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KIDNEYWEEK 2018

San Diego, CA • Oct 23 – 28

Abstract Supplement

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KIDNEYWEEK 2018
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Abstract Supplement

Abstract Publication
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- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
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TH-OR001

Extracellular DNA Drives Cholesterol Crystal Embolism-Related Tissue Injury

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Background: Cholesterol crystal (CC) embolism may be an under recognized cause of acute kidney injury (AKI), especially of catheter intervention- or major surgery- related AKI. Little is known about the pathophysiology of CC embolism-related for the lack of animal models.

Methods: Injecting CC into the left renal artery of C57BL/6N, M*lkl*-/- and *CypD*-/- mice, transcutaneous measurement of GFR after CC injection 24h, quantify renal tubular and endothelial cell injury, crystal clot formation inside arteries, quantify the occlusion of renal arteries of varies sizes. Neutrophil depletion and DNase I interventions were used on mice before CC injection, all experiments same as descripted before.

Results: CC injection to mice caused a sudden drop in glomerular filtration rate (GFR) associated CC embolism and crystal clot formation leading to either partial CC or complete occlusion of numerous *interlobar arcuate*, and *interlobular arteries* documented by histology and 3D reconstructions of vascular contrast micro-CT scans. 24h after CC injection partial obstruction was associated with ischemic necrosis of respective tubular S3 segments, while complete obstruction caused large territorial infarction. Such infarcts were surrounded by massive neutrophil infiltrates apparently also derived from vessels of the renal capsule (rim sign). Necroptosis and mitochondrial permeability transition-related regulated necrosis are known to drive post-ischemic AKI but lack of *Mlkl, CypD* or both had no effect on GFR loss or infarct size probably because crystal clot obstruction remained unaffected. Crystal clots stained positive for platelets, neutrophils, fibrin, and DNA. While neutrophil depletion only partially attenuated GFR loss and infarct size recombinant DNAse I was fully protective as it reduced the number of complete vascular occlusion. *In vitro* studies revealed that CC induce membrane rupture and DNA release from endothelial cells, neutrophils, and platelets and that CC-induced activation of platelets induces neutrophil extracellular traps formation. CC embolism was found in 446 of 92,000 diagnostic kidney biopsies (0.5%).

Conclusions: CC embolism activates numerous cell types to release DNA, which is a central component of crystal clot formation, vascular occlusion, and kidney infarct-related AKI.

Funding: Other U.S. Government Support

TH-OR002

Mitochondrial DNA Leakage Causes Inflammation via the cGAS-STING Axis in Cisplatin-Mediated Tubular Damage

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Background: Cisplatin is an anti-neoplastic drug that induces tubular inflammation. However, its detailed mechanisms are not fully understood. Stimulator of interferon genes (STING) and its upstream or downstream molecules (cGAS-STING axis) play an important role in 3self/non-self DNA-triggered signal transduction, leading to inflammation. Here, we investigated the potential role of STING-mediated inflammation in cisplatin-induced tubular inflammation.

Methods: The human proximal tubular cell line, HK-2, was treated with 10 μM of cisplatin and the renal cortex of C57BL/6 mice, injected with 25 mg/kg of cisplatin for 72 h, was analyzed. The changes in cGAS-STING activation, mitochondrial DNA (mtDNA) leakage, or BAX expression were evaluated using real-time PCR, western blotting, or immunofluorescence analysis. Cisplatin and/or STING siRNA-treated HK-2 culture supernatants were analyzed using cytokine arrays and migration assays. Amlexanox and ethidium bromide (EtBr) were used for cGAS-STING axis inhibition and mtDNA depletion, respectively.

Results: In cisplatin-treated HK-2 or kidney cortex, STING expression was upregulated and translocated from the ER to the Golgi apparatus, indicating STING activation by cisplatin. Subsequently, the cGAS-STING axis(TBK-1, IRF3, and P65) was activated due to cisplatin-mediated phosphorylation. Cisplatin also induced inflammatory cytokine(IL-6, IL-8, ICAM-1, CXCL10, and GMCSF) production and neutrophil chemotaxis, which were ameliorated by STING knockdown ($P < 0.05$). Amlexanox prevented cytokine production via cGAS-STING axis inhibition (IRF3 inactivation). Interestingly, cisplatin-mediated mtDNA leakage to the cytosol activated cGAS-STING axis-mediated inflammation. In fact, EtBr-mediated mtDNA depletion inhibited the inflammation by cisplatin in HK-2. Cisplatin-induced BAX expression, which interacted with the mitochondrial permeability transition pore, suggested that mtDNA leakage was caused by the increase in BAX expression.

Conclusions: mtDNA leakage to the cytosol induces tubular inflammation by activating the cGAS-STING axis in cisplatin nephrotoxicity.

TH-OR003

Knockout of DNA Methyltransferases in Proximal Tubules Preserves Klotho and Improves Kidney Repair after Ischemia/Reperfusion Injury

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Background: DNA methylation, catalyzed by DNA methyltransferases (DNMTs), is an important epigenetic mechanism that has been implicated in renal development, function, and disease pathogenesis. However, the role of DNA methylation in renal ischemia/reperfusion (I/R) injury and subsequent kidney repair remains largely unknown.

Methods: Mice were subjected to: i) 30 minutes of bilateral renal ischemia with 48 hours of reperfusion to examine renal I/R injury, and ii) 30 minutes of unilateral renal ischemia with 2 weeks of reperfusion to analyze post-injury kidney repair. To determine the role of DNA methylation, we established kidney proximal tubule-specific DNMT1 knockout (PT-DNMT1-KO) or DNMT1 and DNMT3a double knockout (PT-DNMT1/3a-DKO) mouse models.

Results: DNMT1 and DNMT3a were markedly increased in renal tubular cells during renal I/R injury as well as post-injury kidney repair. Knockout of DNMT1 or knockout of both DNMT1 and DNMT3a in proximal tubules did not affect renal I/R injury. However, DNMT1 and DNMT3a double knockout (PT-DNMT1/3a-DKO) promoted post-injury kidney repair and attenuated renal fibroblast activation and interstitial renal fibrosis. Two weeks after I/R injury, PT-DNMT1/3a-DKO mice showed lower kidney injury molecule-1 (Kim-1) and vimentin expression than wild type mice, suggesting better kidney repair in DKO mice. Furthermore, DKO mice showed less accumulation of fibronectin and α-SMA (myofibroblast marker) with lower levels of collagen deposition in kidneys, indicating less interstitial fibrosis. Mechanistically, post-injury kidneys showed hypermethylation of Klotho, the anti-aging gene with anti-fibrosis activity. Hypermethylation of Klotho was accompanied by a dramatic decrease of Klotho expression in kidneys. Notably, DNMT1/3a-DKO prevented Klotho hypermethylation and preserved Klotho expression in post-injury kidneys.

Conclusions: These results indicate that DNMT1 and DNMT3a-dependent DNA methylation in proximal tubules plays an important role in kidney repair following renal I/R. Changes in DNA methylation in specific genes, such as Klotho, may lead to aberrant gene expression to promote maladaptive repair and interstitial fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR004

Orphan Nuclear Receptor COUP-TFII Regulates Pericyte Detachment in AKI

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Background: Pericytes are essential to maintain capillary integrity. Acute kidney injury (AKI) causes pericyte detachment from capillaries, triggering endothelial cell injury, capillary rarefaction, and hypoxia, contributing to interstitial fibrosis. The molecular mechanisms underlying pericyte detachment and subsequent transition to myofibroblasts are poorly understood. We hypothesized that Chicken Ovalbumin Upstream Promoter-Transcription Factor II (COUP-TFII) is important for maintaining kidney pericyte function by preventing detachment/activation in the setting of kidney injury.

Methods: COUP-TFII mRNA was measured by quantitative real-time PCR (qRT-PCR) and protein by immunostaining at different times after unilateral ischemia reperfusion (IRI). In vitro, knockdown of COUP-TFII was attained by transfecting a small interfering RNA (siRNA) into CH310T1/2 (pericyte-like cells). Angiopoietin 1 (Ang1, a angiotrophic protein produced by pericyte to maintain vessel stability) expression was evaluated. In addition, we generated CRISPR-cas9 COUP-TFII knock out and tetracycline-inducible COUP-TFII overexpressing CH310T1/2 cells. By modulating COUP-TFII expression, we studied the effect on αSMA expression (a marker of myofibroblast) and cell migration (using scratch motility assay) in CH310T1/2 cells.

Results: COUP-TFII mRNA and protein expression initially decreased at 4 hours after IRI, returned to baseline at 24 hours, and was significantly increased at day 21 post-IRI. In vitro, knockdown of COUP-TFII by siRNA resulted in decreased Ang1 expression in CH310T1/2 cells. Furthermore, knock out of COUP-TFII resulted in increased αSMA mRNA expression and promoted migration compared to wild type CH310T1/2 cells. In contrast, over-expression of COUP-TFII decreased αSMA mRNA expression and inhibited migration compared to control-transfected cells.

Conclusions: Down regulation of COUP-TFII in AKI is an early event regulating pericyte fate. It results in: 1) decreased Ang1 expression, which is important for pericyte-endothelial crosstalk; 2) increased αSMA expression and cell migration, which is important for the pericyte to myofibroblast transdiferentiation. Maintaining COUP-TFII expression may stabilize pericytes, protect endothelial cells in the early phase of AKI, and prevent vascular rarefaction, secondary ischemia and subsequent fibrosis.

Funding: NIDDK Support

TH-OR005

The Orphan Nuclear Receptor RORα Is a Potential Endogenous Protector in Renal Ischemia/Reperfusion Injury

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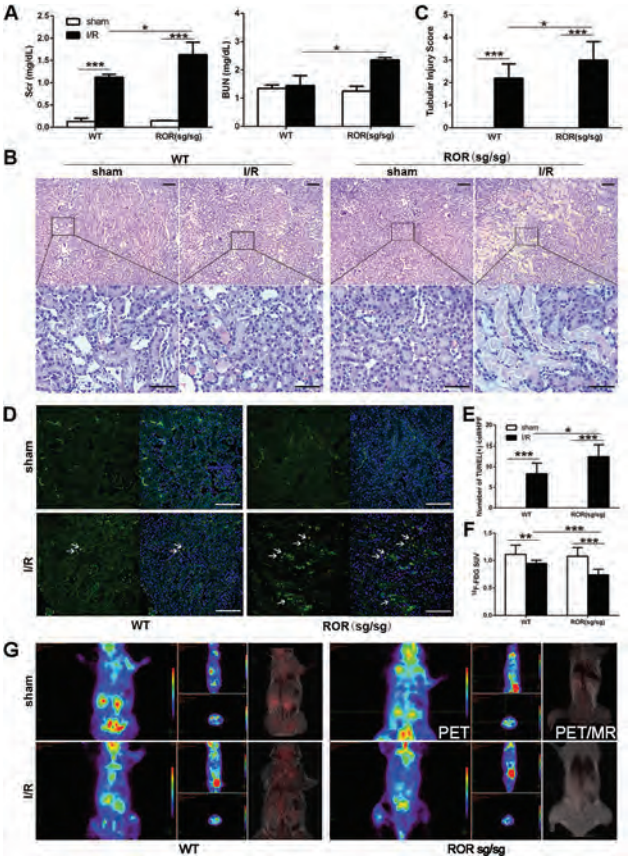
Background: Emerging evidence indicates that retinoid-related orphan receptor alpha (RORα), a member of the ROR nuclear receptor (NR) subfamily, mediates key cellular adaptions to hypoxia and contributes to the pathophysiology of many disease states. However, the effects of RORα in renal ischemia/reperfusion (I/R) injury remain unclear.

Methods: Wild-type C57BL/6 mice, ROR-deficient stagger [ROR (sg/sg)] mice and their wild-type (WT) littermates were used for in vivo studies. Renal I/R injury model was induced by bilateral renal pedicle clamping for 35 minutes. HK-2 cells and human kidney samples were used for in vitro studies. HK-2 cells were treated with hypoxia (1% oxygen) to establish the cell hypoxia/reoxygenation (H/R) model.

Results: We found that RORα was significantly down-regulated after renal I/R injury. RORα-deficient stagger mice displayed dramatically augmented renal dysfunction and morphological damage compared with wild-type (WT) mice at 24 hours post-I/R. Further study revealed that the detrimental effects of RORα deficiency were attributable to tubular epithelial cell apoptosis and, consequently, renal inflammation and oxidative stress. The proapoptotic effect of RORα deficiency was associated with aggravated mitochondrial dysfunction in renal tubular cells after I/R. However, pretreatment of WT mice with the RORα agonist SR1078 ameliorated I/R-induced renal dysfunction and damage and elicited a concomitant decrease in tubular epithelial cell apoptosis.

Conclusions: In summary, our study provides experimental evidence showing that RORα is a novel endogenous protector against renal I/R injury and that RORα activation is a promising therapeutic strategy for the prevention of acute kidney injury.

Funding: Government Support - Non-U.S.



RORα deficiency aggravates renal injury at 24 hours post-I/R.

TH-OR006

Stress Response Gene NUPR1 Protects Renal Tubular Cells from Proliferation-Induced Energy Exhaustion

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Background: Energy depletion in renal tubular cells is a hallmark of acute kidney injury associated with cell death. *NUPR1* (Nuclear protein 1, transcriptional regulator) promotes survival, increases ATP and inhibits proliferation in renal tubular cells. Although proliferation of tubular cells is necessary for kidney repair after resolution of injury, it could increase vulnerability in the context of ongoing injury. The effect of proliferation on energy in cells is unknown. We hypothesized that *NUPR1* protects renal tubular cells from proliferation-induced energy exhaustion.

Methods: Stable renal proximal tubular cell lines were generated from HK-2 cells with inducible expression of *NUPR1* (gain-of-function) or of CRISPR-dCas9-KRAB repression of *NUPR1* (loss-of-function). The cells were transfected with the fluorescent biosensor PercevalHR to visualize the intracellular ATP/ADP ratio and with the intracellular pH sensor pHRed to adjust the ATP/ADP measures. The RatioPlus plugin from Fiji was used to measure ATP/ADP and pH from dual wavelength acquisitions of PercevalHR and pHRed, and the TrackMate plugin was used for monitoring single cell trajectories. The effect of tenovin-1 (p53 agonist for G1/S arrest), rigosertib (PLK1 inhibitor for G2/M arrest), pifithrin-α (p53 inhibitor for G1/S passage) and KU55933 (ATM kinase inhibitor for G2/M passage) on the ATP/ADP ratio was assessed.

Results: *NUPR1* overexpression increased the ATP/ADP ratio in tubular cells. Conversely, *NUPR1* inhibition decreased the ATP/ADP ratio. Modeling proliferative repair after injury by a scratch assay or facilitation of cell cycle passage by pifithrin-α or KU55933 decreased ATP/ADP ratio in migrating and proliferating cells. In contrast, inhibition of proliferation by either contact inhibition, tenovin-1 or rigosertib recapitulated *NUPR1*'s protective effect on ATP/ADP levels. Proliferating cells undergo cyclic variations of the ATP/ADP ratio, with a mitotic peak followed by a sudden drop of ATP/ADP ratio and a gradual recovery.

Conclusions: *NUPR1* protects renal tubular cells from energy depletion caused by proliferation. Proliferation is associated with decreased energy, characterized by cyclic steep diminution of ATP/ADP ratio after mitosis. Delaying proliferation is a potential therapeutic goal to minimize damage during acute kidney injury and prevent maladaptive repair after injury.

Funding: NIDDK Support, Private Foundation Support

TH-OR007

C-Type Lectin Mincle Accelerates Renal Ischemia-Reperfusion Injury

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Background: Evidence has accumulated suggesting that pathogen sensors such as Toll-like receptors contribute to the pathogenesis of various non-infectious diseases. It is also known that Macrophage-inducible C-type lectin (Mincle), a pathogen sensor for *Mycobacterium tuberculosis*, can sense cell death, suggesting the role of Mincle in sterile inflammation. Indeed, we recently demonstrated that Mincle plays an important role in obesity-induced adipose tissue inflammation, thereby regulating systemic insulin resistance. In this study, we investigated the pathophysiologic role of Mincle in a mouse model of acute kidney injury.

Methods: Eight to eleven week-old male Mincle-deficient mice or wildtype mice were subjected to ischemia-reperfusion injury. After 30 minutes of ischemic period, the clamp of left kidney was released to induce reperfusion. The right side of kidney was resected at this time point.

Results: There was a marked upregulation of Mincle mRNA in the injured kidney from 6 hours after the reperfusion. Histological and flow cytometric analysis revealed that most of the Mincle-expressing cells were proinflammatory M1 macrophages infiltrating toward the damaged tubules. All of the Mincle-deficient mice were alive during the experimental period, while about half of wildtype mice died due to renal failure. Consistently, serum concentrations of BUN and creatinine along with mRNA expression of proinflammatory cytokines were significantly ameliorated in the kidney of Mincle-deficient mice compared to wildtype mice. Moreover, wildtype mice were protected against ischemia-reperfusion injury when they received bone marrow transplantation from Mincle-deficient mice.

Conclusions: This study indicates that Mincle in macrophages plays an important role in the pathogenesis of acute kidney injury. Our data also suggest that Mincle senses damaged tubular epithelial cells to accelerate inflammation.

Funding: Government Support - Non-U.S.

TH-OR008

Novel Liposomal Nanocarriers of Preassembled Glycocalyx Restore Renal Microcirculation in Sepsis

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Background: Endothelial cell dysfunction is a weighty contributor to the pathogenesis of sepsis. Endothelial glycocalyx (EG) is a guardian of endothelial functions, but during the course of sepsis its integrity is compromised. We observed that mice with the polymicrobial sepsis exhibit a drastic reduction in the global volume of EG. The loss of EG leads to leukocyte infiltration, impaired microvascular circulation, increased vascular permeability, thrombogenesis, and circulatory collapse, eventuating in the development of multiorgan dysfunction. Therapeutic attempts to prevent EG loss showed success, however, clinically more important restorative therapies of EG have been unsuccessful.

Methods: We have recently invented liposomal nanocarriers of preassembled EG (LNPEG) to expeditiously restore EG and halt vascular complications of sepsis. We used atomic force microscopy, DAF-based NO detection, flow-induced vasodilation and in vivo LPS Laser-Doppler studies.

Results: In vitro testing of LNPEG using atomic force microscopy of cultured endothelial cells showed that they increased thickness of EG and restored mechanoactivation-induced NO production, both severely affected by exposure to LPS. Ex vivo perfused isolated arterioles with degraded EG obtained from LPS-injected mice showed subnormal flow-induced dilation and exhibited increased vascular permeability, whereas perfusion of these vessels with LNPEG restored both and increased flow-induced NO production. In LPS mice,

infusion of LNPEG either systemically or into the renal artery significantly improved renal microcirculation (laser-Doppler imaging and flowmetry). Electron microscopy of kidneys localized LNPEG to be tethered to or embedded into the plasma membrane of glomerular and peritubular capillary endothelial cells. Immunostaining of EG showed its significant restoration after administration of LNPEG.

Conclusions: In conclusion, this is the first demonstration that our invented LNPEG are functionally capable of expeditiously restoring EG and halting vascular complications of sepsis. In summary, wepropose that the early loss of EG facilitates multiorgan failure in sepsis, and treatment with LNPEG has a potential to alleviate it.

TH-OR009

Human Recombinant Alkaline Phosphatase (recAP) Protection from Kidney Ischemia-Reperfusion Injury (IRI) Is Mediated by Dephosphorylation of ATP to Adenosine and Activation of Adenosine A2a Receptors

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Background: Acute kidney injury (AKI) results in high mortality (up to 50%), and surviving patients are at risk for progressive chronic kidney disease (CKD). ATP released from dying cells acts as a potent pro-inflammatory 'danger' signal. Alkaline phosphatase (AP), a common endogenous enzyme that de-phosphorylates ATP, appears to play a significant anti-inflammatory role in host defense and innate immunity. Human recombinant AP (recAP) is currently in Phase 2 clinical trials for treatment of sepsis-associated AKI. We hypothesized that recAP protects kidneys from IRI by metabolizing released extracellular ATP to adenosine, producing anti-inflammatory effects through activation of adenosine A2a receptors (A2aR).

Methods: RecAP (500-2000 U/kg, iv) ± ZM-241,385 (ZM, 20, 200 mg/kg, sc) (adenosine A2a receptor antagonist) were administered 1h before renal ischemia in mice and at times after ischemia in rats; kidney injury in mice was evaluated at 24h.

Results: RecAP dose-dependently decreased kidney injury in WT mice after 26 min ischemia; the 80% decrease in plasma creatinine with 2000 U recAP/kg was prevented completely by co-administration with ZM (20 mg/kg). Enzymatically inactive (mutant) recAP was not protective, suggesting that ATP dephosphorylation is necessary for protection. RecAP also protected *CD73*$^{-/-}$ mice, which lack a 5' ectonucleotidase that de-phosphorylates AMP to adenosine and are more sensitive to IRI than WT mice (22 min ischemia); this beneficial effect of recAP in *CD73*$^{-/-}$ mice (34% of control) was partially blocked by 200 mg/kg ZM (86% of control). In rats recAP ameliorated IRI when administered *after* initiation of acute injury, an effect reversed by ZM, thus providing relevance for therapeutic dosing of recAP clinically. In a CKD ischemic rat model, recAP given after the 3rd instance of IRI also significantly reduced renal injury (61% reduction).

Conclusions: These results strongly suggest that during renal IRI recAP promotes production of adenosine from liberated ATP in injured kidney tissue, thereby amplifying endogenous mechanisms that can reverse tissue injury, in part through A2aR-dependent anti-inflammatory signaling pathways.

Funding: Commercial Support - Pfizer Inc./AM-Pharma B.V.

TH-OR010

Inactivation of Mtorc1 in Proximal Tubular Epithelial Cells Reduces KIM-1-Mediated Kidney Fibrosis and Inflammation in Mice

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Background: Acute kidney injury (AKI) predisposes patients to progressive chronic kidney disease (CKD). Previously we reported that persistent expression, beginning prenatally, of kidney injury molecule-1 (KIM-1) in tubule epithelial cells of the nephron causes murine kidney fibrosis through a mechanism involving mTOR. Since prenatal activation of KIM-1 in this system also decreases nephron number, we tested the hypothesis that postnatal activation of KIM-1 expression specifically in proximal tubular cells (PTCs) would lead to fibrosis independent of any potential effect on kidney development, and evaluated the role of mTOR in this context.

Methods: We created proximal tubular cell specific KIM-1 overexpression transgenic mice by treating Slc34a1$^{CreERT2/+}$;CAG-Z/Kim1-AP$^{tg/+}$ (KIM-1^{PTCtg}) mice with tamoxifen beginning at 4 weeks of age to express KIM-1 in proximal tubules in a postnatal, post kidney development, context. The resulting KIM-1^{PTCtg} mice (and non-KIM-1 overexpression controls) were subjected to bilateral renal ischemia-reperfusion injury (IRI) for 26 minutes, or sham surgery, at 3 months of age and then evaluated at 3 or 6 months later for kidney fibrosis. We also created KIM-1^{PTCtg}/Raptor^{PTCko} mice, where mTORC1 is deleted at 4 weeks of age in KIM-1 overexpressing PTCs, using the same tamoxifen-inducible promoter, and these animals were then evaluated for kidney fibrosis with or without bilateral IRI.

Results: With tamoxifen-induced postnatal KIM-1 overexpression in proximal tubular cells, KIM-1^{PTCtg} mice developed fibrosis with progressive renal insufficiency at 6 months of age. Bilateral IRI in KIM-1^{PTCtg} mice at 3 months of age caused maladaptive repair and a persistence of renal insufficiency post injury, leading to progressive kidney fibrosis and renal failure with an earlier onset (5 months of age) than sham controls. In contrast, KIM-1^{PTCtg}/Raptor^{PTCko} mice subjected to bilateral IRI had less kidney fibrosis and a reduced inflammatory response, demonstrating a role for mTOR in the fibrotic response.

Conclusions: Persistent expression of KIM-1 may play an important role on the link between AKI and progressive CKD. mTORC1 is a potential therapeutic target in KIM-1-mediated kidney injury and fibrosis in mice.

Funding: NIDDK Support, Other U.S. Government Support

TH-OR011

The Hyaluronan Synthase-1 Isoenzyme Promotes Differentiation to a Distinct Subset of Myofibroblasts That Limit Fibrosis Progression

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Background: Renal interstitial fibrosis is a key determinant of CKD progression, and increased synthesis of the glycosaminoglycan, Hyaluronan (HA), in renal tissue correlates with fibrosis and renal outcomes. Factors that regulate HA synthesis therefore influence CKD progression. HA is synthesized by three HA Synthase enzymes (HAS1, HAS2 and HAS3). Our work has specifically shown that increased HAS2 expression is causally linked with fibrosis *in vivo* and is a critical mediator of pro-fibrotic cell phenotype *in vitro*. Furthermore, the anti-fibrotic growth factor BMP7 (Bone Morphogenetic Protein-7) prevents/reverses pro-fibrotic cell phenotype and renal fibrosis in murine models. Recent data shows BMP7 significantly increases HAS1 expression, indicating a possible protective role for this enzyme in fibrosis

Methods: Studies were performed on human proximal tubular epithelial cells our established library of scarring *versus* non-scarring primary fibroblasts. Genetic and histological analysis of kidneys from HAS1, HAS3 and HAS1/3 double knockout mice and Ischaemia Reperfusion Injury (IRI) -induced renal fibrosis were used

Results: In response to TGF-β1, cells primarily expressing the HAS2 isoenzyme assembled large pericellular HA coats tethered to the principal HA receptor CD44-standard. The cells were significantly α-smooth muscle actin (αSMA) positive and had a contractile phenotype. TGF-β1 stimulation in HAS1 isoenzyme expressing cells had negligible HA pericellular coats and enhanced cell-surface expression of the CD44 variant isoform, CD44v7/8. These cells had a limited contractile response, were pro-migratory, with low αSMA expression and laid down different matrix. Mice with IRI have elevated levels of both HAS1 and HAS2 in acute early injury, and HAS2 in late injury; whilst kidneys from HAS1/3 DKO mice were predisposed to pro-fibrotic renal injury

Conclusions: Different HAS isoenzymes have distinct and likely conflicting roles in response to pro-fibrotic stimuli. Whilst HAS2 promotes a pro-fibrotic contractile cell phenotype associated with tissue fibrosis, HAS1 appears to limit pro-fibrotic phenotypes and promotes a distinct subset of myofibroblasts that are pro-migratory and may be involved in reparative processes that limits fibrotic injury

TH-OR012

PINK1-MFN2-Parkin-Mediated Mitophagy Dependent Macrophage Reprogramming Protects against Renal Fibrosis

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Background: Mitophagy, by maintaining mitochondrial quality, plays critical role for normal kidney function. Kidney injury-induced mitochondrial oxidative stress triggers proinflammatory cytokine production by M1 macrophages and their reprogramming towards profibrotic/M2 phenotype. We investigated the role of mitophagy regulatory proteins: PTEN-induced kinase1 (PINK1), Mitofusin 2 (MFN2) and Parkin in macrophage reprogramming during renal fibrosis.

Methods: Renal fibrosis in wild type, PINK1 and Parkin knockout (KO) mice was induced by unilateral ureteral obstruction (UUO) (7-days) or adenine diet (14-days). Renal macrophages from mice and human kidneys were isolated by magnetic beads. Flow cytometry (F4/80, CD11b, Ly6c, CCR1, CX3CR1) and western blots (iNOS, arginase I, mannose receptor-1, fibronectin, rictor, TGFβ1, TGFβR1) were performed to determine macrophage phenotypes and fibrotic response. MitoTracker & MitoSox dyes were used to access mitochondrial membrane potential (MMP) and reactive-oxygen species (mROS). Mitophagy was suppressed by transfection of PINK1-siRNA/Mdivi1 or induced by FCCP treatment.

Results: Obstructed kidneys from PINK1/Parkin KO mice displayed higher expression of FN, MR-1, TGFβ1, TGFβRI & CD45+ mononuclear cells. Renal macrophages from obstructed kidneys of KO mice showed amplified fibrotic response. TGFβ1-treated BMDM from the KO mice displayed greater levels of mROS, rictor, Arg I but not iNOS expressing M1 macrophages. PINK1-knockdown THP-1 human macrophages showed lower phosphorylation at MFN2. Mitochondria from FCCP treated MFN2-KO macrophages showed reduced expression of Parkin and lower MMP. Inhibition of mitophagy in human primary renal macrophages resulted in: i) elevated expression of FN, MR-1, TGFβ1 & CX3CR1, ii) reduced MMP & iii) enhanced mROS production. Human fibrotic kidney showed higher relative mRNA expression of MRC1 (P=0.002), TGFβ1 (P=0.03) and a trend of decrease in Parkin (P=0.07) expression than control kidney.

Conclusions: UUO and adenine diet-induced oxidative stress and renal fibrosis were exaggerated in absence of mitophagy. Deficiency of PINK1 in macrophages resulted in decreased phosphorylation of MFN2, suppressed recruitment of Parkin to mitochondria and rictor-mediated reprogramming of macrophages towards M2/profibrotic phenotype.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR013

Loss of Transcription Factor A (Mitochondrial, Tfam) in Tubule Cells Causes Renal Failure by Linking Metabolic Insufficiency to Enhanced Inflammation

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Background: Renal tubule cells have one of the highest mitochondrial density to keep up with their high energy need. Loss and dysfunction of mitochondria has been proposed to play key role in kidney disease development. On the other hand, the key transcriptional regulator that maintains mitochondrial integrity in renal tubule cells of healthy kidneys have not been defined.

Methods: To investigate the role of Tfam on renal tubule epithelial cells (TECs), we generated and characterized tubule specific Tfam (Transcription Factor A, mitochondrial) knock-out mice (Ksp cre/Tfam $^{flox/flox}$). To perform *in vitro* mechanism studies, we cultured primary TECs from wild-type and WT/Tfam $^{flox/flox}$ mice and infected them with Ad5CMVCre adenovirus to delete Tfam.

Results: Tfam deficient mice were viable at birth but they died by 12 weeks of age. Blood chemistry indicated significant renal damage and azotemia. Structurally, the kidneys were enlarged, the tubules were dilated. There was an increase in inflammatory cells and matrix accumulation. Renal epithelial cells showed abnormally enlarged mitochondria and structural defect. Mitochondrial oxidative phosphorylation associated proteins were decreased with mild lipid accumulation. Mechanistic studies, using primary cultured tubule epithelial cells demonstrated that aberrant mtDNA packaging upon Tfam deficiency results in an escape of mtDNA into the cytosol. These events induced the activation of cytosolic DNA sensing pathway such as Stimulator of interferon genes (STING)-Cyclic GMP-AMP synthase (cGAS), and downstream NF-κB activation. The NF-κB activation was also evident in kidneys of the knock-out mice. Blunting of the NF-κB activation, reduced inflammatory gene expression, proliferation of tubule cells and protected from cellular dedifferentiation.

Conclusions: Collectively, we show Tfam maintains mitochondrial integrity and cellular metabolism at baseline. Loss of Tfam results in NF-κB activation linking metabolic signals to inflammation.

Funding: NIDDK Support

TH-OR014

Novel Rho-Associated Coiled Kinase 2 Inhibitor (ANG4201) Reduces Renal Fibrosis and Improves Kidney Function in Subtotal Nephrectomy Mice Model

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Background: Rho associated coiled kinase 1 (ROCK1) and 2 (ROCK2) are implicated in variety of cellular processes including organ fibrosis. Earlier we demonstrated that kidney ROCK2 and not ROCK1 is upregulated in animal models of renal fibrosis. The present study was done to investigate if inhibiting ROCK2 reduces renal fibrosis and improves kidney function.

Methods: Using core hopping and structure based drug design approach, we synthesized highly selective (>200 fold for ROCK2 vs ROCK1), orally bioavailable ROCK2 inhibitor (ANG4201). We evaluated the antifibrotic effects of ANG4201 in subtotal nephrectomy (Nx) mice model. Adult male SV129 mice were subjected to Nx, wherein poles of one kidney were ablated and contralateral kidneys were removed after two weeks. The Nx were then randomized to vehicle or ANG4201 (20 mg/Kg, PO, BID) and treated for 8 weeks. A week prior to sacrifice, GFR was measured by using FITC-Inulin clearance method. Blood pressure was measured by direct cannulation of the carotid artery. Kidney tissues were analyzed for fibrotic, molecular and inflammatory markers.

Results: Compared to control, Nx mic exhibited increase in both renal ROCK2 expression and phosphorylation of myosin phosphatase, a downstream marker of ROCK2 activity. Treating Nx mice with ANG4201 blocked the upregulation of these proteins. The increase in ROCK2 activity correlated with increase in renal fibrosis characterized by increase in kidney hydroxyproline and α-SMA expression. Nx mice also had elevated blood pressure (MAP; ~165 mm Hg). Intervention with ANG4201 did not affect blood pressure but attenuated hydroxyproline and α-SMA expression which were confirmed with Mason's trichrome and Picrosirius red staining. The reduction in fibrosis was associated with significant improvement in GFR by ~38%, measured by FITC-Inulin clearance method. Urinary EGF, marker of renal function loss was found to be elevated in Nx and subsequently reduced with ANG4201 treatment.

Conclusions: This study demonstrates that ROCK2 upregulation contributes to renal fibrosis and renal functional loss in subtotal nephrectomy mice model. ANG4201 is highly promising orally bioavailable therapeutic ROCK2 inhibitor with potential use in chronic kidney disease.

Funding: NIDDK Support

TH-OR015

Inhibition of Tubulointerstitial Fibrosis by Targeting the p70 Ribosomal Protein S6 Kinase 1

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Background: Tubulointerstitial fibrosis strongly correlates with the decline of renal function in chronic kidney disease (CKD), regardless of the primary etiology. Tubulointerstitial fibrosis is the major characteristic of the patients with aristolochic acid (AA) nephropathy, which is caused by the ingestion of herbs containing AA. Studies using rapamycin suggested that activation of the target of rapamycin (mTOR) might be causally linked to renal fibrosis, but mTOR knockout caused embryonic lethality; mTOR has multiple downstream effectors, including the p70 S6 kinase 1 (S6K1). Here we report the effect of S6K1 knockout on renal fibrosis.

Methods: Induction of tubulointerstitial fibrosis was accomplished by aristolochic acid I (AAI, given at a dose of 3 mg/kg body weight by daily I.P. for 3 consecutive days) or unilateral urethra obstruction (UUO) in wild type and S6K1 knockout mice. Renal lesions, kidney function and mTOR-S6K1 signaling activities were evaluated.

Results: AAI caused a marked increase of kidney injury molecule 1 (KIM-1) and necrosis of proximal tubular epithelial cells. In addition, we observed that the S2 segment of renal proximal tubule is more susceptible to injury than the S1 and S3 segments of proximal tubule in response to AAI treatment. These lesions resulted in a significant decrease in renal function (indicated by elevated serum creatinine and BUN levels) within 3 days, peaked by day 7. AAI treatment or UUO induced massive tubulointerstitial fibrosis within 2-4 weeks, revealed by a marked reduction of renal tubules, proliferation of a-smooth muscle actin-positive cells, Masson trichrome stains, and deposition of extracellular matrix proteins including fibronectin and fibroblast-specific protein 1 (FSP1). Interestingly, mechanistic studies revealed marked activation of S6K1 and ribosomal protein S6 (rpS6) phosphorylation in the kidney in response to either AAI or UUO. Importantly, mice with global (whole animal) homozygous S6K1 knockout were viable and protected from tubulointerstitial fibrosis.

Conclusions: The present study provides the first unequivocal evidence that activation of S6K1 plays an important pathogenic role during the development of tubulointerstitial fibrosis. Thus, specifically targeting S6K1 may represent a viable strategy for the prevention and treatment of renal fibrosis.

Funding: NIDDK Support

TH-OR016

CD47 Blockade Modulates Fibrosis in Chronic Kidney Injury

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Background: Acute kidney injury triggers a complex cascade of cellular esponses that can culminate in maladaptive repair and fibrosis. The matrix protein thrombospondin-1 (TSP1) is known to activate latent TGF-beta, a crucial mediator of fibrosis. We have previously reported that the TSP1 and its receptor CD47 are are induced following kidney injury. However, the role of this axis has not been characterized in chronic kidney disease.

Methods: Age and gender-matched wild-type (WT), CD47$^{-/-}$ and WT mice treated with CD47 blocking antibody (WT+αCD47Ab) were compared in two chronic kidney injury models: ischemia-reperfusion injury and contralateral nephrectomy (RN), and unilateral ureteric obstruction (UUO). All animals underwent analysis of renal function and biomolecular phenotyping. Human and murine WT and CD47$^{-/-}$ renal tubular epithelial cells (rTEC) were studied *in vitro*.

Results: WT, WT + CD47Ab, and CD47$^{-/-}$ RN mice showed no difference in serum creatinine at 4 weeks regardless of injury model, however there was clear amelioration of renal histological changes and fibrosis with blockade or global knockout of CD47, defined by light microscopy and Sirius red staining. WT RN mice showed upregulated mRNA and protein expression of TSP-1 and pro-fibrotic markers TGF-ß, SMAD2, α-smooth muscle actin (SMA), fibronectin and type I collagen. These markers were significantly abrogated in both CD47$^{-/-}$ and WT + αCD47Ab counterparts. Interestingly, both WT and CD47$^{-/-}$ UUO mice at day+7 showed equivalent increases in pro-fibrotic tendency, by histology and qPCR, regardless of overall TSP1 expression. Only treatment with αCD47Ab reduced markers of matrix protein deposition. Renal tubular epithelial cells isolated from WT mice showed robust upregulation of TSP1 and elaborated pro-fibrotic markers under hypoxic stress, which was mitigated in CD47$^{-/-}$ cells. Incubation of rTEC with exogenous TSP1 demonstrated epithelia-to-mesenchyme transition with increased expression of TGF-ß and α-SMA. Immunohistochemistry of human kidney biopsy samples showed upregulated tubular TSP1 expression in stages 3-4 CKD (eGFR 15-59ml/min), and concurrently raised plasma TSP1 levels (8-10 fold) when compared to control samples (eGFR>60ml/min).

Conclusions: These data suggest that renal tubular epithelial cells contribute to fibrosis by activating TSP1-CD47 signalling, and point to CD47 as a target to limit fibrosis following some types of renal injury.

Funding: Government Support - Non-U.S.

TH-OR017

Klotho Overexpression Improves Interstitial Fibrosis, Accumulation of Cell Cycle Arrested Cells, and Increased Levels of Oxidative Stress in the Kidneys of Aging Mice

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Background: Klotho is reported to suppress growth factor signaling by transforming growth factor (TGF)-β1, insulin-like growth factor (IGF)-1, and Wnt. Notably, previous studies have reported that renal function decreases with age, and that interstitial fibrosis, accumulation of cell cycle arrested cells, and increased levels of oxidative stress are major features of the aging kidney. In this study, we investigated whether klotho overexpression improves these factors in the kidneys of aging mice together with the expression of growth factor signaling molecules.

Methods: Male mice that overexpress klotho under the control of the human elongation factor 1 promoter EFmKL46 (KLTG) or wild type 129 mice (WT) were used. Mice at 2 and 24 months old were defined as young mice and aging mice, respectively. Expression of klotho, fibrotic markers (α-smooth muscle actin, vimentin, collagen I, collagen III), cell cycle markers (p16, p21, p53, proliferating cell nuclear antigen), and oxidative stress markers (8-hydroxy-2′-deoxyguanosine, manganese superoxide dismutase, catalase, 3-nitroturosine) were examined using immunohistochemistry, western blotting, and/or quantitative PCR. We also investigated the expression of TGF-β1 (Smad2/3/4), IGF-1 (c-Jun N-terminal kinase, extracellular signal-regulated kinase, p38, protein kinase B, forkhead box protein O1), and Wnt (β-catenin, RAS-related C3 botulinus toxin substrate 1) signaling molecules.

Results: Klotho expression decreased in aging WT mice, whereas it was maintained in aging KLTG mice. Although expression of fibrotic markers did not differ between young KLTG and WT mice, they were significantly suppressed in aging KLTG mice compared with aging WT mice. Similarly, aging KLTG mice demonstrated significantly less expression of cell cycle arrest markers, as well as oxidative stress markers, than aging WT mice. Furthermore, expression of TGF-β1, IGF-1, and Wnt signaling molecules increased in aging WT mice; however, this upregulation was not observed in aging KLTG mice.

Conclusions: Klotho overexpression protects against kidney aging that is characterized by interstitial fibrosis, accumulation of cell cycle arrested cells, and increased levels of oxidative stress in mice, which is accompanied by suppression of signaling for multiple growth factors.

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TH-OR018

Twist1 in Macrophages Attenuates Kidney Fibrosis after Ureteral Obstruction

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Background: Macrophages play a critical role in directing kidney fibrogenesis. The transcription factor Twist1 limits pro-fibrotic cytokine production in macrophages, and we have recently found that activating type 1 angiotensin receptors in macrophages induces Twist1 but paradoxically attenuates renal fibrosis. To directly test the role of macrophage Twist1 in kidney scar formation, we subjected mice with macrophage-specific deletion ("MKO") of Twist1 and controls ("WT") to the unilateral ureteral obstruction model.

Methods: C57BL/6 mice with a floxed allele for the gene encoding Twist1 were bred with LysM-Cre mice to yield Twist1 MKO mice with robust but selective deletion of Twist1 in macrophages (>80% vs. WTs; $p < 0.0001$). Twist1 MKO and WT littermate controls underwent unilateral ureteral ligation with assessment of kidney fibrosis and macrophage phenotype at 14 days.

Results: 2 weeks after UUO, Twist1 MKO mice developed more kidney fibrosis compared to WTs as quantitated by western blots for collagen I (1.5 ± 0.1 vs 1.00 ± 0.1 au; $p = 0.01$) and α-SMA (1.5 ± 0.15 vs 1.00 ± 0.12 au; $p = 0.01$) and hydroxyproline assay (10.7 ± 0.8 vs 8.2 ± 0.6 mg/10mg; $p = 0.02$). As certain MMPs may limit renal fibrosis by degrading extracellular matrix, we profiled kidney MMP expression after UUO and found that the obstructed Twist1 MKO kidneys compared to WTs had blunted mRNA levels for MMP11 (0.65 ± 0. 05 vs 1.00 ± 0.13; $p = 0.03$) and MMP13 (0.38 ± 0.11 vs 1.00 ± 0.20; $p = 0.03$) but preserved expressions of MMP2 and 7 (0.90 ± 0.14 vs 1.1 ± 0.15; $p = 0.78$ and 0.84 ± 0.30 vs 1.0 ± 0.19; $p = 0.66$, respectively). Other gene expression patterns in the Twist1 MKO kidneys consistent with macrophage-driven fibrosis were blunted Arg-1 levels (0.14 ± 0.06 vs 1.00 ± 0.30; $p = 0.05$) and upregulation of Fizz1 (2.35 ± 0.69 vs 1.0 ± 0.19; $p = 0.03$). We therefore used flow cytometry to detect enhanced accumulation of $CD11b^{+}Ly6C^{hi}$ infiltrating monocytes in the obstructed Twist1 MKO kidneys vs WTs (271 ± 41 vs 169 ± 17 cells/mg kidney; $p = 0.049$). Consistent with a role for Twist1 to suppress inflammatory cytokines in myeloid cells, LPS-stimulated peritoneal macrophages from the Twist1 MKO cohort had upregulated IFN-γmRNA compared to WTs (5.9 ± 0.3 vs 1.0 ± 0.2 au; $p < 0.001$).

Conclusions: Twist1 suppresses myeloid cell-dependent fibrosis in the kidney, possibly through effects on matrix degradation.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR019

Smad Anchor for Receptor Activation (SARA) Prevents Pericyte Activation and Protects Kidney from Fibrosis

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Background: Pericytes are a major source of fibrogenic cells in injured kidneys. We previously reported that decreasing SARA expression drives cultured proximal tubular epithelial cell dedifferentiation to a pro-fibrotic phenotype, and last year at ASN showed that pericyte-specific overexpression of SARA prevents interstitial fibrosis induced by aristolochic acid (AA) in mice. Here, we characterize the actions of SARA in pericytes.

Methods: Conditional human SARA-overexpressing mice were bred with PDGFRβ-Cre mice to drive pericyte SARA expression. The offspring were further bred with Z/EGFP or COL1A1-GFP mice to mark cells where Cre or type I collagen transcription is active, respectively. Mice were given AA (2.5 mg/kg, i.p., 3x week, for 3 weeks), then sacrificed after 3 more weeks. Harvested kidneys were enzymatically digested and sorted for GFP^{+} cells to obtain pericytes that were analyzed by flow cytometry and qPCR. A pericyte line ($Gli1^{+}$-iPeri) was isolated from a $Gli1^{+}$ tdTomato Immortomouse.

Results: As anticipated, native SARA mRNA expression was 62% decreased after AA treatment in GFP^{+} cells isolated from both phenotypically wild-type ($SARA^{WT}$; PDGFRβ-Cre^{+}; Z/EGFP) and SARA-overexpressing ($SARA^{Tg}$; PDGFRβ-Cre^{+}; Z/EGFP) mice. Transgene-derived SARA was detected even after AA, only in $SARA^{Tg}$ mice. $SARA^{Wt}$ mice showed significant expansion of the renal interstitial, GFP^{+} pericyte population after AA treatment, but this did not occur in mice with SARA-overexpression in pericytes. GFP^{+} cells isolated from wild-type mice without AA were $NG2^{+}$, $CD90.1^{-}$, confirming their pericyte origin. AA treatment induced 45% of the wild-type GFP^{+} cells to become $CD90.1^{+}$, suggesting pericyte fibroblastic transition. This shift was not observed in GFP^{+} cells isolated from AA-treated, SARA-overexpressing mice. COL1A1 mRNA expression was incrased by 10 fold in GFP^{+} cells from $SARA^{Wt}$ but not $SARA^{Tg}$ littermates. The $Gli1^{+}$-iPeri cell line expressed very little SARA in culture and strongly expressed αSMA. However, transfection with SARA significantly reduced TGF-β1-induced αSMA and COL1A2 promoter activity, suggesting that re-introduction of SARA at least partially reverses the fibrotic nature of $Gli1^{+}$-iPeri cells.

Conclusions: These data suggest that SARA expression in pericytes suppresses their activation to produce extracellular matrix.

Funding: NIDDK Support

TH-OR020

Anti-dsDNA Antibodies Bind to Ku70 in Proximal Renal Tubular Epithelial Cells and Increased Matrix Protein and Cytokine Secretion

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Background: Anti-dsDNA antibodies can lead to immune-mediated kidney injury through complement activation or trigger downstream pro-inflammatory or fibrotic responses after cellular binding. Immune deposition along tubular basement membrane is commonly observed. We investigated the binding of anti-dsDNA antibodies to proximal renal tubular epithelial cells (PTEC).

Methods: Human polyclonal anti-dsDNA antibodies were isolated from the sera of lupus nephritis patients using affinity chromatography and samples demonstrating high binding affinity to PTEC were studied. Cultured PTEC were incubated with serum-free medium, control IgG, or anti-dsDNA antibodies for up to 48h. PTEC plasma membrane proteins were isolated and immuno-precipitated with anti-dsDNA antibodies to identify cross-reactive antigens using LC-MS/MS. The role of Ku70 in inflammatory and fibrotic processes was investigated by gene silencing with RNAi.

Results: The 70 kDa on PTEC cell membrane that bound anti-dsDNA antibodies was identified as Ku70 by LC-MS/MS. Exogenous DNA, histones, or nucleosomes did not affect its binding by anti-dsDNA antibodies. Anti-dsDNA antibodies binding to Ku70 was accompanied by increased fibronectin and laminin expression, and increased MCP-1 and IL-6 secretion ($P<0.05$, for all). Ku70 gene silencing with ninety percent efficacy resulted in reduced PTEC binding by anti-dsDNA antibodies as shown by immunohistochemistry. Ku70 knockdown significantly decreased the expression of fibronectin, laminin, and Bax, and and also the secretion of MCP-1 and IL-6, induced by TGF-β1, MCP-1, IL-1β, and IL-6 ($P<0.05$, for all). Kidney specimens from lupus nephritis patients and NZB/W F1 mice showed markedly increased Ku70 expression in the proximal tubules.

Conclusions: Our data shows that Ku70 mediates the binding of anti-dsDNA antibodies to PTEC, which is accompanied by downstream pro-inflammatory and pro-fibrotic cellular responses.

Funding: Government Support - Non-U.S.

TH-OR021

FGF23 and Falls in SPRINT

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Background: Fibroblast growth factor 23 (FGF23) is elevated in chronic kidney disease and associated with kidney disease progression and increased mortality. There are little data on circulating FGF23 levels and falls despite the fact that FGF23 is derived from bone and regulates phosphorus and 1,25-dihydroxyvitamin D. The purpose of this analysis was to evaluate the relationship between intact FGF23 (iFGF23) and falls in the Systolic Blood Pressure Interventional Trial (SPRINT).

Methods: SPRINT was a randomized multicenter trial evaluating the effects of standard (SBP <140 mmHg) vs. intensive (SBP <120 mmHg) blood pressure lowering on cardiovascular outcomes among older adults without diabetes. iFGF23 was measured among 2488 participants with eGFR < 60 mL/min/1.73m^2. Cox proportional hazards models adjusted for demographics, comorbidities, randomization group, baseline number of antihypertensives, eGFR, and serum calcium, phosphorus, and intact parathyroid hormone identified the relationship between baseline iFGF23 and time to first fall.

Results: Mean age was 73 ± 9 years, 40% were female, and 66% were white. Mean eGFR was 49 ± 11 mL/min/1.73m^2 and median iFGF23 was 66 [52-88] pg/mL. After full adjustment, participants with iFGF23 levels in the highest quartile (compared to the lowest) demonstrated >2-fold increased risk of falling (HR 2.00 [95% 1.20-2.67]), and a doubling of iFGF23 level was associated with an increased risk of fall (HR 2.34 [95% CI 1.28-4.28]). Intact FGF23 did not modify the relationship between randomization to intensive blood pressure lowering and fall (p for interaction 0.96).

Conclusions: Among SPRINT participants with baseline eGFR < 60 mL/min/1.73m^2, iFGF23 was significantly associated with increased risk of falls; however, FGF23 did not modify the relationship between randomization to intensive blood pressure lowering and falls. FGF23 has been associated with frailty in a large cohort of older community-dwelling adults. Our novel finding that FGF23 increases risk of fall supports a link between FGF23 and frailty. Further investigation is necessary.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR022

Genetic Variants Associated with Circulating Fibroblast Growth Factor-23 among Patients with CKD

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Background: Recent genome-wide association studies (GWAS) identified loci associated with differences in fibroblast growth factor 23 (FGF23) concentrations, near genes involved in vitamin D metabolism, ABO blood group system, and renal phosphate transport. These studies were conducted among individuals with preserved kidney function. It is possible that genetic contributions to circulating FGF23 may differ among individuals with mineral metabolism disturbances, such as those with chronic kidney disease (CKD), in whom the biologic implications and potential treatment options are most relevant.

Methods: We examined 5 SNPs previously identified in GWAS of FGF23 (index SNPs) and 44 putatively functional SNPs in the surrounding regions (±250kb) among unrelated individuals of European ancestry (n=1,666) who participated in the Chronic Renal Insufficiency Cohort (CRIC) Study. We additionally tested for interactions of eGFR on the SNP-FGF23 association.

Results: Two index SNPs were associated with FGF23, after adjustment for age, sex, eGFR and BMI: rs11741640 at 5q35.3/*RGS14/SLC34A1* (beta for the G allele: 5.7% higher FGF23 95% CI: 3.6,13.9, p=0.001) and rs2769071 at 9q34.2/*ABO* (beta coefficient for the G allele: 7.3% higher FGF23, 95% CI: 2.8,11.8, p=0.001). When we expanded to surrounding functional variants, 9 SNPs were associated with FGF23 (false discovery rate ≤ 0.05), all within the 5q35.3 region. The strongest association was for rs4075958 in *RGS14* (beta for the A allele: 7.3% lower FGF23, 95% CI: -11.3,-3.1, p=9x10^{-4}). Statistically significant interaction by eGFR was noted for the association of rs17216707 at 20q13.2/*CYP24A1* (p=0.019).

Conclusions: Our findings provide evidence that a subset of genetic variants associated with FGF23 under normal conditions are also associated in the setting of CKD. Larger, more comprehensive studies are needed to fully assess the generalizability of published GWAS findings and to identify potential novel associations in CKD. Both replication and lack of replication of published GWAS findings in CKD provide important information on the genetic etiology and on pathways influencing mineral metabolism disorders.

Funding: NIDDK Support

TH-OR023

Burosumab Improves Phosphorus Metabolism and Fracture Healing in Adults with X-Linked Hypophosphatemia (XLH)

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Background: In an ongoing, Phase 3, double-blind, multicenter study, we examined the efficacy and safety of burosumab, a human monoclonal antibody against FGF23, in 134 adults with XLH.

Methods: Subjects were randomized 1:1 to receive burosumab 1 mg/kg (n=68) or placebo (n=66) subcutaneously every 4 weeks (wks). After 24 wks, subjects receiving placebo crossed-over to receive burosumab, and all subjects received burosumab during wks 24-48, while remaining blinded to prior treatment.

Results: From wks 0 to 24, a significantly greater percentage of burosumab subjects than placebo subjects (94% vs 8%; p<0.0001) attained the primary endpoint of a mean serum phosphorus level within the normal range at the midpoint of dosing intervals; from wks 24-48, phosphorus was within the normal range in both groups (crossover 89%, burosumab-continuation 84%). At baseline, 65 active fractures/pseudofractures (Fx/PFx) were present in 47% (32/68) of subjects in the burosumab group and 91 Fx/PFx in 58% (38/66) of subjects in the placebo group. At wk 24, 43% (28/65) of Fx/PFx fully healed with burosumab and 8% (7/91) healed with placebo (odds ratio of full healing 16.8, p<0.0001). By wk 48, the burosumab-continuation group showed additional Fx/PFx healing, and the crossover group showed healing similar to that of the burosumab-continuation group at wk 24. At wk 48, both groups showed significant decreases from baseline (or wk 24 for crossover) in stiffness, physical functioning, and pain scores (all p<0.001). At wk 48, PTH decreased from baseline by 9% in the burosumab-continuation group and by 7% in the crossover group. Serum creatinine and calcium levels and urine calcium excretion were unchanged. Most subjects had no change in nephrocalcinosis severity score (5-point scale), and no subject had a change >±1 point. Serious AEs were reported in 15 subjects; none were assessed as drug-related.

Conclusions: Inhibition of FGF23 with burosumab was associated with improvements in serum phosphorus levels, pain, stiffness, and physical functioning, and healing of Fx/PFx in adults with XLH. The improvements seen with burosumab at wk 24 were replicated in placebo subjects who crossed over to receive burosumab from wks 24-48.

Funding: Commercial Support - Ultragenyx Pharmaceutical Inc.

TH-OR024

Association of Serum Calcification Propensity with Presence and Progression of Coronary Artery Calcification among Patients with CKD: The CRIC Study

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Background: Coronary artery calcification (CAC) is prevalent among patients with chronic kidney disease (CKD) and predicts the risk of cardiovascular disease and mortality. We hypothesized that a novel measure of serum calcification propensity is associated with CAC among patients with CKD stages 2-4.

Methods: Among 780 participants from the CRIC Study, CAC was measured at baseline and a follow-up visit using electron beam or multidetector computed tomography. Calcification propensity was quantified at baseline as the transformation time (T50) from primary to secondary calciprotein particles, with lower T50 corresponding to higher calcification propensity. Poisson and linear regression were used to estimate associations between T50 and CAC, with a priori stratification by absence or presence of CAC at baseline.

Results: At baseline, 460 (59%) participants had any CAC and 255 (33%) participants had CAC score ≥100 Agatston units. Over an average 3-year follow-up, 65 (20%) participants without baseline CAC developed CAC while 89 participants (19%) with baseline CAC increased ≥100 Agatston units per year. After multivariable adjustment, lower T50 was associated with more severe CAC at baseline and over follow-up among those with baseline CAC (Table).

Conclusions: Among patients with CKD, higher serum calcification propensity is associated with more severe CAC and progression of CAC. Future studies should evaluate

whether T50 predicts the risk of clinical cardiovascular disease and whether its determinants represent novel therapeutic targets.

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Cross-sectional and longitudinal associations of serum calcification propensity and coronary artery calcification

T_{50}, 1 SD (74.9 minutes) Decrease	Age, sex, race/ethnicity, and site-adjusted		Multivariable-adjusted[a]	
	Estimate (95% CI)	P Value	Estimate (95% CI)	P Value
All Participants (n=780)				
Cross-sectional				
CAC >0, Prevalence Ratio	1.02 (0.97-1.07)	0.50	0.98 (0.92-1.03)	0.42
Baseline CAC=0 (n=320)				
Longitudinal				
Change in CAC, √ Transformed Change[b]	0.12 (0.02 to 0.22)	0.02	0.06 (-0.04 to 0.16)	0.24
Incident CAC, Relative Risk	1.07 (0.84-1.36)	0.60	0.95 (0.76-1.18)	0.62
Baseline CAC>0 (n=460)				
Cross-sectional				
CAC Severity, Percent Difference[c]	47% (23% to 75%)	<0.001	35% (12% to 63%)	0.002
Longitudinal				
Change in CAC, √ Transformed Change[b]	0.30 (0.15 to 0.45)	<0.001	0.20 (0.04 to 0.35)	0.01
Increase ≥100 units/year, Relative Risk	1.46 (1.24-1.73)	<0.001	1.23 (1.03-1.48)	0.02

[a] Additionally adjusted for eGFR, proteinuria, diabetes, systolic BP, number of antihypertensive medications, current smoking, history of cardiovascular disease, total cholesterol, use of statin medications, calcium, phosphate, and FGF-23. Covariates were measured at the same visit as the first CT measurement (i.e. baseline).

[b] $\sqrt{CAC}_{follow-up} - \sqrt{CAC}_{baseline}$

[c] Percent difference in baseline CAC score associated with 1 SD decrease in T_{50}

TH-OR025

Serum Bicarbonate Level and Coronary Artery Calcification – A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: There is a graded relationship between the severity of chronic kidney disease (CKD) and coronary artery calcification (CAC), though the mechanism is unclear. Metabolic acidosis, a common complication of CKD, contributes to decreased mineral bone content and may lead to worsening vascular calcification. We hypothesize that low serum bicarbonate level, an expression of metabolic acidosis, is a risk factor for CAC in CKD.

Methods: Serum bicarbonate and CAC were simultaneously measured in 862 CRIC participants at baseline and after 3 years. CAC was measured using electron beam or multidetector computed tomography and calculated using Agatston score. Serum bicarbonate was analyzed both as a continuous and a categorical variable by the following groups: <22 mEql/L (low), 22-26 mEq/L (normal) and >26 mEq/L (high). CAC progression was defined as follows: CAC> 0 at follow-up, if CAC=0 at baseline; annualized change ≥10 Agatston units at follow-up if 0<CAC≤100 at baseline; and annualized percent change (annualized change in CAC score divided by the baseline CAC score) ≥ 10% at follow-up, if CAC > 100 at baseline. Logistic regression models were built to study the association of interest.

Results: The mean eGFR was 43±17ml/min per 1.73m², mean serum bicarbonate was 24.4±3.3 mEq/L, and 42.7% participants had diabetes. A total of 412 (48%) participants experienced CAC progression. Participants with low bicarbonate were more likely to have CAC >400 at baseline, and to experience CAC progression, compared to those in the normal group (57.3% vs 46.2%, p=0.003). The low group had 52% higher risk of CAC progression, compared to normal group (OR1.52; 95%CI: 1.02–2.29), in models adjusted for demographics, baseline co-morbidities, medications, calcium and phosphorus. Addition of eGFR and proteinuria to these models attenuated the association (OR 1.34; 95%CI: 0.87–2.08). In fully adjusted models, each 1mEq/L lower serum bicarbonate was associated with 6% higher risk of CAC progression (OR 1.06; 95%CI: 1.01-1.12).

Conclusions: In a cohort of patients with CKD, low serum bicarbonate level was associated with CAC progression. This association may not be independent of kidney function. Further studies are needed to determine a causal link between low serum bicarbonate and CAC.

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TH-OR026

A Serum Biomarker Panel of Low Bone Turnover Identifies Higher Fracture Risk in Community Dwelling Individuals with CKD

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Background: Individuals with chronic kidney disease (CKD) can have low or high turnover bone disease, either of which could lead to low bone mineral density (BMD). We identified a panel of biomarkers on biopsy that marked low turnover bone disease. Then, in a community-dwelling cohort of persons with CKD, we determined if this panel identified a subset at high risk for fracture.

Methods: Among 58 patients with CKD stage 2-5 who had undergone bone biopsies, we used CART analysis to define a panel of serum biomarkers that could differentiate low turnover from non-low turnover bone disease. We then applied this panel of biomarkers to 676 participants in the Health ABC study who had eGFR < 60 mL/min/1.73m²and had BMD measurements at baseline. We used Cox proportional hazards models to evaluate the association of BMD with fracture risk and to determine whether biomarker defined low- vs non-low bone turnover modified the risk of fracture.

Results: CART analysis in 58 CKD patients defined cut-off points for differentiation of low bone turnover: PTH below the median, soluble a-klotho above the median, and FGF-23 below the median (AUC = 0.6, 0.7, and 0.7, respectively). Among the 676 participants with CKD in Health ABC, mean age was 75±3 years, and were 51% female and 36% African-American. Average eGFR was 48±10 mL/min/1.73m². For every standard deviation (SD=0.16 g/cm²) lower hip BMD at baseline there was higher risk for hip (HR 2.5 (1.9, 3.2)) and spine fractures (HR 1.6 (1.3, 2.1)) during follow-up. This risk differed in individuals with biomarker defined low vs non-low bone turnover ($p_{interaction}$hip= 0.05; spine= 0.07), where individuals characterized as having low bone turnover had higher risk of fracture (Table)

Conclusions: In individuals with CKD, a biomarker panel of PTH, a-klotho, and FGF-23 can be used to identify individuals more likely to have low bone turnover. In such individuals, the relationship of low BMD with risk for incident hip and spine fractures is much higher than in others.

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Table. Association between BMD* and incident fractures stratified by low bone turnover versus non-low bone turnover

	Hip Fractures			
	Unadjusted	Age, gender, race, and site adjusted	Fully adjusted**	P-interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Low Turnover	3.05 (2.01, 4.65)	3.14 (1.91, 5.15)	5.72 (2.67, 12.25)	0.053
Non-Low Turnover	1.80 (1.42, 2.21)	1.81 (1.42, 2.31)	2.23 (1.67, 2.97)	
	Spine Fractures			
	Unadjusted	Age, gender, race, and site adjusted	Fully adjusted**	P-interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Low Turnover	2.66 (1.53, 4.63)	2.58 (1.41, 4.74)	2.67 (1.15, 6.20)	0.066
Non-Low Turnover	1.54 (1.26, 1.87)	1.39 (1.11, 1.74)	1.50 (1.17, 1.93)	

*Per SD lower BMD, which was 0.16 g/cm² in the hip and the spine

**Fully adjusted for age, gender, race, site, BMI, SBP, HTN meds, eGFR, UACR, vitD25(OH)2, smoking status, alcohol use, diabetes, physical activity, osteoporosis meds, and diuretics

TH-OR027

A MicroRNA Approach to Diagnosing Renal Osteodystrophy

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Background: The primary goal of treating renal osteodystrophy (ROD) is reducing high bone turnover with calcitriol and/or calcimimetics while avoiding the development of low turnover. A main obstacle in managing ROD is identifying the underlying bone turnover-type. Bone biopsy, the gold standard to define turnover, is impractical for routine clinical use. Therefore, KDIGO recommends that clinical use (starting/stopping) of these agents is guided by parathyroid hormone (PTH) and bone specific alkaline phosphatase (BSAP). However, bone biopsy studies demonstrated that PTH and BSAP are poor guides for ROD treatment. We hypothesized that 4 circulating microRNAs (miRs) that regulate osteoblast (30b, 30c, 125b) and osteoclast development (155) would provide superior discrimination of low and high turnover than PTH and BSAP.

Methods: In 24 patients with CKD 3-5D, we obtained tetracycline double-labeled iliac crest bone biopsy and measured levels of intact PTH, BSAP and circulating miR-30b, 30c, 125b and 155 (evaluated independently and together as a panel). Spearman correlations assessed relationships between miRs, dynamic parameters of bone biopsy, and PTH and BSAP. Discrimination of low / high turnover were determined by receiver operator curve analysis; areas under curve were compared by χ^2.

Results: miRs moderately correlated with bone formation and adjusted apposition rate (ρ 0.43-0.51; p<0.05) by biopsy but were not correlated with PTH or BSAP. Discrimination of low vs. non-low and high vs. non-high turnover for PTH, BSAP and miRs (both individually and as a panel) are shown in the Table.

Conclusions: These data suggest that a panel of circulating miRs provide accurate non-invasive identification of low and high turnover and individually identified low turnover. Future work will discover and validate additional miR biomarkers of turnover and determine their impact on clinical decision making and outcomes.

Funding: NIDDK Support

Areas under the curve for diagnosis turnover by bone biopsy

	Low vs. Non-Low		High vs. Non-High	
	AUC	95% CI	AUC	95% CI
PTH	0.479	0.209-0.755	0.593	0.296-0.901
BSAP	0.781	0.571-0.991	0.956	0.862-1.000
miR-30b	0.875	0.733-1.000	0.650	0.408-0.892
miR-30c	0.825	0.645-1.000	0.608	0.362-0.855
miR-125b	0.800	0.613-0.987	0.658	0.365-0.951
miR-155	0.767	0.559-0.974	0.558	0.310-0.807
miR Panel	0.983	0.944-1.000	0.800	0.576-1.000

TH-OR028

Cholecalciferol vs Small Doses of Alfacalcidol in Hemodialysis Patients: A Randomized Placebo-Controlled Study

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Background: The ability of extrarenal tissues to convert 25OHD into 1,25(OH)2D and its dependence on substrate levels provide the rationale for supplementing vitamin D in dialysis patients who usually have severe depletion of both: calctriol and vitamin D. The primary aim of the study was to compare effects of cholecalciferol (CHOL, 4000 IU) with frequently used in Europe, small doses of alfacalcidol (ALFA, 0.5 microg) or placebo (PLC), given thrice weekly for 12 weeks, on serum 1,25(OH)2D in hemodialysis (HD) patients with vitamin D deficiency. Secondary outcomes were changes in serum calcium, phosphate, 25(OH)D, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and sclerostin during the treatment.

Methods: This was a prospective, randomized, partly double-blind (CHOL vs PLC), partly open-label (ALFA vs CHOL or PLC) study. Out of 522 patients dialyzed in 5 centers in the Mazovian Province, 93 gave informed consent and met the inclusion criteria: vitamin D and calcimimetics naïve; no history of liver or intestinal disease; serum 25(OH)D <20 ng/ml, iPTH <1000 ->110 pg/ml, calcium <10.2 and phosphate < 6.8 mg/dl. The subjects were stratified by serum iPTH, then randomized into 3 groups according to the treatment

Results: To our knowledge, this is a first study comparing head-to-head these drugs in HD population. There were no significant differences between the groups at baseline. 81 patients completed the study. CHOL normalized serum 25OHD, with a mean rise from 12.9±6.7 to 31.3±10.1 ng/ml (p<0.0001). This was accompanied by a marked increase of $1,25(OH)_2D$ (from 13.8±9.3 to 25.1±14.2 pmol/l (p<0.0001). A rise in serum 1,25(OH)2 was observed also in ALFA treated patients, however much smaller (from 13.5±10.1 to 18.5±11.0 pmol/l; p=0.02). Neither CHOL nor ALFA treatment resulted in significant changes in the remaining parameters.

Conclusions: In most HD patients treatment with CHOL in a dose of 12000 IU/week permits safe correction of vitamin D deficiency and is more effective than small doses of ALFA in rising serum 1,25(OH)2D. This together with a lack of influence on circulating iPTH question the usefulness of this treatment in HD patients.

TH-OR029

Randomized Trial to Evaluate the Effect of Cholecalciferol Supplementation on Parathyroid Hormone in Hemodialysis Patients

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Background: Vitamin D (25VD) supplementation is associated with a decrease in parathyroid hormone (iPTH) in general population, not confirmed in hemodialysis (HD) patients (Pts). The aim of the study was to evaluate if cholecalciferol supplementation can normalize 25VD levels and reduce iPTH in HD Pts with vitamin D deficiency.

Methods: Randomized, controlled trial with 2 arms: cholecalciferol vs placebo. Inclusion Criteria: Adult Pts, on HD for ≥ 3 months, 25VD < 30 ng/ml and iPTH >300 ng/ml. Randomization was done using a table of random numbers, and allocation was blinded for Pts and investigators. Intervention: Pts received one tablet with 5000 IU 25VD or placebo during dialysis thrice a week for 12 weeks. Hemoglobin (Hb), Calcium (Ca), Phosphorous (P), erythropoietin dose (IU/kg/week), Alkaline Phosphatase (AP), 25VD and iPTH were measured at 0 and 12 weeks. Assuming a dropout rate of 15%, sample size of 120 Pts was needed for a 20% reduction on iPTH in 35% of treated Pts. Analysis was done per protocol for the primary outcome. Quantitative data was expressed were compared by t test and categorical by chi square. Significant differences were considered with p values <0.05. Institutional Ethics Committee authorization was obtained.

Results: 118 Pts were randomized, 60 to 25VD and 58 to PLA with no significant differences (Table I). 17 Pts were lost of follow-up, 101 Pts completed treatment (54 with 25VD and 47 with PLA). Pts on 25VD normalized 25VD (increased x 20.9 ± 11.9) significantly more frequently than those on PLA (41 (75.9%) vs 11 (23.4%)). A 20% iPTH reduction was seen in 17 Pts (29.3%) on 25VD (x reduction 45 ± 194) and 9 Pts (19.1%) on PLA (p=0.1). A reduction on AP was seen in 25VD Pts (29.5 ± 84.8, p=0.016) and not on PLA (21.9 ± 81.3).

Conclusions: Significant increase in 25VD was observed in treated group, with a reduction on AP but with no significant effect on iPTH

Funding: Commercial Support - Celsiuss, Government Support - Non-U.S.

Table I. Baseline Characteristics of Pts

	25 vitamin D (n=60)	placebo (n=58)
Gender (M) %	39 (65%)	35 (60.3%)
Age ys x ± SD	68.3 ±14.1	65.6 ±15.1
Diabetics %	24 (40%)	20 (34.5)
AP mU/ml x ± SD	219 ± 180	234 ± 269
25 VD ng/ml x ± SD	16.5 ± 7.6	16.9 ± 7.7
PTH ng/ml x ± SD	692 ± 387	623± 323

TH-OR030

Multicentre Randomized Control Trial of Phosphate Control with a Modified as Compared to Standard Renal Diet

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Background: The standard renal diet fails to distinguish between phytate and non phytate bound phosphorus, despite consensus that the latter is poorly absorbed. A modified renal diet based on the increased use of pulses, nuts and whole grains, the avoidance of P additives and of over-prescription of protein may offer improved or similar [P] levels as the standard renal diet but with a wider food choice.

Methods: We conducted a national, multicentre, pragmatic, parallel arm, open label, randomized controlled trial (1:1 allocation ratio) of 1 month of modified vs. standard diet in 74 prevalent anuric adults on maintenance hemodialysis with a 3 mt mean pre-dialysis serum phosphate ([P]) >1.6mmol/L and a stable phosphate binder and vitamin D prescription. Subjects with a history of severe hyperkalemia, parathyroidectomy or recent acute illness were excluded. Subjects were re-educated on the standard diet or educated on the modified diet by the renal dietitian. Analysis was on a modified intention-to-treat basis of the difference between diets in follow-up [P] minus baseline [P] using an independent sample t test and a 2 sided type 1 error rate of 0.05.

Results: We recruited 74 subjects from 13 university dialysis units. Two patients did not have a follow-up [P], due to an insufficient sample and transplantation and thus could not contribute to the primary analysis. The study population was 96% Caucasian, 69% male, 36% of subjects had diabetes. Both diets were similarly well tolerated. The modified diet resulted in a significantly higher phytate and fiber intake (both p<0.01). Baseline and follow-up [P] in modified diet arm was 2.1 (0.5) and 2.0 (0.7) mmol/L, and in the Standard Diet arm were 2.0 (0.6) and 1.9 (0.6) mmol/l; the mean (95% CI) change in $[PO_4]$ in modified vs. standard arm was 0.01 (-0.24,0.21), p=0.91. The mean (sd) difference in follow-up [K] -baseline [K] in the modified and standard arms was 0.01 (0.7) and 0.09 (0.6) mmol/L respectively; the mean (95% CI) change in $[K^+]$ modified v standard was -0.07(-0.23,0.38), p = 0.63. C terminal FGF23 (n=27) was not significantly different. Limitations of this study include its modest sample size and limited intervention period.

Conclusions: The modified renal diet was well tolerated and was associated with similar [P] control but with a wider food choice and greater fiber intake than the standard diet.

TH-OR031

Combination of Changes in eGFR and Albuminuria and the Risk of Major Clinical Outcomes in Type 2 Diabetes Mellitus (T2DM)

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Background: Whether combining changes in eGFR and UACR more accurately predicts outcomes in T2DM compared with assessing either change alone is unknown. We assessed the association between changes in eGFR and UACR and subsequent risk of the composite of major macrovascular and renal events and all-cause mortality in the ADVANCE-ON study.

Methods: We defined eGFR and UACR change (baseline to 2 years) as ≥40% decrease, <40% decrease to <40% increase (minor change; reference) and ≥40% increase. Follow-up for outcomes commenced at the second eGFR or UACR measurement. Cox regression models (adjusted for demographics, ADVANCE randomized treatment, comorbidities and laboratory measurements [including baseline eGFR and UACR]) were used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) relating changes in eGFR and UACR to the combination endpoint.

Results: Of 8766 patients, from baseline to 2 years, 3% experienced an eGFR decrease ≥40%, 93% experienced a minor change, and 4% experienced an increase ≥40%. For UACR change, the proportions were 29%, 34% and 37%, respectively. 1% experienced both an eGFR decrease ≥40% and a UACR increase ≥40%. Over the next 7.7 years (median), 2191 composite outcome events were recorded. Strong linear associations between eGFR and UACR changes and the subsequent risk of the outcome were observed (p for trend <0.001 for each marker). For eGFR change, the HRs for a decrease ≥40% was 1.59 (95% CI: 1.28-1.97) compared with those with minor change whilst that for an increase ≥40% was 0.82 (0.64-1.04). For UACR change, the HRs were 0.96 (0.85-1.07) for a decrease ≥40% and 1.32 (1.19-1.46) for those with ≥40% increase compared to minor change. Compared to patients with minor changes, patients who experienced an eGFR decrease ≥40% and a UACR increase ≥40% had 2.31 (1.67-3.18) times the risk of the outcome, with evidence of interaction between the 2 markers (p for interaction=0.047).

Conclusions: In patients with T2DM, clinically meaningful decreases in eGFR and increases in UACR over 2 years significantly predicted, independently and in combination, increased risk of major clinical outcomes. Our results suggest that a combined assessment of clinically meaningful changes in both eGFR and UACR compared with separate assessments of the 2 markers may further improve risk stratification in T2DM.

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TH-OR032

Metformin Treatment in Patients with Type 2 Diabetes and CKD

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Background: Metformin is widely used as the first pharmacological option in the patients with type 2 diabetes mellitus. However, use of this drug has not been recommend in individuals with impaired kidney function because of the perceived risk of lactic acidosis. We aimed to assess the efficacy and safety of metformin in patients with type 2 diabetic chronic kidney disease (CKD).

Methods: We conducted a retrospective, observational, cohort study of 10,426 patients with type 2 diabetic CKD who followed the nephrology clinic at two tertiary hospitals from 2001 to 2016. We compared 3,183 patients who used metformin with 7,243 who did not use metformin. Primary outcomes were all-cause-mortality and end-stage renal disease (ESRD) progression. Secondary outcomes were event of metformin associated lactic acidosis and maximal lactate level in all events of lactic acidosis. Cox multivariate analysis and propensity score matching were conducted.

Results: The patients who used metformin had more female proportion, younger, higher eGFR, higher BMI and higher HbA1c level at the time of enrollment. All-cause-mortality for metformin-user group was significantly better than that that of non-metformin user in the multivariable cox analysis (P value <0.001 adjusted hazard ratio [aHR] 0.54, 95% confidence interval [C.I.] 0.48 - 0.62). Also, MFM group has longer duration of ESRD progression. (P value < 0.001, aHR 0.47, 95% CI 0.41 – 0.53). Because two group had significantly different baseline characteristics, we did a propensity score matching by age, gender, hypertension, liver disease, BMI, Hba1c and eGFR. Metformin usage consistently has superiority in all-cause-mortality (P value <0.001, aHR 0.52, 95% CI 0.46 – 0.60) and ESRD progression (P value <0.001, aHR 0.50, 95% CI 0.43 – 0.58) in matched group. There was only one case of metformin associated lactic acidosis event in metformin user group. But there was no difference in maximal lactate level. (P value 0.966)

Conclusions: In Korean diabetic CKD patients, metformin can be safely considered. However, more researches about cumulative dose effect, dose adjustment and monitoring method are needed.

Edit Table - Uni-variate cox analysis about primary outcome in matched group

	Hazard ratio	95% CI	P value
All-cause-mortality	0.52	0.46 - 0.60	<.001
ESRD progression	0.50	0.43 - 0.58	<.001

TH-OR033

CKD Outcomes in Type 2 Diabetes and Moderate-to-Severe CKD Treated with Dulaglutide Versus Insulin Glargine: AWARD-7

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Background: In the Assessment of Weekly AdministRation of Dulaglutide in Diabetes-7 (AWARD-7) study, dulaglutide (DU) treatment was associated with slower decline in estimated glomerular filtration rate (eGFR) compared to insulin glargine (IG) in participants with type 2 diabetes (T2D) and moderate-to-severe chronic kidney disease (CKD). The present analysis is aimed to determine CKD outcomes by treatment group.

Methods: As treatment for T2D, participants with T2D and CKD stages 3-4 were randomized (1:1:1) to receive DU 0.75 mg, DU 1.5 mg, or titrated IG, all added-on to titrated insulin lispro, for 1 year in this open-label (DU dose-blinded), phase 3 clinical study. In this prespecified exploratory analyses, proportions of participants experiencing ≥40% eGFR decline, end-stage renal disease (ESRD), or kidney disease-related death were compared between groups as composite and individual outcomes. For the composite outcome, a time-to-event analysis was conducted using a Cox proportional hazards model.

Results: The age (mean ± SD) of participants was 64.5 ± 8.5 years and 264/549 (48%) were women. At baseline, diabetes duration (mean ± SD) was 18.1 ± 8.8 years, HbA1c was 8.6 ± 1.0%, eGFR was 38 ± 13 mL/min/1.73 m^2, and median (interquartile range) urine albumin-creatinine ratio was 209 (39, 965) mg/g. HbA1c declined similarly in all groups by a mean of approximately 1% over 1 year. The composite outcome was experienced by 47/576 (8.2%) participants: 10/192 (5.2%) in DU 1.5 mg, 16/190 (8.4%) in DU 0.75 mg, and 21/194 (10.8%) in IG (p=0.046, p=0.548 versus IG, respectively). The time-to-event for the composite outcome was significantly better for DU 1.5 mg versus IG (Cox model; p=0.038). Proportions with eGFR decline ≥40% occurred in: 2/192 (1.0%) in DU 1.5 mg, 7/190 (3.7%) in DU 0.75 mg, and 6/194 (3.1%) in IG. Proportions reaching ESRD were: 8/187 (4.3%) in DU 1.5 mg, 14/184 (7.6%) in DU 0.75 mg, and 16/191 (8.4%) in IG. Between-group comparisons were not significant for individual outcomes. No kidney disease-related deaths were reported.

Conclusions: One-year treatment with DU 1.5 mg was associated with a lower rate of CKD outcomes, including the composite outcome of eGFR decline ≥40% or ESRD, compared to IG at similar levels of glycemic control.

Funding: Commercial Support - Eli Lilly and Company

TH-OR034

Reduction in Albuminuria Is Associated with Cardiorenal Protection Independent of Baseline Albuminuria – A Post-Hoc Analysis of the LEADER Trial

Frederik Persson,[1] Stephen Bain,[2] Ofri Mosenzon,[3] Hiddo J. Lambers Heerspink,[4] Johannes F. Mann,[5] Itamar Raz,[6] Thomas Idorn,[7] Soren Rasmussen,[7] Bernt Johan Von Scholten,[7] Peter Rossing.[1] The LEADER Publication Committee on behalf of the LEADER Trial Investigators *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]Institute of Life Science, Swansea University, Swansea, United Kingdom; [3]Hadassah Hebrew University Hospital, Jerusalem, Israel; [4]University Medical Center Groningen, Groningen, Netherlands; [5]KfH Kidney Center, and Friedrich Alexander University of Erlangen, Munich, Germany; [6]Hadassah Hebrew University Hospital, Jerusalem, Israel; [7]Novo Nordisk A/S, Soborg, Denmark.*

Background: We investigated association between changes in urinary albumin-to-creatinine ratio (UACR) and subsequent risk of cardiovascular (CV) and renal events in the LEADER trial according to baseline UACR.

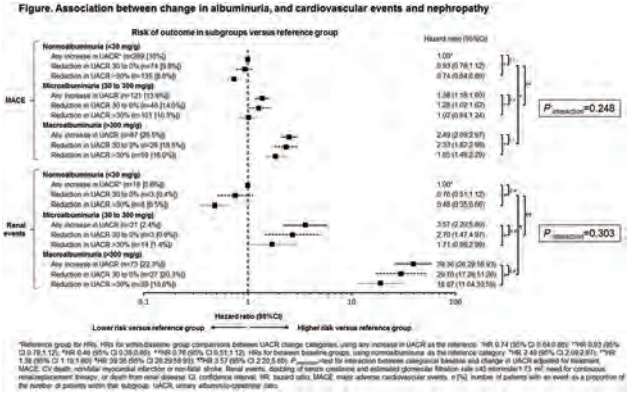
Methods: LEADER was a randomized, double-blind, multicenter, placebo-controlled CV outcomes trial of liraglutide up to 1.8 mg/day vs placebo added to standard care for 3.5–5 years in 9340 patients with type 2 diabetes and high risk for CV disease. Using a Cox regression model including subjects with a UACR measurement at baseline and after 1 year (N=8231 [88%]) adjusted for treatment, we analyzed the risk of major adverse CV events (MACE) and adjudicated renal events (doubling of serum creatinine and estimated glomerular filtration rate ≤45 ml/min/1.73 m^2; the need for continuous renal-replacement therapy; or death from renal disease) from 1 year to end of trial in subgroups defined by first-year change in UACR: >30% reduction, 30-0% reduction, any increase, and according to absolute level of baseline UACR (normo- [<30 mg/g], micro- [30 to 300 mg/g] or macroalbuminuria [>300 mg/g]).

Results: For first MACE, the hazard ratios (HRs) according to baseline UACR groups were: HR=2.49, 95%CI (2.09;2.97) for macro- vs normoalbuminuria and HR=1.38 (1.18;1.60) for micro- vs normoalbuminuria. Correspondingly for first renal event: HR=39.4 (26.3;58.9) and HR=3.57 (2.20;5.80) (Figure). Within each subgroup the risk for CV and renal events was lower in patients with >30% UACR reduction than in those with any UACR increase. There were no interactions between groups (Figure).

Conclusions: These findings highlight the benefit of UACR reduction, even in patients with normoalbuminuria at baseline.

Funding: Commercial Support - Novo Nordisk

Figure. Association between change in albuminuria, and cardiovascular events and nephropathy



TH-OR035

Treatment with Dipeptidyl-Peptidase Inhibitors (DPP4_Rx) Delays Progression of Kidney Disease and Reduces Mortality

Thomas Wiegmann,[1] Olurinde Oni,[1] Peter S. Wiegmann,[2] Archana Goel,[1] Mukut Sharma,[1] Ram Sharma,[1] Maria N. Gomes,[1] Virginia J. Savin,[1] Mariana Garcia-Touza.[1] Cardiovascular and Renal Clinical Research at MidWest BioMedical Research Foundation *[1]Kansas City VA Medical Center, Kansas City, MO; [2]Midwest Biomedical Research Foundation, Kansas City, MO.*

Background: Effects of DPP4_Rx on cardiovascular morbidity are disputed and e ffects on renal function are not known.

Methods: Data from a large cohort of veterans diagnosed with type 2 diabetes mellitus (T2DM) were used to identify patients on DPP4_Rx (group 1). and without DPP4_Rx (group 2). Groups were matched for age (yrs), sex, BMI, initial renal function, follow-up time (FU, minimum 365 days). Propensity score matching (PSM) was used to adjust groups 1 and 2 with a best odds ratio about 1:2. Groups were compared to determine the effect of DPP4_Rx on the progression of CKD and all-cause mortality. Increase in serum creatinine (creat, mg/dl) over time (days) was taken as a measure of progression of CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SPSS and SAS. Results were compared using t-tests, frequency tables, Kaplan Meier survival curves, hazard ratios (HR) and p values.

Results: Results show that subjects in group 1 (N=20,424) had baseline variables (creat 1.061, FU 1117, age 68.2 yrs and BMI 31.9) similar to Group 2 (N=52,118, creat 1.09, FU 1197, age 69.9, BMI 31.7). DM control improved in group 1 (HgbA1c 8.3% to 7.9%,

p < 0.001) but remained worse than group 2 (7.2% to 7.1%) A significant reduction in progression of CKD was seen in group 1. The proportion of patients exceeding creat of 1.5, 3, and 6 mg/dl was reduced by 6.5, 40.8 and 47.4%, all p<0.01 respectively. Time to ESRD (creat >6.0 mg/dl) was delayed also by 143.7 days p < 0.01. Mortality from all causes was reduced by 78.1%, but time to death was not changed.

Conclusions: We conclude that DPP4_Rx associates with a significant reduction in frequency of all-cause mortality and progression toward ESRD independent of glucose control. The data are consistent with a reduction in the number and severity of discrete morbid events that would associate with progressive renal disease and all cause mortality..

Funding: Veterans Affairs Support

TH-OR036

Does Glucose Control Influence the Effect of Empagliflozin on Kidney Outcomes in Type 2 Diabetes (T2D)? Insights from the EMPA-REG OUTCOME® Trial

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Background: In the EMPA-REG OUTCOME® trial, empagliflozin (EMPA), a selective SGLT2 inhibitor given in addition to standard of care, significantly reduced pre-specified kidney outcomes by 39% in T2D patients with established cardiovascular disease (CVD). There is evidence that intensified glycemic control in T2D prevents microvascular complications including progression of kidney disease. We sought to determine whether the renal benefits of EMPA were linked to its effect on HbA1c.

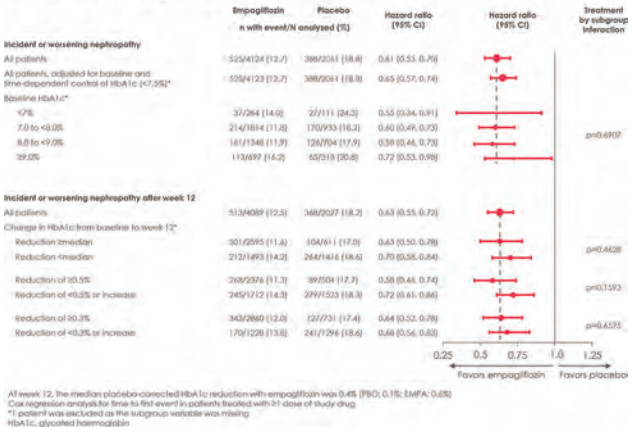
Methods: Patients were randomized (1:1:1) to EMPA 10 mg, EMPA 25 mg, or placebo (PBO). Background glucose-lowering therapy was to remain unchanged for the first 12 weeks. Kidney outcomes were analyzed in the pooled EMPA group vs PBO after adjustment by baseline HbA1c, for HbA1c control during the trial as a time-dependent factor, and by reduction in HbA1c from baseline to week 12. Differences in risk between treatment groups were assessed using a Cox proportional hazards model.

Results: A total of 7020 patients were treated. Median observation time was 3.1 years. The reduction in risk of incident or worsening nephropathy with EMPA vs PBO was found to be consistent irrespective of either HbA1c at baseline or subsequent changes in glycemic control during active study treatment (Figure).

Conclusions: In patients with T2D and established CVD, the beneficial effect of EMPA on kidney outcomes was consistent irrespective of HbA1c prior to and during therapy. EMPA-KIDNEY, the outcome study of heart and kidney protection with EMPA, will provide additional insights into potential glycemia-independent kidney effects of EMPA in patients with and without diabetes.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure. Kidney outcomes adjusted for time-dependent HbA1c control, categorized by baseline HbA1c, and by change in HbA1c from baseline to week 12



TH-OR037

Prediction of the Effect of Dapagliflozin on Renal and Heart Failure Outcomes Based on Short-Term Changes in Multiple Risk Markers

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Background: Sodium glucose cotransporter 2 inhibition with dapagliflozin reduces blood pressure, body weight and urinary albumin:creatinine ratio (UACR) in patients with type 2 diabetes (T2DM). We previously developed an algorithm, the PRE score, to predict how short term effects of a drug on risk factors may translate into long-term changes in clinical outcomes. We applied the PRE score to clinical trials of dapagliflozin to model the effect of the drug on renal and heart failure (HF) outcomes in T2DM patients with impaired renal function.

Methods: The relationships between multiple risk markers and long-term outcome were determined by means of a multivariable Cox model in a subgroup of T2DM patients derived from the ALTITUDE trial. These relationships were applied to short-term changes in risk markers observed in a pooled database of seven dapagliflozin clinical trials to predict the expected drug-induced changes to renal and HF outcomes. Patient characteristics within the background population were matched with respect to UACR and eGFR to those from the dapagliflozin trial participants. The renal outcome was defined as a composite of end-stage renal disease (ESRD) and a sustained doubling of serum creatinine. The heart failure outcome was defined as hospitalization due to HF.

Results: A total of 372 and 136 patients had UACR>30 mg/g and UACR>200 mg/g at baseline, respectively. The PRE score predicted a renal risk reduction of 39% (95% CI 17 to 61%) and 43% (95% CI 4 to 83%) with dapagliflozin 10 mg/day for the UACR>30 mg/g and UACR>200 mg/g subgroups. The predicted reduction in HF events was 21% (95% CI 8 to 35%) and 28% (95% CI 7 to 49%), respectively. Dapagliflozin decreased albuminuria by approximately 35% in both UACR subgroups. Simulation analyses showed that even with a smaller albuminuria lowering effect of dapagliflozin (10%), the estimated renal risk reduction was still 26.5% and 26.8% in the two UACR subgroups.

Conclusions: The PRE score predicted clinically meaningful reductions in renal and HF endpoints associated with dapagliflozin therapy in patients with diabetic kidney disease. These results support a large long-term outcome trial in this population to confirm the benefits of the drug on these endpoints.

Funding: Commercial Support - AstraZeneca

TH-OR038

Canagliflozin Induced Reduction in TNF Receptor 1 Is Associated with a Reduction in eGFR Decline

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Background: Circulating levels of the pro-inflammatory biomarker Tumor Necrosis Factor Receptor 1 (TNFR1) predict the risk of end-stage renal disease (ESRD) in patients with type 2 diabetes. Experimental studies suggested that sodium glucose co-transporter 2 (SGLT2) inhibitors exert anti-inflammatory effects. Here we examined the effect of the SGLT2 inhibitor canagliflozin (CANA) on TNFR1 and assessed whether the change in TNFR1 is associated with eGFR decline.

Methods: TNFR1 levels were measured at baseline, 52 and 104 weeks in plasma samples of 297 patients with type 2 diabetes and urinary albumin:creatinine ratio >15 mg/g participating in a phase 3 clinical trial. Patients were randomly assigned to CANA 100 or 300 mg or glimepiride (GLIM) uptitrated to 6 to 8 mg. Repeated measure models were used to compare effects of CANA vs. GLIM on TNFR1 over 104 weeks follow-up and to assess associations between change in TNFR1 with eGFR change.

Results: During 104 weeks of follow-up, TNFR1 increased in the GLIM group but stabilized or decreased in the CANA 100 and 300 mg groups. Compared with glimepiride, treatment with CANA 100 and 300 mg dose-dependently decreased TNFR1 by 5.9% (1.3 to 10.3; p=0.013) and 9.2% (4.7 to 13.5%; p<0.001). The change in TNFR1 at week 52 (the earliest available time point) was significantly and independently associated with eGFR decline during 104 weeks follow-up (p=0.0234). In increasing tertiles of TNFR1 change, eGFR change during 104 weeks follow-up was -0.4 (95%CI -2.3 to 1.5), -4.7 (95%CI -6.5 to -2.8), and -7.1 (95%CI -9.0 to -5.2) ml/min/1.73m^2. Reductions in HbA1c were similar with GLIM and CANA during follow-up.

Conclusions: The reduction in TNFR1 with CANA and association between changes in TNFR1 and eGFR suggests that TNFR1 may be used to monitor effects of CANA on long-term kidney function.

Funding: Commercial Support - Janssen Research & Development, LLC

TH-OR039

Canagliflozin in Patients with Type 2 Diabetes and Macroalbuminuria: Data from the CANVAS Program

Vlado Perkovic,[1] Brendon L. Neuen,[1] Toshiaki Ohkuma,[1] Bruce Neal,[1] David R. Matthews,[2] Dick de Zeeuw,[3] Kenneth W. Mahaffey,[4] Greg Fulcher,[5] Richard Oh,[6] Qiang Li,[1] Meg J. Jardine.[1] *[1]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia; [2]Oxford Centre for Diabetes, Endocrinology and Metabolism and Harris Manchester College, University of Oxford, Oxford, United Kingdom; [3]University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [4]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA; [5]The Royal North Shore Hospital, University of Sydney, St. Leonards, NSW, Australia; [6]Janssen Research & Development, LLC, Raritan, NJ.*

Background: High levels of albuminuria are associated with increased progressive loss of kidney function in type 2 diabetes mellitus (T2DM). SGLT2 inhibitors reduce glomerular hyperfiltration, which might therefore have particular benefits for people with T2DM and macroalbuminuria.

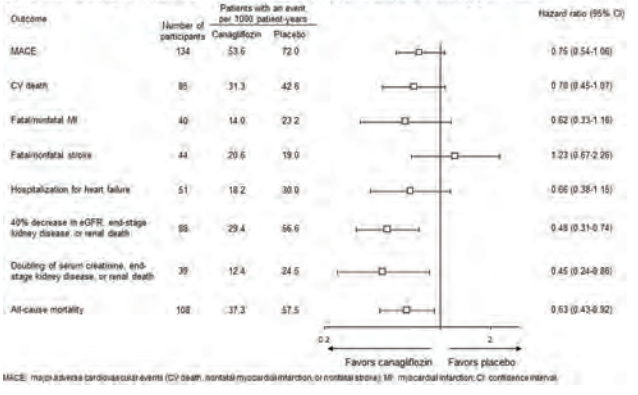
Methods: The CANagliflozin cardioVascular Assessment Study (CANVAS) Program randomized patients with T2DM and a history or high risk of cardiovascular (CV) disease to canagliflozin or placebo. This analysis assessed effects of canagliflozin on renal and CV outcomes in participants with macroalbuminuria at baseline (urinary albumin:creatinine ratio [UACR] >300 mg/g).

Results: The CANVAS Program included 760 participants (7.5%) with macroalbuminuria (mean age 64 y, BP 145/80 mmHg, HbA1c 8.5%, estimated glomerular filtration rate [eGFR] 66 mL/min/1.73 m^2, median UACR 722 mg/g). As compared with placebo, canagliflozin significantly reduced the geometric mean UACR (change from baseline to end of follow-up –36%, 95% CI –43 to –28); slowed the chronic annual decline in eGFR: –1.76 mL/min/1.73 m^2 with canagliflozin vs. –4.77 mL/min/1.73 m^2 with placebo (difference 3.01 mL/min/1.73 m^2, 95% CI 2.03-3.99); and reduced the risk of the composite outcome of end-stage kidney disease or renal death in combination with either 40% decrease in eGFR or doubling of serum creatinine (Figure). Canagliflozin also reduced the risk of all-cause mortality (Figure), while effects on CV outcomes were broadly consistent with those previously reported for the overall trial population.

Conclusions: Canagliflozin lowers albuminuria and improves outcomes in patients with T2DM and macroalbuminuria.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure. Effect of canagliflozin on CV and renal outcomes in participants with UACR >300 mg/g at baseline.



MACE: major adverse cardiovascular events (CV death, nonfatal myocardial infarction, or nonfatal stroke); MI: myocardial infarction; CI: confidence interval.

TH-OR040

Effect of Canagliflozin on Cardiovascular and Renal Outcomes across KDIGO Risk Categories: Analysis from the CANVAS Program

Brendon L. Neuen,[1] Toshiaki Ohkuma,[1] Bruce Neal,[2] David R. Matthews,[3] Dick de Zeeuw,[4] Kenneth W. Mahaffey,[5] Greg Fulcher,[6] Jaime Blais,[7] Qiang Li,[1] Meg J. Jardine,[1,8] David C. Wheeler,[9] Vlado Perkovic.[1,6] *[1]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia; [2]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia; [3]Oxford Centre for Diabetes, Endocrinology and Metabolism and Harris Manchester College, University of Oxford, Oxford, United Kingdom; [4]University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [5]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA; [6]Royal North Shore Hospital, Sydney, NSW, Australia; [7]Janssen Scientific Affairs, LLC, Titusville, NJ; [8]Concord Repatriation General Hospital, Sydney, NSW, Australia; [9]Centre for Nephrology, University College London, London, United Kingdom.*

Background: The CANagliflozin cardioVascular Assessment Study (CANVAS) Program randomized patients with type 2 diabetes to canagliflozin or placebo and demonstrated that the drug reduced the risk of cardiovascular (CV) and renal outcomes. The Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease classification is a risk stratification tool based on estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) and urinary albumin:creatinine ratio (UACR, mg/g).

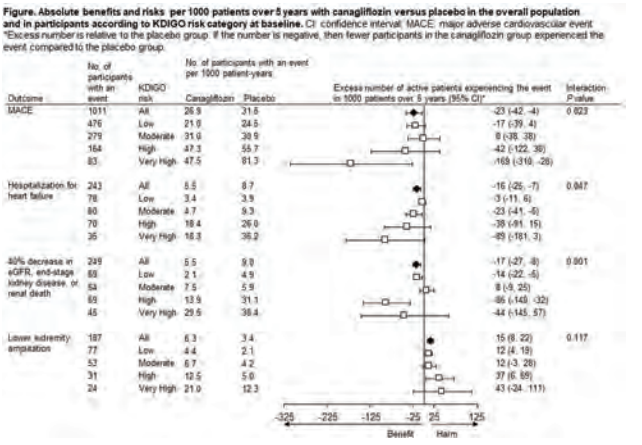
Methods: Absolute effects on CV and renal outcomes were analyzed by baseline KDIGO risk category, defined as low risk (eGFR ≥60 and UACR <30), moderate risk (eGFR 45-<60 and UACR <30, or eGFR ≥60 and UACR 30-300), high risk (eGFR 30-<45 and UACR <30, eGFR 45-<60 and UACR 30-300, or eGFR ≥60 and UACR >300), and very high risk (eGFR <30 with any UACR, eGFR 30-<45 and UACR ≥30, or eGFR 45-<60 and UACR >300).

Results: Of 10,142 participants, 10,031 (98.9%) had available baseline eGFR and UACR data. The proportion of participants in low, moderate, high, and very high risk categories was 58.6%, 25.8%, 10.6%, and 5.0%, respectively. Heterogeneity in absolute effects across KDIGO risk categories was observed for the primary outcome (CV death, nonfatal myocardial infarction, or nonfatal stroke; *P* heterogeneity=0.023), hospitalization for heart failure (*P*=0.047), and the renal composite outcome (40% decrease in eGFR, end-stage kidney disease, or renal death; *P*=0.001; Figure).

Conclusions: The absolute reduction in CV and renal outcomes with canagliflozin may be greater in patients at higher renal risk.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure. Absolute benefits and risks per 1000 patients over 5 years with canagliflozin versus placebo in the overall population and in participants according to KDIGO risk category at baseline. CI: confidence interval; MACE: major adverse cardiovascular event. *Excess number is relative to the placebo group. If the number is negative, then fewer participants in the canagliflozin group experienced the event compared to the placebo group.



TH-OR041

Effects of Hyperoxia with and without Klotho Supplementation in a Murine Model of Post-Natal Nephrogenesis

Mohammed Farhan Ali,[1] Sunil kumar Batlahally venkatarayappa,[2] Merline Benny,[2] Claudia P. Rojas,[3] Naimeh Da Silva,[1] Michael Freundlich,[1] Carolyn L. Abitbol,[1] Marissa J. Defreitas,[1] Karen C. Young.[2] *[1]Department of Pediatrics, Division of Pediatric Nephrology, University of Miami, Miami, FL; [2]Department of Pediatrics, Division of Neonatology, University of Miami, Miami, FL; [3]Department of Pediatrics, Division of Pediatric Pathology, University of Miami, Miami, FL.*

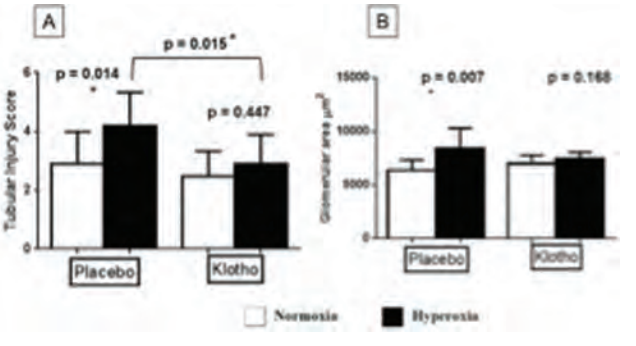
Background: Preterm infants are born during active nephrogenesis and exposure to high oxygen levels has been proposed to cause kidney related injury due to oxidative stress. Studies investigating the effects of hyperoxia on nephrogenesis are limited and have not evaluated whether these effects are reversible by administration of an agent with antioxidant properties. The aim of our study was to determine whether the administration of exogenous Klotho, a multi-functional protein that is known to diminish oxidative stress and apoptosis, attenuates hyperoxia induced glomerular and tubular injury in rats during nephrogenesis.

Methods: Newborn rat pups were raised in hyperoxia (85% oxygen for 3 weeks and then recovered in room air for 3 weeks) or room air (21% oxygen for 6 weeks). Klotho was administered intraperitoneally to half of the pups in both groups every other day for the first 3 weeks. All pups were sacrificed at the end of 6 weeks and the kidneys were assessed for glomerular diameter and area using Image J software, and tubular injury using a tubular injury scoring system (0- no injury, 5- >75% of tubules injured).

Results: Hyperoxia exposed rats had greater glomerular diameter, area and tubular injury scores. The administration of Klotho attenuated tubular injury (Figure A) and prevented glomerulomegaly (Figure B).

Conclusions: The findings of this study demonstrate that hyperoxia exposure during active nephrogenesis in the neonatal rat pups results in increased glomerular size and tubular injury and that the exogenous administration of Klotho in these pups attenuates hyperoxia induced tubular injury and prevents glomerulomegaly at 6 weeks. Future studies aimed at exploring the therapeutic potential of Klotho in neonatal models of kidney injury are needed.

Funding: Private Foundation Support



TH-OR042

Increased Mortality in Underweight but Not Obese Critically Ill Patients – A Secondary Analysis of the AWARE Study

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Background: Obesity is a significant public health problem with an increasing prevalence in both adults and children. The effect of obesity on critical care mortality is controversial and even less is known about the effect of underweight status on mortality. We investigated the prevalence and outcomes of obesity and underweight in a large, critically ill pediatric cohort.

Methods: We conducted a secondary analysis of the prospective, observational, multinational Assessment of Worldwide Acute kidney injury, Renal angina, and Epidemiology (AWARE) study data. PICU patients, 3mos to 25yrs, were eligible but only subjects with documented age, sex, height and weight were analyzed. Patients were divided into 4 groups (under, normal, overweight and obese) based on their BMI percentile-for-age and sex according to WHO (for patients 3mos- 2yrs) and CDC criteria (for patients ≥2yrs). The primary outcome was 28d mortality. We planned for an analysis of a subgroup of septic patients.

Results: A total of 3,719 patients were evaluated of which 542 (14%) had a primary diagnosis of sepsis. Twenty-nine percent of patients were underweight, 44% normal weight, 11% overweight and 16% obese. The 28d mortality rate was 3.5% for the entire cohort and 8.9% for the septic group and differed significantly by weight status (5.7%, 3%, 2.1% and 1.7% for under, normal, overweight and obese subjects, p<0.0001 and 14.9%, 6.5%, 3.5%, 5.3% in the septic group respectively, p=0.003). In a fully adjusted model, 28d mortality risk was 1.8-fold higher in underweight (adjusted Odds Ratio [OR] and 95%CI: 1.2-2.8]) compared to normal weight in the entire group and 3.4 [1.4-8.4] in the septic group with overweight and obese not having increased risk in both cohorts. Interestingly underweight patients had a significantly higher frequency of fluid overload >10% at day 3 (44.0% vs. 32.5%, 26.1%, 19.1% for under, normal, overweight and obese subjects, p<0.0001) without increased frequency of KDIGO-AKI or renal replacement therapy.

Conclusions: Underweight subjects make up a significant proportion of patients in the PICU. Underweight, not obesity, is independently associated with increased risk for mortality which may be associated to their higher frequency of fluid overload during their ICU stay.

TH-OR043

Central Blood Pressure and Measures of Vascular Health in Children with ADPKD

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Background: Hypertension is increasingly recognised in children with Autosomal dominant polycystic kidney disease (ADPKD) but underlying cardiovascular factors such as central blood pressure (cBP) and pulse wave velocity (PWV) may change before overt hypertension. We assessed peripheral BP (pBP), cBP, pulse pressure (PP) amplification ratio, carotid-femoral PWV (PWVcf) and indexed left ventricular mass (LVMI) in children with ADPKD.

Methods: This was a two-centre prospective observational study of children with ADPKD versus age and BMI-matched healthy controls. All children underwent manual pBP, cBP using radial applanation tonometry and PWVcf with a SphygmoCor device. LVMI was measured by 2D m-mode echocardiography. 24-hour ambulatory BP monitoring (ABPM) and urine albumin: creatinine ratio was assessed in children with ADPKD. Estimated GFR was calculated in children where blood tests were performed.

Results: 47 ADPKD and 49 healthy controls (mean ages 11.4 and 11.7 years, 55% and 39% male respectively) were recruited from two paediatric nephrology centres. Children with ADPKD had significantly higher pBP (mean 112/65mmHg vs. 104/60mmHg, systolic p<0.001) and cBP (mean 97/67mmHg vs. 87/61mmHg, systolic p<0.001) compared to healthy children. There was no significant difference between clinic pBP and 24-hour ABPM. 9 children (19%) with ADPKD were on anti-hypertensive medication. Children with ADPKD had a significantly lower PP amplification ratio (1.59 vs. 1.67, p=0.04) compared to healthy children. There was no difference in PWVcf between affected and healthy children (mean 5.74m/s vs. 5.57m/s, p=0.46). Children with ADPKD had a significantly higher LVMI (mean 30.4 g/m$^{2.7}$ vs. 26.2 g/m$^{2.7}$, p=0.01), although only one had frank hypertrophy. There was significantly lower eGFR (mean 89.9ml/min/1.73m^2 vs. 101.4ml/min/1.73m^2, p<0.01) and 42% of children with ADPKD had evidence of microalbuminuria with a raised albumin:creatinine ratio.

Conclusions: This study confirmed that a significant percentage of children with ADPKD have higher blood pressure, with novel cardiovascular findings of normal PWV but significantly lower PP amplification and increased LVMI. These early cardiovascular abnormalities should be amenable to antihypertensive therapy, reinforcing the need for routine screening of children and young people with ADPKD. eGFR and microalbuminaria warrant checking at the same visit.

TH-OR044

Should RAAS Inhibition Be Discontinued in Children with Advanced CKD? Results of the 4C Study

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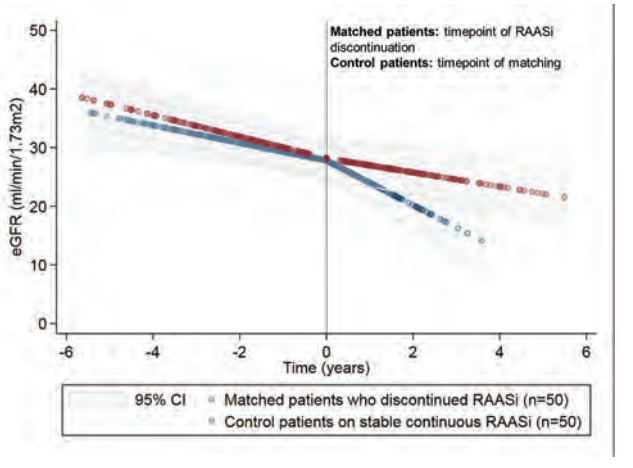
Background: RAAS inhibition (RAASi) is used for renoprotection in children with Chronic Kidney Disease (CKD). RAASi is sometimes discontinued in advanced stages of CKD. We studied the reasons and impact of RAASi discontinuation on important markers of CKD progression and on eGFR decline in the Cardiovascular Comorbidity in Children with CKD (4C) study.

Methods: 69 children with CKD (67% male, mean age 13.7 years, mean eGFR 27 ml/min/1.73m2) who discontinued RAASi during prospective follow-up were studied. Initial 6-month changes in blood pressure, albuminuria and potassium after discontinuation were assessed. The rate of eGFR decline (eGFR slope) during a median of 1.9 years before and 1.2 years after discontinuation were estimated using a linear mixed effects model.

Results: Reported reasons for RAASi discontinuation were increase in serum creatinine (33%), hyperkalemia (23%), and symptomatic hypotension (17%). After discontinuation of RAASi, blood pressure and albuminuria increased whereas potassium decreased. eGFR loss accelerated after RAASi discontinuation from -1.5 (95%CI -2.4 to -0.6) during RAASi treatment to -3.9 (95%CI -5.1 to -2.6) ml/min/1.73m^2 per year (p=0.005). In a matched control group of children who continued RAASi, renal function decline was stable before and after timepoint of matching (eGFR slope -1.8 (95%CI -2.6 to -1.1) versus -1.2 (95%CI -2.0 to -0.4) ml/min/1.73m2/year; p=0.30; Figure).

Conclusions: Discontinuation of RAASi in children with CKD is associated with an acceleration of renal function decline. These results indicate that RAASi is nephroprotective even in advanced CKD and that stopping this therapy, even for good clinical reasons, should be weighed against a potential negative impact on long term renal function.



eGFR over time in patients who discontinued RAASi (blue) and matched controles (red). Grey area: 95%CI per group.

TH-OR045

Uric Acid, Kidney Function, and Cardiovascular Risk among Children with CKD

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Background: Previous studies have shown that high uric acid (UA) is associated with cardiovascular risk factors in adults with and without chronic kidney disease (CKD), but the relationships in children with CKD are not well characterized. We used longitudinal data from the Chronic Kidney Disease in Children (CKiD) cohort study to investigate the relationships between UA, kidney function and cardiovascular outcomes.

Methods: The primary exposure was time-varying UA measured at annual visits. The primary outcomes were blood pressure (BP; clinical and ambulatory) and markers of cardiometabolic health (ie, lipids). Multivariate linear mixed effects models described UA z-scores (scaled within the CKiD population) with BP and lipid outcomes.

Results: A total of 718 participants (mean age= 13, 60% male and 29% with a glomerular-based CKD diagnosis) with at least 1 UA measurement were included in the analysis. At baseline, 47% had a high UA based on age- and gender-specific cutpoints. The figure (below) demonstrates that the UA increased with age, as well as decreasing eGFR even when adjusted for age. Whereas UA was associated with higher clinical and ambulatory BP, the differences were not significant. In models adjusted for age,

gender, race, BMI, CKD diagnosis and eGFR, participants with one SD higher UA had significantly lower HDL (47 vs 50 mg/dL), higher LDL (93 vs 89 mg/dL) and higher total triglycerides (116 vs 110 mg/dL) at baseline compared to those with the average UA. Higher UA was also significantly associated with slower increase in HDL with time (p= 0.002). UA was not associated with longitudinal changes in clinical or ambulatory BP measurements.

Conclusions: There is a strong relationship between eGFR and UA in children with CKD. Higher UA is associated with a more severe lipid profile at baseline and over time, but is not independently associated with hypertension.

Funding: NIDDK Support

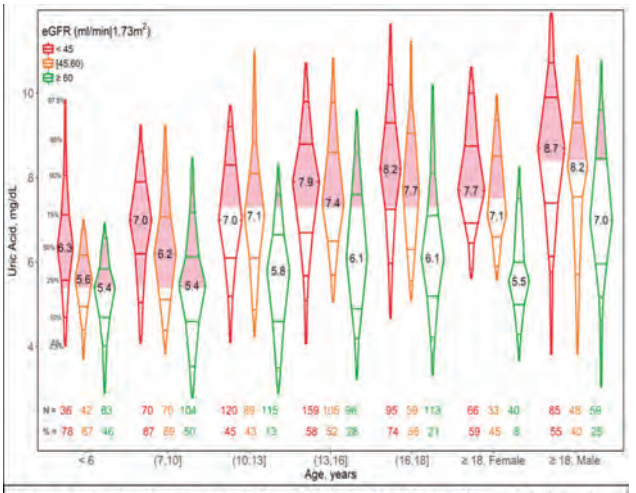

Figure: Association between uric acid and eGFR, stratified by age [N: number of person-visits, %: percentage with high uric acid, shaded area: high uric acid level]

TH-OR046

Kidney Biomarkers for CKD Risk Stratification after Pediatric Cardiac Surgery in the ASSESS-AKI Study

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Background: We have previously demonstrated that children who require surgery for congenital heart disease have increased risk for long-term hypertension and chronic kidney disease (CKD). Biomarkers of ongoing kidney injury and fibrosis after surgery may indicate subclinical kidney disease and assist with prognosis for long-term hypertension and CKD.

Methods: We enrolled children from 1 month to 18 years old undergoing cardiac surgery in the ASSESS-AKI Study. We used Cox proportional hazards regression to assess the association between eight urinary biomarkers (log2 transformed) measured 3 months after cardiac surgery: NGAL, KIM-1, IL-18, L-FABP, uromodulin, MCP-1, YKL-40, and albumin, with the outcomes of incident hypertension (systolic or diastolic BP ≥ 95% for age, height, and gender) and CKD (modified Schwartz eGFR<90 ml/min/1.73m²) at yearly in-person visits over 4 years.

Results: 117 children undergoing cardiac surgery were enrolled. During 48 months of follow-up there were 44 (38%) and 71 (61%) children who developed hypertension and CKD, respectively. After adjustment for sex, AKI during the index hospitalization for surgery, and pre-surgery eGFR, only urine albumin was independently associated with incident CKD (HR, 1.52; 95% CI, 1.20-1.93), but was not associated with incident hypertension (Table). None of the other 7 urinary biomarkers of injury or fibrosis were associated with either outcome.

Conclusions: At 3 months after cardiac surgery, children with higher urine albumin, but not any other tubular injury and fibrosis biomarkers, were more likely to develop CKD.

Funding: NIDDK Support

Table. Multivariate Cox proportional hazard models of the risk of incident hypertension and CKD in children after cardiac surgery with urine biomarkers

	Hypertension HR (95% CI)	CKD HR (95% CI)
Urine biomarker		
NGAL	1.07 (0.91-1.25)	1.05 (0.92-1.20)
KIM-1	0.99 (0.87-1.12)	1.05 (0.93-1.17)
IL-18	1.22 (0.98-1.52)	1.01 (0.85-1.20)
L-FABP	0.92 (0.71-1.20)	1.00 (0.81-1.24)
Uromodulin	0.79 (0.60-1.04)	1.01 (0.82-1.24)
MCP-1	0.95 (0.86-1.06)	1.02 (0.93-1.12)
YKL-40	1.06 (0.90-1.24)	1.07 (0.93-1.23)
Albumin	1.20 (0.90-1.59)	1.52 (1.20-1.93)

Effect size is expressed as the HR for a two-fold increase of each biomarker

Models are adjusted for sex, AKI during the index hospitalization, and pre-surgery eGFR

TH-OR047

Adaptation of the Kidney Failure Risk Equation to Predict Risk of ESRD in Children

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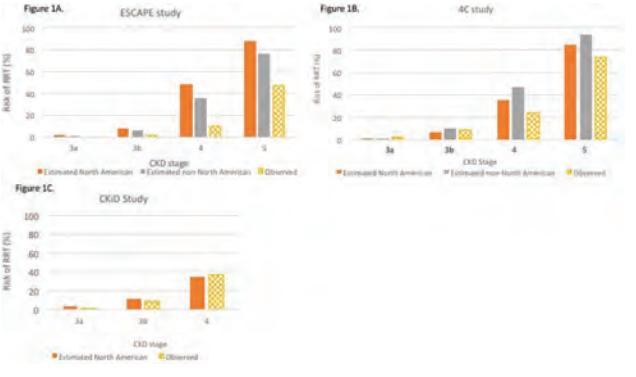
Background: The Kidney Failure Risk Equations (KFREs) have been shown to predict ESRD risk in children with mild-to-moderate CKD in the US. Whether the KFRE accurately predicts progression to ESRD in children with more advanced CKD and children outside of the US is unknown. KFREs to predict ESRD risk in North American (NA) and non-North American (NNA) adults are currently available.

Methods: We studied 653 children from 4C study, 341 children from ESCAPE trial, and 633 children from CKiD study with an eGFR <60 mL/min/1.73 m². The primary predictors were the 4-variable (age, sex, bedside eGFR, albumin-to-creatinine ratio) NA and NNA KFRE score which provides estimates of the risk of ESRD over a 2- and 5-year horizon. C-statistics were used to compare discrimination of the risk for ESRD by the KFRE, and this predicted risk of ESRD was compared to observed failure rates.

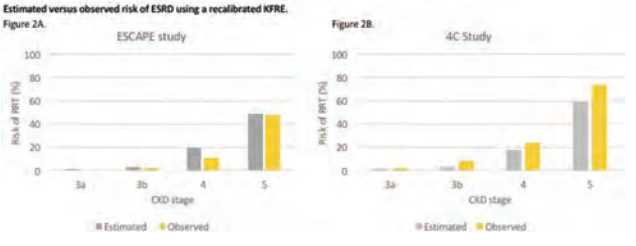
Results: Median follow-up time was 2.8 years in 4C, 4.7 years in ESCAPE, and 3.8 years in CKiD. The NA and NNA 4-variable KFRE strongly discriminated risk of ESRD in children outside the US, with a C-statistic of 0.82 and 0.79 in 4C and 0.90 and 0.87 in ESCAPE over a 2- and 5-year horizon, respectively. The predicted risk closely matched the observed ESRD rates in CKD stage 3, but over-predicted ESRD risk in CKD stage 4-5 across all cohorts (Figure 1). After we re-calibrated the equation, performance of the KFRE in advanced CKD improved (Figure 2).

Conclusions: The KFRE is a simple tool that strongly discriminates the risk of ESRD in children with CKD in the US and internationally, although its performance was less robust in children with advanced CKD. With re-calibration, its performance in more advanced CKD was substantially improved.

Funding: NIDDK Support



Estimated versus observed risk of ESRD using a recalibrated KFRE.



TH-OR048

Children in CKiD with Congenital, Non-Glomerular Form of Progressive CKD Will Experience Renal Replacement Therapy by 40 Years of Age

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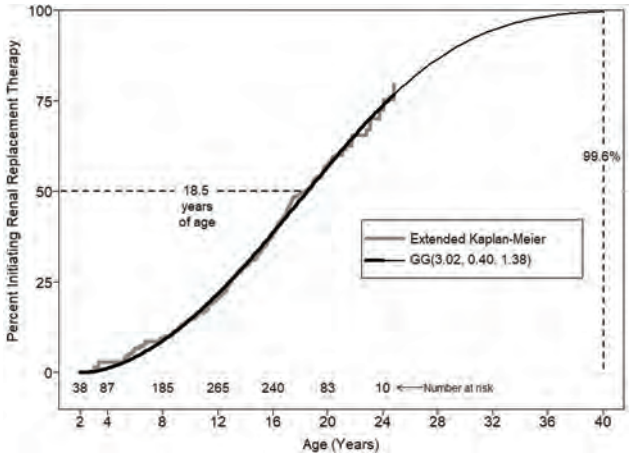
Background: The Chronic Kidney Disease in Children (CKiD) study provides a unique opportunity to prospectively describe a life course characterization of progressive non-glomerular disease prior to renal replacement therapy (RRT). Our aim was to maximize the heterogeneous disease duration at entry in this cohort to estimate the age by which all children with congenital, non-glomerular disease will require RRT.

Methods: The times to RRT in CKiD children were characterized by parametric survival models (generalized gamma (GG) distribution). The time scale was years from NG diagnosis (age) and accounted for late entries due to heterogeneous disease duration at enrollment. Models were fit overall, and stratified by race and gender.

Results: Among 626 children, the median duration of disease at entry was 9 years (range 2 to 18) and median duration at end of follow-up was 15 years (maximum= 27). Three diagnosis groups represented 67%: obstructive uropathy (24%), hypo/dysplasia (24%) and reflux nephropathy (19%). Over approximately 25 years (capitalizing on staggered entries), 186 initiated RRT. The GG fit was excellent and demonstrated that 50% received RRT by age 18.5 and estimated that 99.6% will receive RRT by age 40 (Figure). The times to RRT did not differ significantly by race (p=0.25) or gender (p=0.40), with similar 40 year estimates of RRT for nonblacks (99.9%), blacks (98.8%), males (99.9%) and females (97.9%).

Conclusions: Practically all CKiD participants with progressive non-glomerular disease will receive RRT by 40 years old, much earlier than reports from European registries. This is likely due to a combination of access to care, organ availability and disease severity. Methodologically, these data enable handling right censored observations as interval censored, thus enriching parametric survival methods.

Funding: NIDDK Support



Percent of children with non-glomerular CKD initiating RRT by age

TH-OR049

Racial and Ethnic Disparities in Pediatric Kidney Transplant Outcomes in the United States: Have We Made Any Progress over the Last Twenty Years?

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Background: A recent JASN study demonstrated dramatic reductions in disparities in adult kidney transplant (KT) outcomes in the US. We examined twenty-year trends in pediatric KT outcomes to determine whether pediatric KT disparities also changed over time.

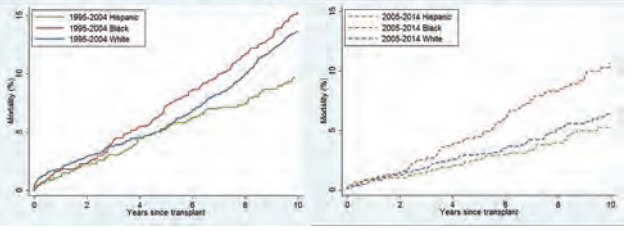
Methods: Using OPTN data, we performed Cox proportional hazards regression models to compare patient outcomes among 3,295 White, 2,049 Black, and 2,073 Hispanic children (aged 0-17 years) who received a KT in the US between January 1, 1995 and December 31, 2014. We adjusted regression models for differences in recipient, donor, and transplant center factors.

Results: From 1995 to 2014, survival after KT improved for all recipients. **(Figure 1)** However, racial/ethnic disparities in long-term survival worsened over time (p<0.05 for statistical interaction). In 1995, compared with long-term mortality in White KT recipients, the adjusted hazard ratio (aHR) for Black recipients was 0.89 (95% CI: 0.67, 1.18) and for Hispanic recipients was 0.51 (95% CI: 0.34, 0.76). In 2014, compared with White recipients, the aHR for Black recipients was 1.84 (95% CI: 1.10, 3.07) and for Hispanic recipients was 0.71 (95% CI: 0.37, 1.35).

Conclusions: In stark contrast to the prior findings of reduced disparities for adult KT recipients, we found that disparities in long-term survival among pediatric kidney transplant recipients worsened over the last two decades in the US. Strategies to elucidate and intervene on mechanisms for disparities in long-term outcomes among pediatric recipients are needed.

Funding: NIDDK Support, Other NIH Support - NHLBI, AHRQ, Other U.S. Government Support, Private Foundation Support

Figure 1. Mortality after Kidney Transplantation among Pediatric Recipients in the United States, by Race/Ethnicity and Time Cohort



TH-OR050

Prevalence of Blood Pressure Control in Children with Kidney Transplant

Pamela D. Winterberg,[1,2] Rouba Garro,[1,2] Devesh S. Dahale,[3] Jens W. Goebel,[4] David K. Hooper.[3] Improving Renal Outcomes Collaborative [1]*Department of Pediatrics, Emory University School of Medicine, Atlanta, GA;* [2]*Children's Healthcare of Atlanta, Atlanta, GA;* [3]*Cincinnati Children's Hospital Medical Center, Cincinnati, OH;* [4]*Children's Hospital Colorado, Aurora, CO.*

Background: Hypertension (HTN) is common in children following kidney transplant (KT) with reported prevalence of 60-90%. Uncontrolled blood pressure (BP) is associated with cardiovascular mortality and decreased graft survival. The Improving Renal Outcomes Collaborative (IROC) is a networked learning health system of 23 pediatric centers dedicated to improving health outcomes and longevity for children with kidney disease by sharing best practices and clinical data, and engaging in quality improvement (QI). We aimed to determine the baseline prevalence of systolic BP control and treatment within the collaborative after implementing standardized processes for BP measurement across centers.

Methods: Patient and KT characteristics were uploaded into the IROC registry via UNOS TEIDI reports. Biometric data, BP measurements, and medications are prospectively entered by centers for each clinic visit. BP percentiles are automatically calculated in the registry using the 2004 NHBPEP 4th Report to determine BP status for each visit (e.g. normal, pre-HTN, stage 1, stage 2). We examined the latest clinic visit for each patient >90 days post-transplant in the registry. Patients were classified by systolic BP control (<90th percentile) and treatment status.

Results: Of the 935 unique patients with at least 1 visit in the registry, 56% had uncontrolled systolic BP (pre-HTN or greater) and/or were on BP medications. Of the 492 pts receiving BP meds, 132 (27%) had uncontrolled systolic BP at last visit. In addition, 31 patients (3% of total) had uncontrolled systolic BP at last visit but no record of BP medication. Of those treated, 80% had one, 16% had 2, and 8% had 3 or more active BP meds. Calcium channel blockers (80%) were most commonly used for treatment of BP followed by renin-angiotensin system blockade (33%), and beta-adrenergic blockade (23%).

Conclusions: HTN is common in pediatric KT patients in the IROC registry. Nearly one-quarter of those treated for HTN have not achieved systolic BP control. Future studies within IROC will evaluate patient- and center-level factors influencing BP control.

		Visit BP Status		
		Normal BP	Uncontrolled BP	Total
BP Treatment	Meds	360 (73% treated are **well-controlled**)	132 (27% treated are **uncontrolled**)	492 (53%)
	No Meds	412 (44% of pts **no treatment required**)	31 (3% pts **untreated, uncontrolled**)	443 (47%)
	Total	772 (83%)	163 (17%)	935

Patients categorized by BP control and treatment status.

TH-OR051

IL-17 Signaling in CD4+ T Cells Control TH17 Responses

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Background: The interleukin-17 family (IL-17A-F) plays a critical role in autoimmune and chronic inflammatory diseases, such as crescentic GN. A heterodimeric receptor complex consisting of IL-17RA and a ligand specific IL-17 receptor subunit (IL-17RB-E), which is expressed by epithelial and endothelial tissue cells, mediates their biological effects. In contrast, the IL-17 receptor expression pattern and function on hematopoietic cells, e.g. $CD4^+$ T cell subsets, remains to be determined.

Methods: Crescentic GN (Nephrotoxic Nephritis, NTN) was induced in IL-17A, IFNγ and Foxp3 triple-reporter mice for *in vivo* cell sorting of renal $CD4^+$ T cell subsets and

subsequent single cell RNAseq of $CD4^+$ T cells using the 10X Single Cell system. The effect of IL-17 signaling in $CD4^+$ T cells was analyzed by CD4 T cell polarization experiments. Moreover, we generated T_H17 cell specific IL-17RA gene-deficient mice to study the role of IL-17 signaling in Th17 cells in the NTN model.

Results: mRNA expression analysis of sorted T cells revealed a predominant expression of IL-17RC and IL-17RE by IL-$17A^{positive}$ T_H17 cells, high IL-17RB expression by $Foxp3^{positive}$Tregs, whereas IL-17RA is ubiquitously expressed by all $CD4^+$ T-cell subsets, demonstrating for the first time a T cell specific expression pattern of IL-17 receptors. *In vitro* T cell polarization experiments revealed that IL-17A-RC signaling downregulates IL-17A expression of T_H17 cells. In line, competitive adoptive transfer experiments of wildtype and IL-$17RA^{-/-}$ $CD4^+$ T cells into nephritic $Rag1^{-/-}$ mice revealed that T_H17 genes were upregulated in cells lacking the IL-17RA, indicating that IL-17 signaling on $CD4^+$ T-cells is instrumental for the control of the T_H17 response. In addition, scRNAseq analysis of 12,971 renal $CD4^+$ T cells revealed that, T_H17 cells lacking the IL-17RA form a distinct cluster which is characterized by upregulation T_H17 marker genes. Most importantly, mice lacking IL-17 signaling specifically in T_H17 cells demonstrated dysregulation of T_H17 immune response with higher production of IL-17A and F after induction of NTN and an accelerated course of the disease.

Conclusions: Our findings indicate that IL-17 receptor signaling in CD4 T cells control T_H17 immune response via a self-inhibitory loop. These findings might provide new insight into the development of more efficient anti-T_H17 treatment strategies.

Funding: Government Support - Non-U.S.

TH-OR052

Bowman Capsule Provides Protective Podocyte Niche: Implications for Crescentic Glomerulonephritis

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Background: A role for CD8+ cytotoxic T cells (CTLs) in peri-glomerular infiltrates during glomerulonephritis (GN) has been proposed, but how and if CTLs can enter Bowman's space remains unclear.

Methods: CD8+ T cells from a newly generated transgenic mouse, termed Jedi (for Just EGFP Death Inducing) T cells that are cytotoxic for any EGFP expressing cells were used. Jedi T cells and lentivirus expressing EGFP were injected into transgenic mice with podocyte-specific EGFP expression mice in normal conditions and in a nephrotoxic serum nephritis (NTSN) model. 4 days after induction of NTSN, Jedi or control CD8+T cells were injected, and the mice were sacrificed at day 12. Proteinuria and blood urea were measured. EGFP+ podocyte areas were analyzed. In biopsies from patients with crescentic GN co-staining of CD8+ T cells and Bowman's capsule were performed.

Results: In control mice, Jedi T cells could not access EGFP+ podocytes. Conversely, when we induced NTSN and injected Jedi T cells, EGFP+ podocyte transgenic mice showed enhanced proteinuria and higher blood urea levels. Morphometric analysis showed greater loss of EGFP+ podocytes, which was associated with severe crescentic and necrotizing GN. Notably, only glomeruli with disrupted Bowman's capsule displayed massive CD8+ T cell infiltrates that were in direct contact with EGFP+ podocytes, causing their apoptosis. Comparable findings were obtained in biopsies from patients with crescentic GN, where infiltration of CD8+ T cells inside Bowman's capsule also only occurred after breaches in the capsule allowed access of CD8+ T cells to the glomerular tuft, resulting in its destruction.

Conclusions: Under control conditions Bowman's capsule provides an immunologically protected niche for podocytes from CTL. However any breach in Bowman's capsule, as occurs during crescentic GN, allows access of CTLs to Bowman's space with catastrophic consequences for the glomerulus, converting a potentially reversible GN into a rapidly progressive GN leading to end stage kidney disease. Translating these mechanistic insights to human crescentic nephritis should direct future therapeutic interventions at blocking CD8+ T cells, especially in progressive stages of rapidly progressive GN.

Funding: Other NIH Support - R01DK078897; R01DK98126, Veterans Affairs Support

TH-OR053

Myeloperoxidase Mediates Renal Damage in Crescentic Glomerulonephritis That Can Be Successfully Targeted In Vivo

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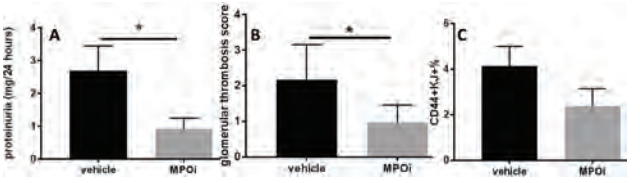
Background: Myeloperoxidase (MPO) released following neutrophil and monocyte activation can lead to host tissue damage by generating ROS and promoting further leukocyte activation. Extracellular glomerular MPO deposition has been shown in ANCA associated vasculitis (AAV) and may promote T and B cell glomerular targeting to enhance crescentic glomerulonephritis (CGN). MPO-deficient mice have less CGN but enhanced T cell activity (Odobasic, 2007). We investigated the role of MPO in mediating glomerular damage and leukocyte activation using a novel MPO inhibitor, AZM198.

Methods: A) We stained renal biopsies from patients with CGN due to SLE, IgA, anti-GBM disease, $ANCA^-$ and $ANCA^+$ GN, for MPO and CD15. B) We measured MPO activity in the supernatants of AAV patient neutrophils and healthy controls, stimulated by different means in the absence and presence of AZM198. C) We induced nephrotoxic nephritis (NTN) in C57BL/6 mice investigating the effect of AZM198 on CGN severity and T cell activity and D) tested the effect of AZM198 on antigen-specific T cell responses using adoptive transfer of DO11.10 lymphocytes into OVA immunised mice.

Results: All biopsies with CGN had extracellular glomerular MPO deposition. In vitro, AZM198 led to a significant reduction in MPO activity measured in the supernatants of PMA (n=16, median(IQR) 37.4(9-175.6) vs12.93(1.9-152.8)U/g, p<0.05), TNF(n=8, 229.2(130.3-950.6) vs108.5(33.3-138.1)U/g, p<0.05) and pANCA(n=6,185.8(79.9-278.9) vs114.3(45.9-340.6)U/g, p=0.19) stimulated neutrophils. In vivo, AZM198 attenuated glomerular inflammation (NTN model), defined by proteinuria (A,p=0.01) and glomerular thrombosis (B,p=0.04,vehicle n=13, MPOi n=15), while reducing CD4 activation. In the adoptive cell transfer model, AZM198 led to a non-significant reduction of CD44 and KJ expression on $CD4^+$ T cells in the draining lymph nodes (C, vehicle n=3, MPOi n=3).

Conclusions: Therapeutic MPO inhibition reduced neutrophil degranulation in patients with AAV and attenuated kidney damage in preclinical models of CGN without augmenting adaptive immune responses, suggesting it may be a novel adjunctive therapy in various forms of CGN.



TH-OR054

Proteinase 3 Promotes Giant Cell Formation and Granulomata In Vitro and In Vivo Implicating a Key Role in GPA Pathogenesis

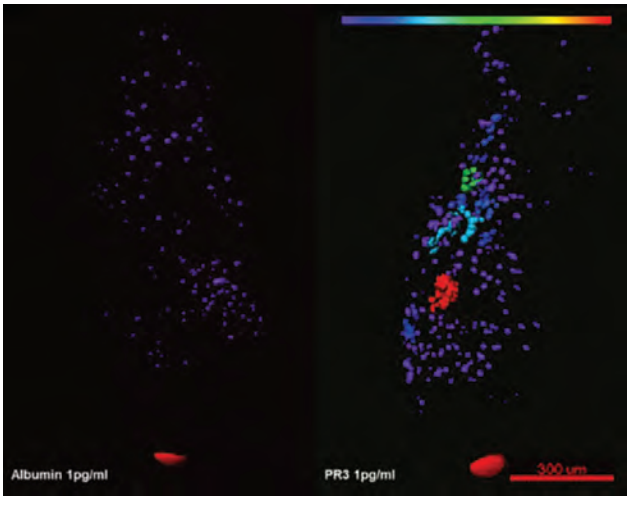
Scott R. Henderson, Maryam Khosravi, Alan J. Greig, Paul Frankel, Alan D. Salama. *University College London, London, United Kingdom.*

Background: Granulomatosis with polyangiitis (GPA) is characterised by ANCA reactivity towards proteinase 3 (PR3), PR3 deposition in granulomatous lesions and increased neutrophil membrane PR3 expression, inhibiting apoptotic cell phagocytosis by macrophages. We investigated whether persistent and excessive PR3 expression in GPA may underlie giant cell and granuloma formation.

Methods: PBMCs were isolated from healthy controls(HC)(n=10), GPA(n=10) and microscopic polyangiitis(MPA)(n=10) patients and monocytes isolated. Cells were stimulated with either enzymatically active (aPR3) or inactive PR3(iPR3) or control auto-antigen myeloperoxidase (MPO). Light, epifluorescence and confocal microscopy was used to confirm cell fusion at different time points. Mpeg:mcherry macrophage zebrafish at 24 hours post-fertilisation were injected with aPR3 or iPR3 or albumin. Fish were imaged by lightsheet microscopy 6 days later.

Results: Monocyte aggregation and giant cell formation occurred following stimulation with both aPR3 and iPR3 with a greater number (p<0.01) and size of aggregates (p<0.001) in GPA patients compared to MPA patients and HC. Typical granuloma were observed using PBMC preparations with a greater number (p<0.001) and size (p<0.001) of aggregates seen in GPA patients. There was no significant difference between aPR3 or iPR3. No effect was seen with MPO. Supernatant profiling implicated specific roles for pro-inflammatory cytokines. In zebrafish (n=9/group), both aPR3 and iPR3 were associated with a significant increase in cell fusion and aggregate volume (p<0.001) when compared to albumin injected controls (figure).

Conclusions: These models support a role for PR3 in promoting monocyte and macrophage fusion and granuloma formation *in vitro* and *in vivo*, and provide an opportunity to test specific therapeutics.



Macrophage aggregation in zebrafish (volume=purple min;red max)

TH-OR055

Sortilin-Related Receptor (SORL1) Mediates Glomerulopathic Light Chain Interactions with Mesangial Cells (MCs)

Guillermo A. Herrera, Jiamin Teng, Xinggui Shen, Chun Zeng, Elba A. Turbat-Herrera. *Louisiana State University Health Sciences Center, Shreveport, LA.*

Background: It has been proven that glomerulopathic (G), but not tubulopathic (T) light chains (LCs) interact with mesangial cells (MCs) using a receptor membrane. Both light chain deposition disease (LCDD) and amyloid- producing (AL) LCs use the same receptor but lead to divergent downstream mesangial cell/matrix alterations. Tubulopathic LCs do not interact with MCs.

Methods: Three AL, two LCDD and one tubulopathic-LCs (10 ug/ml) were incubated with MCs for 30 minutes, cross-linked using DSTTP and subsequently, SPS-PAGE gels were run to identify bands. Bands above 70kD were cut and analyzed using mass spectroscopy (MS). Proteins obtained from various LCs cross linked to MCs were compared to identify receptors shared by the GLCs. TLC was used as a control. Fluorescein-labeled antibody to the SORL1 protein receptor and a second Texas red labeled antibody for the GLCs were used to evaluate for colocalization.

Results: Several transient MC receptors were shared by the 5 GLCs including: G-protein coupled, ligand-gated ion channel/transient receptor potential cation channel, subfamily M, and extracellular matrix linker protein receptor/cell adhesion-molecule extracellular matrix glycoprotein receptors. The one unique membrane receptor shared by the 5 GLCs was SORL1 located on chromosome 11, a lysosomal sorting receptor engaged in directing internalized proteins to the endolysosomal system and participating in microvesicular protein movement inside MCs. SORL1 was colocalized with both AL and LCDD light chains using double fluorescence labeling techniques. No localization was noted with TLC.

Conclusions: SORL1 (238 kD mw) was expressed when GLCs interact with MCs and not when TLCs were incubated with MCs or when MCs were incubated without LCs. Engagement of this receptor serves to direct GLCs, depending on their physicochemical characteristics, to various intracellular compartments where crucial pathogenetic events occur. SORL1 had not been previously identified as a MC receptor but it had been found to be present in the kidneys with no specific localization yet defined prior to this study. SORL1 was colocalized with LCDD and AL-LCs at the cell surfaces and inside MCs. There was no colocalization with TLC.

TH-OR056

Disruption of Endosomal Trafficking of Membrane Bound Nephrin Results in an Earlier Phenotype in Nephrin Deleted Adult Mice

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Background: In a recent publication we reported that deletion of nephrin in an adult mature glomerulus results in FSGS. Following cre-induction a small fraction (10-15%) of nephrin remains at the membrane and is sufficient to maintain the slit diaphragm for 4-6 weeks. *In vitro* studies have suggested that membrane bound nephrin undergoes endocytic recycling. Vesicular trafficking is an important part of cellular development and growth, helping in maintaining a balance between synthesis, degradation and recycling of cellular components. Vps34, an important phosphoinositol kinase that generates PI3P, plays critical role in vesicular trafficking. We hypothesized that in our model recycling is responsible for maintenance of nephrin at the membrane following nephrin deletion.

Methods: Standard biochemical and cell biology techniques were used to analyze kidneys from knock out mice. Cre-loxP system was used to generate podocyte specific deletion of nephrin and vps34.

Results: Nephrin deleted adult animals have normal phenotype at 4-6 weeks age, when mice develop proteinuria. $Vps34^{fl/fl,\ cre+}$ mice have normal phenotype at birth, develop massive proteinuria and accumulation of vesicles by 3 weeks of age and majority of them die by 9 weeks of age. Immunogold EM analysis reveals accumulation of Nephrin in vesicles suggesting involvement of Vps34-dependent endocytic pathway in nephrin's maintenance at the slit diaphragm. In order to examine the role of endocytic recycling of nephrin at the membrane we generated a mouse model where both nephrin and vps34 are simultaneously deleted using tamoxifen in an adult mature mouse podocytes. These double knockout mice develop proteinuria at 1 week of age and die at 10-12 days indicating a earlier phenotype compared to deletion of vps34 or nephrin alone. Immunostaining revealed nephrin in vesicles that are EEA1 and Rab5 positive indicating nephrin localization in early endosomes and not in vesicles originating from the Golgi network.

Conclusions: We report an *in vivo* model that provides evidence for nephrin endocytosis and recycling at the membrane. A small fraction of nephrin is stably present at the membrane once production of new nephrin is stopped. Our data provides evidence of recycling of this nephrin from and to the membrane.

Funding: NIDDK Support

TH-OR057

Induction of a Glomerular Reparative Program in Lupus Glomerulonephritis by a Novel Treg-Enhancing Cytokine Therapy

Rajkumar Venkatadri, Vikram Sabapathy, Marta Stremska, Hongyang Wang, Sun-sang J. Sung, Saleh Mohammad, Shu man Fu, Rahul Sharma. *University of Virginia School of Medicine, Charlottesville, VA.*

Background: Lupus glomerulonephritis (GN) is an autoimmune disease marked with glomerular inflammation and with reduced levels of IL-2 and T-regulatory cell as contributing factors. Earlier we showed that a novel hybrid cytokine IL233 utilizes the synergy of IL-2 and IL-33 to increase Tregs and protect mice from acute kidney injury and onset of accelerated GN in lupus prone NZM2328 mice. Here we investigated whether IL233 can reverse ongoing lupus GN and restore renal structure and function.

Methods: We made use of the recombinant hybrid cytokine (IL233) bearing activities of IL-2 and IL-33 and tested its efficacy to induce a glomerular repair program in three animal model systems: spontaneous lupus GN in NZM2328, adenovirus (Ad)-IFNa-accelerated lupus GN model and MRL/lpr mice.

Results: Treatment of NZM2328 mice after the onset of GN, induced rapid and persistent remission from severe proteinuria in Ad-IFNa-accelerated GN in NZM2328 mice as well as spontaneous lupus GN in NZM2328 and MRL/lpr mice. IL233 strongly inhibited glomerular hypertrophy and mesangial expansion and induced skewing of immune complex deposits towards IgG2b as compared to predominantly IgG2a deposits in control mice. Markers of glomerular integrity (nephrin, podocin, podocalyxin and synaptopodin) were elevated in IL233 treated animals confirming its therapeutic effects. Furthermore, IL233 treatment in mice with established GN also induced elevated levels of renal progenitor markers (Sox9, Six2, Lgr4, Lgr5 and Pax8) indicating an IL233-mediated cellular programming involving regeneration and repair.

Conclusions: We present a novel cytokine therapy of lupus GN with implications for induction of a glomerular reparative program with the use of IL233 hybrid cytokine.

Funding: Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases

TH-OR058

Non-Classical Monocytes Act as Glomerular Sentinels, Sensing Deposited Immune Complexes and Orchestrating the Inflammatory Response via LFA-1 in Experimental Crescentic Glomerulonephritis

Kevin Woollard, Tabitha Turner-Stokes, Ana Isabel Garcia Diaz, H. Terence Cook, Charles D. Pusey. *Imperial College London, London, United Kingdom.*

Background: Non-classical monocytes (NC Mo) crawl along the resting endothelium, orchestrate the inflammatory response in some vascular beds and express high levels of FcγRIII(CD16). They may be important in triggering inflammation to immune complex (IC) deposition in glomerulonephritis (GN). Nephrotoxic Nephritis (NTN) in the WKY rat is a widely used, clinically-relevant model of crescentic GN but the distinct roles of myeloid subsets and the dynamics of their glomerular recruitment are unknown.

Methods: We developed a novel rat transgenic WKY-hCD68-GFP Mo/macrophage reporter. Mo subsets and endothelial cells were sorted from glomeruli of rats with NTN to investigate effector functions. Intravital confocal microscopy, with *in vivo* antibody labelling, was performed in the hydronephrotic kidney of anaesthetised WKY-hCD68-GFP rats, permitting high-resolution glomerular imaging and real-time, *in vivo* visualisation of myeloid recruitment and intravascular behaviour during NTN.

Results: Classical and NC Mo subsets were phenotyped as $GFP^{pos}CD43^{lo}HIS48^{hi}$ and $GFP^{pos}CD43^{hi}HIS48^{int}$ respectively and neutrophils (PMNs) as $GFP^{neg}CD43^{int}HIS48^{hi}$. RNA expression confirmed NC Mo were $CD16^{hi}CX3CR1^{hi}CD14^{lo}CCR2^{lo}$ relative to classical Mo i.e. homologous to mice and humans. During intravital imaging, NC Mo surveyed the glomerular endothelium for prolonged periods in the steady state. Classical Mo and PMNs had only transient endothelial interactions. There were subset-specific differences in the behavioural response to IC deposition during NTN: Increased recruitment of NC Mo vs. increased retention of classical Mo and PMNs. CD16 and pro-inflammatory cytokines (IL-1β, TNFα) were upregulated in NC compared to classical Mo and a unique chemokine axis was overexpressed by the endothelium and NC Mo. LFA-1 blockade inhibited the distinctive migratory phenotype of NC Mo, reducing their recruitment and the retention of PMNs.

Conclusions: LFA-1-mediated endothelial surveillance by $CD16^{hi}$ NC Mo may be an important mechanism for IC detection in GN, orchestrating the subsequent inflammatory response through a unique chemokine axis and cytokine-mediated retention of classical Mo and PMNs. Targeting NC Mo may lead to effective treatments for GN, with fewer side effects.

Funding: Government Support - Non-U.S.

TH-OR059

Classical Monocytes Promote Crescent Formation and Necrosis in ANCA-Associated Necrotizing Crescentic Glomerulonephritis

Anthony Rousselle,[2] Ralph Kettritz,[2,1] Adrian Schreiber.[2,1] *[1]Charite Berlin, Berlin, Germany; [2]ECRC, Berlin, Germany.*

Background: The binding of circulating antineutrophil cytoplasmic autoantibodies (ANCAs) to neutrophils and monocytes and their subsequent activation are key events in the development of ANCA-associated vasculitis (AAV) and necrotizing crescentic glomerulonephritis (NCGN). In contrast to neutrophils, the exact role of monocytes remains poorly described. Murine monocytes are classified into two functionally different subsets: $Ly6C^{hi}$ $CCR2^{+}$ classical (inflammatory) monocytes (CM) and $Ly6C^{lo}$ $CCR2^{-}$ non-classical (patrolling) monocytes (NCM). Differentiation of circulating $Ly6C^{hi}$ monocytes into $Ly6C^{lo}$ monocytes is controlled by the transcription factor C/EBPβ. We showed recently that global monocyte depletion protected from ANCA-induced necrotizing crescentic glomerulonephritis (NCGN) in vivo. We now studied the exact contribution of the two distinct monocyte subsets in AAV.

Methods: To assess the role of both monocyte subsets in vivo, we used our AAV murine model: $MPO^{-/-}$ mice were immunized with murine MPO, sublethally irradiated and subsequently transplanted with hematopoietic cells from either WT, $CCR2^{-/-}$, $C/EBP\beta^{+/+}$ or $C/EBP\beta^{-/-}$ mice (all MPO positive). $CCR2^{-/-}$ mice had a reduction of circulating

Ly6C^{hi} monocytes whereas C/EBPβ$^{-/-}$ mice lacked circulating Ly6C^{lo} monocytes. Mice were sacrificed and analyzed 8 weeks following transplantation. Urine was analyzed by dipstick, albuminuria by ELISA, glomerular necrosis and crescents by histology, and circulating and renal cell influx by flow cytometry.

Results: Blood composition confirmed the expected engraftment as CM and NCM were indeed significantly decreased in CCR2$^{-/-}$ and C/EBPβ$^{-/-}$ chimeric mice, respectively. WT, C/EBPβ$^{+/+}$ and C/EBPβ$^{-/-}$ chimeric mice developed urine abnormalities and glomerular necrosis and crescent formation. In contrast, CCR2$^{-/-}$ chimeric mice did neither develop erythrocyturia and albuminuria nor NCGN. Flow cytometry showed significantly reduced renal infiltration of CM CCR2$^{-/-}$. In contrast, renal neutrophil, macrophage and dendritic cell infiltration remained similar in all groups.

Conclusions: Our findings provide novel experimental evidence that classical monocytes are important contributors of kidney damage in ANCA-mediated NCGN. The exact molecular mechanisms by which classical monocytes promote kidney damage remains to be clarified.

Funding: Government Support - Non-U.S.

TH-OR060

Inflammasome Priming and Activation Glomerular Gene Expression Scores Associate with Poor Outcome in Nephrotic Syndrome

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Background: Recent studies have shown that the inflammasome, a cytoplasmic protein complex that processes interleukins IL-1beta and IL-18, is functional in resident cells of the glomerulus, such as the podocyte. Before activation of the NLRP3 inflammasome, a priming step occurs consisting of upregulation of NLRP3, pro-IL-1beta, and other genes. Here we interrogate glomerular mRNA of patients with nephrotic syndrome to test our hypothesis that gene expression profiles of inflammasome priming and activation (IL-1beta-regulated genes) correlate with eGFR and proteinuria at time of biopsy and outcome measures.

Methods: Using the Nephrotic Syndrome Study Cohort (NEPTUNE), a prospective longitudinal cohort study enrolling patients at time of biopsy, we correlated glomerular gene expression Z-scores of inflammasome priming (5 genes) and activation (100 genes) with clinical characteristics at enrollment (Pearson for eGFR; Spearman for UPCR). Linear GEE models of eGFR and urine protein to creatinine ratio (UPCR) were fit to associate baseline inflammasome Z-scores with disease status over time.

Results: 97 patients with NS (50 FSGS, 47 MCD) were available for analysis. At time of biopsy, both the priming (r=-0.33, p<0.001) and activation (r=-0.45, p<0.001) Z-scores negatively correlated with eGFR. Priming (r=0.23, p=0.02) and activation (r=0.28, p=0.01) Z-scores positively correlated with UPCR as well. Over a follow-up time of 45 months, baseline inflammasome priming and activation Z-scores were associated with lower eGFR over time (-12.6 mg/dL, p=0.028 and -55.4 mg/dL, p<0.001 respectively) in unadjusted models. After adjusting for baseline eGFR and UPCR, diagnosis, age, black race, immunosuppression and time, only the activation Z-score association was significant (-17.4 mg/dL, p=0.05). The inflammasome priming and activation Z-scores did not associate with UPCR over time in adjusted models.

Conclusions: Inflammasome priming and activation Z-scores based on glomerular gene expression profiles significantly correlate with eGFR and UPCR at time of biopsy and associate with lower eGFR, but not UPCR, over time. This approach offers the opportunity to discover novel molecular tests to predict outcome in nephrotic syndrome and highlight pathways for therapeutic intervention.

Funding: NIDDK Support

TH-OR061

Label-Free Imaging of Human Kidney Biopsies Guides Downstream Interrogation

Michael J. Ferkowicz,[1] Seth Winfree,[2] Daria Barwinska,[1] Ken Dunn,[1] Katherine J. Kelly,[1] Timothy A. Sutton,[2] Michael T. Eadon,[3] Pierre C. Dagher,[1] Tarek M. El-Achkar.[1] *[1]Indiana University, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN; [3]Indiana University Division of Nephrology, Indianapolis, IN.*

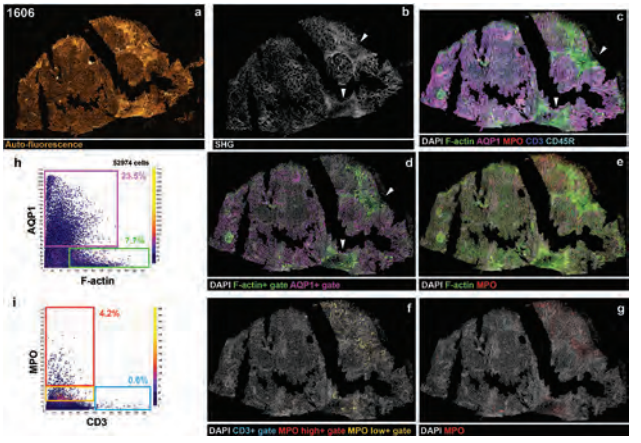
Background: Label-free (LF) imaging of human kidney biopsies is a novel and under-utilized approach to characterize kidney pathology. Unlabeled kidney biopsies have auto-fluorescence (AF) across the visible spectrum that encodes specific signatures of nephron structures and can be correlated with pathology. In addition, AF intensity can be extended using fluorescence lifetime imaging (FLIM) to resolve endogenous fluorophores in health and disease. Second harmonic generation (SHG) by collagen fibers is an LF imaging approach that can be simultaneously acquired, allowing for rapid measurement of fibrosis.

Methods: Scanning multiphoton excitation microscopy was used to rapidly collect AF, FLIM and SHG images of human kidney sections. These same sections were subsequently stained by immuno-fluorescence and imaged with spectral multi-channel three-dimensional laser scanning confocal microscopy. These volumes were then analyzed by 3D tissue cytometry (3DTC).

Results: AF provides LF imaging and identification of tubular sub-segments. Supervised machine learning approaches can automatically and accurately identify tubular sub-segments in AF images. Lifetime imaging of AF provides an additional signature. SHG provides LF imaging of collagen fibrosis. Using 3DTC, LF images can be correlatively integrated into the analysis of stained tubular and infiltrating cells from the same kidney section.

Conclusions: Thus, the label-free imaging of human kidney biopsies using AF, FLIM and SHG will complement our existing confocal spectral imaging approach. This combined multi-dimensional imaging approach will maximize the informational yield of a biopsy when combined with downstream interrogation methods.

Funding: NIDDK Support, Veterans Affairs Support



Label-free imaging informs analysis. A. SHG imaging delineates fibrosis (b) that spatially correlates with spectrally imaged F-actin+ cells (c and d) and inflammatory cells (e, in red and f, in red and yellow).

TH-OR062

SPECTRUM: A Quantitative Pipeline for Optically Cleared Tissue Validated in Crescentic Nephritis

Victor G. Puelles,[1,2] Lena Ortz,[2] Stella Papadouri,[2] Thiago Strieder,[2] Turgay Saritas,[2] Michael Vogt,[2] Christoph Kuppe,[2] David J. Nikolic-Paterson,[3] Marcus J. Moeller.[2] *[1]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]RWTH Aachen University, Aachen, Germany; [3]Monash Medical Centre, Clayton, VIC, Australia.*

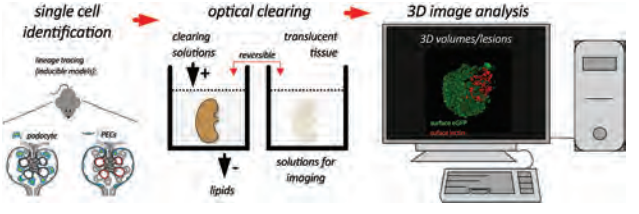
Background: Optical clearing and advanced light microscopy have revolutionised three-dimensional quantification in cell biology. Here, we present a **S**ystematic **P**ipeline of **E**nhanced **C**larification for **T**hree-dimensional **R**endering and **U**nbiased **M**orphometrics (***SPECTRUM***) as a unique tool for the comprehensive analysis of glomerular health and disease.

Methods: ***SPECTRUM*** is based on a combination of single cell identification (ie. lineage tracing), optical clearing, advanced light microscopy with single cell resolution, and 3D morphometrics. Podocytes and parietal epithelial cells (PECs) were genetically labelled with eGFP using inducible mouse systems (POD or PEC -rtTA/H2B-eGFP). Crescentic nephritis was used as a validation model. Several optical clearing protocols were optimized for kidney tissue, including aqueous, hydrogel, and solvent-based approaches. Image acquisition was based on whole structures (ie. glomeruli and lesions) using light sheet, confocal and two-photon microscopy. Subsequent tissue de-clarification with immunolabelling and classical histopathology allowed the combination of 3D and 2D analyses.

Results: While IgG deposition showed a homogeneous distribution among all analysed glomeruli, only 80% showed signs of podocyte loss (podocyte loss per glomerulus of about 60%). Only glomerular lesions showed significant increases in numbers of PECs (sign of PEC activation) in close association with reductions in glomerular capillary volume (sign of capillary injury). PEC activation was confirmed via immunofluorescence in recycled tissue samples (ie. de-novo CD44 expression). Based on 3D analysis of intraglomerular lesion location, we identified a progressive pattern from localised tubular lesions to segmental lesions and development of atubular glomeruli.

Conclusions: ***SPECTRUM*** provides new roadmap for morphometrics in the kidney. In crescentic nephritis, ***SPECTRUM*** revealed that despite of uniform IgG deposition, there was focal lesion development and podocyte loss, and allowed us to characterise for the first time the 3D evolution of extracapillary lesions.

Funding: Government Support - Non-U.S.



TH-OR063

Mass Spectrometry Imaging Rapidly Discriminates between Ischemic Injury in Renal Tissue

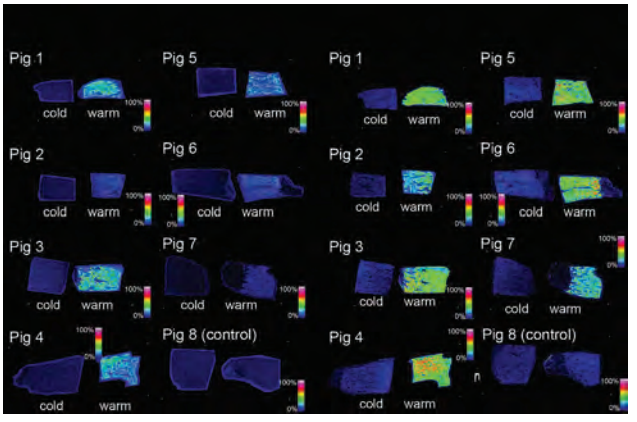
Patrick A. de Hoogt,[1] Tim C. Van smaalen,[1] Maarten G. Snoeijs,[1] Geert willem H. Schurink,[1] Carine Peutz-Kootstra,[1] Berta Cillero pastor.[2] *[1]Maastricht University Medical Center, Maastricht, Netherlands; [2]M4I, Maastricht, Netherlands.*

Background: The increasing analytical speed of mass spectrometry imaging (MSI), leads to growing interest in the medical field. When transplanting donor kidneys, ischemic injury to donor kidneys leads to significant short and long term risk for recipients. No reliable cut-offs are known to decide if a donor kidney can be safely transplanted. Thus, there is a need for new tools to rapidly and accurately assess acute ischemic injury in renal transplantation to aid in graft selection. We investigated the value of MSI to assess acute ischemic kidney tissue in a porcine model.

Methods: A perfusion model was developed where paired kidneys received warm (severe) or cold (minor) ischemia (n=8 per group). First, ischemic tissue damage was systematically assessed by two blinded pathologists. Secondly, MALDI-MSI of kidney tissues was performed to study spatial distributions and compositions of lipids in the tissues.

Results: Histopathological examination revealed no significant difference between kidneys, while MALDI-MSI was capable of a detailed discrimination of warm and cold ischemia by differential expression of characteristic lipid degradation products within 2 hours. In particular lysolipids, including lysocardiolipins, lysophosphatidylcholines and lysophosphatidylinositol, were dramatiaclly elevated after warm ischemia.

Conclusions: This study demonstrates the significant potential of MSI to differentiate and identify molecular patterns of early ischemic injury in a clinically acceptable time frame. The observed changes highlight the underlying biochemical processes of acute ischemic kidney injury and provide a molecular classification tool that can be deployed for graft viability assessment.



TH-OR064

Can Nephrectomy Tissue Be Considered as Normal? A Comparison of the Molecular Expression between Nephrectomy and Donor Kidney Tissue

Samer Mohandes, Huijuan Song, John P. Shapiro, Paolo Fadda, Jianying Zhang, Lianbo Yu, Anjali A. Satoskar, Brad H. Rovin, Samir V. Parikh. *Ohio State University Wexner Medical Center, Columbus, OH.*

Background: The molecular interrogation of kidney tissue provides important information on disease pathogenesis. Uninvolved areas of tumor nephrectomies have been used as normal reference tissue. We postulated that nephrectomy tissue may be remotely affected by the tumor and tested this by comparing compared renal transcript expression of nephrectomy tissue to biopsies of living donor (LD) kidneys at the time of implantation.

Methods: Formalin-fixed paraffin-embedded nephrectomy (n=8) and LD (n=8) tissue was laser dissected and RNA from the glomerular and tubulointerstitial (TI) compartments was extracted. The expression of 564 immune transcripts was analyzed using Nanostring technology. Transcript expression between nephrectomy and LD samples was compared. Differences are reported by fold change (FC) and p-value.

Results: Overall, 116 glomerular transcripts and 67 TI transcripts were differentially expressed between nephrectomy and LD. The top overexpressed nephrectomy glomerular transcripts were FCER1G (FC: 8.5, P: 0.02), CD45RB (FC: 7, P: 0.02), and PDCD1LG2 (FC: 5, P: 0.014), and the top TI transcripts were TNFRSF1B (FC: 6.7, P=0.01), CD45RB (FC: 6, P: 0.02), and C1R (FC: 4.9, P: 0.02). The top under-expressed glomerular transcripts included AIRE (FC: 0.1, P: 0.0001), XCL1 (FC: 0.1, P: 0.02) and IL-20 (FC: 0.13, P: 0.001), and ATM (FC: 0.15, P: 0.03), VTN (FC: 0.16, P: 0.03) and CD160 (FC: 0.17, P: 0.008) in the TI. Panther Pathway analysis revealed upregulation of inflammation mediated by cytokine/chemokines, integrin and interleukin signaling pathways in nephrectomy compared to LD.

Conclusions: To our knowledge, this is the first study comparing the gene expression between nephrectomy and LD. Despite being ostensibly unafflicted by the tumor, the gene expression of nephrectomies was different than LD and reflected overexpression of inflammatory and immune pathways. This study highlights the potential pitfall in using nephrectomy samples as controls, especially when comparing to autoimmune and inflammatory kidney diseases.

Funding: NIDDK Support

TH-OR065

Primary Membranous Nephropathy: Glomerular RNA Sequencing from Archival Kidney Biopsies

Oystein Eikrem,[1,2] Even Koch,[1] Thomas Knoop,[2] Bjorn Egil Vikse,[1,4] Eric Schordan,[5] Hanna Debiec,[3,6] Pierre M. Ronco,[3,6] Sabine Leh,[2,1] Hans-Peter Marti.[1,2] *[1]University of Bergen, Bergen, Norway; [2]Haukeland University Hospital, Bergen, Norway; [3]Inserm UMR_S1155, Paris, France; [4]Haugesund Hospital, Haugesund, Norway; [5]Firalis S.A., Huningue, France; [6]Hôpital Tenon, Paris, France.*

Background: Our study aim was to expand the usability of archival kidney biopsies with primary membranous nephropathy (MN) by next generation sequencing of glomerular mRNA & lncRNA.

Methods: Formalin-fixed & paraffin-embedded (FFPE) renal biopsies from six female and six male adult patients (mean age 55±16 y, mean proteinuria 2.9±3.5 g/d) from the Norwegian Kidney Biopsy Registry (NKBR) with primary MN were divided into: i) PLA2R antibody positive MN (n=6), and ii) PLA2R antibody negative MN (n=6). In addition, we included iii) normal NBKR control samples (n=8; mean age 27±11 y). All subjects had eGFR>60ml/min/1.73m2. RNA inputs of 0.15-3 ng of total RNA per sample from microdissected glomerular cross-sections (High Pure FFPE Extraction kit, Roche) were used for library preparation (Truseq RNA Exome kit, Illumina) and sequenced as 75 bp paired end on a NextSeq500 by Firalis SA, France. Reads were aligned to Homo sapiens hg38 reference genome using Gencode v.26 for mRNA and LNCipedia 5.0 for lncRNA.

Results: From alignment on their databases, 3473 mRNA & 1719 lncRNA were above a threshold of 2 fragments per kilobase of exon per million reads mapped (FPKM). Principal component analyses and heatmaps with differentially regulated mRNA & lncRNA clustered anti-PLA2R positive and anti-PLA2R negative MN together with some separation from normals (esp. lncRNA). Pathways of renal inflammation and of glomerular injury were upregulated in MN (IPA analyses). Overall, 197 mRNA and 59 lncRNA were differentially regulated comparing MN combined to normal controls. Within the two MN groups, 84 mRNA and 19 lncRNA were differentially expressed. Among these 84 mRNA, subgroups of 12 mRNA (e.g. IGFBP2) and 22 mRNA (e.g. MIF) differed also between normal controls and anti-PLA2R positive or negative MN, respectively. Among the 19 lncRNA, subgroups of 4 and 2 lncRNA differed also between normal controls and anti-PLA2R positive or negative MN, respectively. Thus, these mRNA & lncRNA could represent candidates of diagnostic/prognostic markers and of therapeutic targets if confirmed later.

Conclusions: Sequencing of mRNA & lncRNA from microdissected glomerular cross-sections of FFPE kidney biopsies is feasible and potential biomarker & drug target candidates that discriminate anti-PLA2R positive from anti-PLA2R negative MN were identified.

Funding: Government Support - Non-U.S.

TH-OR066

Predicting APOL1 Risk Category from Kidney Donor Biopsies Using Deep Learning

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Background: African Americans (AA) subjects with two *APOL1* gene variants (G1 and G2) are at higher risk (HR) to develop non-diabetic kidney disease, while individuals with 0 or 1 *APOL1* variants are at low risk (LR). Conventional visual histologic analysis of renal biopsies does not identify structural differences between LR and HR subjects with or without kidney disease. In this work we sought to evaluate whether deep-learning (DL) based analysis could help identify phenotypic representations that were predictive of *APOL1* variants from whole slide images (WSI) of kidney biopsies.

Methods: WSI's from kidney allograft implant biopsies stained with H&E from 19 *APOL1* LR and 12 *APOL1* HR AA donors were annotated by a pathologist to identify artifact-free regions of interest (ROIs). The ROIs from the training set (8 LR and 5 HR) were divided into non-overlapping 256x256 patches for processing at 40X magnification. Each patch was assigned a HR or LR label based on the subject's *APOL1* genotype. An 8 layer AlexNet model was trained to predict the likelihood that a previously unseen test input patch belongs to the *APOL1* HR genotype. This patch-wise output was then overlaid as a heatmap on the original image such that red and blue pixels predicts HR and LR class, respectively. Majority voting across the individual patches were aggregated to generated the combined prediction of *APOL1* risk status as either HR or LR. (Figure 1).

Results: The prediction accuracy of trained model was 84.67% and 91.02% for LR and HR cases respectively (n=18, LR=11, HR=7) on the test set.

Conclusions: In this preliminary study, the DL model was able to distinguish between *APOL1* HR and LR genotypes in AA patients. Future work will involve larger scale multi-site independent validation.

Funding: Other NIH Support - National Natural Scientific Foundation of China, Other U.S. Government Support, Government Support - Non-U.S.

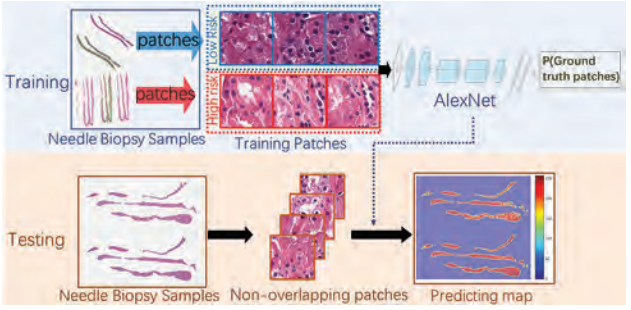

Figure 1: Flowchart illustrating the training and testing for predicting APOL1 risk status, where the bottom right image heatmap is the output from the DL classifier where redder pixels indicate higher likelihood of belonging to the HR class.

TH-OR067

Bevacizumab Associated Glomerulopathy: An Occlusive Hyaline Microangiopathy

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Background: Bevacizumab is a humanized monoclonal IgG1 antibody which neutralizes vascular endothelial growth factor (VEGF) and is used for treating multiple cancer types. As a known and frequent adverse event, it can lead to renal damage including proteinuria and nephrotic syndrome.

Methods: In a retrospective approach we analyzed 16 renal biopsies from patients receiving bevacizumab treatment. We observed a distinctive pseudothrombotic pattern different from the previously reported thrombotic microangiopathy (TMA). Since the newly described pattern includes some features similar to TMA and cryoglobulinemic membranoproliferative glomerulonephritis (MPGN), biopsies with these diagnoses were included for comparison. Clinical, laboratory, light microscopic, immunohistochemical (including a proximity ligation assay (PLA)), proteomic and electron microscopic features were assessed in 16 proteinuric patients after bevacizumab therapy and compared to seven cases of cryoglobulinemic MPGN and six cases of typical acute TMA.

Results: Nephrotic syndrome was present in 14 of the 16 bevacizumab-treated patients. All 16 displayed a patchy pattern of variably PAS-positive hyaline pseudothrombi occluding markedly dilated glomerular capillaries in their biopsies. Mass spectrometry based proteome analysis revealed a special protein pattern demonstrating some features of TMA and some of MPGN, including a strong accumulation of IgG in the thrombi. PLA did not show interaction of IgG with C1q, arguing for accumulation without classical complement activation. Compared to thrombi in TMA cases, the hyaline pseudothrombi did not contain clusters of CD61-positive thrombocytes. Electron microscopy of bevacizumab cases did not show extensive loss of podocyte foot processes.

Conclusions: Bevacizumab therapy can lead to a unique hyaline occlusive glomerulopathy, likely arising from endothelial leakage followed by subendothelial accumulation of serum proteins. Bevacizumab associated glomerulopathy can be diagnosed by light microscopy and is an important differential diagnosis in cancer patients with nephrotic syndrome.

Funding: Government Support - Non-U.S.

TH-OR068

A Nuclear Magnetic Resonance-Based Method for Accurate Assessment of Glomerular Filtration Rate

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Background: Measuring glomerular filtration rate (mGFR) using renal or plasma clearance of an exogenous filtration marker (tracer) is the gold standard for assessing kidney function, but this procedure is time consuming and associated with a high burden for patients. Therefore, GFR is commonly estimated from serum creatinine ($eGFR_{creat}$) or serum cystatin C ($eGFR_{cysC}$). However, there exist different estimating equations for adult and paediatric patients and these equations often perform only moderately outside the cohort in which they were developed.

Methods: We used metabolomics based on nuclear magnetic resonance (NMR) spectroscopy and biostatistical modeling to identify metabolites correlated with mGFR and to combine these metabolites to biomarker networks for accurate GFR prediction. The biomarker networks were established and tested in two separate cohorts from two European centres. These cohorts comprised serum samples from both paediatric and adult patients with various nephrological conditions, covering the whole GFR range from hypo- to hyperfiltration.

Results: By combining creatinine with the uremic toxin myo-inositol, valine as indicator of metabolic acidosis, and a marker of oxidative stress into a metabolic network, we were able to generate reliable results over the whole GFR range. Compared to $eGFR_{creat}$ and $eGFR_{cysC}$, the marker network showed a higher correlation with mGFR (Pearson correlation coefficient r = 0.880 vs. 0.848 and 0.636) and a 31% and 41% reduction, respectively, in overall root mean square error (RMSE 19.2 vs 28.0 and 32.8) in an independent test cohort. Especially in the "creatinine blind spot" between 60-90 ml/min/1.73m^2, it more than halved the variation from 24.5 to 11.0 compared to $eGFR_{creat}$. The marker network increased the percentage of estimated GFR values within 30% of mGFR (P_{30}) from 72% (66%) observed for $eGFR_{creat}$ ($eGFR_{cysC}$) to 82%, which is within the performance range of plasma clearance methods, depending on the tracer used for mGFR measurement.

Conclusions: We developed a metabolomics-based serum test for accurate prediction of GFR in both adult and paediatric patients. It combines the precision of plasma clearance with the convenience of creatinine-based eGFR and obviates the need of invasive tracer application.

Funding: Commercial Support - numares AG

TH-OR069

Histologic Predictors of Renal Outcome in Myeloma Cast Nephropathy: A Multicenter Study

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Background: Cast nephropathy (CN) is the main cause of acute kidney injury (AKI) in multiple myeloma (MM). Renal prognosis is poor and chronic renal impairment strongly affects survival. Whether renal biopsy can help in the management of AKI is unclear. The aim of this study was to investigate the prognostic value of renal biopsy findings in CN.

Methods: We retrospectively reviewed renal biopsies from 161 CN patients in a multicenter cohort (9 centers). Histological features, including the extent of cast formation, were independently scored by 2 pathologists. We assessed reproducibility, correlations with clinical presentation and, in patients with ⟩3 months follow-up (n=135), associations between biopsy findings, hematologic and renal outcomes.

Results: Interclass Correlation (ICC) for inter-reader concordance was good to excellent (⟩0.60) for medullary interstitial inflammation, giant cell reaction around casts, highest and mean cortical and medullary cast numbers. It was moderate (0.40-0.59) for interstitial fibrosis, cortical interstitial inflammation, tubular rupture, interstitial giant cell and Tamm-Horsfall extravasation. We found 46% of kappa CN and 54% of lambda CN. The severity of AKI correlated with higher serum free light chain level (sFLC), ß2-microglobulin, LDH and bone marrow infiltration. The presence of giant cell reaction, highest and mean medullary and cortical number of casts and medullary interstitial inflammation also correlated with a lower initial eGFR. Following therapy, renal response rate was lower with higher age, ß2-microglobulin and baseline sFLC. It was greater with a lower serum creatinine level and greater sFLC reduction. The presence of giant cell reaction, moderate or severe interstitial fibrosis, highest and mean medullary and cortical number of casts and, marginally (p=0.06), medullary interstitial inflammation, also correlated with lower renal recovery rate.

Conclusions: Histologic scoring of CN enables reproducible assessment of morphologic parameters with prognostic significance and may guide the management of MCN. Participants: G. Touchard, H. Fatima, F. Rosenblum, P. Sanders, M. Drosou, M. Rabant, C. Cohen, B. Knebelmann, B. Adam, B. Sis, C. Venner, H. Rennke, S. Motwani, R. Manso, K. Soto, A. Barraca, F. Maletta, D. Rocatello, R. Fenoglio, AM. Asuntis, P. Bianco, A. Pani, A. Angioi.

Funding: Clinical Revenue Support

TH-OR070

Digital Pathology and Computer-Aided Quantitative Analysis for Lupus Nephritis

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Background: The kidney biopsy has allowed a better understanding of the pathogenesis of renal injury in lupus nephritis (LN) and is routinely used for patients with active LN or previously untreated disease. Currently, the ISN/RPS classification system is used to identify subgroups with different prognoses and response to treatment. However, the ISN/RPS classification suffers from poor reproducibility, raising doubts about its validity and clinical application. Thus novel approaches are required to obtain continuous, quantitative data to improve accuracy, reproducibility, and prognostic utility. We have assembled a novel computer-aided digital pathology image analysis pipeline to improve the utility of the kidney biopsy in LN.

Methods: To facilitate our analyses, we have created the University of Michigan Lupus Nephritis Digital Pathology Image Repository (DPIR). Currently it contains 200+ cases with access to clinical data over many years. Slides are scanned to whole-slide images (WSI) at 40x with Leica Biosystems AT2 scanners. We employ QuPath, a cross-platform

open source software for digital pathology and WSI image analysis, for quality control, annotation, and as a framework to run in-house algorithms on WSI. Algorithms to quantitate morphologic features of interest are designed using the image processing package FIJI, a distribution of ImageJ.

Results: Our image analysis pipeline allows supervised WSI annotation (glomeruli, vessels, etc.) and quantitation of glomerular size, glomerular cellularity, mesangial index, interstitial fibrosis and fractional interstitial area, and tubulointerstitial cellularity using PAS and trichrome stained slides. Complete analysis can be performed within one day. Preliminary data comparing glomerular cellularity to ISN/RPS classification groups reveals that cellularity varies widely within each classification group, indicating novel information beyond classification groups are captured.

Conclusions: We have generated a computer-aided, quantitative image analysis pipeline for morphologic features in a lupus nephritis biopsy. The pipeline has a short enough turnaround time suitable for clinical application and generation of an adjunct report wherever cases can be scanned to WSIs. Future studies will seek to improve turnaround time and determine which analyses best predict patient outcome and response to therapy.

Funding: NIDDK Support

TH-OR071

The Role of Megalin in the Regulation of Renal RAS: Investigation Using LC/MS-Based Multiple-Reaction Monitoring Quantification of Angiotensin Peptides

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Background: The mechanisms underlying the regulation of the renal renin-angiotensin system (RAS) are largely unknown. Megalin, an endocytosis receptor in proximal tubular cells, reabsorbs angiotensinogen (AGT) and angiotensin (Ang) peptides filtered through glomeruli. We have developed liquid chromatography (LC)/mass spectrometry (MS)-based multiple-reaction monitoring quantification of Ang peptides. This study aimed to investigate the role of megalin in the renal RAS by measuring Ang peptides in biological samples obtained from kidney-specific, tamoxifen-inducible conditional megalin knock-out mice (KO) and their controls (Ctl).

Methods: Stable isotope-labeled Ang peptides were added to each sample as internal standards. Under the steady condition and 30 min after AGT administration, Ang peptides were extracted by reverse phase chromatography and evaluated by LC/MS-based quantification.

Results: Under the steady condition, Ang-I and -II were quantified in the kidney and plasma without significant differences between KO and Ctl (e.g., kidney Ang-II: 573±257 in KO and 569±172 fmol/g in Ctl). High levels of Ang-I, -II, -1-7 and -1-9 were detected in KO's fresh urine (e.g., Ang-II: 3.8±4.5 pmol/mL), whereas their concentrations were below the limit of detection in Ctl. AGT administration increased kidney Ang peptides without significant increase in plasma. Kidney Ang-II and -1-9 levels in KO administered with AGT were significantly lower than those in Ctl (e.g., Ang -II: 1760±1043 in KO and 2489±836 fmol/g in Ctl, $p<0.05$); kidney Ang-I showed a similar tendency, whereas there was no difference in Ang -1-7.

Conclusions: High-level excretion of Ang peptides in KO's urine indicated that they were produced in the tubular lumen. AGT administration increased kidney Ang peptides independently of the systemic RAS. The increase of kidney Ang-I, -II, and -1-9 induced by AGT administration was suppressed in KO compared with Ctl, whereas there was no difference in Ang-1-7. Ang-I, -II and -1-9 generated in the tubular lumen may be excreted more in KO than Ctl or converted to Ang-1-7. Megalin blockade could be beneficial for modulating the renal RAS by regulating the renal handling of AGT and Ang peptides.

TH-OR072

Cholesterol, a Repressor of Natriuretic Genes

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Background: Salt-sensitivity in Dahl rats is due, in part, to the reduction of hemoxygenase-1 (HO1), cyclooxygenase 2 (COX2), and nitric oxide synthase-2 (NOS2) in the renal medulla. Renal overexpression of HIF1-α, a regulator of HO1, COX2, and NOS2, enhances salt and water excretion and reduces blood pressure. Cholesterol (chol) incorporation into collecting duct (CD) cells, *in vivo or in vitro*, represses COX2 activity in response to tubular flow or fluid shear stress (FSS). We hypothesized that dietary chol ingestion represses flow responsive genes necessary to effectuate salt and water excretion.

Methods: To this end, mice were fed either a 0% or 1% chol diet for up to 12 weeks, injected with SQ isotonic saline at 5% of body weight, and urine collected at 2, 4, and 6 hrs. Kidneys were extracted to measure medullary expression of HO1, COX1, and NOS2. Mice were divided into three dietary time points: (1) 3-5 (2) 6-8 and (3) >9 weeks of diet.

Results: Urine volume was less in the chol group at the 6 hr urine collection for 6-8 wks of diet group (n=8 control and chol; $p<0.05$). Urinary [Na], [K] and osmolality were higher while Na excretion was lower at the 6 hr urine collection time point in the chol ($p<0.05$) vs. control fed mice. Renal medullary HO1 (0.76±0.09; $p<0.05$), and NOS2 (0.76±0.1; $p<0.05$) mRNA levels were reduced compared to controls (HO1, 1.00±0.02; NOS2, 1.00±0.03) while COX2 and HIF1-α were unaffected. ATP-binding cassette transporter (ABCA1), a tissue chol efflux transporter, was increased in the medulla (2.0±0.3 fold; $p<0.05$) of chol vs. control fed mice. To test the flow responsiveness of HO1, COX2, NOS2 and HIf1-α, IMCD3 cells were exposed to 0.4 dynes/cm^2 of FSS for up to 6 hours. HO1 mRNA increased by 350X fold, COX2 by 25X fold, and NOS2 by 8X fold at 6 hrs in sheared (n=4-6; $p<0.01$) vs.static (n=3-6) cells. HIF1-α mRNA increased by ~50% ($p<0.05$) at 4 and 6 hrs. Western blotting of FSS exposed cells demonstrated an increase in HIF1-α and HO1 protein compared to static cells ($p<0.05$). Similar to mouse, chol incorporation into cells raised ABCA1 mRNA levels 3.7±0.2 fold vs. untreated cells.

Conclusions: Dietary chol is associated reduced urine volume and Na excretion at 6 hrs after saline injection and suppressed flow induced HO1 and NOS2 gene expression. Studies will test whether chol incorporation into the tubule represses of natriuretic factors to reduce Na excretion..

Funding: Veterans Affairs Support

TH-OR073

Tubular Deficiency of Heterogeneous Nuclear Ribonucleoprotein F Enhances Development of Hypertension and Kidney Injury via Elevated Renal Angiotensinogen and Attenuated SGLT2 Expression in Mice

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Background: We reported previously that overexpression of the transcription factor, heterogeneous nuclear ribonucleoprotein F (hnRNP F) in renal proximal tubular cells attenuates systolic blood pressure (SBP), kidney injury and renal angiotensinogen (Agt) gene expression in mice with both type 1 and type 2 diabetes (Diabetes 2012, 2017). Here, we investigated whether deletion of hnRNP F in renal tubules would elevate SBP and aggravate kidney injury through increasing renal Agt gene expression.

Methods: Tubule-specific hnRNP F knockout (KO) mice were generated by crossbreeding Pax8-Cre mice with floxed hnRNP F mice on a C57BL/6 background. Both male and female Pax8-hnRNP F KO mice and control littermates were studied. Body weight (BW), SBP, blood glucose (BG), urinary glucose (UG) and albumin/creatinine ratio (ACR) were monitored up to 24 weeks of age. Kidneys were processed for histology. Western blotting and real-time qPCR were used to quantify hnRNP F, Agt, sodium-glucose co-transporter-2 (Sglt2) protein and mRNA expression in renal proximal tubules (RPTs), respectively.

Results: Both male and female Pax8-hnRNP F KO mice developed hypertension and elevated ACR as compared with control littermates with no detectable differences in BW and BG. Intriquingly, both male and female Pax8-hnRNP F KO mice developed glucosuria at 8 weeks of age. However, glucosuria disappeared in male Pax8-hnRNP F KO at the age of 12 weeks, whereas glucosuria was persistent in females. HnRNP F protein and mRNA expression are barely detectable in RPTs of Pax8-hnRNP F KO mice. In contrast, Agt expression was elevated, and Sglt2 expression was attenuated in RPTs of both male and female Pax8-hnRNP F KO mice as compared to controls at 8 and 24 weeks.

Conclusions: Our data demonstrate that hnRNP F plays an important role in the development of hypertension and kidney injury through modulation of renal Agt expression. Pax8-hnRNP F KO mice may provide a novel experimental model to study the development of glycosuria in non-diabetic mice.

Funding: Government Support - Non-U.S.

TH-OR074

Haploinsufficiency of Transcription Factor ETS-1 Improves Renal Autoregulation in Dahl Salt Sensitive Rats

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Background: The mechanisms underlying the susceptibility to hypertension-associated kidney injury are not well defined. Previously, we showed that the transcription factor ETS-1 mediates glomerular injury in Dahl Salt Sensitive (SS) rats. Hypertensive SS rats with a single functioning ETS-1 gene (ES, developed with zinc-finger nuclease (ZFN) technology), exhibit less glomerular injury. Because renal autoregulation is critical for protecting glomeruli from arterial hypertension, we hypothesized that ETS-1 transactivity is involved in afferent arteriolar autoregulatory behavior.

Methods: SS and ES rats were maintained on either a 0.3% (LS SS and LS ES) or a 4% NaCl diet (HS SS and HS ES) for one week.

Results: Assessment of serum creatinine and albuminuria revealed that renal dysfunction was present in the hypertensive HS SS rats, but was abrogated in the HS ES rats despite similar increases in telemetry mean blood pressures. Afferent arteriolar autoregulation was assessed using the *in vitro* blood-perfused juxtamedullary nephron preparation. Average baseline diameter of afferent arterioles were similar across the four groups of rats ($P>0.05$). Afferent arterioles from LS SS and LS ES rats exhibited normal autoregulatory behavior. Decreasing renal perfusion pressure from 100 to 65 mmHg increased arteriole diameter to 118 ± 2% and 119 ± 4% of baseline diameter, respectively. Stepwise increases in perfusion pressure to 170 mmHg decreased arteriolar diameter to 75.4 ± 3% and 72.9 ± 4% respectively. In contrast, pressure-mediated afferent arteriolar responses were markedly impaired in HS SS rats. Baseline diameter averaged 15.1 ± 1.2 μm and remained between 107 ± 3% and 89 ± 4% ($p< 0.05$ vs. LS SS) of baseline over the 65-170 mmHg pressure range tested. Importantly, renal autoregulation was significantly improved in HS ES rats. Baseline diameter averaged 15.6 ± 0.9 μm, and decreasing renal perfusion pressure from 100 to 65 mmHg resulted in a diameter increase to 114 ± 2% while increasing perfusion pressure to 170 mmHg resulted in a pressure-dependent vasoconstriction to 73 ± 3% ($P<0.05$ vs SS HS).

Conclusions: These results show that ETS-1 influences renal arteriolar autoregulation in SS rats and that impaired autoregulation may contribute to hypertension-induced kidney injury in SS rats.

Funding: Veterans Affairs Support

TH-OR075

Renal Artery Stenosis Magnifies Mitochondrial Damage, Aggravating Post-Stenotic Kidney Injury in Pigs with Metabolic Syndrome

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Background: Renal artery stenosis (RAS) often develops in the context of prevalent cardiovascular risk factors, and can induce hypertension, renal injury, and fibrosis. We have shown that metabolic syndrome (MetS) induces mitochondrial damage associated with glomerular hyperfiltration and tubular injury. We hypothesized that superimposition of RAS on MetS would exacerbate mitochondrial damage, aggravating post-stenotic kidney injury in swine.

Methods: Domestic pigs were studied after 16 weeks of either high-fat/high-fructose or standard diet with or without superimposed RAS (n=7 each). Single-kidney GFR was assessed in-vivo with multi-detector-CT, and renal tubular mitochondrial morphology ex vivo by electron microscopy. ATP production was measured by colorimetric/fluorimetric methods in isolated mitochondria and renal fibrosis by trichrome staining.

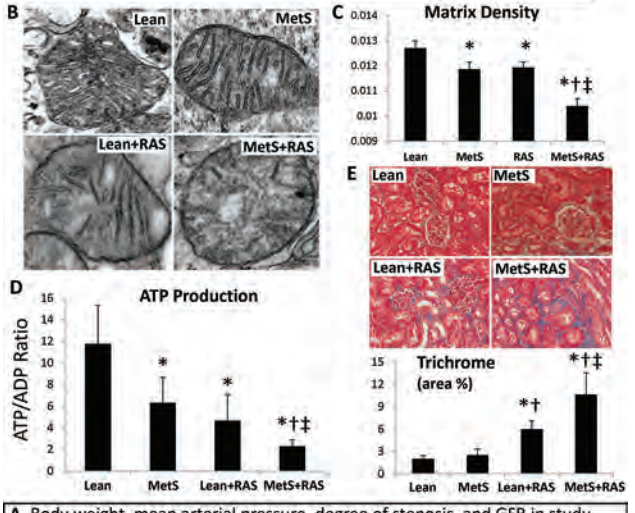
Results: Blood pressure was higher in MetS, Lean+RAS, and MetS+RAS compared to Lean (Table). Both RAS groups achieved significant stenosis. Single-kidney GFR was higher in MetS vs Lean, but decreased in Lean+RAS and MetS+RAS vs. their respective controls. MetS+RAS further decreased renal mitochondrial matrix density (Fig. B-C) and ATP production (Fig. D), and increased renal fibrosis (Fig. E) compared to Lean+RAS.

Conclusions: RAS superimposed on MetS aggravates mitochondrial structural damage and dysfunction, which may contribute to structural injury and dysfunction in the post-stenotic kidney.

Funding: NIDDK Support

A.

	Lean	MetS	Lean+RAS	MetS+RAS
Weight (Kg)	52.5 ± 1.1	93.4 ± 0.9*	50.2 ± 1.4†	92.6 ± 1.5*‡
MAP (mmHg)	102.8 ± 3.6	119.8 ± 5.5*	125.5 ± 9*	121.2 ± 5.9*
Stenosis (%)	-	-	71.7 ± 10.5	68.2 ± 6
Single kidney GFR (ml/min)	76 ± 4	142 ± 7.3*	45.2 ± 3.7*†	113 ± 10.6*†‡



A. Body weight, mean arterial pressure, degree of stenosis, and GFR in study groups. **B.** Electron microscopic images showing mitochondrial swelling and loss of cristae membrane in MetS+RAS. **C.** Mitochondrial matrix density decreased in MetS and Lean+RAS vs Lean, and further decreased in MetS+RAS. **D.** ATP production in similarly decreased in MetS and Lean+RAS compared to Lean, and further decreased in MetS+RAS. **E.** Renal fibrosis assessed by trichrome staining. *p<0.05 vs. Lean; †p<0.05 vs MetS; ‡p<0.05 vs. Lean+RAS.

TH-OR076

Renal Artery Stenosis Induces Renal Cellular Senescence

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Background: Cellular senescence (CS) is an irreversible proliferation arrest with secretory phenotype evoked in response to stress, which can be identified by upregulation of the cyclin-dependent kinase inhibitor $p16^{INK4a}$. Renal artery stenosis (RAS) induces stenotic kidney (STK) ischemia and injury, but whether these involve activation of CS remains unclear. We studied CS in the STK of transgenic INK-ATTAC mice, in which $p16^{INK4a}$-expressing cells can be selectively eliminated by injection of AP20187.

Methods: INK-ATTAC mice were randomized to a 4-week treatment with AP20187 (3.3μg/g, IP, 3/week) or vehicle starting after 2 weeks of RAS or sham (n=6-8 each). Single kidney function (GFR) and oxygenation were studied in vivo using 16.4T magnetic resonance imaging at baseline and 6 weeks after surgery. CS was assessed by plasma levels of Activin-A, and by image cytometry analysis of $p16^{INK4a}$-positive cells in dissociated kidney tissue.

Results: After 6 weeks of RAS blood pressure, Activin-A, STK tissue hypoxia were all elevated, and plasma creatinine tended to be higher compared to sham, whereas STK RBF and GFR were decreased. The percentage of $p16^{INK4a}$-positive cells increased in the STK, many of which expressed epithelial, but not endothelial, cell markers (Fig. E). Clearance of $p16^{INK4a}$-positive cells restored blood pressure, Activin-A, and plasma creatinine levels, and prevented the fall in GFR, and rise in tissue hypoxia (Fig. A-D), whereas RBF remained unchanged.

Conclusions: Renal artery stenosis induces cellular senescence in the stenotic kidney, particularly in tubular epithelial cells, and their clearance improves renal function. These observations suggest a role for cellular senescence in pathogenesis of renal artery stenosis, supporting development of senotherapy.

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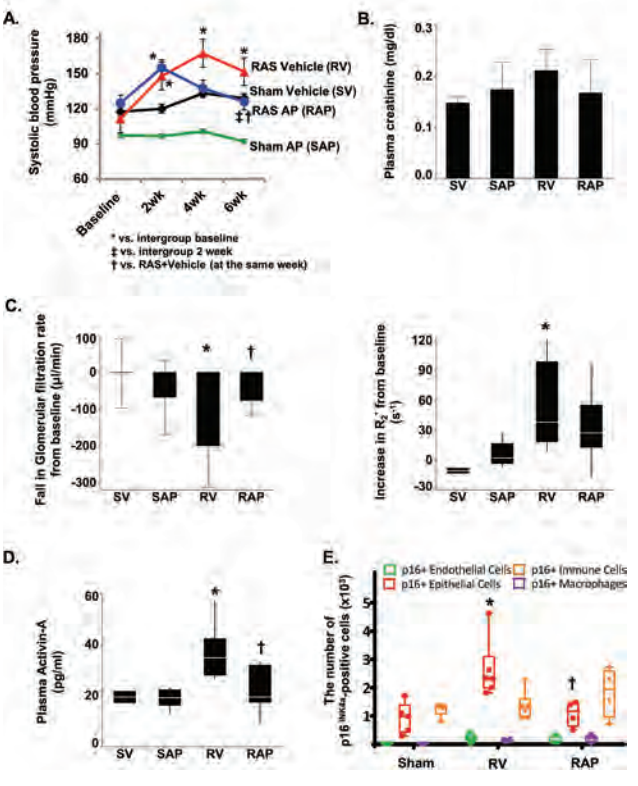
Figure.



TH-OR077

Evidence for Female Protection from Kidney Injury during Angiotensin II Hypertension

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Background: To address resistance to cardiovascular and kidney disease in females (F) vs. males (M), we recently defined sexual dimorphisms in renal transporters' abundance and distribution along the nephron. We reported lower proximal and higher distal Na^+ transporters' abundance and activity along nephrons of F vs. M rats and mice. This study

aimed to examine susceptibility to renal injury during Ang II Hypertension (AngII-HTN) in F vs. M Sprague Dawley rats.

Methods: Rats were either implanted with osmotic minipumps that infused 400 ng/kg/min AngII for 2 weeks or sham operated (n=6/group). Systolic blood pressure (tail-cuff) increased to 190 mmHg in both sexes. Urine was collected overnight in metabolic cages before sacrifice after which blood and kidney were collected. Quantitative immunoblotting was used to assess protein levels of kidney injury molecule-1 (KIM-1), angiotensinogen (aogen) and plasmin in urine and/or renal cortex; serum and urine albumin were quantified via ELISA and BCG method, respectively, and confocal immunohistochemistry (IHC) used to detect endocytosed albumin.

Results: Urinary albumin, similar at baseline in M and F, was 10-fold higher in M vs. F during AngII-HTN ($p<0.001$) associated with a 10% fall in serum albumin in M ($p=0.05$, no change in F). Urinary KIM-1, aogen and plasmin were markedly increased in M during AngII-HTN while near undetectable in F. Higher urinary plasmin in M vs. F correlated with twice as much cleaved (activated) epithelial Na^+ channel gamma subunit during AngII-HTN ($p<0.0001$). In renal cortex homogenates at baseline, KIM-1, aogen and megalin were higher in M vs F; during AngII-HTN cortical megalin increased in F only while KIM-1 and a'ogen were unchanged. AngII-HTN increased cortical albumin in both sexes and endocytosed albumin was evident by IHC in M PT but not F.

Conclusions: Despite similar increases in blood pressure, M vs. F rats exhibit greater susceptibility to renal injury during AngII-HTN, evident as greatly increased urinary albumin, KIM-1, aogen, plasmin associated ENaC activation, and endocytosed PT albumin.

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TH-OR078

Sex Differences in the Renal Hemodynamic Response to Angiotensin II Post-CPAP Therapy in Women and Men with Obstructive Sleep Apnea

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Background: Women have slower loss of kidney function and chronic kidney disease (CKD) progression. The renin-angiotensin system (RAS) and the vascular effects of obstructive sleep apnea (OSA) differ by sex. OSA is associated with glomerular hypertension which can be reversed by continuous positive airway pressure (CPAP) therapy. We sought to determine whether sex differences exist in the effect of CPAP for OSA on renal hemodynamics and the renal RAS in humans.

Methods: Twenty-nine (10 female, 19 male; 49±2y) incident, otherwise healthy, OSA subjects (respiratory disturbance index [RDI]>$15h^{-1}$) with nocturnal hypoxemia (SaO_2<90% >12%/night) were studied in high-salt balance, a state of maximal RAS suppression, pre-CPAP and after 4 weeks of effective CPAP therapy (>4h/night). Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured by para-aminohippurate and inulin clearance technique at baseline and in response to Angiotensin II (AngII) challenge (3ng/kg/min x 30min, 6ng/kg/min x 30min), a marker of renal RAS activity, pre- and post-CPAP. The primary outcome was the effect of CPAP on the renal hemodynamic responses to AngII in women compared to men.

Results: CPAP corrected OSA and nocturnal hypoxemia (RDI: 44±4 vs 4±$1hr^{-1}$, $p<0.001$; duration SaO_2<90%: 45±6 vs 7±2%, $p<0.001$). In women, CPAP was associated with a significant increase in RPF (626±22 vs 718±43 mL/min, $p=0.007$) but no change in GFR (108±2 vs 105±3 mL/min, $p=0.8$), whereas in men, CPAP use was not associated with changes in renal hemodynamics (RPF: 710±37 vs 756±38 mL/min, $p=0.11$; $p=0.7$ vs women; GFR: 124±8 vs 113±6 mL/min, $p=0.085$; $p=0.5$ vs women). Pre-CPAP, there was no difference in the RPF or GFR responses to AngII between women and men. Post-CPAP, there was a significantly greater renovasoconstrictive response to AngII in women (RPF: Δ30min: -100±27 vs -161±25 mL/min, $p=0.007$; Δ60min: -138±27 vs -206±32 mL/min, $p=0.007$), but not in men (RPF: Δ30min: -142±14 vs -154±19 mL/min, $p=0.4$; Δ60min: -168±23 vs -200±23 mL/min, $p=0.053$). Post-CPAP women had a larger initial reduction in GFR in response to AngII compared to men (Δ30min: -5±3 vs 0±2 mL/min, $p=0.039$; vs men).

Conclusions: CPAP therapy for OSA is associated with altered renal hemodynamics and downregulation of renal RAS activity in women but not in men.

TH-OR079

Role of Klotho Genetic Polymorphisms in Salt-Sensitivity Hypertension: A Link between Salt and Aging?

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Background: Hypertension is a common aging-related disorder. Salt intake is one of the main environmental factors contributing to the development of hypertension. Recently, an elegant paper showed that one-half Klotho transgenic mice displayed a spontaneous BP increase and a salt-sensitive hypertension in response to high Na intake. Commonly, serum levels of alpha-Klotho decrease with age and this reduction may be stronger in patients with several aging-related diseases. Aim of the study: to evaluate the role of Klotho polymorphisms in human essential hypertension and salt sensitivity.

Methods: 32 SNPs in Klotho gene identified with a previous GWA were used in the genetic analysis. Selected SNPs were studied for Pressure-natriuresis relationship (PNat) in 677 naïve essential hypertensive patients, never treated before, (NHP) by Acute salt load (NaLoad: 310 mMol in 2 h iv). Salt sensitivty (SS) is defined as mean BP increase (DMBP120) greater than 4 mm Hg at the end of infusion.

Results: We genotyped 32 SNPs within KL gene and 20 kb flanking regions. The best associated SNP with Na sensitivity resulted the missense rs9536314 common SNP, MAF 0.17 for G allele. According to salt sensitivity definition, 64% of NHPs resulted SR, while 36 % were SS. An inverse relationship was found between plasma klotho and DMBP120. Moreover KL rs9536314 GG and GT genotypes are more represented among SS. Again, GG group shows a less steep PNat curve, that is a significant increase in MBP occurred to excrete the same quantity of salt compared to salt resistant subjects.

Conclusions: In summary, this study showed, for the first time, that KLOTHO rs9536314 polymorphism is associate to salt-sensitive hypertension by activating a right shift of the pressure-natriuresis relationship in NHP. Therefore, klotho supplement in those hypertensive patient carrying the GG o mr GT variants may be potential therapeutic strategies for the treatment of salt-sensitive hypertension and kidney damage in elderly patients.

TH-OR080

Malignant Hypertension Can Be Partially Attenuated and Reversed by a 20-Hydroxyeicosatetraenoic Acid Antagonist

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Background: 20-hydroxyeicosatetraenoic acid (20-HETE), the product of cytochrome P450-dependent ω-hydroxylase might potentiate prohypertensive actions of angiotensin II (ANG II) in Cyp1a1-Ren-2 transgenic rats, a model of ANG II-dependent malignant hypertension. Therefore, we evaluated the antihypertensive effectiveness of a 20- HETE receptor antagonist (AAA) in this model.

Methods: Malignant hypertension was induced in Cyp1a1-Ren-2 transgenic rats by activation of the renin gene using indole-3-carbinol (I3C), a natural xenobiotic. Treatment with AAA (N-disodium succinate-20-hydroxyeicosa-6(Z),15(Z)-diencarboxamide) was started either simultaneously with induction of hypertension or 10 days later, during established hypertension. Systolic blood pressure (SBP) was monitored by radiotelemetry, indices of renal and cardiac injury, and kidney ANG II levels were determined.

Results: In I3C-induced hypertensive rats, early AAA treatment reduced SBP elevation (to 161±3 vs. 199±3 mmHg in untreated I3C-induced rats), reduced albuminuria, glomerulosclerosis index and cardiac hypertrophy ($p<0.05$ in all cases). Untreated I3C-induced rats showed augmented kidney ANG II (405±14 vs. 52±3 fmol/g in noninduced rats, $p<0.05$). AAA treatment lowered it to levels not significantly different from that in noninduced rats (72±6 fmol/g). Remarkably, in TGR with established hypertension, AAA also decreased SBP (from 187±4 to 158±4 mmHg, $p<0.05$) and exhibited organoprotective effects in addition to a marked suppression of kidney ANG II levels. In conclusion, 20-HETE antagonist attenuated the development and largely reversed the established ANG II dependent malignant hypertension, likely via suppression of intrarenal ANG II levels.

Conclusions: Intrarenal ANG II activation by 20-HETE is important in the pathophysiology of this model of ANG II -dependent hypertension. 20-HETE antagonists can partially reverse both developing and established hypertension and target organ damage.

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TH-OR081

Urinary Biomarkers of Kidney Damage and Incident CKD in SPRINT

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Background: Randomization to the intensive arm (SBP<120mmHg) in the Systolic Blood Pressure Intervention Trial (SPRINT) was associated with a 3-fold increased incidence of CKD, compared with the standard arm (SBP<140mmHg). However, it is unknown whether incident CKD in the setting of intensive SBP lowering is accompanied by intrinsic kidney injury.

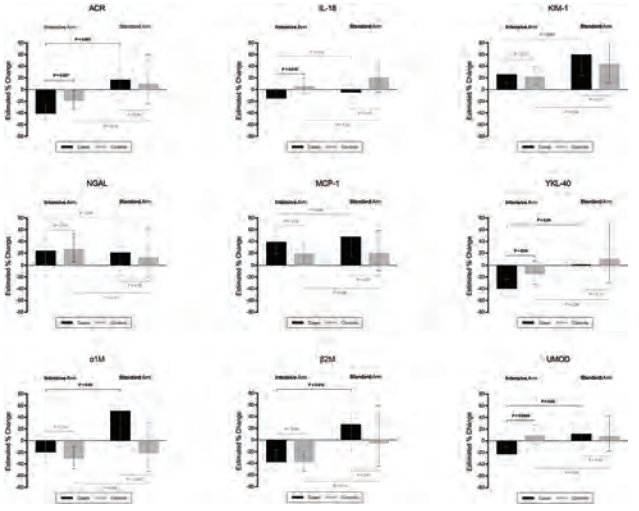
Methods: Among the 162 incident CKD cases (128 in the intensive arm and 34 in the standard arm) that occurred during SPRINT follow-up and 162 controls matched on age, sex, race, baseline eGFR, and randomization arm, we measured 9 validated urinary biomarkers of kidney damage at baseline and 1 year. Linear mixed-effects models adjusting for baseline SBP and urine creatinine estimated 1-year biomarker changes to compare incident CKD cases vs. matched controls in the intensive arm; and to contrast cases in the intensive vs. standard arms.

Results: At 1 year of SPRINT follow-up, incident CKD cases vs. matched controls in the intensive arm had mean eGFR declines of -22 vs. -4 mL/min/$1.73m^2$. However, incident CKD cases in the intensive arm had either significantly greater 1-year reductions or similar changes of kidney damage biomarkers, compared with both matched controls and with cases in the standard arm (**Figure**).

Conclusions: Incident CKD cases in the intensive arm had substantial 1-year eGFR reductions yet did not have relative increases in biomarkers, compared with matched controls; rather, these cases had decreases in several biomarkers, compared with both

matched controls and cases in the standard arm. Thus, incident CKD in the setting of intensive SBP lowering may reflect hemodynamic accommodation rather than intrinsic injury.

Funding: NIDDK Support



1-year percent changes of nine urinary biomarkers among incident CKD cases and matched controls, stratified by randomization arm, in SPRINT.

TH-OR082

Urinary Oxalate Excretion and the Risk of ESRD and CKD Progression

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Background: Kidney failure from oxalate nephropathy is a devastating complication of rare disorders of oxalate metabolism (e.g., primary hyperoxaluria), oxalate over-absorption (e.g., enteric hyperoxaluria), and ingestion of large amounts of oxalate or its precursors. We hypothesized that higher urinary oxalate excretion, even within the typical range of excretion, would be associated with progression of CKD.

Methods: We measured 24h urinary oxalate excretion in stored specimens from 3,123 participants of the Chronic Renal Insufficiency Cohort study. Baseline eGFR was 43 ml/min/1.73m^2. CRIC study participants were followed longitudinally for incident ESRD and/or halving of eGFR. We used Cox proportional hazards models to test whether urinary oxalate excretion was associated with two outcomes: (1) Incident ESRD; and (2) CKD progression, defined as halving of eGFR or incident ESRD. Multivariable models were adjusted for a number of demographic, clinical, and laboratory variables.

Results: The median 24h oxalate excretion in CRIC participants was 18.6 mg (IQR, 12.9 - 25.7 mg). Cross sectionally, higher oxalate excretion was correlated with lower baseline eGFR (r=-0.1, p<0.001) and greater albuminuria (r=0.15, p<0.001). In prospective multivariable-adjusted analyses, those in the highest vs lowest quintile of oxalate excretion had a 1.41-fold (95% CI 1.09-1.83) higher risk of ESRD and a 1.28-fold (95% CI 1.02-1.61) higher risk of CKD progression (p<0.001).

Conclusions: Among individuals with CKD, higher baseline urinary oxalate excretion is associated with greater risk of ESRD and CKD progression. Oxalate excretion should be tested as a potentially modifiable risk factor for progression of kidney disease.

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Risk of ESRD and CKD progression by quintiles of urinary oxalate excretion

	Q1 (1.4-11.5 mg)	Q2 (11.5-16.2 mg)	Q3 (16.2-21.0 mg)	Q4 (21.0-27.7 mg)	Q5 (27.7-102.1 mg)	P value for difference
ESRD events/1000py	2.38	3.18	4.44	4.37	4.90	–
Unadjusted HR	ref	1.33 (1.03-1.73)	1.86 (1.45-2.38)	1.83 (1.43-2.34)	2.05 (1.61-2.62)	<.001
Adjusted HR	ref	1.04 (0.79-1.37)	1.42 (1.09-1.84)	1.33 (1.03-1.73)	1.41 (1.09-1.83)	0.009
CKD progression events/1000py	3.80	4.56	6.89	6.21	7.16	–
Unadjusted HR	ref	1.20 (0.95-1.51)	1.81 (1.46-2.25)	1.64 (1.31-2.04)	1.89 (1.53-2.34)	<.001
Adjusted HR	ref	0.93 (0.74-1.19)	1.31 (1.05-1.65)	1.12 (0.89-1.4)	1.28 (1.02-1.61)	0.006

Adjusted for age, sex, race/ethnicity, systolic blood pressure, diabetes, body mass index, medications, hemoglobin, serum albumin, and baseline eGFR

TH-OR083

Association of Soluble TNFR-1 Concentrations with Long-Term Decline in Kidney Function: The Multiethnic Study of Atherosclerosis

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Background: Tumor necrosis factor receptor-1 (TNFR-1) is a cell surface receptor predominantly expressed in the glomerular and peritubular capillary endothelium and plays a causative role in the development of endothelial cell dysfunction and inflammation. Soluble TNFR-1 (sTNFR-1) concentrations are associated with early glomerular structural lesions and kidney disease progression among persons with established diabetic kidney disease. No studies have assessed the potential impact of sTNFR-1 on long-term changes in kidney function among healthy people.

Methods: We tested associations between sTNFR-1 concentration, measured at study enrollment, and incident decline in eGFR (≥40% decline and annual proportional decline) among 2,551 participants in the Multiethnic Study of Atherosclerosis (MESA). Participants were recruited into the MESA from six U.S. communities and were free of clinical cardiovascular disease at baseline. Serum creatinine concentrations were obtained at enrollment and study years three, five, and ten.

Results: Mean age was 61 years, 53% were women, an equal proportion was White, Black, Chinese or Hispanic (≈25%). Mean baseline eGFR was 79 ± 16 mL/min/1.73m^2. Serum sTNFR-1 was inversely associated with baseline eGFR. Over a median follow-up time of 9.3 years, 110 participants developed a ≥40% decline in eGFR [adjusted hazard ratio, 1.45 (95% CI, 1.18 to 1.78) per standard deviation increment, p=0.0004] Table1. The highest sTNFR-1 tertile was associated with an adjusted annualized decline in eGFR 1.80% (95% 1.10 to 4.70) after multivariate adjustment. Associations were robust across subgroups defined by demographics, hypertension, diabetes, and baseline CKD status.

Conclusions: Serum sTNFR-1 concentrations are associated with long-term decline in eGFR among a healthy, multi-ethnic cohort. Endothelial dysfunction and inflammation may be modifiable targets for the preservation of kidney function in ambulatory patients.

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Table 1. Association of serum TNFR-1 concentration with incident 40% eGFR decline

			Unadjusted	Baseline Demographic adjusted		Multivariable adjusted		Fully adjusted	
Serum soluble tumor necrosis factor receptor 1 (sTNFR-1)	N at risk	N events	Incident Rate (per 1000 person years)	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Tertile 1	851	19	2.6	1.0 (Ref.)	< 0.0001	1.0 (Ref.)	0.009	1.0 (Ref.)	0.09
Tertile 2	849	24	3.3	1.13 (0.61, 2.07)		1.06 (0.57, 1.96)		1.15 (0.61, 2.15)	
Tertile 3	848	67	10.1	2.71 (1.58, 4.65)		1.99 (1.14, 3.48)		1.81 (0.99, 3.32)	
Per SD of sTNFR-1 (406 pg/mL)				1.87 (1.51, 1.84)	< 0.0001	1.48 (1.33, 1.65)	< 0.0001	1.45 (1.18, 1.78)	0.0004

Baseline adjustment: age, age^2, sex, race/ethnicity, and site

Multivariable adjustment: Baseline plus education, BMI, diabetes, and hypertension

Full adjustment: Multivariable plus urine albumin-creatinine ratio, baseline eGFR, and baseline eGFR^2

TH-OR084

Transethnic Genome-Wide Association Studies of Kidney Function Measures Identify Associations at >300 Genomic Loci

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Background: Chronic kidney disease (CKD) affects 10% of the adult population globally. Reduced estimated glomerular filtration rate (eGFR) is the primary measure used to define CKD. Although previous[MW1] genetic studies have revealed many loci associated with eGFR, most of the genetic variation is still unexplained. The CKDGen Consortium is an international collaborative effort aimed at identifying the genetic underpinnings of renal health.

Methods: In an ongoing effort, 121 studies totaling >750,000 participants from five different ethnicities contributed genome-wide association summary statistics relating log-transformed creatinine-based eGFR (CKD-EPI formula) to ~9 million high-quality 1KGP- or HRC-imputed genetic markers, using an additive genetic model adjusted for sex and

age. Summary statistics were combined using fixed-effects inverse variance-weighted meta-analysis.

Results: Across ethnicities, 308 genomic loci (1 Mb-segments, MHC region joined) contained at least one significantly eGFR-associated SNP (p<5E-08). The LD score regression intercept was 1.04, suggesting no residual inflation of the test-statistics. Of the 308 loci, 228 were novel (mapping outside of 500 kb of previously reported index variants), and 80 were consistent with previous findings. Loci were characterized by their association with blood urea nitrogen and CKD, by tissue-specific enrichment of expressed genes, as well as by their heterogeneity correlated with ancestry. Approximate conditional meta-analysis among European-ancestry individuals identified 277 independent trait-associated variants, which together explained 7.6% of the phenotypic variance, almost doubling previous estimates. We fine-mapped 212 non-overlapping regions, of which 46 contained >1 independent SNPs. Credible sets with 99% probability for including a causal variant consisted of 7-74 SNPs (IQR). There were 20 single-SNP sets; for example, rs881858 (close to *VEGFA*) maps to open chromatin and represents a CTCF binding site.

Conclusions: Ongoing analyses include gene expression, tissue enrichment and network analyses of gene expression, and functional follow-up studies. These results of the largest genetic screen of kidney function to date will enhance the understanding of the biologic mechanisms of this trait.

TH-OR085

Genetic and Epigenetic Analysis in Genes Affecting Mitochondrial Function Are Associated with CKD in an Older Population

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Background: The Northern Ireland COhort for the Longitudinal study of Ageing (NICOLA) is a ten-year project exploring health and lifestyle information in 8,504 people ≥ 50 years of age via a computer assisted personal interview with an associated bioresource. Chronic kidney disease (CKD) affects ~10% of the World's population and is more prevalent in older individuals. Optimal renal function is critically dependent upon efficient mitochondria, therefore genetic and epigenetic features that lead to mitochondrial dysfunction may influence CKD.

Methods: The discovery cohort comprised 2,567 white European individuals with body mass index ranging from 18.5 - 40 kg/m^2. Genotyping was performed using Illumina's Infinium CoreExome array (n=551,839 SNPs directly typed), with data imputed to the Haplotype Reference Consortium. Methylation data was generated using Illumina's Infinium MethylationEPIC array (866,554 features with single site resolution). PLINK and Partek Genomics Suite were employed to investigate association with eGFR, serum albumin, urea and creatinine. Replication was conducted in an independent cohort of 402 individuals.

Results: SNPs that demonstrated the most evidence for association include an exonic SNP in the mitochondrial genome *MT-TL2* gene (rs2853498; A12308G; a key SNP defining mitochondrial Haplogroup U) with increased creatinine levels (P=0.000153, OR=1.185, 95% CI=1.0929-1.2812). SNPs in nuclear genes that influence mitochondrial function include rs77790196 within *SLC39A1* (P= 4.4 x10^{-07}, OR=0.0055, 95% CI=0.0007-0.0412) and rs12564199 within *JTB* (P=6.6 x10^{-07}, OR=0.006, 95% CI=0.0008-0.0449) associated with decreased eGFR. Analysis of epigenetic data identified eight genes demonstrating differential methylation with p<10^{-08} and Δβ ±0.2, including *ZBED3*, *ZNF672*, and *AHCTF1* for participants with early stage CKD compared to individuals with CKD stages 3-5.

Conclusions: These analyses have identified novel associations linking CKD with SNPs and CpG sites. This may serve as a future basis for the development of predictive multi-omic biomarkers and/or increased understanding of CKD pathogenesis.

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TH-OR086

Metabolomic Alterations Associated with Proteinuria

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Background: Metabolomic profiling may reveal important pathophysiological mechanisms underlying proteinuria in chronic kidney disease (CKD).

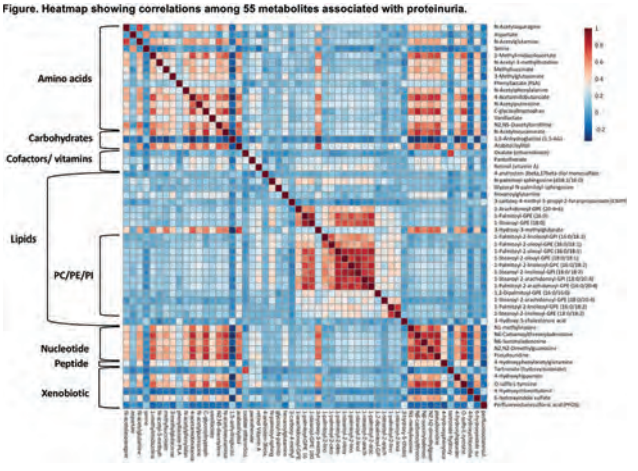
Methods: Among 962 participants in the African-American Study of Hypertension and Kidney Disease (AASK) and 670 participants in the Modification of Diet in Renal Disease (MDRD) Study, we evaluated the cross-sectional association between log-transformed urine protein-to-creatinine ratio (UPCR) and known, non-drug metabolites (N =801) identified in stored serum samples (pre-randomization visit in AASK and 12-month follow-up visit in MDRD) via an untargeted approach. The metabolites with statistically significant associations (adjusted for age, sex, race, trial arm, measured GFR, history of heart disease, smoking, and BMI) after Bonferroni correction were included in a pathway analysis.

Results: In AASK and MDRD, respectively, median UPCR was 80 (IQR: 28-359) and 185 (IQR: 54-894) mg/g, mean age was 56 and 53, 39% were female, 100% and 7% were black, 0% and 5% were diabetic, and mean GFR was 48 and 28 mL/min/1.73m^2. Linear regression identified 64 metabolites associated with proteinuria in one or both cohorts, 55 of which were statistically significant in meta-analysis (p<8x10^{-4}). There were moderate within-pathway correlations among these metabolites (**Figure**). Metabolites with the lowest p-values (p<10^{-17}) included 4-hydroxychlorthalonil, 1,5-anhydroglucitol (1,5-AG), perfluoroctanesulfonic acid (PFOS), and 3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF), all of which negatively associated with UPCR. Pathway analysis showed over-representation of metabolites in the phosphatidylethanolamine (PE) and phosphatidylinositol (PI) pathways.

Conclusions: Metabolomic profiling identified metabolites (including 1,5-AG, CMPF and chemicals such as hydroxychlorthalonil and PFOS), as well as metabolic pathways (such as PE and PI metabolism), that were strongly associated with non-nephrotic range proteinuria in CKD.

Funding: NIDDK Support

Figure. Heatmap showing correlations among 55 metabolites associated with proteinuria.



TH-OR087

An Investigation into the DNA Methylation Patterns of CKD in Older Individuals

Laura J. Smyth, Sharon Cruise, Jill Kilner, Alexander P. Maxwell, Bernadette Mcguinness, Frank Kee, A.J. Mcknight. On behalf of the Northern Ireland Cohort of Longitudinal Ageing collaborative group *Queen's University Belfast, Belfast, United Kingdom.*

Background: Changes in DNA methylation are associated with chronic diseases. The study assessed whether methylation status of CpG sites differs between individuals with and without CKD between the ages of 60 and 79.

Methods: Participants were recruited as part of the Northern Ireland COhort for the Longitudinal study of Ageing (NICOLA), a large-scale population-based prospective cohort study. Estimated GFR was calculated for each individual (n=1,097) using the CKD-EPI formula. CKD stages, based on eGFR, were determined and all individuals with stage 2 CKD (eGFR >60 - <90mL/min/1.73m^2) were removed to increase discrimination between CKD case and control groups. Using the Infinium HD Methylation Assay, MethylationEPIC BeadChips from Illumina, the methylation status of >850,000 CpG sites, gene bodies, promoters and CpG islands were determined in each individual. Blood-derived DNA was processed consistently within our single genetics centre. Partek Genomics Suite 7.0 was utilised for data analysis, with standard quality control applied. In total, 155 individuals had CKD stages 3, 4 or 5 and were compared with 240 individuals with eGFR >90ml/min/1.73m^2 and no evidence of renal disease.

Results: In total, 306 CpG sites were identified as having significantly different levels of methylation in individuals with CKD compared with controls (p<1x10^{-07}). Among the genes identified with altered methylation status, several, including *CLU*, *NOS3*, *IQSEC1* and *NPHP4* have been linked with CKD. High concordance between duplicate samples was also observed for this array. Three of the significantly associated CpG sites demonstrated a graduated increase in the methylation fold change with worsening renal function i.e. comparing control individuals with persons having CKD stages 3, 4 and 5 respectively.

Conclusions: Epigenetic modifications, such as DNA methylation, may represent important biomarkers for the loss of kidney function in individuals with CKD. Data from this longitudinal cohort study provides the opportunity to monitor and assess the relationship between methylation status and CKD over time with a view to identifying new biomarkers or expanding knowledge of those previously identified CKD biomarkers.

TH-OR088

Prognostic Value of Extracellular Fluid Volume in CKD: A Prospective Cohort Study

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Background: Volume overload has been shown to be an independent risk factor for mortality in chronic dialysis patients. However, few studies have analyzed the prognostic value of extracellular fluid (ECF) volume in patients with chronic kidney disease (CKD), not on dialysis. The aim of this study was to analyze the association between ECF volume and end-stage renal disease (ESRD) and mortality in patients with non-dialysis CKD.

Methods: The NephroTest study is a prospective hospital-based tricentric cohort which included 2,084 patients with CKD stage 1-5 of various aetiologies, between 2000 and 2012. ECF volume was measured as the distribution volume of ^{51}CrEDTA, and expressed as a ratio of measured over theoretical ECF (rECF) - the latter being calculated using Moore formula. Measured glomerular filtration rate (mGFR) was assessed from the renal clearance of ^{51}Cr-EDTA. Cause-specific Cox regression models were used to estimate hazard ratios (HR, 95% confidence intervals) of ESRD and death before ESRD associated with rECF tertiles in 1,610 patients with mGFR > 15 ml/min/1.73 m^2.

Results: Mean age of patients was 58.7±15.1years, and 66.8% were men. Baseline mean mGFR was 43.7±18.7mL/min/1.73m^2, mean ECF volume and rECF were 16.1±3.8L and 0.96±0.14, respectively. After a median follow-up of 6.1 [IQR: 3.64;8.37] years, ESRD occurred in 329 (20.4%) patients and 187 (11.6%) patients died before ESRD. After adjustment for age, sex, site, ethnicity, cardiovascular risk factors, underlying renal disease, mGFR, proteinuria, 24-hour sodium excretion, diuretics and diuresis, a higher baseline rECF was significantly associated with ESRD (HR for second vs. first tertile = 1.28 [0.94;1.74], HR for third vs. first tertile = 1.51 [1.08;2.10]), and with mortality (HR for second vs. first tertile = 0.99 [0.63;1.56], HR for third vs. first tertile = 1.81 [1.17;2.80]).

Conclusions: Our data suggest that rECF volume is an independent risk factor of ESRD and mortality. Monitoring and avoiding excessive fluid overload is important for the clinical management of patients with CKD.

TH-OR089

Specific Mitochondrial Genetic Variants Are Associated with Kidney Dysfunction and Injury in Older Adults

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Background: Mitochondrial dysfunction is an important contributor to acute and chronic kidney damage, due to the critical roles of mitochondria for oxidative phosphorylation. Mitochondrial genetic variation has been associated with age-related cardiovascular and functional impairments, but little is known regarding the impact of common inherited mitochondrial DNA (mtDNA) variants on kidney health.

Methods: In this study of 2,728 ambulatory older adults enrolled in the Health, Aging, and Body Composition Study, we evaluated associations of 10 common inherited mtDNA haplotypes and 137 single nucleotide polymorphisms (SNPs) with estimated glomerular filtration rate (eGFR), albumin/creatinine ratio (ACR), and urine concentrations of kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18). DNA was extracted from blood buffy coat specimens and mtDNA genotype was determined using the Illumuna 1M chip. A total of 60 SNPs with minor allele frequency >=1% were examined for associations with kidney outcomes. All analyses stratified participants by European and African ancestry and adjusted for age, sex, and mitochondrial genetic ancestry.

Results: Among persons of European ancestry (n=1,660), m.10589G>A was associated with lower eGFR (57 vs 71 ml/min/1.73m^2; p=0.009) and m.6776T>C was associated with higher ACR (98 vs 29 mg/g; p<0.0001), whereas haplogroup V (1721 vs 1172 pg/ml, p=0.0066) and m.3916G>A (2599 vs 1207 pg/ml, p<0.0001) were each associated with higher urine KIM-1. Among persons of African ancestry (n=1,137), m.15758A>G was associated with higher urine KIM-1 (3476 vs 1074 pg/ml, p<0.0001). There were no statistically significant associations of mtDNA variants with urine IL-18.

Conclusions: Specific inherited mtDNA variants are associated with kidney dysfunction and injury in older adults, suggesting that mitochondrial genetic variability may contribute to risk of kidney disease.

Funding: NIDDK Support

TH-OR090

Provider Perception of Frailty Influences Dialysis Modality Choice for Late Stage CKD Patients Receiving Multidisciplinary Care

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Background: Frailty is common in patients with Chronic Kidney Disease (CKD) and is associated with accelerated aging. While there have been several studies examining frailty in patients with earlier stages of CKD and those on dialysis, little is known about the prevalence and impact of frailty on decisions surrounding renal replacement therapy modalities in patients with advanced CKD (Stages G4-G5). We sought to determine the prevalence of frailty in patients with advanced CKD and the association of these measures with dialysis modality decisions and mortality.

Methods: We studied 587 patients with advanced CKD who were enrolled in multidisciplinary CKD clinics at 4 centers. We collected demographics, comorbid conditions, and laboratory results in addition to objective [Fried Frailty Criteria and Short Physical Performance Battery (SPPB)], and subjective measures (physician and nurse impression) of frailty. Our primary outcomes were choice of dialysis modality based on provider perception of frailty. Our secondary outcomes were agreement between frailty assessment tools and all-cause mortality.

Results: Our cohort had a mean age of 66.3 and 41% were female. Estimates of frailty prevalence varied as 54.8% of the cohort were considered frail according to SPPB, 33.2% according to Fried, 35.2% according to physician impression, and 32.5% according to nursing impression. Agreement between objective frailty assessments was moderate (κ = 0.42), as was agreement between subjective frailty assessments (κ = 0.47). In unadjusted and adjusted analyses, frailty measured objectively using Fried was associated with mortality (HR 2.15 [95% CI: 1.27-3.62]), and frailty measured subjectively (OR 4.20 [95% CI: 1.88-9.76) was associated with choosing in center hemodialysis.

Conclusions: Frailty is common in patients with advanced CKD, but its operational definition can classify different patients as frail. Patients classified as frail by Fried have a higher risk of death, and patients considered frail by nurses and physicians are more likely to choose in-center hemodialysis. Further research to understand the longitudinal trajectory of frailty and its impact on therapeutic choices, morbidity, mortality, and quality of life after the initiation of dialysis is needed.

Funding: Government Support - Non-U.S.

TH-OR091

Twenty-Year Trends in Mortality Due to Myocardial Infarction and Stroke in Dialysis Patients

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Background: In the last decades, important improvements have been made in the prevention and treatment of myocardial infarction and stroke resulting in reduced mortality rates in the general population. However, it is unknown whether mortality rates of myocardial infarction and stroke have also decreased with time in dialysis patients. The aim of this study was to assess the mortality rates due to myocardial infarction and stroke in a large cohort of dialysis patients as compared with the general population for three time periods.

Methods: We included incident dialysis patients from eleven European countries providing data to the ERA-EDTA Registry who started dialysis between 1994 and 2011 and followed them for three years. The causes of death in dialysis patients were compared with the causes of death in the general population in the same time period. We calculated age- and sex-standardized mortality rate ratios (SMRs) with 95% confidence intervals (CIs) by dividing the mortality rates in dialysis patients by the mortality rates in the general population for three time periods (1994-1999, 2000-2005 and 2006-2011).

Results: Of the 201,918 dialysis patients, 79,327 patients died during follow-up of whom 10.3% died due to myocardial infarction and 6.6% due to stroke. In the general population, 19,058,469 persons died during follow-up of whom 7.4% died due to myocardial infarction and 6.1% due to stroke. Compared with the general population, the SMRs of myocardial infarction for dialysis patients were **11.4 (95% CI 10.8-12.0)** between 1994 and 1999, **12.1 (95% CI 11.5-12.8)** between 2000 and 2005 and **14.0 (95% CI 13.2-14.8)** between 2006 and 2011. The SMRs of stroke were **11.0 (95% CI 10.3-11.9)** between 1994 and 1999, **11.7 (95% CI 10.8-12.6)** between 2000 and 2005 and **12.4 (95% CI 11.5-13.3)** between 2006 and 2011.

Conclusions: Mortality rate ratios for myocardial infarction and stroke increased with time. Dialysis patients seem to benefit less of improvements made in the prevention and treatment of myocardial infarction and stroke than non-dialysis patients which may be related to the underlying pathophysiological mechanisms of the atherosclerotic disease or to the limited optimal cardiovascular therapeutic strategies.

TH-OR092

International Comparisons of Mortality Among Hemodialysis Patients in the DOPPS

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Background: Case-mix-adjusted mortality rate among hemodialysis patients has been higher in the US than in Europe or Japan, although this gap has been shrinking. Patient population and clinical practices have changed over time. We are evaluating the effects of case mix, practice patterns, and country factors on mortality rates across countries.

Methods: In DOPPS phase 5 data (2012-15) from hemodialysis facilities in Europe, Japan, and North America, Cox models with cumulative covariate adjustment were fitted to estimate adjusted hazard ratios (HR) for death. Case-mix-based propensities for transplantation or change to peritoneal dialysis (PD) were generated using models based on data from the previous DOPPS phase, while within-country general population all-cause and kidney-related death rates were based on WHO data.

Results: The unadjusted death rate in the US was generally comparable to that of many European countries (figure). Adjustment for case mix, especially age and race, results in lower hazard ratios for most European countries compared to the US, while adjustment for skipped treatments and selected practice measures (fistula use, phosphorous levels <6 mg/dl, intra-dialytic weight gain <5.7% of body weight) increased the hazard ratios for these European countries compared to the US, although most were still somewhat below that of the US. Japan Canada had consistently lower adjusted mortality than the US.

Conclusions: Unadjusted mortality in the US is comparable to that of European countries. Case-mix adjustment yields lower hazard ratios in most countries compared to US, indicating outcomes are still worse in US. Adjustment for practice measures substantially attenuates this effect in some countries, indicating that these factors may provide a means for the US to improve its outcomes. Japan has lower mortality in DOPPS data than any other country; this is not explained by any adjustment explored thus far.

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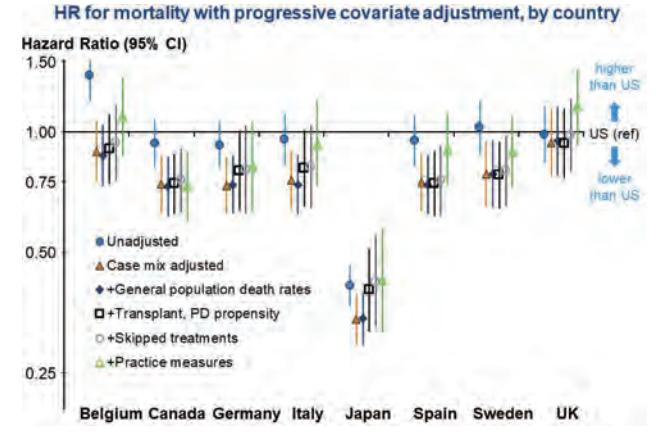

TH-OR093

The Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors (SSRIs) in the Hemodialysis (HD) Population

Magdalene M. Assimon, Jennifer E. Flythe. *University of North Carolina Kidney Center, Chapel Hill, NC.*

Background: HD patients may be particularly susceptible to the lethal consequences of drug-induced QT prolongation due to their tremendous cardiovascular disease burden and recurrent exposure to electrolyte shifts during HD treatments. Electrophysiologic data indicate that citalopram and escitalopram prolong the QT interval more than other SSRIs. Even though 37% of HD patients receive SSRI therapy, the relative cardiac safety of individual SSRIs in this vulnerable population is not well-established.

Methods: Data were taken from a cohort of Medicare-enrolled HD patients in the United States Renal Data System registry (2007–2014). Using a new-user design, we conducted a retrospective cohort study to assess the comparative 1-year risk of sudden cardiac death between HD patients initiating SSRIs with higher (citalopram, escitalopram) vs. lower (fluoxetine, fluvoxamine, paroxetine, sertraline) QT prolonging potential. We used propensity-score weighted survival models, adjusted for numerous demographic and clinical covariates, to estimate adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs). All analyses used an on-treatment analytic approach and treated non-sudden cardiac death as a competing event.

Results: Of 65,654 study patients, 30,932 (47.1%) started an SSRI with higher QT prolonging potential and 34,722 (52.9%) started an SSRI with lower QT prolonging potential. Initiation of an SSRI with higher (vs. lower) QT prolonging potential was associated with an increased 1-year risk of sudden cardiac death, aHR [95% CI] = 1.14 [1.05–1.25]. Observed associations were particularly elevated among females (1.21 [1.07–1.37]); individuals ≥75 years old (1.14 [1.01–1.28]); individuals with structural heart disease (1.13 [1.03–1.23]); and those concurrently using other QT prolonging medications (1.16 [1.04–1.29]). Sensitivity analyses 1) evaluating a composite outcome of sudden cardiac death *or* new-onset ventricular arrythmia, and 2) using an intent-to-treat analytic approach yielded similar results (not shown).

Conclusions: Initiation of an SSRI with higher (vs. lower) QT prolonging potential was associated with an increased risk of sudden cardiac death. When prescribing SSRIs to HD patients, providers should consider the QT prolonging potential of these agents, especially among individuals with sudden cardiac death risk factors.

Funding: NIDDK Support

TH-OR094

Association of Ultrafiltration Rate and Decline in Residual Kidney Function among Thrice-Weekly Hemodialysis Patients

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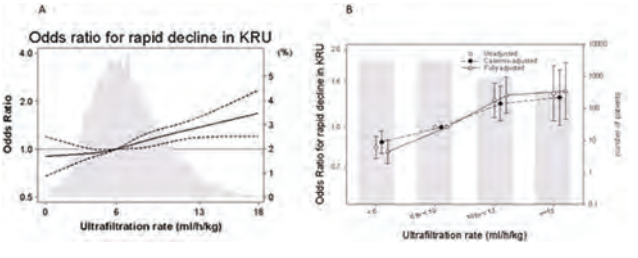
Background: The association between ultrafiltration rate (UFR) and decline in residual kidney function (RKF) has not been well examined in conventional hemodialysis (HD) patients with RKF.

Methods: We retrospectively reviewed a cohort of 7,753 patients who initiated thrice-weekly HD from 2007 to 2011, had available UFR and renal urea clearance (KRU) data at baseline, and had KRU data at 1 year after HD initiation. Patients were categorized into 4 UFR groups (<6, 6 to <10, 10 to <13, and ≥13 mL/h/kg). We defined rapid decline in RKF as a decline in KRU of more than 20% per year. We explored the association between UFR and rapid decline in RKF using logistic regression models with adjustments for case-mix variables, baseline RKF, and maximal change of blood pressure during dialysis.

Results: Mean ± SD UFR level was 7.0 ± 3.1 mL/h/kg. Median (interquartile range) baseline KRU was 3.5 (2.1 – 5.3) mL/min/1.72m^2. Mean annual changes of KRU were -1.1, -1.2, -1.4, and -1.6 mL/min/1.73m^2 in UFR <6, 6 to <10, 10 to <13, and ≥13 mL/h/kg groups, respectively (P = 0.004). In a cubic spline model, higher UFR was associated with increased risk for rapid decline in KRU [figure 1A]. Additionally, we found a graded association between categorized UFR and rapid decline of RKF in the fully adjusted multivariable regression models: odds ratios (95% confidence intervals) were 0.80 (0.72-0.88), 1.33 (1.14-1.57), and 1.39 (1.08-1.80) in UFR <6, 10 to <13, and ≥13 mL/h/kg groups, respectively (reference: UFR 6 to <10 mL/h/kg) [figure 1B].

Conclusions: In incident thrice-weekly HD, higher UFR was associated with rapid decline in RKF. Strategies to avoid high UFR may be useful for RKF preservation in incident HD patients.

Funding: NIDDK Support



TH-OR095

Opioid and Benzodiazepines Use in Patients on Hemodialysis

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Background: Opioid & Concomitant use of benzodiazepines is a public health problem. Little is known about opioids and benzodiazepine prescription in HD patients

Methods: This is retrospective study of USRDS data on ESRD patients ≥18 yrs, on HD, enrolled in Medicare & part D between 2006-2012, excluding those on PD & malignancy. We used ESRD Medicare Prescription Drug Events dataset for narcotics & benzodiazepines. We categorized narcotics into three safety classes per literature (safe, use

caution, unsafe) and analyzed their prescription pattern. We used hospitalization dataset to identify hospitalization with opioid overdose using ICD-9 CM codes, total LOS and ICU LOS

Results: Out of 2,657,352 patients, 643,859 were included, & divided into opioid (n=480,460, 74.6%) and non-opioid group. The biggest difference b/w 2 groups is in the use of benzos (30% in opioid vs 11% in non-opioid P<0.001). There is significant association between opioid & benzo use (OR = 3.27, P<0.001). 6,665,906 narcotic prescriptions were written averaging 13.8 prescriptions/patient. 52.2% patients were prescribed narcotics/year. Each patient got an average of 8 prescriptions/year. 30% of patients who got a prescription for opioid, also got a prescription for a benzo. 56.5% received prescriptions for both within a week of each other. Adverse events (A/E): 2225 patients with narcotic prescription (0.46%) had 3231 admissions with opioid overdose. 4 died. Median LOS is 4d, median ICU LOS is 2d. Benzo use prior to hospitalization was significantly higher in patients admitted for narcotic overdose as compared to others (40% vs 24%, p <0.001). Association between opioid class and A/E: Among the "safe" drugs, fentanyl & hydromorphone were associated with moderately high odds of hospitalization within 30 days (OR 3 and 2.4 respectively). This persisted at 60 & 90 days with fentanyl but decreased with hydromorphone at 90 days (1.6). Methadone was associated with a very high risk of hospitalization at 30 days (OR 5.9), that persisted at 60 & 90 days. Among the drugs to be used with caution hydrocodone had the least OR among all the drugs (1.8, 1.7 and 1.6 at 30, 60 and 90d). Oxycodone was moderate risk and oxymorphone (Opana) was high risk.

Conclusions: opioid and benzodiazpeine prescription in HD patients is very high. Drug safety based on pharmacokinetic profile in dialysis does not translate to clinical safety.

TH-OR096

Prevalence, Indications, and Risks of Muscle Relaxant Use among Hemodialysis Patients

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Background: Muscle relaxants are used to treat musculoskeletal pain and cramping, which are commonly experienced symptoms among hemodialysis patients. However, epidemiologic data characterizing the prevalence, indications, and risks of muscle relaxant use in this population are lacking.

Methods: From the USRDS, we identified 140,899 adults receiving in-center hemodialysis with Medicare Part D in 2011. We determined the prevalence of muscle relaxant use and the presence of a relevant indication, defined by ICD-9 codes, within 60 days preceding the date of a prescription by examining Medicare claims data. Using Cox regression models, we investigated the association between receipt of muscle relaxants (e.g., cyclobenzaprine, baclofen), modeled as a time-varying exposure, and time to first emergency room visit or hospitalization for altered mental status (AMS), fall, and fracture defined by ICD-9 and CPT codes. We adjusted for demographics, comorbidities, duration of muscle relaxant exposure, number of medications, and concomitant medications. Exposure was time-lagged (i.e., ascertained from the prior day) for fall and fracture in order to account for possible effect/cause.

Results: Ten percent (14,312) of the cohort received muscle relaxants, and 17% (24,067) had an episode of AMS, fall, or fracture in 2011. The most common diagnoses associated with muscle relaxant use were musculoskeletal pain other than neck or back pain (72%), back pain (48%), and muscle spasticity (25%). Fourteen percent of patients with a muscle relaxant prescription lacked a relevant indication. Muscle relaxant use was significantly associated with AMS, fall, and fracture (**Table**).

Conclusions: Muscle relaxants are commonly used by hemodialysis patients. They were most frequently prescribed for musculoskeletal pain and spasticity, but a sizeable proportion of patients lacked a clear indication based on claims data. Muscle relaxants are associated with a high risk for AMS, fall, and fracture. Future research to define the appropriate use of these agents in this population is warranted.

Funding: NIDDK Support

Risk of Adverse Outcomes Associated with Muscle Relaxant Use

	Hazard Ratio (95% Confidence Interval)		
	AMS	Fall	Fracture
None	1.00 (ref)	1.00 (ref)	1.00 (ref)
Muscle Relaxant	1.68 (1.53–1.84)	1.29 (1.11–1.49)	1.30 (1.05–1.61)

TH-OR097

Temporal Trend of the Provision of Palliative Care Encounter in Hospitalized Patients with ESRD: A Nationwide Analysis

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Background: End stage renal disease (ESRD) is major cause of worldwide mortality and morbidity. We sought to investigate the temporal trend of the utilization of palliative care (PC) in hospitalized patients with ESRD in United States.

Methods: We conducted a retrospective study using the national inpatient sample to identify patients with ESRD admitted to hospitals from 2006 to 2014. We sought to determine the temporal trend and factors associated with utilizing palliative care in hospital. Multivariate logistic analysis was performed to calculate odds ratios, adjusting for demographics, hospital characteristics, comorbidities and code status. Analysis was performed using Stata 14.0.

Results: A cohort of 6,280,637 patients was identified from 2006 to 2014, of whom 1.65% had a PC consult referral. The incidence of PC contact increased from 0.39% in 2006 to 2.98% in 2014 (aOR 1.11, p<0.01). Patients who received PC contact, compared to who did not, were older (68.79 vs 64.28, p<0.01), had longer hospital stay (8.37 vs. 6.20 days, p<0.01) and were more likely to die in hospital (49.40% vs. 4.04%, p<0.01). Factors associated with more frequent PC referral included more cormobidities, Caucasian race (compared to minorities), teaching hospitals, larger hospitals, hospitals region other than Northeastern area, household income, medicaid or private insurance, and do not resuscitate (DNR) status (shown in Table 1).

Conclusions: The use of palliative care consultation for patients with ESRD who are admitted to hospitals is approximately 1.65%. Race, socioeconomic status, hospital size, region and teaching status all were associated with differential rates of referral. There was a significant increase in palliative care use observed from 2006 to 2014.

Table 1

Predictor for Palliative Care	aOR	95% CI	P
Age	1.03	1.03-1.03	<0.01
Female	0.96	0.92-1.00	0.04
Race			
Caucasian	Reference		N/A
African American	0.76	0.70-0.82	<0.01
Hispanics	0.65	0.59-0.72	<0.01
Asian and Pacific Islander	0.74	0.65-0.83	<0.01
Native American	0.82	0.63-1.07	0.14
Charlson Comorbidity Index			
0-2	Reference		N/A
3-5	1.28	1.19-1.38	<0.01
>6	2.17	1.98-2.39	<0.01
Hospital Teaching Status			
Non Teaching	Reference		N/A
Teaching	1.43	1.29-1.58	<0.01
Hospital Size			
Small	Reference		N/A
Medium	1.18	1.02-1.35	0.03
Large	1.26	1.10-1.44	<0.01
Region			
Northeast	Reference		N/A
Midwest	1.21	1.05-1.40	<0.01
South	1.24	1.09-1.42	<0.01
West	1.26	1.09-1.45	<0.01
Median Household Income			
$1-$38,999	Reference		N/A
$39,000- $47,999	1.12	1.04-1.21	<0.01
$48,000- $ 62,999	1.17	1.08-1.27	<0.01
$63,000 or more	1.25	1.14-1.37	<0.01
Insurance			
Medicare	Reference		N/A
Medicaid	1.12	1.02-1.24	0.02
Private Insurance	1.56	1.41-1.73	<0.01
Self Pay	1.28	0.94-1.73	0.12
Other	0.51	0.17-1.55	0.24
DNR	22.14	20.41-24.00	<0.01

TH-OR098

The Impact of the IDEAL Trial on Early Initiation of Dialysis

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Background: In August 2010, the Initiating Dialysis Early and Late (IDEAL) trial was published and randomized patients with pre-dialysis CKD to planned initiation of dialysis in the eGFR range of 10 to 14 ml/min/1.73m^2 (early start) vs. 5 to 7 ml/min/1.73m^2 (late start). It concluded that earlier initiation was not associated with improved survival or clinical outcomes. The degree by which this information was disseminated and applied in practice is unknown. We aimed to determine the impact of the IDEAL trial on the proportion of patients who initiate dialysis early (eGFR > 10.5 ml/min/1.73m^2).

Methods: A segemented regression analysis was performed including all incident adult dialysis patients from the Canadian Organ Replacement Register (CORR) with at least 90 days of nephrologist care before starting dialysis with a recorded eGFR at dialysis initiation. The primary outcome was the change in the proportion of early dialysis starts (eGFR at initiation > 10.5 ml/min/1.73m^2). Secondary outcomes included the change in the proportion of acute inpatient dialysis initiations, the proportion of patients who received home dialysis as initial therapy, and the proportion of hemodialysis patients who started dialysis with an arteriovenous (AV) fistula.

Results: Following the IDEAL trial we observed an immediate decline in the proportion of early dialysis starts of 4.49% (95% confidence interval 1.24 to 7.74; p = 0.0080), and there was a significant decrease from the pre-trial annual slope of 2.76% (1.68 to 3.84; p = < 0.001), resulting in an annual decrease of 1.44% (0.84 to 2.16; p < 0.001) in the post-trial period. Acute inpatient dialysis initiations increased immediately following the publication by 2.86% (0.10 – 5.62; p = 0.0440), however there was no sustained change. The proportion of patients who received home dialysis as initial therapy and the proportion who initiated hemodialysis with an AV fistula did not have immediate or sustained differences.

Conclusions: The IDEAL trial had a strong and sustained impact on the timing of dialysis initiation in Canada. These changes were accompanied by no sustained effects on home dialysis as initial therapy, AV fistula construction, or acute inpatient dialysis initiation

Funding: Government Support - Non-U.S.

TH-OR099

Impact of Rescheduling a Missed Hemodialysis Treatment on Clinical Outcomes

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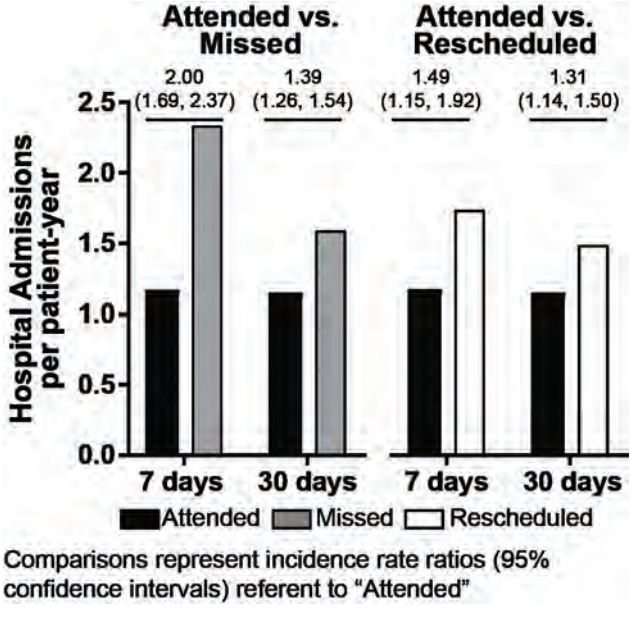
Background: Among patients treated with hemodialysis (HD), a missed treatment is associated with elevated hospitalization risk in the subsequent 30 days. It is not known whether attending a rescheduled treatment on the following day ameliorates this risk.

Methods: This retrospective study used electronic health records and 2014 USRDS claims merged via direct linkage. Eligible patients were adults receiving HD on a Monday/Wednesday/Friday schedule who, as of index, had dialysis vintage ≥90 days, available Medicare A & B claims, and had not missed a treatment for any reason in the 30 days prior to index. For each of 12 index dates, patients were classified based on attending treatment; those who did not were classified as "rescheduled" or "missed" based on whether or not they dialyzed the following day. In separate analyses, "rescheduled" and "missed" patients were each matched (1:5) to patients who attended based on index day of week and propensity score. Hospitalization was considered over the subsequent 7 and 30 days, or until censoring, and compared using generalized linear models.

Results: Prior to matching, patients who missed or rescheduled treatment were of younger age and dialysis vintage than those who attended. All characteristics were balanced after matching. Compared to attending (N=20,725), a missed treatment (N=4145) was associated with a 100% higher rate of hospitalization in the subsequent 7 days, and a 39% higher rate over 30 days. Attending a rescheduled treatment on the day after a missed treatment (N=2308) was associated with a 49% higher rate of hospitalization in the subsequent 7 days, and a 31% higher rate over 30 days, versus attending (N=11,540).

Conclusions: Rescheduling treatment attenuated but did not fully mitigate the hospitalization risk imposed by a missed treatment.

Funding: Commercial Support - This was a research project conducted by the DaVita Institute for Patient Safety and supported by DaVita Kidney Care.



TH-OR100

Association of Baseline eGFR and AKI-D with Early Mortality after ESRD

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Background: Abrupt decline in kidney function and non-recovery of dialysis-requiring AKI (AKI-D) have both been shown to be associated with adverse outcomes in patients with incident ESRD. We hypothesized that distinct patterns of transition to ESRD based on both the mean 1-year baseline eGFR and presence of AKI-D preceding ESRD would help prognosticate 90-day mortality after hemodialysis (HD) initiation.

Methods: We identified a national cohort of Veterans who initiated maintenance HD in 2009-2013 and had outpatient creatine (Cr) measured within 1 year prior to ESRD. Patients were categorized based on A) mean outpatient eGFR within 1 year prior to incident ESRD (≥ or < 30); and B) occurrence of in-hospital AKI-D leading to ESRD. AKI-D was defined using KDIGO criteria of [≥0.3mg/dL rise and/or ≥50% rise in Cr from mean 1-year baseline], *and* inpatient dialysis. The association between patterns of transition and all-cause mortality within 90 days after HD initiation were examined using multivariable Cox models.

Results: Patients with incident ESRD (N=22,815) were 69±11 years old, 98% male, 27% black, and 68% diabetic. 4114 (18%) had mean 1-year outpatient eGFR≥30; 2644 (12%) experienced AKI-D with peak inpatient Cr rise was ≥50% from baseline. Relative to refence group of mean outpatient eGFR<30 and no AKI-D, patients with mean outpatient eGFR≥30 had ~2-fold adjusted risk of 90-day mortality, regardless of presence/absence of AKI-D (Table1). Among patients with mean eGFR<30, those with AKI-D and ≥50% rise in Cr had a small increase in mortality, whereas those with AKI-D and smaller peak Cr (<50% but ≥0.3mg/dl rise) had lower 90-day adjusted mortality.

Conclusions: Nearly 1 in 5 incident ESRD patients had a mean outpatient eGFR≥30 within the 1 year prior to HD initiation. This pattern of abrupt transition to ESRD was strongly associated with early mortality regardless of whether or not AKI-D directly preceded ESRD.

Funding: NIDDK Support

Pattern of Transition	[Death in first 90 days after ESRD] / [Total N] = crude death rate	Unadjusted Hazard Ratio	Fully Adjusted Hazard Ratio**
eGFR<30*, no AKI-D	1229 / 15,484 = 7.9%	Reference	Reference
eGFR<30*, + AKI-D with peak Cr <50% from baseline	39 / 1076 = 3.6%	0.45 (0.32-0.61)	0.62 (0.45-0.86)
eGFR<30*, + AKI-D with peak Cr ≥50% from baseline	170 / 2141 = 7.9%	1.00 (0.85-1.17)	1.31 (1.11-1.55)
eGFR≥30*, no AKI-D	655 / 3611 = 18.1%	2.41 (2.19-2.65)	1.94 (1.75-2.15)
eGFR≥30*, + AKI-D with peak Cr ≥50% from baseline	82 / 503 = 16.3%	2.14 (1.71-2.68)	2.09 (1.66-2.62)

*refers to mean outpatient eGFR within 1 year prior to ESRD. **adjusted for demographics, co-morbidities, and pre-ESRD nephrology care.

TH-OR101

Anti-MicroRNA Screen Uncovers miR-17 Family within miR-17~92 Cluster as the Primary Driver of Kidney Cyst Growth

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Background: We have recently shown that inhibiting miR-17~92 is a potential novel therapeutic approach for autosomal dominant polycystic kidney disease (ADPKD). However, miR-17~92 is a polycistronic cluster that encodes microRNAs (miRNAs) belonging to the miR-17, miR-18, miR-19 and miR-25 families. The relative pathogenic contribution of these miRNA families to ADPKD progression is unknown.

Methods: We performed an *in vivo* anti-miR screen to identify drug targets within the miR-17~92 miRNA cluster. Locked nucleic acid-modified anti-miRs (12 to 16 nucleotides) were used to selectively inhibit either the miR-17, miR-18, miR-19, or miR-25 family in an orthologous model of ADPKD. miRNAs belonging to one family harbor identical seed sequence but there are minor differences in flanking nucleotides. To simultaneously inhibit all members of one family, anti-miRs were designed to Watson-Crick base pair with the majority but not the entire length of cognate mature miRNA sequence. Mice were randomly assigned to receive either 20 mg/kg of anti-miR-17, anti-miR-18, anti-miR-19, or anti-miR-25 family inhibitors, or vehicle at postnatal days (P) 10-12 and 15, and were sacrificed at P18 to assess cyst burden.

Results: Q-PCR analysis showed that anti-miRs specifically inhibit the cognate miRNA family members without affecting the expression of unrelated miRNAs. Treatment with anti-miRs against the miR-17 family reduced cyst proliferation, kidney-weight-to-body-weight ratio, and cyst index. In contrast, treatment with anti-miRs against the miR-18, 19, or 25 families did not affect cyst growth. RNA-seq analysis showed that anti-miR-17 treatment recapitulated the gene expression pattern observed after miR-17~92 genetic deletion. Additional analysis revealed that anti-miR-17 treatment was associated with upregulation of mitochondrial metabolism, suppression of the mTOR pathway, induction of autophagy, and reduction of cyst-associated inflammation (M2-like macrophages).

Conclusions: Our results argue against functional cooperation between the various miR-17~92 cluster families in promoting cyst growth and instead point to miR-17 family as the primary pathogenic component and therapeutic target for ADPKD. This new information is vital because it guides the substantial on-going drug development efforts aimed at targeting the miR-17~92 cluster for the treatment of human ADPKD.

Funding: NIDDK Support

TH-OR102

Kidney Organoids without Cilia Establish a Human Model of Ciliopathy-Associated Polycystic Kidney Disease

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Background: Primary cilia are specialized, antenna-like organelles at the plasma membrane associated with a spectrum of human syndromes called ciliopathies. Phenotypes of polycystic kidney disease (PKD) are commonly associated with ciliopathies, but how cilia function to prevent kidney cysts remains poorly understood. A major barrier to understanding ciliary function is the absence of cellular models that accurately reconstitute the complex human phenotypes of ciliopathies.

Methods: We used the CRISPR-Cas9 genome editing system to introduce mutations in two genes that are required for ciliogenesis, kinesin family member 3A (*KIF3A*) and *KIF3B*, in human pluripotent stem cells (hPSC). Genome modified *KIF3A*$^{-/-}$ or *KIF3B*$^{-/-}$ hPSC were differentiated *in vitro* into kidney organoids containing proximal tubules, distal tubules, and podocytes in nephron-like segments. Structure and composition of organoids were analyzed by immunofluorescence. To determine the mechanistic consequences of ciliary loss, a biochemical assay was used to measure ciliopathy-linked protein levels in both whole cell lysates and extracellular vesicles.

Results: We isolated four independent cell lines with indel mutations in the *KIF3A* gene and three cell lines with indels in *KIF3B*. Immunoblots confirmed that no full-length protein is produced in these mutants. The gene-edited hPSC completely lacked cilia, while ~50% of cells were ciliated in the isogenic controls. Importantly, the absence of cilia did not alter hPSC growth, pluripotency, self-renewal, or their ability to differentiate into kidney organoids. Upon differentiation, however, the cilia-deficient kidney organoids formed large cysts from tubular epithelial cells, which were absent in controls. Defects were furthermore observed in the expression of the disease-associated proteins polycystin-1 and polycystin-2 in kinesin mutants.

Conclusions: Genome modified *KIF3A*$^{-/-}$ or *KIF3B*$^{-/-}$ hPSC establish a general tool for studying the function of human cilia in diverse cell types and organoids. Our findings directly link the loss of ciliary kinesins to polycystin expression defects and kidney cyst formation in human cells. Using this new tool, it is now possible to perform phenotypic screens and mechanistic studies to reveal the functions of human cilia and test interventional strategies for ciliopathy syndromes.

Funding: Private Foundation Support

TH-OR103

Polycystin Signaling: Control of Tubule Cell Shape by Actomyosin-Dependent Apical Constriction

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of end-stage renal disease affecting approximately 1 in 500 adults. Mutations in two genes cause ADPKD. *Polycystic kidney disease 1* (*PKD1*) accounts for 85 % of patients and *PKD2* accounts for the remaining 15 % of patients. Elegant experiments in model organisms have uncovered that the respective proteins, Polycystin-1 (PC1) and transient receptor potential ion channel Polycystin-2 (TRPP2), form a receptor-ion channel complex which is essential for renal morphogenesis and maintenance. The molecular components, however, connecting the two ADPKD proteins to these processes have remained elusive. Or more specifically, the intracellular effectors translating PC1/TRPP2 receptor-ion channel activity into three-dimensional tissue organization connecting genetics, cellular output, and tissue mechanics are unknown.

Methods: We have addressed this issue for the kidney with an unbiased high-resolution mass spectrometry-based screen for TRPP2-binding proteins in polarized renal epithelial cells followed by targeted analyses of PC1/TRPP2 function *in vitro* and *in vivo*. *In vitro* analyses of PC1/TRPP2 and candidate proteins were performed using CRISPR/Cas- and TALEN-based gene-specific knock-out and knock-in Madin-Darby canine kidney (MDCK) cell models. Wild-type and mutant zebrafish, mice, and human samples were used to validate results *in vivo*.

Results: Here we identify an apical junction associated multi protein signaling complex as functional PC1/TRPP2 effector and show: 1) how the PC1/TRPP2 complex controls cellular shape by actomyosin-dependent apical constriction; 2) that this cellular contraction translates on a tissue-scale into a coordinated fine-tuning of renal tubular diameter *in vivo*; and 3) that in human ADPKD kidneys, tubular shape is lost, because of impaired signal integration disconnecting mutant cells from their healthy surroundings.

Conclusions: ADPKD is a prime example for a disease affecting renal morphogenesis and maintenance. We anticipate that our detailed characterization of the various levels of polycystin-dependent renal tubular cell shape control may help to elucidate the complex cellular machinery integrating genetic, cellular, and mechanical inputs in health and renal disease.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR104

Role of the Mechanosensitive Ion Channel Piezo1 in Autosomal Dominant Polycystic Kidney Disease

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Background: Disruption of intracellular calcium (iCa^{2+}) likely underlies the upregulation of cAMP signaling and the proliferative and secretory phenotype of the cystic epithelium in ADPKD. However, the mechanisms by which polycystins reduce iCa^{2+} remain elusive. Impaired flow-induced Ca^{2+} entry through ciliary polycystin complex has been previously proposed as a pathogenic mechanism, but newer evidence suggests the involvement of polycystins in modulation of other mechanosensitive ion channels such as Piezo1, the novel stretch-activated cation channel. We hypothesized that polycystins, through their physical and functional interaction with Piezo1, modulate various cellular responses to mechanical stimulation.

Methods: Wild type inner medullary collecting duct cells (mIMCD3) were stably transfected with genetically encoded biosensors, jRGeco1a and Flamindo2, to study spatiotemporal dynamics of Ca^{2+} and cAMP during live cell imaging, respectively. These cells were also cultured in 3D matrigel matrix. Metanephric embryonic kindeys were cultured and stimualted with forskolin.

Results: Piezo1 is expressed in both WT mIMCD3 cells and PKD_2 null cells (~3 fold higher than wild type). Piezo1 activation by Yoda1 increased cytoplasmic calcium and simultaneously lowered forskolin-induced cAMP (Figure 1A). Additionally, exerting physiological fluid shear stress (FSS) (ibidi pump system) led to reduction in cAMP (Figure 1B). Yoda1 significantly reduced forskolin-induced *in vitro* cystogenesis by 68% in WT and by 48% in PKD_2 null mIMCD3 cells (Figure1C). Low dose Yoda1 (750nM) prevented cyst formation in forskolin-induced cystogenesis of metanephric organ culture (Figure1D).

Conclusions: Piezo1 activation inhibits cystogenesis in matrigel matrices and metanephric organ cultures. Further studies are required to determine *in vivo* effect of Piezo1 on renal cystogenesis.

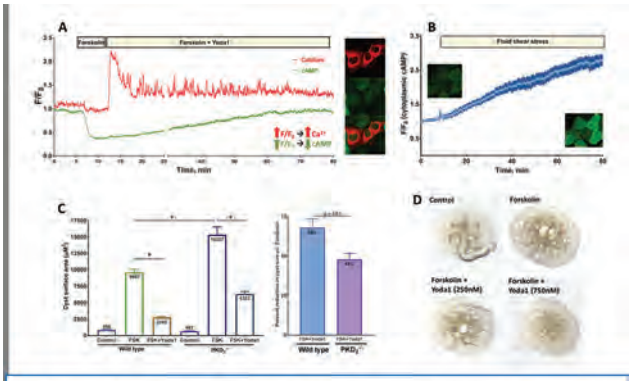

Figure 1: Effect of Piezo1 and fluid shear stress on calcium, cAMP, and cystogenesis. A) Forskolin increased cAMP levels (F/F0 decreased indicating increase in cAMP level). Treatment of cells with both forskolin and Yoda1 led to an increase in cytoplasmic calcium and simultaneously decreased cAMP back to baseline. **B)** FSS gradually decreases cAMP level (Light blue trace is mean F/F0 and dark blue is SD, n=8). **C)** mIMCD3 cells were grown in 3D matrigel and incubated with defined medium (control) +/- forskolin (10uM) and Yoda1 (10uM) for 5 days. Yoda1 reduced forskolin-induced cyst size by 68% in WT and by 48% in PKD2 null cells compared to forskolin alone. D) Yoda1 prevented forskolin-induced cyst formation at a dose of 750 nM.

TH-OR105

Enhanced Protein Folding via XBP1 Activation Ameliorates ADPKD Due to PC1 Misfolding

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Background: *Pkd1* is one of the two genes responsible for autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, ~30% of mutations are missense predicted to result in reduced PC1 function. *XBP1* encodes the main chaperone modulator of the ER unfolded protein response. Here we investigated the role of XBP1 as a "genetic" chaperone therapy which may affect the levels of functional PC1 carrying patient derived missense mutations using the p.R2220W human REJ mutant (p.R2216W in mouse) as a representative candidate.

Methods: The effect of XBP1 on the expression and trafficking of the PC1-R2220W-V5 mutant was determined *in vitro*. A *Pkd1*^{R2216W} knock-in mouse model was generated. Using this backbone, *Pkd1*$^{R2216W/fl}$*;Pkhd1-Cre* and *Pkd1*$^{R2216W/fl}$*;Pkhd1-Cre;XBP1-Rosa-floxstop-TG* mice were examined by morphological, functional and biochemical analyses.

Results: Expression of XBP1 in transiently cells expressing PC1-R2220W-V5 leads to increased expression and GPS cleavage of the mutant protein. Ciliary trafficking of PC1-R2220W was markedly improved by co-expression of XBP1 as compared with PC1-

R2220W alone. At P16, *Pkd1$^{R2216W/fl}$;Pkhd1-Cre* mice developed cystic disease compared with *Pkd1$^{R2220W/+}$* animals as seen via a significant increase in renal parameters [KW/BW, 0.01±0.001 vs. 0.13±0.008, ****p<0.0001; BUN, 33.35±4.44 vs. 102.2±26.4, **p=0.0042; n=10, 7]. Expression of the conditional XBP1 transgene in *Pkd1$^{R2216W/fl}$;XBP1-TG;Pkhd1-Cre* mice at P16 led to a significant decrease in the cystic burden compared to the controls [KW/BW, 0.07±0.006 vs. 0.13±0.008, ****p<0.0001; BUN 50.57±8.47 vs. 102.2±26.49, *p=0.027, n=10, 7]. Using TUNEL and Ki67 assays we found that induction of XBP1 in the cyst lining cells led to a significant reduction in proliferation with no impact on apoptosis suggesting that the improved cystic phenotype in the *Pkd1$^{R2216W/fl}$;XBP1-TG;Pkhd1-Cre* animals is due to a reduction in cyst growth.

Conclusions: Our data raises the possibility that *in vivo* chaperone therapy for the treatment of ADPKD may have a beneficial role for a subset of PC1 missense mutations.

Funding: NIDDK Support, Private Foundation Support

TH-OR106

Cystic Epithelial Cells Modify Their Microenvironment to Promote Fibrosis in Polycystic Kidney Disease

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Background: Progressive tubulo-interstitial fibrosis accompanies cyst expansion in polycystic kidney disease (PKD) and is a major cause for loss of renal function and end stage renal disease. However, the mechanisms for development of renal fibrosis in PKD are currently unclear. A significant number of myofibroblasts, the primary producers of ECM, are often found in the pericystic areas in PKD kidneys. We tested the hypothesis that cystic epithelial cells can activate interstitial myofibroblasts and thus modify the cystic microenvironment to promote fibrosis.

Methods: Renal tubular epithelial-specific vasopressin type-2 receptors (V2R) were stimulated or inhibited in pre-weaning and adult inducible conditional Pkd1 gene knockout mice with cystic kidneys. Wild type and PKD mice were treated with the V2R agonist dDAVP, or the antagonist OPC31260 by daily intraperitoneal injections for 3 days.

Results: Treatment with dDAVP increased myofibroblast numbers and ECM deposition in PKD mouse kidneys, while OPC31260 had the opposite effect. Expression of connective tissue growth factor (CTGF), a matricellular protein, and its transcriptional regulator YAP were increased in the dDAVP treated PKD mouse kidneys. CTGF and YAP were expressed in mouse and human ADPKD renal cystic epithelium, and CTGF secreted by cultured human ADPKD epithelial cells induced myofibroblast activation and migration in vitro. In contrast, YAP inactivation by pharmacological inhibition or renal tubule specific gene deletion suppressed CTGF production and cyst expansion in vitro, and the development of fibrosis in Pkd1 knock out mice.

Conclusions: These results suggest that epithelial specific V2R stimulation can induce YAP dependent CTGF production to activate interstitial myofibroblasts and renal fibrosis in PKD.

Funding: NIDDK Support

TH-OR107

A Central Role of the Enzyme Asparagine Synthetase (ASNS) in Driving Glutamine Anaeplerosis in the Metabolic Rewiring of ADPKD

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Background: We showed that the Warburg effect is a feature of PKD. However, additional pathways involved in the metabolic deregulation of ADPKD are likely present. Here, we explore global metabolomics and isotope tracing experiments to identify new targetable metabolic pathways in PKD.

Methods: 16 newborn (P4) kidneys of *Ksp-Cre;Pkd1$^{flox/-}$* mice and their respective littermate controls were collected. Metabolomics was performed with LC-mass spectrometry (MS). Tracing studies with ^{13}C-labeled carbons from glucose or glutamine were performed in *Pkd1*-mutant cells, using LC-MS.

Results: Metabolomics screen identified 488 significantly altered metabolites. PCA and HCA showed a clear separation between cystic and control samples. The alterations included glycolysis, fatty acid oxidation and biosynthesis, and massive TCA cycle. To test which energy source was fuelling the accumulation of TCA cycle metabolites, alternate labelling with [$^{13}C_6$] glucose or [$^{13}C_5$,$^{15}N_2$] glutamine was performed *in-vitro*. *Pkd1$^{-/-}$* cells had an enhanced glucose uptake, mostly used to produce lactate and minimally funneled into the TCA cycle. To compensate, *Pkd1$^{-/-}$* cells uptake more glutamine and use it both oxidatively and reductively in the TCA cycle to drive fatty acids biosynthesis. Following the fate of the $^{15}N_2$-glutamine, we found a significant increase of ^{15}N-labelled asparagine in *Pkd1$^{-/-}$* cells suggesting that they exhibit increase asparagine synthesis from glutamine. This reaction is catalyzed by Asparagine synthetase (ASNS). Indeed, *Asns* was upregulated in *Pkd1$^{-/-}$* cells and *KspCre;Pkd1* kidneys. Tracing with $^{15}N_2$ and $^{13}C_5$-glutamine showed that silencing of *Asns* reduced significantly the levels of labelled asparagine and glutamine-derived α-KG. Importantly, the down-regulation of *Asns* reduced growth in *Pkd1$^{-/-}$* cells, but not in controls. Combination with glucose starvation was lethal in *Pkd1$^{-/-}$* cells. Microarray analysis on *Pkd1* mutant kidneys (*Pkd1$^{V/V}$*) and human *PKD1* samples confirmed upregulation of ASNS and further validated the global metabolic perturbations observed.

Conclusions: Our data show that increased glutaminolysis, interlinked with asparagine metabolism is an important feature of PKD and targeting ASNS might offer a novel therapeutic opportunity.

TH-OR108

CD8+ T-Cells Regulate Progression of Autosomal Dominant Polycystic Kidney Disease

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Background: Therapeutic strategies to treat Autosomal Dominant Polycystic Kidney Disease (ADPKD) have largely focused on targeting abnormal renal epithelial cell signaling. In cancer, a disease with many parallels to ADPKD, modulating the activity of cells within the microenvironment, specifically CD8$^+$ T-cells, has shown remarkable therapeutic effects. However, the role of CD8$^+$ T-cells and their potential as a novel therapeutic target in ADPKD has not been well studied.

Methods: Using the murine ADPKD model *Pkd1* p.R3277C [RC], as well as stored human ADPKD/Autosomal Recessive PKD (ARPKD) kidney tissue, we explored the role of renal CD8$^+$ T-cells via flow cytometry, *in situ*/immunofluorescence (IF) imaging, qPCR, and pharmacological intervention.

Results: Using flow cytometry and IF, we previously showed that CD8$^+$ T-cells increase in numbers, become selectively activated, and localize to cystic regions in *Pkd1$^{RC/RC}$* vs. wildtype (WT) kidneys. Further, CD8$^+$ T-cell depletion worsened PKD pathology in *Pkd1$^{RC/RC}$* mice. By *in situ* hybridization we now show that *Pkd1$^{RC/RC}$* interstitial and cystic epithelial cells express higher levels of CD8$^+$ T-cell recruiting chemokines (*Cxcl9/Cxcl10*) vs. WT, implying active recruitment of CD8$^+$ T-cells to cystic lesions. We confirmed these findings in human ADPKD/ARPKD vs. healthy control kidneys and demonstrated *in vitro* that human *PKD1$^{-/-}$* renal epithelial cells have higher basal *CXCL9/10* levels, as well as a greater increase in response to IFNg vs. *PKD1$^{+/+}$* cells. To understand how CD8$^+$ T-cells may halt cyst progression, we performed TUNEL and PCNA staining in *Pkd1$^{RC/RC}$* anti-IgG and anti-CD8 treated animals. Mice depleted of CD8$^+$ T-cells had fewer apoptotic and more proliferating cystic epithelial cells vs. control, consistent with CD8$^+$ T-cell-mediated cytotoxicity and IFNg-induced reduction in proliferation.

Conclusions: These data indicate that CD8$^+$ T-cells are recruited specifically to cystic lesions via chemokine production by interstitial and cystic epithelial cells and halt ADPKD progression through modulating cyst expansion via apoptosis/proliferation. Hence, therapeutic strategies aimed at increasing CD8$^+$ T-cell numbers/activity may represent novel treatment approaches to slow ADPKD progression.

TH-OR109

CD4 T Cells Promote Cystic Kidney Disease

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Background: The majority of renal cystic diseases are caused by mutations in proteins localized to the primary cilia or proteins required for cilia assembly. Previous data indicate that renal injury markedly accelerates cyst formation and that macrophage numbers are increased prior to and during cyst formation. Depletion of macrophages reduces renal cysts in multiple models of cystic kidney disease. These data led to the hypothesis that cilia and cilia-related proteins regulate innate immune response and cystic disease following renal injury. However, the involvement of adaptive immune cells in renal injury induced cystic disease remains unknown.

Methods: We set out to identify and define the contribution of adaptive immune cells, particularly CD4 T cells, in an ischemia reperfusion injured cilia mutant model of renal cyst formation and in human patients with autosomal dominant polycystic kidney disease (ADPKD).

Results: Our data show that CD4 T cell numbers are increased prior to the formation of renal cysts and are located in regions adjacent to cysts in conditional cilia mutant mice following injury. Further subtyping of CD4 T cells shows that IL-17A producing CD4 T cells (Th17 cells) are increased prior to the formation of renal cysts whereas T regulatory cells (Tregs) are increased during periods of rapid cyst progression. These data suggest that Th17 cells may contribute to the initial stages of cyst formation whereas Tregs may promote cyst expansion. In support of this idea, genetic deletion of adaptive immune cells (RAG1-/- mouse) or pharmacological depletion of CD4 T cells reduced renal cyst formation. These results are complemented by studies in ADPKD patients where we found an increased number of CD4 T cells in regions adjacent to developing cysts. In addition, our preliminary studies revealed the highest serum levels of IL-17A in young ADPKD patients (<30 yrs old) suggesting that, similar to the mouse model, the number of Th17 cells is also highest in early stages of ADPKD. In contrast, PKD patients with ESRD had increased numbers of Tregs, resembling our data obtained in the mouse. Finally, we point to urinary CD4 T cells as a predictor of renal function decline in ADPKD.

Conclusions: Our results suggest that CD4 T cells are an integral component of renal cystic disease and a candidate marker of the disease activity in ADPKD.

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TH-OR110

Bimodal Activation of Macrophages Promotes Proliferation Independent and Dependent Cyst Expansion in PKD

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Background: Macrophages progressively accumulate adjacent to cyst lining cells in PKD. Macrophage chemoattractant protein-1 (Mcp1) is highly upregulated at the time of cyst initiation following knock-out of Pkd1, and dual deletion of *Mcp1* and *Pkd1* in renal tubules results in less renal macrophages, slower cyst growth, preserved GFR and better survival than deletion of *Pkd1* alone. The current study addresses the mechanisms by which the Mcp1-induced macrophages promote cyst growth.

Methods: Expression profiling was performed by qPCR using RNA from whole kidney and flow sorted macrophages. Multiphoton microscopy was used to analyze tubule morphology from doxycycline-treated *Mcp1$^{fl/fl}$Pkd1$^{fl/fl}$Pax8rtTA;TetOCre* mice (DKO) and *Pkd1$^{fl/fl}$Pax8rtTA;TetOCre* mice (SKO). Tubular cell responses were analyzed using Ki67, BrdU, comet assay and anti-8OHdG staining.

Results: Macrophages that accumulate at cyst initiation (8 weeks age, 2 weeks after doxy induction) express high levels of proinflammatory cytokines Tnfa, Nos2 and IL12, correlating with increased tubular cell injury as judged by Kim1 expression (SKO dCt 0.002 vs DKO dCt 0.0005, p=0.002) and oxidative DNA damage (14.4% 8OHdG$^+$ cells in SKO vs 3.6% in DKO, p=0.009). Analysis of tubular cell proliferation rates and tubule morphology in SKO and DKO kidneys during at cyst initiation shows that the macrophage-dependent component of cyst growth corresponds to decreased tubular epithelial area (tubular cell flattening consistent with injury) and enlarged tubule area (tubule/epithelial area ratio of 3.8±1.0 in SKO vs 1.04±0.02 in control and 1.4±0.5 in DKO p<0.0001) rather than proliferation. At the late cystic stage (18 weeks age), macrophages express high levels of the alternative activation genes Arg1 and Mrc1, with a 3-fold increase in Ki67+ cells in the presence of macrophages (6.4±0.6 in SKO vs. 1.8±0.8 in DKO, p<0.0001), correlating with a late acceleration in cyst growth in the SKO kidneys.

Conclusions: The results demonstrate two distinct effects of macrophages: early proinflammatory induction of tubule cell injury and tubule dilation that is proliferation independent and late alternative activation mediated induction of proliferation-dependent cyst growth.

TH-OR111

AKI in Pediatric Sepsis Is an Independent Risk Factor for Death and New Substantive Disability

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Background: Acute kidney injury (AKI) is common in critically ill children. The incidence of septic AKI and its impact on PICU survivor functional status are unknown. We used data from a multicenter cohort with sepsis to evaluate functional outcomes of children with AKI.

Methods: Using the prospective Life after Pediatric Sepsis Evaluation (LAPSE) study [R01HD073362], we evaluated the association of AKI with a composite of death or new substantive functional disability at day 28 of hospitalization or discharge as a primary outcome. We defined AKI using KIDGO criteria, comparing patients with no AKI or Stage 1 AKI to those with Stage 2 or 3 AKI (Severe AKI). New substantive disability was defined as a Functional Status Scale (FSS) score increase ≥3 points from baseline to 28 days. Wilcoxon rank-sum and likelihood ratio tests were used to compare variable associations between groups. We used multivariable logistic regression to assess the association of AKI with outcomes.

Results: 176 (50.5%) of 348 patients had severe AKI; of those, 38 (21.6%) required renal replacement therapy. Patients with severe AKI had higher median PRISM III scores (excluding creatinine) (12 vs 8; p<0.001), and were treated more often with vasoactive agents (97.7 vs 91.9%; p=0.011), blood products (65.3 vs 44.8%; p<0.001), and corticosteroids (74.4 vs 61.0%; p=0.007). Twice as many patients with severe AKI died or developed new substantive disability (38.1 vs 16.3%; p<0.001). Children with severe AKI had longer PICU stays (11.7 vs 7.1 days; p<0.001), and longer duration of mechanical ventilation (11.0 vs 7.0 days; p<0.001). After adjustment for age, malignancy, and PRISM III score, severe AKI was independently associated with mortality or new substantive disability (adjusted odds ratio 2.77; 95% CI 1.63–4.81, p<0.001). Despite similar baseline FSS scores, children who survived with severe AKI had a greater sustained change in FSS scores at 28 days or hospital discharge than those without AKI (adjusted effect 1.35; 95% CI 0.27–2.43; p=0.014).

Conclusions: In critically ill children with sepsis, severe AKI is common and is independently associated with increased risk of death or new substantive disability. Survivors of sepsis with severe AKI were more likely to have persistent decreased functional status at discharge than those without severe AKI.

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TH-OR112

Long-Term Outcomes after AKI Requiring Dialysis Among Neonates and Children in Ontario: A Population-Based Study

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Background: There is limited knowledge on the long-term impact of an episode of acute kidney injury requiring dialysis (AKI-D) among neonates and children.

Methods: Using health administrative databases housed at the Institute for Clinical Evaluative Sciences, we conducted a retrospective cohort study of all hospitalized neonates and children who received dialysis for AKI across Ontario between 1996 and 2015 and survived to hospital discharge (exposed cohort). We assembled a comparator cohort (up to 4 neonates and children without AKI-D for every patient with AKI-D) matched on demographics and comorbidities. Primary outcomes were all-cause mortality and end-stage renal disease (ESRD, defined as receipt of chronic dialysis or a kidney transplant) and secondary outcomes were *de novo* CKD and hypertension. Incidence rates (IR) were calculated and Cox proportional hazards models were fitted for all outcomes.

Results: There were 466 neonates and 1641 children hospitalized with AKI-D in Ontario between 1996 and 2015, of whom 356 neonates and 1500 children, had matched counterparts without AKI-D. The median follow-up time was 9.2 years (Interquartile Range (IQR) 4.7,12.0) for neonates and 12.4 years (IQR 5.8,16.9) for children. After adjusting for confounders, survivors of AKI-D during the neonatal period had a 21-fold risk of death and a 7-fold higher risk of hypertension, as compared to neonates with no AKI-D. Similarly, children surviving an episode of AKI-D had a higher risk of death, CKD and hypertension as compared to hospitalized children who did not experience AKI-D. (Table 1).

Conclusions: Neonates and children with AKI-D remain at higher risk of long-term adverse outcomes compared to those without AKI-D suggesting that they need a close follow-up after discharge.

	Neonates							
	AKI-D cohort			Comparator cohort				
Primary	N	Person-years (p-y)	IR per 1000 p-y	N	Person-years (p-y)	IR per 1000 p-y	Unadjusted HR (95% CI)[$]	Adjusted[#] HR (95% CI)
ESRD	356		NR			NR	NC[#]	NC
All-cause Mortality	356	2778.7	14.0	1412	12088.6	1.1	12.6 (6.6, 24.1)	20.8 (2.4, 177.5)
Secondary								
De novo CKD	356	2682.3	7.8	1412	NR	0.3	20.8 (7.1, 60.5)	NC
De novo Hypertension	356	2419.1	26.5	1412	11897.5	2.4	8.7 (5.6, 13.6)	6.7 (2.1, 21.6)
	Children							
Primary								
ESRD	1500	16060.0	1.6	5813	NR	0.06	24.1 (7.2, 80.9)	NC
All-cause Mortality	1500	16258.3	7.9	5813	68122.8	0.9	8.53 (6.2,11.7)	5.1 (3.5, 7.6)
Secondary								
De novo CKD	1478	14431.7	12.7	5776	67291.7	0.7	18.2 (12.8, 25.7)	14.8 (9.9, 21.9)
De novo Hypertension	1461	14034.8	17.8	5710	64548.3	5.5	3.2 (2.7, 3.8)	2.4 (1.9, 2.9)

*Not reported (NR) due to the ability to calculate small cells <6
[$]All outcomes were significant at P <0.0001
[#]Adjusted for cardiac surgery, sepsis, and mechanical ventilation during the index hospitalization
[#]Not calculated (NC) due to low event rate

Table 1: Incident rates and hazard ratios of long-term adverse outcomes among neonates and children with AKI-D in Ontario between 1996 and 2015

TH-OR113

Multiple Episodes of AKI and Their Association with Kidney Function and Death

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Background: Recurrent AKI may mediate the risk for future CKD outcomes. Prior studies on recurrent AKI lacked appropriate controls. We compared the incidence of future AKI between hospitalized AKI and nonAKI patients and the impact of AKI on kidney disease progression.

Methods: ASSESS-AKI is a prospective multi-center study of matched AKI and non-AKI patients followed longitudinally beginning 3 months after initial hospitalization. AKI was defined as a 0.3 mg/dl or 50% increase in baseline serum creatinine during subsequent hospitalizations. The determinants of future AKI were examined using multivariate Cox regression. Outcomes included time to event for (1) a composite renal outcome of incident or progressive CKD or ESRD, and (2) the competing risk of death. Predictors of outcome were examined using a multivariable trivariate Weibull regression model, along with a zero-inflated Poisson regression model for the number of AKI events prior to the composite renal endpoint.

Results: Among 769 matched pairs of AKI and non-AKI patients, 465(30%) experienced a future AKI episode over a median follow-up of 57 months. Future AKI was more common among patients with AKI compared to nonAKI status at index hospitalizations, with 8 compared to 5 AKI episodes per 100 person-years (PYs)($p < 0.0001$). After multivariate adjustment, index AKI remained independently associated with the risk for future AKI [aHR 1.5 (95%CI:1.2-1.8)]. The rates of the composite renal outcome were 2, 5, and 6 per 100 PYs among patients with 0, 1, and ≥2 episodes of AKI ($p < 0.0001$). The rates for death prior to a CKD event were 2, 4, and 9 among patients with 0, 1, and ≥2 episodes of AKI ($p < 0.0001$). After multivariable adjustment, the presence of 1 and ≥2 episodes of AKI conferred an increased risk for the CKD outcome [aHR 3.3(2.2-4.9) and 2.8(1.8-4.2)], respectively, compared to patients without AKI. There were incremental increases in the risk of death prior to a CKD event with 1[aHR 1.7(1.2-2.6)] and ≥2[aHR 2.8(1.8-4.2)] episodes of AKI compared to no AKI.

Conclusions: AKI is an independent risk factor for future hospitalized AKI and loss of kidney function. The association between multiple AKI events and future CKD outcomes may be affected by the competing risk of death.

Funding: NIDDK Support

TH-OR114

Post-Discharge Long-Term Cardiovascular Outcome of Dialysis Requiring AKI after Cardiac Surgery

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Background: Dialysis requiring acute kidney injury (AKI-D) is one of the serious complications following the cardiac surgery and it is known to increase in short-term in hospital mortality. Nevertheless, long-term prognosis and risk of major cardiovascular events (MACE) has not been examined yet.

Methods: We conducted a nationwide, population-based cohort study using the data of Korean National Health Insurance System. Adult patients who underwent cardiac surgery in tertiary hospitals between 2006 and 2015 were considered. Patients previously received dialysis were excluded. Then, the patients were divided into those who underwent dialysis after cardiac surgery and those who did not.

Results: Of 52,803 patients received cardiac surgery, 1,261 underwent dialysis during the perioperative period of cardiac surgery. All-cause mortality [adjusted hazard ratio (HR) 2.93 (2.65-3.23), P<0.001], progression to end-stage renal disease (ESRD) [adjusted HR 15.95 (13.89-18.33), P<0.001] and risk of MACE [adjusted HR 2.26 (2.04-2.51), P<0.001] were increased in AKI-D group (Figure 1). In the AKI-D group, all-cause mortality [adjusted HR 1.07 (0.83-1.38), P=0.593] and the risk of MACE [adjusted HR 1.25 (0.94-1.67), P=0.126] were comparable between the continuous renal replacement therapy (CRRT) and intermittent renal replacement therapy (IRRT) group.

Conclusions: Patients required dialysis after the cardiac surgery were associated with high all-cause mortality and rate of dialysis dependence. Although AKI-D patients independently survive, they persistently had increased risk of MACE development. Despite higher patient severity in patients requiring CRRT, outcomes among these patients were not deteriorated, compared to IRRT group.

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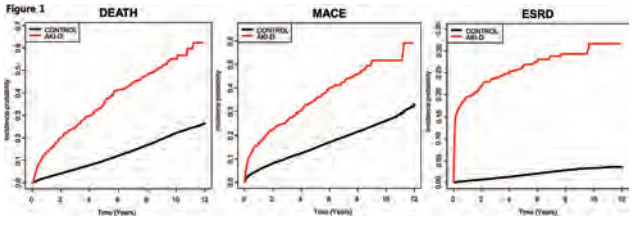

The x-axes represent the time (years), and the y-axes represent the incidence probability. The black, and red lines represent the survival curves of the control, and AKI-D groups, respectively.

TH-OR115

Outcomes after Left Ventricular Assist Device Implantation in Patients with AKI

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Background: Left ventricular assist devices (LVAD) are increasingly used as a bridge to heart transplant and destination therapy for heart failure. Although acute kidney injury (AKI) is a common complication in these patients, there are few multicenter studies on how AKI affects LVAD outcomes. We sought to determine outcomes associated with AKI among patients receiving LVADs in a nationally representative sample of hospitalizations in the US.

Methods: Using the National Inpatient Sample from 2008 to 2013, we identified patients who received a LVAD during a hospitalization using ICD-9 code 37.66. We ascertained AKI and acute dialysis using validated ICD-9 codes. The primary outcome was in-hospital mortality. Secondary outcomes included procedural complications and discharge destination. We used logistic regression to adjust for demographics, hospital-level factors, comorbidities, and acute hospitalization details.

Results: We identified 8362 patients who received a LVAD, of whom 3760 (45%) developed AKI without dialysis (AKI-ND) and 426 (5%) developed AKI-requiring dialysis (AKI-D). In-hospital mortality increased from 4% for patients without AKI, to 12% for patients with AKI-ND, to 48% for patients with AKI-D. We observed similar increases for major bleeding (25% vs 33% vs 49%) and sepsis (9% vs 22% vs 43%). Discharge destination was home for 84% of patients without AKI, 72% of patients with AKI-ND, and 56% of patients with AKI-D. After multivariable adjustment, patients with AKI-ND and AKI-D had higher odds of mortality (OR 3.24, 95% CI 2.04-5.13 and 20.8, 95% CI 9.7-44.2), major bleeding (1.38, 95% CI 1.08-1.77 and 2.43, 95% CI 1.47-4.04), sepsis (2.69, 95% CI 1.93-3.75 and 5.75, 95% CI 3.46-9.56), and discharge to a nursing facility (2.15, 95% CI 1.51-3.07 and 5.89, 95% CI 2.67-12.99). Patients with AKI-ND and AKI-D on mechanical ventilation had a markedly increased adjusted odds of death (14.2, 95% CI 7.5-26.9 and 90.9, 95% CI 41.4-199.6). None of the patients with AKI-D received a heart transplant during the same hospitalization as LVAD implantation.

Conclusions: During a hospitalization in which a LVAD is implanted, patients with AKI are at increased risk of procedural complications and death. The prognosis is particularly poor for patients with AKI-D. This information is necessary to support shared decision-making for patients with advanced heart failure and AKI.

TH-OR116

AKI Is Associated with an Increased Risk of Dementia

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Background: Acute kidney injury (AKI) is associated with long-term adverse outcomes including development of chronic kidney disease, cardiovascular disease and mortality. Acute neurologic complications of acute kidney injury are well described but the long-term consequences of AKI on neurologic outcomes are unclear. We tested the hypothesis that AKI, even with complete kidney function recovery, is associated with a higher risk of developing dementia.

Methods: We performed a retrospective propensity score-matched analysis of 2,082 patients without prior history of dementia from an integrated health care delivery system in Utah, who had a hospital admission between January 1, 1999 and December 31, 2009. AKI was defined by ICD-9 codes and AKI Network serum creatinine values. 1041 patients with AKI followed by complete recovery, defined as discharge creatinine <1.10 times the pre-admission baseline value, were propensity score-matched with 1041 patients without AKI during the index admission. Dementia was defined by ICD-9 codes. Demographic, baseline serum creatinine, prior inpatient visits, season of admission, and all components of the Charlson Comorbidity index were used to generate the propensity score. Proportional hazards analysis was used to compare time to dementia among patients with and without AKI.

Results: After propensity score matching, covariates were well balanced between the groups. The mean (SD) age and baseline creatinine was 61 ± 16 years and 0.9 ± 0.2 mg/dL, respectively. During a median follow-up time of 5.8 years, 97 patients developed dementia. More patients with AKI developed dementia (7.0% vs. 2.3%). Patients with AKI had more than a 3-fold increased risk of developing dementia compared to those without AKI (Hazard Ratio 3.4, 95% CI 2.14 to 5.40).

Conclusions: AKI, even with complete kidney recovery, is associated with a significantly increased risk of hospitalized dementia. Further studies are needed to examine the association of AKI with cognitive dysfunction.

Funding: Other NIH Support - NHLBI

TH-OR117

Recognizing Sepsis: A High-Throughput Non-Invasive Assessment Using Machine Learning and Urinary MicroRNAs

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Background: Identifying early differences between Systemic Immune Response Syndrome, SIRS, and sepsis remains at the fulcrum of surviving sepsis: without early identification, shock and eventual death ensues. MicroRNAs (miRNAs) are non-coding RNAs that regulate gene expression. Given their selective secretion and extensive role in cellular communication, miRNAs have been utilized in diagnosis, prognosis, and therapeutics in various disciplines of medicine. As the kidneys are one of critical organs affected by sepsis, we surveyed the miRNA population in urine at the time of sepsis. Here we isolate urinary exosomes to identify miRNAs that are associated with sepsis in comparison to patients with vascular disease prior to surgery serving as a control group.

Methods: We collected urine samples from 41 patients within 12 hours of sepsis onset and 29 control patients. Using exosomal isolation protocol (Norgen), we extracted miRNAs from urine supernatant. Subsequently, we utilized Affymetrix® RNA Labeling Kit and GeneChip Arrays to obtain expression values of 2,578 miRNAs in each patient. For machine learning, we randomly divided patients into 70% training set for feature selection of microRNAs and prospectively tested the performance in the validation set (30%) using area under the receiver operating curve (AUC).

Results: 94 miRNAs were dysregulated in sepsis ($\log_2$FC > 1, p-value < 0.01). 29 miRNAs were highly associated with the septic cohort. Testing the performance of these miRNAs, the validation set performed well with an AUC of 0.94 (95% CI 0.84 - 1.00). Among these, mir-455 is validated to induce hypoxia signaling, whereas mir-3201 upregulates monocyte chemoattractant protein. The mir-548 family is extensively intercalated in the network of TLR signaling, a pathway at the foundation of sepsis.

Conclusions: Uniting machine learning with miRNA arrays allowed us to identify dysregulated miRNAs and peer deeper into the specific pathways activated at the time of sepsis. Actively, we are utilizing this methodology to delineate expression patterns in septic patients as compared to SIRS+ and control groups to further define the fulcrum between SIRS and sepsis.

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TH-OR118

The Circular RNA ciRs-126 Predicts Survival in Critically Ill Patients with AKI

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Background: Circular RNAs (circRNAs) have recently been described as novel non-coding regulators of gene expression. They might impact on microRNA expression by their sponging activity. The detectability in blood of these RNA transcripts has been demonstrated in patients with cancer and cardiovascular disease. We tested the hypothesis, that circulating circRNAs in blood of critically ill patients with acute kidney injury (AKI) at inception of renal replacement therapy may also be dysregulated and associate with patient survival.

Methods: We performed a global circRNA expression analysis using RNA isolated from blood of patients with AKI as well as controls. This global screen revealed several dysregulated circRNAs in patients with AKI. Most highly increased circRNA-array-based transcripts as well as expression of the circRNA target miR-126-5p were confirmed in blood of 109 patients with AKI, 30 age-matched healthy controls, 25 critically-ill non-AKI patients and 20 patients on maintenance hemodialysis by quantitative realtime-PCR.

Results: Circulating concentrations of 3 novel circRNAs were amplified in blood of patients with acute kidney injury and controls. *Circular RNA sponge of miR-126* (or ciRs-126) was most highly altered compared to healthy controls and disease controls (fold change of 52.1). *CiRs-126* was shown to bioinformatically sponge miR-126-5p, which was found to be highly suppressed in AKI patients and hypoxic endothelial cells. Cox regression and Kaplan-Meier curve analysis revealed *ciRs-126* as an independent predictor of 28-day survival (p<0.01).

Conclusions: Circulating concentrations of circRNAs in patients with acute kidney injury are detectable. *CiRs-126* may potentially sponge miR-126-5p and acts as a predictor of mortality in this patient cohort.

TH-OR119

The Furosemide Stress Test Predicts Severe AKI: A Multicenter Validation

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Background: The Furosemide Stress Test (FST) has been previously shown to predict which patients with Stage 1 or 2 AKI will progress to Stage 3 AKI.

Methods: We conducted a prospective multicenter validation of the FST at 5 centers across North America. Euvolemic or hypervolemic patients with Stage 1 & 2 AKI were given 1 or 1.5 mg/kg of intravenous furosemide, depending on prior exposure. Hourly urine output (UOP) was measured for 6 hours (hrs) to validate the previously published cutoff of 200 ml of urine in the first 2 hrs as well as to explore other cutoffs. We assessed the ability of the FST to predict the development of KDIGO Stage 3 AKI (primary endpoint – 200% increase in serum creatinine or receipt of renal replacement therapy (RRT)) and just the receipt of RRT, as well as occurrence of adverse events.

Results: We prospectively enrolled 92 patients with Stage 1 or 2 AKI who received a mean(SE) dose of 108(3.7) mg of furosemide. Twenty-three (25%) patients developed subsequent Stage 3 AKI, with 10 (11%) receiving RRT. There was no difference in baseline serum creatinine or eGFR, dose of furosemide, cardiovascular SOFA score or APACHE II score between those with and without Stage 3 AKI. Patients who progressed had significantly lower UOP in the 6hrs before the FST (median[IQR]) (241[93-357] compared to 336[199-578] p=0.024). The total UOP for the first 2hrs post-FST provided an AUC(SE) of 0.85(0.05) for progression to stage 3 (p<0.001) and 0.73(0.10) for RRT (p<0.05) (Table) UOP of less than 200ccs in the first 2hrs was 89.8% specific for AKI progression. In terms of adverse events, hypotension developed in 9(10%) patients post FST and 5(6%) patients developed hypokalemia and 5(6%) patients developed hypophosphatemia.

Conclusions: In this multicenter validation, the 2 hour total UOP following FST predicted the progression to Stage 3 AKI and the need for RRT. UOP of less than 200 cc in the first 2hrs post-FST is a highly specific for progression to Stage 3 AKI, while less than 400 cc is highly sensitive for AKI progression.

Funding: Commercial Support - Satellite Healthcare

Sensitivity Analysis for 2 hour UOP following FST to predict Stage 3 AKI

2 hr UOP Cutoff (ccs total)	Sensitivity	Specificity
<100	43.4%	94.2%
<200	73.9%	89.9%
<300	82.6%	84.1%
<400	87.0%	62.3%

TH-OR120

Impact of Echocardiographic Parameters on Mortality in ICU Patients Undergoing CRRT

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Background: Echocardiographic abnormalities have been associated with adverse outcomes in various Intensive care unit (ICU) populations. However, the impact of echocardiographic abnormalities on the prediction of mortality in patients undergoing continuous renal replacement therapy (CRRT) has not been examined.

Methods: Historical cohort study of consecutive adults admitted to the ICUs at one tertiary care hospital from December 2006, through November 2015 who underwent CRRT and had an echocardiogram done within 7 days of CRRT initiation. The primary outcome was 30-day death rate. Logistic regression was used to determine predictors of 30-day mortality.

Results: We included 1,276 patients, 1,040 (81.5%) with acute kidney injury (AKI) and 236 (18.5%) with end-stage renal disease (ESRD). Median patient age was 63 (IQR 53-73) years, and 514 (40%) were female, median Charlson score was 5 (IQR 3-7), and median SOFA score on the day of CRRT initiation was 12 (IQR 10-14). Echocardiographic parameters associated with 30-day mortality on univariate analysis included: Moderate or greater right ventricular (RV) dysfunction (OR 1.47, 95% CI: 1.08-1.60), moderate or greater tricuspid regurgitation (OR 1.67, 95% CI: 1.26 – 2.21) and right ventricular systolic pressure (RVSP) (OR 1.12 per 10 mmHg increase, 95% CI: 1.02-1.23). RV dysfunction (OR 1.54, 95% CI: 1.02-2.32) and tricuspid regurgitation (OR 1.55, 95% CI:1.02-2.32) remained significantly associated with 30-day mortality after adjusting for age, sex, SOFA score, Charlson comorbidity index, need for mechanical ventilation, type of ICU, fluid balance and AKI vs. ESRD using logistic regression analysis.

Conclusions: RV dysfunction and tricuspid regurgitation are associated with increased mortality in patients undergoing CRRT, emphasizing the importance of cardiorenal syndrome among critically-ill patients. Further study will be needed to determine if RV dysfunction is a risk marker or a modifiable risk factor in this patient population.

TH-OR121

Impact of Obesity on Kidney Transplant Outcomes: A Paired-Kidney Analysis

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Background: The prevalence of obesity is increasing in prospective kidney transplant recipients (KTRs). The impact of recipient obesity on long term outcomes is not clear. We sought to evaluate the associations of recipient body mass index (BMI) with transplant outcomes using a paired-kidney model.

Methods: UNOS data were used to identify all deceased donors between 1/2006 and 12/2016 in which each kidney was used for kidney-alone transplant. Recipient BMIs were classified as: 18-25, >25-30, >30-35, and >35 (reference category). Hazard ratios (HR) for graft failure (GF), death-censored GF (dcGF), and patient death were obtained by marginal survival models adjusted for pairing by donor. Odds ratios (OR) for delayed graft function (DGF) were obtained by conditional logistic regression models. Models were adjusted for recipient and transplant factors.

Results: 39,334 paired recipients were evaluated, of whom 4,949 (12.6%) had BMI>35. Median follow up was 43.9 (IQR=22.3-71.8) months, with graft failure in 11.9% and death in 11.0%. Results for adjusted models are shown in table. Compared to patients with BMI>35, patients with BMI 18-25 had lower hazards for both GF and dcGF, but not for death. Patients with BMI >25-30 had lower dcGF. No significant differences seen between BMI >30-35 and BMI>35 for GF, dcGF or death. The odds of DGF were significantly decreased in all BMI groups, compared to BMI>35.

Conclusions: Our paired kidney analysis among a large national transplantation dataset found similar long-term graft and patient outcomes among KTRs with BMI >35 compared to those with BMI 30-35, despite increased DGF. Higher rates of dcGF among all patients with BMI>30 may reflect hyperfiltration, inflammation, subtherapeutic immunosuppression, or increased post-operative complications. Non-inferior patient outcomes among patients with BMI>35 could reflect careful pre-transplant selection among very obese candidates or a survival advantage similar to that of obese dialysis patients. These data support a more favorable consideration of obese patients for kidney transplantation and suggest that the use of a BMI cut off between 35 and 40, while common, is arbitrary and unfounded.

Clinical Outcomes by Body Mass Index Categories (Reference: BMI>35)						
BMI	18-25		>25-30		>30-35	
n	10,683		13,665		10,037	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
GF	0.92 (0.86-0.99)	0.03	0.95 (0.88-1.01)	0.1	0.99 (0.92-1.06)	0.8
DCGF	0.77 (0.70, 0.85)	<0.001	0.84 (0.77-0.92)	<0.001	0.93 (0.85-1.02)	0.1
Death	1.08 (0.99-1.18)	0.08	1.04 (0.96-1.13)	0.3	1.06 (0.97-1.15)	0.2
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
DGF	0.41 (0.35-0.47)	<0.001	0.55 (0.48-0.63)	<0.001	0.71 (0.62-0.82)	<0.001

TH-OR122

Obesity Is Associated with Graft Failure in Pediatric Kidney Transplantation

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Background: Obesity is a potentially modifiable risk factor in kidney transplantation (KT), but recent studies have shown conflicting results regarding the impact of recipient obesity on graft failure in pediatric KT.

Methods: We studied first-time KT recipients 1995-2016 aged 2-17 years at transplant using SRTR data. Using recipients' height and weight at time of KT, we classified them as underweight (BMI <5th percentile), normal weight (BMI 5th to <85th percentile), overweight (BMI 85th to <95th percentile), and obese (BMI ≥ 95th percentile) based on US CDC growth reference charts. Normal weight recipients were the reference group. Survival analysis was used to compare the cumulative incidence of all-cause graft failure (ACGF) between recipients in each BMI category. Multivariable Cox models were used to compare time to ACGF between recipients in each BMI category, adjusting for recipient, donor, and transplant characteristics.

Results: Of 12,247 pediatric KT recipients, 62.7% were normal weight, 6.9% were underweight, 14.3% were overweight, and 16.1% were obese. Obese KT recipients had the highest incidence of ACGF (37% at 10 years vs 34% for normal/overweight and 32% for underweight (Figure)). After adjustment, obesity remained associated with an increased risk of ACGF ($aHR=_{1.09}1.20_{1.31}$, p<0.001).

Conclusions: Obesity at the time of transplantation is associated with increased risk of ACGF in pediatric KT recipients. Obesity may be a modifiable risk factor for graft loss in pediatric KT.

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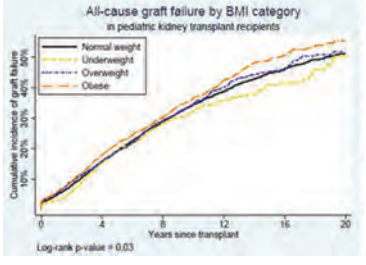

Weight and ACGF in pediatric KT recipients

BMI category	Adjusted hazard ratio
Underweight	$_{0.72}0.82_{0.94}$
Normal weight	Reference
Overweight	$_{0.93}1.05_{1.19}$
Obese	$_{1.09}1.20_{1.31}$

Note: Multivariable Cox regression adjusted for recipient age, recipient sex, recipient race, recipient insurance status, cause of ESRD, years of dialysis prior to KT, donor age, donor sex, donor type (living vs deceased), number of HLA mismatches, peak panel reactive antibody, transplant year

TH-OR123

Association of Pre-Transplant Weight Loss with Mortality after Deceased Donor Kidney Transplantation

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Background: Weight loss is a recognized component of frailty, signaling vulnerability to health stressors. Whether deceased donor kidney transplant (DDKT) recipients who lost weight before DDKT are at higher risk of adverse post-transplant outcomes is unknown.

Methods: Retrospective cohort study, using national registry data, of all DDKT recipients in the United States between January 1, 2005 and December 31, 2014 who were adults (age>=18 years) at wait-listing. We used unadjusted fractional polynomial methods and adjusted Cox proportional hazards models to examine the association of relative change in body weight pre-DDKT with post-DDKT mortality.

Results: Among 96,938 DDKT recipients, there was a non-linear unadjusted relationship between relative pre-DDKT weight change and post-DDKT mortality, with a steep increase in mortality among DDKT recipients who lost 10% or more of their listing body weight compared to those with no pre-DDKT weight change (Figure). In a multivariable Cox model adjusted for recipient and allograft characteristics, waiting time, and dialysis vintage, compared to recipients with weights at DDKT within 5% of their listing weights, recipients who lost 10% or more of their listing body weight before DDKT were 14% more likely to die post-DDKT (adjusted hazard ratio 1.14, 95% confidence interval 1.08-1.21, p<0.001). Pre-DDKT weight gain was not independently associated with post-DDKT mortality after multivariable adjustment. There was no evidence of effect modification by age, dialysis vintage, or body mass index (p>0.10 for interaction terms).

Conclusions: Substantial weight loss before DDKT may indicate increased vulnerability after DDKT. Studies are needed to identify and modify unhealthy weight trajectories among DDKT candidates.

Funding: NIDDK Support

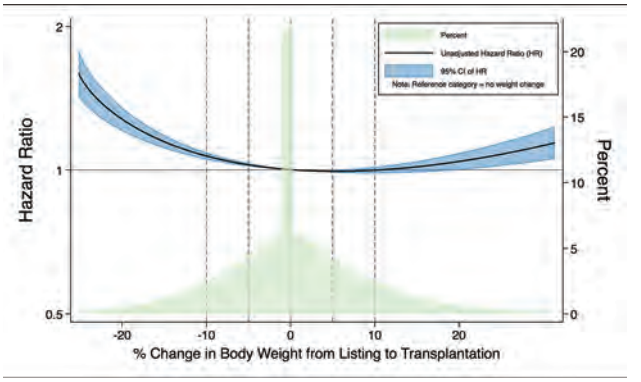

Figure demonstrates the distribution of pre-DDKT weight change (light green) among 96,938 DDKT recipients, and the unadjusted association of pre-DDKT weight change with post-DDKT mortality (black line) with 95% confidence intervals (light blue).

TH-OR124

Metabolic Acidosis Is a Risk Factor for Ischemic Cardiovascular Events in Kidney Transplant Recipients

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Background: Metabolic acidosis is associated with disease progression and death in CKD. However, there is limited information on whether metabolic acidosis is a risk factor for poor outcomes after kidney transplantation.

Methods: We examined the association between mean total serum bicarbonate levels(TCO2) at one-year and the incidence of all-cause mortality, *de novo*ischemic, arrhythmic, or heart failure events in 2018 kidney transplant recipients.

Results: The prevalence of metabolic acidosis defined as TCO2 <24 mEq/L, was 16.9% (n=341). There were 593 deaths and 363 recipients with a CVE over a median follow-up of 3.75 years. CVE included 221 ischemic, 63 arrhythmic, and 178 heart failure events. TCO2 < 22 mEq/L was associated with increased risk of CVE (adjusted HR 2.22; 95%CI 1.41, 3.48). This association was primarily due to ischemic CVE (aHR 2.51; 95%CI 1.43, 4.40). For every 1 mEq/L TCO2 below 24 mEq/L, the risk of all CVE and ischemic events was 18% and 17% higher, respectively (aHR for all CVE 0.82; 95% CI 0.72, 0.94, and aHR for ischemic CVE 0.83; 95% CI 0.71, 0.98). Notably, TCO2 < 22 mEq/L was an independent risk factor for all-cause mortality (aHR 1.85; 95% CI 1.28, 2.68). For every 1 mEq/L TCO2 below 24 mEq/L, the risk of death was 17% higher (aHR 0.83; 95%CI 074, 0.92).

Conclusions: In summary, metabolic acidosis is a risk factor for ischemic CVE and all-cause mortality in kidney transplant recipients. Clinical trials are needed to determine the safety and efficacy of alkali therapy for CVE after renal transplantation.

TH-OR125

Kidney Recipient-Donor KIR-HLA Ligand Mismatch Is Associated with Reduced Graft Survival

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Background: Differences in KIRs between recipients can lead to different KIR-HLA ligand constellations not captured by HLA matching alone. These differences may contribute to variation in allogeneic response to the renal allograft after transplantation.

Methods: We made use of the iGeneTrain consortium and genotyped 162 first kidney transplant recipients and respective HLA-DR matched deceased donors from two centers in Vienna and Prague. KIR types were imputed using KIR*IMP. HLA eplet mismatch was calculated for the HLA-A, -B, -C, -DP, -DQ, and -DR loci. The median follow-up time of the cohort was 5.8 years. KIR HLA ligand mismatches were defined based on the presence of inhibitory KIRs (2DL1, 2DL2, 2DL3 and 3DL1) and activating KIRs (2DS1 and 2DS2) in the recipient and absence or presence of the corresponding ligand in the donor, respectively. Kaplan-Meier analysis and a Cox PH model were used to assess the association of KIR-HLA ligand mismatch with death censored graft loss.

Results: Comparison of the groups of recipients with no- and at least a single KIR-HLA ligand mismatch revealed an elevated risk for graft loss following renal transplantation in the latter group (see figure 1). This association remained significant in a multivariable Cox model after adjustment for full HLA eplet mismatch and donor age (HR: 3.01 CI: 1.06 – 8.56, p-value: 0.039).

Conclusions: Presence of a KIR-HLA ligand mismatch between recipient and donor is associated with graft loss after HLA-DR matched kidney transplantation.

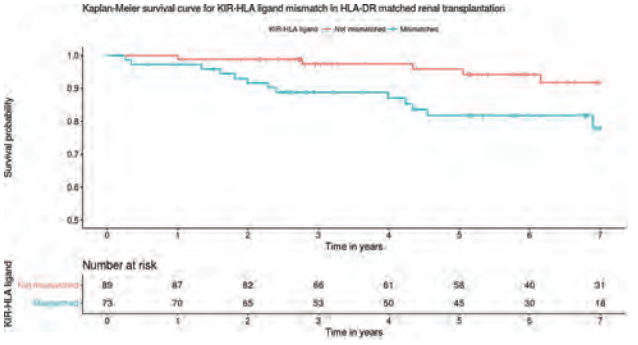

Figure 1: Kaplan-Meier survival curves comparing HLA-DR matched kidney recipient-donor pairs without and with a KIR-HLA ligand mismatch.

TH-OR126

Risk Prediction Score for Allograft Loss in Kidney Transplant Recipients: An International Derivation and Validation Study

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Background: The field of kidney transplantation currently lacks robust models to predict long-term allograft failure, hampering patient care improvement and novel clinical trials. We aimed at developing and validating a score that predicts individual patients' risks of long-term kidney allograft failure.

Methods: This prospective international cohort study included consecutive kidney transplant recipients from a derivation cohort (n=4,000) recruited between 2005 and 2014 in four centres and a validation cohort of 3,557 kidney transplant recipients from six centres recruited in Europe (n=2,129) and North America (n=1,428) between 2002 and 2014. Thirty-three candidate prognostic factors of kidney allograft were assessed. The outcome was the long-term allograft failure (i.e. return on dialysis or pre-emptive re-transplantation); NCT03474003.

Results: Amongst the 7,557 patients included, 1,067 allograft failures occurred (14.12%) after a median follow-up time post-transplantation of 7.12 years (IQR: 3.51-8.77). In the derivation cohort, eight functional, histological and immunological prognostic factors were independently associated with allograft failure and were then combined into an integrative risk prediction score (iBox). This score exhibited accurate calibration and discrimination (C index=0.81; 95% CI, 0.79-0.83). The performance of the iBox was also confirmed in two validation cohorts from Europe (C-index=0.80; 95% CI=0.78-0.84) and the USA (C-index=0.80; 95% CI=0.76-0.84). The iBox was accurate at different times of posttransplant risk evaluation and outperformed conventional prediction model based on functional parameter assessment only. Finally, the performance of the iBox was confirmed in 3 independent randomised controlled therapeutic trials covering distinct clinical scenarios (C-index 0.87; 95% CI=0.82-0.92).

Conclusions: We developed the iBox risk prediction score, which accurately predicts kidney allograft failure and demonstrates generalisability across centres worldwide. This risk prediction score provides an accurate but simple strategy that can be easily implemented to stratify patients into clinically meaningful risk groups, which may help guide patient monitoring in everyday practice and improve the design of future clinical trials.

TH-OR127

Sclerostin Is an Independent Risk Factor of All-Cause Mortality in Older Kidney Transplant Recipients and Graft Loss in Younger Kidney Transplant Recipients

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Background: Immediate graft loss and patient survival after kidney transplantation have improved over the past decade, however, long-term outcomes remain an issue and graft loss is in some centers the leading cause for imitating renal replacement therapy. Sclerostin is a hormone contributing to the bone-vascular wall cross talk and has been implicated in cardiovascular events and mortality in patients with chronic kidney disease (CKD). However, the relationship between sclerostin and mortality or graft failure in renal transplant recipients has not been analyzed so far.

Methods: 600 stable renal transplant recipients were followed for 3 years for all-cause mortality and graft failure. Blood and urine samples for analysis of sclerostin, albumin, creatinine, total cholesterol, HbA1c, 1,25$(OH)_2$D, calcium, phosphorus, iPTH, fasting blood glucose, urinary protein and clinical data were collected at baseline. We performed Kaplan Meier survival analysis and Cox regressions models considering confounding factors such as eGFR, urinary protein excretion, cold ischemia time, donor age, recipient age, time on dialysis and HbA1c.

Results: Elevated baseline serum sclerostin concentrations (>75 ng/ml) is an independent risk factor for all-cause mortality in older(>66y) stable kidney transplant recipients but not in young patients: Kaplan-Meier curves (older patients: P=0.003, log-rank test; young patients: P=0.492, log-rank test); and Cox regression (older patients: relative risk, 0.155; 95% CI, 0.043 to 0.561 ; P=0.004; young patients: relative risk, 1.330; 95% CI, 0.170-10.403; P=0.786). Elevated baseline serum sclerostin concentrations (>75 ng/ml) is an independent risk factor for graft failure in young(≤66y) stable kidney transplant recipients but not in older patients: Kaplan-Meier Curves(older patients: P=0.784, log-rank test; young patients: P=0.023, log-rank test); and Cox regression (older patients: relative risk, 0.227; 95% CI, 0.011 to 4.855 ; P=0.343; young patients: relative risk, 0.244; 95% CI, 0.063-0.944; P=0.041).

Conclusions: Our study showed for the first time that elevated baseline serum sclerostin is an independent risk factor of all-cause mortality in older patients and for graft failure in young patients after kidney transplantation.

TH-OR128

Outcomes for Kidney Transplant Recipients with Hearing, Visual, Physical, and Walking Disabilities

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Background: Lower functional status is associated with higher mortality risk in kidney transplant (KT) recipients. Physical disabilities might also affect post-KT outcomes through similar pathways, but this population has not been well characterized.

Methods: Using a prospective 2-center cohort of 500 KT recipients 6/2013-12/2017, we compared normally able recipients to recipients with self-reported hearing, visual, physical, or walking disabilities. We used hybrid registry-augmented Cox regression to assess the association between disability status and post-KT outcomes (death-censored graft failure and mortality) by adjusting for recipient, donor, and transplant characteristics in the national population (SRTR N=76,112).

Results: Among the 500 KT recipients in our cohort, 24.2% reported a disability: 9.6% had a hearing disability, 16.2% had visual disability, 8.9% had a physical disability, and 11.7% had a walking disability. Compared to recipients that did not report a disability, recipients who reported a disability were more often Black (51.2% vs. 33.8%, p<0.001), spent longer on dialysis (median 2.7 vs. 1.9 years), less often college educated (62.1% vs. 74.6%, p<0.01), less often employed (31.9% vs. 49.7%, p<0.001), and more often on public insurance (67.8% vs. 53%, p<0.01). After adjustment, visual disability was associated with a 3.98-fold higher risk of graft failure and walking disability was associated with a 4.12-fold higher risk of mortality. Other self-reported disabilities were not associated with transplant outcomes (all p>0.05, Table 1).

Conclusions: In this two-center cohort, 24% of KT recipients reported a disability. Compared to recipients without a reported disability, recipients with a visual disability were at higher risk of graft failure and recipients with a walking disability were at higher risk of mortality. These KT recipients might benefit from additional supportive care and monitoring post-transplant.

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Risk of Death-censored Graft Failure and Mortality

	Graft Failure aHR (95% CI)	p-value	Mortality aHR (95% CI)	p-value
Any Disability	1.58 (0.51-4.86)	0.4	1.02 (0.39-2.70)	>0.9
Visual Disability	3.98 (1.38-11.50)	0.01	1.02 (0.37-2.78)	>0.9
Hearing Disability	3.49 (0.95-12.85)	0.06	0.68 (0.14-3.24)	0.6
Physical Disability	0.72 (0.09-6.01)	0.8	1.74 (0.55-5.51)	0.4
Walking Disability	0.55 (0.07-4.32)	0.6	4.12 (1.66-10.24)	0.002

TH-OR129

Outcomes of Kidney Transplant Patients with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab: A Meta-Analysis

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Background: Kidney transplantation in patients with atypical hemolytic uremic syndrome (aHUS) is frequently complicated by recurrence of aHUS, often resulting in thrombotic microangiopathy (TMA) in the renal allograft and graft loss. We aimed to assess the efficacy of eculizumab in the prevention and treatment of aHUS recurrence after kidney transplantation.

Methods: Databases (MEDLINE, EMBASE and Cochrane Database) were searched through March 2018. Studies that reported outcomes of adult kidney transplant recipients with aHUS treated with eculizumab were included. Effect estimates from the individual studies were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018089438).

Results: Fourteen studies (11 cohort studies and 3 case series) that consisted of 167 adult kidney transplant patients with aHUS who received eculizumab for prevention and/or treatment of post-transplant aHUS recurrence were included into the analysis. Among patients who received prophylactic eculizumab, the pooled estimated rates of aHUS

recurrence and allograft loss due to TMA were 7.9% (95%CI: 3.4%-17.5%, I^2 =0%) and 6.6% (95%CI: 2.8%-15.1%, I^2 =0%), respectively. Among patients who received eculizumab for treatment of post-transplant aHUS recurrence, the pooled estimated rates of allograft loss due to TMA was 24.1% (95%CI: 14.8%-36.7%, I^2 =10%). When the meta-analysis was restricted only to cohort studies with data on genetic mutations associated with aHUS, the pooled estimated incidence of allograft loss due to TMA after eculizumab therapy was 22.6% (95%CI: 13.2%-36.0%, I^2 =10%). We found no publication bias as assessed by funnel plots and Egger's regression asymmetry test (P values >0.05 for all analyses).

Conclusions: The use of eculizumab for prevention of aHUS recurrence after kidney transplantation seems to be more effective than treatment with eculizumab after post-transplant aHUS recurrence. Our findings suggest that kidney transplant patients with history of aHUS may have better allograft survival when prophylactic eculizumab is started at the time of kidney transplantation. Randomized control trials are important to further investigate this.

TH-OR130

Outcomes of Kidney Transplantation in AL Amyloidosis Patients

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Background: Therapies for AL amyloidosis have dramatically improved leading to longer patient survival (OS), however more patients reach end stage renal disease. Renal transplantation in patients with AL amyloidosis has been controversial due to lack of long term outcome data and appropriate and validated eligibility criteria.

Methods: We evaluated 52 patients with renal involvement who were followed in the Amyloidosis Center at Boston University Medical Center and underwent renal transplantation at various centers in the United States over the past 30 years.

Results: Median age at renal transplantation was 59.7 years (range 30.7-73.2) with 64% of transplantations from live donors. During a median follow up of 7.1 years (range 0-21), median OS from diagnosis was 16.6 years (range1-27.2), and from renal transplantation was 10.5 years. One, three and five-year graft survival were 92%, 87% and 80%, respectively. Patients with hematologic complete response (CR) or very good partial response (VGPR) at renal transplantation had a better OS than patients with partial response (PR) or no response (NR). Similarly, median time to graft loss in patients with CR/VGPR was 11.7 years (range 0.5-20.3) and with NR/PR was 5.3 years (range, 0.3-15) (HR 2.4, P=0.02). Seventeen patients (32%) had recurrent amyloidosis in the graft with median time from renal transplantation to recurrence of 3.7 years (range 0.3-11.9). Successful treatment mostly prevented graft loss in the setting of disease recurrence in the graft. There was a trend towards better OS and graft survival in patients who underwent high dose melphalan/stem cell transplantation at any time during their disease course vs. patients who were treated only with chemotherapy, however the difference did not reach statistical significance.

Conclusions: This is the largest study of patients undergoing renal transplantation for systemic AL amyloidosis to date. Carefully selected patients, particularly those who had achieved a CR and VGPR to plasma cell directed therapy at the time of renal transplantation demonstrated prolonged OS as well as graft survival. These good outcomes were independent of the type of treatment that was used for the underlying plasma cell dyscrasia. Overall and graft survival of the patients with AL amyloidosis were comparable to outcomes achieved in non-AL amyloidosis patients.

Funding: Private Foundation Support

TH-OR131

Kidney Organoids Generated through Heterochronic Recombination of Progenitors Show Nephron Segmentation and Vascular Connection with Host In Vivo

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Background: In recent years procedures have been developed to differentiate human induced pluripotent stem cells (hiPSC) to renal tissues. In the present study, we investigated the potential of heterochronic recombination of hiPSC-derived kidney progenitors to increase tubular density in hiPSC-derived kidney organoids. Characterization of this technique included organoid engraftment, nephron segmentation, graft vascularization and perfusion in vivo.

Methods: hiPSC-derived kidney progenitors were treated with a WNT/β-catenin agonist for two days to induce epithelialization and were mixed with fresh progenitors, aggregated and cultured at the air-liquid interface. On day 9, these organoids were engrafted under the kidney capsule of NSG mice. Grafts were harvested after 3 weeks and nephron segmentation, vascularization and perfusion were evaluated.

Results: Heterochronic recombination of kidney progenitors induced robust tubulogenesis in kidney organoids compared with unmixed cells. Tubules stained with molecular markers for proximal and distal tubules and revealed segmentation. Podocytes ($Podxl^+$), stromal cells ($Meis1^+$) and endothelial cells ($CD31^+$) were abundant. Engrafted organoids showed differentiation of complex graft-derived glomeruli with vascular networks ($CD31^+$ $Endomucin^+$), podocytes ($Podxl^+$ $WT1^+$), mesangial cells ($Pdgfr\beta^+$), glomerular basement membrane ($Laminin^+$ Col I^+ Col IV^+), and juxtaglomerular cells ($Renin^+$). Proximal tubules (E $cadherin^-$ LTL^+), thick ascending limb of the loop of Henle ($Tamm\text{-}Horsfall\ protein^+$), distal tubule ($BRN1^+$), connecting tubule (E $cadherin^+$ $GATA3^-$ DBA^+), collecting duct ($Troma\text{-}1^+$ $GATA3^+$ DBA^+), and stromal cells ($Meis1^+$ $Pdgfr\beta^+$) were also present in the grafts. Engrafted organoids showed vascularization ($CD31^+$ $Endomucin^+$ SMA^+) and direct connections with host vasculature. All nephron structures and stromal cells in the graft were iPSC derived ($HuNu^+$), whereas endothelial cells were derived from the host ($HuNu^-$).

Conclusions: Heterochronic recombination of kidney progenitors results in vigorous differentiation of human iPSC-derived kidney tissue in vitro and in vivo.

Funding: NIDDK Support

TH-OR132

Mechanistic Analysis of Flow-Enhanced Vascularization in Kidney Organoids

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Background: Multilineage cellular communication is implicated in organ development and cellular maturation. We have recently shown that fluidic shear stress (FSS) promotes the vascularization and maturation of kidney organoids derived from human pluripotent stem cells (hPSCs) *in vitro*. The addition of VEGF is deemed to facilitate vascular formation during kidney organoid development *in vivo*, however, mechanisms of organoid vascularization and maturation under FSS conditions *in vitro* have yet to be identified.

Methods: Early kidney organoids (pretubular aggregate stage) derived from hPSCs were subjected to FSS in printed millifluidic chips. During 10 days of perfusion at a FSS of 0.04 dynes/cm^2, they were given organoid media without growth factors or with either added VEGF (1, 10, 100 ng/mL) or Avastin (250 mg/mL, which inhibits VEGF). The degree, distribution, and maturation of $CD146^+$and $CD31^+$vascular networks were evaluated by immunostaining, RT-qPCR, and image analysis (ImageJ Angiotool plugin). Tubulo-vascular proximity was quantified by distance transformation and surface area contact calculations using Imaris software.

Results: FSS-induced vascularized organoids exhibit upregulated VEGF expression, compared to static controls. Interestingly, total vascular abundance was independent of VEGF signaling under high FSS; however, manipulation of the VEGF pathway reduced vascular invasion to glomeruli and tubulo-vascular surface area contact. Reducing the nephron epithelial communication with vasculature led to an increase in vascular branching and a reduction in average vessel length.

Conclusions: In developing kidney organoids under FSS, modifying the native VEGF intrinsic gradient results in random templating of the same amount of vasculature with less tubular and glomerular integration. Our results indicate that maintenance of intrinsic growth factor production may be critical to develop functional bioengineered kidneys from hPSCs *in vitro*, which may supplant current renal replacement therapies in the future.

Funding: NIDDK Support, Other NIH Support - T32 fellowships, U01, UG3, and R37 awards

TH-OR133

Human Kidney Organoids Model Tubular Injury and Maladaptive Repair with Interstitial Fibrosis In Vitro

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Background: Kidney fibrosis is a unifying feature of diseases that cause progressive loss of kidney function. Upon severe or repeated tubular injury, the adaptive repair response transitions to being maladaptive and pro-fibrotic. Determining the mechanisms involved in maladaptive tubular repair is vital to developing anti-fibrotic therapies. Here we propose kidney organoids as a model for tubular adaptive and maladaptive repair with interstitial fibrosis in human tissue *in vitro*.

Methods: Kidney organoids were generated from hPSCs by our previously established protocol. Organoid maturation was determined by downregulation of developmental genes and upregulation of adult markers using immunostaining, qPCR, flow cytometry, and histone ChIP-seq for epigenetic analysis of chromatin remodeling overtime. Organoids with mature profiles were treated with repetitive cisplatin at 5μM. Cell proliferation, dedifferentiation, partial epithelial-to-mesenchymal transition (pEMT), G2/M cell cycle arrest, pro-inflammatory cytokine expression, myofibroblast activation and interstitial fibrosis were evaluated using a combination of Masson Trichrome, immunostaining, qPCR, and flow cytometry after each treatment.

Results: Organoids exhibited mature gene expression profiles by day 49 of differentiation. LTL^+ tubules exhibited adaptive repair responses following the initial cisplatin treatment, including proliferation ($Ki67^+$), dedifferentiation ($PAX2^+$ and $SOX9^+$), and pEMT (VIM^+ and $SNAIL1^+$). Upon repeated cisplatin injury, LTL^+ cells adopt a pro-fibrotic phenotype characterized by maladaptive repair processes, including further loss of an epithelial phenotype, cell cycle arrest in the G2/M phase, and upregulated pro-inflammatory cytokine expression, followed by tubular atrophy, the transdifferentiation of peritubular fibroblasts ($PDGFR\text{-}\beta^+NG2^-DESM^-$) and pericytes ($PDGFR\text{-}\beta^+NG2^+DESM^+$) into αSMA^+ myofibroblasts, and the advent of interstitial fibrosis (FN and COL1A1).

Conclusions: Human kidney organoids model the transition from adaptive to maladaptive repair in tubular epithelial cells with repeated injury. Human kidney organoids

enable the study of tubular repair, along the continuum from acute injury to fibrosis, and the screening of anti-fibrotic therapeutics in human kidney tissue.

Funding: NIDDK Support, Other NIH Support - T32 (Project DK007527), NHGRI (U54HG009390), Private Foundation Support

TH-OR134

Exo Utero Method to Regenerate Nephrons from Nephron Progenitor Cells in the Living Fetus

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Background: Kidney regeneration using native kidney development has been previously reported. We previously reported that neonephrons could be generated by transplanting nephron progenitor cells (NPCs) into the nephrogenic zone in mice and replacing exogenous cells with host cells. In this cell replacement method, the fetal kidney was used as a scaffold for regeneration. We postulated that direct transplantation of NPCs into the scaffold in utero may obtain a more suitable developmental environment for kidney regeneration. We tried an exo utero method for kidney regeneration was used to examine whether NPCs could be transplanted into the retroperitoneum near the fetal host kidney without fetal sacrifice in vivo, and the development of neonephrons was examined.

Methods: Using an exo utero method to dissect only the myometrial layer of the mouse fetus which has only one clear amnion, cells can be injected to the fetus in utero. This approach allows the fetus in the amniotic membrane to be returned to the uterus after cell transplantation. An exo utero method was used to transplant GFP-expressing NPCs into the retroperitoneum on E13.5. After cell transplantation, the fetus continued to develop in the mother's uterus for 6 days. Following cesarean section on E19.5, histopathological examination was performed to determine NPC differentiation into nephrons. To determine whether cell transplantation in the fetus had a negative effect on fetal growth, fetal body weight and crown-rump-length (CRL) were measured on E19 and compared with those of fetuses who did not receive NPC transplantation.

Results: Glomeruli derived from transplanted NPCs expressed the nephron differentiation markers podocin, nephrin, megalin and aquaporin 1. CD31-positive blood vessels were observed inside the glomeruli. There were no significant differences in body weight or CRL between the fetuses with and without NPC transplantation.

Conclusions: Transplantation of exogenous NPCs into the retroperitoneum using an exo utero method could differentiate into nephrons in vivo. This method, which did not adversely affect fetal growth, is potentially applicable to kidney regeneration using NPCs.

Funding: Government Support - Non-U.S.

TH-OR135

Dose Related Effects of Intra-Renal Autologous Mesenchymal Stem/Stromal Cell Infusion on Renal Hemodynamics, Function, and Cytokine Signaling in Human Atherosclerotic Renovascular Disease

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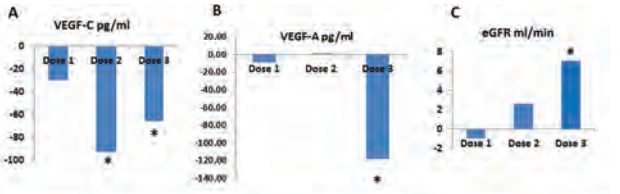
Background: Preliminary data identify increased renal blood flow after intra-renal infusion of mesenchymal stem/stromal cells (MSC) in post-stenotic kidneys. The effects of cell dose on systemic effects and anti-inflammatory activity of autologous MSC in human renovascular disease (RVD) are poorly understood

Methods: We measured cortical and medullary blood flows (MDCT), GFR (iothalamate and eGFR), renal vein cytokine levels, BP, and tissue oxygenation (BOLD MR) in 21 human subjects with atherosclerotic RVD under controlled study conditions, before and 3 mo after MSC delivery. Autologous adipose-derived MSC were administered at 3 dose levels (1, 2.5 and $5.0x10^5$/MSC/kg, n=7 patients each) into one affected kidney, without vascular intervention. Cultured MSC were also studied in vitro..

Results: At the highest dose ($5x10^5$ cells/kg), systolic BP fell (140±11.8 to 128±8.18 mmHg, p<.01), as did urine protein (149±89 to 103±96 mg/dL, p<.01), while single kidney GFR rose (18±10.6 to 21±12.5 ml/min, p<.05). Serum creatinine and renal venous VEGF-A fell only in the highest dose (Figure), whereas VEGF-C and Angiopontin fell at all dose ranges. Increases in treated-kidney tissue oxygenation by BOLD MR were correlated with levels of hepatocyte growth factor secretion by MSC in vitro.

Conclusions: These data reinforce the capability of autologous MSC to improve the renal circulation in human RVD, and reveal their potential to improve renal function, decrease BP, and modify angiogenic signaling from post-stenotic kidneys. The observation that some beneficial effects are dose-dependent and related to in-vitro properties of MSC may serve to optimize this strategy and predict in-vivo efficacy.

Funding: Other NIH Support - R01 DK100081



D

	Pre-Treatment	3 months	p-value
Cortical Blood flow(ml/min)	136 ± 86	159 ±112	p< 0.02
Medullary blood flow (ml/min)	27 ± 15.6	31 ±17.4	p= 0.08
Whole kidney blood flow (ml/min)	163 ± 99	190 ± 125	p=.01
VEGF-C pg/ml	646 ±268	583 ±244	p<.001
Angiopontin pg/ml	2344 ±1298	1867 ± 1198	p=.05
Fraction of whole kidney R2* above 30/s	9.5 ± 6.8	7.1± 5.8	p=.03

A. B. C. Dose specific related changes **D.** Entire cohort changes, between Baseline and 3 months after intra-arterial MSC infusion in ARVD.
* P <0.05

TH-OR136

Therapeutic Effects of Genome-Engineered Angiogenic or Anti-Inflammatory Factor Secreting-Mesenchymal Stem Cells in Mice with AKI

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Background: Stem cell therapy has been proposed as a potential therapeutic strategy for acute kidney injury (AKI). By exploiting genome editing technology, we generated mesenchymal stem cells (MSCs) secreting angiogenic factor (angiopoietin 1: ANG1) or anti-inflammatory factor (erythropoietin: EPO) for therapeutic application in AKI.

Methods: To integrate each gene cassette into the safe harbor locus, AAVS1, of the human umbilical cord-derived MSCs (hUC-MSCs) chromosome, AAVS1-targeting Zinc Finger Nuclease (ZFN) system was exploited. For the application of stem cell therapy *in vivo*, a scaffold-free cell sheet system was established using a temperature-responsive polymer. AKI in C57BL/6 mice was established by bilateral renal pedicles occlusion for 30 min and monitored for additional 7 days after the clamps were removed.

Results: Junction PCR analysis demonstrated the ZFN-aided gene integration in hUC-MSCs. Flow cytometry and osteogenic and adipogenic differentiation assay revealed that genome editing did not affect the stemness. Protein measurement in conditioned media by ELISA and immunoblotting confirmed the production and secretion of each integrated gene product (ANG1 and EPO proteins). The *in vitro* angiogenic function of hUC-MSCs secreting ANG1 was further revealed by the increased cell migration and expression of MMP-9 and Tie-2 mRNAs in co-cultured HUVEC. As a control experiment, a mono-layered sheet of hUC-MSCs was applied to the mice kidney surface *in vivo*. Immunohistochemistry with anti-human nuclei antibody at 1 or 2 weeks after the application demonstrated that hUC-MSCs on the mice kidney surface were intact and specifically labeled. In mice subjected to bilateral renal ischemia and reperfusion, cell sheets of ANG1- or EPO-secreting hUC-MSCs applied to the kidney surface significantly ameliorated renal functional deterioration with lower BUN and creatinine levels, compared with sham control mice as well as mice treated with sheets of GFP-expressing hUC-MSCs. Moreover, treatment of EPO-secreting hUC-MSCs resulted in higher Hct levels.

Conclusions: A novel cell therapy of hUC-MSCs secreting ANG1 or EPO provides the therapeutic effects against AKI *in vivo*.

Funding: Government Support - Non-U.S.

TH-OR137

Bioprinting and Controlled Perfusion of 3D Vascularized Proximal Tubules on Chip

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Background: Building three-dimensional human renal tissues that recapitulate native physiological functions is a grand challenge. To date, progress towards developing 3D proximal tubule (PT) on chip has resulted in significantly improved cell morphology and function, akin to that observed *in vivo*. However, absent a perfusable vasculature that is essential to sustained renal reabsorption, these microphysiological systems are unable to replicate key kidney functions, such as tubulovascular exchange.

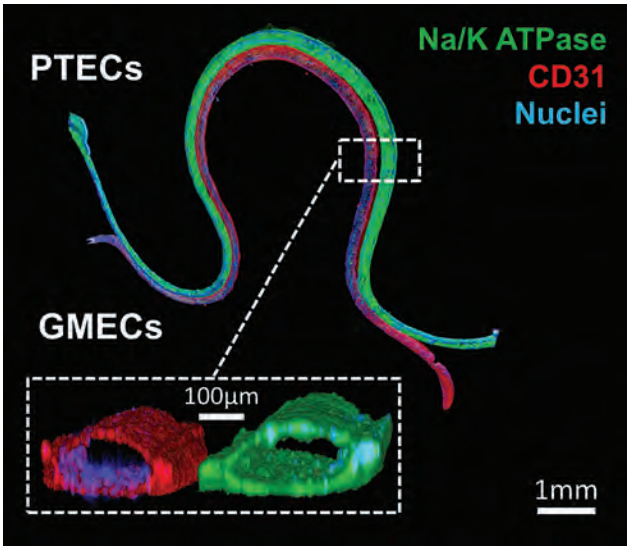
Methods: Here, we report the bioprinting and characterization of a 3D vascularized proximal tubule (PT) on chip that contains two co-localized channels embedded within an engineered extracellular matrix (ECM). In our model, the co-localization of the independently addressable PT and vascular channels combined with the high permeability of our engineered ECM enables effective vectorial transport of solutes. Specifically, we quantitatively measured the vectorial transport of glucose and albumin using a closed-loop perfusion system.

Results: We demonstrated that glucose reabsorption from the PT lumen to the vascular lumen is substantially improved by their 3D lumen geometry and fluid flow. We also observed that the glucose reabsorption by the confluent epithelium is reduced upon administering Dapagliflozin (SGLT2 inhibitor). Finally, to explore a disease state, we

created a hyperglycemic condition by quadrupling the glucose level in the PT channel and studied its effect on confluent endothelium within the vascular channel. We found that hyperglycemia-induced endothelial dysfunction is also reduced by inhibiting glucose transporters in the PT channel.

Conclusions: We have created a 3D vascularized PT on chip model that exhibits renal reabsorptive functions *in vitro*, which is relevant for drug screening, mechanistic safety studies, and disease modeling.

Funding: NIDDK Support, Other NIH Support - (Re)Building a Kidney, an NIDDK-funded consortium, Commercial Support - F. Hoffmann-La Roche



TH-OR138

Endothelialization of Decellularized Porcine Kidneys Sustains In Vivo Perfusion in an Acute Porcine Model

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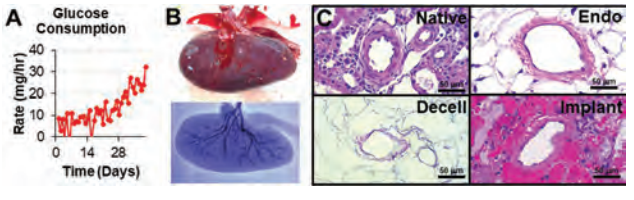
Background: The shortage of donor kidneys forces patients suffering from kidney failure to undergo dialysis as the only alternative to transplantation, the preferred therapy with lower morbidity and mortality rates. Recellularization of kidney extracellular matrix (ECM) scaffolds derived through decellularization is a promising strategy to produce humanized renal tissues for transplantation in a shorter time frame than donor kidneys may become available.

Methods: Porcine kidneys were decellularized via perfusion with mild detergents. The derived ECM scaffolds were repopulated with human umbilical vein endothelial cells (HUVECs) to endow the grafts with thromboresistance. Key metabolic markers were monitored to non-invasively assess cell proliferation, viability, and totality of vascular endothelialization. Re-endothelialized kidneys were functionally assessed by in vitro perfusion with heparinized porcine blood or in vivo anastomosis in an acute porcine implant. Primary epithelial cells were introduced to assess survival in co-culture.

Results: HUVECs engrafted in decellularized kidney scaffolds within both the arterial and venous vasculature. Daily metabolic analysis found that glucose consumption rate (GCR) directly correlated with graft perfusability, and grafts implanted at peak GCR (Fig 1A) sustained higher volumetric blood flow. Implanted grafts anastomosed to the porcine vasculature showed excellent perfusion of the vascular tree, as demonstrated by angiography (Fig 1B). Endothelialization sustained vascular patency during acute in vivo perfusion for up to 1 hour (Fig 1C). Co-culture of endothelialized grafts with epithelial cells showed dual survival in their respective vascular and nephron niches.

Conclusions: Effective engraftment and proliferation of human endothelial cells within porcine kidney scaffolds indicates that the renal ECM retains critical integrin adhesion sites. Sustained perfusion of endothelialized grafts during blood loops and acute implants represents an important step toward chronic transplantation of recellularized whole kidney grafts in human-scale preclinical models.

Funding: Private Foundation Support



TH-OR139

A High-Throughput Microfluidic Model of Proximal Tubule with Active Transport Function

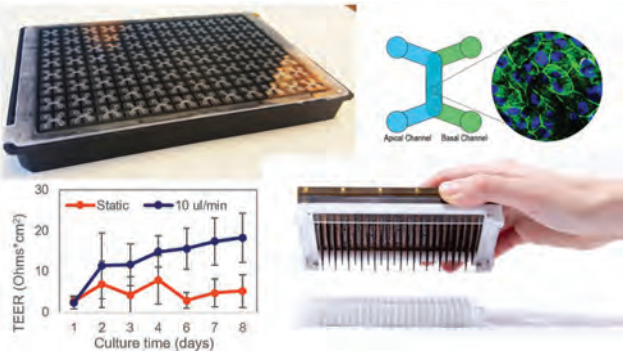
Else M. Vedula, Timothy J. Haggerty, Joseph L. Charest. *Draper, Cambridge, MA.*

Background: Models with kidney-specific function *in vitro* and high-throughput capability will speed kidney disease drug development. Microfluidic models control flow to cultured cells to generate tissue with kidney-specific function. However, high throughput is required for experiments accommodating many drug doses, assays, and biological variables. Microfluidic models have yet to achieve high throughput.

Methods: We developed an *in vitro* kidney model in a high-throughput microfluidic platform, PREDICT-96. PREDICT-96 co-cultured human renal proximal tubule epithelial cells (hRPTEC) and human microvascular endothelial cells (hMVEC) and characterized them via real-time trans-epithelial electrical resistance (TEER) and a high-content screening (HCS) approach quantifying ZO-1 expression, localization. Primary cilia, polycystin-1 (PC1), and transporter expression were characterized via confocal microscopy. Glucose reabsorption via SGLT2 and organic anion transport via OAT-1 were characterized using real-time imaging and spectrophotometric techniques.

Results: hRPTEC and hMVEC formed polarized tissue with barrier integrity and active, kidney-specific transport function. Flow increased TEER, hRPTEC thickness, primary cilia expression with co-localized PC1, and ZO-1 localization. Drug dosing modulated glucose reabsorption from the filtrate to vascular channel, indicating active kidney-specific function. OAT-1 expression and function were characterized to quantify uptake and excretion functions.

Conclusions: Microfluidic flow enhanced tissue structure/morphology, polarization, and function, resulting in *in vitro* tissue with kidney-specific function. Integrated TEER sensing and HCS-capable platform architecture supported real-time data collection. Microfluidic flow-conditioned tissue actively responded to drug dosing, indicating the ability of the model to quantify drug effects. The PREDICT-96 kidney model can generate kidney tissue, study renal toxicity, and evaluate disease progression *in vitro* to speed development of kidney therapeutics.



TH-OR140

Exposure to Fluid Shear Stress Enriches Tip Cell Populations in In Vitro Cultured Ureteric Bud Cells

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Background: Most kidney cells are exposed to fluid shear stress (FSS) from either blood flow or urine flow. Previous studies have shown that changes in FSS may affect the function or induce injury of kidney cells. However, it remains unclear whether FSS influences kidney development when urinary flow starts in the embryonic kidneys, which occurs around embryonic age E15.5 in mouse. In this study, we evaluated the influence of FSS on *in vitro* cultured ureteric bud (UB) cells.

Methods: We used a pumpless microfluidic device, which offers the convenience of conducting parallel cell culture experiments without the need of cumbersome electronic driven equipment. We first validated the function of the device by both mathematical model and experimental measurements. UB cells dissected from E15.5 mouse embryonic kidneys were cultured in the pumpless microfluidic device and subjected to FSS for 48 hrs. Control UB cells were similarly cultured in the device and maintained under a no-flow condition.

Results: We found that the exposure to FSS for up to 48 hrs led to an increase in mRNA expression levels of UB tip cell marker genes (*Wnt11*, *Ret*, *Etv4*) with a decrease in stalk cell marker genes (*Wnt7b*, *Tacstd2*). In further support of the enrichment of UB tip cell population in response to FSS, we also found that exposure to FSS led to a remarkable reduction in the binding of lectin Dolichos Biflorus Agglutinin (DBA), which is a characteristic of UB tip cells.

Conclusions: Results of our present study show that exposure to FSS led to enrichment in UB tip cell populations. Since UB tip cells are known to be the proliferative progenitor cells that contribute to the branching morphogenesis of the collecting system in the kidney, our finding could imply an important link between the FSS from the initiation of urine flow and the development of the kidney.

Funding: Government Support - Non-U.S.

FR-OR001

Relative Survival among Incident Patients on Home Versus In-Center Hemodialysis

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Background: Relatively little research has been aimed at outcomes among incident dialysis patients who undergo home hemodialysis (HHD). Percolating interest in transitional dialysis care may result in greater utilization of HHD during the first year of dialysis. We assessed relative survival among incident patients on HHD versus in-center hemodialysis (IHD).

Methods: We analyzed merged data from the United States Renal Data System. HHD patients initiated at-home treatment with the NxStage System One between January 1, 2006, and December 31, 2012, and within 3 months after dialysis initiation. IHD patients underwent treatment in a dialysis facility at 45 days after dialysis initiation. We followed HHD patients from the day of the first at-home treatment and IHD patients from the 45th day after dialysis initiation; all patients were followed until death, but for a maximum of one year. We used Cox regression to estimate the adjusted hazard ratio (AHR) of death for HHD versus IHD, with adjustment for age, race, sex, primary cause of end-stage renal disease, Medicaid enrollment, comorbid conditions, vascular access type, body mass index, estimated glomerular filtration rate (GFR), and hematocrit; all adjustment factors were ascertained from form CMS-2728.

Results: We identified 1773 HHD patients and 555,366 IHD patients. Relative to IHD patients, HHD patients were younger (mean age, 55.3 versus 60.3 years), more likely white (81.3% versus 62.7%), more likely male (71.1% versus 57.0%), less likely enrolled in Medicaid (9.5% versus 28.3%), and less likely to have heart failure (15.8% versus 31.3%). Mean estimated GFR was 10.5 and 10.4 mL/minute/1.73 m^2 in HHD and IHD patients, respectively. Survival after one year of follow-up was 91.7% and 81.4% in HHD and IHD patients, respectively. After adjustment, the AHR of death for HHD versus IHD was 0.77 (95% confidence interval, 0.66-0.91). Within age strata, corresponding AHRs of death were 0.56 (0.30-1.04) for 20-44 years, 0.74 (0.58-0.94) for 45-64 years, and 0.89 (0.70-1.13) for ≥65 years. Within estimated GFR strata, corresponding AHRs of death were 0.68 (0.51-0.90) for GFR <10 mL/minute/1.73 m^2 and 0.80 (0.65-1.00) for GFR ≥10 mL/minute/1.73 m^2.

Conclusions: Among incident patients, HHD is associated with better survival than IHD. Associations are attenuated with older age and higher estimated GFR at dialysis initiation.

Funding: Commercial Support - NxStage Medical, Inc.

FR-OR002

Efficacy of Mupirocin Prophylaxis for Prevention of Bacteremia in Home Hemodialysis Patients Using Buttonhole Technique for Cannulation

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Background: Buttonhole cannulation (BC) technique is often preferred by home hemodialysis (HHD) patients but has been associated with a significant risk of bloodstream infection (BI). Despite a single center report suggesting a decrease in BI with topical mupirocin prophylaxis (MP), use of MP is not widespread, and indeed, many centers have shied away from using BC altogether. Because our patients have shown a strong preference for BC, we have continued to use BC but began mandating the use of MP in September 2013. This study is a retrospective chart review comparing the incidence of BI in patients using BC before and after we started MP.

Methods: To establish the number of treatments-at-risk for development of access-related BI, HHD billing records from January 2007 through March 2018 were reviewed to assess the total number of HHD treatments performed, as well as the access used for those treatments. Corresponding monthly QA reports were reviewed to identify episodes of BI attributable to the HD access, and confirmed by review of the underlying medical record independently by two clinicians.

Results: From January 2007 through March 2018, 133 patients performed 63,704 HHD treatments, encompassing 298.3 patient-years of observation. Of those, 50 patients performed 28,047 treatments using BC in the period prior to MP and 37 patients performed 14,702 treatments using BC in the period after MP. 21 episodes of access-related BI were observed, with 19 episodes occurring in 14 patients in the pre-MP period, and 2 episodes occurring in 2 patients in the post-MP period. Both patients who developed BI in the post-MP period admitted to non-adherence with MP at the time of BI. When analyzed by observation period, the odds ratio (OR) for BI without MP was 5 (95% confidence interval (CI) = 1.16 to 21.4; p=0.03). In an as-treated analysis, the OR for BI without MP was 21.9 (95% CI=1.3 to 361.7; p=0.03).

Conclusions: Topical mupirocin prophylaxis is effective in prevention of buttonhole cannulation-associated bloodstream infection. Buttonhole cannulation technique can be safely used for HHD if patients are adherent to a prophylaxis protocol.

FR-OR003

Increased Hemodialysis Frequency Is Associated with Improved Clinical Outcomes among Patients in Skilled Nursing Facilities

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Background: In light of hemodynamic instability and frailty, dialysis patients who reside in a skilled nursing facility (SNF), either for short-term rehabilitation or long-term custodial care, may benefit from on-site, frequent hemodialysis (HD). We assessed whether increased HD frequency was associated with risks of death and hospital admission among SNF patients receiving care from a single dialysis provider in the Chicago area.

Methods: We assessed Medicare Parts A and B claims in 2011-2015 to identify HD patients at Affiliated Dialysis Centers (ADC). For each patient-week in 2011-2015, we tallied the number of HD sessions at ADC. We constructed an outcome-exposure model that measured associations of all-cause mortality, all-cause hospital admission (HA), and cause-specific (cardiovascular disease, infection, and other morbidity) HA risks during one calendar week with mean HD frequency during the preceding two calendar weeks, with frequency categorized as ≥4.5 vs. 2.5-4.4 HD sessions/week. We fit logistic generalized estimating equations, with adjustment for age, race, sex, primary cause of end-stage renal disease (ESRD), duration of ESRD, vascular access type, and calendar time.

Results: We identified 3619 unique patients and 78,047 patient-weeks. Mean age was 69.0 years; 59% and 34% of patients were white and black, respectively; 49% were female; and 53% dialyzed with a central venous catheter. Between 2011 and 2015, the percentage of two-week intervals with ≥4.5 HD sessions/week increased monotonically, from 9% in 2011 to 45% in 2015. We observed 641 deaths. The adjusted mortality risk ratio for ≥4.5 vs. 2.5-4.4 HD sessions/week was 0.66 (95% confidence interval, 0.52-0.83). The adjusted all-cause HA risk ratio for ≥4.5 vs. 2.5-4.4 HD sessions/week was 0.91 (0.81-1.02). Corresponding cause-specific HA risk ratios were 0.77 (0.62-0.97), 1.05 (0.88-1.24), and 0.86 (0.74-1.00) for cardiovascular disease, infection, and other morbidity, respectively. For all HAs excluding those attributable to infection, the adjusted risk ratio for ≥4.5 vs. 2.5-4.4 HD sessions/week was 0.83 (0.73-0.95).

Conclusions: In a large study of on-site HD in the SNF setting, increased HD frequency was associated with significantly lower risks of death and all hospital admissions excluding those attributable to infection.

Funding: Commercial Support - NxStage Medical, Inc.

FR-OR004

A Comparison of Technique Survival in Canadian Peritoneal Dialysis and Home Hemodialysis Patients

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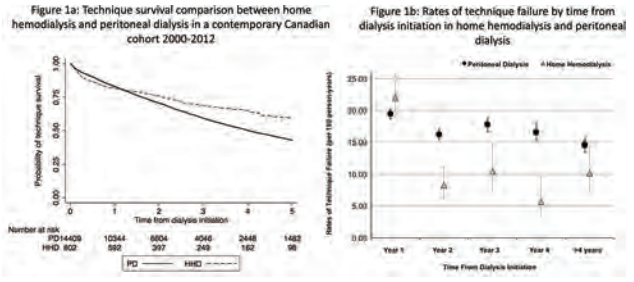
Background: High discontinuation rates remain a challenge for both home hemodialysis (HHD) and peritoneal dialysis (PD). Our study aimed to compare the technique failure risks between HHD and PD in a Canadian cohort.

Methods: We studied adult patients who initiated either HHD or PD within 1 year of dialysis initiation between 2000-2012 in the Canadian Organ Replacement Register. Technique failure was defined as a transfer to any alternative dialysis modality for a period of ≥60 days. We compared technique survival between HHD and PD using a Fine and Gray competing risk model. Secondary outcomes assessed the trajectory of technique survival, the association of patient characteristics with technique failure, causes of technique failure and changes of technique failure rates over time

Results: 15,314 patients were treated with a home dialysis modality between 2000-2012: 14,461 on PD and 853 on HHD. The adjusted risk of technique failure was overall lower with HHD compared to PD (HR 0.79; 95% CI 0.69-0.90). However, comparisons varied over time (Figure 1a). During the first year of therapy, there was no significant difference in technique survival between HHD and PD (HR 1.13; 95% CI 0.94-1.36). Thereafter, the risk of technique failure was significantly lower with HHD. In PD and HHD, crude rates of technique failure were the highest during the first year of therapy (Figure 1b). Among HHD patients, rates were significantly lower subsequent to that. In contrast, the decrease in failure rates was not as pronounced among PD patients. Furthermore, the majority of home dialysis discontinuation occurred for medical reasons in PD (38%) while the majority of HHD patients experienced technique failure due to social reasons or inadequate resources (50%).

Conclusions: In this Canadian study of home dialysis patients, HHD was associated with superior technique survival compared to PD. However, causes and patterns of technique failure differed significantly among these modalities. Strategies to improve patient retention across all home dialysis modalities are needed.



FR-OR005

Effect of Intensive Home Hemodialysis on Right Ventricular Systolic Pressure and Clinical Outcomes

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Background: Increased right ventricular systolic pressure (RVSP) is a marker of pulmonary hypertension in patients with end-stage kidney disease (ESKD). Our primary aim is to examine whether nocturnal home hemodialysis (NHD) will modify RVSP in ESKD patients. Our secondary aim is to ascertain the clinical consequence of normalization of RVSP.

Methods: We conducted a retrospective single center cohort study at the Toronto General Hospital including all patients between 1999 and 2017 with baseline and follow-up echocardiograms on intensive home hemodialysis followed for at least 1 year. Patients were categorized according to RVSP response at the end of follow-up: non-responders with increased RVSP and responders with normal RVSP. Multivariate and cox regression analysis were used to identify risk factors for increased RSVP and reaching clinical composite endpoint (death, cardiovascular hospitalisation, treatment failure), respectively.

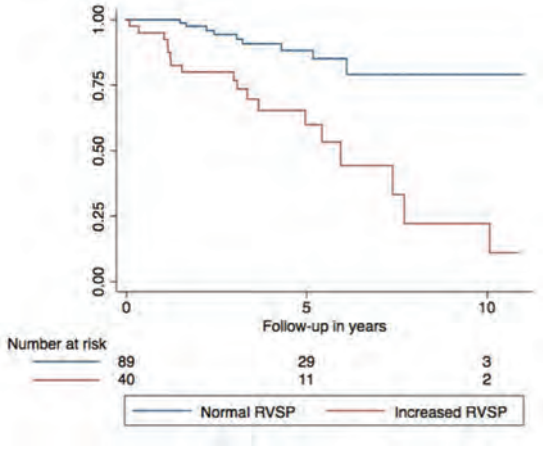
Results: A total of 129 patients were included in the study with a mean follow-up of 4.1 years. 31% (40/129) of patients had increased RVSP (=/> 35 mmHg). 9 (10.1%) out of the 89 responders and 18 (45%) out of the 40 non-responders reached the composite endpoint of death, cardiovascular hospitalization or technique failure. Responder status is an independent predictor for reaching the composite endpoint and is associated with a survival benefit.

Conclusions: Increased RSVP is associated with adverse clinical outcomes in patients on intensive home hemodialysis.

Funding: Private Foundation Support

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Non vs Responders	4.80 (2.15-10.7)	<.01	4.40 (1.93-9.99)	<.01
Diabetes	2.89 (1.30-6.42)	<.01	2.27 (0.97-5.32)	0.06
Age	1.03 (1.00-1.07)	0.02	1.01 (0.98-1.05)	0.28
Smoking Status	0.66 (0.22-1.92)	0.27	0.55 (0.19-1.61)	0.19

Cox proportional hazards analysis of the risk of the composite end point of death, technique failure and CV-related hospitalization.



Composite end point-free survival in responders and non-responders.

FR-OR006

Silicon Nanopore Membrane-Based Implantable Hemodialysis: A Preclinical Proof-of-Concept Study

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Background: Silicon nanopore membranes (SNM) are highly efficient biomimetic and blood-compatible slit-pore membranes. The high efficiency of the membrane enables hemofiltration and hemodialysis by utilizing cardiovascular perfusion pressure to circulate blood over the filters, enabling the prospect of a fully implanted hemodialysis cartridge. This alternative access strategy could offer a solution for patients with complicated conventional access, and lowers barriers to self-care home hemodialysis.

Methods: A 115 x 57 x 18 mm SNM-based parallel-plate hemodialyzer (SNMHD) was prototyped from polycarbonate and stainless steel. The device was implanted subcutaneously in the neck of a healthy Yucatan mini-pig and anastomosed to the carotid artery and jugular vein via ePTFE vascular grafts. Catheters to supply dialysate were tunneled subcutaneously and attached to the SNMHD. The animal was allowed to recover, and 3-hour hemodialysis sessions were performed on the day of surgery, and post-operative days 1, 2, and 3. Dialysate was recirculated in a counter-current fashion at 10-15 mL/min, and blood flow through the SNMHD was between 1.0-1.5 L/min, assessed by pulse wave Doppler ultrasound. Blood samples were collected at the initiation of dialysis, and dialysate sampled every hour to assess solute clearance over time. The animal was treated with daily aspirin and clopidogrel beginning three days before the implant, continuing throughout the post-operative period.

Results: The animal tolerated surgical implantation and subsequent dialysis sessions without complication. Blood flow through the dialyzer remained brisk throughout the three-day study. All dialysis sessions were completed as planned, via recirculation of normal saline through the dialysate catheters. Over the course of the study, normalized creatinine and urea clearances ranged from 11-42 mL/min/$m^2$and 26-74 mL/min/m^2, respectively. Albumin concentration in the dialysate remained below the detection limit throughout the study.

Conclusions: We demonstrated preclinical feasibility of an implantable, pumpless SNM-based hemodialyzer. Further development and refinement of the SNMHD could provide an alternative method for hemodialysis access and facilitate frequent in-home dialysis.

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FR-OR007

International Trends in Mortality Soon after Switch from Peritoneal Dialysis to In-Center Hemodialysis: Results from the INTEGRATED Study Group

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Background: Switching between dialysis modalities is common among patients (pts) with end-stage kidney disease (ESKD) and has been shown to be associated with adverse outcomes. This international registry study describes mortality rates after switch from peritoneal dialysis (PD) to in-center hemodialysis (HD).

Methods: Using four longstanding international registries (ANZ, CORR, ERA, USRDS), and with support from the NIDDK, this study analyzed incident PD pts, defined as starting PD within 180 days of ESKD incidence, who switched from PD to HD for ≥1 day. Pts were grouped into 3 cohorts by year of ESKD incidence (2000-2004, 2005-2009, 2010-2014). Crude mortality rates (per 100 patient-years [PY]) were calculated for the first 180 days after switch, with patients censored on the date of death, transplant, loss-to-follow up, or study end-date.

Results: In each registry, (1) mortality rate was highest during the first 30 days after switch to HD, subsequently declining to a stable rate by 120 to 180 days (Figure); (2) mortality rate decreased from the earliest to the most recent cohort, though remained high soon after switch to HD (Figure).

Conclusions: Transition from PD to HD is associated with high mortality rates internationally, especially during the first 30-day period. The lower mortality rates in recent years may reflect more timely transition and/or improved peri-transition care. Future studies should evaluate optimal timing of switch, as well as modifiable predictors of post-switch mortality, to increase the likelihood of successful transition and to improve clinical outcomes.

Funding: NIDDK Support

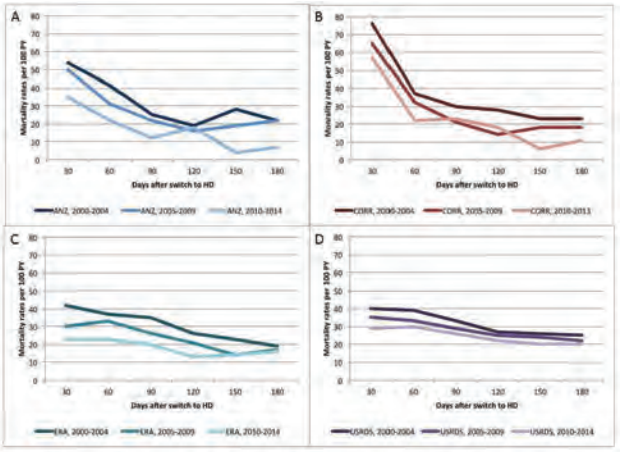
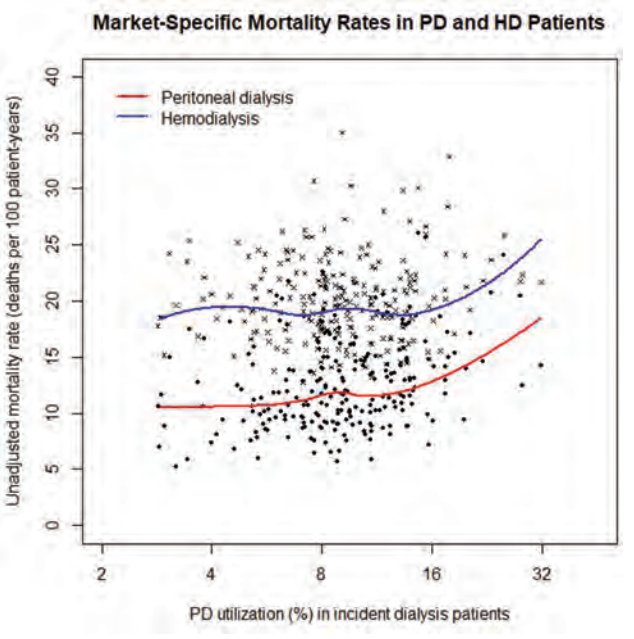


Figure. Mortality rates of incident PD patients who switched to HD for ≥1 day, separated into 3 cohorts, among A) the Australia & New Zealand Dialysis & Transplant Registry (ANZ), B) the Canadian Organ Replacement Register (CORR)*, C) the European Dialysis and Transplant Association (ERA), and D) the United States Renal Data System (USRDS).
*Patients included through 2013 (versus 2014 in the other registries)



FR-OR008

Peritoneal Dialysis Utilization in US markets and Associated Mortality Rate Ratios for Peritoneal Dialysis Versus Hemodialysis

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Background: In the United States, peritoneal dialysis (PD) is associated with lower mortality risk than in-center hemodialysis (HD) during the first year of dialysis. However, increased utilization of PD in a local area may move higher-risk patients from HD to PD, thus attenuating the mortality rate ratio (MRR). We assessed the influence of PD utilization in US markets on MRRs for PD versus HD.

Methods: We analyzed data from the United States Renal Data System. We identified incident dialysis patients in 2006-2013 and retained patients in markets with ≥500 patients. For each area, we calculated the percentage of patients on PD within 3 months of dialysis initiation. Using Poisson regression, we assessed the association of that percentage with the mortality rate between 3 and 36 months after dialysis initiation, without censoring for modality change and with fixed effects for markets.

Results: The cohort included 586,718 incident dialysis patients in 236 markets. Overall PD utilization was 8.8%. Market-specific mortality rates in PD and HD patients are displayed. Market-adjusted MRRs for PD versus HD were 0.56 with local PD utilization of 2-3% (number of markets, 12), 0.55 with utilization of 4-5% (27), 0.58 with utilization of 6-7% (47), 0.61 with utilization of 8-11% (90), 0.65 with utilization of 12-15% (42), 0.64 with utilization of 16-19% (11), and 0.77 with utilization of ≥20% (7). Compared to the market-adjusted MRR with local PD utilization of 2-3%, only the MRR with utilization of ≥20% was significantly different ($P < 0.01$).

Conclusions: Across a gradient of local PD utilization from 2% to 20%, MRRs for PD versus HD are similar. Expanded utilization of PD in incident dialysis patients may have limited negative effect on population survival.

Funding: Commercial Support - NxStage Medical, Inc.

FR-OR009

Peritoneal Fluid Cell Free DNA Is a Versatile Analyte of Peritonitis

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Background: Culture negative peritonitis is common in peritoneal dialysis (PD) patients, especially in the setting of recent antibiotic use. We investigated whether sequencing cell free DNA (cfDNA) extracted from peritoneal fluid supernatants can identify the suspected causative agent(s) in cases of peritonitis.

Methods: We recruited 7 PD subjects: 3 subjects had peritonitis and 4 subjects did not have evidence of peritonitis; and we collected 16 peritoneal fluid specimens. cfDNA was isolated using a Qiagen Circulating Nucleic Acid Kit and a single stranded library preparation was constructed for each specimen. The library was sequenced using an Illumina Next-Seq instrument (75 base pair by 75 base pair). Pathogen identification was performed using the bioinformatics program, GRAMMy.

Results: We obtained approximately 10 million cfDNA reads per specimen. Three PD subjects had an episode of culture confirmed peritonitis (*Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*). cfDNA profiling identified the organisms in all 3 cases and importantly on subsequent days after antibiotic administration which had corresponding same day cultures that were negative. One of the subjects subsequently developed another episode of suspected peritonitis. The subject was treated for peritonitis with intraperitoneal antibiotics, but the peritoneal fluid cultures on admission were negative. The subject continued to have abdominal pain despite intraperitoneal antibiotics. The subject was suspected to have cholecystitis and cullture from a percutaneous cholecystotomy 4 days after admission grew *Enterococcus faecium* and *Parabacteroides distasonis*. cfDNA profiling of peritoneal fluid detected *Enterococcus faecium* and *Parabacteroides distasonis* on admission.

Conclusions: Our pilot data support the use of cfDNA profiling of peritoneal fluid to investigate peritonitis, especially in the setting of antibiotic use, and potentially as a method to investigate occult infections in abdominal organs.

Funding: Private Foundation Support

FR-OR010

Nanoparticles of Lipids with Paclitaxel Reverse Inflammation and Peritoneal Fibrosis in the Peritoneal Fibrosis Model in Uremic Rats

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Background: Increased cellular proliferation and inflammation of the peritoneal membrane (PM) are complications of long term peritoneal dialysis leading to peritoneal fibrosis (PF). Paclitaxel, a potent antiproliferative drug, has therapeutic efficacy, limited by toxicity. Nanotechnology enabled drug release systems that can concentrate the active drug on target tissues. LDE, a LDL similar nanoparticle, was associated to Paclitaxel (NanoPACLI) in order to reduce drug toxicity. NanoPACLI binds to LDL receptors, which are overexpressed on the cell surface of inflamed tissues. In this study, the effects of NanoPACLI administration in a model of experimental PF associated to uremia were analyzed.

Methods: Uremia was induced in male Wistar rats fed with adenine-containing diet during a period of 21 days. Injections of chlorhexedine gluconate (CG) were administrated intraperitoneally (IP) to induce PF. Rats (n=27) were divided into 3 groups: **Control**, normal rats receiving saline injections; **PF/CKD**, uremic rats receiving CG injections; **PF/CKD-NanoPACLI,** uremic rats with PF receiving NanoPACLI injections (IP; 4mg/kg every 3 days). The NanoPACLI treatment was initiated 7 days after PF induction. Euthanasia was performed on day 21. PM thickness, ultrafiltration (UF), inflammatory cell infiltration, and cytokine expression were analyzed.

Results: NanoPACLI significantly decreased peritoneal thickness, prevented UF failure, reduced inflammatory cellular infiltration as well as cytokine concentration in the PM.

Conclusions: NanoPACLI administration was effective in inhibiting the progression of PF and preserving UF in a model of established PF in uremic rats. These findings may be related to the anti-inflammatory effects of paclitaxel delivered locally by NanoPACLI.

Effects of NanoPACLI on PF model in uremic rats

	Control	PF/CKD	PF/CKD-NanoPACLI
BUN (mg/dL)	21±2	97±12**	91±6**
Peritoneal Thickness (µm)	17.2±2.2	91.4±16.3***^	45.9±7.8
UF (ml)	15.9±3.3	-2.2±1.3***^	3.3±1.4
Macrophages (cells/mm^2)	72.4±18.8	347±137^	97.1±32.9
T-cells (cells/mm^2)	11.6±9.2	299.4±64.9**	100.2±74.8
IL-1β (pg/ml)	39.9±5.4	377.3±115.3^	129.4±21.5
TNF-α (pg/ml)	1.7±0.2	50.8±24.3^	4.9±2.6
INF-γ (pg/ml)	9.3±3.06	45.3±12.1**	7.4±2.4

Results were expressed as mean±SEM. *p<0.05;**p<0.01,***p<0.001

FR-OR011

Reducing the Incidence of Post CABG AKI by Early Intervention Guided by Novel Urinary Biomarker (TIMP-2, IGFBP-7): An Institutional Experience

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Background: AKI post cardiac surgery occurs in up to 25% of patients: KDIGO AKI Stage 1 (30%), Stage 2 (10-15%), Stage 3 (2-5%), RRT (1%) and adversely affects prognosis, prolongs hospital stay and increases readmission rate. KDIGO guidelines recommend preventative measures in patients at high risk for developing AKI. In two multicenter studies of critically ill patients, NephroCheck (NC), urinary tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), was validated for risk stratification for moderate-severe AKI. These markers are believed to reflect renal tubular epithelial cell response to stress and can identify patients at risk before injury occurs allowing for interventions to prevent AKI

Methods: Urinary NC was measured in CABG pts (n = 98) at our institution the morning after surgery. All pts with NC > 0.3 (moderate positive) received a modification of the KDIGO support measures. For NC > 0.6 (high positive), nephrology consultation was added. Patients with preoperative CKD were excluded. AKI was defined as rise in creatinine by 0.3 from baseline until hospital discharge. Interventions included goal-directed therapy for optimizing volume status, hemodynamics and renal perfusion pressure, raising the PAD pressure to 14-16 using balanced crystalloid, instituting inotropes for depressed cardiac function, limiting use of diuretics, avoidance of RAAS inhibitors, NSAIDs, and nephrotoxins, extending duration of hemodynamic monitoring, and using a higher transfusion threshold

Results: The AKI incidence (STS registry stage 3 KDIGO) prior to our study was 2.36 %. During the 6-month period using NC, the incidence of Stage 3 AKI fell to 1.25%. One false positive test was seen. One pt with a positive NC had a 2-hour UF post operatively; no other patients required RRT

Conclusions: The use of NC, a urinary biomarker for renal stress, in combination with rapid renal supportive interventions resulted in a 47% relative reduction in AKI in our institution in post CABG patients.

FR-OR012

Preventing AKI and Improving Outcome in Critically Ill Patients Utilising Risk Prediction Score (PRAIOC-RISKS) – A Pilot Study

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Background: Early detection and management of AKI in medical ICU is an unmet goal. Our study used a risk score to identify patients at high risk of developing AKI and apply timely preventive measures.

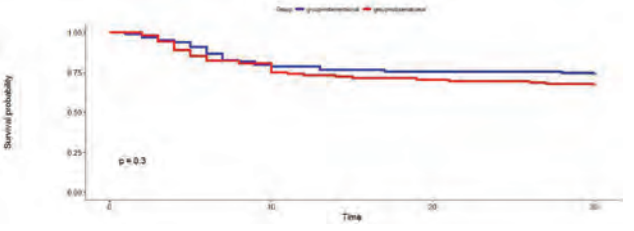
Methods: The study was run at two separate medical intensive care units. A recently validated and published risks score, developed by Malhotra and colleagues was used. A risk score was applied to all patients admitted to the ICU during the study period. Eligible patients were adults, who had mental capacity and who did not have AKI at time of recruitment. Patients who had established AKI at the time of recruitment were excluded from the study. In the (observation) ICU, patients received the standard care. In the (intervention) ICU, high risk patients (risk score ≥5) had very early nephrology review. A package of standardized recommendations was implemented. Measures included optimizing fluid balance, mean arterial pressure, cessation and avoidance of potential nephrotoxic medications and optimal sepsis management. The primary outcome was the incidence of AKI.

Results: During 8 months, we recruited 98 patients in the intervention arm and 108 patients in the observation arm. Baseline characteristics are shown in table 1. There was statistically significant difference in AKI incidence between the two groups (26% in the observation group versus 11% in the intervention group, p=0.002). 30 day-mortality was lower in the intervention group but not statistically significant (25% in the intervention arm versus 32% in the observation arm, p=0.35).

Conclusions: It was feasible to apply very early nephrology intervention to critically ill patient at high risk of developing AKI. The incidence of AKI was significantly lower in the intervention group. Multicentre studies are needed.

	Intervention	Observation	p value
Age (years)	48.01	51	0.23
Female sex n (%)	54(55%)	63(58%)	0.740
Basline creatinine (mg/dl)	1.16	1.07	0.315
SAPS 2	26	27	0.412
AKI risk score	5.32	5.21	0.112
Diabetes n (%)	36 (37%)	39 (36%)	0.326
Hypertension n (%)	33(34%)	42(39%)	0.527
Chronic kidney disease n (%)	13(13%)	10(9%)	0.188
Cardiovascular disease	23(23%)	21(20%)	0.164
30 day Mortality	25	35	0.35

Baseline characteristics



30 days Mortality

FR-OR013

Community AKI Reporting Improves Longer-Term Patient Outcomes

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Background: More than half a million patients develop AKI in England per year. Two-thirds of these occur in the community. AKI episodes have long-term implications with regard to morbidity and mortality. To improve detection of AKI in the community, automated detection systems have been developed to generate an 'AKI Alert' alongside blood test reports. In this study, we assess the outcomes of patients 3 years after the episode of AKI was detected.

Methods: AKI alerts were generated using the UK national AKI algorithm. Only blood tests done in the community were considered. 3-year outcomes were analysed for patients with AKI alerts in December 2014. Worsening renal function was defined as an increase in CKD stage by 1 or more.

Results: 79 AKI alerts were issued over this time period. Of these, 9 were excluded from analysis as 3 were repeat alerts and data was missing for 6. The median age of the patients in which AKI was detected was 80 (Min 22, Max 94). 45 patients had pre-existing CKD with 43% of the total cohort having an eGFR 30-60 and 21% having an eGFR of less than 30. 19 of the 70 alerts were incorrect with 95% overstating the stage of AKI as defined by KDIGO criteria. In cases when AKI was reported correctly, 70% of patients died or had worse renal function 3 years after the episode of AKI. In 71% of cases where an episode of AKI was detected by the algorithm, the alert led to a repeat blood test within 4 weeks. However, in the patients that did not have a repeat blood test in this time frame, there was a higher proportion of falsely reported AKI (45% versus 16%). This might be expected as the clinician may be less likely to repeat the test if deemed not to be a true episode of AKI. Patients in which the alert resulted in a repeat blood test in 4 weeks had a lower incidence of worsening renal function (40% vs 55%) and a composite outcome of death or worsening renal function (69% vs 73%) at 3 years.

Conclusions: A high proportion of patients who have an incidence of 'community' AKI go on to develop worsening CKD or death within 3 years. In cases when the AKI alert led to further investigation, there was a lower incidence of death and progressive renal dysfunction compared to cases where no action was taken. This suggests that a community blood test-based AKI alert system leads to longer lasting improved patient outcomes.

FR-OR014

Impact of Intensive Glycemic Control in the Development of AKI after Cardiac Surgery: A Randomized Clinical Trial

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Background: Hyperglycemia is directly linked to higher rates of morbidity and mortality in hospitalized patients and is recognized as an important risk factor for postoperative complications. We performed a randomized controlled trial to evaluate the impact of an intensive glycemic control strategy in the occurrence of acute kidney injury in patients undergoing cardiac surgery.

Methods: Were included patients who presented blood glucose greater than 200 mg/dl in the first 6 hours of admission to the ICU. Patients aged less than 18 yo, diagnosed with congenital heart disease and heart transplantation were excluded. The patients were allocated in one of the groups: conventional group (CG), glucose target between 140 and 180 mg/dl and the intensive group (IG), glucose target between 90 and 110 mg/dl. The primary endpoint was AKI defined according with KDIGO criteria. The secondary outcomes were mortality, need for dialysis, renal function recovery, hypoglycemia, ICU discharge, length of stay in ICU.

Results: Were included 95 patients, 36 (37.9%) in the IG and 59 (62.1%) in the CG. In the comparison between groups, no significant difference was observed in relation to the surgical risk (p = 0.511) and the risk for acute kidney injury (p = 0.962), measured by the EuroSCORE and Cleveland Clinic Score, respectively. Using vasoactive drugs was higher in the IG as compared to CG (97.2% vs. 83.1%; p = 0.047). There was no difference in the incidence of AKI in IG, when compared with CG (61.1% vs. 49.2%; p = 0.294, respectively). Nevertheless, the return of kidney function to the basal values was smaller in the IG as compared to CG (41.7% vs. 69.5%; p = 0.010, respectively). There was no found any difference between the groups in relation to mortality (p = 0.066), need for dialysis (p = 0.364) and episodes of hypoglycemia (p = 0.151). There was a higher number of ICU discharges in the CG, when compared with IG (98.3% vs. 86.1%; p = 0.028, respectively) as well as shorter length of stay in the ICU (4.2 ± 3.0 vs. 5.7 ± 4.2; p = 0.046, respectively).

Conclusions: The intensive glycemic control strategy used in this study was not associated with decrease in the incidence of acute kidney injury in patients undergoing cardiac surgery also influenced negatively in secondary outcomes.

FR-OR015

One-Year Mortality Follow-Up in Subjects Treated with QPI-1002 at Risk of AKI Following Cardiac Surgery (CS)

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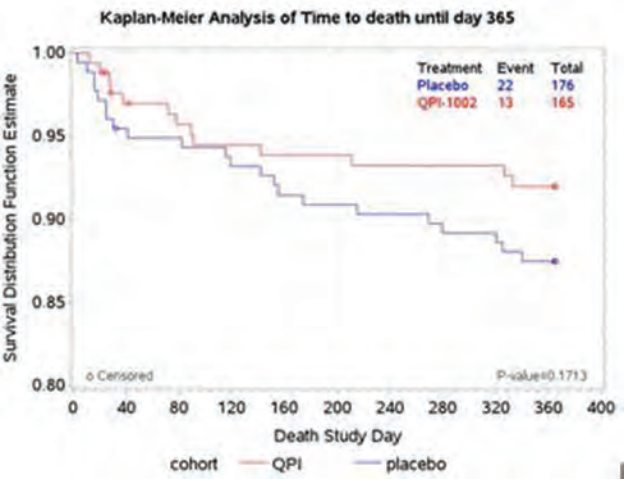
Background: QPI-1002 (QPI), a siRNA targeting p53, is being developed for prevention of Delayed Graft Function (DGF) (NCT#02610296) and for reduction of acute kidney injury (AKI) and its consequences following CS. In a large global Phase 2 double-blind study (N=341: QPI=165, Placebo (PL)=176) (NCT#02610283), QPI reduced the incidence, severity and duration of AKI and reduced the proportion of subjects with major adverse kidney events (MAKE) at Day 90 as previously reported (ASN 2017 Abstract SA-OR124).

Methods: For the primary study, deaths were recorded through Day 90 and causes of death adjudicated by medical dictionary for regulatory activities (MedDRA) coding in a blinded fashion by the medical monitor and safety physician. Longer term mortality was collected at Day 365

Results: Deaths: 22/176 subjects receiving PL and 13/165 subjects receiving QPI died within 365 Days after receiving study drug (p=0.1713). Causes of death were coded to System organ class (SOC): Cardiac Disorders system (3QPI/3 PL), General disorders, (1QPI/5 PL), Infectious disorders (4QPI/4PL), Neoplasm (1PL), Nervous system disorders (2PL), Respiratory disorders (2QPI/2PL), Metabolism (1QPI), Vascular (1QPI) and Not Reported/Unknown(1QPI,5PL). None of the deaths were reported as related to study drug. Eighteen subjects (10 PL and 8 QPI) died within 90 days and 17 subjects (12 PL and 5 QPI) died between D90 and D365.

Conclusions: The results indicate a survival trend through Day 365 in favor of QPI treatment. Additional studies are required to confirm these findings.

Funding: Commercial Support - Quark Pharmaceuticals



FR-OR016

Mortality Outcomes Related to Acute Declines in eGFR following RAAS Inhibition in Patients with Heart Failure

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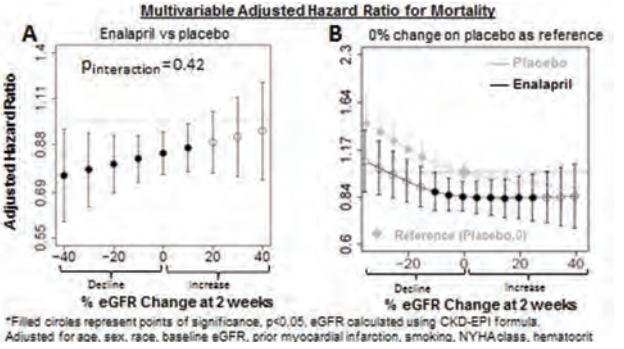
Background: Blockade of the renin-angiotensin-aldosterone system (RAAS) is beneficial for cardiovascular outcomes in heart failure with reduced ejection fraction (HFrEF). However, it is associated with acute declines in estimated glomerular filtration rate (eGFR). Whether the benefit of RAAS inhibition persists for all magnitudes and timing of acute declines remains unclear.

Methods: We performed a retrospective analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) trial, in which patients with HFrEF were randomized to enalapril vs placebo. Multivariable Cox models were used to evaluate the association of % eGFR change from baseline to three follow-up time points (2 weeks, 6 weeks, 12 months) with mortality. We tested for an interaction between treatment group and % eGFR decline. In effort to separate eGFR decline secondary to RAAS inhibition from eGFR decline due to other causes, we also calculated the mortality hazard ratios for enalapril and placebo using the reference point of 0% eGFR decline on placebo.

Results: Using the 2-week follow-up time point, 6,031 participants were included in the analysis (n=3,015 in the enalapril group, n=3,016 in placebo). Compared to placebo, enalapril was associated with a lower hazard of mortality at all levels of eGFR decline, with no significant interaction between treatment assignment and eGFR decline (Figure A). When compared to patients randomized to placebo with 0% eGFR decline, up to 20% decline in the enalapril group was still associated with a lower hazard of mortality (Figure B). Declines of >20% in placebo had higher hazard of mortality compared to placebo with 0% decline, but similar declines in the enalapril group were not. Results were consistent using the time points of 6 weeks and 12 months.

Conclusions: Enalapril decreases mortality at all levels of eGFR decline when compared to placebo. In patients with HFrEF, ACE inhibitors should be continued even if there is an acute decline in GFR up to 20%.

Funding: Other NIH Support - T32 grant: 1T32DK07777



FR-OR017

Thrombotic Microangiopathy Frequency in Patients with Atypical HUS: Discontinuing vs Remaining on Eculizumab Treatment

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Background: Atypical hemolytic uremic syndrome (aHUS) is characterized by thrombotic microangiopathy (TMA). Eculizumab (Ecu), a C5 inhibitor, is the first approved treatment for patients (pts) with aHUS. Using data from the Global aHUS Registry, the largest database of patients with aHUS, we report TMA rate in pts receiving ongoing Ecu vs those who discontinued Ecu.

Methods: Pts enrolled in the non-interventional Global aHUS Registry (NCT01522183) up to 1 January, 2018 were included in this study of real-world data. Pts with unknown treatment status were excluded from this analysis. Additionally, pts with a cobalamin deficiency or diacyl glycerol kinase-ε mutation were excluded from the Ecu treated group. Data were stratified according to Ecu treatment status and descriptive statistics on TMA rate were calculated.

Results: Of the 1475 pts eligible for this analysis, 532 pts were never treated with Ecu and 943 pts were treated with Ecu. Among the latter, 682 pts remained on Ecu without discontinuing treatment, 218 pts discontinued Ecu without restarting and 43 pts discontinued and restarted Ecu. Overall, pts who remained on Ecu had a lower TMA rate than pts who were never treated and pts who discontinued treatment (3.6, 27.5 and 10.7 per 100 pt-years, respectively; Table).

Conclusions: In this, the largest cohort ever analyzed in a real-world, non-randomized setting to address the question of treatment maintenance in aHUS, pts who continued to receive Ecu had a substantially lower risk of TMA than those who discontinued or never received Ecu.

Funding: Commercial Support - Alexion Pharmaceuticals

Clinical characteristics per eculizumab treatment status

		Never treated[a]	Discontinued never restarted[b]	Discontinued and restarted[c]	Ongoing treatment[d]
n		532	218	43	682
TMAs	Pts with TMA (events)	171 (301)	6 (7)	7 (10)	68 (120)
	TMA rate/100 pt-years	27.5	10.7	23.9	3.6
Time on Ecu (years)	Median (IQR)	–	0.6 (0.1–1.2)	2.7 (0.8–3.8)	1.6 (0.5–3.5)
Time to restart Ecu (years)	Median (IQR)	–	–	0.4 (0.1–1.5)	–
Follow-up time (years)	Median (IQR)	1.9 (1.0–3.3)	2.3 (1.2–3.2)	3.0 (2.0–3.9)	2.0 (1.0–3.1)

[a] Pts who were never treated with Ecu (TMAs evaluated from enrollment to last follow up); [b] Pts who discontinued Ecu and never restarted (TMAs evaluated from discontinuation to last follow up); [c] Pts who discontinued Ecu and restarted (TMAs evaluated from first discontinuation to first restart); [d] Pts who never discontinued Ecu (TMAs evaluated from treatment start to last follow up). The definition of TMA was as evaluated by investigator. Decision to treat or discontinue with Ecu was not randomized but made by the investigator.

Ecu, eculizumab; IQR, interquartile range; n, total number in group; pts, patients; TMA, thrombotic microangiopathy.

FR-OR018

Dutch Initiative to Improve Therapy and Economize Healthcare in Atypical HUS

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Background: With the introduction of eculizumab, a new era began for patients with atypical hemolytic uremic syndrome (aHUS); a rare but severe form of thrombotic microangiopathy (TMA). Although the results were promising, a worldwide debate started regarding optimal treatment strategy. Lifelong treatment with this highly expensive orphan drug was advised, despite any evidence. In the Netherlands, an unique and challenging initiative was undertaken by the national working group aHUS, comprising a delegation of (pediatric) nephrologists of all academic hospitals. In 2016, the new Dutch guideline for the diagnostics and treatment of aHUS, drafted by this working group, was implemented. This guideline advocates a restrictive treatment regimen and is monitored by the national, observational, CUREiHUS study. Here we present first preliminary results.

Methods: All known and suspected aHUS patients up till September 2017, were discussed in the working group and included. Patients received plasma therapy and/or eculizumab following the guideline and therapy was evaluated and tapered when patients were stable and in remission. Follow up data were only available from those registered in CUREiHUS study.

Results: In total, 69 patients with TMA have been discussed of which 44 new patients with TMA. In 27 out of the 44, aHUS was suspected and eculizumab was initiated in 25 patients. In the remaining 17 patients, other diagnoses explanatory for the TMA were present, hence no eculizumab treatment was started. Of the 32 patients included in the CUREiHUS study, therapy was adjusted in all. Only 19% of the patients experienced recurrence. After rapid initiation of eculizumab, eculizumab therapy was tapered again with good clinical outcome. A costs reduction of 55% was accomplished.

Conclusions: The new Dutch guideline on the treatment of aHUS regarding a restrictive eculizumab regimen appears safe and effective. Moreover, by critically evaluating eculizumab therapy, aHUS treatment can be economized. Although this first annual report showed promising results, the majority of patients is within their first year of follow up and continuous careful monitoring remains warranted.

FR-OR019

Renal Immune Related Adverse Events in Patients Treated with PD-1 Inhibitors: An Emerging Complication of Immunotherapy

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Background: Inhibition of programmed cell death protein 1 (PD-1) immune checkpoint pathway activates patient's immune system, which is responsible for anti-tumor effect but may cause unwanted immune-related adverse events (IrAE) including renal effects.

Methods: Retrospective review of cases of acute kidney injury (AKI) or nephrotic syndrome while on treatment with PD-1 inhibitors seen at MSKCC between 2012 and 2018. Patients concurrently treated with another checkpoint therapy were excluded.

Results: Thirty-one patients were identified and twenty-three met inclusion criteria. Eight were male and the average age was 61.7 years. Fourteen patients had a biopsy while nine were treated empirically. The mean number of immunotherapy cycles prior to onset of AKI was 5.08 (1-14). In the biopsy group (Table 1), thirteen patients had AIN and one had membranous glomerulonephropathy (MGN). All had either full or partial recovery of renal function. Two patients were re-challenged with PD-1 inhibitors and tolerated 2 and 5 cycles respectively accompanied by low dose steroid therapy. One patient was re-challenged without corticosteroids and AKI recurred after 10 cycles. One patient with biopsy proven AIN received 5 additional cycles without further worsening of renal function. The patient with MGN developed a relapse after re-challenge with checkpoint inhibitor but tolerated additional 5 cycles with supportive care.

Conclusions: Most patients with renal IrAE developed AIN and all recovered kidney function. These patients can be re-challenged with PD-1 inhibitors if clinically indicated with concomitant steroid therapy support.

Funding: Other NIH Support - MSK Cancer Center Support Grant/Core Grant (P30 CA008748)

Patient	Age (years)	Gender (M/F)	Baseline SCr* (mg/dL)	Peak SCr (mg/dL)	Urinalysis findings	Check-point number of cycles	Nephritis treatment	Re-challenge with check point	Last SCr (mg/dl)	Biopsy Findings
1	71	F	0.8	6.5	Pyuria Eosinophil 2%	3	Steroid taper	No	1.3	AIN[a,c]
2	71	F	1.3	2.1	Albumin 100 Pyuria 5-10 RBC/HPF	5	None	No	1.4	AIN
3	83	F	0.9	1.9	Pyuria 9 RBC/HPF	8	None	No	1.0	AIN
4	62	F	0.6	1.3	Pyuria 5 RBC/HPF	3	Steroid taper and maintenance	Yes (2 doses)	1.0	AIN
5	69	M	1.1	1.7	6-10 WBC/HPF	5	Steroid tapers2	Yes (5 doses)	1.5	AIN
6	73	F	0.8	5.1	Albumin 100	1	Steroid taper	No	1.1	AIN
7	58	F	1.2	1.6	Bland	8	Steroid taper	No	1.0	AIN
8	75	M	1.1	1.0	Albumin >1000	6	Steroid taper	Yes-partial remission and recurrence	0.6	MGN† PLA2R Neg
9	73	M	1.0	3.3	Bland	10	Steroid taper	No	1.5	AIN
10	69	M	1.3	3.9	Albumin trace	2	Steroid taper	No	1.4	AIN
11	74	F	0.7	4.5	Albumin trace	7	Steroid taper	No	1.2	AIN
12	50	F	0.6	1.5	Bland	5	Steroid taper	No	1.0	AIN
13	67	F	0.7	1.9	trace hematuria 9RBC/HPF	4	Steroid taper	No	1.2	AIN
14	45	M	0.8	1.5	Bland	3	None	Yes (5 doses)	1.0	AIN

FR-OR020

Polymyxin Hemoperfusion Shows No Benefits on Kidney Outcomes in Severe Sepsis Patients

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Background: Polymyxin B Hemoperfusion (PMX-HP) has been introduced as one of the treatments for sepsis over the past 25 years. Previous randomized control trials (RCT) examining the efficacy of PMX-HP reached different conclusions. We aimed to study the effect of PMX-HP on kidney outcomes in patients with severe sepsis.

Methods: An RCT was conducted in sepsis patients who were admitted at intensive care units and had blood endotoxin activity assay (EAA) level ≥ 0.6. They were randomized into 2 groups. The PMX-HP group received standard treatment plus 2-hour PMX-HP for 2 consecutive days whereas the non PMX-HP group received only standard treatment for sepsis. The primary outcome was Major Adverse Kidney Events by 28 days (MAKE28) which consisted of mortality, renal replacement therapy (RRT) status, and persistent renal dysfunction. Secondary outcomes were the mean or median change in mHLA-DR

expression, CD11b expression, neutrophil chemotaxis, cardiovascular sequential organ failure assessment (CVS SOFA) score, vasopressor dose, and EAA level between day 3 and day 0. Other parameters included serum creatinine on day 7, ICU free days, and ventilator free days.

Results: 59 patients were randomized to PMX-HP (n=29) and non PMX-HP (n=30) groups. At baseline, clinical and immunologic parameters were comparable between groups. The MAKE28 were not significantly different between the two groups, p=1.0. The median change in mHLA-DR expression, parameter of monocyte function, was higher in PMX-HP patients than in non PMX-HP patients, p=0.027. The mean change in CD11b, sparameter of neutrophil activation, was significantly lower in PMX-HP than in non PMX-HP, p=0.002. There were no significant changes in neutrophil chemotaxis, CVS SOFA scores, vasopressor doses, or EAA levels between groups. The serum creatinine on day 7, ICU-free days, and ventilator-free days were comparable between groups.

Conclusions: PMX-HP had no benefits on kidney outcomes in severe sepsis patients. However, it showed beneficial effects on immunomodulation processes. Whether this effects should improve clinical outcomes needs further larger scale clinical trial.

Funding: Commercial Support - Toray provided Polymyxin-B cartridge and endotoxin activity assay kits for use in this study. The company had no influenced on the study design or analysis or on the comment of this article. None of the other authors have any disclosures., Private Foundation Support

FR-OR021

Associations of Tubular Injury, Inflammation, and Repair Biomarkers with AKI in the SPRINT Trial

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Background: Randomization to intensive BP treatment (SBP <120 mmHg) in SPRINT led to higher AKI risk compared to standard BP treatment (SBP <140 mmHg). Whether a greater burden of tubular disease predisposes to AKI has not been well evaluated.

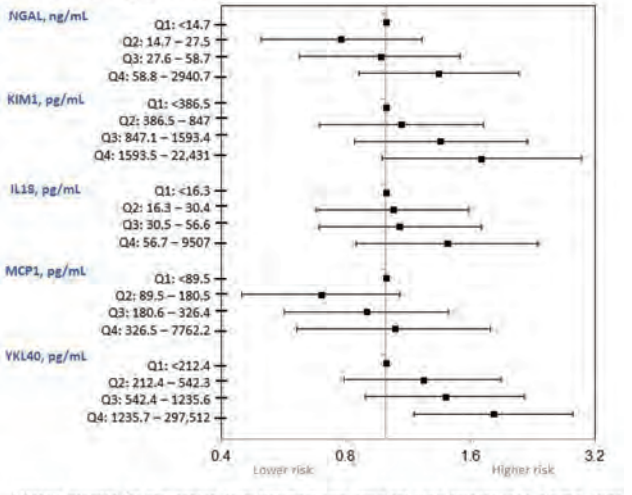
Methods: Among SPRINT participants with CKD (eGFR <60 mL/min|1.73 m^2), we measured baseline urine levels of tubular injury (NGAL, KIM1 and IL18), inflammation (IL18 and MCP1) and repair (YKL40) biomarkers using multiplex panels. Cox proportional hazards models were used to examine whether baseline biomarker levels (log_2-transformed and in quartiles) were independently associated with AKI, defined by hospital discharge AKI diagnosis listed within the top three reasons for hospitalization. We examined whether treatment arm assignment modified these associations by inclusion of interaction terms.

Results: Among 2412 CKD participants with urine biomarkers, the mean age was 73 and mean eGFR 45.9 mL/min/1.73m^2. A total of 190 AKI events occurred over a median 3.2 years of follow-up. YKL40, per 2-fold higher, was independently associated with higher risk of AKI (HR=1.09; 95% CI: 1.01-1.18). The highest versus lowest YKL40 quartile was significantly associated with risk of AKI in adjusted analyses (HR=1.82; 95% CI:1.17-2.83) (**Figure**). Treatment arm assignment did not influence this association. In contrast to YKL40, biomarkers of tubular injury and inflammation were not significantly associated with AKI risk in adjusted analyses.

Conclusions: Higher baseline urine YKL40 levels were associated with higher risk of AKI among SPRINT participants with CKD. These results suggest that CKD patients with greater activation of tubular repair mechanisms are more vulnerable to AKI.

Funding: NIDDK Support

Figure: Association of baseline biomarkers of tubular injury, inflammation and fibrosis with AKI: Hazard Ratio (95% CI)*



*Models adjusted for age; gender; race; treatment arm; prevalent CVD; baseline urine albumin, urine creatinine and eGFR; baseline systolic and diastolic BP; baseline use of ACE-Inhibitors; ARBs or diuretics.. Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; KIM1, kidney injury molecule-1; IL18, interleukin-18; MCP1, monocyte chemoattractant protein-1; YKL40, chitinase-3-like protein

FR-OR022

Plasma Angiopoietin-2 Concentrations Mediate the Contribution of Genetic Variation in the Angiopoietin-2 Gene to Development of AKI Sub-Phenotypes

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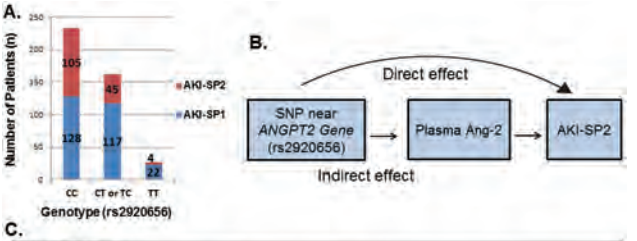
Background: Plasma angiopoietins 1 (Ang-1) and 2 (Ang-2), markers of endothelial stability and dysfunction, have been implicated in the development of acute kidney injury (AKI). Using latent class analysis, we previously identified two AKI sub-phenotypes (AKI-SP1 and AKI-SP2). Critically ill subjects classified as AKI-SP2 had worse clinical outcomes and higher markers of endothelial dsyfuntion (high Ang-2 and low Ang-1) compared to AKI-SP1 (low Ang-2 and high Ang-1). It is unknown whether Ang-1 and 2 are markers of disease or act as a causal mediator in the development of AKI sub-phenotypes.

Methods: A targeted genetic study was performed to identify SNPs within 50 kb of the *Angiopoietin 1 (ANGPT1)* and *Angiopoietin 2 (ANGPT2*) genes associated with AKI- SP2 in 452 AKI subjects from the iSPAAR cohort. Association testing was performed on 190 SNPs. Causal inference analysis was used to determine the role of genetic variation and circulating angiopioetins in the development of AKI-SP2.

Results: An intronic SNP, *rs2920656*, near the *ANGPT2* gene (≈ 30kb downstream to the 3' position) was associated with reduced risk of AKI-SP2 (Bonferroni, p=0.003) and decreased Ang-2 concentrations (p=0.002) adjusting for age, gender, sepsis and 5 principal components of ancestry. Causal inference analysis indicated that the total effect of the SNP (rs2920656) on AKI-SP2 was *Beta* = -0.16 (95% CI -0.23 to -0.09, p=1.0 x 10^{-4}) and the indirect effect was *Beta* = -0.07 (95% CI -0.11, -0.03, p=0.001). This suggests that for each minor allele (T allele) of the genetic variant the risk of developing AKI-SP2 decreases by 16%. When comparing the total effect to the indirect effect through a mediation analysis, 42% of the SNP's prognostic effect was mediated through Ang-2 plasma concentrations (Figure 1).

Conclusions: Our findings support the importance of *ANGPT2* in AKI pathophysiology by mediating plasma Ang-2 levels.

Funding: NIDDK Support, Other NIH Support - NHLBI



C.

ISPAAR Cohort				
Exposure	**Outcome AKI-SP2**			**Mediator (Ang-2)**
	$Beta_{direct}$ (95% CI)	$Beta_{indirect}$ (95% CI)	*Total* (95% CI)	EM (%)
rs2920656	-0.09 (-0.15, -0.04)	-0.07 (-0.11, -0.03)	-0.16 (-0.23, -0.10)	42%

Figure 1: Association between single-nucleotide polymorphism (SNP) rs2920656 and AKI sub-phenotypes and the effects mediated through Angiopoietin-2 (Ang-2) plasma concentrations. (A) Number of patients with AKI-SP2 by SNP. (B) The mediation model. (C) Results of mediation analyses for AKI-SP2. Results are described as observed direct and indirect prognostic effect of the SNP that was mediated through Ang-2 plasma concentrations. 95% CI, p-value and the proportion of the effected mediated (EM%). *Identification of Single Nucleotide Polymorphisms (SNPs) Predisposing to Altered Acute Lung Injury* (iSPAAR)

FR-OR023

Impact of Kinetic Glomerular Filtration Rate Estimation on Medication Dosing in AKI

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Background: Medication dosing during acute kidney injury (AKI) is often based on Cockcroft-Gault (CG) creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) equations (Dowling et al, Pharmacotherapy 2010). However, these equations are not valid in AKI as serum creatinine (SCr) is not in steady state. A kinetic estimate of CrCl or eGFR (keGFR) may be a more accurate method of estimating renal function. The aim of this study was to determine the impact of using kinetic estimates of renal function on drug dosing in critically ill patients with fluctuating SCrs.

Methods: We used data from subjects in the NIH ARDS Network Fluid and Catheters Treatment Trial (Wiedemann et al, NEJM 2006) with more than 2 serial SCrs. SCrs post-dialysis initiation were censored. Daily renal function was calculated using the 1)CG CrCl 2)MDRD and 3)CKD-EPI equations. Kinetic estimates of each formula were calculated using: [Steady State or baseline SCr X CrCl or eGFR/mean SCr at 2 time points]X(1-[(24XΔScr)/(ΔTime (h) X MaxΔSCr/day)]. We evaluated the frequency with which the kinetic estimate of each formula changed medication dosing categories (≥60, 30-59, 15-29, and <15mL/min) compared with the use of CG CrCl, $eGFR_{MDRD}$, or $eGFR_{CKD-EPI}$.

Results: Among 947 subjects, 46.0%, 28.5% and 30.0% of the population required recategorization of the dosing category if the kinetic estimate was used instead of CG CrCl, $eGFR_{MDRD}$, and $eGFR_{CKD-EPI}$, respectively. Recategorization occurred more in those with AKI by AKIN criteria. If CG CrCl was adjusted using the kinetic counterpart, 62.8% of

those with AKI would change dosing categories, compared to 25.6% of patients without AKI.

Conclusions: In a critically ill population, use of kinetic estimates of renal function would change medication dosing in the majority of subjects with AKI on at least one calendar day. Further studies will be needed to test whether use of keGFR in clinical practice would lower the incidence of medication toxicity and avoid subtherapeutic dosing during renal recovery.

Funding: Other NIH Support - T32-DK007219-41

Subjects requiring recategorization using kinetic estimates within 7 days of Acute Respiratory Distress Syndrome

	AKI (n= 521)			No AKI (n=426)		
	No change	±1 category	±2 categories	No change	±1 category	±2 categories
Cockcroft-Gault CrCl	194 (37.2%)	314 (60.3%)	13 (2.5%)	317 (74.4%)	107 (25.1%)	2 (0.5%)
MDRD	291 (55.9%)	220 (42.2%)	10 (1.9%)	386 (90.6%)	39 (9.2%)	1 (0.2%)
CKD-EPI	276 (53.0%)	236 (45.3%)	9 (1.7%)	387 (90.8%)	38 (8.9%)	1 (0.2%)

FR-OR024

Variable Economic Impacts of Clinical Decision Support Algorithms That Predict AKI among Postoperative Patients: A Nationwide Analysis

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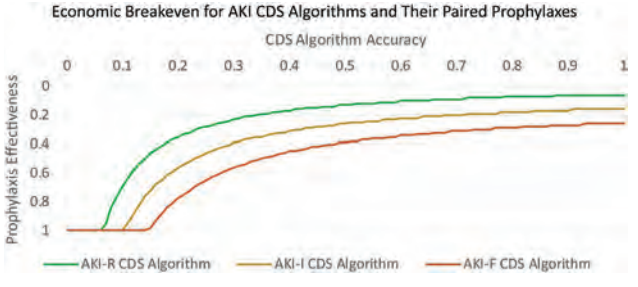
Background: New clinical decision support (CDS) algorithms are being developed to predict the likelihood of AKI among patients who undergo operative treatment. Conceptually those predictions enable early prophylactic interventions that could prevent AKI and thereby avoid its adverse health effects and associated treatment costs. We sought to assess (1) how accurate such CDS algorithms and (2) how effective their paired prophylaxes would have to be to yield a net positive economic impact.

Methods: We searched the 2014 National Inpatient Sample using ICD-9 codes to identify patients ≥18 years old with one or more operative treatments. We combined our findings with data on the incidences and treatment costs of AKI at three RIFLE classification stages. We then performed a sensitivity analysis of the costs associated with the use of CDS algorithms designed to predict AKI-R, AKI-I, and AKI-F in concert with their paired prophylaxes.

Results: We found that CDS algorithms designed to predict AKI-R yielded greater net economic benefits than those designed to predict AKI-I or AKI-F. With an algorithm accuracy of 0.75 and a prophylaxis effectiveness of 0.50, an AKI-R CDS algorithm could create an annual nationwide benefit of $11.6 billion, whereas AKI-I and AKI-F CDS algorithms could create benefits of only $8.3 billion and $4.7 billion, respectively. (**Figure**.) The area under each curve represents the combinations of algorithm accuracy and prophylaxis effectiveness that would produce a net economic benefit for each CDS algorithm.

Conclusions: Our study revealed that lower incidences of AKI-I and AKI-F relative to AKI-R in postoperative patients would likely result in higher false positive rates among CDS algorithms focused on AKI-I and AKI-F. Those higher rates, when combined with likely higher prophylaxis costs to treat potential AKI-I and AKI-F patients, add new costs that, in many cases, overwhelm the costs avoided through early intervention. Barring more effective AKI prophylaxes, future development of AKI-related CDS algorithms should focus on the prediction of AKI-R.

Funding: Other U.S. Government Support



FR-OR025

Defining Kidney Dysfunction in the Community Setting: The ISN 0by25 Initiative

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Background: Community-acquired acute kidney injury (AKI) is common, but often unrecognized in resource-constrained settings. Limited lab assessments and unavailable informationon the prior state of kidney health contribute to this lack of recognition. In this study, we evaluated the efficacy of point of care (POC) serum creatinine (sCr) and urine dipstick tests to identify patients with kidney dysfunction at presentation to community health centres (CHC) and emergency departments (ED), as part of the International Society of Nephrology (ISN) 0by25 Pilot Feasibility Project.

Methods: Patients (pts) presenting at CHC or ED with signs or symptoms associated with high/moderate risk of developing AKI underwent sCr POC test and urine dipstick. At enrollment, pts were classified as chronic kidney disease (CKD) based on prior history, proteinuria(>1+) and/or baseline sCr within 12 mos by estimated GFR (CKD-EPI equation)) <60 mL/min/1.73 m^2; normal renal function (NRF) (no proteinuria and eGFR>75ml/min/1.73 m^2); and Acute Kidney Disease (AKD) neither meeting criteria for CKD or NRF. AKI was confirmed within 7days by sCr increase or decrease of 0.3 mg/dl or 1.5x from the enrollment value. Pt outcomes: progression of AKI, need for RRT, hospitalization, mortality and renal functional recovery, were assessed at 7days and 1, 3 and 6 mos.

Results: 3577pts were screened, 2101enrolled; 91%adults, 9%children. At enrollment, 9% were CKD and 66% AKD. At 7 days, 30% of pts fulfilled criteria for AKI: 67 from NRF (13%), AKD 470 (33%) and CKD 91 (46%). Overall mortality rate was 7.4% at 7 days and increased to 13% at 6 months. In comparison to NRF, AKD and CKD patients had higher mortality at 7 days and follow up, and the development of AKI trended for higher mortality in both AKD and CKD groups. Of 434 patients with 3 months sCr follow up, new onset CKD was encountered in 40(26%) of AKD and 54(33%) of AKI patients. Of patients dying from CKD and AKD groups, non-provision of dialysis occurred in 31 (11%).

Conclusions: Kidney dysfunction is common in CHC and is associated with adverse outcomes. POC tests can identify patients with AKD and CKD at increased risk for AKI, progression of CKD and mortality. Early implementation of targeted interventions may help improve outcomes.

Funding: Private Foundation Support

FR-OR026

Epidemiology of Pediatric AKI in a Nationally-Representative Cohort of American Children

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Background: Acute kidney injury (AKI) significantly increases morbidity and mortality for hospitalized children. However, few studies have evaluated the relationship between race/ethnicity, socioeconomic status (SES) and pediatric AKI. We proposed to evaluate those relationships with the outcome of AKI in a national pediatric cohort.

Methods: The Kids' Inpatient Database, developed by the Agency for Healthcare Research and Quality's Hospital Care and Utilization Program, is a nationally representative database of pediatric discharges from >4100 community hospitals throughout the United States. We conducted a secondary analysis of the most recent data (2012) to assess for racial disparities and socioeconomic differences in the development of pediatric AKI (age 1-20 years) using weighted sampling methods to obtain national estimates. We used logistic regression to assess the relationship between race/ethnicity and SES and the development of AKI, adjusting for comorbidities. SES was defined using three variables: type of insurance (private, Medicaid, other, no insurance), median household income of a patient's zip code in quartiles, and urbanization of patient's home address.

Results: In 2012, approximately 1.2% of all pediatric hospitalizations had an AKI episode, which is a national estimate of almost 30,000 children. After adjusting for chronic illnesses, African American children (Risk difference (RD) 0.00139, 95% CI 0.00064-0.00214) and Asian American children (RD 0.00323, 95% CI 0.00167-0.00478) were at an increased risk for AKI compared to Caucasian children. Children without insurance were more likely to have an episode of AKI compared to those with any form of insurance (e.g., Medicaid versus no insurance has RD of -0.014 with 95% CI -0.016 to -0.012). Based on these data, we estimate that one episode of AKI could be prevented if 73 children currently hospitalized without insurance were provided with Medicaid. No significant differences were seen based on urbanization or median household income.

Conclusions: AKI occurs more frequently in African American and Asian American children compared to Caucasian children. However, the most protective aspect prior to hospitalization is having insurance, regardless of race/ethnicity and type of insurance.

FR-OR027

Reduction in Nephrotoxic Antimicrobial Exposure Decreases Associated AKI in Pediatric Hematopoietic Stem Cell Transplant Patients (HSCT)

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Background: Exposure to nephrotoxic medications (NTMx) is a common risk factor for AKI. Quality improvement work in antimicrobial stewardship and NTMx-associated AKI (NAKI) reduction took place at Cincinnati Children's Hospital from 2013 to 2018. We hypothesized that choosing less nephrotoxic antimicrobial medications for HSCT patients would be associated with lower NAKI rates and no increase in treatment failures.

Methods: We used data from a prospective NAKI monitoring system within our electronic health record. AKI days and severity were extracted for patients exposed to 3+ NTMx or 3+ days of IV aminoglycosides (AG). AKI was defined using KDIGO creatinine criteria. We assessed rates of NTMx exposure and NAKI in all HSCT inpatients from 09/2013 to 03/2018. The percent of repeat positive cultures was used to capture treatment failures. Data were grouped and analyzed by calendar month.

Results: The HSCT division changed frontline fever treatment from piperacillin-tazobactam (pip-tazo) to cefipime, and AG use was limited. Cidofovir use decreased with availability of brincidofovir and antiviral cytotoxic T-lymphocytes. There were no other major changes in supportive care practices. Rates of NTMx exposure, NAKI, and percent of repeat positive cultures all decreased, as shown in Table 1. Mean rates of all stages of NAKI decreased >50% after 01/2016, which coincided with the divisional change from pip-tazo to cefipime. Rates of NAKI have since remained stable.

Conclusions: Reduction of nephrotoxic antimicrobial exposure may decrease the amount and severity of NAKI in HSCT patients without an increase in treatment failures.

Change in Rate of NTMx Exposure, Associated AKI, and Repeat Positive Cultures.

	Period 1: 09/2013 – 01/2016 (Mean per 1000 patient days)	Period 2: 01/2016 – 03/2018 (Mean per 1000 patient days)
Nephrotoxin Exposed Patients	25.46	14.53
All AKI	29.65	12.92
Stage 1 AKI	16.7	6.42
Stage 2 AKI	9.2	4.14
Stage 3 AKI	3.75	1.16
Percent Repeat Positive Blood Cultures	10%	7.3%

FR-OR028

Damage to the Mesangium Mediates the Loss of Podocytes in Glomerular Hypertension

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Background: Glomerular hypertension damages the glomerulus leading to progressive glomerular disease. It is widely believed that increased perfusion pressure exposes the tuft to increased tensile stress challenging the adhesion of podocytes to the GBM favouring their detachment. This hypothesis has been based on the view that podocyte foot processes, like pericyte processes, actively counteract the pressure-driven expansion of the GBM and fail in hypertension. Recent findings have compromised this view. Instead, counteraction of tensile stress to the filtration barrier seems to be almost exclusively performed by the GBM. The GBM displays a non-linear elasticity (Janmey and Tyler Miller 2011, J Cell Sci 124:9) meaning that its distensibility progressively decreases with increasing distension and finally reaches a limit. Thus, the expansion of a glomerular capillary and thus the expansile challenge to podocytes have an upper limit (Kriz and Lemley 2017, Ped.Nephrol 32:405). Podocytes are protected from any unphysiological pressure rises by the GBM.

Methods: High resolutiion light microscopy and transmission electron microscopy.

Results: In hypertensive models and in biopsies from patients with nephrosclerosis local disruptions of mesangial cell GBM connections are a common finding. They are consistently associated with expansions of mesangial spaces and bulging capillaries. These changes have been described in many previous studies. However, the danger that results from such local derangements of the tuft architecture to podocytes has never been adequately recognized. Here we show that such changes are topographically correlated with centrifugal displacements of capillary loops and corresponding podocytes. Depending on the location of the mesangial damage this may lead to a prolapse of podocytes into the urinary orifice with subsequent detachment of podocytes into the urine or to contacts with the parietal epithelium. Such contacts may initiate the formation of a tuft adhesion at any site of the tuft circumference, thus the committed lesion to develop focal segmental sclerosis (FSGS).

Conclusions: A combined failure of mesangial cells and podocytes underlies the development of FSGS in hypertensive glomerular diseases. The same dependence of a podocyte damage on a preceding mesangial failure is also seen in glomerular diseases, in which mesangial-cell-GBM-connections are directly damaged.

FR-OR029

A New Spheroid Model of the Glomerulus

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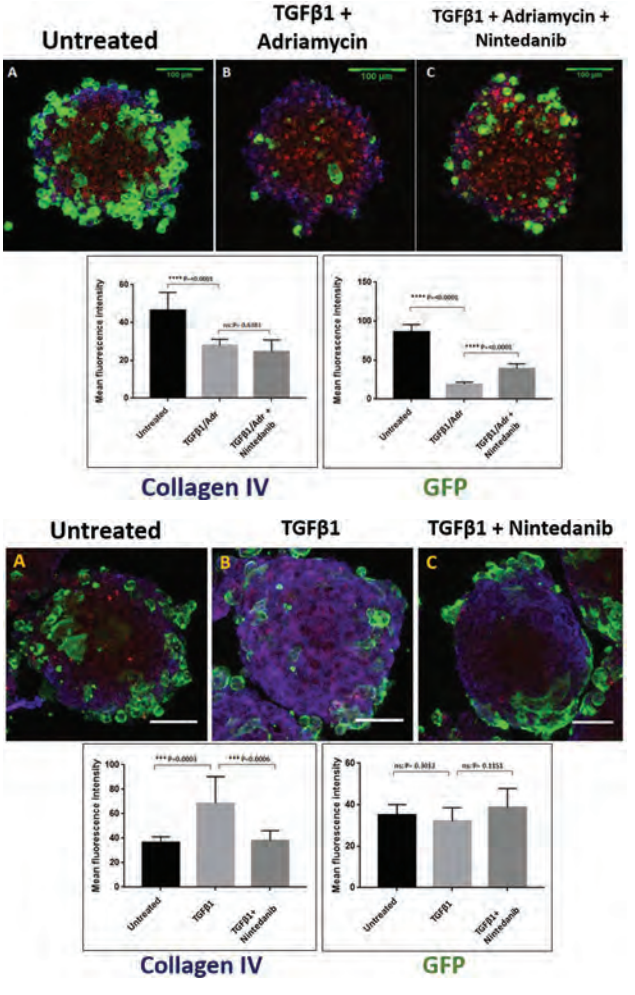
Background: 2D models of glomerular cells are limited in their ability to recreate accurate morphology and protein expression. The purpose of this project was to produce a 3D co-culture of conditionally immortalised human podocytes and glomerular endothelial cells (GEnCs), more translationally representative of glomerular health and disease for medium-throughput pharmaceutical compound screening.

Methods: Magnetic spheroid bio-printing was used to assemble podocytes and GEnCs into organised 3D structures. Fluorescence IHC techniques were used to stain and samples were imaged using confocal, lightsheet and transmission electron microscopy. Western blotting, mass spectrometry-based proteomics and transcriptomics techniques were applied.

Results: Podocytes and GEnCs in spheroid co-culture self-assembled into a glomerulus-like structure, whereby peripheral podocytes wrapped a core of endothelial cells. An organised layer of extracellular matrix formed between the two cell types. A combination of TGFβ and adriamycin caused significant podocyte effacement. TGFβ alone was sufficient to induce a significant increase in expression of the GBM protein collagen IV. Incubation with an antifibrotic compound (Nintedanib) significantly reduced both of these effects.

Conclusions: An in-vitro spheroid model demonstrating two key aspects of glomerulosclerosis (foot-process effacement and matrix dysregulation) has been developed. This model is more physiologically relevant than 2D cultures, whilst being reproducible and scalable.

Funding: Commercial Support - UCB pharma, Government Support - Non-U.S.



FR-OR030

Macula Densa Cells Orchestrate Podocyte Neogenesis

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Background: The recruitment of new podocytes from precursor cells including parietal epithelial cells (PECs) and cells of the renin lineage (CoRL) in response to glomerular

injury has been established, however the mechanism remains elusive. Here we tested the hypothesis that macula densa (MD) cells localized at the glomerular entrance are master organizers of glomerular remodeling, and can be stimulated to recruit new podocytes in the adult kidney.

Methods: Intravital multiphoton imaging (MPM) in genetic mouse models was performed to track the fate and migration pattern of mesenchymal and endothelial precursor cells. RNA seq and gene profiling was used to establish and analyze the gene profile of MD cells under control and stimulating conditions. Immunohistochemistry for podocyte, mesenchymal, and endothelial precursor cell markers p57, WT-1, and CD34 were performed in kidney sections of control WT mice and in a new genetic model of inducible MD-specific Wnt gain-of-function (gof).

Results: MPM provided "smoking gun" direct visual evidence for the migration of single CoRL from the PEC layer to the glomerular tuft (sometimes within 15 s) in the intact mouse kidney. The newly established, exclusively MD-specific secretome includes several angiogenic, patterning, growth factor, and extracellular matrix remodeling peptides including Pappa2, Ccn1, Cxcl14, Wnt10a, Sema3c, Bmp3, Egfl6, Fgf9, Vegfd, Pdgfc, Frem1, etc. In MD-Wnt(gof) mice, glomerular size and podocyte number increased from control 17±3 to 24±3 per unit glomerular volume within 5 weeks. MD-Wnt gof also developed a WT-1+ cell niche at the MD base/extraglomerular mesangium transitioning into the Bowman's capsule, and a CD34+ endothelial precursor cell niche at the glomerular vascular pole. Treatment of Ren1d-Confetti mice with GSK3b inhibitors for only 5 days caused a 3-fold increase in the density of CoRL at the glomerular vascular pole and in PEC layer.

Conclusions: These results suggest that MD cells are central players in the physiological remodeling of the glomerulus via Wnt signaling and secreted paracrine factors, that act on the mesenchymal-to-epithelial transition of glomerular precursor cells to become new podocytes. MD cells also stimulate angiogenesis simultaneously. This new mechanism protects from glomerular injury when augmented, and may be developed further to specifically treat glomerular diseases.

Funding: NIDDK Support

FR-OR031

Glomerular Filtrate Promotes Cell Detachment in Podocyte Injury

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Background: Podocyte detachment is a hallmark of segmental glomerulosclerosis. Although glomerular filtrate may effectively drive cell detachment, it alone is insufficient and needs presumptive structural changes in filtration surface. We analyzed structural background that synergistically drives podocyte detachment in NEP25, a mouse model of uniform podocyte injury.

Methods: Whole glomerular profiles (73 glomeruli, n=6) in NEP25 mice with LMB2 (8-10 days) were photographed by TEM. Entire GBM in all glomeruli were classified into normal, foot process effacement (FPE) or detachment and each length per glomerulus was measured. This method enabled us to identify the localization and continuity of each change within the glomerulus. UUO was performed at day 5 in the above protocol (UUO model, n=3) to identify the effect of filtrate on detachment. Using multiphoton microscopy (MPM), decreased filtration by UUO was visualized. Glomeruli in UUO model were analyzed by TEM in the same way as above.

Results: Detachment occurred only in the glomeruli with >50% FPE lesions. The length of detachment correlated with the length of FPE. Detachment was more in deep cortex than in surface and tended to occur in limited to 1 to 2 local areas within each glomerulus. In examining 43 glomeruli with both vascular and urinary poles, detachment dominantly occurred at the side of urinary pole. Contralateral kidneys of UUO model had severe podocyte detachment, which also occurred dominantly at the urinary pole side (n=61). Filtration effectively decreased in the obstructed kidneys of UUO by MPM and these glomeruli completely lacked podocyte detachment, despite diffuse FPE by TEM (n=55). Podocyte pseudocysts were observed in the contralateral kidneys but rarely in the obstructed kidneys of UUO model.

Conclusions: 1) Podocyte detachment may be caused by synergistic effects of podocyte changes, such as FPE, with hydrostatic forces by filtrate. Biological changes in podocyte that occur in "grouping" may be an additional background. 2) From the fact that the frequency and the length of detachment positively correlated with the extent of FPE and pseudocyst, the cell reaction to strengthen cell-GBM and cell-cell attachment is also a basis for podocyte detachment.

FR-OR032

Promotion of β-Catenin/Foxo Protects against Kidney Fibrosis

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Background: Transforming growth factor β (TGF-β) is the key cytokine in the development of fibrosis. The conflicting roles of TGF-β (profibrotic versus anti-inflammatory) create a dilemma in the treatment of kidney fibrosis. β-catenin/TCF is central to various TGF-β's profibrotic signaling pathways in fibrosis. β-catenin also binds to Foxo in competition with TCF and leads to cell cycle arrest, promoting cell survival under oxidative stress. We propose that promoting β-catenin/Foxo will protect against β-catenin/TCF-mediated profibrotic changes and kidney fibrosis.

Methods: Kidney biopsies of patients with chronic kidney disease (CKD) or a kidney transplant were assessed by Proximity Ligation Assay (PLA) for β-catenin/Foxo and β-catenin/TCF interactions in relation to kidney fibrosis. Murine proximal tubular epithelial C1.1 cells were treated with TGF-β1 (3ng/ml) with or without ICG-001 (5μM), which inhibits β-catenin/TCF. CRISPR/Cas9 gene technology was used to knockout Foxo1 or TCF1. We also evaluated kidney fibrosis in murine unilateral ureteric obstruction (UUO). β-catenin/Foxo and β-catenin/TCF interactions were examined by co-immunoprecipitation (co-IP) and PLA. Profibrotic gene expressions were examined by western blot and immunofluorescence.

Results: PLA of CKD and kidney transplant patient biopsies showed that β-catenin/Foxo correlated negatively (r=-0.7405, P<0.001) and β-catenin/TCF positively (r=0.8061, P<0.001) with kidney fibrosis. TGF-β1 and ICG-001 treatment in C1.1 cells protected against TGF-β1-induced profibrotic gene expression while the protection was absent in Foxo1 KO C1.1 cells. Combined treatment with TGF-β1 and ICG-001 in C1.1 cells showed direct evidence for the promotion of β-catenin/Foxo by PLA and co-IP. UUO mice treated with TGF-β1 and ICG-001 had significantly reduced kidney fibrosis, via promotion of β-catenin/Foxo interaction as shown by PLA.

Conclusions: β-catenin/Foxo protects against TGF-β's profibrotic activity and thereby prevents kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-OR033

An APOL1-Induced FSGS Mouse Model That Mimics Human FSGS Nephropathy

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Background: In the present study, the we aimed to develop a CKD model in mice expressing apolipoprotein L1 (APO1) in order to generate a robust, reproducible model of APOL1 nephropathy. As reported, a bacterial artificial chromosome (BAC) that contains either the human *APOL1* gene (BAC-APOL1 G0) or each of the renal risk variants (BAC-APOL1-G1 and -G2) were used to generate transgenic mice that constitutively expressed APOL1. At baseline, BAC-APOL1 G0, G1, and G2 mice had no renal phenotype despite genetic risk in the latter lines; therefore, we induced hypertension as second hit.

Methods: We used a combination of Saline drinking water, Angiotensin II infusion, uniNephrectomy and Deoxycorticosterone acetate pellets (SAND model)

Results: After 3 weeks, mice developed albuminuria (G0, 2205 ± 84 mg/g, G1, 3840 ± 363 mg/g, G2 3447 ± 111 mg/g, and wild type, 2085 ± 202 mg/g) and uremia, with elevated blood urea nitrogen (BUN). SAND intervention in G1 and G2 mice led to reduced cortical thickness and podocyte number compared to G0 mice. SAND G1 and G2 mouse kidneys showed focal global and segmental glomerulosclerosis (FSGS), as well as glomerular lipid accumulation by oil red O staining. Differentially expressed genes in kidney cortex were identified based on log2 fold change and false discovery rate (FDR) of <0.05. In SAND G1 mice *Aoc1*, *C1q*, *Ncam1*, *Scamp1*, and *Tbca* were downregulated and *Hmgcs2* was upregulated compared to G0 mice. We examined expression of 60 FSGS-related genes, 64 cytokines, 63 cytokine receptors, 52 chemokines and 33 chemokine receptors in order to identify additional differentially-expressed genes in G1 and G2 mice, using a cutoff of log2 fold change of <0.05. *Ccrl2* was shown to be upregulated in G1 and G2 transgenic mice compared to WT and APOL1-G0 mice

Conclusions: In summary, we have shown that with the SAND model of hypertensive nephropathy, BAC-APOL1 G1 and G2 mice manifest more severe proteinuria, FSGS, and distinct patterns of gene expression.

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FR-OR034

PTEN/YAP Mediated Lipid-Accumulation in Podocytes Contributes to Glomerulosclerosis

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Background: The pathogenetic mechanism of focal segmental glomerulosclerosis (FSGS) are largely unknown. Here, we showed that phosphatase and tensin homolog (PTEN) was down-regulated in foamy podocytes in patients with FSGS, however, whether PTEN involves in accumulation of lipid in podocytes and contributes to glomerulosclerosis is undefined.

Methods: PTEN knockout and podocyte-specific PTEN knock-in mice were established.

Results: We revealed that partially deletion of PTEN increased the lipids accumulation in glomeruli segmentally, and boosted albuminuria and glomerulosclerosis. Conversely, podocyte-specific overexpression of PTEN demonstrated a marked alleviation of lipid-retention in podocytes, serum creatinine, UACR, and characteristics of glomerulosclerosis. *In vitro*, PTEN was found down-regulated in cultured podocytes stimulated with ox-LDL. Forced expression of PTEN reduced ox-LDL influx via down-regulating scavenger receptor

A (SR-A), decreasing intracellular cholesterol content, and thus prevented podocytes from lipid loading. In contrast, inhibition of PTEN exhibited aggravated podocytes damage by more lipid accumulation. The lipid retention in ox-LDL treated podocytes was mainly attributed to the lipid uptaking other than lipid effusion or synthesis. Mechanistically, we identified PTEN as a regulator of SR-A by dephosphorylating its nuclear transcription factor, yes-associated protein (YAP), at Ser^{127} in the cytoplasm of ox-LDL treated podocytes.

Conclusions: These findings implicate a central role of PTEN in a signaling cascade that regulates podocytes lipid-loading which contributes to the glomerulosclerosis, and provide evidence for PTEN as a target for HFD-induced FSGS therapy.

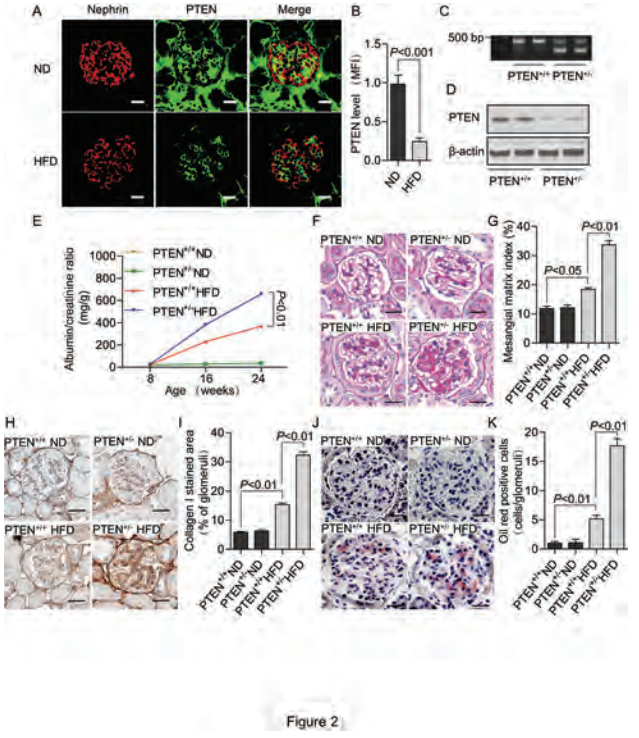

Figure 2

Knockout of PTEN aggravated renal lipid accumulation and glomerulosclerosis in FSGS mice.

FR-OR035

The Role of HDAC Activation in Proteinuric Kidney Disease Progression in Mice and Humans

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Background: As the incidence and prevalence of End Stage Kidney Disease due to proteinuric diseases continue to rise, alternative novel therapies are required.

Methods: An adult-onset proteinuric disease model was generated using doxycycline (DOX)-induced podocyte specific *Talin1* knockout (i*Tln1* KO) mice. Our findings were validated using podocyte specific germline *Dynamin1* and *2* KO (*Dnm* DKO) and *Tln1* KO mice treated with 2 different histone deacetylase (HDAC) inhibitors (valproic acid (VPA) and vorinostat (SAHA)). We generated DOX-induced podocyte specific *Hdac1* and *2* KO or early growth response 1 (*Egr1*) KO mice. Microarray was performed from isolated glomeruli in control and the i*Tln1* KO mice +/- VPA to unearth differentially expressed genes (DEGs). HDAC1 and 2 activities were measured using an activity assay kit. For in-vitro podocyte injury models, lipopolysaccharide (LPS) or protamine sulfate (PS) were used. Observational data in patients on VPA in the Veterans Aging Cohort Study (VACS) was analyzed for estimated glomerular filtration rate (eGFR).

Results: Using Connectivity Map database and Drug Pair Seeker, *Hdac1* and *2* genes and HDAC inhibitors were identified as potential targets regulating or reversing the 188 DEGs in control vs i*Tln1* KO mice glomeruli. Deletion of podocyte *Hdac1* and *2*, in i*Tln1* KO mice where podocyte HDAC1 and 2 are activated, and treatment with VPA, or SAHA ameliorated progression of proteinuria and kidney failure in these mice. VPA also improved survival in *Dnm* DKO and *Tln1* KO mice that die from kidney failure (*Dnm* DKO:35 (median survival (days)), *Dnm* DKO+VPA:77.5, *Tln1* KO:30.5, and *Tln1* KO+VPA:64). From our RNA profiling data, we also identified *Egr1* as a potential VPA regulated target. Loss of *Egr1* in i*Tln1* KO mice mitigated proteinuria and kidney failure (control:0.11 +/- 0.02 (plasma creatinine (mg/dl)), i*Tln1* KO:0.35 +/- 0.02, *Egr1*, i*Tln1* DKO:0.19 +/- 0.02). *Egr1 KO* podocytes stabilized the actin cytoskeleton following LPS or PS in vitro. Longitudinal analysis of VACS revealed reduction in the mean annual eGFR loss among those receiving VPA (-0.48 (ml/year) in VPA user vs -1.10 in non VPA user).

Conclusions: Our results demonstrate inhibition of HDAC1 and 2 activation not only improved proteinuric mice models but also suggests a novel therapeutic strategy in progressive proteinuric human kidney diseases.

FR-OR036

Induced Endothelial Expression of Podocyte Specific Retinoic Acid Receptor Responder 1 (Rarres1) in Glomerular Nephritis (GN) Accelerates Renal Injury

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Background: Glomerular damage, including endothelial dysfunction and podocyte loss, plays an important role in the pathogenesis of diabetic nephropathy (DN). Pathogenesis of microvascular damage in the disease is still poorly understood. High throughput molecular profiling (RNA seq.) identified Rarres1 as a highly podocyte specific protein, that is consistently up-regulated in kidney tissue of DN patients.

Methods: To identify cellular localization of Rarres1, we analysed the expression in human healthy and DN kidneys using immunohistochemical methods and RNA *in situ* hybridization. *In vitro*, we over/underexpress Rarres1 in human podocytes to investigate its functional role. *In vivo*, we generated two novel transgenic mouse lines, enabling cell-specific inactivation and overexpression of Rarres1. We induced crescentic GN model by anti-glomerular basement membrane (anti-GBM) antibodies in podocyte specific knock-out (KO) and endothelial cell (EC) specific knock-in (KI) mice for Rarres1.

Results: In healthy kidney, Rarres1 is specifically expressed by podocytes and not by other glomerular cells. In DN patients, Rarres1 expression is induced in microvascular endothelial cells. *In vitro*, Rarres1 overexpression leads to elevated expression of EMT related genes and activation of NF-kB signaling by interaction with Receptor Tyrosin Kinase Axl. *In vivo*, EC specific Rarres1 KI animals were more prone to anti-GBM-induced damage as they developed higher albuminuria than control animals and showed an accelerated immune response as well as increased levels of fibrotic makers. In contrast to this, podocyte-specific KO animals showed no obvious abnormalities.

Conclusions: In summary, these results suggest that the activation of Rarres1 expression plays a pathogenic role in renal endothelial dysfunction during disease progression by promoting fibrosis and inflammation *in vitro* and *in vivo*.

FR-OR037

Characterization of a New Mechanism of Proteinuria

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Background: A central problem in biology is the mechanism by which cells regulate iron transport. This problem arises because the common oxidized form of iron (ferric-Fe3+) precipitates at physiologic pH, while the reduced form of iron (ferrous-Fe2+) is unstable in oxygenated atmospheres, and produces toxic radicals. To investigate iron transport in the kidney, we performed homology searches with yeast iron transporters and identified Spin, a novel transporter of ferrous iron.

Methods: Using in vivo LacZ reporters and by raising antibodies we found that Spin is specific to the endosomes and lysosomes of the proximal tubule. We constructed a conditional knockout of Spin driven by Megalin-Cre and found iron deposits and intense ferritin staining in the cytosol indicating defective iron localization in the KO.

Results: We saw proximal tubule dysfunction in the KO as measured by proteinuria. Western blot revealed leakage of NGAL and transferrin in the urine, and silver stain showed albuminuria. We investigated this phenotype by intraperitoneally injecting FITC-labeled dextran and found impaired endocytosis in the KO. While megalin expression was unchanged between KO and wild type as seen on confocal microscopy, autophagy appeared to be inhibited in the KO. Electron microscopy showed increased size and number of vesicles in the proximal tubules, and Western blot showed increased abundance of LC3B-II in the homogenate of kidney cortex, suggesting that the Spin KO may hinder autophagosome fusion with the lysosome. The endocytic phenotype appears to be regulated by mislocalized iron because iron deficiency can rescue endocytosis.

Conclusions: In sum, we have found a critical iron transporter that regulates the endocytic functions of the proximal tubule.

Funding: NIDDK Support

FR-OR038

Human Nephron Segmentation: Opportunities to Replicate Cellular Programs In Vitro

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Background: Advances in renal bioengineering have shown how pluripotent stem cells can be differentiated into composite cell-structures called 'kidney organoids'. These technologies can, if harnessed properly, hold potential for human kidney disease modeling, nephrotoxicity screens, and renal replacement therapies. However, the intense interest into the kidney organoids have highlighted our current insufficient understanding of normal human kidney development and raised the question of whether the blueprint for nephrogenesis established in the mouse, frog, and fish, is actually applicable to the human system and the organoid.

Methods: To establish a cellular and molecular understanding of human development we have carefully scrutinized and contrasted it with mouse kidney development using a broad range of technologies including bulk RNA-sequencing (conventional and MARIS-based), single-cell RNA sequencing, in situ hybridization, immunofluorescent stains (three dimensional and two dimensional), and confocal live fate-mapping.

Results: We demonstrate significant conservation between human and mouse patterning programs alongside distinct divergences in anatomies and expression patterns (JASN 2018 PMIDs: 29449453, 29449451, 29449449). Further, our examination of the human system resulted in the proposition of a new model for how nephrons form and pattern. Mesenchymal nephron progenitors are recruited into the forming nephron over a protracted period of time and it is the order of recruitment that dictates the spatial identities and eventual fates of each cell. We demonstrate this model by high-resolution image analyses and 3D reconstructions of human nephrogenesis and confirmed it through direct visualization and cell fate analysis in the mouse kidney organ cultures. Single-cell RNA sequencing of the human nephrogenic niche revealed the molecular events occurring during these early patterning processes and predicted developmental trajectories adopted by nephron progenitor cells in forming segment-specific domains of the human nephron.

Conclusions: The temporal-recruitment model for nephron polarity and patterning provides a framework for how integrated signaling pathways drive mammalian nephrogenesis. Collectively, these studies benchmark human nephrogenesis and predicts why current organoids fall short of replicating the *in vivo* nephron.

Funding: NIDDK Support

FR-OR039

Manipulation of Nephron Patterning Signals Enables Selective Induction of Podocytes from Human Pluripotent Stem Cells

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Background: Podocytes, which play an important filtration role in the kidney, are derived from nephron progenitor cells (NPCs). Recently, we and others have established the induction methods of kidney organoids via NPCs from human induced pluripotent stem cells (hiPSCs). However, it remains a challenge to control the patterning process of nephron development and selectively induce a specific nephron segment.

Methods: We first developed a method to purify NPCs from mouse embryonic kidneys and cultured the NPCs *ex vivo* to investigate the required signals for podocyte induction. We then applied the findings obtained from mouse NPCs to hiPSC-derived NPCs to establish a method to selectively induce human podocytes.

Results: Mouse NPCs differentiation experiments identified that 1) optimal duration and strength of Wnt signaling was essential for mesenchymal-to-epithelial transition and podocyte differentiation, 2) inhibition of TGF-β signaling supported the expansion of proximal segment of renal vesicle, and 3) inhibition of TGF-β signaling in the later step enriched podocyte fraction by suppressing the differentiation of other nephron segments. The resultant protocol was successfully applied to the induction of Nephrin/Podocalyxin-positive podocytes from hiPSCs with more than 90% of efficiency. Importantly, the expression levels of Nephrin and Podocin genes in the induced podocytes were 10^5 to 10^6 times higher than that in the immortalized podocyte cell line and comparable to the sorted human adult podocytes. RNA-seq analysis further confirmed characteristic similarities between induced podocytes and human adult podocytes. Electron microscopy revealed foot process-like protrusions with Nephrin protein expression on the cell surface. Furthermore, exposure of induced podocytes to puromycin aminonucleoside reduced the expression of foot process-associated proteins, suggesting their functional responsiveness.

Conclusions: We elucidated the signals required for podocyte differentiation from NPCs and established a novel method to selectively induce human podocytes from hiPSCs. Induced podocytes exhibited gene expression profiles resembling their counterparts *in vivo* as well as morphological and functional properties of podocytes and will serve as new resources for disease modeling, nephrotoxicity testing, and regenerative medicine.

Funding: Government Support - Non-U.S.

FR-OR040

Nephron Progenitor Commitment Is a Stochastic Process Influenced by Cell Migration

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Background: Nephrons in the mouse kidney are formed from self-renewing mesenchymal progenitors that reside within a niche defined by the cap mesenchyme and ureteric epithelial tip. As the kidney develops, progenitor cells differentiate in response to inductive cues and exit the niche to form nephrons. We previously showed that the cap mesenchyme population is highly dynamic, migrating both within and between domains in response to niche cues. In this study we examine how migrating progenitors initiate nephrogenesis in a precise, spatially regulated manner.

Methods: We used lineage tracing, live timelapse imaging, single cell RNA-seq and computational modelling to characterise the fate of commiting mouse nephron progenitors.

Results: Using a tamoxifen inducible Wnt4-CreERT2 activated reporter we show that committing cells give rise to both the nephrons and a proportion of the progenitor pool. Timelapse imaging reveals a population of cells that are labelled at sites of nephrogenesis but escape commitment and re-enter the progenitor niche. Re-entry occurs continually during kidney development, leading to an accumulation of 'escapers' over time. Single cell RNA-seq reveals that these 'escapers' exist in the same range of transcriptional states as the unlabelled progenitor pool, suggesting that progenitors may traverse the transcriptional hierarchy between self-renewal and commitment in both directions. Consistent with this plasticity, live imaging analysis of individual cell fate suggests that some cells do not commit immediately but remain within the pre-tubular aggregate through branching iterations and contribute to subsequent nephrons.

Conclusions: We propose that nephron progenitor commitment is a stochastic process where the duration of exposure to spatially defined inductive cues is dependant on migration events. Progenitor plasticity may enable robust regulation of nephrogenesis as niches grow and are remodelled during organogenesis.

Funding: Government Support - Non-U.S.

FR-OR041

High Throughput Single Cell RNA Sequencing Reveals a Roadmap to Recreate the Kidney

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Background: The developing mouse kidney represents a valuable model to understand the formation and maturation of renal cell types. High throughput single cell RNA sequencing offers new opportunities to understand the formation of complex tissues.

Methods: We performed single cell RNA-seq on over 6000 cells (median 2896 genes per cell) from E18.5 kidneys on the Chromium 10x platform. Seurat was used for normalisation and clustering of cells, edgeR to test for differentially expressed genes. Findings were investigated using immunofluorescence and lineage tracing.

Results: We used single cell profiling to define cell type-specific profiles and revisit the molecular regulation of kidney development in mouse. A detailed analysis of cellular heterogeneity in the nephron lineage identified multiple *Six2*+ subpopulations including a nephron progenitor 'ground state', a putative committing state with evidence of FGF suppression and Notch activation, and cells expressing markers of both nephron progenitor and stroma. *In vivo* lineage analysis from E12.5 with inducible *Six2*CreERT2 and *Pdgfra*CreER lines supported a rare transition from nephron progenitor to stroma, but not the other way. Several markers thought to be specific to one population were expressed more broadly. For example *Hoxb7* was expressed in collecting duct, distal tubule, and in some endothelial cells. Likewise, most markers considered specific to the ureteric epithelium were also expressed in the distal tubule or connecting segment. Comparative analysis between these populations yielded unique markers for each, which should be useful for distinguishing between these cell types in kidney organoids. An analysis of signaling pathway component expression was performed for each lineage, identifying known and previously unassociated ligands and receptors with progenitor states and stages of maturation in each lineage.

Conclusions: This study offers new insight into the mechanisms of progenitor maintenance and differentiation in the stroma, the ureteric epithelium, and the nephron lineages and therefore provides a roadmap of the signals that regulate differentiation *in vivo*. This information can be used to refine strategies to direct differentiation of mature renal cell types in vitro.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR042

Comparative Analysis of Kidney Organoid and Adult Human Kidney by Single Cell RNA-Seq

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Background: Kidney organoids differentiated from human pluripotent stem cells hold tremendous promise but the similarities and differences between protocols and between pluripotent cell sources is unknown. In addition, how closely organoid-derived kidney cell types model their adult human counterparts is undefined.

Methods: We used Dropseq to generate single cell transcriptomes from two different directed differentiation protocols (Morizane and Takasato), using both iPSC and hES cell lines for each. We analyzed and compared single cell gene expression from 71,390 cells isolated from 38 organoids using unbiased computational approaches. We could detect on average 1,115 genes per cell. We further compared the differentiation state of major organoid kidney cell types against 4,524 single nucleus transcriptomes that we generated from healthy adult human kidney.

Results: Both protocols generate kidney organoids that contain a diverse range of kidney cells at differing ratios but also substantial numbers of non-renal cell types such as muscle and neuron. Some organoids have up to 30% off-target cell types. Organoid-derived cell types are substantially immature compared with adult kidney cells. We could detect 16 different types of adult kidney cell types by single nucleus RNA-seq, including all glomerular cell types, all epithelial cell types including S1-S3 proximal tubule segments and type A and type B intercalated cells, as well as stroma and leukocytes. Disease-related genes predicted by GWAS are predominantly expressed in single cell types in adult kidney and organoids. We also identified lineage-specific expression of transcription factors, receptors and ligands during organoid differentiation and in adult human kidney.

Conclusions: We provide the first direct and comprehensive comparison of separate differentiation protocols using both iPSC and hES cells, revealing important differences in cell ratio, differentiation state and off-target cell types that will be important for investigators

in the organoid field to appreciate. The information provided in this comprehensive dataset will also guide future attempts to improve differentiation protocols, including reduction of off-target populations.

Funding: NIDDK Support

FR-OR043

Reciprocal Antagonism between Ppargc1a and Sim1a Regulates Boundary Formation of the Proximal Straight Segment during Vertebrate Pronephros Development

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Background: The genetic and molecular mechanisms that regulate boundary formation between adjacent segment populations are not fully understood. The pronephros of several vertebrates provides a simplified, tractable model to investigate fundamental mechanisms of segmentation, as this primitive kidney is comprised of proximal and distal segments that are conserved with mammalian nephrons, including humans.

Methods: Through a bioactive small molecule chemical genetic screen, we discovered that peroxisome proliferator-activated receptor (PPAR) signaling is essential for pronephros segmentation. Next, we found that the co-activator, *ppargc1a*, which binds activated PPARs to regulate transcription of target genes, is dynamically expressed in renal progenitors and is requisite for segmentation.

Results: *ppargc1a*$^{sa13186-/-}$ mutants with a T->A substitution that results in a putative null allele have an reduced distal tubule segment and increased proximal tubule domain, which was recapitulated in subsequent knockdown studies and rescued with *ppargc1a* overexpression. Further, *ppargc1a* acts to promote *tbx2b*, a transcription factor necessary for proper formation of the distal segment. Interestingly, *ppargc1a*$^{sa13186-/-}$ have an expanded *sim1a* domain, a transcription factor which is thought to regulate proximal segments. Conversely, *ppargc1a* expression was expanded in *sim1a* deficient embryos. This data suggests a negative regulation between the two factors. To test this interaction, we examined the proximal straight tubule domain in *sim1a* deficient, *ppargc1a* deficient, and doubly deficient embryos. While the loss of *sim1a* resulted in an abrogated proximal straight tubule, loss of *ppargc1a* resulted in expanded proximal straight tubule, but loss of both factors results in a completely restored segment boundary.

Conclusions: Taken together, this data strongly suggests that Ppargc1a and Sim1a act to counterbalance each other in an antagonistic fashion that is necessary for proper nephron segment boundary formation. These findings reveal for the first time how a layer of redundancy within the mechanism of segment boundary delineation is used to mitigate segment formation. Thus, these studies have discovered a useful paradigm to advance our understanding of nephron segmentation mechanisms.

Funding: NIDDK Support

FR-OR044

Deletion of SWI/SNF Chromatin Remodeling Component Brg1 in Nephron Progenitors Causes Renal Hypoplasia

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Background: Regulation of the self-renewal and differentiation capacity of the nephron progenitor (NPC) is a delicately balanced process. Decreased self-renewal or increased differentiation during kidney development can result in decreased nephron number at birth. When severe, this leads to childhood kidney failure. However, even moderate reductions in nephron number are associated with hypertension and chronic kidney disease in adulthood. The molecular mechanisms that modulate expression of genes for expansion of nephron progenitors are not completely understood. Mounting evidence supports a role for the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complex in regulating mesodermal cell fate. The SWI/SNF complex is a large evolutionarily conserved protein complex required for embryonic development. The complex is composed of 10-12 subunits including alternative core ATPase subunits BRM (Brahma) and Brg1 (Brahma related gene 1) that modulate chromatin structure on targeted loci, and regulate lineage restricted gene expression during development. We found that Brg1 associated with Sall1, suggesting that SWI/SNF has a functional role in NPCs.

Methods: We genetically deleted the Brg1 gene (*Smarca4*) in mouse NPCs.

Results: Deficiency of Brg1 in Six2+ NPCs resulted in hypoplastic kidneys by embryonic day (E) 17. The number of Six2+ NPCs was reduced in mutant kidneys as early as E14, which correlated with a significant reduction of phospho-histone H3 positive dividing Six2+ NPCs. The nephron progenitor cells were almost completely lost by the time of birth. Similar to *Sall1* mutants, global gene expression changes in E17 Brg1 mutant kidneys suggested defects in cell adhesion. RNA-seq analysis also showed downregulation of many genes required for mitochondrial respiration, suggesting reduced metabolic fitness of mutant NPCs. Brg1 is not expressed in adult kidney, however upon nephrotoxic injury with aristolochic acid Brg1 was significantly upregulated, indicating that the molecular pathways regulating kidney development may be activated for repair processes after injury.

Conclusions: Together, these data suggest that Brg1 regulates expression of genes that are required for the self-renewal and maintenance of nephron progenitor cells. Our results reveal novel functions of Brg1 in developing kidney.

Funding: NIDDK Support

FR-OR045

Inactivation of Foxi1 Rescues Most of the Hes1-Deficient Mouse Kidney Collecting Duct Defects

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Background: The distal nephron and collecting duct segments of mammalian kidneys consist of intercalated cell types intermingled among Aqp2-expressing (principal) cell types. Notch signaling ensures that a sufficient number of cells select the Aqp2-expressing instead of an intercalated cell state. However, the precise mechanisms by which Notch patterns the collecting ducts is unknown. Here we tested whether Notch signaling simply represses Foxi1, an essential intercalated cell specific transcription factor, to allow for principal cell differentiation.

Methods: Hes1, a direct target of Notch signaling, was inactivated in developing kidney distal nephron and collecting duct segments by generating *Cdh16-Cre;Hes1*$^{f/f}$ mice and compared with *Cdh16-Cre;Hes1*$^{f/f}$*;Foxi1*$^{-/-}$ mice to determine whether the only function of Notch in developing collecting ducts is to repress Foxi1. We also tested whether Hes1 directly regulates principal cell genes in a calcium/calmodulin-dependent protein kinase-II (CaMKII) in *ex vivo* embryonic kidney cultures.

Results: Inactivation of *Hes1* resulted in fewer principal cells, and reduced principal cell specific gene expression, and ability to concentrate urine, along with increased expression of *Foxi1*. Inactivation of *Foxi1* rescues the Hes1-deficient principal cell deficiency and the ability to concentrate urine. However, detailed examination of *Cdh16-Cre;Hes1*$^{f/f}$*;Foxi1*$^{-/-}$ mouse kidneys revealed reduced expression of certain principal cell (PC) specific genes. Consistent with PC specific genes being regulated independent of Foxi1, *Foxi1* inactivation in mice does not result in increased expression of all PC specific genes. Additionally, Hes1 and PC specific genes are down-regulated upon inhibition of Notch signaling in cultured principal cells without activation of *Foxi1* expression. Hes1 can directly activate proximal promoters of *Aqp2*, *Aqp3* and *Elf5* in a CaMKII sensitive manner. The expression of PC specific genes and not *Foxi1* expression is dependent on CaMKII activity in *ex vivo* mouse embryonic kidney cultures.

Conclusions: Notch/Hes1 has at least two roles during collecting duct development: (i) principal cell fate selection by repressing Foxi1 expression and (ii) activation of principal cell gene expression in a CaMKII dependent manner.

Funding: NIDDK Support

FR-OR046

Molecular Programs of the Progenitor Population Directing Branching Morphogenesis and Differentiation of the Collecting Duct Network

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Background: Branching morphogenesis underpins the formation of arborized epithelial networks in many organs including the lung airways and the mammalian kidney collecting duct. Epithelial branch tip cells respond to inductive signals from the adjacent mesenchyme that regulate this process and maintain an uncommitted progenitor identity. Progenitors exit the tip to populate stalk regions where they differentiate into the regionally distinct, organ appropriate, cell types of the epithelial network.

Methods: We employed population-based and single cell RNA-sequencing (scRNA seq) screens to identify tip progenitor cell types and their differentiated progeny in the developing mouse and human kidney and validated key genes by *in situ* hybridization and immunostaining. Several tip-specific genes are being explored through knockout mouse studies to identify their role in tip-niche regulation. To establish lineages from ureteric progenitors to adult collecting duct cell types, we are combining cell fate studies with scRNA seq, facilitated by novel genetic tools.

Results: RNA sequencing has identified a tip-enriched gene set that include all known tip genes and conservation of tip progenitor profiles between the developing mouse and human kidney. Further, conservation is observed in other branching organ systems. Expression studies show that ureteric tips have a complex gene expression pattern and cell fate analysis demonstrates that subsets of cells have lineage restrictions in the establishment of mature cell types. We analyzed the role of *Adamts18*, which encodes a secreted protease in mouse tip cells within the collecting duct and lung. Adamts18 null mutants display enlarged kidneys with double ureters while all mutants exhibit reduced growth of the airways.

Conclusions: Conserved gene regulatory programs organize the kidney tip progenitor niche in mouse and human, and progenitor niches in other branching organs. Lineage-tracing and scRNA seq show mosaicism of progenitor populations and how this determines their potential to form the mature collecting duct cell types. Analyses of Adamts18 mutants give new insights into mechanisms of branching growth in several branching networks.

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FR-OR047

Adult Mouse Aqp2+ Progenitor Cells Maintain and Remodel Connecting Tubule/Collecting Duct

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Background: Embryonic Aqp2^{+} progenitor cells generate all known cell types in the connecting tubule/collecting duct (CNT/CD). Aqp2$^{ECE/+}$ is a highly tamoxifen-inducible principal-cell-specific Cre mouse line with complete fidelity in cell specificity and no leakiness. Here we investigate weather Aqp2^{+} progenitor cells have multipotency and self-

renewal potential during CNT/CD maintenance and lithium-induced remodeling in adult mice.

Methods: *Adult Aqp2$^{ECE/+}$* RFP/+ and Aqp2ECE/+ rainbow/+ were induced with tamoxifen and examined at various time points post induction. Alternatively, tamoxifen-induced adult mice were treated with dietary LiCl for 4, 7 and 14 days, respectively. RFP or GFP co-expression with markers for PC (Aqp2), IC (V-ATPase B1, B2, CAII, AE1, and Pendrin) was investigated by immunofluorescence staining. PC to IC conversion rates ($RFP^+IC^+/(RFP^+IC^+ + RFP^+IC^-)$ and IC derivation from PC rates ($RFP^+IC^+/(RFP^+IC^+ + RFP^-IC^+)$ were determined. Uninterrupted single-colored clones in Aqp2ECE/+ rainbow/+ were grouped into single-cell and multiple-cell ones to represent regular and progenitor cell-like PC, respectively.

Results: *Aqp2$^{ECE/+}$* RFP/+ possessed no PC to IC conversion (no RFP^+ IC^+ cells) at day 1, intermediate state cells (RFP+ PC+ IC+) at day 3, and completely converted cells (RFP+ PC- IC+) at day 60 and 270 post induction. The conversion rate was 5% in the cortex and 0.02% in the medulla at day 60, which were increased to 25% and 4%, respectively, at day 270. IC derivation from PC rates were 47% and 6% in the cortex and medulla, respectively, at day 270. Lithium progressively facilitated PC-IC conversion, with the highest conversion rate reaching to 17.3% in cortex at day 14. Among the total cortical IC population, about 31% IC were derived from PC. Clone size ranged from 1-7 cells, with the largest ones observed at day 270 post induction and day 14 post lithium treatment. The majority of clones were 1-2 cells.

Conclusions: Adult $Aqp2^+$ progenitor cells possess multipotency and self-renewal potential, and contribute to CNT/CD maintenance and remodeling.

Funding: NIDDK Support

FR-OR048

Whole Genome Bisulfate Sequencing and dCas9-Mediated Epigenome Editing Identifies a Key Role for Tumor Necrosis Factor Alpha in Progressive Diabetic Kidney Disease

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Background: Epigenetic changes have been proposed as the biological mechanism that encodes the long-lasting impact of metabolic changes on diabetic kidney disease (DKD) development. Understanding the contribution of methylation changes to DKD has been limited by a lack of comprehensive base resolution methylation data and specific methylome editing.

Methods: We have performed genome-wide based resolution methylation analysis of microdissected human control and DKD kidney tubule samples using whole genome bisulfate sequencing to identify methylation differences in human DKD kidneys. We used RNA sequencing to define transcriptional changes in the same samples. We validated results with larger array-based and animal model results. We applied dCas9-Tet1 system to define the causality of individual cytosine methylation changes and gene expression under specific sgRNAs.

Results: Methylation differences with genome-wide significance were detected in kidney tubule samples of patients with DKD. The changes were replicated by large cohort array-based methylation analysis. Differentially methylated regions (DMRs) were enriched on regulatory regions and associated with gene expression changes; however, it is likely that most changes were actually the result of cell type-specific changes rather than cell-specific changes. Pathway analysis indicated coordinated (methylation and gene expression) changes in metabolic and immune response pathways; specifically, changes in tumor necrosis factor alpha (TNFα) signaling. dCas9-Tet1 based lowering of cytosine methylation level of the TNFα DMR region resulted in an increase in TNF transcription indicating that methylation of this locus plays an important role in controlling gene expression. Increasing the TNF levels in diabetic animal models resulted in high grade albuminuria due to increased cytokine levels and cell death indicating TNFα is functionally important in DKD development.

Conclusions: Our results indicate wide spread methylation differences in DKD kidneys. We propose that epigenetic dysregulation of TNF locus likely contributes to nephropathy in patients with diabetes.

FR-OR049

Aberrant DNA Methylation of mTOR Pathway Promotes Inflammatory Activation of Immune Cells in Diabetic Kidney Disease

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Background: DNA methylation has been implicated in the pathogenesis of diabetic kidney disease (DKD), but the underlying mechanism is unclear. We hypothesize that aberrant DNA methylation in peripheral immune cells may contribute to the inflammation and pathological progression in DKD.

Methods: Whole DNA samples were extracted from human peripheral blood mononuclear cells (PBMCs) and applied to genome-wide methylation analysis. PBMCs were isolated from human whole blood samples to determine the expressions of DNMTs and their relationship with the inflammatory activities. At 8 weeks of age, db/db mice were treated with 5-Aza or PBS twice a week for 12 weeks. Peripheral immune cells were isolated from donor db/db mice with or without 5-Aza treatments and intravenously infused to host diabetic animals. In in-vitro studies, human PBMCs and mouse splenocytes were isolated and applied to the intervention experiments of targeting DNMT1 or mTOR pathway.

Results: The key DNA methylation enzyme DNMT1 increased along with the inflammatory activity of PBMCs in DKD patients. Inhibition of DNMT1 with 5-Aza markedly increased CD4+CD25+ regulatory T (Treg) cells in the peripheral immune cells from DKD patients and in db/db diabetic animals, leading to enhanced immunosuppressive activity. In db/db mice, adoptive transfer of Treg cells from 5-Aza-treated animals beneficially modified the inflammatory phenotype of host immune system, resulting in significant improvement of diabetic albuminuria and chronic kidney injuries. We demonstrated differentially methylated genes in diabetic PBMCs, revealing prominent DNA hypomethylation in the upstream regulatory genes of mTOR pathway. Further mRNA array confirmed the induction of genes predominantly in the positive, rather than negative, regulators of mTOR pathway in DKD. In db/db mice, mTOR activity showed a correlation with the level of global DNA methylation and the inflammatory capacity of kidney immune cells. Finally, mTOR interventions efficiently modified the regulatory effects of 5-Aza on diabetic immune cells.

Conclusions: Chronic hyperglycemia induces aberrant DNA methylation of mTOR pathway, leading to pathogenic activation of immune cells in DKD progression. Our study highlights the therapeutic potentials of targeting epigenetic events in the immune system for treatment of chronic kidney disease and DKD in particular.

FR-OR050

Histone Demethylation near the Serum Amyloid A Promoter: Metabolic Memory Associated Inflammation

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Background: Episodic hyperglycemia increases risk of diabetic complications, also known as "metabolic memory." The study aim was to determine if serum amyloid A (SAA) mediated inflammation is due to demethylation of trimethyl histone 3 lysine 27 (H3K27Me3) near the SAA promoter in podocytes and to correlate indicators of this demethylation with SAA expression in kidneys of humans and mice with diabetes.

Methods: SAA knockout (CRISPR-Cas9) and control mouse podocytes were exposed to advanced glycation end-products (AGE, 300 μg/mL) for 7 days, followed by 7 days without AGE. H3K27Me3 near the SAA promoter was measured via chromatin immunoprecipitation (ChIP). Levels of mRNA for SAA and inflammatory mediators: (CXCL5, CCL5, and CCL2) were measured by qt-PCR. H3K27Me3 demethylation was inhibited (GSK-1, 20 uM) in podocytes exposed to AGE for 1 day. ChIP measured H3K27Me3 near the SAA promoter in the kidney cortex of db/db and wild type mice (C57BLKS). Relationships between expression of JMDJ3 mRNA (H3K27Me3 specific demethylase) and SAA mRNA were determined in kidneys of diabetic and non-diabetic humans and mice (C57- BLKS, DBA/2, eNOS-deficient C57-BLKS, Nephroseq).

Results: H3K27Me3 was reduced (95%, n=6 pooled samples) after 7-day periods of AGE exposure and AGE withdrawal in podocytes. Levels of mRNA increased for SAA (17±6-fold, p=0.025) and inflammatory mediators: CXCL5 (18±12-fold, p=0.004), CCL5 (1.6±0.6-fold, p=0.026), and CCL2 (2.0±0.7-fold, p=0.001). SAA knockout reduced expression of these mediators by ≥60% ($p<0.05$ for all). GSK-1 reduced AGE-induced expression of SAA and these mediators by ≥60% ($p<0.05$ for all). H3K27Me3 was lower in the kidney cortex of db/db mice compared to wild type mice (25±6%, p=0.049, n=6). Expression of JMDJ3 mRNA correlated with SAA mRNA in diabetic and non-diabetic kidney tissue from humans ($r=0.54$, $p<0.001$) and mice ($r=0.54$, $p<0.001$).

Conclusions: Episodic exposure to AGE, a hyperglycemia-related perturbation, caused H3K27Me3 demethylation near the SAA promoter and increased expression of inflammatory mediators in podocytes. Correlative studies showed that indicators of this histone demethylation process and increased SAA expression carried over into kidney tissue of humans and mice.

FR-OR051

Genetic Inactivation of Histone H3 K79 Methyltransferase Dot1l in Aqp2+ Progenitor Cells Causes CKD by Upregulating Endothelin-1 in Mice and Humans

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Background: Histone H3 K79 methyltransferase Dot1l represses aldosterone target genes including endothelin-1 (ET1). $Aqp2^+$ progenitor cells give rise to all known cell types in the connecting tubule and collecting duct. Here we investigate whether genetic inactivation of *Dot1l* in $Aqp2^+$ progenitor cells causes chronic kidney disease (CKD) by upregulating ET1.

Methods: $Dot1l^{f/f}$ Aqp2Cre ($Dot1l^{AC}$) and $Dot1l^{f/f}$ $ET1^{f/f}$ Aqp2Cre (DE^{AC}) mice were generated to disrupt Dot1l with or without intact ET1 in the $Aqp2^+$ progenitor cells, respectively. Aqp2Cre mice were used as WT control. Mice were analyzed at the ages of 12 and 24 months. Alternatively, two-month-old mice were subject to UUO and analyzed 14 days later. Various molecular, cellular and pathological methods were employed to assess the renal function and pathology. Cells with loss of dimethyl K79 ($H3m2K79^-$) were identified and isolated from archived kidney biopsies from patients with diabetic nephropathy (n=50) by laser capture to identify hDOT1L mutations via sequencing.

Results: At both ages, WT mice were apparently normal. $Dot1l^{AC}$ developed slight and severe symptoms mimicking human chronic kidney disease (CKD). The CKD symptoms include extreme polyuria, proteinuria, natriuresis, a variety of tubular abnormalities,

interstitial fibrosis, and mononuclear cell infiltrate. These changes were coupled with upregulated ET1 and fibrotic markers (FSP1, Collagen IV, Vimentin, and a-SMA). However, all of these phenotypic features were ameliorated by inactivation of ET1 in DE^{AC} mice. Consistently, $Dot1l^{AC}$ vs. WT developed more prominent UUO-induced kidney fibrosis, which was partially rescued in DE^{AC} mice. Some CNT/CD cells in DN were $H3m2K79^{-}$. Analysis of the microdissected $H3m2K79^{-}$ cells revealed two single-base deletions and an $E^{129}K$ mutation that is predicted to abolish the methyltransferase activity.

Conclusions: Dot1l is a new potential renoprotective factor by repressing ET1 in both mice and humans. Inactivation of Dot1l in $Aqp2^{+}$ progenitor cells is sufficient to trigger CKD development.

Funding: NIDDK Support

FR-OR052

Single-Cell RNA-Seq of Dissected Glomeruli in a Mouse Model of Diabetic Nephropathy

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Background: Diabetic nephropathy is the most common etiology for end-stage renal disease. In recent years, single-cell RNA-seq (scRNA-seq) has evolved into a reliable tool to interrogate gene expression changes on a single-cell level. Previous scRNA-seq studies on human and animal kidneys failed to capture glomerular cells even when sequencing thousands of cells. Here, we use scRNA-seq on microdissected glomeruli to study changes in a mouse model of diabetic nephropathy (DN).

Methods: Diabetes was induced at 8 weeks of age in IRG/Nphs2.Cre/$eNOS^{-/-}$mice (C57BL/6 background) with 50 mg/g streptozotocin (STZ) over 5 consecutive days. Single-cell suspensions of microdissected whole glomeruli from STZ-treated (DN) and control (Ctrl) mice were used for scRNA-seq on the Fluidigm C1 platform using 800-cell IFCs (v2) according to the manufacturer's instructions. Resulting libraries were sequenced on an Illumina NextSeq500.

Results: We captured 186 and 217 single-cells from control mice, and 188 and 238 single-cells from diabetic mice. After QC filtering 99 and 199 control cells, and 107 and 188 cells from DN were used for downstream analysis. K-means clustering identified 4 cell populations representing endothelial cells (marker genes Kdr, Pecam1, Emcn), podocytes (Nphs1/2, Podxl), mesangial cells (Pdgfrb, Myl9, Gata3), and leukocytes (Cd44, Cd52, Cd53, Cd74, Cd300a). The relative cell type contribution was (Ctrl %/DN %) 47%/62% for endothelial cells, 16%/7% for podocytes, 34%/15.5% for mesangial cells, and 3%/15.5% for leukocytes. Differential analysis of gene expression comparing DN and Ctrl showed genes known to be altered in diabetic glomeruli as well as several interesting candidate genes which have thus far not been demonstrated to be affected in DN.

Conclusions: Single-cell RNA-seq of glomeruli overcomes limitations of previous studies which largely missed glomerular cells altogether. This approach allowed us to confidently identify 3 major cell types of the glomerulus, and the inflammatory response associated in this DN model. The low percentage of podocytes and mesangial from diabetic glomeruli as compared those from control suggests either loss or dedifferentiated of these cells in the diseased condition.

Funding: NIDDK Support

FR-OR053

Modelling Immune Mediated Renal Injury through the Use of Induced Pluripotent Stem Cell Derived Organoids

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Background: The role of inflammatory cells in chronic kidney disease has been well documented, with macrophage infiltration and accumulation implicated in the initiation and progression of renal injury. However, current models of disease fail to accurately reflect the initial cycles of damage and resolution. At the core of this issue remains a fundamental gap in our knowledge of how discrete inflammatory signalling networks converge and interact with renal tissue to cause fibrosis. We have found that plasticity of resident cells and infiltrating cells is reflected by significantly increased levels of the stemness regulator, miR-302 in exosomes of patients with CKD while additionally the TGFβ signalling network was identified as a mediator of macrophage reprogramming.

Methods: IPSCs were differentiated into kidney organoids over a 24 day period. Primitive streak formation was induced by treating cells with CHIR99021 8μM for 3 days. Medium was then changed to APEL medium supplemented with 200ng/ml FGF9 and Heparin 1μg/ml. On day 12, growth factors were removed and organoids were matured until day 24. Organoids were then cultured in conditioned media from peripheral blood mononuclear cells (PBMCs) polarised towards a pro-inflammatory phenotype using lipopolysaccharide 200ng/ml and Interferon γ 20ng/ml and towards a pro-resolving phenotype using interleukin 4 20ng/ml and interleukin 13 20ng/ml. Organoids were subsequently fixed, stained and imaged using confocal microscopy for known markers of renal damage. Similarly, organoids were also treated with the nephrotoxic agent Aristolochic Acid (AA) and co cultured with PBMCs.

Results: Culturing of organoids in conditioned media for a 48 hour period lead to significant increases in the expression of αSmooth Muscle Actin, Fibronectin and KIM-1. Co culture of organoids exposed to AA for up to 24 hours with PBMCs resulted in significant damage to the organoid, accompanied by migration and infiltration of differentiated cells into these damaged organoids.

Conclusions: We propose that this novel model of macrophage induced renal damage can be used to investigate the role of inflammatory pathways which result in fibrosis and that by manipulating the plasticity of resident and infiltrating cells we may inhibit or reverse the progression of fibrosis *in vivo*.

FR-OR054

The NGAL-Macrophage Therapy Improves Diabetic Kidney Disease in db/db Mice by Induction of PI3K/Akt Pathway

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Background: Alternatively activated macrophages (M2) have regenerative properties and shown promise as cell therapy in chronic kidney disease. However, M2 plasticity is one of the major hurdles to overcome. Genetically modified macrophages stabilized by neutrophil gelatinase-associated lipocalin (NGAL) are able to preserve in stable manner their M2 phenotype. Nowadays, little is known about M2 macrophage effects in diabetic kidney disease (DKD). The aim of the study was to investigate the therapeutic effect of both bone marrow-derived M2 (BM-ØM2) and Ø-NGAL macrophages in the *db/db* mice

Methods: Seventeen wk-old mice with established DKD were divided into five treatment groups with their controls: **D+BM-ØM2; D+Ø-BM; D+Ø-NGAL; D+Ø-RAW; D+SHAM and non-diabetic (ND)** (*db*/- and C57bl/6J) animals. We infused $1x10^{6}$ macrophages twice, at baseline and 2 weeks thereafter. Blood, urine samples and kidney tissue were collected. To further ascertain the mechanism by which NGAL macrophage cell therapy is involved in epithelial kidney repair, we co-cultured renal epithelial cells and macrophages *in vitro*. We assessed epithelial proliferation, repair and epithelial phenotype integrity.

Results: BM-ØM2 did not show any therapeutic effect whereas Ø-NGAL significantly reduced albuminuria and renal fibrosis in db/db mice. The Ø-NGAL therapy increased the anti-inflammatory IL-10 and reduced some pro-inflammatory cytokines, reduced the proportion of M1 glomerular macrophages and podocyte loss and was associated with a significant decrease of renal TGF-β1. Furthermore, we demonstrated *in vitro* that NGAL overexpression in macrophages enhanced epithelial markers and healthy epithelial phenotype through the induction of PI3K/Akt pathway. In addition, NGAL activated proliferation markers such as Ki67 and PCNA through the inhibition of PPAR-γ.

Conclusions: Overall, our study provides evidence that NGAL macrophage cell therapy has therapeutic effects on DKD. NGAL acts as a mediator and is a crucial player reducing inflammation, fibrosis and promoting epithelial proliferation.

Funding: Private Foundation Support

FR-OR055

Macrophage-Derived Migrasomes Transfer of IL-11 Is a Novel Mechanism of Renal Interstitial Fibrosis in Diabetic Nephropathy

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Background: Migrasome is a newly discovered, migration-dependent vesicle which differ dramatically from common extracellular vesicles(EVs) and primarily aid in intercellular communications. Macrophages infiltration and fibroblasts activation have been closely associated with renal interstitial fibrosis in diabetic nephropathy(DN). Whether macrophage produce migrasomes and contribute to the pathological processes are unknown.

Methods: Macrophage migrasomes were examined in streptozotocin murine model and Raw264.7 cells by transmission/scanning electron microscopy. Migrasomes isolated from M1/M2 phenotype macrophage, high glucose treated macrophage (M1-mig, M2-mig, HG-mig)interaction with renal fibroblast were assessed and migrasome gene profiling to identify the intercellular signaling.

Results: Ultrastructural analysis revealed that macrophage produce the previously unrecognized vesicles (Fig1.*arrowhead*) that typically grow on the tips or intersections of retraction fibers(Fig1.*triangle*). The vesicles were confirmed as the newly discovered migrasome by morphology and biomarker data that distinguish them from common EVs. We noticed that activated macrophage and HG enhanced migrasome production. Released migrasomes can directly initiate fibroblasts transdifferentiation which fibrosis markers (αSMA, COL1) markedly increased in HG/M1-mig group (by 10-15fold, respectively), while migrasome inhibitor CK636 or Dynasore alleviate fibrosis in DN model. We performed migrasomes gene-profiling to determine what intercellular fibrosis messages might be delivering. Amongst the top ranking genes, notably, we found a specific enrichment of IL-11 mRNA in HG-mig and M1-mig. The knockout IL-11 migrasomes or blocking fibroblasts IL-11RA sharply decreased the fibrosis levels.

Conclusions: Our findings suggest a fundamental, but formerly unrecognized pattern via which macrophage exert their effects through migrasomes and more depth of their functional roles shall be unearthed. IL-11 in HG/M1-mig driving fibroblasts transdifferentiation may be a novel mechanism of fibrosis in DN.

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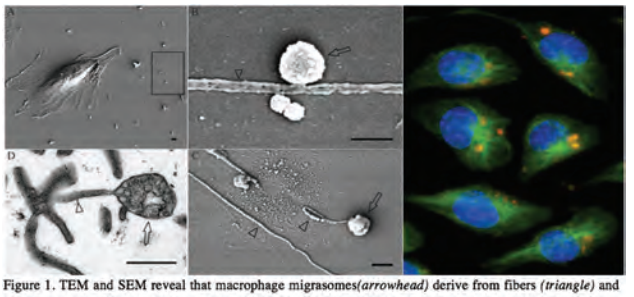

Figure 1. TEM and SEM reveal that macrophage migrasomes*(arrowhead)* derive from fibers *(triangle)* and M1-mig*(orange)*effect on differentiation of fibroblasts (green: αSMA staining) (scale bar, 500 nm)

FR-OR056

TYRO3 Is a Novel Podocyte Protective Factor in Glomerular Disease

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Background: Our previous work demonstrated a protective role of protein S against podocyte loss in early diabetic kidney disease (DKD) [Zong F JASN 2018]. Protein S is known to have anti-inflammatory and anti-apoptotic effects through the activation of Tyro3, Axl, and Mer (TAM) receptors. We find that the biological effects of protein S in DKD are largely mediated by Tyro3 in podocytes. The aim of this study was to determine the role of Tyro3 in podocyte injury in glomerular disease.

Methods: Tyro3 mRNA levels were checked in different datasets of human kidneys with DKD. Tyro3 knockout mice and control WT mice were made diabetes or injected with adriamycin to induce nephropathy. Inducible podocyte-speciifc Tyro3 overexpression mice were generated and crossed with OVE26 diabetic mice or Tg26 mice or induced nephropathy with adriamycin. Albuminuria, kidney histology, and podocyte number were assessed in these mice. Western blot and PCR analysis were used to assess mechanisms of Tryo3 regulation and biological effects in cultured human podocytes.

Results: *TYRO3* mRNA expression is highly enriched in human glomeruli, and immunostaining showed that TYRO3 co-localized with podocyte marker. Glomerular *TYRO3* mRNA expression was suppressed in the progressive DKD. It was also suppressed in focal segmental glomerulosclerosis (FSGS). We showed that genetic ablation of *Tyro3* in murine models of DKD and Adriamycin-induced nephropathy (ADRN) worsened albuminuria and glomerular injury, suggesting a protective effect of TYRO3 in early DKD and FSGS. Conversely, we showed that induction of TYRO3 overexpression specifically in podocytes significantly attenuated albuminuria and kidney injury in mice with DKD, ADRN and HIV-associated nephropathy. Mechanistically, we found that TYRO3 expression was suppressed by activation of TNF-α/NF-κB pathway, which may contribute to decreased TYRO3 expression in progressive DKD and FSGS, and TYRO3 confers anti-apoptotic effects through the activation of AKT pathway in podocytes.

Conclusions: In conclusion, we demonstrate that TYRO3 has a critical role to maintain normal podocyte function and could be a potential new drug target to treat glomerular disease.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR057

Development of a Peptide Inhibitor of a Novel Target to Retard Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the major cause of end-stage renal disease worldwide, and remains suboptimally treated medically. A large body of compelling data from our group have demonstrated a critical role of CDA1 in DN and validated CDA1/CDA1BP1 interaction as a promising target to retard diabetic nephropathy. We have developed a prototype inhibitor, CHA-061, to target this novel axis.

Methods: This study focuses on the assessment of CHA-061 for its efficacy to attenuate parameters relevant to renal fibrosis in two models of diabetes. The first model is an insulin deficient model using streptozotocin (STZ)-induced diabetes in ApoE KO mice, a model relevant to type 1 diabetes. The second is a type 2 diabetes model using db/db mice which initially become obese and subsequently diabetic as a result of the leptin receptor mutation. Both non-diabetic control and diabetic mice with established DN after diabetes was developed for 10 weeks were randomly allocated to receive either vehicle or CHA-061 treatment (10 mg/kg IP injections twice a week) for 10 weeks.

Results: The analysis of kidney tissues showed that, in the vehicle treated ApoE KO mice, diabetes was associated with >2-fold increase in gene expression of sclerotic molecules such as collagens I and III as well as proinflammatory genes such as TNFα and MCP1. Immunohistochemical staining of collagen III was increased >10-fold and the glomerulosclerosis index (GSI) as assessed by PAS staining was increased >2-fold in diabetic ApoE KO mice. These parameters were significantly attenuated in CHA-061 treated diabetic ApoE KO mice. Similarly, CDA1 expression levels were increased ~2-fold in diabetic db/db mice accompanied by >2-fold increase in gene expression of sclerotic molecules such as CTGF, fibronectin, collagens I, III and IV when compared to the non-diabetic dbh mice. CHA-061 treatment reduced these parameters in the diabetic db/db mice to levels similar to those in the non-diabetic controls. These results were consistent with our previous target validation data using CDA1 KO and CDA1BP1 KO mouse strains.

Conclusions: Taken together, the current study has demonstrated the efficacy and feasibility to pharmacologically target the novel CDA1/CDA1BP1 axis to retard nephropathy in both type 1 and type 2 diabetes by targeting not only fibrotic but also proinflammatory pathways.

Funding: Government Support - Non-U.S.

FR-OR058

Chloride-Insensitive WNK4 Mice Reveal Differential NCC Regulations by Dietary Potassium

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Background: With-no-lysine (WNK) kinases critically regulate sodium chloride cotransporter (NCC) in the distal nephron. Earlier works reveal that intracellular chloride ion ($[Cl^-]i$) binds to a hydrophobic pocket of WNKs and inhibits autophosphorylation and activity of WNKs in non-transporting *in vitro* condition. Substitution of two leucine residues (L319, L321) surrounding the hydrophobic pocket with phenylalanine makes WNK4 less sensitive to $[Cl^-]i$. The Cl^--sensing character of WNK4 hasn't been validated *in vivo*.

Methods: We generated the Cl^--insensitive L319F/L321F WNK4 mice using CRISPR/Cas9.

Results: The Cl^--insensitive L319F/L321F WNK4 mice displayed hypertension, hyperkalemia, and metabolic acidosis along with hyperactive NCC and impaired urinary potassium excretion, mimicking pseudohypoaldosteronism type II. To test the Cl^--sensing character of WNK4 in response to dietary potassium, we fed L319F/L321F WNK4 mice diets with various potassium contents. Potassium deprivation failed to further enhance NCC in L319F/L321F WNK4 mice. Chronic potassium-rich diet still dephosphorylated NCC in L319F/L321F WNK4 mice. These results suggest that Cl^--insensitive WNK4 is an NCC stimulator, and the physiological $[Cl^-]i$ in the distal nephron suppresses WNK4 activity. Potassium deprivation enhances NCC through ameliorating Cl^--mediated inhibition on WNK4. In chronic potassium adaptation, other mechanism(s) overrides the constitutively active WNK4 to suppress NCC.

Conclusions: In sum, this study provides compelling evidence supporting that WNK4 is a bona fide NCC stimulator and Cl^- sensor in the distal convoluted tubule. The Cl^--sensing mechanism of WNK4 play an important role in potassium deprivation.

Funding: Government Support - Non-U.S.

FR-OR059

Regulated Dephosphorylation of NCC Shapes the Renal Potassium Switch Pathway

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Background: The Renal Potassium Switch Pathway stimulates the thiazide-sensitive sodium chloride cotransporter (NCC) to limit urinary potassium loss at the expense of retaining sodium and elevating blood pressure. It has been established that low extracellular potassium ($[K^+]_o$) activates the WNK4-SPAK kinase cascade to drive NCC phosphorylation, but it remains mysterious how NCC is dephosphorylated in response to a rise in $[K^+]_o$. It has been assumed that high $[K^+]_o$ turns off WNK4-SPAK mediated NCC phosphoactivation, allowing phosphatase activity to dephosphorylate WNK4, but this remains unclear.

Methods: Kinase-activating mutations were introduced in SPAK, the terminal kinase in the WNK signaling pathway, and renal expression of the constitutively active (CA) SPAK mutant was specifically targeted in mice to the early DCT. NCC abundance (tNCC) and phosphorylation (pNCC) were evaluated in vivo and in isolated tubules, together with telemetric blood pressure (BP) measurements in response to changes in dietary potassium and $[K^+]_o$. CA-SPAK were compared to Control mice.

Results: CA-SPAK mice display NCC hyperphosphorylation and thiazide-treatable hypertension. BP remained elevated in CA-SPAK mice, compared to control, over a wide range of $[K^+]_o$, as predicted. However, BP dropped in CA-mice when $[K^+]_o$ exceeded 5mM, and this was coincident with a reduction in pNCC/tNCC, revealing a $[K^+]$-regulated dephosphorylation mechanism. Acute elevation in $[K^+]_o$ decreases pNCC in isolated DCT from WT but not CA-SPAK mice. However, chronic potassium loading for 2 or 5 days reduces pNCC abundance with an IC50 of ~4.1mM in WT. pNCC is also reduce in CA-SPAK mice under the same conditions but with a rightward shift in pNCC vs. $[K^+]_o$ curve (IC50 ~ 5.5mM), suggesting chronic activation of a protein phosphatase (PP). Subsequent RNA profiling studies revealed a network of PP-subunits are regulated to decrease pNCC in response to increased $[K^+]_o$.

Conclusions: Because CA-SPAK drives NCC phosphorylation independent and downstream of WNK, these observations provide strong support for a potassium-activated phosphatase that directly dephosphorylates NCC. Thus $[K^+]_o$–regulated phosphorylation as well as dephosphorylation of NCC shape the Renal Potassium Switch Pathway. Regulated NCC dephosphorylation provides new mechanism to explain why high dietary K^+ consumption alleviates salt-sensitive hypertension.

Funding: NIDDK Support

FR-OR060

Differential Functions of Chloride Channels Clc-k1 and Clc-k2 in Mouse Kidneys

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Background: Two voltage-gated ClC chloride (Cl^-) channels, ClC-Ka and ClC-Kb, conduct urinary Cl^- reabsorption in renal tubules. Genetic alterations on ClC-Ka/ClC-Kb result in human diseases with abnormal blood pressure. Previous studies have shown that rodent ortholog Clc-k1 and Clc-k2 expressed in the renal medulla and cortex, respectively. The physiological roles of these two Cl^- channels have not been compared.

Methods: We created Clc-k1 knockout and Clc-k2 knockout mice sharing the same genetic background using the Ksp-Cre system.

Results: Clc-k1 deficiency resulted in polyuria with a blunted response to vasopressin and relatively normal extracellular fluid. In contrast, Clc-k2 deficiency led to uncompensated renal salt wasting, hypovolemia, and impaired renal function. The sodium transporters in distal nephron were unanimously upregulated in Clc-k1 knockout mice but downregulated in Clc-k2 knockout mice. Various vasopressors, including catecholamine, endothelin, and serotonin, were stimulated in Clc-k2 knockout mice but not in Clc-k1 knockout mice. Patchy interstitial inflammation & fibrosis, hyperplasia of juxtaglomerular apparatus, and renal scarring were observed in Clc-k2 knockout mice. High salt diet rescued the renal function and ameliorated the interstitial inflammation and fibrosis in Clc-k2 knockout mice. In embryonic kidneys, Clc-k2 transcript first expressed in the nephron progenitors on E13.5 and gradually extended into the inner medulla along with NKCC2. Clc-k1 was not detected in the embryonic kidneys and found in inner medulla on P1 after birth.

Conclusions: Clc-k1 and Clc-k2 express and function differentially in the embryonic and adult kidney. The critical roles of Clc-k2 in distal salt reabsorption and embryonic kidney explain the uncompensated salt wasting in Clc-k2 knockout mice.

Funding: Government Support - Non-U.S.

FR-OR061

A Single Gastric K+ Load Induces Acute Diuresis in Mice

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Background: K^+ balance relies on regulated renal K^+ excretion to match variable dietary K^+ intake. Upon a K^+ rich meal, rapid and effective urinary K^+ excretion is obligatory. The renal adaptation to an acute K^+ load involves an increase of the driving force for K^+ secretion by shifting the distal tubular Na^+ reabsorption from being electroneutral (NCC) to electrogenic (ENaC). In addition, K^+ secretion in the CD is stimulated by increased luminal flow. Here we asked, if a high K^+ intake acutely increases urinary flow.

Methods: Mice were K^+ challenged through gavage, diets or a combination of these. After K^+ loading urinary volume, $[K^+]_u$ and $[Na^+]_u$, plasma osmolality, $[K^+]_p$ and $[Na^+]_p$ were measured.

Results: 1) Mice switched from a 1% to a 2% K^+ diet increased their diuresis markedly within 12h. **2)** Mice switched from a 1% to a 0.01% K^+ diet had a biphasic diuretic response. During the first 12h their diuresis decreased, whereas it increased from 12 to 36h. **3)** A single K^+ load, by gastric gavage, corresponding to 25-50% of daily K^+ intake induced diuresis within 30 min. This occurred despite augmented plasma osmolality. $[K^+]_u$ remained unchanged and therefore the increased urinary K^+ excretion depended on the volume effect **4)** K^+ gavage did not changes urinary creatinine excretion suggesting a constant GFR. **5)** Subsequently, a possible direct and acute effect of a plasma $[K^+]$ ($[K^+]_{bl}$) increase was tested in isolated perfused mTALs and CDs. An acute $[K^+]_{bl}$ increase (from 3.6 to 6.5 mM) did not affect TAL NaCl absorption (measured 5 and 25 minutes post K^+ jump). In contrast, the same manoeuver reduced the CDs sensitivity to stimulated AVP-mediated water absorption (measured 10 minutes post K^+ jump).

Conclusions: Dietary K^+ load induces a rapidly on setting diuresis. This increase in urinary volume appears crucial for a powerful K^+ elimination since it appears prior to alteration in $[K^+]_u$. Based on preliminary data we suggest that the physiological mechanism of K^+-induced diuresis involves AVP desensitization of the CD.

Funding: Government Support - Non-U.S.

FR-OR062

SPAK Is Rapidly Dephosphorylated in the Distal Convoluted Tubule during Acute Potassium Loading

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Background: The thiazide-sensitive sodium chloride cotransporter (NCC) of the distal convoluted tubule (DCT) is phosphorylated and activated by WNK acting through SPAK. High extracellular potassium leads to rapid NCC dephosphorylation and inactivation. However, the molecular mechanism remains unknown. Here, we examined the roles of SPAK in this process: specifically, testing the hypothesis that ***SPAK is dephosphorylated by high extracellular K in cultured cells and in vivo.***

Methods: 1) SPAK-transfected HEK293 cells were treated with 0mM to 10Mm (high) KCl, for one hour. Cell extracts were analyzed by western blot. 2) Kidney slices were incubated for 30 minutes in 0 Mm K to increase NCC phosphorylation and then treated with 3mM or 10mM K for 30 minutes. Slices were snap frozen. 3) C57/BL6 mice were gavaged with either vehicle or 3% KCl for 15 mins. Blood collected was used for electrolyte measurement by iSTAT. One kidney was processed for western blot and the other kidney was either perfused for IF or cortex-rich kidney poles were isolated and snap frozen.

Results: In HEK293 cells, raising medium $[K^+]$ for one hour led to a reduction in transfected and endogenous SPAK phosphorylation at S383. This *in vitro* finding was replicated *ex vivo* in kidney slices by western blot analysis. We saw parallel decrease in NCC and SPAK phosphorylation levels in kidney slices incubated in high K (10mM) vs normal K (3mM) buffer. We used a model similar to Loffing and colleagues to test whether SPAK dephosphorylation by high K^+ occurs in a physiologically relevant setting. C57/BL6 mice gavaged with 3% KCl for 15 minutes showed an increase in plasma $[K^+]$ and a corresponding decrease in SPAK phosphorylation in the cortex, but not in whole kidney. Immunofluorescence studies also showed decreased SPAK-S383 primarily in parvalbumin-positive 'early' DCT1 upon K loading. Cytosolic total-SPAK puncta observed in control kidneys rapidly disappeared after K loading, suggesting a rapid alteration in SPAK localization as well as phosphorylation by extracellular K.

Conclusions: Although prior work suggested that SPAK is not involved in rapid NCC dephosphorylation, the current data indicate that SPAK is rapidly dephosphorylated *in vivo* primarily along the DCT during short term K treatment. Further work will be necessary to establish that this effect is essential for rapid NCC dephosphorylation.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR063

Phosphorylation of β1Pix by AMPK and Its Role in ENaC Inhibition in Kidney Epithelial Cells

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Background: AMP-activated kinase (AMPK) inhibits the epithelial Na^+ channel (ENaC) by increasing the binding of the ubiquitin ligase Nedd4-2 to ENaC. We recently showed that AMPK inhibits ENaC by direct phosphorylation of Nedd4-2 at a site critical for Nedd4-2 stability. We also demonstrated that the Pak-interacting exchange factor β_1Pix is required for ENaC inhibition by AMPK and for Nedd4-2 stability in mouse kidney cortical collecting duct (CCD) cells. AMPK activators increase the binding of β_1Pix to 14-3-3. Thus, AMPK may enhance Nedd4-2-dependent ENaC degradation by promoting the formation of a β_1Pix/Nedd4-2/14-3-3 complex. Here, we further investigate the mechanisms of how AMPK promotes a β_1Pix-14-3-3 interaction and whether 14-3-3 binding is important for ENaC inhibition by AMPK.

Methods: Protein mass spectrometry (MS), *in vitro* translation and phosphorylation assays were used to detect AMPK phosphorylation sites in β_1Pix. Various constructs were transiently expressed in polarized mpkCCD$_{c14}$ cells. An epithelial volt-ohmmeter was used to measure amiloride-sensitive equivalent short-circuit currents in mpkCCD$_{c14}$ cells ± combined treatment with the AMPK activators AICAR and A-769662 for 24 h. Coimmunoprecipitation assays were used to examine modulation of β_1Pix/14-3-3/Nedd4-2 interactions by AMPK.

Results: AMPK directly phosphorylates β_1Pix *in vitro*, and six potential AMPK phosphorylation sites were detected by MS. Among these sites, the Ser-71 phosphorylation site on β_1Pix was found to be functionally significant. Compared to wild-type β_1Pix, overexpression of the β_1Pix-S71A mutant significantly reduced ENaC inhibition and the binding of both β_1Pix and Nedd4-2 to 14-3-3 caused by AMPK activation in mpkCCD$_{c14}$ cells. Moreover, overexpression of a β_1Pix-Δ602-611 mutant unable to bind 14-3-3 decreased the interaction between Nedd4-2 and 14-3-3. Finally, in preliminary studies, overexpression of the R18 peptide, which inhibits 14-3-3-target interactions, reduced the binding of both β_1Pix and Nedd4-2 to 14-3-3 and attenuated ENaC inhibition by AMPK in CCD cells.

Conclusions: Our results suggest that phosphorylation of β_1Pix at Ser-71 by AMPK is involved in the formation of a β_1Pix/Nedd4-2/14-3-3 complex, which promotes ENaC degradation caused by AMPK activation.

Funding: NIDDK Support, Private Foundation Support

FR-OR064

A Pivotal Role of WNK1/OSR1 Pathway in Regulation of Renal Proximal Sodium Transport

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Background: In renal proximal tubules (PTs) we and others have shown that insulin stimulates both apical Na^+/H^+ exchanger (NHE)3 and basolateral Na^+/HCO_3^- co-transporter (NBCe1) via PI3K/Akt signaling. Pioglitazone (Pio) also stimulates both NHE3 and NBCe1 via non-genomic PPARg/ERK signaling (Cell Metab 2011). In human PTs, angiotensin (Ang)II stimulates both transporters via NO/ERK signaling (JASN 2014). However, the mechanism underlying this coordinate regulation in apical and basolateral PT sodium transport is poorly understood. In this study, we investigated the role of WNK1/OSR1 pathway in regulation of PT sodium transport.

Methods: By using a pH-sensitive dye BCECF we measured the basolateral NBCe1 activity and apical NHE3 activity in freshly-isolated rat PTs as well as human PTs, the latter obtained during surgery for renal cell carcinoma. We also measured the NBCe1 activity in rat PTs incubated overnight with siRNA against WNK1, WNK3, OSR1 or SPAK. Protein phosphorylation was analyzed by Western blotting in rat and human kidney cortex tissue.

Results: In freshly-isolated rat and human PTs, insulin and Pio markedly stimulated both NHE3 and NBCe1 activities, and an OSR1/SPAK inhibitor, Closantel (10mM) completely suppressed these stimulatory effects. Closantel also completely suppressed the AngII-stimulated NBCe1 and NHE3 activities in human PTs. Immunostaining analysis confirmed the expression of OSR1 protein in rat and human PTs. In rat and human kidney cortex, Closantel suppressed the insulin-induced OSR1/SPAK phosphorylation without affecting the Akt phosphorylation. Similarly, Closantel suppressed the OSR1/SPAK phosphorylation by Pio and AngII without affecting the ERK phosphorylation. In overnight incubated rat PTs, siRNA against WNK1 but not WNK3 abolished the stimulatory effects of Pio and insulin on NBCe1. Moreover, siRNA against OSR1 but not SPAK abolished the stimulatory effects of Pio and insulin.

Conclusions: These results indicate, for the first time to our knowledge, that diverse stimuli depending on the distinct signaling cascades converge into WNK1/OSR1 pathway, which may work as a master regulator of PT sodium transport and hence represent a novel therapeutic target in hypertension and/or volume expansion.

Funding: Government Support - Non-U.S.

FR-OR065

G-protein Pathway Suppressor 2 Abolished the WNK4-Mediated Inhibition of the Large Conductance Ca2+ Activated Potassium (BK) Channels

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Background: G-protein pathway suppressor 2 (GPS2) is a multifunctional protein and transcriptional regulation factor. We have recently reported that GPS2 enhances BK channel activity and its protein expression by reducing ERK1/2 signaling-mediated degradation of the channel. Previous studies reported that WNK4 inhibits BK channel activity and protein expression through stimulating ERK 1/2 signaling pathway. Our yeast-two hybrid screening data showed that WNK4 interacts with GPS2. Thus, we hypothesized that GPS2 increases BK protein expression through interfering with the WNK4-mediated effect on BK.

Methods: Cell culture, transfection, western blot analysis, co-immunoprecipitation, and cell surface biotinylation were used in the experiments.

Results: To determine whether GPS2 modulates the WNK4-mediated inhibitory effect on BK, we first wanted to confirm whether GPS2 interacts with WNK4. In HEK293 cells cotransfected with HA-WNK4 and either myc-vector or myc-GPS2, co-immunoprecipitation (co-IP) experiments showed that myc-GPS2 co-immunoprecipitates WNK4, whereas myc-vector does not. To further confirm their interaction, we performed the reciprocal co-IP experiments in HEK293 cells cotransfected with HA-GPS2 and either myc-vector or myc-WNK4. We found that myc-WNK4 co-immunoprecipitates HA-GPS2 while myc-vector does not. To further assess the effects of GPS2 on WNK4-mediated inhibitory effects on BK, we performed the western blot analysis in HEK293 cells cotransfected with BK and WNK4 in the presence or absence of GPS2. We found that WNK4 significantly inhibits BK protein expression as expected. However, in the presence of GPS2, BK protein expression is restored to the control level. We further did cell surface biotinylation experiments in Cos-7 cells co-transfected with BK and WNK4 in combination with increasing doses of GPS2. We showed that WNK4 significantly inhibits total and surface BK protein expressions and GPS2 reversed the WNK4-mediated inhibition of BK in a dose-dependent manner. We further showed that GPS2 reversed the WNK4-mediated inhibition of BK protein expression by partially reducing the BK degradation through a lysosomal pathway.

Conclusions: These data suggested that GPS2 abolishes the WNK4-mediated inhibition of BK by partially reducing BK degradation through a lysosomal pathway.

Funding: Veterans Affairs Support

FR-OR066

Response of Intercalated Cell (IC) BKα Knock-Out Mice to a High K (HK) Diet

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Background: Flow-induced K secretion (FIKS) in the cortical collecting duct (CCD) is mediated by BK channels, which also contribute to the renal adaptation to a high K diet (HKD). BK channels are expressed in both ICs and principal cells (PCs) in CCDs. We generated a mouse with a targeted deletion of BKα, the pore forming subunit of the BK channel, in ICs (IC-BKα-KO) by crossing floxed BKα mice with B1 V-ATPase Cre mice. Perforated cell recordings of ICs in CCDs in these KO mice revealed reduced charybdotoxin (CTX)-sensitive K currents vs. those in floxed controls, suggesting that the KO would have a limited capacity for FIKS and renal adaptation to a HKD. In fact, KO mice exhibited a higher blood [K] vs. controls (5.5±0.8 vs. 5.0±0.7 mM; p<0.05), yet rates of urinary K excretion in response to volume expansion were similar in both groups.

Methods: See results.

Results: To confirm the contribution of IC BK channels to FIKS and K adaptation, we measured net transepithelial transport (Jx, in pmol/min.mm) of Na and K, in control (n=4) and KO (n=6) microperfused CCDs from mice fed a HKD x 10 d. Similar rates of flow-stimulated JNa were observed in control and KO CCDs (43.3±6.5 and 26.9±8.3, respectively, p=NS), but FIKS, present in control CCDs (-5.0±0.6), was absent in KO tubules (-1.1±0.6; p<0.05). Although CTX-sensitive K currents in PCs were upregulated in KO mice (454±40 pA; n=6) vs. those in controls (304±28 pA; n=5; p=0.02), the failure to detect FIKS in KO CCDs underscored the critical role of ICs vs. PCs in BK channel-mediated K secretion. ROMK immunolabeling of kidney cryosections revealed a 16% increase in apical membrane relative to whole cell expression in calbindin-positive DCTs of KO mice vs. controls.

Conclusions: We conclude that in the absence of IC BKα, mice have a limited capacity for adaptation to a HKD, as evidenced by the higher blood [K], and lack of FIKS, confirming a critical role of IC BK channels in K homeostasis. We speculate that upregulation of alternate K secretory channels, including ROMK, in other segments of the nephron occurs to enable K secretion in the absence of BK channel activity in ICs.

Funding: NIDDK Support

FR-OR067

Calcineurin Homologous Protein 1 Regulates the Renal Na-K-2Cl-Cotransporter

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Background: The Na-K-2Cl-cotransporter (NKCC2) of the thick ascending limb (TAL) is essential for renal salt handling. Its activity depends on phosphorylation and dephosphorylation steps. Our previous work suggested that calcineurin is involved in dephosphorylation and deactivation of NKCC2. Calcineurin activity can be modulated by members of the calcineurin homologous protein family (CHP). Among these, CHP1 has been implicated in the regulation of several membrane proteins including ion transporters. We hypothesized that CHP1 participates in calcineurin-dependent regulation of NKCC2 activity.

Methods: Immunofluorescence, immunoblotting, co-immunoprecipitation and GST pull down assays were applied in rodent kidneys and cultured cells to characterize physical and functional interactions between NKCC2, CHP1 and calcineurin.

Results: Double labeling of CHP1 and NKCC2 revealed their close co-localization in rat TAL. Both products co-immunoprecipitated, suggesting their interaction. GST pull down assays with recombinant N-terminal NKCC2 mutants, mimicking its (de)phosphorylation at functionally relevant residues (T96, T101, T114, and S126), suggested that CHP1 and calcineurin may compete for the binding with phosphorylated NKCC2. Overexpression of CHP1 in cultured macula densa cells significantly increased NKCC2 phosphorylation at baseline and upon low-chloride stimulation. Acute stimulation of NKCC2 by administration of desmopressin in rats promoted the interaction of NKCC2 with CHP1, while attenuating its binding with calcineurin.

Conclusions: Our data suggests that CHP1 protects NKCC2 from calcineurin-dependent dephosphorylation and deactivation.

FR-OR068

APOL1 Antisense Oligonucleotide Treatment Ameliorates IFNγ-Induced Proteinuria in Genomic APOL1 Transgenic Mice

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Background: APOL1 risk variants (G1/G2) strongly associate with CKD in African Americans. Not all individuals homozygous for the risk variants, however, develop renal disease suggesting that a second hit is required. In this study, we sought to develop a physiologically-relevant mouse model of APOL1-associated renal disease.

Methods: We generated genomic APOL1 G0 or G1 transgenic mice via random transgenesis of a human APOL1-containing fosmid, resulting in APOL1 expression in similar tissues as that identified in humans and at similar relative levels of expression. Mice were challenged with recombinant IFNγ and APOL1 induction was measured by qRT-PCR. Proteinuria was measured by albumin ELISA and normalized using urine creatinine levels measured by a clinical chemistry analyzer.

Results: Naïve APOL1 G1 Tg mice failed to show a differential renal phenotype compared to APOL1 G0 mice. A single dose of IFNγ, however, caused robust proteinuria only in G1 mice, despite inducing kidney APOL1 expression in both G0 and G1 mice. We identified an antisense oligonucleotide (IONIS-APOL1$_{Rx}$) against APOL1 that is potent with an excellent safety profile. Administration of IONIS-APOL1$_{Rx}$ to G1 Tg mice prior to IFNγ challenge prevented APOL1 induction and IFNγ-induced proteinuria in a dose-dependent manner. Treatment with a hepatocyte-targeting version of IONIS-APOL1$_{Rx}$, however, provided incomplete protection against IFNγ-induced proteinuria, suggesting that local expression of APOL1 in kidney is critical for pathogenesis. In search of a kidney-specific target engagement biomarker, we detected APOL1 mRNA in urinary shed cells from mice and humans and correlated its reduction to kidney APOL1 mRNA reduction in APOL1 Tg mice.

Conclusions: We developed a novel APOL1 transgenic mouse model that recapitulates the physiological attributes of APOL1 and exhibits a kidney phenotype in G1 mice upon IFNγ challenge. APOL1 ASO treatment in this model prevents IFNγ-induced proteinuria in G1 mice, demonstrating that the kidney disease cell type is sensitive to APOL1 ASO

treatment and that IONIS-APOL1$_{Rx}$ may be an effective therapeutic for APOL1-associated nephropathies.

Funding: Commercial Support - Ionis Pharmaceuticals, AstraZeneca

FR-OR069

Kidney Compartment Specific eQTL Studies Highlight Causal Genes and Pathways for Renal Disease Development

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Background: Chronic kidney disease (CKD) is a common disease condition affecting more than 1 in 10 people in the general population. Genome wide association studies (GWAS) have identified more than 100 regions where nucleotide variants are significantly and reproducibly associated with kidney function. Expression quantitative trait locus (eQTL) analysis aim to identify gene expression changes in cell and tissue samples driven by the underlying genetic variation. By combining GWAS and eQTL studies we can identify gene expression change driven by disease associated genetic variation. Genes for which expression are influenced by GWAS signals are likely candidates for disease development.

Methods: We conducted eQTL analyses separately on glomerular and tubular portions of healthy human kidney samples obtained from 151 subjects of European descent. We complemented our compartment-based eQTL studies with kidney-specific epigenome maps and single-cell RNA-sequencing results. Focusing on the *DAB2-C9* CKD GWAS locus, we induced kidney injury by folic acid administration and unilateral ureter obstruction to test the effect of *DAB2* and *C9*. To understand the mechanism of Dab2-induced kidney damage, we cultured primary renal tubule cells from Dab2$^{flox/+}$ mice and infected them with Cre-eGFP or control adenovirus.

Results: We identified eQTLs and generated a searchable public eQTL database from human whole kidney, tubules and glomeruli samples. Kidney-specific eQTLs showed significant enrichment for genetic variants associated with renal traits. We identified eQTLs at 27 genes that colocalize with CKD GWAS signals. Putative causal genes were enriched for proximal tubule expression and endolysosomal function. *DAB2* appeared to be a central gene among the putative causal genes. *In vivo* studies, using mice with reduced tubule epithelial-specific gene expression demonstrated that Dab2 protects mice from CKD development. *In vitro* results indicate that Dab2 in tubule cells plays an important role in TGFβ-induced profibrotic gene expression.

Conclusions: This in-depth follow-up analysis of CKD GWAS, defines a novel framework for CKD development, and identifies DAB2 and endolysosomal pathway as key mechanism for kidney disease pathogenesis.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim, the Eli Lilly Co., Private Foundation Support

FR-OR070

Allele-Specific Expression Studies Identify Tubule Epithelial DACH1 as a Kidney Disease Gene

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Background: Genome wide association analysis (GWAS) have identified significant associations between over 100 genetic loci and kidney disease development. However, finding causal genes, cell types and biological mechanisms underlying such associations remains a challenge. High throughput RNA-seq data allows transcriptome-wide scan of millions of variants and their impact on gene expression variation (eQTLs) in specific cells and tissues. Furthermore, incorporating allele-specific expression (ASE) analysis enables us to improve statistical power for such screening methods while controlling for biases and potential confounding factors.

Methods: We generated genotype and gene expression data of kidney tissue samples obtained from 121 healthy individuals of European descent. Additionally, we generated mice with tubule-specific dose reduction of *Dach1* (Ksp^{cre}/*Dach1*$^{flox/+}$). Kidney injury was studied in aging mice or following folic acid administration. We cultured primary renal tubule epithelial cells (TECs) from *Dach1*$^{flox/+}$ mice for Cre adenovirus infection. Furthermore, we performed single cell RNA-sequencing on control and Ksp^{cre}/Dach1$^{flox/flox}$ mouse kidneys.

Results: We identified 41 ASE loci (compared to 27 eQTL loci) with genome-wide significant associations to kidney function. Interestingly, kidney compartment-based ASE analysis identified a significant tubule-specific association between the CKD risk variant rs716877 genotype and *DACH1* level, but not in glomeruli. The GWAS risk allele was associated with decreased *DACH1* levels. By single cell RNA-sequencing analysis, we found that *Dach1* is expressed in the loop of Henle, distal convoluted tubules and collecting ducts. Mice with reduced tubule-specific Dach1 level demonstrated worsened renal damage at baseline and following nephrotoxic injury. Reducing Dach1 expression in primary TECs directly increased profibrotic gene expression. Single cell RNA-sequencing analysis of Ksp^{cre}/Dach1$^{flox/flox}$ mice indicated a significantly increased expression level of proliferating tubule cells.

Conclusions: Combining ASE and GWAS integration analysis, we identified 41 putative causal associations between genetic variation and kidney development. In particular, we show that reducing tubule epithelial *Dach1* level induces kidney fibrosis development via TEC proliferation.

Funding: NIDDK Support

FR-OR071

GWAS of Urinary Metabolite Concentrations among CKD Patients Identify 90 Loci

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Background: The kidneys play a central role in metabolite handling. Genetic studies of metabolite concentrations can identify proteins performing these functions. Reduced GFR may represent a challenge model for metabolite handling, facilitating the identification of such loci.

Methods: We carried out GWAS of the urinary concentrations of 1,172 metabolites among 1,221 European ancestry GCKD study participants with eGFR of 30-45 ml/min/1.73m^2 and UACR <30 mg/g, with further replication among 406 individuals. Dilution-corrected urinary metabolite concentrations were related to HRC-imputed genome-wide genotypes of minor allele frequency >1%, using an additive genetic model and multivariable adjustment. Statistical significance was defined as p<4.3e-11 (5e-8/1172) in a meta-analysis of discovery and replication, with concordant effect sizes.

Results: After correction for multiple testing, there were 246 genome-wide significant associations for 211 metabolites, distributed across 90 independent loci. These included previously identified loci in screens of urine (n=15) and blood (n=55) metabolite concentrations in the general population, and 20 novel loci. Associations between lead SNPs and urinary metabolite concentrations were strong, with p-values as low as <1e-550. Compared to associations of the same genetic variants and urinary metabolites in a healthy population, effects were significantly stronger among CKD patients on average (p<2e-16). The number of metabolites associated with a locus' lead variant ranged up to 30 for missense rs13538 in *NAT8*, consistent with the function of N-acetyl-transferase in detoxification reactions. Relating genome-wide genotypes to modeled relationships between metabolites (pairwise ratios, clusters) resulted in additional insights such as the identification of candidate substrates for renal transport proteins, a functional readout of renal enzymes, detoxification reactions of drugs commonly prescribed among CKD patients, and facilitated the de-orphanization of SNP-associated metabolites of previously unknown identity.

Conclusions: Our study increases the number of loci associated with urinary metabolite concentrations from 26 to 90, highlights the value of studying genetics of renal metabolism among CKD patients, and provides many novel insights into human renal (patho)physiology.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR072

Rho Guanine Nucleotide Exchange Factor β-PIX Is Required for the Maintenance of Podocyte Architecture and Glomerular Function in Adult Mice

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Background: Activation of Rac1 (a small GTPase) in podocytes has been implicated in the development of proteinuria and focal segmental glomerulosclerosis (FSGS). Previously, we identified Arhgef7 (β-PIX) as a predominant GEF (guanine nucleotide exchange factor) that interacts with Rac1 in human podocytes (HP) using a proximity-based ligation assay, BioID. Furthermore, we confirmed that β-PIX is expressed in podocytes both *in vitro* and *in vivo*. However, its functional role remains unknown.

Methods: Cultured mouse podocytes (MP) with β-PIX knockdown (KD) and their controls were established using shRNA. Cell size was quantified in fixed cells stained with phalloidin. Cell migration and adhesive property were studied by wound healing assay and attachment assay, respectively. Cell proliferation was studied by MTT assay. Podocyte specific β-PIX deficient (KO) mice were generated by crossing β-PIX floxed mice with NPHS2-Cre mice. Urine albumin to creatinine ratio (ACR) and renal histology were studied up to 13 weeks of age. Data are provided as the mean ± SE.

Results: Compared to control MP, β-PIX KD MP were significantly smaller. Cell motility and adhesive property were modestly decrease in β-PIX KD MP. Proliferation rate was not different. Podocyte specific β-PIX KO mice presented no obvious renal phenotype up to 2-3 weeks of age, but developed progressive proteinuria starting at around 7-8 weeks of age (8 wk: KO: 117±44 x10^2 vs Control: 49±15 μg/mg, n=7-11, p<0.01; 13 wk: 255±128 x10^2 vs 238±90 μg/mg, n=4-7, p<0.05). In addition, by PAS staining, 13-week-old KO mice showed global/segmental glomerulosclerosis, parietal cells proliferation, and tubular casts in the kidney.

Conclusions: Our findings demonstrate the previously unrecognized importance of β-PIX in maintaining podocyte function. To the best of our knowledge, this is the first evidence that a Rho GTPase GEF plays a critical role in podocytes.

FR-OR073

Tight Regulation of Crkl Isoforms Account for the Etiology and Pleiotropic Effect of the 22q11.2 Microdeletion Syndrome (DiGeorge) on Kidney and Urinary Tract Development

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Background: We recently showed that haploinsufficiency and point mutations in *CRKL* drive kidney and urinary tract malformations in the DiGeorge, or 22q11.2, syndrome and in sporadic CAKUT, respectively. We examined the developmental necessity of two *Crkl* transcript isoforms using conditional mutant mouse models.

Methods: Bulk RNAseq data from E15.5 mouse kidneys were analyzed for expression of *Crkl* T1 and T2 expression. Phenotypic analyses were carried out on conditional mouse mutants generated by breeding *Crkl(Ex1)$^{f/f}$* or *Crkl(Ex2)$^{f/f}$* with either *Six2*-, *Hoxb7*- or *Pax2-Cre* mice to delete either both splice variants by removing the first of three exons (Ex1), or by removing T1 only via Ex2 excision.

Results: Analysis of RNAseq data show T1 and T2 expression at a mean TPM of 39.5 and 9.3, respectively, (n=4) in E15.5 mouse kidneys. This is comparable to TPM data for housekeeping (*Gapdh*=55.5) and kidney & urinary tract genes (*Pax2*=10.4, *Hoxb7*=54.9, *Six2*=24.1). The two isoforms exist also in human embryonic kidneys. At P0, phenotypic analysis of *Six2-Cre;Crkl(Ex1)$^{f/f}$* and *Six2-Cre;Crkl(Ex2)$^{f/f}$* mice shows severe renal hypoplasia. When both *Crkl* transcripts were removed in ureteric-bud derived structures via *Hoxb7-Cre*, both unilateral and bilateral ureteropelvic dilation and early hydronephrosis developed by P0. However, in *Hoxb7-Cre;Crkl(Ex2)$^{f/f}$* mice, where only T1 is absent, there was a decreased frequency and severity of obstructive phenotypes. Lastly, when bred with *Pax2-Cre* mice, both crosses show mild renal hypoplasia at P0 and E18.5.

Conclusions: These data suggest a tight regulation of both *Crkl* isoforms during mouse embryonic development with possible tissue-specific synergistic and modulatory effects. On the one hand, the presence of both *Crkl* isoforms in the metanephric mesenchyme is necessary for normal kidney development, but when inactivated in both compartments, hypoplasia was less severe. When T1 was removed from UB-derived structures, the presence of only T2 was sufficient to prevent abnormal development and obstructive uropathy, which were only observed with absence of both *Crkl* isoforms. These findings provide further insight into the pleiotropic effect of human *CRKL* mutations on kidney and urinary tract development.

Funding: NIDDK Support

FR-OR074

The LMX1βR246Q Mutation Causes FSGS through Dysregulation of Chloride Intracellular Channel Expression and Focal Adhesion Dynamics

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Background: We previously reported a heterozygous missense mutation of LMX1β as a cause of nail-platella-like renal disease in two families with hereditary FSGS. Currently, there are no targeted therapies for $LMX1\beta_{R246Q}$-induced glomerulopathy. We hypothesized that $LMX1\beta_{R246Q}$ disrupts the expression of disease-relevant molecular targets that may be amenable to pharmacotherapy. To test this hypothesis, we performed an unbiased, RNA-seq analysis in our established $LMX1\beta_{WT}$ and $LMX1\beta_{R246Q}$-overexpressing podocyte lines to uncover potential therapeutic targets.

Methods: We conducted RNA-seq, qPCR, immunoblot, immunofluorescence, and scratch wound healing assays in $LMX1\beta_{WT}$ and $LMX1\beta_{R246Q}$-overexpressing podocytes to evaluate the effects of the $LMX1\beta_{R246Q}$ mutation on podocyte dysmotility.

Results: We detected significantly reduced Chloride Intracellular Channel 5 (*CLIC5*) expression in $LMX1\beta_{R246Q}$ podocytes relative to $LMX1\beta_{WT}$ controls by RNA-seq and qPCR. CLIC5 protein expression was similarly reduced as was the expression of CLIC3 and CLIC4. Given the established roles of CLIC proteins in the regulation of foot process architecture (i.e. CLIC5) and β1-integrin recycling (i.e. CLIC3 and CLIC4), we evaluated motility in $LMX1\beta_{R246Q}$ podocytes. $LMX1\beta_{R246Q}$ podocytes displayed decreased wound closure, β1-integrin expression, FAK phosphorylation and paxillin activation. Focal adhesion density was increased in $LMX1\beta_{R246Q}$ podocytes relative to controls as evidenced by an increase in VASP staining by immunofluorescence. Gene expression of PKG II, an upstream activator of VASP, was also significantly downregulated by RNA-seq and qPCR in $LMX1\beta_{R246Q}$ podocytes. To determine the effect of NO/sGC/PKG pathway agonists on podocyte motility, we treated $LMX1\beta_{R246Q}$-overexpressing podocytes with vardenafil (PDE5 inhibitor), cinaciguat (sGC activator) or riociguat (sGC stimulator). These NO/sGC/PKG agonists ameliorated podocyte dysmotility.

Conclusions: The $LMX1\beta_{R246Q}$ mutation may cause FSGS, in part, through the dysregulation of CLIC-mediated foot process architecture and β1- integrin recycling and through impaired of PKG-mediated VASP activation in focal adhesions. NO/sGC/PKG pathway agonists may be effective in ameliorating $LMX1\beta_{R246Q}$-induced podocyte dysmotility.

Funding: NIDDK Support, Private Foundation Support

FR-OR075

Enzymatic Degradation of Cystine Decreases Nephrolithiasis in a Mouse Model of Cystinuria

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Background: Cystinuria is a genetic disease characterized by frequent recurrent stone formation in the kidneys requiring multiple procedural interventions with an increased risk of chronic kidney disease. Stone formation is the result of increased urinary excretion of insoluble cystine due to mutations in the *SLC3A1* and/or *SLC7A9* genes. Current disease management with hyperhydration, alkalization and cystine binding thiol drugs (CBTD) is challenging and problematic. Effectiveness is limited with continued stone formation and frequent adverse effects to CBTD requiring treatment withdrawal in some patients (Biyani and Cartledge, EAU-EBU update series 4, 2006). We investigated the potential of an alternative approach to disease management utilizing novel cystine degrading enzyme derived from human cystathionine gamma lyase (CGL).

Methods: *In vivo* efficacy of ACN00107 was tested in a murine model of cystinuria (SLC3A1-/-) that develops stones between 4 and 7 weeks of age (PMID: 28165480). ACN00107 (100 mg/kg, i.p., every other day) was administered to 5-week-old SLC3A1 -/- mice for up to 6 weeks. At specific timepoints prior to, during, and after ACN00107 treatment, bladder and kidneys were weighed and imaged by micro computed tomography (μCT) analysis.

Results: μCT analysis demonstrated a reduction in both volume and number of total kidney stones after 6 weeks of treatment which was associated with reduced kidney weights. A trend towards reduced bladder weight and total bladder stone volume compared to control was also observed.

Conclusions: This study demonstrates for the first time that enzymatic degradation of cystine reduces the propensity for kidney and bladder stone formation in a mouse model of cystinuria. Given the high morbidity, frequent requirement for procedural intervention, and the safety and tolerability profile of current medical approaches, enzymatic degradation of cystine warrants further investigation as a new potential approach for disease management.

Funding: Commercial Support - Aeglea BioTherapeutics, Inc.

FR-OR076

TFCP2L1 Mutations Cause a Novel Distal Tubulopathy in Humans

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Background: An underlying monogenic cause of early-onset chronic kidney disease (CKD) can be detected in 20% of individuals. To date, >250 monogenic causative genes have been identified for the most common etiologies of CKD evident before age 25 years suggesting mechanisms of renal pathogenesis.

Methods: We performed whole exome sequencing to identify novel monogenic causes of CKD in ~1,000 families with renal tubulopathy/ echogenic kidneys.

Results: We discovered 2 different recessive, homozygous mutations in *TFCP2L1* (Transcription Factor CP2 Like 1) in 2 consanguineous families with CKD. Family B2003 with CKD at the age of 2 years, episodes of severe hypochloremic, hypokalemic alkalosis, cataracts, seizures, developmental delay, and hypotonia encoded a homozygous Ser290Phefs*5 mutation. A second child encoded a homozygous Gln168Arg mutation in A5048 with onset of CKD by 2 years of age, loss of urinary potassium and chloride, hypotonia and deafness. The variants are disease causing by SIFT, MutTaster and PolyPhen2 prediction programs and are absent from gnomAD database. Gln168Arg is located in the DNA-binding domain positioned at the start of the L10 loop pointing into the DNA minor groove. *Tfcp2l1* is a transcription factor expressed in the thick limb of Henle, distal convoluted tubule, connecting segments and especially in the intercalating cells (ICs) in collecting ducts. *Tfcp2l1* alone is sufficient to induce tubulogenesis in rat progenitors and is required for normal maturation of the distal nephron and collecting ducts in mice (Yamaguchi, Development, 2006; Werth, Elife, 2017). *Tfcp2l1* knockout mice display loss of expression of direct binding targets of Tfcp2l1 including ion transporters in different segments of the distal nephron and regulatory proteins determining cell identity. A knockout caused renal hypoplasia, polyuria, renal potassium and chloride loss (Yamaguchi, Development 133:4737, 2006) and disruption of collecting duct patterning characterized by the deletion of ICs (Werth, eLIFE, 2017). Consistently, in *Xenopus* larvae skin *tfcp2l1* localizes to *foxi1+* ICs.

Conclusions: We here identified *TFCP2L1* mutations as a potential novel cause of distal tubulopathy in humans. Modeling these mutations in mice and segment specific deletions will reveal the full functions of *Tfcp2l1*.

FR-OR077

CHRNA3 Mutations Cause Neurogenic Bladder and Dysautonomia

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are the most prominent cause (>45%) of chronic kidney disease (CKD) in the first 3 decades of life. Although about 40 monogenic causes have been implicated in human CAKUT so far, many causes remain unknown.

Methods: To identify novel monogenic causes of CAKUT we applied whole exome sequencing (WES) to 144 families with CAKUT.

Results: By WES, we discovered a homozygous frameshift mutation (p.Thr337Asnfs*81) in the gene *CHRNA3* (*cholinergic receptor nicotinic alpha 3 subunit*) in a patient of consanguineous descent with CKD stage 3 secondary to neurogenic bladder, vesicoureteral reflux (VUR) and bilateral hydronephrosis. Screening WES data of 703 further patients with CAKUT revealed three different homozygous recessive *CHRNA3* mutations in 3 families with neurogenic bladder (p.Ser340*; c.267+2T>G obligatory splice site mutation; p.Arg110His). *CHRNA3* codes for an ion channel subunit in the urothelium and interacts with other ion channels in the neuronal network governing bladder reflexes and smooth muscle contraction. A *Chrna3* knockout mouse has impaired bladder reflexes, a distended urinary bladder, dribbling urination, urinary tract infections, urinary stones and mydriasis (Xu *PNAS* 96:5746, 1999). Given the mydriasis in mice we inquired for constant mydriasis in the patients. This was confirmed for the index patient with p.Thr337Asnfs*81 and two affected siblings with the p.Ser340* mutation.

Conclusions: We identified *CHRNA3* recessive mutations as the first cause of neurogenic bladder in humans. The mutations caused additionally extrarenal dysautonomic phenotypes such as constant mydriasis. Our findings may disclose a pathophysiological sequence, in which neurogenic bladder secondarily causes CAKUT.

FR-OR078

Confidence in Women's Health: An International Survey of Nephrologists

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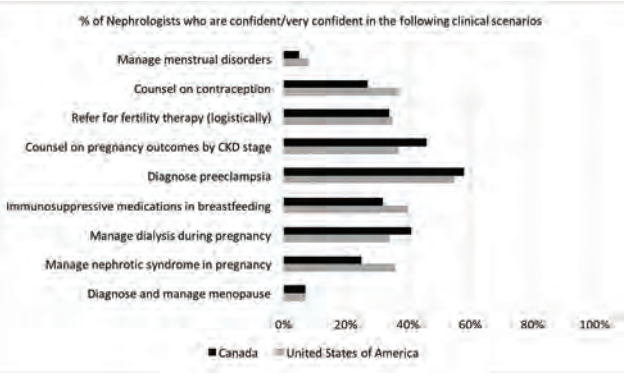
Background: A broad range of women's health issues are intimately related to kidney disease, yet little is known about providers' confidence in these issues. The women's health working group of CureGN sought to assess adult Nephrologists' exposure to women's health, their confidence in counseling and management, and ways to improve future care.

Methods: A 25-question survey was disseminated via the CureGN email network, the Canadian Society of Nephrology and ASN *Kidney News*. Demographics, practice characteristics, and response prevalence were summarized with descriptive statistics. Responses across country of practice (United States vs Canada) were compared using Pearson's chi squared test.

Results: Of the 154 respondents, 58% were from the US, 53% were women, and the median age was between 41-45. The majority (77%) identified their practice setting as academic. 55% of the respondents had fellowship training in women's health, which was similar across country of training (p=0.325). Nephrologists from both countries lacked confidence across a spectrum of issues (Figure 1). Most provided contraception (64%) and pre-conception (68%) counseling to less than one woman per month though counseling occurred significantly more frequently in the US. In their career, 91% have cared for less than five pregnant women on dialysis. Only 12% had access to interdisciplinary clinics. Finally, 89% felt that interdisciplinary guidelines and/or continuing education seminars would improve knowledge.

Conclusions: As women with chronic kidney disease experience adverse maternal outcomes and remain at risk for disease progression postpartum, we must do better to bolster provider knowledge and comfort level. Further research is warranted to identify barriers to counseling about women's health issues, identify best mechanisms to enhance physician confidence, and facilitate formation of interdisciplinary clinics. Interdisciplinary guidelines and case based materials may be a starting point.

Funding: NIDDK Support



Nephrologists' Confidence Managing Women's Health

FR-OR079

The Effect of Plasma Exchange and the Effect of Reduced-Dose Oral Glucocorticoids during Remission Induction in Severe ANCA-Associated Vasculitis

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Background: Whether plasma exchange reduces the risk of end-stage renal disease or death in anti-neutrophil cytoplasm antibodies (ANCA) -associated vasculitis is uncertain. Also uncertain is whether lower doses of oral glucocorticoids reduce the risk of infection without increasing the risk of end-stage renal disease or death.

Methods: We performed a 2-by-2 factorial randomized controlled trial to separately evaluate plasma exchange and two different regimens of oral glucocorticoids in patients with severe ANCA-associated vasculitis. Participants were randomly assigned to 7 treatments of plasma exchange or no plasma exchange. Participants were also randomly assigned to either a reduced-dose regimen that <60% of the cumulative oral glucocorticoid dose or a standard regimen by 6 months or the standard regimen. All patients received immunosuppression. Patients were followed for up to 7 years for the primary composite outcome of death from any cause or end-stage renal disease.

Results: Amongst 702 participants, the primary outcome occurred in 28% of patients allocated to plasma exchange compared to 31% in the no plasma exchange group (hazard ratio 0.86, 95% confidence interval [CI] 0.65 to 1.13; p=0.27). The primary outcome occurred in 28% of patients in the reduced glucocorticoid group and 26% in the standard glucocorticoid group (absolute risk difference 2.3%, 90% CI -3.4% to 8.0%; met non-inferiority hypothesis). Serious infections in the first year occurred less often in the reduced glucocorticoid group compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52 to 0.94; p=0.02).

Conclusions: Plasma exchange did not reduce the risk of end-stage renal disease or death. Compared to a standard dose, reduced glucocorticoids did not substantially increase the risk of death or end-stage renal disease and resulted in fewer serious infections.

Funding: Other U.S. Government Support

FR-OR080

Membranous Nephropathy: Response to Rituximab Is Dependent on Anti-PLA2R1 Epitope Spreading and Gender

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Background: Membranous nephropathy (MN) is a rare autoimmune kidney disease, yet one of the leading causes of nephrotic syndrome (NS) in adults. Clinical evolution is complex and treatment controversial. There is a need for better biomarkers to identify patients at risk of severe disease and orient therapy. Phospholipase A2 receptor 1 (PLA2R1) was identified as the major autoantigen in 70% of patients with MN. Proteinuria and PLA2R1 antibody titer predict outcome in PLA2R1-related MN.

Methods: We evaluated the additional predictive role of PLA2R1 epitope spreading from the immunodominant CysR domain to CTLD1 and CTLD7 domains in 117 consecutive, rituximab- treated patients with PLA2R1-related MN and nephrotic syndrome. Primary outcome was complete (proteinuria <0.3 g/24h) or partial remission (proteinuria <3.0 g/24h and >50% reduction vs basal). Non-spreaders had antibodies restricted to the CysR domain while spreaders had additional antibodies to CTLD1 and/or CTLD7 domains.

Results: Higher basal anti-PLA2R1 titer associated with higher probability of spreading. All patients with titer >400 RU/ml were spreaders. Fifteen of the 79 spreaders (19%) were females vs 16 of the 38 non-spreaders (42%; p=0.008), and 15 of 31 females (48%) were spreaders vs 64 of 86 males (74%; p<0.01). During a median (IQR) follow-up of 32.2 (16.4-50.5) months, 77 patients (66%) achieved the combined endpoint of

complete or partial remission. Female gender (p=0.004), shorter duration of proteinuria (p=0.004), lower proteinuria (p=0.004), lower antibody titer (p=0.036), and no epitope spreading (p=0.009) predicted remission. Compared to spreader males, the HR (95% CI) for the endpoint was 5.15 (2.73-9.70; p<0.0001) in non-spreader females, 2.09 (1.16-3.77, p=0.014) in spreader females, and 1.85 (0.95-2.59, p=0.069) in non-spreader males.

Conclusions: In MN, anti-PLA2R1 titer and epitope spreading monitoring help to predict response to rituximab. Better response of females could be explained, at least partially, by protection against PLA2R1 epitope spreading. VB and PR contributed equally as first authors, GL and GR contributed equally as last authors.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR081

Non-Invasive Diagnosis of Primary Membranous Nephropathy using Phospholipase A2 Receptor Antibodies

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Background: Kidney biopsy is the current gold standard to diagnose membranous nephropathy (MN). Approximately 70-80% of patients with primary MN have circulating anti-PLA2R antibodies. We hypothesized that PLA2R antibody testing without the need for a biopsy is a valid strategy to make a non-invasive diagnosis of MN in the setting of preserved renal function and negative work up for secondary causes such as autoimmunity, malignancy, medications and paraproteinemias.

Methods: The medical records of all Mayo Clinic patients with positive serum PLA2R antibody tests between July 2015 and December 2017 were reviewed.

Results: A total of 1065 PLA2R tests were ordered on 675 unique patients. Of these, 113 had a positive PLA2R antibody test, of which 105 had native renal biopsies performed. The primary diagnosis in all biopsies was MN. Eighty-four patients had a negative work up for secondary causes of MN. Fifty of the 84 patients had preserved renal function (eGFR >60 ml/min/1.73m^2). In none of these 50 patients, kidney biopsies provided significant information that altered diagnosis or management. Among the 34 patients with eGFR <60 ml/min/1.73m^2, additional findings that altered the treatment plan included acute interstitial nephritis (n=1), superimposed diabetic nephropathy (n=1) and cellular crescents (n=1). Potential secondary causes were identified in 21 cases (positive ANA test = 4, malignancy = 9, NSAID = 3, monoclonal protein = 5). A detailed review of the clinical data revealed that these were co-existing findings and not true secondary MN.

Conclusions: In patients with preserved renal function and no evidence of secondary causes, a positive PLA2R test confirms the diagnosis of MN. A kidney biopsy does not add significant data in this context.

FR-OR082

PLA2R1 as the Major Autoantigen in Membranous Nephropathy: From New Epitope Identification to Personalized Medicine

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Background: Membranous nephropathy (MN) is a rare autoimmune kidney disease yet the most common cause of nephrotic syndrome. Clinical evolution is complex and treatment controversial. There is a need for better biomarkers to identify patients at risk of severe disease and orient therapy. In 2009, PLA2R1 was identified as the major autoantigen, with circulating autoantibodies in 70% of patients. The severity of MN and clinical outcome is associated with anti-PLA2R1 titer and the presence of multiple antibodies. PLA2R1 epitopes have been identified in the CysR (CR), C1 and C7 domains and may be linked by a mechanism of epitope spreading. However, their exact number and location including controversial findings concerning their presence in the CR and C1 domains require further studies. The aim of this work was to clarify the number of PLA2R1 domains containing epitopes.

Methods: To clarify the conundrum between CR and C1 N-terminal domains, we expressed in HEK293 cells a series of CR-FnII-C1 triple domains with insertion of protease cleavage sites between each domain. Reactivities were tested with different patients' sera before and after protease cleavage. To further investigate the number of epitope domains in the distal region of PLA2R1, we expressed a series of individual PLA2R1 domains and tested their reactivity for a cohort of >150 MN patients by ELISA.

Results: The triple domain CR-FnII-C1 was recognized by all patients' sera when tested before cleavage. After cleavage releasing isolated domains, some sera had reactivities limited to CR or C1 while others reacted with both CR and C1, demonstrating the presence of independent epitopes targeted by different antibodies. The ELISA screening of a cohort of 150 patients towards individual PLA2R1 domains led us to identify C5 and C8 as two new epitope-containing domains.

Conclusions: Our results show that patient's autoantibodies can target up to 5 PLA2R1 domains: CR, C1, C5, C7 and C8 with different prevalence's. The clinical association between reactivity towards these 5 PLA2R1 domains and disease activity is currently being analyzed and may help to design new diagnosis and prognosis tools towards better personalized medicine. JJ and VB contributed equally as first authors.

Funding: Government Support - Non-U.S.

FR-OR083

CD-19 Targeted Rituximab Is Safe and Effective in Adult Steroid Dependent/Resistant but Calcineurin Inhibitor Dependent Podocytopathy

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are common podocytopathies causing nephrotic syndrome (NS) in children and adults. A significant proportion of patients are either steroid dependent (SD) or resistant (SR), requiring alternate therapies. Long-term calcineurin inhibitors (CNI) use is associated with dyslipidemia, impaired glucose tolerance and, nephrotoxicity. Rituximab is a potential candidate in this group of patients, with a more favourable safety profile, so the present study was undertaken to evaluate the efficacy and safety of rituximab in SD/SR MCD/FSGS dependent on CNIs to maintain remission.

Methods: This was a prospective observational study conducted from July 2014 to February 2018. SD-NS or SR-NS (biopsy proven MCD/FSGS), who were CNI dependent were enrolled. All patients received rituximab at a dose of 375 mg/m^2 at entry in the study. CD-19 levels were monitored monthly and patients having CD-19 levels >5/μL and/or >1% received additional low-dose (100 mg) of rituximab. Patients were followed up monthly for a period of 12 months, and the clinical and biochemical parameters prior to and following rituximab administration were compared. Outcome: Cumulative percentage of patients who experienced remission (Complete remission (CR), partial remission (PR)) at 6 and 12 months.

Results: A total of 24 patients was enrolled and followed for 12 months. Mean age at enrolment was 22.77±7.45 years. At the end of 6 and 12 months, 87.50% and 79.16% of the patients achieved remission, respectively. CR and PR at 6 and 12 months were observed in 14 (58.33%) and 7 (29.17%), and 13 (54.16%) and 6 (25%), patients, respectively. Relapse occurred in 7 (29.16%) patients during the follow-up, requiring steroids (4, 57.14%) or CNIs (3, 42.85%). The mean dose of rituximab was 791 mg. Rituximab was well-tolerated, with infusion reactions, respiratory tract infection and oral candidiasis in 5 (20.83%), 5 (20.83%) and 1 (4.17%) patient, respectively.

Conclusions: CD-19 targeted rituximab is a safe and effective agent in the management of adults with CNI dependent MCD/FSGS. At 12 months, over three-fourth of the patients with CNI dependent podocytopathy maintain clinical remission.

FR-OR084

Nephrotic Syndrome Is Significantly Associated with Increased Risk of Ischemic Stroke

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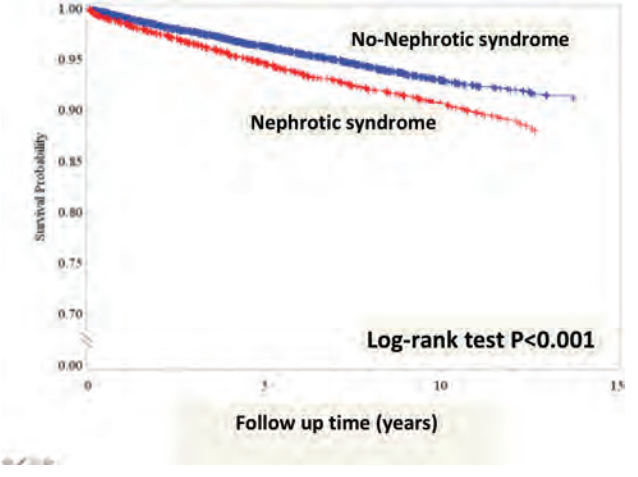
Background: Evidence on the risk of ischemic stroke in patients with nephrotic syndrome is scarce.

Methods: We conducted a retrospective nationwide cohort study by analyzing the registry data of the National Health Insurance Research Database in Taiwan. Adult patients who were aged ranged 18 to 110 years and had received a diagnosis of nephrotic syndrome were included in the nephrotic syndrome cohort. For each patient with nephrotic syndrome, the corresponding controls were selected 1:4 on the basis of matched age, sex, Charlson comorbidity index, and index date to evaluate the risk of stroke, especially the ischemic stroke.

Results: The first three-year incidence rates of ischemic stroke were 25% and 15.9% in 3496 patients with nephrotic syndrome and 13984 comparison control cohorts, respectively. Overall, 9% patients with nephrotic syndrome developed ischemic stroke in 9.1±2.9 years follow-up period. A higher risk of stroke was observed in patients with nephrotic syndrome than in controls, adjusted hazard ratio (aHR) 1.37; 95% confidence interval (CI) 1.21-1.54, p<0.001. Regarding the risk of different stroke subtypes, including ischemic stroke and hemorrhagic stroke, the aHR for ischemic stroke was 1.38 (95% CI 1.21-1.57, p<0.001) and that for hemorrhagic stroke was 1.26 (95% CI 0.84-1.88, p=0.266) in patients with nephrotic syndrome compared with controls, after adjustment for age, sex, and comorbidities.

Conclusions: This study provides first significant evidence that patients with nephrotic syndrome had an increased risk of ischemic stroke.



FR-OR085

Treatment Response in Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

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Background: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) usually results from an occult hematologic clone, making treatment challenging.

Methods: The Mayo Clinic pathology and Columbia U. Glomerular Ctr database were used to identify patients with PGNMID. Response to each treatment (Rx) regimen for native renal disease was evaluated. "Renal response" was defined as decrease in proteinuria (UPRT) by >50% without worsening of serum creatinine (Scr); "complete remission" as return to within 10% of normal Scr with <1 g/d UPRT; "renal progression" as reaching ESRD, death or need for another Rx. Chi-square, Fisher's exact and Log-rank test were utilized for statistical analysis.

Results: Rx outcomes in 83 PGNMID patients were evaluated. Most had no known hematologic clone (87%). Median Scr at presentation was 1.6 mg/dL (1.2-2.3) with UPRT 4.12 g/d (2.71-8.07). Over a median follow up period of 2.8 yrs, 30% (25/83) reached ESRD, 5% (4/83) died and a median of 2 (1-3) and total 139 Rx were received. "Renal response" differed significantly between the Rx regimens (p=0.012). This was primarily due to worse outcomes with conservative Rx and a superior response with cyclophosphamide (Table). "Renal progression" occurred with 60% Rx regimens over a median time of 216 days (104-545). Time to progression was lesser with conservative vs immunosuppressive Rx (p=0.012) but not different among the 5 immunosuppresive regimens (p=0.369). Anti-plasma cell Rx was less often used as 1st Rx as compared to other regimens (p=0.011).

Conclusions: PGNMID results in poor renal outcomes especially when immunosuppression is not used. Cyclophosphamide was most likely to lead to renal remission in our cohort but surprisingly, anti-plasma cell Rx, which is most appropriate targeted therapy in expert opinion, was not found to have improved outcomes. This may be due to use of this Rx later in disease course. Further prospective studies are needed to identify the best Rx in PGNMID.

Rx Regimen (N=139)	Renal Response	P-value	Complete Remission	P-value
Conservative	11.8% (2/17)	0.001**	11.8% (2/17)	0.194
Steroids alone	42.1% (8/19)	0.522	15.8% (3/19)	0.344
Mycophenolate based	47.8% (11/23)	0.909	26.1% (6/23)	0.843
Cyclophosphamide based	71.4% (15/21)	0.025**	38.1% (8/21)	0.115
Anti-plasma cell	56% (14/25)	0.434	24% (6/25)	0.953
Anti-B cell	52.9% (18/34)	0.590	26.5% (9/34)	0.754

FR-OR086

Hypertension or Complement-Associated Thrombotic Microangiopathy Diagnostic Implications and Response to Eculizumab

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Background: Malignant hypertension is listed among the causes of secondary thrombotic microangiopathy (TMA), but the presence of pathogenic mutations in complement genes have been recently reported in patients with hypertension-induced. No studies have investigated the frequency and severity of hypertension (HTN) in primary, complement-mediated atypical hemolytic uremic syndrome (aHUS).

Methods: Seventy-five patients with primary aHUS were collected in 21 hospitals in Spain and Portugal. Primary outcome was hematologic and renal response. Patients were classified according to the severity of HTN in normal blood pressure (8 patients, 10%), stage 1 HTN (13, 17%) and stage 2 HTN (54, 72%). Among the latter, malignant HTN (defined by the presence of hypertensive retinopathy grades III/IV) was found in 24 (55%) out of 43 patients in whom retinal examination was performed.

Results: Median age was 34 years and 27 patients (36%) had history of HTN. Fifty-five (75%) patients required acute hemodialysis at presentation. Plasmapheresis was performed in 64 patients and 35 received eculizumab. Abnormalities in complement genes were found in 36 /64 patients (56%) in whom genetic study was performed (68% among patients with malignant HTN). Response was significantly lower after plasmapheresis (25%) than after eculizumab (82%), as well as the rate of dialysis discontinuation (38% and 79%, respectively). Response to eculizumab was similar in normotensive (100%), stage 1 HTN (71%), stage 2 HTN (84%) and malignant HTN patients (90%) and was independent of the presence of genetic abnormalities. Renal survival was significantly higher in patients treated with eculizumab (87% at 1, 3 and 5 years) compared to patients who did not receive this treatment (55%, 46% and 38% at 1, 3 and 5 years, respectively).

Conclusions: Severe hypertension is very common in aHUS, frequently fulfilling the criteria of malignant HTN. The efficacy of eculizumab was observed also in patients with HTN, having or not abnormalities in complement genes.

FR-OR087

Long-Term Effects of Sparsentan, a Dual Angiotensin and Endothelin Receptor Antagonist in Primary Focal Segmental Glomerulosclerosis (FSGS): Interim 84-Week Analysis of the DUET Trial

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Background: DUET is a phase 2, randomized, active-control study of patients (pts) 8–75 years with primary FSGS, estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2, and urine protein-to-creatinine ratio (UP/C) ≥1 g/g. Pts (N=109) were randomized to sparsentan (SPAR; 200, 400, or 800 mg/d) or irbesartan (IRB; 300 mg/d) for 8-week double-blind (DB) treatment in addition to current standard of care (including immunosuppressive treatments), followed by SPAR only (SPAR:SPAR, IRB:SPAR) in the open-label extension (OLE). This interim analysis was performed at Week 84.

Methods: In the OLE, UP/C, blood pressure (BP), eGFR, and FSGS partial remission endpoint (FPRE; UP/C ≤1.5 g/g and >40% UP/C reduction) were assessed every 12 weeks and compared with baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR).

Results: UP/C, BP, and eGFR data are in the Table. SPAR:SPAR and transition to SPAR, at Week 8 in IRB:SPAR, led to statistically significant reductions in UP/C and BP, sustained to Week 84. FPRE was achieved by 27/45 (60%) SPAR:SPAR and 13/26 (50%) IRB:SPAR pts at Week 84. In both groups, eGFR decreased initially and stabilized with increasing follow-up duration, possibly reflecting early hemodynamic effects of the drug. During SPAR treatment, adverse events were reported in 63 (94%) SPAR:SPAR and 32 (91%) IRB:SPAR pts; headache, peripheral edema, and hypotension occurred in >20% of pts in SPAR:SPAR or IRB:SPAR.

Conclusions: Sparsentan achieved sustained protein-lowering and BP-lowering effects in primary FSGS over 84 weeks, suggesting long-term nephroprotective potential of the drug.

Funding: Commercial Support - Retrophin, Inc., San Diego, CA

Table. UP/C, Systolic BP, and eGFR in the DUET Open-Label Extension

	Week							
	0	8	24	36	48	60	72	84
SPAR:SPAR (N)*	67	67	64	64	60	55	50	45
Systolic BP, mmHg, mean ± SD	131.5 ±11.6	116.1† ±13.0	121.8† ±14.1	120.4† ±14.5	122.9† ±13.3	121.0† ±14.9	121.7† ±17.5	121.9† ±16.3
UP/C, g/g, median (range)	2.8 (0.3, 14.0)	1.6† (0.0, 14.2)	1.2† (0.0, 14.3)	1.3† (0.2, 13.8)	1.3† (0.0, 12.0)	1.2† (0.0, 8.7)	1.2† (0.0, 14.2)	0.9† (0.0, 10.8)
eGFR, mL/min/1.73 m^2, median (range)	69 (28, 192)	65 (27, 158)	66† (25, 180)	64† (21, 176)	65† (21, 195)	62† (20, 162)	63† (22, 186)	64† (17, 163)
IRB:SPAR (N)*	—	35	34	33	29	28	27	27
Systolic BP, mmHg, mean ± SD	—	124.2 ±13.3	117.8† ±11.9	119.3 ±11.9	121.3 ±13.5	118.4† ±12.7	118.7† ±12.8	119.4† ±16.1
UP/C, g/g, median (range)	—	2.3 (0.4, 10.1)	1.5† (0.1, 13.1)	1.6† (0.1, 7.0)	1.5† (0.0, 4.6)	1.6† (0.0, 4.0)	1.1† (0.0, 4.9)	1.1† (0.0, 8.4)
eGFR, mL/min/1.73 m^2, median (range)	—	63 (26, 216)	55† (25, 195)	55† (26, 153)	65† (23, 155)	60† (24, 157)	62† (21, 157)	61† (20, 155)

*N for SBP shown; Ns for UP/C and eGFR not shown. †95% confidence interval for mean change from baseline (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR) excludes 0.

FR-OR088

An Autologous Cellularized In Vivo Engineered Vascular Graft Capable of Remodeling to a Non-Thrombogenic Blood Vessel upon Arteriovenous Grafting in Adult Goats

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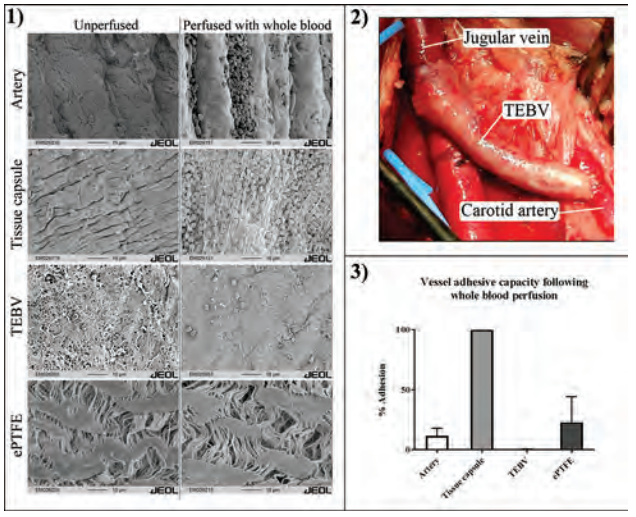
Background: The durability of prosthetic vascular grafts used for hemodialysis access is poor due to venous stenosis, limiting vascular access. We present a method to create tissue engineered blood vessels (TEBVs) capable of developing *in vivo* towards a functional vascular graft.

Methods: Polymeric rods are implanted subcutaneously in goats for 1 month, resulting in the formation of fibrocellular tissue capsules (TC's) with sufficient mechanical strength to restrain arterial pressure. The TC's then are grafted as arteriovenous conduit between the carotid artery and jugular vein. After 1 or 2 months in the vasculature the grafts were harvested.

Results: *Ex vivo* perfusion showed grafts were less thrombogenic than initial TCs, and also when compared to ePTFE grafts. At 1 month the TEBVs were composed of vascular smooth muscle cell-like cells, with confirmed contractility. At 2 months, complete endothelialisation and elastin formation was also observed, while *in vivo* graft patency was comparable to ePTFE.

Conclusions: Here, we demonstrate the *in vivo* remodelling capacity of TC into TEBV, and their potential as replacements for prosthetic vascular grafts.



FR-OR089

Lysyl Oxidase Determines Postoperative Vascular Stiffness and Neointimal Formation after Arteriovenous Fistula Creation

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Background: The transformation of a vein to a fistula is one of the most intriguing processes in vascular biology. The desired scenario is that the fistula matures becoming a larger vessel with increased luminal area and a thicker wall. Unfortunately, arteriovenous fistulas (AVFs) frequently fail (~40%) because venous stenosis compromises blood flow. Lysyl oxidase (LOX) is the main enzyme that catalyzes the oxidative deamination of lysine/hydroxylysine residues (ε-amino groups) in proteins to facilitate spontaneous intra/intermolecular covalent crosslinks formation. The most recognized substrate of LOX is collagen. In fact, collagen tensile strength relies upon LOX mediated crosslinking. LOX is critical for vascular and connective tissue formation; however, deregulated LOX increases collagen stiffness and prevents its degradation, thereby contributing to fibrosis.

Methods: Herein, our goal was to demonstrate that upregulated LOX in the venous limb of the AVF mediates improper remodeling, which causes stenosis and failure.

Results: We first demonstrated that immature and mature collagen crosslinks (using UPLC-ESI-MS/MS) were more abundant in failed human AVFs than in fistulas that matured successfully (N=10/group, p< 0.05). Increased crosslinking correlated with vascular accumulation of LOX as determined by immunohistochemistry. Interestingly, LOX appeared in the interstitial space and in the nuclei of smooth muscle cells (SMCs) and neointimal cells, in agreement with prior reports detecting LOX within the nuclei of cultured fibroblasts. The nuclear location of LOX in SMCs was further demonstrated using cell fractioning techniques. The LOX inhibitor β-aminoproprionitrile (BAPN) decreased SMC growth in culture, which suggests a potential role of this enzyme in the postoperative expansion of the intima. Finally, we demonstrated that systemic and local inhibition of LOX with BAPN increases blood flow and elasticity, and prevents medial fibrosis and intimal hyperplasia in a rat model of AVF.

Conclusions: In conclusion, these data indicate, for the first time, the importance of LOX-mediated crosslinking in AVF failure and the potential role of this enzyme not only in vascular stiffness but also in the control of SMC fate and growth.

Funding: NIDDK Support

FR-OR090

Inhibition of MicroRNA-92a Enhances Arteriovenous Fistula Development

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Background: The Hemodialysis Fistula Maturation Consortium Study showed that endothelial health was associated with the development of arteriovenous fistulas (AVFs). MicroRNA (MiR)-92a is a major contributor to vascular endothelial dysfunction. We recently reported that patients with chronic kidney disease (CKD) had increased serum miR-92a levels when compared to non-CKD control subjects, and that serum miR-92a was likely derived from the endothelium. Thus, we investigated the relationship between miR-92a and AVF development in animal models.

Methods: In young male Wistar rats with normal kidney function or with adenine diet-induced CKD, we created femoral AVFs and then assessed AVF lumen diameter by ultrasound and AVF tissue miR-92a levels by RT-PCR at 4 weeks after creation. In a mouse carotid-jugular AVF model, miR-92a inhibition was achieved using genetic and pharmacological approaches: (1) whole-body knockout (miR-92a$^{-/-}$) with C57BL/6 mice used as wild-type (WT) controls; or (2) nanoparticles (NPs) that encapsulate miR-92a inhibitors and target inflamed endothelium (un-encapsulated miR-92a inhibitors and saline were used as no-NP and no-treatment controls, respectively). C57BL/6 mice received the inhibitor treatment (8 mg/kg body weight) intravenously at 1 day after AVF creation and were sacrificed 1 week later. Mouse AVF cross-sectional lumen area was quantified by histology.

Results: When compared to AVFs in non-CKD rats, AVFs in CKD rats had increased miR-92a expression (3-fold, $p<0.05$) and smaller AVF lumen diameter (1.0 ± 0.51 in CKD vs. 1.55 ± 0.65 mm in non-CKD, $p<0.05$). In the knockout study, the percent open lumen area of AVF veins was larger in miR-92a$^{-/-}$ mice (72% of total area) than in WT mice (12%). In the inhibitor study, both NP-encapsulated (41%) and un-encapsulated (23%) miR-92a inhibitors resulted in larger open lumen area than saline control (5%), and the effect of encapsulated inhibitors was more pronounced.

Conclusions: In our rat model, CKD increased the AVF tissue miR-92a levels and decreased the AVF lumen area. Further, inhibition of miR-92a improved AVF development. Nanomedicine may offer a novel and effective therapeutic approach to enhance AVF maturation in CKD patients.

Funding: NIDDK Support

FR-OR091

Does Sex Matter? The Transcriptomics of Sex Differences in Arteriovenous Fistula Failure

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Background: Over 260,000 women depend on a vascular access to receive hemodialysis to prolong their lives. Since women have a higher risk of arteriovenous fistula (AVF) maturation failure compared to men, they are more likely to initiate dialysis with grafts and central venous catheters, further increasing their risk for hospitalization and complications. The reasons for sex disparities in AVF maturation have not been well studied despite the unmet clinical need.

Methods: Herein, we explored the nature of sex-related differences in AVF remodelling using high-throughput RNA sequencing of human pre-access veins and AVFs, and functional assessment of experimental fistulas.

Results: We first confirmed that women are at higher risk of maturation failure in a cohort of 161 patients. Failure was associated with female sex independently of preoperative luminal diameter (>4 mm), age and diabetes. Failure among women was associated with postoperative medial fibrosis. Interestingly, experimental AVFs in female rodents had lower blood flow and were stiffer than those in their male counterparts as determined by high precision pressure myography. The persistence of sex disparities in animal models that lack the confounding factors of human cohorts highlight the importance of sex-related biological effects in fistula maturation. Transcriptomic profiling of sex-biased AVF remodeling revealed strong pre-existing (veins) and postoperative (fistulas) sex-related differences in gene expression, and uncovered novel molecular targets of maturation failure associated with sex effects. In women's veins, 748 genes were significantly associated with nonmaturation, while 537 distinct genes were differentially expressed between men's veins that matured or failed. The transcriptomic disparity persisted after fistula creation. Only 33 out of the 763 differentially expressed genes in AVFs that matured vs. failed were common between sexes.

Conclusions: These results demonstrate that mechanisms leading to maturation or failure are sex dependent, and highlight the necessity of sex-oriented therapies in preventing hemodialysis access failure.

Funding: NIDDK Support

FR-OR092

Temporal Activation of Notch Improves Arteriovenous Fistulas Maturation

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Background: maturation of arteriovenous fistula (AVFs) requires arterialization of the venous arm in order to sustain increased blood flow and repeated punctures. Proliferation and migration of vascular smooth muscle cells (VSMCs) are required for thickening the venous wall of AVFs. But excessive VSMC accumulation forms a neointima, ultimately, leading to AVF failure. Notch signaling determine the artery fate. Earlier, we demonstrated that Notch signaling in AVFs stimulates vascular remodeling, but complete inhibition of Notch signaling pathway block AVF arterialization. Does temporally controlled Notch activation balance AVF arterialization and neointima formation?

Methods: AVFs created in wild type (WT) and conditionally inducible, VSMC-specific Notch KO mice (RBP-Jk$^{VSMC-KO}$). Temporal Notch activation was controlled by addition of tamoxifen to KO Notch transcription factor, RBP-Jk, in VSMCs. The VSMCs were labeled and tracked; VSMC dedifferentiation, activation, and neointima formation were determined.

Results: in AVF anastomoses, VSMC contractile markers were decreased; proliferation and migration markers were markedly increased. These results document VSMC activation and dedifferentiation. In neointimas, activated Notch was present in VSMC nuclei and it induced VSMC contractile markers thereby promoting neointima formation. Pre-operative KO of RBP-Jk in VSMCs blocked expression of contractile markers causing non-arterialization of AVFs. However, when RBP-Jk was KO in VSMCs in day 10 or day 20 after AVF surgery, the VSMCs in the neointima expressed VSMC markers even

without RBP-Jk expression. Consequently, arterialization of the AVF was induced and the neointima area was smaller in AVFs created in RBP-Jk$^{VSMC-KO}$ mice VS. WT mice. Thus, Notch signaling is required to initiate the expression of VSMC markers. But, the signaling pathway is not required for maintaining VSMC fate. As occurred in AVF, KO or inhibition of Notch signaling suppressed PDGF-BB-induced differentiation of progenitors into VSMCs. Notch overexpression promotes PDGFRβ expression plus differentiation VSMCs from their progenitors.

Conclusions: Temporal activation of Notch improves AVF arterialization and maturation.

Funding: NIDDK Support

FR-OR093

Targeting Zero Infection in Hemodialysis Patients: An Experience of an Intra-Hospital Hemodialysis Unit with None Catheter-Related Blood-stream Infection in 633 Days

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Background: Patients undergoing hemodialysis (HD) through tunnelled central venous catheter are exposed to several risks, including infection and trombosis. Catheter-related bloodstream infection (CR-BSI) is the second major cause of death in this population. To reduce the incidence of CR-BSI we conducted an intervention study aimed in lowering these rates.

Methods: An quasi-experimental, pre-post intervention study was conducted in an intra-hospital hemodialysis unit with 15 HD machines and attending 70 patients. In 2011, we implemented an evidence-based intervention package aiming at elimination of all preventable CR-BSI, including the following measures: 1. Alcohol based gel delivery system fixed in every HD machine for hand hygiene 2. Catheter external cleaning with alcoholic chlorhexidine before manipulation for at least 1 minute 3. A scrub-the-hub protocol with strictly aseptic technic for catheter manipulation in any intervention 4. Use of chlorhexidine-impregnated dressing 5.Training all nurse staff admitted, annual re-training and evaluation of performance with infection rate feedback 6. The use of citrate 30% as lock solution.

Results: During the follow-up period (January 2011 to January 2018) a mean of 34 patients (range 30-38) used tunnelled catheter as vascular access each year. The median age was 72 years (range 20-90 years), and 35% of patients were diabetic. After implementation of the intervention package, we observed a continuous reduction in the CR-BSI rate: from 1.1/1000 catheter-days in 2010, the year before the intervention measures; to 0.6/1000, 0.6/1000, 0.1/1000, 0.1/1000, 0.2/1000, 0.2/1000 and 0.0/1000 catheter-days from 2011 to 2017, respectively. Between April 2016 and January 2018, we reached the longest period without CR-BSI events: 633 days, interrupted by a *Serratia marcenses* CR-BSI with tunnel infection in a recipient of pancreas transplant.

Conclusions: Implementation of several evidence-based practices and continuous education can reduce CR-BSI in HD patients to a very low and sustained level. Targeting zero infection proposing eliminate all preventable infection should be routine practice of all dialysis units.

FR-OR094

Arteriovenous Fistula Maturation Outcomes Following Local Perianastomotic Delivery of Sirolimus

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Background: Arteriovenous Fistula (AVF) creation and maturation have many obstacles limiting successful cannulation in a timely manner. Time to first cannulation and rates of AVF suitability for dialysis remain unacceptable; 80% of ESRD patients initiate dialysis with a catheter; many require use for ≥90 days. The use of locally delivered perianastomotic sirolimus may help maturation of AVF in a predictable timeframe by attenuating the development of neointimal hyperplasia. We now report the combined findings of our single arm Phase 2 trial and open label portion of our ongoing US Phase 3 multicenter, randomized controlled clinical trial (NCT02513303).

Methods: All patients underwent creation of an AVF for hemodialysis. The phase 2 trial included 30 patients. The open label phase 3 trial, to date, includes 22 patients. For all patients, after creation of a successful end-to-side vascular anastomosis, sirolimus–eluting collagen membranes (Drug product; Vascular Therapies, Cresskill, NJ) were implanted around the anastomosis and outflow vein. Time to First dialysis (TTFD) defined as use with 2 needles and 300 mL/min flow (2N/300) for 3 consecutive sessions, proportion of AVF in use with 2N on or before day 90, Fistula Suitability at 6 months (FSD6) defined as fistula use (2N/300) for two-thirds of the dialysis sessions during a 30 day period commencing on day 150, and thrombosis/abandonment rates are reported.

Results: Fifty two patients, 51 with ESRD on dialysis and 1 with CKD, were enrolled (Male 67%, mean, age 56±17 y, diabetic 42%; radiocephalic AVF 65%). There were no product related serious adverse events. By 6 months, 9 AVF were abandoned: 7 thrombosed (6 within 2 wks), 1 for central vein occlusion and 1 for pseudoaneurysm. Abandoned AVF are included in the calculations shown in Table. Median days (Q1, Q3) to first dialysis was 49 (39, 67).

Conclusions: 1. In comparison to historical controls local delivery of sirolimus resulted in improved AVF outcomes 2. 73% of sirolimus treated AVF were mature by 3 months (HFM: 25%) 3. Suitability for Dialysis at 6 months was 82% (DAC: 40%)

Funding: Commercial Support - Vascular Therapies

	Proportion of AVF in use with 2 needles on or before day 90	Fistula Suitability for Dialysis at 6 Months
No. eligible for evaluation	51	50
Outcome	37/51 (73%)	41/50 (82%)

FR-OR095

GlomCon Trivia: A Live Web-Based Interactive Fellows Curriculum

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Background: Sufficient exposure during nephrology training to the variety of glomerulonephritides (GN) is difficult due to their rare and heterogeneous presentations. GN diagnosis/management and renal pathology interpretation are topics recently identified as areas needing further instruction (JASN 2017; 28:1983–1990). Glomerular Disease Case Conference (GlomCon) Trivia, recipient of the 2017 ASN Innovation in Kidney Education Award, was created to enhance the GN education of trainees, and connect training programs to foster a culture of collaborative learning.

Methods: Using GlomCon's live web-based video platform, the "Trivia" series was created for nephrology training programs to provide topic-based didactic webinars. These sessions include an interactive Q&A audio/video chat forum centered around board-style Q's answered by participants in real time. Participants access the webinars via institutional video conference setup, personal computers, or smartphones. A selected number of multiple-choice Q's (MCQ) from the Webinar were shared with the general public through social media (Twitter). An anonymous survey was obtained to assess participant's perception and experience.

Results: From 9/17-5/18, 11 sessions have been held by different training programs. 100% of the survey responders agreed that the sessions enhanced awareness of GN, and 94% either "completely agreed" or "agreed" that the sessions contributed to their overall knowledge base. In terms of educational quality, 84% rated it as "outstanding" or "above average". In addition, 73% of participants "completely agreed" that the session supplemented their individual program's curriculum. On Twitter, an average of 78 people responded to each publicly presented MCQ.

Conclusions: GlomCon Trivia Interactive Fellows' Curriculum is a global initiative with the potential to 1) Enhance education in GN for trainees, 2) Allow participants to interact and collaborate beyond geographical boundaries, 3) Facilitate discussion of diagnosis and management approaches which can be region or center specific. This program adds to the expanding list of training tools with free open access, which will hopefully improve the education of our trainees and increase interest in the field of nephrology for potential applicants.

FR-OR096

Demystifying Glomerular Disease: A Worksheet Teaching Tool

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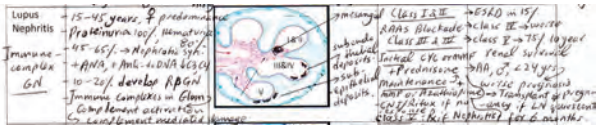
Background: Learners of all levels express apprehension about glomerular diseases. This may herald from an incomplete understanding of the pathophysiology, and a focus on memorization. For example, understanding that IgA Nephropathy begins with an abnormal IgA protein helps the learner conceptualize symptoms and principles of treatment. This curriculum uses active learning and is broadly applicable to students, residents, and fellows. The goals of this worksheet include: 1) Reduce anxiety when approaching glomerular disease, 2) Complete a worksheet that can be used as a study guide, 3) Use illustration to understand the pathophysiology and histologic representation of glomerular diseases.

Methods: The learner is given a 4-page worksheet with 20 glomerular diseases, arranged by order of the most frequently encountered. Each disease is represented by 1 row. The facilitator is provided a detailed written guide, and the teaching session does not require power point. The learners collectively discuss each disease, but must begin by illustrating pathophysiologic immune marker and/or key histologic appearance of the disease. Next, the clinical presentation, treatment, and prognosis are discussed. The worksheet includes select prompts and mnemonics to aid in material retention and can be completed within a 90 minute session.

Results: We piloted a total of 3 sessions with 42 independent learners - medical students (19), internal medicine residents (13), and Nephrology fellows (10). Over 90% of respondents 'did not feel comfortable treating glomerular disease' prior to the workshop. Over 90% (n=40) of participants agreed or strongly agreed that the worksheet was easy to complete. 85% of respondents plan to use use the completed worksheet as a study guide. One representative comment was 'Excellent review on a topic I struggle with!'

Conclusions: Educators need a teaching tool to help trainees demystify glomerular diseases. The glomerular worksheet can be completed on-the-fly, emphasizes pathophysiology / histology, and can be used as a study guide.



FR-OR097

Easing the Difficult Job of Giving Bad News: Using a Decision Aid to Match Patient Values to a Dialysis Modality

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Background: Nephrologists say telling patients they need dialysis is the worst part of the job—and patients do not want this "bad news". Yet, little is known about how nephrologists describe the options or tailor information to patients' values—or whether decision support can make this challenging topic less traumatic and more effective.

Methods: *Design:* A 2-phase prospective, intervention study of audiorecorded conversations between nephrologists and stage 4-5 non-dialysis CKD patients at 2 WI clinics. *Phase 1:* 6 nephrologists and 32 patients; no decision support offered. *Phase 2:* 6 nephrologists and 30 patients; patients used an online, values-based decision aid—*My Life, My Dialysis Choice (My Life)* before the visit and shared the 1-page summary of their values/dialysis preferences with the nephrologist. *Data:* Phase 1 vs. Phase 2: conversations for tailoring information to (1) Values, (2) Patients' surveys for dialysis preference, and (3) Nephrologists' surveys.

Results: ***Results*** *Sample:* Nephrologists had a mean age of 40 and 7.5 mean years of practice. Patients' mean eGFR was 20; mean age was 70; 90% were non-Hispanic white; 73% did not finish college. Phase 1: The dialysis conversation segment was the most difficult. 0% of nephrologists elicited patients' values. Nephrologists tailored dialysis information for only the 4 (13%) activated patients who inserted their values; 4 (13%) patients preferred home dialysis. Nephrologists said they wanted a tool to aid the dialysis discussion. Phase 2: The summary served as a dialysis conversation icebreaker. Nephrologists proactively addressed patients' values 97% of the time and tailored their modality information accordingly (P<0.001 vs. Phase 1). Nephrologists said it "alleviated the need to give bad news." 15 (50%) patients preferred home dialysis (P <0.01 vs. Phase 1).

Conclusions: Patient use of *My Life* (~20 minutes) eased a difficult conversation for both nephrologists and patients, and increased patient preference for home dialysis modalities in this small study.

Funding: Commercial Support - Amgen supported Phase 1

Conversation Analysis Results

Conversation Analysis	Phase 1: No Decision Aid n=32	Phase 2: Decision aid n=30	P value
MD elicited/addressed patients	0 (0%)	29 (97%)	<.001
Patients inserted their own values	4 (13%)	0 (0%)	<.001
POST-VISIT PATIENT SURVEY			
Would choose home dialysis	4 (13%)	15 (50%)	<.01
Undecided about a type of dialysis	12 (38%)	6 (20%)	0.134

FR-OR098

Harnessing Technology to Enhance Medical Student Learning

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Background: Various studies have shown that active learning is more effective than passive learning for long-term retention of concepts for students. Moreover, in this day and age, young learners seem to be familiar, adept, and excited about engaging with online learning material. Therefore, we have designed online leaning materials which allow medical studnents to interact with them in an active manner that leads to improved long-term retention of renal pathophysiological principles.

Methods: Our medical school curriculum at the University of Wisconsin transformed in the fall of 2016 and as a part of this process we created numerous online enduring learning activities (ELA) in addition to the traditional in class lectures and medium group discussions for first year medical students. Some ELAs teach basic science concepts in an innovative way involving technologies like the lightboard. Other ELAs utilize Articulate Storyline, which allows the students to interact with online simulated cases to apply basic science concepts such as sodium, water, and acid- base balance to clinical care. Students receive immediate feedback during these activities through the use of embedded self-assessment activities. Suggested by their name, ELAs are designed to be enduring; they are stored in a in a repository and are easily searchable with the intention that students revisit their content during their clinical years.

Results: To determine if active learning promoted better long-term retention of renal pathophysiological concepts, we compared the students' scores for content taught in-class during traditional lectures to concepts that were taught through ELAs for the renal exam. Our data shows that students performed better on questions from ELA content (Table 1).

Conclusions: Our preliminary data indicates that active learning methodologies such as delivering content through online ELAs is an effective way to teach difficult renal pathophysiology concepts. Feedback indicates that students find these online activities more engaging, and the ELAs offer better student interaction with the material and this likely translates to improved long-term retention of the material in our students.

Number Of Students	Total Number of students	Mean of Students with correct response	Standard Deviation	p-Value
In- Class Content	173	130.01 (75.15%)	31.23 (18.05%)	
ELA Content	173	139.77 (80.79%)	25.19 (14.56%)	P < 0.0001

Table 1: Student scores for content taught through ELAs compared to traditional didactic format

FR-OR099

The Acute Dialysis Orders Objective Structured Clinical Examination (OSCE): Results of Administration to 117 Nephrology Fellows Nationwide

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Background: Few quantitative, validated, Nephrology-specific simulations assess ACGME fellow competency performance. We developed, validated and administered a formative OSCE during 2016 and 2017 to 117 Nephrology fellows nationwide to assess medical knowledge, patient care, and systems-based practice in acute dialysis.

Methods: Fellows use institutional protocols and order sets to write dialysis orders and answer evidence based questions on 3 acute dialysis scenarios (49 test items; 58 possible points). 10 board-certified clinical nephrologists validated the test, determining a pass threshold of 46 points.

Results: The 2016 administration included 25 fellows (4 programs), and the 2017 administration included 92 fellows (15 programs). 51 first year fellows and 66 second/third year fellows completed the OSCE. All tests were scored by the 2 Principal Investigators. Median time to take the test was 65 minutes. 75% of fellows passed Scenario 1 (Acute CRRT), with 92% correctly prescribing a greater than 20 ml/kg/hr effluent dose, and 63% able to calculate CRRT clearance as effluent volume. 43% passed Scenario 2 (Urgent outpatient initiation) with 75% using a correct 3-4 meq/L K+ dialysate, but only 12% able to identify the 2 absolute, urgent indications for chronic dialysis initiation. Fellows performed poorly on Scenario 3 (Management prior to and dialysis prescription for acute hyperkalemia in ESRD). 6% passed, with only 20% correctly checking for rebound hyperkalemia with 2 separate lab draws. However, 83% were correct in not giving IV sodium bicarbonate as acute medical management for hyperkalemia. 32% of fellows passed the overall OSCE. No significant difference was found between first and second year fellow performance (overall score 42.7 ± 5 vs. 44.4 ± 4; p= 0.049; 24% vs. 39% pass rate; p= 0.082) with no correlation between second year fellow ITE and OSCE scores. The fellow satisfaction survey had a 56% response rate. 78% strongly agreed/agreed that the OSCE was useful in assessing proficiency in ordering acute renal replacement therapy.

Conclusions: The Acute Dialysis OSCE can provide quantitative data for fellow ACGME sub-competency assessments, and identify opportunities for dialysis curriculum development.

Funding: Other U.S. Government Support

FR-OR100

Nephrology Business Leadership University: Filling a Gap in Fellowship Education

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Background: Historically, fellowship training programs have not focused on the knowledge and skills fellows need to successfully transition from training to practice. Concurrently there is dissatisfaction with nephrology as a career choice and interest in nephrology has declined. As a specialty we have focused on attracting trainees into nephrology but not on ensuring fellows have the skills to navigate their career post fellowship. To address this need we developed a weeklong conference, Nephrology Business Leadership University (NBLU), in partnership with practicing nephrologists and industry experts. Our goal was to provide fellows with education in the business aspects of nephrology not taught in traditional nephrology training programs.

Methods: During NBLU fellows attended workshops on topics ranging from the job search to growing a practice to retirement planning. Fellows also participated in sessions on leadership roles in nephrology. Pre- and post-course surveys, interactive feedback sessions, and exit interviews were used to assess the program. A Pre/Post Knowledge Level Survey (5-point Likert Scale) assessed improvements in knowledge level in 24 different content domains. Scores were compared using a paired two sample means t-test. Follow up surveys will be sent at the end of the academic year to assess implementation of this knowledge into the attendees job search.

Results: 31 fellows attended NBLU, representing 22 programs in 15 different states. The pre-survey confirmed that the areas covered in NBLU were absent in traditional training; only 2 out of 30 respondents stated "yes" to having previous instruction in any

business aspects of medicine. The Knowledge Survey demonstrated statistically significant increases in knowledge in all 24 areas. Median knowledge level in the 24 areas was 1.72 prior to and 4.11 post course ($p<0.05$) .100% of surveyed fellows would recommend NBLU.

Conclusions: Education on the business aspects of nephrology is lacking in traditional fellowship training. NBLU is an innovative and effective program for educating fellows on areas they will need when they transition into practice. Fellows were satisfied with their experience and would recommend the program to others. Results of follow up will further assess if learned skills were useful during their job search and in the early days of practice.

Funding: Commercial Support - US Renal Care, Clinical Revenue Support

FR-OR101

The Need for Nephropathology Teaching Worldwide: The ISN-Clinical Nephropathology Course Survey

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Background: The epidemiology and pathology of kidney disease is still unknown in large parts of the world that are burdened with high rates of CKD, in part due to inability to adequately process and interpret kidney biopsies. Clinical Nephropathology Certificate (CNC) Program is a joined educational initiative of the International Society of Nephrology (ISN) and American Nephrologists of Indian Origin (ANIO) primarily focusing on needs of nephrologists and pathologists in parts of the world with suboptimal nephropathology training and service. The CNC program(started 2013) includes over 40 recorded online lectures and 12 live webinars run by a pathologist and a nephrologist (one each month) made available over a one-year period.

Methods: We surveyed previous and current participants of the ISN CNC program to better understand the worldwide nephropathology practices. This voluntary survey was emailed to participants with 12 questions regarding the nephropathology service in their institutions and respective countries.

Results: The survey response was received from 293 out of 494 current or former participants (response rate 59%) from 63 countries. The data were evaluated using ISN regions and world bank economy classification. Results are summarized in Table below.

Conclusions: The survey responses suggest a large gap between the nephropathology practices in well-developed countries and the rest of the world. Even when existent in L/LM/UMIC, EM services are available for select cases and not routinely. The lack of trained nephropathologists and inability to adequately process samples is a common problem for the most of Africa, Asia, and Latin America, leading to underutilization of kidney biopsy procedures for diagnostic purposes. The lack of financial resources in these countries is still a significant limiting factor in establishing functional nephropathology laboratories. Programs like ours help bridge the education gap that exists in these countries.

Survey results stratified by world bank classification with regards to nephropathology services available in respondents' countries and institutions where they practice

WHO Nation types	n (%)	Electron microscopy in respondents' countries	Nephropathology in respondents' institutions
Low income(LI)	14 (5%) - 5 countries	None	No renal lab - 50%; LM only 36%; LM and IF 12%; EM 0%
Lower middle income(LMI)	122 (59%) - 20 countries	Available in rare labs in 7 out of 20 countries, but not routinely	No renal lab - 23%; LM only 23%; LM and IF 36%; EM 18%
Upper middle income(UMI)	36 (12%) - 12 countries	Exists in all countries but not routinely performed	No renal lab -20%; LM only 11%; LM and IF 23%; EM 46%
High income(HI)	71 (24%) - 26 countries	Commonly present and used routinely in labs in 23 out of 26 countries	No renal lab - 23%; LM only 1%; LM and IF 35%; EM 41%

FR-OR102

Impaired Renal Iron Handling Leads to Iron Overload through an ET-1 Dependent Pathway

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Background: Elevated plasma endothelin-1 (ET-1) reported in sickle cell disease correlates with microalbuminuria, an independent risk factor for renal disease progression. In humanized sickle cell mice (HbSS), long-term ET_A receptor antagonism significantly attenuated renal tubular iron deposition in proximal tubules (PT). Evidence suggests a pathophysiological links between ET-1, renal iron deposition and early sickle nephropathy, therefore we hypothesize that ET-1 regulates renal iron trafficking in iron overload-associated sickle nephropathy.

Methods: To determine the involvement of ET-1 in renal iron handling mouse primary PT cells (from wild type, HbSS and control (HbAA) mice) were exposed to ET-1 and iron trafficking mediators were assessed by PCR.

Results: Expression of the iron import transporter transferrin receptor 1, TfR-1, and the iron storage protein, H-ferritin, were increased in a concentration-dependent manner by ET-1 in mouse primary PT cells. Also, ET-1 treatment resulted in a decrease in iron exporter ferroportin-1, FPN-1 (65% reduction), which was associated with a doubling in expression of hepcidin, HAMP, a key regulator of FPN-1 and iron removal from the cell. Exposure of PT cells to plasma from HbSS mice, increased cellular iron uptake compared to plasma from control HbAA mice (98±17 vs. 4±1 pg/μl, $p<0.05$). The ET_A antagonist, BQ123, completely prevented ET-1-mediated alterations in all iron mediators, suggesting involvement of ET_A receptors in iron trafficking mechanisms. Moreover, plasma ET-1 was positively correlated with renal iron deposition in HbSS mice ($R^2=0.72$, $p<0.0001$). PT cells isolated from HbSS mice showed significant elevation in expression of TfR-1, DMT-1, H-ferritin, and HAMP along with significantly lower FPN-1 expression compared to control mice. 10-week treatment (from weaning) with an ET_A receptor antagonist (ambrisentan 10mg/kg/day) prevented the induction of DMT-1, preserved FPN-1 and reduced HAMP expression in PT cells from HbSS mice.

Conclusions: These results uncover a novel role for ET-1 in PT iron trafficking and provide a rationale for the use of selective ET_A receptor blockade as a therapeutic approach in iron overload-associated sickle nephropathy.

Funding: NIDDK Support, Other NIH Support - Excellence in Hemoglobinopathies Research Award "The Role of Endothelin-1 in Sickle Cell Disease (U01 HL117684)" to D.M. Pollock, Other U.S. Government Support, Private Foundation Support

FR-OR103

Inability to Regulate Fatty Acid Oxidation or Glycolysis Increases Renal Fibrosis

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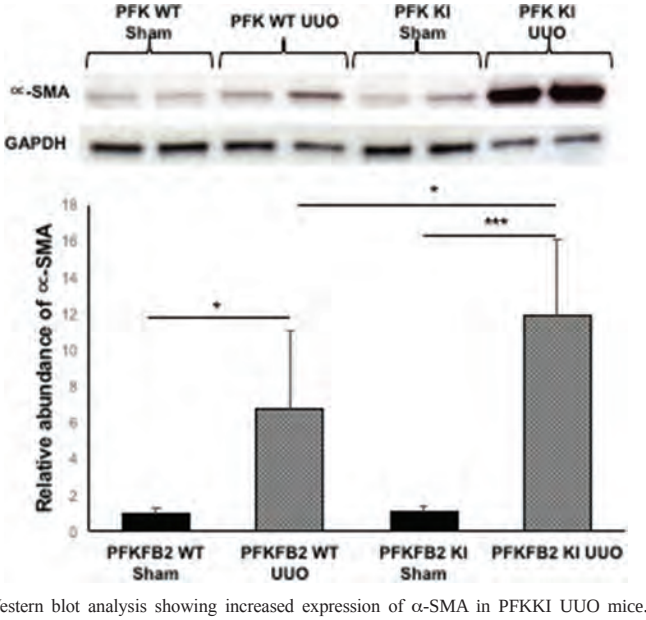
Background: Changes in energy metabolism are emerging as a key contributor to renal fibrosis. Expression of genes regulating fatty acid metabolism is reduced in fibrotic kidneys and aerobic glycolysis increases in some renal disease models. We aimed to determine the role of phosphorylation events that control fatty acid oxidation (FAO) and glycolysis in renal fibrosis.

Methods: The folic acid nephropathy (FAN) and unilateral ureteric obstruction (UUO) models were induced in mice with knock-in mutations of phosphosites in acetyl CoA carboxylase 1 and 2 (ACC1/2KI mice), the major regulator of FAO, and 6-phosphofructo-2kinase/fructose-2,6-biphosphatase (PFKFB2KI mice), the major regulator of glycolysis. Metformin, which activates AMPK to increase phosphorylation of ACC and PFKFB2, was administered to mice with FAN.

Results: ACC Ser79 phosphorylation was reduced in folate-treated tubular epithelial cells ($p<0.01$) and WT mice with FAN ($p<0.05$). Mutation of these sites in ACC1/2 KI mice with FAN or UUO caused lipid accumulation (Oil Red O $p<0.01$), increased triglyceride ($p<0.01$), increased collagen (PicroSirius red $p<0.001$; Masson's Trichrome $p<0.01$; qRT-PCR $p<0.01$) and increased α-SMA (Western blot $p<0.05$; qRT-PCR $p<0.01$). Metformin administration was associated with reduced fibrosis (PicroSirius red $p<0.01$) and lipid accumulation (Oil Red O $p<0.05$) in WT mice, but not in ACC1/2KI mice. To determine the role of control of glycolysis, UUO was induced in PFKFB2KI mice. WT mice with UUO had reduced PFKFB2 Ser483 phosphorylation ($p<0.01$). PFKFB2KI UUO mice had increased collagen (Picrosirius red $p<0.001$), increased fibronectin (Western blot $p<0.05$; qRT-PCR $p<0.05$), increased α-SMA (Western blot, $p<0.05$) (Fig.1) and glycogen accumulation (PAS, $p<0.05$).

Conclusions: These data suggest that reduced phosphorylation of ACC and PFKFB2 are deleterious following renal injury. Drugs that reverse this, such as metformin, may be useful in preventing and treating renal fibrosis.

Funding: Other NIH Support - National Health and Medical Research Council of Australia



Western blot analysis showing increased expression of α-SMA in PFKKI UUO mice. *P<0.05, ***P<0.001

FR-OR104

Amphiregulin Drives Kidney Fibrosis in Mice and Its Elevated Serum Levels Correlate with CKD Outcomes in Humans

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Background: We have shown that ADAM17-released EGFR ligands in proximal tubule cells (PTCs) drive kidney fibrosis in IRI and UUO kidney injury models (Kefaloyianni et al, JCI Insight 2016). Which specific EGFR ligands are involved remains unknown. We showed that amphiregulin (AREG) is the most upregulated EGFR ligand after kidney injury in mice and the most potent EGFR ligand in inducing pro-inflammatory and pro-fibrotic genes in human PTCs (HPTCs) *in vitro*. Soluble AREG (sAREG) is significantly elevated in the urine of AKI and CKD patients and AREG protein is elevated in CKD biopsies, as compared to healthy controls. It is not known whether AREG has a key role in mediating injury-induced kidney fibrosis in mice and humans.

Methods: We used tamoxifen inducible AREG$^{fl/fl}$-Slc34a1$^{GCE+/-}$-tdTomato^{+} (AREG-PTC KO) mice and ADAM17$^{fl/fl}$-Slc34a1$^{GCE+/-}$-tdTomato^{+} (ADAM17-PTC KO) mice and their respective wt littermates, as well as HPTCs transfected with control or YAP1 siRNA. We also developed and extensively validated a sensitive bead-based ELISA for sAREG in human serum samples.

Results: We found that sAREG can uniquely sustain EGFR activation in HPTC *in vitro* via YAP1-dependent upregulation of its own transcript, followed by ADAM17-dependent release of sAREG (positive feedback). *In vivo*, AREG-PTC-KO reduced IRI-induced sustained EGFR phosphorylation, as well as upregulation of pro-inflammatory cytokines and pro-fibrotic markers. We show that in ADAM17-PTC-KO mice, which cannot release any injury-induced EGFR ligand in PTC, injection of sAREG alone is sufficient to induce production of pro-inflammatory and pro-fibrotic factors to the levels of ADAM17 wt mice. Finally, we show that sAREG serum levels correlate positively with serum creatinine and CKD stage and negatively with eGFR in a nephrectomy cohort (n=69) of patients with various diagnosis and levels of fibrosis.

Conclusions: These results suggest that AREG is a major driver of kidney fibrosis in mice and humans, acting via a YAP1-dependent positive feedback loop that sustains EGFR activation and induces pro-inflammatory and pro-fibrotic cytokines, and represents a potential functional marker of fibrosis and CKD progression.

Funding: NIDDK Support

FR-OR105

The Effects and Potential Role of Circulating Macrophage in Renal Fibrosis

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Background: Macrophages plays an important role in the process of renal fibrosis. Recent studies have suggested that circulative macrophages are the major source of myofibroblasts, which is contradicted with traditional view, that only a few myofibroblasts were derived from bone marrow-derived cells. In this study, we looked for changes in CKD lesions and macrophages at different stages to find better classification of macrophage

Methods: Firstly, we adopted a bone marrow transplantation (BMT) model using GFP mouse bone marrow cells. Secondly, a parabiosis + I/R model or UUO model was constructed using GFP mice. To further understand the link between macrophage with myofibroblast, CSF1r-GFP mice were adopted in parabiosis + I/R model. Otherwise, we used the chlorophosphate liposome (CL) to knockout macrophages. CCR2-/- mice were adopted to construct parabiosis + I/R models to observe the effect of circulating macrophage in renal fibrosis. To directly explore the mechanism of macrophage on renal injury, we sorted Ly6c+ inflammatory macrophages from I/R kidneys and injected under kidney capsule of immunodeficient mice. At the same time, fibrosis-related markers were detected after co-culture the sorted Ly6c+ cells with fibroblasts.

Results: BMT+I/R model found that 22.55% of renal myofibroblasts were derived from bone marrow-derived cells, and 14.6% of myofibroblasts were derived from peripheral macrophages. The parabiosis + I/R or UUO model by using CSF1r-GFP mice proved that 5-9% of myofibroblasts in the kidney expressed GFP. With the treatment of CL, operated mice had early renal injury and delayed atrophy, and renal tubular injury was alleviated. Then we used CCR2-/- mice and observed that mice knocked out of peripheral macrophages reduced renal fibrosis; CCR2-/- mice were constructed parabiosis model with WT mice, in which peripheral macrophages can be replenished, and their kidney damage and fibrosis are aggravated. The sorted Ly6c+ inflammatory macrophages direclty lead to increased fibroblast activation and fibrosis.

Conclusions: The results indicated that peripheral derived macrophages are not the main source of myofibroblasts. The sorted Ly6c+ macrophages have the effect on promoting renal fibrosis. Knockout peripheral inflammatory macrophages reduce renal fibrosis. Ly6c+ inflammatory macrophages can directly lead to normal kidney damage and fibrosis and can promote fibroblast activation.

Funding: Government Support - Non-U.S.

FR-OR106

DOT1L Inhibition Attenuates Renal Fibrosis through Suppressing Multiple Profibrotic Signaling Pathways and Preserving Expression of Smad7 and Klotho

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Background: Disruptor of telomeric silencing-1 like (DOT1L) protein specifically catalyzes the methylation of histone H3 on lysine-79 and is implicated in leukemia and some solid tumors, but its role in tissue fibrosis remains unknown.

Methods: In this study, we examined the role of DOT1L in renal fibroblast activation, epithelial-mesenchymal transition and renal fibrosis development in vitro and in vivo.

Results: We demonstrated that injury to the kidney increased DOT1L expression and H3K79 dimethylation (H3K79me2) in renal tubules and myofibroblasts in a murine model of unilateral ureteral obstruction. Administration of EZP5676, a highly selective inhibitor of DOT1L, attenuated renal fibrosis as evidenced by decreased activation of renal interstitial fibroblasts and reduced deposition of extracellular components. Treatment with EZP5676 or DOT1L siRNA also inhibited transforming growth factor β1 and serum -induced activation of renal interstitial fibroblasts and epithelial-mesenchymal transition (EMT) in vitro. Moreover, blocking DOT1L abrogated injury-induced epithelial G2/M arrest; reduced expression of Snail and Twist, two transcription factors that drive EMT; downregulated Notch1, a transmembrane receptor protein associated with renal fibrosis; and inactivated several profibrotic signaling molecules, including Smad3, epidermal growth factor receptor, platelet growth factor receptor, STAT3, AKT as well as NF-κB in the injured kidney. Conversely, DOT1L inhibition increased expression of phosphatase and tensin homolog, a protein associated with dephosphorylation of tyrosine kinase receptors, and prevented decline in levels of klotho and Smad7, two renoprotective factors.

Conclusions: Our data indicate that targeting DOT1L inhibits activation of renal fibroblasts, EMT and renal fibrosis by suppressing activation of multiple profibrotic signaling pathways and retaining expression of renoprotective factors. DOT1L could be a novel therapeutic target for treatment of fibrotic renal diseases.

Funding: NIDDK Support

FR-OR107

Osteocrin, a Bone-Derived Humoral Factor, Exerts a Renoprotective Role in Ischemia-Reperfusion Injury in Mice

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Background: Natriuretic peptides (NPs; atrial, brain and C-type NPs: ANP, BNP and CNP) constitute the hormonal basis of the heart-kidney network, in which the remote organs influence each other under physiological and pathophysiological conditions. We recently reported that osteocrin (Ostn), originally identified as a secretory peptide in the bone and muscle, exerted bone elongation and cardioprotective effects through antagonizing NP clearance receptor NPR3. Of note, SNPs of the *Ostn* and *NPPA/NPPB* gene loci are reportedly related to a renal function decline risk by genome-wide association studies. However, the role of Ostn in the kidney has not been clarified yet.

Methods: To investigate the role of Ostn, we generated systemic Ostn knockout (KO) mice, and mated with liver-specific SAP promoter-driven Ostn-transgenic mice (KO-Tg). Wild-type (WT), KO and KO-Tg mice were subjected to ischemia-reperfusion injury (IRI) by unilateral renal artery clamping. Samples were collected at 3 weeks after IRI. Ostn expression in the kidney was evaluated by X-gal immunostaining using Ostn-LacZ knockin mice.

Results: In atrophic and fibrotic kidneys after IRI of WT, Ostn mRNA was increased in parallel with NPR3 and CNP upregulation, but not in the contralateral or pre-IRI kidneys. Furthermore, CNP expression was markedly suppressed in the contralateral kidney after IRI. These changes were either enhanced or suppressed in KO or KO-Tg, respectively, suggesting that Ostn affects the regulation of CNP and NPR3 expression in the kidney. In KO kidneys, mRNA expression of neutrophil gelatinase-associated lipocalin (NGAL) and IL-1b was further enhanced. In KO-Tg, fibrosis and atrophy were significantly ameliorated compared to WT and KO, together with the decreased expression of pro-fibrotic (aSMA, TGF-b), pro-inflammatory (IL-1b, TNFa) and tubular injury maker (NGAL, KIM-1) genes. X-gal immunostaining revealed that endogenous Ostn expression was induced by IRI in the tubular epithelial cells of corticomedullary junction in the kidney.

Conclusions: Exacerbation of IRI-induced kidney injury in Ostn-deficient mice was attenuated by ectopic overexpression of Ostn. Our data suggest a renoprotective role of Ostn, and could provide a potential therapeutic strategy against acute kidney injury.

FR-OR108

Temporal and Tissue-Specific Activation of AHR Signaling in Discrete Renal Diseases

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Background: Aryl hydrocarbon receptor (AHR) signaling is emerging as an important mediator of uremic toxicity regulating several manifestations of uremic solutes. While previous studies showed AHR activation in whole organs in response to uremia, no studies have examined cell- type specific AHR activation in vivo in uremic and non-uremic conditions in discrete models of kidney diseases.

Methods: Transgenic mice containing two dioxin-response elements upstream of a beta-galactosidase (β-gal) reporter gene were subjected torenalanischemia/areperfusioninjury(I/R), andanaAdenine-induced CKD, oranda recently developed Indoxylsolute specific animal modelss. TCDD, a canonicalAHRligand served as a positive control. β-gal protein expressionswaserecompared using a recently validatedquantitativecolor-based image segmentation quantitative image analytical techniqueanalysis. Double label immunofluorescence was used to analyze cell specific expression of β-gal. mRNA was analyzed with qRT-PCR. Plasma was analyzed for levels of blood-urea nitrogen (BUN), creatinine.

Results: In all the models, β-gal expression in kidneys predominated in both the proximal and distal renal tubules, but distinctly sparedwas absent fromthe glomeruli. In I/R model, β-gal expression significantly increased within 24 hours of injury ($p<0.05$) and decreased at both 48 and 96hrs post-surgery, while renal function continued to remains significantly altered at all these time points ($p<0.01$). Along with renal tubules, CKD and solute specific AHR models showed significant increase β-gal expression in endothelial, smooth muscle cells of the aorta and liver ($p<0.05$). A trend towards increased AHR activation in cardiomyocytes and neuron cells bodies was observed. Xxx Uremic solutes

Conclusions: The current study represents the first use of this reporter animal in disease-specific models. The model demonstrated a broad sensitivity in uremic kidney diseases and also in uremia-independent mechanisms such as hypoxia. While supportive of our previous observations in uremic thrombosis, AHR activation in some of the organs provide a hypothesis-generating insight. The model demonstrated a broad sensitivity in uremic kidney diseases and also in uremia-independent mechanisms such as hypoxia.

Funding: Other NIH Support - NHLBI 1R01Hl123235 (VCC), T32 HL70024 (JAW)

FR-OR109

CKD Impairs Muscle Protein Synthesis via a Demethylase Mechanism That Regulates Ribosomal Biogenesis

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Background: the report that patients with chronic kidney disease (CKD) require diets with 1.5 g protein/kg/d is based on the premise that a high protein diet will overcome a block in muscle protein synthesis. Such a diet, however, would cause metabolic acidosis, hyperphosphatemia, etc. To prevent these outcomes we are investigating mechanisms that can improve muscle protein synthesis even with dietary protein is restricted. We have identified a CKD-stimulated, chromatin-modifying, nucleolar protein, NO66 and show that it suppresses both ribosomal DNA transcription and muscle protein synthesis

Methods: we studied mice with CKD (subtotal nephrectomy) with BUN >80 mg/dL, similar to values in ESRD patients.

Results: NO66 demethylates histone proteins, H3K4ME3 and H3K36ME3, regulating growth. In muscles of both mice and patients with CKD, we found high levels of NO66 mRNA and protein. These increases were found to be stimulated by inflammation and mediated by changes in NF-κB: NO66 expression was suppressed by a NF-κB inhibitor. In support of this conclusion, we identified 3 NF-κB binding sites in the NO66 promoter. Does NO66 cause loss of muscle mass in mice with CKD? To address this possibility, we created global KO of NO66 in mice (NO66-/-) or satellite cell-specific NO66 KO (NO66-Pax7-cre) or muscle-specific NO66 KO (NO66-MCK-cre) mice. In response to CKD, NO66 KO mice developed an increase in muscle mass (28±8%) and protein synthesis (71±15%) vs. results in control mice. From a RNA-seq analysis of soleus muscles of $NO66^{-/-}$ and $NO66^{flox/flox}$ mice, we found that NO66 absence in muscle stimulates ribosomal biogenesis. Consistent with the RNA-seq results, both rRNA and the ribosomal translational capacity were increased in muscles lacking NO66 vs. results from control, $NO66^{flox/flox}$ mice. In addition, NO66 overexpression was found to suppress pre-rRNA expression in C2C12 muscle cells. Finally, a CHIP assay revealed that NO66 represses the transcription of ribosomal DNA via a demethylase mechanism

Conclusions: we have uncovered a new mechanism that regulates protein synthesis and ultimately, muscle mass

Funding: NIDDK Support

FR-OR110

The Kidney Makes Gas in Defense against Urinary Bacteria

Katherine Xu, Tian Shen, Abraham D. Levitman, Max Werth, Jonathan M. Barasch. *Columbia University, New York, NY.*

Background: The kidney expresses a variety of powerful defense mechanisms to limit urinary infection including iron scavenging, a process called "nutritional immunity". We previously demonstrated that the intercalated cells generate the archetype of the urinary iron defense, a lipocalin called NGAL which binds Enterochelin (Strong, FHCC), a bacterial siderophore. However, because urinary bacteria can evade the bacteriostatic effects of NGAL by modifying Enterochelin and by producing additional siderophores, other mechanisms of "nutritional immunity" are anticipated.

Methods: We utilized a cell type specific method of RNA isolation (adapted from Gay, Oregon). A promiscuous form of phosphoribosyltransferase (UPRT) was cloned into the Rosa26 locus using a floxed-stop design which we activated in a cell specific fashion with HoxB7Cre or Atp6v1b1Cre. Thiouracil was introduced 12hr and 24hrs after infection. Hmox1 was detected with a luciferase based reporter (Contag et al, Stanford). CO was detected with a novel metal-based probe synthesized at Columbia (adapted from Liu, China).

Results: A survey of classical iron transporters revealed segment specific expression of megalin (proximal tubule), TfR1 (TALH), and DMT1 (TALH-DCT). Nonetheless, despite ferritin accumulation, we failed to identify the mechanism of iron import in intercalated cells. Isolation of RNA directly from intercalated and principal cells revealed synthetic (*NPAS-BMAL-ALAS*), transport (*Hrg1, Flvcr1*) and metabolic enzymes (*Hmox*) of heme metabolism. Functional reporters demonstrated Hmox expression and the production of CO gas from cortical>medullary sources *in vivo* and from AtpCre-mTmG FACS isolated intercalated cells *in vitro*. Urinary bacteria (UPEC) with heme transport mutations were not competitive in the colonization of the kidney but conversely were markedly stimulated by heme, suggesting bacterial-host competition for heme capture and metabolism. In fact, infection upregulated both heme synthetic and metabolic genes, suggesting that CO production is induced by infection. Exposure to CO terminated the growth of UPEC.

Conclusions: We have identified an unusual iron trafficking system in the collecting ducts that mirrors the nutritional requirements of UPEC to achieve pyelonephritis. Many of these components are specific to the intercalated cells, consistent with the notion that these cells defend the urinary tract.

Funding: NIDDK Support

FR-OR111

Whole-Kidney Three-Dimensional Imaging Reveals the Progression of Renal Sympathetic Denervation after Ischemia-Reperfusion Injury

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Background: The sympathetic nervous system is critical in maintaining the homeostasis of renal functions. Its three-dimensional (3D) structures in the kidney, however, have not been elucidated because of the limitation of conventional imaging methods. CUBIC (Clear, Unobstructed Brain/Body Imaging Cocktails and Computational analysis) is a newly developed tissue clearing technique, which enables 3D imaging of whole-organ with single-cell resolution. Here, we apply CUBIC to the kidney research, visualizing the 3D structure of renal sympathetic nerves, showing the process of denervation after ischemia-reperfusion injury (IRI).

Methods: Eight-week-old male C57BL/6 mice were subjected to sham operation or bilateral IRI for 45 minutes, and sacrificed 28 days after surgery. The kidneys were optically cleared using CUBIC protocol. After making kidneys transparent, the sympathetic nerves were labeled with 3D immunofluorescent staining. Whole-kidney imaging was acquired by a light-sheet fluorescent microscopy.

Results: The spatial distribution of sympathetic nerves was clearly visualized. Compared with the sham group (figure 1A), the nerve density in the cortical lesion was significantly decreased in the IRI group (figure 1B).

Conclusions: The new 3D imaging technique has demonstrated the sustained renal sympathetic denervation after IRI. Dysfunction of sympathetic nerves might be related to the progression of chronic kidney disease.

Funding: Government Support - Non-U.S.

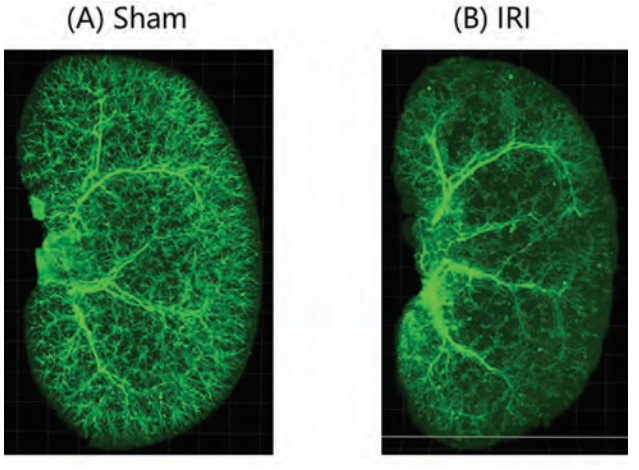

Figure 1. The representative 3D imaging of sympathetic nerves in the kidney. (A) Sham-operated group, (B) Bilateral IRI group.

FR-OR112

The Epidemiology of CKD from 1990 to 2016 in the United States of America: An Analysis of the Global Burden of Disease Study

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Background: Over the last 3 decades, the United States experienced significant changes in demographic, social, and epidemiologic trends; these changes likely have contributed to changes in chronic kidney disease (CKD) epidemiology.

Methods: We used the Global Burden of Disease (GBD) study data and methodologies to describe the change in burden of CKD from 1990 to 2016 involving disability adjusted-life years (DALYs) and death.

Results: Between 1990 and 2016, CKD DALYs increased by 104.7% from 945,627 (UI: 837,774-1,053,428) to 1,935,953 (1,747,356-2,124,794). Death due to CKD increased by 149.5% from 33,080 (UI: 3 2,382-33,721) to 82,539 (UI: 80,297-84,652). All states exhibited increase in CKD burden, but there was remarkable heterogeneity in rate of change. In 2016, the burden varied greatly by state, where Mississippi (the state with the highest burden) had twice the age-standardized CKD DALY rate compared to Vermont (the state with the lowest burden), 697(UI:619-778) and 321 (UI:280-363), respectively. In the US, 37.8%, 35.6%, and 26.7% of the increase in DALYs was attributable to increased risk factor exposure, population growth, and aging, respectively. Decomposition analyses showed substantial increase in metabolic, and to a lesser extent dietary, risk factors which manifested in increase in CKD due to diabetes, and to a lesser extent hypertension. CKD due to diabetes was the primary contributor for increased probability of death due to CKD among those aged 20-54; among those aged 55-89, the increase in probability of death was driven by CKD due to diabetes and decreased probability of death from causes other than CKD. Improvement in socio-demographic (SDI) development was coupled with an increase in age-standardized DALY rates. Rate of change in burden of CKD outpaced rate of change of other non-communicable diseases, and rate of change of CKD in all SDI levels.

Conclusions: The US toll of CKD is significant, rising, and substantially variable among states; it is driven by increased risk factor exposure and demographic expansion leading to increased probability of death from CKD among working adults; the rate of change in CKD burden outpaced other diseases in the US and CKD in other areas of the world.

Funding: Veterans Affairs Support

FR-OR113

Cumulative All-Cause Hospitalization Trajectories and Risks of ESRD and Death in the Chronic Renal Insufficiency Cohort (CRIC) Study

Anand Srivastava,[1] Xuan Cai,[1] Jungwha Lee,[1] Rupal Mehta,[1] David I. Chu,[2] Sarah J. Schrauben,[3] Milda R. Saunders,[4] Clarissa J. Diamantidis,[5] Katherine T. Mills,[6] Jonathan J. Taliercio,[7] Tariq Shafi,[8] Chi-yuan Hsu,[9] Sushrut S. Waikar,[10] James P. Lash,[11] Tamara Isakova.[1] CRIC Study Investigators *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [3]Division of Renal, Electrolytes, and Hypertension, University of Pennsylvania, Philadelphia, PA; [4]University of Chicago, Chicago, IL; [5]Duke University School of Medicine, Durham, NC; [6]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [7]Glickman Urological and Kidney Institute, Cleveland, OH; [8]Johns Hopkins University School of Medicine, Baltimore, MD; [9]University of California San Francisco, San Francisco, CA; [10]Harvard Medical School, Boston, MA; [11]University of Illinois at Chicago, Chicago, IL.*

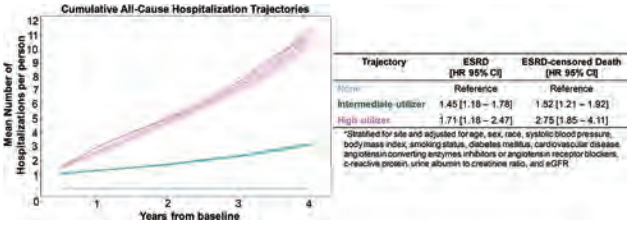
Background: Prior studies have not evaluated whether trajectories of all-cause hospitalization identify high-risk sub-phenotypes of patients with chronic kidney disease (CKD).

Methods: We evaluated data on 3012 participants of the CRIC Study who were alive and did not reach end stage renal disease (ESRD) during the first 4 years of follow up. To identify clinically distinct trajectories of cumulative all-cause hospitalization during 4 years, we performed trajectory analyses using latent class model. Trajectory analyses allow agnostic detection of subpopulations with distinct longitudinal patterns. Next, we fit multivariable-adjusted Cox proportional hazards models to assess the associations of trajectories of all-cause hospitalization with ESRD and with ESRD-censored death in participants who survived beyond their 5th annual visit.

Results: Trajectory analyses identified 3 discrete groups based on cumulative all-cause hospitalizations within the first 4 years of follow-up: none (n=1090), intermediate-utilizer (n=1785), or high-utilizer (n=137). Participants in the high-utilizer group were more likely to be black, have greater prevalence of diabetes mellitus and cardiovascular disease, have higher body mass index and albuminuria, and lower estimated glomerular filtration rate (eGFR). During a median follow-up time of 5.6 years, there were 544 ESRD events and 437 ESRD-censored deaths. High and intermediate utilizer trajectory groups were associated with a higher risk of ESRD and ESRD-censored death (Figure).

Conclusions: Trajectories of cumulative all-cause hospitalization identify subgroups of patients with CKD who have increased risks of ESRD and death independent of known risk factors including eGFR and albuminuria. Population health interventions should focus on patients with CKD with increasing cumulative all-cause hospitalizations.

Funding: NIDDK Support



Trajectory	ESRD [HR 95% CI]	ESRD-censored Death [HR 95% CI]
None	Reference	Reference
Intermediate-utilizer	1.45 [1.18 – 1.78]	1.52 [1.21 – 1.92]
High utilizer	1.71 [1.18 – 2.47]	2.75 [1.85 – 4.11]

*Stratified for site and adjusted for age, sex, race, systolic blood pressure, body mass index, smoking status, diabetes mellitus, cardiovascular disease, angiotensin converting enzymes inhibitors or angiotensin receptor blockers, c-reactive protein, urine albumin to creatinine ratio, and eGFR

FR-OR114

Efficacy and Safety of Evolocumab in CKD: Data from the FOURIER Trial

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Background: The efficacy and safety of PCSK9 inhibition in patients (pts) with CKD is undefined. We analyzed outcomes by kidney function in FOURIER.

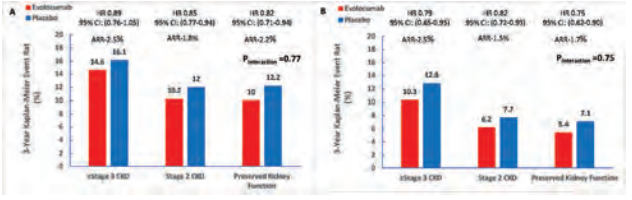
Methods: FOURIER randomized 27564 pts with stable atherosclerosis and LDL-cholesterol (C) ≥70 or non-HDL-C ≥100 mg/dL to the PCSK9 inhibitor evolocumab or placebo. The primary endpoint (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), key secondary endpoint (CV death, MI or stroke), and safety outcomes were analyzed by CKD stage estimated from baseline CKD-EPI eGFR.

Results: 8077 pts had eGFR ≥90 mL/min/1.73m^2, 15,034 stage 2 (eGFR 60-89), and 4443 ≥stage 3 CKD (eGFR <60). Age and comorbidity prevalence increased with worse CKD. LDL-C reduction with evolocumab vs placebo at 48 weeks was similar across CKD groups at 58.2%, 59.4% and 58.7%, respectively. In the placebo arm, the primary and key secondary endpoint rates were higher with worsening CKD, especially those with ≥stage 3 vs. preserved kidney function (primary-16.1% vs. 12.2%, P<0.01; secondary-12.8%

vs. 7.1%, P<0.001, Figure). Relative risk reduction (RRR) with evolocumab was similar regardless of CKD stage (P_{int}=0.77 and 0.75, respectively). However, the absolute RRs for the key secondary endpoint tended to be larger among those with ≥stage 3 CKD (2.5%, 95% CI: 0.4%-4.7%) compared with individuals with preserved kidney function (1.7%, 95% CI 0.5%-2.8%). Adverse events, including eGFR decline ≥30%, were similar regardless of CKD stage.

Conclusions: LDL-C lowering and the relative efficacy and safety of evolocumab was preserved across CKD groups in patients with clinically evident atherosclerosis and hyperlipidemia on statin therapy. Absolute reduction in CV death, MI or stroke with evolocumab tended to be greater with more advanced CKD.

Funding: Commercial Support - Amgen



Kaplan-Meier event rates at 3-years according to treatment group. (A) Primary endpoint. (B) Key secondary endpoint. ARR-absolute risk reduction. HR-hazard ratio. CI-confidence interval.

FR-OR115

RAAS Inhibitors and Risk of ESRD and Mortality in Advanced CKD

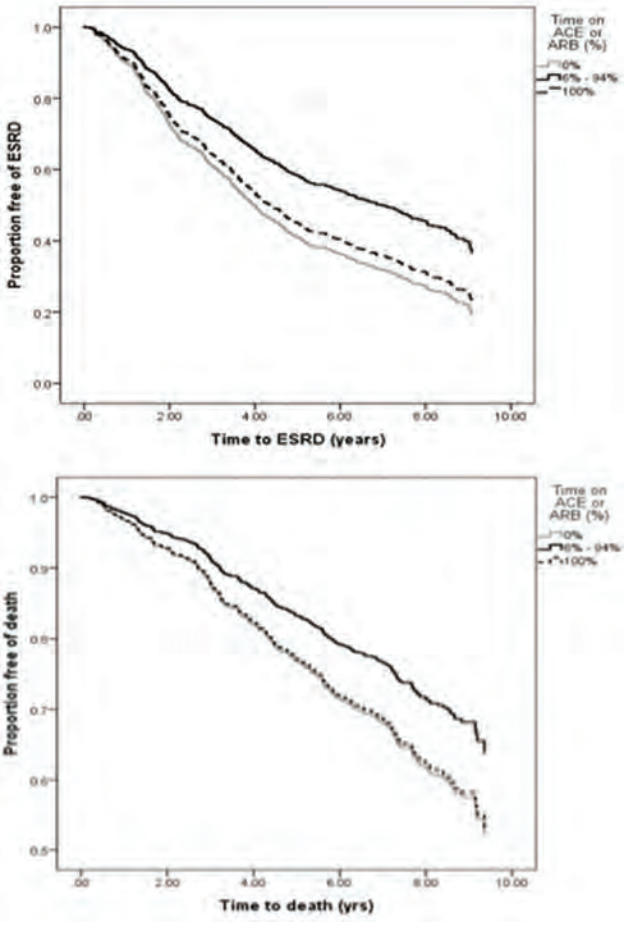
Nayan Arora, Ronit Katz, Nisha Bansal. *UW, Seattle, WA.*

Background: Inhibition of the renin-angiotensin-aldosterone system (RAASi) is standard of care in early to moderate CKD. However their use in advanced CKD is controversial due to lack of data on safety and efficacy. We described the use of RAASi among a large advanced CKD cohort and tested the association of differing patterns of RAASi use with clinical outcomes.

Methods: We identified participants of the Chronic Renal Insufficiency Cohort (CRIC) study with eGFR <30 mL/min/1.73m2. A physician reviewed all available longitudinal study visit data and classified participants into groups based on RAASi use (defined as use of ACEi or ARBs): (1) no RAASi use; (2) continuous RAASi use; and (3) treated dynamically with periods off and on RAASi during advanced CKD. Cox models were used to test the association of patterns of RAASi use with risk of ESRD and mortality, adjusting for potential confounders.

Results: Of the 761 participants with advanced CKD (mean eGFR 25 ml/min/1.73 m2), 167 (22%) did not take a RAASi throughout the study period, 319 (42%) took a RAASi continuously and 275 (36%) had a dynamic approach to RAASi use. Dynamic treatment with RAASi was associated with the lowest cumulative rates of ESRD and mortality (Figure). In multivariable models, a dynamic treatment strategy was associated with a 46% lower risk of ESRD (HR 0.54, 95% CI: 0.41,0.71) and a 23% lower risk of death (HR 0.77, 95% CI: 0.46, 0.97) compared with no RAASi use. The association of continuous ACEi/ARB use with clinical outcomes did not significantly differ from no RAASi use.

Conclusions: In a large, multi-center cohort of participants with advanced CKD, there was heterogeneity in patterns of use of RAASi. A dynamic, personalized approach to RAASi use in advanced CKD may be linked with lower risk of ESRD and mortality



KM curves for ESRD and death by patterns of RAASi use in advanced CKD

FR-OR116

Real World Dosing Practices of Renin-Angiotensin-Aldosterone System Inhibitors Is Associated with Risk of Adverse Clinical Events in CKD Patients

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Background: This study estimated real-world relationships between renin-angiotensin-aldosterone system inhibitors (RAASi) dosing in chronic kidney disease (CKD) patients and the incidence of all-cause mortality and major adverse cardiovascular events (MACE).

Methods: Data from the UK Clinical Practice Research Datalink and linked Hospital Episode Statistics between Jan 2006 and Dec 2015 were used to identify adult non-dialysis patients with incident CKD stage 3+ (based on codes or eGFR ≤60 mL/min/1.73m^2). Kaplan-Meier survival curves were stratified by <50% and ≥50% of guideline-recommended RAASi dose. Adjusted odds ratios (ORs) relating RAASi dosing to mortality and MACE were estimated using Generalized Estimating Equations.

Results: 100,572 patients were included in the study (mean follow-up 6 years). Mortality rates for patients prescribed <50% and ≥50% of recommended RAASi dose were 58 and 11 events per 1,000 patient-years, respectively; the corresponding rates of MACE were 141 and 82 events respectively. Risk of mortality over time was greater for patients prescribed <50% RAASi dose compared to those prescribed ≥50% (Figure 1). Adjusted ORs for mortality and MACE were 3.77 and 1.57 (both p<0.0001), respectively, comparing patients prescribed <50% and ≥50% RAASi dose.

Conclusions: CKD patients prescribed <50% RAASi dose were at significantly higher risk of mortality and MACE compared to those prescribed ≥50%. Although adjustment for factors such as clinician risk appreciation was not possible, the results highlight the need for treatment strategies that allow the prescription of recommended RAASi doses to optimize patient benefit.

Funding: Commercial Support - AstraZeneca

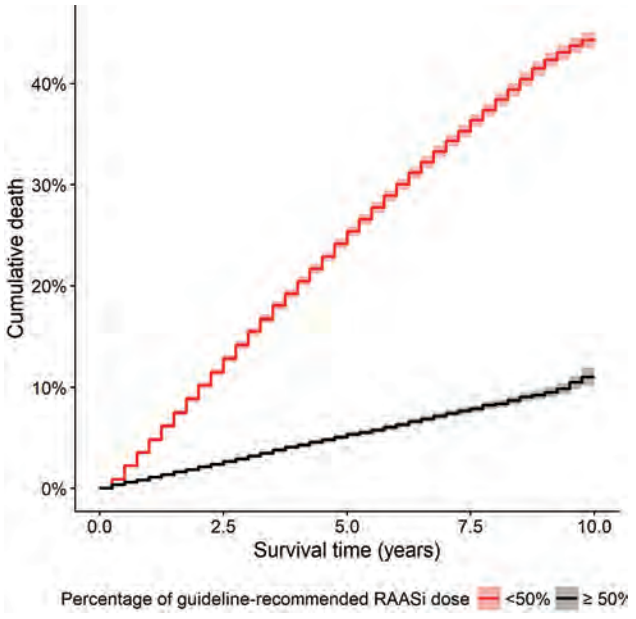

Figure 1. Mortality rates stratified by RAASi dose

FR-OR117

Benefits and Risks of Oral Anticoagulant Therapy in CKD: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: The effects of anticoagulation in chronic kidney disease (CKD) are uncertain. The aim of this systematic review was to study the benefits and risks of oral anticoagulant therapy in CKD.

Methods: Electronic databases were searched for randomized controlled trials with ≥3 months follow-up in CKD patients (Stage 3-5D) that evaluated oral anticoagulant therapy. Treatment effects were summarized using random-effects meta-analysis.

Results: Nine trials (1341 participants) compared a vitamin K antagonist (VKA) to placebo, no study medication, aspirin, or low molecular weight heparin (LMWH). Twenty-three trials (27849 participants) compared a non-vitamin K oral anticoagulant (NOAC) to VKA, placebo, aspirin, or LMWH. Only 7 VKA trials (663 participants) included patients with advanced CKD, including dialysis patients. There were no clear differences in the risk of all-cause death (7 trials, RR 0.92, 95%CI 0.71, 1.18), and major bleeding (6 trials, RR 1.08, 95%CI 0.61, 1.92) between the VKA and combined control groups. Data on venous thromboembolism (VTE) and stroke or systemic embolism in atrial fibrillation (SSE-AF) with VKA were scant. Compared to VKA, NOAC reduced the risk of SSE-AF (5 trials, RR 0.82, 95%CI 0.70, 0.96), major bleeding (8 trials, RR 0.71, 95%CI 0.51, 0.97), hemorrhagic stroke (3 trials, RR 0.42, 95%CI 0.20, 0.65), and intracranial hemorrhage (3 trials, RR 0.43, 95%CI 0.26, 0.60); and had similar risk of VTE/VTE-related death (4 trials, RR 0.86, 95%CI 0.47, 1.58), and all-cause death (4 trials, RR 0.91, 95%CI 0.78, 1.06). There were no clear differences in the risk of all-cause death (6 trials, RR 0.95, 95%CI 0.82, 1.11), VTE/VTE-related death (7 trials, RR 0.56, 95%CI 0.29, 1.09), and major bleeding (14 trials, RR 1.04, 95%CI 0.74, 1.44) between the NOAC and combined control groups. Compared to placebo, the effect of NOAC on major adverse cardiovascular events was uncertain (3 trials, RR 0.85, 95%CI 0.73, 1.01).

Conclusions: NOAC have a benefit-risk profile superior to VKA in early stages of CKD, with significant reductions in SSE-AF and major bleeding. However, there is insufficient evidence to conclude whether patients with advanced CKD derive benefit from VKA or NOAC.

FR-OR118

Trends in Use of Prescription Opioids by Those with CKD in the United States, 1999 to 2014

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Background: High rates of opioid prescribing in the United States have contributed to a national opioid epidemic. Those with chronic kidney disease (CKD) likely have not been immune, and may, in fact, have an increased probability of opioid prescription due to a high prevalence of pain and frequent contact with healthcare systems. We sought to elucidate trends in prescription opioid use in the CKD population over time, by levels of kidney function, and among CKD-relevant subgroups.

Methods: We examined trends in prescription opioid use from years 1999-2014 among adult National Health and Nutrition Examination Survey participants with creatinine-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or albumin-creatinine ratio (ACR) ≥ 30 mg/g. Differences in opioid use by racial/ethnic and other demographic characteristics and CKD-relevant comorbidities were described.

Results: 7.5% of the CKD population used a prescription opioid compared to 5.4% among those without CKD (P < 0.001). Both reduced eGFR and albuminuria were associated with opioid use: 8.4% among those with eGFR < 60 ml/min/1.73m^2 compared to 5.6% (P < 0.001) among those without reduced eGFR, and 7.4% among those with ACR ≥ 30 mg/g compared to 5.6% (P < 0.001) among those without albuminuria. No temporal trend in unadjusted prevalence of opioid use in the CKD population was seen. In an age, sex, and race/ethnicity adjusted model, the most recent era 2011-2014 vs. 1999-2002 was associated with increased opioid use in the CKD population (adjusted odds ratio 1.43, 95% CI 1.05-1.95). Other multivariate associations (P < 0.05) were age 40-64 years, female sex, diabetes mellitus, hypertension, BMI ≥ 30 kg/m^2, history of cancer, and arthritis. After statistical adjustment, no difference was seen among racial/ethnic minorities in the CKD population.

Conclusions: Prescription opioid use is more prevalent among the CKD population than in the general U.S. population with 28% of opioid use among those with CKD attributable to the association with CKD. Multiple comorbidities, which to varying degrees increase risk for pain and/or exposure to healthcare systems, were associated with increased prevalence of prescription opioid use.

FR-OR119

Geographic and Environmental Inequities and the Prescription Opioid Epidemic among Elderly CKD Patients in the United States

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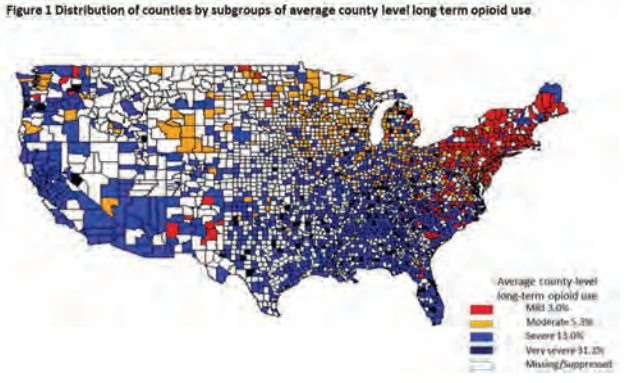
Background: CKD patients are vulnerable to opioid abuse due to high burden and suboptimal management of pain. We assessed geographic variation and the impact of environmental factors on long-term opioid use in elderly CKD patients.

Methods: We used a linked dataset from Medicare 5% sample claims data (2006-09), the American Community Survey Data (2005-09) and the Health Resources and Services Administration (HRSA) Primary Care Service Area (PCSA) data (2007). Medicare Part D enrollees age ≥65 years were included. County-level long-term opioid use was measured as % patients prescribed opioids for more than 90 days during a 1-year period after CKD diagnosis. County-level environmental factors included % of general physicians, elderly, population residing in Medically Underserved Areas (MUAs) and area deprivation index. A mixture model separating counties into different risk categories with subgroup analysis, was applied to investigate the relationship between environmental factors and county-level long-term opioid use.

Results: : The mixture model (Fig) clustered counties (n=1,794) into 4 risk subgroups. The average proportion of long-term opioid use of subgroups, which corresponded to mild, moderate, severe and very severe long-term opioid use were 3.0%, 5.3%, 13.0% and 31.2%. Counties in the Northeast and Midwest were more likely in mild and moderate risk groups, while the West andSouth counties were more likely in the severe and very severe group. Counties with aging adults and higher deprivation index were associated with greater long-term opioid use. Counties in MUAs were most likely in the very severe group.

Conclusions: Several environmental factors are associated with long-term prescription opioid use among elderly patients with CKD. This association varied across counties, highlighting the importance of allocating resources for this epidemic at county level.

Funding: NIDDK Support



FR-OR120

Efficacy and Safety of Oral Ferric Maltol (FM) in Treating Iron-Deficiency Anemia (IDA) in Patients with CKD: Randomized Controlled Trial

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Background: IDA is common in CKD and is a leading cause of morbidity and mortality. Oral ferrous products for IDA may be poorly tolerated due to gastrointestinal (GI) adverse events (AEs). Intravenous iron can be inconvenient and has the risk of allergic

reactions or iron overload. Patients with CKD and IDA would benefit from effective, well tolerated oral iron replacement therapy. FM is an oral iron replacement therapy for IDA formulated to improve GI absorption. A phase 3 multicenter double-blind, randomized controlled trial (NCT02968368) evaluated the efficacy and safety of FM in patients with stage 3/4 CKD.

Methods: Patients aged ≥18 years with CKD (estimated GFR ≥15 to <60 mL/min/1.73 m²) and IDA (hemoglobin [Hb] ≥8.0 to <11.0 g/dL, and either ferritin <250 µg/L with transferrin saturation [TSAT] <25% or ferritin <500 µg/L with TSAT <15%) were randomized 2:1 to oral FM 30 mg or placebo twice daily for 16 weeks. The primary endpoint was change in Hb from baseline to Week 16 using analysis of covariance of the intent-to-treat population. Also reported are data on all iron parameters measured in the trial; changes from baseline in ferritin, TSAT, and serum iron were assessed at Weeks 4, 8, and 16.

Results: Of 167 patients randomized (FM 111, placebo 56), 77% completed double-blind treatment (FM 81%, placebo 70%). All iron parameters were significantly improved with FM vs placebo over 16 weeks (Table). GI disorders were the most common drug-related AEs (FM 18%, placebo 7%). Serious AEs occurred in 21% in each group; none was considered to be study-drug related. Two patients died (one in each group), both considered unrelated to study drug.

Conclusions: FM resulted in statistically significant and clinically meaningful increases in Hb concentration and all iron parameters from baseline to week 16 vs placebo, supporting the efficacy of oral FM in treating IDA in patients with stage 3 or 4 CKD. FM was generally well tolerated, with only minor differences in the safety profile and overall GI AEs vs placebo.

Funding: Commercial Support - Shield Therapeutics Ltd

Least-square mean change from baseline to Week 16

	FM (n=111)	Placebo (n=56)	p-value
Hb	0.50 g/dL	–0.03 g/dL	0.0149
Ferritin	25.49 µg/L	–8.25 µg/L	0.0004
TSAT	3.78%	–0.69%	<.0001
Serum iron	1.58 µmol/L	–0.21 µmol/L	0.0037

FR-OR121

Benefits and Harms of Dual Antiplatelet Therapy in CKD: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Dual antiplatelet therapy (DAPT) is the standard of care in coronary artery disease. Despite the high burden of cardiovascular disease in chronic kidney disease (CKD), the role of DAPT in improving outcomes in CKD has not been systematically studied. The aim of this systematic review was to study the benefits and harms of DAPT in CKD.

Methods: Electronic databases were searched for randomized controlled trials (RCT) that included CKD patients (stage 3-5D or proteinuria) and evaluated the effect of DAPT on cardiovascular outcomes with ≥3 months follow up. Treatment effects were summarized using random-effects analysis.

Results: Eleven trials (13628 participants) compared DAPT to a single antiplatelet agent (6 trials), placebo (3 trials), or no study medication (2 trials). DAPT interventions were aspirin/dipyridamole (5 trials) and aspirin/P2Y12 inhibitor (6 trials). Compared to the control group, DAPT reduced the risk of major adverse cardiovascular events (4 trials, risk ratio [RR] 0.87, 95%CI 0.78, 0.97), myocardial infarction (5 trials, RR 0.76, 95%CI 0.61, 0.92), and stroke (6 trials, RR 0.81, 95%CI 0.68, 0.94). There were no differences in risk of cardiovascular death (7 trials, RR 0.95, 95%CI 0.76, 1.14), all-cause death (10 trials, RR 0.92, 95%CI 0.82, 1.03), and major bleeding (8 trials, RR 1.36, 95%CI 0.98, 1.73) between DAPT and control group. Three other trials (6239 participants) compared DAPT using aspirin/P2Y12 inhibitor to DAPT. Compared to aspirin/clopidogrel, aspirin plus ticagrelor or prasugrel reduced the risk of all-cause death (2 trials, RR 0.74, 95%CI 0.6, 0.88); and with no differences for major adverse cardiovascular events (2 trials, RR 0.88, 95%CI 0.61, 1.14), and major bleeding (3 trials, RR 0.93, 95%CI 0.37, 1.48). Overall, 4 trials included dialysis patients (1860 participants); 5 trials excluded dialysis patients (13725 participants); 2 trials did not include advanced CKD (stages 4-5) (372 participants); and 3 trials did not report the lower threshold of renal function for exclusion (3910 participants).

Conclusions: DAPT improved cardiovascular outcomes in early stages of CKD. However, there is insufficient evidence to conclude whether patients with advanced CKD derive benefit from DAPT.

FR-OR122

Skeletal Muscle Inflammation and Fibrosis Contribute to Weakness in Patients with CKD

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Background: Muscle dysfunction is an important cause of morbidity among patients with chronic kidney disease (CKD). Although muscle fibrosis is present in a CKD rodent model, its existence in humans and its impact on physical function are currently unknown. In animal models of muscle injury, TNF-α secreted by macrophages prevents muscle fibrosis by limiting the expansion of fibro/adipogenic progenitor cells (FAPs).

Methods: We examined isometric leg extension strength and measures of skeletal muscle fibrosis and inflammation in vastus lateralis muscle from CKD patients (n=10, stage 4 and 5 CKD) and healthy, sedentary controls of similar age (n=10). Histochemistry and immunohistochemistry were used to assess muscle collagen and macrophage and FAP cell populations, and RT-qPCR was used to assess muscle-specific inflammatory marker expression.

Results: Muscle collagen content was significantly greater in CKD compared with control (18.8 ± 6.7% vs. 11.7 ± 2.0% collagen area, p=0.008), as was staining for collagen I, pro-collagen I, and a novel collagen-hybridizing peptide that binds remodeling collagen. Muscle collagen was inversely associated with leg extension strength in CKD (r= -0.74, p=0.01) but not control (r=0.40, p=0.28). FAP abundance was increased in CKD, was highly correlated with muscle collagen (r=0.84, p<0.001), and was inversely associated with TNF-α expression (r= -0.65, p=0.003). TNF-α, CD68, CCL2, and CCL5 mRNA were significantly lower in CKD than control, despite higher serum TNF-α and IL-6. Immunohistochemistry confirmed fewer CD68+ and CD11b+ macrophages in CKD muscle.

Conclusions: Skeletal muscle collagen content is increased in humans with CKD and is functionally significant. Muscle fibrosis correlated with increased FAP abundance resulting from insufficient macrophage-mediated TNF-α secretion. These data provide a foundation for future research elucidating the mechanisms responsible for this newly identified human muscle pathology.

Funding: NIDDK Support

FR-OR123

Intramuscle Fat Infiltration in Non-Dialysis CKD: Clinical Determinants and Association with Mortality

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Background: Intramuscle fat infiltration (IFI) is an important feature of aging currently understood as a cause of muscle weakness in elderly. Compared to healthy controls, IFI has been reported elevated in chronic kidney disease (CKD) patients. Its determinants and consequences, however, are unknown.

Methods: Cross-sectional study with mortality follow-up of 195 nephrology-referred patients with non-dialysis CKD stages 3-5. Mean age was 60±11 years, 61% were men and glomerular filtration rate (creatinine clearance) was 25±12 ml/min/1.73 m². We used computed tomography (CT) scan (Slice-O-Matic software version 5.0) of the third lumbar vertebra to quantify the degree of IFI (reported as % of fat within muscle area). Muscles evaluated by CT were psoas, transversus abdominis, rectus abdominis, external and internal obliques, erector spinae and quadratus lumborum. Coronary artery calcification score (CAC) was evaluated by CT, muscle strength by dynamometry (handgrip strength, HGS) and shown as standard values to normative tables.

Results: IFI was higher in women than in men (9.7±6 vs 6.3±4%, P<0.05), and was positively correlated (Spearman test) with age (rho =0.37), Charlson comorbidity score (rho=0.19), CAC (r=0.16) and CT-derived visceral (rho=0.37) and subcutaneous fat (rho =0.57). IFI was negatively associated with HGS (rho=-0.25) and CT-derived skeletal muscle mass (rho=-0.37). In multiple linear regression analysis, male sex (ß=-0.66; P<0.01), older age (ß=0.40 per 1-SD increase; P<0.01), higher muscle mass (ß=0.48 per cm/m² increase; P<0.01) but lower muscle strength (ß=-0.15 per % decrease in HGS) were independent predictors of IFI% (r^2=0.33). During 40±13 months of follow-up, 57 patients died. Increased IFI was associated with the risk of death (adjusted hazard ratio 1.60 per 1-SD increase, 95% CI: 1.21 to 2.11) independently of sex, age, diabetes, CKD stage, CAC, subjective global assessment and standard HGS.

Conclusions: IFI is associated with lower muscle strength in non-dialysis CKD patients and predicts the risk of death, regardless of muscle stores. These data are consistent with the notion that intramuscle fat infiltration worsens muscle quality.

FR-OR124

Pro-Inflammatory Diets Increase Risk of ESRD in US Adults with CKD

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Background: CKD progression can be accompanied by chronic low-grade inflammation marked by elevated concentrations of inflammatory markers. We hypothesized that proinflammatory diets increase risk of kidney disease progression and systemic inflammation is a mediator of progression of kidney disease.

Methods: We analyzed a cohort study of 1084 adults with CKD (eGFR 15-59 ml/min/1.73m^2) aged≥ 20 years in the 1988-1994 National Health and Nutrition Examination Survey linked with the US Renal Data System, allowing for assessment of ESRD as an outcome over a follow-up period of 14 years. The Adapted Dietary Inflammatory Index (ADII, based on 26 components) was calculated at baseline from a 24-hr dietary recall. We used regression analysis to examine the association between ADII and an inflammatory score (IS) computed from C-reactive protein, serum albumin, white blood cell count, and mean platelet volume, adjusting for demographics, body mass index, physical activity, HbA1C, systolic blood pressure, total cholesterol. The Fine Gray competing risk model was used for exploring the association between (i) IS and ESRD, and (ii) risk of incident ESRD and per standard deviation (SD) increase in ADII. The models were adjusted for the above mentioned covariates and estimated glomerular filtration rate and urinary albumin–to-creatinine ratio (ACR). IS was considered as a mediator of CKD progression using Valeri and Vanderweele's method.

Results: 120 participants with CKD (11.1%) developed ESRD. A 1 SD increase in ADII was associated with a higher IS (β [95% CI]: 1.05[0.89-1.22]). IS was also associated with ESRD (relative hazard [RH]: 1.12 [95% CI: 1.02-1.25]). ADII was associated with increased risk of incident ESRD (RH per SD increase: 1.40 [1.04-1.78]). Mediation analyses showed that 25% of the total effect of the ADII on ESRD was explained or mediated by IS. Interaction tests showed a higher risk of ESRD per SD increase in ADII in adults with ACR≥30mg/g (RH 1.55 [1.12-1.96] than those with ACR<30 mg/g (RH 0.96 [0.55-1.38]; $p_{interaction}$<0.001).

Conclusions: A proinflammatory diet is independently associated with risk of ESRD which is mediated by the inflammatory markers. These findings have implications for prevention of ESRD using dietary approaches.

Funding: Other U.S. Government Support

FR-OR125

Multicenter Randomized Controlled Study of the Efficacy of Low-Protein Rice for Dietary Protein Restriction in Patients with CKD

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Background: The benefits of dietary protein restriction in chronic kidney disease (CKD) remain unclear, largely due to poor adherence to low-protein diet in most clinical studies. Rice, a major staple food globally, is a primary source of dietary plant proteins, especially in Asia. We examined the efficacy of low-protein rice (LPR) for dietary protein restriction in CKD patients.

Methods: This open multicenter randomized controlled study aimed to compare the efficacy of dietary protein restriction [0.7 g/kg ideal body weight (IBW)/day] between CKD patients without LPR (no LPR group) and those with LPR (LPR group) to be eaten in at least 2 meals per day for 24 weeks (UMIN000015630). We enrolled 104 patients (age, 62.7 ± 10.8 years) with CKD (stages G3aA2 and G4) from Niigata University Medical & Dental Hospital and 7 affiliated hospitals from August 2014 to December 2017. Patients in both groups were given regular instruction by dietitians to meet the nutritional goal. Maroni's formula was used to estimate protein intake.

Results: Analysis of covariance was performed adjusted by protein intake at the start of the study. After 24 weeks, estimated protein intake decreased from 0.99±0.23 to 0.80±0.20 g/kg IBW/day in the LPR group and from 0.99±0.23 to 0.91±0.21 g/kg IBW/day in the no LPR group, respectively. The change was significantly higher in the LPR group than in the no LPR group by 0.11 (95% CI, 0.03 to 0.19) g/kg IBW/day (P = 0.001). Energy intake did not differ significantly between the groups; salt intake decreased significantly at 24 weeks in the LPR group. Creatinine clearance did not differ significantly between the groups, but urinary protein excretion decreased significantly at 24 weeks in the LPR group. Also, nutritional indices including diagnostic markers of protein-energy wasting and quality of life showed no significant difference between the groups.

Conclusions: LPR has potential as a feasible tool for dietary protein restriction in CKD patients. Long-term studies are needed to investigate LRP diet and suppression of CKD progression.

Funding: Commercial Support - Kameda Seika Co.,Ltd., Sato Foods Industries Co.,Ltd., Biotech Japan Co.,Ltd., Forica Foods Co.,Ltd.

FR-OR126

Dietary Fiber Intake, Myocardial Injury, and Major Adverse Cardiovascular Events among ESRD Patients: A Prospective Cohort Study

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Background: Dialysis patients are frequently advised to restrict fruits, vegetables, wholegrain or nuts intake due to their high potassium or phosphate content. The importance of fiber intake in relation to cardiovascular health in dialysis patients is not known.

Methods: Two hundred and nineteen prevalent dialysis patients was prospectively recruited from a university teaching hospital and regional dialysis center and followed for 4 years. Dietary fiber intake was estimated using a 7-day validated food frequency dietary questionnaire and examined in relation to a composite of major adverse cardiovascular events (MACE).

Results: Higher fiber intake was associated with less inflammation, lower serum cardiac troponin T, N-terminal pro-brain natriuretic peptide and less cardiac hypertrophy. During 4 years' follow-up, 127 patients were complicated with one or more MACE. Higher fiber intake (hazard ratio [HR], 0.87, 95% confidence intervals [CI], 0.80 – 0.94) and higher fiber intake density (HR, 0.85, 95% CI, 0.74 – 0.97) were associated with a lower risk of MACE on univariate analysis. In the multivariable Cox regression analysis, higher fiber intake predicted a lower risk of MACE (adjusted HR, 0.89, 95% CI, 0.81 – 0.97, P=0.008) independent of other clinical, demographic, biochemical, hemodynamic, adequacy parameters, dietary protein and energy intake, as well as inflammatory and cardiac markers. Similarly, fiber intake density retained significance in predicting MACE both as a continuous variable [adjusted HR, 0.87, 95% CI, 0.77 – 0.99] and when stratified into tertiles, adjusting for the same confounders. Those in the lower tertile of fiber intake density showed an increased hazard for MACE [adjusted HR, 1.78, 95% CI, 1.13 – 2.80] compared to those in the upper tertile.

Conclusions: Higher dietary fiber intake and fiber nutrient density were associated with less inflammation, less myocardial hypertrophy and injury and predicted a lower risk of MACE in dialysis patients. These data form an important basis for a randomized controlled trial to examine the effects of fiber supplementation on cardiovascular outcomes in dialysis patients.

Funding: Government Support - Non-U.S.

FR-OR127

Resistant Starch Supplementation Reduces Indoxyl Sulfate Levels in Hemodialysis Patients: A Randomized, Double-Blind, Crossover, Placebo-Controlled Study

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Background: Protein-bound uremic toxins produced from intestinal bacterial protein fermentation, including indoxyl sulfate (IS) and p-cresyl sulfate (p-CS), tend to accumulate in chronic kidney disease (CKD) patients. These patients have a gut microbiota imbalance that leads to loss of gut barrier integrity, facilitating the passage of IS and p-CS into the bloodstream. Both solutes are linked with the progression of renal disease, as well as, cardiovascular disease (CVD). Strategies like prebiotic supplementation may be effective to restore the balance of the gut microbiota. This study tested whether prebiotic resistant starch (RS) supplementation would reduce IS and p-CS plasma levels in hemodialysis patients (HD).

Methods: Thirty eight stable HD patients were randomized in RS (n=19) or Placebo (n=19) groups to receive alternately 9 cookies/day (dialysis days) and 1 sachet/day (non-dialysis days) containing 16 g of RS (Hi-Maize 260, Ingredion®) or manioc flour for 4 weeks and then after the washout period (4 weeks) were crossed over to the alternative for an additional 4 weeks. Fasting pre-dialysis plasma IS and p-CS were analyzed by reversed-phase high-performance liquid chromatography. Food intake was also recorded. Intention-to-treat analysis were performed in order to verify the variation of IS and p-CS plasma levels according to allocation groups, by means of mixed linear models is SAS.

Results: Twenty six patients concluded the study, 12 in RS-Placebo group (42% male, 54.8±7.9 years, 53.0±40.5 months of HD, 26.7±5.1 Kg/m^2) and 14 in Placebo-RS group (71% male, 54.2±11.9 years, 44.1±23.0 months of HD, 26.2±4.8 Kg/m^2). After 4 weeks, IS plasma levels were significantly reduced in the RS group [-6.2 (-9.7/-3.3)mg/L] compared to placebo [2.2 (-5.9/4.5)mg/L] (p=0.006). No significant alterations was observed in plasma p-CS levels or food intake (besides fiber intake has increased with RS).

Conclusions: Prebiotic RS supplementation seems to be an effective nutritional strategy to reduce plasma IS levels in CKD patients on HD. These findings support the hypothesis that prebiotics may be a new non-pharmacological intervention to modulate gut microbiota.

Funding: Government Support - Non-U.S.

FR-OR128

Probiotic Dietary Supplementation in Hemodialysis Patients: A Double-blind, Randomized, Placebo-Controlled Trial

Sixiu Liu, Hongli Jiang. *First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, China.*

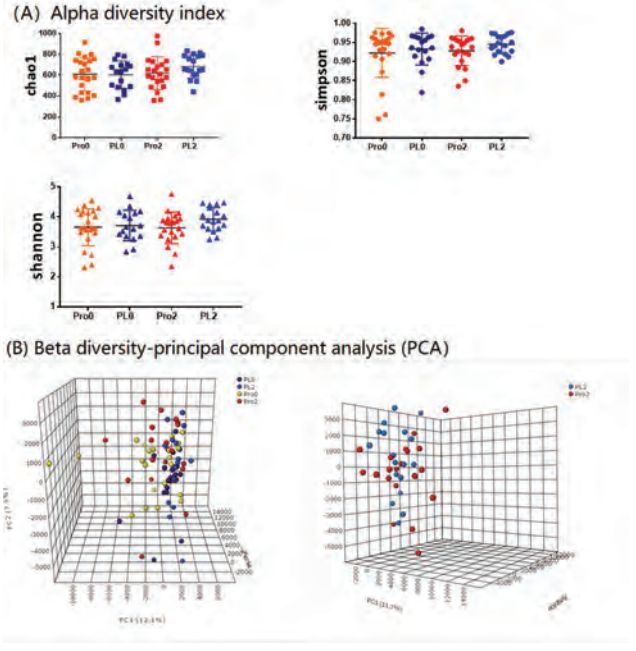
Background: Recent studies have highlighted that gut microbiota is a key origin of uremic retention solutes in patients with chronic kidney disease, and is involved in triggering systemic microinflammation. The objective of this study was to evaluate the effects of probiotics on the gut microbiota profile and inflammatory markers in hemodialysis (HD) patients.

Methods: This was a randomized, double-blind, placebo-controlled study. Fifty HD patients were assigned to receive 1 of 2 treatments: probiotic (Pro0,n = 25; Enterococcus faecalis, Lactobacillus acidophilus, Bifidobacterium longum, 4 capsules each, twice daily, totally containing 30 billion colony-forming units per day) or placebo (PL0,n = 25) daily for 6 months. Blood samples and feces samples were collected at baseline and after intervention. The gut microbiota profile, inflammatory markers (IL-6, TNF-α and hs-CRP) and endotoxin were assessed.(Trial registration number NCT02929225.)

Results: Twenty-three patients remained in the probiotic group(Pro2) and 22 in the placebo group(PL2). Compared with the placebo group, probiotics did not induce major changes in the faecal microbiome. The alpha and beta diversity of gut microbiota in probiotic group were not significantly different from placebo group(Fig.1(A)and(B)). However, according to the Linear discriminant analysis coupled with effect size measurements (LEfSe) further identified four bacterial families that significantly changed. Particularly, Family Enterococcaceae was increased, while Ruminococcaceae was reduced in probiotic group. In addition, the plasma levels of inflammatory markers and endotoxin were not affected by probiotics.

Conclusions: In HD patients, probiotics did not significantly induce major alterations in the fecal microbiome but several specific bacteria relative abundance were restored.

Funding: Government Support - Non-U.S.



FR-OR129

Dysbiosis in Renal Failure Causes Insulin Resistance and Leaky Gut

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Background: Chronic Kidney disease (CKD) leads to clinically relevant insulin resistance (IR), which is a novel cardiovascular risk factor in patients with CKD. However, the pathophysiology of IR in CKD remains unclear. Recently, gut microbiota alterations have been reported to be associated with the etiology and progression of CKD. Using germ-free mice, we sought to determine whether dysbiosis in renal failure (RF) contributes to CKD-associated IR.

Methods: RF was induced in 7-week-old male ICR mice by feeding a diet containing 0.2% adenine for 6 weeks; these were compared with a control group that was fed a normal diet. Fecal microbiota transplantation (FMT) was performed by oral gavage on the 8-week-old, germ-free, male, ICR mice using cecal microbiota obtained from either the control group (control-FMT) or RF group (RF-FMT). The vehicle group was gavaged with only sterile phosphate-buffered saline. Two weeks after inoculation, glucose and insulin tolerance and intestinal microbiota and barrier function were evaluated in each group.

Results: In the mice from the RF group, whose body and adipose tissue weight were markedly lower, IR was evident where insulin stimulation failed to activate insulin signaling in skeletal muscles and adipose tissues. The expression of tight junctions in the colon was also reduced. In the RF-FMT group, glucose and insulin tolerance were impaired compared with those in the control-FMT and vehicle groups; insulin-induced signal transduction was attenuated, especially in skeletal muscles. Additionally, adipose tissue weight, adipocyte size and tight junction protein expression in the colon were lower in the RF-FMT group compared with those in the control-FMT group. These results mimicked those of the RF and the control groups. The differences in gut microbiota between the RF and control groups were mostly consistent between the RF-FMT and the control-FMT groups, including a decrease in *Bacteroides* and *Prevotella* species and an increase in *Clostridium* species in the RF and RF-FMT groups.

Conclusions: The gut microbiota from mice with RF induced IR along with impaired adipose tissue maturation, and disruption of the intestinal barrier associated with RF. Our data demonstrated for the first time, that uremic dysbiosis directly affects CKD-related metabolic abnormality.

FR-OR130

CKD Attenuates the Plasma Metabolome Response to Insulin

Baback Roshanravan,[1] Leila R. Zelnick,[2] Jessica A. Alvarez,[3] Jorge Gamboa,[4] Thomas Ziegler,[5] Kristina M. Utzschneider,[6] Steven E. Kahn,[6] Bryan R. Kestenbaum,[6] Daniel Raftery,[6] Ian H. de Boer.[7] *[1]University of Washington - Kidney Research Institute, Seattle, WA; [2]Kidney Research Institute, Seattle, WA; [3]Emory University SOM, Atlanta, GA; [4]Vanderbilt University, Nashville, TN; [5]ASN, Lilburn, GA; [6]University of Washington, Seattle, WA; [7]Division of Nephrology and Kidney Research Institute, University of Washington, Seattle, WA.*

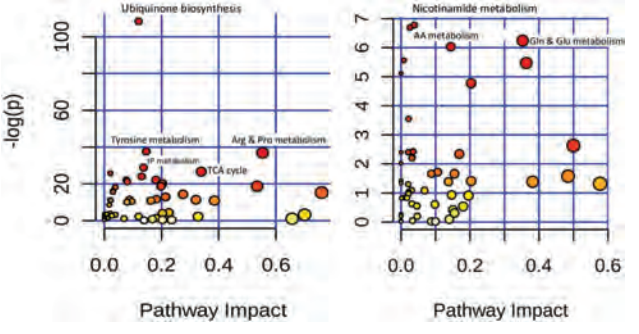
Background: Chronic kidney disease (CKD) leads to decreased sensitivity to the metabolic effects of insulin contributing to protein energy wasting and muscle atrophy. Targeted metabolomics profiling during hyperinsulinemic euglycemic insulin clamp testing may help identify potential aberrant metabolic pathways contributing to insulin resistance among patients with CKD.

Methods: Using a targeted metabolomics profiling, we examined the plasma metabolome in 95 adults without diabetes in the fasted state (58 with moderate-severe CKD, 37 with normal glomerular filtration rate (GFR)) of whom 60 had plasma collected during a hyperinsulinemic-euglycemic clamp (40 with CKD). We assessed heterogeneity in fasting metabolites and the response to insulin to identify potential cellular metabolic pathways linking CKD with insulin resistance. Differences and changes in metabolite concentrations by CKD status and with insulin clamp testing were adjusted for potential confounders of age, sex, race/ethnicity (white versus non-white) and body weight. Pathway analysis was performed using Metaboanalyst

Results: Mean GFR among participants with CKD was 37.3 mL/min per 1.73m^{2}compared to 89.3 ml/min per 1.73m^{2}among controls. In the fasting state, differences between CKD and control subjects included significant abnormalities in tryptophan metabolism, ubiquinone biosynthesis, and the TCA cycle (Figure). Insulin infusion markedly decreased plasma metabolite levels, predominantly amino acids and their metabolites. CKD was associated with attenuated insulin-induced changes in nicotinamide, arachidonic acid, and glutamine/glutamate metabolic pathways (Figure).

Conclusions: Targeted plasma metabolomics profiling suggests broad disruption in amino acid metabolism and mitochondrial function as putative manifestations or mechanisms of the impaired anabolic effects of insulin in CKD.

Funding: NIDDK Support



Comparison of fasting (left panel) and insulin clamp (right panel) metabolic pathway differences between CKD and controls.

FR-OR131

Endurance Exercise-Derived Exosomal miRNA Exerkines Attenuate Progressive CKD

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Background: Progressive CKD is still an unmet biomedical challenge because no effective therapies are available as of yet for clinical use. While various studies across multiple organs which demonstrated that endurance exercise (EE) protects from progressive organ failure by endocrine-like signalling via specific nucleic acids (so-called exerkines), little consideration has been paid as to whether any exerkines are released in a manner other than direct discharge into the circulation. It is becoming increasingly apparent that one of the main mechanisms by which scelettal muscle cells and distant organs communicate

is by the release of cell-derived extracellular exosomes. Based on these pre-requisits, we here aimed to gain insights into the molecular mechanisms underlying successful reno-protection and to explore whether such pathways could be therapeutically targeted.

Methods: EE was performed in *C57BL/6*mice for 4 weeks before challenging with unilateral ureteral obstruction (UUO) for 7 days without EE. Exosomal miRNA signatures were analyzed by unbiased array-based approaches and confirmed by qRT-PCR in sclettal muscles, plasma exosomes and corresponding kidneys. By using miRNA mimics administered systemically, miRNA candidates for succesful protection during EE were confirmed for therapeutical implications.

Results: We identified a unique miRNA signature in muscle-derived exosomes and kidneys specifically during endurance exercise, associated with attenuation of progressive CKD. Systemic administration of miRNA mimics was equally effective to attenuate progressive CKD, supporting that endurance exercise-derived exosomal miRNAs are involved in reno-protection. On a mechanistic level, we provide evidence that exosomal miRNAs directly target and degrade *PAI-1*, associated with activation of the tPA/uPAR/plasmin pathway. Increased tPA/uPAR/plasmin stimulates ECM remodelling and degradation by activation of latent MMPs, in particular MMP-2 and MMP-9.

Conclusions: In summary, we here provide evidence that EE attenuates progressive CKD by enrichment of exosomal miRNA exerkines modulating ECM remodelling and degradation in chronically injured kidneys. Because miRNA mimics equally protect from progressive CKD, these findings further support therapeutical implications of exosomal exerkines as nature's exercise pill.

FR-OR132

Genome-Wide Non-HLA Incompatibility between Donor and Recipient Contributes to Kidney Allograft Attrition

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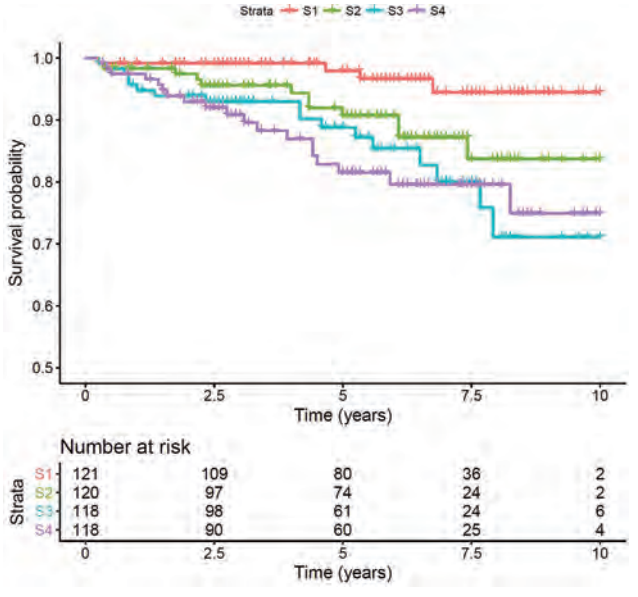
Background: The introduction of HLA matching of donors and recipients was a breakthrough in kidney transplantation but epidemiological data suggest also a fundamental role of non-HLA alloimmunity.

Methods: 477 deceased donor and first kidney transplant recipient pairs from a prospective multi-center transplant cohort study were successfully genotyped and genome-wide genetic mismatches in nsSNPs were calculated to identify incompatibilities in transmembrane and secreted proteins. Association of nsSNP mismatch and graft loss was estimated in a Cox model adjusting for HLA mismatch and clinical covariates. Customized peptide arrays were generated to screen for antibodies against genotype-derived mismatched epitopes.

Results: The median nsSNP mismatch in immune-accessible transmembrane and secreted proteins between donors and recipients was 1,892 with an interquartile range (IQR) of 86. The degree of nsSNP mismatch was independently associated with graft loss in a multivariable model adjusted for HLA eplet mismatch *(HLA-A, B, C, DP, DQ, DR).* Each increase by a unit of one IQR exhibited a HR of 1.68 (95% CI 1.17-2.41, p=0.005). Five-year death censored graft survival was 98% in the quartile with the lowest mismatch but only 82% in the highest quartile (p=0.003, logrank test).(Figure). Customized peptide arrays verified a donor-specific alloimmune response to genetically predicted mismatched epitopes for selected transmembrane proteins.

Conclusions: Genetic mismatch of non-HLA haplotypes coding for transmembrane or secreted proteins is associated with an increased risk of functional graft. DSAs can be identified against genotype derived non-HLA epitopes.



FR-OR133

Single Cell Transcriptome Analysis of Human Kidney Allograft

Hemant Suryawanshi,[2] Hua Yang,[3] Milagros T. Lagman,[4] Michelle L. Lubetzky,[5] Thomas Tuschl,[7] Manikkam Suthanthiran,[6] Thangamani Muthukumar.[1] *[1]Weill Cornell Medicine, New York, NY; [2]The Rockefeller University, New York, NY; [3]Weill-Cornell, New York, NY; [4]Weill Medical College of Cornell University, New York, NY; [5]Division of Nephrology and Hypertension, New York, NY; [6]Weill Cornell Medical College, New York, NY; [7]Howard Hughes Medical Institute, New York, NY.*

Background: Unbiased transcriptome-based clustering analysis of cells within the kidney allograft may help identify cell type-specific injury and has the potential to redefine the current pathology-based classification of allograft rejection/injury.

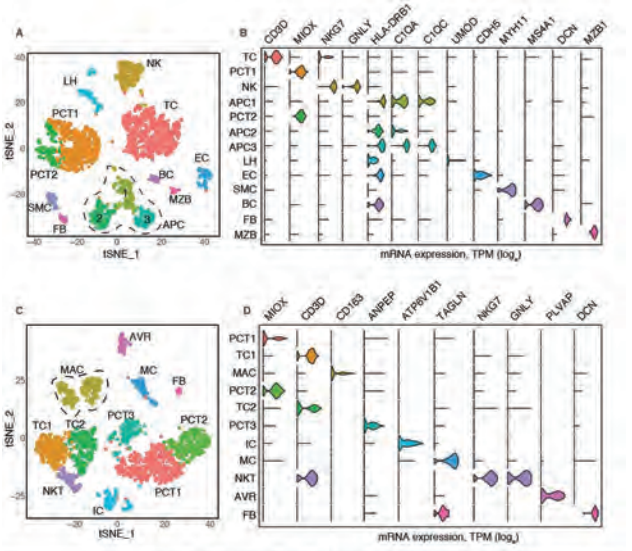
Methods: Kidney allograft tissue obtained at the time of core needle biopsy (n=2, TK1 and TK2, Figure 1) was digested to generate single cell suspension. Droplet-based 10X Chromium platform (10X Genomics) was used to capture single cells in emulsion, followed by cDNA synthesis, sequencing, and analysis.

Results: We obtained 2,657 (TK1) and 2,207 (TK2) high-quality scRNA-seq profiles and identified 13 and 11 major cell clusters, respectively (Figure 2). In both biopsies, T cells (27% TK1 and 24% TK2) were abundant despite the differences in histopathology findings. Cell types restricted to TK1 were NK, MZB and SMC, whereas cell types restricted to TK2 were NKT, MC and IC. Only TK2 had fibrosis but we found FB cells in both the samples.

Conclusions: Our single cell expression atlas of human kidney allograft has deciphered the complex cellular environment of kidney allograft and provides a powerful step towards better understanding of the cellular basis of kidney allograft dysfunction.

Clinical and histopathological characteristics

Variable	Transplant Kidney Biopsy #1 (TK1)	Transplant Kidney Biopsy #2 (TK2)
At the time of transplant		
Recipient		
Age at transplant, years	29	51
Gender	M	F
Donor		
Age	28	49
Gender	F	M
Deceased donor organ	No	No
From transplant to biopsy		
Acute rejection	Yes	Yes
At the time of biopsy		
Time from transplantation, months	84	42
Time from prior rejection, months	8	16
Creatinine, mg/dl	1.69	2.63
Urine albumin creatinine ratio	0.22	4.8
Biopsy findings	Minimal glomerular changes Mild peritubular capillaritis No acute rejection	Transplant glomerulitis Transplant glomerulopathy Peritubular capillaritis
Banff lesion score		
g (glomerulitis)	0	3
t (tubulitis)	0	0
i (interstitial inflammation)	0	0
v (vascular inflammation)	0	0
ptc (peritubular capillary inflammation)	1	3
cg (chronic glomerulopathy)	0	3
ct (tubular atrophy)	0	2
ci (interstitial fibrosis)	0	2
cv (chronic vascular changes)	1	1
ah (arteriolar hyalinosis)	2	0
cptc (ptc BM multilayering)	0	0
C4d staining	Negative	Negative
Donor Specific anti-HLA Antibodies	Yes (Class II)	No



Single-cell expression atlas of human kidney allograft

(A and C): Cell type assignment following *t-SNE*-based visualization of expression differences for 2,657 and 2,207 single cells for TK1 and TK2 samples, respectively, using established lineage markers. (B and D): Violin plots showing expression of selected lineage markers for TK1 and TK2 samples, respectively for all the cell types arranged in the order of decreasing number of cells. *TC, T cell; PCT, proximal convoluted tubule; APC, antigen-presenting cell; LH, loop of Henle; EC, endothelial cell; SMC, smooth-muscle cell; BC, B cell; FB, fibroblast; MZB, marginal zone B cell; MAC, macrophage; IC, intercalated cells; MC, mesangial cell; NKT, natural killer T cell; AVR, ascending vasa recta.*

FR-OR134

Accelerated Podocyte Detachment Early after Kidney Transplantation and Relationship to Long-Term Allograft Loss-of-Function

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Background: Kidney allograft half-life has not improved despite excellent short-term survival. Recent long-term surveillance biopsy studies identify accumulating glomerulosclerosis associated with late allograft loss. While podocyte depletion is well-known to drive proteinuria and glomerulosclerosis in animal models and human glomerular diseases, its role in renal allograft loss-of-function is not generally recognized.

Methods: To address these questions, we collected urine from 125 kidney transplant recipients in the first post-transplant year for urine pellet mRNA and protein analysis, with a median follow up of 4.5-years.

Results: Using multivariable linear models adjusted for proteinuria, transplant, recipient and donor factors, we observed that the **average rate of podocyte detachment in the first post-transplant year was significantly associated with eGFR decline**. The relationship between podocyte detachment rate and eGFR decline persisted **even among recipients who were non-proteinuric (<0.3g/g creatinine) and who had no recurrent or *de novo* glomerular disease identified on 1yr protocol biopsy**.

Conclusions: These findings support the concept that in kidney allografts **accelerated podocyte loss precedes proteinuria**, is associated with inferior long-term allograft outcomes as measured by eGFR decline. Modulating factors driving early podocyte detachment after kidney transplantation may help improve long-term outcomes.

Funding: NIDDK Support, Other NIH Support - O'Brien and Michigan Nutrition and Obesity Research Center

Predictors of eGFR slope over median 4.5 years of follow-up: Multivariable analysis.

Variable	β Coef.	Std. Err	P value	LCL	UCL
Log UPodCR	-2.17	0.62	0.001	-3.41	-0.93
Log UProtCR	0.15	0.59	0.81	-1.03	1.33
GGS >10% (ref: GGS <10 %)	-4.20	1.65	0.01	-7.50	-0.94
Glomerular Disease (TG or Recurrent disease)	-5.77	2.04	0.006	-9.83	-1.70

Adjusted for recipient & donor factors (age,race,sex, race,BSA), transplant factors (HLA mismatch, cold ischemia time), first year events (de novo DSA and rejection), average of other urine mRNA markers (UTGFbeta1CR,UAqp2CR) and IFTA.

Abbreviations: UpodCR, urine podocin mRNA to urine creatinine ratio; UAqp2CR, urine aquaporin2 mRNA to urine ratio; UTGFbeta1CR, urine transforming growth factor beta mRNA to creatinine, UProtCR; urine protein to creatinine ratio.

FR-OR135

The Banff Working Group Classification of Polyomavirus Nephropathy: A Validation Study in the Modern Era

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Background: The Banff multicenter working group on polyomavirus nephropathy (PVN) recently proposed a morphologic, clinically significant PVN classification scheme with three disease classes based on the histologic degree of intra-renal PV replication and the Banff-ci score. Transplant recipients with definitive PVN managed between 1996-2010 were analyzed (JASN 29: 680, 2018). Aim: To evaluate the validity of the proposed PVN classification in the modern transplant era.

Methods: 652 consecutive adult renal allograft recipients transplanted at UNC after 1/1/2009 were enrolled. In patients with definitive PVN, the first diagnostic biopsy (index biopsy) was scored and PVN classes defined. Clinical and histologic data were statistically analyzed following the Banff working group approach (JASN 29: 680, 2018). Biopsies with TCMR (type II/III), ABMR or other severe renal diseases were excluded from some analyses.

Results: PVN affected 57/652 patients (incidence 8.7%; 39 (68%) males; median age 54 years). 2/57 patients were excluded due to recurrent disease at time of index biopsy. PVN class I: 29/55 (53%), class II: 25/55 (45%), class III: 1/55 (2%; small case number in class III precluded further statistical analysis). Class I was diagnosed earlier (median 18 weeks post grafting) than class II (24 weeks). Baseline S-Cr levels before index biopsy were similar between class I and II: class I 1.4 mg/dl, class II 1.3 mg/dl, p=0.823. At index biopsy, class I compared to II had only a minor rise of S-Cr: median % change from baseline, 10% class I, 37% class II, p=0.004. Over 12-month follow-up, class I showed minimal increase in S-Cr levels compared to baseline (+0.2 mg/dl; median change) in contrast to class II (+0.6 mg/dl; p=0.003). In the study cohort, graft failure was rare: overall 3/55 (5%); class I: 2/29 (7%), class II: 1/25 (4%), class III: 0/1 (0%).

Conclusions: The histologic classification of PVN as proposed by the Banff working group also carries clinical significance in the modern era. PVN class I characterizes cases with stable graft function. Overall graft failure rates for this single site are lower (5%) than reported by the Banff working group (30%). The PVN disease classification provides additional clinical information, therefore it should be incorporated into diagnostic and scientific communications.

FR-OR136

Archetype Analysis Identifies Distinct Profiles in Renal Transplant Recipients with Transplant Glomerulopathy Associated with Allograft Survival

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Background: Transplant glomerulopathy (TG) is a common glomerular lesion observed after kidney transplantation and a well-known contributing factor for allograft loss. However, overlapping pathways, associated etiologies and clinical courses have not been addressed at a population level.

Methods: All consecutive kidney transplant recipients from 3 referral centers from France and 1 in Canada with a diagnosis of TG (Banff cg score≥1) in biopsies performed between January 2004 and January 2014 were included and assessed by light microscopy, immunohistochemistry, immunofluorescence and electron microscopy. All patients underwent circulating anti-HLA donor-specific antibodies testing at the time of TG diagnosis.

Results: Among the 8,207 post-transplant allograft biopsies performed during the inclusion period in the 4 centers, 552 presented with TG (incidence of 6.7%). The median time to TG diagnosis post-transplant was 33.18 months (IQR: 12.12 – 78.72 months). Kidney allograft survival rates after TG diagnosis were 69.4%, 57.1%, 43.3% and 25.5% at 3, 5, 7 and 10 years, respectively. Unsupervised learning method integrating clinical, functional, immunological and histological parameters revealed 5 TG archetypes characterized by distinct features, and associated etiologies. The 5 TG archetypes unraveled distinct allograft survival profiles with incremental 5-year allograft loss rates between archetypes (Fig 1).

Conclusions: A probabilistic data-driven archetypical approach applied in a large well defined multicentric cohort, refines the diagnostic and prognostic features associated with TG, reducting heterogeneity, which might help improving disease characterization and individual patient risk stratification, opening avenues for an archetype-based strategy for TG treatment.

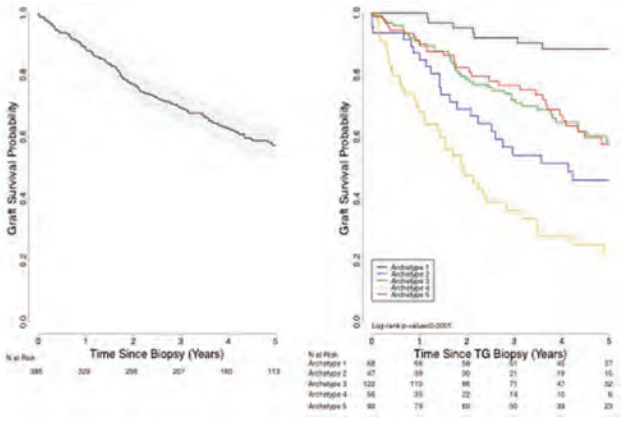

Figure 1: Kidney allograft survival after TG diagnosis overall (A) and archetype-based (B). The overall difference between the five archetypes was significant (p-value<0.0001).

FR-OR137

A Phase-I Clinical Trial of Donor-Derived MIC Cell Infusion for the Induction of Donor-Specific Hyporesponsiveness after Living Donor Kidney Transplantation (TOL-1 Study)

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Background: MIC cells are donor-derived monocytes that gain immunosuppressive properties after incubation with the proliferation inhibitor mitomycin C.

Methods: PBMCs were harvested from living donors by leukapheresis and MIC cells were manufactured under GMP conditions. Transplant recipients received either 1.5x10E6 MIC cells/kg body weight on day -2 (N=3,group A), 1.5x10E8 MIC cells/kg body weight on day -2 (N=3,group B) or day -7 (N=4,group C) before living donor kidney transplantation. Patients received immunosuppressive therapy with CyA,EC-MPS and CS. Primary outcome measure was the frequency of adverse events (AE) on day 30.

Results: A total of 72 AEs (3 severe AEs) occurred in treated patients that were unrelated to MIC cell infusion. No positive cross match results, de novo donor specific antibodies, or rejection episodes but 2 infectious complications were recorded. Median serum creatinine on day 30 was 1.4 mg/dL with no significant proteinuria. In vitro, MIC cells were capable of inducing tolerogenic dendritic cells with low expression of costimulatory molecules CD80, CD86 and a 30% increase of immunosuppressive molecule CD103. Beyond day 30 after surgery, serum creatinine remained stable (median 1.48 mg/dL on day 180) with no significant proteinuria (median 10 g/mol creatinine on day 180) and no rejection episodes. The patients from group C who received low-dose CyA and low-dose EC-MPS during the observation phase had no or only minimal reactivity against irradiated donor lymphocytes in mixed lymphocyte culture while reactivity against 3rd party lymphocytes was preserved. CD19+ B cells increased to a median of 300/µL until day 30 but decreased to a median of 35/µL on day 180.CD19+CD24highCD38high transitional Bregs increased from a median of 2% on day 30 to a median of 20% of the total CD19+ B cell pool on day 180. There was an increase in the plasma IL-10/TNFalpha ratio from a median of 0.05 before cell therapy to a median of 0.11 on day 180.

Conclusions: MIC cell therapy represents a promising option for individualized immunosuppression after living donor kidney transplantation.

FR-OR138

The Effect of Pulse Steroids/IVIG/Rituximab on Circulating Lymphocytes and Cytokines in Kidney Transplant Recipients with Chronic Active ABMR)

Nancy A. Wilson,[1] Natalie M. Bath,[1] Sarah E. Panzer,[2] Arjang Djamali,[3] Shannon Reese.[1] *[1]University of Wisconsin, Madison, WI; [2]University of Wisconsin Madison, Madison, WI; [3]School of Medicine and Public Health, Madison, WI*.

Background: There is no information on the effect of combination therapy with pulse steroids/IVIG/Rituximab on circulating T-cell and B-cell phenotypes and cytokines in kidney transplant recipients (KTR) with chronic active antibody mediated rejection (cABMR).

Methods: We examined this questions in 8 KTR with cABMR who underwent follow up evaluation with a repeat protocol biopsy within 3 months of the initial diagnosis. PBMC subsets were identified using flow cytometry. Plasma was analyzed using Luminex 45-plex assay for cytokines. Paired Wilcoxon rank sum test was utilized to assess the effect of therapy on pre and post samples. Pre-treatment samples were also compared to a group of 11 healthy volunteers matched for age, gender, and race.

Results: Median age at the diagnosis of cABMR was 48 years. The diagnosis was made at a median of 9.8 years post-transplant. Median Scr and urine PC at biopsy were 2.43 mg/dL and 1.24 g/g. Treatment with pulse steroids/IVIG/Rituximab was associated with a statistically significant decline in ptc and mvi Banff scores ($p<0.05$) at the three-month protocol biopsy. Similarly, B cells, Naïve B cells, plamablasts, and transitional B cells were significantly reduced ($p<0.05$ for all). However, treatment was associated with a significant increase in CD3 T cells and IL17 levels ($p=0.02$ for both). There was no significant difference in other Banff scores, kidney function, and Treg or Breg populations. Compared to controls, KTR had significantly lower naïve B cells, plasmablasts, and transitional B cells, while cirtculating fractaline, IL1-alpha, IL7, IL13, IL15, PDL1, and VEGF levels were significantly increased ($p<0.04$ for all).

Conclusions: In conclusion, KTR with ABMR have significantly different circulating B cell and cytokine profiles than healthy volunteers. Short term therapy with Pulse steroids/IVIG/Rituximab effectively inhibits disease activity in cABMR. However, treatment is associated with an upregulation of T cell response suggesting a negative feedback role for B cells in cABMR.

FR-OR139

G2/M Cycle Arrest in Human Transplanted Kidneys Correlates to Fibrosis, Functional Decline, and Graft Loss

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Background: Kidney transplantation (KTx) is the only curative treatment of end-stage renal failure. However, some KTx recipients suffer from long-term graft loss associated with interstitial fibrosis and tubular atrophy (IF/TA), especially after delayed graft function (DGF) due to acute tubular injury (ATI). Maladaptive repair, characterized by G2/M arrested tubular cells, has emerged as a key mediator of IF/TA after ATI in animal experiments, although little is known about its role in human kidney fibrosis. In this retrospective study, we studied the relation between G2/M cell cycle arrest in tubular cells in biopsies and histological and functional outcome of kidney allografts.

Methods: We included 64 patients, of which 32 presented with DGF and 32 with early graft function (EGF). Surveillance biopsies taken at 3 months after KTx were evaluated for G2/M cell cycle arrest by staining for the G2/M marker pHH3 and the proliferation marker Ki67. ATI was quantified morphologically in the indication biopsies taken approximately 7 days after KTx in the DGF group. Renal outcome was evaluated by fibrosis 2 years after KTx (Remuzzi score), kidney function decline in 2 years (CKD-epi), and 10-year death-censored graft survival.

Results: At 3 months after KTx, DGF kidneys had more G2/M arrested cells (median 1.17 cells/mm2 [0.0-3.8] vs median 0.6 cells/mm2 [0.0-1.8]; $p<0.05$) and the number of arrested cells/mm2 correlated to acute histological damage in the 7 day biopsy ($\rho=-0.78$ $p<0.0005$), to histological severity of fibrosis in biopsies taken 2 years after transplantation ($\rho=0.52$, $p<0.01$), and to functional decline over these 2 years ($\rho = -0.44$, $p<0.01$). Finally, the amount of G2/M arrested cells was associated with a higher risk of 10- year death-censored graft survival (univariate cox regression, HR=3.98, $p<0.01$).

Conclusions: Our data suggest that in the regenerative response following ATI damaged cells in kidney allografts can get arrested in G2/M and subsequently contribute to progressive IF/TA, functional decline and eventually graft loss.

Funding: Commercial Support - Astellas Pharma inc.

FR-OR140

Clinical Utilization of Donor-Derived Cell-Free DNA (AlloSure) for Monitoring Kidney Transplants: The Colorado Experience

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Background: Cell-free DNA is released by cellular apoptosis or damage. Donor-derived cell-free DNA (dd-cfDNA) released from kidney allografts can be differentiated from recipient cfDNA and correlates with graft injury due to rejection. Dd-cf-DNA may be an effective biomarker for monitoring immunologic risk and damage in kidney transplants. We recently implemented dd-cfDNA surveillance in all eligible kidney transplant recipients within three years of transplant at our center. Here we present our early experience.

Methods: All eligible kidney transplant recipients within three years of transplant at our center were enrolled in the surveillance protocol. Blood samples for dd-cfDNA are collected at 1, 2, 3, 4, and 6months post-transplant and then quarterly for the first 3years. A dd-cfDNA proportion of >1.0% was considered positive based on published data. Management of positive results were left to clinical discretion. Patients also undergo surveillance biopsy at 3 months post-transplant per our institutional protocol.

Results: In the first four months of the protocol, 394 samples have been collected from 256 patients. The dd-cfDNA was negative (<1.0%) in 95.2% (n=375) of samples analyzed. Nineteen samples from 18 patients were positive (>1.0%) with 13 patients undergoing subsequent biopsy. Six biopsies (46.2%) were confirmed diagnosis of rejection (2 with clinical rejection, 4 with subclinical rejection). Seven biopsies were not diagnostic of rejection (3 with no pathologic abnormality, 1 with ATN, 1 with glomerular disease, 1 with moderate glomerulitis, 1 with borderline cellular rejection). Twelve patients have had dd-cfDNA monitoring (a total of 22 samples, all <1.0%) and 3-month surveillance biopsies. Biopsies demonstrated no pathologic abnormality in 11 of 12 surveillance biopsies (91.7%).

One biopsy had moderate peritubular capillaritis, moderate glomerulitis, and negative staining for C4d. The patient has stable graft function and no DSA.

Conclusions: To our knowledge, this is the largest published series to date using dd-cfDNA to monitor immunologic risk in kidney transplant recipients. A positive dd-cfDNA (>1.0%) had a PPV of 46.2% for biopsy-proven acute rejection, and importantly, 4 out of 6 of these cases were subclinical. A negative dd-cfDNA (<1.0%) had a NPV of 91.7% on 3-month surveillance biopsies.

Funding: Commercial Support - CareDx

FR-OR141

Gene Expression Profiles of Post-Transplant Glomerular Disease

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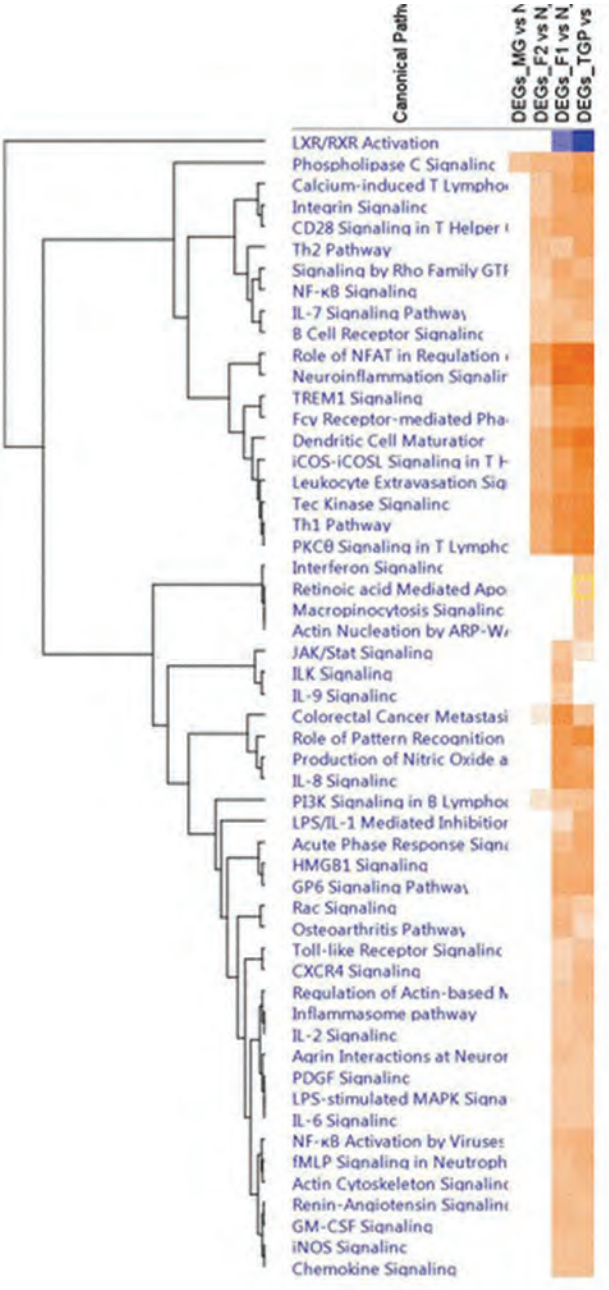
Background: Intragraft gene expression profiles of glomerular disease after kidney transplantation has not been well described other than transplant glomerulopathy (TG) which develops due to chronic rejection. We aimed to evaluate intragraft gene expression profiles of post-transplant glomerular disease including membranous glomerulopathy (MG), secondary or primary focal segmental glomerulosclerosis (FSGS), comparing to normal and TG biopsies.

Methods: The gene expression profiles of the 83 kidney biopsy specimens were studied by Affymetrix HuGene 1.0 ST expression arrays. TG (n=33), MG (n=10), secondary/late FSGS (n=16), and primary FSGS (n=6) were compared to normal transplant kidney biopsies (n=16).

Results: Gene Ontology analysis showed that all 4 glomerular disease groups had increased expression of gene transcripts related to activation, regulation, and differentiation of T cells, B cells, leukocytes, cytokines, chemokines, chemotaxis, and immune response compared to normal biopsies. Ingenuity Pathways Analysis demonstrated majorly overlapping differentially expressed genes between different comparisons indicating majorly common pathways and gene expression (Figure). Comparing canonical pathways the MG was least aggressive in terms of gene expression differences, followed by the secondary/late FSGS when compared to normal allografts. Primary FSGS and TG had the most differentially expressed genes, with most of them involved in inflammatory pathways and immune response. ILK signaling pathway and IL9 signaling pathway were uniquely activated in primary FSGS. All 4 groups demonstrated increased interferon gamma and rejection, cytotoxic T cell and macrophage associated pathogenesis based transcript expression.

Conclusions: Post-transplant glomerular disease including MG and FSGS had intragraft gene transcripts associated with increased immune activity similar to rejection and share overlapping gene transcripts with TG.



SA-OR001

Frailty and Age Disparities in Access to Kidney Transplantation

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Background: Older age is a known barrier to kidney transplantation (KT). One mechanism to explain age disparities is frailty, a decreased physiologic response to stressors associated with poor outcomes after KT.

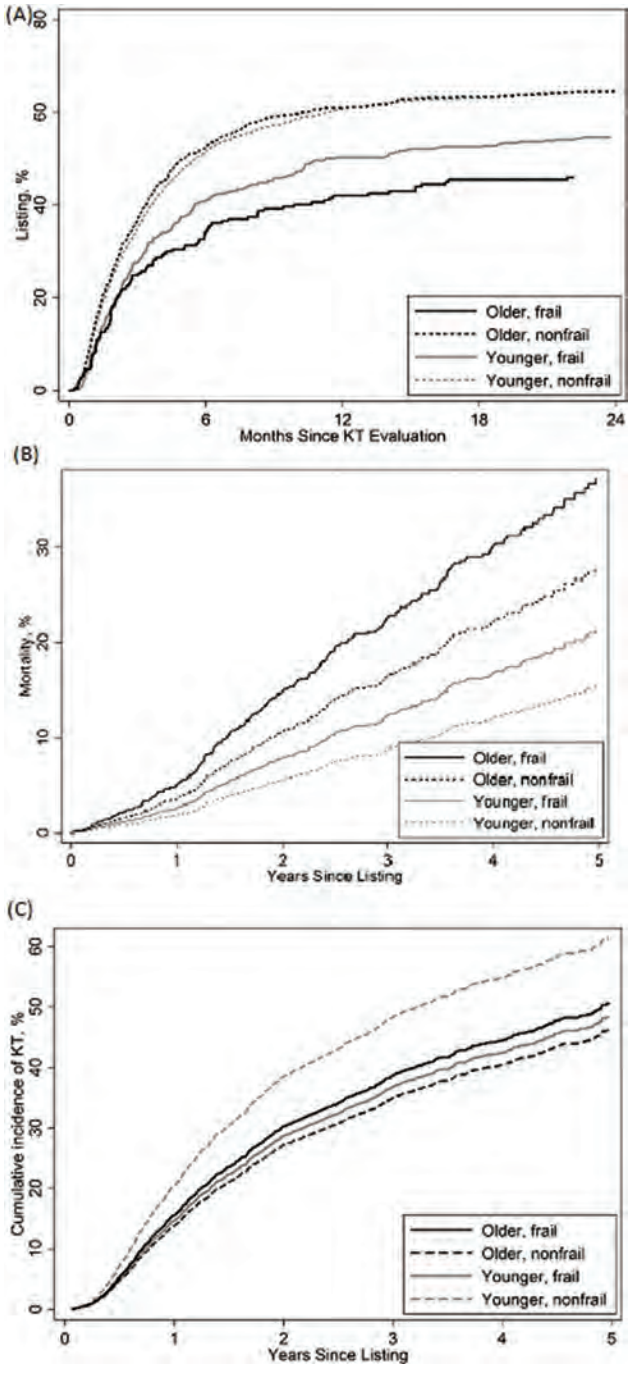
Methods: We studied 3,548 KT candidates (2009-2017) in a multi-center cohort study of frailty. We estimated time to listing, waitlist mortality, and transplant rate using Cox proportional hazards, competing risks, and Poisson regression.

Results: The association between KT listing and candidate age varied by frailty status (interaction p=0.03): Older (age≥65) frail candidates were 27% less likely to be listed compared to older nonfrail candidates (aHR:0.73,95%CI:0.59-0.92,p<0.01), whereas younger (age:18-64) frail candidates were 23% less likely to be listed for KT (aHR:0.77,95%CI:0.68-0.88,p<0.001) (Figure 1A). Both older (aSHR:1.97,95%CI:1.54-2.53,p<0.001) and frail (aSHR:1.38,95%CI:1.05-1.83, p=0.02) KT candidates had higher waitlist mortality; but there was no synergistic effect (interaction p=0.12) (Figure 1B). The association between candidate age and transplant rate differed by frailty status (interaction

p=0.02): younger frail KT candidates were transplanted less frequently than younger nonfrail candidates (aIRR:0.68,95%CI:0.55-0.83,p<0.001). However, older frail KT candidates had similar transplant rates to older nonfrail candidates (aIRR:1.12,95%CI0.78-1.61,p=0.5) (Figure 1C).

Conclusions: The synergistic effect of older age and frailty is associated with a lower chance of listing, but not seen in older frail candidates with regards to waitlist mortality. Frailty assessment at KT evaluation can help guide patient counseling for candidates all of all ages, and prehabilitation strategies to improve pre-KT outcomes.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, F32AG053025, R01AG055781



SA-OR002

Identification of Factors That Explain Racial Disparities during the Evaluation Process for Kidney Transplantation

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Background: Racial disparities between blacks and white patients are observed in evaluation completion rates, a step required for kidney transplantation (KT) listing. However, the role of patient-level demographics and medical comorbidities as explanatory factors for these disparities is unclear. We compared the risk of listing in black versus white adults referred to clinic for KT evaluation and identified whether the association of socio-economic factors and medical co-morbidities account for racial disparities in listing for KT.

Methods: As part of a prospective multi-center cohort study of aging and ESRD, 3,540 black and white candidates were enrolled at evaluation for KT (1/2009-12/2017). Self-reported demographic data, education, income, employment, and frailty status was collected at time of first evaluation. Medical comorbidities were ascertained from self-report and chart review. Time to listing in the first year was our primary outcome. We used multivariate Cox proportional hazard models to estimate incidence for listing and the association of patient-level factors between black and white participants. Mediation analysis was performed using percent reduction in beta coefficient for race in expanded model versus a base model, adjusted for age and sex.

Results: Among 3,540 participants, the mean age was 54.7 years (sd=13.5) with 41.2% female and 49.2% self-reported black race. Overall, 1,930 patients were listed for KT in the first year. Likelihood of listing was lower for blacks compared with whites (HR=0.77, 95% CI:0.70-0.84) after adjusting for age and gender. Racial differences in listing rates were partially explained by socio-economic factors (% reduction in beta coefficient, 38.5%) and partially explained by medical co-morbidity (% reduction in beta coefficient, 35.6%). After accounting for age, gender, patient-level socioeconomic factors, and medical comorbidity, disparity by race persisted (adjusted HR 0.89, 95% CI 0.81-0.98, % reduction in beta 47.6%).

Conclusions: Racial disparities during the listing stage of KT are partly explained by differences in patient-level socio-economic factors and medical comorbidity. Higher socio-economic status may indicate greater personal resources to navigate the transplant process and could direct future intervention.

Funding: Other NIH Support - NIA, 2T32-HL00718041A

SA-OR003

Exploring the Viability of Kidneys Discarded in the US: A Comparison of Kidney Utilization Patterns and Outcomes in the US and France

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Background: Approximately 2,000 donated kidneys are discarded in the US each year. Some transplant leaders have questioned the viability of these lost organs, while others suggest instead that allocation inefficiencies or risk-aversion due to center report cards are responsible for the high discard rates. However, few studies have examined whether kidneys discarded in the US might be transplanted with acceptable outcomes in other countries.

Methods: Using UNOS registry and the Paris Transplant Group prospective cohort data from 2004 – 2014, we compared kidney quality and outcomes between the US and France.

Results: During this period, 125,936 kidneys in the US and 4,287 kidneys in the Paris Transplant Group cohort were procured for transplant. As shown in the upper panel, a much higher proportion of transplanted French kidneys were higher-risk organs (as measured by the kidney donor profile index, KDPI) compared to the US (median 65 [39-90] vs 42 [19-67] in the US, p<0.0001). During the decade, the KDPI of US kidneys only increased modestly (from a mean KDPI of 42 to 44), while in France, a steadily rising KDPI (from a mean KDPI of 54 to 67) reflected a trend of more aggressive organ use. We used the Kaplan-Meier method to estimate death-censored graft survival for higher-KDPI kidneys transplanted in France. Three and five-year survival for KDPI 80 – 90 kidneys was 88 and 83%, for KDPI 91-99 kidneys was 83 and 79% and for KDPI 100 was 81 and 78%. Finally, we fit a logistic regression model to predict kidney discard in the US (AUC 0.80) and estimated the probability that kidneys transplanted in France would have been discarded if instead allocated in the US. Many transplanted French kidneys would have had a high probability of discard in the US system. Using 951 transplanted kidneys in France randomly selected according to their probability of being discarded in the US, we calculated that the use of those kidneys in the US would have translated to a 3,000 allograft life-years saved.

Conclusions: In summary, these results provide fresh evidence that some kidneys discarded in the US are a lost opportunity that could have benefitted some wait-listed patients.

SA-OR004

Clinical Utility and Interpretation of CKD Stages in Living Kidney Donors

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Background: Current definitions of chronic kidney disease (CKD) staging define any individual with estimated glomerular filtration rate (eGFR)<60 as having stage 3 or higher CKD. Nearly half of living kidney donors (LKDs) have post-donation eGFR below this threshold, but the clinical interpretation of eGFR<60 in donors is unknown, and the "CKD" label may not be appropriate. Evidence of risk associated with decreased post-donation eGFR is needed to inform international guidelines and best practices for donor followup and care management.

Methods: Using national registry data, we studied end-stage renal disease (ESRD) risk in 67,571 LKDs 1999-2015 with at least one reported postdonation serum creatinine

(SCr). eGFR was calculated via the CKD-EPI equation. Measurements with eGFR<15 were excluded from analysis. We modeled the association between eGFR category (≥60, 45-59, 30-44, 15-30, corresponding to no CKD, CKD stage 3, stage 4A, and stage 4B) using Cox regression with eGFR category as a time-varying exposure and adjusting for donor age, sex, race (black vs nonblack), BMI, and 1st-degree biological relationship to recipient.

Results: 117,051 CKD measurements were reported at median (IQR) 11 (4-14) months post-donation (90th percentile 25m post-donation). Of these, 33.9% were in the range 45-59, 5.7% were in the range 30-45, and 0.8% were in the range 15-29. Lower eGFR categories were associated with greater ESRD risk: 5-fold higher risk for eGFR 30-45 (aHR = 5.3 (2.1-13.3)) and 54-fold higher risk for eGFR 15-29 (aHR=53.7 (4.8-421.3); both p<0.001). Donors with eGFR 45-60 had elevated risk but the association was not statistically significant (aHR=1.9 (0.9-3.8), p=0.08).

Conclusions: There is insufficient evidence to support the category eGFR 45-60 as clinically meaningful "CKD stage 3" among LKDs. Nevertheless, eGFR category is associated with ESRD risk among donors with eGFR<45, and our results support current guidelines recommending longitudinal followup of renal function in living kidney donors.

Funding: NIDDK Support

eGFR range	Unadjusted HR (ESRD)	Adjusted HR (ESRD)
≥60	Reference	Reference
45-59	0.81 **1.50** 2.79	0.92 **1.86** 3.77
30-44	1.80 **3.94** 8.60	2.11 **5.30** 13.26
15-29	5.41 **40.29** 299.77	6.83 **53.66** 421.33

SA-OR005

Variation in Access to Transplant Referral and Evaluation Start among Dialysis Facilities

Laura J. McPherson,[1] Derek Dubay,[3] Matthew J. Ellis,[4] Heather Jones,[9] Carlos F. Zayas,[2] Laura L. Mulloy,[5] Brenda B. Thrasher,[8] Joseph A. Gulotta,[6] Shannon Wright,[7] Reem Hamoda,[1] Stephen O. Pastan,[1] Rachel E. Patzer.[1] on behalf of the Southeastern Kidney Transplant Coalition *[1]Emory University School of Medicine, Atlanta, GA; [2]Augusta University (MCG) School of Medicine, Augusta, GA; [3]Medical University of South Carolina, Charleston, SC; [4]Duke University Medical Center, Durham, NC; [5]Medical College of Georgia, Augusta, GA; [6]IPRO, Lake Success, NY; [7]IPRO ESRD Network of the South Atlantic, Morrisville, NC; [8]Carolinas Medical Center, Charlotte, NC; [9]Vidant Medical Center, Greenville, NC.*

Background: Variation exists in transplant access across US dialysis facilities. However, little is known about the proportion of end-stage renal disease (ESRD) patients who initiate or complete transplant steps prior to waitlisting. We describe dialysis facility-level variation in referral and evaluation start among dialysis facilities in ESRD Network 6 using our regional pre-transplant data registry.

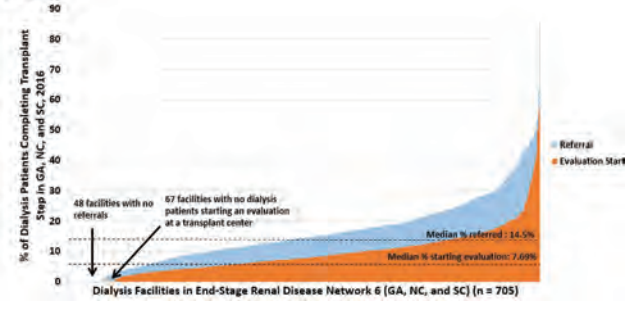
Methods: In collaboration with the community-based Southeastern Kidney Transplant Coalition, patient-level data from all 9 transplant centers in ESRD Network 6 (GA, NC, and SC) on kidney transplant referral (date referral form was received by transplant center) and evaluation start (date patient started evaluation) were collected from January 1, 2012 to December 31, 2016. Referral and evaluation start data were linked with ESRD Network data, including prevalent patients by dialysis facility and year, to calculate the proportion of patients referred and starting evaluation.

Results: Among 47,804 prevalent dialysis patients from all ESRD Network 6 dialysis facilities in 2016 (n=705) with a median of 60 patients/facility, approximately 16.1% (n=7717) were referred for evaluation and 9.2% (n=4406) started an evaluation. The median proportion of patients referred in 2016 was 14.5% (IQR: 8.9-21.2%), with 48 facilities not referring any patients (Figure 1). The median proportion of patients starting an evaluation in 2016 was 7.7% (IQR: 4.2-12.2%); 67 facilities had no patients start evaluation in 2016.

Conclusions: In the Southeastern United States, a small proportion of dialysis patients are referred for kidney transplant evaluation, and fewer start the evaluation at a transplant center. There is considerable variation in the proportion of patients referred and starting evaluation across dialysis facilities in ESRD Network 6. Interventions targeting these early steps in the kidney transplant process could improve equitability in transplant.

Funding: NIDDK Support

Figure 1.



SA-OR006

Favorable Cardiac Remodeling Following Ligation of Arteriovenous Fistula in Stable Renal Transplant Recipients: A Randomized Controlled Study

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Background: Cardiovascular morbidity and mortality remains high in recipients of kidney transplantation. Persistence of a functional arteriovenous fistula (AVF) post-transplant may contribute to maladaptive cardiovascular remodeling. In this study we aimed to determine whether ligation of AVF would improve myocardial mass in stable kidney transplant recipients, assessed at baseline and 6 months after closure using cardiac magnetic resonance imaging (CMR).

Methods: We recruited 63 adult kidney transplant recipients with stable kidney function and functioning AVF. Participants were randomly assigned to AVF ligation versus no intervention, after a baseline CMR scan followed by a repeat scan six months following AVF ligation. Primary outcome was assessment of left ventricular(LV) mass at 6 months. Secondary outcomes were changes in left and right ventricular volumes, pulmonary flows, left and right atrial areas.

Results: Of the 93 participants assessed for eligibility, 63 eligible participants underwent randomisation: 32 to the intervention and 31 to non-intervention. 54 out of 63 participants completed the study. At the end of 6 months, a decrease of 21.6 gm (95% CI -32.1to -11.0, p<0.001) was observed between the mean LV mass in the AV fistula closure group compared to no significant change in the non-intervention control group. The difference in LV mass index (gm/m^2) was a drop by 11.7 gm (95 % CI -17.2 - -6.1, p<0.001) in the intervention group from the baseline versus no change in the control group. Decrease in LV end diastolic volume, LV end systolic volume, right ventricular and bi-atrial volumes were also observed in the AVF closure group. No significant complications were noted after AVF ligation.

Conclusions: Elective ligation of AVF in adults with stable kidney transplantation and functioning AVF is associated with marked reduction in both absolute and indexed measurements of myocardial mass. (Funded by the Royal Adelaide Hospital Research Foundation grant; Australian and New Zealand clinical trials registry, number ACTRN12613001302741)

Funding: Private Foundation Support

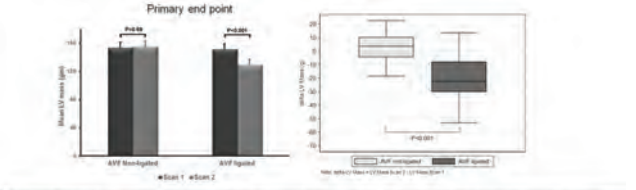

Figure 1. (a) Difference in absolute LV mass between the groups (b) Difference (delta) in the LV mass between the two scans in each group

SA-OR007

Gut Microbiota Dysbiosis Is a Novel Risk Factor for Urinary Tract Infections in Kidney Transplant Recipients

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Background: The gut is the presumed source of urinary tract infection (UTI) but direct evidence for this supposition is lacking.

Methods: We recruited 169 kidney transplant recipients for serial collection of fecal specimens and profiled 516 fecal specimens using 16S rRNA gene deep sequencing of the V4-V5 hypervariable region. Among the cohort, 36 subjects developed *Escherichia* bacteriuria within the first 6 months of transplantation (*Escherichia* Group) and 133 subjects did not (No *Escherichia* Group); 36 subjects developed *Enterococcus* bacteriuria (*Enterococcus* Group) and 133 subjects did not (No *Enterococcus* Group).

Results: The relative gut abundance of *Escherichia* was significantly higher in the fecal specimens in the *Escherichia* Group than in those in the No *Escherichia* Group (P<0.001, Wilcoxon rank sum test) (Fig 1A) and the relative gut abundance of *Enterococcus* was significantly higher in the fecal specimens in the *Enterococcus* Group than in those in the No *Enterococcus* Group (P<0.001) (Fig 1B). Using a Cox Regression with gut abundance as a time-dependent covariate, a relative gut abundance of 1% *Escherichia* was a risk factor for future development of *Escherichia* bacteriuria (HR= 3.2, P<0.001), and a relative gut abundance of 1% *Enterococcus* was a risk factor for future development of *Enterococcus* bacteriuria (HR = 2.6, P= 0.006). Strain analysis of the *Escherichia coli* in paired urine-fecal specimens using shotgun metagenomic sequencing revealed that the *E. coli* strain in the urine specimens was most similar to the *E. coli* strain in the fecal specimens from the same subject, supporting the gut as the source of the urine strain (Fig 1C).

Conclusions: Our findings support the hypothesis that gut microbial composition is a contributor to UTI in kidney transplant recipients. Modulating the gut microbiota may be a novel and effective strategy for preventing this frequent complication.

Funding: Other NIH Support - NIAID

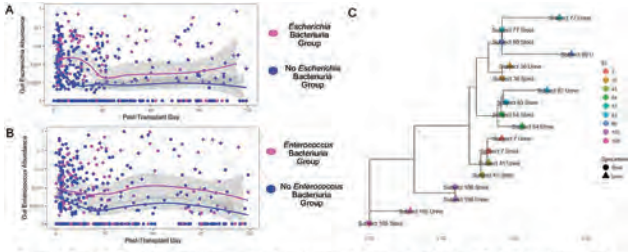

Figure 1. Panel A. Each point represents a fecal specimen with the gut abundance of *Escherichia* (y axis) and time in days after transplantation (x axis). Panel B. Each point represents a fecal specimen with the gut abundance of *Enterococcus* (y axis) and time in days after transplantation (x axis). Panel C. Consensus strains for *Escherichia coli* were constructed using Strainphlan and a phylogenetic tree was constructed based on these strains. *E. coli* in the urine specimens was most similar to *E. coli* in the fecal specimens from the same subject.

SA-OR008

Association of Recipient APOL1 Kidney Risk Alleles and Hepatitis C Status with Kidney Transplant Outcomes

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Background: African-Americans (AA) are more likely to have worse kidney transplant outcomes compared to non-AA transplant recipients. The mechanism is unknown but the *APOL1* risk alleles (RA) have been postulated as likely contributors. Given the high prevalence of *APOL1* RA in AA a two-hit theory has been embraced. We examined the outcomes of kidney transplant recipients (KTR) stratified by *APOL1* RA and hepatitis C virus (HCV) antibody status.

Methods: We conducted a multicenter observational prospective study of incident KTR. Incident KTR were genotyped for *APOL1* RA. Baseline characteristics and graft survival rates were compared by number of *APOL1* RA and/or by HCV antibody presence.

Results: Among 221 participants, approximately 43% had 2 *APOL1* RA. The prevalence of HCV antibody in the cohort was 17%. KTR with 2 *APOL1* RA were younger compared to those with none or one *APOL1* RA [51.8 vs 42.2 years old, P<0.0001]. Two *APOL1* RA was associated with early (prior to 1500 days) [1.98 (95% CI 1.01-3.85); P=0.045], but not late graft failure (up to 2000 days) [HR 1.39 (95% CI 0.79-2.45); P=0.25] adjusted for acute rejection and age at transplant. However, recipients with both two *APOL1* RA and HCV antibodies demonstrated lower graft survival compared to recipients with only one or none of those risk factors. [HR 2.74(95%CI 1.06-7.10); P=0.04].

Conclusions: Our study demonstrates the effect of *APOL1* risk status in KTR on graft survival. Furthermore, it illustrates that the effect of recipient *APOL1* RA on graft outcome may be altered by viral infections such as HCV and is likely time dependent.

Funding: NIDDK Support

SA-OR009

Characteristics and Outcomes of Deceased Donor Kidney Transplants Performed in the US Based on Donor HCV NAT and Recipient HCV Ab Status

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Background: HCV nucleic acid testing (NAT) testing for deceased donors has become routine since April 2014. Comparative outcomes of deceased donor renal transplants (DDRT) based on HCV NAT and antibody (Ab) testing in different donor-recipient pairs are not well known.

Methods: We queried the UNOS dataset for DDRT performed between April 2015 and September 2017. Pediatric age, multiorgan transplants, and cases with unknown HCV NAT / Ab status were excluded. The final study cohort (N=27,930) were stratified into 4 groups: 1) Donor (D) Ab-/NAT- Recipient (R) Ab- (reference group, n=27,070); 2) D Ab+/ NAT- R Ab- (n=133); 3) D Ab+ / NAT+ R Ab- (n=65); 4) D Ab+/NAT+ R Ab+ (n=662). A propensity score was calculated based on donor KDPI, recipient age, race, and underlying kidney diagnosis. An exact propensity score matching was performed 1:4 ratio between the reference group and other 3 stratified groups. Primary outcomes were overall allograft survival (failure defined as death or graft failure), acute rejection at 1 year and DGF.

Results: The results are shown in Table 1.

Conclusions: HCV NAT + kidneys do have similar outcomes compared to NAT negative donors. Utilization of HCV NAT + kidneys should be encouraged.

Characteristics and outcomes of DDRT based on HCV NAT and Ab testing

	DAb-/NAT-RAb-N=20,070	DAb+/NAT-RAb-N=133	D Ab+/NAT+ RAb-N=65	D Ab+/NAT+ RAb+ N=662	P-value 4-way
Donor age, mean(SD)	38.8 ±15.8	36.7±11.7	32.4±8.6	32.6±8.2	<.001
Donor gender, male %	61.4	48.9	61.5	67.8	<.001
Donor race, White %	67.6	90.2	92.3	84.3	<.001
DCD donor %	21.2	16.5	7.7	8.2	<.001
ECD donor, %	13.5	6	0	1.5	<.001
KDPI, %	47±26	57±19	49±15	49±16	<.001
Recipient age, mean (SD)	518±13.5	57.8±10.8	60.1±7.5	59.8±7.7	<.001
Recipient gender, male %	61.4	48.9	61.5	67.8	<.001
Recipient race, White %	36.8	37.6	47.7	26.1	<.001
ESRD diagnosis, DM %	26	33.8	36.9	39.4	<.001
Dialysis duration>3 yr, %	70.3	68.4	14.3	41	<.001
Transplant factors and outcomes					
CIT, hr	17.9±8.7	19.8±7.3	20.7±8.6	18.4±8	<.001
National allocation, %	16.3	60.2	55.4	48.8	<.001
Length of stay, days	6.4±7.2	6.1±5.1	6.4±5.7	6.1±4.9	<.001
HLA mismatch >3, %	71	81	73	83	<.001
Acute rejection at one-year, %	4.4	0	1.5	3.6	<.001
Propensity matched overall graft survival at one year, %	93.7	89.7	98.1	94	<.001
DGF, %	28.7	17.3	23.1	18.9	<.001

SA-OR010

BK Virus Nephropathy: Characterization of an Interferon Signature and Identification of Risk Factors for Graft Failure

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Background: BK virus nephropathy(BKVN) is an important cause of allograft failure. Identification of its immune pathways may help design better therapeutics.

Methods: We measured urinary cell mRNAs in 53 BKVN patients and 43 patients with normal protocol biopsies. Among the 53 BKVN cases, 18 grafts failed within 3 years post diagnosis and none in the normal group. Levels of mRNA were measured using kinetic, quantitative polymerase-chain assays. We compared mRNA levels of 53 BKVN vs. 43 normal patients, and within BKVN group, the 18 BKVN with graft loss vs. 35 BKVN without graft loss.

Results: Among the transcripts quantified in a total of 96 renal graft recipients, urinary cell levels of 18S rRNA, IP-10 and MIG were significantly higher in the BKVN group vs. normal group (all P<0.0001)(Table 1). Of the 53 BKVN cases, 18 lost their grafts and they were more likely to have received a deceased-donor renal transplant(DDRT) (P=0.03) and a higher creatinine(SCr) at time of BKVN diagnosis (2.88+/-1.18 mg/dl vs. 1.96+/-0.69 mg/dl;P=0.005). Urinary cell levels of PAI-1 mRNA predicted graft failure(Figure 1). Multivariate analysis demonstrated that PAI-1 mRNA level (OR: 2.6;P= 0.005), biopsy SCr (OR: 9.1;P<0.001) and DDRT (OR: 8.3;P=0.01) were independent predictors of graft failure.

Conclusions: BKVN is associated with an inflammatory milieu characterized by an interferon signature. Urinary cell levels of the acute phase reactant PAI-1 offer a noninvasive means to predict graft failure after BKVN diagnosis.

	Control (N=43)	BKVN (N=53)	P Value
Age (mean+/-SD) (years)	53.98+/-10.22	54.74+/-15.03	0.63
Male, n (%)	27 (63%)	37 (70%)	0.47
Race			0.6
Non-African American, n (%)	27 (63%)	36 (68%)	
African American, n (%)	16 (37%)	17 (32%)	
Type of Transplant			0.05
Living-Donor Transplant (100%), n (%)	25 (56%)	20 (44%)	
Deceased-Donor Transplant (100%), n (%)	18 (35%)	33 (65%)	
Creatinine at Biopsy (median) (mg/dl)	1.4	2	<0.0001
Gene Expression Data			
18S (median) (copies/ug of RNA)	1.24E+09	4.51E+09	<0.0001
Ln(CD3:18S) (median)	0.477	0.0138	0.45
Ln(IP10:18S) (median)	-0.828	0.978	<0.0001
Ln(MIG:18S) (median)	-0.476	1.34	<0.0001
Ln(FOXP3:18S) (median)	-3.41	-3.606	0.71
Ln(TGFb1:18S) (median)	1.64	1.556	0.79
Ln(PAI1:18S) (median)	-0.0268	-0.3419	0.07

Table 1.

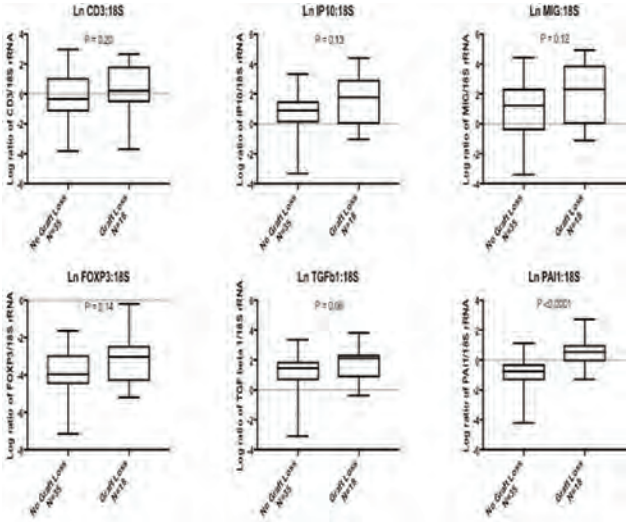

Figure 1.

SA-OR011

Alpha 2 Adrenergic Receptor Blockade Prevents AKI to CKD Transition

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Background: Increased sympathetic nerve activity and norepinephrine (NE) levels are of importance in the onset and the early development of end stage renal disease. We reported that renal denervation (DNx) can prevent renal fibrosis and inflammation in renal fibrogenesis models. However, the underlying mechanism by which renal denervation prevents the long-term sequelae of acute kidney injury (AKI) remains to be elucidated.

Methods: Based on our data, we hypothesized that NE mediates its effect through activation of alpha 2 adrenergic receptors (α2ARs). In this study, we investigated whether genetic or pharmacological inhibition of α2ARs prevents ischemia/reperfusion injury (IRI)-induced CKD progression.

Results: IRI resulted in severe kidney fibrosis in medullary region over 2 weeks with tubular cast and atrophy and massive macrophage infiltration. Renal DNx and pharmacological inhibition of α2AR did not affect renal functional and histological damage in the acute phase of the IRI. However, renal tubular damage, inflammation, and fibrosis progression was suppressed 2 weeks post-IRI by renal DNx and pharmacological inhibition of α2AR with downregulation of downstream targets of NE-α2AR axis, including angiotensinogen, fibrogenic factors and inflammatory cytokines. Similar with results in pharmacological inhibition of α2A-AR subtype, blockage of α2C-AR subtype by pharmacological or genetic manipulation prevented the long-term sequelae of IRI, including renal tubular atrophy, inflammation and fibrosis progression.

Conclusions: Collectively, inhibition of α2AR subtypes prevents IRI-induced AKI to CKD transition through inhibition of persistent renal tubular injury and inflammation, and fibrosis progression, suggesting that targeting α2ARs may be a potential therapeutic strategy to prevent long-term sequelae of ischemic AKI.

Funding: Private Foundation Support

SA-OR012

Regeneration of Proximal Tubules after Severe Injury Depends on Clonal Proliferation of eR1-Active Subpopulation of Proximal Tubular Cells

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Background: Proximal tubular cells (PTC) are considered to repair injured proximal tubules by their own proliferation. However, whether this process depends on stochastic proliferation of surviving PTCs or expansion of a specific population of PTCs is still debated, and whether severity of injury affects the repair process is uncertain. In mammals, RUNX transcription factors are essential in diverse biological processes. Along with the elucidation of the roles of Runx1 in hematopoietic homeostasis and blood malignancies, a Runx1 enhancer named Runx1+24mCNE (eR1) has been identified recently, and shown to be active in adult long-term hematopoietic stem cells and gastric stem cells, but the role of eR1 in the kidney is unknown.

Methods: We first compared the proliferation of PTCs after 30- (moderate injury) and 60-min ischemia reperfusion injury (IRI) (severe injury) by bromodeoxyuridine (BrdU) labeling. We next explored the role of eR1 in kidney injury, utilizing eR1-ECFP and eR1-Cre^{ERT2} mice.

Results: As indicated by BrdU incorporation, PTCs of the superficial cortex were more proliferative in 60-min IRI than in 30-min IRI, whereas proliferation rate was comparative in the deep cortex. While ECFP$^+$ PTCs were almost absent in healthy kidneys of eR1-ECFP mice, ECFP$^+$ cells increased to about 20% of total PTCs in the superficial cortex after 60-min IRI, but not after 30-min IRI. Then, we subjected eR1-ECFP:eR1-Cre^{ERT2}:R26-tdTomato mice to 60-min IRI, and showed that ECFP$^+$ and tdTomato$^+$ PTCs mostly overlapped in acute phase even without tamoxifen. This result indicated that eR1-Cre^{ERT2} mice show leaky Cre^{ERT2} activity when eR1 was highly activated, and could be used to trace the fate of PTCs with strong eR1 activity. In acute phase of 60-min IRI, tdTomato$^+$ PTCs showed a higher rate of BrdU incorporation than other PTCs, and clustered with several tdTomato$^+$ PTCs. Clonal analysis using eR1-Cre^{ERT2}: R26-Confetti multicolor reporter mice revealed that clusters of PTCs were mostly labeled with a single color, indicating the clonal expansion of labeled cells. Notably, tdTomato$^+$ PTCs in acute phase were mostly positive for Kim-1 and vimentin, and negative for PTC markers such as aquaporin 1.

Conclusions: In severe injury, transiently dedifferentiated eR1-active PTCs clonally expand and repair superficial proximal tubules.

SA-OR013

Tubular HIF-1α Activates Macrophages via Exosomal MicroRNA-23a to Promote Tubulointerstitial Inflammation

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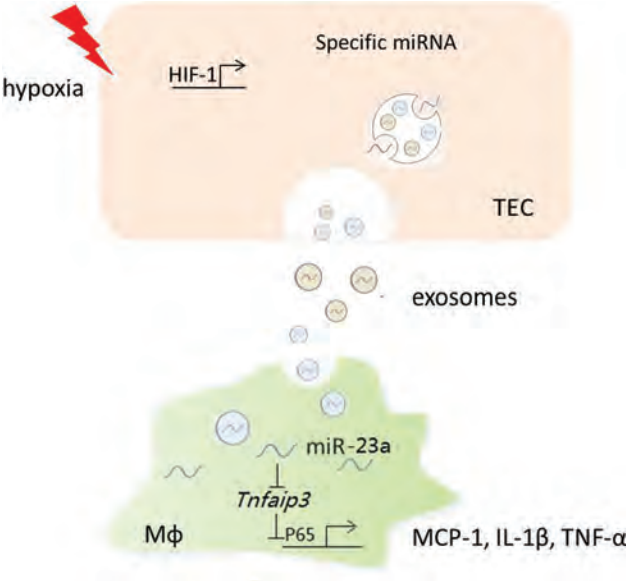
Background: Hypoxia is a key instigator of tubulointerstitial inflammation (TI) which has been assumed related with hypoxia inducible factor-1 (HIF-1), a master regulator response to hypoxia. While the exact mechanism of HIF-1 on this pathophysiological process is still largely unclear.

Methods: Hypoxia-related TI was induced in I/R injury and UUO models. Exosomes from hypoxic kidney and hypoxic TECs were isolated. The role of HIF-1 on miR-23a expression was studied using CHIP-PCR. Besides, exosomal miR-23a was inhibited or overexpressed to explore its functional role in macrophage. *In vivo*, TECs exosomes overexpressed or silenced miR-23a was transferred to mice via kidney parenchyma injection. Furthermore, treatment of miR-23a inhibitor in I/R model was also performed.

Results: TI was highly associated with the time-course expression of tubular HIF-1α in I/R injury and UUO mice. Meanwhile, the kidney exosomal miR-23a was markedly increased. *In vitro*, hypoxic TECs presented with higher HIF-1α and upregulation of NF-κB as well as exosomal miR-23a. HIF-1α could transcriptionally regulate miR-23a in exosomes. Exosome from hypoxic TECs could develop more severe macrophage activation compared to exosome from normal TECs. Furthermore, we demonstrated that exosomal miR-23a directly suppressed its target A20, leading to macrophage activation. Inhibition of miR-23a reversed macrophage activation. *In vivo*, TI was significantly increased when mice transferred with miR-23a enriched exosomes, which was not shown by miR-23a silenced exosomes. Furthermore, treatment of miR-23a inhibitor in I/R model could ameliorate TI significantly.

Conclusions: Our study firstly demonstrates that tubular HIF-1 regulated macrophage function via exosomal miR-23a to promote hypoxia-related TI. The finding provides a novel strategy to target HIF1α-miR-23a axis in preventing hypoxia induced kidney injury.

Funding: Government Support - Non-U.S.



SA-OR014

Arginase 1 Knockout Macrophages Fail to Promote Epithelial Proliferation and Impair Kidney Repair after AKI

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Background: Renal ischemic injury induces epithelial cell death which leads to an innate immune response that includes initial proinflammatory macrophage activation that promotes additional epithelial injury followed by alternative activation that is required for

kidney repair. Alternative activation is marked by the expression of several genes including arginase 1 (Arg1), mannose receptor (Mrc1) and macrophage scavenger receptor (Msr1), but the actual function of the protein products of these genes in the injured kidney is not known. This work addresses the role of Arg1 expression by reparative macrophages in kidney repair.

Methods: AKI model: Unilateral renal ischemia reperfusion with contralateral nephrectomy in $Arg1^{f/f}$;$LysMCre^{/+}$ (Arg1ko: knock-out of Arg1 in macrophages) and $Arg1^{+/+}$;$LysMCre^{/+}$ (Arg1con: control) mice. RNA was isolated either from whole kidney or from flow sorted macrophages (CD45+F4/80+). Gene expression profiling by qPCR. Immunohistology performed on paraffin embedded kidney sections.

Results: $Arg1^{ko}$ (n=8) and $Arg1^{Ctrl}$ (n=9) mice were therefore subjected to 27 minutes of unilateral IR with contralateral nephrectomy. The initial rise in creatinine on day 1 was equivalent in the 2 groups (1.55±0.05 and 1.61±0.05 mg/dl, p=ns). 85% of the control mice survived to day 7 after IR, whereas only 37% $Arg1^{ko}$ mice survived until day 7, with mortality observed on day 3. Renal macrophage expression of Arg1 on day 7 after IR is 0.755±0.484 in control mice but only 0.020±0.012 in $Arg1^{ko}$ mice (dCt relative to Hprt1, p=0.04). Quantification of F4/80+ cells in the kidney on day 3 revealed no difference in macrophage numbers between control and $Arg1^{ko}$ mice (298±83 vs. 315±17 F4/80+ cells/mm^2, p=ns), whereas tubular cell proliferation as determined by Ki67 positivity was significantly reduced in $Arg1^{ko}$ kidneys (343±86 vs. 110±33 Ki67+ cells/mm^2, p=0.03). Finally, morphometric analysis of day 7 kidney sections showed a pronounced loss of healthy tubular mass in $Arg1^{ko}$ kidneys compared to control kidneys (normal tubule/section: 34.2%±2.7 vs. 44.7%±0.5, p=0.004).

Conclusions: These results indicate that the upregulation of macrophage Arg1 expression facilitates tubular regeneration by promoting epithelial cell proliferation and limiting nephron loss at the site of injury.

Funding: Other NIH Support - NIH RO1-DK093771

SA-OR015

Tamm-Horsfall Protein (Uromodulin) Inhibits Systemic Oxidative Stress by Inactivating the TRPM2 Channel

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Background: Tamm-Horsfall protein (THP) is produced exclusively in the thick ascending limb (TAL) of the loop of Henley. In TAL cells, THP is secreted apically in the urine but also released basolaterally in the interstitium and circulation. We previously showed that THP downregulates inflammatory signaling in S3 proximal tubules. Here, we investigate potential targets of THP on these cells and the role of systemically released THP.

Methods: We used THP+/+ and THP -/- mice. Various assays and technologies as described in results

Results: We performed laser microdissection on S3 and TAL tubules for transcriptomic studies. Bioinformatic analysis determined that, in the setting of THP deficiency, JNK stress kinase signaling is activated in S3 segments but not in TAL. JNK activation uniquely in S3 segments was confirmed by 3D tissue cytometry. Additional proteomic studies on S3 segments and human proximal tubular cell suggested that THP inhibits oxidative stress and Rac-1 activity, both known to be upstream of JNK. This was confirmed in vivo using intravital imaging and other measures of oxidative stress. Furthermore, we observed that THP deficiency increased oxidative injury not only in the kidney, but also systemically and in distant organs, such as the lungs. Since TRPM2, a nonvoltage activated nonselective cationic channel, is implicated in regulating oxidative stress, we investigated if THP modulates its activity. Indeed, TRPM2 is expressed in the kidney, lungs and other organs. In HEK-293 recombinant cells with inducible TRPM2, we show that THP specifically inhibits TRPM2 dependent calcium influx in a dose dependent manner. Furthermore, pharmacological inhibition of TRPM2 in THP-/- mice reduced systemic oxidative damage.

Conclusions: We show that THP inhibits oxidative stress not only in the kidney but also systemically in other organs. This effect is likely mediated through the circulating form of THP. Our data suggest that this effect, in part, is due to inhibition of the TRPM2 channel, which in some tissue types, conditions and experimental models, is known to cause downstream oxidant injury. These findings underscore the importance of THP in mediating a systemic cross-talk between the kidney and other organs and identify, for the first time, a molecular target for circulating THP.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR016

Inhibition of Orai1-Mediated Ca2+ Signaling Ameliorates AKI-to-CKD Transition Following Ischemia and High Salt Diet

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Background: Store-operated Ca^{2+}entry (SOCE) through Orai1 channels raise intracellular Ca^{2+}concentrations in T cells, which induce proliferation and cytokine production in immune cells. The Orai-1 gene has been linked to SCID, and loss-of-function mutation of Orai-1 in murine T cells shown to be protective in models of autoimmune disease, due to impaired production of the cytokine IL-17. T-helper 17 (Th17) cells increase following renal injury and exposure to high-salt diet and IL-17 blockade reduces AKI-to-CKD progression. We have recently identified Orai-1 expression in AKI primed renal T cells and hypothesize that Orai1-mediated Ca^{2+}signaling may influence Th17 differentiation and modulate CKD progression.

Methods: Rats were allowed to recover from renal ischemia for 1 week and CD4+ lymphocytes were analyzed for $Ca^{2+}$and IL-17 responses in vitro. In other studies, rats were subjected to bilateral I/R and allowed to recover 24 hours with or without SOCE antagonist YM-58483 (1mg/kg). To study CKD progression, rats following unilateral ischemia were allowed to recover for 5 weeks 0.4% NaCl diet. CKD was hastened by Unx and elevated dietary NaCl (4%) for 4 weeks. In this study, rats were fed YM-58483 or vehicle daily during the high salt treatment.

Results: AKI primed CD4+ lymphocytes manifested an induction of IL-17 production in vitro to angiotensin II and 170 mMol/L Na^+while ~30% of cells manifested an increase in cytosolic Ca^{2+}; these responses were blocked by 10mM YM-58483. Rats treated with YM-58483 were protected from bilateral ischemia as indicated by lower serum creatinine (vehicle 3.3±0.4; YM-58483 2.2±0.5 mg/dl; p£0.05) and significantly reduced by ~40% Th17 infiltration. When post ischemic rats were exposed to 4% dietary salt, there was an increase in inflammatory cells and fibrosis. YM 58483 initiated during high salt feeding significantly attenuated renal CD4+, CD8+, B cells and dendritic/macrophage cells by ~50%. Th17 cells (CD4+/IL17+) were also reduced significantly (vehicle 19425±23086, YM-58483 6494±1146 cells/g; p£0.05). In addition, YM-58343 treatment also attenuated the development of interstitial fibrosis by ~86% relative to vehicle (p< 0.05).

Conclusions: Taken together, these data suggest that Orai1 activity is enhanced by renal ischemia and that Orai1-mediated Ca^{2+}signaling increases Th17 activity and AKI-CKD progression.

Funding: NIDDK Support

SA-OR017

Hepcidin Mitigates Sepsis-Induced AKI through Its Antibacterial and Anti-Inflammatory Effects

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Background: Sepsis-induced acute kidney injury (AKI) is a common cause of in-hospital morbidity and mortality. Sepsis induces hepcidin-dependent iron sequestration to limit iron availability to pathogens. Hepcidin can limit inflammation. Therefore, we investigated if hepcidin pretreatment would mitigate endotoxin- and peritonitis-induced systemic pathology and AKI.

Methods: C57BL/6 mice were treated with saline or 50 µg hepcidin, 24 hours before LPS injection (*Escherichia coli O111:B4*, 6.5 mg/kg) or subjected to Cecal ligation and puncture (CLP) to induce peritonitis. Some mice underwent splenectomy (SPLX) and were challenged with LPS, with and without Hepcidin. Mice undergoing CLP received another dose of hepcidin, 2 hours prior to CLP. Renal injury and inflammatory markers were assessed. After CLP, mice were euthanized at different time points. Mouse macrophages (J774A) were treated with SiRNA to H-ferritin or scramble, treated with 1µg/mL Hepcidin for 4 hours, and cultured with 1 ng/mL LPS for 6 hours.

Results: LPS-induced AKI (plasma creatinine, renal NGAL and KIM-1 gene expression) were significantly reduced by hepcidin pretreatment. Hepcidin also reduced LPS-induced renal Cox-2, loss in PGC1a and enzymatic activity of cytochrome c oxidase. Hepcidin induced higher splenic H-ferritin, reduced splenocytes apoptosis, and inflammation. SPLX reduced LPS-induced AKI, and hepcidin did not provide additional protection in these settings. In CLP model, Hepcidin significantly reduced bacteremia, AKI, and mortality (colony forming units in the blood, renal NGAL and KIM-1 gene expression) and increased survival (up to 6 days in hepcidin-treated mice compared to approximately 24 hrs in PBS-treated mice). Compared to scramble siRNA, H-ferritin-deficient macrophages treated with Hepcidin secreted more LPS-induced IL-6.

Conclusions: Our results demonstrate a protective role of hepcidin in endotoxin- and peritonitis-induced pathologies and AKI, exerted through H-ferritin-dependent anti-inflammatory effects, and antibacterial property. Splenectomy protects against LPS-induced AKI.

Funding: NIDDK Support

SA-OR018

TLR9 Mediated IL-17A Responses Are Associated with the Pathogenesis of Polymicrobial Septic AKI

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Background: Toll-like receptor 9 (TLR9) contributes to the development of polymicrobial septic AKI. Recently, interleukin (IL) -17A has been shown to play a pathogenic role in septic AKI. According to the previous study, TLR 9 mediated IL-17A responses were associated with the pathogenesis of many conditions, including murine hypersensitivity pneumonitis, mycobacteria-elicited pulmonary granuloma, and neurotoxicity induced by microglia. However, its role in septic AKI remains unclear. We hypothesized that TLR9-mediated IL-17A responses are associated with the pathogenesis of polymicrobial septic AKI.

Methods: Tlr9-knockout (Tlr9KO) mice and IL-17A knockout mice (IL-17AKO) and both wild type (WT) littermates were subjected to cecal ligation and puncture (CLP) operation to induce polymicrobial sepsis. We performed functional and pathological assessment of the kidney and splenic apoptosis evaluated by immunohistochemistry of caspase 3 at 18 hours after CLP. Survival were assessed for the following 7 days after CLP. We assessed IL-17A consentrations in plasma and ascites from Tlr9KO and WT mice at 3,

6, 18 hours after CLP by enzyme-linked immunosorbent assay (ELISA) also. Furthermore, we examined IL-17A production of immune cells in spleen by flow cytometry.

Results: Although WT mice developed kidney injury at 18 hours after CLP, Tlr9KO and IL-17AKO mice exhibited decreased serum creatinine levels, expression of Kidney Injury Molecule-1 in proximal tubular cells, and improved tubular damage score in cortex. Splenic apoptosis were decreased at 18 hours after CLP in both Tlr9KO and IL-17AKO mice compared with WT mice. Mortalities were less in both Tlr9KO and IL-17AKO mice compared with WT mice after CLP. Furthermore, IL-17 A levels of both plasma and ascites were significantly higher in WT mice than Tlr9KO mice at 18 hours after CLP, and IL-17A levels in ascites tended to increase in earlier phase than in plasma. IL-17A production of splenic γδ T cells was less in Tlr9KO mice compared to WT mice at 3 hours after CLP.

Conclusions: We showed that Tlr9KO and IL-17AKO could protect against polymicrobial septic AKI, and Tlr9KO mice decreased IL-17A secretion in plasma, ascites, and splenic γδ T cells. These findings suggest that TLR9 mediate IL-17A production, and this pathway is associated with the pathogenesis of septic AKI.

SA-OR019

Renal Ischemia Resistant Rat Strains and Ischemic Preconditioned (IPC) Kidneys Share Upregulated Mitochondria Proteins

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Background: Brown-Norway (BN) rats are resistant to renal ischemia reperfusion injury as compared to Sprague-Dawley (SD) or Dahl Salt Sensitive (DS) rats. This resistance is linked to 3 chromosomes in BN rats. Also IPC kidney mitochondria have significant changes in their proteome. The study goal was to identify mitochondria proteins that are over-expressed in both IPC and genetically resistant tissues. Quantitative proteomic analysis of mitochondria was performed in IPC kidneys and compared to sham conditioned kidneys. A second set of comparisons was performed on kidney cortex mitochondria isolated from BN rats and DS rats.

Methods: Mitochondria were isolated from renal cortex of BN rats, DS rats, IPC and IPC sham treated kidneys of SD rats. 4 animals were used for each group with 3 replicant samples. Mitochondria proteomes were identifed using label free quantitative proteomic analysis using LC-MS/MS. LS-MS/MS data were collected in Thermo Q Exactive Orbitrap High Field (HF) MS coupled to Dionex UltiMate 3000 RP HPLC system. Raw data were analyzed using MaxQuant and Andromeda search engines. Highest stringency conditions were used in protein identification in all searches. Proteins were identified by searching against the rat protein sequences database from Uniprot. Relative protein quantitation was performed using the MaxQuant LQF algorithm.

Results: Greater than 1300 proteins were identified in the sham versus IPC mitochondria, 571 proteins are significantly overexpressed in the IPC group (p values <0.05). In the proteomic comparison between BN and DS rats, 1184 proteins were identified with high confidence. Of the 1184 proteins 770 proteins were expressed 1.8-fold or greater in BN versus SS rats (p values <0.05). Comparing the two groups revealed 78 common proteins. Ingenuity pathway analysis revealed enhanced pathways that include response to drug, negative regulation of apoptosis, protein transport, metabolic processes and redox homeostasis.

Conclusions: 78 endogenous mitochondria proteins are significantly overexpressed in mitochondria from kidney cells in an ischemic preconditioned state or isolated from a rat strain with genetic resistance to ischemia. These proteins represent important targets for pharmacologic exploration to develop preventative agents for acute kidney injury.

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SA-OR020

Transcriptional Trajectories of Human Kidney Disease Progression

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Background: The molecular understanding of the transcriptional program determining the progression from acute to chronic kidney injury in humans is limited.

Methods: We performed RNAseq-based transcriptional profiling on protocol biopsies obtained from 42 kidney transplant recipients at 4 time points (before and after reperfusion, 3 and 12 months after transplantation) and we applied machine learning techniques to identify and group patient responses over time. Our previously described mouse model of ischemia/reperfusion injury was used for data validation.

Results: In the first hours after reperfusion all patients underwent a similar response characterized by a biphasic transcriptional program under the control of immediate early response genes. In the following months we identified two main transcriptional trajectories corresponding to recovery and to a sustained injury response leading to fibrosis and renal function deterioration. The molecular map generated by this computational approach delineated the transcriptional program determining the transition from acute to chronic kidney injury: genes associated with mitochondrial dysfunction, kidney injury/repair and innate immunity were followed by genes related to fibrosis and adaptive immunity. Moreover, the computational model highlighted early markers of kidney disease progression (e.g. EP300). The characterization of a similar process in mice showed evidence for substantial similarities in the response to kidney injury across species and expanded the relevance of the findings beyond kidney transplantation.

Conclusions: The integration of multiple transcriptomes from serial biopsies in advanced computational algorithms overcame the analytical hurdles related to interindividual variability and identified shared transcriptional elements of kidney disease progression. For the first time, this new concept allowed an unsupervised analysis of the molecular mechanisms of kidney disease in a clinical setting.

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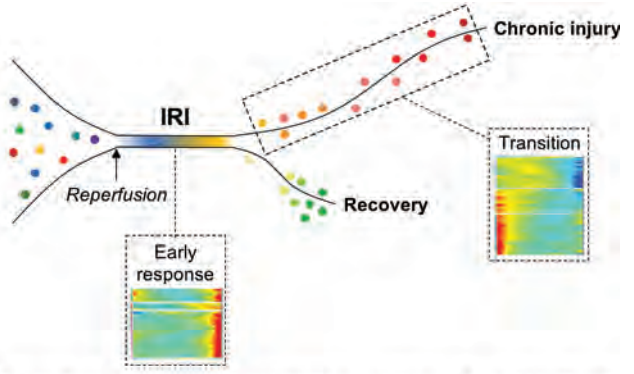

Conceptual summary. Computational analysis of transcriptional responses in kidney tissue from renal transplant patients identified common early injury outcome with divergent longer-term outcomes: recovery versus the initiation of a chronic injury signature.

SA-OR021

Decreased KAT5 Expression Impairs DNA Repair and Induces DNA Methylation in Diabetic Nephropathy Podocytes

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Background: Podocytes are terminally differentiated cells with a very low capacity of regeneration. Therefore, the mechanism of DNA damage repair in podocytes is expected to be highly significant. We have recently reported that podocyte specific deletion of DNA double strand break (DSB) repair factor KAT5 causes glomerulosclerosis in mice (KAT5 KO mice) (ASN Kidney week 2017). Here we investigated the role of KAT5 in the pathogenesis of diabetic nephropathy (DN).

Methods: We generated tamoxifen-inducible podocyte-specific KAT5 knockout mice (iKO) to investigate the physiological role of KAT5 excluding its role in the maturation of podocytes. Expression of KAT5 was examined in streptozotocin (STZ)-induced DN mice model and the effect of KAT5 gene transfer was evaluated. We performed in vitro studies using cultured human podocytes to examine the mechanism of KAT5-associated epigenetic changes.

Results: KAT5 iKO mice showed massive albuminuria (WT 40±9 mg/gCr, iKO 2455±153 mg/gCr, p<0.01) and FSGS lesion with foot process effacement of podocytes after 12 weeks induction of KAT5 knockdown, similar to the KAT5 KO mice. Nephrin expression was significantly decreased, as shown by both isolated podocytes and glomerular immunofluorescence staining. Interestingly, thickening of glomerular basement membrane was observed in some glomeruli of KAT5 iKO mice just like in DN, which was observed especially in the glomeruli near the corticomedullary junction. Podocyte KAT5 expression was decreased in DN mice, accompanied by increased DNA DSBs and DNA methylation and restoration of decreased KAT5 by gene transfer attenuated albuminuria and glomerulosclerosis. In cultured human podocytes, knockdown of KAT5 increased DNA DSBs and decreased nephrin expression with increased DNA methylation of the nephrin promoter region. High-glucose treatment (30mM) induced KAT5 reduction and overexpression of KAT5 increased nephrin expression with decreased DNA DSBs and decreased DNA methylation at the same nephrin promoter region, indicating that KAT5-mediated DNA repair may be related to the DNA methylation status.

Conclusions: KAT5-mediated DNA repair is essential for podocyte maintenance and has relation to the changes in DNA methylation status in DN. KAT5 may be a good therapeutic target for DN.

SA-OR022

Selective Deletion of EGFR in Podocytes Protects against Nephropathy in Type II Diabetes

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Background: Previous studies by us and others have indicated that renal epidermal growth factor receptor (EGFR) signaling is activated in DN and EGFR inhibition protects against DN. In the present study, we examined whether selective EGFR deletion in podocytes affected development of DN in type II diabetes.

Methods: *db/db* mice with selective podocyte EGFR deletion (podocin-Cre; $EGFR^{f/f}$; *db/db*: $\mathbf{EGFR^{podKO}}$**;*db/db***) and an accelerated type II diabetic model ($eNOS^{-/-}$; *db/db* mice) with selective podocyte EGFR deletion (podocin-Cre; $EGFR^{f/f}$; $eNOS^{-/-}$; *db/db*: $\mathbf{EGFR^{podKO}}$**; $\mathbf{eNOS^{-/-}}$; *db/db***) were generated and used. Genotypes were confirmed before sacrifice. A mouse podocyte cell line was used for *in vitro* studies.

Results: Selective podocyte EGFR deletion was confirmed by reduced EGFR co-IF with WT1. Podocyte EGFR deletion had no effect on body weight and fasting blood sugar in either *db/db* or eNOS$^{-/-}$; *db/db* mice. However, podocyte EGFR deletion led to marked reduction in albuminuria in both *db/db* and eNOS$^{-/-}$; *db/db* mice [albumin vs. creatinine ratio (μg/mg): 175 ± 11 vs. 495 ± 16 in 40 week old *db/db* , $P < 0.01$; 2185 ± 175 vs. 3434 ± 418 in 20 week old eNOS$^{-/-}$; *db/db* mice, $P < 0.05$]. Glomerulosclerosis index was lower in EGFR^{podKO}; eNOS$^{-/-}$; *db/db* mice than in eNOS$^{-/-}$; *db/db* mice at 20 weeks. In eNOS$^{-/-}$; *db/db* mice, podocyte EGFR deletion produced less podocyte loss, as indicated by increased mRNA levels of podocin and higher podocyte number per glomerulus section (10.7 ± 0.5 vs. 7.0 ± 0.2, $P < 0.001$), in association with decreases in proinflammatory cytokine/chemokine levels, including iNOS, IRF5, IL-23, IL-1α, IL-1β, CCL-3, TNF-α and IL-6 as well as pro-fibrotic and fibrotic components, TGF-β1 and collagen I and IV. Both *in vivo* and in cultured podocytes exposed to high glucose, inhibition of podocyte EGFR signaling suppressed the mTOR/p70 S6K signaling pathway, leading to stimulation of a podocyte protective autophagic pathway, as indicated by increased beclin 1 and decreased rubicon, an inhibitor of beclin 1, and decreases in the autophagic substrate, p62.

Conclusions: These studies indicate that activation of a podocyte EGFR signaling pathway contributes to progression of diabetic nephropathy, at least in part due to activation of an EGFR/mTOR/p70 S6K pathway, leading to inhibition of podocyte autophagy and subsequent cell injury.

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SA-OR023

Exosome-Mediated miR-26a Treatment Attenuates Muscle Atrophy and Kidney Fibrosis in Diabetic Mice

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Background: The treatment of muscle wasting is well known to be accompanied by benefits in other organs. However, how the muscle communicates with these organs is less understood. Exosomes, natural carriers of many signal molecules including microRNA (miR), mediate organ to organ communication. We hypothesized that intramuscular injection of miR-26a would counteract both muscle wasting and renal fibrosis through exosome-mediated muscle-kidney crosstalk in diabetic mice.

Methods: We used an engineered exosome vector which contains an exosomal membrane protein gene - lysosomal-associated membrane protein 2b (Lamp2b) fused with kidney specific surface peptide [(KKEEE)^{3}K] for kidney targeting delivery. Exosome encapsulated miR-26a (Exo/miR26) were generated in cultured skeletal muscle satellite cells, collected from conditioned media, and injected into the tibialis anterior muscle of diabetic mice. Diabetes mellitus was induced by low dose STZ injection (5-days). A NanoSight instrument was used to quantify exosomes. MiR deep sequencing and qPCR were used to identify microRNA expression. The In-Vivo Xtreme camera system was used to detect exosomes *in vivo*.

Results: miR-26a was decreased in skeletal muscle and kidney of diabetic mice. Diabetic serum enhanced secretion of miR-26a exosomes from cultured skeletal satellite cells and HEK293 kidney cells. The delivery of exogenous Exo/miR26a into muscle increased the levels of miR-26a in skeletal muscle and kidney, as well as increasing muscle cross-sectional area and decreasing diabetes-induced upregulation of atrogin-1 and MuRF1. Interestingly, renal fibrosis lesions were partially depressed, and α-SMA, connective tissue growth factor (CTGF), fibronectin and collagen1α were decreased in diabetic kidney with intramuscular injection of Exo/miR-26a. Blood urea nitrogen was decreased in diabetic mice treated with Exo/miR26a. Using fluorescent dye labeled Exo/miR26a, we found that the fluorescence intensity in kidney was linearly correlated with skeletal muscle.

Conclusions: overexpression of miR-26a in muscle prevents diabetes-induced muscle loss and attenuates renal fibrosis via exosome-mediated muscle-kidney crosstalk. These results could provide new approaches for developing therapeutic strategies for kidney diseases with muscle wasting.

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SA-OR024

miR-379 Knockout Mice and CLASH Technique Reveal Fis1 as a Novel miR-379 Target Related to Diabetic Nephropathy

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Background: We recently showed that microRNAs (miRNAs) in the miR-379 megacluster and the host noncoding RNA (lncMGC) are co-regulated by endoplasmic reticulum stress, are upregulated in kidneys of diabetic mice and promote features of early diabetic nephropathy (DN). Here we hypothesized that miR-379-mutant mice created by CRISPR-Cas9 editing (miR-379-knockout, KO) are valuable tools to examine the in vivo functions of the miR-379 cluster and miR-379 in DN. Furthermore, new miR-379 targets identified using miR-379KO mouse mesangial cells (MMC) and the CLASH technique (crosslinking, ligation, and sequencing of hybrids) can uncover new therapeutic targets for DN.

Methods: Cas9 nickase and two guide RNAs (gRNAs) were injected into mouse eggs to create miR-379KO mice. To identify new miR-379 targets, UV-crosslinked RNA-protein complexes from wild type (WT) and miR-379KO mouse mesangial cells (MMC) were sonicated, immunoprecipitated (IP) with Ago2 antibody and ligated. Hybrid RNAs were subjected to RNA sequencing (CLASH).

Results: Several founders identified by PCR were crossed with WT mice, and homozygous miR-379KO mice (harboring 36bp deletion in the miR-379 locus) were obtained. Multiple miR-379 hybrid sequences were identified by CLASH and RNA-seq. Fis-1 (mitochondrial fission) was confirmed as a bonafide miR-379 target by Ago2 IP qPCR and Fis1 3'UTR reporter assays. siRNA-mediated Fis1 knockdown reduced key mitochondrial signals in MC, suggesting Fis1 is a new player in mitochondrial dysfunction in DN. Notably, miR-379-KO mice were protected from early features of DN, and Fis1 expression was decreased in kidneys of diabetic WT but not diabetic miR-379KO mice.

Conclusions: Combination of miR-379-mutant mice created by CRISPR-Cas9 editing and CLASH technique identified Fis1 as a new miR-379 target with key mitochondrial functions in the diabetic kidney. Fis1 could be a novel therapeutic target for DN.

Funding: NIDDK Support

SA-OR025

Mice with Drp1-S600 Knockin Mutation Exhibit Reduced Mitochondrial Fission and Attenuation of Diabetic Nephropathy

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Background: Mitochondrial fission has been linked to the pathogenesis of diabetic nephropathy (DN), but how this process affects progression of DN *in vivo* remains elusive. We have previously reported the role Dynamin-related protein1 (Drp1), a key component of mitochondrial fission, and its phosphorylation at serine 600 on mitochondrial dynamics in podocytes *in vitro*. We now report the *in vivo* consequences of S600 phosphorylation in progression of DN in a mouse model of Type 2 diabetes.

Methods: We generated a S600 phospho-dead Drp1 knockin mouse on the C57BL/6 background *via* point mutation of serine 600 to alanine. Following C57Bl6/J ES cell electroporation, selection, and screening of colonies by southern blot and PCR analysis, we identified several positive clones and generated chimeric S600A mice. We next generated heterozygous S600$^{+/A}$ and homozygous S600$^{A/A}$ mice. We crossed the Drp1-S600 mice with *Lepr$^{db/+}$* mice, a well-established model of Type 2 diabetes, to generate homozygous diabetic Drp1-S600$^{A/A}$ mice (Lepr$^{db/db}$; Drp1-S600$^{A/A}$).

Results: Diabetic Drp1-S600 mutant mice were followed over the course of 16 weeks. Diabetic mice did not exhibit any differences in their body weight or blood glucose levels. In contrast, as compared to diabetic *wild-type*, both hetero- and homozygous diabetic Drp1-S600A mice exhibited significantly reduced albuminuria. Histological analysis by Periodic-Schiff's Acid (PAS) stain and quantification of glomerular area positive for PAS stain, revealed attenuated mesangial matrix expansion in glomeruli of db/db;Drp1-S600$^{A/+;A/A}$ compared to controls. Transmission electron micrographs (TEM) also revealed reduced podocyte foot process effacement and reduced glomerular basement membrane thickening in diabetic Drp1-S600$^{A/+;A/A}$ compared to diabetic controls. TEM of podocytes also revealed elongated mitochondria and increased aspect ratio in mitochondria from *db/db*;Drp1-S600A mice compared to *wild-type* diabetic mice. Our results are consistent with preservation of mitochondrial morphology and structure in S600 mutant mice.

Conclusions: These findings demonstrate that a single phosphorylation site in Drp1 regulate mitochondrial fission and progression of DN and elucidate a potential role for targeting Drp1-S600 phosphorylation in DN.

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SA-OR026

Inhibition of Complement C5a/C5a Receptor 1 Decreases Renal Injury in Diabetic Kidney Disease via Metabolic Reprogramming

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Background: The complement system plays a central role in the activation of innate immunity, inflammation and tissue remodelling. The complement activation fragment C5a is a potent pro-inflammatory effector molecule. We have shown complement activation in patients with diabetes including renal deposition of the canonical C5a receptor C5aR1 and C5a/C5aR1 activation in experimental diabetes. This study aimed to determine whether genetic deletion or pharmacological inhibition of C5aR1 could confer renoprotection in diabetes.

Methods: Streptozotocin (STZ)-induced diabetic C57BL/6 mice were treated with the highly selective C5aR1 antagonist, PMX-53 (2mg/kg/day) in drinking water for 24 weeks (n=10). C5aR1 deficient mice (*C5ar1-/-*) and their wild type littermates were rendered diabetic with STZ and followed for 24 weeks (n=10). Kidney injury was assessed by urinary albumin excretion and glomerulosclerosis (GSI). Immunohistochemistry for Collagen IV, FoxP3+ regulatory T cells and F4/80+ cells was performed. Transcriptomics of renal cortex was performed by RNA-sequencing using the Illumina platform and pathway analyses using Gene Set Enrichment Analysis.

Results: Diabetic *C5ar1-/-* mice showed protection against renal injury with decreased albumin excretion. Treatment of diabetic mice with PMX-53 led to a reduction in proteinuria, inhibition of glomerular injury and fibrosis and resolution of inflammation via a decrease in F4/80+ macrophages and activation of FoxP3+ regulatory T cells. Transcriptomic analyses showed that the diabetes gene signature was reversed by PMX-53. Pathways that were reduced by PMX-53 in diabetic mice were related to mitochondrial function and lipid

metabolism. The top differential gene downregulated in the diabetic kidney was acyl-CoA dehydrogenase 10 *(Acad-10)*, which participates in the beta-oxidation of fatty acids in mitochondria. Blockade of C5aR signalling in diabetic mice restored *Acad-10* expression.

Conclusions: Our findings demonstrate that genetic or pharmacological disruption of C5aR1 is renoprotective in diabetes via restoration of pathways involved in fatty acid oxidation and by suppressing the pathogenic inflammatory response. This study indicates that targeting the C5a/C5aR1 pathway may provide a substantial therapeutic benefit for this devastating complication of diabetes.

Funding: Private Foundation Support

SA-OR027

Klotho Ameliorates Diabetic Nephropathy via AMPK-PGC1α Mediated Renal Mitochondrial Protection

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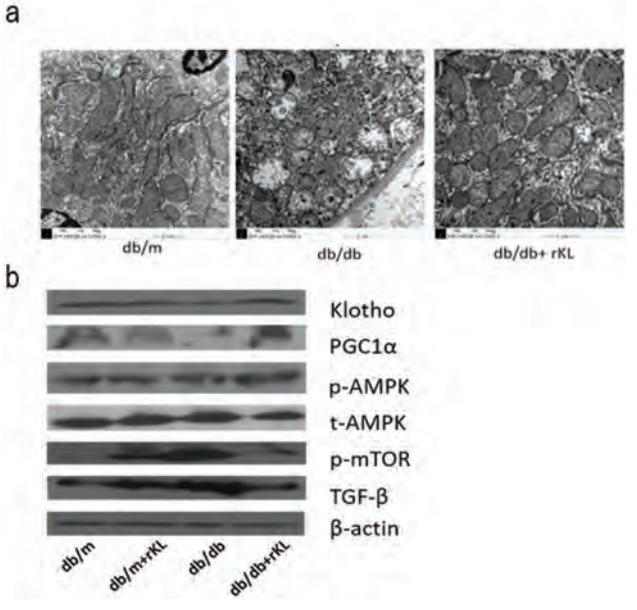
Background: Diabetic nephropathy(DN) is associated with renal mitochondrial injury, and decreased renal klotho. Klotho is known as ageing suppressor, and mitochondrial dysfunction is the hallmark of ageing. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) is a master regulator of mitochondrial biogenesis, and adenosine monophosphate-activated protein kinase(AMPK) is known as a guardian of mitochondria. Here, we report that recombinant klotho protein (rKL) is protective against DN in db/db mice by PGC1α-AMPK mediated mitochondrial recovery in the kidney.

Methods: We injected rKL into db/db and db/m mice for 8 weeks, and collected the serum and the kidney. Also, we treated rKL to various renal tubular cells *in vitro*, with or without 30mM high glucose (HG) exposed.

Results: rKL-treated db/db mice showed recovered renal proximal tubular mitochondria, as well as significantly reduced renal ROS and serum glucose, compared to vehicle-treated db/db mice. Also, rKL increased renal p-AMPK, PGC1α, and down-regulated mTOR/TGF-β in db/db mice. Moreover, we confirmed that rKL treatment ameliorated HG-mediated cellular damage, with an increase of PGC1α-AMPK induced mitochondrial recovery in cultured renal tubular cells.

Conclusions: Our data suggest a mitochondrial protective role of klotho against diabetic kidney disease by inducing AMPK-PGC1α expression.

Funding: Government Support - Non-U.S.



a) renal mitochondiral recovery by rKL in db/db mice, and b) rKL increased renal p-AMPK and PGC1α expression in db/db mice.

SA-OR028

Effects of Sodium Glucose Cotransporter 2 Deletion on Bone and Mineral Metabolism

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Background: Type 2 diabetes mellitus (T2DM) and chronic kidney disease are associated with an increased risk of developing bone and mineral metabolism abnormalities. A new class of glucose-lowering agents, sodium-glucose cotransporter 2 (SGLT2) inhibitors, promotes urinary glucose excretion and improves renal and cardiovascular outcomes in patients with T2DM. However, SGLT2 inhibitors are associated with increased risk of bone fractures. Because loss of SGLT2 function may decreases urinary phosphate, we hypothesize that inhibition of SGLT2 induces mineral metabolism alterations that could contribute to increased bone fragility.

Methods: Slc5a2 nonsense mutation in Sweet Pee (SP) mice results in total loss of SGLT2 function in proximal tubules. To understand the effects of loss of SGLT2 function on mineral metabolism, urine and serum was collected from fasted wild type (WT) and SP mice. Levels of fractional excretion of calcium and phosphate; serum phosphate, calcium, PTH, $1,25(OH)_2D$, and FGF23 were evaluated at 15 and 25 weeks. To determine the longitudinal impact of loss of SGLT2 function on bone metabolism, bone architecture, remodeling, and mineralization was assessed in SP mice and WT mice at 15 and 25 weeks of age.

Results: At 25 weeks, SP mice showed significantly decreased body weight compared to WT mice (21.6±3.8 vs 25.1±2.9 g, $p<0.05$). Consistently, femoral length was significantly shorter in SP mice compared to WT mice (14.1±0.4 vs 14.5±0.2 mm, $p<0.05$). Overall renal function was not impaired in SP mice compared to WT mice (blood urea nitrogen: 18±4 vs 21±5 mg/dL, NS). Fasted SP mice did not show modification of fractional excretion of calcium. Serum calcium, PTH, and $1,25(OH)_2D$ levels were similar between WT and SP mice at 15 and 25 weeks. Fractional excretion of phosphate was significantly higher at 25 weeks in SP mice compared to WT (5.5±2.0 vs 2.5±1.9 %, $p<0.05$), despite unchanged levels of FGF23. SP mice had reduced cortical bone mineral density, compared to WT mice at 25 weeks (1240±16 vs 1264±14 mg/cm^3, $p<0.05$).

Conclusions: These results suggest that loss of SGLT2 function in the absence of T2DM may contribute to bone fragility. Future studies are required to determine how loss of SGLT2 function impacts bone fragility in T2DM.

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SA-OR029

Unravelling Reno-Protective Effects of SGLT2 Inhibition in Human Proximal Tubular Cells

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Background: Large clinical trials recently demonstrated that SGLT2 inhibitors (SGLT2i) slow the progression of kidney function decline in type 2 diabetes independently of their glucose lowering effects. However, the underlying molecular mechanisms of these beneficial renal effects are unknown. As the proximal tubule (PT) is supposed to play a role as initiator and contributor in early pathogenesis of diabetic kidney disease, we conducted a systematic molecular approach to study the effects of SGLT2i on gene expression in human PT cells. Utilizing two SGLT2i, namely empagliflocin and canagliflocin, we investigated their effects on differential gene expression in the presence and absence of TGF-ß1, a well established pro-fibrotic ligand.

Methods: human proximal tubular cell culture (HK-2 and RPTEC/TERT1), microarray hybridization, pathway enrichment analysis, real-time PCR, ELISA

Results: Microarray hybridization analysis identified 94 genes that were both upregulated by TGF-ß1 and downregulated by two SGLT2i in HK-2 and RPTEC/TERT1 cells (n=2). Functional annotation of these genes revealed 152 involved pathways in 7 annotation clusters (EASE score < 0,05). Within the top-ranked clusters (enrichment score > 3), annotations for extracellular matrix organisation ($p=6,4x10^{-7}$) and extracellular space ($p=2,8x10^{-6}$) showed the highest significance. Differential gene expression of 3 annotated genes of interest within this pathway, namely thrombospondin 1 (THBS1), tenascin C (TNC) and platelet derived growth factor subunit B (PDGFB), was verified on mRNA level in HK-2 and RPTEC/TERT1 cells: While TGF-ß1 significantly induced mRNA expression of THBS1 (5-fold), TNC (8-fold) and PDGFB (4,2-fold), SGLT2i significantly downregulated basal mRNA expression of THBS1 (0,2-fold), TNC (0,5-fold) and PDGFB (0,5-fold). Administration of SGLT2i in the presence of TGF-ß1 resulted in a significant inhibition of TGF-ß1-induced THBS1 and TNC mRNA expression by approximately 50 % (n=4; $p<0,05$). TGF-ß1-induced PDGFB protein expression was almost completely blocked in the presence of SGLT2i (n=6; $p<0,001$).

Conclusions: We conclude that SGLT2i block basal and TGF-ß1-induced expression of key mediators of renal fibrosis and kidney disease progression, namely of THBS1, TNC and PDGFB in two independent human PT cell lines.

SA-OR030

Dysregulated Translation and Differential p53 Isoform Expression in the Kidney during Diabetes

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Background: Over 30 million people in the US have diabetes and it remains the leading cause of ESRD. Critically missing from investigation into the pathogenesis of diabetic nephropathy (DN) is the detailed examination of translation, the fundamental process linking gene expression to the synthesis of functional proteins. In this study we use a mouse model of diabetes to examine differential and sequential changes in global translation as well as expression of p53, an important regulator of transcription and translation during cell stress, in the kidney.

Methods: Transcriptional (RNA-seq) and translational (polysome, Ribo-seq) profiling are used to study changes in the translatome during progression of diabetes in the kidney of db/db (B6.BKS(D)-Lepr ^{db}/J) mice. p53 isoform expression is examined by biochemical, proteomic, and translational profiling in db/db mice and nondiabetic background (WT) mice.

Results: Transcriptional profiling reveals that pathways regulating translation are the most differentially altered in the kidney of db/db mice as the diabetic state progresses from 8 weeks to 12 weeks old. Significant changes are observed broadly across ribosomal proteins and regulators of both ribosomal biogenesis and translation. Direct analysis of translation by polysome profiling demonstrates translational activity is increased by 50% in 12 week-old compared to 8 week-old db/db mice. In addition, Ribo-seq confirms the increase in translational activity in the kidney from db/db mice as compared to WT mice. Further analysis of Ribo-seq data reveals four general variations of ribosomal kinetics in the kidney of db/db mice as compared to WT mice. Given the relationship between cell stress and altered translation, we examined p53 isoform expression in the kidney of db/db mice. Immunoblotting reveals the presence of a ~44kDa band consistent with ΔNp53, a translationally-regulated (IRES-mediated) p53 isoform modulating aging and metabolism, in the kidney of db/db mice that is absent in WT mice. Proteomic analysis and ribosome footprint profiling (Ribo-seq), an indispensable method to examine IRES-mediated generation of proteins, further substantiate the differential generation of ΔNp53 in the kidney of db/db mice.

Conclusions: Dysregulated translation in the diabetic state is associated with ΔNp53 expression that can in turn alter translation and contribute to DN.

Funding: NIDDK Support

SA-OR031

The Renal Na-Cl and Na-K-2Cl Cotransporters Are Increased in Urinary Exosomes of Patients with Severe Preeclampsia

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Background: Arterial hypertension (AH) in preeclampsia (PE) is in part due to increased sodium reabsorption in the kidney. One of the major pathways for salt reabsorption is the Na-Cl cotransporter (NCC), whose expression and activity is modulated by female hormones (AJP Renal, 2015). Here we assessed the presence of NCC and NKCC2 in urinary exosomes of women with PE as compared with women with healthy pregnant (HP).

Methods: We included ten women diagnosed with severe PE (ACOG 2013; SBP ≥160mmHg or DBP ≥ 110mmHg, protein/creatinine ratio > than 0.3mg/dl), which were matched with a HP patients by age and gestation weeks. The urine sample was taken at the time of detection of arterial hypertension with criteria of severity. Urinary exosomes were used for Western Blot analysis for total and phosphorylated NCC, NKCC2 and the kinase SPAK. Serum and urinary electrolytes were measured.

Results: Mean age (years), gestation (weeks) and mean blood pressure (mmHg) were 28 ± 4.6, 36 ± 3.7 and 123 ± 11 for PE group and 25 ± 6.7, 37 ± 3.9 and 83 ± 8.5 in HP, respectively. A remarkable increase in the expression of NCC was found in PE group vs HP, 3.0 ± 0.77 vs 1.0 ± 0.7321 ($p<0.01$, Fig 1). There was no difference in the expression of NKCC2, but a significant increase in the phosphorylated form was observed in PE group (2.56 ± 1.11 *vs* 1.00 ± 0.15, p=0.015, Fig. 1). Additionally, increase in the expression and activation of SPAK/OSR1 were observed in the PE group. Serum K^+ was similar between PE and HP groups (p=NS).

Conclusions: Our data revealed increased expression/activation of NCC and NKCC2 in PE, suggesting the participation of these cotransporters in the development of AH. The increased phosphorylation of SPAK/OSR1 suggests that these kinases are responsible for NCC and NKCC2 activation.

Funding: Government Support - Non-U.S.

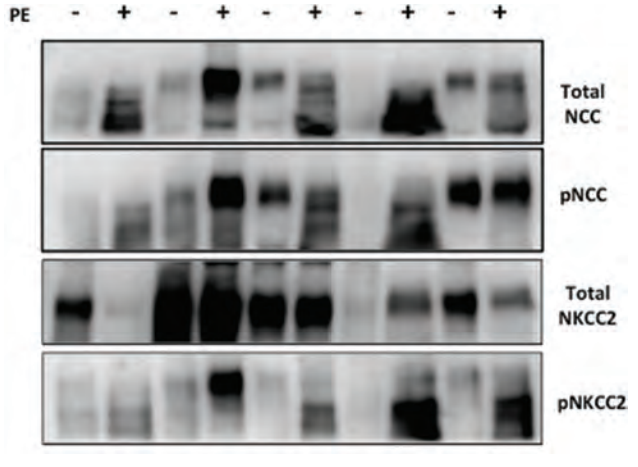

Figure 1. Total and phosphorylated NCC and NKCC2 in five PE and HP patients

SA-OR032

Intense Renal Sodium Retention in Healthy Individuals Subjected to a Potassium Deprived Diet

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Background: Diets poor in potassium (K) have been associated with hypertension, cardiovascular disease and all-cause mortality. Our study aims to quantify sodium (Na) balance in the setting of total dietary potassium deprivation of brief duration while keeping dietary sodium constant.

Methods: 10 male healthy volunteers were studied in the clinical research unit while on a strict calorie and electrolyte balanced liquid diet for a 10 day control period followed by a 5 day study period with total dietary K deprivation. The Na intake was kept constant throughout the entire study period (1.8 mEq/KBW) and the intake of K was reduced from 1.5 mEq/KBW to 0 mEq/KBW. Body weights, systolic and diastolic blood pressure (SBP, DBP), serum and 24 hour urine electrolytes were collected daily.

Results: At the end of the control period, urinary K was 81 ± 8.6 mEq/24hrs and fell to 16 ± 1.68 mEq/24Hr (p=0.0006) by day 5 of the K deprived diet. After 5 days on a K deprived diet the cumulative K deficit was -132 ±10 mEq with a fall in plasma K from 4.54 ±0.15 to 3.68 ±0.05 mEq/dL (p=0.0016) by the end of the study period. Urinary Na excretion fell on day one on the K deprived diet, and by day 5 renal Na retention resulted in a positive Na balance of 507 ± 3.8 mEq/L. Bodyweight did not significantly increase during the initial 5 days of the study diet (from 91.6 ± 5.2kg to 91.8 ± 5.3kg; p=0.71). SBP at the end of 5 day increased slightly, but not significantly from 111.2 ± 2 .58 mmHg to 115.49 ± 2.94 mmHg; p=0.083, and DBP decreased but not significantly from 72.6 ± 1.6 mmHg to 71.3 ± 2.4mmHg; p=0.50. There was a marked fall in hematocrit by day 5 with a fall from 45.6 ± 0.53% to 42 ± 0.44% (p=0.01). From the change in hematocrit and body weight plasma volume was estimated to have increased by 192mL (from 3483 ± 379 mL to 3675 ± 409 mL; p=0.005) over the 5 day period.

Conclusions: This study shows that total dietary K deprivation is a potent stimulus for the kidney to rapidly retain Na over a very short period of time. Even more striking was the observed magnitude of the positive Na balance of 507 mEq/L with only a small increase in plasma volume along with no significant increase in body weight or blood pressure. This observation supports recent evidence of a large Na reservoir with the ability to store significant amounts of Na, thus limiting its impact on body weight and blood pressure.

Funding: NIDDK Support

SA-OR033

Sodium Concentration in Tissues of Dialysis Patients

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Background: Dialysis patients are unable to fully remove sodium (^{23}Na). Thus, ^{23}Na is buffered in the skin, muscle and skeleton (osmotically inactive, but not biologically inert). We measured ^{23}Na content in these reservoirs using novel ^{23}Na MRI, in dialysis patients and healthy controls.

Methods: We undertook a pilot cross-sectional study of 26 subjects (10 controls and 16 dialysis - 9 peritoneal dialysis and 7 hemodialysis - patients). Subjects participated in a study session, which included collection of baseline information, bloodwork and a ^{23}Na MRI study using a multinuclear-capable 3.0T MRI (Discovery MR750, General Electric Healthcare). An axial proton T1-weighted fast-low-angle-shot sequence was acquired to delineate the anatomy; followed by a ^{23}Na MR image obtained with a custom-made lower-leg ^{23}Na coil and ^{23}Na-optimized pulse sequence (DA-3DPR). Maps of absolute tissue ^{23}Na concentration were generated using calibration vials of known ^{23}Na concentration included in the field-of-view. Four regions of interest were drawn, highlighting different tissues: 1) pre-tibial skin, 2) posterior leg skin (included because ^{23}Na distribution in skin was inhomogeneous), 3) soleus muscle, and 4) tibia.

Results: ^{23}Na concentrations in the different tissues for both groups are shown in Fig. 1. Dialysis patients had statistically significant higher ^{23}Na levels in all four regions ($p<0.05$). Dialysis modality and gender did not have a significant effect.

Conclusions: Dialysis patients have significantly higher ^{23}Na level in their skin, muscle and bone compared to healthy controls.

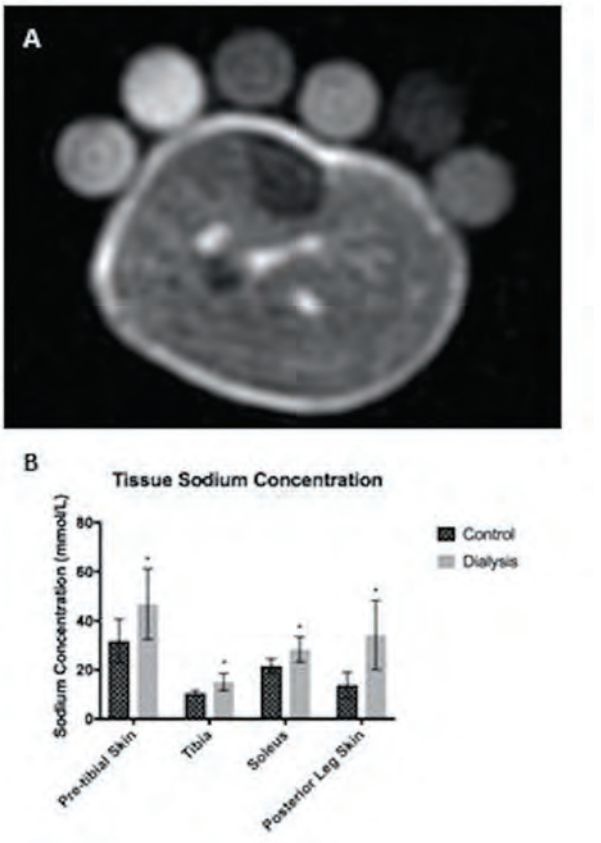

Fig. 1: A: ^{23}Na concentration map of the lower leg and calibration vials for a dialysis patient. B: ^{23}Na concentration in different tissues in dialysis patients and controls. Error bars = standard deviation. * = statistically significant differences ($p<0.05$)

SA-OR034

Incidence and Outcomes of Hyperkalemia in Solid Organ Transplant Recipients

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Background: Hyperkalemia is a serious complication resulting in a critical adverse event. Solid organ transplant (SOT) recipients can experience hyperkalemia contributed by both pathophysiological and medication related mechanisms. We examined incidence and outcomes of hyperkalemia in SOT recipients receiving acute care.

Methods: In a multi-center national sample (Cerner Health Facts database, 1/1/2000 to 6/30/2016), we examined patients with first hospitalization after transplant surgery or during the study period, whichever occurred earlier. Based on the peak potassium (K) level in mEq/L during the index admission, we classified K as normal ≤5.0, mild 5.1-5.5, moderate 5.6-6.0, and severe >6.0; hyperkalemia was defined as moderate or severe K groups. By logistic regression, we analyzed the effect of hyperkalemia and its severity on in-hospital mortality/hospice discharge and 30-day readmissions after adjustment for major confounders.

Results: Of the 14,684 SOT recipients, 65% kidney; 8% heart; 17% liver; and 10% other transplants. The cohort was 60% male with median age of 56 years (Q1, Q3, 45, 64) and median creatinine of 1.6 mg/dL (Q1, Q3, 1.2, 2.7). Overall, 16% experienced hyperkalemia (K levels: 69% normal; 15% mild; 8% moderate; 8% severe); frequency of hyperkalemia across organ type ranged between 13% and 17%. Overall in-hospital mortality was 2.6%; hyperkalemia group 6.1% vs. others 2.0% ($p<0.001$); mortality by K class was 1.6%, 3.7%, 5.4% and 6.8%, respectively ($p<0.001$). Hyperkalemia increased the risk of death [adjusted odds ratio (aOR), 3.1; 95% confidence interval (CI), 2.5-4.0]; compared to normal level, the severity of K class was associated with a graded increase in risk of death: mild K, aOR 2.2; 95% CI, 1.7-3.0; moderate K, aOR 3.4; 95% CI, 2.4-4.7; severe K, aOR 4.6; 95% CI, 3.3-6.2. There was a synergistic interaction between hyperkalemia and type of SOT, which was statistically significant ($p=0.025$). Hyperkalemia also increased risk of 30-day readmissions, 27% vs. others 18% ($p<0.001$); aOR 1.5; 95% CI, 1.4-1.7.

Conclusions: Hyperkalemia occurs in 1-in-6 SOT recipients during acute care; it is associated with a 3-fold increase in the risk of hospital mortality and 1.4-fold increase in the risk of readmission. Hyperkalemia prevention or treatment during acute care may improve patient survival in transplant recipients.

Funding: Clinical Revenue Support

SA-OR035

Urine Citrate Excretion Reliably and Non-Invasively Identifies Acid Retention in CKD 2 Patients without Metabolic Acidosis

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Background: Dietary acid (H^+) reduction slows eGFR decline in CKD stage 2 (eGFR=60-89 ml/min/1.73 m^2, CKD 2) patients without metabolic acidosis (conventionally defined as plasma total CO_2 <22 mM) (Mahajan et al, Kid Int, 2010) but who have H^+ retention identified using cumbersome and invasive methods. Earlier studies from this laboratory supported the potential utility of urine citrate excretion to non-invasively identify H^+ retention in such patients but its reliability to do so was not assessed.

Methods: We measured H^+ retention and 8-hour urine citrate excretion ($U_{citrate}V$) in macroalbuminuric, non-diabetic CKD 2 (n=40) and CKD stage 1 (eGFR >90 ml/min/1.73 m^2, CKD 1, n=26) patients with hypertension-associated nephropathy but without metabolic acidosis (mean plasma total CO_2 25.9±0.8 and 26.4±0.6 mM, respectively). H^+ retention was measured by comparing observed to the expected increase in plasma [HCO_3] in response to retained HCO_3 (dose minus $U_{HCO3}V$) 6 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body weight HCO_3 apparent space of distribution.

Results: H^+ retention was higher in CKD 2 than CKD 1 (28.1±9.4 vs. 5.2±12.0 mmol, respectively, $p<0.01$) but $U_{citrate}V$ was lower in CKD 2 than CKD 1 (187±40 vs. 335±125 mg, respectively, $p<0.01$). Overall Pearson correlation for $U_{citrate}V$ with H^+ retention was -0.76 ($p<0.001$) and a mixed effects regression model showed lower $U_{citrate}V$ to be strongly predictive of higher H^+ retention ($p<0.001$). Using the 90th percentile of H^+ retention in CKD 1 (19.5 mmol) as normal, $U_{citrate}V$ of 230 mg in CKD 2 patients had sensitivity 93.7%, specificity 62.5%, positive predictive value 90.9%, negative predictive value 71.4%, and an accuracy of 87.5% to predict H^+ retention.

Conclusions: Lower $U_{citrate}V$ reliably identifies CKD 2 patients with higher H^+ retention in the absence of metabolic acidosis by acid-base parameters. Because <2% of CKD 2 patients have metabolic acidosis (Shah et al, AJKD, 2009), follow-up studies should further refine this simple, non-invasive method to identify CKD 2 patients who are candidates for dietary H^+ reduction which might reduce their risk for nephropathy progression.

SA-OR036

A Multicenter, Randomized Pilot Study of Oral Sodium Bicarbonate Supplementation in Non- to Mildly-Acidotic CKD: The BASE Pilot Study

Kalani L. Raphael,[1] Tamara Isakova,[2] Joachim H. Ix,[3] Dominic S. Raj,[4] Myles Wolf,[5] Linda F. Fried,[6] Jennifer J. Gassman,[7] Brett Larive,[7] Kevin C. Abbott,[8] Susan R. Mendley,[8] Geoffrey A. Block,[9] Ping Li,[4] John P. Middleton,[5] Stuart M. Sprague,[10] Donald E. Wesson,[11] Alfred K. Cheung.[12] The CKD Pilot Studies Consortium *[1]VA Salt Lake City Health Care System, Salt Lake City, UT; [2]Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]UCSD, San Diego, CA; [4]GWU Medical Faculty Associates, Washington, DC; [5]Duke University, Durham, NC; [6]VA Pittsburgh Healthcare System, Pittsburgh, PA; [7]Cleveland Clinic, Cleveland, OH; [8]The National Institutes of Health, NIDDK, Bethesda, MD; [9]Colorado Kidney Care, Denver, CO; [10]NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; [11]Baylor Scott and White Health and Wellness Center, Dallas, TX; [12]University of Utah, Salt Lake City, UT.*

Background: Chronic oral $NaHCO_3$ may preserve GFR in CKD, even in those with normal serum (S) HCO_3^-. However, definitive proof of efficacy and the optimal dose have not been demonstrated. We performed a randomized, double-blinded, placebo-controlled multicenter pilot study to determine the safety, tolerability, compliance, and pharmacodynamics of two doses of oral $NaHCO_3$ and the feasibility to conduct a multicenter Phase-3 trial.

Methods: Individuals (n=194) with mean age 68 yrs, eGFR 37 ml/min/1.73m^2, ACR 530 mg/g, and S-HCO_3^- 24 meq/L (range 20-28 meq/L) were randomized to higher-dose (HD) (0.8 meq/kg-LBW/d; n=90) or lower-dose (LD) (0.5 meq/kg-LBW/d; n=52) $NaHCO_3$ or placebo (Plac; n=52) for 28 weeks. The dose was adjusted depending on clinical and laboratory side-effects. The prescribed dose at study completion was the primary outcome. Feasibility for a Phase 3 trial was defined a priori as ≥67% of participants completing the study on full dose and ≥80% on ≥25% of the dose. Pharmacodynamics were assessed by S-HCO_3^-, 24-hour urine NH_4^+ (U-NH_4^+) and pH (U-pH).

Results: 87% in HD, 98% in LD, and 88% in Plac completed the study on full dose, while 91% in HD, 98% in LD, and 94% in Plac completed the study on ≥25% of the dose. Compliance by pill count was ≥88%, with >80% of participants having ≥80% compliance in all arms during follow-up. BP, weight, and S-K^+ were similar between Plac, LD and HD during follow-up. Table 1 shows dose-response effects of $NaHCO_3$ on S-HCO_3^-, U-pH and U-NH_4^+.

Conclusions: In persons with non- to mildly-acidotic stage 3/4 CKD, safety, tolerability and compliance of HD and LD NaHCO3 were each comparable to Plac. $NaHCO_3$ had a mild effect on S-HCO_3^- and substantial dose-dependent effects on U-NH_4^+ and U-pH, but no significant effect on BP, weight, or S-K^+. A Phase-3 multicenter trial using $NaHCO_3$ 0.8 meq/kg-LBW/d is feasible.

Funding: NIDDK Support

Dose response effects of NaHCO3 on acid-base indices

Acid-Base Indicator	Higher-Dose NaHCO3 vs. Placat week 28		Lower-Dose NaHCO3 vs. Plac at week 28	
	Estimate	95% CI	Estimate	95% CI
S-HCO3- (meq/L)	1.4	0.6 to 2.2	0.1	-0.8 to 1.1
24-hr U-NH4+, % difference	-48	-57 to -36	-33	-47 to -16
24-hr U-pH	0.8	0.6 to 1.0	0.6	0.3 to 0.8

SA-OR037

The Effects of Sodium Bicarbonate in CKD Stages 3 and 4: A Randomized, Placebo-Controlled, Multi-Center Clinical Trial

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Background: The chronic metabolic acidosis associated with kidney disease may contribute to muscle dysfunction, bone disease and progression of kidney disease.

Methods: We enrolled 149 patients with CKD stages 3 and 4 and randomized them to either placebo or sodium bicarbonate (NaBicarb) (0.4 mEq/kg ideal body weight/day) between 7/2011 and 4/2016 at 3 clinical sites across the US. Participants were seen at baseline, 2, 6, 12 and 24 months. The dual primary outcomes were muscle function assessed by sit-to-stand-to-sit test and bone mineral density. At each visit, blood pressure (BP), weight, a 5-repetition sit-to-stand-to-sit test, and laboratory studies were conducted. Bone mineral density scans were performed at baseline, 12 and 24 months.

Results: Of the 149 participants, 74 were on NaBicarb, 75 were on placebo. Mean age was 61.0 years (standard deviation(SD) 12.6), 54% were women, 58% were non-Hispanic black, 13% were Hispanic and 27% were non-Hispanic white, 62% had diabetes mellitus and 93% had hypertension at baseline. Baseline serum bicarbonate level was 23.5 (SD 1.7) mEq/L, baseline eGFR was 36.3 (SD 11.2) ml/min/1.73m^2 and baseline systolic BP was 137 (SD 17) mmHg. There were no differences in baseline characteristics by treatment group. 104 participants completed the 24 months study. At 2, 6, 12 and 24 months, the mean serum bicarbonate levels in the NaBicarb arm were 26.4 mEq/L (SD 2.2), 25.5 mEq/L (SD 2.3), 25.6 mEq/L (SD 2.6) and 24.4 mEq/L (SD 2.8). These were significantly higher than in the placebo group (p<0.001). NaBicarb caused a significant decrease in serum potassium levels by approximately 0.1 mEq/L (p= 0.047). There were 14 patients in the NaBicarb group who had a potassium level >5.0 mEq/L over the course of the study compared to 30 patients in the placebo group (p=0.005). There were no significant differences in sit-to-stand-to-sit time, bone mineral density, BP or weight between the randomized groups.

Conclusions: NaBicarb therapy in patients with CKD stages 3 and 4 significantly increases serum bicarbonate and decreases serum potassium levels. There were no differences in muscle function or bone mineral density between the randomized groups. Larger trials are required to evaluate effects on kidney function.

Funding: NIDDK Support

SA-OR038

Therapeutic Efficacy and Safety of Human Adipose-Derived Stem Cells for Anti-GBM Nephritis

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Background: Mesenchymal stem cells (MSCs), which exert immunomodulatory function, would be one of the promising therapeutic agents for inflammatory disorders. We have been intensively studied adipose derived stem cells (ASCs) cultured under low serum conditions (LASCs) and recently demonstrated that systemic administration of syngeneic LASCs ameliorated anti-GBM nephritis in rats more effectively than ACSs grown under high serum conditions (HASCs). In the current study, we investigated therapeutic potency of human LASCs for rat anti-GBM nephritis.

Methods: Anti-GBM nephritis was induced by intravenous injection of TF78, a monoclonal anti-glomerular basement membrane antibody, to female WKY/NCrj rats. 2×10^6 human LASCs, HASCs or bone marrow derived MSCs (BMMSCs) were administrated to them on day 0, 2, 4 and sacrificed on day 7. Therapeutic efficacy was evaluated by proteinuria during observation period and serum creatinine (sCr), BUN, histological renal damage on day 7. Distribution of administrated MSCs was observed by In Vivo Imaging System. The clotting time after addition of MSCs into plasma was measured. The expression of tissue factor on the MSC surface was analyzed by flow cytometry.

Results: ASC-treatment demonstrated significant amelioration in TF78-induced renal dysfunction. Histologically, crescent formation and accumulations of CD68$^+$ or CD163$^+$ macrophages in inflamed glomeruli were significantly decreased in ASC-treated groups compared with the BMMSC-treated group. Although the therapeutic efficacy of HASC slightly surpassed that of LASC, therapy-related animal death caused by pulmonary accumulations of administrated-ASCs occurred in 4 out of 12 HASC-treated rats, while none in LASC-treated animals. Procoagulant function, which has emerged as a critical aspect in clinical application of ASCs, was remarkably diminished in LASCs compared with HASCs as evidenced with similar clotting time and tissue factor expression to BMMSCs.

Conclusions: Human ASCs have therapeutic potential for anti-GBM nephritis as well as syngeneic ASCs compared with BMMSCs. Although HASCs shows slightly superior efficacy, it has a serious safety drawback compared with LASCs. From a comprehensive perspective, LASCs would be advantageous in therapeutic potential for clinical use.

SA-OR039

Neutralizing the Th1 Effector Cytokines, TNFα and IFNγ, in Experimental Autoimmune Myeloperoxidase ANCA Associated Glomerulonephritis (MPO-ANCA GN)

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Background: Anti-cytokine monoclonal antibody (mAb) therapies have been effective in many autoimmune diseases but have not been successfully trialled in MPO-ANCA associated vasculitis. This study assessed the efficacy of blocking key CD4$^+$ Th1 subset signature effector cytokines, TNFα and IFNγ in MPO-ANCA GN. Assessing therapeutic efficacy of these anti-cytokine mAbs is now complicated by our recent discovery that Th subset dominance during the development of MPO autoimmunity is biphasic with initial transient Th17 dominance followed by persistent Th1 responses.

Methods: Anti-MPO autoimmunity was induced in C57BL/6 mice by MPO immunization and GN triggered using anti-GBM Ig during early and late development of anti-MPO autoimmunity, and GN assessed 4 days later (days 20 and 32, respectively). mAb treatment began 4hrs post GN triggering.

Results: Administration of anti-TNFα mAb early in anti-MPO development (day 20) had no effect on kidney injury compared with vehicle treated controls: albuminuria [5.7±1.7 vs 5.5±1.7 mg/24hr, P=0.9]; glomerular segmental necrosis [GSN: 50±4 vs 43±3%, P=0.1]. Similarly, anti-IFNγ mAb was ineffective in attenuating GN at this timepoint [GSN: 48±6 vs 45±3%, P=0.53]. Failure of these treatments is concordant with our observation that early developing anti-MPO autoimmunity is Th17 dominant. In contrast, anti-TNFα therapy during established anti-MPO GN (day 32) markedly attenuated kidney injury [GSN: 27±2 vs 50±4%, P=0.01]. TNFα blockade acts locally in the kidney as systemic MPO specific IFNγ and IL-17 recall responses from lymph nodes draining MPO immunization sites were similar to vehicle treated controls. Neutralizing IFNγ at this late timepoint induced a phenotypic switch from Th1 responses to a protective Th2 with increased in serum MPO-ANCA [1.19±0.25 vs 0.48±0.13 OD_{450nm}, P=0.02], increased IL-4 production from MPO challenged LN cells and increased the proportion of activated M2 macrophages [F4/80$^+$CD206$^+$: 29.3±3.2 vs 16.0±0.9%, P=0.01]. However, 4 days of anti-IFNγ treatment was insufficient to improve GN.

Conclusions: In conclusion, Th1 anti-MPO effector responses direct established anti-MPO nephritogenic autoimmunity and glomerular injury (day 32). Therapeutic TNFα neutralizing mAb initiated after triggering GN effectively attenuates kidney injury.

Funding: Government Support - Non-U.S.

SA-OR040

BB-Cl-Amidine Limits Neutrophil Extracellular Trap Formation and Inflammation in Murine Experimental Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody Associated Glomerulonephritis

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Background: Accumulating evidence suggests that dysregulation of neutrophil extracellular traps (NETs) could be associated with the pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA) vasculitis. Peptidyl arginine deiminases (PADs) are enzymes that generate citrullinated proteins, which are pro-inflammatory in both innate and adaptive immune responses. Citrullination of histone 3 (H3Cit) by PAD2 and PAD4 facilitates generation of both macrophage extracellular traps (METs) and NETs. BB-Cl-amidine is a second generation pan (PAD) inhibitor which reduces citrullination of H3Cit and subsequent NET formation. This study investigates the contribution of NETs in the pathogenesis of experimental anti-myeloperoxidase ANCA associated glomerulonephritis (MPO-ANCA GN) and the therapeutic possibility of BB-Cl amidine disrupting NET formation in vivo, and attenuating anti-MPO GN.

Methods: Experimental anti-MPO GN was induced in C57BL/6 mice by myeloperoxidase (MPO) immunisation and GN triggered using a subnephritogenic dose of anti-glomerular basement membrane globulin. BB-Cl-amidine treatment (1mg/kg/daily, n=6 or vehicle, n=7) was administered to disrupt NET formation after the establishment of MPO autoimmunity until termination of the experiment.

Results: NET accumulation identified by co-localisation of extracellular DNA, H3Cit, PAD4, and MPO, was prominent in glomeruli of untreated (vehicle) mice compared to BB-Cl-amidine treated mice (2.1 ± 0.4 vs 0.4 ± 0.1, P=0.004). Histological assessment of kidneys demonstrated prominent glomerular segmental necrosis in the untreated group versus a reduction in mice receiving BB-Cl-amidine (88 ± 3% vs 41 ± 3%, P=0.004). BB-Cl-amidine significantly attenuated glomerular leukocyte infiltration; CD4 T cells (1.2 ± 0.3 vs 0.3 ± 0.1, P=0.03), macrophages (1 ± 0.1 vs 0.4 ± 0.06, P=0.008) and neutrophils (3 ± 0.5 vs 1.6 ±0.3, P=0.03), compared to untreated mice. BB-Cl-amidine treated mice had increased numbers of CD4+FoxP3+ T regulatory cells in lymph nodes compared to the untreated mice (7.1 ± 0.9% vs 3.7 ± 0.3% P= 0.001).

Conclusions: PAD inhibtion with BB-Cl-amidine successfully attenuates in vivo formation of NET formation in experimental anti-MPO GN, reduces kidney injury, glomerular pathology, and supresses inflammation.

Funding: Government Support - Non-U.S.

SA-OR041

Tolerogenic Dendritic Cells Attenuate Autoimmune Vasculitis by Inducing Interleukin 10-Expressing Regulatory T Cells

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Background: Tolerogenic dendritic cells (DCs) are an attractive immunoregulatory tool for the treatment of inflammatory diseases, but their therapeutic efficacy has not been tested in autoimmune renal vasculitis. These studies sought to determine whether tolerogenic DCs can suppress experimental anti-myeloperoxidase (MPO)-associated vasculitis.

Methods: Tolerogenic DCs (BAY-DCs) were generated by culturing bone-marrow cells with an NFkB inhibitor BAY-11-7082. MPO-pulsed BAY-DCs or vehicle were administered to mice with established anti-MPO or anti-methylated bovine serum albumin (mBSA) immunity, after which immune responses and vasculitis were assessed. BAY-DCs were also transferred to DREG mice (expressing diphtheria toxin [DT] receptor under the Foxp3 promotor) in which foxp3+ regulatory T cells (Tregs) were depleted using DT. BAY-DC-induced Tregs or vehicle were administered, with or without a neutralizing anti-IL-10 receptor antibody, to mice with established anti-MPO immunity, and immune responses and vasculitis assessed.

Results: MPO-pulsed BAY-DCs attenuated established anti-MPO T cell autoimmunity (proliferation, IL-17A/IFNg production) and, after glomerulonephritis was triggered by anti-basement membrane globulin, vasculitis (glomerular injury and leukocyte accumulation), in association with an induction of IL-10-producing Tregs in lymph nodes. MPO-pulsed BAY-DCs did not affect immune responses against mBSA. They also failed to inhibit anti-MPO responses in Treg-depleted DREG mice, showing that Tregs are required for BAY-DC-mediated effects on MPO-specific immunity. Furthermore, Treg transfer/IL-10 receptor blocking experiments showed that BAY-DC-induced Tregs suppressed established anti-MPO immunity and glomerulonephritis via IL-10.

Conclusions: Tolerogenic BAY-DCs attenuate established anti-MPO autoimmunity and consequently vasculitis in an antigen-specific manner by inducing IL-10-expressing Tregs. This suggests that tolerogenic DCs may represent a novel therapeutic option for the treatment of autoimmune renal vasculitis.

Funding: Government Support - Non-U.S.

SA-OR042

Targeting CD103+ Dendritic Cells Using Flt3 Inhibitors for Treatment of Kidney Disease: Relevance to Human Kidney Disease

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Background: Whereas CD103+ dendritic cells (DCs) were previously considered to be a minor DC subset in kidney disease. we and others have proven that they have a major role. Flt3 is a receptor specifically expressed on tissue CD103+ DCs. Flt 3 inhibitors are currently used for cancer treatment. In this study, our aims are 1. To examine CD141+ DCs (human homologue of mice CD103+ DCs) in human kidney diseases. 2. To explore the role of CD103+ DCs and therapeutic potential of targeting CD103+ DCs by repurposing Flt3 inhibitors in experimental kidney diseases.

Methods: For a human study, we included 294 patients who underwent kidney biopsies from 01/07/2016 to 01/04/2017. For animal experiments, we are using Adriamycin Nephropathy (AN), anti-GBM disease and ischemia reperfusion injury (IRI).

Results: In humans, the number and proportion of CD141+ DCs were significantly increased in proliferative glomerulonephritis and acute tubular necrosis (ATN). CD141+ DCs were found mainly in tubulointerstitium, except in lupus nephritis where they were also present in glomeruli. CD141+ DC numbers correlated with increasing severity of ATN ($P<0.001$) as well as increasing severity of fibrosis in IgA nephropathy ($P=0.025$), but not in diabetic nephropathy. In murine AN, anti-GBM disease and IRI, the number and proportion of kidney CD103+ DCs were significantly increased. In AN, CD103+ DCs played a pathogenic role through activation of CD8+ T cells. Treatment with a Flt3 inhibitor specifically depleted CD103+ DCs and significantly reduced renal injury. The effect of Flt3 inhibition is currently being studied in anti-GBM disease and IRI.

Conclusions: Kidney CD103+ DC numbers correlate with severity of human kidney disease. In experimental kidney disease, CD103+ DCs play a pathogenic role through activation of CD8+ T cells. Targeting CD103+DCs with Flt3 inhibitors effectively reduces renal injury, suggesting a novel therapeutic strategy with accelerated translational potential through drug repurposing.

SA-OR043

Epigenetic Changes in Dendritic Cells in Patients with Systemic Lupus Erythematosus (SLE) with Renal Involvement

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Background: SLE is a systemic autoimmune disease that affects the kidneys in about 50% of patients. The pathogenesis of lupus is still unclear and requires further research. There is a mounting evidence that changes in the dendritic cell (DC) function is associated with SLE development.

Methods: 51 patients with lupus nephritis were enrolled to the project. The study group (SG) consisted of 9 men and 42 women, the average age was 44.05 (range: 21-69) years. The control group (CG) consisted of 22 people with no history of autoimmune diseases (5 male and 17 female) with average age 35 (range: 22-60) years. Each participant of the study was cytometrically examined for DCs subpopulations (mDC - myeloid DC, pDC - plasmacytoid DC), including DC activity assessed. The global DNA methylation, histone H3 methylation was estimated. Cytokine profile analysis of both groups was performed with Luminex platform.

Results: In the SG as compare to CG, the percentage of DCs ($HLA\text{-}DR^+$ Lin^{2-}) was significantly lower ($p=0.0259$) and it was accompanied by a significant decrease in the $CD123^+$ pDCs subpopulation ($p=0.006$). There were no statistical differences between the SG and CG in the mDCs ($CD11c^+$) subpopulations ($p=0.133$). However, in the mDCs subpopulation a significant increase in the expression of activation markers was found in SG (for $CD80^+$ $p=0.002$). The study of epigenetic changes in DCs did not show significant differences in the global DNA methylation between groups. However, a statistically significant decrease in methylation histone H3K27me3 in mDCs was found in CG ($p=0.0005$), which suggests increasing transcriptional activity of DCs in this group. The strongest increase in activity was present in INF-inducible genes such as IRF8 (pDC $p=0.0002$; mDC $p=0.037$). In both subpopulations of DCs, the second strongly activated gene in patients with SLE was the TNF gene (pDC $p=0.0049$; mDC $p=0.0198$). Changes in gene activity translate directly into the cytokine profile. The level of proinflammatory cytokines was statistically higher in SG: TNFα ($p=0.0007$), IL8 ($p=0.0029$).

Conclusions: DCs are vital factors in the pathogenesis of SLE. Epigenetic and transcriptomic studies of DCs and analysis of serum proteins have demonstrated their significant role in the genetic modification of the autoimmune process.

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SA-OR044

Transcriptomic and Proteomic Profiling Identifies Patients with Elevated Inflammatory and Immune Signaling in Nephrotic Syndrome

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Background: Despite the high cost associated with renal disease, the reliability and availability of information to guide patient care using a precision medicine approach prior to reaching end-stage is relatively sparse. To address this, patient specific profiles were generated for major signaling pathways to understand the diversity of patient level signaling in a nephrotic syndrome cohort.

Methods: Transcriptomic profiles were generated from isolated glomeruli (glom) and tubulointerstitium (TI) samples from subjects with nephrotic syndrome in the NEPTUNE cohort. Patient-specific transcriptional profiles were generated from a curated set of genes for activated TNF, JAK-STAT, and major immune cell types. Patient-specific profiles were correlated with urine biomarker profiles generated from a panel of 54 markers to identify relevant surrogate markers. NMF clustering was used to identify disease-relevant molecular subtypes. Patient-specific profiles and clustering approaches were utilized in a blinded retrospective analysis to evaluate the use of high dimensional data to predict patient outcomes and help guide treatment decisions.

Results: Across the cohort, TNF and JAK-STAT pathway activation profiles in the tubulointerstitium were both positively correlated with IFTA ($p<0.001$). In select cases, profiles were identified with high pathway activation with little to no IFTA. MCP-1 and TIMP1 were identified as biomarkers for TNF activation with a C-statistic of 0.86. Urine IP-10 was correlated with intrarenal JAK-STAT activation ($p<0.001$), and together with immune cell signatures were predictive of intrarenal inflammation and immune activation. NMF clustering of glom and TI profiles from subjects each revealed four patient clusters that were associated with outcome; the poorest prognosis cluster was enriched for inflammatory and innate immunity pathways. In individual cases, profiling results were qualitatively consistent with pathology descriptors.

Conclusions: Patient-specific transcriptional and urine biomarker profiles were identified that can indicate degree of intrarenal signaling and damage, and by combing data from other domains, can be used to identify patients that may be best suited for targeted therapy approaches and/or pharmacodynamic patient monitoring in clinical settings.

Funding: NIDDK Support

SA-OR045

Molecular Profiling of Serial Kidney Biopsies to Identify Markers That Predict Long Term Outcomes in Lupus Nephritis

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Background: Proliferative lupus nephritis (LN) is treated with induction therapy followed by prolonged maintenance therapy for several years. The intra-renal molecular changes that occur during this treatment period is unknown. Here we present results of molecular profiling of the LN glomeruli using protocol kidney biopsies to identify markers of long term response.

Methods: A protocol kidney biopsy was done at flare (Bx1), after induction therapy (Bx2) and after 3 years of maintenance therapy (Bx3) in 9 LN patients. Controls were living donor transplant biopsies (n=6). Glomeruli were laser dissected and RNA was extracted and analyzed by nanostring. Transcript expression from LN glomeruli was compared to controls, and complete responders (CR, n=5) were compared to non-responders (NR, n=4). Response was determined by proteinuria level and renal function at Bx3. All patients were treated with standard induction and maintenance therapy for LN.

Results: There were 110 differentially expressed glomerular transcripts between NR and CR. Pathway analysis revealed upregulation of several T cell pathways in NR compared to CR including Th1, Th2, NFAT, ICOS-ICOSL, CD28 and PKC signaling in T lymphocytes. Additionally, toll-like receptor, trem1, complement, and interferon signaling were upregulated in NR. The expression of 8 glomerular transcripts significantly increased in NR and decreased in CR from Bx1 to Bx3. This included *HLA-DQA1* (FC:3.9 P: 0.03), *LAIR1* (FC:4.2, P:0.004), *GBP1* (FC:2.7, P:0.001), *CCR1* (FC: 3.4 P:0.04), *JAK1* (FC:2.0, P:0.02), *C1R* (FC:2.5, P:0.01), *CTSC* (FC:2.6, P:0.04), and *C1QA* (FC:4.2, P:0.01).

Conclusions: Transcript expression from serial kidney biopsies in LN after prolonged maintenance therapy predicts T cell activation and persistent inflammation in NR compared to CR glomeruli. These pathways could be specifically targeted to improve response in NR. Several glomerular transcripts were identified to predict response in this cohort. These transcripts should be studied further to determine their utility as predictive markers of long-term outcomes in LN.

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SA-OR046

The Influence of Microbiome Composition on the Development and Progression of IgA Nephropathy

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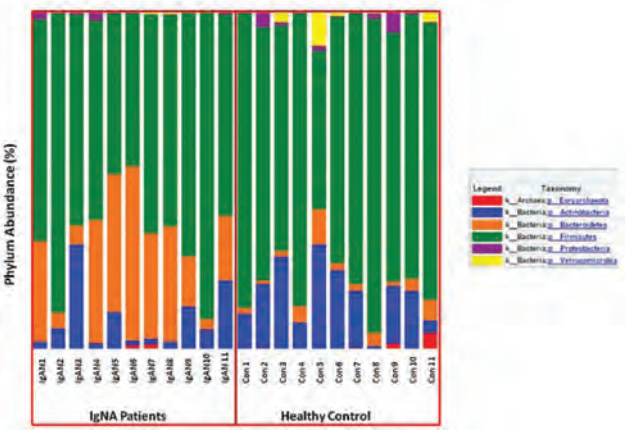
Background: IgA Nephropathy (IgAN) is an auto-immune dis., characterized by abnormal deposition of IgA1 antibody with aberrant O-glycosylation in the glomerular mesangium, resulting in local inflammation. Aberrantly glycosylated IgA1 may be synthesized in response to a mucosal infection and may include deregulated innate immune responses. IgAN usually characterized with variability in its manifestation between different patients. The human microbiome is involved in normal host physiology & several metabolic diseases. It was shown that IgAN patients had an altered fecal microbiota, but the exact relationship between microbiome composition and IgAN is still understood.

Methods: Stool sample from 26 IgAN patients and 26 healthy control individuals subjected to microbiome array and to taxonomic analysis, to characterize their microbiome compositions. Creatinine, albumin and urine proteinuria levels are used for evaluate the renal function of each IgAN patient. The clinical and laboratory evaluations will be crossed with the taxonomic data using statistical analysis.

Results: Preliminary result with 11 IgAN patients and 11 healthy controls, there are significant differences in the microbiome composition between the two groups. IgAN patients have a significant increase in the Bacteroides phylum accompanied with a significant decrease in the amount of both the Actinobacteria and Verrucomicrobia phyla, compared with the healthy individuals (Fig.1). At the genus level, there is a significant increase in the Prevotella bacteria in the IgAN subjects compared with the healthy individuals.

Conclusions: 1. A strong association between specific bacteria population and IgAN 2. To isolate specific population of bacteria that leads to IgAN or even aggravate its manifestation. 3. Develop disease-specific therapies based on microbiome modulations and manipulations by modifying the gut microbiota through diet, antibiotic Tx, probiotic interventions, fecal transplants.



SA-OR047

Molecular Phenotype of Lupus Nephritis Histological Lesions

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Background: The current classification of lupus nephritis (LN) solely relies on histological features and does not incorporate any information about molecular changes that characterize pathologic features. Inclusion of molecular phenotype in histologic scoring may provide insights into disease pathogenesis, prognosis, and aid in surveillance. As a first step towards achieving a more comprehensive molecular-histopathological description of kidney tissue in LN, we evaluated the transcriptional changes associated with various histologic phenotypes in LN.

Methods: 54 kidney biopsies from 53 sequential patients were dissected and separated into glomerular and interstitial compartments. RNA was extracted and amplified. cDNA was hybridized to affymetrix Genechips, processed and data normalized. Descriptive statistics were used for patient demographics. Differential mRNA expression was evaluated according to the presence or absence of the histologic lesion of interest using Wilcoxon Rank Sum test, then using Spearman's Rank Correlation, mRNA expression levels were correlated with lesion severity (on a semiquantitative scale). Pathway analysis of significant transcripts was later performed. A subset of transcripts were validated in an indepndent population.

Results: Histological lesions in LN demonstrated different patterns of expression. The most notable glomerular transcripts reflecting disease activity were osteopontin (OPN) and fibronectin (FN1), which correlated with cellular proliferation, and galectin 3 (LGALS3) which correlated with cellular crescents. On the other hand, interstitial podocin, TLR4, and ITGA1 expression were associated with interstitial fibrosis, and glomerular expression of NEAT1 and CYTIP were associated with glomerular sclerosis. Interestingly, cluster analysis demonstrated clear separation based on tissue type (glomerular vs interstitial), and not by ISN/RPS class or NIH activity and chronicity indices. OPN, FN1, and LGALS3 correlated with proteinuria in the validation cohort.

Conclusions: Histological lesions of LN demonstrate different patterns of expression that do not reflect distinct immunological/inflammatory processes. Some of the identified gene transcripts (OPN, FN1, LGALS3) deserve further evaluation as biomarkers of LN activity, as they correlated with histological activity and proteinuria in two independent cohorts.

SA-OR048

Genomic Characterization of Monogenic Hypertension in a Multiethnic Cohort

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Background: Hypertension is a major risk factor for adverse outcomes, but secondary hypertension may not be not appropriately diagnosed. We sought to ascertain prevalence of monogenic hypertension mutations, and their associations with blood pressure and clinical outcomes.

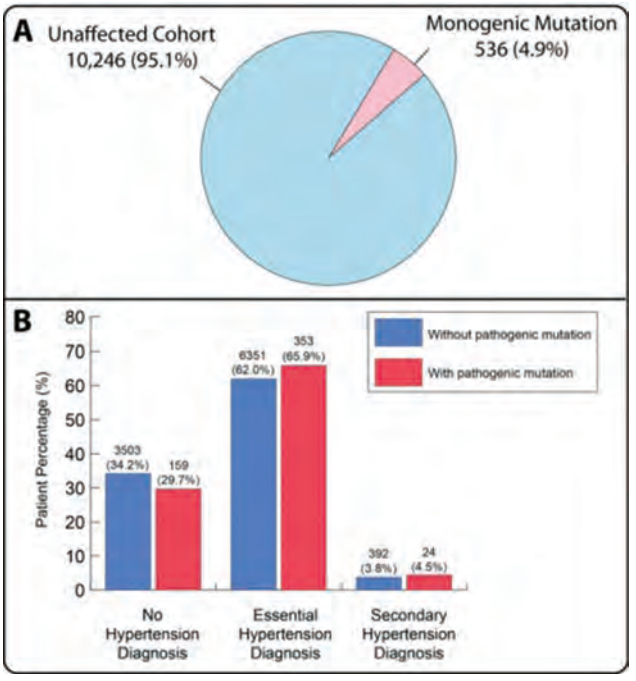
Methods: In 10,782 individuals of predominantly African (n=4,502) or Hispanic/Latino (n=4,621) ancestry, we examined Clinvar mutations pathogenic for secondary hypertension with systolic, diastolic, and mean arterial blood pressures; hypertension-associated composite clinical outcome; acute systolic blood pressure elevation rates, and appropriate diagnosis.

Results: 536 individuals (4.9%) possessed pathogenic mutations. Individuals with pathogenic mutations had 11% increased risk for adverse outcomes (95% CI 1.01-1.20) and had elevated mean arterial (2±0.36 mmHg; p<0.01), systolic (3.22±0.55 mmHg, p<0.001), and diastolic (1.19±0.34) blood pressures. Individuals with a pheochromocytoma and paraganglioma-associated mutation had 2.5-fold higher rates (95% CI 1.8-3.4) for acute

SBP elevations above 200 mmHg. Only 4.5% of individuals with pathogenic mutation had appropriate diagnoses of secondary hypertension and 5.4% received appropriate biochemical evaluations. The majority were diagnosed with essential hypertension (65.9%). (Figure 1)

Conclusions: Pathogenic mutations were more frequent in Hispanic Americans. Individuals with pathogenic monogenic mutations for secondary hypertension have higher blood pressures, increased rates of acute blood pressure elevation, and elevated risk for adverse clinical outcomes. The majority of individuals with pathogenic mutations were not appropriately evaluated or diagnosed. These results suggest a need for diversity in the study of rare genetic diseases, and that a genotypic approach for diagnosis of hypertension may be beneficial.

Funding: NIDDK Support



SA-OR049

The New 2017 ACC/AHA Guideline for High Blood Pressure in Adults: How It Impacts Mexican Population and Healthcare System? An Analysis of the SALMEX Cohort

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Background: The new 2017 ACC/AHA High Blood Pressure Guidelines for Adults lower the threshold to define hypertension (HT). The impact of these new definitions on populations and health systems is poorly understood.

Methods: SALMEX was a cross-sectional study to evaluate Na^+ and K^+ intake as well as chronic non-communicable diseases prevalence in adults. Participants were recruited from 2010 to 2012. We included data from all subjects aged 20-64 yrs (n=990). HT prevalence and pharmacological treatment (TX) requirement were determined according to both: JNC 7 and 2017 ACC/AHA. Data was extrapolated to sex- and age-adjusted Mexico City's (CDMX) population and annual costs of medical follow-up was calculated. The need for pharmacologic TX was assessed with the Atherosclerotic Cardiovascular Disease (ASCVD) score, and compared to Framingham scores (lipids and BMI).

Results: HT prevalence in the SALMEX cohort increased from 16.2% to 37.4% (18% to 39.3% adjusted to CDMX population). The proportion of subjects requiring pharmacological and non-pharmacological TX increased from 17.7% to 19.0% and from 17.7% to 37.4%, respectively (19.4% to 21.8% for pharmacological and 19.4% to 39.3% for non-pharmacological TX, adjusted to CDMX population). Medical follow-up annual costs for hypertensive subjects in CDMX would increase an estimated $59,278,928 USD. The indication to initiate pharmacological TX was similar when assessed by Framingham risk score with serum lipids values or with BMI, as compared to the ASCVD score, with correlation kappa indexes of 0.981 and 0.972 respectively.

Conclusions: The adoption of the new HT guidelines in Mexican population not only has implications on its prevalence but also on medical follow-up costs. Further pharmacoeconomic analysis is required to evaluate the potential impact of this new HT definition. Framingham BMI score represents the most cost-effective alternative to assess cardiovascular risk at diagnosis.

Funding: Commercial Support - Danone Institute, Mexico

Prevalence, treatment and cost differences according to ACC/AHA 2017 and JNC 7 hypertension guidelines		
Hypertension Prevalence	2017 ACC/AHA	JNC 7
a) SALMEX (%)	37.4%	16.2%
b) Mexico City, age-adjusted§ (%)	39.3%	18.0%
Non-pharmacological treatment	2017 ACC/AHA	JNC 7
a) SALMEX, n (%)	370 (37.4)	175 (17.7)
b) Mexico City, age-adjusted§, n (%)	2,083,155 (39.3)	1,027,171 (19.4)
Pharmacological treatment	2017 ACC/AHA	JNC 7
a) SALMEX, n (%)	188 (19.0)	173 (17.7)
b) Mexico City, age-adjusted§, n (%)	1,154,547 (21.8)	1,027,171 (19.4)
Cost of hypertension follow-up and treatment in Mexico City healthcare systemΩ	2017 ACC/AHA	JNC 7
1) Pharmacologically treated subjects	$91,209,213	$81,146,509
2) Non-pharmacologically treated subjects	$49,216,224	$0
3) Mexico City population-cost increase per year	$59,278,928	N/A

§Adjusted to 2010 age-sex distribution of Mexico City adult population.
Ω Based on costs of a public hospital in Mexico City, adjusted to 2018 USD.

SA-OR050

The DASH Diet and Blood Pressure among Black Americans with and without CKD: The Jackson Heart Study

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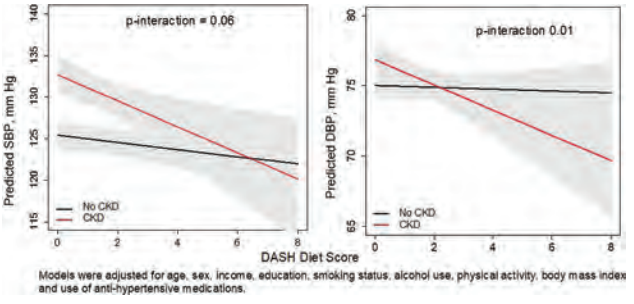
Background: Hypertension control rates are low among Black Americans, particularly among Blacks with CKD. CKD raises blood pressure (BP) through complex mechanisms. Therefore, therapies may have a different effect on BP for those with and without CKD. The DASH diet lowers BP in adults without CKD but its effect in CKD is not clear. Our preliminary data showed that markers of kidney dysfunction are associated with better BP response to the DASH diet. We tested the hypothesis that greater DASH diet accordance has a stronger association with lower BP among Blacks with CKD compared to those without CKD.

Methods: This cohort study of Jackson Heart Study participants involved 3135 Black adults enrolled between 2000 and 2004 (Exam 1) with data on office BP and habitual diet from food frequency questionnaires. We examined the cross-sectional relation of a modified-DASH diet score (excluding sodium intake; range 0-8) to SBP and DBP using linear models adjusting for demographic, behavioral, and clinical factors. We tested for interaction between the DASH score and CKD status (defined as eGFR <60 ml/min/1.73 m^2 and/or urine albumin-to-creatinine ratio ≥30 mg/g).

Results: Mean age was 55 years, 60% had hypertension, and 19% had CKD. Overall, the median DASH score was 1.0 (interquartile range [IQR]: 0.5-2.0), which was similar among participants with and without CKD (1.0 [IQR: 0.5-2] and 1.0 [IQR: 0.5-1.5], respectively). Among those *without* CKD, the DASH score was not associated with SBP (-0.4 [95% confidence interval: -1.0, 0.1] mmHg) or DBP (-0.1 [-0.4, 0.2] mmHg). Among those *with* CKD, a higher DASH score by one point was associated with lower SBP (-1.6 [-2.6, -0.5] mmHg) and DBP (-0.9 [-1.5, -0.3] mmHg; Figure).

Conclusions: CKD status modified the relation of the DASH score to SBP and DBP. Despite poor diet quality overall, greater DASH diet accordance was more strongly associated with lower BP among Blacks with CKD compared to those without CKD.

Funding: Other NIH Support - NHLBI, NIMHD



SA-OR051

Long-Term Kidney Effects of Intensive (INT) SBP Lowering in Persons with Type 2 Diabetes Mellitus (T2DM): ACCORD BP and ACCORDION

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Background: We recently reported that INT SBP lowering increased the risk of incident CKD in T2DM. It is unclear whether this risk persists long-term after discontinuation of INT SBP control.

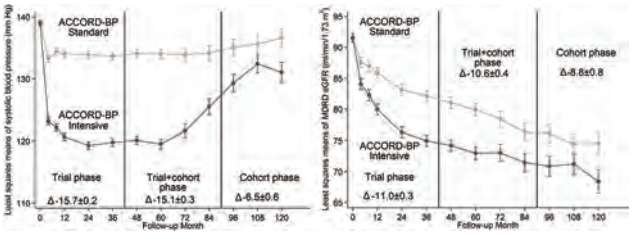
Methods: ACCORD BP tested the effects of SBP goal < 120 vs. < 140 mm Hg on CV outcomes in T2DM. ACCORDION was a long-term, post-trial, off-intervention, cohort follow-up of ACCORD participants. We examined the long-term trajectories of SBP and

eGFR using mixed models. In separate Cox regression models, we related the intervention to incident CKD (defined as a >30% decrease in eGFR to a value <60 ml/min/1.73 m²) in participants without CKD at baseline (N = 4305) and to a composite of 50% decline in eGFR or incident stage IV CKD (<30 ml/min/1.73 m²) in all participants (N = 4733).

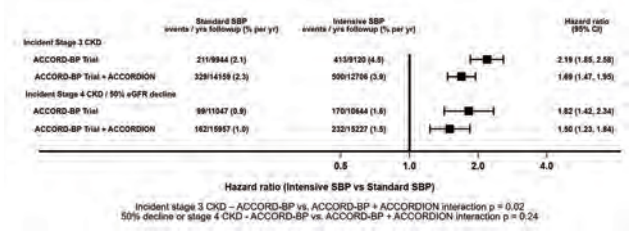
Results: SBP and eGFR trajectories are depicted in Fig 1. Mean differences in SBP and eGFR between the treatment arms are also summarized in Fig 1. INT SBP lowering resulted in increased risk of incident CKD in ACCORD BP which attenuated after the intervention was discontinued during ACCORDION (Fig 2), interaction p = 0.02; the pattern was similar for 50% decline/ stage IV CKD but the interaction p value (0.24) was not significant.

Conclusions: In persons with T2DM, INT SBP lowering resulted in a decline in eGFR and higher risk of kidney events which appeared to attenuate after discontinuation of the intervention.

Funding: NIDDK Support



SBP and eGFR trajectories



Hazard ratios for kidney events with INT SBP lowering in ACCORD BP and ACCORDION follow-up

SA-OR052

The Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury in a Subgroup of Participants in the ACCORD Trial

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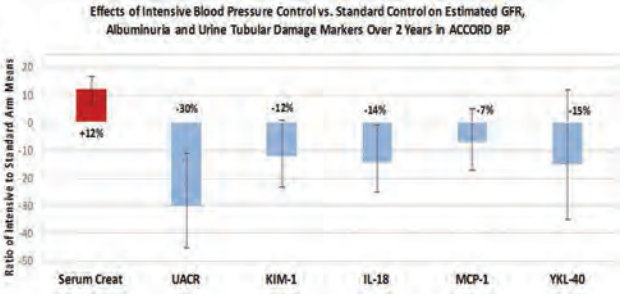
Background: Randomization to the intensive (SBP<120 mm Hg) arm in the ACCORD-BP trial resulted in more rapid decline in estimated glomerular filtration rate (eGFR) than in the standard arm (SBP <140 mm Hg). Whether this change reflects hemodynamic effects or accelerated intrinsic kidney damage is unknown.

Methods: Longitudinal sub-group analysis of 529 participants in the ACCORD-Blood Pressure clinical trial. We measured urine biomarkers of tubule injury (kidney injury molecule-1 [KIM-1], interleukin-18 [IL-18]), repair (YKL-40) and inflammation (monocyte chemoattractant protein [MCP-1]) at baseline and year 2. We compared changes between arms using ANCOVA.

Results: Of the 529 participants, 260 were randomized to intensive and 269 to standard blood pressure arm. Mean age was 62 ± 6.5 and eGFR 90 ml/min/1.73m². Baseline clinical characteristics, eGFR, urinary albumin-to-creatinine ratio (ACR), and all 4 biomarkers were similar between arms. Compared to the standard arm, eGFR was 9.2 ml/min/1.73m² lower in the intensive arm at year 2. Despite the reduction in eGFR, ACR was 30% lower in the intensive arm and 4 urinary biomarkers were unchanged or lower at year 2 in the intensive arm (Figure). Moreover, participants in the intensive arm with the largest declines in eGFR had greater reductions in urine IL-18 and YKL-40. In a subgroup analysis stratified by incident CKD development (sustained 30% decline and eGFR < 60 ml/min/1.73 m², n=77), ACR and 4 biomarkers were flat to decreased in the intensive arm, whereas the urinary biomarkers were unchanged or increased in those that developed CKD in standard arm.

Conclusions: Among a subgrop from the ACCORD trial, randomization to intensive BP control reduced eGFR but did not increase injury markers. These findings support the hypothesis that eGFR decline in intensive BP arm of ACCORD predominantly reflect hemodynamic alterations.

Funding: NIDDK Support



SA-OR053

Modification of Effect of Intensive Blood Pressure Lowering on Cardiovascular (CV) Outcomes by Baseline eGFR in the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial

Adhish Agarwal, Man Li, Jianing Ma, Alfred K. Cheung. *University of Utah, Salt Lake City, UT.*

Background: The SPRINT trial reported CV benefits of intensive (INT) systolic blood pressure (SBP) target of <120 mm Hg vs. <140 mm Hg in patients with and without CKD. However, SPRINT excluded patients with a history of stroke. The SPS3 trial examined the CV effects of INT SBP control in patients with previous stroke and found a non-significant reduction in all (recurrent) stroke (hazard ratio [HR] 0.81, 95% CI 0.64-1.03) and the CV composite outcome of myocardial infarction (MI) or vascular death (HR 0.84, 95% CI 0.68-1.04). We conducted a post hoc analysis of the SPS3 trial to examine whether baseline eGFR modified the effects of INT SBP control on CV events in patients with a history of stroke.

Methods: 3,020 patients with recent MRI-defined symptomatic lacunar infarctions were randomized to a SBP target of <130 mm Hg vs. 130-149 mm Hg. Among 3,017 patients with valid baseline eGFR measurements, we evaluated the effects of INT SBP control on the risk of recurrent stroke and CV composite outcome (stroke, acute MI or death) during the 3.7 years of mean follow-up in two strata defined by baseline eGFR (<60 or ≥60 ml/min/1.73m²) using Cox proportional models. We also tested the interaction between treatment group and baseline eGFR.

Results: Non-significant rate reduction by INT SBP control was seen for all (recurrent) stroke and the composite outcome in both eGFR strata. In the eGFR <60 ml/min/1.73m² subgroup (N=303, mean eGFR 51.22 ml/min/1.73m²), the HR was 0.84 (95% CI, 0.46-1.56) for all stroke, and 0.92 (95% CI, 0.58-1.44) for the CV composite outcome. In the eGFR ≥60 ml/min/1.73m² subgroup (N=2714, mean eGFR 90.08 ml/min/1.73m²), the HR was 0.83 (95%, 0.64-1.07) for all stroke, and 0.90 (95%, 0.74-1.09) for the CV composite outcome. Baseline eGFR did not significantly modify the effect of INT SBP control on either all stroke ($P_{interaction}$=0.74) or the CV composite outcome ($P_{interaction}$=0.45).

Conclusions: Baseline eGFR did not modify the effects of INT SBP lowering on CV events among patients with previous stroke. Studies with adequate statistical power in patients with a wide range of kidney functions are needed to provide conclusive evidence of SBP targets in CKD.

SA-OR054

Influence of Intensive Glycemia Intervention on the Effects of Intensive Systolic Blood Pressure (SBP) Lowering in Type 2 Diabetes Mellitus: Reconciling Results from ACCORD BP and SPRINT

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Background: Intensive systolic blood pressure (SBP) lowering significantly reduced cardiovascular disease (CVD) events in the Systolic Blood Pressure Intervention Trial (SPRINT) but not in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP).

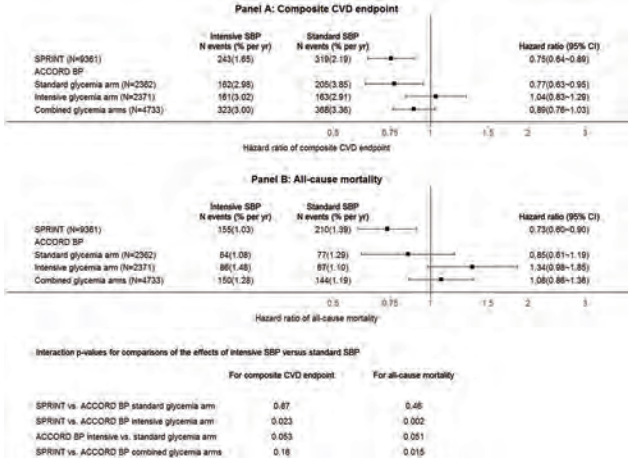
Methods: SPRINT (N =9361) tested the effects of intensive (<120 mm Hg) versus standard (<140 mm Hg) SBP goals on CVD events and all-cause mortality. Using 2x2 factorial design, ACCORD BP (N = 4733) tested the same SBP intervention in addition to an intensive versus standard glycemia intervention. We compared the effects of intensive SBP lowering on the composite CVD endpoint and all-cause mortality in SPRINT with its effects within each of the glycemia arms in ACCORD BP.

Results: As shown in the figure, intensive SBP lowering decreased the hazard of the composite CVD endpoint similarly in SPRINT and the ACCORD BP standard glycemia

arm (interaction p=0.87). However, the effect of intensive SBP lowering on the composite CVD endpoint in the ACCORD BP intensive glycemia arm was significantly different from SPRINT. Patterns were similar for all-cause mortality.

Conclusions: The effects of intensive SBP control on CVD events and all-cause mortality were similar in persons without diabetes and in persons with diabetes on standard glycemic control. An interaction between intensive SBP lowering and intensive glycemic control may have masked beneficial effects of intensive SBP lowering in ACCORD BP.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS



Hazard ratios for CVD events and ACM for intensive vs. standard SBP goals in SPRINT and ACCORD BP glycemia arms

SA-OR055

Safety and Efficacy of High Dose Spironolactone in Loop Diuretic Resistant Acute Decompensated Heart Failure

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Background: Secondary hyperaldosteronism plays a key role in pathogenesis of volume overload and resistance to loop diuretics. However, Athena-HF trial failed to show response to high dose spironolactone in ADHF subjects. We aim to evaluate the safety and efficacy of high dose spironolactone with patiromer exclusively in loop diuretic resistant ADHF subjects.

Methods: ADHF subjects admitted with one symptom and one sign of hypervolemia were given spironolactone 100mg daily if they lost <1lb/day despite IV furosemide>160mg/day (at least one dose of 80mg/day) or equivalent dose of other loop diuretics or remained significantly dyspneic despite 48hrs after admission. The dose was up titrated to 200mg based on response with no change in dose of loop diuretic. Subjects received oral patiromer if serum potassium was >4.3mEq/L. They were followed until achievement of euvolemia or hospital discharge.

Results: Twenty of 48 enrolled subjects with ADHF were loop diuretic resistant. One subject was withdrawn due to mechanical ventilation. The mean±SD age was 61±15yr, 60% male, and 50% Hispanics. Nine did not respond to furosemide >160 mg/day and ten remained symptomatic after 48hrs. Median[IQR] dose of furosemide was 160[120,230] mg/day a day before intervention. Mean ejection fraction was 27.9±19% and 14 subjects had pulmonary hypertension with mean PASP 47.3±11.5 mmHg. All 19 subjects except one responded to addition of spironolactone. Mean±SD weight change was -3.0±3.4lb on day1 and -6.5±4.5lb by day2 ($p<0.001$, ANOVA) on spironolactone. Mean urine output increased from 1712±686 ml a day prior to spironolactone to 2732±1374ml on day1 and 3439±1565 ml ($p=0.002$, ANOVA) on day2 on spironolactone. Eight subjects required 200mg dose. One subject sustained worsening renal function in setting of hypotension due to worsening of underlying cardiac dysfunction. None of the subjects had serum potassium >5.5mEq/d. Three subjects were given patiromer for protocol indication and it was well-tolerated.

Conclusions: Addition of high dose spironolactone to ADHF patients resistant to loop diuretic provided significant decongestion without causing hyperkalemia or worsening renal function. A larger randomized trial is warranted in loop diuretic resisant ADHF patients.

Funding: Commercial Support - Relypsa, Inc

SA-OR056

Elevated Tissue Na+ Deposition in Hemodialysis Patients with Cardiovascular Disease Detected by 23Na-Magnetic Resonance Imaging

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Background: Disturbances in Na^+ homeostasis with accumulation of Na+ in tissues are present in salt sensitive hypertension and correlate with left ventricular hypertrophy. Tissue Na^+ distribution could be recently visualized in vivo by ^{23}Na-magnetic resonance imaging (^{23}Na-MRI). We used ^{23}Na-MRI to quantify Na^+ in skin and muscle of hemodialysis (HD) patients either with or without concomitant cardiovascular disease (CVD). We hypothesized that tissue Na^+ might accumulate to a higher extent in HD patients co-diagnosed with CVD.

Methods: We used ^{23}Na-MRI at 3.0 Tesla to quantify Na^+ content in skeletal muscle and skin of the left lower leg. We determined tissue Na^+ content using a Na^+ volume coil in 19 HD patients with a positive history of a CV event (MI, CABG, arrhythmia, stroke or PAD IV) and in 41 age-matched control HD patients. Additionally, total body water content, including extra- and intracellular water space, were determined using Body Composition Monitoring technique (BCM).

Results: Compared to control HD patients ^{23}Na-MRI detected an increased Na^+ content in muscle tissue (20.97 ± 3.60 vs. 24.59 ± 7.10 mmol/L, $p<0.05$) and skin tissue (21.95 ± 7.26 vs. 29.80 ± 10.91 mmol/L, $p<0.05$) of HD+CVD patients. Simultaneously measured excess extracellular water content detected by BCM was significantly higher in the HD+CVD group (1.17 ± 1.48 vs. 2.31 ± 1.61 liter, $p<0.05$). .

Conclusions: ^{23}Na-MRI detected increased Na^+ in muscle and skin tissue as well as higher excess extracellular water content in HD+CVD patients. Our findings provide evidence that the history of a cardiovascular event is associated with disturbances in tissue Na^+ and water content in HD patients.

SA-OR057

Balancing eGFR Loss and Albuminuria Suppression during Intensive BP Control

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Background: Intensive BP lowering often lowers GFR. This GFR decline is thought to be hemodynamic, benign, and potentially necessary for albuminuria (ACR) suppression. We hypothesized that the Kidney Failure Risk Equation (KFRE) which predicts 5-yr risk of ESRD (using age, sex, eGFR, ACR) could help guide the risk-benefit tradeoff between eGFR loss vs. ACR suppression during intensive BP lowering.

Methods: We determined the tradeoff between GFR loss and ACR suppression that could be theoretically tolerated during intensive BP lowering to maintain the same predicted 5-year ESRD risk (based on the mathematical relationship of eGFR and ACR in the KFRE). We then determined the % of participants in African American Study of Kidney Disease and Modification of Diet in Renal Disease (MDRD) trials (two trials of intensive BP lowering) who achieved adequate ACR suppression during intervention. We confirmed that the KFRE predicted risk of ESRD (henceforth KFRE score) at baseline and at 6 mos (after intensification of BP control) both provided good risk discrimination for ESRD.

Results: To maintain the same KFRE score, substantial ACR suppression was needed to counter even small declines in eGFR (Table). For example, a 3 mL/min/1.73 m^2 decline in eGFR would require 50% ACR suppression to maintain the same KFRE score. Only 21% of 1523 trial participants had sufficient suppression of ACR that maintained or improved their KFRE score given the large magnitude of eGFR changes that occurred during BP lowering. The KFRE score discriminated risk of ESRD before and after intensive BP lowering well, with C-statistic of 0.85 (strict BP) and 0.87 (usual BP) at baseline, and c=0.88 for both treatment arms at 6 mos. Every 10% worsening of KFRE score predicted higher observed risk of ESRD (HR 1.93 [95% CI 1.66-2.25]) in the strict BP arm.

Conclusions: De-intensification of BP control should be considered when aggressive BP lowering leads to declines in eGFR without sufficiently large corresponding ACR suppression to maintain (or improve) the same predicted ESRD risk by the KFRE.

Funding: NIDDK Support

Change in eGFR (final-initial) (mL/min/1.73 m^2)	% albuminuria suppression required to maintain same ESRD risk
0	0
-1	25%
-3	50%
-4	63%
-5	71%
-10	92%
-15	98%
-20	99%

SA-OR058

Clinical Significance of Crescent Formation in IgA Nephropathy – A Multicenter Validation Study

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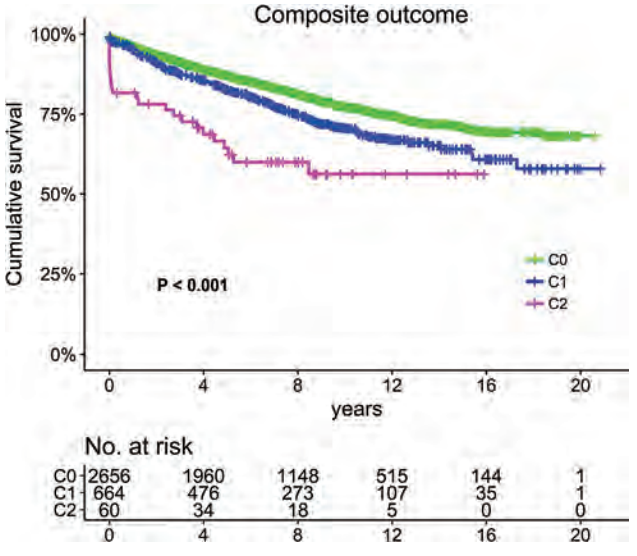
Background: Additional validation study was warranted to confirm the clinical significance of C score, which was recently added to the Oxford classification for immunoglobulin A (IgAN).

Methods: We performed a multicenter retrospective cohort study in four hospitals in Korea. Patients who had biopsied glomeruli less than eight or inadequate follow-up information were excluded. Clinicopathologic parameters, including the degree of cellular or fibrocellular crescents, were collected and included in multivariable model for Cox regression analysis. The main outcome was a composite renal outcome, defined as a merge of progression to end-stage renal disease (ESRD) and halving of estimated glomerular filtration rate (eGFR) from baseline.

Results: Among included 3,380 biopsy-confirmed IgAN patients, there were 664 (19.6%) patients with C1 and 60 (1.8%) patients with C2 scores in the study population. Although C0 and C1 patients shared similar baseline characteristics, C2 patients frequently had more clinicopathologic risk factors for poor prognosis of IgAN. Both C1 [adjusted HR 1.33 (1.11-1.58), P=0.002] and C2 [adjusted HR 2.24 (1.46-3.43), P<0.001] scores were associated with increased risk of the composite outcome. C2 was a strong predictive parameter associated with both progression of ESRD and halving of eGFR, whereas C1 was mainly associated with the increased risk of halving of eGFR. Notably, the proportion of crescent showed a linear association with the risk of adverse renal outcome.

Conclusions: The C score in the Oxford classification is a valid predictive parameter for IgAN prognosis. Additional clinical attention is necessary for IgAN patients with identified cellular or fibrocellular crescents



SA-OR059

Percentage of Glomerular Crescents Predicts Renal Outcomes in Children with IgA Vasculitis – A Midwest Pediatric Nephrology Consortium Study

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Background: While crescents on kidney biopsy predict poor outcome for children with IgA vasculitis, evidence-based thresholds for %crescents most predictive of renal risk are not established. The International Study of Kidney Disease in Children (ISKDC) used 50% and 75% thresholds to grade severity of crescentic glomerulonephritis. MEST-C scoring for IgA nephropathy has also been proposed for IgA vasculitis: 1 point for any glomerular crescent and 2 when crescents involve >25% of glomeruli.

Methods: To test the validity of 25, 50, and 75% thresholds for crescents in IgA vasculitis, we identified 62 patients (13 centers) in the IRB-approved Midwest Pediatric Nephrology Consortium Glomerulonephritis with Crescents Registry (18% of total). Enrollment included patients <21 yo with >1 crescentic glomerulus on biopsy from 2004-16. Primary outcome was end stage kidney disease (ESKD) at 1 year. Secondary outcomes included estimated glomerular filtration rate (eGFR) at 1 year and change in eGFR over time. Crescents were defined by local renal pathologist.

Results: The cohort was 47% female, 53% white, 3% black, 18% Hispanic, and 3% Asian. Median age at biopsy was 8 years (range 6-11) with 2.6 years median follow-up (IQR 1.7-4.8). A median of 36 glomeruli were sampled per biopsy (IQR 27-57). The median %crescents was 10.8 (IQR 7-18%, max 83%). Cellular crescents were seen in 95% of biopsies; fibrous crescents in 27%; both in 23%. Only 2% of children had crescents in >50% of glomeruli, and only one in >75% of glomeruli. One child with 13% cellular and 3% fibrous crescents advanced to ESKD at 26 months post-biopsy. Median change in eGFR was +2.8 mL/min/1.73m^2/year (IQR -20 to +24) at 1 year and -1.5 (IQR -7 to +6) at latest follow-up. Change in eGFR was 2-fold greater for children with >25% crescents (-3.6) vs. those with <25% (-1.6).

Conclusions: Children with higher %crescents present with lower GFRs but most have significant recovery of eGFR at 1 year. Utility of the ISKDC thresholds for grading crescents in IgAV is limited, due to low prevalence of biopsies with crescents >50%. Long term, the 25% threshold for cellular crescents appears to predict worsening GFR decline.

SA-OR060

Relationship between Complement Activation and the Oxford Classification Score and Their Combined Effects on Renal Outcome in Early Stage IgA nephropathy

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Background: Complement activation has been highlighted in the pathogenesis of IgA nephropathy. However, it is unknown how the complement is connected to the downstream phenotype of IgA nephropathy. In this study, we investigated the association of the mesangial C3 deposition with the Oxford classification and their joint effects on the prognosis of IgA nephropathy.

Methods: We included 408 patients with biopsy-proven early stage IgA nephropathy [T0 and estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m^2] between 2009 and 2016 at Yonsei University Health System. C3 deposit was defined as the immunofluorescence intensity of C3 ≥2+ within the mesangium. The study subjects were classified according to the combination of C3 deposits and each lesion of the Oxford classification. The primary endpoint was the development of a ≥ 30% decline in eGFR during follow-up.

Results: Among the Oxford lesions, M1 (mesangial proliferation), S1 (segmental sclerosis), and crescent were significantly correlated with C3 deposit, whereas E1 (endocapillary proliferation) was not. During a median follow-up of 32.5 (18.0 – 61.8) months, primary endpoint occurred in 32 patients (7.9%). In individual multivariable-adjusted analyses, the presence of M1, S1, and C3 deposit was significantly associated with increased risk of primary outcome. In combined analyses with C3 deposit and each of the Oxford lesions, HRs were significantly higher in the presence of C3/M1 and C3/S1, and C3/crescent than in the presence of each single lesion alone.

Conclusions: C3 deposition was significantly associated with the Oxford M-, S-, and crescent scores. In addition, risk of adverse renal outcome was consistently highest when C3 deposition was added to each score. These findings suggest that complement activation can strengthen the significance of the Oxford score and the presence of both components portends a poorer prognosis in IgA nephropathy.

SA-OR061

Relationship between IgA1 Lectin-Binding Specificities, Mesangial C4d Deposits, and Clinical Phenotypes in IgA Nephropathy

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Background: The reason why mesangial C4d deposits are detected in only certain biopsies of IgA nephropathy, remains unclear. In this study, we analyse the association between different patterns of IgA1 glycosilation, mesangial C4 deposition and clinical phenotypes, in IgA nephropathy

Methods: This cross-sectional study included 145 patients with idiopathic IgA nephropathy. We measured the serum levels of three different IgA1 lectin-binding specificities, using enzyme-linked-immunosorbent assays, and we analysed the relationship between these specificities, C4d mesangial deposits and clinical profiles at diagnosis.

Results: C4d-positive vs. Cd4-negative patients had higher proteinuria (median: 3.1 g/g [0.9-4.2] vs. 1.8 g/g [1-2.2]; p=0.000), hematuria (223 cel/µL [32-278] vs 99 cel/µL [25-186], p=0.000), and higher levels of IgA1 with ability to bind Helix Aspersa (HAA IgA1) (150.6 ± 52 U vs 96.2 ± 64.1 U, p= 0,000), Triticum vulgaris (TVIgA1) (85.1 ± 31.7 U vs 42.2 ± 26.9U, p= 0.000) and Canavalia ensiformis (ConAIgA1) (32.5 ± 18U vs 16.7 ± 9.38U, p=0.000) but similar levels of total galactose-deficient IgA1 (338 ± 64 U vs 324 ± 43U p: 0.15). The levels of HAAIgA1, TVIgA1 and ConAIgA1 were all associated with the mesangial deposition of C4d, extracapillary proliferation and the presence of acute kidney injury. HAAIgA1, TVIgA1 and ConAIgA1 had a similar ability to discriminate between C4d positive ad C4d-negative biopsies (AUC: 0.72 ± 0.04, 0.83 ± 0.03 and 0.81 ± 0.04, respectively, p=0.000 in all cases). In logistic models, TVIgA1 and ConAIgA1 were the only independent predictors of mesangial C4d deposits

Conclusions: In IgA nephropathy, the severity of the disease is associated with the level of desialylation of galactose-deficient IgA1 whereas C4d deposits are associated with elevated levels of IgA1 glycoforms involving aberrantly glycosilated N-linked glycan residues.

SA-OR062

An Open-Label Pilot Study of ACTH in the Treatment of IgA Nephropathy at High Risk of Progression

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Background: Patients with IgAN and elevated proteinuria despite renin-angiotensin inhibition (RASI) are at risk of progressive CKD, and therapeutic options are limited. ACTH has been shown to lower proteinuria in certain proteinuric kidney diseases. We hypothesized that it may be effective in lowering proteinuria and preserving renal function in patients with IgAN at high risk of progression.

Methods: We conducted a prospective open-label pilot study in patients with IgAN using ACTH (H.P. Acthar® Gel) at a dose of 80 units SC twice weekly for a total of 6 months (m) and followed patients for a total of 12m. Patients had to have urinary protein (UP) > 1 g/24 hr despite adequate RASI & eGFR >30 ml/min at enrollment. Secondary IgAN & those with hepatitis were excluded. Glucocorticoids could not have been used for the prior 3m. Primary endpoint was defined as achieving CR (24 hr UP <300 mg & ≤10% reduction in eGFR) or PR (≥50% reduction in UP and ≤25% reduction in eGFR).

Results: Twenty patients were enrolled. One was removed from the study at 3m as he was hepatitis B positive. Another patient withdrew at 6m due to progression of IgAN but was included in the analysis at 12m. At baseline, the mean age was 34.5 ± 10.5 yrs with 11 males & 8 females, 14 Caucasian & 5 Asians. At 12m there was a statistically significant decline in 24hr UP from 2.8 to 1.9 g (P=0.006) and significant increase in serum albumin (3.79 to 3.93, P=0.02). There was no significant change in eGFR (65.5 to 61.1 ml/min, P=0.1). There were 8 PRs (42%). There were total of 4 infections (1 pneumonia, 1 otitis media, and 2 sinus infections) that required antibiotics. Most common adverse events included acne, hot flashes, and anxiety.

Conclusions: Patient with IgAN with >1 g/24 hr UP and eGFR >30ml/min had a significant reduction in 24hr UP with stable eGFR at 12m follow up after being treated with 6 months of ACTH.

Funding: Commercial Support - Mallinckrodt

Patients' clinical and renal charactersitics

	Baseline (n=19)	12 months (n=19)	P value
sBP (mmHg)	124.2 ± 20.2	118.8 ± 11.1	0.24
dBP (mmHg)	76.0 ± 8.2	76.6 ± 9.8	1.0
BMI (kg/m2)	27.7 ± 7.4	28.5 ± 7.0	0.18
Serum creatinine (mg/dL)	1.40 ± 0.49	1.55 ± 0.64	0.1
eGFR - CKD-EPI (ml/min)	65.5 ± 28.8	61.1 ± 31.1	0.1
Serum albumin (g/dL)	3.79 ± 0.54	3.93 ± 0.39	0.02
24 hour urinary proteia (mg)	2821 ± 1234	1963 ± 1668	0.006

SA-OR063

Using Long Term Outcome Data to Redefine Proteinuria and eGFR End Points for Lupus Nephritis Trials

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Background: Lupus Nephritis (LN) is a common & severe manifestation of systemic lupus erythematosus (SLE) that can lead to renal failure (ESRF). Reviews of Euro-Lupus Nephritis & MAINTAIN cohorts suggest a less stringent cut off proteinuria at 1yr (<0.8g/d & <0.7g/d respectively) better predicted good renal outcome at 7yrs than usual complete remission (CR) criteria (<0.5g/d). This cut-off has yet to be validated using urinary protein creatinine ratio (uPCR) or in a larger real world cohort.

Methods: Data were reviewed for LN biopsies 1/1/1996 to 1/1/2016. Definition CR:uPCR (mg/mmol) <50 & estimated glomerular filtration rate (eGFR mls/min/1.73m^2) ≥60, or if b/l <60, no fall >20%; Partial remission (PR):uPCR <300 with ≥50% improvement & eGFR as CR; Non-remission (NR):no PR by 1yr. Factors predicting good outcome, defined as 1-46yr survival with eGFR >60, assessed by multiple logistic regression (LR) with correction & receiver operating characteristic (ROC) curves.

Results: 476 patients had 819 biopsies. Median age diagnosis:SLE 29yrs; LN 32yrs. Female:82%. Ethnicity:32% S Asian, 27% Black, 26% White& 3% SE Asian. At latest f/up since diagnosis LN (median 9yrs(0-46): majority, 293(62%) had good outcome; ESRF: 68(14%), median 5yrs(0-43); died: 31(7%), 7yrs(0-19). LR identified 1yr eGFR and uPCR as predictors of good outcome: eGFR odds ratio (OR) 2.186 (95% CI 1.529-3.126) p<0.001 for each rise 10; uPCR OR 0.547 (0.356-0.841) p=0.006 for increase between ranges (0-50,50-100,100-300,300-500,500-1000,>1000). ROC curves identified 1yr uPCR <68 (AUC0.70,p<0.0001,sens 67%,spec 65%) & eGFR >80.5 (AUC 0.83,p<0.0001,sens 77%,spec 76%) predictive of good outcome. Standard CR&NR definitions fail to predict good outcome; in contrast, achieving uPCR & eGFR identified by ROC curves strongly predicted good outcome OR 5.68 (95% CI 2.367-13.635, p<0.001); OR good outcome if not achieved 0.42 (95% CI 0.188-0.926, p=0.032).

Conclusions: Our "real world" multi-ethnic cohort, the largest to date, support Eurolupus and MAINTAIN data: less stringent proteinuria thresholds (<68mg/mmol) and excellent renal function (>80.5ml/min/m^2) at 1yr better predict long term outcome than current trial endpoints. As the key outcome that matters to patients, we argue it is time to change definitions of success of treatments in LN trials.

SA-OR064

Infectious Complications in Lupus Nephritis Treatment: A Systematic Review and Meta-Analysis

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Background: Infection is an important concern in lupus nephritis treatment, but few studies have primarily focused on this complication. We investigated the incidence rate of infections, their associated risk factors, and outcomes reported in the literature.

Methods: Randomized controlled trials (RCTs) on lupus nephritis Class III/IV/V published between January 1980 and December 2016 and identified from Pubmed/Medline were included in the meta-analysis. Infection risk associated with different immunosuppressive medications was presented as risk ratio (RR) with 95% confidence interval (CI) using the Mantel-Haenszel method.

Results: Thirty-two RCTs involving 3834 patients were included. Estimated incidence rates of overall and serious infections were both higher during the induction phase than maintenance phase. The rate of serious infections ranged from 8.2-50 per 100 patient-years during the induction phase, and 3.5 per 100 patient-years during maintenance phase. The rates of serious infections were 4.1-25% in Asia and 4.4-8.5% in non-Asian countries; with infection-related mortality rates of 0-6.7% in Asian, compared to 0-2.1% in non-Asian locations. Mycophenolate mofetil as induction treatment was associated with lower overall infection risks than cyclophosphamide in non-Asian countries (RR, 0.60; 95% CI, 0.48–0.75; p<0.001). Recent data (since 2011), predominantly from Asia, suggested that tacrolimus used as induction immunosuppression was associated with lower rates of overall infections compared with mycophenolate mofetil (RR, 0.50; 95% CI, 0.33–0.76; p=0.001).

Conclusions: Infection remains a serious complication in patients with lupus nephritis, especially in Asia, but the reported rates varied markedly. Mycophenolate mofetil was associated with lower infection rates in non-Asian patients, compared with cyclophosphamide; and further experience is required to confirm the infection risk associated with tacrolimus.

Funding: Private Foundation Support

SA-OR065

Lupus Nephritis Flare after Withdrawal of Immunosuppression Is Predicted by Kidney Biopsy Findings during Maintenance Therapy: A Prospective Observational Cohort Study

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Background: The optimal duration of maintenance immunosuppressive therapy in lupus nephritis (LN) is unclear. Withdrawal of immunosuppression is generally based on a patient achieving a sustained clinical remission (CR). However, a significant proportion of patients in CR continue to have persistent histologic activity on kidney biopsy. We postulated that patients with ongoing histologic activity are at risk of LN flare when maintenance therapy is tapered, and designed a prospective observational study to test this hypothesis.

Methods: Patients with Class III/IV±V LN on maintenance therapy who had received at least 3 years of immunosuppression and were in complete CR for at least the last year of treatment were recruited to undergo a kidney biopsy. Maintenance therapy was withdrawan after the kidney biopsy and patients were followed prospectively for 2 years. The primary endpoint of the trial was LN flare.

Results: Out of 44 recruited patients, 36 completed the study. Patients withdrew due to pregnancy, non-renal lupus flare, or by choice. Biopsy showed that 20 patients (55.6%) had achieved complete histologic remission with an NIH activity index (AI) of 0, nine patients (25%) had an AI of 1 or 2, and 7 patients had an AI between 3 and 5. LN flared in 11 patients (30.5%), all but one flare (91%) occurred in patients with persistent histologic activity, and everyone with an AI>2 flared. In multivariable analysis AI and duration of SLE were independent predictors of LN flare, and these variables could discriminate between future flare and no-flare with 100% sensitivity, 88% specificity, an 8.3% misclassification rate, and an area under the ROC curve of 0.98. Among the individual components of the AI, endocapillary proliferation and subendothelial deposits were both significantly associated with the odds of future flare, but endocapillary proliferation was a more robust marker.

Conclusions: Persistent histologic activity in kidney biopsies of LN patients in complete CR on maintenance immunosuppression, especially persistent endocapillary proliferation, is a risk factor for future LN relapse. A kidney biopsy during maintenance immunosuppression may help inform the decision of whether to withdraw or continue maintenance therapy in LN.

Funding: Government Support - Non-U.S.

SA-OR066

A Phase III Study of Abatacept on Standard of Care in Patients with Active Class III or IV Lupus Nephritis

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Background: Novel treatments (tx) for active class III or IV lupus nephritis (LN) are needed. This study compared IV abatacept (ABA) vs placebo (pbo) on background therapy for tx of active proliferative LN.

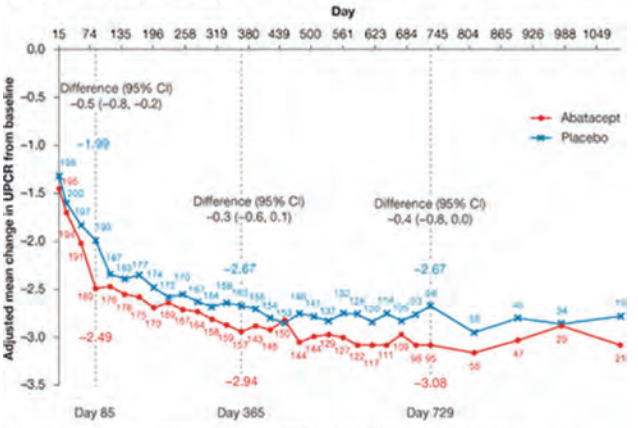
Methods: This was a 24-month (M), randomized, Phase III, double-blind study with long-term extension. Patients (pts) were randomized to pbo or IV ABA every 4 wks on background of MMF + corticosteroids (CS). Primary endpoint: complete response (CR; UPCR ≤0.5, preserved eGFR, no cellular casts, CS ≤10 mg/day) at Year (Yr) 1. We report all blinded data up to Yr 3 of tx.

Results: 405 pts were randomized (ABA n=202; pbo n=203). At baseline: mean age=33 yrs, UPCR=3.78, eGFR=95 mL/min. ABA 77%, pbo 79% completed Yr 1; fewer discontinued during Yr 2 (ABA 14%, pbo 22%). There were no differences between tx arms in CR rates at Yr 1 (ABA 35.1%, pbo 33.5%, p=0.73; primary endpoint). Sustained CR (two successive visits) were more frequent and occurred earlier in ABA pts. CR rates were higher and non-response rates lower in ABA arm in Yr 2 and 3. Benefits were driven by improvement in proteinuria, seen as early as 3 M and sustained up to 3 yrs (Figure). There was no between-group difference in eGFR over 3 yrs. Safety in Yr 1 was consistent with the known profile of ABA (serious AE [SAE] rate ABA 24%, pbo 19%). SAE rates after Yr 1 were lower (ABA 6%, pbo 13%). More sustained improvements in SLE-related biomarkers (C3, C4, anti-dsDNA) were seen in ABA-treated pts over 3 yrs.

Conclusions: The study failed to meet its primary endpoint. Up to 3 yrs of tx, abatacept-treated pts had more rapid improvement in proteinuria, which led to earlier, sustained CR with a favorable safety profile. Writing assistance provided by Caudex.

Funding: Commercial Support - Bristol-Myers Squibb

Figure: Adjusted Mean Change in UPCR Over Time (all Patients)



Adjusted mean change is estimated from longitudinal model repeated mixed model which includes stratification factors (race, ACEi/ARBs use) treatment group, time, time*treatment group interaction and baseline UPCR as continuous covariate
ACEi=angiotensin-converting enzyme inhibitor; ARBs=angiotensin receptor blockers; UPCR=urine protein-to-creatinine ratio

SA-OR067

Correlation of Albuminuria and Hypoalbuminemia with Area Under the Curve Levels of Mycophenolic Acid in Lupus Nephritis

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Background: Mycophenolate mofetil (MMF) is the mainstay of therapy for lupus nephritis (LN). Studies have shown targeting an area under the curve (AUC) leads to better outcomes in these patients. Therefore, it is critical to identify factors modifying AUC of MMF. Mycophenolic acid (MPA) the active metabolite of MMF binds avidly to albumin. Since patients with lupus often have profound albuminuria and hypoalbuminemia, we hypothesized that it might influence MPA-AUC.

Methods: 51 subjects with biopsy confirmed LN on 1500 mg of MMF twice daily, were included in this study. MPA levels were obtained at 0, 1, 2 and 4 hours. The MPA-AUC values calculated using the linear trapezoidal rule. Spearman correlations were used for correlations between urine albumin creatinine ratio (UACR), serum albumin and MPA-AUC.

Results: Subjects mean age was 33±13 years. The mean serum albumin was 3.3± 0.9 g/dL. 90 % of patients had albuminuria with a median of median of 874 mcg/mg [IQR: 365, 2150]. In univariate analysis there was a statistically significant correlation between AUC and UACR (Rho=-0.34, P=0.02) and serum albumin (Rho=0.48, P=0.004) (Figure-1A and 1B). In multivariate analyses serum albumin remained an independent predictor of AUC when controlled for age and proteinuria [R^2=0.21 p=0.03], but not for renal function[p=0.06]. Hypoalbuminuria was a predictor of AUC only for an eGFR > 60 ml/min/1.73 mt2.

Conclusions: Our results reveal that hypoalbuminemia is associated with lower therapeutic levels of MMF, particularly in those with normal renal function. Patients with hypoalbuminemia are more likely to have severe disease warranting higher doses of MMF. We will discuss the implications of these findings with regard to the monitoring of MMF-AUC to ensure adequate therapeutic doses in such patients.

Figure-1A

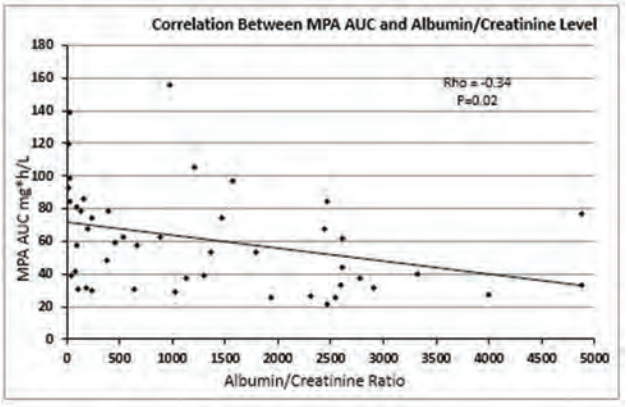
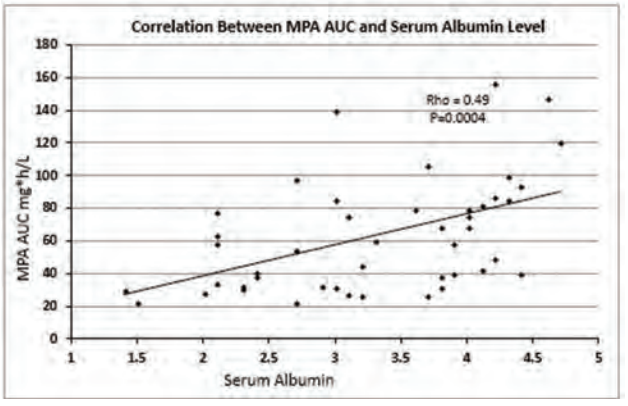


Figure-1B



SA-OR068

A Randomized Controlled Trial of Albumin Versus Saline for the Prevention of Intradialytic Hypotension in Hypoalbuminemic Patients

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Background: Intradialytic hypotension (IDH) is a frequent complication in hypoalbuminemic patients with AKI or ESRD limiting adequate fluid removal and increasing the risk for vascular access thrombosis, early hemodialysis (HD) termination, and mortality. Albumin infusion before and during therapy has been used for preventing and treating hypotension with varying results. We evaluated the efficacy of albumin infusion in preventing intradialytic hypotension during HD.

Methods: A randomized, crossover trial was performed in 65 patients with albumin<3g/dl with AKI or ESRD who required HD during hospitalization. Patients were randomized to receive 100mL of either 0.9% sodium chloride or 25% albumin intravenously prior to their first dialysis session and alternated between the two solutions for up to 6 sessions. Patients' vital signs and ultrafiltration removal rate were recorded every 15 to 30 minutes during HD. All symptoms associated with hypotension as well as interventions during the dialysis were recorded. IDH was assessed by different definitions reported in the literature (Table).

Results: 65 patients completed 249 sessions; mean age was 58(+/-12), 46(70%) were male with a mean weight of 76 (+/-18) kg. Presence of IDH was lower during albumin sessions based on all definitions. The risk of hypotension was significantly decreased based on the KDOQI, decrease in systolic blood pressure (SBP)<30 and 20mmHg and a nadir<90mmHg definitions.

Conclusions: In hypoalbuminemic patients who need IHD, administration of albumin before dialysis results in fewer episodes of intradialytic hypotension. Albumin infusion may be of benefit to improve safety of IHD in high-risk patients

Intradialytic hypotension definition and frequency in NS and Albumin groups

Term	Definition	Albumin	NS	P
Nadir90	Min IHD SBP< 90 mmHg	22 (17.7%)	31 (24.8%)	0.09
Nadir100	Min IHD SBP<100 mmHg	55 (44.4%)	56 (44.8%)	0.92
Fall20	Pre-HD SBP-min IHD ≥ 20	44 (35.8%)	59 (48.0%)	0.02
Fall30	Pre-HD SBP-min IHD ≥ 30	29 (23.6%)	40 (32.5%)	0.04
Fall20Nadir90	Pre-HD SBP-min IHD ≥ 20 and min IHD SBP <90	4 (3.3%)	14 (11.4%)	0.01
Fall30Nadir90	Pre-HD SBP-min IHD ≥ 30 and min IHD SBP <90	3 (2.4%)	9 (7.3%)	0.09
KDOQI	Pre-HD SBP-min IHD ≥ 20 and symptoms of cramping, headache, lightheadedness, vomiting, or chest pain during HD	9 (7.3%)	19 (15.4%)	0.002
HEMO	Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration	16 (12.9%)	26 (20.8%)	0.07

P values based on Generalized Estimating Equations to analyze the effect of albumin on hypotension outcome.

SA-OR069

Thirst, Xerostomia, and Inter-Dialytic Weight Gain in the Sodium Lowering in Dialysate (SoLID) Trail

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Background: A number of observational studies and clinical trials have shown that lower dialysate [Na^+] is associated with reduced fluid intake in hemodialysis (HD) patients. We report the effect of lower dialysate [Na^+] on thirst, xerostomia, and inter-dialytic weight gain (IDWG) in the Sodium Lowering in Dialysate (SoLID) trial (ACTRN12611000975998, www.solid.org.nz).

Methods: The SoLID trial randomised 99 participants on home or self-care HD from 11 sites in New Zealand to the control group (dialysate [Na^+] of 140mM) or intervention group (135mM) for 12 months. Thirst and xerostomia were scored by validated inventories - the Dialysis Thirst Inventory or DTI (Bots 2004), and the Xerostomia Inventory or XI (Thomson 2011). IDWG was measured as the weight gain between dialysis sessions averaged over a two-week period. Outcomes were ascertained at baseline, 6 and 12 months, and analysed using generalized linear models on an intention-to-treat basis.

Results: Results are tabulated in Table 1. IDWG was lower in the intervention group compared to the control group at all time-points There was little or no difference in thirst and xerostomia between the control and intervention groups at either 6 or 12 months.

Conclusions: In the SoLID trial, lower dialysate [Na^+] clearly reduced fluid intake, consistent with previous clinical trials. The intervention did not change DTI and XI, however, despite previous observational studies showing positive correlation between DTI and XI with IDWG (Bots 2004). Further research is underway to determine the relationship between IDWG and the individual items within the DTI and XI instruments. It may be that the DTI and XI are invalid in prospective settings due to recall bias or other reasons, and that other methods are more suitable for determining the longitudinal effects of different interventions on thirst and xerostomia.

Funding: Commercial Support - Fresenius Medical Care (Australia), Private Foundation Support, Government Support - Non-U.S.

Mean difference (p-value) in outcomes between control and intervention group at 6 and 12 months

	Dialysis Thirst Inventory (DTI) score	Xerostomia Inventory (XI) score	IDWG in kg
6 months	-1.22 (0.38)	-0.62 (0.53)	-0.559 (0.001)
12 months	0.57 (0.68)	0.38 (0.70)	-0.569 (<0.0005)

SA-OR070

Subgroup Analysis of Impact of Extended Hours Dialysis on Quality of Life in the Active Dialysis Trial

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Background: The ACTIVE Dialysis trial of extended hours (≥24 hours per week) versus standard hours (≤18 hours per week) haemodialysis demonstrated a significant improvement in QOL as measured by Short Form-36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS). We aimed to determine if the effect of extended hours dialysis on quality of life (QOL) in the ACTIVE Dialysis trial differed according to pre-specified subgroups.

Methods: The ACTIVE Dialysis trial was an open-label randomised, blinded endpoint assessment trial. Two hundred participants were enrolled from four countries and randomised to 12 months of standard or extended hours dialysis. The SF-36 was administered by a blinded interviewer at 3-month intervals. Mean difference between extended and standard arms was assessed by mixed linear regression. The overall effect sizes (Cohen's *d*: where 0.2-0.5 is a small effect, 0.5-0.8 a moderate effect and >0.8 a large effect) were calculated as the ratio of mean difference to standard deviation. Subgroup variables were added to the regression model with an interaction with treatment group to test for effect modification.

Results: Extended hours dialysis was associated with significant improvement in PCS (2.30 [95% CI 0.55-4.06]; p=0.010) and MCS (2.54 [95% CI 0.48-4.60]; p=0.016). The effect size on both measures was small (PCS 0.24 [95%CI 0.06-0.42; p=0.010], MCS 0.24 [95%CI 0.04-0.43; p=0.016]). The effect of extended hours dialysis did not vary significantly by baseline score, region (China vs Australia, Canada, New Zealand), dialysis location (home vs in-centre/satellite) or dialysis vintage (≤6 months vs >6 months).

Conclusions: Extended hours dialysis leads to a small improvement in physical and mental QOL. These effects did not differ significantly between key demographic and clinical subgroups.

Funding: Commercial Support - Baxter International, Government Support - Non-U.S.

SA-OR071

Bioelectrical Impedance Analysis (BIA) Versus Clinical Criteria for Setting Ultrafiltration (UF) in Chronic Hemodialysis (HD) Patients

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Background: This study compared the laboratory, echocardiographic and clinical outcomes of patients where dry weight (DW) was determined using BIA or clinical evaluation, thus guiding UF.

Methods: A prospective randomized study involving chronic stable HD patients, 21 in BIA and 21 in Clinical-group, managed based on a structured protocol to set UF. The effect on volume status and CV indices after 3 months was evaluated. BIA was done fortnightly for BIA-grp while hypo- or hypervolemia was observed every HD session for the other group. CBC, electrolytes were done monthly, inferior vena cava (IVC) size and collapsibility index (CI), Left ventricular (LV) size, cardiac index and ejection fraction were done at baseline and month 3. Intradialytic events were noted.

Results: DW decreased by 1.12 kg in BIA-grp (p=0.012). Lab results were similar in both groups. IVC and LV size decreased by 0.1 cm in BIA-grp but remained unchanged in Clinical-grp, although not significant (p=0.2183, p=1.000). IVC CI significantly increased to 49.5% in BIA-grp but dropped to 40.8% in Clinical-grp (p=0.0186) suggesting a decrease in right atrial (RA) pressure and attainment of euvolemia in the former group. There was a non-significant increase (4%) in the EF in BIA compared to Clinical (2%) group (p=0.527). Significant change in diastolic BP (7 mmHg drop) and MAP (8 mmHg drop) were seen in the BIA-grp (p=0.034, p=0.043). Intradialytic episodes of muscle cramps, chest pain/palpitations, and dizziness occurred only in BIA-grp (p=0.000).

Conclusions: BIA-guided determination of UF resulted in a significantly reduced dry weight, DBP, MAP, and RA pressure in a chronic HD population while other cardiac indices had a tendency to improve. All these may result in improved cardiac function and CV outcomes.

Funding: Commercial Support - Fresenius Medical Care

TABLE 1. Echocardiographic Findings and Dialytic Profile

CHARACTERISTICS		TOTAL (Mean ± SD) (n=42)	BIA GROUP (Mean ± SD) (n=21)	CLINICAL GROUP (Mean ± SD) (n=21)	P-VALUE
IVC Diameter (cm)	Baseline	1.8 ± 0.5	1.7 ± 0.4	1.8 ± 0.6	0.5323
	After 12 weeks	1.7 ± 0.5	1.6 ± 0.4	1.8 ± 0.6	0.2183
IVCCI (%)	Baseline	45.8 ± 11.5	45.9 ± 12.2	45.8 ± 11.0	0.9780
	After 12 weeks	45.5 ± 11.6	49.5 ± 9.4	40.8 ± 12.4	0.0186
Cardiac Index (L/min/m2)	Baseline	4.0 ± 1.7	3.8 ± 1.1	4.2 ± 2.2	0.4648
	After 12 weeks	4.1 ± 1.5	4.2 ± 1.5	3.9 ± 1.4	0.5105
LV size (cm)	Baseline	5.2 ± 0.5	5.3 ± 0.5	5.2 ± 0.6	0.5639
	After 12 weeks	5.2 ± 0.6	5.2 ± 0.6	5.2 ± 0.6	1.0000
Ejection Fraction (%)	Baseline	56.9 ± 13.3	58.1 ± 12.2	55.5 ± 14.7	0.5399
	After 12 weeks	59.8 ± 12.5	62.0 ± 10.9	57.2 ± 14.1	0.2314
DW (kg)	Baseline	55.7 ± 14.4	56.8 ± 15.0	54.6 ± 14.0	0.6285
	After 12 weeks	55.7 ± 14.7	55.7± 15.8	54.6 ± 13.9	0.8112
Kt/V	Baseline	1.8 ± 0.4	1.8 ± 0.3	1.8 ± 0.4	1.0000
	After 12 weeks	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.0000
SBP (mmHg)	Baseline	159 ± 23	162 ± 21	155 ± 24	0.3265
	After 12 weeks	151 ± 22	152 ± 18	150 ± 26	0.7749
DBP (mmHg)	Baseline	88 ± 12	91 ± 10	86 ± 13	0.1777
	After 12 weeks	86 ± 13	84 ± 13	88 ± 13	0.3307
MAP (mmHg)	Baseline	112 ± 13	114 ± 11	109 ± 15	0.2323
	After 12 weeks	107 ± 14	106 ± 13	108 ± 15	0.6493
Intra-dialytic hypotension		9	4 (44.4%)	5 (55.6%)	0.4798
Intra-dialytic muscle cramps		9	9 (100.0%)	0 (0.0%)	0.0000
Intra-dialytic chest pain/palpitations		2	2 (100.0%)	0 (0.0%)	0.0000
Intra-dialytic dizziness/headache		3	3 (100.0%)	0 (0.0%)	0.0000

** IVC, inferior vena cava; IVCCI, inferior vena cava collapsibility index; LV, left ventricle; DW, dry weight; Kt/V, measure of hemodialysis adequacy; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure*

SA-OR072

Online Haemodiafiltration Improves Inflammatory State in Dialysis Patients: A Longitudinal Study

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Background: We conducted this study to evaluate and compare the effect of online haemodiafiltration(OL-HDF) and conventional haemodialysis(C-HD) on the level of inflammatory markers (hs-CRP,IL1, IL6 and TNF- α) in Chronic Kidney Disease V (D).

Methods: In this prospective observational study we measured levels of hs-CRP, IL-1, IL-6 and TNF-alpha at baseline, 3months and 6 months. 60 patients (5 excluded, underwent transplant) with CKD V on C-HD for minimum 3 months were included. Study population was divided in two groups; 27 patients were continued on C-HD; 28 patients shifted on OL-HDF. Follow-up period was 6 months after randomization.

Results: Mean age was 50.22yrs. Mean Kt/v and dry weight were similar in both groups at baseline. Kt/v (P=0.78) & dry weight (P=0.591) remained stable in both groups after 6 months. Mean hs-CRP levels were similar in both groups at baseline (2.66±1.86 mg/dl vs 2.60±1.96 mg/dl; p=0.916) and at 6 months, there was significant reduction of hsCRP in the HDF group by 33%(p-0.007). Mean IL-1 levels were similar at baseline in both groups (177.30±41.86pg/ml vs 166.57±30.29pg/ml; p=0.280) and at 6 months, IL- 1 levels in HDF group decreased significantly (p<0.001) by 13 %. Mean IL-6 levels were similar at baseline in both groups (14.18±9.46pg/ml vs 12.74±7.63pg/ml; p=0.536) and at 6 months IL-6 levels in HDF group decreased significantly (p=0.001) by 33%. Mean TNF-α levels were similar at baseline in both groups (15.47±7.60pg/ml vs 14.87±7.48pg/ml; p=0.771) and at 6 months, TNF-α levels in HDF group decreased significantly (p=0.017) by 22 %. Mean Haemoglobin was similar in both groups at baseline (8.90±1.50gm/dl vs 9.16±1.33 gm/dl; p=0.498). At 6 months, haemoglobin was stable in HD group(p=0.426), while in HDF group it increased significantly (p=0.001) to 10.05±1.53gm/dl. This was associated with a significant decrease on rhEPO requirement in HDF group by 14% (p – 0.043). Mean S. phosphorous was similar in both groups at baseline (6.12±1.72mg/dl vs 6.07±2.05mg/dl; p=0.923). At the end of 6 month reduction in phosphorous in HDF group was significantly higher (p<0.001).

Conclusions: This study showed that CKD related inflammation improved significantly with online-HDF, with significantly decreased level of hs-CRP : 33%, IL-1 : 13%, IL-6 : 33%, THF- α : 22% after 6 months.

SA-OR073

Using IVC Collapsibility and Lung Ultrasound to Determine Ultrafiltration Goal in Hemodialysis Patients

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Background: Intra-dialytic hypotension (IDH) and pulmonary congestion are two problems at the opposite ends of the spectrum of the problems related to volume status management in ESRD patients. Current clinical assessment tools to predetermine ultrafiltration (UF) goal in hospitalized patients are inadequate. We sought to determine the utility of employment of hand-held ultrasound at the bedside to adjust goal UF in hospitalized HD patients.

Methods: Hospitalized patients receiving HD for AKI or ESRD in the MSH inpatient dialysis unit were eligible for participation in this pilot study at Mount Sinai Hospital. HD encounters were randomized to the ultrasound-assisted UF goal (intervention group) vs. standard of care to determine UF goal (control arm). In the intervention group, the UF rate ordered by the treating nephrologists was additionally adjusted based upon IVC collapsibility and lung ultrasound patterns assessed immediately prior to the start of HD, as shown in the **Table**. The primary outcomes were A. Intradialytic hypotension (IDH) and B. Moderate to severe congestion on the end of HD.

Results: There were 26 HD encounters in the intervention arm and 26 in the control arm. Based on the US findings, the UF goal was changed in 12 out of 26 (46%) HD patients in the intervention group; Among those 12, 6 patients were classified as hypervolemic and had their UF goal increased, and 6 patients were classified as hypovolemic and had their UF goal decreased. IDH was observed in 1 patient in the intervention arm vs. 4 patients in the control arm. Post-dialysis pulmonary congestion was seen in 2 patients in the intervention arm vs. 4 patients in control group.

Conclusions: This pilot study suggests that adjusting UF goal based on US findings may improve precision of the optimal UF for that HD session and has the potential to decrease incidence of IDH and post-dialysis pulmonary congestion.

Intervention Arm Protocol for UF Adjustment

CVP based on IVC	Lung US	INTERPRETATION	UF adjustment
>10	B line pattern	Hypervolemic	1L more than last time
6-10	A line pattern	Euvolemic	UF not adjusted
≤6	A line pattern	Hypovolemic	≤1L

SA-OR074

The Relationship between Non-Transferrin Bound Iron (NTBI) and Iron Utilization for Erythropoiesis in Maintenance Hemodialysis Patients

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Background: The relationship between non-transferrin bound iron (NTBI) derived oxidation stress and arteriosclerosis in maintenance hemodialysis (MHD) patients has been reported. In this study, we investigated the determinant of serum NTBI and the relationship between NTBI and iron utilization for erythropoiesis in MHD patients who did not receive the iron preparations.

Methods: Study design: multicenter cross-sectional study. We evaluated the blood levels of hemoglobin (Hb), β2-microglobulin (βMG), total cholesterol, triglyceride, iron, hepcidin, ferritin, total iron binding capacity (TIBC), NTBI, Interleukin(IL)-6, tumor necrosis factor (TNF)-α, and high sensitive (hs) CRP in 126 MHD patients who did not receive the iron preparations for the past three months. To evaluate the relationship between serum NITB and iron utilization for erythropoiesis, patients were divided into 4 groups according to Hb and ferritin levels (Hb<10 g/dL and ferritin<50 ng/mL, Hb<10 g/dL and ferritin≥50 ng/mL, Hb≥10 g/dL nad ferritin<50 ng/mL, and Hb>10 g/dL and ferritin≥50 ng/mL).

Results: There was no significant difference in the NTBI levels in patients with or without diabetes and hepatitis C. Moreover, there was no significant correlation among NTBI, age, hemodialysis duration, and inflammation index (IL-6, TNF-α, hsCRP). In multivariate analysis, only serum ferritin was selected as a significant (β=0.69, p<0.0001) predictor of serum NTBI levels. Even after adjusting according to the dose of ESA, the serum NTBI of patients with Hb<10 g/dL and ferritin≥50 ng/mL (0.72± 0.5(μM Fe)) had significantly higher levels than other groups ((Hb<10 g/dL and ferritin<50 ng/mL: 0.57±0.35 (μM Fe), Hb≥10 g/dL and ferritin<50 ng/mL: 0.58±0.28 (μM Fe), and Hb>10 g/dL and ferritin≥50 ng/mL:0.62±0.41 (μM Fe).

Conclusions: In this study, we revealed that serum NTBI levels in MHD patients were related to the iron storage and iron utilization for erythropoiesis. Although, repleted iron storage patients with anemia who suspected dysutilization of iron for erythropoiesis already showed significantly higher serum NTBI levels; iron administration to these patients might cause further higher NTBI levels related with arteriosclerosis of MHD patients.

SA-OR075

Phase 3, Multicenter, Open-Label Study of Intermittent Oral Roxadustat in Peritoneal Dialysis CKD Patients with Anemia

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Background: Roxadustat is an oral HIF-PHI in late-stage development for treatment of anemia in CKD. This Phase 3 study evaluated the efficacy and safety of roxadustat in Japanese CKD patients on peritoneal dialysis (PD).

Methods: This 24-week, randomized, open-label study enrolled adult, Japanese, anemic CKD patients on PD into two groups based on prior ESA treatment. Patients not treated with ESA (ESA Untreated) were randomized to roxadustat 50mg or 70mg; patients treated with prior ESA (ESA Treated) were switched to roxadustat 70mg or 100mg depending on prior ESA dose. Dose was adjusted throughout the study to maintain a target hemoglobin (Hb) level of 10.0-12.0 g/dL. Efficacy endpoints were maintenance rate of target Hb level at Weeks 18-24, cumulative response rate at the end of treatment (two Hb thresholds, 10.0 g/dL and 10.5 g/dL; and Hb increase, ≥1.0 g/dL), average Hb levels at Weeks 18-24 and its change from baseline, and rate of rise in Hb levels from Week 0 to Week 4. Safety was assessed by occurrence of adverse events (AEs).

Results: 56 patients were enrolled (ESA Untreated, n=13; ESA Treated, n=43). Maintenance rates were 92.3% (95% CI: 64.0, 99.8; ESA Untreated) and 74.4% (95% CI: 58.8, 86.5; ESA Treated). Maintenance rates of patients with at least one Hb value at Weeks 18-24 were 92.3% (95% CI: 64.0, 99.8; ESA Untreated) and 86.5% (95% CI: 71.2, 95.5; ESA Treated). In the ESA Untreated Group, cumulative response rate for both Hb thresholds was 100%. Mean of average Hb levels at Weeks 18-24 were 11.05 g/dL (95% CI: 10.67, 11.42; ESA Untreated) and 10.93 g/dL (95% CI: 10.73, 11.13; ESA Treated); mean change in average Hb at Weeks 18–24 from baseline was 1.69 g/dL (95% CI: 1.06, 2.33; ESA Untreated) and 0.14 g/dL (95% CI: –0.12, 0.39; ESA Treated). In the ESA Untreated Group, mean (SD) rate of rise in Hb levels from Week 0 to Week 4 was 0.193 (0.203) and 0.556 (0.408) g/dL/week with roxadustat 50mg and 70mg, respectively. The most common AEs were nasopharyngitis, back pain, catheter site infection, diarrhea, vomiting, abdominal pain, conjunctivitis, constipation, nausea, and pruritus.

Conclusions: Roxadustat was well tolerated and effective in achieving and maintaining Hb levels within the target range in Japanese CKD patients on PD previously treated or untreated with ESA.

Funding: Commercial Support - Astellas Pharma Inc

SA-OR076

Effect of Intradialytic Exercise on Physical Performance and Echocardiographic Findings in Maintenance Hemodialysis Patients

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Background: Poor physical performance (PP) is frequently observed and related to a high risk of mortality, cardiovascular events, and hospitalizations in dialysis patients. We aimed to investigate the effect of intradialytic exercise (IDE) on PP and echocardiographic findings in maintenance hemodialysis (MHD) patients.

Methods: This study randomly assigned ambulatory MHD patients aged≥20 years on dialysis≥6 months, to 4 groups: aerobic exercise (AE), resistance exercise (RE), combination exercise (CE), and control. A stationary bike was used for AE at moderate intensity and a TheraBand®/theraball for RE at vigorous intensity. A 12-week IDE program (3 times/week) was completed in the AE (n=11), RE (n=10), and CE (n=12) groups. The control group (n=13) received only warm-up stretching. At baseline and 12-week follow-up, a sit-to-stand for 30 seconds test (STS30), a 6-minute walk test (6-MWT), and echocardiography were performed in all patients.

Results: We observed significant increases in STS30 (times/30 s) and 6-MWT (meters) in the AE (18.7±5.4 vs 16.5±4.8 and 459±122 vs 434±111, respectively), RE (24.6±4.9 vs 21.0±5.0 and 530±106 vs 510±102, respectively), and CE (24.8±10.7 vs 21.6±9.6 and 514±165 vs 492±167, respectively) groups at 12 weeks compared with baseline, while no improvement was observed in the control group. When comparing between-group changes in STS30 and 6-MWT, there were significant increases in the AE (2.3±2.2 vs -0.5±2.2 and 25±29 vs -26±41, respectively), RE (3.6±2.7 vs -0.5±2.2 and 20±21 vs -26±41, respectively), and CE (3.3±3.1 vs -0.5±2.2 and 22±12 vs -26±41, respectively) groups compared with the control group. In the echocardiographic analysis, the 12-week IDE group interventions (AE, RE, and CE) showed no significant change on left ventricular (LV) ejection fraction (%) (2.5±5.2, -0.7±5.3, and -0.3±5.4 vs 0.3±3.9, respectively), LV mass index (g/m^2) (-1.5±16.7, 0.8±16.3, and -0.5±32.0 vs -11.7±30.1, respectively), and myocardial performance index (0.09±0.19, -0.02±0.18, and 0.12±0.21 vs 0.08±0.18, respectively) compared with the control group.

Conclusions: Although IDE does not affect the echocardiographic parameters measured, it appears to be clinically beneficial in improving PP. It may suggest that IDE can also contribute to improve PP even before any significant benefits in cardiac function is achieved in MHD patients.

SA-OR077

Effects of Age and Hemodialysis on Frailty Prevalence, Gait, and Balance in Diabetic Patients: A Randomized Controlled Trial

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Background: Motor skills deteriorates with aging. Some conditions may magnify this deterioration. This study examined whether diabetes and hemodialysis (HD) would negatively impact gait, balance, and physical frailty beyond aging.

Methods: Seventy-three elderly adults with diabetes (age=71.4±5.4 years, BMI=30.8±5.9, 49% were on HD) and seventy-eight mid-age adults with diabetes (age=56.7±5.7 years, BMI=31.1±7.2, 50% were on HD) were recruited. Gait and balance performances were objectively measured using validated wearable sensors at HD clinic. Frailty status was determined by Fried Frailty Criteria.

Results: Aging deteriorated motor-functions (gait and balance) in people with diabetes irrespective of dialysis (9%-46% deterioration, Cohen's *d*effect size=0.22-0.42), with largest effect size observed for double support in gait performance (p=0.011). In addition, deteriorations in gait and balance caused by aging were more pronounced among diabetics with HD (19%-65% deterioration, d=0.41-0.75, p<0.05), when compared to diabetics without HD (1%-14% deterioration, d=0.01-0.20, p>0.05). The largest effect size for gait deterioration among diabetics with HD was observed in double support test (d=0.75,p = 0.002, Fig. 1), and the largest effect size for balance deterioration was observed in ankle stability test (d=0.48, p = 0.042, Fig. 1). Diabetics with HD, irrespective of age, had 3 times higher prevalence of frailty than diabetics without HD (42% vs. 14%, p=0.017).

Conclusions: Our study showed that HD deteriorates gait and balance and magnifies prevalence of frailty by factor of 3 beyond aging in people with diabetes. Immobility caused by prolonged HD (4-hour, 3 times per week) and post-dialysis exhaustion may contribute to poorer motor function in older diabetics leading to frailty. This study demonstrated practicality of wearable sensors to assess motor performance in dialysis clinics with opportunity to capture early deterioration.

Funding: Government Support - Non-U.S.

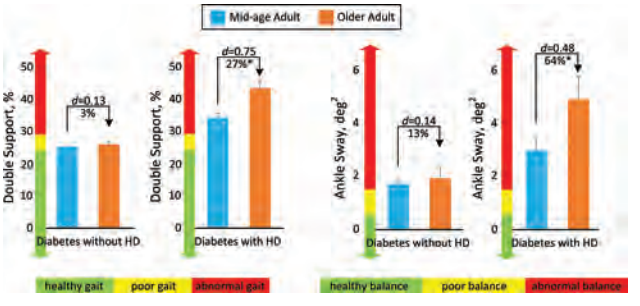

Fig. 1: Gait and balance comparison between mid-age and elderly diabetic patients with and without HD.

SA-OR078

Higher eGFR at Ten Years in CKD Stage 2 Patients Treated with Chronic Oral NaHCO3 Despite No Metabolic Acidosis Is Associated with Prevented Worsening of Underlying Acid Retention

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Background: Chronic oral $NaHCO_3$ but not eqimolar NaCl preserves eGFR compared to placebo in CKD stage 2 (eGFR=60-89 ml/min/1.73 m^2, CKD 2) patients (Mahajan et al, KI, 2010) without metabolic acidosis (conventionally defined as plasma total CO_2 <22 mM). Because amelioration of underlying H^+ retention with dietary alkali in experimental CKD models without metabolic acidosis helped preserved GFR (Wesson et al, Kid Int 2010), we explored if eGFR preservation in CKD 2 patients without metabolic acidosis receiving $NaHCO_3$ was associated with amelioration of underlying acid (H^+) retention.

Methods: We randomized 120 CKD 2 non-diabetic, macroalbuminuric subjects with hypertension-associated nephropathy without metabolic acidosis (plasma total CO_2 > 24 mM) to receive 0.5 meq/kg bw/day $NaHCO_3$ (HCO3, n=40), 0.5 meq/kg bw/day NaCl (NaCl, n=40), or to usual care (UC, n=40) and assessed them yearly for 10 years. We measured Cystatin C-based estimated GFR (eGFR) and H^+ retention by comparing observed to expected increase in plasma total CO_2 in response to retained HCO_3 (dose minus $U_{HCO3}V$) 2 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body weight HCO_3 apparent space of distribution.

Results: Baseline eGFR was not different among groups, was lower than their respective baseline for each group at 10 years, but the 10-year value was higher ($p<0.01$) in HCO_3 (60.3±4.8 ml/min/1.73 m^2) than NaCl and UC (52.2±5.8 and 51.4±4.6 ml/min/1.73 m^2, respectively). Baseline H^+ retention was not different among groups and the 10-year vs. baseline value was not different for HCO_3 (15.7±12.6 vs. 18.1±14.87 mmol, p=0.90). By contrast, 10-year H^+ retention was higher than baseline in NaCl (27.5±15.2 vs. 19.2±16.7 mmol, respectively, $p<0.01$) and UC (22.1±11.2 vs. 17.4±9.9 mmol, $p<0.01$)

Conclusions: Better eGFR preservation in $NaHCO_3$-treated CKD 2 patients without metabolic acidosis was associated with no worsening of underlying H^+ retention whereas H^+ retention worsened in NaCl and UC with less eGFR preservation. The data support that worsening H^+ retention, without metabolic acidosis, contributed to nephropathy progression in CKD. The data suggest that more aggressive $NaHCO_3$ dosing might reduce H^+ retention, rather than preserve its level, possibly yielding even greater eGFR protection.

SA-OR079

Serial FGF23 Concentrations and Risk of ESRD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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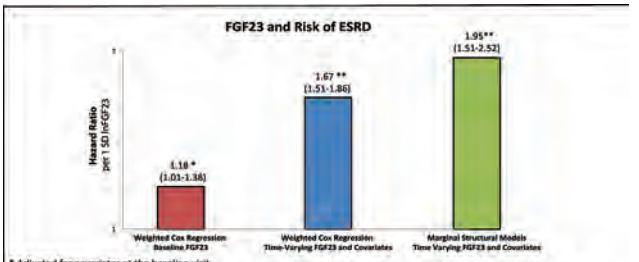
Background: Studies using a single FGF23 value suggest that elevated plasma FGF23 is associated with increased risk of ESRD in patients with CKD. However, the data are inconsistent and do not include serial assessments of FGF23.

Methods: To test the association between serial plasma FGF23 and ESRD risk, we performed a case-cohort study within the CRIC Study. We included 1597 individuals with serial FGF23 measurements: 1135 randomly selected individuals, of whom 266 reached ESRD, and 462 individuals outside the random subcohort who also reached ESRD. FGF23 values were available at 2–5 annual time points in all individuals (mean 4.0 ± 1.2). We used weighted Cox proportional hazards models adjusted for baseline and time-varying covariates. To account for the possibility that eGFR could be a time-dependent confounder, we used marginal structural models. We performed group-based trajectory modeling and adjusted the analyses for baseline and final eGFR and eGFR trajectory.

Results: In all models using baseline and time-varying FGF23, elevated plasma FGF23 was independently associated with increased risk of ESRD (Figure). In group-based trajectory analyses, compared to individuals with plasma FGF23 in the stable trajectory group, individuals in the slowly and rapidly rising trajectory groups were at ~3-fold and ~22-fold greater risk of ESRD (Table).

Conclusions: In multiple modeling approaches using serial FGF23 measurements, elevated plasma FGF23 was independently associated with risk of ESRD. Mechanistic studies are needed to test whether exposure to elevated and rising FGF23 levels contributes to accelerated CKD progression.

Funding: NIDDK Support



FGF23 Trajectories and Risk of ESRD

FGF23 trajectory group	Total N	ESRD N	Unadjusted	Model 1	Model 2	Model 3	Model 4	Model 5
Stable lnFGF23/year = 0.03	643	70	Reference	Reference	Reference	Reference	Reference	Reference
Slowly rising lnFGF23/year = 0.14	409	193	7.45 (5.54 – 10.03)	8.62 (6.22 – 11.93)	3.63 (2.43 – 5.42)	3.85 (2.57 – 5.78)	3.95 (2.55 – 6.12)	2.94 (1.89 – 4.56)
Rapidly rising lnFGF23/year = 0.40	111	91	43.80 (26.57 – 72.20)	52.25 (30.14 – 90.59)	23.52 (13.03 – 42.45)	29.69 (16.04 – 54.96)	34.13 (16.56 – 71.51)	21.89 (10.94 – 43.98)

Up to 5 annual time points, median duration of subsequent follow-up time 3.2 years in 1163 total participants at risk
Covariate adjustment are for final covariate values (time 0) except when stated
Model 1: stratified by center, adjusted for age, sex, race, and ethnicity
Model 2: Model 1 plus eGFR, UACR (baseline), serum albumin, hemoglobin, CRP (V3), and IL-6 (V3)
Model 3: Model 2 plus diabetes, smoking, SBP, BMI, history of coronary artery disease, heart failure, stroke, and peripheral vascular disease, number of hypertension medications, and ACE/ARB use
Model 4: Model 3 plus calcium, phosphate, PTH, lnFGF23, and baseline eGFR
Model 5: Model 4 plus eGFR trajectory (remove all other eGFR variables)

SA-OR080

Febuxostat for Patients with CKD Stage G3 with Asymptomatic Hyperuricemia: A Randomized Trial

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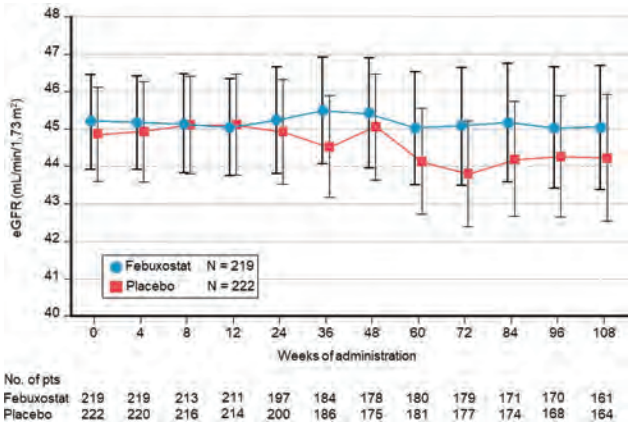
Background: Epidemiological and clinical studies have suggested that urate-lowering therapy may slow the progression of chronic kidney disease (CKD). However, clinical evidence is still scarce.

Methods: We conducted a randomized, double-blind, placebo-controlled trial in patients with CKD stage G3 [estimated glomerular filtration rate (eGFR) < 60 and ≧ 30 ml/min/1.73m^2] with asymptomatic hyperuricemia (n = 467) at 55 sites in Japan. Participants were randomly assigned, in a 1:1 ratio, to receive febuxostat (loading daily dose: 10 mg on days 1 to 28; maintenance daily dose: 40 mg at weeks 8 to 108) or placebo. The primary endpoint was the slope (mL/min/1.73 m^2 per year) of the eGFR. The mean eGFR slope, time-course changes in eGFR, and serum uric acid from baseline through week 108 were measured.

Results: Among 443 patients who underwent randomization, 220 received febuxostat and 222 received placebo. No significant difference was found in the mean eGFR slope between febuxostat (0.23 ± 5.26) and placebo (-0.47 ± 4.48) (difference, 0.70 mL/min/1.73 m^2 per year; 95% confidence interval, -0.21 to 1.62) (Figure). A subgroup analysis revealed a significant between-group difference in the kidney function decline-suppressing effect in patients who were negative for proteinuria (difference, 1.79; 95% confidence interval, 0.55 to 3.03) and whose serum creatinine concentration was lower than the median (difference, 1.76; 95% confidence interval, 0.44 to 3.07). The incidence of gouty arthritis was significantly lower (P = 0.007) in the febuxostat group [0.91% (2/219)] than in the placebo group [5.86% (13/222)]. Adverse events specific to febuxostat did not occur.

Conclusions: Febuxostat failed to show a statistically significant renoprotective effect as compared with placebo in Japanese patients with CKD stage G3 with asymptomatic hyperuricemia.

Funding: Commercial Support - Teijin Pharma Limited



SA-OR081

Reduction in Albuminuria with Dapagliflozin Cannot Be Predicted by Baseline Clinical Characteristics or Changes in Most Other Risk Markers

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Background: The sodium glucose co-transporter 2 inhibitor dapagliflozin (DAPA) has been shown to decrease the urine albumin:creatinine ratio (UACR). This effect varies markedly among individual patients. This study assessed the baseline characteristics and concurrent changes in other cardiovascular risk markers that could be associated with UACR response to DAPA.

Methods: A pooled analysis of 11 phase 3, randomized, controlled clinical trials was performed. UACR change from baseline post 24 weeks treatment with DAPA (10 mg/day) in 531 patients with type 2 diabetes and UACR ≥30 mg/g was determined. UACR response was defined as >30% reduction from baseline at 24-weeks and UACR non-response was defined as ≤30% reduction at 24-weeks.

Results: A total of 288 (54%) patients were classified as responders and 243 (46%) as non-responders. At 24 weeks, the UACR adjusted mean change from baseline appeared to be bimodal: −71.2% (95% CI: −73.7 to −68.3) in responders and 25.9% (95% CI: 17.1 to 35.4) in non-responders (Table). Baseline UACR, HbA1c, estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), body weight, cardiovascular disease history, and concomitant anti-diabetic medication use were similar between responders and non-responders. Changes in HbA1c, body weight, and haematocrit were also similar between the two groups. Responders showed a numerically larger reduction in SBP and eGFR compared to non-responders (Table). The incidence of hypoglycaemia and other adverse events was similar between the two groups.

Conclusions: UACR reduction to DAPA is an individual characteristic that cannot be predicted by baseline clinical features. It is associated with a modestly larger concurrent reduction in SBP and eGFR. Whether UACR responders compared to non-responders show improved long-term renal and cardiovascular outcomes remains to be determined.

Funding: Commercial Support - AstraZeneca, Gaithersburg, MD, USA.

Table: Adjusted mean change from baseline at week 24*

	UACR responders (N=288)	UACR non-responders (N=243)
UACR† (%)	−71.2 (−73.7, −68.3)	25.9 (17.1, 35.4)
HbA1c (%)	−0.9 (−1.1, −0.7)	−0.7 (−0.9, −0.6)
Body weight (kg)	−2.3 (−2.8, −1.9)	−2.3 (−2.8, −1.9)
Haematocrit (%)	2.0 (1.7, 2.3)	2.6 (2.2, 2.9)
SBP (mm Hg)	−8.7 (−10.2, −7.2)	−3.5 (−5.3, −1.8)
eGFR (mL/min/1.73 m²)	−2.4 (−4.0, −0.8)	−0.3 (−1.9, 1.3)

*Numbers are adjusted mean and 95% confidence interval (CI); †UACR was log transformed for analysis and exponentiated back for presentation. Abbreviations: eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; SBP: systolic blood pressure; UACR: urine albumin:creatinine ratio

SA-OR082

Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop Collaboration by the NKF, EMA, and FDA

Andrew S. Levey. Planning and Operations Committees and Analytic Group *Tufts Medical Center, Boston, MA.*

Background: The workshop was held on March 15-16, 2018. We used observational studies, clinical trials and simulations to address the research aims (Table). At the ASN meeting, we will present updated and more detailed results.

Methods: For observational studies, we included 20 studies comprising 585,723 participants with 7047 clinical endpoints (ESKD) for ACR change (or equivalent PCR change) and 14 studies, 3,373,368 participants, 14348 endpoints for eGFR slope. For clinical trials, we included 43 trials comprising 30,078 participants with 3939 clinical endpoints (ESKD, eGFR <15 and Scr doubling) for ACR change and 47 trials, 59,074 participants, 6883 endpoints for eGFR slope. For simulations, we performed 1000 independent simulations for >1200 scenarios for parameters related to eGFR trajectories and study design to compare power and type 1 error for eGFR slope with the clinical endpoint (ESKD or Scr doubling).

Results: For observational studies, after adjustment for measurement error, relationships between change in ACR or eGFR slope and the clinical endpoint were strong and consistent. For clinical trials, relationships of treatment effects on change in ACR and eGFR slopes with the clinical endpoint were moderately strong and strong, respectively. The magnitude of relationships was similar across cohorts and trials for both ACR change and eGFR slope (30% ACR reduction or eGFR slope improvement by 0.5-1.0 ml/min/1.73 m2 per year were associated with a HR of approximately 0.7 for the clinical endpoint). For simulations, eGFR slope can substantially reduce the required sample size and duration of followup compared to the clinical endpoint in some circumstances, particularly when baseline eGFR is high.

Conclusions: These analyses suggest that both change in albuminuria and GFR slope can fulfill criteria for surrogacy for use as endpoints in clinical trials for CKD progression under some conditions (characteristics of the clinical population, intervention and trial design), with stronger support for GFR slope than for albuminuria change. Implementation requires understanding conditions under which one or the other surrogate is likely to perform well and restricting its use to those settings.

Funding: Private Foundation Support

NKF-EMA-FDA Workshop Research Aims

1. Examine associations of changes in ACR with subsequent adverse outcomes (ESRD and mortality), and examine consistency of associations across subgroups (level of ACR and GFR, disease, and interventions) as well as implications of measurement error.
2. Examine associations of slope of GFR with subsequent adverse outcomes (ESRD and mortality), and examine consistency of associations across subgroups (level of ACR and GFR disease, intervention) as well as implications of measurement error.
3. Examine associations of treatment effects on early change in ACR with treatment effects on established endpoints, and consistency across subgroups (level of ACR and GFR, disease, and intervention)
4. Examine associations of treatment effects on GFR slope (acute, chronic and total slope) with treatment effects on established endpoints, and consistency across subgroups (level of ACR and GFR, disease, and intervention).
5. Develop methods to combine early change in ACR and GFR for combined endpoint

SA-OR083

Change in Albuminuria and Subsequent Risk of ESRD: A Consortium Meta-Analysis

Josef Coresh.[1,2] CKD Prognosis Consortium and CKD Epidemiology Collaboration *[1]CKD Prognosis Consortium, Baltimore, MD; [2]CKD Epidemiology Collaboration, Boston, MA.*

Background: A recent NKF-FDA-EMA Workshop evaluated candidate surrogate endpoints for clinical trials to slow kidney disease progression, particularly among participants with relatively preserved baseline glomerular filtration rate (GFR). Here we analyze the strength and consistency of the association between changes in albuminuria and end-stage kidney disease (ESKD) risk across a wide range of cohort studies.

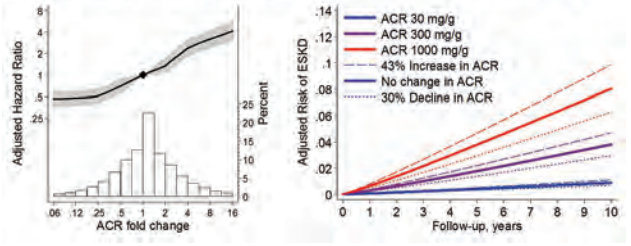
Methods: We included 20 studies with 585,732 individuals and 7,047 ESKD events. Using linear regression of log albuminuria, we quantified the percent change in albuminuria during a baseline period of 1, 2, and 3 years. Associations with subsequent ESKD were quantified using Cox regression in each cohort, followed by random-effects meta-analysis. Further adjustment for regression dilution was used to take into account the high variability of albuminuria to relate risk to true reductions in albuminuria.

Results: Change in urine albumin-to-creatinine ratio (ACR) was strongly related to ESKD risk (**Figure**). The adjusted hazard ratio of ESKD following a 30% decrease in ACR during a 2-year baseline period was 0.83 (95% CI 0.74-0.94); after further adjustment for regression dilution it was 0.77 (95% CI 0.65-0.92). Adjusted hazard ratios were relatively consistent across subgroups and study types but were somewhat stronger at higher ACR (p-interaction<0.05). Among persons with ACR >300 mg/g, a true reduction in ACR of 30% over 2-years was estimated to confer >1% absolute reduction in 10-year ESKD risk even at preserved GFR (**Figure**). Results were similar and slightly stronger for PCR.

Conclusions: Change in albuminuria was consistently associated with later risk of ESKD across a wide range of settings lending support to its use as a surrogate endpoint for CKD progression trials. Adjustment for high ACR variability was needed to demonstrate the similar magnitude of observational associations to clinical trials.

Funding: NIDDK Support, Private Foundation Support

Figure: Distribution of ACR fold change over 2-years and hazard ratio of ESKD (left) and absolute adjusted (eGFR 60) risk of ESKD over follow-up by baseline ACR groups and magnitude of change in ACR over 2-years (right, dashed lines show regression dilution adjusted risk for 30% decline and 43% increase=1/(1-30%))



SA-OR084

Early Albuminuria Change as Surrogate End Point for Kidney Disease Progression – Individual Patient Meta-Analysis of Randomized Controlled Trials: A Report from an NKF-FDA-EMA Workshop

Hiddo J. Lambers Heerspink. Chronic Kidney Disease-Epidemiology Collaboration *University Medical Center Groningen, Groningen, Netherlands.*

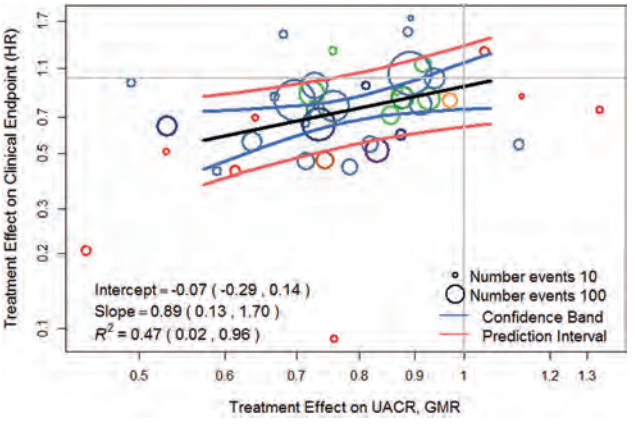
Background: A recent NKF-FDA-EMA Workshop evaluated candidate surrogate endpoints for clinical trials to slow kidney disease progression. Change in albuminuria (UACR) may have advantages as it occurs earlier than kidney failure or GFR decline.

Methods: Using a pooled dataset including 30078 patients from 43 RCTs with UACR data at baseline and 6 months post-randomization, we estimated treatment effects on UACR and the composite clinical end point of ESRD, eGFR < 15 or doubling of serum creatinine using separate intent-to-treat analyses in each RCT. We then performed Bayesian mixed models to relate the treatment effects on UACR to treatment effects on the clinical endpoint and to compute the predicted hazard ratio for the clinical endpoint given a specified magnitude of treatment effect on UACR.

Results: Treatment reduced 6-month UACR by a geometric mean ratio (GMR) 22% (95%CI18-26). The figure shows a statistically significant association of treatment effects on change in UACR compared to that of the clinical endpoint. The association was strengthened when analyses were restricted to those with baseline UACR > 30mg/g [R^2 47% (95%CI 2-96) vs 72% (5-99)]. For a 30% true change in UACR, the HR for the clinical endpoint was predicted to be 0.68 (95%CI 0.47-0.95) vs 0.93 (0.63-1.35) with no treatment effect on UACR. Results were consistent by subgroups of baseline eGFR, and disease.

Conclusions: In conjunction with results from epidemiological studies presented at the workshop, the moderately strong association between treatment effects on early changes in albuminuria and treatment effects on the clinical endpoint for UACR > 30mg/g supports the use of sufficiently large reductions (~> 30%) in albuminuria as a surrogate end point for kidney failure in clinical trials of kidney disease progression.

Funding: Private Foundation Support



The colours represent different interventions. GMR, geometric mean ratio. HR, hazard ratio

SA-OR085

Performance of eGFR-Based Surrogate End Points by Statistical Simulation: A Report from an NKF-FDA-EMA Workshop

Tom Greene,[1] Jian Ying.[2] CKD-Epidemiology Collaboration *[1]University of Utah, Salt Lake City, UT; [2]Univrsity of Utah, Salt Lake City, UT.*

Background: Analyses at the individual and trial level support the validity of 30% or 40% eGFR declines and eGFR slope as surrogate endpoints for randomized clinical trials (RCTs) of CKD. We apply statistical simulation to determine conditions in which eGFR-based surrogate endpoints a) increase statistical power, allowing shorter follow-up or reduced sample size compared to the clinical endpoint of doubling of SCR or kidney failure (CEP), and b) preserve low risk of false positive conclusions if the treatment does not affect the CEP (Type 1 error).

Methods: Using a dataset of 59,074 patients from 47 RCTs, we determined input parameters for simulations of eGFR trajectories and the relationships of these trajectories with kidney failure and death. 1,000 independent simulations were performed for > 1,200 scenarios for eGFR trajectories and specific study designs. We compared the total sample size (N) required for 90% power and evaluated Type 1 error for mean eGFR slope from baseline (total slope) and from 3 months follow-up (chronic) and for composite time-to-events endpoints based on 30%, 40% declines or kidney failure vs. the CEP.

Results: The table displays the required N for each endpoint for 9 scenarios defined by the acute effect of the treatment on eGFR and the type of long-term treatment effect (uniform across fast and slow progressors), proportional (greater for fast progressors), or intermediate. Other simulations show that in the absence of a positive acute effect, Type 1 error favoring the treatment is preserved for each method except chronic slope. Type 1 error for chronic slope may be inflated if a negative acute effect attenuates as eGFR declines.

Conclusions: eGFR-based surrogate endpoints can substantially reduce the required N vs. the clinical endpoint, particularly when baseline eGFR is high and there is no acute effect. The optimum eGFR-based endpoint depends on the rate of eGFR decline, type of treatment effect and study design.

Funding: Private Foundation Support

Acute Effect (ml/min/1.73m²)	Long Term Effect	Baseline eGFR (ml/min/1.73m²)	Ratio of Required N vs. CEP				Total N required for CEP
			Chronic Slope	Total Slope	30% eGFR decline	40% eGFR decline	
None	Uniform	42.5	0.29	0.26	0.52	0.63	5,210
None	Intermediate	42.5	0.55	0.47	0.79	0.77	2,490
None	Proportional	42.5	0.94	0.86	1.06	0.80	1,280
None	Uniform	67.5	0.08	0.07	0.21	0.31	22,090
None	Intermediate	67.5	0.26	0.23	0.42	0.49	5,320
None	Proportional	67.5	0.49	0.47	0.54	0.60	2,060
-1.25	Uniform	42.5	0.19	0.53	1.81	0.95	6,490
-1.25	Intermediate	42.5	0.40	1.18	2.49	1.13	2,580
-1.25	Proportional	42.5	0.65	1.70	2.67	1.08	1,430

Required Ns for 90% power with 2-sided α=0.05. Mean (SD) chronic slope in control group = -3.25 (4) ml/min/1.73m²/yr, mean baseline eGFR = 42.5 ml/min/1.73m², follow-up is 2.5 - 4 yrs, 25% treatment effect.

SA-OR086

GFR Slope as a Surrogate End Point for Kidney Disease Progression – Individual Patient Meta-Analysis of RCTs: A Report from an NKF-FDA-EMA Workshop

Lesley Inker. Chronic Kidney Disease-Epidemiology Collaboration *Tufts Medical Center, Boston, MA.*

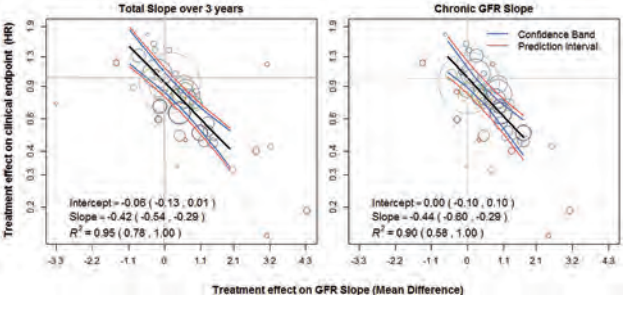
Background: A recent NKF-FDA-EMA Workshop evaluated candidate surrogate endpoints for clinical trials to slow kidney disease progression. GFR slope may provide an advantage over time to event endpoints by increasing power but has limitations, in particular when early acute changes differ from longer term changes.

Methods: Using a pooled dataset of 59074 participants from 47 studies, we computed GFR slope from randomization to 1, 2, and 3 years (total slope[TS]) as well as after excluding the initial 3 months after randomization (chronic slope[CS]). We performed Bayesian mixed models to relate the treatment effects on GFR slope to those on the clinical endpoint (CE), defined as ESKD, eGFR<15 or doubling of creatinine and to compute predicted hazard ratio (HR) for the clinical endpoint given a specified magnitude of treatment effect on slope.

Results: The figure shows associations of treatment effects on 3-year TS and CS compared to that of CE. For TS, associations weaken but persist at 2 years [R^2 0.82 (0.46, 0.97)], and deteriorate at 1 year [R^2 0.47 (0.09, 0.78)], likely related to presence of acute effects. For CS, sensitivity analyses using truncated data seem to show similar associations with follow-up time of 18-24 months. Results were consistent across eGFR, ACR and disease subgroups. For a 0.75 ml mean difference in 3-year TS and CS, predicted HR on the CE was 0.69 (0.59, 0.81) and 0.72 (0.60, 0.87), respectively.

Conclusions: Treatment effects on 3-year TS and CS have strong associations with those on the CE. TS over lesser time periods needs to consider presence of acute effect. These results, combined with analyses of epidemiological associations and simulation studies presented at the Workshop, support the use of GFR slope as a surrogate endpoint in clinical trials of kidney disease progression.

Funding: Private Foundation Support



Colours represent different interventions. Size of the circle is proportional to number of events

SA-OR087

Association between GFR Slope and Subsequent ESKD and the Impact of Adjustment for Measurement Error: Meta-Analysis of Observational Studies

Morgan Grams. CKD Prognosis Consortium *CKD Prognosis Consortium (CKD-PC), Baltimore, MD.*

Background: A recent NKF-FDA-EMA Workshop evaluated candidate surrogate endpoints for clinical trials to slow kidney disease progression, particularly among participants with relatively preserved baseline glomerular filtration rate (GFR). Here, we investigate difference in GFR slope as a candidate surrogate endpoint using observational studies assembled by the CKD-PC.

Methods: We evaluated the strength of association between GFR slope and the clinical endpoint of end-stage kidney disease (ESKD), including the impact of error in slope measurement and the length of the observation period in which slope is observed, using random-effects meta-analysis of 14 cohorts including 3,373,368 participants followed for a mean of 4.4 years.

Results: In covariate-adjusted analyses, a reduction in eGFR decline of 0.75 ml/min/1.73 m^2/year was protective for ESKD in participants with baseline GFR ≥60 ml/min/1.73 m^2 (adjusted hazard ratio using 1-year slope, 0.93, 95% CI: 0.92-0.94). Associations were stronger among participants with GFR <60 ml/min/1.73 m^2 (0.88, 95% CI: 0.86-0.91), when slopes were observed over longer observation periods (2-year slope, 0.80, 95% CI: 0.78-0.82; 3-year slope, 0.71, 95% CI: 0.69-0.74), and when adjusted for measurement error (1-year slope 0.80, 95% CI 0.77-0.83; 2-year slope, 0.71, 95% CI: 0.69-0.74; 3-year slope, 0.64, 95% CI: 0.60-0.67). Compared to a control group with baseline GFR of 60 ml/min/1.73 m^2 and an expected 2-year GFR decline of 3 ml/min/1.73 m^2/year, an intervention that slows GFR decline by 0.75 ml/min/1.73 m^2/year would be expected to result in an absolute 10-year risk reduction of ESKD of 1.3% (0.9% to 3.6% risk reduction for a baseline eGFR of 75 to 45 ml/min/1.73 m^2, respectively).

Conclusions: Slope of GFR is associated with subsequent ESKD, with stronger associations after adjustment for measurement error as well as when observed over longer periods. These results, combined with analyses of clinical trials and simulation studies, may support the use of GFR slope as a surrogate endpoint in clinical trials.

Funding: NIDDK Support, Private Foundation Support

SA-OR088

CyTOF Analysis Identifies Antibody-Secreting and Memory B Cells >1 Year Prior to Antibody-Mediated Rejection (AMR) Development in Pediatric Kidney Transplant Recipients

Clara Fischman,[1] Miguel Fribourg,[1] Fabrizio Ginevri,[2] Patrizia Comoli,[2] Michela Cioni,[2] Arcangelo Nocera,[2] Chiara Cantarelli,[1,3] Laura Perin,[4] Paolo Cravedi.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]IRCCS G Gaslini, Genoa, Italy; [3]Az. Osp. Univ. Parma, Gattatico (Reggio Emilia), Italy; [4]Childrens Hospital Los Angeles, Los Angeles, CA.*

Background: Development of anti-HLA donor specific antibodies (DSA) is associated with antibody mediated rejection (AMR) and reduced graft survival. Changes in circulating T and B cells before AMR development have not been investigated systematically.

Methods: We used time-of-flight mass cytometry (CyTOF) to comprehensively characterize T and B cells in prospectively collected PBMC from 10 pediatric kidney transplant recipients who developed DSA and 11 matched controls who did not develop DSA. PBMC were obtained at 2 months post-transplant, 3 months prior to DSA development, and at DSA detection (PBMC from controls were collected at the same time-points).

Results: DSA^+ and DSA^- patients had similar baseline characteristics and comparable T cell frequencies across the different time-points. Patients who developed DSA had significantly more B cells with an antibody-secreting phenotype ($CD27^+CD38^+$) compared to DSA^- controls 3 months prior to DSA detection (p=0.01; **Figure 1A,B**). Within DSA^+ patients, only those that developed AMR (n=5; 18±3.6 months post-DSA detection) had increased B cells with a memory phenotype ($CD27^+CD95^+IgD^-$) at the time of DSA detection (p=0.009; **Figure 1A,C**). There was no difference in DSA titers between patients who developed AMR and those who did not (13,687±4,159 vs. 11,375±1,894 MFI, respectively; p=0.63).

Conclusions: Our extensive phenotypic analysis by CyTOF showed that, while circulating T cells do not differ between patients with or without DSA, antibody-secreting and memory B cells are detectable prior to the development of DSA and AMR, offering a potential target for this serious condition.

Funding: NIDDK Support, Private Foundation Support

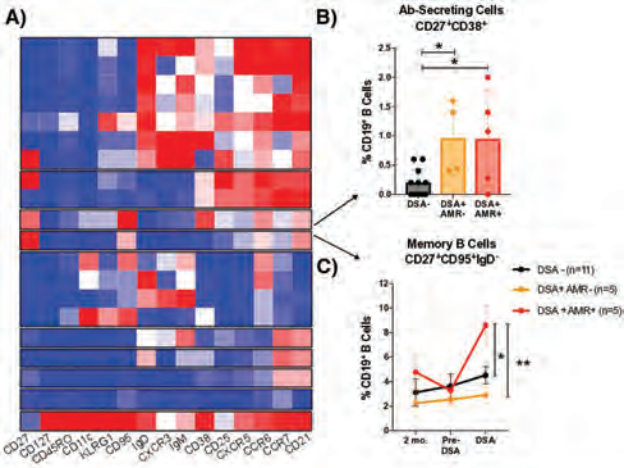


Figure 1. Increased antibody-secreting and memory B cells detected in DSA^+ AMR^+ recipients by CyTOF. **A)** B cells from all patients were pooled together and 20 subclusters identified by Phenograph using 15 cellular markers (shown below heatmap). Heatmap of normalized marker expression across the 20 Phenograph B cell subclusters. **B)** Frequency of $CD27^+CD38^+$ antibody secreting cells pre-DSA stratified by DSA and AMR status. **C)** Frequency of CD27 $^+CD95^+IgD^-$ memory B cells at all time-points. Plots show mean ± SEM. *p<0.05 and **p<0.01.

SA-OR089

Concerns over the Safety and Maturity of Nephron-Like Structures after Renal Subscapular Transplantation of Kidney Organoids Derived from Human iPS Cells

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Background: For chronic kidney disease, regeneration of lost nephrons in human kidney organoids derived from induced pluripotent stem (iPS) cells is proposed to be an attractive potential therapeutic option, but it remains unclear whether kidney organoids transplanted into kidneys *in vivo* would be safe or functional.

Methods: Kidney organoids were differentiated from the CMC11 iPS cell line using the protocols decribed previously. The harvested kidney organoids were transplanted into subcapsular space of kidneys of immunodeficient male NOD/SCID mice.

Results: Kidney organoid grafts survived for months after transplantation and were vascularized from host mouse endothelial cells. Transplantation of kidney organoids into mouse kidneys revealed nephron-like structures with more mature characteristics, compared with kidney organoids *in vitro*, but they remained immature. Ultrastructural analysis revealed the filtration barrier-like structures, capillary lumens and tubules with brush border in the transplanted kidney organoids, which were more mature than those of the kidney organoids in vitro but not organized as adult mammalian kidneys. Stroma of transplanted kidney organoid grafts were filled with vimentin-positive mesenchymal cells, and cells in nephron-like structures were similarly not fully differentiated. Chondrogenesis and cystogenesis were observed in the transplanted kidney organoid grafts in the long term, characteristics reminiscent of teratoma tumors.

Conclusions: Our data suggest that kidney organoids derived from iPS cells may be transplantable but strategies for overcoming the immaturity and maldifferentiation are needed before they can be used in humans as a therapeutic option for nephron loss.

SA-OR090

MicroRNA Expression in Human Kidney Allografts Is Associated with Future Development of Fibrosis

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Background: Biomarkers that foretell tubulointerstitial fibrosis (IFTA) of the kidney allograft may help redefine management of kidney transplant recipients.

Methods: We studied 16 kidney allograft surveillance biopsies from 16 recipients at 3 months post–transplantation. All biopsies had Banff ci score (interstitial fibrosis) and ct score (tubular atrophy) of zero. Based on the presence of IFTA in the 12-month surveillance biopsy, 10 recipients were classified as 'Progression to IFTA' (Group A, ci score ≥2 and ct score ≥2) and 6 as 'No Progression to IFTA', (Group B, ci/ct scores=0). We did RNA sequencing of the 16 biopsies and compared the differential abundance of miRNA between Group A and Group B. We did qRT-PCR assay of the top differentially abundant miRNAs.

Results: Sixteen miRNAs were differentially abundant between the groups; 11 increased and 5 decreased in Group A comapred to Group B (Figure 1). All 16 miRNAs,

as reported in prior studies, were associated with organ fibrosis. By qRT-PCR assay, the miRNAs discriminated the groups with high degree of accuracy (Figure 2).

Conclusions: miRNA expression in kidney allograft in 3-month surveillance biopsies is associated with IFTA in 12-month surveillance biopsies.

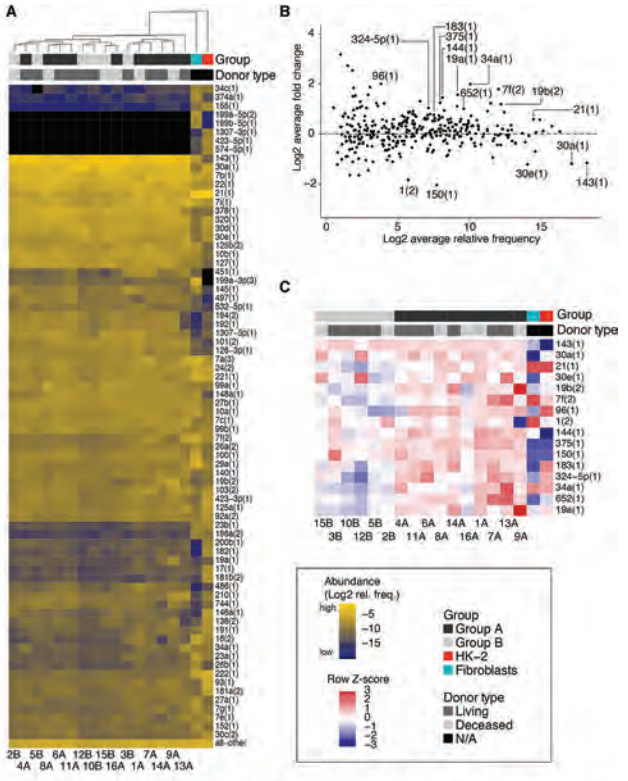

Figure 1. Kidney Allograft MicroRNA Profiles Generated by Small RNA Sequencing.
(A) Heat map after unsupervised clustering of the cumulative top 90% abundant individual miRNAs of 16 kidney allograft biopsy samples obtained at 3 months after transplantation.
(B) MA-plot showing the result of the differential analysis between Groups A and B.
(C) Heat map of 16 differentially expressed miRNAs selected for qRT-PCR.

miRNA	Area Under ROC	95%CI	P
96-5p	0.98	0.93-1.00	0.002
34a-5p	0.98	0.91-1.00	0.002
183-5p	0.95	0.85-1.00	0.003
21-5p	0.93	0.81-1.00	0.005
652-3p	0.93	0.79-1.00	0.006
375	0.89	0.73-1.00	0.01
7f-5p	0.86	0.67-1.00	0.02
324-5p	0.82	0.58-1.00	0.04
144-3p	0.78	0.51-1.00	0.07
19a-3p	0.76	0.51-1.00	0.09
19b-3p	0.73	0.45-0.99	0.14

Figure 2. Discrimination between Group A and Group B by miRNAs.
qRT-PCR assay of the 11 miRNAs increased in Group A (Progression to Fibrosis) comapred to Group B (No Progression to Fibrosis). At the time of reverse transcription we spiked the RNA sample with 1ul of 1nmol synthetic cel-miR-54 (Integrated DNA Technologies). We did qRT-PCR assay in QuantStudio™ 6 Flex Real-Time PCR System (ThermoFisher Scientific). Absolute levels of miRNAs were measured in PCR assays by the incorporation of a customized 73-bp BAK amplicon-based standard curve. The spike-in control, cel-miR-54 copies, and the endogenous control, RNU-44 copies, were not different between Group A and Group B (P=0.1 and P=0.15, respectively). For each sample, we created ratios of individual miRNAs to miR-143, the most abundant miRNA in kidney, in the same sample. We did receiver operating characteristic (ROC) curve analysis and assessed the ability of the miRNAs to discrimiante Group A and Group B by the area under the ROC curve.

SA-OR091

Change of Gut Microbiome after Kidney Transplantation and Its Impact on Acute Rejection

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Background: Gut microbiota regulates immune responses and its dysbiosis is associated with various kinds of diseases, although very few studies have been conducted in kidney transplantation recipients. The purpose of this study is to analyze the changes of gut microbiome after renal transplantation and to evaluate the association between bacterial composition and post-transplantation outcomes.

Methods: We prospectively enrolled renal transplant recipients at 2 tertiary centers. We gathered their fresh feces before and three-month after receiving transplantation. The Illumina MiSeq system was used for sequencing of the 16S rRNA V4-V5 variable region from the extracted stool DNA. We explored gut microbiome profile change before and after transplantation and its impact on transplantation outcomes such as acute rejection (AR) and infection occurrences.

Results: From 76 recipients, we analyzed 76 feces before transplantation and 39 feces after transplantation. Microbial diversity decreased significantly in three months after transplantation than pre-transplantation period ($p<0.001$). At the phylum level, *Proteobacteria* significantly increased in post-transplantation state ($p=0.046$). At the genus level, relative proportions of *Oscillibacter* ($p=0.001$), *Subdoligranulum* ($p=0.018$), and *Alistipes* ($p=0.005$) significantly decreased, whereas the genera *Clostridium_g24* significantly increased ($p=0.016$) in post-transplantation period. When we compared gut microbiome profiles between patients with and without transplantation outcomes, both observed operational taxonomic unit ($p=0.029$) and microbial diversity ($p=0.014$) were significantly lower in AR group. AR group tended to have lower phylum *Bacteroidetes*, higher phylum *Proteobacteria*, and lower abundance of the genera *Faecalibacterium* than non-AR group, although insignificant. Recipients with infection episodes had lesser the genera *Oscillibacter* ($p=0.019$) than those without. In addition, they had higher abundance of the genera *Bacteroides* ($p=0.037$) than those without.

Conclusions: In this study, we demonstrate significant sequential changes as well as a decreased diversity of gut microbiota after kidney transplantation. Interestingly, transplantation outcomes including AR and infection episodes were associated with changes of gut microbiota in recipients.

SA-OR092

Histone Deacetylase-8 Inhibition Is Protective in Renal Ischemia-Reperfusion Injury

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Background: Ischemia/reperfusion injury (IRI) is a major source of morbidity in renal transplantation and other surgical scenarios, and has no specific therapy. In renal transplantation, IRI contributes to poor outcomes and early graft loss. Histone deacetylases (HDACs) regulate diverse cellular processes. We have previously shown that class I HDAC 1 and 2 have reciprocal effects on renal ischemia-reperfusion injury (IRI) with HDAC1 deletion increasing vulnerability and HDAC2 protection providing profound protection. HDAC8, another Class I HDAC, is structurally distinct from other members and is specifically targetable, making it a molecule of interest in IRI.

Methods: Whole-body tamoxifen-inducible HDAC -8 deficient (HDAC8 KO), and tamoxifen-treated WT female mice, as well as B6 female mice treated with specific HDAC8 inhibitor (OJ-1) or DMSO control were used. Mice were subjected to warm renal IRI through unilateral clamping of the renal pedicle and contralateral nephrectomy under strict temperature control. Creatinine and BUN were examined at 24-, 48-, 72-, and 96-h post IRI.

Results: HDAC8 KO (Figure 1A& 1B) and inhibitor-treated (Figure 1C & 1D) mice developed significantly less renal injury after renal IRI than controls, with significantly decreased post-operative BUN and Cr ($p<0.0001$ for all).

Conclusions: HDAC8 knockout and pharmacologic inhibition appears to be proactive in a standard model of renal warm IRI. The benefit of short term HDAC8 pharmacologic inhibition represents an important finding, demonstrating highly novel translational potential. Further clinical correlation and mechanistic understanding is needed for this candidate molecule.

Funding: NIDDK Support

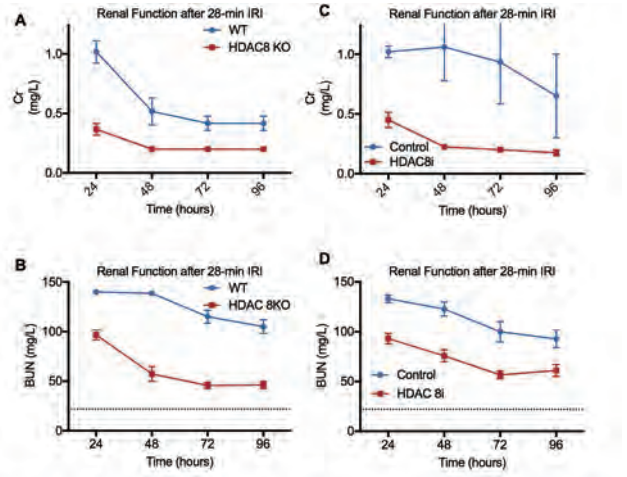

Figure 1. A&B) HDAC8 KO demonstrated significantly improved BUN (p<0.0001) and Cr (p< 0.0001) at each time point post IRI. C&D) HDAC8 inhibition demonstrated significantly improved BUN and Cr (p<0.0001) relative to DMSO control

SA-OR093

Urinary Microvesicular Biomarkers for Delayed Graft Function and Overall Outcome after Living Donor Kidney Transplantation

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Background: With a cargo of specific proteins and nucleic acids, urinary microvesicles represent a source for cellular material, that can be isolated easily and non-invasively. Despite this, their application in routine diagnostics are still a subject of investigation. Kidney biopsies remain the gold standard procedure in the diagnosis of transplant failure. We hypothesize that the addition of non-invasive biomarkers could benefit this method minimize the risk of a sampling error.

Methods: Via a protocol of differential centrifugation, we isolated urinary microvesicles from living kidney transplant recipients and their donors over the course of 40 kidney transplantations. Urine samples were collected on day -1 (donor sample), 0, 1 and 3 months after transplantation (recipient samples). Microvesicular protein content was measured using quantitative mass spectrometry. We detected proteins, that linearly change their abundance corresponding to clinical parameters, e.g. GFR measured at 6 and 12 Months after transplantation in a set of 20 transplantations, by linear regression models. These results were validated in a cohort of 20 additional transplantations.

Results: We identified >1500 proteins present in at least 50% of the first sample set. In hierarchical clustering analysis, the proteomic profiles depicted a clear clustering by time point of urine collection. Microvesicular proteins of glomerular (e.g. nephrin, podocin) or tubular origin (e.g. V-ATPase and Slc transporters) were regulated over the course of transplantation. Overall, specific proteomic time course patterns were apparent over the course of transplantation. Depending on low statistical error and high stability in a leave-one-out cross-validation of the linear models correlating to GFR values after transplantation, we created a list of 64 candidate proteins. This candidate list was validated in a targeted proteomics analysis in the samples of the follow-up cohort.

Conclusions: With this study, we present the first analysis of the changes in the human urinary microvesicular proteome over the course of kidney transplantation. We believe, the validated biomarkers of all 40 Transplantations to hold the potential to further aid the diagnosis of graft survival and possibly transplant rejection.

Funding: Government Support - Non-U.S.

SA-OR094

Simvastatin Modulates the Immunoregulatory Phenotype of Vascular Endothelial Cells

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Background: Evidence suggests that HMG-CoA reductase inhibitors (statins) reduce the incidence of acute and chronic allograft rejection and have immunomodulatory effects. However, their mechanism of function to regulate alloimmunity is poorly understood. We hypothesize that statins modulate the immunogenicity of donor graft endothelial cells (EC) and the costimulation of recipient CD4+ Teffector cells thereby promoting a pro-tolerogenic intragraft microenvironment.

Methods: Pooled populations of CD4+T cells and memory CD45RO+ subsets were isolated from PBMC, and were co-cultured with untreated human umbilical vein EC (HUVEC) or EC pre-treated with simvastatin (Simva, 0.1-10μM for 24 hrs) in the presence of mitogen (PHA 0.1-0.3μg/ml). The ability of EC to transcostimulate CD4+T cell proliferation was measured after 72 hours using either [3H] thymidine incorporation or CFSE dilution by FACS. Released cytokines were analyzed by Luminex and by ELISPOT, and the direct effect of Simva on the phenotype of EC was evaluated by RNAseq and validated by qPCR. Controls were Simva-treated fibroblasts.

Results: We found a significant reduction ($P<0.001$, n=6) in the proliferation of CD4+T cells following coculture with Simva-pretreated EC vs. untreated cells. Furthermore, inhibition of memory CD4+T cell proliferation was dose dependent using up to five concentrations of simva (0.1-10μM, n=3). Multianalyte luminex assays of coculture supernatants revealed a reduction in several pro-inflammatory cytokines, and ELISPOT assays confirmed a notable effect on the reduction of IL-2, IFNg and IL-6 production following coculture with Simva-pretreated EC vs. untreated cells. In contrast, fibroblasts pretreated with Simva failed to inhibit PHA-induced proliferation of CD4+T cells as a control, indicating that there are cell intrinsic effects of Simva on the EC phenotype. To determine mechanism, we evaluated RNAseq and performed mRNA gene arrays on Simva-treated EC vs untreated and found increased expression of immunoregulatory genes including LGALS family molecules and reduced expression of IL-6, IL-8 and OX40L.

Conclusions: Simvastatin modulates the immunogenicity of EC and their function in the activation of memory $CD4^+$T cells. These studies support the use of simvastatin as an adjunct immunomodulatory therapy to augment tolerance and promote long-term graft survival.

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SA-OR095

Single Cell RNA-Seq of Sequential Kidney Biopsies in Antibody Mediated Rejection Reveals a Highly Diverse Inflammatory Response

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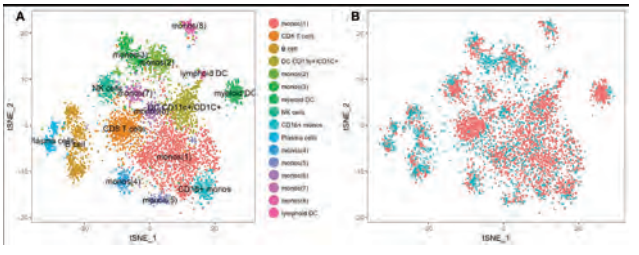
Background: Antibody mediated rejection (AMR) remains a major cause of allograft failure yet current treatments are suboptimal reflecting our poor understanding of this disease process. To better understand the impact of current AMR treatments we performed single cell RNA-seq on human kidney biopsies both at AMR diagnosis and at 1 month post treatment.

Methods: Single cell suspensions were prepared by enzymatic digestion. The 10X Genomics platform was used for library preparation. Libraries were sequenced to a depth of ~50k reads/cell. Gene-cell matrices were obtained using CellRanger and the downstream analyses were done using R and Seurat.

Results: 11,592 cells (1,841 genes/cell) and 5,581 cells (1,253 genes/cell) from the pre- and post-treatment biopsy, respectively, were included in the final analysis of each biopsy. AMR treatment included rituximab, bortezomib, IVIG, high dose steroids and tocilizumab. Allograft function did not return to baseline and post treatment histology showed no improvement in Banff scores. We detected all major epithelial cell types. A combined analysis of all immune cells from both biopsies revealed 16 separate immune cell clusters (Fig A). These included distinct monocyte(x8), dendritic cell(x3), CD8 T cell, NK cell, B cell and plasma cell clusters. Treatment resulted in a modest reduction in B cell and plasma cell proportions of 0.56 to 0.44 and 0.6 to 0.4, respectively (Fig B; red, pre-treatment cells; blue, post-treatment cells). By contrast, the number of these cells expressing TNFRSF17 (BMCA, B cell maturation antigen) increased from 1.2% to 24.9%, before and after treatment. Furthermore, the number of TNFSF13B (BAFF, B cell activating factor) expressing cells remained high after treatment (42% to 32%).

Conclusions: Aggressive anti-B cell and anti-plasma cell therapy failed to substantially reduce intra-graft antibody secreting cell numbers. Elevated intra-graft antibody secreting cell number may be maintained by BAFF-BCMA signaling. scRNA-seq provides a quantitative description of the cellular landscape in rejection.

Funding: NIDDK Support



SA-OR096

IgG Glycosylation Causes Podocyte Injury in Transplant Glomerulopathy via Calcium Calmodulin Kinase IV

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Background: Transplant glomerulopathy(TG) is a major cause of late allograft loss. Increase in urine podocin/creatinine ratio in TG signifies acceleration of podocyte detachment from glomerular basement membrane. We evaluated the mechanism by which antibodies lead to podocyte injury in transplant glomerulopathy. We focused on calcium calmodulin kinase IV(CAMKIV), a serine threonine kinase which we have shown to be upregulated in immune podocytopathies.

Methods: Expression of CaMKIV in transplant biopsy kidney specimens was evaluated by immunofluorescence. Immortalized human podocytes were examined for actin cytoskeleton changes after exposure to IgG from patients with TG versus controls. We subjected IgG from TG patients to deglycosylation and silenced the podocyte expressed neonatal Fc receptor (FcRn) by CRISPR technology and siRNA.

Results: CaMKIV was increased in podocytes of transplant kidney biopsies from patients with TG but not in samples without TG. Culture of podocytes in the presence of IgG from TG patients or patients who eventually developed TG, led to increased CAMKIV expression in a dose dependent manner along with reduction in expression of nephrin and alpha actinin 4, podocyte migration and significant actin cytoskeleton changes. This was not seen with IgG from normal transplant subjects. Silencing of FcRn reduced the entry of IgG into podocytes. IgG from patients with TG subjected to N-deglycosylation failed to increase the expression of CaMKIV. CAMKIV deficiency or pharmacologic inhibition preserved nephrin and alpha actinin 4 expression and prevented the disruption of actin cytoskeleton in podocytes. CAMKIV inhibited GSK3beta by phosphorylating it at serine 9 which led to stabilization of transcription factor SNAIL and subsequent repression of nephrin transcription.

Conclusions: We conclude that targeting CaMKIV may represent a novel biomarker for the early detection of transplant glomerulopathy and a pathway for development of novel therapeutics in this disease. Furthermore, glycosylated IgG from patients with TG enters podocytes through the FcRn causing an increase in CaMK4 and transcriptional repression of nephrin. The ability of IgG in the sera of patients with TG vs controls to disrupt structure and function of podocytes can serve as a bioassay for impending TG. Targeting the glycosylation of IgG may prevent allograft failure.

Funding: NIDDK Support

SA-OR097

Late B Lymphocyte Action in Dysfunctional Tissue Repair Following Kidney Injury and Transplantation

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Background: Immune-mediated injury contributes to unsatisfactory long-term outcomes after kidney transplantation, but the mechanisms initiating late immunoreactivity are poorly understood.

Methods: In this translational study, we combined transcriptional profiling of serial protocol biopsies after kidney transplantation in humans (RNAseq analysis from 163 protocol biopsies) with the extensive characterization of immunological processes up to 18 months after ischemia/reperfusion injury (IRI) in mice (RNAseq, immunofluorescence, B cell receptor analysis and autoantibody detection).

Results: In human kidney allografts, a transcriptional B cell signature correlated with fibrosis and reduced graft function. The presence of a B cell signature at 1 year was associated with an injury/repair response earlier after transplantation, not primarily related to episodes of allograft rejection. In the mouse model, we identified a sustained immune response in the absence of foreign antigens in conjunction with the transition to chronic kidney disease. The late intrarenal response after IRI was characterized by the appearance of ectopic lymphoid structures hosting the proliferation and maturation of B lymphocytes into antibody secreting cells. The B cell receptor analysis was consistent with a process of clonal expansion and affinity maturation of B lymphocytes in the damaged kidney. In the absence of foreign antigens this process resulted in the production of systemically detectable broadly-reacting antibodies.

Conclusions: These findings highlight stage specific immunological responses to kidney injury shared between the mouse and human kidney and suggest a new disease model for chronic forms of injury and rejection after transplantation with dysfunctional kidney repair as the *primum movens* of late B cell mediated immunity.

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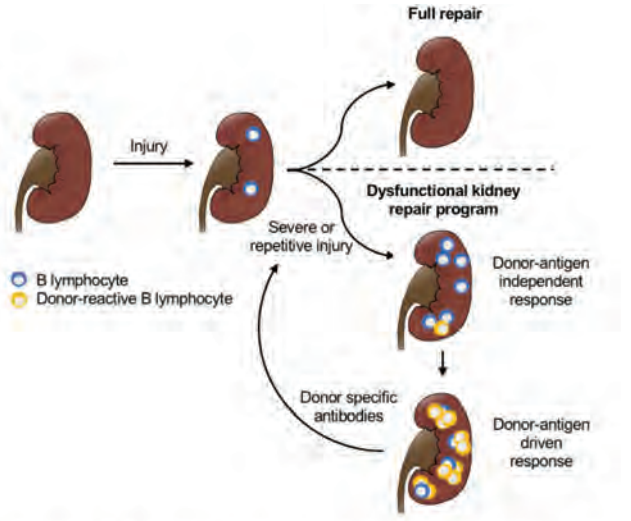

New model to understand late alloreactivity after kidney transplantation. Severe or repetitive kidney injury induces a dysfunctional repair program leading to a sustained immune response in the kidney. Over time, the local immune response leads to the recruitment and activation of donor reactive B cell clones, which differentiate to plasma cells and produce donor specific antibodies, further contributing to tissue injury in a deleterious feedback mechanism.

SA-OR098

Glycerol-3-Phosphate Is a Novel FGF23 Regulator Derived from the Injured Kidney

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Background: Disorders of FGF23 are associated with significant morbidity and mortality, but an understanding of what regulates FGF23 in bone is lacking. Because the kidney is the major end-organ of FGF23 action, we hypothesized that it releases a factor that regulates bone FGF23 synthesis.

Methods: Using aptamer based proteomics and liquid chromatography-mass spectrometry (LC-MS) based metabolomics, we profiled >1600 molecules in renal venous plasma obtained from human subjects. After identifying the molecule that has the strongest correlation with FGF23, we used *in vitro* techniques and genetically modified mice to investigate its effects on bone FGF23 production. Further, we examined the association between the molecule and FGF23 levels in an ischemia-reperfusion (IRI) model of acute kidney injury (AKI) in mice, and in 26 individuals who did (cases) or did not (controls) develop AKI after cardiac surgery.

Results: Renal vein glycerol-3-phosphate (G-3-P) had the strongest correlation with circulating intact FGF23 (iFGF23) levels (r^2 = 0.76, P = 5.2x10^{-6}) in humans. Injection of G-3-P, as well as its downstream product lysophosphatidic acid (LPA) in mice increased plasma iFGF23 and c-terminal FGF23 (cFGF23) levels at 24 hours. G-3-P increased LPA levels in bone marrow and in osteoblast cell culture, and this effect on LPA as well as G-3-P's stimulatory effect on FGF23 production, were blocked with the glycerol-3-phosphate acyltransferase (GPAT) inhibitor FSG67 *in vivo* and *Gpat2* knock-down *in vitro*. The stimulatory effect of G-3-P and LPA on FGF23 production were similarly abrogated in *Lpar1* deficient cells and mice. In mice subjected to IRI, kidney tissue G-3-P levels rose rapidly; the increase in iFGF23 levels following IRI was significantly attenuated with GPAT inhibition or *Lpar1* deletion. In humans undergoing cardiac surgery, plasma G-3-P levels increased significantly and correlated with the plasma iFGF23 levels (r^2 = 0.31) in AKI cases but not controls.

Conclusions: Our findings establish G-3-P as a molecule released from the injured kidney, that is converted to LPA via GPAT-2 in bone where it triggers FGF23 production through LPAR1. This is a novel mechanism in mineral metabolism and outlines potential targets to modulate FGF23 production during kidney injury.

Funding: NIDDK Support

SA-OR099

DMP1 Prevents Bone Alterations, FGF23 Elevations, and Cardiac Hypertrophy in Mice with CKD

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Background: Disordered bone and mineral metabolism is a common complication of CKD. Excessive secretion of the osteocyte-derived hormone fibroblast growth factor 23 (FGF23) during CKD progression is independently associated with increased risk of cardiovascular disease and mortality, perhaps by contributing to development of left ventricular hypertrophy (LVH). Dentin matrix protein 1 (DMP1), an extracellular matrix protein produced by osteocytes, is an established inhibitor of FGF23 production and a promoter of bone mineralization. We hypothesized that overexpression of DMP1 in CKD would improve bone health and prevent FGF23 elevations and consequent adverse cardiovascular outcomes in CKD.

Methods: We studied the Col4a3^{KO} mouse, an established model of progressive CKD, which typically shows a shortened lifespan (21.4±0.6 weeks). We overexpressed DMP1 (DMP1$^{Tg\text{-}3.6Kb\ Colla1\ promoter}$) in the bone of WT (DMP1^{Tg}) and Col4a3^{KO} (Col4a3^{KO}/DMP1^{Tg}) mice and we assessed renal function, serum FGF23 and phosphate (Pi) levels, bone and cardiac phenotype in 20 week-old mice, and overall survival.

Results: Col4a3^{KO} mice showed impaired renal function (blood urea nitrogen: 94±18 vs 25±2 mg/dL), reduced bone mineral density (BMD: 1154±14 vs 1194±5 mg/cm^3), altered osteocyte morphology and connectivity, an 8-fold increase in serum FGF23 levels, hyperphosphatemia (serum Pi: 9.2±0.6 vs 6.2±0.2 mg/dL), and LVH (LV Mass: 124±7 vs 101±4 mg) ($p<0.05$ vs WT for each). Overexpression of DMP1 in Col4a3^{KO}/DMP1^{Tg} did not improve renal function but corrected the reduction in BMD by 40% and fully prevented osteocyte alterations. Col4a3^{KO}/DMP1^{Tg} also showed lower FGF23 levels (631±124 vs 1161±196 pg/mL) resulting in higher serum phosphate levels (11.4±1.0 mg/dL) ($p<0.05$ vs Col4a3^{KO} for each). As opposed to Col4a3^{KO}, Col4a3^{KO}/DMP1^{Tg} mice did not have LVH (LV Mass: 93±5 mg; NS vs WT) and showed improved survival (24.2±0.9 weeks; $p<0.05$ vs Col4a3^{KO}).

Conclusions: DMP1 prevented CKD-associated osteocyte alterations, FGF23 elevations and LVH, and improved survival, despite persistently impaired renal function and worsened hyperphosphatemia. This supports the contribution of FGF23 excess to cardiac injury in CKD and suggests that DMP1 represents a novel therapeutic approach to improve bone and cardiac outcomes in CKD.

Funding: NIDDK Support

SA-OR100

The Osteocyte Is Not the Only Source of FGF23 in Folic Acid-Induced AKI

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Background: Fibroblast growth factor 23 (FGF23) is thought to be produced predominantly by osteocytes in bone and to exert a phosphate-regulating action in the kidneys. Its levels increase with development of chronic kidney disease and acute kidney injury (AKI) and are linked to morbidity and mortality. Recently, other tissues were reported to be additional sources of FGF23 in kidney injury or iron deficiency. However, it is unclear to what extent the extra-skeletal sources contribute to the baseline and the massively elevated serum FGF23 levels in AKI.

Methods: FGF23$^{fl/fl}$ mice carrying loxP sequences flanking exon 1 of *Fgf23* gene were bred with Zp3-Cre and DMP1-Cre lines to produce global (FGF23-null) and osteocyte-specific FGF23 (^{Ocy}FGF23-KO) KO mice, respectively. AKI was induced after a single folic acid (FA) injection in adult male and female ^{Ocy}FGF23-KO and control mice and circulating intact and c-terminal FGF23, PTH, and mineral levels as well as Fgf23 mRNA expression in various tissues were determined 24 hours after induction of AKI.

Results: The FGF23-null mice recapitulated serum and skeletal phenotypes of the previously reported germ-line FGF23 KO mice, validating our gene KO strategy. Basal serum FGF23 and PTH levels in the ^{Ocy}FGF23-KO mice were 39-50% and 48-67% lower (depending on sexes) compared to control mice, respectively. While serum cFGF23 levels were increased by AKI more robustly in control (6904±1272 pg/ml) vs ^{Ocy}FGF23-KO mice (3178±836.1 pg/ml) ($p<0.05$), the fold-change over baseline value was similar between the 2 groups (35 in control vs 41 fold in KO mice, p=0.69). Accordingly, AKI induced higher PTH levels in control (2583±339.5 pg/ml) vs ^{Ocy}FGF23-KO mice (1349±363.9 pg/ml, $p<0.05$), despite no difference in phosphate, calcium, and BUN levels between the two mouse groups after 24 hrs of AKI. As expected, FA did not increase FGF23 mRNA levels in the bone of ^{Ocy}FGF23-KO mice, but raised FGF23 mRNA levels in their kidney and spleen by 5-10 fold.

Conclusions: We conclude that although the osteocytes contribute greatly to baseline FGF23 levels and to the increase of FGF23 in AKI, extra-skeletal tissues, particularly spleen and kidney, are also significant sources of FGF23 at physiological and injury states.

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SA-OR101

Dietary Phosphate Restriction Attenuates Renal Cystic Disease in pcy/pcy Mice

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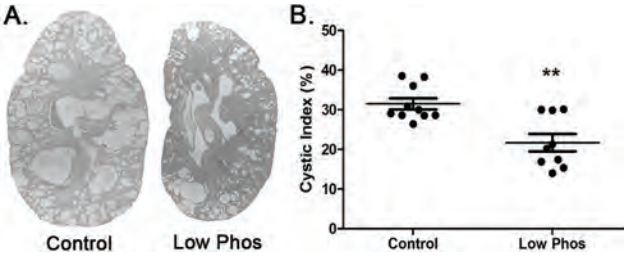
Background: Abnormalities in phosphate metabolism strongly predict future development and progression of chronic kidney disease (CKD); however, the mechanism remains undefined. Previously, we showed that dietary phosphate restriction reduced tubular injury in mice with glomerulonephritis. Here, we determined if dietary phosphate restriction slows renal cyst growth and fibrosis in *pcy/pcy* mice, a slowly progressive model of polycystic kidney disease (PKD).

Methods: At 7 weeks of age, *pcy/pcy* mice were randomized to receive either a control phosphate (0.54%) or low phosphate (0.02%) diet (n=10/group) until 20 weeks of age. All other major dietary constituents, including protein source and content were comparable between diets. Mice were sacrificed for measurement of kidney weight to body weight (KW/BW), cystic index (% cystic area), and renal expression of early markers of fibrosis.

Results: *Pcy/pcy* mice that received the low phosphate diet had a 25% lower KW/BW (low phosphate 2.9±0.3% vs. control 4.3±0.6%; $P<0.001$) and 30% lower cystic index (low phosphate 21.7±6.6% vs. control 31.5±4.4%; $P<0.01$). When examining the renal gene expression of markers of fibrosis, *pcy/pcy* mice fed the low phosphate diet had a 50% reduction in the expression of collagen 1a1 ($P<0.05$) and a 40% reduction in the expression a-smooth muscle actin ($P<0.01$).

Conclusions: Dietary phosphate restriction attenuates PKD progression and renal gene expression for early markers of fibrosis in *pcy/pcy* mice.

Funding: NIDDK Support



Effect of dietary phosphate on cyst burden in *pcy/pcy* mice. (A) Cross-sections of kidneys from 20 week-old *pcy/pcy* mice receiving either a control diet or low phosphate diet. **(B)** Kidney cystic index scoring from *pcy/pcy* mice receiving either control or low phosphate diet. **P<0.01

SA-OR102

Dietary Magnesium Prevents Vascular Calcification and Bone Mineralization in Klotho Knock-Out Mice

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Background: Klotho is a key modulator of the phosphate (Pi) and calcium (Ca^{2+}) balance and is diminished in chronic kidney disease (CKD). Klotho knock-out ($^{-/-}$) mice are therefore an important model for CKD, mimicking all essential features including hyperphosphatemia and development of calcification. In CKD, serum magnesium (Mg^{2+}) inversely correlates with incidence and severity of vascular calcification. The mechanisms by which Mg^{2+}prevents vascular calcification are poorly understood. Therefore, this study aims to determine the effects of Mg^{2+}on development of aortic calcification using Klotho$^{-/-}$mice.

Methods: Klotho$^{-/-}$and Klotho$^{+/+}$mice were fed a normal (0.05% w/w) or high (0.48% w/w) Mg^{2+}diet from birth. Aortic calcification was detected by Von Kossa staining and RNA-sequencing was performed. Serum electrolyte and hormone concentrations were determined. MicroCT was used to study bone integrity.

Results: Von Kossa staining revealed that aortic calcification developed extensively in Klotho$^{-/-}$mice on a normal Mg^{2+}diet and was absent in Klotho$^{+/+}$mice. Strikingly, high Mg^{2+}diet prevented calcification in Klotho$^{-/-}$mice. Moreover, Mg^{2+}rescued increased expression of RUNX2 and osteopontin as well as upregulation of matrix gla protein, demonstrating the preventive effect of Mg^{2+}on pro-osteogenic signaling. Potential novel mechanisms by which Mg^{2+}prevented calcification were studied by RNA sequencing, revealing that pathways mediating inflammation and extracellular matrix remodeling enriched in Klotho$^{-/-}$mice were reversed by Mg^{2+}. Though Mg^{2+}prevented calcification, klotho$^{-/-}$mice on high Mg^{2+}diet had reduced weight and smaller stature. Interestingly, high Mg^{2+}impaired bone formation in Klotho$^{-/-}$mice as femoral mineral-bone density decreased by 20% compared to mice on normal Mg^{2+} diet. High Mg^{2+}did not change known mineralization modulators parathyroid hormone, 1.25-dihydroxyvitamin D and Ca^{2+}in serum. Interestingly, Mg^{2+}prevented calcification despite increasing fibroblast growth factor-23 and Pi concentration in Klotho$^{-/-}$mice.

Conclusions: This study shows that Mg^{2+}prevented vascular calcification in Klotho$^{-/-}$mice. Importantly, Mg^{2+}prevented mineralization in the aortic media as well as bone,

potentially involving anti-inflammatory signaling and disruption of extracellular matrix remodeling.

Funding: Government Support - Non-U.S.

SA-OR103

Cinacalcet Ameliorates Cardiac Valve Calcification in CKD via Suppressing Endothelial-to-Osteoblast Transition

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Background: Clinical studies found cinacalcet (CINA) markedly ameliorated cardiac valve calcification in chronic kidney disease (CKD) patients, but it underlying mechanisms are still unknown. Previous studies demonstrated endothelial cell participate in ectopic calcification in part by mediating endothelial-to-mesenchymal transition (EndMT) that could be transitioned into mesenchymal stem cells and further differentiated into osteoblast. Thus we investigated whether cinacalcet ameliorated cardiac valve calcification in two CKD models via suppression of endothelial-to-osteoblast transition.

Methods: SD rats were randomly divided into three group: control group (CTL, n=10), CKD group(n=30), and CINA treatment group(n=30). CKD group were established by 5/6 nephrectomy (n=15) or 0.75% adenine (n=15) for 4 weeks, both followed with 2.0% phosphorus diet for next 8 weeks. Meanwhile, rats of CINA treatment group were orally administered CINA (10 mg/kg one day). The expression of EndMT and osteoblast markers in valve was examined with the use of western blot, real time PCR, immunofluorescence staining and immunohistochemistry. Pathological examinations of the valves included histological characterization and Von Kossa staining. And we finished echocardiography for three groups. Besides, the important makers of Notch signal pathway were also detected in our study with the use of western blot and real time PCR.

Results: In CKD rats, CINA treatment significantly decreased the serum PTH concentration, calcium but did not affect the elevated levels of serum creatinine, blood urea nitrogen and phosphorus. Besides, CINA significantly attenuated aortic valve calcification, and inhibited the expression of osteogenic markers (osteopontin and osterix). Moreover, CINA treatment largely abolished the up-regulation of mesenchymal markers (FSP1 and α-SMA), stem cell markers (CD44 and CD10) and down-regulation of the endothelial marker (CD31, E-cadherin), which accompanied calcification in CKD aortic valve samples. Besides, Notch signal pathway was activated with Notch1, NICD, HES and HEY increased, while CINA could ameliorates this process.

Conclusions: These findings suggest CINA could attenuate valve calcification by abrogating Notch mediated endothelial-to-osteoblast transition in rats with CKD.

SA-OR104

Pharmacokinetic and Pharmacodynamic Evaluation of a New Vascular Calcification Inhibitor (INS-3001) in Rats

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Background: Morbidity and mortality of patients with CKD increase with the progression of vascular calcifications. In the context of the development of drugs capable of reducing pathological crystallization, *myo*-inositol hexaphosphate (IP6) has been shown to be a promising candidate but needs to be administered *via* intravenous infusion. This study demonstrates the *in vivo* inhibitory effect of an IP6 analog (INS-3001), and characterizes its pharmacokinetic profile in uremic and non-uremic rats.

Methods: Efficacy of INS-3001 versus IP6 to prevent severe vascular calcification was studied in non-uremic rats (vitamin D3 model, n = 5 – 11/group), while the PK of INS-3001 was determined after after single i.v. or s.c dosing of 10mg/kg in uremic rats (adenine diet model) and non-uremic controls (n = 6/group). Vascular calcifications were visualized by von Kossa staining and calcium tissue content measured by ICP-MS. INS-3001 concentrations in EDTA plasma were measured using a HILIC-MS/MS bioanalytical method.

Results: INS-3001 significantly blunted carotid calcification reducing the amount of calcium in tissues by a factor of two compared to controls (p=0.017) while a numerical decrease was observed at the level of abdominal aorta (p>0.05). Treatment with IP6 could not be completed due to the appearance of necrotic lesions at the injection site. INS-3001 displayed high s.c. bioavailability. In the s.c. group, uremic rats displayed higher AUC, mean residence time and Tmax than non-uremic controls (1327.1 vs 802.3 μg/mL*min; 124 vs 66 min; 23 vs 50 min, respectively) whereas Cmax remained unchanged (8348 vs 8325 ng/mL). Similar trends were observed following i.v. administration.

Conclusions: IINS-3001 is a potent inhibitor of vascular calcification after Vitamin D overdose in rats, in addition INS-3001 has a beneficial effect on the renal function of animals in this model. The uremic state appeared to significantly influence the rat plasma PKs of INS-3001 after s.c. and i.v. administration. The data suggests that uremia extends plasma exposure of INS-3001 without increasing peak plasma levels and that therapeutic levels can be attained following s.c. administration in the context of uremia.

Funding: Government Support - Non-U.S.

SA-OR105

Inhibition of Tissue-Nonspecific Alkaline Phosphatase Protects against Medial Arterial Calcification in the CKD-MBD Mouse Model

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Background: Medial arterial calcification (MAC), the main manifestation of chronic kidney disease - mineral and bone disorder (CKD-MBD), is a serious complication of patients with CKD. The overexpression of tissue-nonspecific alkaline phosphatase (TNAP) on vascular smooth muscle cells is reported to accelerate MAC formation. The aim of this study was to assess the inhibitory effect of SBI-425, novel and potent pharmacological TNAP inhibitor, on MAC formation in a CKD-MBD mouse model.

Methods: Eight-week-old C57/BL6J male mice in CKD groups (Vehicle, SBI-10 and SBI-30) (n=10 each) mice were fed a 0.2% adenine and 0.8% phosphorus (Pi) diet for 6 weeks to induce CKD, followed by a high phosphorus (0.2% adenine and 1.8% Pi) diet for 6 weeks. Mice in the SBI-10 and SBI-30 groups were administrated 10mg/kg and 30mg/kg of SBI-425 by gavage once per day, respectively, from 14 to 20 weeks of age. Control group mice (n=6) were fed a standard chow (0.8% Pi) from 8 to 20 weeks of age. At sacrifice, animals were scanned by computed tomography (CT) and aorta, kidney and blood samples were harvested.

Results: In contrast to major MAC formation in the vehicle group, administration of SBI-425 drastically halted MAC formation confirmed by aortic calcification volume (CT imaging), percentage calcified area in histology (positive Von Kossa staining) and aortic tissue calcium content (OCPC assay). Aortic tissue mRNA expression of osteoblastic trans-differentiation-related genes including TNAP were upregulated in the Vehicle group, while they were suppressed to Control levels in the SBI-10 and SBI-30 groups. Plasma and aortic tissue TNAP activities were increased in the Vehicle group, and they were suppressed by SBI-425 administration. Blood levels of urea nitrogen and creatinine, phosphorus, intact PTH and FGF-23 were higher in the CKD groups than in the Control group and were comparable between CKD groups. Plasma pyrophosphate (PPi) levels were shown to be higher in SBI-10 and SBI-30 group than the others.

Conclusions: These results showed that TNAP inhibition protects the vascular media from MAC formation in a mouse model of CKD-MBD. As PPi is a potent protective agent for calcification, elevated PPi concentrations in the SBI-425 treated groups, resulting from TNAP activity suppression, reduced MAC.

SA-OR106

The Direct Inhibitory Effect of Ferric Citrate on Phosphate-Induced Calcification and Osteoblastic Trans-Differentiation via Suppression of HIF1a Expression in Human Vascular Smooth Muscle Cells

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Background: Vascular calcification is a life-threatening pathophysiological abnormality in chronic kidney disease (CKD). Phosphate (P) is known as its main inducer, and it was recently reported that P enhances HIF1a expression, leading to osteoblastic trans-differentiation and calcification of cultured vascular smooth muscle cells (VSMCs). Because iron degrades HIF1a via activation of proryl hydroxylase (PHD), we examined direct effects of ferric citrate (FC), an iron-containing P binder, on P-induced calcification, osteoblastic trans-differentiation, and HIF1a expression in VSMCs.

Methods: Human VSMCs were cultured in DMEM plus 10%FCS and 2.0mM P with 0, 1, 5, 10, 50, 100, or 500mM FC for one or two weeks. The precipitated calcium (Ca) contents and expression of calcification inducers or inhibitors were evaluated.

Results: At 1 week, moderate to high concentrations (>=5mM) of FC equally decreased P-induced calcification by about 80% (p<0.01), while, at 2 weeks, FC inhibited calcification in a concentration-dependent manner and high concentrations (>=50mM) of FC reduced calcification by almost 90% (p<0.01). Moderate to high concentrations (>=5mM) of FC not only suppressed expression of osteoblastic trans-differentiation inducers (BMP2, RUNX2, SOX9, MSX2, PiT1, and MMP2), but also increased expression of calcification inhibitors, OPG and MGP (p<0.01). Moreover, moderate to high concentrations of FC inhibited expression of HIF1a and VEGF, a downstream gene of HIF1 (p<0.01). Expression of HIF1a and VEGF positively correlated with precipitated Ca content and expression of BMP2, RUNX2, SOX9, MSX2, PiT1, and MMP2, respectively (p<0.01), and negatively correlated with OPG and MGP expression (p<0.01).

Conclusions: FC, an iron-containing P binder, can directly inhibit P-induced calcification and osteoblastic trans-differentiation via suppression of HIF1a expression in cultured human VSMCs.

Funding: Government Support - Non-U.S.

SA-OR107

Sucroferric Oxyhydroxide (PA21) Improves Mineral Homeostasis, Reduces Vascular Calcification, and Exerts a Beneficial Effect on Renal Function in a Rat Model with CKD

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Background: PA21 (or sucroferric oxyhydroxide) is an efficacious, well-tolerated iron-based phosphate binder and a promising alternative to existing compounds. We aimed to evaluate the effect of PA21 on renal function, mineral homeostasis and vascular calcification in a CKD rat model.

Methods: To induce stable CKD, 64 male Wistar rats were administered a 0.25% adenine diet during for 8 weeks. CKD rats were assigned to 4 treatment groups: (i) vehicle (n=16), (ii) 2.5 g/kg/day PA21 (n=16), (iii) 5.0 g/kg/day PA21 (n=16) and (iv) 3.0 g/kg/day $CaCO_3$ (n=16). Evolution in renal function and mineral metabolism was followed by measurement of serum creatinine, phosphorus, calcium, 1,25 $(OH)_2$ vitamin D, PTH and FGF-23. Serum ionized calcium, iron, hematocrit, hemoglobin, pH and bicarbonate were also measured. Calcification was assessed by determining the calcium content in the arteries.

Results: Vehicle treated CKD rats developed severe renal impairment, with creatinine values around 3.5-4 mg/dL, and anemia as indicated by decreased serum hematocrit and hemoglobin levels. CKD went along with hyperphosphatemia, hypocalcemia, low 1,25 $(OH)_2$ vitamin D and high PTH and FGF-23 levels. Both PA21 and $CaCO_3$ treatment showed efficient phosphate binding capacity and prevented the pronounced increase in serum PTH. CKD rats treated with 2.5 or 5 g/kg PA21 showed significant lower serum creatinine and phosphorus levels and higher ionized calcium levels after 8 weeks of daily treatment as compared to vehicle treated CKD rats. The better preserved renal function with PA21 treatment went along with less severe anemia. Both PA21 doses prevented the dramatic increase in FGF-23, whereas $CaCO_3$ did not. Daily treatment with PA21 did not increase circulating iron levels. Finally, PA21 treatment significantly reduced the calcium content in the aorta as well as the carotid and femoral arteries, whereas $CaCO_3$ did not affect calcification in the arteries.

Conclusions: In contrast to $CaCO_3$, treatment with PA21 had, aside from its phosphate lowering capacity, a beneficial impact on the development towards severe CKD and prevented the pronounced rise in serum FGF-23. Arterial calcification was significantly reduced by PA21 treatment.

Funding: Commercial Support - Vifor (International) Ltd.

TH-PO001

Interventions in Patient Pathways Reduce the Incidence and Complications of AKI

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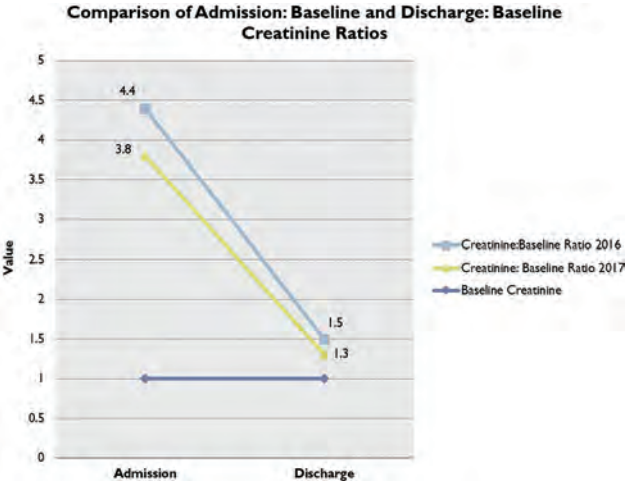
Background: We investigated the management and outcomes of patients developing AKI-3 in the South Tyneside area of the North East of England (population:153,700, census 2011). We proactively introduced interventions to aide early recognition and management of AKI. These interventions included intensive education for clinical staff in the community and hospitals, the launch of a nephrology outreach service in the South Tyneside Hospital and an online AKI health pathway tool. The study aims to scrutinize any changes in outcomes since interventions were delivered.

Methods: Methods: Data was gathered by interrogating the regional pathology database for all patients who developed AKI 3 during the periods of 1st October 16 – 31st December 2016 and subsequently from 1st October 2017 – 31st December 2017. Paediatric patients, palliative care patients and those on renal replacement therapy were excluded.

Results: We demonstrate an overall reduction of 17% in the development of AKI3 during the study period (68 vs 82 cases) additionally; we demonstrate a 29% reduction in the development of AKI-3 in hospital. The discharge to baseline creatinine ratio improved from 1.5:1 to 1.3:1. The admission to baseline creatinine ratio improved from 3.8:1 to 4.4:1. The overall mortality rates remain at 30.88% and the overall hospital stay did not change (16.1 days vs 16.2 days).

Conclusions: In conclusion, we demonstrate a significant improvement in the incidence of AKI-3. There is early recognition of AKI and significant improvement in the renal function on discharge. We recognise that there was no improvement in overall mortality and the total number of in-patient days did not improve. Our data suggests that simple interventions at multiple levels in a patient's pathway can lead to significant improvement in outcomes.



Comparison of Admission: Baseline and Discharge: Baseline Creatinine Ratios

TH-PO002

Real-Time, Model-Driven Diagnostic and Therapeutic Evaluation of Patients at Risk of AKI: A Pilot and Feasibility Study

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Background: Acute kidney injury is typically defined by a rise in serum creatinine, but this is a late marker of the syndrome. Real-time, updated modeling of AKI risk using electronic health record (EHR) parameters may allow for targeting of diagnostic and therapeutic interventions earlier in the course of AKI.

Methods: We deployed a time-updated AKI prognostic model into the EHR of a large, tertiary care hospital. The model alerted study team members when any hospitalized adult had a greater than 30% risk of developing AKI within the next 48 hours: the "pre-AKI Alert". Study personnel took urine and blood samples, examined the medical record, and followed patients for the development of creatinine-defined AKI. Our primary goal was to determine the feasibility of providing tailored pre-AKI recommendations in this clinical setting.

Results: Of 98 patients who met eligibility criteria, 68 were unable or refused to consent to study participation. Of the 30 who were enrolled, 5 developed AKI within 24 hours, 1 additional patient within 48 hours, and 1 later during the subsequent hospital admission. Lower-than-expected AKI rates were seen due to difficulty obtaining consent from the highest-risk patients. At the time of pre-AKI alert, 3 patients were receiving a potentially nephrotoxic agent, 24 had at least one electrolyte abnormality that could be addressed, and 3 had mean arterial pressure < 65mmHg (Table). Oxygen saturation was significantly lower in those who went on to develop AKI compared to those who did not with median (IQR) SPO2 94 (92 - 94) compated to 97 (95-98), p=0.03.

Conclusions: A real-time updated model successfully identified a group of patients at high risk for AKI, many of whom had nephrotoxin, electrolyte, blood pressure, or oxygenation abnormalities that could be proactively addressed. Model-based pre-AKI interventions are feasible and their efficacy should be explored in a larger study.

Funding: NIDDK Support

Characteristics at Pre-AKI Alert

	AKI within 48h (N=5)	No AKI Within 48h (N=25)	Total (N=30)
Potassium > 5.4 meq/L	1	2	3
Bicarbonate < 22 meq/L	3	18	21
MAP < 65 mmHg	1	2	3
Receiving Nephrotoxin	0	3	3
Scheduled for Contrast Study	0	2	2

TH-PO003

Epidemiology of Emergency Department AKI

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Background: The epidemiology of Acute Kidney Injury (AKI) diagnosed in the Emergency Department (ED) is poorly described. This study describes the incidence, demographics and outcomes of patients diagnosed with AKI in the ED (ED-AKI).

Methods: Between April and August 2016 20,421 adult patients attended the ED of a University Teaching Hospital (UK) and had a serum creatinine measurement. Using an electronic AKI reporting system, 548 incident ED-AKI patients were identified and compared to a randomly selected cohort of non-AKI ED patients (n=571). Admission, short term and 12-month follow-up data was collated and compared.

Results: 572 patients had a confirmed eAlert AKI (548 incident cases), giving an incidence of ED-AKI of 2.8%. ED-AKI was associated with a 24.4% inpatient mortality of which 22.3% of deaths occurred in the first 24-hours and 58% within 7 days. Progression of admission AKI stage to a higher AKI stage was associated with a 38.8% mortality compared to a 21.4% mortality in those who did not progress (p<0.001). In multivariate analysis ED-AKI was an independent risk factor for mortality (HR, 6.293; 95% CI, 1.887 to 20.790, p=0.003). For those discharged from hospital 20.4% of ED-AKI patients were re-admitted within 30-days (non-AKI 7.6%, p<0.001). At 90-days following hospital discharge 10.0% of the discharged ED-AKI group died (non-AKI discharged 90-day mortality 1.4%, p<0.001). 12-months post discharge 17.8% of ED-AKI group developed CKD progression or de-novo CKD compared to 6.0% in the non-AKI cohort.

Conclusions: AKI diagnosed in the ED is a strong independent predictor of death. ED-AKI mortality is predominantly in the first days following presentation, but for those surviving to discharge there is significant long-term morbidity and mortality

TH-PO004

Derivation of a Prediction Model for Emergency Department AKI

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Background: Acute Kidney Injury (AKI) is an independent risk factor for death. Over 50% of community acquired AKI cases are identified in the Emergency Department (ED), which is the main route for acute hospital admissions. Accurate risk stratification is essential to facilitate prompt medical investigation and treatment. This study aimed to derive a hospital front-door model for predicting AKI in the ED (ED-AKI).

Methods: Between April and August 2016 20,421 adult patients attended the ED of a University Teaching Hospital in Wales and had a serum creatinine measurement. A retrospective analysis was conducted on 1119 cases (548 incident ED-AKI patients and 571 randomly selected non-AKI ED patients). Univariate and stepwise backwards removal of insignificant variables in a multivariate analyses were used to derive a pragmatic model for predicting and risk-stratifying AKI. The primary outcome was ED-AKI.

Results: An 18-point model using four variables was derived for assessing patients on ED arrival, where 0 is low chance of ED-AKI and 18 a high chance. The adjusted odds ratios for AKI were: age 1.03; male gender 1.45; known Chronic Kidney Disease 2.08; and number of comorbidities (from 0 to 10) 1.31. At a score of >2, the sensitivity was 99.8% (95%CI 99.0-11.0), and specificity was 5.1% (95%CI 3.4-7.2). At a score of >5.5, the sensitivity was 85.8% (95%CI 82.6-88.6), and specificity was 52.7% (95%CI 48.5-56.9). At a score of >11, the sensitivity was 15.0% (95%CI 12.1-18.2), and specificity was 96.5% (95%CI 94.6-97.8). The probability of AKI increased with score groups (chi-squared <0.0001). The AUROC was 0.745 (95%CI 0.720-0.772; p<0.0001; R^2 18%). There were positive correlations between the score and peak creatinine (r=0.415; p<0.0001) but not with AKI stage.

Conclusions: A simple, pragmatic 18-point score for predicting probability of ED-AKI on ED arrival has been derived. This now requires refinement and prospective validation.

TH-PO005

Comparison of Community and In-Hospital Acquired AKI in the Clinical Emergency Department at a University Tertiary Hospital

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Background: Prospective studies comparing frequency and outcomes of community and in-hospital (IH) acquired acute kidney injury (AKI) in patients (pts) admitted to the Emergency Department (ED) are scarce, especially in developing countries.

Methods: This study aimed to compare the frequency, characteristics and outcomes of community AKI (CAKI) vs. IH acquired AKI diagnosed by RIFLE or/and KDIGO (serum creatinine criteria - SCr) in pts admitted to the ED through a referred emergency room (ER) of a tertiary university hospital. All pts ≥ 18 years old hospitalized in the ED were included. Exclusion criteria: decline to sign the informed consent, IH < 48 h, chronic kidney disease stage 5, pts on palliative care and renal transplant. Pts were assessed until the hospitalization day 7 or discharge. SCr(mg/dl) was assessed at admission and daily or every 48h. Pts were divided in the following groups: non-AKI, community-acquired AKI (CAKI), AKI by RIFLE (ARIFLE), AKI by KDIGO (AKDIGO) and ARIFLE negative AKDIGO positive (K+R-). The assessed outcomes were length of IH stay (LoS, d), and IH mortality. Data are presented as median (minimum-maximum values) or percent (%). Statistical significance is set at p<0.05.

Results: A total of 788 pts were included, mean age 63 y (18-98y), 55.1% were male, LoS was 8d (2-132) and IH mortality was 16.7%. A total of 231 pts (29.3%) developed IH AKDIGO – mostly KDIGO I (69.7%) and 167 pts (13.6%) presented CAKI, resulting in 398 AKI pts (50.5%) Causes of hospitalization were pulmonary (36.2%), cardiovascular (11.3%), gastric (16.3%) and others (36,2%). Major outcomes among AKI groups and Non-AKI group (IMAGE1):

Outcomes vs. AKI	NON- AKI	CAKI	ARIFLE	AKDIGO	K+ R -
% (N)	49.5 (390)	21.1(167)	18.8(148)	29.4 (231)	10.5 (83)
AGE (Y)	57 (18-95)	64 (18-98) ***	64 (18-98) *	65 (18-98) ***	66 (20-95) **
LOS (D)	5.0 (2-132)	9 (1-132)	10 (2 - 95) *	9 (2 -95)	8 (2-78)
IH MORTALITY (%)	9.5% (37)	17.4(29) &	31.1(46) &	28.5 (66) &	24.1(20) &

* p<0.05 vs Non-AKI; **p<0,01 vs no AKI; ***p<0,001 vs no AKI; & IH mortality was significantly different among groups (p<0.0001).

Conclusions: The frequency of AKI at reference ER admission and IH acquired in the first 7d of hospitalization was strikingly high in the clinical ED. CAKI showed high frequency and mortality. KDIGO criteria diagnosed more pts than RIFLE criteria IH pts. IH mortality of AKI pts was significantly higher than non-AKI pts at the ED.

Funding: Government Support - Non-U.S.

TH-PO006

Transition of Hospital-Associated AKI to Acute Kidney Disease and CKD

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Background: Acute kidney injury (AKI) is closely tied bidirectionally to the pathogenesis and public health burdens of chronic kidney disease (CKD) together with increased risks for hospital readmission, endstage kidney disease, and death. Bridging transient AKI and CKD, acute kidney disease (AKD) may represent a potentially modifiable stage in the natural history of kidney disease.

Methods: We performed a retrospective analysis of hospitalization data from the electronic health records for Geisinger, a large healthcare delivery system in Central Pennsylvania and New Jersey, 2013-2017 inclusive of baseline SCr and eGFR values 12-18 months preceding hospital admission. We examined AKI events (KDOQI criteria, duration 7 days or less), length of stay, AKD (persistent AKI based on SCr during Days 8 to 89 post-AKI start date), incident CKD (patients with baseline eGFR <60ml/min/1.73m^2), and CKD progression (eGFR ≥5 ml/min below baseline eGFR).

Results: Of 282,418 patient admissions, we identified 53,741 hospital admissions characterized by AKI events (19.0%). Length of stay (LOS) was increased following an AKI event (5.8 days) and exceeded 7 days in 24.7% of AKI patients versus a LOS of 3.7 days in non-AKI patients. Among admissions with AKI events, AKI transitioned to acute kidney disease in 38.2% of occurrences. Moreover in 35,190 patients admitted with a baseline eGFR ≥60 ml/min, 18.8% of patients developed incident CKD following either AKI or AKD within 1 year of the AKI start date. Combining AKI and AKD occurrences in 9,245 patients with baseline CKD prior to hospital admission, 29.0% of patients exhibited post-AKI/AKD progression of their CKD within 1 year of the AKI event.

Conclusions: Hospital-associated acute kidney injury is observed to occur in conjunction with increased hospital length of stay, a relatively high transition rate to acute kidney disease, and both incident and progression of chronic kidney disease within 1 year of an event. Close clinical follow-up of AKI survivors is needed to promote renal recovery and/or delay progression of kidney disease.

Funding: Private Foundation Support

TH-PO007

Predictive Factors of Renal Recovery Following AKI

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Background: AKI is frequent and predictors of renal recovery are incompletely understood. We aimed to determine the association between clinical characteristics and risk factors for AKI with renal recovery.

Methods: This prospective observational study was conducted among intensive care unit patients from 25 centers in 9 countries. AKI was defined as an increase in creatinine of at least 0.3 mg/dl within 48 hours, and renal recovery, as a creatinine at hospital discharge within less than 0.5 mg/dl of reference creatinine.

Results: Between 2008 and 2018, 14,460 patients were screened, of whom 4,241 (29%) developed AKI. A total of 2,009 (47%) of AKI patients had sufficient data. Median age was 64 years (IQR 50-74), 63% were male, 67% were Caucasian, 19% Asian and

7% were Black. Thirty-two percent came from emerging countries and 44% had CKD. Thirty-six percent underwent surgery, 47% had sepsis, and 47% received vasopressors. APACHE III scores at ICU admission was 61 (IQR 43-83). Within the first 7 days of AKI, 43% had hypotension, 14% received iodinated contrast, 26% required anesthesia and 72% received nephrotoxins (including any antibiotics). In-hospital mortality was 20%, and 19% received dialysis during hospital stay. Seven percent of 1613 survivors were dialysis-dependent at discharge, while 72% recovered their renal function. A lower probability of renal recovery was associated with older age, residence in an emerging country, presence of diabetes and liver disease, medical reason for ICU admission and provision of dialysis, while administration of vasopressors was associated with a better probability of renal recovery. Additional risk factors for AKI were not associated with a lower probability of renal recovery.

Conclusions: In our study, older age, residence in an emerging country, diagnosis of diabetes and liver disease, medical reason for ICU admission, as well as severe AKI were independently associated with a lower renal function at hospital discharge. However, ongoing risk factors for AKI within days of diagnosis did not modify renal prognosis at discharge.

Funding: NIDDK Support

TH-PO008

Post-Discharge Major Adverse Cardiovascular Events of Intensive Care Unit Survivors Who Received Acute Renal Replacement Therapy: A Nationwide Population Based Study

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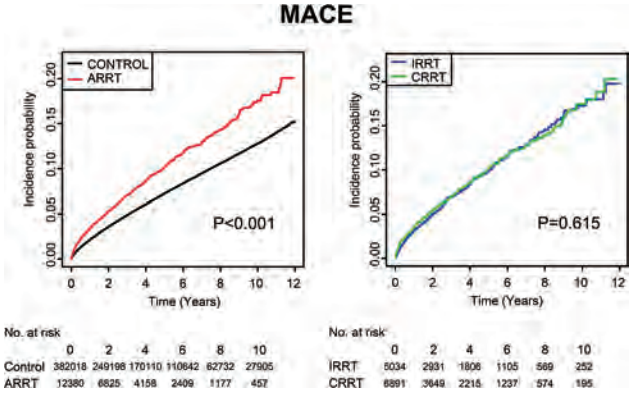
Background: The long-term risk of a major adverse cardiovascular events (MACE) in intensive care unit (ICU) survivors who underwent acute renal replacement therapy (ARRT) requires further investigation.

Methods: We performed a nationwide population-based study using the claims database of Korea, including ICU survivors in over 40 government-designated tertiary hospitals from 2005 to 2016. The study group consisted of ICU survivors who underwent ARRT, and the control group consisted of those without ARRT. Patients were excluded if they 1) were under age 20, 2) expired within 30 days after discharge, 3) received ICU care for less than 24 hours, 4) had a previous ICU admission, 5) had a history of MACE or MACE-related cardio/cerebrovascular diseases. The outcomes of the patients who received CRRT were compared with those of patients who received only intermittent renal replacement therapy (IRRT). The main outcome was MACE, including acute myocardial infarction, revascularization, and acute ischemic stroke. Patient mortality and progression to end-stage renal disease were also evaluated.

Results: We included 12,380 ARRT patients and 382,018 patients in the control group. Among the study group, 6,891 patients were included in the CRRT group, and 5,034 in the IRRT group. The risks of MACE [adjusted hazard ratio (HR) 1.463 (1.323-1.619), P<0.001], all-cause mortality [adjusted HR 1.323 (1.256-1.393), P<0.001], and end-stage renal disease [adjusted HR 18.110 (15.779-20.786), P<0.001] were higher in the ARRT patients than the control group. When we compared the CRRT patients to the IRRT patients, the risk of a MACE was comparable [adjusted HR 1.049 (0.888-1.239), P=0.575].

Conclusions: Clinicians should note the increased risk of a long-term MACE in ARRT survivors and consider appropriate risk factor management. Receiving CRRT did not increase the risk of MACE when compared to receiving IRRT only.



TH-PO009

Simple Postoperative-AKI Risk (SPARK) Classification in Major Non-Cardiovascular Surgery

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Background: We aimed to develop a patient-oriented outcome-based postoperative acute kidney injury (PO-AKI) risk index and classification for planning PO-AKI monitoring before performing major non-cardiac surgery.

Methods: We performed an observational cohort study in two tertiary referral hospitals, each consisting a discovery and validation cohort. Patients who underwent a major non-cardiac operation (≥ 1 hour) were included. We fitted a proportional logistic regression model for an ordinal outcome consisting of the following three categories: no PO-AKI, low-stage AKI, and critical AKI. Critical AKI was defined as KDIGO AKI stage ≥ 2, post-AKI death, or renal failure within 90 days after surgery. PO-AKI events not fulfilling the definition of critical AKI were defined as low-stage AKI.

Results: A total of 50,792 and 39,537 patients were included in the discovery and validation cohorts, respectively. After building a robust model with variables that could be collected or estimated when surgery was scheduled, further simplification was performed. The final Simple PO-AKI RisK (SPARK) index included scores of the following ten variables: age, sex, eGFR, surgery duration, emergency operation, diabetes mellitus, renin-angiotensin-aldosterone system blockades, hypoalbuminemia, anemia, and hyponatremia. The calibration and discrimination results were acceptable. The AUC for low-stage AKI and critical AKI was 0.701 and 0.779 in the validation cohort. When we designated cutoff values to define four classifications, the incidences of the outcomes showed class-dependent increments.

Conclusions: The SPARK index and classification prior to surgery reflects not only the risk of PO-AKI but also the severity and patient-oriented outcomes associated with PO-AKI.

Risk factors	Scores
Age (years)	
< 40	0
≥40 and <60	6
≥60 and <80	9
≥80	14
eGFR (mL/min/1.73 m^2)	
≥ 60	0
≥ 45 and <60	7
≥ 30 and <45	13
≥ 15 and <30	21
Urine albuminuria (≥ 1+)	5
Sex	
Female	0
Male	7
Surgical duration (hours)	×4
Emergency operation	8
Diabetes mellitus	4
RAAS blockade use	5
Hypoalbuminemia (< 3.5 g/dL)	8
Anemia (<12 g/dL female, 13 g/dL male)	3
Hyponatremia (<135 mEq/L)	4

SPARK class	Score	AKI	Critical AKI
A	< 20	less likely	minimal
B	≥ 20 and < 40	possible	less likely
C	≥ 40 and < 60	at risk	possible
D	≥ 60	definite risk	at risk

TH-PO010

Geographic Correlation Between Dialysis-Requiring AKI and Recovery from ESRD

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Background: We recently reported that about 5% of incident end stage renal disease (ESRD) patients in the U.S. recover enough kidney function to discontinue maintenance

dialysis (Lee AJKD 2017). Large geographic variations in rates of renal recovery among ESRD patients have also been reported (Mohan PLoS One 2013). We hypothesized that this may be related to variation in rates of dialysis-requiring acute kidney injury (AKI-D).

Methods: Incidence rates of AKI-D hospitalization in 2011 for AZ, AR, CA, FL, IA, KY, MA, MD, MI, NJ, NM, NY, NV, OR, RI, SC, VT and WA were calculated from the State Inpatient Database using validated diagnostic and procedure codes. Rates of renal recovery among ESRD patients in 2011 were calculated using U.S. Renal Data System data. U.S. Census data were used to define underlying population sizes. Correlation (unadjusted) was determined using Pearson's r.

Results: We found a positive correlation between rate of renal recovery and incidence of AKI-D, both overall (Figure) and in subgroups (Table).

Conclusions: Rates of renal recovery among incident ESRD patients varied considerably across states and correlated with geographic variation in AKI-D incidence. These findings support the hypothesis that renal recovery among ESRD patients mostly represents recovery from AKI-D. When reporting counts of "end-stage" renal disease, subtracting those who recovered renal function (which ranges in magnitude from 3% to 8% in the sampled states) might be a consideration.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support, Government Support - Non-U.S.

State-level correlation between AKI-D incidence and rate of renal recovery among ESRD patients stratified by age and sex

	Pearson Correlation r	P
age 45 – 64 yrs	0.63	0.005
age 65 – 74 yrs	0.58	0.012
age ≥ 75 yrs	0.69	0.001
Male	0.68	0.002
Female	0.58	0.012

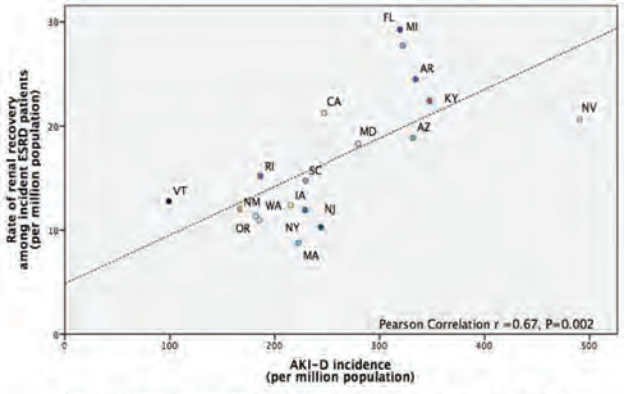

Figure State-level correlation between AKI-D incidence and rate of renal recovery among incident ESRD patients 2011

TH-PO011

Population-Based Trends in Pediatric AKI (2008-2016): The Kaiser Permanente Experience

Rishi V. Parikh,[1] Thida C. Tan,[1] Elaine Ku,[2] Tracy Y. Jonelis,[1] Alan S. Go.[1]
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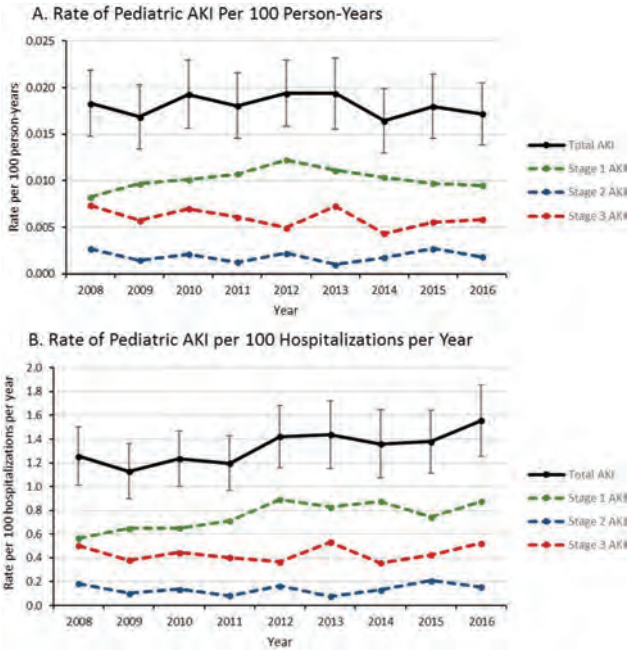
Background: Acute kidney injury (AKI) may lead to long-term consequences in children but its epidemiology has not been well-described outside of ICU settings. We evaluated recent temporal trends in rates of AKI in a large, diverse pediatric population receiving care within an integrated healthcare delivery system.

Methods: We identified calendar year-based cohorts from 2008-2016 of Kaiser Permanente Northern California members <18 years old. We excluded those <1 year old or who received prior renal replacement therapy before entry into a yearly cohort. Hospitalized AKI was identified and its severity assessed using KDIGO criteria. Baseline SCr was defined as the most recent outpatient, non-emergency department value 7-365 days before admission, and eGFR was calculated using the bedside Schwartz equation. We examined age- and sex-adjusted incidence of AKI per 100 person-years and per 100 hospitalizations per year, directly standardized to the 2008 population. Trends were evaluated using Poisson regression.

Results: Among 1,500,546 pediatric members, mean age was 9.8 years and 48.9% were female. The age-and sex-adjusted incidence of hospitalized AKI did not change significantly across the study period. There were 69,645 hospitalizations during the study period, with the hospitalization rate in the population declining from 1.45 per 100 PY in 2008 to 1.12 per 100 PY in 2016 (p<0.001). Among hospitalizations, the age-and sex-adjusted incidence of Stage 1 AKI increased from 2008 to 2016, with borderline significance.

Conclusions: Population-level pediatric AKI incidence did not significantly change between 2008-2016, but Stage 1 AKI incidence slightly increased over time among the subset of hospitalized children.



TH-PO012

Theophylline Use to Mitigate AKI in Infants Undergoing Total Body Cooling for Perinatal Asphyxia

Kyle Merrill, Jennifer G. Jetton, Jonathan M. Klein, Jason Misurac. *University of Iowa, Iowa City, IA.*

Background: Perinatal asphyxia is a common cause of acute kidney injury (AKI) and hypoxic ischemic encephalopathy (HIE). Theophylline is protective against AKI in infants with HIE who are not treated with total body cooling. However, there is a paucity of information on the effect of theophylline to protect against AKI in infants with HIE treated with total body cooling.

Methods: Single-center retrospective cohort analysis of infants diagnosed with HIE treated with total body cooling from 1/2007 to 12/2017. Inclusion criteria were: moderate or severe HIE, gestational age > 36 weeks, measurement of at least two serum creatinine (SCr) values at least 12h apart, and absence of prenatally diagnosed renal disease. Included infants were stratified based on receipt of theophylline and theophylline dose strategy: either a single dose of 5-8 mg/kg on day of life (DOL) 0 (standardized) or multiple doses (non-standardized). AKI was defined according to a Kidney Disease: Improving Global Outcomes (KDIGO) definition modified for neonates: SCr ≥50% above the lowest previous baseline; increase in SCr of ≥0.3 mg/dL within 48h; or urine output (UOP) ≤1 ml/kg/h for 24h.

Results: There were 116 infants who met the inclusion criteria. Among included infants, SCr was missing on 374/812 days (46%) from DOL 0-6, limiting the detection of AKI by SCr. AKI incidence was 63/116 (54%). There was no significant difference in AKI incidence between groups (χ^2=0.18, p=0.91). AKI severity was higher in the no theophylline group but the difference was not significant (χ^2=3.9, p=0.42). UOP was different between groups on DOL 1 (p=0.008) but not on DOL 2-6.

Conclusions: In this cohort of infants with HIE treated with total body cooling, theophylline administration was not associated with a significant difference in the incidence or severity of AKI.

	No Theophylline (n=58)	Standardized Theophylline (n=46)	Non-standardized Theophylline (n=12)
AKI (UOP or SCr)	32/58 (55%)	24/46 (52%)	7/12 (58%)
AKI (SCr only)	6/58 (10%)	8/46 (17%)	2/12 (17%)
AKI Stage	Stage 1 – 17/58 (29%) Stage 2 – 7/58 (12%) Stage 3 – 8/58 (14%)	Stage 1 – 17/46 (37%) Stage 2 – 3/46 (7%) Stage 3 – 4/46 (9%)	Stage 1 – 6/12 (50%) Stage 2 – 0/12 (0%) Stage 3 – 1/12 (8%)
UOP DOL 1 (ml/kg/hr)*	1.3 (0.8-2.1)	1.9 (1.3-2.7)	1.5 (0.6-2)
Nephrotoxins Received**	1 - 72% ≥2 - 25%	1 - 25% ≥2 - 3%	1 - 58% ≥2 - 8%
HIE Severity	Mod. - 78% Severe - 22%	Mod. - 70% Severe - 30%	Mod. 50% Severe 50%
Mortality (DOL 0-6)	2/58 (3.4%)	4/46 (8.6%)	1/12 (8.3%)

*Median (IQR) **Gentamicin, vancomycin, piperacillin/tazobactam, acyclovir, and captopril

TH-PO013

Hyponatremia and AKI in Critically Ill Children

Cassandra L. Formeck,[3,1] Emily L. Joyce,[3,1] Priyanka Priyanka,[1] Shashank Badavanahalli Rajashekar,[1] Juan Carlos Ayus,[2] John A. Kellum,[1] Michael L. Moritz.[3] *[1]The University of Pittsburgh, Pittsburgh, PA; [2]Renal Consultants of Houston, Houston, TX; [3]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.*

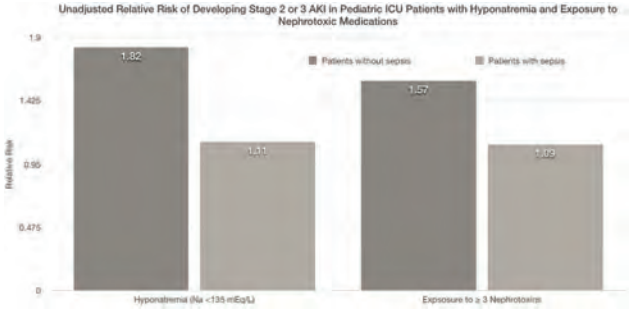
Background: Hyponatremia is associated with increased morbidity and mortality in hospitalized patients for unknown reasons. Hyponatremia is also associated with osmotic cellular stress. Renal tubular epithelial are exposed to numerous stressors in critically ill patients. We hypothesized that hyponatremia would be associated with a greater rate of acute kidney injury (AKI) in critically ill children. Our objective was to evaluate the association between hyponatremia and AKI, controlling for sepsis, a primary coexposure.

Methods: Using a pediatric ICU database of 12,806 admissions, we included patients with a measured sodium value within 6 hours of ICU admission, and excluded patients with AKI or significant chronic renal dysfunction. We analyzed the association between hyponatremia (serum Na < 135 mEq/L), sepsis and known nephrotoxic drug exposure within 48 hours of ICU admission, on the development of stage 2 or 3 AKI within 7 days. For the primary analysis, we stratified by the presence or absence of sepsis at ICU admission, and compared rates of AKI in patients with and without expsoure to hyponatremia or 3 or more nephrotoxic medications.

Results: A total of 5,300 patients (male 58%; mean age 7.5 years) were included in the analysis. 16.1% of patients had hyponatremia, 7.0% nephrotoxic medication exposure and 30.1% developed sepsis. The incidence of stage 2 or 3 AKI was 8.8% in hyponatremic patients with sepsis compared to 14.7% in hyponatremic patients without sepsis. Patients with hyponatremia and nephrotoxic medication exposure were at increased risk for AKI in the absence of sepsis (p <0.001, p 0.008). Patients with hyponatremia, with and without sepsis, were more likely to develop AKI compared to patients with normonatremia (RR 1.11, RR 1.82). In children without sepsis, patients with hyponatremia were at higher risk of developing AKI than patients with exposure to 3 or more nephrotoxic medications (RR 1.82, RR 1.57).

Conclusions: Hyponatremia is a significant risk factor for AKI in critically in children in the absence of sepsis.

Funding: NIDDK Support



TH-PO014

Hyperuricemia Is Associated with AKI and All-Cause Mortality in Hospitalized Patients

Min woo Kang,[1] Minjung Kang,[2] Soie Kwon,[3] Ho Jun Chin,[4] Dong Ki Kim,[1] Kwon Wook Joo,[1] Yon Su Kim,[5] Sejoong Kim,[4] Seung Seok Han.[5] *[1]Seoul National University Hospital, Seoul, Republic of Korea; [2]Seoul National University Hospital, Seoul, Republic of Korea; [3]Seoul national university, Seoul, Republic of Korea; [4]Seoul National University Bundang Hospital, Seong nam, Republic of Korea; [5]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Hyperuricemia as a risk factor of high morbidity and mortality has been documented in several disease status. Nevertheless, the relationship between uric acid (UA) and the risks of acute kidney injury (AKI) and mortality remains unresolved in hospitalized patients.

Methods: All patients (aged ≥ 17 years old) admitted to Seoul National University Bundang Hospital from January 2013 to December 2013 were retrospectively reviewed. UA at the time of admission was categorized based on the quartiles. Odds ratio (OR) for AKI and hazard ratio (HR) for all-cause mortality were calculated after adjustment of multiple variables. All the analyses were stratified by gender.

Results: The 4th quartile UA group (male, UA ≥ 6.8 mg/dL; female, UA ≥ 5.4 mg/dL) showed a higher risk of AKI than the 1st quartile group (male, UA < 4.4 mg/dL; female, UA < 3.5 mg/dL) as following ORs: 2.3 (1.76-2.90) in males (P < 0.001); and 2.5 (1.86-3.32) in females (P < 0.001). There were more patients who did not recover from AKI in the 4th quartiles than in the 1st quartiles, as following ORs: 1.5 (1.11-1.95) in males (P < 0.001); and 2.5 (1.63-3.98) in females (P < 0.001). The 4th quartile group had a higher risk of all-cause mortality than the 1st quartile group, as following HRs: 1.5 (1.30-1.71) in males (P < 0.001); and 1.3 (1.08-1.52) in females (P = 0.004). The in-hospital mortality risk was also higher in the 4th quartile than in the 1st quartile, which was only significant in males: OR, 2.4 (1.56-3.77) (P < 0.001).

Conclusions: Hyperuricemia increases the risks of AKI and all-cause mortality in hospitalized patients.

Figure 2. Kaplan-Meier curves of the ESRD risk

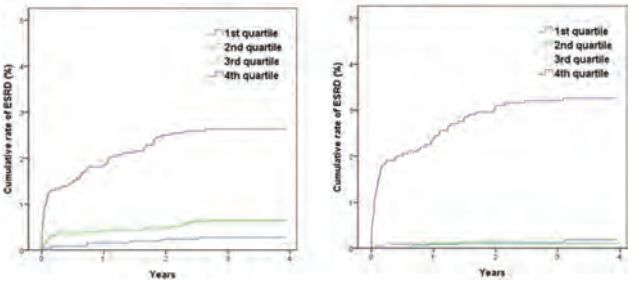
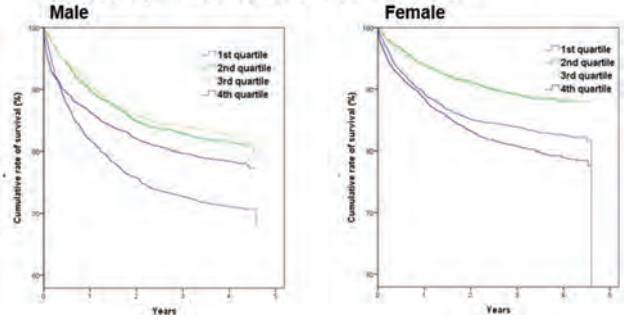


Figure 3. Kaplan-Meier curves of the survival rates



TH-PO015

Improvement of the Renal Angina Index Clinical Application Through Multiple Baseline Creatinine estimation Methods

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Background: The Renal Angina Index (RAI) is a validated screening tool used at 12h of pediatric intensive care unit (PICU) admission that predicts severe AKI on PICU day 3. A baseline serum creatinine (SCr) value is essential for AKI diagnosis as well as RAI, yet, is often not available. In this situation, our RAI algorithm uses a validated height-dependent imputation method (Baseline SCr (mg/dL) = 0.413 x height (cm) / 120ml/min/1.73m^2), yet patient height often is not available in the medical record within 12 hours of PICU admission. To improve the reliability of the RAI algorithm, we compared the height-dependent method with an age-based, height-independent baseline SCr calculation.

Methods: In April 2017, we implemented an electronic algorithm to automatically generate an RAI score for every patient (pt) admitted to our PICU. We reviewed 157 pt records from May 2017, selecting those who had an appropriate calculation of their RAI at 12h. We compared the RAI using an age-based SCr imputation method of Pottel to the RAI using a SCr imputed by the height-dependent method. Our primary outcome was a change in fulfillment of the RAI positivity threshold (RAI≥8). A secondary outcome compared height-based imputed and age-based baseline SCr to assess for a discrepancy of >25% between the two methods.

Results: We found 15/157 false positive RAI results on screening due to a lack of previously measured SCr and height, 42 without SCr measurement within 12h of their admission, leaving 100 that had sufficient data for RAI calculation. Only 2/100 pt had the RAI reclassified when using the Pottel imputed baseline SCr (one in each direction). 20% of pt had a discrepancy of 25% or more between the two methods. A Cochrane-Mantel-Haenszel Chi-square test confirmed that being small for age (<3rd percentile of height) or being older (≥14 years old) were both independently associated with an overestimation of the baseline SCr when using the age-based method.

Conclusions: The age-based method to estimate baseline SCr offers a viable height-independent alternative for RAI calculation. While being less precise than a height-based approach, this lack of precision rarely leads to reclassification of pt RAI status.

TH-PO016

U-Shape Association of Serum Albumin Level and AKI Risk in Hospitalized Patients

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Background: While an association between hypoalbuminemia and increased risk of acute kidney injury (AKI) is well-established, the risk of AKI development and its severity among patients with elevated serum albumin is unclear. The aim of this study was to evaluate the risk of AKI in hospitalized patients stratified by various admission serum albumin levels.

Methods: This single-center retrospective study was conducted at a tertiary referral hospital. All adult hospitalized patients who had admission albumin levels available between January 2009 and December 2013 were enrolled. Admission albumin was categorized based on its distribution into six groups (≤2.4, 2.5-2.9, 3.0-3.4, 3.5-3.9, 4.0-4.4, and ≥4.5 mg/dL). The primary outcome was the incidence of hospital-acquired AKI (HAKI). Logistic regression analysis was performed to obtain the odds ratio of AKI for various admission albumin strata using the albumin 3.5 to 3.9 mg/dL (lowest incidence of AKI) as the reference group.

Results: Of the total 9,552 studied patients, HAKI occurred in 1,556 (16.3%) patients. The incidence of HAKI among patients with admission albumin ≤2.4, 2.5-2.9, 3.0-3.4, 3.5-3.9, 4.0-4.4, and ≥4.5 mg/dL was 18.3%, 14.3%, 15.5%, 14.2%, 16.7%, and 26.0%, respectively. After adjusting for potential confounders, admission serum albumin levels ≤2.4 and ≥4.5 mg/dL were associated with an increased risk of HAKI with odds ratios of 1.52 (95% CI 1.18-1.94) and 2.16 (95% CI 1.74-2.69), respectively. While stage 1 HAKI was significantly more frequent among patients with admission albumin ≥4.5 mg/dL (23.0% vs. 11.6%, P<0.001), incidence of stage 3 HAKI was higher in those with albumin ≤2.4 mg/dL (2.8% vs 0.3%, P<0.001).

Conclusions: Admission serum albumin levels ≤2.4 and ≥4.5 mg/dL were associated with an increased risk for HAKI. Patients with admission albumin ≥4.5 mg/dL had HAKI with a lower intensity when compared with those who had admission albumin levels ≤2.4 mg/dL.

TH-PO017

Admission Calcium-Phosphate Product Levels and Risk of AKI in Hospitalized Patients

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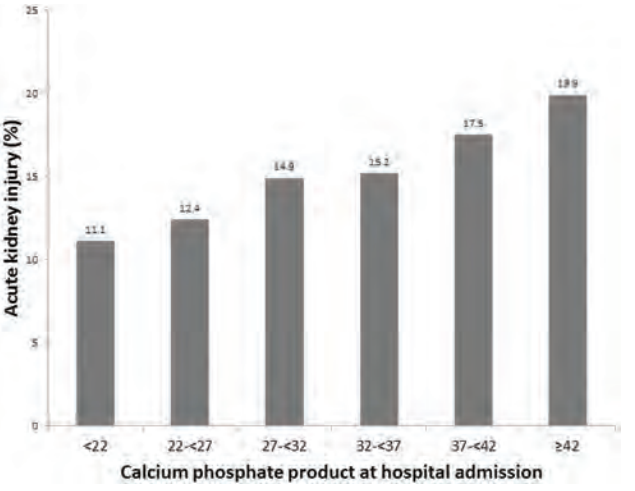
Background: An increased serum calcium-phosphate product (CaP) can result in acute kidney injury (AKI) due to tubular and interstitial calcium phosphate deposits. In addition, CaP of >55 mg^2/dL^2 is associated with systemic calcification. However, the risk of AKI development among hospitalized patients with different calcium-phosphate product levels on admission remains unclear.

Methods: All adult hospitalized patients who had both admission serum calcium and phosphate levels available between years 2009 and 2013 were enrolled. Admission CaP was categorized based on its distribution into six groups (<22, 22-<27, 27-<32, 32-<37, 37-<42 and ≥42 mg^2/dL^2). The odds ratio (OR) of in-hospital mortality by admission CaP, using the CaP category of <22 mg^2/dL^2 as the reference group, was obtained by logistic regression analysis.

Results: After excluding patients with end stage renal disease (ESRD), without serum creatinine measurement, and those with AKI at presentation, a total of 9,864 patients were studied. In-hospital AKI occurred in 1,478 (15.0%) patients. The incidence of AKI among patients with admission CaP <22, 22-<27, 27-<32, 32-<37, 37-<42 and ≥42 mg^2/dL^2 was 11.1%, 12.4%, 14.9%, 15.2%, 17.5%, and 19.9%, respectively. After adjusting for potential confounders, CaP >37 mg^2/dL^2 was associated with an increased risk of developing AKI, with ORs of 1.53 (95% CI 1.19-1.96) and 1.63 (95% CI 1.25-2.14) in patients with admission CaP 37-<42 and ≥42, respectively. Among a subgroup of patients with available serum albumin, after adjusting for potential confounders, corrected CaP >27 mg^2/dL^2 was associated with an increased risk of developing AKI with ORs of 1.50 (95% CI 1.06-2.15), 1.49 (95% CI 1.06-2.13), 1.85 (95% CI 1.30-2.67) and 1.69 (95% CI 1.16-2.49) when CaP were within 27-<32, 32-<37, 37-<42 and ≥42 mg^2/dL^2, respectively.

Conclusions: Elevated admission CaP was associated with an increased risk for in-hospital AKI.



TH-PO018

Lower Serum Bicarbonate Is Associated with an Increased Risk of AKI

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Background: Lower serum bicarbonate levels are associated with an increased risk of kidney disease progression. Whether lower serum bicarbonate levels are associated with an increased risk of developing acute kidney injury (AKI) is unclear. We tested the hypothesis that lower serum bicarbonate levels are associated with a higher risk of developing AKI.

Methods: We included 8,393 patients from the Systolic Blood Pressure Intervention Trial (SPRINT). Serum bicarbonate levels were measured at baseline in the SPRINT study. AKI was a predetermined adjudicated adverse event that was determined by hospital admission and discharge records with AKI as a recorded diagnosis. Serum bicarbonate was examined in clinically significant cutoffs ≤ 24, 25-28 and >28 mEq/L, with 25-28 mEq/L as the reference group. Cox proportional hazard models were used to examine the association between serum bicarbonate and development of AKI.

Results: The mean (SD) age, estimated glomerular filtration rate (eGFR), and serum bicarbonate level at baseline were 68 (9) years, 77 (23) ml/min/1.73m2 and 26.3 (2.6) mEq/L, respectively. Participants with serum bicarbonate levels ≤ 24 mEq/L were more likely to be male and to have lower baseline eGFR. After a median follow-up time of 3.3 years, 293 participants developed AKI. More patients in the lower bicarbonate group developed AKI (6.1% vs 2.8% in the 25-28 mEq/L and 2.1% in the >28 mEq/L). A bicarbonate level ≤ 24 mEq/L was associated with a significantly increased risk of AKI compared to those with a bicarbonate level of 25-28 mEq/L after full adjustment (HR 1.42, 95% CI 1.1 to 1.8).

Conclusions: Lower serum bicarbonate levels are an independent risk factor for the development of AKI.

Funding: Other NIH Support - NHLBI

Hazard Ratio (95%CI) of AKI

Serum Bicarbonate mEq/L	Unadjusted	Model 1*	Model 2**
≤ 24	2.11 (1.7-2.7)	1.42 (1.1-1.8)	1.42 (1.1-1.8)
25-28	1.00	1.00	1.00
> 28	1.14 (0.8-1.6)	0.99 (0.7-1.4)	1.01 (0.7-1.4)

*Model 1: adjusted for age, gender, race, treatment assignment, smoking status, history of cardiovascular disease, heart failure, baseline body mass index, blood pressure and eGFR.

**Model 2: adjusted for model 1 plus class of antihypertensive medication.

TH-PO019

Risk Factors for Community-Acquired Kidney Disease

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Background: Risk factors for the development of AKI in the community, either presenting to Community Health Center (CHC) or emergency departments (ED), have not been well studied in Low and Lower-Middle Income Countries (LLMIC). A key limitation is the heterogeneity of diseases and a lack of a standardized approach to evaluating renal

dysfunction. We evaluated the risk factors associated with acute kidney disease (AKD) within the International Society of Nephrology 0by25 Pilot Feasibility Project, designed to improve detection and management of community acquired-AKI in LLMIC.

Methods: Patients (pts) presenting to CHC or ED were screened for signs or symptoms *a priori* associated with risk of developing AKI. Pts with high/moderate risk underwent a serum creatinine (sCr) POC test and a urine dipstick. Pts were classified as chronic kidney disease (CKD) based on prior history, proteinuria (>1+) and/or baseline sCr within 12 mos by estimated GFR (CKD-EPI equation)) <60 mL/min/1.73 m^2; normal renal function (NRF) (negative proteinuria and eGFR>75ml/min/1.73 m^2); Acute Kidney Disease (AKD) neither meeting criteria for CKD or NRF. AKI was confirmed within 7 days by sCr increase or decrease of 0.3mg/dl, or 1.5x from the reference value.

Results: 3,577 pts were screened; 319 CKD and 379 children <12 years old were excluded from this analysis. Of 2,879 remaining pts, 1248 (43%) were classified as AKD at enrollment; 496 had NRF; and 1,135 with low risk for AKI, were assumed to have a normal renal function. Over the first 7 days, 438(3.5%) from AKD and 58(35%) from NRF group met criteria for AKI. In comparison to NRF, pts with AKD had a higher frequency of diabetes (13% AKD vs. 9%NRF), hypertension (22%AKD vs.16%NRF) and chronic liver disease (5%AKD vs. 2%NRF). Dehydration associated with vomiting and low oral intake was the most common risk factor for AKD, followed by diarrhea, hypotension and appetite loss. Pts with AKD were more often hospitalized and had high mortality rates; 9% at 7 days and 15% at 6months.

Conclusions: Comorbidities and a set of signs and symptoms can identify adult patients at risk for AKD and can be used to select patients that may benefit from POC testing in CHC. Crucially, identification of kidney dysfunction can help discriminate patients who may benefit from higher levels of care.

Funding: Private Foundation Support

TH-PO020

National AKI Risk Estimates After a Variety of Inpatient Surgeries

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Background: Postoperative acute kidney injury (AKI) is not well studied in non-cardiac procedures. Our aim was to quantify the risk of AKI and dialysis-requiring AKI (AKI-D) after various inpatient surgeries.

Methods: We used the National Inpatient Sample (NIS), which is a nationally representative sample of hospitalizations in the United States and includes records from all payers (including the uninsured). We identified 37 types of surgeries from 1/1/2013 to 9/30/2015 in adults (age ≥18 years) on first 2 days of hospitalization, excluding patients with end stage renal disease. Procedures, AKI and AKI-D were defined using ICD-9-CM diagnosis and procedure codes. Certain same-day surgery combinations were identified as well. Weighted frequencies and proportions of AKI and AKI-D were calculated for each surgery with 95% confidence intervals (CI).

Results: Our study sample of 2,504,894 surgical hospitalizations represented 12,524,470 hospitalizations when weighted. AKI and AKI-D risk was plotted in figure 1 sorted by AKI risk. Surgeries with the highest AKI-D percentages were heart transplant (2.6%, 95% CI 1.0-4.2), liver transplant (3.7%, 95% CI 2.4-4.9) and abdominal aortic aneurysm repair (4.2%, 95% CI 3.4-5.0). Small bowel surgery had the highest AKI risk among bowel surgeries (8.7%, 95% CI 8.3-9.0) and had even higher risk when combined with colon surgery (18.3%, 95% CI 17.4-19.3) or with exploratory laparotomy (14.2%, 95% CI 13.5-14.8). Exploratory laparotomy combined with an abdominal procedure (except gastric and cesarean procedures) had significantly higher AKI risk (range of percentage difference 0.4-5.5).

Conclusions: Using nationally representative data, we estimated the risk of AKI and AKI-D in a large population of surgical hospitalizations including certain same-day surgery combinations.

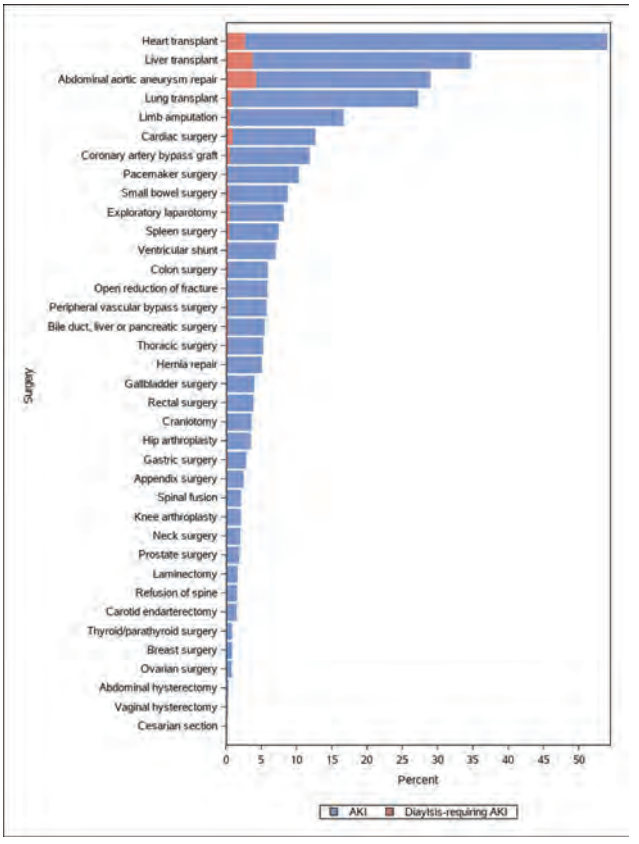

Figure 1. AKI Risk After Inpatient Surgeries

TH-PO021

Predictors for AKI in Old Age

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Background: Acute kidney injury (AKI) is a feared condition especially in old age. Data on incidence rates however as well as predictors are scarce. The Berlin Initiative Study (BIS) evaluates the incidence of AKI and potential predictors in older adults.

Methods: The BIS is a prospective population-based cohort initiated in 2009 whose participants are members of a German insurance company with the largest fraction of older adults. Patients are documented biannually by a standardized questionnaire. All intermediate hospitalizations with referral and acute ICD-10 (N17.xx) diagnoses were provided by the insurance company. N17.xx events during hospitalizations were identified. From the group without incident AKI 16 patients with prevalent events were excluded. Multivariate Cox-PH regression analysis was used to detect predictors for the first incident AKI.

Results: As of May 04, 2018, 2053 participants (47.4% male, mean age 80.3 at inclusion) were observed for 7.4±0.4 years. Of those, 189 (9.2%) experienced at least one AKI during the observation. In total, 292 events were observed (incidence ratio / 100.000 person-yrs: 1900). At baseline, patients with incident AKI were about 2.4 years older, more frequently male (57 vs. 47%), had a worse waist-hip-ratio (WHR, median 1.0 vs. 0.9), $eGFR_{(BIS2)}$ (median 49 vs. 60 mL/min per 1.73m^2) and albumin-creatinine ratio (median 17 vs. 10 mg/g) and suffered more often from comorbidities at baseline (hypertension 91 vs. 77%, diabetes 40 vs. 25%, myocardial infaction 22.0 vs 13%, stroke 15 vs. 8%, anemia 32 vs. 16%). Of the 189 patients with AKI, 26 (13.8%) were admitted to the hospital with an N17.xx ICD-10 code, all other patients with other primary referral diagnoses; the median number of hospitalization during the observation period was 7 (median duration of stay 11 days). Of the patients without AKI, 41% had hospitalizations with a median number of 4 (median duration of 7.6 days). In the multivariate model, $eGFR_{(BIS2)}$ (OR=0.873 [0.83;0.92] per 5 units), waist-hip-ratio (OR=1.47 [1.24;1.74] per 0.1 units), hypertension (OR=2.00 [1.18;3.38]), diabetes (OR=1.61 [1.19;2.18]), and anemia (OR=1.52 [1.09;2.12]) were predictive for AKI in older adults.

Conclusions: With 1900 per 100.000 person-yrs AKI is frequent in a representative sample ≥70 yrs. Potential predictors apart from $eGFR_{(BIS2)}$ were WHR, hypertension, diabetes and anemia.

Funding: Veterans Affairs Support

TH-PO022

AKI Mortality and Weekend Nephrologist Consultation

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Background: Admission to the hospital on weekends (WKD) is associated with increased mortality for acute illnesses than weekdays (WDAY). Previous analysis showed that this phenomenom also occurs in patients with acute kidney injury (AKI). However, there is still no data about this association and nephrologist consultation. Aim: analyse the impact of the day of the week of nephrologist consultation on the mortality in patients with AKI.

Methods: Database of patients over 18 years with AKI between 1srt January 2012 and 28st February 2018. Patients were analyzed according to the day of the week of first nephrologist consultation.

Results: During the period 6177 patients diagnosed with AKI were attended. The mean age was 64.1±15.7 years. They were classified in KDIGO I (46.3%), KDIGO II (26.5%) e KDIGO III (27.2%) at the nephrologist's called. The mean SOFA was 7.3 ± 4.7, 34.1% dialyzed and global mortality was 37.1%. WDAY called group has 4761 (77.1%) and WKD, 1416 (22.9%) patients. SOFA (7.8±4.7 *vs* 7.1±4.6, p<0.001) and mortality (41.5% *vs* 35.8%, p <0,001) were higher on WKD group. The following mortality risk factors were identified: age (OR 1.02; IC 1.02-1.03; p<0.001), obstructive AKI (OR 0.39; IC 0.26-0.58; p<0.001), sepsis (OR 1.26; IC 1.10-1.45; p=0.001), liver disease (OR 1.40; IC 1.11-1.77; p=0.004), cancer (OR 1.17; IC 1.19-2.62; p=0.005), dialysis (OR 1.54; IC 1.31-1.80; p<0.001), SOFA at the moment of the call (OR 1.18; IC 1.16-1.20; p<0.001) and at the first dialysis (OR 1.07; IC 1.05-1.08, p<0.001). In the model with only patients hospitalized in intensive care unit (ICU) (3283 patients; 53.14%), nephrologist consultation at WKD (OR 1.22; IC 1.02-1.46; p=0.028), age (OR 1.01; IC 1.01-1.02; p<0.001), obstructive AKI (OR 0.51; IC 0.27-0.96; p=0.037), cancer (OR 2.30; IC 1.34-3.94; p=0.002), dialysis (OR 1.57; IC 1.31-1.88; p<0.001), SOFA at the moment of the call (OR 1.11; IC 1.09-1.13; p<0.001) and at the first dialysis (OR 1.08; IC 1.07-1.10; p<0.001) were identified as risk factors of mortality.

Conclusions: First nephrologist consultation at WKD was associated a higher mortality, particularly those hospitalized in ICU. This association can be due to the highest severity of this population.

TH-PO023

Incidence and Risk Factors of AKI After Coronary Artery Bypass Grafting

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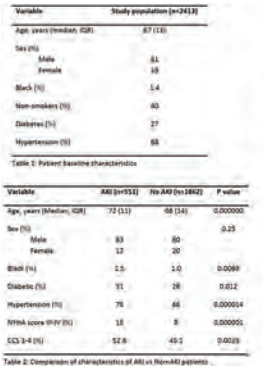
Background: Acute kidney injury (AKI) Post-coronary artery bypass graft (CABG) is common, but the exact incidence remains controversial, and contributing risk factors varies in different studies. We aimed to investigate the true incidence and risk factors of AKI post Cardiopulmonary bypass (CPB) CABG; in a large inner-city, multi-ethnic, population.

Methods: We examined 2413 patients undergoing first time CPB CABG in a large tertiary care, UK hospital. Creatinine measurements (on isotope dilution mass spectroscopy or spectrometry) were derived from hospital records, pre-surgery and post-surgery days 1,2,3 and 4. AKI was defined as a rise of serum creatinine 26.4 μmol/L or 50% or 1.5-fold from baseline creatinine.. All data for the study was recorded prospectively, as a part of institutional audit process. All statistics were done using SPSS 17 and p value<0.05 was considered significant.

Results: Baseline characteristics of the patients are shown in table 1. The incidence of AKI was 23%. Majority of new AKI cases occurred on the second day post-operatively with 19% occurring on day 2 compared to 6%, 9% and 3% occurring on days 1, 3 and 4 respectively. Patients who developed AKI were older, with higher proportion of blacks, diabetics, hypertensives, higher CCS score (Canadian Cardiovascular Society grading of angina) and higher NYHA class compared to non-AKI patients (table 2). Incidence of AKI was associated with increased in-hospital mortality (4.4% vs 0.5%; p=0.000) and length of stay (8[IQR5] vs 6[IQR3] days; p=0.000). On multiple regression analysis, the independent predictors of AKI were age, CCS score 3-4, hypertension, emergency nature of surgery, insulin dependent diabetes and raised pre-operative creatinine (table 3).

Conclusions: In a multi-ethnic, inner-city population the incidence of AKI was 23% in first time CPB CABG patients and the independent risk factors were age, CCS score 3-4, hypertension, emergency surgery, diabetes and CKD.



Variable	Study population (n=2413)
Age, years (median, IQR)	67 (13)
Sex (%)	
Male	61
Female	39
Black (%)	14
Non-smokers (%)	40
Diabetes (%)	27
Hypertensives (%)	88

Table 1: Patient baseline characteristics

Variable	AKI (n=551)	No AKI (n=1862)	P value
Age, years (Median, IQR)	72 (11)	68 (14)	0.000000
Sex (%)			0.25
Male	83	80	
Female	17	20	
Black (%)	1.5	1.0	0.0069
Diabetic (%)	31	28	0.012
Hypertension (%)	79	66	0.000014
NYHA score III-IV (%)	18	8	0.000001
CCS 3-4 (%)	52.6	49.1	0.0019

Table 2: Comparison of characteristics of AKI vs Non-AKI patients

Variable	Odds ratio	95% CI	P value
CCS 3-4	1.32	(1.08-1.62)	0.008
Hypertension	1.39	(1.10-1.74)	0.012
Emergency	2.78	(1.42-5.44)	0.000014
Insulin dependent diabetes	1.99	(1.43-2.77)	0.00004
Age	1.05	(1.04-1.06)	0.000000
Pre-op creatinine	1.02	(1.02-1.03)	0.000000

Table 3: Multivariate regression analysis of predictors of AKI following CPB CABG.

Tables on baseline characteristics; comparisons & predictors of AKI

TH-PO024

Patient-Centered AKI: Baseline Characteristics of the Change AKI Study

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Background: Hospital-related AKI carries a threat of poor outcomes that persist after discharge, yet few interventions support patient-centered AKI awareness and self-management beyond the hospital. We describe the study protocol and baseline characteristics of the ongoing Change AKI Study, a pilot study testing the feasibility and acceptance of an mHealth-based educational intervention for AKI survivors.

Methods: Hospitalized AKI survivors at Duke University Hospital seen by the inpatient nephrology service were recruited in 2017-2018. Eligible participants complete baseline surveys including questions regarding their outpatient safety behaviors (e.g. regular use of pain medication such as NSAIDs), perceived AKI knowledge (e.g. "Which of the following statements best describe how much you know about what causes AKI?"), and perceived risk of AKI outcomes (e.g. "How likely do you think it is that you will develop AKI in the future?"). Participants are then randomized to receive an mHealth educational program promoting AKI awareness/self-management, or usual care. Surveys are repeated by phone 1-month after discharge to evaluate changes in behaviors, perceived knowledge, and perceived risk.

Results: To date, 56 participants have completed baseline (28 intervention, 28 control). Half (50%) are female, 57% are aged 45-64 years old, and 42% are Black. Most have completed high school (98%), with a high proportion reporting a history of hypertension (61%) and diabetes (50%). Over half reported regular pain medication prior to hospitalization. Despite receiving a nephrology consult, only 28 (50%) report being aware of their AKI diagnosis – 23% report being told by their primary hospital team. Perceived AKI-related knowledge was variable: what kidneys do (95%), what is AKI (36%) causes of AKI (59%), what to do after AKI (48%). Most (70%) were concerned about recurrent AKI, 52% felt it was likely. While 63% reported confidence in knowing what questions to ask their outpatient provider about AKI, only 50% felt confident they had information to lower their future AKI risk.

Conclusions: AKI awareness, perceived knowledge, and self-management are suboptimal among hospitalized survivors receiving inpatient nephrology care. Interventions designed to improve these patient-centered outcomes may prevent recurrence.

TH-PO025

Risk Factors for AKI in High-Risk Populations: Systematic Review and Meta-Analyses

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Background: Predictive models help identify patients at increased risk for Acute kidney injury (AKI) for preventive care. It is unclear how various risk factors perform in different clinical settings. We systematically reviewed predictive models for AKI in four high risk settings and performed meta-analyses of common AKI risk factors

Methods: We searched MedLine, EMBASE, CINAHL and Cochrane Library, and performed hand searches of the retrieved reference lists, from 2010 through 2017 for English language studies of prediction models for hospital-acquired AKI (KDIGO, AKIN or RIFLE criteria) in adult hospital populations, patients undergoing cardiac surgery, patients in intensive care unit (ICU) and those undergoing contrast procedures. PRISMA-P 2015 statement was used for data extraction and study appraisal. For the meta-analyses of risk factors, studies with insufficient or non-standardized data and unadjusted risk factors were excluded. Random effects meta-analyses were used to assess pooled adjusted odds ratio (OR) for diabetes (DM), congestive heart failure (CHF) and chronic kidney disease (CKD) for developing AKI

Results: 74 studies testing AKI prediction models in the four clinical settings were included. Of these, 10 were in the general hospital setting, 8 were in the ICU, 27 in

percutaneous coronary interventions, and 29 in cardiac surgery. There was considerable heterogeneity among studies in the choice and definition of predictors. Meta-analyses included 14 studies reporting diabetes (135955 patients), 16 studies reporting CKD (137846 patients) and 22 studies reporting CHF (180224 patients). Stratified analyses based on high-risk clinical settings were consistent with the overall results (Table 1)

Conclusions: In the combined as well as sub-populations, DM, CKD, and CHF are associated with increased risk for AKI. Analyses of differential risk levels in sub-populations was limited by heterogeneity. Using uniform definitions for AKI and its risk factors in the development of predictive models for AKI is essential for their clinical application

Funding: Private Foundation Support

Meta-analyses results

	Overall estimate OR (95% CI)	Percutaneous coronary intervention OR (95% CI)	Cardiac surgery OR (95% CI)
Diabetes	1.72 (1.38-2.14)	1.86 (1.47-2.34)	1.26 (1.01-1.56)
CKD	1.47 (1.32-1.64)	2.53 (1.10-5.83)	1.31 (1.15-1.51)
CHF	1.78 (1.54-2.06)	2.07 (1.62-2.65)	1.55 (1.31-1.83)

TH-PO026

Frequency and Consequences of AKI in Patients with CKD in Public Nephrology Practices in Queensland, Australia

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Background: It is recognised that acute kidney injury (AKI) contributes to, and complicates, CKD and can exacerbate its progression. We describe acute kidney injury (AKI) documented in hospital episodes in patients enrolled in the CKD.QLD registry, based in the public nephrology sector in Queensland.

Methods: Queensland Health supplied data on CKD.QLD patients on admissions to all Queensland hospitals, public and private, as well as associated costs, and deaths, from May 2011 to June 2016. We describe the frequency of AKI and associated conditions, recognised by ICD codes.

Results: Among 6,365 CKD.QLD patients, 2,198 (34.5%) had a total of 4,711 hospital encounters with an AKI diagnosis. 550 patients had three or more AKI-related admissions. 64.9% of AKI admissions were through the emergency department. People with AKI were somewhat older (68.2 vs 64.6 yr) and more often male (57.1% vs 52%), than those without AKI, p<0.001 for both. Leading diagnoses associated with AKI were congestive heart failure, urinary tract infection, myocardial infarction, dehydration, pneumonia and COPD, gastroenteritis/colitis, and sepsis, and diabetic nephropathy was the leading underlying renal condition. Of those with AKI, 553 (25.2%) subsequently died in the 5 year interval and 238 (10.8%) started renal replacement therapy (RRT), compared with 282 (12.8%) who died and 295 (13.4%) who started RRT among those who did not have AKI, p<0.001 for each. Adjusted for all other significant factors, the hazard ratio (95%CI) of AKI patients relative to those without AKI for death without RRT was 3.32 (CI 2.8-3.9), p<0.001, and for RRT was 1.21 (CI 1-1.5), p=0.06.

Conclusions: AKI that comes to clinical attention is very common among these CKD patients. It usually presents through unplanned, emergency admissions. It is associated with strikingly increased rates of death but only marginally increased rates of RRT. Preventable causes of AKI should be better understood and addressed.

Funding: Commercial Support - AMGEN Australia, Government Support - Non-U.S.

TH-PO027

Characteristics of Patients Readmitted to Hospital One Year Following an Episode of AKI

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Background: Acute kidney injury (AKI) is a risk factor for further episodes of AKI. We have analysed the characteristics of a cohort of patients who had an AKI identified by an AKI e-alert and who were readmitted within a 1 year

Methods: Data was gathered on patients admitted to a teaching hospital who had an AKI e-alert (2015 - 2017) and who were subsequently readmitted within 1 year. The electronic health care records (EHR) of these patients were reviewed

Results: 2010 patients were identified of which 1513 patients had an initial length of stay〈 30 days. Initial review of 302 patient EHR from this subgroup (n=1513) excluded 52 patients who did not have a clinical episode of AKI. The remaining cohort (n=251) had a mean age of 73 yrs (25-99 yrs) with 135 (54%) males and 116 (46%) females. The mean length of stay was 16 days and the cause of AKI was poorly documented in the EHR. The reason for admission was multifactorial (30%) sepsis (26%), cardiac failure (15%), hypovolaemia (8%), malignancy (8%) obstruction (5%), trauma (5%) and abdominal surgery (3%). The 1 yr mortality was 37% and this increased with age; 20.9% (〈 60 yrs), 33.3% (〈 60-79 yrs) and 42.2% (〉80yrs). At 3 months recovery of kidney function to the original eGFR occurred in 20.3% of patients. 10.7% of patients experienced a reduction in kidney function to〈 50% of their baseline eGFR. Recovery of eGFR to baseline at 3 months did not result in improvement in 1 year mortality rate 32.8% versus 29.2% in those patients whose kidney function did not return to baseline eGFR. The mean time to readmission was 68.4 days (range 1-336 days). The cause for readmission was the same in only 20% of patients. Only 23.9% of those readmitted had a further episode of AKI either at the time of readmission or throughout the subsequent length of hospital stay.

Conclusions: Acute kidney injury has been identified as a risk factor for recurrent episodes of AKI. In our ongoing analysis of a large cohort of patients only 23.9% of those readmitted had an episode of AKI at the time of readmission or throughout the subsequent length of hospital stay. The reason for readmission was the same for only 20% of the patients. Nearly 80% of patients fail to fully recover kidney function by 3 months. Further analysis of the characteristics of this cohort are ongoing and will be presented.

TH-PO028

Temporal Trends in the Inpatient Mortality of Patients with AKI After Coronary Revascularization in a Nationwide Study

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Background: The major modalities of coronary revascularization - coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) both carry high risk of acute kidney injury (AKI). Our previous studies have shown that both CABG and PCI were associated with increasing temporal trends in AKI incidence over the years; and in-hospital mortality after CABG was more than 40% higher than that of PCI. In this study, we compared the temporal trends of total in-hospital mortality, and in-hospital mortality associated with AKI after CABG vs PCI.

Methods: We generated a propensity-matched cohort of 274,464 hospitalizations that had first time CABG or PCI for multi-vessel coronary disease in 2004 to 2012 from the National Inpatient Sample. Patients received concomitant valvular repair or both CABG and PCI on same admission, history of organ transplant, CKD stage V or ESRD on dialysis were excluded. Both groups were propensity score matched. The odds ratios were estimated by the random intercept logistic regression model.

Results: The temporal trends of in-hospital mortality in CABG-AKI group had been decreasing from 16.52 % in 2004 to 6.51% in 2012 whereas in the PCI- AKI group, the in-hospital mortality has been stable, 14.17% in 2004 to 13.11% in 2012. Compared to PCI-AKI group, the likelihood of in-hospital death for CABG- AKI group in 2004 was 20 % higher (OR 1.20, 95% CI 0.89-1.61, P=0.35). But after 2004, the odds reversed.. From 2005 to 2012, the odds of in-hospital death in the patients with post-CABG AKI became 23%-54% lower than the PCI-AKI group (OR 0.77, 95% CI 0.60-0.99, P=0.05; OR 0.46, 95%CI 0.36-0.59, P<0.0001). Interestingly, when we compared the overall in-hospital mortality between both groups irrespective of the kidney function, CABG was associated with higher in-hospital mortality from 2004-2010 than PCI group with down-trending ORs. In 2011 and 2012, PCI was associated with higher in-hospital mortality.

Conclusions: CABG patients with post procedural AKI have shown a decreasing temporal trends in in-hospital mortality over the years whereas the in-hospital mortality remains high in the PCI patients with AKI.

TH-PO029

Incidence and Outcomes of Dialysis-Requiring AKI in Taiwan—A Nationwide Study 2003-2014

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Background: Dialysis-requiring acute kidney injury (AKI-D) is associated with high morbidity and mortality. Despite increasing incidence of AKI-D, information pertaining to trends and prognosis remains limited due to underreporting of discharge code of AKI code and differences in definition. We identify first in-hospital dialysis using procedure code to evaluate the time trend and outcome of AKI-D over a twelve-year period in Taiwan.

Methods: In a retrospective nationwide study based on National Health Insurance Database 2000-2015, all adults requiring the first hospitalized dialysis treatment between 2003 and 2014 were identified. Patients with previous renal transplantation or chronic dialysis were excluded. Through cross-linking of several administrative datasets, information pertaining to comorbidity, concurrent surgical interventions and sepsis, and clinical outcome were ascertained.

Results: A total of 203,071 first hospitalized dialysis was retrieved. Among them, 22,746 patients (11.2%) had advanced chronic kidney disease (CKD); 121,054 patients (59.6%) had history of CKD; 59,271 patients (29.2%) received dialysis during admission without documented CKD. Among patients without pre-existing CKD, 46.7% had sepsis; 6.6% were related to cardiac surgery; 91.2% had been admitted to ICU and 42.5% received CRRT. Patients without pre-existing CKD showed the highest in-hospital mortality (71.1%). However, only 47% of patients without pre-existing CKD could be identified with ICD-9 code of acute kidney injury (584). Time trend analysis showed that there were decreased trends of in-hospital mortality and increased trends of long-term dialysis from 2003 to 2014. For those who was discharged without receiving regular dialysis, 25% and 12% of patients died within 1 and 2 years after discharge.

Conclusions: In a nationwide retrospective study of 1st hospitalized dialysis treatment using procedure code, we found AKI-D was underreported and associated with high mortality. For the AKI-D survivors, high mortality was also noted.

TH-PO030

Kinetic Estimated Glomerular Filtration Rate (KeGFR) in Liver Transplantation: An Early Predictor of Significant AKI

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Background: Acute kidney injury (AKI) is a common clinical problem in patients undergoing liver transplantation (LT) and up to 20% of these patients progress to CKD. Kinetic estimated glomerular filtration rate (KeGFR) is a recommended formula in non-steady states. Aim: to evaluate the diagnostic yield of KeGFR for early prediction of AKI in patients following LT.

Methods: We retrospectively studied all patients who underwent LT from 06/ 2017 to 04/2018. Clinical data and all SCr measurements during the first 5 days after transplantation were recorded. SCr before surgery was considered as baseline. Significant AKI was defined as an increase of at least 2 times in SCr baseline or requirement of renal replacement therapy (RRT). Early decline of eGFR was defined as a decreased of more than 50% from baseline eGFR in the first postoperative 24 hours. Early decline of eGFR was evaluated by the KeGFR, Cockfort-Gault, CKD-EPI, and MDRD-4 formulas and compared with the development of significant AKI in the first 5 postoperative days.

Results: Forty nine patients were included, mean age of 47.3 ± 11.68 y, 55.1% were female. Median baseline SCr was 0.7 mg/dL (range 0.43 - 3.03). Three patients had significant AKI prior transplantation. Twenty-four (49.0%) patients developed significant AKI in the first 5 days postoperative, of which 33.3% required RRT and 12.5% died. Diagnostic performance of studied formulas is shown in Table 1.

Conclusions: KeGFR was the only formula that predicted significant AKI within the first 24 hours, with a high sensitivity (87%) and a strong negative likelihood ratio (0.17) and improved area under the curve (0.846). The KeGFR formula is an affordable diagnostic tool, which improves our capability of significantly detecting AKI in patients following liver transplantation.

Table 1. Diagnostic performance (early decline in eGFR) at 24 hours following liver transplantation

Formula	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	-LR	Diagnostic yield (%)	AUC†
Kinetic eGFR	87.5	72.0	75.0	85.7	3.13	0.17	79.6	0.846
Cockroft-Gault	25.0	100.0	100.0	58.1	∞	0.75	63.3	0.774
CKD-EPI	25.0	100.0	100.0	58.1	∞	0.75	63.3	0.787
MDRD-4	29.2	96.0	87.5	58.5	7.29	0.74	63.3	0.776

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, +LR: positive likelihood ratio, -LR: negative likelihood ratio, AUC: area under the curve, †AUC obtained from ROC analysis using the maximum proportional decline in eGFR from baseline in the first 24 hours for each patient.

TH-PO031

Using Kinetic Glomerular Filtration Rate to Predict AKI

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Background: Monitoring renal function changes during critical illness is difficult as current MDRD and CKD-EPI GFR estimating equations usually under or overestimate renal function during an episode of acute kidney injury (AKI). The kinetic glomerular filtration rate (KeGFR) equation (J Am Soc Nephrol 2013; 24: 877–888) has been developed to better evaluate rapid changes in renal function. We hypothesized that changes in KeGFR would predict the development of AKI in critically ill patients.

Methods: We prospectively evaluated 208 patients admitted to our general ICU. Serum creatinine (sCr) was measured daily for 7 days. KeGFR was calculated from the change in consecutive values of sCr (ICU baseline sCr and 24 h ICU sCr). In patientswith no baseline sCr available we back calculated sCr using MDRD equation (for an eGFR = 75 ml/m/1.73m^2). Patients diagnosed with AKI in the first 24 hours after ICU admission according to the KDIGO definition were excluded. AKI was defined as an increase of sCr value 1.5 times the baseline value or 0.3 mg/dl above the baseline within 48 hours to 7 days after ICU admission. The predictive performance of KeGFR was assessed by the receiver operator characteristic analysis to determine the area under the curve (AUC).

Results: From 208 patients enrolled in the study 98 patients developed AKI (47 %). Age, baseline serum creatinine, and eGFR (CKD-EPI) were not different between patients with and without AKI. At 24 h post ICU admission AKI patients had lower KeGFR (47.7 ml/m vs. 81.1 ml/m; p < 0.0001); at this time point KeGFR predicted AKI with an AUC of 0.778 (95% CI 0.689 - 0.867; p < 0.001). A KeGFR reduction from a baseline eGFR (ICU admission) ≥ 22.6% had a sensitivity of 95.3% and a specificity of 87.5% for predicting subsequent AKI development within 48 h and 7 days of ICU admission with an AUC of 0.969 (95% CI 0.932 – 1.000; p < 0.001). This reduction in KeGFR percentage from a baseline eGFR had an odds ratio of 4.5 (95% CI 1.675 – 12.090; p = 0.002) for subsequent development of AKI after 48 h of ICU admission.

Conclusions: The use of KeGFR accounts for non-steady state conditions and could improve clinical risk prediction models for AKI development in the ICU. sCr measurements, which can be obtained at modest cost, remain useful to guide early management of AKI if performed frequently.

TH-PO032

Early Biomarkers in the Detection and Risk Stratification of Sepsis Patients

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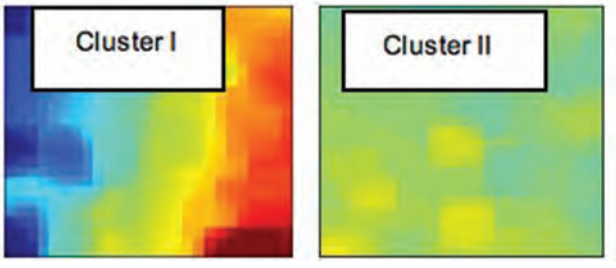
Background: Treatment of sepsis requires early hemodynamic support and antibiotic initiation, making timely diagnosis and risk stratification critical to improving survival. The reliance on clinical judgment, rather than diagnostic guidelines, to diagnosis and risk stratify sepsis patients results in a wide range of clinical outcomes.

Methods: In a prospective cohort study of 157 sepsis patients in a surgical ICU, we used 42 biomarkers that includes laboratory and vital measurements as well as age and Charlson comorbidity index using the earliest measurement within 48 hours of sepsis onset. We used hierarchical clustering to group patients with similar clinical characteristics. We compared clinical characteristics and outcomes between two main clusters identified using Fisher's exact test for categorical variables and student's t-test or Wilcoxon rank sum test for continuous variables as appropriate. Composite biomarker mosaic images were created using clustering variables.

Results: We identified two main clusters with 18 and 139 subjects in Clusters I and II, respectively. Cluster I consisted of more septic shock patients (78% vs 17%) who had early multiorgan failure and acute physiologic derangements in the first 24 hours of sepsis onset (median APACHE II score of 30 vs 16 and total SOFA score of 13 vs 5, respectively, p<.0001). Chronic diseases that differentiated the two clusters were cardiovascular and renal diseases (p<.0001). Renal biomarkers were significantly elevated two to three folds with higher prevalence of AKI (93% vs 45%) in cluster I compared to cluster II (p<0.01). Cluster I had significantly higher hospital mortality of (33% vs 2.2%, p<.0001) and one year mortality (50% vs 18%, p=0.005).

Conclusions: Using early biomarkers, we were able to identify two major clusters that had clinically different profiles which were reflected in composite biomarker mosaic images. We would be able identify patients at risk for adverse outcomes using our clustering and imaging methodology in order to improve hospital and long-term outcomes.

Funding: Other NIH Support - National Institute of General Medical Sciences



TH-PO033

Identification of AKI Subtypes in Patients with Sepsis Using Unsupervised Clustering

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Background: Acute kidney injury is highly prevalent in critically ill patients. Physicians recognize that subphenotypes of sepsis associated AKI exist. Our goal was to identify subphenotypes of AKI in patients admitted to the intensive care unit with sepsis.

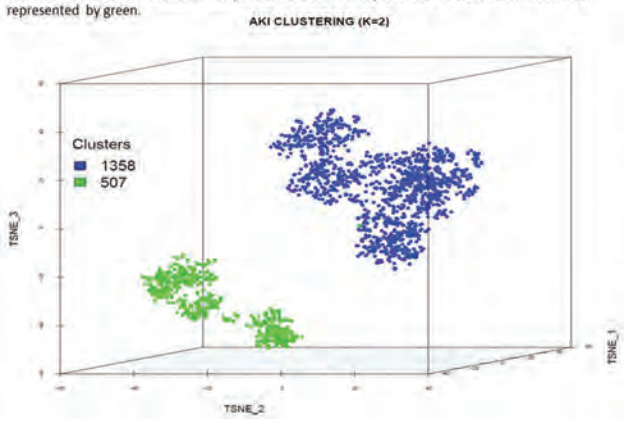
Methods: This was a retrospective analysis using the Medical Information Mart for Intensive Care (MIMIC)-III database. We identified AKI using the Kidney Disease Improving Global Outcomes criteria and sepsis utilizing the Clinical Classification Software. We used unsupervised machine learning to identify clusters using laboratory results and vital signs prior to AKI diagnosis.

Results: 1,865 patients were identified with sepsis associated AKI. After data processing and feature selection, 59 features, of which 28 were measures of variability, remained for inclusion into our unsupervised machine learning model. We utilized k-means clustering with k ranging from 2 – 10; k=2 had the highest silhouette score (0.62). Cluster 1 had 1,358 patients while Cluster 2 had 507 patients. There were no significant differences between clusters on age or gender. Small but significant differences were found on comorbidities, several laboratory results, and vital sign parameters. In-hospital mortality was significantly higher in cluster 2 patients (25%) vs. cluster 1 (20%, p=0.008). Features with the largest differences between clusters included basophil variability, eosinophil variability, ALT variability, and Creatine Kinase values.

Conclusions: To our knowledge this is the first study to identify two distinct subphenotypes of sepsis associated AKI utilizing electronic medical record data. Variability among laboratory values was important for clustering. Future studies in other cohorts and additional features are needed to validate and expand on the results of our study.

Funding: NIDDK Support, Government Support - Non-U.S.

Figure 1: 3-D Representation of clusters utilizing t-Distributed Stochastic Neighbor Embedding (t-SNE) method. This method condenses the 59 features into 3 transformed values which allows for 3-D representation. Each dot represents a single patient. The separation between two dots represents differences of features between two patients. Cluster 1 is represented in blue, while Cluster 2 is represented by green.



TH-PO034

AKI Predicts 30 Day Mortality in Community Acquired Infection

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Background: The National Institute for Health and Care Excellence has recently introduced new guidance for sepsis that risk stratifies patients to high, moderate and low risk based on clinical observations from the National Early Warning Score (NEWS). Laboratory assessment for Acute Kidney Injury (AKI) is mandated in patients with moderate risk, and if present warrants intravenous antibiotics within one hour. Our aim was to evaluate the association between AKI in suspected community acquired (CA) infection (I) and 30 day mortality.

Methods: Data of hospital admissions with CA-I (defined as prescription of antibiotics within 24 hours from A&E arrival) were extracted from the Electronic Patient Records from 07/2013 to 02/2018. Dialysis patients were excluded. CA-AKI was defined as AKI alerting within 24 hours. NEWS score was analysed in groups 0 (low risk), 1-4 (moderate risk) and >4 (high risk). A binary logistic model was used to assess associations with 30 day mortality. The model was tested separately in each group of NEWS. AKI 2 and 3 were analysed together as AKI2&3.

Results: There were 3764 patients aged 61 ±22 years, 2047 (54.4%) females, 292 (7.8%) CA- AKI {AKI 1, 201 (5.3%), AKI 2 60 (1.6%) and AKI 3 31 (0.8%)}. Lactate was tested in 1382 (36.7%) patients and was above 2 in 398 (10.6%) cases. NEWS was 0 in 1140 (30.3%), 1-4 in 2150 (57.1%) and >4 in 474 (12.6%) cases. 316 patients (8.4%) died within 30 days. In logistic regression analysis for the whole cohort age (OR 1.07 CI 1.06-1.08, p=<0.001), male (OR 1.48, CI 1.15-1.91, p= 0.002), lactate (OR 1.67, CI 1.19-2.34, p= 0.003), NEWS 1-4 (OR 2.23, CI 1.54-3.29, p=0<.001), NEWS>4 (OR 4.58, CI 2.99-7.01, p=0<.001), AKI 1 (OR 2.14 CI 1.44-3.20, p=<0.001) and AKI2&3 (OR 4.12 CI 2.46-6.90, p=<0.001) were associated with 30 day mortality. AKI2&3 retained a significant association in NEWS=0 group (20(1.8%) cases of AKI2&3 OR 5.41 CI 1.62-18.13, p =0.006),(Table 1)

Conclusions: CA-AKI is associated with an increased risk for mortality in CA-I even in patients with normal clinical observations. Convergence of sepsis and AKI guidance should be prospectively assessed.

30 Day Mortality

Total (N=3448)		NEWS=0 (N=1140)		NEWS=1-4 (N=2150)		NEWS>4 (N=474)	
HR (CI)	P value	HR (CI)	P value	HR (CI)	P value	HR (CI)	P value
1.47 (1.15-1.89)	<0.001	1.09 (1.06-1.13)	<0.001	1.07 (1.06-1.09)	<0.001	1.05 (1.03-1.07)	<0.001
1.47 (1.15-1.89)	0.002	1.45 (0.72-2.94)	0.302	1.79 (1.28-2.49)	0.001	1.09 (0.68-1.76)	0.719
2.34 (1.70-3.22)	<0.001	6.28 (2.66-14.76)	0.000	1.71 (1.09-2.68)	0.019	1.08 (0.58-2.00)	0.814
2.255 (1.52-3.35)	<0.001	0.89 (0.20-4.77)	0.983	2.44 (1.49-3.98)	<0.001	1.79 (0.81-3.93)	0. 148
4.04 (2.41-6.76)	<0.001	5.41 (1.62-18.13)	0.006	2.65 (1.24-5.66)	0.012	5.46 (2.11-14.12)	<0.001

TH-PO035

Association of AKI on Outcomes in Patients with ARDS - Secondary Analysis of LUNG-SAFE Patient Cohort

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Background: The impact of Acute Kidney Injury (AKI) in Adult Respiratory Distress Syndrome (ARDS) is poorly understood. We addressed this in a secondary analysis of the large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE) patient cohort. LUNG SAFE was an international, multicentre, prospective cohort study of patients with severe respiratory failure conducted during 4 consecutive weeks in winter 2014, in 459 intensive-care units (ICU) in 50 countries across six continents.

Methods: Patients undergoing invasive mechanical ventilation (IMV) with a diagnosis of ARDS at D1 or D2 post onset of acute hypoxic respiratory failure (AHRF) with no history of chronic kidney disease (eGFR<60ml/min/1.73m2) and not transferred from another ICU were included in the analysis. Patients were categorised based on worst serum creatinine (Scr) or urine output between D1-D7 post diagnosis of ARDS into (1) no AKI Serum creatinine <1.5mg/dl or urine output >0.5mL/kg/h (2) Moderate AKI: Scr 1.5-4mg/dl or min urine output<0.5mL/kg/h or (3) severe AKI: Scr >4mg/dl or Renal Replacement Therapy (RRT) during D1-D7 following onset of ARDS.

Results: 2016 patients were included in the analysis; 1193 (59%) with no AKI, 619 (31%) moderate AKI and 204 (10%) with severe AKI. RRT was required in 1.2% of patient with no AKI, 24.6% of moderate AKI and 100% of severe AKI over the 28 day follow-up period. Sequential organ failure assessment score was higher with worsening category of AKI (8.8±3.8, no AKI, 11.5±3.7 moderate AKI, 12.2±3.8 severe AKI, p<0.001). Lower pH, PaO2-FiO2 ratio and higher positive end-expiratory pressure were noted with advancing AKI category. Ventilatory free days was lower and ICU mortality and hospital mortality was higher with advancing AKI category (table 1).

Conclusions: The development of AKI, even in those who do not require RRT is associated with a substantial increase in mortality in patients with ARDS, with over half of these patients dying in hospital.

Funding: Government Support - Non-U.S.

Association of AKI on outcomes in patients with ARDS

Category of AKI	No AKI N=1193	Moderate AKI N=619	Severe AKI N=204	P-value
Ventilator Free days, median (IQR), days	17.0 [0.0;23.0]	0.0 [0.0;19.0]	0.0 [0.0;12.0]	<.001
ICU Mortality No. (%)	306(25.6%)	276(44.6%)	116(56.9%)	<.001
Hospital Mortality, No. (%)	355(29.9%)	310(50.2%)	125(61.3%)	<.001

TH-PO036

Assessment of Fluid and Nutritional Status Using Bioimpedance Methods in AKI Patients Treated with Continuous Renal Replacement Therapy

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Background: Bioelectrical impedance analysis is an essential method for maintenance hemodialysis patients to assess nutritional and fluid status, however, there is still a lack of research on the value of bioelectrical impedance analysis in evaluating the prognosis of acute kidney injury (AKI) patients treated with continuous renal replacement therapy (CRRT).

Methods: Patients with severe AKI treated with CRRT in the first affiliated hospital of Nanjing medical university from 2014 to 2017 were prospectively enrolled. They were divided into death group and survival group according to 28-day survival. Logistic regression was used to analyze 28-day survival and Lean Tissue Index (LTI), Fat Tissue Index (FTI), the ratio of extracellular water(ECW) and body cell mass (BCM) (ECW/BCM), and overhydration (OH) were recorded.

Results: A total of 145 patients were included. The average age was 62.6±15.6 ys, average APACHE II score 21.7±6.5, SOFA score 9.4±3.6, and body mass index of 24.1±4.3 kg/m2. The pre-CRRT body composition analysis parameters were as followed:OH 3.9 ± 3.1L, LTI 12.4 ± 3.4kg/m2, FTI 10.3 ± 4.5kg/m2, ECW 18.0 ± 4.2L, BCM 18.6 ± 7.3L. The 28-day mortality rate was 44.8%.The pre-CRRT OH values and ECW/BCM values in survival group and death group were 3.4±3.2L, 4.6±3.0L and 1.0±0.4,1.1±0.4 (P<0.05), respectively. The changes of OH values and ECW/BCM values between CRRT 1st day and CRRT 7th day were 1.4±2.2L, 3.0±3.0L and 0.08±0.22,0.25±0.27 (P<0.05), respectively in two groups. Univariate and multivariate logistic regression analysis showed that pre-CRRT high OH values and high ECW/BCM values were associated with 28-day death, while LTI values and FTI values were not significant correlated with 28-day death; After CRRT initiation, the changes of OH values and ECW/BCM values between CRRT 7th-1st day were significantly associated with 28-day mortality.

Conclusions: The pre-CRRT fluid status(indicators of OH and ECW/BCM)were associated with 28-day mortality in patients with AKI, while the nutritional indicators LTI and FTI were not significantly related to short-term mortality. The correction of fluid overload by CRRT within 7 days may reduce the 28-day risk of death.

Funding: Government Support - Non-U.S.

TH-PO037

Body Composition for Predicting Exertional Rhabdomyolysis-Induced AKI During Intensive Physical Training Program for Military Recruits

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Background: Exertional rhabdomyolysis-induced acute kidney injury (AKI) is a life-threatening condition. The risk factors for developing this condition are partially documented and changing in the body composition of these population is still poorly understood.

Methods: A prospective cohort study in the military recruits between May to July 2017 were conducted. Demographic and laboratory data including body mass index (BMI), serum creatinine, electrolyte, creatine phosphokinase (CPK), and body composition using dual frequency body impedance analysis (BIA) were measured before training and every 2 weeks until program had been completed.

Results: Total of 301 participants with mean age of 22 ± 2.5 years old were included. The incidence of exertional rhabdomyolysis-induced AKI was 19.2 %. At baseline, subjects who developed exertional rhabdomyolysis-induced AKI had lower frequency of exercise before recruitment (1.02 ± 0.13 times/week vs 3.49 ± 0.93 times/week, p <0.001), lower total body water (TBW) (45.08 ± 2.95 % vs 54.31 ± 5.21%, p < 0.001) and lower plasma potassium (3.6 ± 0.3 mEq/L vs 4.0± 0.4 mEq/L, p < 0.001). Along the course of training, AKI group had a significant loss of muscle mass (-5.65 ± 2.55% vs -4.06 ±1.75%, p < 0.001) and fat mass (-3 ± 1.41% vs -2.17 ± 0.98% p < 0.001) in the first 2 week. Moreover, there was a statistically significant increased in percentage of TBW at week 2 (2.57 ± 4.95% VS 0.24 ± 2.41 P<0.001) in AKI group compared with non-AKI group. Multivariate analysis revealed that low baseline of total body water (OR 5.51 (5.15-10.75), p < 0.01) and increased TBW at week 2 (OR 2.46 (1.49-2.97, p < 0.01) were the strong independent predictors for exertional rhabdomyolysis-induced AKI.

Conclusions: The study demonstrates that lack of adequate exercise before recruitment, low baseline potassium, low baseline TBW and increased TBW in early training period are the additional risk factors for exertional rhabdomyolysis-induced AKI. To our best knowledge this is the first study which explore the body composition change for prediction of exertional rhabdomyolysis induced. Early detection of these parameters should be implemented for AKI prevention program.

TH-PO038

Trajectories of AKI in Chronic Critical Illness After Sepsis

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Background: Acute kidney injury (AKI) is one of the most common complications among hospitalized patients. Besides the severity of an initial episode of AKI, the timing and duration of renal recovery are required to characterize the natural history of this complex condition and its effect on kidney health. We have determined the epidemiology of persistent AKI and renal recovery, the development of chronic critical illness (CCI), hospital outcomes, and long-term survival in sepsis patients. We hypothesize that patients with persistent AKI, especially those without renal recovery, have worse hospital and long-term outcomes after sepsis.

Methods: In the prospective observational study of 245 sepsis patients, AKI types were adjudicated using KDIGO criteria and ADQI recommendations. In contrast to rapidly reversed AKI, persistent AKI is characterized by the persistence of KDIGO creatinine beyond 48 hours of the onset. Patients whose renal function did not completely recover at discharge were considered to have no recovery. Development of CCI and six-month survival were compared using Fisher's exact and log-rank test, respectively.

Results: Two percent (6/245) had preexisting end-stage renal disease (ESRD) and 15% (36/245) had pre-existing chronic kidney disease (CKD). Among non-ESRD subjects, while about 46% (109/239) developed AKI within 48 hours of sepsis onset, overall 59% (140/239) developed AKI; 28% (39/140) having rapidly reversed AKI and 72% (101/140) having persistent AKI. Among 101 patients who had persistent AKI, 41% (58/140) did not recover at discharge and they had had longer ICU stay, more days on mechanical ventilation, greater prevalence of CCI (55%), and higher hospital mortality (27%). Patients with no recovery had lower 6-month cumulative survival (43%) compared to patients with recovery (88%) and no AKI (94%) (p<0.0001). Among CCI patients, survival was significantly worse for patients with no complete recovery compared to patients who recovered (p=0.0003) or did not develop AKI among patients with CCI (p=0.0001). Among non-CCI patients survival was similar across groups.

Conclusions: Among critically ill septic patients, persistent AKI and absence of renal recovery are significant risk factors for adverse outcomes and long-term mortality.

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TH-PO039

Improved Mortality of Critically Ill Patients with AKI: Population-Based Cohort Study in Korea Between 2008 and 2015

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Background: Although there is still no specific treatment facilitating renal tubule regeneration in acute kidney injury (AKI), the rapid increase aging population with more comorbidities and advance in critical care management were expected to change the epidemiology of AKI. However, few recent studies dissecting the current epidemiology characteristics of critically ill patients with AKI. We investigated the recent epidemiologic changes of AKI in critically ill patients.

Methods: All adult admissions to intensive care units (ICU) in Korea from 2008 to 2015 were screened using the national health insurance review and assessment database, and a total of 1,744,235 patients were included. The clinical characteristics and change in incidence and mortality rate of AKI were analyzed.

Results: The incidence of AKI increased from 7.4% in 2008 to 8.3% in 2015 (p for trend <.001). The age-standardized AKI rates in were 7018.6 per 100,000 person-years. The in-hospital mortality was significantly decreased from 39.1% in 2008 to 37.2% in 2015 (p for trend <.001) with 2427.6 deaths per 100,000 person-years. Patients with AKI showed higher in-hospital mortality, prolonged ICU length of stay, and higher total cost. Multivariable analysis showed increased risk of in-hospital mortality (OR 6.25), mechanical ventilation (OR=4.63), ECMO (OR=18.22), and vasopressor requirement (OR=4.02) in AKI patients.

Conclusions: Recent advances in medical management for AKI have attenuated in-hospital mortality of critically ill patients with AKI despite increase of the elderly population as well as the incidence of AKI.

TH-PO040

Association of Serum Potassium Level at the Initiation of Renal Replacement Therapy with All-Cause Mortality Among Burn Intensive Care Unit Patients with AKI

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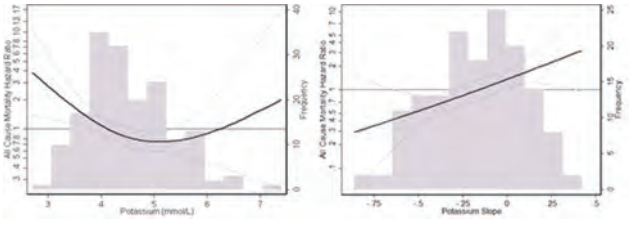
Background: Burn injury is associated with serious complications including acute kidney injury (AKI) requiring renal replacement therapy (RRT). There is little data on the association between baseline serum potassium (K) and outcomes in burn patients initiated on RRT. Therefore, we evaluated the association of K at the RRT initiation with survival in a cohort of burn patients.

Methods: We examined 170 burn patients enrolled in a multicenter observational study in eight burn centers across the United States. We used Cox regression models with adjustments for covariates including severity of illness, laboratory values, urine output, total burn surface area, and vasopressor requirement to evaluate the association of K level at RRT initiation with in-hospital all-cause mortality. We further explored the association between K slope, from the initiation to 48 hours after beginning of RRT, and mortality, using the same multilevel Cox models. Patients without either baseline or 48 hours K measurements were excluded from the slope analysis.

Results: The cohort was comprised of 169 AKI patients who required RRT and had a baseline K. 20% of patients were female with a mean±SD age of 51±17 years. Hypokalemia was associated with a higher risk of subsequent mortality. 150 patients were included in the slope analysis. There was a linear association between increasing K slope and higher mortality based on the result of restricted cubic splines.

Conclusions: While baseline hypokalemia at the time of RRT initiation was associated with higher risk of mortality, increasing K at 48 hours was also associated with worse outcomes in patients with burn-associated AKI. This finding may be due to inadequate dialysis, ongoing tissue destruction, or both. Future investigations are needed to examine the mechanisms which can explain these observations.



TH-PO041

Comparison Between Creatinine vs Urinary Output Criteria in RIFLE and KDIGO Definitions for AKI Post Major Elective Non-Vascular Abdominal Surgeries

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Background: Most of the studies using RIFLE and KDIGO AKI definitions are solely based on serum creatinine (SCr) changes. However, the urinary output (UO) criteria may be more sensitive especially for surgical patients. Therefore, the aim of this study was to compare the efficacy of SCr and UO criteria for RIFLE and KDIGO AKI diagnosis and outcome of patients (pts) submitted to major elective non vascular abdominal surgeries (MENVAS) admitted to the ICU.

Methods: Two hundred and twenty five pts were prospectively evaluated, peri-operatively, from the ICU admission until 7 days of hospitalization. Serum creatinine (mg/dl) was measured before surgery and once a day until day 7 or ICU discharge. Hourly UO (ml/kg/h) was measured daily. AKI was diagnosed using either SCr or UO according to RIFLE and KDIGO definitions. Data are presented as mean ± SD or frequencies. Statistical significance was set at $p<0.05$.

Results: A total of 225 pts were analysed, 126 (56%) developed AKI. Most frequent types of surgery were: hepatectomy, sleeve gastroplasty, gastrectomy, hepatectomy + cholecystectomy, gastroduodenopancreatectomy and, adrenalectomy. AKI pts were older 57.6 ± 1.2 vs. 50.8 ± 1.6 Non -AKI ($p = 0.0007$). Duration (min) of surgery in AKI pts was 365.6 ± 18.3 vs. 341.5 ± 16.8 Non-AKI (NS). The AKI diagnoses according to RIFLE were: 118 by UO and 38 by SCr criteria. According to KDIGO definition: 118 by UO and 39 by SCr criteria. In addition, 31 pts fullfilled both criteria simultaneously. Using the SCr criteria alone for AKI diagnosis, a total of 87 patients in RIFLE group and KDIGO group would be overlooked while only one additional patient was diagnosed by KDIGO. AKI pts (KDIGO definition) diagnosed by UO or SCr criteria changes, presented, compared to Non-AKI pts: hospital LoS 21.4 ± 1.9 vs. 25.6 ± 3.8 ($p <0.0004$), ICU LoS 3.6 ± 0.3 vs 5.8 ± 0.97 ($p < 0.0001$). Mortality in the AKI group was 10.2% vs. 2.0 % in Non-AKI ($p=0.0149$).

Conclusions: Utilization of SCr criteria instead of UO for RIFLE and KDIGO definitions in surgical patients would overlook a very high number of AKI patients (69%). Urinary output criteria seems to be pivotal for early AKI recognition in these patients. Furthermore, AKI post MENVAS is frequent and carries worse outcome and mortality.

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TH-PO042

FGF23 and AKI in SPRINT

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Background: Fibroblast growth factor 23 (FGF23) is elevated in chronic kidney disease and associated with kidney disease progression and increased mortality but data on FGF23 in humans with acute kidney injury (AKI) are limited. We hypothesize that high circulating intact FGF23 (iFGF23) concentrations will identify individuals at high risk of AKI and may modify the relationship between randomization to intensive blood pressure lowering and AKI in the Systolic Blood Pressure Interventional Trial (SPRINT).

Methods: The SPRINT study was a randomized multicenter trial evaluating the effects of standard (SBP <140 mmHg) vs. intensive (SBP <120 mmHg) blood pressure lowering on cardiovascular outcomes in older adults without diabetes. iFGF23 was measured in 2488 subjects with GFR < 60 mL/min/1.73m^2. Cox proportional hazards models adjusted for demographics, comorbidities, randomization group, and baseline number of antihypertensives, eGFR, and serum calcium and phosphorus identified the relationship between baseline iFGF23 and time to first AKI event.

Results: Mean age was 73 ± 9 years, 40% were female, and 66% were white. At baseline, mean eGFR was 49 ± 11 mL/min/1.73m^2 and median FGF23 was 66 [52-88] pg/mL. After full adjustment, there was no significant association between baseline iFGF23 and time to first AKI event; HR for Q4 (vs. Q1) was 0.93 (95% CI 0.60-1.44) and HR for iFGF23 modeled as a continuous variable was 0.96 (95% CI 0.75-1.23). FGF23 did not modify the relationship between randomization to intensive blood pressure lowering and AKI (p for interaction 0.12).

Conclusions: Among SPRINT participants with baseline eGFR < 60 mL/min/1.73m^2, there was no significant association between baseline iFGF23 and AKI events. iFGF23 did not modify the relationship between randomization to intensive blood pressure lowering and AKI.

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TH-PO043

Exosomal Mitochondrial DNA Is a Prognostic Factor in Septic AKI Patients

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Background: We reported the amount of circulating mitochondrial DNA (mtDNA) was increasing in septic rodent models and contributed development of AKI via toll-like receptor 9. The levels of mtDNA in septic patients have varied according to reports, which might occur because of the difference of the blood plasma fraction due to different centrifugal processing. We assayed mtDNA according to blood plasma fractions and evaluated whether mtDNA in circulating exosome was a prognostic factor in septic shock and septic AKI patients.

Methods: Septic patients who needed polymyxin B immobilized hemoperfusion (PMX) in intensive care unit of Hamamatsu University School of Medicine from November 2013 to March 2017 were enrolled. Patient's plasma was collected from just before the PMX initiation followed by centrifugation at 17,000g for 15 minutes to remove dead cell and cell debris. Exosome was obtained by ultracentrifugation at 200,000g for 1 hour. We extracted exosomal DNA and quantified exosomal mtDNA (Ex-mtDNA) by using real-time PCR. We prospectively observed their outcomes.

Results: The level of Ex-mtDNA in septic shock patients with hospital death (n=6) was significantly higher than those survivors (n=16) and health volunteers (n=4) (log2.80±1.19 vs log0.91±0.81 vs log-0.56±1.09, $p<0.05$). The ROC curve analysis revealed that Ex-mtDNA is the best prediction for in-hospital death compared with total mtDNA and blood lactic acid and SOFA score and urine volume [AUC: 0.90 (0.74-1.08) vs 0.86 (0.69-1.03), 0.80 (0.58-1.03), 0.84 (0.64-1.06)] and has high sensitivity and specificity and also odds ratio [0.83 (0.36-1.00), 0.93 (0.66-1.00), 65.0 (2.27-125), $p<0.05$, cut-off value: log1.91] The level of Ex-mtDNA in AKI patients was also higher than those in non-AKI patients (log1.84±1.20 vs log0.63±1.10, $p<0.05$) but was not better prediction than blood lactic acid and SOFA score [AUC: 0.76 (0.53-1.00) vs 0.82 (0.63-1.01), 0.85 (0.67-1.02)].

Conclusions: Ex-mtDNA has a potential as a good predictor of survival and AKI in septic shock patients.

TH-PO044

Exosomal MicroRNAs in Urine Are Associated with Children's Blood Pressure and Renal Biomarkers: An Exploratory Cross-Sectional Study

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Background: Urinary extracellular microRNAs are potential biomarkers of renal health and disease that may originate from epithelial cells in the renal or urogenital tract. Traditional analytical methods examine individual miRNA biomarkers; here we employ a mixtures approach to identify combinations of miRNAs associated with renal health.

Methods: We assessed the association between a mixture of exosomal miRNAs and systolic blood pressure (SBP), as well as 8 protein biomarkers measured in spot urine samples collected from 103 healthy children aged 4-5 years. We performed differential centrifugation and visualized exosomes using electron microscopy. miRNA were extracted and analyzed for 754 miRNAs using OpenArray qPCR. Expression data were normalized using the global mean. A miRNA was considered 'detectable' if it produced reliable qPCR signal in ≥70% of participant samples. We applied weighted quantile sum (WQS) regression to create a composite renal biomarker index of 252 'detectable' miRNAs, and tested for association between the miRNA mixture with either SBP or the 8 protein biomarkers, adjusting for age, BMI, sex, and parental report of indoor smoking. We analyzed the levels of 8 proteins (albumin, cystatin C, clusterin, osteopontin (OPN), α-1-microglobulin (A1M), kidney injury molecule-1 (KIM-1), TFF (trefoil factor 3), β2-microglobulin (β2M)). We considered substantive contributors to the mixture index as those with ≥ 2% weight.

Results: Increased SBP was associated with the miRNA index (β: 0.08, 95%CI: 0.1, 1.5; $p=0.02$), driven by miR-590 and miR-885 (out of 13 total miRNA with weights ≥2%). Seven proteins (albumin, A1M, KIM1, TFF3, B2M and clusterin were positively associated with the miRNA mixture. Levels of cystatin C were not associated with the miRNA index. Notably, the associations of A1M, clusterin, and KIM-1 with the miRNA mixture were consistently driven by miR-574; the associations of TFF and OPN were consistently driven by miR-146b. The mRNA targets of miR-146b and miR-574 are enriched for nephrotoxic functions including renal inflammation, nephritis, tubule damage, and necrosis.

Conclusions: These findings highlight combinations of exosomal miRNAs as potential sensitive and non-invasive early life biomarkers of renal health.

Funding: Other NIH Support - NIEHS

TH-PO045

Urine Biomarkers and AKI Associations with CKD and Hypertension 3 Months Post-Cisplatin in Children

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Background: Cisplatin (CisP) causes acute kidney injury (AKI) and may lead to chronic kidney disease (CKD) and hypertension (HTN) in children. Aims: 1) Describe 3-month post-CisP CKD/HTN; 2) Determine if a) AKI during CisP treatment and b) urine neutrophil gelatinase-associated lipocalin (uNGAL) and kidney injury molecule-1 (uKIM-1) near end of CisP therapy are associated with 3-month CKD/HTN.

Methods: 12-site prospective pediatric study. Exposures: a) Serum creatinine (SCr)-AKI during CisP therapy (KDIGO definition); b) Electrolyte AKI(eAKI): low serum Mg^{++}, K^{+} or PO_4^{-} during therapy; c)uNGAL/KIM-1 at discharge from a late CisP cycle. Outcomes: a) CKD: urine albumin/creatinine ratio≥3mg/mmol(≥7.5mg/mmol if <2 years old), urine protein/creatinine ratio≥15mg/mmol or SCr-estimated glomerular filtration rate<90mL/min/1.73m^2; b) HTN: blood pressure≥95thpercentile (adults:≥140/90mmHg) or treated for HTN. Univariate tests and multiple logistic regression were performed to evaluate exposure-outcome relations and adjusted associations.

Results: Of 154/158 with 3-month data: 77(50%) boys; median[IQR] age: 6[3-12] years. 96/142(68%) had CKD; 14/141(10%) had HTN; 100/154(65%) had CKD or HTN. SCr-AKI, ≥Stage 2 SCr-AKI and eAKI+SCr-AKI were associated with 3-month HTN(Table). AKI was not associated with CKD(Table). Adjusting for age and gender, only ≥Stage 2 SCr-AKI was associated with 3-month HTN (adjOR 4.4(95% CI 1.1-18.4)). Biomarkers were not associated with CKD or HTN(Table).

Conclusions: CKD and HTN are common 3 months after CisP. AKI is associated with 3-month HTN. Ongoing 3-year follow-up will determine if associations change and/or persist. Measures to reduce HTN after cancer therapy are needed.

Funding: Government Support - Non-U.S.

Association of different AKI phenotypes with 3 month CKD and HTN

AKI Exposure	% with outcome	
	%With CKD	% With HTN
SCr-AKI	45/61 (74%)	10/61 (16%)*
No SCr-AKI	51/81 (63%)	4/80 (5%)
≥ Stage 2 SCr-AKI	13/19 (68%)	5/18 (28%)*
< Stage 2 SCr-AKI	83/123 (67%)	9/123 (7%)
eAKI	91/134 (68%)	14/135 (10%)
No eAKI	5/8 (63%)	0/6 (0%)
eAKI + SCr-AKI	43/57 (75%)	10/59 (17%)*
No eAKI + SCr-AKI	53/85 (62%)	4/82 (5%)

Table: AKI *vs.* non-AKI prevalence of CKD and HTN at 3 months post CisP therapy completion (**TOP**) and end of CisP NGAL and KIM-1 concentrations between patients with *vs.* without CKD and HTN (**bottom**).
Legend:
SCr-AKI: AKI defined using the KDIGO definition (peak SCr throughout CisP therapy over baseline/pre-cisplatin treatment SCr.
eAKI: presence of low serum phosphate, magnesium or potassium throughout treatment.
eAKI+SCR-AKI: presence of both AKI phenotypes throughout treatment.
*Indicates significant difference between AKI *vs.* non-AKI groups.

Association of late CisP therapy biomarkers with 3 month CKD and HTN
Median (upper & lower IQR biomarker values)

Biomarker Exposure	With CKD	No CKD	With HTN	No HTN
uNGAL ng/mg creatinine	20 [5.8-40] N=73	9.7 [5.2-20] N=30	23 [5.9-175] N=11	15 [5.6-30] N=95
uKIM-1 pg/mg creatinine	1628 [421-4723] N=75	787 [428-2300] N=30	3757 [1859-8240] N=11	1251 [401-3804] N=96

TH-PO046

Markers of Kidney Tubule Cell Function and Risk of AKI

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Background: Novel biomarkers can quantify kidney tubular functions including proximal tubule reabsorption (alpha 1 microglobulin [a1m], and beta 2 microglobulin [b2m]) and tubule protein synthesis (uromodulin [umod]). Associations of tubule function measures with acute kidney injury (AKI) risk are uncertain. We evaluated associations of markers of kidney tubular function with AKI risk in participants with chronic kidney disease (CKD) in the SPRINT Trial.

Methods: Among 2351 participants with CKD (eGFR<60 ml/min), urine a1m, b2m and umod were measured by multiplex immunoassay (MesoScale Diagnostics) at the randomization visit. Cox proportional hazard models evaluated log-transformed biomarker levels as risk factors for AKI during 3.8 years mean follow-up. Sequential models adjusted for demographics, randomization arm, and urine creatinine (Model 1); baseline eGFR, uACR, and AKI risk factors (Model 2); and the other tubule function biomarkers (Model 3).

Results: Lower urine umod and higher a1m levels were each associated with higher AKI risk (Table). The association with uromodulin was independent of baseline eGFR and uACR (Model 2). Adjustment for all 3 tubule function markers strengthened associations of a1m which was independently associated with AKI in the final model. Results were similar in analyses stratified by randomization arm.

Conclusions: Assessment of tubule function by measurement of urine umod and a1m provides information of AKI risk independent of eGFR and albuminuria in persons with hypertension and CKD but without diabetes. Future studies should evaluate if dynamic changes in these markers can predict AKI risk in those exposed to intensive blood pressure lowering.

Funding: NIDDK Support

	Hazard Ratio (95% CI) Per Doubling of Marker	P Value
# AKI events/# at Risk	184/2351	
- Uromodulin		
– Model 1	0.72 (0.64, 0.81)	<.001
– Model 2	0.78 (0.67, 0.90)	0.001
– Model 3	0.71 (0.59, 0.85)	<.001
- Alpha-1 microglobulin (α1m)		
– Model 1	1.22 (1.11, 1.34)	<.001
– Model 2	1.08 (0.98, 1.19)	0.13
– Model 3	1.17 (1.04, 1.32)	0.01

TH-PO047

Combination of ITRAQ-Based Quantitative Proteomics and Parallel Reaction Monitoring Identifies Biomarkers for the Early Diagnosis of AKI Following Percutaneous Coronary Intervention

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Background: In this study, we used Isobaric Tags for Relative and Absolute Quantitation(ITRAQ) to identify novel diagnostic biomarkers and to explore the underlying mechanisms of acute kidney injury (AKI) following percutaneous coronary intervention (PCI).

Methods: 114 patients (>60yrs) admitted for elective PCI were included in the study. We identified 14 elderly patients with PCI-AKI, 14 patients of whom did not develop AKI were selected as controls, matched by age, gender. Urine samples were collected before PCI, and 24 hours post-PCI. Blood collected for serum creatinine (Scr) concentrations and biochemical analysis. Isobaric Tags for Relative and Absolute Quantitation (ITRAQ) technology followed by Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) was used to discover differentially expressed proteins (DEPs) in a training set of PCI-AKI (n=6) and controls (n=6). DEPs were then investigated in an independent cohort of PCI-AKI (n=8) and controls (n=8) using parallel reaction monitoring (PRM). We also identified DEPs potentially involved in PCI-AKI pathogenesis by analyzing biological processes, cellular components, molecular functions, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and protein-protein interactions (PPI).

Results: Comparing to patients before PCI, a total of 167 DEPs (106 upregulated proteins and 61 downregulated proteins) were identified in the urine of PCI-AKI patients (24h post-PCI). Among the upregulated proteins, 12 proteins were overlapped in both comparisons of AKI-24h/AKI-Pre and AKI-24h/CON-24h. Using the PRM approach, we successfully confirmed the differential accumulation of Haptoglobin (HPT), apolipoproteins A-I (APOA1) and Peroxiredoxin-2 (PRDX2) at 24h post-PCI comparing to pre-PCI and controls in the validation set. And they were earlier than Scr for diagnosis PCI-AKI. GO and KEGG pathway analysis described that these proteins were mainly involved in the peroxisome pathway(PRDX2), and the PPARγ signaling pathway (APOA1).

Conclusions: Our research showed HPT, APOA1 and PRDX2 were potential urine biomarkers and may play key roles in the pathogenesis of PCI-AKI. And these biomarkers might be prospective to made into "AKI panel" similar to myocardial enzyme for the diagnosis of PCI-AKI in the future.

TH-PO048

Identification of Urine Potential Biomarkers of AKI Patients with Cirrhosis by iTRAQ-Based Quantitative Proteomics

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Background: To identify novel diagnostic biomarkers and to explore the underlying mechanisms of acute kidney injury (AKI) patients with cirrhosis.

Methods: We performed a prospective nested case-control study. We collected urine samples of cirrhotic patients with risk factors of AKI (bacterial infections, bleeding from oesophageal varices, large volume paracentesis (>3L/d), increased dosage of diuretics, and receiving contrast medium) at the time of risk factors occurred and 1d after the risk factors. Blood was collected for serum creatinine (Scr) concentrations and biochemical analysis. iTRAQ technique followed by Liquid Chromatography tandem Mass Spectrometry (LC-MS/MS) was used to screen differentially expressed proteins (DEPs). And DEPs were also

analyzed by Gene Ontology (GO),Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and protein-protein interactions (PPI) analysis.

Results: 90 cirrhotic patients with risk factors of AKI were included in the study. Among these patients, 11 patients were diagnosed as AKI (KDIGO AKI criteria, 2012), and 9 patients were selected as controls (matched by age and gender). Using iTRAQ approach,a total of 289 DEPs (64 upregulated proteins and 225 downregulated proteins) were identified in the urine of AKI group (1d after risk factors occurred) comparing to controls. 20 biological process, 20 cellular components, 20 molecular functions and 20 significant KEGG pathways were identified. Among them, renin-angiotensin system pathways, and apoptosis pathways may play a role in the pathogenesis of AKI with cirrhosis. Combined with the PPI results, alpha-1-antitrypsin precursor(SERPINA1), S100 calcium binding A9(S100A9)and mucin-5AC(MUC5AC)were significantly up-regulated at 1d after risk factors occurred in AKI group. And they were earlier than Scr which significantly rose in both comparisons of AKI-48h/AKI-Pre and AKI-48h/CON-48h till at 48h for diagnosis of AKI with cirrhosis.

Conclusions: iTRAQ technology was useful in the selection of DEPs from proteomes, and might provide a theoretical basis for the study of biomarkers and mechanisms in AKI with cirrhosis. The identified panel of SERPINA1, S100A9 and MUC5AC proteins might serve as potential biomarkers and thereby aid in the detection of AKI with cirrhosis.

TH-PO049

Predictive Value of Current Biomarkers for Early Reversal of AKI

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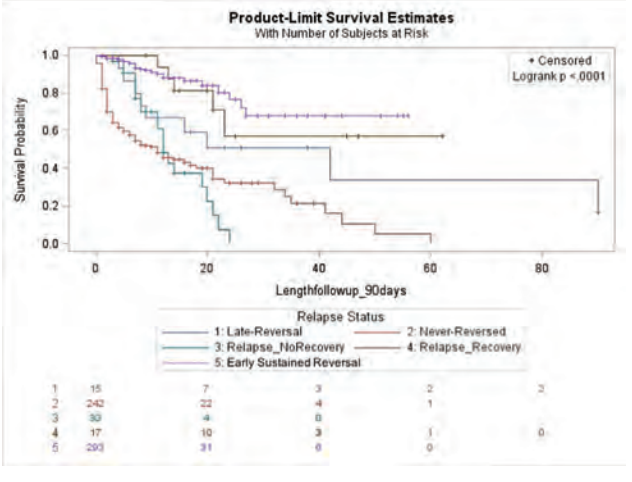
Background: Acute kidney injury (AKI) is associated with various recovery patterns. Early reversal of AKI is common in critically ill patients and associated with good outcomes. The predictive role of current biomarkers for reversal of AKI is still unknown.

Methods: Using data from an ancillary study to a large randomized trial, including 1,341 patients with septic shock we focused on patients with stage 2 or 3 AKI at presentation or manifesting within the first day of hospital admission. Early reversal of AKI was defined as no longer meet any criteria for AKI (for at least 24 hours) on any day within the 7 days after first documented AKI. Any subsequent AKI episode after initial reversal was considered a relapse. Final recovery status was then assessed at hospital discharge. Several urinary biomarkers were measured at 24 hours after enrollment and used for prediction of early reversal.

Results: Among the 604 patients with KDIGO stage 2 or 3 AKI, 345 (57.1%) patients had early reversal of renal function. Of these, 50 (14.5%) patients had a relapse of AKI during their hospital stay after early reversal. A total of 327 (54.1%) patients finally had recovery at hospital discharge. About 40% of patients never reversed AKI. None of the urinary biomarkers TIMP-2●IGFBP7, NGAL, Kim-1, L-FABP, or type IV collagen were predictive of early reversal of AKI (C-statistics: 0.37, 0.45, 0.49, 0.48, 0.45, respectively). Patients who had early sustained reversal of renal function experienced the best survival at day 90, while those who had relapse of AKI and those who never recovered had the worst outcomes.

Conclusions: Currently available AKI biomarkers are not useful for prediction of early reversal of renal function after AKI. Novel predictive biomarkers for renal recovery are needed.



Survival by recovery patterns.

TH-PO050

Circulating Cardiac Stress, Vascular Dysfunction, and Inflammatory Biomarkers Predict AKI in French Type 2 Diabetes Patients: The SURDIAGENE Cohort

Benedicte Sautenet,[1] Pierre Jean Saulnier,[3] Gand Elise,[3] Ronan Roussel,[6] Stephanie Ragot,[5] Gilberto Velho,[6] Samy Hadjadj.[3] *[1]CHRU Tours, Tours, France; [3]CHU Poitiers, Poitiers, France; [5]University of Poitiers, Poitiers, France; [6]INSERM, Paris, France.*

Background: Acute kidney injury (AKI) is related to chronic kidney disease and death in patients from the general population, with or without type 2 diabetes. Nevertheless AKI biomarkers are rarely validated in diabetes population. We aimed to explore the individual and combined prognostic value of 8 circulating candidate markers for AKI.

Methods: We prospectively followed-up 1345 (565 women/780 men) type 2 diabetes participants of a French single-centre hospital-based cohort (SURDIAGENE) with baseline GFR≥30 ml/min/1.73m2 and no renal replacement to onset of AKI, death, or December 31, 2015. Intrahospital AKI was diagnosed and staged using the KDIGO criteria. We assessed 3 markers of cardiac and endothelial dysfunction (mid-regional-pro-adrenomedullin [MRproADM], angiopoietinlike-2 [ANGPTL2], N-terminal prohormone brain natriuretic peptide [NTproBNP]), 1 of oxidative stress (fluorescent advanced glycation endproducts [AGE], carbonyls), 1 for cardio-renal pathways (copeptin [CTproAVP]), and 1 of inflammation (soluble TNF receptor 1 [TNFR1]). Cox models were used to estimate the risk of AKI for each biomarker at baseline after adjustement for usual risk factors: sex, diabetes duration, HbA1c, systolic blood pressure, GFR, ACR, use of antihypertensive, and history of cardiovascular disease. Hazard ratios were reported per 1 SD increment of the logarithm of the biomarker concentration.

Results: At baseline, mean±SD age was 64±11 years, diabetes duration 14±10 years, HbA1c 7.8±1.6%, and eGFR 77±21 ml/min/1.73m^2, and median (IQR) ACR 3 (1-10) mg/mmol. During a median follow-up of 4.7 years, 449 (33%) patients developed an AKI. In univariate analysis, each biomarker was significantly associated with AKI, and 6 remained associated after multivariable adjustment (Table). The addition of a multimarker score summing standardized and weighted values of these 6 markers to the model including usual risk factors significantly improved C-statistics (0.724 to 0.759, $P<0.0001$), and 5-year risk-predictive performance (relative integrated discrimination improvement index=0.435, $P<0.0001$).

Conclusions: A panel of 6 biomarkers representing cardiac, vascular and inflammatory pathways improved the prediction of AKI over usual risk factors in patients with type 2 diabetes.

TH-PO051

Heat Shock Protein 72 (Hsp72) Is a Useful Biomarker for AKI in Liver Transplant

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Background: Acute Kidney Injury (AKI) after liver transplantation (LT) is a frequent complication and an important risk factor for mortality. We have shown that Hsp72 is an early AKI biomarker in animal models of ischemic acute renal injury and in a variety of critically ill patients in the ICU (EMBO MM 2011 and Plos One 2014). Since the LT program in our institute performs one transplant per week, we designed the present study to determine the incidence and risk factors of AKI during the postoperative period of LT, and to assess whether Hsp72 can be a useful tool to predict AKI.

Methods: We conducted a single-center prospective and observational study for LT patients (N=26). AKI was defined as a two-fold increase in baseline serum creatinine (SCr). Urine samples were collected before LT and at 0, 6, 12, 24 and 48 hours after. Urinary samples were resolved in SDS-PAGE gels and analyzed by western blot with a monoclonal anti-Hsp72 antibody. Hsp72 values were adjusted to urinary creatinine concentration.

Results: The mean age of our cohort was 49±10.58 years with 57.7% females. Hepatitis C infection was the main etiology for cirrhosis (42.3%). 14 patients (53.8%) developed AKI in the 5 days post-LT, and four of them required dialysis. Multivariate analysis showed that AKI was associated with encephalopathy prior to LT (OR 10.99, p=0.029). Based on SCr, AKI was diagnosed with a median of 24 h post-LT. Conversely, Hsp72 levels significantly increased at 6 h post-LT in patients that developed AKI vs. the non-AKI (p=0.042). The AUC-ROC analysis revealed that at 6 h Hsp72 predicts AKI with an AUC of 0.732.

Conclusions: Our observations indicate that urinary Hsp72 increases in patients that develop AKI in the post-LT several hours before they reach AKI criteria based on SCr, suggesting that Hsp72 could be a useful biomarker for the development of AKI.

Funding: Government Support - Non-U.S.

TH-PO052

Utilizing Neutrophil Lymphocyte Ratio to Detect Early AKI

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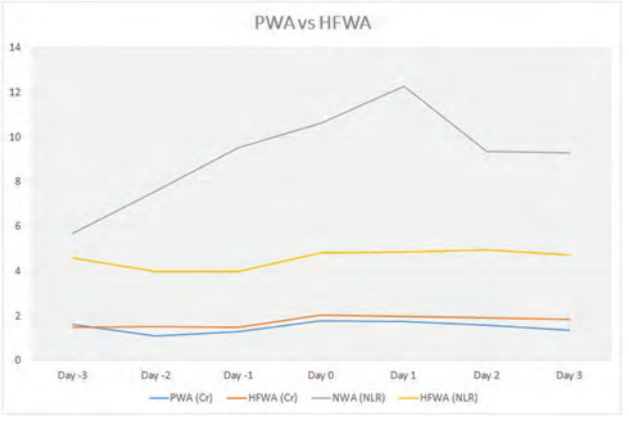
Background: The ability to detect early Acute Kidney Injury (AKI) prior to elevation of Cr has always been a challenge to physician. Traditionally, serum Cr level is used

to diagnose AKI. However, it has been shown to be poor predictor of AKI occurrence. Multiple inflammatory markers for AKI have been studied, but they are expensive and their clinical values remain limited. NLR has been found to be strongly associated with inflammatory states in last decade, thus can potentially be used as marker for AKI. Our primary objective is to investigate the role of NLR in prediction of early AKI prior elevation of Cr. We compared NLR's predictive power of AKI in both inflammatory and non-inflammatory conditions.

Methods: Retrospective study included 413 patients with age ≥ 18 who were admitted with the diagnosis of pneumonia without AKI (PWOA) and those admitted with pneumonia who developed AKI (PWA) as well as the patients admitted with diagnosis of heart failure without AKI (HFWOA) and those admitted with heart failure who developed AKI (HFWA). NLR and renal function were compared from 3 days before Day 0, and 3 days after Day 0. Day 0 represents as the day of diagnosis of AKI in PWA and HFWA groups; Day 0 is also represented by day of diagnosis of pneumonia or heart failure in PWOA and HFWOA groups. Subjects with ESRD, contrast induced AKI, drug induced AKI, hematologic proliferative diseases, on immunosuppressive agents or chronic steroid were excluded from the study.

Results: Patients in PWOA group has significantly hight NLR value (p value <0.0001) and longer lenght of stay (pvalue: <0.01) when compared to HFWOA, owing to higher sensitivity of NLR. Significant rise in NLR was also observed 72 hours earlier than serum Cr in PWA group (p value <0.0001). Thus, NLR not only strongly associated with AKI rather than infectious process, but also able to predict AKI significantly earlier than serum Cr level.

Conclusions: Our result suggests that NLR that was found to be associated with inflammatory conditions, can potentially be utilized as a marker to detect early AKI.



PWA vs HFWA

TH-PO053

Remote Ischemic Preconditioning in the Prevention of Contrast Induced Nephropathy in Patients Undergoing Peripheral Angiography: A Pilot Randomized Controlled Trial

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Background: Contrast induced nephropathy (CIN) is a leading cause of hospital acquired acute Kidney injury (AKI). Remote ischemic preconditioning (RIPC) has been found to be protective against AKI in patients undergoing coronary surgery This project aims to evaluate the potential of RIPC prior to vascular angiography in preventing CIN.

Methods: This study is a single centre, experimental, randomised controlled trial of the effect of RIPC with the induction of brief episodes of upper limb ischemia followed by reperfusion using blood pressure cuffs to determine protection against CIN in advanced peripheral arterial disease undergoing elective angiography. The inclusion criteria for this study are: patients above age of 21 yrs undergoing elective peripheral arterial angiography/ angioplasty who have an eGFR≥ 45ml/min and have given written informed consent. There are two arms of this trial: Control and preconditioned arm (RIPC). Patients will be randomised 1:1. Group 1(Control arm) : IV hydration with 0.9% normal saline (1ml/kg/ hour) prior to angiographic procedure Group 2 (RIPC) : patients will receive IV hydration prior to procedure, similar to control group. Additionally patients will receive RIPC, where a blood pressure cuff will be placed around one arm of the patientand inflated to a pressure of 250mm Hg for 5 minutes, deflated and allow arm to re-perfuse for 5 min. This is repeated for atotal of 3 ischemia-reperfusion cycles. Patients in both arms had serial measurements of serum creatinine as wellas serum cystatin and urinary NGAL at 2 hours, 24 hours, 48 and 72 hours post procedure

Results: There was no signicant differences between Control and RIPC groups with regards baseline characteristics. There was no reduction in development CIN in the RIPC group compared to Control.

Conclusions: RIPC did not offer any protection against development of CIN in our group of patients with eGFR >45ml/min over and above the standard therapy ie. intravenous hydration. The protective effect of RIPC in patients with more advanced chronic kidney disease needs further study

	RIPC (n = 19)			Control (n = 20)			p-value		
Biomarker	Baseline	48-hour	% change from baseline	Baseline	48-hour	% change from baseline	Interaction	Group	Time
Serum Creatinine (μmol/L)	99.7 ± 39.7	109.9 ± 43.0	11.1 ± 14.4	95.9 ± 26.9	93.8 ± 23.7	-1.3 ± 14.0	0.011		
Urine NGAL	155.4 ± 253.5	171.2 ± 248.3	164.4 ± 284.4	49.1 ± 78.8	57.6 ± 66.1	235.6 ± 462.4	0.87	0.056	0.60
Serum Cystatin	1.54 ± 0.52	1.51 ± 0.55	-2.96 ± 10.67	1.38 ± 0.38	1.31 ± 0.33	-3.91 ± 9.49	0.59	0.24	0.054

Table 1.RIPC versus Control

TH-PO054

The Effect of Remote Ischemic Preconditioning for Preventing Contrast-Induced AKI in CKD Patients Undergoing Elective Coronary Angiography

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Background: Despite the increasing use of pre- and post-hydration protocols and low-osmolar contrast media, the incidence of Contrast-Induced Acute Kidney Injury (CI-AKI) is still significant. The underlying mechanism has been attributed in part to ischemic kidney injury. Remote ischemic preconditioning (RIPC) is a non-invasive, safe, and low-cost method to reduce ischemic reperfusion injury. We aim to investigate whether RIPC, as an adjunct to standard preventive measures, reduces CI-AKI in chronic kidney disease (CKD) patients who are in high risk of CI-AKI.

Methods: This randomized double-blind control trial compared standard care with or without ischemic preconditioning (4 cycles of intermittent arm ischemia) in patients with impaired renal function (estimated glomerular filtration rate, eGFR < 60 mL /min/1.73 m2 by CKD-EPI equation) undergoing elective coronary angiography in the Police General Hospital between May 2017 and February 2018. The primary outcome was the incidence of CI-AKI, defined as an increase in serum creatinine > 0.3 mg/dL or 1.5 times above baseline at 48 hours after contrast medium exposure.

Results: A total of 50 patients, 55 episodes were enrolled, out of which 28 were in the RIPC group, and 27 were in the control group. The medians of contrast media volume, serum creatinine, and eGFR at baseline did not differ between the groups. The primary outcome, CI-AKI, occurred in a total of 7 episodes, consisting of 2 (7%) in the RIPC group and 5 (18%) in the control group, with no significant difference between the two groups (p=0.21).

Conclusions: RIPC cannot reduce the incidence of CI-AKI after contrast administration in CKD patients who are at risk of CI-AKI.

TH-PO055

AKI Is Common in Patients Receiving Immune Checkpoint-Inhibitors (CPIs)

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Background: Immune CPI use for first-line or salvage cancer immunotherapy is rapidly increasing. Because acute interstitial nephritis may complicate CPI therapy, the American Society of Clinical Oncology suggests holding CPIs and evaluating any patient (pt) whose serum creatinine (SCr) rises at least 1.5-fold above baseline (BL) i.e., ≥ grade 1 AKI. Empiric steroid therapy is recommended for pts with a Grade ≥ 2 AKI without an alternate cause. We sought to determine the frequency, severity, and predictors of AKI in a real-world population receiving CPIs.

Methods: We included all pts on CPIs from 2011-2017 at our institution. We determined CPI start date by oncology infusion records. BL SCr was established by averaging all SCr values during the 6 months prior to CPI start date. We compared all SCr values within 6 months after starting CPIs to the BL SCr to determine the fold-change from BL. We used logistic regression to determine if age, sex, race, hypertension, diabetes, cirrhosis or baseline CKD (GFR < 60) predicted AKI.

Results: 1843 pts started CPI therapy. 1039 (56%) had sufficient data to determine a BL SCr and had ≥1 SCr checked within 6 months of starting CPIs. Average age was 63 (SD, 13) yrs, 60% were male and 91% were Caucasian. The mean BL SCr was 0.9 (SD, 0.4) mg/dl, and 175 (17%) had CKD at BL. Pts had a median of 7 (IQR, 2-14) SCr values measured during the BL period, and 12 (IQR, 8-18) SCr values measured in the 6 months after CPI. 140 pts (13.5%) had an AKI event within 6 months of starting CPI therapy; 79 (56%) were grade 1 (>1.5-2-fold rise in SCr), 46 (33%) were grade 2 (>2-3-fold rise in SCr) and 15 (11%) were grade 3 (>3-fold rise in SCr or needed dialysis). Of the 140 pts with AKI, 42 (30%) had multiple AKI events within the first 6 months of starting CPIs. The first AKI event occurred on average 67 (SD, 52) days after starting CPIs. 69 pts (6.6% of the total cohort) had a sustained AKI event lasting > 48 hours. No baseline pt characteristics, including BL SCr, predicted AKI in a multivariable models.

Conclusions: AKI events are common in pts receiving CPIs. BL CKD does not appear to be a risk factor for AKI after CPIs. Nephrologists are likely to be increasingly called upon to evaluate the cause of AKI and assist oncologists in determining the best course of therapy in pts receiving CPIs.

TH-PO056

Incidence of AKI Among Critically Ill Patients with Brief Empiric Use of Anti-Pseudomonal Beta-Lactams with Vancomycin

Diana J. Schreier,[1] Kianoush Kashani,[2] Ankit Sakhuja,[2] Kristin C. Mara,[4] Mohammad samie Tootooni,[5] Heather A. Personett,[1] Sarah Leung,[1] Andrew D. Rule,[2] James Steckelberg,[3] Aaron J. Tande,[3] Erin F. Barreto.[1] *[1]Department of Pharmacy, Mayo Clinic, Rochester, MN; [2]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN; [3]Division of Infectious Diseases, Mayo Clinic, Rochester, MN; [4]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN; [5]Department of Health Sciences Research, Mayo Clinic, Rochester, MN.*

Background: Nephrotoxins contribute to 20-40% of acute kidney injury (AKI) cases in the intensive care unit (ICU). The combination of piperacillin/tazobactam and vancomycin (PTZ/VAN) has been identified as nephrotoxic, but existing studies focus on extended durations of therapy rather than the brief empiric courses often used in the ICU. The objective of this study was to compare the risk of AKI with a short course of PTZ/VAN to other anti-pseudomonal beta-lactam/vancomycin combinations

Methods: Retrospective cohort of 3299 ICU patients that received at least 24 hours, but no more than 72 hours of an antipseudomonal beta-lactam and vancomycin [(PTZ/VAN, cefepime (CEF/VAN), or meropenem (MER/VAN)]. The risk of developing stage 2 or 3 AKI was compared between antibiotic groups with multivariable logistic regression adjusted for relevant confounders. We also compared the risk of persistent kidney dysfunction, dialysis dependence, or death at 60-days between groups.

Results: The overall incidence of stage 2 or 3 AKI was 9%. Brief exposure to PTZ/VAN did not confer a greater risk of stage 2 or 3 AKI after adjustment for demographics, baseline serum creatinine, AKI risk prediction score, severity of illness, or sepsis [PTZ/VAN vs. CEF/VAN: adjusted OR, 95% CI 1.11 (0.85, 1.45); PTZ/VAN vs. MER/VAN 1.04 (0.71, 1.42)]. No significant differences were noted between groups at 60-day follow up in the outcomes of persistent kidney dysfunction (P = 0.081), new dialysis dependence (P = 0.15), or death (P = 0.091).

Conclusions: Short courses of PTZ/VAN were not associated with a greater risk of short- or long-term adverse renal outcomes compared to other empiric broad-spectrum combinations.

TH-PO057

AKI After Intravenous Vancomycin Compared to Other Common Intravenous Antibiotics

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Background: Vancomycin is a mainstay treatment for Gram-positive infection, but it may be associated with nephrotoxicity and acute kidney injury (AKI). AKI contributes to short-term morbidity, mortality, and increased risk of chronic kidney disease (CKD). The study aimed to evaluate the 2-week risk of AKI after ≥3 days of intravenous (IV) vancomycin treatment compared to patients treated with a comparator using U.S. commercial claims data.

Methods: From Truven MaketScan claims data (United States), we identified patients with a first hospitalization with IV vancomycin or comparator treatments with similar clinical indications (**table 1**) for ≥3 days with a treatment onset ≤ five days after hospital admission (2000-2015). Patients with claims for prior AKI, CKD, or use of immunosuppressive medications were excluded. We estimated incidence rates (IR) and hazard ratios (HR) with cox-regression adjusted for age, sex, main diagnosis, surgical procedure, and 1-year history of comorbidities and co-medication.

Results: We identified 32,997 hospitalized patients with vancomycin or comparator mono-therapy. The mean age was 50 (±15) years and 60% were female. Covariates were evenly distributed across treatment cohorts. Vancomycin was used in 5,449 (17%) patients and in 83% a comparator. Overall, there were 129 cases of AKI, and the IR of AKI was 9.32 (95% CI: 7.84-11.07) per 100 person-years. The crude HR comparing vancomycin vs. comparators was 1.04 (95% CI: 0.85-1.90). After adjustment the HR for vancomycin vs. all comparators was 0.74 (95% CI 0.45-1.21). Similarly, separate adjusted models for individual comparators did not result in elevated HR for vancomycin.

Conclusions: Our study using US claims data did not demonstrate an association between treatment with vancomycin alone and an increased risk of AKI compared to other commonly used intravenous antibiotics in hospitalized patients.

Table 1.

	N	Cases	Person-years	Incidence rate* (95%CI)	Crude HR (95%CI)		Adjusted HR (95%CI)	
Vancomycin (Index group)	5,449	22	229	9.62	(6.34-14.62)			
Comparators	27,548	107	1156	9.25	(7.66-11.18)	1.04	(0.85-1.90)	0.74	(0.45-1.21)
Cefazolin	20,124	58	846	6.86	(5.30-8.87)	1.40	(0.86-2.29)	1.01	(0.55-1.83)
Linezolid	251	6	10	57.63	(25.89-128.28)	0.17	(0.07-0.42)	0.17	(0.01-0.46)
Piperacillin	3,885	25	162	15.39	(10.40-22.78)	0.63	(0.35-1.11)	0.47	(0.24-0.91)
Cefepime	433	2	18	11.07	(2.77-44.28)	0.87	(0.45-3.70)	0.80	(0.19-3.69)
Meropenem	379	7	16	44.44	(21.18-93.21)	0.22	(0.09-0.51)	0.21	(0.10-0.52)
Ertapenem	2,205	8	93	8.65	(4.32-17.29)	1.11	(0.51-2.50)	0.47	(0.19-1.17)
Daptomycin	271	1	11	8.80	(1.24-62.51)	1.09	(0.15-8.11)	0.99	(0.12-8.19)

*per 100 person-years

TH-PO058

Levetiracetam and the Risk of AKI: A Population-Based Cohort Study

Kevin Yau,[1,2] Eric McArthur,[2] Racquel Jandoc,[2] Flory T. Muanda,[1,2] Chirag R. Parikh,[3] Ron Wald,[4] Amit X. Garg.[1,2] *[1]Western University, London, ON, Canada; [2]Institute for Clinical Evaluative Sciences, London, ON, Canada; [3]Yale University and VAMC, New Haven, CT; [4]St. Michael's Hospital, Toronto, ON, Canada.*

Background: Regulatory agencies warn about the risk of acute kidney injury (AKI) with levetiracetam use based on information contained in case reports. We conducted this population-based cohort study to determine whether new levetiracetam use versus non-use is associated with AKI.

Methods: We performed a population-based retrospective cohort study in Ontario, Canada. Adults who received a new outpatient prescription for levetiracetam from an outpatient pharmacy between January 1, 2004 and March 1, 2017 were matched to two non-users on stage of chronic kidney disease, recorded seizure in the prior 90 days, and logit of a propensity score for levetiracetam use. The primary outcome was a hospital encounter (emergency department visit or hospitalization) with AKI within 30 days of cohort entry. Secondary outcomes were AKI within 180 days and change in the serum concentration of creatinine. We assessed the primary outcome using health care diagnosis codes. We evaluated the change in the concentration of serum creatinine in a subpopulation with laboratory measurements.

Results: We matched 3,980 levetiracetam users to 7,960 non-users (mean age 55 years, 51% women). Levetiracetam use was not significantly associated with a higher risk of AKI within 30 days (13 [0.33%] events in levetiracetam users and 21 [0.26%] events in non-users [odds ratio, 1.24; 95% CI, 0.62-2.47]). Similarly, there was no significant association with AKI within 180 days (odds ratio, 0.70; 95% CI, 0.43-1.13). The change in the concentration of serum creatinine did not significantly differ between levetiracetam users and non-users.

Conclusions: In this population-based study it is reassuring that levetiracetam use was not associated with a higher risk of AKI.

Funding: Private Foundation Support, Government Support - Non-U.S.

Outcomes Assessed Using Database Codes

	Levetiracetam users (n=3,980)	Non-users (n=7,960)	OR (95% CI)	P-Value
Acute kidney injury (30 days)	13 (0.33%)	21 (0.26%)	1.24 (0.62-2.47)	0.55
Acute kidney injury (180 days)	23 (1.15%)	65 (1.63%)	0.70 (0.43-1.13)	0.15
Rhabdomyolysis (180 days)	10 (0.50%)	14 (0.35%)	1.43 (0.64-3.22)	0.39
Acute dialysis (180 days)	0 (0.00%)	≤5 (≤0.06%)	-	-
Acute interstitial nephritis (180 days)	5 (≤0.12%)	≤5 (≤0.06%)	-	-

To comply with privacy regulations to minimize the chance of identifying a study patient, numbers of patients were suppressed in the case of 1 to 5 patients (reported as ≤5).

TH-PO059

Longer-Interval Regimen of Colistin Reduces Nephrotoxicity in Kidney-on-a-Chip

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Background: Potential nephrotoxicity of colistin is of growing concerns due to relative high incidence and recent extensive use; however, which dosing regimen is less nephrotoxic remained uncertain. Previous animal and clinical studies have showed conflicting results for less toxic dosing regimen. We investigated whether bolus-mimicking regimens or continuous infusion regimen of colistin may be less nephrotoxic using microfluidic organ-on-a-chip device applying the Pharmakokinetic profile of colistin.

Methods: We introduced colistin to the kidney epithelial cells on kidney-on-a-chips under physiological shear stress condition(1 dyn/cm^2) and separated chip devices into two groups: bolus-mimicking regimen group and continuous infusion regimen group. Two drug treatment regimens were given the same total colistin dose over a 48 h period. Bolus-like regimen mimicked pharmacokinetic profiles for human bolus injection with starting colistin concentration of 1138 μg/ml and reducing by half every 9 h known as half-life of colistin in critically ill patients. Continuous Infusion regimen groups were exposed at colistin concentration of 400 μg/ml for 48 h.

Results: The bolus-mimicking regimen injured 1.64% out of total observed cells, whereas the continuous infusion regimen damaged 3.44% after 48-hour colistin exposed period. ($P < 0.05$). Bolus-mimicking regimen sustained lower transmembrane permeability of FITC-albumin and tight junction protein expression ZO-1 and occludin compared to the prolonged exposed regimen.

Conclusions: We found that a bolus-mimicking regimen dramatically alleviates kidney injury compared to the continuous infused regimen. Longer interval regimens may help to reduce nephrotoxicity in long-term colistin-using patients. In addition, kidney-on-a-chip experiments could be useful for selecting optimal dosing regimen of nephrotoxic drugs.

Funding: Government Support - Non-U.S.

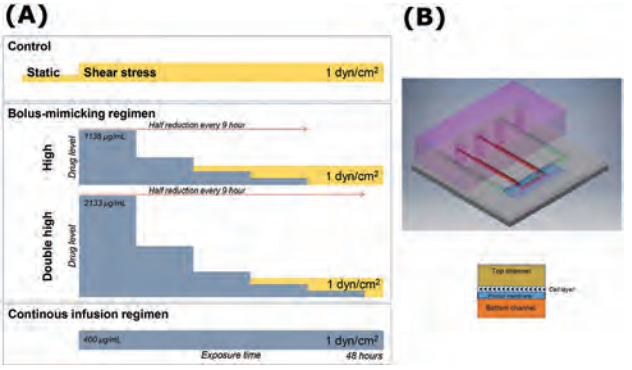

Figure 1. (A) Two different administration regimen of colistin: Bolus-mimicking regimen and continuous infusion regimen (B) The schematic design of kidney-on-a-chip used in this study

TH-PO060

The Characteristic of Drug Spectrum That Induced AKI and Clinicopathological Features of Drug-Induced AKI

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Background: To analyze the changes and characteristics of drug spectrum, and to analyze the kidney pathological characteristics of drug-induced acute kidney injury.

Methods: Retrospective analysis the characteristics of the patients of our center in 2012 January to October 2016, who were diagnosed of drug-induced AKI. According to the data of medical history and clinical manifestations, record the related drugs, analysis of the changes of drug composition and the renal pathological characteristics.

Results: There are 228 patients diagnosed drug-induced AKI, and 51 patients underwent renal biopsy. In 228 patients, 70 patients were caused by antibacterial and antiviral drugs, 63 patients were caused by non-steroidal anti-inflammatory drugs, 17 patients were caused by Chinese herbal medicine, and other drugs including the ACEI / ARB drugs, proton pump inhibitors, weight-loss drugs, lipid-lowering drugs, anti-hepatitis B virus medicine, antidepressants, albumin, platinum chemotherapy drugs, colchicine, calcineurin inhibitors. 14 patients cannot named which drugs. There were 31 patients had 2 or 3 types of drugs used before kidney injury. The antibiotics and antiviral drugs were the most frequently drugs associated with AKI, including cephalosporins, acyclovir, azithromycin, clindamycin, levofloxacin. In the 51 underwent renal biopsy patients, 12 patients showed allergic interstitial nephritis, 19 cases of patients showed interstitial nephritis, 8 patients showed renal tubular epithelial cell injury, and 2 cases showed Minimal Change Nephropathy, 2 cases showed IgA nephropathy, 2 cases of mild mesangial hyperplasia with glomerulosclerosis.

Conclusions: The first three types of drugs induce AKI were antibiotics and antiviral drugs, non- steroidal anti-inflammatory drugs and Chinese herbal medicine. In the group of antibacterial drugs and antiviral drugs, the most common drugs were cephalosporins, acyclovir, clindamycin, azithromycin and levofloxacin, but not aminoglycosides. Allergic interstitial nephritis, interstitial nephritis and tubular epithelial cell injury is the main pathological manifestations of drug - induced AKI, but some patients had no obvious changes of the pathological performance.

TH-PO061

NSAID Use and NSAID-Associated AKI Before and After Implementation of Pennsylvania's Prescription Drug Monitoring Program

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Background: Few studies describe the influence of prescription drug monitoring programs (PDMPs) on NSAID use or NSAID-associated adverse effects. We asked whether implementation of Pennsylvania's PDMP, designed to reduce narcotic use, was associated with changes in inpatient NSAID administration or NSAID-related Acute Kidney Injury (AKI) in western Pennsylvania (UPMC) hospitals.

Methods: We examined retrospective data from 16 UPMC hospitals in three PA PDMP phases: pre-PDMP (Jan 1-Aug 25, 2016), voluntary PDMP participation (Aug 26-Dec 31, 2016), and mandatory PDMP participation (Jan 1-Dec 31, 2017). Patients with ICD-10 codes indicating ESRD or kidney transplant were excluded. Outcomes included percent of admissions with any NSAID use and with prolonged NSAID use (≥ 4 days) and frequency of NSAID-associated AKI. AKI was defined by presence of both a creatinine-based electronic flag and an ICD-10 code for atraumatic, non-obstructive AKI. Outcomes were compared during each phase using chi-square tests, and interrupted time-series analyses were used to examine the impact of each phase over time.

Results: Inpatient visits in the pre-, voluntary, and mandatory PDMP phases totaled 95,550; 52,344; and 151,251, respectively. Across the three phases, hospitalizations with any NSAID use increased (77.1% pre- vs 78.3% voluntary vs 79.5% mandatory PDMP, p<0.001). Additionally, hospitalizations with prolonged NSAID use increased across the three phases (32.1% pre- vs 32.6% voluntary vs 33.9% mandatory PDMP, p=0.001). In interrupted time series analysis, receipt of any NSAIDs increased 1.4% with implementation of the voluntary phase (p <0.001), and AKI incidence increased 0.7% with implementation of the mandatory phase (p=0.06). Across all phases, patients with CKD were particularly susceptible to NSAID-associated AKI with prolonged NSAID use, as 42.0% of CKD patients receiving NSAIDs for ≥ 4 days experienced AKI, compared to 29.9% of CKD patients receiving < 4 days of NSAIDs (p = 0.001).

Conclusions: We find that implementation of the PA PDMP was associated with a significant increase in NSAID use and duration in inpatient UPMC facilities and a marginally significant and temporally correlated increase in AKI. Further analyses will examine whether AKI increased more dramatically in specific high-risk patient subsets.

Funding: NIDDK Support

TH-PO062

Bortezomib-Induced Tumor Lysis Syndrome in Patients with Untreated Symptomatic Multiple Myeloma: A Retrospective Study

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Background: Tumor lysis syndrome (TLS) causes acute kidney injury (AKI) and is a complication of cancer chemotherapy. TLS risk is classified by malignant disease type. Although multiple myeloma (MM) is a low-risk disease, treatment by novel therapies, including bortezomib (Bor), may increase TLS risk. Thus, we evaluated the association between Bor-based therapy and TLS in MM patients.

Methods: We retrospectively reviewed patients who received first-line therapy for untreated symptomatic MM between May 2007 and December 2017. Patients treated by Bor-based therapy comprised the Bor group; all remaining patients (i.e., those treated by conventional anti-cancer agents) comprised the Non-Bor group. Incidences of laboratory and clinical TLS (LTLS and CTLS) during first-line therapy were compared between groups.

Results: There were 129 and 75 patients in Bor and Non-Bor groups, respectively. Baseline laboratory data were similar between groups. More patients received prophylactic administration for hyperuricemia in Bor group than in Non-Bor group. However, LTLS incidence was significantly higher in Bor group than in Non-Bor group (12.4% vs. 4.0%, P<0.05); CTLS was observed in eight patients (6.2%) in Bor group and one (1.3%) in Non-Bor group [Table]; these patients were diagnosed with CTLS due to elevated serum creatinine. Three CTLS patients with AKI were in Bor group. No CTLS patients died or referred for dialysis during treatment period.

Conclusions: Bor-based therapy may increase risk of AKI in LTLS and CTLS, even with prophylactic interventions. TLS risk must be further evaluated in low-risk diseases such as MM, as an increasing number of novel therapies can achieve tumor shrinkage.

Table. The incidences of laboratory TLS and clinical TLS in patients treated by bortezomib-based regimen (Bor group) and Non-bortezomib-based regimen (Non-Bor group).

	No. of patients (%)		P value
	Bor group (n=129)	Non-Bor group (n=75)	
Laboratory TLS	16 (12.4)	3 (4.0)	<0.05*
Clinical TLS	8 (6.2)	1 (1.3)	0.159

All nine patients were diagnosed with CTLS due to elevated serum creatinine >1.5 × upper limit of normal range.

TLS: Tumor lysis syndrome

P values were determined by Fischer's exact test.

TH-PO063

Risk of AKI and Hyperkalemia Among Older Patients Prescribed Non-Steroidal Anti-Inflammatory Drugs

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat pain and inflammation. Clinical guidelines caution against NSAID use in older patients due to high risk of acute kidney injury, but better evidence is needed to inform clinical care for those most at risk. The objective of this study was to determine the risk of acute kidney injury and hyperkalemia associated with long-term prescription NSAID use among older patients, and risk factors associated with these outcomes.

Methods: We conducted a population-based retrospective cohort study using linked healthcare data from Ontario, Canada. We identified patients >66 years with a new NSAID prescription with a day supply >14 days between 2007 and 2015. We propensity-score matched NSAID users to non-users and performed conditional logistic regression on 30-day risk of acute kidney injury, hyperkalemia, all-cause mortality, and hospital encounter with ventricular arrhythmia. We also developed a logistic regression model of predictors for acute kidney injury or hyperkalemia among NSAID users.

Results: We identified 61,219 eligible NSAID users and 156,589 eligible non-users. We matched 46,107 NSAID users to 46,107 non-users (mean age 74 years, 58% female). NSAID users were significantly more likely to develop acute kidney injury and hyperkalemia compared to non-users (see Table). Our prediction model included six baseline factors that were significantly associated with acute kidney injury or hyperkalemia (C-statistic adjusted for Harrell's optimism: 0.72, 95% CI: 0.70-0.74): older age, male gender, lower baseline estimated glomerular filtration rate, higher baseline serum potassium, angiotensin converting enzyme inhibitor or angiotensin receptor blocker prescription, and diuretic prescription. This model will be available as an online calculator through the QxMD Calculate application.

Conclusions: Older patients prescribed NSAIDs for more than 14 days are at greater risk for acute kidney injury and hyperkalemia compared to non-users. We have developed an online calculator to help inform clinical decision making for NSAID prescribing in this population.

Funding: Government Support - Non-U.S.

Outcome	NSAID users, n (%)	Non-users, n (%)	Odds ratio (95% CI)	Risk difference (95% CI)	Number needed to harm (95% CI)
Acute kidney injury	380 (0.82)	272 (0.59)	1.41 (1.20-1.65)	0.23 (0.13-0.34)	427 (292-787)
Hyperkalemia	184 (0.40)	123 (0.27)	1.50 (1.20-1.89)	0.13 (0.06-0.20)	756 (485-1715)
All-cause mortality	66 (0.14)	79 (0.17)	0.83 (0.60-1.16)	-0.03 (-0.08-0.02)	N/A
Hospital encounter with ventricular arrhythmia	71 (0.15)	76 (0.16)	0.93 (0.67-1.29)	-0.0001 (-0.06-0.70)	N/A

TH-PO064

Routine Laboratory Monitoring Following Initiation of an ACEi or ARB and the Association with Adverse Outcomes

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Background: Clinical guidelines recommend serum creatinine and potassium monitoring shortly after initiating an Angiotensin Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB). However, it is unclear if monitoring prevents adverse outcomes. The objective of this study was to identify the association between obtaining laboratory monitoring shortly after initiating an ACEi or ARB prescription and adverse outcomes across two large North American regions.

Methods: We conducted two population-based retrospective cohort studies using healthcare data from Kaiser Permanente Northern California and the Institute for Clinical Evaluative Sciences, Ontario, Canada. We included patients initiating an ACEi or ARB prescription between 2007 and 2015. We compared patients with both outpatient serum creatinine and potassium tests in the 30 days following the prescription date to a group without such tests, where we randomly assigned a test date. Patients with and without follow-up tests were matched using high dimensional propensity scores to have similar indicators of baseline health. We assessed outcomes of all-cause mortality and hospitalization with acute kidney injury or hyperkalemia within 30 days of the test date using Cox proportional hazards regression.

Results: In the Kaiser cohort, 55,487 (34%) eligible patients received follow-up outpatient serum creatinine and potassium tests (mean 12 days after ACEi / ARB initiation). The final cohort included 54,274 patients with follow-up tests matched to 54,274 without tests (mean age 63 years). There was no significant difference in 30-day all-cause mortality between patients with follow-up tests compared to patients without tests (see Table). Patients with follow-up tests were more likely to be hospitalized with acute kidney injury, but not hyperkalemia, compared to patients without tests. The findings were similar in the Ontario cohort (mean age 75 years).

Conclusions: Routinely measuring serum creatinine and potassium after initiation of an ACEi or ARB does not appear to prevent adverse outcomes compared to no such measurements.

Funding: Government Support - Non-U.S.

Outcome	Kaiser Permanente Northern California Cohort				Ontario Cohort			
	Follow-up test, n (%)	No follow-up tests, n (%)	Hazard Ratio (HR) (95% CI)	Adjusted HR (95% CI)	Follow-up tests, n (%)	No follow-up tests, n (%)	HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality	85 (0.16)	108 (0.20)	0.78 (0.59-1.03)	0.70 (0.46-1.06)	144 (0.24)	111 (0.19)	1.29 (1.01-1.66)	1.20 (0.86-1.66)
Hospitalization with acute kidney injury	93 (0.17)	52 (0.09)	1.82 (1.30-2.57)	2.44 (1.40-4.26)	60 (0.67)	26 (0.29)	2.23 (1.41-3.54)	4.86 (1.56-15.17)
Hospitalization with hyperkalemia	22 (0.04)	11 (0.02)	2.00 (0.97-4.12)	N/A*	14 (0.16)	9 (0.10)	1.56 (0.67-3.59)	N/A*

*Adjusted models did not converge

TH-PO065

Incidence, Pathology Findings, and Outcomes of Patients with Kidney Biopsy Proven Acute Interstitial Nephritis

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Background: Acute interstitial Nephritis (AIN) is a common cause of AKI. However, there have been no recent studies that have reviewed the incidence, and/ or etiology of AIN.

Methods: Using our Health System's kidney biopsy database, we reviewed charts of total 322 patients who underwent kidney biopsies in last 1 year. Patients with pathological diagnosis of AIN were analyzed for related clinical presentations and concurrent pathological findings. Patients with pure AIN were then compared to patients with AIN and associated kidney pathology findings using students t-tests and chi-square.

Results: AIN was present in 13% (42/322) patients. 38% had pure tubulo-interstitial diseases (Pure AIN) and 62% also had findings of other kidney diseases. 44% had simultaneous glomerular pathologies including primary and secondary FSGS (3 cases with collapsing glomerulopathy, 2 with secondary FSGS and 1 with primary FSGS), diabetic nephropathy, membranous nephropathy, immune complex GNs and lupus nephritis. To our surprise, concurrent oxalate deposition was seen in 12% patients. Mean age of patients with AIN was 54.2 years and 61% were females. Overall mean peak Scr was 3.9mg/dl and last known mean Scr post treatment was 2.5mg/dl. Mean proteinuria was 2.8 grams for both groups. There was no statistical difference in both groups in terms of age, proteinuria at baseline, and change Scr. Pure AIN group presented with a higher mean Scr (4.8) compared to AIN with concurrent glomerular disease group(3.2)(p= 0.09). Urine eosinophils were present only in 2 of 11 patients who were tested, and up trending peripheral eosinophilia was seen in only 9 patients. 10/42 patients received treatment with corticosteroids only. 11 patients required hemodialysis(HD). Pure AIN group was more likely to require HD (64% vs. 36%). Beta lactam antibiotics (13.9%), NSAIDs (11.6%) and proton pump inhibitors (6.9%) were most common agents causing AIN.

Conclusions: AIN remains a prevalent cause of AKI. AIN with concurrent kidney pathology is more common than pure AIN. Patients with Pure AIN presented with higher Scr and were more likely to require treatment with HD. Although few patients with AIN were noted to have up-trending peripheral eosinophil counts, neither eosinophiluria nor peripheral eosinophilia were associated with predicting the kidney biopsy findings.

TH-PO066

Prevention of Cisplatin-Induced AKI by Magnesium Supplementation: A Systematic Review and Meta-Analysis

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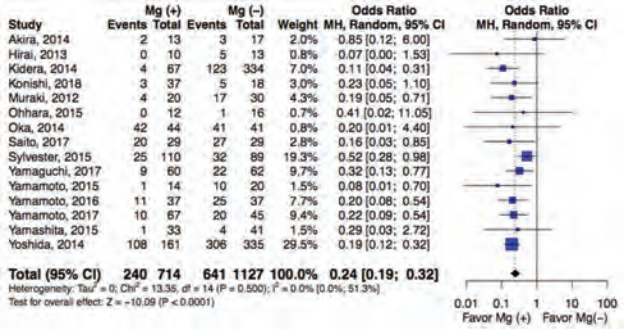
Background: Cisplatin-induced AKI (CIA) is a serious adverse event that affects 30-40% of exposed patients. To date, no prevention method has demonstrated its indisputable effectiveness. Nevertheless, magnesium appears to play a nephroprotective role, partly through its action on the Organic Cation Transporter 2 (OCT2), a renal proximal tubular receptor. The aim of this work is therefore to study the potential nephroprotective effect of magnesium supplementation on CIA.

Methods: After a systematic review on Pubmed, Embase and Web of Science, from January 1978 to January 2018, without language restriction, we performed a meta-analysis with a random effect model. Primary outcome was the occurrence of a CIA, according AKI-KDIGO classification and grading (2012). Heterogeneity between studies was quantified (I^2) and the analysis completed by a meta-regression to adjust the results for potential confounders. This study is registered in the PROSPERO International Prospective Register of systematic reviews, registration number CRD42018090612.

Results: Within the 1125 eligible records, 15 studies fulfilling the selection criteria were included in this work (4 prospective and 11 retrospective cohort studies), for a total of 1841 patients. The meta-analysis showed a significant nephroprotective effect of magnesium supplementation on grade 2 (OR=0.22, 95% CI 0.14-0.33, I^2=0.0%), grade 3 (OR=0.25, 95% CI 0,08-0.76, I^2=0.0%) and all combined grades of CIA (OR=0.24, 95% CI 0.19-0.32, I^2=0.0%). This effect remained after adjustment for all potential confounding factors (sex, age, cumulative dose of Cisplatin, baseline renal function, performance status index, type of cancer, stage of disease and type of comolecule).

Conclusions: Today, relatively unknown, magnesium supplementation could become, in the future, an effective method of low-cost prevention for CIA. In any case, these promising results encourage the implementation of a large-scale randomized trial.



TH-PO067

High Incidence of Early AKI in Cord Blood Transplantation (CBT) Recipients

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Background: CBT can be curative in patients with high-risk hematologic malignancies but may be associated with a risk of acute kidney injury (AKI).

Methods: We analyzed AKI incidence and risk factors in adult CBT recipients (18-65 years) transplanted for hematologic malignancies with cyclophosphamide/ fludarabine/ thiotepa / TBI 400, cyclosporine (CSA)/ mycophenolate mofetil and double unit CB grafts from 2006-2016. Maximum grade AKI (KDIGO criteria 1, 2 or 3) was calculated using day 0 - +100 creatinines. If patients had multiple episodes, the highest AKI grade was analyzed.

Results: 154 patients (median age 51 years) were transplanted. No patient had chronic kidney disease. Median age-adjusted hematopoietic cell transplantation comorbidity index (aaHCT-CI) was 3 (range 0-9). 58 (38%) patients also received haploidentical CD34+ cells. 96% engrafted, 74% had grade II-IV acute graft-*vs*-host disease (aGVHD), and 138 (90%) were alive/ disease-free at day 100. 125 patients had AKI (41 grade 1, 62 grade 2, 22 grade 3) for a grade 1-3 cumulative incidence of 82% (median onset 30 days, range 0-96) and 54 % for grade 2/3. High-toxic CSA levels (3 day average greater than 350) were seen immediately prior to AKI in 11/41 (27%) patients with grade 1 *vs* 33/84 (39%) of grade 2-3 patients. There were 29 patients who did not have an AKI event. Significant variables associated with AKI are shown in Table 1.

Conclusions: CBT recipients are at significant risk for AKI. Early recognition and prompt intervention are critical to lessen severe injury. Strategies to mitigate AKI are required as well as analysis of the effect of AKI on long-term renal function.

Table 1a: Association between pre/ post CBT characteristics & AKI

Variable	*Any AKI Hazard Ratio (95 % CI)*	*P-value*	*Grade 2-3 AKI Hazard Ratio (95 % CI)*	*P-value*
Patient & Graft Variables				
CMV positive	**1.4 (1.0-2.0)**	**0.06**	**1.49 (1.0-2.3)**	**0.08**
aaHCT-CI score > / = 3	**1.2 (0.9-1.8)**	**0.25**	**1.50 (1.0-2.3)**	**0.07**
Haplo-CD34+ cells	**1.3 (0.9-1.9)**	**0.15**	**1.62 (1.1-2.5)**	**0.03**
Post-CBT Variables				
ICU admission	**1.5 (1.2-1.9)**	**< 0.001**	**1.76 (1.3-2.4)**	**< 0.001**
Nephrotoxic med(s)*	**1.2 (1.0-1.5)**	**0.05**	**1.5 (1.3-1.8)**	**< 0.001**

Table 1b: Multivariate analysis for grade 2-3 AKI

Variable	*Grade 2-3 AKI Hazard Ratio (95 % CI)*	*P-value*
aaHCT-CI score > / = 3	**1.2 (0.9-1.6)**	**0.08**
Haplo-CD34+ cells	**1.5 (1.2-1.9)**	**0.001**
ICU admission	**4.1 (2.6-6.4)**	**< 0.001**
Nephrotoxic med(s)*	**1.4 (1.1-1.9)**	**0.008**

Non-significant variables: age, gender, African ancestry, pre-existing hypertension or diabetes, high-very high Disease Risk Index, bacteremia (any organism excluding coagulase negative Staphylococcus), baseline serum albumin.
* Nephrotoxic medications: foscarnet, amikacin, amphotericin, or intravenous cidofovir.

TH-PO068

AKI in Hospitalized Patients with Solid Organ Cancer Who Undergo Cancer Treatment

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Background: Acute Kidney Injury (AKI) is common in patients with cancer and associated with interruptions in therapy, increased testing and procedures, and higher healthcare costs. However, the epidemiology of AKI complicating solid organ cancer is not well-understood. We aimed to explore correlates and consequences of AKI in patients hospitalized for treatment of solid organ cancer in the United States.

Methods: Using the National Inpatient Sample (NIS) database from 2012 we included patients over the age of 20 with a primary diagnosis of solid organ cancer with a concomitant diagnosis code for cancer treatment category (surgery, chemotherapy or radiation). We excluded patients with a diagnosis code for end-stage renal disease (ESRD), or if they had a procedure code for dialysis without associated AKI. In our analysis we created separate models for the interaction between cancer type and treatment category and the outcomes: AKI, hospitalization length of stay (LOS) and cost. Multivariate models were adjusted for age, sex, comorbidities, region, primary payer, bedsize and teaching status of the hospital.

Results: The weighted sample had 321,345 hospital admissions for solid organ cancer treatment. Approximately half were for women and >60% were for persons over the age of 60. More than half had hypertension, more than one in five had diabetes. Overall, 5.5% of patients who underwent surgical treatment had AKI, compared to 11% and 9% of patients who received chemotherapy and radiation therapy (XRT) respectively. After adjustment for covariates, patients with the highest risk of AKI were those admitted for kidney and liver cancer XRT who had a 32% (CI 13%-50%), and 23% (CI 7%-40%) probability of AKI respectively, followed by admissions for XRT of colon cancer 19% (CI 11%-27%), and chemotherapy for prostate cancer 18% (CI 2%-34%). After adjusting for cancer type, treatment type, and covariates, hospitalizations with AKI had on average, double LOS (CI 1.92-2.11) and 1.78 times higher hospitalization costs (CI 1.70-1.86).

Conclusions: The probability of AKI in hospitalized patients with solid organ cancer is significantly different among different cancer types and treatment modalities. Presence of AKI is associated with increases in hospitalization costs and LOS. Further analysis will evaluate risk factors and inform clinical decision making.

TH-PO069

AKI Drives Papillary Renal Cell Carcinoma Formation from Tubular Progenitor Cells

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Background: Renal cell carcinoma (RCC) accounts for 2% of all cancers, with about 190,000 new cases per year worldwide. As the Notch pathway has a critical role in kidney injury and repair, and Notch hyperexpression was reported in patients with RCC, we hypothesized that a persistent activation of the Notch pathway may drive tubular epithelial cell (TEC) hyperplasia, leading to cancer formation. Other risk factors for RCC include obesity, diabetes, hypertension and genetic factors, but the majority of cancers occur in apparent absence of clear risk factors. As tissue injury is an important cofactor for many types of cancers, we proposed to verify whether acute kidney injury (AKI) plays a role in RCC development.

Methods: We developed mouse models in which the intracellular domain of Notch 1 (NICD1) is expressed constitutively by all Pax8+ TECs (Pax8/NICD1) or only by Pax2+ renal progenitors (Pax2/NICD1) upon induction in adult mice. Both models were further bred with Confetti mice, allowing clonal analysis of the lesions. Following induction, the mice were either left to age for 9 months or underwent unilateral ischemia-reperfusion injury (IRI), an experimental model of AKI, and were sacrificed at 28 days.

Results: At 9 months, Pax8/NICD1 mice presented a significant decline of renal excretory function as well as numerous, multicentric and progressive pretumoral and tumoral lesions. Histological analysis indicate the presence of papillary RCCs (pRCCs). In Pax8/NICD1/Confetti mice, we observed that most of the pRCCs were mono- or biclonal, suggesting that they could originate from a local stem cell/progenitor population. Pax2/NICD1 mice presented exclusively papillary tumors. Lineage tracing in Pax2/NICD1/Confetti mice identified single Pax2+ tubular progenitors as the source of pRCCs. Mice subjected to IRI presented mono- and biclonal papillary tumors in only 28 days, indicating that AKI strongly accelerated the development of pRCCs.

Conclusions: These mouse models represent useful new tools to study the mechanisms of tumor development in the kidney and indicate Pax2+ renal progenitors as the cell of origin of pRCC. Additionally, this study provides the first experimental demonstration of the link between AKI and the development of papillary tumors, with important clinical implications for RCC patients.

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TH-PO070

Epidemiology and Outcomes of AKI in Hospitalized Cancer Patients in China

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Background: Acute kidney injury (AKI) is a common complication in cancer patients, but the data are lacking in Asian countries. We aimed to assed the epidemiology, correlated risk factors and outcomes of AKI in cancer patients from China.

Methods: We conducted a nationwide cohort study of cancer patients who were admitted to 25 general and children hospitals across China from January 1, 2013 to December 31, 2015. We obtained patient-level data from the electronic hospitalization information system and laboratory databases of all inpatients who had at least two serum creatinine tests within any 7-day window during their first 30 days of hospitalization. AKI was defined and staged according to Kidney Disease Improving Global Outcomes criteria. Incidence rate and risk factor profiles for AKI were examined. Outcomes of interest included in-hospital mortality, length of stay and daily costs.

Results: A total of 136,834 adult cancer patients were assessed in our study. The overall incidence of AKI was 7.6%, of which 1.6% were community acquired and 5.9% hospital acquired. The top three cancer types with high incidence of AKI were bladder cancer, leukemia, and lymphoma. Risk factors for community-acquired and hospital-acquired AKI were similar, including age, increased baseline serum creatinine, shock and urinary tract obstruction. In-hospital occurred in 12.0 % with AKI versus 0.9% cancer patients without AKI. After adjustment for confounders, the severe AKI was associated with higher risk of in-hospital death, prolonged length of stay and higher daily costs.

Conclusions: Clinicians should increase their awareness of AKI in hospitalized cancer patients.

TH-PO071

AKI in Stem Cell Transplant Patients: Role of Hemoglobinuria

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Background: The available evidence regarding the risk factors of hemoglobinuria shortly after hematopoietic stem cell transplant (HSCT) and its association with outcomes including acute kidney injury (AKI), mortality, and engraftment is very limited.

Methods: The objectives of this study were: 1. Identify risk factors of hemoglobinuria within 24 hours of HSCT **2.** Assess whether hemoglobinuria is a risk factor for early post-HSCT AKI **3.** Assess outcomes (mortality, engraftment, and infection) with AKI as the predictor in the group of patients with post-HSCT hemoglobinuria. **Methods:** Retrospective cohort study of adults that underwent hematopoietic stem cell transplantation from January 6, 1999, to November 6, 2017. Patients that underwent bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) were included in the study (n= 5992). Of these, we identified 50 patients that developed gross hemoglobinuria within 24 hours after HSCT (In 7 out of 50 patients gross hemoglobinuria was confirmed with urinalysis).

Results: Univariable analysis showed that post-HSCT hemoglobinuria was associated with graft type (BMT vs. PBSCT, OR 12.99 CI 7.3-23.16), underlying disease (lymphoma OR 13.82, CI 4.2-45.43, acute leukemia OR 7.79, CI 1.94-31.22, reference group: multiple myeloma) and fludarabine-based conditioning regimen (OR 2.4, CI 1.09-5.47). In multivariable analysis these associations persisted for all predictors except for acute leukemia. Of the 11 patients that underwent allogeneic HSCT and had hemoglobinuria, only one had a transplant with ABO mismatch (bidirectional). ABO incompatibility hence, was not included in the analysis. Additionally, post-HSCT hemoglobinuria was also associated with early (48-72h) posttransplant AKI (OR 6.3, CI 3.4 -11.7) in univariable analysis. Finally, AKI in patients with hemoglobinuria was associated with delayed platelet engraftment (P= 0.049) but not white blood cells (WBC) engraftment (P=0.11), infection (P=0.77) or 100-day mortality (P=0.52).

Conclusions: Our study demonstrated a significant association between post-HSCT hemoglobinuria and graft type (BMT), fludarabine-based conditioning regimen and underlying disease (lymphoma). Hemoglobinuria was also associated with early post-Tx AKI. Future studies should focus on preventing post-HSCT hemoglobinuria induced AKI in these high-risk patients.

TH-PO072

Temporal Trends and Impact on Mortality of AKI in Cancer Patients

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Background: Recently, overall death rate in cancer patients has been improved in virtue of advanced preventive and treatment modalities. Acute kidney injury (AKI) is one of serious complication associated with worse outcomes, although its temporal trend and impact on outcome remain unclear in cancer patients.

Methods: This study retrospectively assembled newly diagnosed cancer patients at Seoul National University Hospital between January 2005 and December 2013. Among a total of 98,284 incident cases of cancer, we excluded patients with multiple primary cancer, age under 18 years-old, advanced renal dysfunction with eGFR less than 15 ml/min/1.73m^2. We evaluated annual trends of AKI occurrence within the first year after diagnosis of cancer.

Results: We finally included 68,302 patients after exclusion, and 14,152 (23.4%) patients in them developed AKI within the first year after cancer diagnosis. Overall incidence of AKI was highest in lung cancer (289.5 /1000 person-year), followed by genitourinary tract cancer (260.8/1000 person-year) and hematologic malignancies (217.1 /1000 person-year). As times go by, cancer patients has been older, more hypertensive and more diabetic, and exposed more radiocontrast. With this trend, annual AKI development has increased from 21.0% to 27.8% (P for trend <0.001). On the contrary, 5-year mortality has decreased from 42.9% to 26.5% (P for trend <0.001). Multivariate analysis showed adjusted odd ratio of AKI on mortality has been increasing continuously.

Conclusions: Although overall death rate has decreased, AKI incidence and the impact of AKI on mortality have been increasing over time in cancer patients. Our study suggested that appropriate preventive strategy and adequate management for AKI in patients with malignancy, which is an important role of nephrologists.

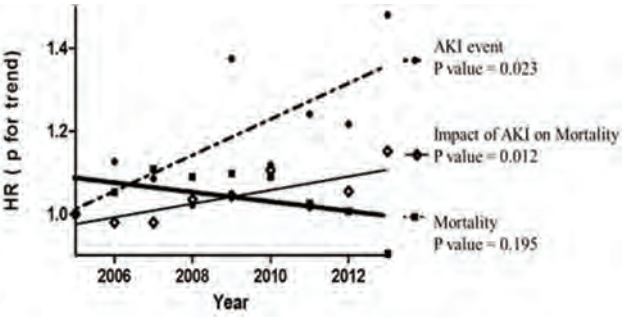

Figure 1. Temporal trends of AKI incidence and Impact on Mortality from 2005 to 2013.

TH-PO073

Partial Nephrectomy Is Associated with Increased Risk of AKI Compared to Radical Nephrectomy for Renal Cell Cancer

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Background: Acute kidney injury (AKI) is a common complication after major surgery including partial (PN) or radical nephrectomy (RN).

Methods: We evaluated if nephron-sparing surgery is associated with lower incidence of acute kidney injury (AKI). We used data from the national surgical quality improvement program (NSQIP) from Jan 2005 to Dec 2013. The primary endpoint was the occurrence of AKI as defined as over 200% increase in serum creatinine within 72 hours after surgery which is coded by the NSQIP. The main secondary endpoint was the occurrence of progressive kidney failure (PKF) as defined as a need for renal replacement therapy during the course of hospital stay or within 30 days of surgery. In order to identify the confounding variables for the occurrence of AKI and PKF, initially univariate analyses were performed and those factors and covariates which had a trend of significance (P<0.10) were included in multivariable binary logistic regression model. Propensity weighted analyses were then performed between the PN and RN groups for the occurrence of AKI and PKF, using confounding factors and covariates which were significant contributors of AKI and PKF.

Results: There were more male patients in both groups and the RN patients were older. PN patients had lower preoperative weight. Patients who underwent RN had higher prevalence of hypertension, CAD, CHF, dyspnea on exertion, dependent functional status, CKD as defined by eGFR <60 ml/min/1.73m^2, disseminated neoplastic disease, significant weight loss of history of bleeding episodes. PN patients had higher serum hematocrit, but lower serum creatinine values. AKI was observed in a total of 143 patients. Multivariable analysis showed increasing age, female gender, eGFR <60 ml/min/1.73m2 and increased operative times were significantly associated with increased risk of AKI. Post-operative progressive renal failure, occurred in 149 patients. In multivariable analysis only age, sex, GFR weight loss serum albumin and operative time were significant. Propensity analysis showed increased risk of AKI with PN compared to RN (OR: 1.683 (95% CI;1.073-3.181). PN also had a trend in increasing the risk of postoperative progressive kidney failure (OR: 1.683(95% CI:0.980-2.229)

Conclusions: PN was associated with increased risk of AKI.

TH-PO074

Burden and In-Hospital Mortality of Dialysis-Requiring AKI (AKI-D) Among Hospitalized Adults with Granulomatosis with Polyangiitis (GPA)

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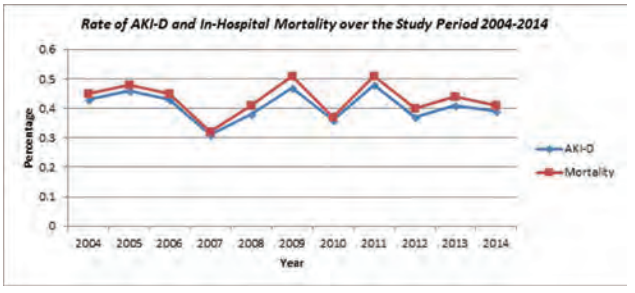
Background: To describe the incidence of acute kidney injury (AKI) requiring renal replacement therapy (dialysis-requiring AKI, AKI-D) and the impact on in-hospital mortality among hospitalized adults with granulomatosis with polyangiitis (GPA).

Methods: We reviewed the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample (NIS) Database, a large nationally representative sample of inpatient hospital admissions, to identify all adult hospitalizations with AKI-D and primary or secondary diagnosis of granulomatosis with polyangiitis (GPA) from 2004–2014. We investigated the trend of AKI-D in each disease for each year and performed multivariate logistic regression to evaluate the impact of AKI-D and co-morbidities on in-hospital mortality.

Results: Among 339,856 hospitalizations with AKI-D, the proportion of GPA as an associated diagnosis remained stable at 0.31-0.47% per year. From 2004-2014, AKI-D complicated 0.32% of hospitalizations with GPA as a primary or secondary diagnosis. The age-adjusted odds of in-hospital mortality associated with AKI-D in patients with GPA decreased over the study period, from 0.92 (95% CI 0.88–0.96) in 2008 to 0.79 (95% CI 0.75–0.82) in 2014. Compared to other causes of AKI-D, GPA was significantly associated with lower in-hospital mortality with adjusted OR 0.64 (95% CI 0.55 - 0.76).

Conclusions: These data suggest that the incidence of dialysis-requiring AKI among hospitalized adults with GPA remained stable; however, the in-hospital mortality seemed to decrease and significantly lower than other causes of severe acute kidney injury.



TH-PO075

AKI in Pediatric Cancer Patients: Incidence and Outcome

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Background: Pediatric patients with cancer are known to experience acute kidney injury (AKI) but its incidence and clinical impact has not been well established. The purpose of this study is to analyze the incidence of AKI within 1 year of diagnosis of cancer in children, and to assess its impact on the development of impaired renal function and the development of proteinuria.

Methods: Retrospective review of medical records was done on patients who were diagnosed and treated for cancer at Seoul National University Hospital between 2004 and 2013. Patients who were 18 years old or younger at diagnosis of cancer and who had their Cr levels measured at least two times within one year of diagnosis were eligible. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: stage 1 as 0.3 mg/dL rise of Cr within two days or 1.5 times rise within seven days, stage 2 as two times rise, stage 3 as three times rise or Cr above 4 mg/dL. Impaired renal functionof eGFR of cancer survivors less than 90ml/min/1.73m^2, and development of proteinuria were also assessed.

Results: Among 2,170 candidate patients assessed, 1,868 patients were eligible. Patients were diagnosed with cancer at a median age of 7.9 years old. Their median initial eGFR at diagnosis was 90.0ml/min/1.73^2. A total of 983 patients (52.6%) developed AKI and the cumulative incidence of AKI within two weeks, three months, and one year of diagnosis were 28.9%, 39.6%, 53.6%, respectively. The 1-year cumulative incidence of AKI was the highest in patients with acute myeloid leukemia (88.4%) and lowest in patients treated for retinoblastoma (14.1%). Within the 1 year of cancer diagnosis, AKI occurred once in 520 (27.8%), 2-3 times in 349 (18.7%), more than 4 times in 114 (6.1%) patients. 18.7%, 22.1%, and 11.8% of the patients had stage 1, stage 2, and stage 3 AKI respectively. 22.6% of the survivors had impaired renal function. Male sex, lower eGFR at diagnosis, frequent AKI occurrence and nephrectomy was independent risk factor. Also, 8.2% of the survivors developed proteinuria and female gender, older age were the associated independent risk factors.

Conclusions: Current study showed that AKI occurred in a relatively large percentage of pediatric patients with cancer and that it may adversely affect their long-term renal function.

Funding: Government Support - Non-U.S.

TH-PO076

Platelet Count and Serum Creatinine in the Differential Diagnosis of TMA: An Analysis from the CESAR Study

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Background: Thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing *E. coli* hemolytic uremic syndrome (STEC-HUS), and atypical HUS (aHUS) require a fast differential diagnosis in order to initiate urgent therapy. TTP may be excluded by an ADAMTS13 activity assay result of >5–10%, however, this test is not immediately available at many centers. Data from the CESAR study[1] were used to assess whether routine laboratory parameters can be used to predict/rule out TTP.

Methods: CESAR was a cross-sectional, multicenter, epidemiologic study of the relative incidence of aHUS, TTP and STEC-HUS in Germany. We developed an algorithm to predict severe ADAMTS13 deficiency in adult patients at clinical presentation. All available variables were analyzed for correlation with final diagnosis. Thresholds were identified maximizing the sum of sensitivity and specificity (Youden Index: J=sensitivity+specificity-1) and then rounding to the nearest easy-to-recall value.

Results: A total of 219 adult patients with a mean (SD) age of 56.2 (18.9) years were enrolled, of whom 31 (14%) were diagnosed with TTP. Platelet (Plt) and serum creatinine (SCr) levels significantly correlated with TTP diagnosis ($p<0.01$). Multivariate analysis (Table 1) revealed that if Plt and SCr levels are above threshold values (Plt: 30 x 10^9/L and SCr: 1.8 mg/dL), TTP is almost certainly ruled out (negative predictive value 98.1 and 92.3 for one or both values, respectively, above threshold).

Conclusions: This analysis shows that Plt and SCr are strong predictors to rule out a diagnosis of TTP. This finding confirms previous studies[2] and may help to accelerate differential diagnosis of TMA. [1]Schoenermarck U, et al. 2017; presented at ASN Kidney Week [SA-PO421] [2]Coppo P, et al. PLoS One 2010;5(4):e10208.

Funding: Commercial Support - Alexion Pharma GmbH

Table. Multivariate analysis to predict TTP diagnosis

Criteria	Specificity	Sensitivity	PPV	NPV
Plt ≤30x10^9/L	84.0	61.3	38.8	92.9
SCr ≥1.8 mg/dL	54.8	90.3	25.0	97.1
Plt ≤30x10^9/L AND SCr ≥1.8 mg/dL	90.8	54.8	50.0	92.3
Plt ≤30x10^9/L OR SCr ≥1.8 mg/dL	54.6	93.5	25.7	98.1

Values expressed as %. NPV, negative predictive value; Plt, platelets; PPV, positive predictive value; SCr, serum creatinine.

TH-PO077

Outcomes of Renal Function After Urinary Diversion for AKI among Patients with Obstructive Uropathy Secondary to Malignancy Admitted in a Tertiary Hospital

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Background: Acute kidney injury secondary to malignant obstructive uropathy is associated with poor prognosis. Urinary diversion with percutaneous nephrostomy or DJ ureteral stenting have been used to manage this potentially life-threatening condition. The study aimed to compare the renal function outcomes of patients with malignant obstructive uropathy and to determine the predictors of poor renal function after urinary diversion.

Methods: A retrospective cohort study was conducted to collect data on 112 patients admitted in a tertiary training hospital in Metro Manila from January 2015 to January 2018. EpiInfo 6 was used to compute for the sample size. Both descriptive and inferential statistics were used to describe the baseline patient characteristics and to compare the pre- and post-urinary diversion renal function outcomes.

Results: The mean age of patients was 51.52 ± 11 years with majority being females, 96/112 (85.71%). The mean number of days from admission to urinary diversion was 10.31 ± 13.08 days while the mean hospital days from admission to discharge was 24.45 ± 16.38 days. In paired t-test, there was a significant improvement in the post-urinary diversion renal function parameters including BUN, creatinine, GFR, sodium, potassium, and calcium (all p-value < 0.05) but not albumin (p-value 0.0785). Recovery of renal function (i.e. creatinine reduction of more than 25% from baseline) was achieved by 79/103 (76.7%) of patients. On multiple linear regression, for every one year increase in age, there was a corresponding 0.81 ml/min/1.73 m^2 reduction in GFR (95% CI -1.35 - -0.27, p-value 0.004) while for every one day delay in urinary diversion from admission, there was a corresponding 1.09 ml/min/1.73 m^2 reduction in GFR (95% CI -1.86 - -0.31, p-value 0.007). On multiple logistic regression, the significant predictors of poor GFR (<60 ml/min/1.73 m^2) post-urinary diversion were age (OR 1.11, 95% CI 1.03-1.19, p-value 0.006) and number of days delay from admission to urinary diversion (OR 1.24, 95% CI 1.02-1.51, p-value 0.034).

Conclusions: Prompt urinary diversion significantly improved renal function outcomes. Urinary diversion should not be delayed especially in the older patient population.

TH-PO078

Immunophenotypic Analysis of Humanized Mouse Kidney in Comparison with Human Kidney

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Background: Most positive intervention studies in mice fail in human trials, in part due to fundamental differences between mice and humans. Humanizing mouse tissue aims to bring the mouse experimental model closer to human responses. Given the strong data supporting immune cells in acute kidney injury pathogenesis and repair, it is important to test relevance to humans. However, there is little information on immune phenotype of humanized mouse kidney in comparison to normal human kidney. We evaluated immune cell composition in the kidneys of two humanized mice strains and compared it to that of normal human kidney tissue.

Methods: For humanization, 4 week old NOG and NOGEXL female mice were irradiate (100 cGy) and $1x10^5$ human cord blood derived CD34+ hematopoietic stem cells transferred intravenously. Kidneys were harvested from well perfused humanized NOG (huNOG) and huNOGEXL mice, 20 weeks post engraftment. Normal human kidney samples were collected from visibly unaffected portion of nephrectomies from renal cell carcinoma. Kidney mononuclear cells isolated from mouse and human kidneys were analyzed for human CD45, TCR, CD4, CD8, CD20, CD16, CD14, CD11c and CD206 using flow cytometry. n=3/group each humanized mouse strain and human kidney.

Results: The frequency (mean%±SEM) of human CD45+ cells was higher (p=0.04) in huNOG (12.5±2.9) mouse kidney compared to normal human kidney (6.4±1.3). Similarly, the frequency of CD11c+ cells was higher (p=0.02) in huNOG (28.0±4.1) kidney compared to normal human kidney (17.8±1.4). The frequency of CD16+ cells was significantly reduced in both huNOG (7.6±5.5, p=0.03) and huNOGEXL (4.9±1.0, p=0.01) kidney compared to human kidney (31.5±6.3). CD8 T cell frequency was significantly lower (p=0.03) in huNOGEXL (17.2±2.6) compared to human kidney (34.8±4.4). There was no statistically significant difference in the frequency of TCR+, CD4+, CD20+, CD14+ and CD206+ cells between humanized mice kidney and human kidney.

Conclusions: These data demonstrate that huNOG and huNOGEXL kidneys have significant numbers of human immune cells. Furthermore, there are key similarities and differences between different background strains compared to human kidney. Humanizing mice to study kidney disease is a useful approach however it is important to know key strengths and limitations of this approach.

Funding: NIDDK Support

TH-PO079

Role of Toll Like Receptors in the Pathogenesis of Myeloma Kidney

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Background: Free light chains (FLCs) lead to kidney injury (KI) in myeloma patients. We previously demonstrated that inflammatory pathways triggered by endocytosis of FLCs in proximal tubule cells (PTCs) lead to KI. The role of innate immunity mediated by toll-like receptors (TLR) in FLC-associated KI has not been previously investigated. Here we present our initial observations on the role of TLRs in FLC-induced KI in PTCs *in-vitro*.

Methods: Human kidney PTCs cultures were exposed to κ and λ FLCs. Cell supernatant and pellets were used for ELISA and gene expression studies. Cell proliferation was checked through MTS assay. Data were analyzed using one-way ANOVA with post hoc Tukey test and P values <0.05 were considered significant.

Results: Both κ and λ FLCs induced TNFα secretion and suppressed proliferation of PTCs in a dose- and time-dependent manner. Several innate-immunity (TLRs 2, 3, 4, 6, 9, HMGB1, MYD88, TICAM1), inflammatory (IL6, IL18, IL1B, IL2, TNFα, TGFβ), apoptotic (BCL2, TP53), and KI markers (HAVCR1, ABCB1, LCN2) were assayed. Increased lipocalin 2 (LCN2) and decreased TP53 appeared as the most prominent KI biomarkers for both FLC subtypes. FLCs increased the expression of TLRs 2, 3, 4, 6 and 9, with marked increases in TLR4 gene and in HMGB1 protein levels. Our data show that HMGB1 significantly increases the expression of TLR4 gene in PTCs with or without FLCs exposure. Knock-down of HMGB1 through R, S- Sulforaphane inhibits FLC-induced TLR4 expression suggesting HMGB1 as a likely candidate damage-associated molecular pattern (DAMP) activating TLR4 in FLC exposed PTCs.

Conclusions: PTCs exposed to FLCs release HMGB1, which induces TLR4 expression and downstream inflammation leading to KI. TLRs may be novel diagnostic biomarkers and therapeutic targets for KI in myeloma.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO080

Kidney Proximal Tubular TLR9 Exacerbates Ischemic AKI

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Background: Ischemic acute kidney injury (AKI) is a major clinical problem. Although Toll-like receptor 9 (TLR9) mediates cell death and inflammation in the liver, the role for kidney TLR9 in ischemic AKI is unknown. Here, we tested the hypothesis that renal proximal tubular TLR9 activation exacerbates ischemic AKI by promoting renal tubular apoptosis and inflammation.

Methods: Wild type mice (WT, TLR9fl/fl) or renal proximal tubular TLR9 null mice (TLR9fl/fl PEPCK Cre) were subjected to sham surgery or 30min kidney ischemia/reperfusion (IR) injury. A separate cohort of mice was pretreated with a selective TLR9 agonist (1mg/kg ODN-1668) or control ODN and subjected to 20min renal IR injury. Cultured mouse proximal tubule cells or immortalized human proximal tubule (HK-2) cells were treated with a selective TLR9 agonist (1-5 μM ODN-BW006) to determine whether TLR9 activation induces renal proximal tubular pro-inflammatory cytokines and NFκB activation in vitro.

Results: Renal proximal tubular TLR9 null mice were protected against renal IR injury with decreased plasma creatinine (1.8±0.2mg/dL), NGAL mRNA (362.6±61.6 fold increase over sham), neutrophil infiltration and TUNEL positive cells compared to WT mice (Cr=2.6±0.1mg/dL, NGAL=667.6±122.3 fold increase over sham, N=8 for all groups). In addition, renal proximal tubular TLR9 deletion reduced pro-inflammatory cytokine synthesis, caspase 3 and 8 activation when compared to WT mice after renal IR injury. Consistent with this, a selective TLR9 agonist exacerbated renal IR injury in WT mice (Cr=1.4±0.1mg/dL, 0.93±0.04mg/dL of vehicle) but not in renal proximal tubular TLR9 null mice (Cr=0.7±0.02mg/dL, 0.73±0.02mg/dL of vehicle, N=5 for all groups). In HK-2 cells, a TLR9 selective ligand induced NFκB activation, pro-inflammatory cytokine mRNA synthesis as well as caspase 3 and 8 activation. In primary cultures of mouse proximal tubule cells from TLR9fl/fl PEPCK Cre mice, TLR9 selective ligand induced significantly less pro-inflammatory cytokine mRNA synthesis compared to cells from WT mice.

Conclusions: Taken together, our studies suggest that renal proximal tubular TLR9 activation exacerbates ischemic AKI by promoting renal tubular inflammation and apoptosis after IR via NFκB, caspase 3, and 8 activation. Our studies provide novel insight to the pathophysiology of kidney proximal tubule TLR9 in ischemic AKI, suggesting a potential therapy for ischemic AKI.

TH-PO081

Role of Interleukin-4 Receptor-JAK3-STAT6 Signaling in the AKI-to-CKD transition

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Background: Mineralocorticoid receptor (MR) antagonism is highly efficient to prevent both acute injury and the progression to chronic kidney disease (CKD) after an ischemic episode by enhancing a macrophage M2 polarization in the early post-ischemic phase and might be therefore an efficient repair mechanism. Interleukin-4 (IL-4) receptor activation in myeloid cells appears to be part of the protective mechanism. The exact contribution of IL-4 receptor downstream signaling potentially through JAK3-STAT6 in renal protection mediated by finerenone remains unclear. We tested the involvement of IL-4 receptor signaling induced by MR inhibition in the development of kidney fibrosis after an ischemic acute kidney injury (AKI) episode.

Methods: Thirty male C57/B6 mice were divided in: sham, renal ischemia for 22.5 min (IR), IR plus treatment with the non-steroidal MR antagonist finerenone (10 mg/kg) at -48, -24 and -1 h before IR and two groups of mice subjected to IR and receiving finerenone plus a STAT6 or JAK3 inhibitor. The mice were followed-up during 4 weeks to test for AKI to CKD transition. In another set of mice, the macrophages were sorted from kidneys after 24 h of reperfusion and flow cytometry characterization was performed.

Results: The progression of AKI to CKD after 4 weeks of renal ischemia in the untreated mice was characterized by a 40% increase in plasma creatinine, a 6-fold increase in proteinuria, severe tubule-interstitial fibrosis and increased mRNA levels of NGAL, Kim-1, alpha-SMA, fibronectin, TGF-beta and collagen-I. The mice that received finerenone were protected against all these alterations. MR inhibition promoted increased IL-4 receptor expression and phosphorylation in the whole kidney and in isolated macrophages. The protective effect conferred by MR antagonism was partially reversed by STAT6 inhibition as evidenced by a 5-fold increase in proteinuria and by the JAK3 inhibitor which partially reversed the tubule-interstitial fibrosis protection, and completely prevented the reduction in Kim-1 and fibrosis related gene expression.

Conclusions: Finerenone modulates the IL-4 receptor-JAK3-STAT6 signaling pathway, leading to macrophage phenotype switching and protection against AKI to CKD transition.

Funding: Government Support - Non-U.S.

TH-PO082

Mineralocorticoid Receptor Antagonism Prevents the Acute and Chronic Effects of Ischemic AKI in the Large White Pig

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Background: In rodent models of kidney ischemia/reperfusion (IR), mineralocorticoid receptor (MR) antagonism has shown beneficial effects against acute kidney injury (AKI) and its progression to chronic kidney disease (CKD); whether these findings might be translated to the human pathology remains to be clarified. The Large White pig is a useful

preclinical animal model to test the effectiveness of therapeutic strategies aimed to protect against AKI due to the kidney similarities between the human and the pig. In this study we evaluated the effect of MR antagonism against the acute and chronic effects of ischemic AKI in the Large White pig.

Methods: Eighteen Large White male pigs were divided in three groups: sham, pigs that received vehicle and underwent bilateral renal ischemia for 60 min and a group of pigs subjected to renal ischemia and receiving Soludactone (potassium canreonate). Soludactone (7mg/kg, i.v.) or vehicle doses were given at 48 h, 24 h and 30 min before the induction of the ischemia and 24 h and 48 h after reperfusion. Urine collection and blood sampling was carried out at days 1, 3, 5, 7, 11, 14 and 90. Kidney biopsies were taken at days 14 and 90.

Results: Renal IR induced kidney dysfunction in the untreated pigs at day 1 (plasma creatinine: 443±7 mmol/L). In contrast, the pigs that received canrenoate showed an impressive prevention of plasma creatinine elevation (145±3 mmol/L). Tubular injury was evidenced by a significant increase in urinary NGAL, KIM-1, L-FABP and NAG excretion and by histological abnormalities at day 14 (tubular injury and increased inflammatory infiltrate). Canreonate treatment decreased by 50% the excretion of these markers and prevented the histological damage. At day 90, the untreated pigs presented kidney fibrosis which was absent in the canreonate-treated pigs. Plasma creatinine was higher in untreated pigs at day 90 (120±2 mmol/L) as compared to the treated pigs (92±4 mmol/L)

Conclusions: MR antagonism is effective against the acute and chronic kidney dysfunction and structural injury in a preclinical model of AKI in the Large White pig. These findings support clinical trials testing the potential benefits of MRAs in AKI.

Funding: Government Support - Non-U.S.

TH-PO083

Knockout of Interleukin-36 Receptor Prevents Fibrosis in Mice Models of AKI-to-CKD Progression

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Background: IL-36, a newly named member of the IL-1 cytokine family, includes 3 isoforms, IL-36α, IL-36β, and IL-36γ, all of which bind to a heterodimer containing IL-36 receptor (IL-36R). Little is known about the role of the IL-36 axis in fibrosis during AKI to CKD progression. We examined IL-36 function using mice AKI to CKD models and clinical samples.

Methods: We evaluated IL-36 function in two models of AKI to CKD progression by using IL-36R knockout (KO) and wild-type (WT) mice. First model, left renal ischemia was performed for 35min and right kidney was removed 21days later, and left kidney analyses at 28 days (IRI). Second model, we used aristolochic acid toxic nephropathy (AAN) in mice at 28 days. We evaluate the renal function and histological analysis of KO and WT mice in both models. Fibrotic changes were evaluated by RT-PCR, Western blot analysis, and immunohistological analysis of collagen type IV, CTGF, and Masson trichrome staining. In clinical study, we performed immunohistological examination of IL-36α in AKI to CKD patients and minimal change renal biopsy sample.

Results: IL-36R was found to be expressed in the kidney mainly in proximal tubules in WT mice. IL-36R KO mice had significantly lower Cr and BUN at 28 days compared to WT mice in both models. Immunohistological examination showed mild tubular injury and fibrotic change in IL-36R KO mice compared to WT mice in both models. IL-36α/β/γ levels were increased after IRI and AAN, and IL-36α was expressed in lymphocytes and renal tubular cells. Immunohistologial analysis of collagen type IV and CTGF, and Masson trichrome staining revealed that massive fibrotic changes were observed in WT mice compared to KO mice in both models. Protein expression of collagen type IV and CTGF were also increased in WT mice compared to KO mice. Notably, IL-36α staining in renal-biopsy samples of AKI to CKD patients was enhanced.

Conclusions: Our results demonstrate that IL-36α is up-regulated in renal tissues in both mouse and human AKI to CKD transition, and that IL-36α stimulates collagen type IV and CTGF in AKI to CKD transition models. Thus, IL-36α/IL-36R blockage could serve as a potential therapeutic target in AKI to CKD transition.

TH-PO084

Deficiency of IKKα in Macrophages Mitigate the Fibrosis Progression of Kidney After Renal Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI) could lead to chronic kidney disease (CKD) and the macrophages play key roles in this process. The aim of this study was to the discovery the role of IκB kinase α (IKKα) in macrophages in the process of AKI-to-CKD transition.

Methods: We crossed lyz2-Cre mice with IKKa floxed mice to generate mice with IKKα ablation in macrophage (Mac IKKa-/-). Mice renal ischemia/reperfusion injury (IRI) model was induced by clamping the renal artery for 45 min. Treated mice were evaluated for blood biochemistry, tissue histopathology and epithelial mesenchymal transition (EMT) markers. Macrophages isolated from peritoneal cavity for co-culturing with tubular epithelial cells (TEC)and flow cytometry analysis.

Results: We found that mice with Mac IKKa-/- significantly alleviated the fibrosis and ameliorated the kidney function loss after IRI compare with wide type (WT) mice. The expression of EMT markers and the infiltration of M2 macrophages were decreased in kidneys of Mac IKKa-/- mice after IRI. The in vitro experiment showed that the IRI TECs co-cultured with IKKa-/- macrophages (KO MΦ) downregulated the EMT accompany with downregulating Wnt/β-catenin signal.

Conclusions: These data support the hypothesis that IKKα was involved in mediating the macrophage polarization and elevating the fibrotic promoting inflammatory factor in macrophages. So knockdown the IKKα in macrophage may be a potential method that can be used to alleviate the AKI-to-CKD transition after IRI.

TH-PO085

Divergent Sphingosine 1-Phosphate (S1P) Signaling Pathways Control Pericyte Function in AKI to CKD Transition

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Background: Acute kidney injury (AKI) can lead to chronic kidney disease (CKD). S1P, a sphingolipid that regulates AKI and fibrosis, is produced by two different kinases, sphingosine kinase (SphK) 1 and 2, and after its export can bind to S1P1-S1P5 receptors. S1P1, a key player during AKI and CKD, is expressed in both endothelial cells (EC) and pericytes (PC; *Foxd1Cre*$^{+}$) and plays an important role in angiogenesis and EC-PC communication. We showed previously that EC S1P1 is protective after ischemia reperfusion injury (IRI) and that the global *Sphk2 KO* has less fibrosis after AKI, however the role of S1P signaling in pericytes is unknown.

Methods: Folic acid (FA; 250 mg/kg) or vehicle (0.3 M $NaHCO_3$, Veh) was given ip to 12-14 wk old male *Foxd1Cre*$^{+}$*Sphk2*$^{fl/fl}$ (*Sphk2KO*), *Foxd1Cre*$^{-}$ *Sphk2*$^{fl/fl}$ (WT control), *Foxd1Cre*$^{+}$*S1P1*$^{fl/fl}$ (*S1P1KO*), and *Foxd1Cre*$^{-}$*S1P1*$^{fl/fl}$ (WT) mice. For IRI kidneys were clamped for 26 min ischemia followed by 24h reperfusion (8-10 wk old mice). AKI (24-72h) was assessed by plasma creatinine (PCr), blood urea nitrogen (BUN), qPCR (*Kim-1* and *Ngal*) and histology (H&E staining). 14 days after injection of FA or Veh to *Sphk2* mice, PCr and BUN were measured, and kidneys were analyzed for fibrosis by picrosirius red staining and by qPCR for expression of fibrotic markers.

Results: After bilateral IRI, in *S1P1KO* mice PCr was lower than in WT (0.91 vs. 0.55). After FA, in *S1P1KO* mice PCr was lower (0.78 vs. 0.23 mg/dl, $p<0.05$), as was ATN score (78.6 vs. 53.6%, $p<0.05$), Kim1 (0.63 vs. 0.33 $p<0.01$) and Ngal (0.85 vs. 0.50, $p<0.05$). There was no difference between Sphk2KO and its WT control in PCr, BUN, *Kim-1, Ngal* or histology (days 1-3). However, by day 14, FA-treated *Sphk2KO* mice had less fibrosis (by histology), smaller increases in BUN (39.6 vs. 55.5 mg/dL, $p<0.05$), and smaller increases in expression of fibrosis-related genes (Col1a1, Col3a1, Acta2, fibronectin, and vimentin) than WT control mice.

Conclusions: These divergent results suggest that: 1) sphingolipid signaling through *SphK2* and *S1P1* in perivascular cells is critical in controlling the phenotype in AKI and CKD and 2) controlling intracellular S1P through sphingosine kinases and extracellular *S1P1* may serve as specific therapeutic targets in both AKI and AKI-CKD transition.

Funding: NIDDK Support

TH-PO086

Neutrophil Depletion Alters Macrophage (Mo) Phenotype and Modulates Inflammation in Unilateral Ureteral Obstructed (UUO) Kidney

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Background: UUO is a model to study inflammation and fibrosis in the kidney. Neutrophils (Neu) are the first line of defense in response to injury. Mo closely coordinate with Neu to regulate inflammation. This study investigated if neutrophil depletion can alter macrophage infiltration and inflammation in UUO fibrosis.

Methods: UUO surgery was done by the method adapted from the Vanderbilt O'Brien Center. Neutrophil depletion was done by injecting clone 1A8 to a cohort of five mice labeled (ND), 3 days pre and 2 days post UUO. An equal number of mice underwent UUO but did not receive any treatment (UT). Contralateral kidneys were used as control (C). Mice were sacrificed 3 days and 10 days after UUO. Neu, Mo, and macrophage phenotype M1 and M2 were determined by flow cytometry. Inflammation markers MCP1, IL1β, and fibrosis marker α-smooth muscle actin (SMA) were assessed by immunoblot.

Results: There was no significant influx of Mo and trace levels of inflammatory markers in C, hence comparison was made between ND and UT. 3 days after UUO, Neu levels in the blood and kidney of UT were 28% and 60% respectively. In contrast, Neu levels in ND blood and kidney was <1% and <12% respectively, suggesting significant neutrophil depletion. 3 Day UUO: Mo influx in the kidney of ND was significantly lower than UT. The M1 phenotype in UT was 1.5 fold higher ($p<0.05$) and M2 phenotype was 2 fold lower than ND ($p<0.05$). Kidney MCP-1 and IL-1β of UT was 3 fold ($p<0.01$) and 2.5 fold ($p<0.01$) higher than ND, respectively. Kidney SMA was not significantly altered between the groups. 10-day UUO: The M1 phenotype in UT was still 1.5 fold higher ($p<0.05$) than ND but the difference in M2 phenotype between UT and ND was not significant. MCP-1 and IL-1β were 2 and 1.5 ($p<0.05$) fold higher in UT, suggesting sustained inflammation in UT. SMA levels in the ND kidney were 1.8 fold higher than UT but was not statistically significant.

Conclusions: Chronic inflammation frequently leads to fibrosis, however, the mechanisms are not clearly understood. In the ND cohort the decrease in M1 phenotype (thought to be proinflammatory) and increase in M2 (reparative type) following neutrophil depletion can explain the reduced inflammation but not fibrosis. This suggests controlling inflammation at an early stage may not positively modulate fibrosis.

TH-PO087

Selenoprotein-T Exerts a Protective Role in Cisplatin-Induced AKI by Suppression of ER Stress

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Background: Selenium (Se) is an essential trace element with important roles in human health. Acute kidney injury (AKI) as well as chronic kidney disease are often associated with low serum and tissue levels of Se. Se is incorporated with a wide range of Se-dependent enzymes, also known as selenoproteins, at its active site. Selenoprotein-T (Sel-T), a member of the selenoprotein family, is a novel thioredoxin-like enzyme. However, it's role, especially in ER stress, during renal disease remains unexplored. In this study, we aim to explore the role of Sel-T in the pathogenesis of cisplatin-induced AKI.

Methods: Twenty C57 mice were randomly divided into four groups (n=8-10): sham, AKI-1d, AKI-2d and AKI-4d. Western blot or immunohistochemistry was used to detect the expression of Sel-T, NGAL, cleaved-caspase-3, caspase-12, Bax, Bcl-2 and GRP78. In vitro, NRK-52E cells were exposed to cisplatin (20uM) for 6h, 12h and 24h respectively. Lentivirus transfection or non-specific Sel-T agonists, PACAP and db-cAMP, were utilized to regulate Sel-T before cisplatin stimuli. Flow cytometry and commercial kit were adopted individually for apoptosis and ROS detection.

Results: Comparing to sham groups, the expression of Sel-T was significantly down-regulated in the AKI-4d group. Meanwhile, the levels of NGAL, cleaved-caspase-3 and Bax were increased with the reduction of Bcl-2. Consistently, in vitro Sel-T was lessened, especially after 24h of cisplatin exposure. And Sel-T deficiency aggravated cisplatin induced ER-stress as well as cell apoptosis and ROS generation in NRK-52E cells. Pretreatment of non-specific Sel-T agonists ameliorated the ER stress in cisplatin group.

Conclusions: Sel-T deficiency is occurred in cisplatin-induced AKI in which ER stress-associated apoptosis and oxidative stress are the underlying mechanisms. Hopefully, Sel-T agonists may be effective remedies for cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

TH-PO088

TGF-β Promotes Fibrosis After Severe AKI by Enhancing Renal Macrophage Infiltration

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Background: TGF-β, a central mediator of renal fibrosis, signals through a heterotetrameric receptor complex composed of two type I and two type II transmembrane subunits. Although macrophages are implicated as mediators of renal fibrosis and produce TGF-β1, macrophage TGF-β1 deletion did not prevent fibrosis after severe renal I/R injury. The current studies investigated the role of macrophage TGF-β signaling in post AKI fibrosis.

Methods: Male C57BL/6 wild type (WT, $Tgfbr2^{f/f}$) or LysM-Cre;$Tgfbr2^{f/f}$ ($TGF\beta RII^{-/-}$) mice underwent uninephrectomy plus 29 min renal I/R and were sacrificed after 4 weeks. Both in vitro and in vivo chemotaxis assays were performed.

Results: At 4 weeks after injury, there was increased renal expression of TGF-ß1 and tubulointerstitial fibrosis in WT mice. TGFßRII-/- mice had markedly decreased renal fibrosis and decreased renal macrophages. TGF-ß is a potent chemoattractant. The *in vitro* chemotactic response to a known chemotaxin, f-Met-Leu-Phe, was not different between isolated bone marrow monocytes (BMMs) from WT and TGFßRII-/- mice. Although TGF-ß was also a potent chemoattractant to WT BMMs, TGFßRII-/- BMMs did not respond. The SMAD inhibitor, SIS3, markedly inhibited the chemotactic response to TGF-ß in WT BMMs, but had minimal effect in TGFßRII-/- BMMs. To confirm these findings in an *in vivo* setting, we utilized a chemotaxis assay using matrigel plugs. Matrigel suffused with either f-Met-Leu-Phe or TGF-ß1 was injected subcutaneously into the subscapular regions of WT or TGFßRII-/- mice. After 6 days, f-Met-Leu-Phe induced equal numbers of macrophage infiltration into the matrigel plugs of WT and TGFßRII-/- mice. TGF-ß also induced matrigel macrophage infiltration in WT mice but not in TGFßRII-/- mice. To determine macrophage infiltration into post AKI kidneys, we determined the number of PKH26 labeled BMMs infiltrating into WT kidneys for 3 days 12 days after AKI. There were significantly more PKH26 labeled WT BMMs than TGFßRII-/- BMMs.

Conclusions: Macrophage TGFßRII deletion protects against the development of tubulointerstitial fibrosis following severe ischemic renal injury. Chemoattraction of macrophage to the injured kidney through a TGF-β/TGFßRII axis is a heretofore undescribed mechanism by which TGF-ß can mediate renal fibrosis during progressive renal injury.

Funding: NIDDK Support

TH-PO089

Inhibition of H3K4 Trimethylation Attenuates Renal Senescence in Mice with Ischemic Reperfusion Injury

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Background: Renal senescence is induced by not only aging, but also various stimuli, and plays important roles in the development of renal inflammation and fibrosis. Recently, accumulation of $p16^{INK4a}$-positive cells in the kidney has been considered a molecular feature of renal senescence, which is regulated by Mixed-lineage leukemia 1 (MLL1)/WD-40 repeat protein 5 (WDR5)-mediated histone 3 lysine 4 trimethylation (H3K4me3). In this study, we investigated whether MLL1/WDR5 complex inhibitor MM-102 attenuates renal senescence together with renal inflammation and fibrosis in ischemic reperfusion injury (IRI) mice and cultured renal fibroblasts.

Methods: Male C57BL/6 mice were subjected to IRI (renal pedicle was clamped for 30 minutes), and administered MM-102 every 24 hours for 7 days postoperatively. Expression of MLL1, WDR5, H3K4me3, and $p16^{INK4a}$ was examined by western blotting and immunohistochemistry. Senescence-associated β-galactosidase (SA-β-gal) staining was performed as a senescence marker. Renal fibrosis was examined by the expression of transforming growth factor (TGF)-β1, α-smooth muscle actin (αSMA), and collagens. The effect of MM-102 on inflammation was investigated by the expression of nuclear factor-κB (NF-κB), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and CD11b. For the *in vitro* study, TGF-β1-stimulated normal renal fibroblasts with and without MM-102 preincubation were examined for expression of MLL1, WDR5, H3K4me3, and $p16^{INK4a}$. Chromatin immunoprecipitation assays were performed to clarify the status of $p16^{INK4a}$ gene promoter as an H3K4me3-enrichment region.

Results: MM-102 suppressed expression of $p16^{INK4a}$ and β-gal in IRI mice, accompanied by decreased expression of MLL1 and WDR5 as well as H3K4me3. MM-102 also attenuated renal fibrosis and inflammation in the kidneys of IRI mice. In the *in vitro* study, TGF-β1 induced expression of MLL1, WDR5, H3K4me3 and $p16^{INK4a}$. Finally, the $p16^{INK4a}$ promoter was revealed to be an H3K4me3 site in renal fibroblasts.

Conclusions: The MLL1/WDR5 inhibitor MM-102 ameliorates IRI-induced renal senescence together with renal fibrosis and inflammation through a reduction in H3K4me3.

Funding: Government Support - Non-U.S.

TH-PO090

Long-Term Sequelae of AKI: A Year-Long Male and Female Murine Model

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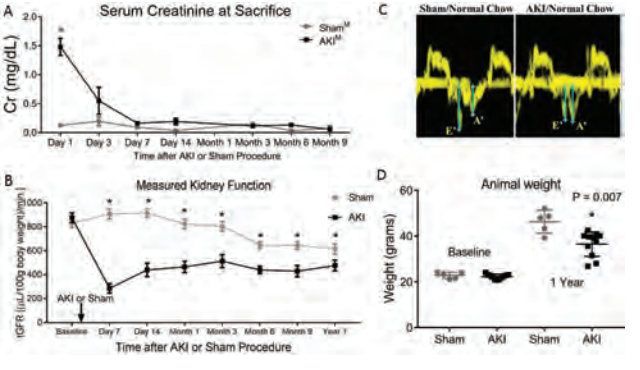
Background: There is growing appreciation that acute kidney injury (AKI) leads to systemic sequelae as well as chronic kidney disease (CKD), however most murine models of disease evaluate AKI and CKD as distinct entities, thus limiting their translational value. Herein, we performed a 1 year study of male and female BLK6 mice to determine the long-term renal and systemic sequelae of AKI.

Methods: Male and female adult BLK6 mice underwent bilateral ischemia reperfusion injury or sham procedure. Female mice underwent longer clamp times (34 min compared to 24 min) to overcome the protective effects of estrogen. Renal and systemic outcomes were tracked longitudinally in the males (1, 3, 7, 14 days, 1, 3, 6, 9, and 12 months) and at 12 months in the females.

Results: Measurements of glomerular filtration rate (tGFR), systemic inflammation, and diastolic dysfunction remained abnormal for the duration of the study.

Conclusions: Despite early normalization of serum and urine biomarkers of renal function, long-term renal and systemic sequelae were evident in both the male and female cohorts following AKI.

Funding: Private Foundation Support



Representative data from the male cohort of AKI vs sham. (A) serum creatinine normalizes within several days following bilateral ischemia-reperfusion injury. (B) Measured transcutaneous glomerular filtration rate (tGFR) remains persistently low in the AKI group compared to sham. (C) Echocardiography demonstrates diastolic dysfunction with inversion of A' E' following AKI. (D) 1 year after AKI, mice weigh less than mice that underwent sham procedure.

TH-PO091

AKI to CKD Transition After Acute Cardiorenal Syndrome in the Mouse

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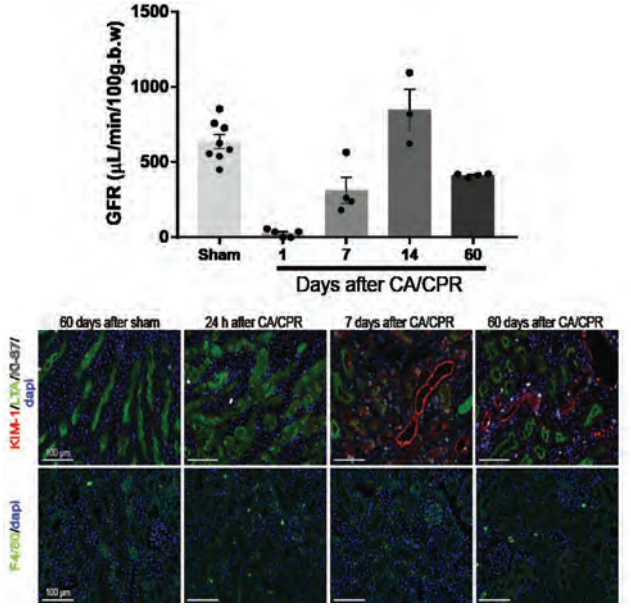
Background: Acute cardiorenal syndrome (CRS type 1, CRS1) is an common cause of acute kidney injury (AKI) with high mortality and significant potential to transition to chronic kidney disease (CKD). Mechanistic data from translational models is lacking. We report AKI-to-CKD transition following CRS1 in a mouse model, accompanied by long-term renal inflammation.

Methods: CRS1 was modeled in male C57BL/6 mice (n=16) using potassium-induced 8 minute cardiac arrest followed by cardiopulmonary resuscitation (CA/CPR) and compared with sham (n=8). α-smooth muscle antibody, KIM-1, cleaved caspase-3, Ki-67, macrophage F4/80, and CD3 were quantified from immunohistology 1, 7, 14, and 60 days later. Glomerular filtration rate (GFR) was measured by FITC-sinistrin transcutaneous clearance and serum urea nitrogen by autoanalyzer.

Results: Sham survival was 100%. 24h survival after CA/CPR was 100% and 60 day survival was 88%. CA/CPR induced severe AKI with near-zero GFR at 24h, and early macrophage infiltration demonstrated by robust F4/80 signal. 7 days after CA/CPR, KIM-1, F4/80, and CD3 revealed severe tubular injury, predominantly of proximal tubules, and inflammation with extensive cell proliferation, although GFR was recovering. At 14 days, GFR had normalized, but at 60 days GFR was again significantly below baseline, accompanied by elevated serum urea nitrogen, continued macrophage and t-cell infiltrate, apoptotic cell death, and widespread tubulointerstitial fibrosis.

Conclusions: Acute cardiorenal syndrome induces extensive tubular injury and inflammation in the renal cortex and outer medulla which progresses to renal fibrosis and chronic kidney disease despite initial functional recovery. We present a clinically relevant mouse model of AKI-CKD transition which we expect to provide insight into the the mechanisms underlying renal sequelae of cardiac arrest.

Funding: NIDDK Support, Veterans Affairs Support



TH-PO092

Binding of Cell Surface Carboxypeptidase M Contributes to Tubulo-Protective Effects of Fibrinopeptide Bß15-42

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Background: Acute and chronic kidney disease is often associated with activation of the coagulation cascade and with parallel activation of the fibrinolytic system. During fibrinolysis the peptide Bβ15-42 is cleaved off the end of the fibrin Bβ chain. Previous studies have demonstrated a protective effect of Bβ15-42 in sepsis, myocardial infarction and renal ischemia/reperfusion. The responsible molecular mechanism was attributed to binding of Bβ15-42 to endothelial VE-cadherin. Our preliminary work had shown that Bβ15-42 also has a direct protective effect on renal tubular cells. It was the goal of the present study to clarify this VE-cadherin independent mechanism.

Methods: Repetitive doses of Bβ15-42 (3 mg / kg i.v.) or control peptide were tested in vivo in unilateral ureteral obstruction (UUO) and in aristolochic acid nephropathy (AAN). Kidneys were examined at different time points by histomorphology and damage marker expression. In vitro, renal tubular cells were stressed by AA or staurosporine before treatment with Bβ15-42 or control peptide. Target proteins were knocked-down by siRNA and cell damage was quantified by LDH release and qPCR. Bβ15-42 binding partners were identified by ligand-receptor capture (LRC) technology LRC-TriCEPS. Carboxypeptidase M activity was measured by Dansyl-Ala-Arg-OH trifluoroacetate assay.

Results: In vivo, Bβ15-42 improved the tubular damage pattern after induction of AAN and after UUO. To identify potential new Bβ15-42 interaction partners on tubular cells, we used LRC-TriCEPS and found the membrane protein carboxypeptidase M (CBPM) as a highly specific binding partner. Despite its strong tubular expression the physiological role of renal CBPM which modifies a variety of candidate signal peptides by C-terminal cleavage is unknown. CBPM enzymatic activity was significantly inhibited by Bβ15-42, both in vitro and in vivo. Knockdown of CBPM by siRNA resulted in a marked reduction in the protective effect of Bβ15-42.

Conclusions: The fibrinopeptide Bβ15-42 has a direct protective effect on tubular epithelial cells, which is largely determined by binding to CBPM and inhibition of CBPM enzymatic activity. Our results show a novel mode of action for Bβ15-42 and suggest that CBPM may represent a new target that can be used therapeutically for nephroprotection.

TH-PO093

Loss of Proximal Tubular Krüppel-Like Factor 6 Is Protective Against Renal Injury

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Background: Transcriptional regulators of DNA-damage pathways leading to kidney fibrosis are relatively unknown. Krüppel-like factor 6 (KLF6), a zinc finger transcription factor, has diverse roles in various tissues. KLF6 is highly expressed in the proximal tubule (PT) and upregulated in renal ischemia-reperfusion injury and sepsis models, but its specific role in PT DNA damage and tubulointerstitial fibrosis is unknown. Our aim was to investigate the role of PT KLF6 in the setting of DNA damage, using the PT-specific DNA damaging toxin aristolochic acid I (AAI).

Methods: PT-specific *Klf6* knockdown (*Klf6^{PTKO}*) mice were generated by breeding *Klf6$^{fl/fl}$* and *Pepck*-Cre mice. *Klf6$^{fl/fl}$* littermates were used as controls. Mice were given 3mg/kg AAI or vehicle DMSO i.p. every 3 days for 3 weeks (active phase), followed by 3 weeks without injections (remodeling phase), and euthanized. Renal damage was assessed by: serum creatinine and urea nitrogen (SUN); histology (H&E, PAS and trichrome staining with blinded scoring for inflammation and fibrosis); IF for deposition of collagen 1A1 (COL1A1); and qRT-PCR for vimentin and E-cadherin expression. RNA-Seq was undertaken in active and remodeling phase samples. Data were analyzed using ANOVA with corrections for multiple comparisons.

Results: AAI caused renal damage and significantly increased serum creatinine and SUN in all mice. These were significantly lower in *Klf6^{PTKO}* mice versus *Klf6$^{fl/fl}$* mice in the acute phase, with lower vimentin expression, and preserved PT area and E-cadherin expression. In the remodeling phase, *Klf6^{PTKO}* kidneys had maintained weight, preserved PT area and less inflammation, fibrosis, COL1A1 deposition and vimentin expression, compared to *Klf6$^{fl/fl}$* kidneys. RNA-Seq combined with ENCODE ChIP-Seq data showed that many integrin signaling components that contribute to fibrosis were upregulated by AAI in *Klf6$^{fl/fl}$* mice, which was reversed in *Klf6^{PTKO}* mice with AAI, and contain KLF6 binding sites. Likely protective genes were upregulated by AAI and upregulated further in *Klf6^{PTKO}* mice, e.g. Gas6, which has a predicted KLF6 binding site.

Conclusions: PT-specific loss of KLF6 protects against renal injury and fibrosis in the setting of DNA damage. This may have relevance for DNA damaging nephrotoxic chemotherapeutic drugs e.g. cisplatin.

Funding: NIDDK Support

TH-PO094

Using Transdermal Measurement of GFR to Evaluate Long-Term Outcomes in Mouse Models of AKI

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Background: There are no specific treatments for patients with acute kidney injury (AKI). In part this relates to the preclinical studies that have been used to assess therapeutic efficacy: these are often short-term studies, commonly using cisplatin or ischemia reperfusion (IR) injury. However, to identify target populations with meaningful long-term outcomes, therapeutic efficacy should be tested in a range of models over longer periods, including the long-term effects of therapy on the development of progressive chronic kidney disease (CKD) after episodes of AKI.

Methods: We established a range of mouse models of AKI that reflect the diverse injuries seen in human AKI and allow long-term functional analyses of CKD progression: 1) unilateral IR with a delayed contralateral nephrectomy (Nx), modeling profound renal hypoperfusion; 2) repeat-dosing cisplatin, modeling the injury in patients receiving cisplatin chemotherapy; 3) reversible UUO with delayed contralateral Nx, modeling the relief of urinary obstruction; and 4) rhabdomyolysis, modeling crush injury, sepsis and cardiopulmonary bypass-associated AKI. We are currently developing new models in female and diabetic mice, to recapitulate more complex clinical scenarios. To evaluate the effects of these injuries on CKD progression, we used transdermal monitors to assess glomerular filtration rate (GFR) in conscious mice by detecting the clearance of exogenous FITC-sinistrin through the skin 26-46 days after the initial injury.

Results: Here, we present for the first time, data on the long-term effects of AKI on GFR in multiple mouse models of AKI. GFR was significantly reduced in several models, but not in the rhabdomyolysis model (Table).

Conclusions: We have assessed the use of transdermal GFR measurement in a range of mouse models of AKI. This method of assessing renal function is more clinically relevant than standard methods and will be useful for preclinical efficacy testing of novel therapeutics on long-term renal outcomes in mouse models of AKI.

Funding: NIDDK Support, Other U.S. Government Support

Transdermal GFR measurement in a range of mouse models of AKI

Injury Model	Mean GFR (µl/min)		p-value
	Control mice	Injured mice	
IR-AKI with delayed Nx (day 26)	306.21 n=5	153.16 n=5	0.0001
Repeat-dosing cisplatin (day 26)	355.84 n=4	180.63 n=7	0.0133
Reversible UUO (day 46)	432.54 n=4	166.02 n=9	<.0001
Rhabdomyolysis (day 26)	314.50 n=6	266.48 n=8	0.1395

TH-PO095

Myo-Inositol Oxygenase Promotes Ferroptosis in Cisplatin-Induced AKI

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Background: Over-expression of myo-inositol oxygenase (MIOX), a kidney tubular specific enzyme, exacerbates renal redox injury in cisplatin-induced AKI. Recently, a newly coined term, i.e., ferroptosis, has been reported, which is closely associated with lipid peroxidation and it plays a significant role in the pathogenesis of AKI. Whether or not MIOX exacerbates tubular damage by accelerating ferroptosis in cisplatin-induced AKI needs to be investigated.

Methods: CD1 mice were subjected to intraperitoneal cisplatin injection with or without Fer-1, a potent ferroptosis inhibitor. Samples were collected for various studies three days later.

Results: Fer-1 substantially decreased the blood creatinine and urine protein excretion, and ameliorated renal pathological changes in cisplatin-treated mice. Wild-type (WT) mice, MIOX-overexpressing transgenic (MIOX-TG) mice and MIOX-Null (MIOX-KO) mice were injected with cisplatin. In comparison to cisplatin-treated WT mice, MIOX-TG mice had a relatively greater increase in blood creatinine and urine protein excretion, and severe renal pathological changes. These perturbations were minimal in cisplatin-treated MIOX-KO mice. Various ferroptosis metabolic sensors, including lipid peroxidation, GPX4 activity, NADPH, GSH, ferritinophage, mitochondrial deformation and lysosomal permeability, had undergone severe perturbations in MIOX-TG compared to WT mice, and these were not observed in MIOX-KO mice. In vitro studies revealed that cisplatin-induced HK-2 cell death was considerably reduced by Fer-1, DFO (iron cleator), and VAD (apoptosis inhibitor), but not by Nec-1 (necroptosis inhibitor). Also, cisplatin-treated HK-2 cells had severe perturbations in ferroptosis metabolic sensors, which were further accentuated by transfection of MIOX-pcDNA, while ameliorated by MIOX-siRNA.

Conclusions: In conclusion, these findings indicate that ferroptosis, conceivably integral to the pathogenesis of cisplatin-induced AKI, is modulated by the expression of MIOX.

Funding: NIDDK Support

TH-PO096

Cisplatin-Induced AKI Is Attenuated in Hepatic Sulfotransferase (Sult) 1a1-Deficient Mice by Suppressing Production of Indoxyl Sulfate (IS) and Oxidative Stress

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Background: The toxicological process leading to cisplatin-induced AKI is caused by several mechanisms, including inflammatory responses, oxidative stress and apoptosis in renal tubules. We have reported that IS, a sulfate-conjugated uremic solute, accumulates extensively in serum and kidney of animal models of cisplatin AKI. IS is derived from the liver through metabolic process by hepatic CYP2A6/2E1 and Sult1a1, however, pathophysiological role of Sult1a1 in cisplatin AKI has not been elucidated. We generated the Sult1a1 gene-deficient mice (Sult1a1$^{-/-}$), and evaluated the toxico-pharmacological role of IS in cisplatin AKI.

Methods: C57BL/6 mice (WT) and Sult1a1$^{-/-}$ were treated with cisplatin (20 mg/kg) by intraperitoneal injection. In additional experiments, Sult1a1$^{-/-}$ were treated with IS after cisplatin administration. Gene expression of Sult1a1 and other Sult species were determined by qRT-PCR. IS and indoxyl-β-D-glucuronide (IG) levels were determined by LC-MS/MS. Accumulation of IS and 4-hydroxy-2-nonenal (4-HNE), an oxidative stress marker, in renal tissue were examined immunohistochemically. BUN, serum creatinine, Kim-1 and Ngal were determined. Cisplatin concentration in serum and kidney was measured as the ^{194}Pt levels using ICP-MS.

Results: Sult1a1 mRNA expression was not detected in the liver of Sult1a1$^{-/-}$, and was significantly elevated (5.9-fold) in WT liver with cisplatin AKI, whereas mRNA expression of other Sult gene family members were not significantly differed between WT and Sult1a1$^{-/-}$ after cisplatin treatment. In cisplatin-treated Sult1a1$^{-/-}$, kidney injury markers, renal IS level and 4-HNE accumulation were markedly reduced compared with those in WT kidney. IG concentrations in serum and kidney were elevated in cisplatin-treated Sult1a1$^{-/-}$, suggesting that glucuronidation serves as an alternative detoxification pathway for indoxyl. Administration of IS to cisplatin-treated Sult1a1$^{-/-}$ reproduced severe AKI as observed in WT. Renal accumulation of ^{194}Pt showed no significant difference between Sult1a1$^{-/-}$ and WT.

Conclusions: IS could be one of exacerbation factors in cisplatin AKI by accelerating oxidative stress. Hepatic Sult1a1 was the enzyme responsible for deriving IS, suggesting a potent preventive target for cisplatin nephropathy.

Funding: Government Support - Non-U.S.

TH-PO097

MUTYH, a DNA Repair Enzyme, Protects Against Cisplatin-Induced AKI

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Background: MutY homolog (MUTYH) is a DNA Repair Enzyme and plays a key role in base excision repair (BER) for mitochondria (type I MUTYH works for mitochondrial DNA repair) and nuclear genome (type II MUTYH works for nuclear DNA repair). The current study aimed to evaluate the role of MUTYH in cisplatin-induced acute kidney injury.

Methods: *In Vivo*, Male MUTYH-/- mice and littermate WT controls were treated with cisplatin (20 mg/kg, ip). *In vitro*, mouse proximal tubular cells (mPTCs) with stable overexpression of MUTYH I or II were treated with cisplatin (5 mg/mL).

Results: In WT mice, cisplatin strikingly reduced MUTYH protein expression by 40%. MUTYH deficiency aggravated cisplatin-induced renal dysfunction (Scr: MUTYH -/- 112.5±18.8 vs. WT 33.60±9.14 mM, p<0.01; BUN: MUTYH -/- 67.65±4.0 vs. WT 37.83±4.99 mM p<0.01). Meanwhile, the renal tubular injury markers of KIM-1 and NGAL in MUTYH -/- mice were also further enhance by 191% and 94.11%, respectively, as compared with the WT mice after cisplatin treatment. The levels of cleaved caspase-3 and the number of TUNEL-positive cells in the kidneys of cisplatin-treated MUTYH-/- mice were higher than those in the kidneys of WT mice, showing the aggravated apoptotic response. Moreover, MUTYH deficiency resulted in the accumulation of 8-OHdG (indicating more severe DNA damage) and the aggravation of mitochondrial dysfunction. *In vitro*, Overexpression of type II MUTYH strikingly ameliorated cell apoptosis and oxidative stress induced by cisplatin, while MUTYH I overexpression showed a marginal role against cisplatin-induced cell injury.

Conclusions: MUTYH II but not MUTYH I played a significant role in protecting against cisplatin-induced acute kidney injury. Targeting type II MUTYH could be a promising strategy for the treatment of AKI.

TH-PO098

Treatment of Cisplatin-Induced AKI with Renal Selective Nanotherapy

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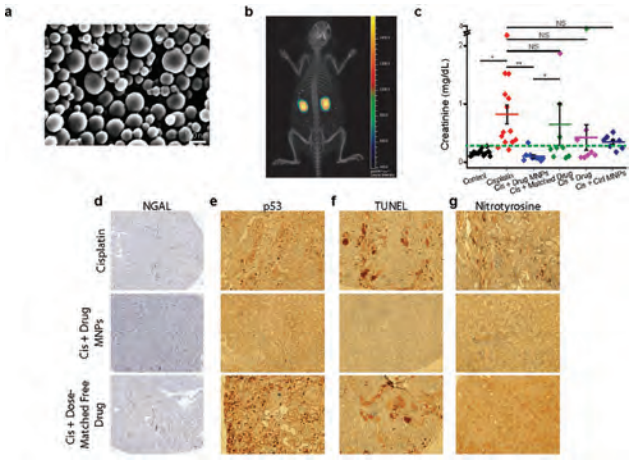
Background: Acute kidney injury (AKI) occurs in up to 30% of patients treated with cisplatin and up to 25% of patients in intensive care. AKI is linked to increased morbidity and mortality. Unfortunately there are no effective interventions for the treatment or prevention of AKI in humans. In prior work, we developed mesoscale nanoparticles (MNPs) that selectively localize to the kidneys primarily to the proximal tubular epithelium. We hypothesize that these MNPs can be used a delivery platform of small molecules for the treatment of AKI.

Methods: We synthesized nanoparticles from poly(lactic-*co*-glycolic acid) and polyethylene glycol (PLGA-PEG) which were encapsulated with the reactive oxygen species scavenger edaravone. The particles are approximately 400 nm in diameter with a negative surface charge. AKI was induced wit cisplatin induction (25 mg/kg IP) followed by intravenous injection of therapeutic MNPs (50mg/kg) loaded with edaravone(3.9 mcg/100 mg MNP) or the free drug alone 24 hours after induction of AKI. Mice were sacrificed after 72 hours.

Results: Compared to cisplatin alone, mice treated with drug-encapsulating MNPs had a significant reduction in serum creatinine. We stained for the renal injury marker NGAL, DNA-damage induced protein p53, TUNEL for apoptosis, and nitrotyrosine for oxidative stress. In each, we found significantly increased injury and staining in mice with cisplatin alone or cisplatin plus dose-matched free drug, with reduced or baseline levels in mice receiving therapeutic MNPs.

Conclusions: These studies demonstrate the therapeutic efficacy of our MNP as a delivery system of drugs to the proximal tubules for the treatment of cisplatin induced AKI. This approach may result in the development of novel therapeutic strategies for patients affected by AKI of different etiologies.

Funding: Other NIH Support - NCI



a) Electron micrograph of MNPs. b) MNP localization to the kidneys c) Serum creatinine in mice treated with therapeutic nanoparticles or edaravone

TH-PO099

C-Terminal Binding Protein 2 (CtBP2), a NADH-Dependent Transcription Regulator Contributes to Renal Cell Dysfunction and AKI

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Background: Worldwide, acute kidney injury (AKI) occurs in more than 13 million patients annually. AKI is associated with high short-term morbidity, a long-term risk of chronic kidney disease (CKD) as well as adverse cardiovascular events. Mechanistically, renal tubular cell dysfunction and cell death is the hallmark and the underlying cause of AKI. However, the transcriptional regulators that control shifts in epithelial cell gene expression that triggers renal tubular cell death and dysfunction remain underexplored. Here we have examined the role of NADH-dependent transcription regulator C-terminal binding protein 2 (CtBP2) in the pathogenesis of AKI.

Methods: We have used three AKI-associated mouse models, namely cisplatin nephrotoxicity (30 mg/kg, i.p.), rhabdomyolysis (50% glycerol, 7.5 ml/kg, i.m.) and ischemia reperfusion injury (30 bilateral ischemia) and determined the mRNA and protein expression of CtBP2 during kidney injury. Furthermore, we have examined the effect of CtBP2 inhibition on AKI by using a pharmacological inhibitor (MTOB) and CtBP2-specific siRNA knockdown (hydrodynamic intravenous injection). Finally, to uncover the associated mechanisms, we carried out chromatin-immuno-precipitation (ChIP) experiments and gene expression analysis to identify CtBP2 target genes in renal epithelial cells.

Results: Renal protein expression analysis showed that CtBP2 levels are very low in normal murine kidneys. However during the early phase of cisplatin, ischemia or rhabdomyolysis induced AKI, there is a striking increase in CtBP2 protein expression in renal epithelial cells. Functional *in vivo* studies showed that pharmacological or genetic inhibition of CtBP2 function significantly mitigates renal impairment (BUN, Serum Creatinine and renal damage score, Control vs. CtBP2 inhibition group, $p>0.05$) in all the three mouse models of AKI. Through ChIP and RNA expression analysis, we have identified a CtBP2 target gene expression signature that likely contributes to renal dysfunction associated with AKI.

Conclusions: Here we have identified CtBP2 as an essential regulator of renal dysfunction and AKI. Future development of CtBP2 targeting small molecules could provide a therapeutic strategy for the prevention or treatment of AKI.

Funding: Private Foundation Support

TH-PO100

PGC1α in Complex Models of AKI

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Background: Acute kidney injury (AKI) in patients is often complex, arising in the context of background chronic kidney disease (CKD) or even recent AKI from a different etiology. In experimental models of simple AKI, we have identified a critical role for the mitochondrial biogenesis regulator PPAR-γ coactivator-1α (PGC1α) in resistance to and recovery from AKI. Renal PGC1α expression is markedly reduced in both septic and post-ischemic mice. And PGC1α knockout (KO) mice suffer worse renal function and overall survival after transient renal ischemia, whereas PGC1α induction in the renal tubule improves AKI recovery and survival. The potential role for PGC1α in a more translatable "multi-hit" experimental model of AKI, however, remains unexplored.

Methods: 1st AKI insult: PGC1α KO and WT mice underwent 15 minutes of bilateral renal ischemia. Serum creatinine measurements were collected at 24 hours, 1 month, and 6 months after ischemia reperfusion injury (IRI). 2nd AKI insult: Six months following the initial renal IRI, mice were administered cisplatin (intraperitoneal, 10 mg/kg), then monitored for 72 hours post-injection.

Results: PGC1α KO mice exhibited increased serum creatinine relative to WT littermates at 24 hours after IRI. At 1 month and 6 months post-IRI, creatinine in both genotypes had recovered to normal levels. However, 6-month survival in KO mice was 83% compared to 100% survival in WT mice. Within 48 hours of the second AKI insult, survival was 33% in KO versus 75% in WT.

Conclusions: PGC1α may impact both kidney function and overall survival after AKI. Despite KO survivors of the initial AKI insult recovering to indistinguishable and normal serum creatinine as compared to control littermates, PGC1α KO mice suffered worse outcomes after the second insult. The results suggest that PGC1α, and by extension mitochondrial homeostasis, may have important effects on the renal response to cumulative insults. Given the increasingly appreciated connections between AKI and CKD, models of repeated AKI may illuminate mechanisms of transition from acute insult to chronic impairment.

Funding: NIDDK Support

TH-PO101

Dysregulated Tubular Autophagy Promotes Maladaptive Kidney Repair and Interstitial Fibrosis During AKI-CKD Transition

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Background: Tubular cell injury is a key pathological feature of AKI. Renal tubules have the capacity to regenerate after injury, but kidney repair following severe AKI is often incomplete, leading to interstitial fibrosis and CKD. The mechanisms underlying AKI-CKD transition are poorly understood. Autophagy is induced in tubular cells during AKI and protects against injury. Recent work further reveals a profibrotic role of tubular autophagy in UUO. However, the role of autophagy in kidney repair and fibrosis after AKI remains unknown.

Methods: We established an inducible, conditional knockout mouse model where *Atg7* can be ablated specifically from renal tubules at a desired time. Using this model we examined the role of tubular autophagy in the development of chronic renal pathologies after ischemic AKI.

Results: Mice underwent 30-min unilateral renal ischemia followed by reperfusion for up to 4 wks. Autophagy was persistently activated in proximal tubules of post-ischemic kidneys, as indicated by LC3-II accumulation and increased formation of both autophagosomes and autolysosomes. We generated a doxycycline-inducible, renal tubule-specific *Atg7* knockout mouse model (i*Atg7* KO) where *Atg7* was specifically deleted from renal tubules only during the recovery phase after AKI without affecting initial injury. The inducible *Atg7* KO blocked autophagy in renal tubules and also suppressed post-ischemic fibrosis. Proliferation and activation of fibroblasts was inhibited in i*Atg7* KO mice, so was the accumulation of ECM components. Wild-type (WT) mice had 10.1% interstitial fibrosis 2-wk after AKI and 17.5% at 4-wk, which were reduced to 6.7% at 2-wk and 9.9% at 4-wk respectively in i*Atg7* KO mice. AKI in WT mice led to decreased staining of brush border marker LTL and increased expression of vimentin in renal tubules indicating tubular degeneration, which were reversed in i*Atg7* KO mice. Renal tubules in WT mice displayed remarkable senescent changes after ischemic AKI, which were significantly attenuated by autophagy deficiency. Under these conditions, G_2/M cell cycle arrest was also induced in renal tubules of WT but suppressed in i*Atg7* KO kidneys.

Conclusions: These results suggest that autophagy in renal tubules may contribute to maladaptive kidney repair during AKI-CKD transition by promoting interstitial fibrosis via tubular atrophy, senescence, and cell cycle arrest.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO102

Metabolic Reprogramming in Sepsis-Associated AKI

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Background: AKI significantly contributes to the morbidity and mortality. Therapeutic strategies are limited due to incomplete understanding of its pathogenesis. Changes in tubular metabolism in response to cellular stress during sepsis may play an important role. A sepsis-associated AKI (s-AKI) model induced by cecal ligation and puncture (CLP) was used to investigate the early and late changes in mitochondrial function and tubular metabolism in s-AKI.

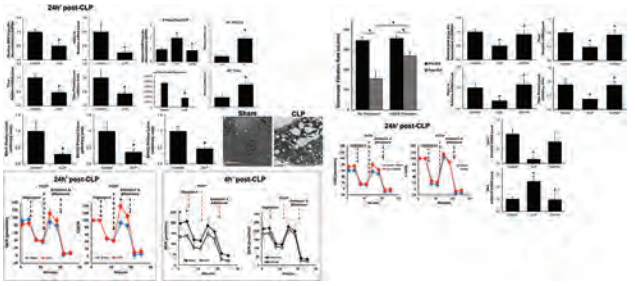
Methods: C57bl/6 mice underwent CLP or sham surgery. Mitochondrial biogenesis, content and dynamics were examined at 4 hours (4 h') and 24 hours (24 h') post CLP. Mitochondrial respiration is freshly isolated proximal tubules was examined with XF96 Seahorse analyzer. Expression of glycolytic enzymes and other assays of tublar metabolism were performed. Lastly, the role of AMP-activated protein kinase (AMPK), the principal cellualr metabolic sensor, was also investigated.

Results: Mitochondrial DNA copy number, PGC1α and Tfam expression were increased at 4 h' but significantly decreased at 24h' post-CLP. Mitochondrial fusion proteins were unchanged at 4' but decreased significantly at 24h' in CLP kidneys. Basal respiration in proximal tubules was significantly diminished in CLP at 4h'. At 24h', a significantly increased maximum respiration rate was observed, suggesting a shift to glycolytic metabolism. The expression of phosphofructokinase (PFK), a rate-limiting glycolytic enzyme, was significantly elevated, while carnitine palmitoyltransferase I (CPT1), a rate-limiting enzyme of lipid oxidation, was dramatically reduced at 24h'. Treatment with AICAR, an AMPK activator, prevented CLP-induced alteration of mitochondrial function (dynamics and biogenesis) and improved GFR.

Conclusions: Our novel findings demonstrate early changes in mitochondrial function and metabolic preprogramming in s-AKI. Mitochondrial dysfunction with a shift to glycolytic metabolism with dimished fatty oxidation under cellular stress is seen. Activation of AMPK improves mitochondrial function by improving mitochondrial biogenesis and

fusion. Additional effects on tubular metabolic reprogramming with AMPK activation is being investigated.

Funding: NIDDK Support, Veterans Affairs Support



TH-PO103

Hsp70 Induction by GGA Treatment Attenuates the Proapoptotic Unfolded Protein Response and Inhibits Gentamicin-Induced Renal Cell Death

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Background: Exposure to nephrotoxic antibiotics damages the proximal tubule epithelial cells and causes substantial morbidity and mortality. Gentamicin is a common nephrotoxic antibiotic that promotes proximal tubule damage and acute kidney injury (AKI). However, the lack of a unifying mechanism for gentamicin-induced renal cell injury limits AKI therapy. We hypothesize that computational analysis of an unbiased, broad-based shRNA cell signal screen will identify a "best fit" mechanism(s) of renal cell injury as well as targeted drugs to ameliorate gentamicin-induced AKI.

Methods: Dual shRNA screens of 25,000 individually barcoded signal pathway genes were performed in gentamicin-exposed human proximal tubule cells. Differentially expressed shRNAs were analyzed by Ingenuity Pathways Analysis (IPA) software. Predictions based on computational data were then tested using Unfolded Protein Response (UPR) markers: ATF6, CHOP, BiP and XBP1. Additionally, protein ubiquitination, protein misfolding (thioflavin T staining), oxidative stress (4HNE), mitochondrial integrity (MitoTracker), endoplasmic reticulum (ER)-mitochondrial association (ER Tracker), and cell death (cleaved PARP and propidium iodide staining) were measured.

Results: Interference RNA screening detected 226 differentially expressed shRNAs. Pathway analysis of these shRNAs identified the UPR as the "best fit" mechanism of cell injury and suggested Hsp70 as a potential cytoprotectant. Gentamicin exposure increased protein ubiquitination, protein misfolding, oxidative stress, activated all 3 UPR arms, caused mitochondrial fragmentation followed by mitochondria-ER dissociation, and finally, induced cell death. Chemical induction of Hsp70, a protein that regulates several UPR steps, markedly reduced protein ubiquitination, misfolding, oxidative stress, suppressed both mitochondrial fragmentation and dissociation from ER, and dramatically improved renal cell survival.

Conclusions: This study suggests that the proapoptotic UPR contributes to gentamicin-induced renal cell injury. Hsp70 induction by chemical treatment ameliorates the proapoptotic UPR events and significantly improves renal cell survival during gentamicin exposure.

Funding: NIDDK Support

TH-PO104

Sex-Specific Regulation of Sirtuin-3 Mediates Differences in Ischemia-Reperfusion Kidney Injury

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Background: Sex influences susceptibility to kidney ischemia-reperfusion injury (IRI), and sex hormones play a crucial role. We previously showed that a pathway from stanniocalcin-1 (STC1) mediated AMPK activation to induction of mitochondrial sirtuin-3 (mtSIRT3) suppresses ROS and confers resistance to kidney IRI. Current observations reveal increased baseline kidney expression of STC1 and SIRT3, and AMPK activation in female vs male mice. We hypothesized that SIRT3 mediates sex differences in response to IRI.

Methods: Male and female wild-type (WT) or SIRT3 transgenic (Tg) mice were subjected to bilateral kidney IR (clamping of renal pedicles for 30 min). Male or female WT mice were treated with testosterone for 2 weeks (s.c. implantation of 21-day release, 200mg pellet). HEK cells were treated with 17β-estradiol, testosterone or vehicle.

Results: pAMPK and mtSIRT3 expression are higher in kidneys of WT female mice vs. males; pAMPK and SIRT3 decline with age but sex differences persist. At age 6 months, male WT kidneys display tubular vacuolization, which is absent in male SIRT3Tg mice. Male SIRT3Tg mice demonstrate resistance to IR [preserved creatinine clearance (CrCl) and morphology; less ROS] and better survival vs WT males; outcomes similar to WT females. In WT females, kidney mtSIRT3 expression correlates positively with plasma estradiol and negatively with testosterone levels. In WT males, kidney mtSIRT3 only correlates negatively with plasma testosterone. Testosterone administration to 6 months-old WT males causes kidney injury (decreased CrCl; increased tubular vacuolization), and decreases kidney mtSIRT3 expression with no effect on whole cell SIRT3. Testosterone administration to WT females increases whole cell- and mtSIRT3 (maybe due to associated rise in plasma estradiol) and causes no measurable kidney injury. In HEK cells, estradiol dose-dependently increases SIRT3 mRNA, whole cell- and mtSIRT3 protein, and ERβ and ERRα mRNA. Testosterone dose-dependently decreases mtSIRT3 protein expression with no effect on whole cell SIRT3 protein or SIRT3 mRNA.

Conclusions: The data suggest: 1) SIRT3 ameliorates kidney IRI; 2) decreased SIRT3 expression underlies increased susceptibility to ischemic injury in male mice; 3) sex steroids regulate mtSIRT3 expression, estrogen via transcriptional regulation and testosterone via reduced mitochondrial targeting.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO105

Pubertal Surge of Sex Hormones Induces Kidney Maturation but Confers Ischemic Vulnerability to Postnatal Kidney

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Background: While neonatal kidney is still immature and maturation continues after birth, comprehensive studies on postnatal kidney maturation are limited, and how kidney maturation affects disease susceptibility has not been evaluated.

Methods: We set out to characterize female kidney maturation from infancy to adulthood by morphological analysis and comprehensive gene expression analysis. We also aimed to assess the impact of pubertal sex hormones on postnatal kidney maturation and disease susceptibility.

Results: Comprehensive analysis revealed the increase of transcripts encoding transporters and metabolic enzymes during puberty, associated with the elongation of brush borders of proximal tubules in the deep cortex. Upregulated transporters included solute carriers that transport sodium, organic anion, phosphate, glucose and amino acids, and the most enriched motif near the transcription start sites of these genes was the binding motif of *hepatocyte nuclear factor 4a*, a transcription factor essential for proximal tubule differentiation, presumably indicating the differentiation of proximal tubule during puberty. Notably, the maturation of adult mice was attenuated by the ovariectomy before puberty, whereas the administration of estrogen, but not progesterone reversed these changes. Unexpectedly, adult mice ovariectomized before puberty unexpectedly showed tolerance to renal ischemia, whereas adult mice ovariectomized after puberty were vulnerable to renal ischemia. Latter result was consistent with recent studies on the protective effects of estrogen against injury. Importantly, insulin-like growth factor 1 receptor (IGF-1R) protein in the kidney decreased during puberty, whereas kidneys of adult mice ovariectomized before puberty showed high expression of IGF-1R like infant kidney, indicating that pubertal sex hormone surge decreases IGF-1R expression. In vivo knockdown of IGF-1R in proximal tubules substantially reduced renal IGF-1R expression, and significantly attenuated ischemic tolerance of adult mice ovariectomized before puberty, implying that IGF-1R signaling in proximal tubule contributes to the tolerance of these mice.

Conclusions: Pubertal sex hormones accelerate kidney maturation but paradoxically confer ischemic vulnerability to postnatal kidney, possibly by inhibiting IGF-1R signaling in proximal tubules.

TH-PO106

Remote Ischemic Preconditioning Confers Renoprotection Against Septic AKI via Exosomal miR-21

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Background: Renal ischemic preconditioning is beneficial for multiple organs in response to ischemic injury. Whether limb remote ischemia preconditioning (limb rIPC) functions as a protective effector against sepsis-associated AKI is unclear, and the underlying mechanism has not been fully elucidated. Our study aimed to explore the protective role of limb rIPC in mice with AKI induced bycecal ligation and puncture (CLP).

Methods: In vivo, we preconditioned CLP-challenged mice with remote ischemia and reperfusion in the bilateral femoral arteries, which were subjected to 4 cycles of clamping for 5 minutes and unclamping for 5 minutes. Organ function and indicators of inflammation and apoptosis were examined, and the potential mechanism was determined. In vitro, we extracted myocyte-derived exosomes under hypoxia and re-oxygen preprocessing, and these exosomes were pre-added to lipopolysaccharide (LPS)-treated mouse tubular epithelial cells (mTECs).

Results: In vivo, limb rIPC protected polymicrobial septic mice from multiple organ dysfunction and morphological damage, via anti-inflammatory and anti-apoptotic effects. However, limb rIPC could not attenuate CLP-induced renal injury in miR-21 knockout mice. rIPC enhanced local miR-21 expression in ischemic limbs in a hif-1α dependent way, and miR-21 expression in serum exosomes and remote organs, such as the kidney and lung, was up-regulated. This beneficial effector was potentially transmitted in circulation by exosomal transfer. Meanwhile, an elevation in miR-21 was detected in exosomes derived from myocytes with hypoxia and re-oxygen pretreatment. The exosomal preconditioning resulted in renal protection and a reduction in inflammatory cytokines and in mTEC apoptosis in response to septic injury. We further found that high miR-21 expression inhibited miR-21 target genes, exerting anti-inflammation and anti-apoptosis effects.

Conclusions: Enhanced exosomal miR-21 that is induced by limb remote ischemia preconditioning contributes to renoprotection against sepsis. Our data suggest a novel and promising therapeutic strategy for septic AKI.

Funding: Government Support - Non-U.S.

TH-PO107

Myeloid Heavy Chain Ferritin Mitigates Ischemic AKI

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Background: Acute kidney injury (AKI) stimulates crosstalk between damaged renal tubular epithelium and infiltrating inflammatory cells by chemokine and cytokine release. Perpetual inflammation drives worsened kidney function, structural damage and fibrosis, highlighting the importance of understanding immune cell trafficking in AKI. Heavy chain ferritin (FtH), a protein with ferroxidase activity responsible for iron metabolism, is implicated in macrophage polarization. Here, we investigate the role of myeloid FtH in immune cell trafficking and resolution of AKI.

Methods: We subjected mice deficient in myeloid FtH ($FtH^{LysM-/-}$) and floxed controls ($FtH^{fl/fl}$) to bilateral renal ischemia-reperfusion injury (IR, 20 minutes). We measured renal function, structural damage, chemokine and cytokine expression, and inflammatory cell infiltration.

Results: $FtH^{fl/fl}$ and $FtH^{LysM-/-}$ mice experience similar functional (serum creatinine; SCr levels ($FtH^{fl/fl}$ 1.6 ± 0.11 mg/dL; $FtH^{LysM-/-}$ 1.3 ± 0.12 mg/dL) and structural damage at day 1. At day 2, only $FtH^{LysM-/-}$ mice continue to worsen (2.4 ± 0.38 mg/dL), which subsequently results in significant mortality. $FtH^{LysM-/-}$ mice also exhibit elevated levels of *growth differentiation factor-15*, a marker of renal injury, at day 2 while $FtH^{fl/fl}$ levels are significantly decreased. Interestingly, day 2 after IR, while chemokine and cytokine expression in $FtH^{fl/fl}$ mice is reduced, levels of intrarenal inflammatory markers, such as *CXCL2* and *IL-6*, and serum IL-5 remain elevated in $FtH^{LysM-/-}$ mice. Following IR, the absolute number of intrarenal $F4/80^{int/low}$ $CD11b^{+}$ $Ly6C^{low/neg}$ $CD11c^{+}$ mononuclear phagocytes in $FtH^{fl/fl}$ mice increases, while this cell population does not change from sham levels in $FtH^{LysM-/-}$ mice. After IR, $FtH^{fl/fl}$ mice have a robust induction of neutrophil elastase, an enzyme important for digestion of cellular debris, while it is significantly blunted in $FtH^{LysM-/-}$ mice.

Conclusions: Our findings demonstrate that, while deletion of myeloid FtH does not influence the ischemic insult to the kidney, it regulates the resolution of AKI potentially via activation of pro-resolving macrophages. This study underscores the significance of harnessing macrophages in immunotherapy for AKI resolution and prevention of chronic kidney disease.

Funding: NIDDK Support

TH-PO108

The Role of Hemopexin as a Protectant Against AKI

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Background: In ischemic and nephrotoxic acute kidney injury (AKI), renal heme content and plasma heme levels are increased. Heme is prooxidant, proinflammatory, and nephrotoxic. Levels of heme are restrained by degradation by heme oxygenase (HO) and by the binding of heme to hemopexin (HPX). HPX is also anti-inflammatory. We questioned whether induction of HPX occurs in AKI and its functional significance.

Methods: Renal HPX mRNA and protein expression was assessed by RT-PCR and western analysis respectively. Renal function was evaluated by serum creatinine and blood urea nitrogen (BUN). Multiple AKI models were employed, including glycerol-induced, heme protein-mediated AKI, and AKI induced by either acute ischemia, endotoxin, or hemoglobin.

Results: HPX mRNA and protein were vigorously induced in the kidney exposed to hemoglobin, along with the receptor for the HPX-heme complex CD91. We thus examined the effect of glycerol-induced, heme protein-mediated AKI in $HPX^{+/+}$ and $HPX^{-/-}$ mice. Renal function was comparable in these mice prior to the administration of hypertonic glycerol and on days 1 and 2 after the induction of AKI. However, $HPX^{-/-}$ mice as compared to $HPX^{+/+}$ mice exhibited significantly higher BUN at day 3 (166 ± 24 vs 104 ± 17 mg/dl) and day 4 (142 ± 23 vs 82 ± 11 mg/dl) following the induction of AKI; similarly, serum creatinine values were also higher on day 3 (1.4 ± 0.2 vs 0.8 ± 0.1 mg/dl) and day 4 (1.2 ± 0.2 vs 0.7 ± 0.1 mg/dl) in $HPX^{-/-}$ mice compared with $HPX^{+/+}$ mice. In ischemia-induced AKI, HPX mRNA and protein are also vigorously induced in the kidney, along with CD91. However, no differences were observed in renal function in $HPX^{+/+}$ and $HPX^{-/-}$ mice at days 1 and 2 following ischemia. No differences in renal function were observed in $HPX^{+/+}$ and $HPX^{-/-}$ mice at days 1 and 2 following endotoxin-induced AKI, and at days 1 and 7 following hemoglobin-induced AKI.

Conclusions: HPX is significantly induced in both nephrotoxic and ischemic models of AKI. A beneficial, functional effect of such induction is observed in glycerol-induced, heme protein-mediated AKI, but only in the recovery phase of such AKI. We suggest that when HO-1, the potent, broad-based protectant in AKI, is intact, HPX provides a secondary backup system for guarding against heme toxicity.

Funding: NIDDK Support

TH-PO109

Trib1 Is Involved in Renal Recovery and Regeneration in a Mouse Model of Ischemia/Reperfusion Injury

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Background: Acute kidney injury (AKI) is one of the most common serious complications in hospitalized patients. Despite tremendous effort has been made, AKI is still strongly associated with poor outcomes. Maladaptive repair after AKI exhibit a persistently increased risk of progression to chronic kidney disease (CKD). Macrophages are implicated in the initial injury after ischemic/reperfusion (I/R) and also participate in tubular repair after I/R. Macrophages are classified into two subsets, M1 (inflammatory) and M2 (anti-inflammatory). M1 macrophages play a pathogenic role in boosting inflammatory and kidney injury, whereas M2 macrophages exhibit an anti-inflammatory and wound healing. Evidence demonstrates that macrophage polarization plays a critical role in the process of kidney recovery and chronic fibrosis, hence, enhancement of M1 to M2 phenotype transition might promote renal recovery after I/R. Trib1 is critical for the differentiation of macrophages, therefore, we aimed to investigate the role of trib1 in the process of kidney recovery following I/R and the link between trib1 and macrophage phenotype.

Methods: We used lentiviral vector mediated RNA interfering (RNAi) to knock down expression of trib1 in mice to investigate the role of trib1 in the process of renal repair.

Results: Our results showed that mice with down regulation of trib1 showed markedly reduced renal function, severe renal pathological damage, and exacerbated inflammation. Inhibition the expression of trib1 resulted in an impaired ability to form M2 macrophages in the kidney, whereas coincided with increased M1 macrophages. Expression of TNF-α, IL-6, and IL-12 increased markedly in the trib1 suppressed mice accompanied with a decreased expression of IL-4 and IL-10. Inhibition of Trib1 led to reduced PCNA and Ki67-positive proliferating tubular cells.

Conclusions: Our results showed that trib1 is involved in kidney recovery and regeneration through the regulation of macrophage polarization. This might be a viable therapeutic option to enhance renal repair after I/R injury.

Funding: Government Support - Non-U.S.

TH-PO110

Arginase 2 as a Mediator of Ischemia-Reperfusion Injury in the Kidney Through Regulation of Nitrosative Stress

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Background: Arginase 2 (Arg2) is expressed exclusively in the kidney and catabolizes the hydrolysis of L-arginine, which is common substrate for nitric oxide synthase, to produce L- ornithine and urea. There were several reports that administration of arginase blockade protected hepatic and myocardial ischemia-reperfusion injury. However, the role of Arg2 for renal ischemia-reperfusion injury is still poorly unknown.

Methods: Human renal tubular epithelial cells, (HK-2 cells) were cultured under 6-hour hypoxic condition (1% O_2) and subsequent 24-hour reoxygenation (21% O_2) (H/R). To knockdown Arg2, cells were transfected with *Arg2* siRNA. Eight to ten week-old wild type (WT) and Arg2 knockout (Arg2KO) male mice were subjected to clamping of bilateral renal pedicles for 28 minutes and euthanized 24 hours after reperfusion (I/R).

Results: The level of *Arg2* mRNA and ARG2 protein was increased at 24 h after I/R in mouse kidney. Immunohistochemistry revealed that ARG2 was localized specifically in renal proximal tubules and increased after I/R. In HK-2 cells, the immunofluorescent signals of ARG2 were significantly elevated after H/R. ARG2 distributed in a punctate pattern throughout the cytoplasm and partly colocalized with mitochondrial marker. *Arg2* knockdown in HK-2 cells resulted in attenuated 3-nitorotyrosine (3-NT) formation after H/R, though the extent of apoptosis was not changed. Arg2KO mice were markedly resistant to ischemic kidney injury as measured by serum urea nitrogen (WT 150 ± 23 vs Arg2KO 106 ± 34 mg/dL, p <0.05) and creatinine (WT 1.06 ± 0.65 vs Arg2KO 0.43 ± 0.45 mg/dL, p <0.05). The level of 3-NT in ARG2KO kidney was decreased as compared to WT at 24-h reperfusion.

Conclusions: Arg 2 was strongly induced after renal I/R injury particularly in tubular epithelial cells. Suppressing Arg2 by knockdown or knockout method resulted in reduced 3-NT in renal tubular cells. Deficiency of ARG2 significantly alleviated I/R injury in mouse kidney. Our results suggest that ARG2 is a cause of nitrosative stress and inhibition of ARG2 may be beneficial for treatment of renal I/R injury.

TH-PO111

Lowering of Pathological Asymmetric Dimethyl Arginine by a Novel Dimethylarginine Dimethylaminohydrolase Improves Kidney Function After Ischemia-Reperfusion Injury

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Background: Asymmetric dimethyl arginine (ADMA) is an endogenously produced inhibitor of nitric oxide synthase (NOS) which contributes to endothelial dysfunction, endothelial to mesenchymal transition, reduced organ perfusion, and fibrosis. High

levels of ADMA are produced in patients with kidney disease and in response to renal ischemia which may contribute to the pathogenesis of kidney disease. In this study, we have investigated ADMA lowering and therapeutic efficacy of novel dimethylarginine dimethylaminohydrolase (DDAH) in the setting of acute kidney injury produced by ischemia-reperfusion (I/R).

Methods: DDAH gene was cloned and expressed in E. coli to generate recombinant DDAH (rDDAH). In vivo circulating DDAH activity was determined at various times after i.v. administration to rats using a colorimetric assay. I/R injury in rats was produced by renal artery ligation for 40 min followed by reperfusion in male Sprague-Dawley rats. The effect of I/R injury on renal DDAH was measured by changes in DDAH mRNA and enzymatic activity. rDDAH was post-translationally modified by PEGylation (M-DDAH) to achieve prolonged in vivo activity. The effect of M-DDAH on I/R injury in rats was determined by changes in creatinine and histology.

Results: DDAH mRNA expression and activity rapidly declined following renal I/R injury in rats, and were ~20% of the values in sham-operated controls within 6 hours ($P<0.05$). Reduction in DDAH was accompanied by increased ADMA in the kidney from 0.14±0.05 uM/mg protein at baseline to 0.42±0.09 uM/mg protein at 6h ($P<0.05$). Native rDDAH was rapidly cleared within 15 min after i.v. administration to rats, whereas PEGylated DDAH (M-DDAH) exhibited 15-fold greater in vivo half-life than the native rDDAH. M-DDAH treatment attenuated the degree of renal injury in the I/R model as indicated by reduced serum creatinine (2.23±0.38 mg/dL I/R vs 1.15±0.17 mg/dL M-DDAH, $P<0.05$) and the degree of renal tubular damage.

Conclusions: Our studies are first to synthesize a novel pharmacologically viable DDAH molecule which lowered ADMA in rats. M-DDAH significantly improved renal function in a model of I/R in rats, suggesting that M-DDAH may offer a new therapeutic approach for improving endothelial function in the setting of AKI.

TH-PO112

GDF15 Marked Stressed Tubular Epithelium and Alleviated Ischemic AKI

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Background: Renal ischemia reperfusion injury (IRI) frequently triggers tubular damage leading to acute kidney injury (AKI) in varied clinical settings including kidney transplantation. We identified *Gdf15* (Growth/differentiation factor 15) as one of the genes rapidly activated in the mouse nephron following ischemic AKI; a similar induction is observed after transplant of the human kidney. First identified as an autocrine regulatory molecule associated with macrophage activation, *Gdf15* was induced by proinflammatory cytokines and activated by various stressors including inflammation, oxidative stress and DNA damage. The role for endogenous GDF15 in ischemic kidneys is unclear.

Methods: To study *Gdf15* expression and function in the mouse kidney, we generated a mouse line ($Gdf15^{nuGFP\text{-}CE}$)producing a truncated GDF15 missing C-term 210 a.a. and fused with P2A-nuclearGFP-F2A-CREERT2. We examined GFP and tamoxifen dependent TDT expression in $Gdf15^{nuGFP\text{-}CE/+}$, $R26^{TDT/+}$ mice and compared the acute and chronic renal response to IRI in *Gdf15* heterozygous and *Gdf15* null mice by qRT-PCR, histology and immunofluorescence. To validate the clinical relevance of our findings, we performed a *GDF15*-related single nucleotide polymorphism association study in a cohort of kidney transplant recipients.

Results: In steady state, GDF15 was produced mainly by the Apq1- thin descending limb of the Henle's loop (tDLH), by the S3 segment of the proximal tubule and by principal cells in the collecting duct. After moderate bilateral renal IRI, Gdf15 was predominantly activated in proximal tubules, Aqp1+ tDLH, principal cells in the collecting ducts and connecting tubules. Moreover, GDF15 deficiency exacerbated acute tubular injury, enhanced inflammatory response and facilitated adaptive immunity following ischemia. Consistently with the immune-regulatory effect observed in the mouse model, we found that single nucleotide polymorphisms previously linked to lower circulating GDF15 concentration, were associated with an increased incidence of biopsy proven acute rejection in the first year after kidney transplantation.

Conclusions: GDF15 is a functionally relevant, conserved element with reno-protective and immune-regulatory properties in the immediate response to ischemic AKI.

Funding: Other U.S. Government Support

TH-PO113

Proximal Tubule β2 Adrenergic Receptor Is Responsible for Formoterol-Induced Recovery of Mitochondrial and Renal Function After AKI

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Background: Numerous cell types play a role in the pathogenesis of AKI, including immune, endothelial, and renal proximal tubule cells. Our laboratory demonstrated that the β_2 adrenergic receptor (β_2AR) agonist formoterol stimulates mitochondrial biogenesis (MB) and accelerates the recovery of renal and mitochondrial function in mice following ischemia-reperfusion injury (IRI). However, the cell type(s) responsible for this recovery remains unknown.

Methods: $ADRB2^{Flox/Flox}$ (WT) mice were mated with γGT-Cre mice to generate γGT-Cre:$ADRB2^{Flox/Flox}$ (KO) mice with proximal tubule deletion of the β_2AR. These mice were subjected to renal IRI and were treated once daily with formoterol or vehicle beginning at 24 h and euthanized at 144 h.

Results: Compared to WT, KO mice had 80% lower renal cortical ADRB2 mRNA and DNA. At 24 h following IRI, WT and KO mice had a similar loss of renal function as measured by serum creatinine. At 144 h following IRI, both WT and KO mice treated with vehicle exhibited persistent renal dysfunction as measured by elevated serum creatinine (SCr), KIM-1 protein, and tubular necrosis. Following treatment with formoterol, WT mice, but not KO mice, exhibited accelerated recovery of renal function. Treatment with formoterol increased mitochondrial protein expression and mtDNA copy number in WT but not KO mice. Sham-operated KO mice also had fewer mitochondria than WT mice as assessed by transmission electron microscopy. Formoterol restored mitochondrial number and density in WT but not KO mice.

Conclusions: Following AKI, formoterol activates the β_2AR and stimulates MB in proximal tubule cells to accelerate the recovery of renal function. The β_2AR also regulates mitochondrial homeostasis in healthy proximal tubule cells. These data underscore the importance of the proximal tubule cell as a therapeutic target for AKI. Thus, targeting compounds that induce MB in renal proximal tubule cells may provide more effective treatments for AKI.

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TH-PO114

Inhibition of Semaphorin-3a Suppresses Lipopolysaccharide-Induced AKI

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Background: Acute kidney injury (AKI) is a common and catastrophic complication in sepsis-associated patients. Endotoxin is a common cause of sepsis-associated AKI. Lipopolysaccharide (LPS) is the major component of endotoxin derived from gram-negative bacteria and has been found to be involved in the pathogenesis of AKI. Semaphorin-3a (Sema3A), a soluble axon guidance cue, appears to play an important role in the development of AKI. However, the role of Sema3A in sepsis related AKI remains unknown.

Methods: Lipopolysaccharide (LPS) was used to simulate sepsis-associated AKI in male C57BL/6 mice and NRK-52E cells (rat tubular epithelial cells). The role of Sema3A in LPS-induced AKI was investigated in *vivo* and in *vitro*. Firstly, mice were intraperitoneally injected by LPS with different times to examine Sema3A expression. Next, (-)-Epigallocatechin-3-gallate (EGCG) was administrated to inhibit Sema3A. Then, Renal function, kidney injury, inflammation, and apoptosis were measured to investigate the effect of Sema3A in LPS-induced AKI. Furthermore, to explore the mechanism of Sema3A regulates inflammation and apoptosis in *vitro*, NSC23766 (a specific Rac1 inhibitor) and SP600125 (a specific JNK inhibitor) were used. Then, the mRNA expression of IL-6 and TNF-α, cell apoptosis, the expression of Rac1/NF-κBp65 and JNK signaling molecules were examined.

Results: The expression of Sema3A was upregulated in renal tubular epithelial cells (TECs) in LPS induced AKI model. Similar change was found in NRK-52E cells incubated with LPS (5μg/ml). Notably, inhibition of Sema3A by EGCG significantly reduced renal inflammation and the apoptosis of TECs in LPS induced AKI mice. EGCG intervention also ameliorated LPS-induced inflammation and apoptosis in NRK-52E cells in *vitro*. Our results also indicated that Rac1/NF-κBp65 and JNK signaling were involved in Sema3A-mediated inflammation and apoptosis of TECs, respectively.

Conclusions: Our results suggested that the upregulation of Sema3A probably play a pathogenic role in LPS-induced AKI, which promote renal inflammation and TECs apoptosis. Rac1/NF-κBp65 and JNK signaling pathways might be involved in the inflammation and cell apoptosis respectively.

TH-PO115

PAC-Mediated AKI Protection Is Critically Dependent on Cell-Derived Microvesicles

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Background: Acute Kidney Injury (AKI) significantly worsens the prognosis of hospitalized patients. In recent years, cell-based strategies have been established as reliable option for improving AKI outcomes in experimental AKI. Own studies focused on so-called Proangiogenic Cells (PACs). Mechanisms that contribute to PAC-mediated AKI protection include production / secretion of extracellular vesicles (EV). In addition, the cells act by paracrinic processes (secretome). The current study evaluated whether AKI may be preventable by the administration of either PAC-derived EV and / or the secretome alone.

Methods: AKI was induced in male C57/Bl6N mice (8-12 weeks) by bilateral renal ischemia (IRI - 40 minutes). Syngeneic murine PACs were stimulated with either melatonine, Angiopoietin-1 or -2, or with Bone Morphogenetic Protein-5 (BMP-5) for one hour respectively. PAC-derived EV and the vesicle-depleted supernatant were subsequently collected and i.v. injected post-ischemia. Mice were analyzed 48 hours later.

Results: IRI induced significant kidney excretory dysfunction as reflected by higher serum cystatin C levels. The only measure that improved AKI was the injection of EV, collected from native PACs. The following conditions worsened post-ischemic renal function even further: EV+Ang-1, EV+BMP-5, EV+melatonin, and EV+secretome+Ang-1.

Conclusions: Together, our data show that PAC-mediated AKI protection critically depends on the availability of cell-derived EV. The secretome, either collected from native or preconditioned cells does not prevent mice from ischemia-induced dysfunction. Certain PAC preconditioning protocols may even worsen the renal prognosis of EV(/secretome)-treated animals.

TH-PO116

Early Inflammatory Response to Pyelonephritis Induced by Uro-Pathogenic E. coli Requires P2Y2 Receptor Activation

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Background: Urinary tract infections are exceedingly common and severe infections including pyelonephritis are often caused by *E. coli* that produces the pore-forming virulence-factor alpha-hemolysin (HlyA). We have previously demonstrated that HlyA releases cellular ATP directly through its membrane pore and that the associated erythrocyte lysis is completely prevented by blocking ATP-signalling. Renal epithelia are not lysed by the toxin. Instead the released ATP causes $P2Y_2$-receptor dependent intracellular [Ca^{2+}] oscillations followed by epithelial IL-6 release. Thus, we speculated that $P2Y_2$ receptor deficient mice may be more susceptible to pyelonephritis as a result of inadequate epithelial-induced immune activation.

Methods: Acute pyelonephritis was induced by injecting 100 million HlyA-producing, uropathogenic *E. coli* into the urinary bladder of balb/c mice. After 24 hours, pyelonephritis was confirmed by culture of the right kidney, the urine and plasma were collected and the left kidney was isolated for histology after perfusion fixation.

Results: The mice showed relatively modest change in overall behaviour in response to the renal infection compared to vehicle controls and the survival or degree of infection was similar in $P2Y_2^{-/-}$ and $P2Y_2^{+/+}$ mice after 24 h. The $P2Y_2^{+/+}$ mice with confirmed pyelonephritis, showed marked elevation of plasma IL-6 (42.0±7.3 pg/ml) compared to control (12.2±4.5 pg/ml, p=0.001). Preliminary data show reduced plasma IL-6 in $P2Y_2^{-/-}$ mice with confirmed pyelonephritis (24.7±10.3 pg/ml). Similarly, we found significant elevation in keratinocyte chemoattractant (KC, a murine homologue of IL-8) in plasma of $P2Y_2^{+/+}$ mice subjected to HlyA-producing *E. coli* (91.3±27.4 pg/ml) compared to control (23.9±7.1 pg/ml, p=0.003). In contrast, plasma KC were markedly lower in $P2Y_2^{-/-}$ mice with pyelonephritis (33.6±14.7 pg/ml). These changes are likely to reflect early interaction between bacteria and renal epithelium, since the degree of neutrophil infiltration had not increased in pyelonephritic kidneys at this early time point.

Conclusions: These results indicate that ATP signalling via the $P2Y_2$ receptor plays a pivotal role in the early response to pyelonephritis with HlyA-producing *E. coli*. Data on ATP release to the urine, survival and immune reaction after 3 days are pending.

Funding: Government Support - Non-U.S.

TH-PO117

The Effect of Adenosine Kinase on Acute Renal Injury

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Background: Numerous studies have demonstrated that several mechanisms, including necrosis, apoptosis, inflammatory reaction and oxidative stress are closely linked to acute kidney injury. Adenosine, emerging as a key regulatory molecule, is mostly protective in the pathophysiology of inflammatory diseases. Previous study showed that some of the adenosine receptors led to renal-protection against ischemia-reperfusion injury. However, these adenosine receptors agonists lack a useful therapeutic index due to cardiovascular side effects. We hypothesized that inhibition of adenosine kinase exacerbates extracellular adenosine levels to reduce cisplatin and ischemia reperfusion-induced renal injury.

Methods: 1.(1)C57BL/6 mice(24g, 6-8week, male) were randomly divided into 4 groups: Control, ABT-702, Cisplatin, and ABT-702+ Cisplatin, (2)C57BL/6 mice were randomly divided into 4 groups: sham operation group (Sham), ABT-702, ischemia-reperfusion (IR), ABT-702 +IR group (ABT-702+IR), kidney pathological changes, and protective effects were observed. 2.(1) HK-2 cells were pretreated with 1uM ABT-702 then incubated with cisplatin at 20uM concentration for 24 h. (2) HK-2 cells were treated with the ADK small interfered RNA, then incubated with Cocl2 at 250uM concentration for 12 h to induce chemical hypoxia, followed by reperfusion for 24 h. The apoptosis-associated protein (cleaved caspase-3, Bcl-2, Bax), ROS, and four types of adenosine receptors were detected. Four receptors antagonists were added before ABT-702 to detect the changes in cell viability.

Results: In this study, inhibition of adenosine kinase could markedly attenuate cisplatin-induced and renal ischemia reperfusion-induced acute kidney injury, tubular cell apoptosis, oxidative stress and inflammation in the kidneys. Consistent to in vivo results, the inhibition of ADK suppressed cisplatin and Cocl2-induced apoptosis, ROS production and inflammation in HK2 cell. Additionally, the protective effect of ADK inhibition was abolished byA1 or A2Badenosine receptors inhibition and enhanced by A2Aor A3 adenosine receptors inhibitor.

Conclusions: Inhibition of ADK increases adenosine and attenuates acute renal injury by anti-inflammatory, antioxidant stress and anti-apoptosis mechanism and partly dependents on A1 and A2b receptors to protect HK2 cells injury.

Funding: Government Support - Non-U.S.

TH-PO118

Acute and Chronic Renal Ischemia-Reperfusion Injury and Angiotensin II-Induced Hypertension Are Attenuated in Mice with Proximal Tubule-Selective Deletion of Angiotensin AT1a Receptors

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Background: The present study tested the hypothesis that genetic deletion of angiotensin II (ANG II) AT_{1a} receptors selectively in the proximal tubule of the kidney attenuates renal ischemia-reperfusion injury and ANG II-induced hypertension in mice.

Methods: Proximal tubule-specific AT_{1a} receptor-knockout mice (PT-AT_{1a}-KO) were generated using the standard Cre/LoxP recombination approach. Adult male C57BL/6J (WT), global AT_{1a}-KO, and PT-AT_{1a}-KO mice were subjected to sham surgery or 45 min bilateral renal ischemia, followed by reperfusion for 24 h or 7 days. ANG II-dependent hypertension was induced by infusing ANG II at 1.5 mg/kg/day, i.p., for 2 weeks. Systolic blood pressure (SBP), renal function, glomerular, tubuointerstital, and perivascular fibrotic responses were determined and compared

Results: Basal systolic blood pressure was 22 ± 5 mmHg lower in global AT_{1a}-KO or 11 ± 3 mmHg lower in PT-AT_{1a}-KO mice ($p<0.05$ vs. WT). WT mice developed significant glomerular, cortical tubulointerstitial and perivascular injury 24 h or 7 days after renal ischemia-reperfusion was induced ($p<0.01$). Ischemia and reperfusion renal injury was not prevented in global AT_{1a}-KO mice (n.s. vs. WT), but it was significantly attenuated in PT-AT_{1a}-KO mice 24 h or 7 days after renal ischemia-reperfusion was induced ($p<0.05$ vs. WT or AT_{1a}-KO). WT developed severe ANG II-induced hypertension, as expected, but it was significantly attenuated in PT-AT_{1a}-KO mice ($p<0.01$ vs. WT).

Conclusions: We concluded that AT^{1a} receptors in the proximal tubule of the kidney play a key role in the pathogenesis of renal ischemia-reperfusion injury and ANG II-dependent hypertension.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO119

Necroptosis and Ferroptosis Inhibitors Have Significant Benefit in Acute Ischemic Kidney Injury In-Vivo and In-Vitro

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Background: We aimed to determine if necroptosis or ferroptosis inhibitors are beneficial in murine ischemia reperfusion injury, and if necroptosis or ferroptosis occur in human tubular cells.

Methods: Mice were subjected to 18m of bilateral renal ischemia with 24 or 48h reperfusion. Highly specific RIPK1 inhibitor, GSK547a, or ferroptosis inhibitor Liproxstatin-1 were given from 4h *after* injury. Outputs included creatinine, acute tubular necrosis (ATN) score, phosphorylated MLKL (pMLKL, end effector of necroptosis) stain, TUNEL stain and qPCR. Human renal tubular cells (HK-2) underwent 3 models of ischemia in-vitro +/- necroptosis/ferroptosis inhibitors.

Results: With drug given 4h *after* injury, both RIPK1 inhibitor and liproxstatin-1 significantly reduced serum creatinine (mmol/L)(Vehicle:239.8 (+/- 51.8), RIPK1 inhibitor:103.9 (+/- 48.2) $p<0.001$, Liproxstatin-1:43.1 (+/-14.4) $p<0.001$) and ATN score (Vehicle: 3/4 (3-4), RIPK1 inhibitor: 2/4 (1-2) $p=0.008$, Liproxstatin 1: 2/4 (1-2) $p<0.001$)(9/group) 48h after injury. 24h after injury there was extensive pMLKL in vehicle treated injured kidneys. pMLKL, ATN score and TUNEL stain were significantly reduced by RIPK1 inhibition(N=6). There was median 5-fold increase in renal RIPK3 expression 48h after injury compared to sham animals, this was significantly reduced by RIPK1 inhibition ($p=0.004$) but not by liproxstatin-1 ($p=0.67$) (N=9). A20 (necroptosis inhibitor) expression was significantly higher vs vehicle in RIPK1 inhibitor ($p=0.02$) and liproxstatin-1 ($p=0.01$) treated kidneys. Despite less ATN, Liproxstatin-1, but not RIPK1 inhibitor treated kidneys demonstrated *higher* expression of MCP-1 ($p=0.002$) and TNF-α ($p<0.001$) compared to vehicle. In in-vitro ischemic HK2 cell injury, there was evidence of both necroptosis (MLKL phosphorylation) and ferroptosis (iron dependent lipid peroxidation) with associated benefit for cell survival from necroptosis and ferroptosis inhibitors (N=3-6), although to different extents depending on the type and severity of injury.

Conclusions: Both necroptosis and ferroptosis contribute to ischemic kidney injury. There may be differential effects of related inhibitors on inflammatory genes. Further study is required to determine if this impacts long term renal function after an ischemic injury.

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TH-PO120

Novel Imaging Technique Visualizing Spatiotemporal ATP Dynamics During AKI Predicts Renal Prognosis and Provides Proof-of-Concept for Hypothermia

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Background: The kidney constantly utilizes adenosine 5' triphosphate (ATP), and mitochondrial dysfunction, which leads to ATP depletion, plays an important role in the pathogenesis of kidney diseases. In spite of importance of ATP dynamics, however, lack of technology to visualize *in vivo* ATP dynamics has hindered further analysis. Here we enabled the visualization of spatiotemporal renal ATP dynamics and analyzed whether the ATP dynamics during AKI could predict the renal prognosis.

Methods: To enable intravital ATP imaging, we generated a novel mouse line, which expressed the FRET-based ATP biosensor systemically. We monitored renal ATP dynamics in both warm and cold ischemic reperfusion (IR) models with two-photon microscope. Furthermore, we performed the quantification of fibrosis two weeks after IR, and assessed the correlation between the ATP recovery in acute phase and fibrosis in chronic phase.

Results: The ATP level of proximal tubules (PTs) rapidly decreased to the basal level in only 2 minutes after ischemia induction, whereas that of distal tubules (DTs) was maintained even after 30 minutes. The ATP dynamics in PTs after reperfusion was variable depending on the duration of ischemic time. The longer ischemic time led to slower and more insufficient ATP recovery in PTs. The ATP recovery after 15, 30, and 60 minute-warm IR took 2, 5, and 30 minutes to reach a peak plateau, and the % ATP recovery were 90%, 83%, and 69%, respectively, while the ATP recovery after 30 and 60 minute-cold IR took 2 and 4 minutes, and the % ATP recovery were 90% and 87%, indicating rapid and complete ATP recovery in cold ischemia. Interestingly, the fibrosis in chronic phase was inversely well correlated with the ATP recovery of PTs in acute phase in both warm and cold IR.

Conclusions: We, for the first time, succeeded in visualizing the spatiotemporal ATP dynamics in the kidney and revealed the tolerance of DTs to ischemia from the point of ATP dynamics. After reperfusion, the ATP recovery in PTs was variable depending on the severity of injury, and the ATP dynamics in acute phase might determine the outcome in chronic phase. In addition, cold ischemia results in much more rapid and complete ATP recovery than warm ischemia, which provides proof of concept for renal hypothermia.

TH-PO121

No-Reflow in Experimental AKI

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Background: In acute kidney injury (AKI), multiple redundant pathways contribute to renal failure. Renal microvascular congestion has been observed in clinical AKI. We sought to test the hypothesis that inadequate reperfusion, activation of coagulation and microthrombi are significant factors that result in renal failure following ischemia. We have previously (Dominguez et al, J Am Soc Neph 28:3533) demonstrated improvement in multiple abnormal pathways of injury with exosome therapy.

Methods: The role of activated coagulation, microthrombi formation and fibrinolysis were examined in a model of ischemic AKI using multiphoton, intravital imaging performed 48 hours postischemia. Four groups of rats were studied: sham surgery, bilateral renal ischemia/reperfusion (IR)/vehicle, IR/exosomes, IR/urokinase. Exosomes derived from renal tubular epithelia, urokinase or vehicle (0.9% NaCl) was administered 24 hours postischemia when renal failure was established.

Results: Diffuse renal microvascular thrombi resulted in a heterogeneous decrease in intrarenal blood flow within postischemic kidneys. Administration of exosomes after renal failure occurred, resulted in improved renal blood flow and decreased inflammation, fibrin formation and immunoreactive tissue factor. Urokinase, given after renal failure, improved intrarenal blood flow and decreased renal fibrin and tissue factor, but had less effect on inflammation. Renal function improved rapidly in both the exosome and urokinase groups.

Conclusions: Our data indicate that the no-reflow phenomenon follows global renal ischemia and contributes to heterogeneous, ongoing ischemia leading to a cycle of inflammation, tissue injury and postischemic renal failure. In this model, fibrinolysis improves renal function postischemia.

Funding: Veterans Affairs Support, Private Foundation Support

RENAL PARAMETERS 48 hours postischemia/24 hours post therapy (exosomes or urokinase)

Experimental group		Serum creatinine (mg/dl)	Mean RBC velocity (um/sec)	RBC velocity <200um/sec (%)	RBC velocity >1000um/sec (%)	Microvascular diameter (um)	PMN (number/hpf)	Tissue factor (% area of staining)	Fibrin(% area of staining)
sham	vehicle	0.46±0.08*	824±37*	0*	25*	8.9±0.2	0.6±0.2*	0.19±0.00*	0.31±0.00*
IR	vehicle	1.71±0.18	351±17	38	4	8.9±0.3	2.3±0.3	2.4±0.29*	3.3±0.5
IR	exosomes	0.74±0.03*	760±32*	7*	27*	10±0.5	0.9±0.03*	0.25±0.05*	1.1±0.2*
IR	urokinase	0.84±0.1*	707±33*	14*	20*	9.3±0.5	1.6±0.07*#	0.78±0.24*	1.2±0.3*

*p<0.05 v ischemia/vehicle; #p<0.05 v ischemia/exosomes; PMN, polymorphonuclear neutrophil

TH-PO122

Selective Decontamination of Digestive Tract Attenuates Kidney Ischemia/Reperfusion Injury and Distant Organ Damage via Immune Modulatory Effect

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Background: Emerging evidence suggests the critical role of gut as an amplifier of systemic inflammation in diverse pathological conditions. Selective decontamination of digestive tract (SDD) is known to inhibit colonization by aerobic gram-negative bacilli while preserving anaerobic microflora and is currently being used to prevent infection and also to reduce mortality in critically ill patients. We aimed this study to examine the effect of SDD on the severity of kidney injury as well as on distant organ damage and also the underlying mechanisms.

Methods: We used male C57L/B6 mouse bilateral ischemia/reperfusion injury(IRI) after SDD, which was the mixture of three antibiotics (neomycin 25mg/kg, ampicillin 60mg/kg, and metronidazole 25mg/kg) given by orogastric gavage once daily for 12 days. The renal function, colon immunity, local and systemic inflammation level was assessed. We measured liver function test to check distant organ injury.

Results: Kidney IRI but not bilateral nephrectomy provoked increased intestinal permeability. The "leaky gut" following IRI was accompanied by increased colon apoptosis, decreased claudin-1 expression. Ly6G+ neutrophil infiltration and M1proinflammatory macrophages increased in colon after kidney IRI. SDD before IRI but not bilateral nephrectomy resulted in significant attenuation of kidney injury and inflammation as well as distant organ injury. The protective effect of SDD was associated with better preservation of intestinal permeability, reduced colon apoptosis and restored claudin-1 expression. SDD also led to the expansion of M2 anti-inflammatory macrophages and Tregs in colon. Spleen Tregs and Foxp3 expression were also increased in SDD mice. Mesenteric lymph node cells from SDD mice showed reduced proliferative response upon TCR stimulation, suggesting the state of immune tolerance compared to control mice.

Conclusions: Our results showed the critical role of intestine as an amplifier of kidney injury, inflammation and distant organ damage after IRI. We also showed the protective effect of SDD might be partially mediated by immune modulatory effect through expansion of M2 macrophages and Tregs. Strategies aimed at restoring intestinal integrity, microbiome and intestinal mucosal tolerance could be novel therapeutics in acute kidney injury.

TH-PO123

Spatially-Preserved, Multiplexed Expression Analysis of the Normal and Injured Human Kidney

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Background: Tissue obtained by renal biopsy is a useful substrate for understanding the biology of human acute tubular injury (ATI) with preservation of spatial context - including interactions between resident renal cells and those of the immune system. However, the small amount of tissue obtained in biopsies places a practical limitation on the number of markers that can be analyzed by conventional immunostaining, thereby limiting discovery.

Methods: Imaging mass cytometry (IMC) is a mass spectrometry-based technology that allows for simultaneous analysis of up to 40 protein and mRNA markers on a single section of formalin-fixed paraffin-embedded tissue, with no spectral overlap or background fluorescence. Using a prototype imaging mass cytometer and human kidney obtained by nephrectomy, we have sought to validate a panel of metal-conjugated monoclonal antibodies for use in mapping the human kidney with IMC, while also developing technology to simultaneously interrogate mRNA targets.

Results: We have developed and validated a panel of over 20 metal-conjugated monoclonal antibodies detectable by IMC in the kidney. We have successfully generated two-dimensional reconstructions to 1 micron resolution of reference and injured kidneys simultaneously stained with over 15 metal-tagged antibodies, better defining the spatial relationships between cell types.

Conclusions: With our current panel of antibodies, we will be able to interrogate true normal biopsies from living kidney donors and banked biopsies from patients with ATI. This will allow us to construct semi-quantitative two-dimensional atlases of the resident cell types, immune cells, and markers of cellular injury, stress, activation, regeneration and death in the normal and acutely injured human kidney.

Funding: NIDDK Support, Private Foundation Support

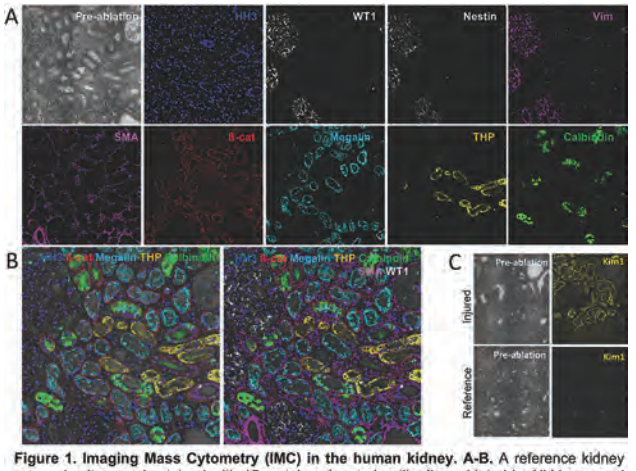

Figure 1. Imaging Mass Cytometry (IMC) in the human kidney. A-B. A reference kidney was simultaneously stained with 15 metal-conjugated antibodies, ablated by UV laser, and atomized particles detected in an imaging mass cytometer; reconstructed false-colored IMC images are shown for 9 markers: histone H3 (a pan-nuclear marker), cytoplasmic WT1 (podocytes), Nestin (podocytes), Vimentin (fibroblasts, podocytes and mesangium), alpha SMA (smooth muscle), ß-catenin (tubular epithelium), Megalin (proximal tubule), Tamm-Horsfall protein (thick ascending loop of Henle) and calbindin (distal convoluted tubule). "Pre-ablation" image is a light microscopic image generated from the tissue area of interest prior to UV laser ablation and IMC. **B.** Merged images overlayed onto the pre-ablation image in A for the indicated markers. **C.** An injured versus reference human kidney stained with a metal-conjugted antibody to Kim1, an injury marker. Note positive staining in the injured kidney and absence of epithelial staining in the reference kidney.

TH-PO124

An Unbiased Functional Genomic Screen Identifies Fibroblast Growth Factor 9 as a Novel Regulator of AKI

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Background: Renal epithelial cell death and dysfunction are the hallmark and underlying cause of acute kidney injury (AKI), a common disorder characterized by sudden loss of renal function, high mortality and lack of therapeutic options. Identification of therapeutic strategies to prevent AKI is an essential but unmet medical need. Here we have used an unbiased functional genomic screen to identify therapeutic and druggable targets for AKI.

Methods: In this study, we carried out an unbiased siRNA-based high throughput screen (HTS) using a mouse renal tubular cell line. In this screen, 5169 druggable genomic genes (number of 384-well plates: 68; quadruplicate) were silenced in BUMPT cells and their effect on cisplatin-mediated cell death was examined by Cell Titer Glo assay. The siRNAs that significantly protected cells from cisplatin-induced cell death were selected for confirmatory secondary screens. Subsequently, by using a pharmacological inhibitor and renal tubule specific knock-out mice (GGT-Cre and FGF9 flox mice), one of the top hits from these screens was validated as a potential therapeutic target in three mouse models of AKI, namely cisplatin-, ischemia-, and rhabdomyolysis-induced AKI. In these mouse models, renal impairment was determined by accumulation of nitrogenous waste (blood urea nitrogen and serum creatinine), biomarkers of kidney injury (KIM1 and NGAL expression) and histological analysis (H&E staining and renal damage score).

Results: Our primary and confirmatory screens identified FGF9 as one of the regulators of renal cell death and injury. Infigratinib, a pan inhibitor of FGF9 receptors, mitigated kidney injury (KIM1, NGAL and renal damage score) and significantly improved renal function (blood urine nitrogen and creatinine) in three mouse AKI models (Vehicle vs. Infigratinib group, $p \leq 0.01$). Furthermore, renal tubule specific FGF9 knock-out mice exhibited significant protection from AKI as compared to their control littermates.

Conclusions: Using a novel HTS mediated functional genomic screen, we have identified FGF9 associated signaling network as a crucial modulator of renal dysfunction and AKI. Proof-of-principle experiments also suggest that pharmacological or genitic inhibition of FGF9 signaling can mitigate AKI.

TH-PO125

Translating Ribosome Affinity Purification (TRAP) Molecular Profiling of Kidney Cell Types: A Data Resource

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Background: The Translating Ribosome Affinity Purification (TRAP) methodology was developed in the labs of Nathaniel Heintz and Paul Greengard at Rockefeller University in order to overcome the inherent cellular complexity of tissues and to obtain cell-type specific translational profiles of critically relevant cell types in these tissues (Doyle et al., Heimann et al., Cell, 2008). Using bacTRAP transgenic mouse lines licensed from Rockefeller University or generated at Takeda, California, we here apply the TRAP methodology to profile relevant kidney cell types, both in a basal state as well as in models of acute kidney injury.

Methods: We employed the TRAP methodology in order to obtain translational profiling data from multiple kidney cell types. Transgenic mice expressing the EGFP-ribosomal L10a fusion protein under kidney cell type specific promoters were generated using standard techniques and characterized for EGFP-L10a expression in the cell types of interest. For collection of TRAP samples, whole kidneys were isolated from several mice, homogenized, and processed following standard TRAP protocols. Total tissue mRNA and cell-type enriched TRAP mRNA samples were amplified, libraries prepared, and sequenced following routine protocols.

Results: We have collected kidney TRAP data covering two general areas: 1. Baseline data, collected from unperturbed transgenic bacTRAP mice, targeting specific cell types (podocytes, proximal tubule epithelial cells (PTECs) and subsets of PTECs, and perivascular mesenchymal cells) 2. Data from disease model studies (sepsis, bilateral ischemia-reperfusion).

Conclusions: Here we demonstrate that bacTRAP is a powerful tool for translational profiling of kidney cell types. In order to make best use of our kidney TRAP datasets, we are making this data available to the greater scientific community. This data is an invaluable resource for identification of potential drug targets and biomarkers for kidney disease, as well as for elucidating the mechanism of action for kidney disorders and drug response. In addition to the RNAseq data, we have access to many TRAP mouse lines on the C57Bl6/J strain which are also available. Details of data and transgenic mouse lines will be available at this poster session.

Funding: Commercial Support - Takeda California, Inc

TH-PO126

Optogenetic Stimulation of Either Efferent or Afferent Vagus Neurons Protects Kidneys from Ischemia-Reperfusion Injury

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Background: We recently reported that electrical vagus nerve stimulation (VNS) in the neck protects mouse kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway (CAP). Stimulation of vagal efferent neurons is believed to be essential to the activation of CAP. However, we found that electrical stimulation of the cephalic end of a divided vagus nerve was equally effective against IRI. It is therefore still unclear whether afferent or efferent VNS is most important in ameliorating renal IRI.

Methods: Channelrhodopsin-2 (ChR2) is a light-sensitive, non-selective cation channel that is opened only during blue light application. We crossed *loxP-STOP-loxP ChR2* mice with choline acetyltransferase (*Chat*)-*cre* and vesicular glutamate transporter 2 (*Vglut2*)-*cre* mice to generate *Chat-ChR2* and *Vglut2-ChR2* mice expressing ChR2 in vagal efferent and afferent neurons, respectively. Illumination of the cervical vagus nerve with blue laser selectively stimulated vagal efferent and afferent neurons ("efferent VNS" and "afferent VNS") in *Chat-ChR2* and *Vglut2-ChR2* mice, respectively. Optogenetic stimulation with blue laser (wavelength: 473 nm) of left cervical vagus nerve was performed with 50 Hz (10 sec) to observe physiological changes and with 5 Hz (10 min) in renal IRI experiments to minimize physiological changes. IRI surgery was performed 24 h after optogenetic VNS; mice were euthanized 24 h later.

Results: Blue laser (50 Hz) applied to the cervical vagus nerve, decreased heart rate markedly (300→180 bpm) with no change in respiratory rate in *Chat-ChR2* mice and completely paused breathing by activation of Hering-Breuer inflation reflex in *Vglut2-ChR2* mice, proving selective efferent VNS and afferent VNS. Both efferent VNS (plasma Cr: 1.53±0.20 vs. 0.48±0.05 mg/dL) and afferent VNS (plasma Cr: 1.09±0.22 vs. 0.44±0.06 mg/dL) with 5 Hz protected kidneys from IRI, improved kidney histology and decreased renal *Kim-1* expression. Splenectomy abolished the protective effect in both groups.

Conclusions: Afferent VNS as well as efferent VNS protects the kidneys from IRI. In both cases protection requires the spleen. These results support the hypothesis that CAP underlies the beneficial effect of efferent VNS on IRI and propose that a sympathetic reflex mediates the protective effect of afferent VNS.

Funding: NIDDK Support

TH-PO127

Enhancer and Super-Enhancer Dynamics in Kidney Repair

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Background: The endogenous repair process of the mammalian kidney allows rapid recovery after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. There is currently limited understanding of which transcriptional regulators activate these repair programs. Here we investigate the existence of enhancer dynamics in the regenerating mouse kidney.

Methods: RNA-seq and ChIP-seq (H3K27ac, H3K4m3, BRD4, MED1, POL2) were performed on samples from repairing kidney cortex 4 hours and 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and

super-enhancer dynamics. Further, we investigated the role of super-enhancer activation after IRI through pharmacological BET inhibition via the small chemical compound JQ1 in vitro and in AKI models *in vivo*.

Results: AKI leads to genome-wide alterations in enhancer repertoire *in vivo*. We identified 16,781 enhancer sites (H3K27ac / BRD4 positive, H3K4me3 negative) active in Sham and IRI samples; 6,512 lost and 9,774 gained after IRI. The lost and gained enhancer sites could be annotated to 62% and 63% of down- and up-regulated transcripts after AKI, respectively. The top 5 transcription factor binding motifs enriched in lost enhancer sites are Hnf4a, Esrrb, PPARE, RXR and Esrra. In contrast Fra1, Fosl2, Atf3, Jun-AP1 and BATF binding motifs are enriched in gained enhancer sites after injury. Both transcription factor groups show corresponding mRNA changes after injury. Super-enhancer analysis reveals 164 lost and 216 gained super-enhancer sites after IRI. 385 super-enhancers maintain activity before and after injury. Pharmacological inhibition of super-enhancer activity by BRD4 inhibition (JQ1 50 mg/kg/day) before IRI led to suppression of 40% of injury-induced transcripts associated with cell cycle regulation, and significantly increased mortality between days 2 and 3 after AKI.

Conclusions: These results are the first demonstration of enhancer and super-enhancer function in the repairing kidney. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET proteins that are already being tested in clinical trials. Our comprehensive analysis of enhancer changes after kidney injury *in vivo* has the potential to identify new targets for therapeutic intervention.

Funding: NIDDK Support, Other NIH Support - Marie Curie, Austrian Science Fund

TH-PO128

Application of New Hypertension Guidelines to Renal Transplant Recipients: Impact on Cardiovascular Outcome and Graft Survival

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Background: Based on data of the SPRINT trial, American national guidelines recently reduced the blood pressure goal from 140/90 mm Hg to 130/80 mm Hg for subjects with increased cardiovascular risk, e. g. those with chronic kidney disease. To date it remains elusive whether renal transplant recipients benefit from these goals as well.

Methods: We performed a retrospective analysis of 877 patients who underwent kidney transplantation between 1997 and 2011 in three transplant centers in Germany (Berlin and Bochum) with a follow-up of 12 - 120 months. Blood pressure was obtained at regular follow-up examinations in the transplant outpatient clinic. Patient and graft survival was defined as composite endpoint. Subjects were stratified according to mean systolic blood pressure values < 130 mmHg, 130-139 mmHg, or ≥ 140 mmHg.

Results: Mean SBP of the overall follow-up period was significantly associated with patient and graft survival. Cumulative survival was significantly higher for those patients with a systolic blood pressure (SBP) < 130 mmHg than those with 130-140 mmHg. Survival was lowest in renal transplant recipients with a mean SBP ≥ 140 mmHg. Analogously, mean SBP of the first 12 months posttransplant < 130 mmHg was associated with better cumulative patient and graft survival than higher blood pressure values in Kaplan Maier analyses.

Conclusions: Renal transplant recipients who achieve a mean systolic blood pressure < 130 mmHg have a significantly lower mortality and a better allograft outcome than with the conservative blood pressure goal < 140 mmHg. The new blood pressure targets should be considered suitable for renal transplant recipients as well.

TH-PO129

Progression of Cardiovascular Calcification in Renal Transplant Recipients

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Background: Cardiovascular disease is the leading cause of death in renal transplant patients. We conducted a study to determine the progression of cardiovascular calcification in renal transplant recipients.

Methods: 192-slice computed tomography was used to longitudinally examine abdominal and thoracic aortic calcification (AAC, TAC) and CAC in 34 renal transplant recipients at time of transplantation, at 6 months (n=28), and at 12 months (n=24). Univariate analyses were used to assess risk factors for CAC progression. Transplant patients were matched to 50 dialysis patients. Linear regression was used to adjust for baseline CAC in evaluating groups' calcification progression.

Results: Boxplots for AAC, TAC and CAC scores are shown in fig. 1. Pre-transplant square root of CAC volume (SqrtCACVol) correlated with serum calcium (r=.44, p=.012), magnesium (r=.43, p=.018), male gender (r=.56, p=.001), CAD (r=.49, p=.004) and age (r=.65, p < .001), but not with presence of diabetes, phosphorous, or dialysis vintage. None of these variables were associated with 1-year changes in SqrtCACVol. In the matched groups, transplant patients gained less SqrtCACVol compared to dialysis patient (Transplant: 1.3, 95% CI -0.4 - 3.1; Dialysis: 3.9, 95% CI 1.9 – 5.9, fig. 2), though this difference was not significant (p = 0.07).

Conclusions: Renal transplantation does not stop or reverse vascular calcification; however the rate of progression was less compared to dialysis patients.

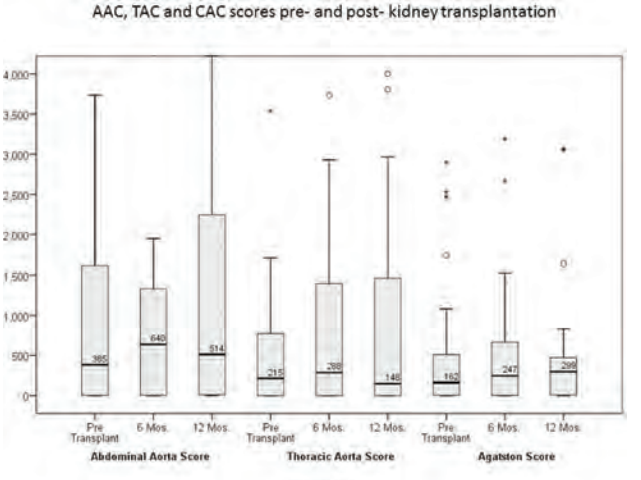

Figure 1.

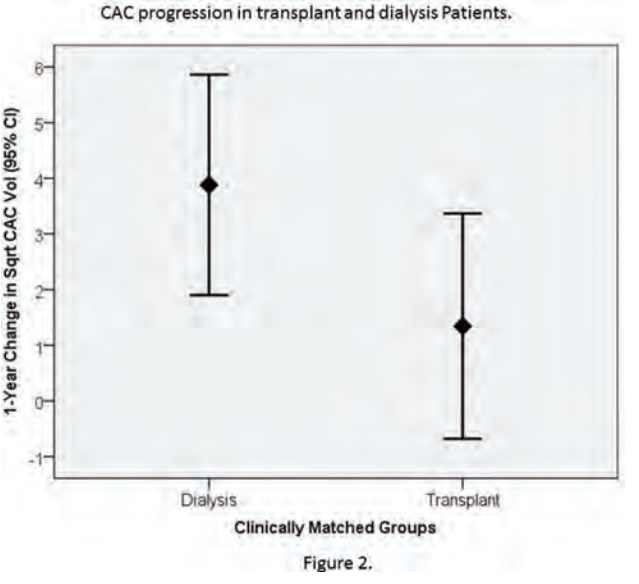

Figure 2.

TH-PO130

Vascular Calcification Slows but Does Not Regress After Renal Transplantation

Harish R. Alappan,[2] Payaswini Vasanth,[1] Shumila Manzoor,[3] W. Charles O'Neill.[1] *[1]Emory University, Atlanta, GA; [2]Emory University - Undergraduate, Atlanta, GA; [3]Renal Division,Department Of Medicine, Emory University, Atlanta, GA.*

Background: While prevention of uremic vascular calcification has been extensively studied, it is not clear whether this lesion is reversible. To address this, we measured the change in breast arterial calcification (BAC), a marker of generalized medial arterial calcification, after successful kidney transplantation (Tx) in women without other risk factors for medial arterial calcification.

Methods: Women with kidney transplantation between 2009 and 2016 who had BAC and at least 2 digital mammograms performed at this institution after Tx were included. Women with diabetes, warfarin use, or serum creatinine > 1.4 were excluded. Breast arterial calcification (BAC) was measured on serial mammograms and linear regression was performed on each patient. Comparison was made to randomly selected cohorts of women with ESRD or eGFR ≥ 60 ml/min/1.73 m^2.

Results: Characteristics of the final cohort of 16 patients (with ranges) were: mean age at Tx, 56 (39-67); mean pre-Tx ESRD duration, 7.0 years (0.3-14); mean serum creatinine at most recent mammogram, 1.05 mg/dl (0.60-1.40); median baseline BAC, 41 mm/breast (2-776); mean number of mammograms, 3.6 (2-6). The slopes of BAC vs. time showed a mean increase of 5.3 ± 2.6 mm/breast/y or 9.8 ± 5.2 %/y, which was significantly ≥0 (p<0.05). This was significantly less than the rate of 18.1 ± 5.6 mm/breast/y in 23 ESRD women (p=0.017) and similar to the rate of 4.3 ± 0.7 mm/breast/y in 43 women with eGFR ≥ 60 ml/min/1.73 m^2. The rate decreased in all 3 patients in whom it could also be measured pre-Tx. The post-Tx slope was negative in 7 patients but within the error of the measurement. In the 10 patients with >2 mammograms, none showed consistent decreases in BAC with each mammogram. There was no difference in age, pre-Tx ESRD duration, baseline BAC, or serum creatinine between patients with positive and negative slopes.

Conclusions: We conclude that medial arterial calcification significantly slows but does not regress after renal transplantation. This irreversibility emphasizes the importance of strategies to prevent vascular calcification during CKD and ESRD.

Funding: Clinical Revenue Support

TH-PO131

Factors Associated with Coronary Artery Calcification Score in Renal Transplant Recipients

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Background: Coronary artery calcification (CAC) is associated with cardiovascular morbidity. The presence and severity of CAC amongst renal transplant patients may vary because of heterogeneity within the population. We sought to determine factors associated with CAC using baseline data from a clinical trial.

Methods: Prevalent renal transplant patients recruited to a clinical trial of vitamin K supplementation (ViKTORIES: ISRCTN22012044) were included. Biochemical tests were performed and demographic data recorded at the baseline visit. Coronary artery calcification (CAC) was determined by non-contrast CT coronary calcium (Agatston) score; score >160 was considered high. Binary logistic regression analysis was used to determine factors associated with high CAC score. Analyses were conducted using *stats* and *oddsratio* for R statistical software.

Results: There were 68 trial participants included: 70.6% were male; 97.1% were Caucasian. Patients with high CAC score (58.8%; median score 1269, IQR 502-3245) were older (60.8 vs 54.7 years; p=0.01) with similar systolic blood pressure (152 vs 144 mmHg; p=0.08) and proteinuria (urine protein creatinine ratio 98 vs 72 mg/mmol; p=0.56), but had longer time since renal transplant (11.2 vs 7.4 years; p=0.05) and time since first renal replacement therapy (17.0 vs 9.8 years; p=0.002). There was no difference in graft function (GFR 50.6 vs 54.2 ml/min; p=0.54) and both groups had controlled calcium, phosphate and parathyroid hormone. Vitamin D insufficiency (vitamin D <30 ng/nl) was common in both groups (71.4 vs 65.0%; p=0.58). On binary logistic regression analysis, factors associated with high CAC score were older age (OR 1.18 per 10-year increase; 95% CI 1.05-1.33), longer duration of non-transplant RRT (OR 1.02 per year; 95% CI 1.01-1.04) and current or previous smoking history (OR 1.35; 95% CI 1.09-1.67).

Conclusions: In a diverse group of renal transplant recipients, high CAC score was associated with older age, dialysis vintage and smoking status, but not with traditional markers of CKD mineral and bone disorder or vitamin D insufficiency. These offer few modifiable risk factors for intervention, though smoking cessation may be worthwhile. Activity of calcification inhibitors may be important in this patient group and warrant further study.

Funding: Private Foundation Support

TH-PO132

High Molecular Weight Adiponectin Inhibits Vascular Calcification in Renal Allograft Recipients

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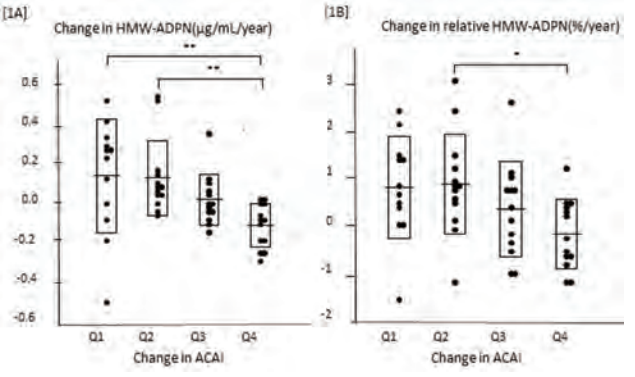
Background: Adiponectin (ADPN) prevents the development/recurrence of cardiovascular events via its anti-atherogenic effects. However, few long-term studies have examined the changes in serum ADPN levels and arterial calcification seen in renal allograft recipients.

Methods: The effects of the serum ADPN level on arterial calcification were examined in 51 Japanese renal allograft recipients. Abdominal aorta calcification was evaluated on computed tomography using the aortic calcification area index (ACAI). The change in the ACAI and serum high-molecular-weight (HMW) - ADPN fractions were studied over an 8-year period. The arterial expression of ADPN, ADPN receptors (AdipoR)1 and 2, and T-cadherin (cadherin-13) were also examined by immunohistochemistry.

Results: 1) The change in the ACAI were grouped into quartiles and compared with the alterations in the serum levels of each ADPN fraction over an 8-year period. The change in the ACAI was much lower in the patients with highly elevated HMW-ADPN levels. 2) Multiple regression analysis demonstrated that an advanced age at transplant and a history of cardiovascular complications were associated with an increased change in the ACAI, while higher HMW-ADPN concentrations were associated with improvements in the ACAI. Serum HDL-C level was also identified as a positive factor to increase serum HMW-ADPN level. 3) In immunohistochemical examinations, ADPN was detected on CD31-positive arterial endothelial cells from renal allograft biopsy samples. ADPN co-localized with T-cadherin and AdipoR1, but only partially co-localized with AdipoR2.

Conclusions: Both HMW-ADPN and HDL-C might inhibit the progression of vascular calcification by promoting ADPN binding to vascular endothelial cells via T-cadherin and AdipoR in Japanese renal allograft recipients.



TH-PO133

Serum Calcification Propensity and Fetuin-A: Biomarkers of Cardiovascular Disease in Long-Term Kidney Transplant Recipients

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Background: "T50," shortened transformation time from primary to secondary calciprotein particles, may reflect deranged mineral metabolism predisposing to vascular calcification, and cardiovascular disease [CVD]. The glycoprotein fetuin-A is a major T50 determinant.

Methods: The FAVORIT cohort, is a completed, large, multiethnic controlled clinical trial cohort of chronic, stable kidney transplant recipients (KTRs). We conducted a longitudinal case-cohort analysis using a randomly selected subcohort of patients, and all individual cases who developed CVD. Serum T50 and fetuin-A were determined in this total of n=685 FAVORIT trial participants at randomization.

Results: 311 incident or recurrent CVD events occurred during a median surveillance of 2.18-years. Shorter T50 (minutes), or reduced fetuin-A concentrations (g/L) were associated with CVD after adjustment for treatment assignment, systolic blood pressure, age, sex, race, pre-existing CVD and diabetes, smoking, body mass index, total cholesterol/HDL cholesterol, kidney allograft vintage and type, calcineurin inhibitor, or lipid lowering drug use, estimated glomerular filtration rate, and urinary albumin/creatinine: tertile 1 (lowest) to tertile 3 (highest) comparisons, T50, [HR= 1.86; 95% CI= (1.20, 2.89)]; fetuin-A, [HR=2.25, 95% CI= (1.38, 3.69)]. Elevated high sensitivity c-reactive protein [hsCRP] was an effect modifier of both these associations.

Conclusions: Shortened T50, as well as reduced fetuin-A levels, ostensible promoters of vascular calcification, remained associated with greater risk for CVD outcomes, after adjustment for major CVD risk factors, measures of kidney function and damage, and KTR clinical characteristics and demographics, in a large, multiethnic cohort of long-term KTRs. Increased hs-CRP was an effect modifier of these CVD risk associations.

Calcification propensity/T50 (minutes), Fetuin-A (g/L), & CVD outcomes in FAVORIT: A Case-Cohort Analysis

T50 per SD decrease‡	T1: 114-311 (median=276)	T2: 312-367 (median=339)	T3: 368-552 (median=410)
HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1: 1.33 (1.15, 1.54)*	Model 1: 2.28 (1.56, 3.33)	1.53 (1.04, 2.25)	(referent)
Model 2: 1.21 (1.01, 1.44)**	Model 2: 1.86 (1.20, 2.89)	1.41 (0.88, 2.26)	(referent)
Model 3: 1.22 (1.03, 1.46)***	Model 3: 1.85 (1.18, 2.90)	1.44 (0.90, 2.31)	(referent)
Model 4: 1.23 (1.03, 1.48)****	Model 4: 2.00 (1.27, 3.15)	1.49 (0.90, 2.45)	(referent)

Fetuin-A per SD decrease‡	T1: 0.19-0.38 (median=0.34)	T2: >0.38-0.46 (median=0.42)	T3: >0.46-0.71 (median=0.51)
HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1: 1.39 (1.19, 1.62)*	Model 1: 2.32 (1.60, 3.37)	1.56 (1.05, 2.30)	(referent)
Model 2: 1.29 (1.07, 1.56)**	Model 2: 2.21 (1.37, 3.57)	1.59 (0.97, 2.60)	(referent)
Model 3: 1.31 (1.09, 1.58)***	Model 3: 2.25 (1.38, 3.69)	1.67 (1.01, 2.77)	(referent)
Model 4: 1.29 (1.07, 1.56)****	Model 4: 2.19 (1.33, 3.62)	1.65 (0.99, 2.76)	(referent)

Total case-cohort n=685: random subcohort n=433, median follow-up=3.7 years, 311 total CVD events in full case-cohort sample during follow-up; ‡T50, in minutes, mean=340, SD=70.4; Fetuin-A in g/L, mean=0.42, SD=0.08; *T50 or Fetuin-A unadjusted, per SD increase, & across tertiles; **Model 2: adjusted for systolic blood pressure, age, sex, race, pre-existing CVD or diabetes, smoking, body mass index, total cholesterol/HDL cholesterol ratio, kidney allograft vintage and type (deceased vs. living donor), calcineurin inhibitor use, & lipid lowering drug use; ***Model 3: adjusted for all the variables in Model 2, plus eGFR and natural log urinary albumin/creatinine. **** Model 4: adjusted for all variables in Model 3, plus natural log plasma hsCRP. Total case-cohort sample with hsCRP available, n = 691, including n=431 in random subcohort, and n=309 CVD cases

TH-PO134

Impact of Hypertension and White Coat Hypertension on Renal Function and Blood Pressure Post Kidney Donation

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Background: The effects of nephrectomy on blood pressure (BP) and renal function in kidney donors with hypertension (HTN) and white coat HTN are unclear. This study is a pilot of a planned larger project aimed at investigating this in UK kidney donor population.

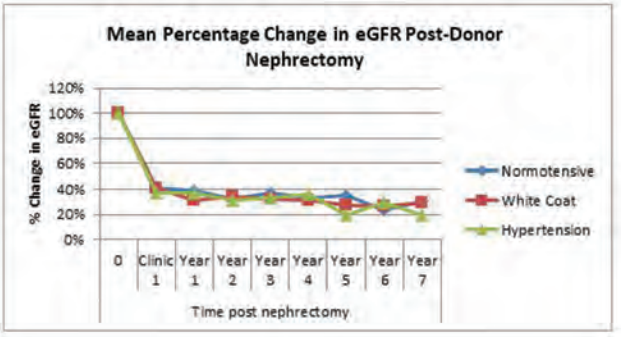
Methods: Living donors with HTN and white-coat HTN (BP >140/90 but normal ABPM) between January 2010 to December 2014 were identified. Matched normotensive donors were chosen as controls.

Results: N=30, 10 in each category. Table 1 shows demographics pre-donation. There was no significant difference in percentage reduction of eGFR post-donation across all donor groups (Figure 1). No donor had proteinuria pre-donation. Post-donation, donors with normal BP and white coat HTN did not develop proteinuria. However 20% donors

in HTN group developed proteinuria. All normotensive donors had normal BP readings post-donation. No donors in the white coat HTN group took anti-hypertensive medication pre-donation; post-donation, 40% required medication. All donors in HTN group took anti-hypertensive medications pre-donation; of these, 70% had raised BP post-donation needing uptitration of medications.

Conclusions: There was no significant difference in change in renal function across all 3 groups. Our observations of higher incidence of proteinuria and uptitration of BP medications in donors with HTN, and significant proportion of donors with white coat HTN requiring antihypertensive medications post-donation merits further investigation. Our future work will investigate the impact of pre-donation HTN and white coat HTN on renal function and cardiovascular health in a large cohort of kidney donors.

	Normotension	White Coat HTN	HTN
Age (years) - Median (Range)	49 (32-64)	47.5 (34-61)	51 (45-66)
Gender	60% male, 40% female	50% male, 50% female	40% male, 60% female
Ethnicity	90% Caucasian, 10% Caribbean	80% Caucasian, 10% African, 10% Other	80% Caucasian, 20% Asian
eGFR (mls/min) - Median (Range)	92 (72-114)	95.5 (68-119)	94.5 (64-103)
ACR (mg/g)	<5	<5	<5-16.1
Clinic BP (mmHg) - Median (Range)	128/79 (121/76-129/86)	144/94 (124/76-162/104)	145/88 (124/68-158/96)
Follow up time (months) - Median (Range)	60 (48-84)	84 (1-84)	72 (36-96)



TH-PO135

Association Between Malnutrition – Inflammation Score and Bone Fractures in Prevalent Kidney Transplant Recipients

Miklos Z. Molnar,[1,4] Abduzhappar Gaipov,[1] Orsolya Cseprekál,[2] Praveen Kumar Potukuchi,[1] Kairat Kabulbayev,[5] Manish Talwar,[6] James D. Eason,[7] Istvan Mucsi,[3] Csaba P. Kovesdy.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]Semmelweis University, Budapest, Hungary; [3]University of Toronto, Toronto, ON, Canada; [4]Transplant Nephrology- Methodist Le Bonheur, Memphis, TN; [5]Kazakh national medical university, Almaty, Kazakhstan; [6]UTHSC, Germantown, TN; [7]University of TN/Methodist Transplant Institute, Memphis, TN.*

Background: Kidney transplant recipients (KTR) have a 4-fold higher risk of fracture compared to the general population. Chronic inflammation and protein energy wasting (PEW) syndrome are common in KTR and associated with poor outcomes. The presence of inflammation and PEW syndrome can directly affect bone resorption and bone formation, leading to bone loss and fractures. We assessed the association between Malnutrition-Inflammation Score (MIS) a marker of PEW and bone fractures in KTR.

Methods: This prospective cohort study included 839 prevalent KTR. MIS is a semiquantitative instrument for the evaluation of Malnutrition–Inflammation Complex Syndrome, was calculated at the study entry. Self-reported history of fractures was recorded during the 2-year follow-up period. The association between MIS and bone fractures was examined in logistic regression analyses with adjustment for age, gender, eGFR, smoking habits, history of pre-transplant bone fractures and acute rejection.

Results: Mean age was 51±13 years and 56% of patients were males. Fifty-five (7%) patients experienced bone fractures during the follow-up period. In logistic regressions, MIS score showed linear association with increased risk of fracture (Figure 1). Each 1-point higher MIS was associated with 23% higher risk of bone fractures (odds ratio (OR) and 95%CI: 1.23, 1.12–1.34), which remained significant after multivariable adjustments (OR: 1.17, 95%CI: 1.06–1.29).

Conclusions: The MIS is independently associated with new bone fractures in prevalent KTR.

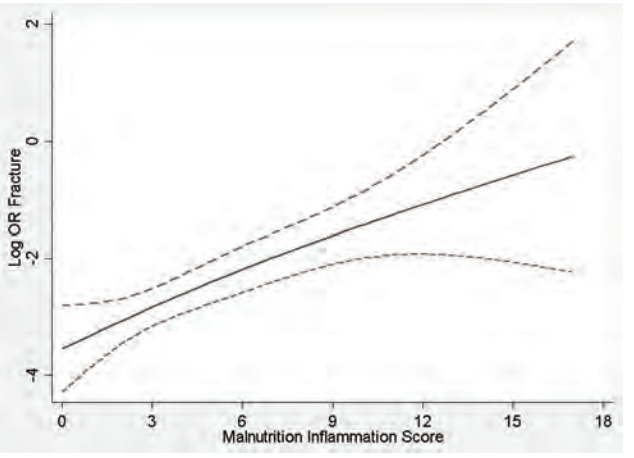


Figure 1. An association of MIS with bone fractures using cubic splines

TH-PO136

Association Between Serum Pre-Albumin Level and Outcomes in Prevalent Kidney Transplant Recipients

Miklos Z. Molnar,[1,3] Abduzhappar Gaipov,[1] Christopher D. Jackson,[1] Manish Talwar,[1,3] Vasanthi Balaraman,[1,3] Arijit Chakravarty,[1,3] Orsolya Cseprekál,[2] Zoltan Mathe,[2] Adam Remport,[2] Csaba P. Kovesdy,[1] James D. Eason,[1,5] Istvan Mucsi.[4] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]Semmelweis University, Budapest, Hungary; [3]Transplant Nephrology- Methodist Le Bonheur, Memphis, TN; [4]University of Toronto, Toronto, ON, Canada; [5]University of TN/Methodist Transplant Institute, Memphis, TN.*

Background: Prealbumin, a transport protein mostly synthesized in the liver, is a marker of nutrition. While decreased prealbumin levels are associated with increased mortality in end stage kidney disease patients, its association with mortality in kidney transplant recipients remains unknown. We evaluated the association between prealbumin levels and outcomes in kidney transplant recipients.

Methods: This prospective cohort study included 991 kidney transplant recipients enrolled from December 31, 2006 to December 31, 2007 and followed over a 6-year period. Sociodemographic, past medical history, clinical and laboratory data were collected at the study entry. Associations between prealbumin levels and death with functioning graft, all-cause mortality and graft loss were examined using survival models.

Results: Serum prealbumin levels showed significant negative correlation with eGFR (R=-0.28, p<0.001), and hsCRP (R=-0.24, p<0.001) (Figure 1). Each 5 mg/dL lower serum prealbumin level was associated with 20% higher risk of death with functioning graft (Hazard Ratio (HR) [95% Confidence Interval (CI)]: 1.20 [1.08–1.35], p=0.001), which persisted after multivariable adjustments (HR [95%CI]: 1.13 [1.00–1.28], p=0.039) (Figure 2). Qualitatively similar trend was observed in all-cause mortality; however, there was no association between prealbumin levels and graft loss (Figure 2).

Conclusions: Lower serum prealbumin level is associated with increased risk of death with functioning graft and all-cause mortality in prevalent kidney transplant recipients.

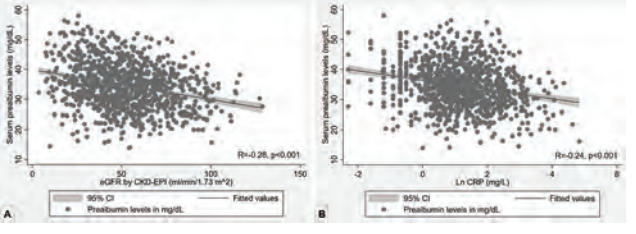


Figure 1: Association between serum prealbumin level with eGFR (panel A) and serum C-reactive protein (panel B).

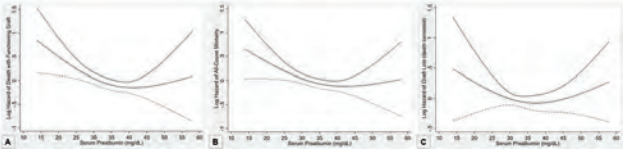


Figure 2: An adjusted association of serum prealbumin levels with death with functioning graft (panel A), all-cause mortality (panel B) and death censored graft loss (panel C) using cubic splines

TH-PO137

Myocardial Perfusion Reserve Is Preserved in Patients with Kidney Transplant

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Background: Chronic kidney disease (CKD) has been associated with decreased myocardial perfusion reserve (MPR), the ratio of stress and rest perfusion. MPR reflects the capacity of vascular bed to increase perfusion and reflects the endothelial function and microvascular responsiveness. The effect of kidney transplantation on MPR is unknown. In this study our aim was to assess MPR of kidney transplant patients.

Methods: 10 healthy subjects and 19 kidney transplant patients without manifest atherosclerotic disease and with mild to moderate kidney impairment were included in the study. The average age of kidney transplant patients was 37 +/-23 months. Myocardial perfusion (MP) was measured by means of [^{15}O]H_2O PET (positron emission tomography) at rest and during adenosine infusion.

Results: MP was statistically significantly higher at rest in the kidney transplant patients than in the healthy controls (p=0.0015). After correction by cardiac work load (basal MP_{corr}, corrected basal myocardial blood flow, [(MP/own RPP)xRPP average of the healthy]) the difference between the groups disappeared. Coronary vascular resistance (CVR) at rest and CVR and MP at stress were comparable between the groups. Although MPR was reduced, MPR_{corr} (=stress flow/basal MP_{corr}) did not differ between the kidney transplant patients and the healthy controls.

Conclusions: MP and CVR during stress are preserved in the kidney transplant patients with mild to moderate CKD. The reduced MPR is explained by increased resting MP which is likely linked with increased cardiac workload due to sympathetic overactivation in the transplant patients.

Funding: Private Foundation Support

	Kidney transplant patients	Controls
	N=19	N=10
Basal MP (ml/min/g)	1.3 (0.4)*	1.0 (0.2)
RPP	10053 (2878)*	6723 (1112)
Basal MP corr (ml/min/g)	0.9 (0.2)	1.0 (0.3)
Stress MP (ml/min/g)	3.8 (1.0)	4.0 (0.9)
MPR	3.0 (0.9)*	4.2 (1.0)
MPR corr	4.3 (1.6)	4.1 (1.1)
CVR basal [mmHgmL(-1)min(-1)g(-1)]	83 (19)	93 (21)
CVR stress [mmHgmL(-1)min(-1)g(-1)]	27 (9)	22 (8)

Values are mean (SD),

*P<0.05 controls versus kidney transplant patients

TH-PO138

Arterial Stiffness and Immunosuppressive Regimen in Renal Transplants Recipients

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Background: Reduction of cardiovascular influences on the long-term survival rates of renal transplant recipients (RTRs) The aim of the study was to assess the relation between immunosuppression and pulse wave velocity in RTRs.

Methods: 103 RTRs, who were visiting outpatient clinic in February 2018 were enrolled into the study. eGFR was calculated with the CKD-EPI formula. Arterial stiffness was assessed by means of brachial-ankle and carotid-femoral pulse wave velocity (baPWV, cfPWV) measured by ABI-system 100. Patient characteristics and results were described by median and interquartile range (IQR) for continuous variables and by frequencies for categorical variables.

Results: Median age of 103 studied RTRs was 53 (37-61) years, 64 (62.1%) patients were male. Details are presented in figure 1. The immunosuppressive regimen was as follow: calcineurin inhibitors (CNI) (68.9/17.5% on TAC/CsA, respectively), antiproliferative agents (48.5/47.6% on MPS/MMF, respectively), steroids (39.8/7.8/3.9% on methylprednisolone/prednisolone/prednisone, respectively), belatacept (6.8%). There was linear correlation between CsA level and cfPWV (p <0,05). CsA concentration/dose (C/D) ratio correlated with baPWV (p<0,05). Neither tacrolimus daily dose nor concentration correlated with baPWV and cfPWV, respectively. C/D ratio of TAC correlated with cfPWV p<0,05). There were observed linear correlations between age of the patients, duration of renal replacement therapy and baPWV, cfPWV (p<0,05). eGFR correlated negatively with cfPWV (p<0,05)

Conclusions: CsA and TAC were administered in the majority of the study population. CNI increased the arterial stiffness. Both CsA and TAC C/D ratio had the influence on PWV. Age, RRT duration time and eGFR correlated with arterial stiffness markers

Parameter	Median (IQR) value	unit
Time after KTx	61 (22-110)	month
Total time of RRT	134 (73-188)	month
eGFR	52 (38-72)	ml/min/1,73m^2
Creatinine level	1.41 (1.05-1.88)	mg/dl
baPWV	11,9 (10.9-13.6)	m/s
cfPWV	8.1 (6.9-9.7)	m/s
TAC (dose/day)	3.5 (2.5-5.0)	mg
TAC (concentration of drug)	5.84 (4.71-7.76)	ng/ml
TAC (concentration/dose ratio)	1,716 (1.127-2.303)	-
CsA (dose/day)	150 (120-240)	mg
CsA (concentration of drug)	87.59 (73.79-102.2)	ng/ml
CsA (concentration/dose ratio)	0,554 (0.359-0,821)	-

Figure1. The values of median

TH-PO139

Progression of Endothelial Dysfunction, Atherosclerosis, and Arterial Stiffness in Kidney Transplant Patients

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Background: Cardiovascular events are the commonest cause of mortality and morbidity in kidney transplant recipients, yet little is known about the changes in vascular structure and function with time. This pilot study investigated changes vascular structure and function over time, in stable kidney transplant patients (KTxPs) compared to controls.

Methods: Brachial artery flow-mediated dilation (FMD), nitroglycerine-mediated dilation (NMD), carotid-femoral pulse wave velocity (cf-PWV), ankle-brachial pressure index (ABPI), and common carotid artery intima-media thickness (CCA-IMT) were assessed in 18 KTxPs and 17 controls at baseline and 3-6 months after. All subjects were recruited after written consent and all measurements were done in our vascular laboratory under standard conditions.

Results: There were more dyslipidaemics in KTxPs compared to controls (10 vs. 3; *P*=0.02). There was no difference in age (51.28 ± 13.29 vs. 45.82 ± 10.85; *P*=0.19), body mass index (25.56 ± 5.18 vs. 24.59 ± 2.59; *P*=0.49), or diabetes status (3 vs. 0; *P*=0.08). No difference existed in vascular markers between KTxPs and controls at baseline: FMD (4.34 ± 3.45 vs. 4.63 ± 3.02 %; *P*=0.79), NMD (15.15 ± 6.08 vs. 16.00 ± 5.47 %; *P*=0.67), cf-PWV (7.83 ± 1.76 vs. 6.96 ± 1.26 m/s; *P*=0.10), ABPI (1.27 ± 0.15 vs. 1.18 ± 0.08; *P*=0.47), CCA-IMT (5.73 ± 0.95 vs. 5.54 ± 1.08 mm; *P*=0.05). Vascular measurements did not change in controls upon follow-up (see table 1). In KTxPs, FMD decreased (-1.52 ± 2.74 %; *P*=0.03), cf-PWV increased (0.62 ± 1.06 m/s; *P*=0.03), and CCA-IMT increased (0.35 ± 0.53 mm; *P*=0.02).

Conclusions: Markers of vascular structure and function worsened in stable kidney transplant patients follow-up. We propose that after initial improvement in cardiovascular health immediate post-transplant; the newly acquired cardio-vascular risk factors, immunosuppression and persistent mild CKD may cause further deterioration explaining the elevated risk for CV events.

Table 1. Changes in cardiovascular structure and function from baseline to second visit

Parameter	Healthy controls (n=17)			KTxPs (n=18)			Between-group comparison
	Baseline visit	Second visit	P-value	Baseline visit	Second visit	P-value	Baseline results P-value
Brachial FMD (%)	4.63 ± 3.02	3.51 ± 2.73	0.33	4.34 ± 3.45	2.82 ± 2.18	0.03	0.79
Brachial NMD (%)	16.00 ± 5.47	17.17 ± 5.18	0.31	15.15 ± 6.08	15.74 ± 3.88	0.68	0.67
Cf-PWV (m/s)	6.96 ± 1.26	7.17 ± 1.50	0.51	7.83 ± 1.76	8.44 ± 2.28	0.03	0.10
Mean ABPI	1.18 ± 0.08	1.21 ± 0.11	0.43	1.27 ± 0.15	1.23 ± 0.14	0.34	0.47
Mean CCA-IMT (mm)	5.54 ± 1.08	5.73 ± 1.34	0.22	5.73 ± 0.95	6.07 ± 0.98	0.02	0.05

Legend: n number of participants, KTxPs kidney transplant patients, FMD flow-mediated dilation, NMD nitroglycerin-mediated dilation, Cf-PWV carotid-femoral pulse wave velocity, ABPI ankle-brachial pressure index, CCA-IMT common carotid intima-media thickness

Data presented as mean ± SD (95% confidence interval)

Table showing the changes in vascular abnormalities over time in kidney transplant patients and controls

TH-PO140

Incidence of Cardiovascular Diseases in Pediatric Solid Organ Transplant Recipients

Sandeep Brar,[1,2] Stephanie Dixon,[5,8] John M. Paterson,[5,7] Joseph Kim,[1,2] Diane Hebert,[1,3] Jade S. Dirk,[5] Emma J. Hahn,[6] Rulan S. Parekh,[3,1] Rahul Chanchlani.[4] *[1]Department of Medicine, University of Toronto, Toronto, ON, Canada; [2]Division of Nephrology and the Kidney Transplant Program, University Health Network, Toronto, ON, Canada; [3]The Hospital For Sick Children, Toronto, ON, Canada; [4]McMaster Children's Hospital, Hamilton, ON, Canada; [5]Institute for Clinical Evaluative Sciences, London, ON, Canada; [6]Institute of Clinical Evaluative Sciences, London, ON, Canada; [7]Institute of Health Policy, Management, and Evaluation, Toronto, ON, Canada; [8]Department of Epidemiology and Biostatistics, Western University, Toronto, ON, Canada.*

Background: Cardiovascular disease (CVD) is a long-term complication in pediatric solid organ transplant (SOT) recipients; however, the incidence is not well described.

Methods: We conducted a cohort study comparing CVD rates in children with SOT (heart, liver, lung, kidney, small bowel) at the Hospital for Sick Children in Toronto,

Canada (n = 979) with a random sample of healthy, non-transplanted children in Ontario (n = 1,000,000) between 1993 and 2014 using provincial health administrative data. Outcomes included non-fatal CVD events, CVD-specific death, and a composite of non-fatal and fatal CVD events. Non-fatal CVD events were defined as atherosclerotic (acute myocardial infarction, stroke, peripheral vascular disease, carotid endarterectomy, percutaneous coronary intervention, coronary artery bypass grafting) and non-atherosclerotic (congestive heart failure, arrhythmia, cardiac defibrillation, insertion of pacemaker, out of hospital cardiac arrest).

Results: Among SOT recipients, 41% had a kidney transplant, 32% had a liver transplant and 22% had a cardiac transplant. The remaining 5% had lung, small bowel or multi-organ transplants. Mean age at index was 7.7 and 8.1 years in the transplant and non-transplant group, respectively. During an overall median follow-up time of 11.0 years (interquartile range: 5.7-17.5 years), CVD events were at least 50 times more likely to occur in SOT recipients versus healthy, non-transplanted children (table).

Conclusions: The increased incidence of CVD in children post transplantation highlights the need for surveillance and prevention during transition into early adulthood.

Events and incidence rate ratios for cardiovascular outcomes in pediatric solid organ transplant recipients

Outcome	Number of events	Event rate per 1000 person-years	Incidence rate ratio (per 1000 person-years) (95% CI)
Non-fatal composite			
Non-transplant	5727	0.5	Reference
Transplant	260	32.5	68.2 (60.2, 77.2)
Non-fatal, atherosclerotic CVD			
Non-transplant	3104	0.3	Reference
Transplant	167	19.5	75.7 (64.8, 88.4)
Non-fatal, non-atherosclerotic CVD			
Non-transplant	4422	0.4	Reference
Transplant	167	19.5	52.9 (45.5, 61.5)
CVD-specific death			
Non-transplant	633	0.1	Reference
Transplant	76	9.5	180.3 (142.1, 228.7)
Non-fatal and fatal composite			
Non-transplant	6072	0.5	Reference
Transplant	278	34.7	68.8 (61.0, 77.5)

TH-PO141

Obesity as a Predictor of Renal Allograft Function

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Background: While being underweight in ESRD is associated with increased morbidity and mortality, obesity in these patients leads to unfavorable post-transplant outcomes. The aim of this study is to explore associations between pre-transplant obesity and early readmission (ERA), as well as renal allograft function at 12 months post-transplantation.

Methods: Demographic data of 84 patients receiving a kidney transplantation from January to December 2014 were retrieved. The patients were categorized into non-obese and obese groups based on BMI. ERA, defined as any admission within 30 days after the discharge date from transplant admission, and eGFR was associated with pre-transplant obesity status.

Results: Of all 83 patients, 53 were non-obese and the remaining 30 patients were obese with mean BMIs of 24.65±3.08 and 34.12±2.98, respectively (95% CI -10.85, -8.09, p <0.001). Pre-transplant diabetes were lower in the non-obese group than in the obese group (30% vs 60%, p 0.015); otherwise, all other baseline characteristics between non-obese and obese groups were similar. There were 19, 4, and 2 patients who had 1, 2, and 3 ERA, respectively. One patient died at the early post-transplant period. The remaining 57 patients were never readmitted. Obese patients had 33% higher odds of being readmitted when compared to non-obese patients (OR 1.33, 95% CI 0.50, 3.51, p 0.562). Among 50 non-obese and 28 obese patients with functioning allografts at 12 months post-transplantation, mean eGFR at 12 months was 59.4±19.55 and 50.9±15.81 ml/min/1.73 m^2, respectively. Obese patients had a decrease in eGFR of 8.56 ml/min/1.73 m^2 at 12 months post-transplantation compared to non-obese patients (95% CI -17.17 to 0.04, p 0.051). After adjusted for all variables including age, race, type of kidney transplantation, induction immunosuppressive medications, pre-transplant diabetes, hypertension, hyperlipidemia, and smoking, obese patients had a significant decrease in eGFR at 12 months post-transplantation by 10.10 ml/min/1.73 $m^2$when compared to non-obese patients (95% CI -20.18 to -0.02, p-value 0.0495).

Conclusions: Although ESRD patients who are underweight are at risk of poor outcomes during the pre-transplant period, pre-transplant obesity increases the risk of poorer renal allograft function. Patients who will undergo a kidney transplantation should control and maintain their weight in a normal range.

TH-PO142

Overweight and Size Mismatch Are Risk Factors of De Novo Focal Segmental Glomerulosclerosis After Kidney Transplantation from Parent to Child

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Background: Proteinuria among transplant recipients is an important factor for allograft and patient survival. In addition, the mean age of donor is increasing in Japan. The aging donor is a risk factor of de novo focal segmental glomerulosclerosis (FSGS) due to podocytopenia and loss of nephron number. The aim of this study is to evaluate the risk factor in de novo FSGS after kidney transplantation (KTx) from parent to child.

Methods: This is an observational case control study. The subjects were 45 patients who underwent KTx from parent to child between 2009 Apr to 2016 Aug in our Hospital and whose allograft survived to have allograft biopsy not showing FSGS at both 0 and 12 months. Cases of recurrent FSGS (N=1), IgA nephropathy (N=1), and nephrosclerosis of 0h biopsy (N=1) and those without protocol biopsy at 12 months (N=3) were excluded, leaving total of 39 patients. We examined clinical and histological features, with all values are expressed as mean ± standard error (SE).

Results: Five out of 39 recipients showed FSGS in biopsy which was done after > 12 months (FSGS group). Comparing FSGS group vs non-FSGS group, male accounted for 100% vs 61.8 %, the ages were 41.2 ± 3.3 vs 35.0 ± 1.3 (p=0.088), body weight (BW) were 74.9 ± 6.1 vs 59.5 ± 2.4 kg (P=0.024), body mass index (BMI) were 26.2 ± 2.0 vs 21.9 ± 0.8 kg/m^2(P = 0.049), the donor age was 68.8 ± 3.2 vs 62.4 ± 1.2 (p=0.069), and the donor eGFR was 72.3 ± 6.2 vs 77.6 ± 2.4 ml/min/1.73m^2, respectively. So, there were significant differences for BW and BMI of recipients. Before KTx, the difference between the recipient and donor's BW was significantly higher in FSGS group [18.3 ± 7.3 vs 1.4 ± 2.8 kg (p=0.038)]. At protocol biopsy of 12 months after KTx, BW and BMI in FSGS group were also significantly higher than non-FSGS group [BW; 78.0 ± 6.1 vs 60.6 ± 2.3 kg (P=0.012), BMI; 27.3 ± 1.9 vs 22.3 ± 0.8 kg (P=0.027)]. The duration to FSGS diagnosis after KTx was 1066 ± 277 day. The Columbia classification of FSGS group was all NOS variant (no perihilar). The range of foot process effacement was not diffuse, indicating these FSGS were secondary.

Conclusions: Overweight of the recipient and size mismatch are risk factors of de novo FSGS after 12 months post-KTx from parent to child.

TH-PO143

Obesity Is a Risk Factor for ESRD in Prior Living Kidney Donors

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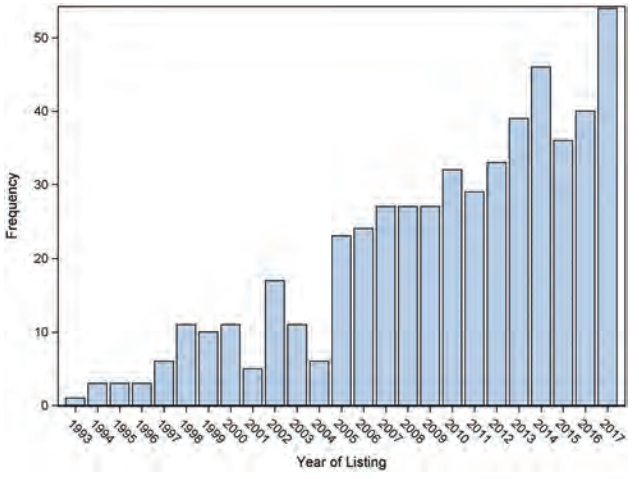
Background: Living donors undergo extensive evaluation prior to donation. Despite that some living kidney donors (LKDs) progress to end stage renal disease (ESRD). We evaluated the trends and characteristics of LKDs who were waitlisted for kidney transplantation.

Methods: We used the United Network for Organ Sharing data to identify 524 LKDs who were listed for kidney transplantation from 1993-2017. For qualitative variables, frequencies were computed and the tests of association were performed using the chi-square test.

Results: In this cohort, 59.8% (n=313) were men and 40.2% (n= 211) women. Cause of ESRD was diabetes in 17.5%, hypertension in 32% and other in 44%. Forty six % were White, 38.5% Black, 10% Hispanic, 2.2% Asian, 1.9 % Native -American and 1.1% were multiracial. Mean age at listing was 55 yrs ±11.4. **Figure 1** shows the increasing number of prior LKDs who waitlisted from 1993- 2017. The number of Black LKDs who waitlisted were disproportionately higher (38.5%) as compared to the proportion of Black LKDs in this time period varying from 8% to 12%. Hypertension as a cause of ESRD was observed to be much higher in Blacks (41.1%) and Hispanics (32%) as compared to Whites (26%), p= 0.02. Mean BMI at time of waitlisting was 29.5 ± 5.2 kg/m^2. Among LKDs who were listed for transplantation, majority were overweight (36%) or obese (43.%). Forty-one percent of (n=100) white, 46% (n=93) black, 46 % Hispanic (n=24) and 25.3% (n=7) multiracial prior LKDs were obese (>30kg/m^2) at time of wait listing, p=0.18.

Conclusions: Transplantation centers now approve more medically complex obese LKDs without supporting data. Informed consent with obese individuals are critical in those considering LKD. Life style changes and modifications should be addressed in those with normal BMI at time of donation to avoid future obesity. Long-term studies are needed to understand risks associated with hypertension and obesity focused on minority LKDs



TH-PO144

Association of Visceral Obesity After Kidney Transplantation with Graft Survival in Living Kidney Transplant Recipients: A Retrospective Cohort Study

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Background: Excessive weight gain is common after kidney transplantation. However, the relationship between visceral obesity and kidney allograft outcome remains unclear. We measured the visceral fat area by computed tomography and examined the relation with the kidney allograft survival.

Methods: We identified 254 recipients who underwent living kidney transplantation from 2004 to 2014. Of those, 196 recipients evaluated metabolic risk factors and visceral fat area at the level of the umbilicus on abdominal computed tomography before transplantation and 12 months after transplantation and were followed until February 2018. Visceral obesity was defined as visceral fat area of ≥100cm^2. Metabolic syndrome was defined by the NCEP ATP III criteria modified for the Japanese population. Treatment-resistant hypertension was defined as an office blood pressure of ≥130/80 mmHg, despite receiving ≥3 antihypertensives including diuretics, or ≥4 drugs usage. The adverse graft outcomes were defined as a decline of 50% or more of estimate glomerular filtration rate with baseline one month after transplantation or initiation of renal replacement therapy.

Results: Recipients with visceral obesity were seen in 69 (35.2%) at 12 months post-transplantation. Compared to recipients with no visceral obesity, they were more likely to be male, older, have a higher weight gain from 1 month to 12 months after kidney transplantation (7.0 ± 7.5 vs. 4.6 ± 8.8%, P <0.05), prevalence of metabolic syndrome (23.2 vs. 3.9%, P <0.01), and treatment-resistant hypertention (17.4 vs. 7.1%, P <0.05), and have a lower glomerular filtration (44 ± 12 vs. 48 ± 15 ml/min/1.73m^2, P <0.05). During median 9.5-year follow-up, they also had higher adverse graft outcome (3.2 vs 1.3 per 100 patient-years, P <0.05). In multivariate analysis, visceral obesity independently remained as a risk factor for kidney allograft outcome (hazard ratio, 2.27 ; 95% confidence interval, 1.11–4.72, P=0.033).

Conclusions: Visceral obesity at 1 year post-transplantation becomes a risk factor for metabolic syndrome and graft survival, which emphasizes the importance of management of obesity after transplantation.

TH-PO145

Effect of Obesity on Transplant Outcome One Year Post Kidney Transplant

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Background: Kidney transplant is the preferred option of treatment for patients with Chronic kidney disease, studies have shown poor outcome for obese patients BMI≥30kg/m2 and more perioperative complications, the aim of this study is to compare outcomes of obese patients BMI ≥30kg/m2 to patients with BMI<30kg/m2.

Methods: A retrospective single center cohort study of adult kidney transplant recipients between 1/2014 - 1/2016 compairing 308 patient BMI<30 to110 patients BMI≥30, one year patient and graft survival, incidence of delayed graft function, average hospital stay, wound and cardiac complications, new onset diabetes after transplant (NODAT), proteinuria and rejection.

Results: Table1 shows obese patient with BMI≥30kg/m2 were older, diabetics, on peritoneal dialysis, had higher incidence of delayed graft function worse patient suvival in one year, other complcations were not significantly different among both groups

Conclusions: Kidney transplant recipients with BMI ≥30kg/m2 have higher incidence of mortality, delayed graft function than patients with BMI <30kg/m2. Dietery counseling and referral for bariatric surgery is recommended for weight loss to improve post transplant outcome.

	BMI <30kg/m2	BMI≥ 30kg/m2	P value
Number of patients	308	110	
SEX			0.24
Females	125(40.5%)	44(40%)	
Males	183(59.5%)	66(60%)	
Mean age SD	50	53.7	0.02
Dialysis Modality			0.12
HD	237(77%)	79(72%)	
Peritoneal dialysis	52(17%)	26(23.9%)	
Predialysis	20(7%)	4(3.7%)	
living donor	57(18%)	8(7.3%)	0.02
Deceased donor	251(81.9%)	102(92.7)	
DM	94(30.5%)	48(43.6%)	0.01
Death 1 year	2(0.65%)	4(3.6%)	0.024
Graft failure	6(1.9%)	3(2.7%)	0.63
creatinine mean 1year	1.4mg/dl	1.6mg/dl	0.22
Delayed graft function	55(17.9%)	38(35%)	<.001
NODAT	19(6.2%)	8(7.3%)	0.69
Days in hospital >5Days	122(39.6%)	44(37.6%)	0.67
Drain	29(7%)	30(27.3%)	<.001
Wound Infection	3(1%)	0(0%)	0.3
Post transplant proteinuria>0.5gm/d	55(17.9%)	24(22%)	0.174
Rejection 1Year post transplant	10(3.2%)	4(3.6%)	0.58
Ischemic cardiac events	8(1.9%)	0(0%)	0.09
Arrhythmias	11(3.6%)	5(4.6%)	0.65

TH-PO146

Advanced Glycation End Products and Risk of Late Graft Failure and Cardiovascular Mortality in Renal Transplant Recipients: A Prospective Cohort Study

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Background: Advanced glycation endproducts (AGE) have been implicated in the pathogenesis of chronic transplant dysfunction and cardiovascular (CV) disease of renal transplant recipients (RTR), but no prospective studies have been performed to date. We investigated the association of plasma AGE levels with graft failure (GF) and CV mortality in a cohort of RTR with long-term follow-up.

Methods: Tandem mass spectrometry was performed to simultaneously measure the AGE N$^{\varepsilon}$-(Carboxymethyl)lysine (CML) and N$^{\varepsilon}$-(Carboxyethyl)lysine (CEL) levels in hydrolysates of plasma proteins. Multivariate-adjusted Cox-proportional hazards regression analysis was used to assess prospective associations with clinical outcomes.

Results: We included 555 RTR (mean (SD) age 51±12 years old, 56% males). During median follow-up for 6.9 [IQR, 6.2-7.2] years, 67 (12%) RTR developed GF, and 122 (22%) died (52% were due to CV causes). In analyses adjusted for potential confounders, including age, sex, estimated Glomerular Filtration Rate (eGFR) and proteinuria, CML levels were not independently associated with GF, but they were with CV mortality (Table 1). In similar analyses, CEL levels were independently associated with GF and CV mortality (Table 1). The association of CML levels with GF was modified by renal function (P_{int}<0.001), with a significant and independent association in RTR with eGFR≤45 mL/min/1.73m^2 (HR, 1.75; 95% CI, 1.06-2.89; P=0.03).

Conclusions: High plasma levels of the AGE CML and CEL were independently associated with increased risk of GF and premature CV mortality. These results strengthen the quest for studying AGE-targeted interventions as potential therapeutic strategy to improve long-term outcomes in RTR.

Funding: Government Support - Non-U.S.

Table 1. Multivariate-adjusted associations of plasma CML and CEL levels with GF and CV mortality in RTR.

Outcomes	CML, µmol/L		CEL, µmol/L	
	HR (95% CI)	P value	HR (95% CI)	P value
Graft Failure	1.44 (0.89-2.33)	0.14	2.71 (1.26-5.81)	0.01
Cardiovascular mortality	1.90 (1.22-2.95)	0.004	2.77 (1.13-6.83)	0.03

Hazard ratios are adjusted for age, sex, eGFR, proteinuria, primary renal disease, pre-transplant dialysis vintage, time between transplantation and inclusion, BMI, total cholesterol, systolic blood pressure, personal history of diabetes mellitus and CV disease, and familiar history of CV disease.

TH-PO147

Fruit and Vegetable Consumption and Cardiovascular Mortality in Renal Transplant Recipients: A Prospective Cohort Study

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Background: We investigated the associations of fruit and vegetable (F&V) consumption after kidney transplantation with risk of CV mortality in an extensively phenotyped cohort of renal transplant recipients (RTR) with long-term follow-up.

Methods: F&V consumption were assessed by means of an item-specific food-frequency questionnaire. Multivariable-adjusted Cox-proportional hazards regression analysis was performed to assess the risk of CV mortality.

Results: We included 400 RTR (age 52±12 (SD) years old, 54% males). At a median follow-up of 7.2 [interquartile range, 6.7-7.6] years, 93 (23%) patients died, of which 49 (53%) were due to CV disease. Overall, fruit consumption was not associated with CV mortality, whereas vegetable consumption was inversely associated with risk of CV mortality (Table 1). This association remained independent of adjustment for several potential confounders. The association of fruit consumption with CV mortality was significantly modified by renal function (P_{int}=0.01) and proteinuria (P_{int}=0.01), with significant inverse associations in patients with estimated Glomerular Filtration Rate (eGFR)>45 mL/min/1.73m^2 (HR, 0.56; 95% CI, 0.35-0.92; *P*=0.02) or absence of proteinuria (HR, 0.62; 95% CI, 0.41-0.92; *P*=0.02).

Conclusions: In RTR, a relatively high vegetable consumption is independently and strongly associated with lower risk of premature CV mortality. A relatively high fruit consumption is also associated with lower risk of premature CV mortality, although particularly in RTR with eGFR>45 mL/min/1.73m^2 or absence of proteinuria. Further studies are warranted to investigate whether increasing F&V consumption may open opportunities for interventional pathways to decrease the burden of CV mortality in RTR.

Funding: Government Support - Non-U.S.

Table 1. Association of fruit and vegetable consumption with CV and all-cause mortality of RTR

Outcome	Fruit consumption, servings/day		Vegetable consumption, tablespoons/day	
	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular mortality	0.90 (0.64-1.27)	0.55	0.50 (0.35-0.72)	<.001
All-cause mortality	0.91 (0.71-1.16)	0.45	0.73 (0.56-0.95)	0.02

Hazard ratios are adjusted for age, sex, income, educational level, physical activity, eGFR, proteinuria, time since transplantation, primary renal disease, total cholesterol, blood pressure, BMI, diabetes and smoking status.

TH-PO148

The Incidence and Related Factors of Post-Transplantation Diabetes Mellitus within 1-Year After Kidney Transplantation: Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT)

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Background: Posttransplantation diabetes mellitus (PTDM) is associated with poor graft survival and greater mortality. The incidence of PTDM after kidney transplantation (KT) reported to date is varied from 10-74% and varies by country and race. There are few nationwide cohort study reports on the incidence of PTDM and associated risk factors in Korea. The purpose of this study was to evaluate incidence and related factors of PTDM early after KT in Korea.

Methods: A total of 1,080 recipients were enrolled in KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) between July 2012 and August 2016. This study included 723 recipients, excluding 273 patients with pretransplant DM and 84 patients lost of follow-up within 1-year after KT. We evaluated associated factors of PTDM within 1-year after KT.

Results: Among the 723 recipients, 85 (11.8%) was diagnosed and treated with PTDM. In the univariate logistic regression analysis, pretransplantation variables that showed significant associations with PTDM were older recipient age, end-stage renal disease due to polycystic kidney disease, smoking history, high body mass index, waist–hip ratio (WHR), HbA1C levels, numbers of HLA total and HLA-DR mismatches and lower transferrin saturation. Posttransplant variables that were significantly associated with PTDM were high WHR, triglyceride/high density lipoprotein ratio, and serum triglyceride levels, low serum albumin levels, acute rejection, statin use, and vitamin D replacement. In the multivariate logistic regression analysis, predictors of PTDM were older recipient age, high WHR and HbA1C before KT, and statin use after KT.

Conclusions: In Korean cohort study, the incidence of PTDM was 11.8%. Risk factors for PTDM within 1-year after KT were older recipient age, higher WHR and HbA1C before KT. To prevent PTDM, it is important to control the overweight and abdominal obesity through life style modification prior to KT.

TH-PO149

Withdrawal of Antihypertensive Medication One Year After Kidney Transplantation: Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT)

Seungyeup Han,[1,2] Seong Sik Kang,[1,2] Hayeon Park,[1] Jin hyuk Paek,[1,2] Sang Mok Yeo,[1] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park.[1,2] KNOW-KT Study Group *[1]Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea.*

Background: Cardiovascular disease (CVD) is a major cause of graft and patient loss in kidney transplant (KT) recipients. Inadequate control of hypertension in KT recipient is associated with an increased risk of CVD. Therefore blood pressure control after KT is important and it is also important to evaluate the related factors. The purpose of this study was to evaluate the incidence and related factors of withdrawing antihypertensive (AH) medication early after KT.

Methods: A total of 1,080 patients were enrolled in KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) between July 2012 and August 2016. The study included 857 recipients who had been treated for hypertension prior to KT and followed-up for 1-year after KT. We evaluated associated factors of withdrawing AH medication within 1-year after KT.

Results: Among 857 the recipients, 278 (32.4%) withdrawn AH medication within 1-year after KT. The medication withdrawn (MW) group was younger than the medication continued (MC) group and the proportion of female, nondiabetic patients, and non-smokers were higher. In the pre-transplant evaluation, the MW group had lower systolic blood pressure (SBP), body mass index (BMI), triglyceride/high density lipoprotein (TG/HDL) ratio, and serum TG levels and showed thinner left ventricular posterior wall thickness (LVPWT) and smaller left atrial diameter in echocardiography. One year after KT, the MW group had lower BMI, TG/HDL ratio, and serum TG levels and had a lower incidence of delayed graft function (DGF), acute rejection (AR), and coronary artery disease (CAD). In multivariate logistic regression analysis, predictors of withdrawing AH medication after KT were female, lower SBP before KT and thin LVPWT in pre-transplant echocardiography.

Conclusions: In a Korean cohort study, 32.4% of recipients who were treated with hypertension before KT stopped AH medication 1-year after KT. For better control of BP and prevention of additional administration of AH medication after KT, it is important not only to prevent DGF, AR, and CAD after KT, but also to control SBP and prevent cardiovascular remodeling before KT.

TH-PO150

New Onset Diabetic Foot Ulcer After Renal Transplantation Increases Risk of Transplant Failure

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Background: Patients with diabetic kidney disease are at high risk of diabetic foot ulcers (DFU). Whether this risk is modified after renal transplant is unclear. There is a paucity of information on the burden and risk factors for DFU development after transplantation and impact of DFU on renal transplant viabilty.

Methods: We evaluated the incidence and predictors of new onset DFU post renal transplant in a single centre retrospective study. Patients who underwent renal transplant for diabetic kidney disease between 2004-2016 were evaluated. In total 144 (66% male, 26% Type 1, 74% Type 2) diabetic patients were evaluated. Median (range) follow up was 6 (3 to 13) years. Median (range) age was 62 (28 to 80) years and duration of diabetes 23 (7-60) years. Electronic patient medical notes were reviewed.

Results: Over the follow up period 22 (15%) patients developed a new DFU. Patients with a DFU were of similar age, body mass index, diabetes duration and had similar pre-transplant haemoglobin, as compared to those without a DFU. Patents who developed a DFU were more likely to have Type 1 than Type 2 diabetes (29% vs. 10%), history of peripheral vascular disease (PVD) [32 % vs. 8%], had higher pre-transplant HbA1c, mean ± standard deviation (7.5 ±1.2% vs. 6.8±1.4%) and serum creatinine (809±243µmol/l vs. 660±202µmol/l) p<0.05 for all. Of the cohort 8 patients had a history of DFU pre-transplant and all 8 developed a new onset DFU post-transplant. Median (range) duration of healing was 5 (1-26) weeks. Nearly 50% of all DFU occurred within the first 1000 days post-transplant. Of the 22 cases, 6 needed a minor amputation; no major amputations were documented. Mortality was 27.3% in patients with DFU compared to 20.3% without DFU p=0.25. Patients with DFU had more than twofold increased risk of transplant failure as compared to those without DFU (50% vs 23.3% p=0.02).

Conclusions: Nearly 1 in 7 patients post renal transplant develop a new onset DFU. Type 1 diabetes, higher pre-transplant HbA1c, serum creatinine and history of PVD and prior DFU are associated with increased risk of new onset DFU post-transplant. DFU increases risk of transplant failure nearly twofold. Our results indicate a high burden of DFU post-transplant and emphasises the requirement for regular foot surveillance by renal and diabetes clinical teams in this high-risk population.

Funding: Government Support - Non-U.S.

TH-PO151

Glucose Metabolism After Renal Transplantation: Oral Glucose Tolerance Test-Derived Insulin Release and Insulin Sensitivity Under Tacrolimus versus Belatacept-Based Immunosuppression

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Background: In our previous oral glucose tolerance test (OGTT)-based study (PMID23656979), calcineurin inhibitor-treated kidney transplant recipients (KTRs) showed lower insulin release but higher insulin sensitivity than non-KTRs. We aimed at refining our analysis, using only Tacrolimus-treated KTRs (Tac-KTRs) vs Belatacept-treated KTRs (Bela-KTRs) as controls.

Methods: We revisited our database and analysed indices of insulin release and insulin sensitivity from OGTTs of 67 Tac- vs 26 Bela-KTRs.

Results: Our center's outpatient records showed 38 Tac-KTRs vs 0 Bela-KTRs among 113 KTRs with treated posttransplant diabetes mellitus. The randomly assigned OGTTs among KTRs with unknown glycemic status differed between Tac- vs Bela-KTRs: 11 vs 0 diabetics (2-h glucose [2-h G] ≥200 mg/dL), 24 vs 2 prediabetics (2-h G 140-199) and 32 vs 24 with normal glucose tolerance (NGT) (2-h G <140) [*p<0.01*]. Tac- vs Bela-KTRs with NGT had similar age, body mass index, 0-h and 2-h G, but higher HbA1c and insulin sensitivity and lower insulin release (Table and Figure).

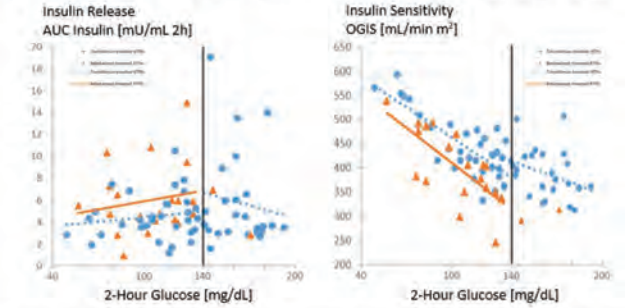
Conclusions: In line with our previous study, impaired insulin release was the main pathophysiological feature for diabetes development in Tac-KTRs, while Bela-KTRs had no impaired glucose metabolism. It is tempting to speculate that impaired insulin secretion, due to beta-cell damage, in Tac-KTRs is compensated by increased insulin sensitivity, but this mechanism seems more complex and deserves further study.

Table: Characteristics and OGTT-derived indices of stable kidney transplant recipients (time since transplantation >6 month) with different immunosuppression randomly assigned to an OGTT

	<140 mg/dL			≥140 mg/dL		
	Tacrolimus n=32	Belatacept n=24	*p-value	Tacrolimus n=24	Belatacept n=2	*p-value
Age	47 ± 14	51 ± 12	0,31	61 ± 12	45 ± 17	0,09
Male, %	56	71	0,26	75	50	0,44
Time since Transplantation, years	4,1 ± 4,8	4,9 ± 4,3	0,51	4,5 ± 5,8	6,2 ± 1,2	0,7
BMI on transplantation, kg/m²	24,2 ± 5	25,1 ± 3,6	0,45	24,1 ± 3	28,2 ± 3,8	0,1
Glucocorticoid, %	97	100	0,38	88	100	0,59
Dose, mg	4,4 ± 1,9	4,7 ± 0,8	0,43	5,8 ± 4,4	5 ± 0	0,8
Uric acid, mg/dL	7,9 ± 7,2	5,8 ± 1,4	0,2	7,6 ± 1,6	5,8 ± 0,2	0,12
Serum creatinine, mg/dL	1,7 ± 0,7	1,2 ± 0,3	0,006	1,7 ± 0,5	2,1 ± 0,9	0,39
Serum albumin, g/L	49,5 ± 30,6	45,1 ± 3,5	0,5	42,5 ± 3,7	43,5 ± 1,1	0,74
HbA_{1c}, relative %	5,6 ± 0,5	5,3 ± 0,4	0,002	6 ± 0,6	5,45 ± 0,45	0,21
Glucose 0h, mg/dL	90,6 ± 10,2	88,2 ± 10,8	0,4	100,8 ± 14	100 ± 2	0,94
Glucose 2h, mg/dL	108 ± 24	105 ± 20	0,6	163 ± 15	159 ± 13	0,68
Insulin, AUC, mU/ml 2h	4,6 ± 2	6 ± 3,1	0,05	5,9 ± 4,3	4,9 ± 2,1	0,77
OGIS, mL/min m²	446 ± 64	401 ± 73	0,03	387 ± 50	301 ± 11	0,03
AUC Insulin/AUC Glucose	312 ± 131	394 ± 180	0,07	302 ± 233	259 ± 153	0,8

Boldface numbers indicate findings with $P < 0.05$. AUC, area under the curve; OGIS, oral glucose insulin index; *unpaired two-tailed Student's t test for continuous variables, chi-square test for dichotomous variables.

Figure: Comparison of OGTT-derived parameters: Tacrolimus- versus Belatacept-treated kidney transplant recipients



Insulin release, shown as OGTT-derived AUC insulin by 2-hour glucose (left) and insulin sensitivity, shown as OGTT-derived oral glucose insulin sensitivity (OGIS) index by 2-hour glucose (right). Within each of the two patient groups (Tacrolimus, Belatacept), a regression line was modelled for 2-hour glucose values <140mg/dL. In Tacrolimus-treated kidney transplant recipients, a regression line was also modelled for 2-hour glucose between 140 and <200 mg/dL.

TH-PO152

Empagliflozin in Posttransplantation Diabetes Mellitus: Effect on Glucose Metabolism and Fluid Volume

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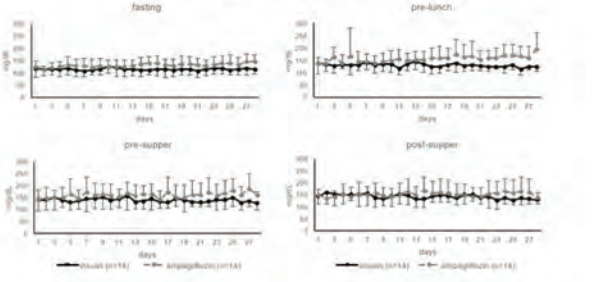
Background: Empagliflozin decreases cardiovascular morbidity and mortality in type 2 diabetics, but safety and efficacy in patients with posttransplant diabetes mellitus (PTDM) is unknown.

Methods: We conducted a prospective non-inferiority trial, converting stable kidney transplant recipients with PTDM from insulin (<40 IU/day) to 10 mg empagliflozin, aiming at eliminating exogenous insulin. Oral glucose tolerance tests, fluid volume status and adverse events were compared from baseline to 4 weeks after empagliflozin conversion (clinicaltrials.gov:NCT03113110).

Results: 14 patients (the required sample size, using change in intra-individual 2-hour glucose as primary endpoint) completed the study visits. The primary endpoint was negative (*p=0.06*) but glucose control was clinically inferior after insulin withdrawal (27.2±10.5 IU/day; Figure & Table). Insulin sensitivity and bioimpedance spectroscopy-derived extracellular fluid volume decreased with empagliflozin therapy. No patient developed ketoacidosis, 3 had bacterial urinary tract infections (UTIs).

Conclusions: Despite risk of UTIs and moderatly inferior glucose control under empagliflozin monotherapy following exogenous insulin therapy, empagliflozin is a valuable antidiabetic for PTDM patients which should be studied as add-on therapy. Plasma volume contraction might contribute to the cardiovascular risk reduction observed in type 2 diabetics.

Patients' self-monitored blood glucose profiles



Self-monitored blood glucose profiles over 28 days. During the first three days of empagliflozin treatment, the insulin dosage was washed out. Comparisons between empagliflozin and insulin treatment were calculated using a mixed linear model. Mean differences: fasting [19.4 mg/dl (95%CI -0.5-37.3) p=0.06], pre-lunch [24.4 mg/dl (95%CI -0.19-48.9) p=0.05], pre-supper [mean 20.7 mg/dl (95%CI -4.2-45.7) p=0.1] and post-supper [mean 7.9 (95%CI -21.0-36.8) p=0.6]. Means and standard deviations of blood glucose levels are displayed as bold lines (blood glucose levels during insulin treatment) and dotted lines (blood glucose levels during empagliflozin treatment).

Kidney function, metabolic parameters and anthropometric measures

Variables	baseline	visit 2	p
Creatinine mg/dL, mean (SD)	1.3 (0.4)	1.4 (0.4)	**0.01**
eGFR mL/min/1.73m², mean (SD)	53.9 (23.0)	45.2 (16.4)	**0.006**
Uric acid mg/dL, median (IQR)	7.5 (6.7-9.4)	6.2 (5.9-7.1)	**0.04**
Glucosuria mg/dL, median (IQR)	3.0 (0.0-6.0)	1,741.5 (584.0-2,255.8)	**0.01**
Glucose, 0h mg/dL, mean (SD)	111 (21)	144 (45)	**0.005***
Glucose, 2h mg/dL, mean (SD)	232 (82)	273 (116)	0.06*
Glycated hemoglobin %, mean (SD)	6.4 (0.8)	6.6 (0.7)	0.08
Homeostatic model assessment – insulin resistance, mean (SD)	2.23 (1.36)	4.16 (3.46)	**0.03**
Beta-cell glucose sensitivity, pmol $min^{-1}m^{-2}mM^{-1}$, mean (SD)	28.6 (17.1)	36.6 (23.5)	0.06
Oral glucose insulin sensitivity index mL/min/m², mean (SD)	390 (66)	328 (85)	**0.01**
PREDIcted M mg kg -1min-1, mean (SD)	4.2 (2.0)	3.5 (1.8)	**0.02**
Waist circumference cm, mean (SD)	103.1 (14.4)	97.4 (13.5)	**0.01**
Weight kg, mean (SD)	74.8 (17.2)	73.2 (17.4)	**0.02**
Total body fluid volume L, mean (SD)	36.5 (9.5)	35.5 (9.1)	**0.008**
Extracellular fluid volume (ECV) L, mean (SD)	18.2 (5.1)	17.2 (4.6)	**<0.001**
Fluid volume overload L, mean (SD)	2.7 (2.1)	1.8 (1.8)	**0.006**
Fluid volume overload % ECV, mean (SD)	13.4 (7.4)	9.7 (7.7)	**0.02**

SD, standard deviation; eGFR, estimated glomerular filtration rate;
* one sided comparison due to the non-inferiority design of the EmpTra-DM study

TH-PO153

Cardiovascular Events After Kidney Transplantation: Seven-Year Follow-Up of the Vienna Treat-to-Target Trial of Basal Insulin in Post-Transplant Hyperglycemia (TIP)

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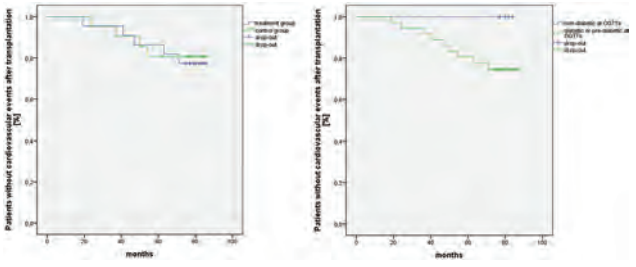
Background: In our previous proof-of-concept clinical trial, basal insulin therapy early after kidney transplantation significantly reduced the odds of posttransplant diabetes mellitus (PTDM) throughout 1 year of follow-up (PMID22343119). We investigated whether the occurrence of cardiovascular events (CVEs) differed by insulin therapy, respectively by oral glucose tolerance test (OGTT)-derived glycemic status.

Methods: We obtained ethics approval for following up on the Vienna TIP-study patients, in order to compare CVEs in those who had received insulin versus standard of care control treatment; and in patients with normal glucose tolerance (NGT, 2-hour glucose [2-h G] <140 mg/dL), versus in prediabetics (2-h G 140-199) plus diabetics (2-h G ≥200), per OGTT-result at 3, 6 and 12 months posttransplantation.

Results: Seven of the original 50 TIP-study patients were lost to follow-up. Occurrence of CVEs differed by diabetic status, but not by treatment status (Figure). None of the patients with NGT experienced any CVE, but NGT patients were significantly younger (Table).

Conclusions: The present results lead to the hypothesis that PTDM might be a read-out for older, potentially sicker patients, and that CVE occurrence might not be modifiable by antidiabetic treatment.



	Insulin	Control	p*	Diab. + prediab.	NGT	p*
N patients	22	21		36	7	
Males (%)	14 (64)	14 (66)	1,0	24 (67)	4 (57)	0,68
Females (%)	8 (36)	7 (34)	1.0	12 (33)	3 (43)	0,68
Age ± SD	54±12,1	56,6±13,3	0,55	**57,3±12,1**	**45,6±10,9**	**0,02**
Inclusion [months] ± SD	76,6±15,1	76,6±10,1	1,0	75,9±13,8	80,1±3,2	0,42
Height [cm] ± SD	168,7±8	171,3±3	0,33	170±8,1	171,3±10	0,67
Weight [kg] ± SD	73±12,3	80,6±13,8	0,06	76,6±14	77,1±10,9	0,92
2-h G month 3 [mg/dL]	156	205	0,07	**195**	**107**	**<0,01**
2-h G month 6 [mg/dL]	149	156	0,62	**160**	**117**	**<0,01**
2-h G month 12 [mg/dL]	151	157	0,77	**163**	**112**	**<0,01**

Diab. + prediab. = diabetics + prediabetics; NGT = normal glucose tolerance; SD = standard deviation, 2-h G = 2-hour glucose at the oral glucose tolerance test. *p-values were determined, using the unpaired two-tailed Student t test for continuous variables, and the unadjusted chi square test for categorical variables. †Determined at transplantation. **OGTTs in the original TIP-study were not performed in patients who were receiving anti-diabetic therapy (accounting for the lack of signifcance between 2-h G in insulin treatment-versus control patients; for further details, please refer to PMID22343119).

TH-PO154

High Incidence of Recurrent Diabetic Nephropathy in Kidney Transplant Alone (KTA) Recipients

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Background: Improving long-term kidney allograft survival is a major challenge. Recurrent diabetic nephropathy (RDN) in kidney transplant recipients is not well studied. We aimed to determine the incidence, timing and severity of recurrent diabetic nephropathy (RDN) in recipients with pre-transplant type 1 (T1DM) and type 2 diabetes (T2DM).

Methods: We studied 118 diabetic transplant recipients (recs) -T1DM (simultaneous kidney pancreas [SPK] and KTA), and T2DM (all KTA) transplanted between 2002 and 2009. Recs with SPK had functioning pancreas allograft at 5y post transplant. All recs underwent surveillance protocol kidney biopsy at 4 months, 1y, 2 y and 5 y post transplant. RDN was diagnosed based on light microscopy according to Banff 2015 criteria (MM score) and/or as described by pathologist if MM score was not assigned. Advanced RDN was diagnosed if MM score was >1. Patients with immune complex diseases were excluded.

Results: We identified 52 T1DM (46% SPK and 54% KTA) and 66 T2DM (all KTA) recs. T1DM were younger (47y ± 1.3 vs. 62.1y±1.2 for T2DM; p<0.001). BMI was comparable (31.2 T1DM vs. 33.2 T2DM). The earliest RDN was seen at 1 year post transplant. At 5 years, the incidence of RDN was only 4.3% in T1DM SPK, compared to 34% in T1DM with KTA and 46% in T2DM with KTA (p<0.05). BMI was higher in those with RDN (34.5 vs 29.9; p<0.05) regardless od diabetes type. 13 (11%) recs developed advanced RDN (mm>1) at 5 years. Those recs were more likely to be T2DM (74% vs. 26% for T2DM and T1DM, respectively, p<0.05). Mean HbA1C in this group at 5 y was 8.12%±1.8. Creatinine has not changed over the 5 years post transplant (mean delta creatinine 0.03 ± 0.38). Mean albuminuria at 5 y was 52 mg/24h ± 345. 7 (53 %) of recs with advanced RDN did not have significant albuminuria at 5 years (30 mg/24 h or less).

Conclusions: Histologic changes of RDN can be seen as early as 1 year post kidney transplant and have high incidence at 5 years. HIgh BMI is a risk factor. Pancreas transplantation is associated with histological protection. Advanced RDN is significantly more common in T2DM recipients and may be clinically silent. Future studies should focus on identifying risk factors for RDN, its impact on graft survival and development of better noninvasive biomarkers of histologic injury.

TH-PO155

Liraglutide May Be Safe After Kidney Transplantation

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Background: Kidney transplant has offered better outcomes for patients with end stage renal disease (ESRD). Diabetes is a common comorbidity in patients with renal transplants which requires treatment. Diabetes is the most common cause of ESRD. Patients could develop post-transplant DM (PTDM), or have pre-existing diabetes mellitus. Management of DM after transplant (whether the patient had it from before or after the transplant) is challenging. Different medications could be used to manage PTDM. Those medications have good safety and efficacy record in the general population and patients with mild degrees of kidney disease.

Methods: We conducted a retrospective single center analysis of safety and efficacy of Liraglitude after kidney transplant. The study was approved by institutional review board. We collected data (demographics, laboratory tests and any symptoms or hospitalizations) for 32 consecutive patients for 18 months.

Results: All 32 patients received subcutaneous Liraglitude at an average of 1.2 mg/day throughout the study period. Patients' average age was 64. 18 were females and all from Middle Eastern decent and had kidney transplant on average 32 months when they were included in the study. 13 patients had DM before the transplant and the rest had PTDM. 15 patients were on metformin and 10 were on insulin while the rest were not on any other medications. Average baseline creatinine was 1.2 mg/dL (106.3 mmol/L) and glycated hemoglobin (HbA1c) of 8.4 g/dL while creatinine was 1.1 mg/dL (97.5 mmol/L) and HbA1c was 7.2 g/dL at the end. HbA1c dropped 1.2 on average within 6 weeks of initiating Liraglitude and was maintained for the rest of the study. Urine protein did not change significantly throughout the study. One patient developed acute myocardial infarction during the study and another patient was hospitalized with acute pancreatitis. A third patient developed an opportunistic infection. Ten patients developed nausea and vomiting following the initiation of Liraglitude but that resolved 4 weeks later with lowering the dose. No allergic reactions or hypoglycemia episodes were reported. The average weight dropped 2.4 kg during the study and body mass index changed from 28.6 to 27.8. Only one patient stopped the medication due to acute pancreatitis.

Conclusions: In this retrospective analysis, Liraglitude seems to be safe and efficacious after kidney transplant. It can be considered to manage DM after transplant.

TH-PO156

Linagliptin May Be Safe After Kidney Transplant

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Background: The incidence and prevalence of end-stage renal disease (ESRD) is increasing. The most common cause of ESRD is diabetes mellitus (DM). Kidney transplantation offers better quality of life and survival for patients with ESRD. Patients could develop post-transplant DM (PTDM). Management of DM after transplantation (whether the patient had it from before or after the transplant) is a challenge. Different medications could be used to manage PTDM. Those medications have good safety and efficacy record in general population and patients with mild degrees of kidney disease.

Methods: We conducted a retrospective single center analysis of safety and efficacy of Linagliptin post kidney transplantation. The study was approved by institutional review board. We collected data (demographics, laboratory tests and any symptoms or hospitalizations) for 28 consecutive patients for 16 months.

Results: All 28 patients were initiated on Linagliptin throughout the study period. Patients' average age was 62. Fifteen were females and all from Middle Eastern decent and had kidney transplant on average of 25 months when they were included in the study. Twelve patients had DM before the transplant and the rest had PTDM. 13 patients were on metformin and 8 were on insulin while the rest were not on any other medications at the start of the study. Baseline average creatinine was 1.5 mg/dL (132.9 mmol/L) and glycated hemoglobin (HbA1c) of 8.2 g/dL at the start of the study while creatinine was 1.6 mg/dL (141.8 mmol/L) and HbA1c was 7.4 g/dL at the end. HbA1c dropped 0.8 on average within 5 weeks of starting Linagliptin and was maintained at the same level for the rest of the study. Urine protein did not change significantly throughout the study. Two patients developed acute myocardial infarction during the study and a third patient was hospitalized with an opportunistic infection. Two patients had urinary tract infections. 3 patients had nausea and vomiting after starting Linagliptin but that resolved 2 weeks later. No allergic reactions, hypoglycemia or acute pancreatitis episodes were reported. The average weight and body mass index did not change throughout the study. None of the patients stopped the medication.

Conclusions: In this retrospective analysis, Linagliptin seems to be safe and efficacious after kidney transplantation. It can be considered in the management of diabetes post kidney transplantation.

TH-PO157

Serum Bicarbonate Levels Are Associated with Graft Survival and Mortality in Swiss Kidney Transplant Recipients

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Background: Metabolic acidosis (MA) is a frequent complication of chronic kidney disease (CKD) and an independent risk factor for kidney disease progression. MA is also highly prevalent after kidney transplantation (12%-58%). A recent study has shown that MA after kidney transplantation was associated with increased risk of graft loss and death indicating an impact of MA on long-term graft function. However, the cohort had a fairly low prevalence of MA. Also a cut-off value for bicarbonate of 22 mEq/L, as commonly used for the definition of MA, may be questionable since kidney outcome and mortality have been shown to correlate best with TCO_2 values of 24-28 mEq/L. Thus, we wanted to investigate if serum bicarbonate is associated with graft outcome and mortality in Swiss kidney transplant recipients (KTRs).

Methods: We performed a single-center retrospective study including adult (≥ 18 years) patients that have been subjected to *de novo* kidney transplantation between 1999 and 2015. Cox proportional hazard model was used to analyze a possible association between time-dependent serum bicarbonate measurements and graft loss (defined as re-entry to dialysis or second kidney transplantation) or death

Results: 430 KTRs were included in the analysis with a mean age of 50.9±13.4 years. Mean observation time was 4.7±2.8 years. 284 (66%) were male and 318 (74%) had received a deceased donor kidney transplant. Mean bicarbonate and eGFR levels one year post-transplant were 22.7±3.1 mmol/L and 61±26 ml/min, respectively. Prevalence of MA (defined as bicarbonate <22 mmol/L) was 51.2% after transplantation and decreased to 30.8% one year post-transplant. 14 (3%) patients died and 31 (7%) suffered from graft failure. Higher bicarbonate levels were associated with significantly lower hazards for graft failure (HR=0.88; 95% CI, 0.79-0.98; p=0.022) and mortality (HR=0.79; 95% CI, 0.66-0.93; p=0.006) after adjusting for potential confounders such as age, type of donor and time-varying eGFR.

Conclusions: Our analysis showed that higher serum bicarbonate levels are associated with long-term graft and patient survival in Swiss KTRs. Thus, serum bicarbonate may serve as a predictor for graft and patient outcome after kidney transplantation as has been previously shown for patients with CKD.

TH-PO158

Prevalence of Gout in the Surviving US Solid Organ Transplant Population

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Background: Although incidence and survival are frequent topics within the solid organ transplant (SOT) literature, there are no recent publications on the total size of the surviving SOT population. Existing studies of gout in SOT have focused on the incident SOT population. This analysis was performed to characterize the prevalent SOT population and the prevalence of gout within it.

Methods: 2017 U.S. population sizes of kidney, heart, liver, and lung recipients were estimated by combining Organ Procurement and Transplantation Network (OPTN) primary transplant cohort sizes (1988-2017) with previously published survival rates for each annual cohort's time since transplant (0-29 yrs), adjusted for recent improvements in 1-5 yr survival. Gout among prevalent SOT patients was assessed via 2 administrative claims databases: Medicare Fee-For-Service Limited Data Set (5% sample) and a commercial claims sample (IQVIA™ Real-World Data Adjudicated Claims – US). Definitions used were – SOT: a claim with an SOT procedure code OR any claim with a history of SOT status code; Gout: ≥1 claim with any gout diagnosis code. Total gout prevalence was calculated by weighting Medicare and commercially insured patient estimates by OPTN payer distribution.

Results: 637,231 U.S. patients received a primary kidney (393,953), liver (142,186), heart (66,637), or lung (34,455) transplant between 1988 and 2017. An estimated 355,000 (55.8%) recipients were alive in 2017, comprising nearly two-thirds (233,000) kidney, as well as 78,700 liver, 29,300 heart, and 14,700 lung recipients. Gout was identified in 11% of prevalent SOT patients in 2016. Higher rates of gout were seen in kidney (13%) and heart (13%) recipients compared to liver (6.4%) and lung (5.3%) recipients (p<0.0001 in both datasets).

Conclusions: Hundreds of thousands of U.S. patients are living with an organ transplant today and these numbers are likely to increase. Within the SOT clinical picture, gout is a frequent co-morbidity of which physicians should be aware. This study suggests a markedly higher rate of gout for the most common SOT types (11%) compared to established rates reported for the general population (e.g. 3.9%). Kidney recipients, with the largest surviving population and high rates of gout, bear much of this disease burden.

Funding: Commercial Support - Horizon Pharma

TH-PO159

Gout Severity in Kidney Transplant Recipients

Lauren Radeck,[1] Clive M. Mendonca,[1] Isabel Lang,[1] Jeffrey Kent,[2] Brian Lamoreaux,[2] Richard J. Johnson.[3] *[1]Trinity Partners, Waltham, MA; [2]Horizon Pharma, Lake Forest, IL; [3]University of Colorado Denver, Aurora, CO.*

Background: Gout is a frequent co-morbidity of solid organ transplant (SOT), especially among kidney recipients. Less well understood are any differences in gout severity and treatment success between gout patients with and without SOT. This retrospective analysis of medical patient chart data was performed to compare disease severity and treatment history in recent gout case examples with vs. without a history of kidney transplant.

Methods: An online survey was completed using a panel of board certified U.S. nephrologists. Respondents were asked to pull de-identified patient charts for their 3 most recent gout patients. Measures evaluated included: SUA level, numbers of swollen/tender joints (at visit), visible tophi (at visit), gout flare events (prior 12 months), gout drug treatment history, and presence of "severe, uncontrolled gout" defined as: SUA ≥7.0 mg/dL, 1 or more visible tophi AND 2 or more gout flares, and history of xanthine oxidase inhibitor treatment. Case examples were weighted by number of visits in last 12 months and respondents' overall gout treatment volume.

Results: 23 out of 299 (7.7%) Rx-treated patients had a history of kidney transplant (N=104 nephrologist respondents). Compared to non-SOT patients, SOT patients were more likely to meet severe uncontrolled gout criteria (25% vs. 7%, p<0.05). Univariate analysis found that SOT patients, compared to non-SOT patients had: higher prevalence of visible tophi (32% vs. 13%, p<0.01), lower allopurinol treatment rates (28% vs. 50%, p<0.05), and higher rates of failure or contraindication to febuxostat (22% vs. 4%, p<0.01).

Conclusions: This study provides preliminary evidence that gout is more severe and poses more challenges for pharmacologic management in kidney transplant patients compared to other nephrology gout patients. Although gout has been linked to a higher all-cause mortality rate among kidney recipients in the literature, to our knowledge there are no published comparisons of gout severity among such patients vs. the general nephrology patient population. Further investigation of symptom severity and unmet need in appropriate, effective treatment options in transplant recipients with gout is warranted.

Funding: Commercial Support - Horizon Pharma

TH-PO160

Immunosuppressant Use and Gout in the Prevalent Solid Organ Transplant Population

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Background: Gout is a frequent co-morbidity of solid organ transplant (SOT). Cyclosporine (CsA) is often cited as the main cause of gout in SOT, as other immunosuppressant (IS) regimens were associated with lower gout rates (e.g. 1980s studies of azathioprine monotherapy). In most guidelines & institutions, tacrolimus (TAC) has replaced CsA in SOT IS regimens. However, two questions are largely unknown: (1) to what degree is CsA still used among prevalent SOT patients? (2) can CsA fully explain high rates of gout still seen among SOT patients? This retrospective patient claims data analysis was performed to evaluate IS use and gout in the prevalent SOT population.

Methods: IS regimens and gout prevalence among prevalent SOT patients were assessed via commercial claims data (IQVIA™ Real-World Data Adjudicated Claims – US). Definitions used were – SOT: claim with an SOT procedure code OR any claim with a history of SOT status code; IS: ≥1 claim for a given IS drug in the calendar year; Gout: ≥1 claim with any gout diagnosis code. IS use at time of transplant for 2016 recipients was obtained from the Organ Procurement and Transplantation Network (OPTN).

Results: The proportion of prevalent SOT patients on CsA declined from 2012 to 2016: heart 22% to 18%, kidney 21% to 17%, lung 16% to 11%, liver 15% to 12% (all p<0.01). TAC use increased: heart 66% to 73%, kidney 67% to 74%, lung 75% to 80%, liver 77% to 82% (all p<0.01). CsA use was higher in prevalent vs. incident SOT populations (e.g. 17% vs. 1.7% kidney 2016, p<0.0001). 2016 gout prevalence was 16% vs. 8% among CsA vs. non-CsA patients. Among all SOT patients with gout, 69% and 26% were on TAC and CsA, respectively.

Conclusions: Despite declining CsA use, gout remains a problem in SOT patients. For one, this study finds that many prevalent SOT patients still receive CsA. Additionally, gout prevalence in the non-CsA population was much higher (8%) than established rates reported in the general population (e.g. 3.9%). This suggests CsA is not the sole driver of gout in SOT. In fact, this analysis finds that post SOT, more than twice as many gout sufferers are on TAC than on CsA. Physicians should be aware that with any transplant IS regimen including calcineurin inhibitors, gout is likely to remain a frequent co-morbidity of SOT.

Funding: Commercial Support - Horizon Pharma

TH-PO161

Role of Coronary Interventions in High Cardiovascular Risk Patients on Kidney Transplant Waitlist

Bayiha daho Klaud francheska, Maria Fernandez, Ahmad Salha, Racquel M. Lowe-Jones, Debasish Banerjee. *St George's University Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: High cardiovascular risk patients on the kidney transplant list often undergo cardiac interventions to improve their outcome and survival following

transplantation. However the benefits of these interventions are currently unknown and were explored in this study.

Methods: The study, approved by hospital Clinical Effectiveness and Audits Committee, included 164 episodes in 126 patients discussed in discussed in a multidisciplinary cardio-renal MDT, between 1-10-2014 to 30-09-2017 and followed until 23-05-2018.

Results: 126 patients were discussed in the multidisciplinary meeting, some more one than once. Clinical characteristics of the 164 patient episodes were; age 61±8years, BMI 28±5kg/m^2, cholesterol 4.0±1.1mmol/L, 61% diabetes, 96% hypertension, 63% haemodialysis and 27% pre-dialysis. After discussion 96 cardiac procedures were suggested and performed, including stress echocardiogram (68%), echocardiogram (9%), coronary angiogram (13%), percutaneous coronary intervention (4%), and coronary artery bypass graft (4%). The non-invasive tests resulted in further 19 angiograms, 10 PCI and 1 CABG. Thirty-five percent of patients had no cardiac intervention performed; 44% had a single intervention and 21% had multiple interventions. 28 patients had an event (death, ACS or stroke) during follow-up, who were more likely to be diabetic, the clinical characteristics are in table 1. 37% (n= 13) of patients who had invasive cardiac intervention developed an event, while 16% (n=7) of patients who did not receive any cardiac tests or intervention developed an event (p=0.246). Of the 91 patients who did not have invasive procedures, only 15 (16%) had an event as opposed to 13 (37%) in the remaining cohort who had invasive procedures done (Figure 1).

Conclusions: Out of 126, events occurred in 28 patients, mainly cardiovascular. Cardiac interventions including angiograms, CI or CABG were unable to lower the CV event rate in high-risk patients on transplant waitlist..

	Patients with no events (n=98)	Patients with events (n=28)	P value
Age	61 ± 8.8	62.6 ± 6.3	0.256
Men (%)	60	60.7	0.543
Diabetes (%)	53.1	75	0.009
Haemodialysis (%)	57.1	78.6	0.014
BMI	27.9 ± 4.8	28.5 ± 5.2	0.506
Cholesterol	4.14 ± 1.1	3.7 ± 1.2	0.025
Positive DSE (%)	11.2	14.3	0.532
Angio/PCI/CABG (%)	19.4	46.4	0.246

Table 1: Clinical characteristics of patients with cardiac events vs. without cardiac events

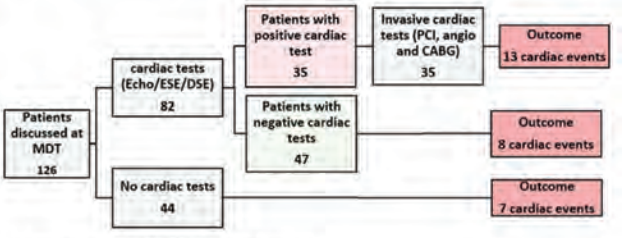

Figure 1: Flowchart of the 126 patients discussed

TH-PO162

Non-Skeletal Effects of High Doses Versus Minimum Recommended Intake of Vitamin D3 in Renal Transplant Recipients in a Prospective, Multicenter, Double-Blind, Randomized Study

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Background: High doses of vitamin D_3 (cholecalciferol, CL) have been advocated to reduce the risk of diabetes mellitus (DM), major cardiovascular events (MACE), and cancer, which are frequent complications in renal transplant recipients (RTR).

Methods: The VITALE study is a prospective, multicenter (30 French transplantation departments), double-blind, controlled trial (NCT01431430). Adult RTR with serum 25(OH)-vitamin D levels (25OHD) <30 ng/mL, were randomized between 12 and 48 months after transplantation to receive either high doses (HD, 100,000 IU) or low doses (LD, 12,000 IU corresponding to the minimum recommended intake, MRI) of CL every 2 weeks for 2 months then monthly for 22 months. The primary objective was to evaluate the effect of HD vs LD on a composite endpoint: DM, MACE, de novo cancer, and patient death. The sample size calculation was based on the assumption of an incidence of a first event of the composite endpoint of 22% in the LD group *versus* 13% in the HD group. The inclusion of a total of 480 RTR was required to test this hypothesis with a power of 80%.

Results: Between January 2012 and December 2013, 536 RTR (mean (SD) age 50.8 (13.7) years, 335 males) were included. Baseline clinical and biological characteristics did not differ between HD (n=269) and LD (n=267) groups. In the HD and the LD group, 25OHD was 20.2 (8.1) vs 19.2 (7.0) ng/mL at D0 and 43.1 (12.8) vs 25.1 (7.4) ng/mL after 24 months (<0.0001). The intention to treat analysis showed that the number of events of the composite endpoint did not differ between HD and LD groups (15% vs 16%, respectively). There was also no difference for infections (51% vs 47%), acute rejection episodes (3% vs 2%) and graft loss (0.37% in both groups). The number of patients with incident hypercalcemia or hyperphosphatemia did not differ between groups (17% vs 13%, p=0.24, and 5% vs 4%, p=0.41, in HD and LD group respectively). Of note, evolution of valvular calcifications was not significantly different between groups (p= 0.59).

Conclusions: In conclusion, HD of CL are well-tolerated but do not reduce the incidence of non-skeletal complications in RTR when compared to the MRI.

Funding: Commercial Support - Crinex Laboratory (France), Government Support - Non-U.S.

TH-PO163

A Prospective Observational Study Comparing Bone Loss in Renal Transplant and Dialysis Patients

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Background: Bone loss has been reported with chronic dialysis and after renal transplantation. This study compared the differences in longitudinal changes in BMD between dialysis and transplant patients using quantitative computed tomography (QCT).

Methods: Total hip BMD was assessed using QCT in 29 renal transplant recipients at the time of transplantation, at 6 months (n=25), and at 12 months (n=19). In addition 50 dialysis patients of similar gender, age, race, dialysis vintage, diabetes, non-smoking status, coronary artery disease, and exercise were studied. BMD at baseline and after 12 months was compared between the two groups.

Results: In transplant patients, total hip BMD by QCT decreased from a mean of 0.88 g/mm^3 at time of transplantation to 0.83 g/mm^3 at 6 months after transplant, then stabilized at 0.83 g/mm^3 at 12 months for an average loss of 0.05 ± SE 0.02 g/mm^3 (fig. 1). While the average dialysis patient lost 0.02 ± SE 0.01 g/mm^3 of BMD at the hip over 12 months (p= 0.07, Figure 2). The average bone loss was higher for transplant patients with normal baseline BMD compared to patients with low BMD (Normal: -0.05 g/mm3; Low: -0.02, p=0.314).

Conclusions: Significant bone loss occurs in renal transplant recipients during the first 6 months then stabilized at 12 months. This bone loss is more than what is observed in matched dialysis patients. Normal BMD is still of concern because bone loss may be higher compared to patients with low BMD.

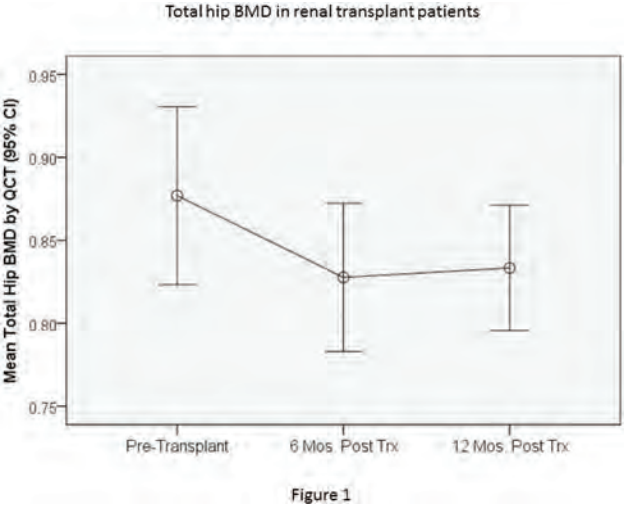

Figure 1

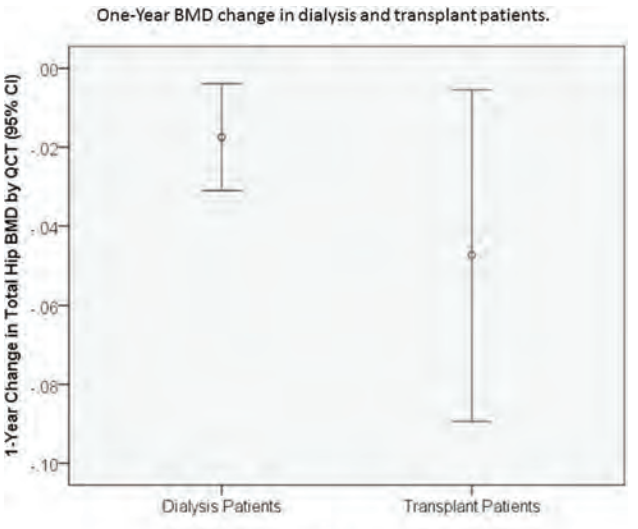

Figure 2

TH-PO164

Association of Post-Transplant Calcium and Phosphate Levels with Graft Outcomes

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Background: Alterations in Ca and P are observed with varying impact on post-transplant outcomes and its implications in graft function are unclear. Our study assesses the relation between serum P and Ca during the first year and graft outcomes

Methods: Longitudinal single centre cohort study, we analyse 1524 first transplants, since 1991 to 2016. Our data was prospectively collected in the national kidney transplant registry. The primary outcome was graft failure and association with P and Ca on first year. We include patients >18 years and immunosuppression MMF + CNI + steroids. We categorized the P and Ca as low, normal or high. The analysis include Kaplan Meier and cox regression

Results: The age was 47.9 y (SD13.9), donor age 43.2 (SD13.3), 64.4% male, 59% HD, 29.5% PD, and 10.1% pre emptied, HLA mean 3.35 (SD1.5), time to fail 8.2 y (SD5.0), 297 grafts failed (18.4%), 85.1% has P<0.7 mmol/L the first year 0.52 (SD0.15), reached at 26.9 (SD46) days, 35.9% Ca >2.6 mmol/L, reached at 74.7 (85.9) days. The KM analysis show increase graft failure with low P or Ca pre transplant (p:0.03), better outcomes with low P at 1, 6 and 12 m (p:0.014, 0.04, 0.004), and high Ca at 1 month, but not so at 6 and 12 m (p:0.03, 0.7 and 0.6). Cox regression show HR 0.60; 95% CI 0.29 to 1.26 with low P and HR 0.71; 95% CI 0.52 to 0.98 with high Ca for graft failure

Conclusions: The derangements in Ca and P are frequent post transplant and develop the first months. The post transplant hypercalcemia is associated with better graft outcomes however the hypophosphatemia not. Futures trials will investigate if the treatment of these conditions would be a risk factor in these patients

Cox regresion model for High Calcium at 1st month

Variables	Sig.	Exp (B)	95% CI LL	95% CI UL
Minimum P (mmol/L)	0.04	0.71	0.52	0.98
Rejection	0.01	1.93	1.33	2.81
Age (Years)	0.01	1.04	1.03	1.05
DGF (days)	0.01	1.04	1.02	1.07

Table 01. General characteristics between phosphate and calcium subgroups.

Ca and P mmol/L	P >0.7	P <0.7	p	Ca <2.6	Ca >2.6	p
Recipient age	50.9 (14.1)	48.4 (14.2)	0.003	49.8 (14.0)	47.1 (14.5)	0.001
Donor age	46.5 (12.7)	43.8 (13)	0.001	44.8 (13.2)	43.2 (12.6)	0.04
HLA total	3.4 (1.6)	3.3 (1.4)	0.58	3.4 (1.5)	3.3 (1.5)	0.34
PGEN %	17.7 (26.7)	12.5 (22.7)	0.004	13.3 (23.6)	13.4 (23.3)	0.94
DGF (days)	3.4 (8.1)	1 (3.4)	0.001	1.3 (3.9)	1.5 (5.3)	0.39
Time to death (y)	5.5 (3.4)	6.6 (3.7)	0.001	6.5 (3.8)	6.3 (3.5)	0.87
Time to fail (y)	5.4 (3.3)	6.4 (3.7)	0.001	6.3 (3.7)	6.2 (3.5)	0.79
HD vinatge (y)	3 (2)	2.8 (2.8)	0.41	2.6 (3.0)	3.2 (2.0)	0.001
eGFR 1st month	45.3 (20.3)	62.9 (19.3)	0.001	58.8 (19.4)	63.4 (21.7)	0.003
Sex (M/F) %	69.2 / 30.8	63.8 / 36.2	0.12	62.0 / 38.0	68.9 / 31.1	0.007
CMV Donor (+) %	35.9	35	0.79	37.5	31.2	0.02
CMV recipient (+) %	40.2	35.9	0.24	36	37.6	0.54
Rejection %	16.3	10.4	0.01	11.8	10.5	0.43
Death %	11.7	10.8	0.69	12.2	8.8	0.04
Failed graft %	17.8	17.1	0.82	19.2	13.9	0.009

TH-PO165

Effects of Denosumab on Bone Metabolism and Bone Mineral Density in Kidney Transplant Patients: A Meta-Analysis

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Background: The uses of immunosuppressive agents, are associated with increased risks of bone loss in kidney transplant (KTx) patients. Denosumab, a potent anti-resorptive agent, has been shown to increase bone mineral density (BMD) in patients with CKD. However, its effects on bone metabolism and BMD in KTx patients remain unclear.

Methods: A literature search was conducted using MEDLINE, EMBASE and Cochrane Database from inception through April 2018 to identify studies evaluating the effects of denosumab on changes in bone metabolism and BMD from baseline to post-treatment course in KTx patients. Study results were pooled and analyzed using a random effects model. The protocol for this meta-analysis is registered with PROSPERO (CRD42018095055).

Results: 5 studies (a clinical trial and 4 cohort studies) with a total of 162 KTx patients were identified. Majority of patients had baseline eGFR ≥ 30 mL/min/1.73 m2. After the treatment (≥6 to 12 months), there were significant increases in BMD with standardized mean differences (SMDs) of 3.26 (95%CI 0.88-5.64) and 1.83 (95%CI 0.43 to 3.22) for lumbar spine and femoral neck, respectively. There were also significant increases in T scores with SMDs of 0.92 (95%CI 0.58 to 1.25) and 1.14 (95%CI 0.17 to 2.10) for lumbar spine and femoral neck, respectively. There were no significant changes in serum Ca or PTH from baseline to post-treatment course (≥ 6 months) with mean differences (MDs) of 0.52 (95%CI, -0.13 to 1.16) mmol/L and -13.24 (95% CI, -43.85 to 17.37) ng/L, respectively. Data from a clinical trial demonstrated that asymptomatic hypocalcemia occurred more common in denosumab group (12 episodes in 39 patients) than in control (1 episode in 42 patients). From cohort studies, the pooled incidence of hypocalcemia following denosumab treatment was 1.7% (95%CI 0.4% to 6.6%). All reported hypocalcemic episodes were mild and asymptomatic, but majority of patients required Ca and Vit D supplements.

Conclusions: Among KTX patients with good allograft function, denosumab effectively increases BMD and T scores in the lumbar spine and femur neck. From baseline to post-treatment, there are no differences in serum Ca and PTH. However, mild hypocalcemia can occur following denosumab treatment, requiring monitoring and titration of Ca and Vit D supplements.

TH-PO166

Safety and Efficacy of Patiromer in Kidney and Liver Transplant Recipients

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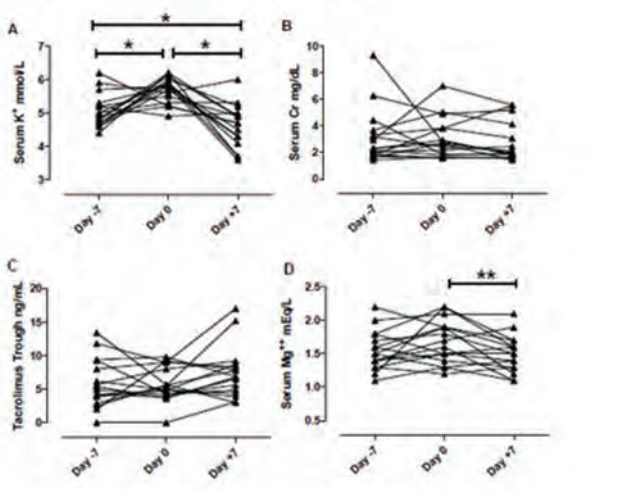
Background: Patiromer has been FDA approved for the management of chronic hyperkalemia, however, there is a paucity of data regarding its safety and efficacy in transplant recipients.

Methods: We retrospectively reviewed the use of patiromer in 16 transplant recipients at our center from 2016 to 2018 including 9 Kidney, 6 Liver, and 1 Kidney after Liver recipients. Patiromer was given mid-day, separated from immune suppression medications by 3 hours. It was started a median of 24 (8-548) days (d) post-transplant and used for a median of 44 (1-160) d. Maximum dose used was 8.4 g/d in 7, 16.8 g/d in 6, and 25.2 g/d in 3 patients. In 5 (31.3%) patients, patiromer was added to other therapies for hyperkalemia: fludrocortisone in 3, diuretics in 3, and discontinuation of sulfamethoxazole/trimethoprim in 2 for an alternative agent.

Results: Mean serum K decreased (Fig. 1A) though serum Cr did not change (Fig. 1B). Patiromer did not appear to interfere with tacrolimus absorption as 13 (81.3%) patients were within goal tacrolimus trough range 1 week after starting patiromer and no change in mean tacrolimus troughs was seen (Fig. 1C). Serum magnesium decreased from initiation to 1 week later but post-initiation levels were not different from pre-initiation levels (Fig. 1D). 10 (62.5%) patients required magnesium repletion. There were no adverse events attributed to patiromer and no observed episodes of rejection. 1 patient stopped patiromer due to intolerance, but later resumed the medication without issue. 3 patients were readmitted with hyperkalemia: 1 in the setting of AKI, 1 after self-discontinuing patiromer, and 1 after provider-instructed dose reduction.

Conclusions: In this observational cohort, patiromer appears to be both safe and effective for treating hyperkalemia in kidney and liver transplant recipients.

Figure 1: Serum Values Before and After Patiromer Initiation



*= P<0.01. ** = P<0.05 A: Serum K 7 days before (5.06±0.50), on day of (5.69±0.38) and 7 days after (4.61±0.65) initiation of patiromer. B: Serum Cr 7 days before (3.15±2.06), on day of (3.05±1.52) and 7 days after (2.74±1.49) initiation of patiromer. C: Tacrolimus trough 7 days before (5.86±3.66), on day of (5.78±2.61) and 7 days after (7.45±3.91) initiation of patiromer. D: Serum Mg 7 days before (1.55±0.29), on day of (1.69±0.28) and 7 days after (1.50±0.07) initiation of patiromer.

TH-PO167

Potential Beneficial Association of Renin-Angiotensin-Aldosterone-System Blockade and Graft Prognosis in Allograft IgA Nephropathy

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Background: Clinical evidence supporting suggestions of using renin-angiotensin-aldosterone-system blockades (RAASB) for proteinuric recurrent glomerulonephritis after renal transplant was scarce. For allograft IgA nephropathy (IgAN), benefits of RAASB for graft prognosis remained controversial although the medication is consisting the mainstay for treatment of native IgAN.

Methods: We performed a bi-center retrospective cohort study on kidney transplant recipients diagnosed for IgAN in allograft biopsy. The included patients were stratified according to their prescribed maintenance hypertensive medication types within 6 months from their diagnosis. Patients those had follow-up duration less than 6 months were not considered in the analysis. The main outcome was 5-year death-censored-graft-failure (DCGF). Additional adjustment for other variables including presence of acute rejection or time-averaged eGFR after 3 months from diagnosis of allograft IgAN was performed, as clinicians may prescribe RAASB to those who were at stable allograft function.

Results: Among 558 patients with allograft IgAN, there were 38 patients who only received RAASB, and 33 patients who received single agent of CCB or BB. The other 121 patients were prescribed for other medications, mostly combination therapies. The RAASB group had relatively higher eGFR at the time of diagnosis for allograft IgAN but had higher degree of albuminuria and worse pathologic findings. The group of patients who received single antihypertensive agent other than RAASB (calcium channel blockers (CCB) or beta blockers (BB)) had significantly increased risk of DCGF (adjusted HR 2.68, 95% CI 1.08-6.67, P=0.03) than those who received single RAASB agent, and this was also similar in patients who received multiple antihypertensive medications (adjusted HR 2.20, 95% CI 1.02-4.74, P=0.04). In addition, this possible beneficial association of RAASB usage and graft prognosis was more prominent in patients who had albuminuria at the time of allograft IgAN diagnosis.

Conclusions: Usage of RAASB during the time of allograft IgAN diagnosis was associated with better prognosis compared with using other antihypertensive drugs. Our study is one of evidences encouraging the usage of RAASB in allograft IgAN patients.

TH-PO168

Relationship of Systolic Blood Pressure with GFR Decline in Kidney Transplant Recipients: The FAVORIT Trial

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[1]UCSD, San Diego, CA; [2]University of Washington, Seattle, WA; [3]Tufts Medical Center, Boston, MA; [4]University of Utah, Salt Lake City, UT; [5]UCSD, San Diego, CA; [6]Rhode Island Hospital, Providence, RI.

Background: In chronic kidney disease, intensive systolic blood pressure (SBP) control reduces mortality, but increases rate of estimated glomerular filtration (eGFR) decline and acute kidney injury risk. The optimal blood pressure target in KTRs is uncertain. Prior observational studies from FAVORIT demonstrate lower mortality at lower SBP levels, but the relationship of SBP with kidney allograft function is largely unknown. We investigated the relationship of baseline SBP with risk of kidney allograft failure and eGFR slope during long-term follow-up among stable KTRs.

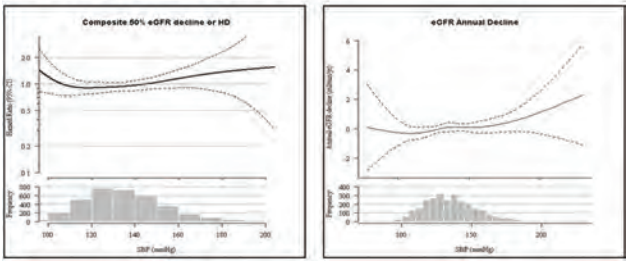
Methods: The FAVORIT trial, a multicenter, double-blind, randomized trial examining the effect of B-vitamin therapy on CVD and mortality, recruited KTRs who were at least 6 months post-transplant. SBP was measured at baseline, and subsequent eGFR values and kidney failure events were assessed. Cox proportional hazards and multivariable linear regression models were used to determine association of SBP with time to ≥50% eGFR decline or dialysis dependence, and annualized eGFR decline, respectively. Restricted cubic spline plots were developed to evaluate the functional form of the relationships. Models were adjusted for demographics, transplant characteristics, baseline eGFR, urine ACR and comorbidities.

Results: Among 3,598 KTRs, mean age was 52±9 years, mean baseline SBP was 136±20 mmHg and mean eGFR was 49±18 ml/min/1.73m^2. There were 369 ≥50% eGFR decline or dialysis dependence events during mean follow-up of 4.0±1.5 years. The relationships of SBP with both ≥50% eGFR decline or dialysis (SBP: $P_{\text{nonlinearity}} = 0.2$) and annualized eGFR slope (SBP: $P_{\text{nonlinearity}} = 0.8$) were linear without evidence of J or U shaped relationships (figure).

Conclusions: In a large sample of stable KTRs, we found no evidence of threshold at which lower baseline SBP was related to higher risk of eGFR decline. While reassuring in light of prior findings of mortality benefit at lower SBP, future trials are required to establish optimal BP targets in KTRs.

Funding: NIDDK Support

Figure: Adjusted spline plots for risk of ≥ 50% eGFR decline or hemodialysis dependence and annualized eGFR decline over the range of baseline systolic blood pressure



TH-PO169

Triglyceride to HDL-Cholesterol Ratio and Risk of Major Cardiovascular Events in Renal Transplantation Recipients

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Background: Dyslipidemia is common in renal transplant recipients(RTRs). Recent studies have shown that TG/HDL-C ratio may be a better predictor of cardiovascular(CV) events and CV mortality than other lipid parameters. We analyzed the TG/HDL of the first year of transplantation to identify the risk factors for major cardiovascular events(MACE). MACE was defined as heart failure, coronary artery disease with percutaneous coronary artery intervention(PCI), and cerebrovascular disease confirmed as an imaging study.

Methods: We retrospectively included 1301 RTRs who had lipid profile after 1 year of transplantation between 2000-2018. We identified TG/HDL from the lipid profile at 1 year and classified it into 3 groups as follows: low; less than 1, moderate; 1 to 2.5, high; 2.5 or more. After then, we explored an association between TG/HDL group and MACE.

Results: The mean age of included patients was 40.9 years and male sex was 61.7%. The prevalence of diabetes was 29.1%. Statin was prescribed in 30.3% of RTRs within 1 year after transplantation. RTRs with higher TG/HDL tended to be more men, more obese and diabetic. Proportion receiving statin was lowest in moderate TG/HDL group. During follow-up, 80 patients experienced MACE. Time to MACE occurrence was 92.7 month. As expected high TG/HDL group showed elevated MACE risk even after adjustment with age, sex, BMI, DM, prior history of CVD, and statin use (adjusted HR 1.98 [1.20-3.29] p=0.008), compared with moderate TG/HDL group. Interestingly, also low TG/HDL group revealed higher risk of MACE, compared to moderate TG/HDL group (adjusted HR 2.14[1.03-4.47] p=0.041). These associations were represented similarly in statin users, whereas only low TG/HDL group, not high TG/HDL group, showed elevated MACE risk in non-statin users.

Conclusions: High TG/HDL of 2.5 or more may be a risk factor for cardiovascular events in RTRs, especially in patients requiring statin therapy. Additionally, our study suggested low TG/HDL may paradoxically increase cardiovascular risk, especially in low risk patients.

TH-PO170

Pre-Transplant NT-proBNP, Dialysis Duration, and Post-Transplant Mortality in Renal Transplant Recipients

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Background: Pre-transplant dialysis duration is associated with increased mortality in renal transplant recipients (RTRs) due to intradialytic volume overload and subsequent progression of left ventricular hypertrophy. As a result, the cardiovascular system could deteriorate into a worse state in potential RTRs. N-terminal pro brain natriuretic peptide (NT-proBNP), a protein released by stretch of ventricular cells caused by volume overload, is a prognostic predictor of mortality in end-stage renal disease patients. The aim is to assess if dialysis duration (DD) is independently associated with mortality in RTRs and if NT-proBNP explains the association between DD with mortality in RTRs.

Methods: 648 patients, transplanted (1995-2005) in the University Medical Center Groningen, were prospectively analyzed after exclusion of 225 patients without sera NT-proBNP and 39 patients with graft failure within 1 year after transplantation. Multivariable Cox regression models were used to study the association of DD and NT-proBNP with all-cause mortality. Mediation analysis was performed to evaluate whether the associations between DD and mortality were mediated by NT-proBNP.

Results: In multivariable Cox regression DD was associated with increased risk for post-transplant mortality, independent of potential confounders including age, gender, creatinine, diastolic blood pressure, diabetic nephropathy, donor type, delayed graft function, pre-emptive transplantation and CMV seropositivity (Hazard ratio [HR]: 1.39; 95% confidence interval [CI]: 1.11-1.75; *P*=0.004). This association weakened after adjustment for NT-proBNP (HR: 1.25; 95% CI: 0.99-1.58; *P*=0.06). NT-proBNP was independently associated with all-cause mortality in RTRs (HR: 1.46; 95% CI: 1.23-1.74; *P*=<0.001). In mediation analysis NT-proBNP was found to explain 47.3% of the effect of DD on all-cause mortality in RTRs.

Conclusions: DD is a predictor of mortality in RTRs and variation in NT-proBNP at the time of transplantation to a large extent captures and mediates the effect of DD on mortality risk in RTRs. Future studies are needed to evaluate the potential value of NT-proBNP as check of cardiac patency of patients on the transplantation waiting list.

TH-PO171

Epidemiology and Prognostic Importance of Atrial Fibrillation in Kidney Transplant (KT): A Meta-Analysis

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Background: This meta-analysis was conducted with aims to summarize all available evidence on prevalence of pre-existing atrial fibrillation (AF) and/or incidence of AF following kidney transplantation and the outcomes of KT recipients with AF.

Methods: A literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through March 2018. We included studies that reported 1) prevalence of pre-existing AF or incidence of AF following kidney transplantation or 2) outcomes of KT recipients with AF. Effect estimates from the individual study were extracted and combined utilizing random-effect, generic inverse variance method of DerSimonian and Laird. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018086192).

Results: 8 cohort studies with 137,709 kidney transplant recipients were enrolled. Overall, the pooled estimated prevalence of pre-existing AF in patients undergoing kidney transplantation was 7.0% (95%CI: 5.6%-8.8%) and pooled estimated incidence of AF following kidney transplantation was 4.9% (95%CI: 1.7%-13.0%). Meta-regression analyses were performed and showed no significant correlations between year of study and either prevalence of pre-existing AF (p =0.93) or post-operative AF after kidney transplantation (p =0.16). The pooled OR of mortality among KT recipients with AF was 1.86 (3 studies; 95%CI: 1.03-3.35). In addition, AF is also associated with death-censored allograft loss (2 studies; OR: 1.55, 95%CI: 1.02-2.35) and stroke (3 studies; OR: 2.54, 95%CI: 1.11-5.78) among KT recipients.

Conclusions: The overall estimated incidence of AF following kidney transplantation is 4.9%. Despite advances in medicine, incidence of AF following KT doesn't seem to decrease over time. In addition, there is a significant association of AF with increased mortality, allograft loss, and stroke after kidney transplantation.

TH-PO172

Autoantibodies to Apolipoprotein A-1 as Independent Predictors of Cardiovascular Mortality in Renal Transplant Recipients

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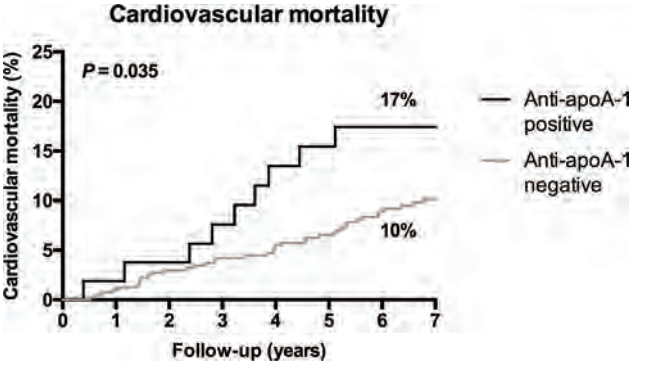
Background: The aim of this study was to determine i) the prognostic value of autoantibodies against apoA-1 (anti-apoA-1 IgG) for incidence of cardiovascular disease (CVD) specific mortality, all-cause mortality and graft failure in renal transplant recipients (RTR), patients known to have a high CVD burden only partly explained by traditional CVD risk factors, and ii) to delineate the relationship of anti-apoA-1 IgG with HDL functionality.

Methods: 462 prospectively included RTR were followed for 7.0 years. Baseline anti-apoA-1 IgG were determined and associations with incidence of CVD mortality (n=48), all-cause mortality (n=92) and graft failure (n=39) were tested.

Results: HDL functionality assessed in vitro by measuring anti-oxidative and cholesterol efflux capacity was not associated with anti-apoA-1 IgG levels. Kaplan–Meier analyses demonstrated significant associations of anti-apoA-1 IgG with CVD mortality (log rank test among tertiles: P=0.048). Adjusted Cox regression analysis showed that for each standard deviation increase of log transformed anti-apoA-1 IgG values, there was a 4-fold increase (hazard ratio [HR]: 4.00; 95% confidence interval [95%CI]:1.32-12.11; p=0.01) in risk for CVD mortality and a more than 2-fold increase for all-cause mortality (HR:2.69, 95%CI:1.25-5.83; P=0.01), independent of CVD risk factors, renal and HDL function. The association with all-cause mortality disappeared after excluding cases of CVD specific mortality. The sensitivity, specificity, positive predictive value, and negative predictive value of anti-apoA-1 positivity for CVD mortality were 18.0%, 89.3%, 17.0%, and 90.0%, respectively.

Conclusions: In conclusion, this prospective study demonstrates that in RTR, anti-apoA-1 IgG are independent predictors of CVD mortality. In RTR, anti-apoA-1 IgG are not associated with HDL functionality.



TH-PO173

High-Quality 3D MRA for Transplant Renal Artery Stenosis with NATIVE TrueFISP

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Introduction: Renal artery stenosis is a common complication after transplantation. In our institution, we have experienced a high rate of false-positive Doppler ultrasound and "confirmatory" non-contrast time-of-flight MRA studies that needlessly go to invasive catheterization. We present one of many of our cases which show the utility of high-quality 3D MRA using a non-flow dependent non-contrast technique, NATIVE TrueFISP.

Case Description: A 13-year-old male with a history of idiopathic dilated cardiomyopathy and end-stage renal disease underwent a combined cardiac transplant and deceased donor kidney transplant. Two months after the transplant, the patient was admitted for respiratory distress, pulmonary edema, and worsening cardiac function. On admission, the patient was mildly hypertensive. Further investigation showed an increase in serum creatinine to 1.6 mg/dl. A Doppler study showed elevated peak systolic velocity of the transplant renal artery anastomosis, up to 434 cm/sec. To confirm the sonographic suspicion of renal artery stenosis, a non-contrast 3D MRA was requested which showed tight juxta-anastomic stenosis (see Figure 1A). A diagnostic angiogram confirmed the pre-invasive imaging findings with nearly 1:1 correlation with the MRA 3D volume-rendered images (see Figure 1B). Angioplasty of this lesion was achieved by serial balloon dilation. Follow-up ultrasounds up to six-months post angioplasty show interval normalization of the renal artery velocities and blood pressure.

Discussion: The correct diagnosis of post-transplant renal artery stenosis is critical to avoid unnecessary, risky, costly, and time-consuming procedures. Under the supervision of a qualified radiologist, we have found our initial experience with NATIVE TrueFISP MRA technique to be reliable in evaluating transplant renal artery stenosis without the need for intravenous contrast.

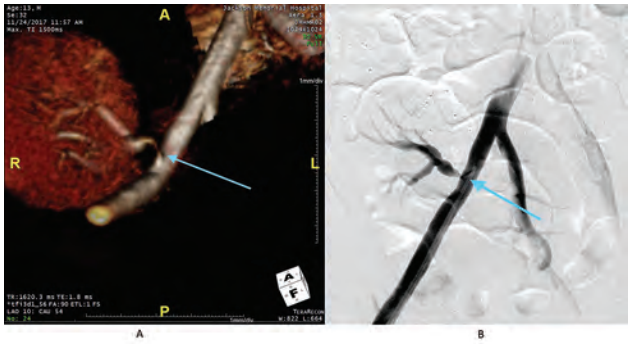

Figure 1 (A) 3D volume-rendered MRA shows tight juxta-anastomotic narrowing. (B) Conventional angiogram shows nearly 1:1 correlation of the stenosis as compared with the MRA.

TH-PO174

Clinical Outcomes of Adult Kidney Transplant Recipients with Post-Transplant Metabolic Acidosis: A Retrospective Cohort Study

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Background: Metabolic acidosis as defined as serum bicarbonate of <22 mmol/L is commonly seen in patients with advanced chronic kidney disease, and is observed among Kidney transplant recipients (KTRs) due to maladaptive changes during early post-transplant causing subacute kidney injury despite preserved estimated glomerular filtration rate. Post-transplant metabolic acidosis is potentially an early marker of chronic allograft nephropathy, and eventual graft loss. However, graft survival is not well studied due to lack of periodic determination of serum bicarbonate post-transplant. This study aims to determine clinical outcome of graft loss among patients with post-transplant metabolic acidosis.

Methods: This is a single-centered retrospective cohort study, which included 132 eligible subjects from January 1995-December 2012 at the St. Luke's Medical Center, Quezon City. Laboratory measurements were determined at 12 months post-transplant, which included serum bicarbonate, creatinine, and proteinuria. Clinical outcomes were determined as graft loss, either by death or death censored graft failure, based on follow-up records.

Results: A total of 132 recipients were analyzed for baseline characteristics according to serum bicarbonate at 12 months post-transplant. The low serum bicarbonate (<22 mmol/L) group included 26 patients, with an incidence rate of 19.7%. Risk factors for metabolic acidosis include: eGFR of 15- 30 ml/min, deceased donor status, presence of one DR mismatch, acute rejection, presence of proteinuria, and use of alkalinizing agents. Graft loss, death, and death censored graft failure were not significantly associated with post-transplant metabolic acidosis, with the following risk ratios for graft loss (HR=2.293, 95% CI 0.849-6.191, p=NS), mortality (HR=1.885, 95% CI 0.311 -11.436, p=NS), and death censored graft failure, (HR=2.502, 95% CI 0.759-8.246, p=NS). The mean allograft survival with metabolic acidosis is 124.8 months, compared with 134.1 months in the group without metabolic acidosis.

Conclusions: Post-transplant metabolic acidosis has fairly high incidence rate of 19.7%. Graft loss, death, and death censored graft failure were not significantly associated with post-transplant metabolic acidosis. Periodic monitoring of serum bicarbonate is recommended to yield a well-represented large prospective cohort study in the future.

TH-PO175

Phosphate levels: Early Determining Factors and Influence in Long Term Graft Outcome in a Cohort of Renal Transplanted Patients

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Background: Renal transplantation (RTx) only partially corrects certain metabolic alterations, especially in mineral metabolism (MM). We aim to examine the effect of RTx during the 1st year of RTx on P levels, exploring the factors related and influencing P levels after 1 month (T1) and 12 months (T2) of RTx. The impact on long term graft outcome of 1st year average P levels (P-avr) will also be explored.

Methods: In 132 RTx pts (age: 48[37;58] yrs – 87 males), up to the 476 transplanted in our unit between 2006 and 2015, clinical parameters, blood and urinary samples were collected at T1 and T2. In addition, in all the patients intact FGF23 (iFGF23) was tested at T1 and T2. Median follow up (FU) was 5[3-9] yrs.

Results: 84% percent of patients received a kidney from a deceased donor; 68% and 23% of patients were treated with haemodialysis and peritoneal dialysis before RTx. Dialysis vintage was 49[27-64] mths. Cold ischemia time was 13[11-16]h. MM parameters at T1 were: Ca 9.7[9.3-10.2]mg/dL, iPTH 68[42-114]pg/mL, ALP 94[72-127]U/L, 25OHVitD 12[8-17]ng/mL. Between T1 and T2, an increase of P levels was noted (T1:2.3[1.9-2.8] mg/dL – T2 3.1[2.7-3.6] mg/dL, p<0.001). iFGF23 was reduced (T1: 80[6-1360] pg/mL–T2 62[14-489] pg/mL, p=0.01). P-avr was 2.7[2.3-3.1]mg/dL. Thirty-five percent and 11% of patients were treated with active and native vitamin D during the first year of RTx. In multivariate analysis, T1-iFGF-23, T2-ALP and T2-Ca resulted the most influencing parameters of T1-P, T2-P and P-av (p=0.009, p=0.03 and p=0.002 resp.). No relationship between T2-P and T2-iFGF23 as like as between P-av and renal function was found. No influence of immunosuppressive therapy was found. During FU, 8 patients restarted dialysis (D+). D+ were different to those patients with functioning graft only for higher T2-PTH (p=0.01) and P-av (p<0.0001). In Cox and ROC curve analysis, P-av was the best predicting and discriminatory factor for graft loss (Cox: p<0.0001; ROC: AUC 0.71±0.10– p=0.04).

Conclusions: Our data confirm that RTx has an impact to MM from the beginning, and that P levels are influenced by different factors at T1 and T2. However, independently to renal function, P-av might influence long-term graft outcome.

TH-PO176

Early Post-Transplant Hypophosphatemia Predicts Better Graft Function After Kidney Transplantation

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Background: Hyperphosphatemia is a well-established and independent risk factor for fracture, cardiovascular disease, and mortality in dialyzed and non-dialyzed patients with chronic kidney disease. Recent studies showed that high serum phosphate is associated with rapid decline in kidney function. Kidney transplantation dramatically decreases serum phosphate levels; however, the association of hypophosphatemia with graft survival remains unclear.

Methods: This was a single-center, retrospective study comprising 90 patients who underwent a kidney transplant at our institution between 2008 and 2016. Patients were divided into two groups, with and without hypophosphatemia. The hypophosphatemia was defined as those with less than or equal to the lowest quartile of serum phosphate levels at 3 months post-transplant. The endpoints were defined as 30% decrease in the eGFR. The cumulative kidney survival rates were calculated for each group using the Kaplan–Meier method, and the adjusted hazard ratio (HR) was calculated using the Cox regression model.

Results: No significant differences were observed in age, diabetes, living donor, pre-emptive kidney transplantation, ABO incompatibility, donor-specific antigen, or biochemical parameters of mineral bone disorders at transplantation between the two groups. The proportion of male recipients was higher in the hypophosphatemia group than in the control group (88% vs. 65%). The hypophosphatemia group received a higher proportion of cinacalcet prescriptions during the dialysis period than the control group (33% vs. 14%). The median follow-up duration was 47.5 months, and the 90 transplantations resulted in 6 cases of graft loss, 2 of mortality, and 37 of 30% decline in eGFR. The Kaplan–Meier analysis revealed that patients in the hypophosphatemia group had a significantly lower risk of 30% decline in eGFR than those in the control group. After adjusting for confounding factors, hypophosphatemia was associated with a significantly lower risk of 30% decline in eGFR [HR, 0.37; 95% confidence interval (CI), 0.14–0.88] compared with the control group.

Conclusions: The results of the present study suggested that hypophosphatemia at 3 months post transplant is a favorable sign for the successful outcome of transplantation.

TH-PO177

To Study the Effect of Variable Protein Intake on Nitrogen Balance in Renal Transplant Recipients with Underlying Graft Dysfunction

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Background: It is essential to determine the optimum nutrition (protein intake) in renal transplant recipients on steroids with renal dysfunction to maintain a neutral nitrogen balance. It was our aim to study the effect of variable protein intake [i.e.higher (1.2g/kg/d) and lower (0.8g/kg/d) protein intake] on nitrogen balance, body composition, glomerular filtration rate and proteinuria in renal transplant recipients with low eGFR (15–44 ml/min/1.73m^2).

Methods: This prospective, open-labelled, randomized, cross-over, interventional study enrolled 35 patients who were ≥ 4 months post-transplant and who had an eGFR between 15 - 44 ml/min/1.73m^2. Thirty-two patients completed the study. The subjects were randomised to either Group 1 [Diet: proteins (1.2 g/kg/day) and 35 kcal/kg/day] or Group 2 [Diet: proteins (0.8 g/kg/day with 50% first class proteins) and 35 kcal/kg/day] for one month. The subjects crossed over to the other diet for the second month. The body composition analysis, sr. creatinine, blood urea nitrogen, sr. protein, sr. albumin, 24 hours proteinuria, GFR measurement (24 hours creatinine clearance), three day diet recall and nitrogen balance estimation were performed at baseline and at the end of the first and second months. Statistical analysis was performed using SPSS version 21.

Results: The three day diet recall showed that the daily protein and energy consumption was 1.2 g/kg and 36.47 kcal/kg with the higher protein diet and 0.94 g/kg protein with 31.94 kcal/kg with the lower protein diet. The nitrogen balance was positive with both the diets, +3.61 g/d with the higher protein diet (p=0.0002) and +1.66 g/d with the lower protein diet. The waist hip ratio showed a significant decrease on the higher protein diet (p=0.011) and increase on the lower protein diet (p=0.011). There was significant gain in muscle mass (0.70 kg gain; p=0.0317) with the higher protein diet. Significant increase was noted in blood urea nitrogen (p=0.0048) and GFR (p=0.0114) with the higher protein diet. 24 hours urinary protein excretion increased significantly after consuming the higher protein diet (320mg/d, p=0.010).

Conclusions: Renal transplant recipients remained in positive nitrogen balance with both diets. Muscle mass and proteinuria increased significantly with the higher protein diet.

Funding: Private Foundation Support

TH-PO178

The Efficacy of Exercise Training in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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Background: The effectiveness of exercise in kidney transplant recipients is not well established. We therefore performed a systematic review of the effects of exercise training in kidney transplantation recipients.

Methods: We searched two electronic databases for articles up to April 2017. Inclusion criteria were as follows: randomized controlled trial and kidney transplant recipients aged 18 years or older. The main outcomes were allograft function (estimated glomerular filtration rate, eGFR), exercise tolerance (VO2 peak), and quality of life (QOL).

Results: After screening of 1,303 references in PubMed and Ichushi, six randomized control trials were analyzed. For kidney transplant recipients, supervised exercise training was shown to significantly improve VO2 peak (mean difference, 2.42; 95% confidence interval (95%CI) 0.22–4.63) and QOL (mean difference, 7.23; 95%CI 0.94–13.52). However, exercise training did not improve allograft kidney function (mean difference, 6.22; 95%CI -13.00–25.44). No reporting bias was observed in any of the outcomes.

Conclusions: Exercise training for kidney transplant recipients significantly improved exercise tolerability and QOL, but a significant improvement was not obtained with respect to allograft kidney function.

TH-PO179

Fibroblast Growth Factor 23 and Arterial Stiffness in SPRINT

Anna J. Jovanovich,[1,2] Zhiying You,[3] Charles Ginsberg,[4] Joachim H. Ix,[4] Mark A. Supiano,[5] Michael Shlipak,[6] Alfred K. Cheung,[7] Michel Chonchol,[2] Kristen L. Nowak.[8] *[1]Denver VA, Denver, CO; [2]University of Colorado, Aurora, CO; [3]UC Denver, Aurora, CO; [4]UCSD, San Diego, CA; [5]University of Utah Geriatrics Division, Salt Lake City, UT; [6]San Francisco VA Medical Center, San Francisco, CA; [7]University of Utah, Salt Lake City, UT; [8]University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.*

Background: Fibroblast growth factor 23 (FGF23) and arterial stiffness are both associated with cardiovascular disease and mortality in chronic kidney disease (CKD). The relationship between FGF23 and arterial stiffness needs further investigation. We hypothesized that higher serum FGF23 levels would be associated with greater arterial stiffness in participants with CKD in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: The SPRINT study was a randomized multicenter trial evaluating the effects of standard (SBP <140 mmHg) vs. intensive (SBP <120 mmHg) blood pressure lowering on cardiovascular outcomes among older adults without diabetes. Intact FGF23 (iFGF23) was measured at baseline among 2384 participants with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2. Multivariable linear regression determined the association between baseline iFGF23 and pulse pressure (PP; a surrogate measure of arterial stiffness) (N = 2384) and aortic pulse wave velocity (aPWV) (N = 202), the latter of which was measured in an ancillary study. Models were adjusted for demographics, comorbidities, randomization group, baseline number of antihypertensives, eGFR, albuminuria, and serum calcium and phosphorus.

Results: In the PP analysis, mean age was 73 ± 9 years, mean eGFR was 49 ± 11 mL/min/1.73m^2, and median iFGF23 level was 71 [53-95] ng/mL. There was no significant association between baseline iFGF23 and PP (β: -0.08, 95% CI: -1.06 to 0.89). Notably, baseline serum phosphorus was significantly associated with PP (β: 1.33, 95% CI: 0.23 to 2.43) in the fully adjusted model. In the ancillary study, mean age was 73 ± 10 years, mean eGFR was 47 ± 12 mL/min/1.73m^2, and median iFGF23 level was 71 [53-95] ng/mL. In the unadjusted model, higher iFGF23 was significantly associated with lower aPWV (β: -0.009, 95% CI: -0.02 to -0.003). However, in the fully adjusted model, this association was no longer significant (β: -0.003, 95% CI: -0.01 to 0.004).

Conclusions: Among SPRINT participants with baseline eGFR < 60 mL/min/1.73m^2, iFGF23 was not associated with arterial stiffness as measured by PP and aPWV. However, higher serum phosphorus was associated with increased PP. The analysis of aPWV was limited due to a smaller sample size.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO180

Fibroblast Growth Factor 23 (FGF23) and Cystic Liver Disease in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Previous studies have demonstrated that the cystic liver from ADPKD patients markedly expresses FGF23 mRNA and protein. Epidemiological studies have reported an elevation in circulating FGF23 levels in adult ADPKD patients compared to non-ADPKD patients with similar kidney function. We hypothesize that elevated serum iFGF23 levels are associated with greater increases in cystic liver volume in early ADPKD.

Methods: 440 participants with early ADPKD and normal kidney function (mean eGFR 92± 18mL/min/1.73m^2) who participated in HALT Study A were included in this analysis. The cross-sectional and longitudinal (5-year) association of iFGF23 with liver volume, measured as baseline total liver volume and change in total liver volume by magnetic resonance imaging, respectively, were evaluated using linear regression models. iFGF23 levels were measured using stored serum samples obtained at baseline

Results: Participants had a mean (SD) age of 37 ± 8 years. Mean (SD) serum phosphate level and the median (IQR) iFGF23 level were 3.4 ± 0.5 mg/dL and 43 (33–56) pg/mL, respectively. The median (IQR) baseline liver volume was 1790 (1572-2088)ml. After adjustment for age, sex, body mass index, randomization group, systolic blood pressure, estimated glomerular filtration rate, urinary albumin excretion, serum calcium, phosphate, parathyroid hormone level and PKD genotype, higher circulating iFGF23 levels were not associated with liver volume at baseline (ß=35.39, [95% CI -86.75 to 157.53; p=0.60] per doubling in iFGF23). Similarly, higher circulating iFGF23 was not associated with greater percentage increase in liver volume (ß=-1.94, [95% CI -17.04 to 13.15; p=0.80]) per doubling in iFGF23.

Conclusions: Our results indicate that circulating iFGF23 is not independently associated with liver volume in ADPKD patients. FGF23 does not appear to represent a valid therapeutic target or a pertinent biomarker for liver cysts progression in patents with early ADPKD.

Funding: NIDDK Support

TH-PO181

The Effect of Intensive Blood Pressure Lowering on Markers of Mineral Metabolism in Persons with CKD in SPRINT

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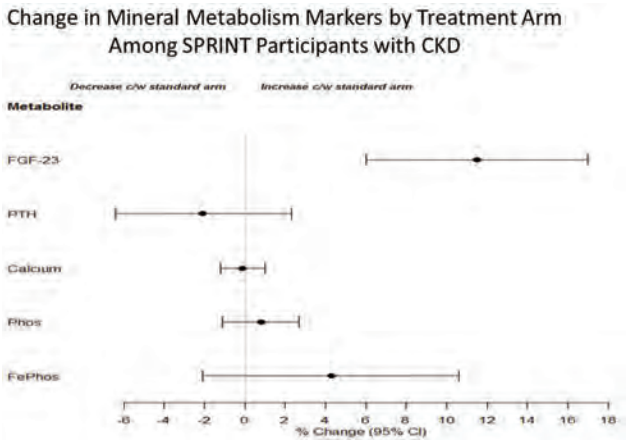
Background: Serum fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) concentrations are high in chronic kidney disease (CKD) and have been associated with increased cardiovascular disease (CVD) risk. The SPRINT trial demonstrated that intensive blood pressure (BP) lowering reduced risk of CVD despite more rapid eGFR decline. The effects of intensive blood pressure lowering on serum FGF23 and PTH are currently unknown.

Methods: Among individuals with CKD (eGFR < 60ml/min/1.73m^2), we randomly selected 1000 participants and measured serum intact FGF23 (iFGF23; Kainos ELISA), intact PTH (iPTH), calcium, phosphate, and urine phosphate/creatinine at baseline and year 1. Thirteen were missing serum samples, resulting in 987 for analysis. We used linear mixed models to assess the effect of intensive BP lowering on iFGF23 and iPTH, in addition to changes in serum calcium, phosphate and fractional excretion of phosphate (FePhos).

Results: Mean age was 72±9 years, 42% were female, and mean eGFR was 46±10 ml/min/1.73m^2. Demographics, baseline BP, kidney function, iFGF23, and iPTH were well-balanced across arms. Randomization to the intensive arm resulted in an increase in iFGF23 over 1 year compared with the standard BP arm (p=0.01) but no change in PTH [-1.6% (95% CI -6.1, 2.9]. After adjustment for 1 year changes in eGFR and albuminuria, persons in the intensive arm experienced an 11.2% (95% CI 6.2, 17.5) increase in serum iFGF23 compared with the standard arm. Randomization to the intensive arm did not impact calcium and phosphate or FePhos

Conclusions: In SPRINT participants with CKD, compared with the standard arm, randomization to the intensive BP arm led to an increase in iFGF23 that was independent of changes in eGFR. Future studies should determine whether increasing iFGF23 in persons receiving intensive BP therapy impacts CVD risk.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program, NHLBI, NINDS, National Institute on Aging, Private Foundation Support



TH-PO182

Change in FGF23 and PTH1-84 and Subsequent Cardiovascular and Renal Events in Patients with Advanced CKD

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Background: Elevated levels of parathyroid hormone (PTH1-84) and fibroblast growth factor 23 (FGF23), measured at a single time, are associated with increased risk of cardiovascular (CV) and renal events in patients with CKD. Few studies have examined the longitudinal association between bone mineral biomarkers (BMB) and outcomes. We sought to describe changes in PTH1-84 and FGF23 over time and their association with subsequent CV and renal events.

Methods: Using data from a prospective cohort of 1078 patients with advanced CKD in Canada under the care of nephrologists (2008-2013), we measured serial PTH1-84 and FGF23 (3 time-points) in a central laboratory using sensitive DiaSorin assays. Adjudicated CV (coronary artery disease, congestive heart failure, stroke, sudden cardiac death) and renal outcomes (initiation of renal replacement therapy (RRT)) were recorded over 3 years of follow-up after the last BMB measurement. We used group-based trajectory models to characterize patterns of change in BMB, and Cox regression models to relate these changes to CV and renal outcomes.

Results: Mean age was 69.9, 62% were male, 45% were diabetic and 45% had pre-existing CV disease. Mean eGFR was 27mL/min/1.73m^2; 28%, 34% and 38% had eGFR <20, 20-29 & >30mL/min/1.73m^2 respectively. We identified 3 distinct patterns of BMB change over time: low & stable (reference group), mid-level & stable, high & slowly rising. The proportions of patients in each category for PTH1-84 were 26%, 55% and 20% respectively. A small subgroup of patients (6%) had a high & rising pattern for FGF23. During median follow-up of 29 months, 11% experienced a CV event and 13% initiated RRT. Compared with the reference group, patients with mid-level & stable and high & rising patterns of each BMB had higher risk of CV events and RRT (Table). In multivariable models, only the high & rising patterns of PTH1-84 and FGF-23 demonstrated increased risk of CV events.

Conclusions: The majority of patients with advanced CKD had stable BMB values over time. A subgroup of patients had a high & rising pattern of change in PTH1-84 and FGF23 which conferred increased risk of CV events.

Funding: Commercial Support - DiaSorin

Table 1: Associations of BMB Change Patterns with Cardiovascular and Renal Outcomes

BMB Change Pattern (% patients)	CV Event (Unadjusted) HR	95% CI	CV Event (Adjusted) HR	95% CI	RRT (Unadjusted) HR	95% CI	RRT (Adjusted) HR	95% CI
i(PTH(1-84))								
Low Stable (26%)	Reference		Reference		Reference		Reference	
Mid Stable (55%)	2.053	1.169 - 3.606	1.657	0.933 - 2.942	1.919	1.109 - 3.322	1.152	0.641 - 2.069
High Rising (20%)	3.417	1.880 - 6.212	2.063	1.059 - 4.019	6.338	3.666 - 10.955	1.292	0.711 - 2.349
FGF-23								
Low Stable (59%)	Reference		Reference		Reference		Reference	
Mid Stable (35%)	2.009	1.359 - 2.971	1.560	1.560 - 2.492	5.727	3.736 - 8.780	1.235	0.768 - 1.988
High Rising (6%)	3.375	1.858 - 6.130	2.383	1.117 - 5.085	17.039	10.165 - 28.561	1.045	0.546 - 1.999

TH-PO183

Adjustment for ProBNP Substantially Attenuates Prognostic Implications of Plasma FGF23 Levels in CKD

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Background: Various epidemiological studies linked high plasma levels of the phosphatonin FGF23 with cardiovascular events in non-dialysis CKD. It remains enigmatic whether high FGF23 exerts adverse cardiovascular effects, or whether it reflects detrimental effects of residual confounders. Earlier epidemiological studies adjusted for chronic kidney disease – mineral bone disease (CKD-MBD) regulators of FGF23 rather than for recently discovered non-CKD-MBD regulators, among which iron deficiency and heart failure are of particular importance. Moreover, they used c-terminal FGF23 assays (cFGF23) rather than more specific intact FGF23 assays (iFGF23).

Methods: The *CARE FOR HOMe* study analyzed plasma ferritin, hepcidin, iFGF23, cFGF23 and proBNP along with conventional risk factors, among 575 CKD G2-G4 patients. The participants were followed 5.1 ± 2.1 years for the occurrence of atherosclerotic events and hospitalization for acute decompensated heart failure, respectively.

Results: cFGF23 correlated strongly with high iFGF23, fairly with high proBNP and weakly with low ferritin; correlation coefficients of iFGF23 with proBNP and ferritin were numerically lower. In Kaplan-Meier analyses, both endpoints were predicted by cFGF23 and iFGF23. In Cox regression models, cFGF23 remained an outcome predictor after adjustment for conventional risk factors and iron deficiency. This prediction was largely eliminated when further adjusting for proBNP. iFGF23 was less consistently associated with adverse outcome in partly adjusted models, and failed to predict outcome in fully adjusted models.

Conclusions: In summary, iron deficiency and heart failure affect plasma FGF23. As adjustment for proBNP virtually eliminates the prognostic implications of plasma FGF23, we speculate that high FGF23, rather than exerting detrimental cardiovascular effects, merely mirrors prevalent heart disease.

TH-PO184

Effect of Renal Transplantation on Carotid Intimal Medial Thickness (CIMT), Left Ventricular Mass Index (LVMI), and CKD-MBD Markers: A Longitudinal Study

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Background: Various nontraditional risk factors (NTRFs) including serum markers of CKD-MBD (serum calcium, phosphorus, intact PTH, vitamin D & FGF-23) & increased LVMI have been implicated for high cardiovascular (CV) mortality in CKD. Renal transplant (RT) by correcting uremic milieu improves most NTRFs. However compared to general population, CV mortality remains high post RT. This could be due to new risk factors or legacy effect of previous CKD period. CIMT is marker of structural atherosclerosis & has been shown to decrease after correction of risk factors in some clinical settings. This prospective, longitudinal study in CKD 5D patients looks at any change in CIMT & LVMI post RT & their correlation with changes in CKD-MBD markers.

Methods: 83 consecutive, eligible & consenting patients aged 18-65 years undergoing first live RT were enrolled. All investigations, CIMT & LVMI assessments were done at baseline (≤1 week prior to RT) & at 6 & 12 months post RT. Patients with pre-transplant diabetes, established coronary/valvular heart disease & those having persistent eGFR <40 ml/min post RT were excluded

Results: 74 patients completed study, 91.8% were male, mean age was 35.5±10.6 years & median dialysis vintage was 14 months. All were on MMF, steroids & calcineurin inhibitors. At baseline CIMT did not correlate with any of CKD-MBD parameters while LVMI correlated positively with FGF-23 (correlation coefficient 0.57, p-value <0.001). There was a significant reduction in CIMT & LVMI at 6 & 12 months post RT & improvement some CKD-MBD markers (table). There was however no correlation between changes in CIMT & LVMI & changes in CKD-MBD markers

Conclusions: In low risk CKD-5D population we document a significant decline in CIMT & LVMI post RT. Though there was significant improvement in CKD-MBD markers post RT they did not correlate with change in CIMT & LVMI

Parameter	Baseline	6 month	12 month	P-value I vs II, I vs III
CIMT mm	0.57±0.07	0.55±0.08	0.55±0.07	0.001, 0.001
LVMI g/m2	161.9±14.4	160.8±12	149.3±13.6	<.001, <0.001
S. Calcium mg/dl	9.2±1.4	9±0.8	9±0.7	0.16, 0.3
S. Phosphorus mg/dl	5±1.6	2.9±0.8	3.3±0.6	<.001, <0.001
Intact PTH pg/dl median (range)	57.8 (9.3-1297.7)	33 (3-297)	12.9 (3-210)	0.29, 0.01
25 (OH) Vit D ng/dl median (range)	10.5 (4.9-52.6)	10.5 (4.9-52.6)	16.6 (3.9-38.2)	0.54, 0.08
Intact FGF-23 pg/dl median (range)	2649.2 (157.8-3244.2)	72.2 (2.3-2481.3)	68.6 (5.7-2939.5)	<.001, <0.001

TH-PO185

FGF23 as a Risk Factor for Cardiovascular Events and Mortality in Patients in the EVOLVE Trial

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Background: Risk factors for all-cause mortality and cardiovascular events in dialysis patients with CKD-MBD have not been fully elucidated. Historically, analyses using mineral metabolism biomarkers to predict clinical outcomes have used neither FGF23 nor clinically-adjudicated events.

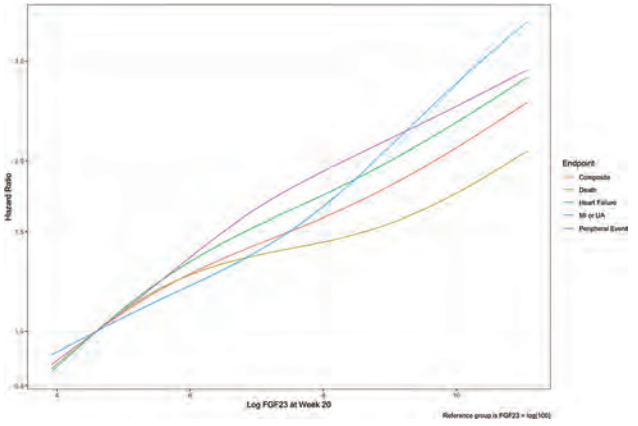
Methods: We evaluated FGF23 and other risk factors using data from EVOLVE, a randomized, double-blind placebo-controlled, event-driven trial (N=3883 with CKD-MBD) in which subjects were followed for up to 64 months. EVOLVE compared cinacalcet to placebo with a composite endpoint of death, myocardial infarction, hospitalization for unstable angina, heart failure (HF), or peripheral vascular event. Inclusion criteria included PTH ≥300 pg/mL, calcium ≥8.4 mg/dL, and phosphorus ≥5.3 mg/dL. Our study quantified FGF23-associated risk following dose titration (week

20). We used Cox proportional hazards models to estimate the relative risk of the composite endpoint and its components, adjusting for age, albumin, race, sex, smoking status, Hb, P, Ca, PTH, and alkaline phosphatase as well as history of diabetes, coronary artery disease, HF, and stroke. Laboratory values and age were modeled using penalized splines to allow for a flexible relationship between the measure and risk (e.g., S or U-shaped).

Results: We included 2,411 patients who were event-free at week 20, and had an FGF23 measure. There were 1100 events (526 deaths and 574 non-fatal events). In adjusted models, higher log FGF23 was associated with a higher risk of the composite endpoint and its components. See Figure.

Conclusions: FGF23 appears to be an important, independent risk factor for mortality and CV events in addition to those traditionally associated with CKD-MBD.

Funding: Commercial Support - This study was funded by Amgen, Inc.



Association of Log(FGF23) with the Composite Endpoint and its Components

TH-PO186

Interactions Between FGF23 and Genotype in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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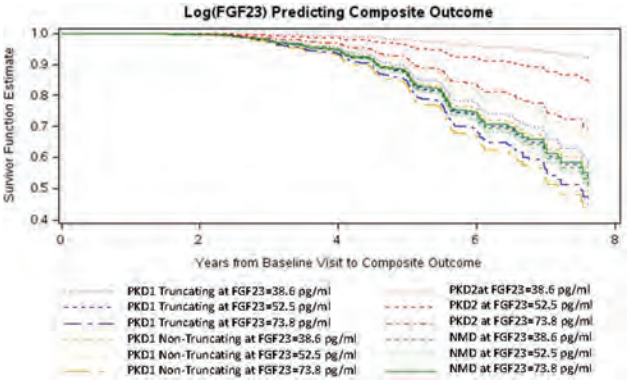
Background: Among individuals with ADPKD, higher serum intact fibroblast growth factor 23 (iFGF23) was associated with disease progression in participants in the HALT-PKD study. PKD mutation is also an important determinant of ADPKD progression. We hypothesized that serum levels of iFGF23 and vitamin D metabolites (1,25-dihydroxyvitamin D [1,25$(OH)_2$D] and 25-hydroxyvitamin D [25[OH]D]) differed in adults with ADPKD according to ADPKD mutation and that the interaction between genotype and mineral metabolites would predict clinical endpoints.

Methods: 921 individuals with ADPKD who participated in the HALT-PKD study A or B and had measurement of mineral metabolites (1,25$(OH)_2$D, 25(OH)D, and iFGF23) were categorized by PKD mutation (PKD1 truncating, PKD1 non-truncating, PKD2, or no mutation detected [NMD]). The longitudinal (5-yr) association of the interactions of genotype * iFGF23 and genotype * 1,25$(OH)_2$D with clinical endpoints of (a) 50% decline in eGFR; b) end-stage renal disease (ESRD); c) composite of 50% decline in eGFR, ESRD, or death) were evaluated using cox proportional hazards regression.

Results: Median (IQR) 1,25$(OH)_2$D differed (PKD1 truncating: 31.0 (24.4, 39.1); PKD1 non-truncating: 32.0 (24.8, 40.1), PKD2: 33.9 (24.8,41.0); NMD: 38.2 (27.8, 46.4) pg/ml; p=0.01) and iFGF23 tended to differ (PKD1 truncating: 55.9 (40.5, 76.2); PKD1 non-truncating: 49.9 (37.7, 72.2); PKD2: 48.6 (33.9, 69.8); NMD: 49.8 (39.7, 65.8) pg/ml; p=0.07) according to PKD genotype. There was a significant interaction between FGF23 and genotype ($p<0.01$) for the composite endpoint in the fully adjusted models (Figure), but no significant interaction between 1,25$(OH)_2$D and genotype for clinical endpoints.

Conclusions: ADPKD genotype interacts significantly with FGF23 to influence clinical endpoints, with the worst outcomes in individuals with a PKD1 truncating or non-truncating mutation and the highest tertile of iFGF23.

Funding: NIDDK Support



TH-PO187

Association of Serum Bicarbonate Levels with Serum Fibroblast Growth Factor-23 Levels

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Background: The regulation of fibroblast growth factor-23 (FGF23) is not understood. *In vitro* studies have found that metabolic acidosis increases FGF23. However, small pilot studies have found that treatment of low bicarbonate levels with sodium bicarbonate increases FGF23 levels. We tested the hypothesis that lower serum bicarbonate levels are associated with higher levels of FGF23.

Methods: We included 822 patients from the HALT-PKD Study A (n=540; mean eGFR = 91±17 ml/min per 1.73 m2) and B (n=462; mean eGFR = 48±12 ml/min per 1.73 m2) with serum bicarbonate and FGF23 levels measured at baseline. Bicarbonate was examined as a continuous variable and in categories (≤ 24, 25-28 and >28 mEq/L, with 25-28 mEq/L as the reference group). We used linear regression models to examine the cross-sectional association between baseline serum bicarbonate and FGF23 levels.

Results: The mean (SD) age and estimated glomerular filtration rate (eGFR) was 43 ± 10 years and 70 ± 26 ml/min/1.73m2. The mean (SD) serum bicarbonate level was 26.7 ± 2.4 mEq/L and the median (IQR) serum FGF23 level was 53 (39-74) pg/mL. Participants with bicarbonate levels ≤ 24 mEq/L had lower baseline eGFR and higher systolic blood pressure. In unadjusted analysis, every 1 mEq/L increase in serum bicarbonate was associated with a decrease of 1.25 pg/mL in FGF23 levels (β -1.25, 95% CI -2.48 to -0.01). However, after adjustment for demographics, randomization group, baseline eGFR, smoking, cardiac history, body mass index, blood pressure, serum calcium and phosphorus, the association was no longer significant (p=0.20). A serum bicarbonate ≤ 24 mEq/L trended towards an increased risk of higher FGF23 in unadjusted analysis but it did not reach statistical significance (p=0.05).

Conclusions: Serum bicarbonate levels are not associated with FGF23 levels in patients with polycystic kidney disease. Further studies are needed to examine the relationship between metabolic acidosis and FGF23 in other causes of kidney disease.

Funding: Other NIH Support - NHLBI

TH-PO188

Genome-Wide Association Study Reveals That Distinct Genetic Factors Regulate Intact and C-Terminal FGF23 Levels in Humans

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Background: Elevated fibroblast growth factor 23 (FGF23) levels have been associated with chronic kidney disease (CKD) progression, cardiovascular disease (CVD) and increased mortality. FGF23 also directly induces cardiac myocyte hypertrophy. Recently, non-mineral factors such as iron, anemia, inflammation and erythropoietin (EPO) have been identified in FGF23 production. Such factors are also associated with CKD progression, CVD and mortality. Thus, several lines of evidence suggest that FGF23 could play an important link. However, no studies have examined genetic factors underlying FGF23 levels in humans. We conducted the first-ever genome-wide association study (GWAS) study of FGF23.

Methods: We measured both the active, intact form (iFGF23), and the total amount of FGF23 as measured by c-terminal form (cFGF23) via ELISA in a population of 1,400 Finnish men aged 58+7 (SD) yrs. and eGFR 85+15 ml/min/1.73 m^2. We performed GWAS mapping using a linear mixed model removing, SNPs with less than 5% minor allele frequency.

Results: We identified suggestive loci for cFGF23 on chromosomes 3 ($p = 4.3 \times 10^{-7}$) and 21 ($p = 8.9 \times 10^{-8}$), and suggestive for iFGF23 levels on chromosomes 7 ($p = 3.6 \times 10^{-6}$), 12 ($p = 3.6 \times 10^{-6}$) and chromosome 18 ($p = 4.5 \times 10^{-6}$). The locus influencing iFGF23 levels on chromosome 7 is near the erythropoietin (*EPO*) gene, which stimulates hematopoiesis

and is deregulated in CKD patients. It is known that serum EPO and recombinant EPO administration are associated with FGF23 levels. Genetic manipulation of FGF23 has been shown to regulate erythropoiesis through EPO, indicating that regulation of EPO and FGF23 is complex. Our results show that genetic variants near *EPO* regulate iFGF23, raising the possibility that iFGF23 is genetically controlled by EPO. In contrast, the cFGF23 levels were not associated with the locus near *EPO* possibly due interindividual variation in FGF23 cleavage.

Conclusions: Our results improve the understanding of the complex regulation between FGF23 and EPO. Our results provide evidence that complex and distinct genetic factors are involved in the regulation iFGF23 and cFGF23 that may help identify populations with different FGF23 levels at similar GFR, and indicate that natural genetic variation near *EPO* is involved in the regulation of FGF23.

Funding: Other NIH Support - NIH T32

TH-PO189

Effects of Induced Whole-Body Hypoxia on FGF23 in Obese Men

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Background: Higher fibroblast growth factor 23 (FGF23) is associated with higher risk of heart disease and mortality in patients with chronic kidney disease (CKD). Recent evidence shows that Hypoxia Inducible Factor 1α (HIF-1α) is a direct transcriptional activator of FGF23. No study has directly tested the effect of induced hypoxia on FGF23 levels.

Methods: In a single-arm study design, 8 healthy obese men (BMI: 32.7 ± 3.7 kg/m^2; age: 28 ± 3 years) were exposed to 10 consecutive nights of moderate hypoxia (15 ± 0.5% O_2, simulating oxygen tension at 2400 m elevation) using hypoxic tents. Blood specimens and skeletal muscle and adipose biopsies were taken at baseline and after 10 days of hypoxic exposure. The primary outcomes were change in plasma intact FGF23 (iFGF23), c-terminal FGF23 (cFGF23) and FGF23 ratio (cFGF23:iFGF23). Paired t-test analysis was used to examine changes in log transformed values for iFGF23, cFGF23 and the FGF23 ratio. We also examined associations of muscle and adipose HIF-1α expression with FGF23.

Results: There were no statistically significant changes in either cFGF23 or iFGF23 after induced hypoxia. There was a statistically significant increase in the FGF23 ratio (1.05±0.11 to 1.08±0.11) post exposure to hypoxia (p=0.02)**(Table).** HIF-1α expression in muscle was significantly associated with iFGF23 (r=0.86,*p*<0.05) but not cFGF23 (r=0.11,*P*=0.45).

Conclusions: Exposure to hypoxia significantly increased the FGF23 ratio in obese men. In addition, muscle expression of HIF-1α was associated with iFGF23 plasma levels, suggesting that hypoxia influences FGF23 transcription and cleavage in humans.

Geometric mean Change (95%CI) in plasma FGF23 and arithmetic mean change (±SD) in FGF23 ratio with exposure to hypoxia.

	Baseline	Post-Exposure	p-value
cFGF23	71.1 (26.4,190.9)	75.3 (27.1,209.2)	0.48
iFGF23	58.9 (18.5,188.3)	55.2 (16.0,189.8)	0.38
FGF23 Ratio	1.05 ± 0.11	1.08 ± 0.11	0.02

TH-PO190

FGF23, Erythropoietin, and Erythroferrone Levels in Autosomal Dominant Polycystic Kidney Disease Patients

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Background: Circulating FGF23 levels are higher in patients with autosomal dominant polycystic kidney disease (ADPKD) compared to patients with similar kidney function and other causes of CKD. Although bone is the major source of FGF23, erythropoietic bone marrow cells may also express FGF23 in response to erythropoietin (EPO), levels of which increase in ADPKD. We tested whether serum EPO levels in ADPKD patients are associated with circulating and bone FGF23. We also assessed serum levels of the EPO-responsive hormone erythroferrone (ERFE).

Methods: 20 adult subjects with ADPKD and normal kidney function (mean ± SD eGFR 97 ± 29 ml/min/1.73m^2) and 9 healthy controls participated in the study. We measured circulating C-terminal (total) FGF23 (cFGF23), intact FGF23 (iFGF23), EPO, ERFE, phosphate, calcium, PTH, 25D, 1,25D, iron, ferritin, hepcidin, and hemoglobin. Quantitative bone FGF23 levels were determined by immunohistochemical staining from bone biopsies.

Results: Circulating total FGF23 was higher in ADPKD subjects than in controls (geometric mean (95% CI) 109 (78, 153) vs. 73 (56, 95) RU/ml, p=0.050). Intact FGF23 tended to be higher (67 (57, 80) vs. 51 (39, 67) pg/ml, p=0.073). Quantitative bone FGF23 levels did not differ between the groups. Serum EPO levels were higher in ADPKD subjects (11.1 ± 6.7 vs. 6.1 ± 3.8 mIU/ml, p=0.019). Consistent with increased EPO, serum ERFE levels were also increased (17.6 ± 7.4 vs. 7.6 ± 6.2 ng/ml, p=0.001). The ADPKD subjects had higher phosphate (4.0 ± 0.5 vs. 3.6 ± 0.4 mg/dl, p=0.036) and lower 1,25D (44 (39, 49) vs. 61 (45, 82) pg/ml, p=0.039). Serum calcium, PTH, 25D, iron, ferritin, hepcidin, and hemoglobin did not differ between the groups. In the ADPKD subjects, EPO correlated with Log cFGF23 (r=0.55, p=0.021), and tended to correlate with Log iFGF23 (r=0.42, p=0.069), but not bone FGF23. After adjusting for phosphate, EPO remained associated with Log cFGF23 (β=0.58, p=0.011) and Log iFGF23 (β=0.44, p=0.053).

Conclusions: ADPKD patients with normal kidney function have increased EPO levels, which are associated with increased ERFE, and may contribute to increased circulating FGF23. EPO-induced marrow FGF23 expression has been demonstrated in rodents, and may explain the observation that EPO is associated with circulating FGF23 but not bone FGF23.

TH-PO191

Associations of Food Environment with Bone Mineral Disorders in the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Access to fast food outlets may influence eating behaviors and contribute to disordered mineral metabolism through increased consumption of phosphates. The influence of food outlet density on mineral disorders has not been studied in chronic kidney disease (CKD).

Methods: Baseline cross-sectional analysis of the association between food outlet density (within 1 km of census block group) and phosphate ≥5.3 mg/dL, fibroblast growth factor 23 (FGF23) ≥100 RU/mL, and parathyroid hormone (PTH) ≥100 pg/mL using multivariable logistic regression. Data on food outlets included a count of fast food restaurants (unhealthy), convenience stores (unhealthy), and grocery stores (healthy). A food outlet index was categorized as *no food outlets*; *only unhealthy outlets*; *few healthy food outlets* (a ratio of healthy to unhealthy ≤0.2); or *mostly healthy (*a ratio of >0.2).

Results: The study included 2,484 participants with CKD (mean age 58 years, 46% female, 42% white, 39% black, and mean eGFR 44 ml/min/1.73 m^2). A total of 455 (18%) participants had no food outlets within 1 km, 973 (39%) had only unhealthy food, 716 (29%) had few healthy food outlets, and 340 (14%) had mostly healthy outlets. Hyperphosphatemia was rare (n=50, 2%); 73% and 41% of participants had excess FGF23 and PTH, respectively. The table summarizes analyses. Compared to persons living in an area with only unhealthy food, increased availability of healthy food outlets was significantly associated with increased odds of hyperphosphatemia [OR=2.3 (1.1, 4.9)].

Conclusions: Our results highlight the possibility that changes to the food environment at the neighborhood level may impact important health indicators in CKD. Increased food availability may influence behaviors, and access to healthy food may not prevent unhealthy choices.

Funding: NIDDK Support, Other U.S. Government Support

Multivariable Logistic Regression for Association* Between Food Outlet Density and Markers of Mineral Disorders

Variables	Only unhealthy food outlets		No food outlets		Few healthy food outlets		Many healthy food outlets	
	Median (IQR)	OR (95% CI)	Median (IQR)	OR (95% CI)	Median (IQR)	OR (95% CI)	Median (IQR)	OR (95% CI)
Phosphate ≥5.3 mg/dL	3.7 (3.3-4.2) mg/dL	1.0 (ref)	3.6 (3.2-4.1) mg/dL	0.75 (0.23, 2.5)	3.7 (3.3-4.2) mg/dL	0.92 (0.42, 2.0)	3.7 (3.3-4.2) mg/dL	2.3 (1.1, 4.9)
FGF23 ≥100 RU/mL	152 (99-243) RU/mL	1.0 (ref)	137 (92-216) RU/mL	0.93 (0.70,1.2)	155 (95-252) RU/mL	0.93 (0.72, 1.2)	163 (105-279) RU/mL	1.1 (0.79, 1.2)
PTH ≥100 pg/mL	57 (37-95) pg/mL	1.0 (ref)	47 (33-78) pg/mL	1.2 (0.92,1.5)	55 (36-90) pg/mL	1.0 (0.80, 1.3)	60 (38-97) pg/mL	1.1 (0.80, 1.4)

*Adjusted for center, age, sex, race/ethnicity, income, eGFR, diabetes, activated vitamin D and phosphorus binder use.

TH-PO192

Effect of Ferric Citrate Hydrate on FGF23 and Serum α-Klotho in Hemodialysis Patients with Hyperphosphatemia and Controlled Serum Phosphate Levels: ASTRIO Study, Supplementary Analysis

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Background: Elevated serum Fibroblast Growth Factor (FGF) 23 level is an independent risk factor for the progression to ESRD, and high FGF23 levels are reportedly associated with cardiovascular events. There is growing interest in α-klotho, a co-receptor for FGF23, as a biomarker of kidney function, because low α-klotho levels have been associated with adverse kidney disease outcome. However, the effect of phosphate binders (PBs) on α-klotho has not been extensively evaluated.

Methods: ASTRIO was a prospective, randomized, multicenter, 24-week study. 93 HD patients who had been taking non-iron based PBs were randomized to Ferric Citrate

Hydrate (FC) group (n=45) or Control group (n=48). In Control, patients maintained treatment with their existing PBs. Serum P and Hb were controlled within 3.5 to 6.0 mg/dL and 10.0 to 12.0 g/dL, respectively. The primary endpoint was change in ESA dose; we also evaluated serum FGF23 and α-klotho.

Results: Serum P was maintained in both groups. C-terminal FGF23 (cFGF23) significantly decreased in FC compared to Control (p=0.04). There were no statistical differences in the changes in intact FGF23 (iFGF23) and α-klotho between groups. Serum ferritin and TSAT were significantly increased in FC compared to Control.

Conclusions: In this study, while there was no difference in the change of serum P between the groups, cFGF23 significantly decreased in FC compared to Control, but did not change iFGF23 and α-klotho.

Parameter	FC (N=40) Mean (SD) Change (from baseline to EOT**)	Control (N=42) Mean (SD) Change (from baseline to EOT**)	Adjusted Mean Difference (FC minus Control)	p-value
P (mg/mL)	0.24 (1.59)	-0.17 (1.53)	0.55	0.06
Ferritin (ng/mL)	79.0 (81.5)	2.9 (79.3)	79.5	<0.01
TSAT (%)	8.6 (12.1)	0.5 (11.8)	9.0	<0.01
cFGF23 (pg/mL)*	-0.2 (0.8)	0.2 (0.8)	0.7	0.04
iFGF23 (pg/mL)*	-0.1 (0.8)	0.1 (0.9)	0.8	0.33
α-klotho (pg/mL)	2.0 (91.5)	-8.9 (145.3)	-11.1	0.58

*Logarithmic transformation, **End of treatment

TH-PO193

Soluble Klotho Is Associated with Cardiovascular Disease Events in Patients with Hemodialysis: Prospective Cohort Study

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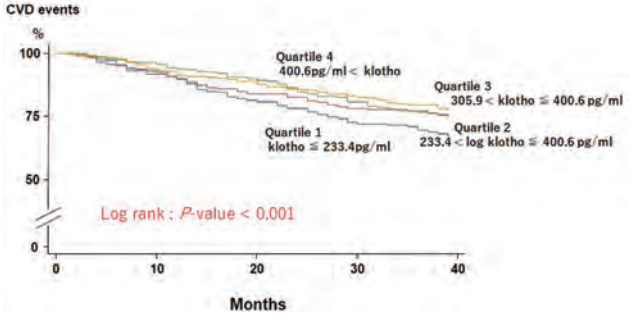
Background: Patients with hemodialysis are higher mortality and their main cause of death is CVD events. Mineral bone disorder recently has been regarded as the important risk factors of CVD events. Klotho, which is known as an antiaging gene, serves as the cofactor for fibro blast growth factor 23 (FGF23) and regulate phosphorus and vitamin D metabolism. We aimed to evaluate whether serum soluble klotho levels are associated with CVD events in hemodialysis patients.

Methods: This prospective cohort study analyzed 1029 hemodialysis patients. We divided the study population into four groups based on serum Klotho levels. In this study, we defined the primary outcome was cardiovascular events, defined as a composite of death due to cardiac disease, sudden death, ischemic heart disease, heart failure requiring hospitalization and cerebral vascular events including cerebral hemorrhage and cerebral infarction. Association between Klotho levels and CVD events were analyzed using Cox proportional hazard model.

Results: The median soluble Klotho level was 305.9 (233.4-400.6) pg/ml. Their mean age (±standard deviation) was 63.1 (±11.9) years and median dialysis vintage was 109 (38-153) months. During follow up, 394 CVD events occurred. CVD events were more frequent in the lowest than highest soluble Klotho quartile [hazard ratio, 1.50; 95% confidence interval, 1.04-2.18; *P*-value, 0.032]. These associations were confirmed in patients with higher age (>65 years), higher phosphate levels (> 6.0mg/dl), or cinacalcet.

Conclusions: In this study, we found that soluble klotho is associated with CVD events in hemodialysis patients.



TH-PO194

Association of Serum Mineral Parameters with Mortality in Hemodialysis Patients: Data Analysis from Korean ESRD Registry

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Background: We investigated the association between mineral metabolism parameters and mortality in Korean hemodialysis patients to identify optimal targets in Korean population.

Methods: Among hemodialysis patients registered in the End-stage renal disease Registry of the Korean Society of Nephrology between March 2012 and June 2017, those with serum calcium, phosphorus, and intact parathyroid hormone (iPTH) measured at enrollment were included. Analysis for the association of serum levels of calcium, phosphorus, and iPTH with all-cause mortality was conducted.

Results: Among the total 21,433 enrolled patients, 3,135 (14.6%) patients died during 24.8 ± 14.5 months follow-up period. After multivariable adjustment, patients in the 1st quintile of corrected calcium was associated with lower mortality (HR, 0.84; 95% CI, 0.71-0.99; *P*=0.003), while those in the 5th quintile of corrected calcium was associated with higher mortality (HR, 1.39; 95% CI, 1.20-1.61; *P*<0.001) compared with those in the 3rd quintile. For phosphorus, only the lowest quintile was significantly associated with increased mortality (HR, 1.24; 95% CI, 1.08-1.43; *P*=0.003). The lowest (HR, 1.18; 95% CI, 1.02-1.36; *P*=0.026) and the highest quintile of iPTH (HR, 1.24; 95% CI, 1.05-1.46; *P*=0.013) were associated with increased mortality. Regarding target counts achieved according to the KDOQI guideline, patients who achieved none of the mineral parameter targets had higher mortality than those who achieved all of the 3 targets (HR, 1.37; 95% CI, 1.12-1.67; *P*=0.003).

Conclusions: In Korean hemodialysis patients, high serum calcium, low phosphorus, as well as high and low iPTH levels were associated with increased all-cause mortality.

TH-PO195

Changes in Serum Phosphorus (sP) Among Patients with Hyperphosphatemia (sP >5.5 mg/dL) Switched to Sucroferric Oxyhydroxide for Two Years

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Background: Hemodialysis (HD) patients are advised to keep sP levels ≤ 5.5 mg/dl through diet modification and use of phosphate binders (PB). Sucroferric oxyhydroxide (SO) has been prescribed to hemodialysis patients for the control of sP as part of routine clinical care. This database analysis retrospectively analyzed sP and PB pill burden in patients who had a mean sP level > 5.5 mg/dl at baseline and were prescribed SO for up to two years.

Methods: The analysis included adult HD patients with sP > 5.5 mg/dl at baseline (3-month, -Q1) who were switched to SO as part of routine care for up to two years (Q1-Q8). Patients were stratified into 3 groups based on baseline sP: Group 1: sP 5.6-7 mg/dl, Group 2: sP 7.1-8.5 mg/dl, and Group 3: sP >8.5 mg/dl. Mixed effects linear regression was used for significance testing.

Results: There were 2067, 1381, and 479 patients in Groups 1, 2, and 3, respectively. 84% had recorded PB prescriptions at baseline with the majority prescribed sevelamer. Table 1 shows the percent of patients who achieved sP ≤5.5 mg/dl and mean sP levels by group. In Groups 1 and 2, 42% and 22% of patients had sP ≤5.5 mg/dl after 2 years of follow-up. In the group with the highest baseline sP level, Group 3, sP ≤ 5.5 mg/d was achieved in 8.3% of patients, and the mean sP for this group decreased from 9.36 mg/dl to 7.62 at Q8, a 19% reduction in sP (-1.74 mg/dl). On average, the PB pill burden was reduced in groups 1, 2, and 3 from 8.7, 9.7, and 9.9 PB pills/day at baseline to 4.9, 5.3 and 5.4 SO pills/day at Q8, respectively.

Conclusions: Patients with elevated sP levels at baseline switched to sucroferric oxyhydroxide for up to two years as part of routine care, experienced significant reductions in sP along with a >40% reduction in PB pills/day and increase in patients with sP ≤5.5 mg/dl.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

sP at baseline	-Q1	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
% patients with sP <= 5.5 mg/dL										
Group 1: 5.6 - 7 mg/dL	0%	28.50%	34.90%	39.30%	40.90%	39.40%	41.30%	39.20%	42.40%	
Group 2: 7.1 - 8.5 mg/dL	0%	9.70%	13.20%	16.70%	18%	20.20%	20.60%	20.60%	21.90%	
Grouo 3: > 8.5 mg/dL	0%	2.50%	5.90%	6.80%	7.80%	10.50%	10.80%	9.50%	8.30%	
Mean serum phosphorus (mg/dL)										P-values
Group 1: 5.6 - 7 mg/dL	6.31	6.14	6	5.93	5.9	5.9	5.93	5.97	5.9	<0.0001
Group 2: 7.1 - 8.5 mg/dL	7.64	7.08	6.9	6.8	6.83	6.74	6.75	6.72	6.74	<0.0001
Group 3: > 8.5 mg/dL	9.36	8.34	8.15	7.96	7.95	7.75	7.66	7.65	7.62	<0.0001

TH-PO196

Serum Phosphorus (sP) Lowering Effect of Sucroferric Oxyhydroxide (SO) in Phosphate-Binder (PB) Naïve Hemodialysis Patients (pts) over 12 Months

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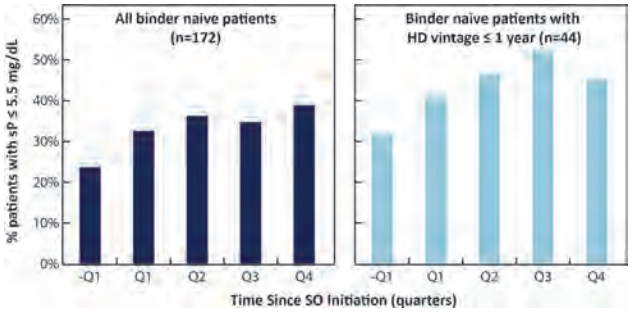
Background: Achieving recommended levels of sP ≤5.5 mg/dL by restricting dietary phosphate alone can be a major challenge and may compromise nutritional status leading to poor outcomes in hemodialysis (HD) pts. Whereas most HD pts are prescribed PB therapy to control sP, the efficacy and bill burden vary substantially across agents. We hypothesize that SO can effectively control sP with a low PB pill burden in pts naïve to PB.

Methods: Data, rendered de-identified, were extracted for all adult, HD pts with their first SO prescription between 3/1/2014-3/1/2015 and SO prescription for 12 months. 172 adult HD pts with SO prescribed as a first-line PB were identified. A subset of 44 pts prescribed SO as late as one year after dialysis start were also analyzed. Baseline (BL) was defined as the 3 months before SO (-Q1) and SO follow-up was divided into quarters (Q1-Q4).

Results: Pts were 54 (±14) years old with a dialysis vintage of 49 (±52) months. Comparing BL vs SO follow-up (Q1-Q4) among all 172 pts, there were consistent improvements in pts achieving target sP ≤5.5 mg/dL (increased from 23.7% at BL to 32.6%-38.8% during SO treatment, p<0.0001) [Figure]. Pts were prescribed between 4.0–4.1 SO pills/day. For the subset of 44 pts prescribed SO during the first year of dialysis, 31.8% of pts had sP ≤5.5 mg/dl at BL and during SO follow-up, 40.9%-52.4% of pts had a sP ≤5.5 mg/dl, a 29%-65% increase from baseline. Mean PB pills/day for this subset ranged from 3.7 to 3.9 pills/day during Q1-Q4.

Conclusions: SO was effective in achieving sP ≤5.5 mg/dL as a first line PB with a low pill burden (4.0–4.1 pills/day) in HD pts. This was confirmed in a subset of pts who began HD as late as one year of starting SO.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group



TH-PO197

Serum Phosphorus and Phosphate Binder (PB) Pills/Day Among Hemodialysis Patients Prescribed Sucroferric Oxyhydroxide (SO) for a Year Compared to Patients Who Discontinue SO and Are Prescribed Other PB

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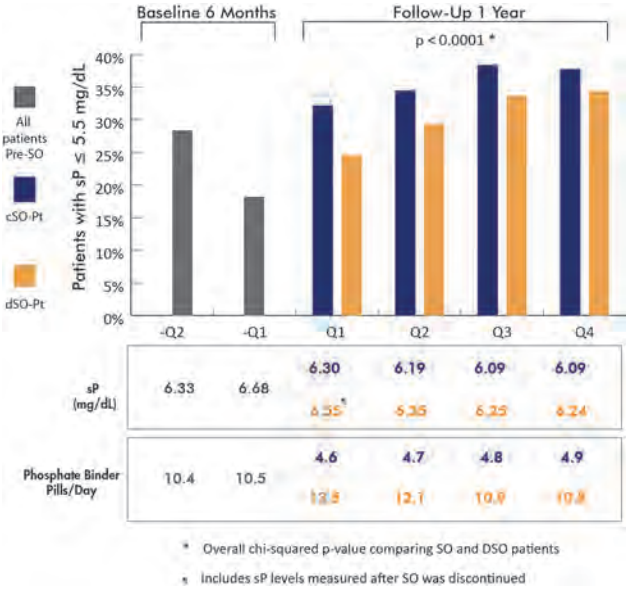
Background: The high pill burden of most PBs has been associated with hemodialysis (HD) patients' lack of adherence to prescribed therapy. SO is an iron-based PB indicated for the control of serum phosphorus (sP) in patients with chronic kidney disease on dialysis with a starting dose of 3 pills/day. This retrospective database analysis compared sP levels and PB pills/day for patients who continued use of SO and patients who discontinued SO.

Methods: Analysis included adult, HD patients prescribed PB for 12 months as part of routine care with sP measurements recorded during the quarter (Q) before and 4 Q after switch to SO. Continued use of SO was defined as SO monotherapy for 12 months (cSO-Pt). Discontinuing SO (dSO-Pt) was defined as discontinuation of SO within 90 days of initiation followed by a switch to other PB(s). Pre-SO baseline was 6 months (-Q2 and -Q1) and follow-up was 12 months (Q1 to Q4). Statistical analysis was conducted using chi-square test.

Results: 653 cSO-Pt and 2294 dSO-Pt were analyzed. 74% of dSO-Pt had a switch to sevelamer after discontinuing SO. Up to 38.4% of cSO-Pt achieved sP ≤5.5 mg/dL compared to up to 34.4% for dSO-Pt [Figure]. During a 12-month follow-up, crude mean sP was 6.19 mg/dL for cSO-Pt and 6.37 mg/dL for dSO-Pt (p<0.0001). After controlling for age, gender, baseline sP, and baseline serum albumin, the follow-up mean sP was 6.22 mg/dL for cSO-Pt and 6.39 mg/dL for dSO-Pt, p<0.0001. The mean PB pill/day was 4.8 for cSO-Pt and 9.2 for dSO-Pt.

Conclusions: During a 12-month follow-up, SO patients had a lower mean sP, were more likely to achieve in-sP ≤5.5 mg/dl, and were prescribed 50% fewer pills/day than patients who discontinued SO and were prescribed other PB(s).

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group



TH-PO198

Hepcidin, Iron Indices, and Bone Mineral Metabolism in Non-Dialysis CKD

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Background: There have been some small studies which have reported that intravenous iron replacement was associated with levels of bone mineral metabolism markers. Disordered bone mineral metabolisms are also well-known risk factors of erythropoietin (EPO) resistance. Hepcidin is a key peptide for the EPO resistance and iron metbolism. Although the intimate association between hepcidin, iron indices, and bone mineral metabolism was expected, particularly in non-dialysis chronic kidney disease (CKD) patients, it has been studied sparsely. Therefore, we performed this study.

Methods: We reviewed data of 2,238 patients from a large-scale multicenter prospective Korean study (2,011–2,016), and excluded 214 patients with missing data on markers and related-medications of iron and bone mineral metabolism, hemoglobin, blood pressure and causes of CKD. Multivariate linear regression analysis was used to identify the association between iron and bone mineral metabolism.

Results: The proportion of CKD stage 1-5 were 16.2%, 18.7%, 37.1%, 21.6%, and 6.4%, respectively. Per each 10% increase in transferrin saturation (TSAT), there was a 0.013 mmol/l decrease in phosphorus [95% confidence interval (CI) -0.021—0.004; *P* = 0.003] and a 0.022 nmol/l increase in logarithmic 25-hydroxyvitamin D (Ln-25OHD) levels (95% CI 0.005–0.040; *P* = 0.019). A 1 pmol/l increase in Ln-ferritin was associated with a 0.080 ng/l decrease in Ln-intact parathyroid hormone (Ln-iPTH) (95% CI -0.122—0.039; *P* <0.001). Meanwhile, beta (95% CI) per 1 unit increase in phosphorus, Ln-25OHD, and Ln-iPTH for the square root of the serum hepcidin were 0.594 (0.257–0.932; *P*= 0.001), -0.270 (-0.431—0.108; *P* = 0.001), and 0.115 (0.004–0.226; *P* = 0.042), respectively. In subgroup analysis, the relationship between phosphorus, 25OHD, and hepcidin was strongest in the positive-inflammation group.

Conclusions: Increased TSAT was associated with decreased and increased phosphorus and 25OHD levels, respectively, while increased ferritin was associated with decreased iPTH levels. Increased phosphorus and iPTH and decreased 25OHD were independently associated with increased hepcidin levels.

TH-PO199

Effects of Patiromer on Markers of Mineral Metabolism in Patients with Hyperkalemia and Hyperphosphatemia

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Background: Patiromer (PAT) is a once-daily K binder for hyperkalemia (HK) treatment; Ca is the counterexchange ion. In TOURMALINE (NCT02694744) patients (pts) with serum K >5.0 mEq/L were randomized to PAT 8.4 g QD without/with food for 4 wks, with doses adjusted to achieve/maintain serum K 3.8-5.0 mEq/L (target range). The primary endpoint (% of pts in target range at wk 3/4) was met in 83% dosed without food and 87% with food, with overlapping 95% CIs. We report the effects of PAT on markers of mineral metabolism in the pts with baseline (BL) hyperphosphatemia (HyperP, serum phosphate >4.8 mg/dL).

Methods: BL and wk 4 serum and 24-hr urine phosphate and Ca, and other markers, are reported for all HyperP pts combined (without/with food). Time-corrected 24-hr urine phosphate/Ca values were normalized to each pt's mean of the time-corrected urine creatinine (Cr) level.

Results: 16 pts had HyperP; 11 dosed without and 5 with food. All had CKD (median [Q1, Q3] eGFR 18.0 [11.5, 20.5] mL/min/1.73m^2) and hypertension; 14/16 had diabetes. Two pts were on stable doses of sevelamer during the study. The primary endpoint was met in 14/16 pts (10/11 without and 4/5 with food in target range). There were significant reductions in serum and 24-hr urine phosphate (Table). Mean serum Mg decreased significantly. Mean serum Ca and 24-hr urine Ca were not different from BL at wk 4. Serum PTH levels decreased at wk 4 (P=0.19). Overall, 15/16 had ≥1 post-BL serum phosphate assessment; 9/15 had serum phosphate in the normal range by wk 4.

Conclusions: The decrease in serum and urine phosphate in the small number of HyperP pts in this study supports that intestinal phosphate is bound to some of the released Ca when PAT is used to lower serum K. These findings suggest that PAT may aid in the management of HyperP in pts with CKD requiring both K and phosphate binders.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

Markers of Mineral Metabolism in HyperP Patients in TOURMALINE

		Baseline		Week 4		P-value
		Mean (SD)	N	Mean (SD)	N	
Serum electrolytes (mg/dL)	Calcium	9.1 (0.5)	16	9.3 (0.3)	13	0.58
	Magnesium	2.3 (0.4)	16	2.1 (0.4)	13	0.004
	Phosphate	5.3 (0.4)	16	4.7 (0.9)	13	0.017
24-hour Cr-normalized urine electrolytes (mg/24 hr)	Calcium	31.0 (19.9)	6	32.3 (20.0)	6	0.73
	Phosphate	722.8 (331.9)	9	573.7 (304.7)	9	0.025
Other markers of mineral metabolism (pg/mL)	Fibroblast growth factor 23	483.2 (587.2)	16	470.2 (695.6)	13	0.29
	Parathyroid hormone	136.8 (81.7)	14	93.2 (48.4)	13	0.19

TH-PO200

Effects of Lanthanum Carbonate on Mineral Metabolism in Normophosphatemic Patients with CKD: Secondary Analysis of the COMBINE Trial

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Background: Disordered mineral metabolism is a nearly universal complication of reduced kidney function that develops early in the course of CKD and is associated with adverse clinical outcomes. Strategies aimed at reducing dietary phosphate absorption may prevent abnormalities in markers of mineral metabolism, but data from large and long-term interventional studies are lacking.

Methods: The COMBINE trial was a randomized, double-blinded, 12-month, 4-group parallel trial of nicotinamide and lanthanum carbonate vs. placebo in 205 CKD stage 3–4 patients that tested the effects of active therapies on serum phosphate and FGF23 levels and on safety and tolerability. The primary results demonstrated that compared to placebo (n=51), lanthanum carbonate (n=50), nicotinamide (n=51) or dual treatment (n=53) did not significantly lower serum phosphate or FGF23. To determine the efficacy of each individual therapy, we performed secondary analyses to test the main effects of lanthanum carbonate (treated, n=103 vs. untreated, n=102) and nicotinamide (treated, n=104 vs. untreated, n=101).

Results: At baseline, mean eGFR was 33±7 ml/min/1.73m^2, serum phosphate was 3.7±0.5 mg/dL, FGF23 was 103.6 [IQR 76.8, 145.1] pg/ml, and PTH was 96 ± 64 pg/ml. Baseline characteristics were well-balanced across comparison groups. In intention to treat analyses, the overall 12-month effect of lanthanum carbonate treatment on serum phosphate was -0.051 mg/dL (95% CI= -0.191 to 0.089, P=0.48); FGF23 was -14.0% (95% CI= -24.2 to -3.7, P=0.0077); PTH was -6.7% pg/mL (95% CI= -20.1 to 6.9, P=0.33); FEPI was -3.56 (95% CI= -5.76 to -1.36, P=0.0016); and 24 hr urine phosphate/creatinine was -0.042 mg/dL (95% CI= -0.081 to -0.003, P=0.033). No significant effects were observed with nicotinamide treatment.

Conclusions: In a secondary analysis of the COMBINE trial, we demonstrated that lanthanum carbonate treatment decreased urinary phosphate excretion and reduced FGF23 levels. Our findings provide support for targeting dietary phosphate absorption to modify FGF23 levels in patients with CKD stages 3-4.

Funding: NIDDK Support, Commercial Support - Shire

TH-PO201

Effectiveness of Sucroferric Oxyhydroxide in Phosphate Binder-Naïve and -Experienced Patients: A Real-World Retrospective Database Analysis

Charles Chazot,[4] Rosa Ramos,[5] Attilio Di Benedetto,[6] Manuel A. Ferreira,[3] Birgit Kagermeier,[2] Hans-Juergen Arens,[7] Sebastian Walpen,[1] Viatcheslav Rakov,[1] Stefano Stuard.[2] *[1]Vifor Fresenius Medical Care Renal Pharma, Glattbrugg, Switzerland; [2]Clinical & Therapeutical Governance, Fresenius Medical Care, Bad Homburg, Germany; [3]Nova Medical School, Lisbon, Portugal; [4]NephroCare France, Fresnes, France; [5]Nephrology, NephroCare Spain, Madrid, Spain; [6]Medical Direction, NephroCare Italy, Naples, Italy; [7]Contract Clinical Services, Fresenius Medical Care, Bad Homburg, Germany.*

Background: Retrospective analysis of a clinical database (EuCliD5) assessed the real-world effectiveness of an iron-based phosphate binder (PB), sucroferric oxyhydroxide (SFOH), to control serum phosphorus (sP) levels in hemodialysis (HD) patients (pts) in European countries.

Methods: De-identified data were extracted from electronic records for adult HD pts in 4 countries (France, Italy, Spain, Portugal) who were newly prescribed SFOH as part of routine care between Jan 2016 and Oct 2017. Baseline (BL) was defined as the 3-month period prior to SFOH prescription. Mean PB pill burden and sP levels were analyzed for Months 1–3 (Q1) and Months 4–6 (Q2) of SFOH treatment using mean values from the BL period as the reference. Effectiveness of SFOH for control of sP levels was evaluated for pts who had not received PB therapy during BL (PB-naïve) and those who had (PB-experienced).

Results: 1347 pts were included (mean age: 61.6 years; 63.5% male), of whom 605 pts were PB-experienced and 742 were PB-naïve. Characteristics of pts in these subgroups were generally comparable; median dialysis vintage was longer in PB-experienced vs. -naïve pts (50 vs. 34 months). The % of pts with sP control (≤5.5 mg/dL) during BL was lower in the PB-experienced (31.6%) vs. the PB-naïve (44.9%) subgroup (**Figure**). In both subgroups, the % pts achieving sP ≤5.5 mg/dL increased significantly from BL through Q1 and Q2. For PB-experienced pts, these sP improvements were achieved with a reduction in PB pill burden.

Conclusions: In routine practice, SFOH therapy improved sP control in both PB-naïve and PB-experienced HD pts, with a relatively low daily pill burden.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma

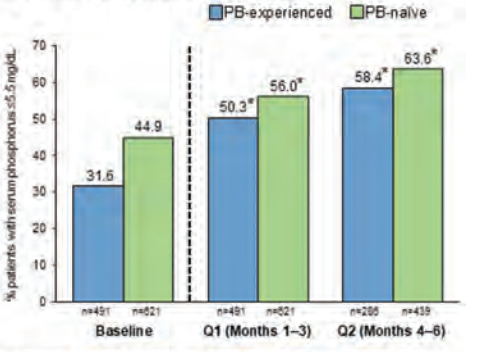
Figure: Serum phosphorus control during the follow-up

a) **Mean ± SD serum phosphorus concentrations (mg/dL) and changes from BL in each treatment period**

	PB-experienced	PB-naïve
Baseline	n=491: 6.1 ± 1.1	n=521: 5.7 ± 1.2
ΔBL to Q1 (Months 1–3)	n=491: −0.4 ± 1.2*	n=521: −0.4 ± 1.1*
ΔBL to Q2 (Months 4–6)	n=286: −0.6 ± 1.2*	n=439: −0.6 ±1.2*

*$p<0.0001$ for change from baseline

b) **% pts achieving serum phosphorus control (≤5.5 mg/dL) and mean PB pill burden in each treatment period**



	Baseline		Q1 (Months 1–3)		Q2 (Months 4–6)	
Mean SFOH pill burden (pills/day)	0	0	1.4	2.2	1.5	2.4
Other PB pill burden (pills/day)	5.1	0	2.3	0.2	2.4	0.4
Mean total PB pill burden (pills/day)	5.1	0	3.7	2.5	3.9	2.7

*$p<0.0001$ for change from BL in % pts with sP ≤5.5 mg/dL

TH-PO202

Association Between Serum Phosphorus level and Decline of Glomerular Filtration Rate in Heathy Individuals

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Background: High serum phosphorus levels are strongly and independently associated with a more rapid decline of renal function in patients with advanced chronic kidney disease (CKD). We hypothesized that phosphorus was also associated with decline of Glomerular Filtration Rate (GFR) in heathy individuals.

Methods: We identified 1,340 healthy individuals with measured serum creatinine from the Rugao aging cohort over the period of Nov 2014 (baseline) to Nov 2017 (2nd follow-up). The association of phosphorus at the 2nd follow-up (Nov 2017), which was not measured at the baseline, with decrease of GFR between baseline and 2nd follow-up was examined using logistic models with adjustment for baseline demographics characteristics and laboratory variables.

Results: The mean age (mean±SD) of the cohort was 75±4 years old and included 55% females, 7% diabetics, and 44% hypertension. Mean GFR estimated by CKD-EPI equation at baseline and the 2nd follow-up was 88.0 (±10) and 85.9 (±12) ml/min/1.73m^2, respectively, with an average of 2 ml/min/1.73m^2 decrease across the 3 years. Mean serum phosphorus level was 1.17(±0.16) mmol/l. Serum phosphorus was not associated with GFR at the baseline (P=0.1) or at the 2nd follow up (P=0.5). However, each 1-mmol/l increase in phosphorus concentrations was associated with approximately 3-fold increased risk for rapid GFR decline (defined as at least 4.5ml/min/1.73m^2 decrease during the 3 years) after adjusted for age, gender, smoking, hypertension, cardiovascular disease, BMI, Low-density lipoprotein, triglyceride, albumin, and baseline GFR (OR 3.1, 95%CI 1.3-7.2, P = 0.01).

Conclusions: Higher phosphorus levels are associated with GFR decline in heathy individuals. Further studies are needed to validate this finding.

TH-PO203

Using Machine Learning to Help Predict Elevated Serum Phosphate Levels in Patients with ESRD

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Background: According to USRDS, over two-thirds of patients treated with hemodialysis had serum phosphate (PO_4) greater than the KDIGO guidelines of 4.5 mg/dl (USRDS 2017, KDIGO 2009). In practice, most clinicians try to achieve PO_4 levels between 3.0 and 5.5 mg/dl (Handbook on dialysis 2015). Proactively identifying patients who may transition from the normal clinical range to greater than 5.5 mg/dl may help clinicians target their interventions and avoid elevated PO_4 levels.

Methods: We built a machine learning model with over 1000 variables to predict which HD patients will realize a PO_4 lab value greater than 5.5mg/dl during the following month. We restrict our model to patients using a pharmacy specializing in renal medications with all PO_4 draws less than 5.5 mg/dl in the last 180 days. Some of the variables included in this model are history of lab values, treatment vital signs, treatment no shows, comprehensive assessments from dieticians and social workers, and PO_4 binder medication possession ratios. To train the XGBoost machine learning model, we utilized data from patients who were treated in Fresenius Medical Care North America clinics between January 2016 and October 2017. The results shown below are from un-seen test data with 16639 patients in 2017.

Results: For the patients enrolled in the specialty pharmacy who have all PO_4 values less than 5.5 mg/dl in the previous 180 days, the prevalence of having next month's lab draw greater than 5.5 mg/dl is approximately 10%. Results from the test data include area under the receiver operating curve (AUROC) of 0.75, sensitivity of 72% and specificity of 66%. The confusion matrix for test data is shown in Table 1.

Conclusions: We created a predictive model to help identify patients who may unexpectedly have elevated PO_4 lab values in the next month. Identifying these patients may help to target interventions that mitigate negative consequences associated with high PO_4 levels.

Funding: Commercial Support - Fresenius Medical Care North America

Confusion matrix for test data (n = 16639)

		Actual PO4 >5.5 mg/dl	
		Positive	Negative
Prediction for PO4 >5.5 mg/dl	Positive	7.3%	30.6%
	Negative	2.9%	59.1%

TH-PO204

Safety, Efficacy, and Cost-Effectiveness of Mg/Al Type Hydrotalcite Drug versus Conventional Phosphate Binders in Hemodialysis CKD Patients with Hyperphosphatemia

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Background: Hyperphosphatemia is a risk factor for the increased of mortality rates in chronic kidney disease (CKD) patients and associated to several clinical diseases. In this study, we assess safety, efficacy and clinical cost between Mg/Al hydrtoalcite (Talcid) and conventional non-calcium, non-aluminum phosphate binders (Lanthanum carbonate, LC) for hemodialysis (HD) chronic kidney disease (CKD) patients with hyperphosphatemia.

Methods: In this open-label, randomized, parallel-group study, 64 maintenance hemodialysis patients were matched to our selected procedure. Serum phosphate levels were over 1.78 mmol/L (5.5 mg/dl) and they were randomized to treat Talcid 1000 mg three times/day or LC 500 mg two or three times/day for 6 months. Serum calcium, phosphate, parathyroid hormone (iPTH) and alkaline phosphatase (ALP) levels were examined serially for 6 months.

Results: In hemodialysis patients with hyperphophatemia, both Talcid and LC significantly moderated serum phosphate levels, from 2.323±0.392 to 1.702±0.360 mmol/L(P<0.01) and from 2.379±0.393 to 1.890±0.403 mmol/l (P<0.01), respectively. Serum calcium and intact parathyroid hormone (iPTH) level in the both groups did not significantly change when comparing to baseline parameters during the study. No severely adverse events were reported on both groups. Total cost of 6-month treatment with Talcid was 839.79±96.97 RMB while 6-month treatment with LC was 10292.96±4018.10 RMB (P<0.01).

Conclusions: The efficacy and safety of hydrotalcite are similar to LC but it presents higher reaching-target rate and lower economic burden in hemodialysis CKD patients with hyperphosphatemia. It can be severed as another option for dialysis patients with hyperphosphatemia patients.

Comparisons of the daily average cost and total cost between Talcid group and LC group during 6 months treatment.

6 months	Talcid group	LC group	p-value
Average dose / day(mg)	2687.50±310.34	1191.31±465.06	<.001 **
Total cost(RMB)	839.79±96.97	10292.96±4018.10	<.001 **

Data are presented as mean+SD

** P < 0.001, Talcid group verse LC group

TH-PO205

Acute Mineral Metabolism Disorders Following Kidney Donation Are Not Different Compared to Those Observed in Other Surgical Procedures

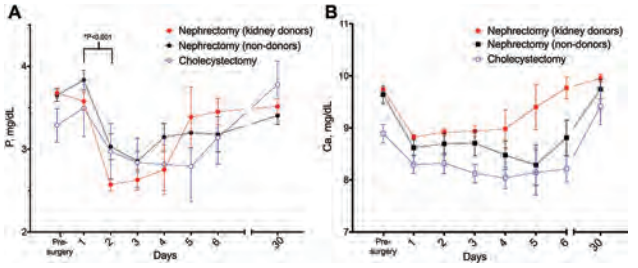
Jorge I. Fonseca-Correa,[1] Luis Tamez Pedroza,[1,3] Lucas Porto-Silva,[1,2] Josefina Alberú,[1] Ricardo Correa-Rotter,[1] Juan Carlos Ramirez-Sandoval.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; [2]Benemérita Universidad Autónoma de Puebla, Ciudad de México, Mexico; [3]Universidad Autonoma de Baja California, Ciudad de M?xico, Mexico.*

Background: Emerging studies have suggested that living kidney donors (LKD) have acute mineral metabolism (MM) abnormalities after unilateral nephrectomy related to loss of eGFR, in particular significant disturbances in P and Ca. Nevertheless, these changes have not been compared to controls undergoing other major surgical procedures. Our aim was to analyze acute MM abnormalities (serum Ca y P levels) in 3 groups: following laparoscopic (LN) vs. open nephrectomy (ON) and elective laparoscopic cholecystectomy (LC).

Methods: Single-center retrospective cohort study (n=293). Biochemical parameters were evaluated before and after surgery on days 1-6 and 30, in 100 consecutive LKD undergoing LN, compared with 91 subjects undergoing ON for kidney cancer or urolithiasis, and 102 subjects with gallstone disease undergoing elective LC. We excluded cases with CKD G4.

Results: LN group was younger compared to ON and LC groups (41±19, 58±14, and 58±19 years; p<0.001), and eGFR was higher in LN compared to ON and LC (101±17, 79±23, and 85±28 mL/min/1.73m^2; p<0.001). As expected, only LN and ON reduced eGFR by day 2: -11.4 (-27 to 6) and -14 (-51 to 3) mL/min/1.73m^2 respectively. Serum P levels did not change significantly from baseline to day 1, but decreased by day 2 in all groups (LN=-1.2 [-1.6 to -0.2], ON=-1.0 [-1.7 to -0.1] and LC=-0.6 [-1.0 to 0.0] mg/dL) before normalizing by day 30 (Figure). Serum P decline was not modified by concurrent changes in eGFR in any group. Moderate hypophosphatemia (reduction to 1-2 mg/dL) was similarly present in all groups (LN 14%, ON 7%, and LC 12%; p=0.16). No hypophosphatemia <1 mg/dL occurred during follow-up. Transient non-corrected hypocalcemia and hypoalbuminemia appeared by day 3 in all groups.

Conclusions: Acute MM disturbances (serum P and Ca) occur after surgical procedures independent of changes in eGFR, and are not related to kidney donation or nephrectomy indicated for other causes. Postoperative slight hypophosphatemia is frequent and appears to be a multifactorial.



TH-PO206

Hyperphosphatemia and Acid-Base Equilibrium Disorders Are Newly Recognized Risk Factors for Mönckeberg's Sclerosis of Vascular Access Artery

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Background: Medial arterial calcification (MAC), also known as Mönckeberg's sclerosis, in vascular access (VA) artery is reported to be observed with high frequency in end-stage renal disease (ESRD) patients with advanced age and/or diabetic nephropathy. MAC in VA artery is also associated with increased risk of VA failure and cardio-vascular disease (CVD) events. The purpose of this study was to clarify risk factors for MAC formation in VA arteries of patients with ESRD.

Methods: Forty-one patients with ESRD, who underwent VA operation at the initiation of hemodialysis therapy, were enrolled in this study. In addition to clinical information (primary disease, age, gender, blood biochemical and computed tomography (CT) imaging findings etc.), the presence of calcification was examined pathologically by Von Kossa staining of arterial specimens (radical artery).

Results: MAC was observed in 21 patients (51.2%), and their serum phosphorus (Pi) (6.2 *vs* 4.9), Ca x Pi product (53.3 *vs* 42.4), blood urea nitrogen (79.7 *vs* 60.7), urinary osmolality (U-OSM) (333 *vs* 246) levels were significantly higher, while HCO_3^- (20.1 *vs* 23.0), base excess (-5.45 *vs* -2.33) and urinary pH (5.80 *vs* 6.47) levels were significantly lower than the averages of 20 patients without MAC formation (48.8%). Other biochemical parameters (e.g. i-PTH, FGF-23, α-klotho and pyrophosphate) and patients' age, gender and treatment history did not differ between MAC positive and MAC negative patients. The ROC analysis revealed that the area under curve for serum phosphorus and U-OSM were the highest, 0.771 and 0.874, respectively. By Fisher's test, a serum phosphorus level of 4.8 mg/dl or more significantly increased the probability of MAC (66.7% *vs* 17.65%, $p<0.0037$), and its odds ratio was 9.33 times. The U-OSM of 312 mOsm or more significantly increased the incidence of MAC (76.9% *vs* 9.1%, $p<0.0013$) with an odds ratio of 33.3.

Conclusions: It was shown that higher serum phosphorus level and severer renal dysfunction and acid-base equilibrium disorders at the start of hemodialysis were risk factors for MAC in VA artery. Particularly, patients with hyperphosphatemia over 4.8 mg/dl were highly likely to display MAC in VA artery, so that attention should be paid to potential VA failure and CVD events.

TH-PO207

Intestinal Phosphorus Absorption Assessment by Kinetic Modeling of 33P Radiotracer in Hemodialysis Patients

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Background: Intestinal phosphorus (P) absorption is an important component of P homeostasis. In CKD, limiting P absorption is the goal of many pharmacologic therapies. 24-hr urine P has been used as a surrogate for P absorption, but recent balance studies demonstrate that this measure is highly variable and not related to net P absorption (Stremke, CJASN 2018). Further, 24-hr urine P is not useful in oliguric/anuric patients. Changes in serum P are equally problematic due to diurnal variation, fluxes with dialysis, and erratic dietary intake. We tested a ^{33}P absorption method as a sensitive and direct assessment of P absorption in humans that can be used for clinical research in hemodialysis (HD) patients.

Methods: HD patients with stage 5D CKD were enrolled. Following 10 days of controlled study diet (~800 mg/d P), patients underwent HD and then were admitted as inpatients to a clinical research center for 2 days for P absorption testing. ^{33}P radiotracer was administered PO with a meal containing a load of ~300 mg P, and blood sampled over 24-hr. The next day, a second dose of ^{33}P was administered by IV and blood sampled for another 24-hr, followed by a second HD treatment. Serum ^{33}P activity was measured by liquid scintillation, adjusted for decay and expressed as % of dose. The ^{33}P data were analyzed by compartmental modeling using WinSAAM software. Intestinal absorption was calculated as the fraction moving into blood vs. moving down the intestinal tract into stool. Descriptive results from 14 unique subjects are presented.

Results: Serum P increased during the 48-hr of study that was during an interdialytic interval. To estimate how much additional P (i.e., over absorption) was entering the system, a second model was used. Average fractional P absorption was 58±17%. The absorption test was well-tolerated by patients in the study. Complications were limited to difficulties with venous access in some patients.

Conclusions: Fractional P absorption can be estimated directly by a test using oral and IV ^{33}P administration; the test is feasible and well-tolerated in HD patients. This novel methodology can be used for clinical studies aimed at assessing physiology, pathophysiology, or interventions related to P absorption in HD patients.

Funding: NIDDK Support, Other NIH Support - Partial support from Grant # UL1TR001108 (A. Shekhar, PI) from NIH, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award, Commercial Support - Chugai Pharmaceutical, Co, Ltd.

TH-PO208

Phosphate Binders for Preventing and Treating CKD-Mineral and Bone Disorder (CKD-MBD)

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Background: Phosphate binders are used to reduce positive phosphate balance for people with CKD to prevent tissue calcification, cardiovascular events and mortality, and bone complications. In this Cochrane review we aimed to update the available evidence for phosphate binders to manage CKD-MBD.

Methods: We searched the Cochrane Kidney and Transplant Specialised Register through 30 November 2017 for all randomized trials (RCTs) of adults with any stage of CKD comparing a phosphate binder with another phosphate binder, placebo or usual care. Key outcomes were cardiovascular events, all-cause and cause-specific mortality, symptomatic bone disease, adverse events, and surrogate measures of vascular calcification. We used random-effects meta-analysis, the Cochrane risk of bias tool, and the GRADE process to adjudicate evidence certainty.

Results: 104 RCTs (13,744 adults) were eligible. Placebo-controlled RCTs were generally in CKD G3-5 not requiring dialysis, while active comparator RCTs involved CKD 5D on dialysis. In CKD 3a to 5, compared with placebo or usual care, sevelamer, lanthanum, iron, and calcium-based phosphate binders had uncertain effects with respect to all-cause and cardiovascular mortality, myocardial infarction, stroke, fracture, or coronary artery calcification. In patients on dialysis, sevelamer may decrease all-cause mortality (RR 0.53, CI 0.30-0.91; low certainty evidence) and induce less hypercalcemia (RR 0.30, CI 0.20-0.43) compared with calcium-based binders, while the evidence indicates that sevelamer had uncertain effects with respect to cardiovascular mortality, myocardial infarction, stroke, or fracture, coronary artery calcification, or fracture. Compared with calcium, lanthanum had uncertain effects with respect to all-cause or cardiovascular mortality, myocardial infarction, stroke, fracture, or coronary artery calcification.

Conclusions: For patients with CKD G3a to 5 not requiring dialysis, there is no evidence that phosphate binders improve clinical vascular and bone outcomes. For dialysis patients, sevelamer lowers all-cause mortality compared to calcium-based binders and incurs less treatment-related hypercalcemia. Data for patient-centered outcomes of lanthanum and iron-based binder treatment and placebo-controlled trials in the dialysis setting are limited.

TH-PO209

Hidden Hypocalcemia at the Initiation of Dialysis as a Risk Factor for Cardiovascular Disease and All-Cause Mortality

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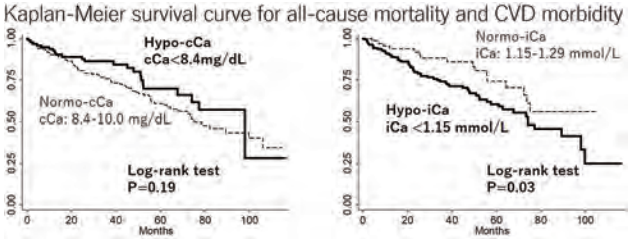
Background: Lower corrected calcium (cCa) levels were reported to be associated with better prognosis among incident dialysis patients. On the other hand, hypocalcemia (HypoCa) often leads to arrhythmia and heart failure. Prognostic importance of true calcium (Ca) status defined by ionized calcium (iCa) remains to be revealed.

Methods: We performed a retrospective cohort study of incident hemodialysis (HD) patients. We collected the latest data just before the initiation of HD. We divided patients into 3 categories: Apparent HypoCa (low iCa: <1.15 mmol/L and low cCa: <8.4 mg/dL), Hidden HypoCa (low iCa and normal cCa), and Normocalcemia (NormoCa: normal iCa and normal cCa). The primary outcome was the composite outcome of all-cause death and cardiovascular diseases (CVD) after the initiation of HD. Using log-rank tests, Kaplan-Meier curves, and cox proportional hazards models, we examined whether Ca status predicts the primary outcome.

Results: Among the enrolled 321 patients, 75% of the patients showed true HypoCa defined as iCa <1.15 mmol/L, 57% of whom showed Hidden HypoCa. Over a median follow-up period of 31.5 months, 31% of the patients reached the primary endpoint. The risk for the primary outcome was not significantly different between HypoCa and normocalcemia defined by cCa. In contrast, patients with true HypoCa had higher risk than patients with normal iCa levels (Figure). In univariate analysis, Hidden HypoCa was significantly associated with increased risk for death or CVD compared with NormoCa (hazard ratio [HR], 2.35; 95% confidence interval [CI], 1.27-4.32), whereas Apparent HypoCa was not. Even after adjustment for age, sex, eGFR, diabetes, QTc prolongation, serum albumin, phosphate, and ALP levels, Hidden HypoCa was associated with significantly higher risk (HR, 2.28; 95% CI, 1.08-4.80).

Conclusions: Hidden HypoCa at the initiation of dialysis was a significant risk factor of the combined outcome of all-cause mortality and CVD morbidity, independently of QTc prolongation, phosphate, and ALP, suggesting the importance of measuring iCa.



TH-PO210

Combined Impact of Phosphorous and Calcium on Mortality Risk in 109,205 Hemodialysis Patients

Antonio Aguirre,[1] Christina Park,[1] Jui-Ting Hsiung,[1] Carola-Ellen Kleine,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh,[1] Elani Streja.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

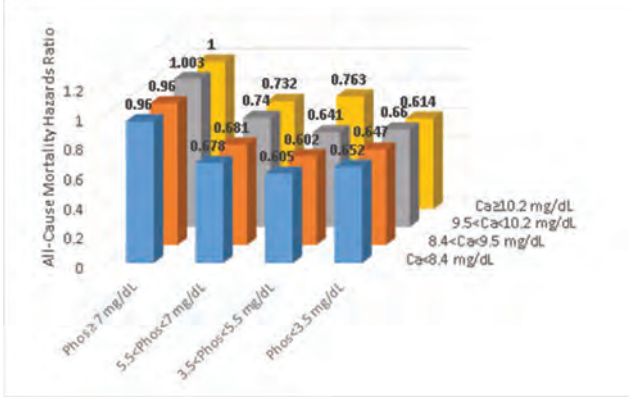
Background: Mineral and bone disorder (MBD) is highly prevalent in patients with chronic kidney disease (CKD). Serum phosphorus (Phos), calcium (Ca) and calcium phosphorus product have been shown to be independently associated with mortality risk in hemodialysis patients. We sought to examine whether evaluating the combination of Phos and Ca can better predict mortality rates among dialysis patients.

Methods: Our analytical cohort consists of 109,205 incident hemodialysis patients receiving treatment from a large dialysis organization between 2007 and 2011. Associations between combined serum Phos and Ca values for the first dialysis quarter (dialysis start + 91 days) and mortality were estimated using Cox proportional hazard models with adjustment for demographics and markers of malnutrition and inflammation.

Results: Mean patient age was 63 ±15 years, while 44% were female, 32% were African American, and 58% were diabetic. The mean amount of Phos in the total cohort was 4.9 ± 1.1 mg/dL and the mean amount for Ca was 9.1 ± 0.6 mg/dL. Compared to the reference group (Phos ≥10.2 mg/dL and Ca ≥7 mg/dL), all-cause mortality tended to be lowest in patients with Phos 3.5-<5.5 mg/dL and Ca 8.4-<9.5 mg/dL (Hazard Ratio 0.60, 95% CI 0.44, 0.82). Besides, patients in the highest Phos group (≥ 7mg/dL) had the highest mortality risk across all strata of serum Ca. (Figure 1)

Conclusions: In hemodialysis patients, keeping serum Phos and Ca within or close to the physiological range might result in better survival. Further studies are needed to examine this association.

Funding: NIDDK Support



TH-PO211

Association Between Serum Magnesium and Arterial Calcification in Incident Hemodialysis Patients

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Background: Animal studies demonstrate that magnesium (Mg) supplementation inhibits arterial calcification in CKD. In humans, both CKD and diabetes mellitus (DM) are independent risk factors for arterial calcification; however, it is unknown if Mg influences calcification in CKD patients and whether DM alters this potential relationship. We tested the hypotheses that higher serum Mg concentration was associated with lower coronary artery calcification (CAC) and thoracic aortic calcification (TAC) scores in incident hemodialysis (HD) patients and that these associations, if any, were modified by DM.

Methods: We performed cross-sectional analyses of 367 incident HD patients in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) cohort. Serum Mg was measured on a non-HD day. CAC and TAC were quantified with computed tomography, which was done at a median time of 3.6 months after initiation of HD. We used logistic regression to study the association of Mg with CAC (>0 vs. 0) and TAC (>0 vs. 0) scores among all participants and linear regression for log-transformed CAC among those with CAC >0. Models were tested for interaction with DM status and adjusted for age, sex, race, smoking, body mass index, serum calcium, phosphate, parathyroid hormone, albumin, hemoglobin, low-density lipoprotein and Kt/V.

Results: Mean age was 55 years; 40% were female; 72% were black and 58% had DM. Mean serum Mg was 1.8±0.2 mEq/L; 63% had CAC >0 and 50% had TAC >0. DM did not modify the association between Mg and CAC. Among all participants, Mg was not associated with CAC. However, among those with CAC >0, per 0.1 mEq/L higher Mg, CAC score was 15% lower [% change: -15% (95% CI: -25%, -3%), p=0.02]. DM modified the association between Mg and TAC (p for interaction=0.003). Per 0.1 mEq/L higher serum Mg, the odds of having TAC >0 was 34% lower [OR: 0.66 (95% CI: 0.47, 0.92), p=0.02] among non-diabetics, but was 55% greater [OR: 1.55 (95% CI 1.08, 2.23), p=0.02] among diabetics.

Conclusions: Consistent with animal studies, higher serum Mg was associated with a lower CAC score among incident HD patients with CAC >0 and with a lower odds of having TAC >0 among non-diabetics. Why Mg was associated with a higher odds of having TAC >0 among diabetics remains to be elucidated.

Funding: NIDDK Support, Private Foundation Support

TH-PO212

Serum Magnesium Value at 1 Year After Initiation of Hemodialysis Is a Significant Predictive Factor of All-Cause Mortality

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Background: Recent studies reported that higher levels of serum magnesium (Mg) were associated with better prognosis in patients undergoing hemodialysis. However, it remains unclear which measurement point of the serum Mg value is crucial for vital prognosis after initiation of hemodialysis. In this study, we evaluated the association of serum Mg for 3 years after initiation of hemodialysis with subsequent all-cause mortality.

Methods: We conducted a single-center retrospective cohort study in 205 patients who initiated hemodialysis between March 2004 and May 2014 and could be followed-up for at least three years or more. We analyzed the influence of annual serum Mg value on all-cause mortality for 3 years using Cox's hazard proportional model. The hazard ratio (HR) of all-cause mortality was adjusted for demographic data, 3-year-averaged laboratory data and medications.

Results: The median follow-up period was 6.1years and fifty patients reached the outcome. Since the median of 3-year-averaged Mg level was 2.6mg/dl, we evaluated the significance of Mg≥2.6mg/dL versus Mg<2.6mg/dL using Cox's proportional hazard model. Although, at the time of initiation of hemodialysis, HR of Mg≥2.6mg/dL was 1.15[0.52-2.26], HRs of Mg≥2.6mg/dL at 1 year, 2 years and 3 years after initiation of hemodialysis, were 0.33[0.15-0.74], 0.41[0.15-0.74] and 0.30[0.16-0.53] and found to be significant factors in univariate analysis. Even adjusted for age, presence of diabetes, 3-year-averaged serum albumin and phosphorus and use of non-calcium containing phosphate binder, which were also significant factors in univariate analysis, HRs of Mg≥2.6mg/dL at 1 year, 2 years and 3 years were 0.48[0.26-0.87], 0.45[0.25-0.82] and 0.50[0.26-0.96], respectively, showing that Mg≥2.6mg/dL was a significantly better prognostic factor at 1 year or longer after hemodialysis initiation.

Conclusions: In this study, we found that higher levels of serum Mg at 1 year or later after initiation of hemodialysis were associated with subsequent better prognosis.

TH-PO213

Hypomagnesemia and Body Composition in Maintenance Hemodialysis Patients

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Background: The aim of this study was to investigate the relationships between serum magnesium (Mg) levels and body composition, clinical parameters, or survival in maintenance hemodialysis (MHD) patients.

Methods: The subjects were 215 MHD patients on dialysate Mg of 1.0 mEq/L. Pre-dialysis laboratory data collection and post-dialysis body composition analysis with the Body Composition Monitor® (Fresenius Medical Care) were performed at the baseline. The patients were divided into serum Mg tertiles [T1-3]. Kaplan-Meier survival, and logistic regression analyses for T1 were examined.

Results: Among all patients, the mean age was 72±12 years, 39.1% were diabetics, and the median dialysis vintage was 44 (8-96) months. The serum Mg values of T1 (n=67),

T2 (n=76) and T3 (n=72) were <2.3, 2.3-2.5 and >2.5 mg/dl, respectively. The differences in body cell mass index (BCMI) among T1, T2, and T3 were significant (5.7±1.9, 6.4±2.1, 6.6±2.2 kg/m^2, p<0.05), as were those in overhydration/extracellular water ratio (OH/ECW) (15.1±16.5, 7.1±11.1, 9.1±14.2%, p<0.01), but no significant differences were seen for the body mass index (20.2±5.3, 22.1±6.4, 20.3±4.9 kg/m^2), lean tissue index (11.2±2.6, 12.0±3.3, 12.1±3.0 kg/m^2), or fat tissue index (8.0±3.7, 9.1±4.4, 8.7±4.6 kg/m^2). T1 exhibited a significantly greater age (75±11, 73±12, 69±13 years), a shorter dialysis vintage, and lower normalized protein nitrogen appearance (nPNA), serum albumin (3.2±0.5, 3.3±0.4, 3.4±0.5 g/dl) and uric acid values (6.5±1.7, 6.9±1.4, 7.2±1.4 mg/dl) but higher C-reactive protein levels (1.4±2.4, 1.1±2.7, 0.9±1.9 mg/dl) compared with T2 and T3 (p<0.05). During the 3 years, 47 (21.9%) patients died. Three-year survival rates were 57.7% and 67.9% in T1 and T2+T3, respectively (p<0.05). Multivariate analyses included all significant variables in the univariate analyses showed that T1 was significantly associated with the BCMI [Odds ratio (OR) 0.83, 95% confidence interval (CI) 0.70-0.97] or OH/ECW [OR (95%CI): 1.03 (1.01-1.06)], respectively, independent of age, dialysis vintage, nPNA, serum albumin and uric acid levels (p<0.05).

Conclusions: Hypomagnesemia is associated with lower 3-year survival rate, and worse body composition parameters such as BCMI and OH/ECW, which reflect muscle depletion and overhydration, respectively, in MHD patients.

Funding: Private Foundation Support

TH-PO214

Hypomagnesemia May Not Cause Increased Mortality as Agent Provocateur in Maintenance Hemodialysis Patients

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Background: It is unclear whether hypomagnesemia causes increased mortality as agent provocateur or bystander in maintenance hemodialysis (MHD) patients. This study aimed to investigate the associations between hypomagnesemia and mortality, and to study the factors related to hypomagnesemia in MHD patients.

Methods: The subjects were 353 Japanese MHD patients. Laboratory parameters including the serum magnesium (Mg), coronary artery calcium score (CACS) and medication use were studied at baseline. The subjects were stratified into baseline Mg level quartiles (Q). Kaplan-Meier survival, Cox proportional hazards models for the factors associated with mortality and logistic regression analyses for Q1 were examined.

Results: Among all patients), the median age was 68 (60-78), 39.7% were diabetics, and the median dialysis vintage was 75 (32-151) months. The Mg values of Q1 (n=86), Q2 (n=97), Q3 (n=99), and Q4 (n=71) were <2.2, 2.2-2.4, 2.5-2.7, and >2.7 mg/dl, respectively. The patients in Q1 exhibited significantly lower serum albumin, phosphate, uric acid, fibroblast growth factor 23, Kt/V_{urea} and normalized protein nitrogen appearance (nPNA) levels (P<0.01), but significantly higher serum high sensitivity C-reactive protein (hsCRP) levels (P<0.05) than the patients in Q2-4. During the 3 years, 91 patients died. The 3-year cumulative survival rate was 54.4%, 70.3%, 84.3%, and 85.2% in Q1, Q2, Q3, and Q4, respectively (P<0.05), and 3-year cardiovascular (CV) mortality was also significantly higher in Q1/Q2 than in Q3/Q4 (P<0.05). The Q1 was significantly associated with 3-year all-cause mortality [Hazard ratio (HR) 2.09, 95% confidence interval (CI) 0.96-4.49, P<0.01] and 3-year CV mortality [HR (95%CI): 3.03 (1.02-8.84), P<0.05], independent of Log (CACS+1), age, dialysis vintage, serum hsCRP and uric acid but the significance was lost in the model which included serum albumin, nPNA and medication use. The most significant determinant of Q1 was serum albumin levels (g/dl) [Odds ratio (95% CI): 0.10 (0.02-0.37), p<0.01], and Q1 was not found to be related to CACS or medication use including sevelamer or proton pump inhibitor.

Conclusions: Hypomagnesemia per se may not cause increased 3-year all-cause and CV mortality as agent provocateur but associated with malnutrition in MHD patients.

Funding: Private Foundation Support

TH-PO215

The Influence of Age on PTH/Vitamin D Relationship in Non-dialytic CKD

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Background: Hypovitaminosis D is recognized as a worldwide epidemic. It is associated with elevation in parathormone (PTH), increasing the risk of fractures. Studies on general population have reported that the relationship between PTH and 25vitamin D (PTH/vitD) is influenced by aging. However, in chronic kidney disease (CKD) patients, the effect of on PTH/vitD remains unknown. This study aims to analyze the impact of age (≥ 65 years old) on PTH/vitD in non-dialytic CKD patients.

Methods: This is a cross-sectional study that analysed data from digital medical records of stage 3 CKD patients of outpatient Nephrology service of Hospital das Clínicas, Universidade de São Paulo. PTH/vitD was analyzed for the following categories: renal function, sex, furosemide and hydrochlorothiazide intake, serum calcium, oral cholecalciferol supplementation, phosphate binder and omeprazole.

Results: 1178 patients (506 women and 672 men) with glomerular filtration rate (GFR) = 44.03 ± 8.74 mL/min/1.73m2 were analyzed. Elderly and women accounted for 57 and 48.7% of total patients, respectively. PTH/vitD was higher in women [2.81(1.79-4.18) vs. 2.5 (1.6-3.97), p<0.0001], elderly [2.83(1.91-4.38) vs. 2.33 (1.54-3.61); p<0.0001], CKD stage 3b [2.9 (1.95-4.55) vs. 2.34 (1.49-3.52), p<0.0001], furosemide [3.48 (2.22-5.58) vs. 2.5 (1.59-3.69), p<0.0001] and cholecalciferol users [2.9 (1.82-4.44) vs. 2.46 (1.57-3.55), p<0.0001]; and lower in hydrochlorothiazide users [2.54 (1.6-3.66) vs. 2.7 (1.7-4.3), p = 0.018]. We did not find any association with phosphate binders or omeprazole. There was a correlation between PTH/vitD and serum calcium (r= -0.140; p <0.0001). The multivariate analysis revealed that PTH/vitD was dependent on eGFR, sex, furosemide intake, serum calcium and age.

Conclusions: Our data shows that, elderly patients with CKD present higher PTH levels when compared with young adults with similar eGFR, calcium and vitamin D levels. Prospective studies are required to determine whether cholecalciferol reposition has an impact on vitamin D and PTH levels in this population.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO216

Evaluation of Intact and Biointact PTH Assays in Chronic Hemodialysis Patients

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Background: Clinical management of chronic kidney disease - mineral and bone disorder is largely based on parathyroid hormone (PTH) concentrations, measured at regular intervals. The existence of PTH fragments, detected by first and second generation (“intact”) PTH (i-PTH) assays, led to the development of third generation (“biointact”) whole PTH (w-PTH) assays detecting only full length PTH. Despite efforts to use only w-PTH assays, i-PTH assays, which are usually less costly, are still being used and marketed, such that it may be indispensable to convert PTH values from one assay to another. We aimed at assessing the technical performance of a novel i-PTH assay, in comparison to 2 widely used w-PTH assays and to another i-PTH assay.

Methods: PTH levels of 134 patients on chronic hemodialysis were measured at 2 timepoints within 3 months, using: the novel new i-PTH assay by Siemens Healthcare (SH) and Roche Diagnostic (RD), respectively; the w-PTH assay by RD and DiaSorin (DS), respectively. All concentrations were measured in pg/ml by automated analyzers: Advia Centaur CP (SH), Cobas e 602 (RD) and Liaison XL (DS). Statistical methods included Passing-Bablok regression analyses and Bland Altmann plots.

Results: The i-PTH SH was slightly higher calibrated than i-PTH RD. Compared with w-PTH assays, the i-PTH SH assay yielded 2.5-fold higher results, while i-PTH RD was about 2-fold higher. Among the w-PTH(1-84) assays a rather good concordance was observed, with a mean bias of 12 ± 45.6 pg/mL (±2 SD) by Bland Altmann plots. In contrast, there was a substantial bias of -88.7 ± 183.4 pg/mL between the two iPTH assays (RD minus SH).

Conclusions: The table provided above enables method conversions, which are of interest, if a laboratory switches the assay or if a patient changes the treatment center.

Funding: Commercial Support - Simens Healthcare

Y =	intercept [pg/ml]	+	slope	* X	r
i-PTH SH =	-7.2	+	1.32	* i-PTH RD	0.99
i-PTH SH =	-23.8	+	2.50	* w-PTH RD	0.97
i-PTH SH =	4.6	+	2.47	* w-PTH DS	0.96
i-PTH RD =	5.5	+	0.76	* i-PTH SH	0.99
i-PTH RD =	-13.2	+	1.90	* w-PTH RD	0.98
i-PTH RD =	6.9	+	1.89	* w-PTH DS	0.98
w-PTH RD =	9.5	+	0.40	* i-PTH SH	0.97
w-PTH RD =	6.9	+	0.52	* i-PTH RD	0.98
w-PTH RD =	13.8	+	0.99	* w-PTH DS	0.99
w-PTH DS =	-1.9	+	0.40	* i-PTH SH	0.96
w-PTH DS =	-3,7	+	0.53	* i-PTH RD	0.96
w-PTH DS =	-14.0	+	1.01	* w-PTH RD	0.99

TH-PO217

Peritoneal Dialysis Mineral Metabolism Disorders: Results from the BRAZPDII

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Background: Few studies evaluate mineral and bone disorders (MBD) in patients treated with peritoneal dialysis (PD), and the main guideline guiding their treatment were based on studies performed in patients treated with hemodialysis. BRAZPDII is a cohort of patients from 114 dialysis centers in Brazil, which contains data from 9.905 patients on peritoneal dialysis. We analyzed biochemical markers related to MBD (calcium (Ca), phosphorus (P) and parathormone (PTH)), categorized patients in accordance with the targets proposed guideline Kidney Disease: Improving Global Outcomes (KDIGO), and

compared the survival index between the groups which maintained the biochemical markers within or without the normal ranges

Methods: We recruited 844 patients from BRAZPDII, who had MBD biomarker data, and followed them up for 24 months. Cox proporcional was used to eliminate potencial variable confounders, and Kaplan-Meier estimator was used to compare the survival rate between the groups.

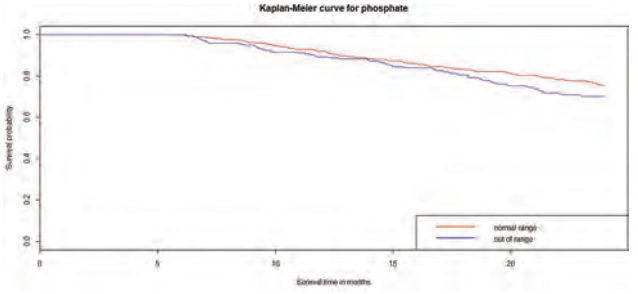
Results: Patients with Ca and P within the normal range using KDIGO definitions (8.4-10.2mg/dL and 3.5-5.5mg/dL, respectively) were associated with lower mortality (p<0.05; HR 1.63 and 1.79, respectively). PTH levels were not associated with mortality, regardless of the ranges proposed by KDIGO guideline (150-600).

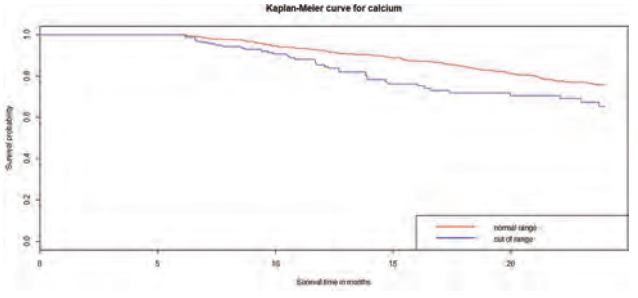
Conclusions: Keeping calcium and phosphate within the range as suggested by KDIGO was associated with lower mortality in PD patients. PTH levels were not associated with mortality risks.

Funding: Commercial Support - Baxter

Relative risk of mortality and biochemical parameters out of range (KDIGO)

Biochemical parameter	HR	95% CI	p-value
Calcium	1.63	1.12-2.38	0.01
Phosphate	1.79	1.26-2.54	0.001
PTH	0.99	0.99-1.00	0.56





TH-PO218

Hypoparathyroidism and Malnutrition – Two Sides of the Same Coin?

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Background: Chronic kidney disease-mineral and bone disorder has been recognized as a risk factor for dialysis patients survival. Clinical guidelines identify secondary hyperparathyroidism (SHPT) as the main target for therapeutic measures leaving aside the low level of parathyroid hormone (PTH). We used data from Czech Registry of dialysis patients (RDP) to analyze occurence of hypoparathyroidism in incident hemodialysis patients and its association with clinical outcomes.

Methods: In RDP we found 4878 patients who started dialysis from 2012 to 2015. Data of 576 patients treated by hemodialysis (HD) and 2615 patients treated by hemodiafiltration (HDF) were examined using multivariable regression, log-rank test and Cox survival models. Patients treated by peritoneal dialysis and patients with incomplete data were excluded. Laboratory values are recorded in RDP every 3 months in all patients, for analysis we used their respective mean values over entire follow-up.

Results: Mean follow-up of 3191 patients was 1394 days, 3-years survival 71% in all patients, 74% in HDF and 55% in HD subgroups. Mean age of patients was 65.3 years, proportion of diabetics 45%. Mean PTH < 150 pg/ml was found in 31.8% of patients, PTH 150-600 pg/ml in 64.4% and PTH > 600 pg/ml in 3.8% patients. We merged patients with PTH > 150 pg/ml into single group and compared all variables between subgroups with discriminating value of PTH 150 pg/ml (low PTH vs high PTH). Low PTH was associated with lower BMI, lower albumin and phosphate level, higher age and Kt/V. 3-years survival was significantly better in high PTH group, 65% vs 74%, this association was preserved after adjustment for mean serum calcium, phosphate, Kt/V, dialysis method (HD vs HDF), age, BMI and diagnosis of diabetes. The difference in survival between low and high PTH group dissapeared after adjustment for serum albumin. The same proportion of patients treated with phosphate binders was found in both groups. Proportion of patients treated with PTH-lowering drugs (cinacalcet, paricalcitol, calcitriol) was significantly lower in low PTH group.

Conclusions: In our study one third of incident dialysis patients have low PTH which was associated with decreased survival. Low PTH behaves as a marker of malnutrion not related to diabetes and treatment of SHPT. Whether therapeutic measures increasing PTH translate into better patient outcome warrants prospective studies.

TH-PO219

Factors Affecting Progressive Vascular Calcification in Hemodialysis Patients

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Background: It is known that patients who have done dialysis due to end stage renal disease have progressive vascular calcification, and that the more severe it is, the more frequent the occurrence and resulting death of cardiovascular disease. But so far very little is known about the causes of progressive vascular calcification. We aimed to investigate the risk factors for progressive abdominal aortic calcification in patients doing hemodialysis.

Methods: We conducted cross-sectional study of 281 subjects at six centers who agreed to this study and underwent lateral lumbar radiography. Kauppila score was used to measure abdominal aortic calcification, and progressive vascular calcification was defined as a median vascular calcification score of 7 or more. Radiographs of the lateral lumbar spine were analyzed by two staff members and the identities of the Kauppila scores between the two were 91%.

Results: The mean age of the 281 hemodialysis patients was 62.7 years, and 250 patients (89%) had calcification. The distribution of the abdominal aortic calcification score was 49.5% in 0-6, 28.5% in 7-12, 17.1% in 13-18, and 5% in 19-24. The risk factors for progressive vascular calcification were Kt / V (OR 8.2, 95% CI 2.39-28.1), cardiovascular disease (OR 2.54, 95% CI 1.27-5.06), DM (OR 2.38, 95% CI 1.21-4.68), age (OR 1.05, 95% CI 1.03-1.08), serum Ca (OR 1.63 1.13-2.34), total CO2 (OR 1.15, 95% CI 1.04-1.27), serum Na (OR 0.86 95% CI 0.79-0.93) and serum chloride (OR 0.88, 95% CI 0.82-0.94).

Conclusions: Several factors were associated with progressive vascular calcification. Further longitudinal studies are needed to determine the association of these factors with progressive vascular calcification.

TH-PO220

Trabecular Bone Score May Manifest as CKD-Mineral and Bone Disorder (CKD-MBD) Phenotype Reciprocal to Major Cardiovascular Outcome

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Background: In general population, trabecular bone score (TBS) represents bone microarchitecture and predicts fracture risk independent of bone mineral density (BMD). A few studies reported that TBS is significantly reduced in dialysis patients. Chronic kidney disease-mineral and bone disorder (CKD-MBD) are accompanied by increased fracture risk and cardiovascular morbidity and mortality. We investigated whether TBS is associated with comorbidity related to CKD-MBD or frailty in hemodialysis patients.

Methods: In this cross-sectional study, TBS was obtained using the TBS iNsight software program (Med-Imaps) with BMD dual energy x-ray absorptiometry (DXA) images (L1–L4) from prevalent hemodialysis patients. For frailty evaluation, Tilburg frailty indicator was used. Hand grip test and bio-impedance (InBody) were measured. Patient generated subjective global assessment (PG-SGA) was measured as nutritional assessment. History of major adverse cardiovascular event (MACE) was collected. Demographic, clinical, laboratory and biomarker data were also collected.

Results: Total 57 patients were enrolled. Mean age of population was 56.8 ± 15.9 years old. Female was 50.9%. Diabetes mellitus (DM) was 40.4% and MACE was prevalent in 36.8 %. Mean TBS value was 1.44 ± 0.10. TBS was significantly reduced in MACE group (1.48 ± 0.10 vs. 1.38 ± 0.08, p<0.01). Multivariable regression analysis was conducted adjusting age, sex, dialysis vintage, DM, MACE, phase angle and intact parathyroid hormone. Age (ß=-0.003; p<0.01) and MACE (ß =-0.053; p=0.02) were significant predictors of TBS. α-klotho neither showed any significant difference in MACE outcome (MACE vs. no MACE, 474.0 ± 370.0 pg/mL vs. 582.8 ± 740.1 pg/mL, p=0.54), nor association with TBS (r=-0.001, p=0.41). During the period of follow up after TBS measure (about 20 months), 4 deaths, 7 new onset fractures, and 6 new onset MACEs were recorded. Lower TBS was associated with mortality (p<0.05) or new onset fracture (p<0.01, by log-rank test).

Conclusions: TBS was associated with age and MACE in hemodialysis patients. TBS may manifest as phenotype of frailty, also may manifest as CKD-MBD phenotype reciprocal to MACE.

TH-PO221

Progression of Abdominal Aortic Calcification in Kidney Transplantation Recipients and Hemodialysis Patients

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Background: Vascular calcification is a critical complication of chronic kidney disease (CKD), and its mechanism is multifactorial. It has been reported that kidney transplantation (KT) may slow down the progression of vascular calcification along with the improvement of kidney function. However, there is a paucity of data about the comparison of the progression of vascular calcification between KT and hemodialysis (HD) patients. The aim of the present study is to compare the progression of abdominal aortic calcification between KT recipients and incident HD patients.

Methods: Ninety-one patients who underwent KT from January 2008 to January 2016 and 56 patients who initiated hemodialysis from December 2012 to June 2014 in our institutes were included in this study. We assessed the abdominal aortic calcification index (ACI) using a non-contrast computed tomography. The timing of assessment of the baseline and follow-up ACI was as follows; KT group: at the time of KT and at 1~2 years after KT, incident HD group: at the time of HD initiaion and at 1 year after HD initiation, respectively. The progression of ACI (ΔACI (%/year)) was calculated and compared between KT recipients and incident HD patients.

Results: The KT group included 17 pre-emptive KT (PKT) recipients (Living donor; n= 17, Deceased donor; n= 0) and 74 non-PKT recipients (Living donor; n= 69, Deceased donor; n= 5). The dialysis vintage was 51.2±55.6 months in the KT group. The KT group had significantly lower ΔACI compared to the incident HD group. Even after excluding the patients with pre ACI=0 (KT; n=34, incident HD; n=4), its relationship remained significant among the two groups. The baseline characteristics showed that the incident HD group had significantly higher prevalence of diabetes mellitus (DM) and higher age and body mass index (BMI) compared to the KT group. After adjustment for these traditional risk factors for vascular calcification using a propensity score matching, baseline ACI was comparable among the two groups, but the KT group had significantly lower ΔACI compared to the incident HD group.

Conclusions: Our findings suggest that KT slows the progression of ACI compared to HD initiation.

TH-PO222

Progression of Medial Arterial Calcification in CKD and ESRD

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Background: Medial arterial calcification, as distinguished from atherosclerotic calcification, is common in chronic kidney disease (CKD) and portends poor clinical outcomes, but its progression relative to the severity of CKD and the role of other risk factors is unknown. Calcification of breast arteries detected by mammography, a marker of generalized medial calcification, was used to measure progression in women with CKD and end-stage renal disease (ESRD).

Methods: Women with and without CKD were identified from a computerized search of medical records. Subjects with current warfarin use, which is associated with medial arterial calcification, were excluded. Estimated glomerular filtration rate (eGFR) was determined by the four-variable MDRD formula and ESRD was defined as chronic outpatient hemodialysis. The lengths of calcified segments of breast arteries on digital mammograms were summed and expressed as millimeters per breast. Results are presented as medians and interquartile ranges with analysis by the Mann-Whitney U or Kruskall-Wallis test.

Results: Progression of calcification was measured in 60 control subjects (estimated glomerular filtration rate (eGFR) ≥ 90 ml/min/1.73 m^2) and 137 subjects with CKD (eGFR <90 ml/min/1.73 m^2) divided into tertiles by eGFR (Table). Progression in control subjects was linear over time and independent of age. An increased rate of progression was observed only in the lowest CKD tertile (eGFR <40 ml/min/1.73 m^2), p=0.006. Progression accelerated markedly in ESRD (n=36), with a median of 20 mm/breast/y (7.4-51), p=0.006 vs CKD 3rd tertile. Diabetes significantly augmented progression in CKD (2-fold, p=0.029) and ESRD (4.4-fold, p=0.004) but not in the absence of CKD:4.0 (1.1-8.5) vs. 3.9 (0.7-7.8) mm/breast/y.

Conclusions: CKD is a risk factor for medial arterial calcification but only when advanced (eGFR < 40 ml/min/m^2). This is consistent with hyperphosphatemia rather than earlier derangements in mineral metabolism as a contributing factor. Progression is markedly accelerated in ESRD patients, suggesting the possibility of dialysis-specific effects. Diabetes is a significant risk factor in the presence of CKD or ESRD.

Funding: Clinical Revenue Support

eGFR (ml/min/1.73 m^2)	90-170	53-90	40-52	6-39
Age	77.0 ± 1.0	74.4 ± 1.2	78.3 ± 1.0	73.4 ± 1.5
Diabetes (%)	28	33	26	33
Δ BAC (mm/breast/y)	3.9 (0.7-8.0)	3.3 (0.3-6.2)	4.2 (0.3-10)	8.1 (2.4-23) *

* p = 0.006

TH-PO223

The Prognostic Value of Serum Galectin 3 to Abdominal Aortic Calcification Progression in Maintenance Hemodialysis Patients

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Background: Heterotopic vascular calcification is one of the complications of maintenance hemodialysis (MHD) patients contributed to adverse prognosis. Basic research results indicated the relation of Galectin-3 (Gal-3) with cardiovascular calcification. However whether serum Gal-3 is associated with uremic vascular calcification has not been investigated yet.

Methods: A prospective cohort study was performed. Eligible patients undergoing hemodialysis during July 2014 enrolled from Blood Purification Center of Ruijin Hospital were followed up for 3 years. Twice AAC assessment have been performed at the baseline and after 3-year follow-up respectively. Baseline laboratory measurement results, clinical data and blood samples were collected. Serum Gal-3 was detected by quantified ELISA kits. SPSS 23.0 and Medcalc 11.4.2.0 were used to analyze data.

Results: 152 patients were recruited. Mean Gal-3 concentration was 29.24±10.15ng/ml. All patients has finished first lateral lumbar X-ray examination and 104 patients finished repetitive examination 3 years later. Serum Gal-3 was positively associated with blood phosphonium, baseline abdominal aortic calcification score (AACS), andΔAACS of MHD patients. Logistic regression analysis indicated that serum Gal-3 was an independent risk factor to both severe AAC and AAC progression in 3 years. ROC analysis revealed a significant prognostic value of serum Gal-3 to severe AAC and AAC progression in 3 years. High serum Gal-3 was one of the characteristics of patients with rapid AAC progression.

Conclusions: Serum Gal-3 is a novel biomarker of vascular calcification in uremic patients. Our research first demonstrated that serum Gal-3 was a promising biomarker predicting severe AAC and AAC progression in 3years of MHD patients. Serum Gal-3 maybe a potential intervention target for vascular calcification of MHD patients.

Funding: Government Support - Non-U.S.

Table 1. Binary Logistic regression analysis of AAC progression after 3-year follow-up. Model 1: Adjusted by sex, age, dialysis vintage, ALB, ALP, TC, Ca, P, PTH, 25(OH)D, and Gal-3, Method: Forward LR; Model 2: Adjusted by sex, age, dialysis vintage, ALB, ALP, TC, Ca, P, PTH, 25(OH)D, and Gal-3 Tertiles, Method: Forward LR; Gal-3 T1: Gal-3≤23.94ng/ml, Gal-3 T2: 23.94<Gal-3≤33.19ng/ml, Gal-3 T3: Gal-3>33.19ng/ml.

Terms	Univariate			Model 1: AAC progression			Model 2: AAC progression		
(N=104)	OR (95%CI)	B	P	OR (95%CI)	B	P	OR (95%CI)	B	P
Male	1.113(0.509, 2.432)	0.107	0.789	-	-	NS	-	-	NS
Age	1.034(1.001, 1.011)	0.033	0.045	1.042(1.004, 1.081)	0.041	0.028	1.048(1.009, 1.089)	0.047	0.016
Dialysis vintage	1.003(0.995, 1.011)	0.003	0.433	-	-	NS	-	-	NS
ALB	0.853(0.729, 0.997)	-0.159	0.046	-	-	NS	-	-	NS
ALP	1.002(0.993, 1.011)	0.002	0.692	-	-	NS	-	-	NS
TC	0.987(0.692, 1.412)	-0.013	0.942	-	-	NS	-	-	NS
Ca	2.880(0.486, 17.050)	1.058	0.244	-	-	NS	-	-	NS
P	1.940(0.946, 3.975)	0.663	0.070	-	-	NS	-	-	NS
PTH	1.001(1.000,1.002)	0.001	0.109	1.001(1.000, 1.002)	0.001	0.035	1.001(1.000,1.002)	0.001	0.032
25(OH)D	1.000(0.988,1.013)	0.000	0.998	-	-	NS	-	-	NS
Gal-3	1.076(1.031, 1.122)	0.073	0.001	1.089(1.039, 1.140)	0.085	<0.001	/	/	/
Gal-3 Tertiles	-	-	<0.001	/	/	/	-	-	<0.001
T1	1.000(1.000,1.000)	-	-	/	/	/	1.000(1.000,1.000)	-	-
T2	5.881(1.950,17.738)	1.772	0.002	/	/	/	7.702(2.293,25.869)	2.042	0.001
T3	8.667(2.960,25.372)	2.159	<0.001	/	/	/	13.294(3.902,45.294)	2.587	<0.001

TH-PO224

Ankle-Brachial Index Predicts Vascular Calcification in Hemodialysis Patients with Severe Hyperparathyroidism

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Background: Vascular calcification, which is a common complication of secondary hyperparathyroidism (sHPT), is related with high mortality in chronic kidney disease (CKD) patients. Besides the increase of intact parathyroid hormone (iPTH), high levels of phosphorus induce phenotypic changes in vascular smooth muscle cells (VSMC) that differentiate on osteoblast-like cells causing calcification at the media of arterial wall. This study aims to correlate ankle-brachial index (ABI) with biochemical abnormalities and presence of vascular calcification on X-Ray exams.

Methods: We analyzed thirty hemodialysis (HD) patients over eighteen years of age and with iPTH higher than 1000pg/ml. All patients underwent an assessment of their clinical history, laboratory data and radiographic evaluation. ABI was measured by portable Doppler Medpej®DF 7001.

Results: The age was 44.8±8.7yo, 70% women, HD vintage 136.8±61.6 months, serum phosphorus 6.1±1.0mg/dl and iPTH 2883.7±1165.2pg/ml. 66% of patients had Adragão Score>3, 76% had arteriovenous fistula (AVF) calcification and 52% had lumbar aortic calcification. Adragão Score correlated with AVF calcification (r=0.5;p<0.01) and lumbar aorta (r=0.70;p<0.01). The ABI was 1.79±0.96 and correlated with Adragão score (r=0.54;p<0.01), AVF calcification (r=0.47;p<0,05) and phosphorus level (r=0.84;p<0.05). In sHPT evaluation, we routinely use a simple vascular calcification score on plain radiographic films of pelvis and hands (Adragão score). We verified significant correlation between this score compared to AVF and lumbar aortic calcifications. Moreover, ABI, a simple clinical tool performed at bedside, was strongly correlated with serum phosphorus, Adragão score and AVF calcification. All this findings corroborate with the role of phosphorus in osteoblastic differentiation of VSMC and vessel stiffness caused by media calcification.

Conclusions: We observed high prevalence of vascular calcification in hemodialysis patients with severe hyperparathyroidism using conventional image methods and the ABI was a practice tool for this diagnosis in this population.

Funding: Government Support - Non-U.S.

TH-PO225

Enarodustat (JTZ-951), an Oral HIF-PH Inhibitor, Elevates and Maintains Hemoglobin Levels over 30 Weeks in Japanese Anemic Patients with CKD Not on Dialysis

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Background: The dose response in Hb and safety of enarodustat administered for 6 weeks in anemic patients with CKD not on dialysis (ND-CKD) was assessed in a placebo-controlled, randomized, double-blind manner (period I). In addition, the maintenance dosage and safety of long-term treatment with enarodustat was assessed in an open-label manner for 24 weeks (period II).

Methods: ESA naïve subjects (G1) and subjects receiving a stable dose of ESAs (G2), who have protocol specified Hb criteria, were respectively randomized in 1:1:1:1 ratio to receive either enarodustat doses of 2, 4, 6 mg or placebo once daily. Subjects, who completed the period I and were eligible for the period II, received long-term treatment with enarodustat that was adjusted in the range of 2 to 8 mg to maintain Hb in a target range of 10.0-12.0. Use of IV iron was prohibited by the end of period I.

Results: The weekly Hb elevation rate in G1 was significantly increased with dose. In G2, the changes in Hb from baseline at endpoint were also increased with dose. In period II, the proportion of subjects who maintained Hb level within the target range at end of treatment in G1 and G2 were 71.4% and 83.1%, respectively. While Hb levels over the course of Period II stayed in a target range, more than 70% subjects experienced ≤ 1 dose adjustment during the period II. Median hepcidin and ferritin levels were decreased across all the enarodustat arms during period I in contrast with increase in TIBC levels. These parameters remained stable during period II. Enarodustat was generally well tolerated.

Conclusions: Enarodustat corrected and maintained Hb levels in anemic patients with ND-CKD with minimum dose adjustment requirement. Furthermore, better iron availability and utilization by enarodustat are suggested to be contributed to erythropoietic responses, which is expected to provide alternative and more physiologic treatment option to ESA for anemic patients with CKD. The efficacy and safety compared with ESA and long-term studies are being examined in phase 3 studies.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO226

Enarodustat (JTZ-951), an Oral HIF-PH Inhibitor, Maintains Hemoglobin Levels Switching from ESAs over 30 Weeks in Japanese Anemic Patients with CKD Receiving Maintenance Hemodialysis

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Background: The dose response in Hb and safety of enarodustat administered for 6 weeks was assessed in anemic patients with CKD receiving maintenance hemodialysis (HD-CKD) in a placebo-controlled, randomized, double-blind manner (period I). In addition, the maintenance dosage and safety of long-term treatment with enarodustat was assessed in an open-label manner for 24 weeks (period II).

Methods: Subjects, who have been receiving a stable dose of ESAs and have protocol specified Hb criteria, were randomized in 1:1:1:1 ratio to receive either enarodustat doses of 2, 4, 6 mg or placebo once daily and switched from ESAs. Subjects, who completed the period I and were eligible for the period II, received long-term treatment with enarodustat that was adjusted in the range of 2 to 8 mg to maintain Hb in a target range of 10.0-12.0. Use of IV iron was prohibited by the end of period I.

Results: In period I, the changes in Hb from baseline at endpoint were increased with dose. In period II, the proportion of subjects who maintained Hb level within the target range on Ext Week 24 and end of treatment were 70.9% and 65.1%, respectively. Beside Hb levels were within a target range, approximately 80% subjects experienced ≤ 2 dose adjustments during period II. Mean prescribed dose was 4.30 mg/day. Median hepcidin and ferritin levels were decreased across all the enarodustat arms during period I in contrast with increase in TIBC levels. These parameters remained stable during period II. Enarodustat was generally well tolerated.

Conclusions: Enarodustat maintained Hb levels in anemic patients with HD-CKD switching from ESAs with minimum dose adjustment requirement. Furthermore, iron availability and utilization by enarodustat are suggested to be contributed to erythropoietic responses, which is expected to provide alternative and more physiologic treatment option to ESA for anemic patients with CKD. The efficacy and safety compared with ESA and long-term studies are being examined in phase 3 studies.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO227

Efficacy and Safety of Daprodustat on Anemia Management in Japanese Hemodialysis Patients Not Using Erythropoiesis-Stimulating Agents

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Background: This Phase 3, open-label, non-comparative, multi-center study (funded by GlaxoSmithKline) examined the efficacy and safety of daprodustat (Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitor) over the 24 weeks in 28 Japanese hemodialysis (HD) subjects not using erythropoiesis stimulating agents (ESA).

Methods: Subjects on newly started dialysis or maintenance dialysis with hemoglobin (Hgb) of 8.0-<10.0 g/dL not using ESA were enrolled to receive daily oral daprodustat. After the first 4 weeks of the fixed starting dose of 4 mg, doses were adjusted monthly to achieve a Hgb target of 10.0–12.0 g/dL over the 24 weeks, utilizing doses ranging from 1-24 mg. The primary endpoint was to evaluate Hgb at Week 4. All subjects received the full ophthalmologic examinations (best corrected visual acuity, intraocular pressure, an anterior segment exam, and a fundoscopic exam) at baseline, Week 12 and the end of study.

Results: The mean baseline Hgb value was 9.10 g/dL. After the first 4 weeks, the mean change in Hgb from baseline was 0.79 g/dL (95%CI: 0.53, 1.05). No subjects experienced a rapid Hgb increase, defined as > 2 g/dL over the first 4 weeks. The mean Hgb value increased and reached the target range (10-12 g/dL) at Week 8 (10.76 g/dL), and was maintained within the target range at Week 24 (11.12 g/dL). At Week 24, 23 subjects (82%) had a Hgb value within the target range, and 18 (64%) subjects reached the lower target Hgb value without a dose adjustment. Ninety-two percentage of on-therapy AEs were reported as either mild or moderate in severity. There were no AEs leading to withdrawal/discontinuation of study treatment and no pre-defined ocular AEs of special interest were reported from the full ophthalmologic exam.

Conclusions: Daprodustat 4mg safely and effectively increased Hgb over the initial first 4 weeks of treatment. Daprodustat had an ability to achieve and maintain Hgb within target range and was generally well tolerated over the 24-week of treatment.

Funding: Commercial Support - GlaxoSmithKline

TH-PO228

Randomized, Placebo-Controlled Phase 2 Trials of Vadadustat, an Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI), to Treat Anemia of CKD

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Background: The HIF-PHI vadadustat (VDT) was investigated in two phase 2, randomized, double-blind, placebo-controlled trials in Japanese subjects with anemia due to non-dialysis-dependent (NDD) or dialysis-dependent (DD) CKD.

Methods: Trials consisted of a 6-wk fixed-dose, placebo-controlled, primary efficacy period and a 10-wk dose adjustment period. In each trial, subjects were randomized to VDT 150 mg, 300 mg, 600 mg, or placebo. After 6 wks, subjects randomized to placebo were switched to VDT, and all subjects had their dose adjusted according to Hb response. For the primary efficacy analysis in each study, an ANCOVA model was used in the MITT population to compare mean change in Hb from baseline to Wk 6 between the VDT and placebo groups. Last observation carried forward (LOCF) was used for missing Hb data.

Results: Fifty-one and 60 subjects were randomized in the NDD and DD studies, respectively. Mean changes in Hb from baseline to Wk 6 were statistically significant in all VDT treatment arms compared with placebo (Table). Treatment with VDT 300 mg or 600 mg was associated with statistically significant increases in total iron binding capacity and decreases in ferritin and hepcidin from baseline to Wk 6 compared with placebo (P<0.01). Incidence of AEs during the 6-wk period in the VDT groups (150 mg, 300 mg, 600 mg) and placebo was 33%, 58%, 54%, and 36% (NDD study) and 53%, 73%, 40%, and 40% (DD study). During the 16-wk treatment period and 2-wk follow-up, the most common AEs reported were hypertension and viral upper respiratory infection (NDD study) and nasopharyngitis, diarrhea, and headache (DD study). 13 SAEs in 11 subjects (NDD study) and 10 SAEs in 7 subjects (DD study) were reported. No deaths were reported.

Conclusions: These data support continued development of VDT for patients with renal anemia.

Funding: Commercial Support - Akebia Therapeutics, Inc.

Table. Changes in Hemoglobin (g/dL) Between Baseline and Week 6: Vadadustat vs Placebo

	NDD-CKD			DD-CKD		
	n	Mean Change, g/dL	P-value	*n*	Mean Change, g/dL	P-value
VDT 600 mg	12	1.62	<.0001	11	0.44	<.0001
VDT 300 mg	12	1.13	<.0001	13	0.08	<.0001
VDT 150 mg	13	0.43	0.0045	13	-0.28	0.0004
Placebo	14	-0.47	–	6	-1.48	–

TH-PO229

Effects of Dosing Frequency on the Efficiency of EPO Administration in Hemodialysis Patients

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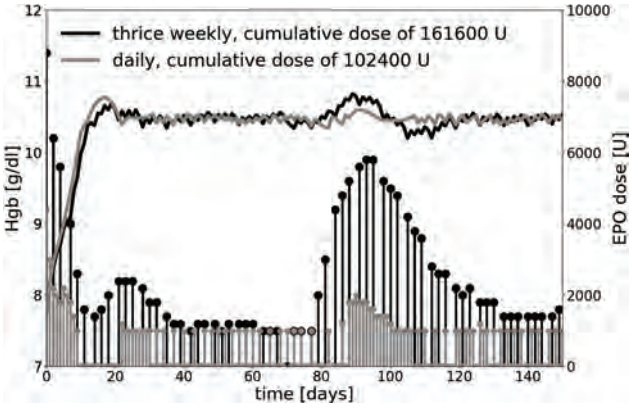
Background: Achieving target hemoglobin (Hgb) levels in hemodialysis (HD) patients treated with short-acting erythropoietin (EPO) is challenging. It is highly desirable to keep drug doses low to mitigate adverse events and to reduce costs. Based on a mathematical model of erythropoiesis we developed a model predictive control (MPC) algorithm for patient-level EPO dose optimization.

Methods: Using an individualized model of erythropoiesis (Fuertinger et al, PLoS ONE 2018) an MPC algorithm is designed for computation of EPO doses at predefined dosing frequencies. The MPC aims to stabilize Hgb levels at 10.5 g/dl. Hgb variability and total amount of administered EPO are compared in an in-silico study in 60 chronic HD patients over a period of 150 days for a thrice weekly versus a daily EPO administration regimen.

Results: Daily and thrice weekly administration maintain Hgb levels equally within the target Hgb range of 10-12 g/dl except one patient reaching the target range only via daily administration. Compared to thrice weekly EPO administration, the daily administration scheme reduces Hgb variability by 8.9% and lowers the cumulative EPO dose by 18.1%. Figure 1 shows the results obtained in a single patient.

Conclusions: Our analysis shows a clear potential for reducing the risk of adverse events and saving costs by increasing the EPO dosing frequency and thereby reducing the required amount of EPO to correct the patient's anemia. Clinical studies are warranted to validate these findings.



TH-PO230

Recombinant Erythropoietin Reduces Endothelium-Mediated Vasodilation in Patients with CKD – A Prospective Controlled Study

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Background: Recombinant erythropoietin (rhEPO) is used for the treatment of CKD-associated anaemia, despite the hypertension and cardiovascular risks. Postulated mechanisms include endothelial dysfunction. Given the emergence of non-rhEPO treatments, elucidating the vascular effects of rhEPO in CKD-associated anaemia is important for comparative studies with non-rhEPO treatments.

Methods: We conducted a single centre open-label prospective non-randomised matched-control study in pre-dialysis rhEPO-naïve patients with CKD (n=12) and matched-healthy controls (n=12) to assess the effect of rhEPO on endothelial function (NCT02987465). Forearm blood flow responses to intra-arterial acetylcholine (ACh endothelium-dependent vasodilator), noradrenaline (NA) and BQ123 (ETA receptor antagonist) were assessed using venous occlusion plethysmography in CKD patients before and 6-weeks after rhEPO and in controls at baseline. Blood pressure, blood parameters and aortic stiffness (carotid-femoral pulse-wave velocity PWV) were measured. The primary outcome was change in log-transformed forearm blood flow compared using mixed-effects ANOVA.

Results: Baseline characteristics were similar between CKD patients and controls (age±SD 65±16 vs 64±16 years, male 83% vs male 83%). Although median eGFR (16, IQR 13-25 vs 83, IQR 78-90 ml/min, p<0.001) and haemoglobin (Hb 97±11 g/L vs 140±9 g/L, p<0.001) were lower, mean arterial pressure (110±21 vs 92±9 mmHg, p=0.02) and PWV (11.5±4.8 vs 8.3±2.2 m/s, p=0.04) were higher in patients with CKD. Response to ACh did not differ significantly between CKD patients and controls at baseline. In the CKD group, rhEPO increased haemoglobin (Hb) to 110 ± 17g/L (p<0.001) after 6 weeks, and reduced endothelium-dependent vasodilation by 23% (95% CI, 5% to 40%, p=0.009). The response to BQ123 did not differ after rhEPO treatment (-5%, 95% CI, -13% to 2%, p=0.15), but there was a greater vasoconstrictor response to NA (10%, 95% CI, 2% to 17%, p=0.01). Blood pressure and arterial stiffness did not change significantly after rhEPO.

Conclusions: Endothelium-dependent vasodilation is impaired after rhEPO treatment in patients with CKD, and NA-induced vasoconstriction is enhanced, suggesting possible mechanisms for rhEPO-associated hypertension and adverse cardiovascular outcomes.

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TH-PO231

Erythropoietin Stimulating Agents (ESA) Hyporesponsiveness and Outcomes: Patient Characteristics and Major Adverse Cardiovascular Events (MACE)

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Background: Studies of ESA hyporesponsivness prior to 2011 showed increased morbidity and mortality potentially associated with high doses of ESA. US ESRD payment change (bundling), introduced in 2011, contributed to lower ESA use and lower targeted hemoglobin and may have altered the relationship of ESA hyporesponse to clinical outcomes.

Methods: Using the CROWNWEB clinical database from 2012-14, we characterised ESA hyporesponder patients (HR) on dialysis and, using inpatient diagnosis codes, evaluated rates of MACE in this population compared to ESA normoresponders (NR). MACE outcomes were modelled using negative binomial regressions. HR were identified using ESA resistance index (ERI) or dose; for epoetin alfa an ERI of ≥2.0 U/kg/wk/g/L or dose of ≥450 U/kg/wk was used.

Results: 119,742 patients met inclusion criteria; 43% (51,544) were classified as HR. At baseline, most were on hemodialysis (HD) (95.7% HR and 97.0% NR) and receiving epoetin alfa (97.0% HR and 95.6% NR); the mean dose (U/kg/wk) in the 2 months prior to index date was 336.0 in HR and 69.5 in NR. HR had a longer dialysis duration (5.7 vs. 4.9 years) and more comorbidities, with a Charlson Comorbidity Index of 3.8 vs. 3.2. Heart failure and coronary artery disease were more common in HR vs. NR, 47.8% vs. 36.3% and 41.1% vs. 35.0%, respectively. However, rates of T2DM were similar (51.5% in HR vs. 53.9% in NR). Over one year of follow up, 23% of patients died (24.1% HR vs. 22.6% NR). MACE and thromboembolic event-related hospitalizations were significantly higher for HR vs. NR (0.14 vs. 0.09 hospitalizations per patient-month). Non-adjusted and adjusted models for MACE incidence rate ratio comparing HR vs. NR are presented in the table below.

Conclusions: Our analysis showed ESA HR and NR have similar one year mortality rates despite epoetin alfa doses 4.8 times higher in HR. However, ESA hyporesponsivness was associated with increased risk of MACE and thromboembolic event related hospitalizations.

Funding: Commercial Support - GlaxoSmithKline

MACE event model results

	Unadjusted model HR vs. NR		Adjusted model HR vs. NR	
Hospitalizations related to:	Incidence rate ratio	(95% CI) p-value	Incidence rate ratio	(95% CI) p-value
Heart-failure	1.58	(1.55; 1.62) < 0.001	1.38	(1.36; 1.41) < 0.001
Myocardial infarction	1.27	(1.22; 1.33) < 0.001	1.16	(1.11; 1.22) < 0.001
Stroke	1.29	(1.24; 1.35) < 0.001	1.21	(1.16; 1.26) < 0.001
Thromboembolic event	1.63	(1.56; 1.70) < 0.001	1.37	(1.31; 1.43) < 0.001

TH-PO232

Effects of Erythropoietin-Stimulating Agents on Blood Pressure in Patients with Non-Dialysis CKD and Renal Anemia

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Background: Erythropoietin-stimulating agents (ESAs) are widely used for treating renal anemia in patients with non-dialysis chronic kidney disease (CKD). Elevation of blood pressure (BP) is an adverse event of ESA treatment. Rigorous BP control has an important role in managing and treating non-dialysis CKD. Therefore, investigating the effects of ESA treatment on BP is important. This randomized, open-label, parallel-group, controlled study investigated that the effects of two main long-acting ESAs (continuous erythropoietin receptor activator [CERA] and darbepoetin alfa [DA]) on office BP and the ambulatory BP profile in 36 patients with non-dialysis CKD and renal anemia. We also examined the relationships of ESAs with progression of CKD and CVD events.

Methods: Participants were randomly assigned to receive CERA or DA treatment. The doses of ESAs were adjusted to maintain hemoglobin levels within the target range of 10–12 g/dL. In both groups, the antihypertensive therapy was aimed at achieving the target office BP. The primary outcomes were office BP and the ambulatory BP profile at 24 weeks after randomization.

Results: Hemoglobin levels of the two groups were within the target range at 24 weeks after randomization. There were no significant differences in office BP and the ambulatory BP profile, including short-term BP variability, between the CERA and DA groups. Although

some patients required an increase in antihypertensive agents in the CERA and DA groups, the rate of these patients was comparable between the two groups. ESA treatment did not increase BP in both groups. There were no significant differences in vascular function, renal function, and the urinary protein/creatinine ratio between the CERA and DA groups.

Conclusions: Our results suggest that CERA and DA have similar effects on BP in patients with non-dialysis CKD and renal anemia. ESAs can improve anemia without worsening the BP profile with adequate use of antihypertensive agents.

TH-PO233

Real-World Experience with C.E.R.A. in Pediatric Dialysis Patients Fits Modeling-Based Predictions: Results from the IPDN Registries

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Background: The International Pediatric Dialysis Network (IPDN, www.pedpd.org) maintains two global registries with children on chronic peritoneal dialysis (IPPN) and hemodialysis (IPHN). We compared registry data to PK/PD modeling and simulation results to validate the modeling approach for Continuous Erythropoiesis Receptor Activator (C.E.R.A.) in children and to examine the use of C.E.R.A. in pediatric patients (pts).

Methods: Among a total of 3225 (IPPN) and 673 (IPHN) pts registered by April 2018 with at least one update, 126 (IPPN) and 32 (IPHN) pts received C.E.R.A. sc (IPPN) or iv (IPHN) and were included in a retrospective assessment of pts characteristics, efficacy (Hb, ferritin) and safety (hospitalization in past 6 months). A model-based evaluation of clinical trial data was conducted in parallel. Subsequent prospective simulations in pediatric pts were performed, i.e. without adjusting for baseline characteristics of IPDN pts.

Results: The mean age (SD) of pts at last visit was 12.0 (6.4; IPPN) yrs and 14.2 (5.3; IPHN) yrs. With median [Q1;Q3] monthly doses (µg/kg body weight) of 3.0 [2.2;4.9] for IPPN and 1.7 [1.1;3.0] for IPHN, mean (SD) Hb levels (g/dL) were 10.8 (1.7; IPPN) and 10.5 (1.8; IPHN). Mean (SD) ferritin levels (µg/L) were 264 (289; IPPN) and 499 (3339; IPHN). In pts with longitudinal follow-up, Hb and ferritin levels were stable during C.E.R.A. treatment. The most common causes of 132 (IPPN) and 41 (IPHN) reported hospitalizations were hypertension and peritonitis (n=19, both) in IPPN and hypertension (n=7) and pyelonephritis (n=5) in IPHN. Results of prospective simulations were in excellent accordance with observed IPDN data: simulated mean [95% CI] Hb levels (g/dL) were 10.9 [10.5;11.3] for sc and 11.0 [10.6;11.3] for iv. Simulated median [95% CI] doses (µg/kg every 4 weeks) after Hb stabilization were 2.7 [2.0;3.9] for sc and 2.3 [1.6;3.2] for iv.

Conclusions: The real-world outcomes regarding steady state C.E.R.A. doses and Hb responses confirm simulations based on models developed with adult and pediatric clinical trial data. With C.E.R.A. the Hb and ferritin levels were within clinical target ranges in peritoneal and hemodialysis settings. No new safety signals were observed.

Funding: Commercial Support - Baxter, Fresenius Medical Care

TH-PO234

Simultaneous Dosing of Iron and ESA Using Model Predictive Control (MPC)

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Background: Advances have been made to assist the dosing of erythropoietic stimulating agents (ESA) beyond the use of a "paper protocol". These methods have been dependent on either assuming that iron stores are replete or that a separate iron dosing protocol is followed. Since ESA response is influenced by the iron status and changes as patients become iron replete, it would be beneficial to perform these dosing procedures in parallel. We tested the hypothesis that we could develop a MPC algorithm for the simultaneous dosing of both ESA and iron.

Methods: ESA dose prediction was performed using our previously published work (J Am Soc Nephrol 25:159-66 2014). Dose determination is based on an estimate of the red blood cell life span, sensitivity to the ESA and dose of ESA. Further, a close-loop design was used to "feed back" the error between observed and desired Hb. A second MPC model was developed for Iron dosing that determines the dose of iron based on baseline ferritin, iron and Tsat sensitivity to iron administration based on our previously published model (Clin J Am Soc Nephrol 5:576-81, 2010). The current model was developed in Matlab/Simulink. We simulated several iron deficient states with ferritin between 80 and 120 with ESA sensitivity values from 0.1 to 2.0. Simulations were performed to determine the impact of iron supplementation on ESA dose.

Results: The results of the simulations are shown in the following table where the effect of simultaneous iron dosing on total ESA dose is shown. Total iron administered was independent of ESA dosing in this simulation and resulted in 10,000, 8,000 and 4,000 mg over 2 years for ferritins of 80, 100, and 120, respectively.

Conclusions: We simulated the effect of concurrent ESA and iron dosing in ESRD using advanced computational approach. The algorithm optimizes both, ESA and iron dose. Further work needs to be performed on the dynamics of the response during all phases of iron repletion and in the face of elevated ferritin levels due to inflammation.

Funding: NIDDK Support

Total ESA dosed over 2 years when model preforms iron dosing (Iron Dosed) or does not (No Iron Dosed)

Iron Dosed	Ferr=80	Ferr=100	Ferr=120	No Iron Dosed	Ferr=80	Ferr=100	Ferr=120
K=0.1	6455	6975	6925	K=0.1	8435	7830	7240
K=0.5	1805	2000	1905	K=0.5	5715	2240	2000
K=1.0	935	1030	980	K=1.0	3060	1170	1045
K=2.0	475	550	495	K=2.0	1565	595	535

TH-PO235

Effects of Targeting 11 to 13 g/dL of Hb on Renal Outcome in Non-Diabetic Patients with Advanced CKD: A Randomized Control Study, PREDICT

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Background: Anemia, a common complication of chronic kidney disease (CKD) is associated with high mortality. Target hemoglobin (Hb) levels using erythropoiesis stimulating agent for CKD remain controversial between 10 and 12g/dL, especially in non-diabetic patients with CKD.

Methods: The open-label randomized controlled trial, PREDICT, aims to study the impact of targeting Hb levels of 11–13 g/dL using darbepoetin alfa with reference to a low Hb target of 9–11 g/dL. The primary outcome is a renal composite endpoint (starting chronic dialysis, kidney transplantation, eGFR 6 mL/min/1.73m^2 or less, and 50% decrease in eGFR).

Results: The study enrolled 479 non-diabetic Japanese patients with eGFR 8–20 mL/min/1.73m^2. Of the 479 patients evaluated, 239 were assigned to maintain high Hb and 240 were assigned to maintain low Hb. Mean Hb level reached at 11.0g/dL at 16 week in high Hb group and maintained at 11.1g/dl during the study, while it was maintained at 10.0 g/dL in low Hb group. Mean doses of darbepoetin alfa in high and low Hb groups were 317 and 185µg/12 weeks, respectively. The renal composite endpoint occurred 105 (43.9%) in high Hb group and 116 (48.3%) in low Hb group (p=0.315 for log-rank test, Cox HR 0.78, p=0.075). Mean GFR reduction rate from baseline was significantly lower in high Hb group than in low Hb group at 24 week (-3.1 vs -11.0 %, p=0.001), 48 week (-11.0 vs -17.6 %, p=0.016), and 72 week (-9.34 vs -18.3%, p=0.024). Cardiovascular events occurred in 19 patients (7.9%) assigned to high Hb group and in 16 patients (6.7%) to low Hb group (HR 1.07, p=0.841). All cause death occurred 14 patients (5.9%) in high Hb group and 11 patients (4.6%) in low Hb group (HR 1.28, p=0.561).

Conclusions: Maintaining Hb at 11-13g/dL compared with Hb 9-11 g/dL by use of darbepoetin alfa did not improve renal outcome in patients with advanced CKD without diabetes, while it did not exacerbate cardiovascular outcome or all cause death. (ClinicalTrials.gov No. NCT01581073).

Funding: Private Foundation Support

TH-PO236

Effect of Epoetin on Cardiovascular Disease in Patients Who Initiate Dialysis

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Background: Anemia is a common complication in chronic kidney disease (CKD) patients and is a risk factor for increasing the incidence of cardiovascular disease (CVD). Epoetin used to treat these anemia has also been shown to increase CVD incidence in CKD patients. However, the risk of CVD of Epoetin use in dialysis patients has not yet been determined.

Methods: Data were collected from a prospective observational study in Clinical Research Center for ESRD (CRC-ESRD) registry. A total of 857 patients were enrolled in this study, all of whom received Epoetin and were enrolled in the registry at initiation of dialysis. The relationship between the incidence and mortality of CVD and Epoetin dose was analyzed. The patients were divided into groups by median hemoglobin (Hb) value and dialysis modality, and were analyzed.

Results: A mean dose of Epoetin was 4454.2±5114.0 IU/week. Median Hb level was 10.7g/dL and mean Hb level was 10.9±1.1 g/dL. There was no difference in Hb levels between hemodialysis (HD) patients and peritoneal dialysis (PD) patients. However, Epoetin dose was 4850.1±5370.5 IU/week in HD patients, which was significantly higher than 2753.2±3335.7 IU/week in PD patients (p<0.001). In the low Hb group, the mean Hb was 10.1±0.6 g/dL and the epoetin dose was 6206.2±5651.5 U/week. In the high Hg group,

the mean Hb was 11.7±0.8 g/dL and the epoetin dose was 2732.1±3811.8 IU/week. Hb level and epoetin dose were significantly different between the two groups. The dose of Epoetin has a correlation with CVD event in HD patients ($p<0.001$), but not in PD patients ($p>0.05$). The incidence of CVD was 77 cases in the low Hb group which is significantly high than 49 cases in the high Hb group ($p=0.003$). The Epoetin dose and CVD incidence were related in low Hb and high Hb group, respectively (each $p<0.05$). The CVD mortality was also associated with Epoetin dose in HD patients ($p=0.009$).

Conclusions: Epoetin dose is associated with CVD incidence and mortality in patients who initially initiate hemodialysis.

TH-PO237

Renal Outcome by Different Target Hemoglobin Levels Using Epoetin Beta Pegol in Predialysis CKD Patients with ESA Hyporesponsiveness: A Multicenter Open-Label Randomized Controlled Study (RADIANCE-CKD)

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Background: Although ESA hyporesponsiveness has emerged with respect to a poor renal and overall survival in CKD patients, appropriate ESA treatments to patients with ESA hyporesponsiveness remain uncertain.

Methods: We randomly assigned 362 predialysis CKD patients with ESA hyporesponsiveness to the intensive treatment group (target hemoglobin [Hb] level ≧ 11g/dl) and conservative treatment group (target Hb level; baseline Hb levels ± 1g/dl) using epoetin beta pegol (CERA). The primary renal composite endpoint was a transition to renal replacement therapy, a reduction of eGFR to less than 6ml/min/1.73m2 or a reduction of eGFR more than 30%. The observation period was 21 months from the assignment.

Results: Mean age was 74.7 years and 58.6% were male. Mean baseline eGFR in the intensive and conservative groups were 15.3 and 15.9ml/min/1.73m2, respectively. Mean baseline hemoglobin level was similar of 9.9g/dl in both groups despite an appropriate and similar median dose of ESA (86 and 100 μg/month for CERA, P 0.913; 120 and 80 μg/month for darbepoetin alfa, P 0.136, respectively). Mean Hb levels during observation period in each group were 10.44 and 10.05 g/dl ($P < 0.0001$) and median doses of CERA were 120.0 and 96.3 μg/month, respectively ($P < 0.0001$). Kaplan-Meier analysis showed no significant difference in the primary end point between the two groups (99 and 109 events; log-rank test, P 0.837). Cox proportional hazards analysis also showed no significant difference between the two groups (Hazard ratio, 0.972; 95% confidence interval, 0.74 to 1.28; $P = 0.84$. The incidence of cardiovascular events (CVEs) was not different in both groups [20 (10.9%) and 24 (13.4%) patients, respectively (P 0.522)]. Heart failure accounted for approximately 65% of CVEs in both groups.

Conclusions: Although there was no significant difference in renal outcome, our results suggest that targeting Hb level of 11g/dl or higher using CERA may be safe in terms of CVEs in predialysis Japanese CKD patients with ESA hyporesponsiveness. This study is funded by Chugai Pharmaceutical Co., Ltd.

Funding: Commercial Support - Chugai Pharmaceutical Co., Ltd.

TH-PO238

The Pursuit of a More Physiologic Iron and ESA Treatment: Results from a Triferic and Individualized ESA Protocol QA Project

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Background: We implemented a new standard of care (SOC) anemia protocol using a web-based tool that individualizes Aranesp treatments and uses Triferic for iron supplementation. The objective was to observe changes in anemia parameters.

Methods: A QA project was conducted in a single hemodialysis (HD) clinic in 6/16-4/18: the standard bi-weekly Aranesp protocol and Venofer (phase A), Triferic replacing Venofer (phase B, 2 months "washout"+6 months), a new web-based weekly Aranesp dose titration tool and Triferic (phase C, 2 months "washout"+6 months). Target Hgb range was 9-11 g/dL with means 10 and 10.2 in phases A-B and C, respectively, and Tsat>30%. Monthly stats included patients who *received at least one Aranesp dose during the recent 3-months period.* We compared clinic-level monthly means for anemia related variables corresponding to standard SOC (6 months prior to phase B) and phases B and C using ANOVA with repeated measures and Cuzick's nonparametric test for trend.

Results: A total of 105 patients were treated at the clinic during the 3 project phases. Monthly totals varied due to transfers, transplantation, and death (11, 10.5%). Demographics mean (SD) age 61.6 (15.4) years, 52 female (50%), 35 Latino (33%), 25 (24%) white, 20 (19%) black, 6 (6%) Asian, and 19 (18%) unknown. Anemia results for each phase are shown in Figure 1. Hgb means increased with the higher target mean; mean ferritin levels were significantly lower in phase C vs phase A or phase B ($p<0.001$); Tsat levels modestly decreased compared to phase A but remained on target; and mean Aranesp and mean total iron (Venofer and/or Triferic) were lower but statistically similar across protocols.

Conclusions: A more frequent dosing schedule, which integrates Triferic for iron management with a web-based tool for individualized Aranesp treatments, performed better than a standard anemia protocol in HD patients. Patients were more likely to have Hgb in the target range or higher, lower but not significantly different dosages of Aranesp and total iron, reduced Ferritin levels and maintain Tsat levels on target.

Funding: Commercial Support - Rockwell Medical Inc.

Variables	Phase A	Phase B	Phase C	Cuzick's Trend Test	ANOVA	A=B	A=C	B=C
	mean (SD)	mean (SD)	mean (SD)	p-value	p-value	p-value	p-value	p-value
Sample Size	45.5 (2.8)	62.3 (3.6)	57.5 (2.7)					
Hgb (g/dL)	9.8 (0.2)	10.0 (0.3)	10.3 (0.1)	0.006	0.006	0.02	<0.001	0.006
< 9 (%)	16.1	13.8	10.9					
[9, 11] (%)	75.5	71.2	68.1	0.26	0.23	0.29	0.08	0.44
> 11 (%)	8.3	15.0	21.0					
Tsat (%)	36.2 (3.5)	30.0 (4.1)	30.9 (2.2)	0.04	0.02	0.002	0.005	0.54
Ferritin (ng/mL)	1005 (45)	919 (53)	730 (44)	<0.001	<0.001	0.004	<0.001	<0.001
Aranesp (mcg)	105 (18.7)	113.6 (17.6)	95.2 (12.0)	0.45	0.27	0.40	0.39	0.11
Total Iron (mg)	175.6 (42.5)	143.5 (55.7)	146.1 (37.1)	0.26	0.29	0.16	0.20	0.91

TH-PO239

Intravenous Ferric Carboxymaltose Is Efficacious and Safe in Management of Iron Deficiency Anemia Among Hemodialysis Patients

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Background: Anemia has a high prevalence among hemodialysis patients. Therapy mainly includes erythropoietin (EPO) and iron supplementation. Ferric carboxymaltose is a recent intravenous iron that proved to be efficacious among nondialysis CKD patients with no data regarding its use among dialysis patients. The aim of this study is to assess the efficacy and safety of Ferric carboxymaltose among hemodialysis patients.

Methods: In this prospective randomized study, 104 patients on maintenance hemodialysis were recruited. Inclusion criteria included: anemia (hemoglobin less than 10 gm/dL) and inadequate iron status (ferritin level < 200 mg/dL and TSAT < 20%). Exclusion criteria included: patient received other forms of iron within the last 4 weeks or a patient has recent blood loss event. Patients were randomized to receive either intravenous Ferric carboxymaltose (once weekly)or Iron *Sucrose* (three times weekly). Hemoglobin hematocrit, ferritin, and TSAT were recorded at baseline and after 4 and 8 weeks. The dose of EPO was kept the same as before the study for patients already on EPO and on a fixed initial EPO dose for naive patients. Adverse effects including pain at injection site, allergy, fever were documented. ANOVA test was performed to compare the means of hemoglobin and iron studies. Chi x2 test was performed to compare the frequency of adverse effects between the two groups. Linear regression analysis was done to assess the likelihood of response to IV Ferric carboxymaltose.

Results: The mean age of patients was 56.4 ± 12.2 years. Female patients were 46%. In the Ferric carboxymaltose group, the mean ferritin increased from 148 ± 34 to 634 ± 154 ng/mL (95% CI: -527.07 to -444.92, p. value < 0.001). in Iron *Sucrose* group, mean ferritin increased from 134 ± 42 to 596 ± 112 ng/mL (95% CI: -491.8 to -432.12; p-value < 0.001). There was no significant difference in the increase in both ferritin and TSAT between the two groups. In addition, There was no difference in the frequency of adverse effects among the two groups.

Conclusions: Intravenous Ferric carboxymaltose is efficacious in restoring iron repletion with tolerable adverse effects.

TH-PO240

Real World Experience: A Conversion of Haemodialysis Patients from Iron Sucrose to Iron Isomaltoside

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Background: Anaemia is common in haemodialysis (HD) patients, and associated with significant morbidity and mortality. Intravenous (IV) iron combined with erythropoietin (EPO) is the mainstay treatment of anaemia in these patients. Iron isomaltoside 100, 5% (Diafer) is the newest IV iron available to HD patients in the UK. **Objective:** To assess the efficacy and safety of converting patients from iron sucrose (IS) to iron isomaltoside (IIM).

Methods: The clinical notes of 880 HD patients were retrospectively reviewed for the period between September 2015 - April 2017. 633 were prescribed IIM of which 97 patients made a direct switch from IS to IIM. Haemoglobin (Hb), ferritin (FER), transferrin saturation (TSAT), and EPO dose were collected 1 month before conversion (T-1), month of first IIM dose (T0), 6 (T6) and 12 (T12) months post conversion. ANOVA or Friedman tests were used for statistical analyses with post-hoc adjustment for multiple comparisons using T0 as control.

Results: Differences in clinical variables are shown in the table. There was a statistically significant effect on Hb over time although after converting (T0), there was no significant change at 6 or 12 months. There were significant improvements in ferritin and TSAT over time, which remained at 6 months for both ($P<0.01$) and at 12 months for TSAT ($P<0.05$). There was an overall decrease in weekly iron dose that was significant at 12 months ($P=0.02$) and no change in EPO dose. In total there were 28,125 prescriptions of IIM and 8,145 of IS with no difference in reported adverse events during the audit period (6 each, none required adrenaline).

Conclusions: Hb, TSAT and FER were maintained at satisfactory levels for at least 12 months post-conversion, indicating that the drugs have similar efficacy with no difference in reported adverse events.

	T -1	T0	T6	T12	P value
Hb (g/L) (M / SD)	108.5±13.7	112±13.7	114.3±12.2	111.7±10.9	<.01
Ferritin (ug/L) (mdn / IQR)	305 (204-398)	288 (204-404)	374 (255-490)	338 (220-447)	0.01
TSAT (%) (mdn / IQR)	21.5 (16-28)	20 (15-27)	25.5 (19-34)	24 (16-32)	<.001
Weekly Fe dose (mg) (mdn / IQR)	50 (50-100)	50 (50-50)	50 (25-100)	50 (25-50)	<.001
Weekly EPO dose (U) (mdn / IQR)	9000 (4000-12000)	9000 (4000-12000)	6000 (3000-12000)	8000 (3000-12000)	0.4

TH-PO241

When It Comes to Intravenous Iron, More or Less, Outcomes Are Same

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Background: Intravenous (IV) iron supplementation is required in the management of anemia in most chronic hemodialysis patients. Although iron supplementation will replete iron stores and provide available iron to maximize effectiveness of erythropoietin stimulating agents (ESAs), it is a potent oxidant and known for having several potentially toxic side effects including worsening of infections and iron overload. Thus, lower doses of iron would be preferable, provided anemia is adequately managed and ESA requirements are not increased as a result.

Methods: In a single hemodialysis unit of 48 male veterans, we prospectively treated patients with standard dosing of IV sodium ferric gluconate (loading dose: 1000mg when transferrin saturation (Tsat) <20% and/or ferritin <100 μg/L or maintenance dose: 500mg when Tsat 20-50% and ferritin 100-800 μg/L), to maintain a hemoglobin (hb) level of 10-11 g/dL. Iron loading dose was 125mg IV with each dialysis treatment X 8 doses and maintenance dose was 125mg IV weekly X 4 weeks. The subsequent six months, iron dosing was reduced by half, and all other treatments were continued per protocol. Hb and iron parameters were assessed throughout the treatment periods, along with dosing requirements of erythropoietin and iron.

Results: There were no differences seen in the hb and iron profile during the standard vs reduced dosing periods, hb (mean 10.46 g/dL SD 1.57 vs mean 10.41 g/dL SD 1.39, p=0.72), Tsat (mean 22.83% SD 11.99 vs mean 24.76% SD 12.69, p=0.086) and ferritin (mean 565 μg/L SD 410 vs mean 606 μg/L SD 419, p=0.11). During the 6 month standard dosing period, 19.1% of the patients received IV iron and 23.8% during the reduced dosing period. The average amount of iron administered was 126.6mg/month in the standard dosing group and 51.2mg/month in the reduced dosing group. Erythropoietin dosage was similar during the two periods: 16,517 units/week (SD 8413) vs 14,064 units/week (SD 8612) respectively, p=0.055, however, more patients required erythropoietin treatment (32.8% vs 52.4%).

Conclusions: In our study population, iron stores were equally maintained during the standard dosing compared to a 50% reduction in IV iron administration, but more patients required ESA therapy. Implementation of a lower dosing IV iron regimen may mitigate potential adverse effects of iron supplementation without effecting iron stores.

TH-PO242

Risk of Infection Post Intravenous Iron Therapy in Patients with Anemia of CKD

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Background: The use of intravenous (IV) iron therapy has escalated in the treatment of anemia of chronic kidney disease (CKD) in order to optimize hemoglobin outcomes with the use of erythropoiesis-stimulating agents. The risk of infection associated with IV iron administration in patients with non-dialysis-dependent CKD has not been well defined. The purpose of this study was to investigate the risk of infection in patients with non-dialysis-dependent CKD who have received IV iron versus those patients who have not received IV iron within 3 months post index date.

Methods: This was a retrospective cohort, single center study of patients receiving care at the VA San Diego Healthcare System. Patients were included if they were enrolled in an outpatient CKD clinic from January 1, 2014 to June 1, 2017. Patients were excluded if they had end stage renal disease, active infection, or had an active prescription for immunosuppression therapy. The treatment arm included patients who had received at least one dose of IV iron for treatment of anemia of CKD. The control arm included patients enrolled in CKD clinic who did not receive IV iron during the study period. Control patients were matched to the treatment arm patients in a 3:1 ratio based on the season of their index date. Infection was defined as prescription of IV or PO antibiotic within 3 months post index date. Chi square test was performed to determine statistical significance for our primary outcome.

Results: 33 out of the 411 (8.0%) control patients and 22 out of the 136 (16.2%) IV iron patients developed at least one infection over the course of 3 months after the index date (p=0.006). CKD patients who received IV iron where twice as likely to develop an infection versus CKD patients who did not receive IV iron (OR=2.21, 95% CI 1.2-3.9).

Conclusions: This study provides support that the use of IV iron is associated with increased infection risk in the non-dialysis-dependent CKD population. This study however is limited in the ability to account for all baseline confounding variables between our study populations as it is retrospective in nature. A prospective study will be imperative to further investigate this increased risk of infections associated with IV iron therapy. Thoughtful consideration of the risks and benefits are warranted in prescribing IV iron for the treatment of iron deficiency anemia in CKD.

TH-PO243

Effect of Intravenous Ferumoxytol on Serial Platelet Counts in CKD Patients with Iron Deficiency Anemia

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Background: Iron deficiency often leads to reactive thrombocytosis; theoretically, its correction should lead to a lowering of the platelet count (PLT). Only a few studies have investigated this aspect, with some showing a reduction in PLT, whereas others did not. We investigated the effect of iron repletion with intravenous (IV) ferumoxytol (Fm) on serial PLT counts in CKD patients with iron deficiency anemia (IDA).

Methods: We conducted a retrospective chart review, including all patients with CKD and IDA who were treated with IV ferumoxytol at our medical center during a 24-month period. Patient demographics were recorded, as were baseline laboratory values for creatinine, eGFR, hemoglobin (Hgb), hematocrit (HCT), iron, transferrin saturation, ferritin and PLT. The serial counts for Hgb, HCT and PLT continued to be recorded at 1, 2, 3, 4, 6, 8, 12 and 16 weeks after the Fm dose. If data was unavailable at the exact time point, the nearest date was used if within a week.

Results: A total of 264 doses of IV ferumoxytol (each 510 mg) were given in 119 patients with age 57±13 years, Creatinine 3.1±1.5 mg/dL, eGFR 26±12 mL/min, Hgb 10.2±1.3 g/dL, T-sat 16.5±6 % and PLT 242±85. All CKD stages were represented in the study sample. Hgb and Fe stores improved post-dose. The change in post-dose PLT over time is depicted in the table below. In fact, PLT were reduced compared to baseline throughout the 16-week period of follow-up, reaching statistical significance at weeks 3, 6, 8, 12 and 16.

Conclusions: Correction of iron deficiency significantly lowered PLT in CKD patients with IDA who received IV ferumoxytol. This finding stands in contrast to some previous evidence that PLT counts were not significantly reduced with IV iron dextran used as total dose infusion. Our findings may help guide choice of IV iron therapy, given the possibility that increased PLT in the short-term post-dose period may contribute to the thrombotic events noted in clinical trials of erythropoiesis stimulating agents in CKD patients.

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	Week 16
N	264.00	51.00	56.00	45.00	54.00	79.00	108.00	130.00	121.00
PLT	241.73	218.16	219.73	200.44	220.28	208.19	217.15	212.66	222.43
SD	85.20	71.71	68.52	95.61	104.40	88.35	61.11	61.49	76.67
P-value vs baseline		0.06	0.07	0.00	0.11	0.00	0.01	0.00	0.03

TH-PO244

Once Daily versus Twice Daily Oral Iron for Iron Repletion in CKD: A Randomized, Controlled, Open Label Trial

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Background: In healthy individuals, the amount of iron absorbed with once daily (OD) dosing has been shown to be as good as with twice daily (BD) dosing despite double cumulative dose with BD dosing. Increase in serum hepcidin impairs absorption from subsequent dose when multiple doses are given. Oral iron supplementation, given as divided daily doses, is commonly prescribed in pre-dialysis CKD as iron deficiency and anemia are common. Therefore, in view of recent findings of impaired iron absorption with multiple daily dosing in normal individuals, we decided to compare iron repletion by OD versus BD oral iron dosing in subjects with stage G3-4 CKD and iron deficiency. The primary objective was difference in change in % transferrin saturation (%TS) between groups over 12 weeks. The main secondary objectives were differences in change in serum ferritin and blood hemoglobin over 12 weeks.

Methods: In this open label, randomized, controlled trial (CTRI/2017/02/007799 at ctri.nic.in), stable adult subjects with CKD stage G3-4 and iron deficiency (%TS <30 % and serum ferritin <500 ng/ml) were randomized (1:1) to receive tablets of ferrous ascorbate (equivalent to 100 mg elemental iron) in either OD (one tablet daily, total 100 mg) or BD (one tablet twice daily, total 200 mg) dosage. Hemoglobin <9 g/dL, iron use in last 3 months, previous gastrointestinal disease, bleeding or use of anti-acid drugs were exclusion criteria. Repeated measure ANOVA was used to assess change in % TSAT and serum ferritin over 2, 6 and 12 weeks in either dosage group and test the interaction of dosage form with change in % TSAT and serum ferritin in study population.

Results: Out of 328 screened subjects, 80 were enrolled. At baseline, the groups were similar except for higher hemoglobin and eGFR in the OD group. In both groups, there were significant effects (increase) of the dosage group on % TS and serum ferritin. However, there were no interaction between the dosage group and change in %TS [Wilks' Lambda=0.951, F (3, 222) = 1.359, p=0.258] or change in serum ferritin [Wilks' Lambda=0.916, F (2.533, 187.450) = 2.666, p=0.059] or change in hemoglobin. Interestingly, there was significant interaction of dosage group with change in MCHC with significant rise in OD group ($p < 0.001$).

Conclusions: Iron incorporation in hemoglobin might be better with OD dosing.

Funding: Government Support - Non-U.S.

TH-PO245

Effect of Oral Ferric Maltol on Iron Parameters in Patients with CKD and Varying Degrees of Inflammation; A Randomized, Controlled Trial

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Background: The incidence of anemia increases with the severity or stage of CKD. Further, some patients with CKD have chronic inflammation, which can reduce the absorption and utilization of iron, including that from oral ferrous iron products. Alternative intravenous iron administration can be inconvenient and has the risk of allergic reactions or iron overload. Patients with CKD and iron-deficiency anemia (IDA) would benefit from an oral iron replacement therapy that is effective irrespective of the degree of underlying inflammation.

Methods: In this phase 3, multicenter, randomized, controlled trial (NCT02968368), patients aged ≥18 years with CKD (estimated glomerular filtration rate ≥15 to <60 mL/min/1.73 m²) and IDA were randomized 2:1 to ferric maltol or placebo orally 30 mg twice daily for 16 weeks. IDA was defined as hemoglobin ≥8.0 g/dL to <11.0 g/dL, and either ferritin <250 µg/L with transferrin saturation (TSAT) <25% or ferritin <500 µg/L with TSAT <15%. Changes in iron storage indices were assessed at weeks 4, 8, and 16 for different levels of high-sensitivity C-reactive protein (hsCRP).

Results: 111 patients were randomized to ferric maltol and 56 to placebo. In the intent-to-treat population (last observation carried forward), the mean change in ferritin from baseline to week 16 for ferric maltol vs placebo was 25.32 vs –3.67 µg/L for those with hsCRP <1 mg/L, 32.54 vs –3.88 µg/L for those with hsCRP ≥1 to ≤3 mg/L, and 23.78 vs –12.87 µg/L for those with hsCRP >3 mg/dL. Corresponding changes in TSAT concentrations from baseline to week 16 were 3.95% vs –1.89% in ferric maltol recipients vs placebo recipients with hsCRP <1 mg/L, 3.31% vs –0.12% in those with hsCRP ≥1 to ≤3 mg/L, and 3.86% vs –0.97% in those with hsCRP >3 mg/dL.

Conclusions: Ferric maltol improved iron parameters – ferritin and TSAT – from baseline to week 16 vs placebo in patients with IDA and CKD irrespective of the degree of chronic inflammation.

Funding: Commercial Support - Shield Therapeutics Ltd

TH-PO246

Effect of Oral Iron on Serum Hepcidin and Erythroferrone in CKD Patients

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Background: Hepcidin regulates iron metabolism by blocking iron egress from iron-handling cells. Erythroferrone (ERFE) is a hormone that is stimulated by erythropoietin and directly inhibits hepcidin production. Despite the key role of both hormones in iron metabolism, little is known about the change in hepcidin and ERFE in response to oral iron in CKD patients.

Methods: A total of 24 patients with stage 3b-4 CKD and iron deficiency were randomized to take either ferric citrate (FC;n=12, 2 gms tid with meals) or ferrous sulfate (FS;n=12, 325 mg tid) for 12 weeks. Follow-up visits were done 2, 6 and 12 weeks after baseline, at which time serum samples were collected to measure hepcidin and ERFE. Linear mixed models were used to examine changes in hepcidin and ERFE overtime and whether this differed by treatment arm.

Results: There were no significant differences in baseline characteristics by treatment arm [Figure1]. Serum TSAT and ferritin increased by 10% and 37%, respectively, in the FC arm and 0.1% and 6%, respectively, in the FS arm after 12 weeks. The change in serum hepcidin differed by randomization arm (P=0.03). Hepcidin concentrations significantly increased in participants taking FC but not those taking FS [Figure2]. There was no significant change in serum ERFE over time in either group.

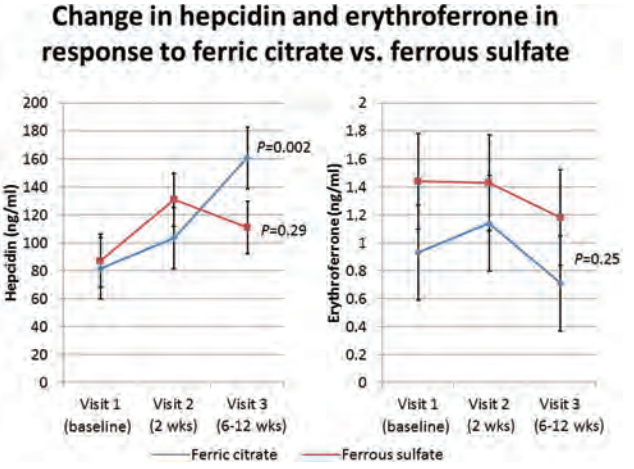
Conclusions: Treatment with FC, but not FS, increased serum hepcidin in CKD patients. Neither drug significantly changed ERFE.

Funding: Commercial Support - Keryx Biopharmaceuticals

Table: Baseline characteristics

	Ferric citrate	Ferrous Sulfate	*P*
N	12	12	
Age, years	60.2 (12.2)	62.0 (11.8)	0.71
Male sex, N (%)	4 (33)	5 (42)	0.67
Black race, N (%)	7 (58)	5 (42)	0.41
eGFR, ml/min/1.73m²	29.8 (11.5)	22.9 (8.5)	0.11
% saturation	18.3 (5.1)	16.5 (6.4)	0.48
Ferritin, ng/ml	116.5 (87.1)	76.4 (36.2)	0.16
Hemoglobin, g/dL	11.4 (1.2)	10.8 (1.3)	0.26
Hepcidin, ng/ml	81.7 (61.2)	87.3 (47.9)	0.80
Erythroferrone, ng/ml	0.93 (1.43)	1.44 (1.26)	0.36

Results shown as mean (SD) or N (frequency)



TH-PO247

Oral Iron Administration (OIA) Transiently Increased Serum Malondialdehyde Modified Low-Density Lipoprotein (MDA-LDL) and Non-Transferrin Bound Iron (NTBI) in Hemodialysis (HD) Patients

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Background: Intravenous iron administration may increase NTBI which appears in iron overload and cause organ damage through free radical production. OIA is not considered to increase NTBI because of slow iron adsorption rate. Aim of this study is to assess the kinetics of transferrin saturation(TSAT), NTBI and MDA-LDL in HD patients after OIA.

Methods: 16 HD patients without any iron load within 4 weeks, whose Hb<12g/dl, ferritin<100ng/ml and CRP<1.0mg/dl and 8 healthy volunteers were enrolled. Both groups received oral ferrous sulfate 105mg. We evaluated the following markers before and at 1,2,3,4 and 48 hours(hrs) after OIA : MDA-LDL, NTBI, Hepcidin-25(HPC), serum iron(Fe), TSAT, ferritin and standard hematological parameters. Vitamin C(VC) and selenium(Se) were measured before and 48hrs. Other 9 HD patients without OIA were also enrolled as HD control. MDA-LDL was measured by ELISA. NTBI was measured by recently described reliable method(Clin Chim Acta437:129-135, 2014).

Results: 1. Fe before OIA was 30(24-49)µg/dl and significantly increased at 1hr and reached the peak level of 272(104-320)µg/dl at 4hrs (medians(interquartile range)). 2. MDA-LDL before OIA was 97(68-124)U/L and significantly increased to 116(73-166)U/L at 1hr and reached the peak level of 121(81-165)U/L at 3hrs and decreased to 117(79-134) U/L at 48hrs, not significantly different from the level before OIA. 3. TSAT before OIA was 12(7-17)% and significantly increased at 2hrs, reached the peak level of 70(34-80)% at 4hrs. 4. NTBI before OIA was 0.02(0-0.10)µM and significantly increased to 0.15(0.03-0.56) µM at 4hrs. 5. HPC before OIA was very low (0.55(0.14-1.78)ng/ml) and unchanged during 48hrs. 6. In healthy and HD controls Fe, MDA-LDL, TSAT, NTBI and HPC were not significantly changed during 48hrs. 7. VC before OIA in HD patients was 3.0(1.8-6.2) mg/ml and significantly lower than that in healthy volunteers (7.7(6.5-10.7) mg/ml). 8. Se before OIA in HD patients was 14.5(12.5-16.1) mg/dl and significantly lower than that in healthy volunteers (18.4(17.6-20.3) mg/dl).

Conclusions: Fe and MDA-LDL at 1hr, TSAT at 2hrs, and NTBI at 4hrs significantly increased after OIA in HD patients. The lower anti-oxidant level in HD patients may influence the early increase of MDA-LDL.

Funding: Private Foundation Support

TH-PO248

Economic Burden of Anemia-Related Transfusions in Medicare Dialysis Patients

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Background: Red blood cell transfusions are unwanted outcomes of poor anemia management, and remain important enough that Medicare has instituted a quality measure to ensure adequate care of dialysis patients. Previous studies investigated the burden of transfusions in Medicare dialysis patients, but did not investigate anemia-related transfusions (in the absence of another acute medical indication), or costs of inpatient transfusions due to anemia. We estimated Medicare spending for both inpatient and outpatient transfusions administered solely to manage anemia.

Methods: We used the USRDS dataset to analyze patients receiving dialysis in 2014. We included Medicare Parts A/B patients on dialysis at the beginning of 2014 and those initiating dialysis during 2014. Transfusions were identified using an algorithm requiring

ICD-9 procedure and/or revenue center codes. We identified hospitalizations with 0- or 1-day stays with anemia as the principal diagnosis and no evidence of another reason for the hospitalization based on other diagnosis, procedure, and DRG codes. We identified outpatient, emergency department (ED), and observation (Obs) stays that appeared to be solely for transfusions. We calculated associated total Medicare paid costs by identifying costs directly associated with the transfusion and related costs for screening or monitoring in the pre- (day -3 to day -1) and post- (day 1 to day 3) period, and post-transfusion-related complications.

Results: We identified 9669 transfusions associated with anemia in the absence of other acute illness: 974 inpatient, 1264 ED/Obs, 7431 other outpatient. Total Medicare payments for these transfusions were $13.78 million: $7.37 million inpatient, $1.47 million ED/Obs, $4.95 million other outpatient. Inpatient transfusions accounted for 10% of total anemia-related transfusions, but for over 50% of total transfusion costs.

Conclusions: Costs related to anemia-induced transfusions are substantial. Savings can be potentially achieved by more closely following anemia treatment guidelines, and using outpatient settings in lieu of more expensive care settings.

Funding: Commercial Support - Amgen

Setting for Transfusions	N	Transfusion Costs	Related Costs	Total Costs	Costs per Transfusion
Inpatient	974	$7,362,817	$4,271	$7,367,088	$7,564
ED/Obs	1,264	$1,451,228	$15,392	$1,466,620	$1,160
Other outpatient	7,431	$4,741,086	$206,339	$4,947,425	$666
Total	9,669	$13,555,131	$226,002	$13,781,133	$1,425

TH-PO249

Anemia Treatment Patterns in CKD: Results from Three International Surveys Among Physicians

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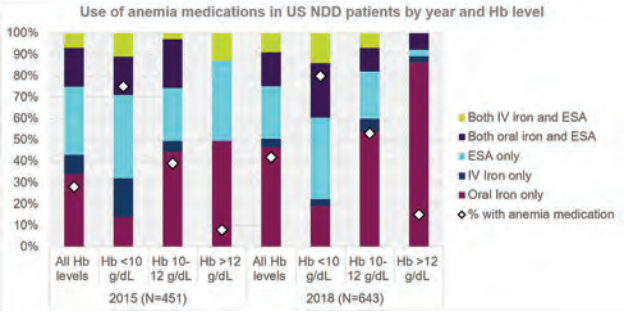
Background: Patients with chronic kidney disease (CKD) are at risk of developing anemia. We describe the use of anemia medications, internationally and in the US, by year, by Hb level and across CKD stages.

Methods: Data were drawn from the 2012, 2015 & 2018 Adelphi CKD Disease Specific Programmes. The real-world, point in time surveys included data from physicians (mostly nephrologists) and a random sample of their CKD patients across France, Germany, Italy, Spain, United Kingdom (EU5; included in 2012 and 2015), US (all years) and China (2015 only). Disease and treatment information, including oral iron, IV iron and erythropoiesis-stimulating agents (ESAs), was provided by the physicians and was analyzed descriptively. Blood transfusions were not considered.

Results: Data were available from 5488 non-dialysis (NDD) and 3490 dialysis (DD) patients (1350 and 1255 from the US, respectively). The overall prevalence across regions of Hb<10 g/dL was 8%, 7%, 15%, 20%, and 19% in patients CKD stage 3a, 3b, 4, 5 and dialysis, respectively, which increased slightly over time. Across regions, these patients were more likely to be treated for anemia in higher CKD stages. Although treatment rates varied by practice type, the overall proportion of US patients prescribed anemia medication increased to 42% of NDD patients (and varied by Hb levels; **figure**) and 80% of DD patients in 2018. The proportional use of ESAs in US NDD patients decreased from 75% to 49%, yet was stable in DD patients. In 2015, proportional ESA use in NDD patients was higher in EU5 countries than in the US.

Conclusions: CKD-anemia is most often treated in DD patients. Medication rates in NDD patients increased over time, yet anemia prevalence also increased, suggesting that anemia management can be optimized.

Funding: Commercial Support - AstraZeneca



TH-PO250

Associations of Hemoglobin Levels and Quality of Life in Patients with CKD: Pooled Results from Three International Surveys

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Background: Anemia is a common comorbidity in patients with chronic kidney disease (CKD), which can affect patients' quality of life (QoL). The current study aims to determine the burden of anemia in CKD, by analyzing patients' QoL by CKD stage and hemoglobin (Hb) levels.

Methods: Data were drawn from the 2012, 2015 & 2018 Adelphi CKD Disease Specific Programmes. The real-world, point in time surveys included data from physicians and a random sample of their CKD patients across France, Germany, Italy, Spain, United Kingdom (EU5), USA and China. Data were pooled to create a large cross-sectional dataset. Patient demographics, disease characteristics and concomitant conditions were provided by the physicians. Patients completed the Kidney Disease Quality of Life Instrument (KDQOL), including the short form 12 (SF-12), and the EuroQol Visual Analog Scale (EQ VAS). Multivariable analyses were performed on SF-12 and EQ VAS scores, adjusting for age, sex, CKD stage, common comorbidities and CV risk.

Results: KDQOL and EQ VAS results were available for 2781 and 2789 NDD patients and 1749-1726 DD patients, respectively. As CKD stage increased, patients' QoL deteriorated across all KDQOL domains. In the total population, lower Hb levels were associated with lower KDQOL and EQ VAS scores (Table). This association was also apparent within CKD stages. Adjusted analyses showed statistically significant positive associations between Hb level and the SF-12 physical and mental summary scales as well as EQ VAS scores (all $p<0.001$), which were numerically strongest in patients not on dialysis.

Conclusions: This study revealed a consistent relation between lower Hb level and deteriorated QoL, which was significant when adjusted for potential confounding factors. Anemia should be recognized as a contributing factor to lower QoL in patients with CKD.

Funding: Commercial Support - AstraZeneca

	Non-dialysis patients			Dialysis patients		
QoL outcomes (mean, SD)	*Hb <10 g/dL*	*Hb 10-12 g/dL*	*Hb >12 g/dL*	*Hb <10 g/dL*	*Hb 10-12 g/dL*	*Hb >12 g/dL*
Symptoms/problems	74.8 (19.3)	79 (17.9)	85.4 (15.6)	73.5 (18.7)	76.2 (17.5)	79.4 (14.9)
Effect of kidney disease	70.0 (20.1)	72.5 (20.2)	79.4 (18.3)	60.4 (20.9)	62.2 (21.9)	67.6 (18.3)
Burden of kidney disease	48.6 (28.6)	55.9 (27.5)	65.3 (26.1)	38.3 (25.9)	40.8 (27.4)	40.5 (24.3)
SF-12 physical summary score	37.9 (9.7)	40.3 (9.4)	43.8 (9.7)	35.2 (9.4)	37.6 (9.7)	38.6 (9.7)
SF-12 mental summary score	44.3 (10.2)	45.7 (9.5)	48.7 (9.3)	43.7 (10.5)	45.2 (10.4)	47.3 (9.4)
EQ VAS score	63.0 (17.9)	66.4 (16.7)	71.9 (15.8)	58.4 (19.4)	60.7 (19.6)	62.9 (18.7)

TH-PO251

Incidence, Prevalence, and Correlates of Anemia and Iron Deficiency in US Veterans with Non-Dialysis Dependent CKD (NDD-CKD)

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Background: Anemia in CKD is often multifactorial, including from low erythropoietin production, absolute (true) iron deficiency, and functional iron deficiency related to a chronic inflammatory state. However, there is limited evidence regarding the incidence, prevalence, and correlates of anemia and iron deficiency in NDD-CKD, which is the objective of this study.

Methods: We identified persons with NDD-CKD receiving care through the Veterans Affairs healthcare system from 2005-2015. Eligible patients had ≥2 eGFRs <60ml/min/1.73m^2 separate by >90 days and a Hgb measured within 180 days of the 2nd measured eGFR. We calculated incidence and prevalence of anemia (Hgb<12g/dl), characterized concurrent iron parameters (iron deficiency: absolute, transferrin saturation [TSAT] ≤20% and ferritin <100ng/ml; functional, TSAT ≤20% and ferritin ≥100ng/ml), and identified correlates of iron deficiency status using logistic regression.

Results: We included 944,175 persons with NDD-CKD and measured Hgb. At incident eGFR <60, 78.4% were non-anemic, 16.9% had mild (Hgb 10-<12g/dl), 4% moderate (Hgb 8-<10g/dl), and 0.6% severe anemia (Hgb <8g/dl). Incidence of anemia among 686,649 at-risk patients was 110.3 (95%CI; 109.9-110.7) per 1000 patient years. Iron parameter measurement varied with presence and severity of anemia: the proportion with both transferrin saturation and ferritin varied from 37.1% in the severely anemic, to 5.2% among those without anemia (Table). In the multivariable analysis, the only significant predictor of absolute iron deficiency anemia was prior GI bleed, and there were no significant predictors of functional iron deficiency.

Conclusions: One in five patients had anemia at CKD diagnosis; among those without it, 11 of 100 developed it for each year of follow-up. Prevalence of both absolute and functional iron deficiency increased with severity of anemia at incident CKD. Outcomes associated with absolute and functional iron deficiency anemia merit further studies.

Funding: Commercial Support - Keryx

Table. Iron parameters, by anemia severity, among persons with NDD-CKD and iron panel measurement.

No anemia (Hgb ≥ 12g/dl)				
Ferritin (ng/ml)	Transferrin saturation ≤ 20%	20 - 25%	25 - 30%	> 30%
≤ 100	22.9	10.9	7.3	8.5
100 - 200	7.8	6.5	5.3	7.5
> 200	4.8	4.8	4.6	9.2
Mild anemia (Hgb 10 to < 12g/dl)				
Ferritin (ng/ml)	Transferrin saturation ≤ 20%	20 - 25%	25 - 30%	> 30%
≤ 100	31.5	7.6	4.0	4.0
100 - 200	11.2	5.5	3.6	3.8
> 200	10.1	6.1	4.7	7.9

Moderate anemia (Hgb 8 to < 10g/dl)				
Ferritin (ng/ml)	Transferrin saturation ≤ 20%	20 - 25%	25 - 30%	> 30%
≤ 100	34.1	3.5	2.0	2.5
100 - 200	12.0	3.4	2.2	2.3
> 200	16.4	6.9	4.8	9.7
Severe anemia (Hgb < 8g/dl)				
Ferritin (ng/ml)	Transferrin saturation ≤ 20%	20 - 25%	25 - 30%	> 30%
≤ 100	35.0	2.3	0.9	2.1
100 - 200	7.4	2.5	1.4	1.5
> 200	21.7	5.5	4.1	15.6

Cell contents are percentages of persons in each anemia category with transferrin saturation and ferritin within the specified ranges.

TH-PO252

The Impact of Newly Developed Inflammation, Characterized by Rise in C-Reactive Protein, on Anemia Management Practices in Hemodialysis Patients: A Before-After Design in the DOPPS

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Background: Inflammation, as assessed by a rising C-reactive protein (CRP), may lower hemoglobin (Hgb) level and lead to increased ESA dose to support the unmet need.

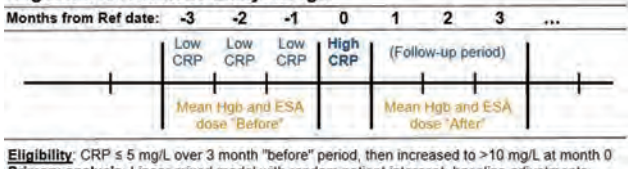
Methods: Using data from Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 4-6 (2009-2018) in 10 countries where CRP is routinely measured, we identified hemodialysis patients who had a new inflammation event, defined here as CRP >10 mg/L following a 3-month period with all available CRP measurements ≤5 mg/L. In a "before-after" design treating patients as their own controls, we used adjusted linear mixed models to estimate within-patient effects of inflammation on changes in Hgb and log-transformed ESA dose, comparing mean values from the 3 months "before" vs. "after" observing high CRP. Sensitivity analyses used different CRP thresholds as a proxy for a new inflammation event (e.g., ≤3 to >10 mg/L, ≤5 to >20 mg/L).

Results: Among 12389 patients, 40158 CRP values (21% of all measurements) were >10 mg/L, and 3752 measurements (from 2976 patients) met the eligibility criteria (Fig). In the "before" vs. "after" periods, mean Hgb was 11.2 vs. 10.9 g/dL and mean ESA dose was 6347 vs. 6994 units/week. In 56% of the cases, patients experienced either a Hgb drop of >0.5 g/dL (40% of cases) or a >20% increase in ESA dose (33% of cases). In adjusted models, the average within-patient change was 0.26 g/dL (95% CI: 0.22, 0.30) lower Hgb and an 8.6% (95% CI: 6.4, 10.8) increase in ESA dose. Results were robust to sensitivity analyses varying the CRP thresholds.

Conclusions: After patients experienced an inflammation event, Hgb levels declined and ESA doses rose, suggestive of increased ESA resistance. Routine measurement of CRP is not practiced in the US but could help identify inflamed patients. These patients may benefit from proactive adjustment of medications or, in the future, anemia therapies that may be less subject to effects of inflammation.

Funding: NIDDK Support, Commercial Support - This analysis was supported by AstraZeneca. The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects and countries is provided by AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Keryx, Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Proteon, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karaboyas directly., Private Foundation Support, Government Support - Non-U.S.

Figure. Illustration of study design



TH-PO253

Factors Associated with Anemia in Nondialysis CKD

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Background: Anemia is common among chronic kidney disease (CKD) patients with increased hospitalizations and mortality and is associated with inflammatory cytokines and iron status. **Objective**: To assess factors associated with anemia in nondialysis CKD patients.

Methods: We analyzed 100 nondialysis CKD outpatients no erythropoiesis-stimulating agent. Anemia was defined as hemoglobin (Hb) concentration <13.0 g/dL for men and <12.0 g/dL for women. Thus, 63 patients were in anemia group and 37 in non-anemia group. We performed analyzes of demographic data, CKD-EPI, Hb concentration, albumin, iron status, serum sFas, iPTH, inflammatory cytokines and erythropoietin (Epo) levels. We used correlations to all variables. We performed comparisons between two groups and multiple linear regression was used to determine the factors associated with Hb concentration when p<0.1.

Results: The primary causes of CKD were diabetes and hypertension followed by chronic glomerulonephritis. We observed in all patient together positive correlation between Hb and transferrin saturation (r=0.20, p=0.04), Hb and CKD-EPI (r=0.42, p<0.001), Hb and albumin (r=0.39, p=0.003). There was negative correlation between Hb and sFas (r=-0.50, p<0.001). We observed lower CKD-EPI (48±23, 27±10 mL/min; p=0.001), Hb (14.1±1.4, 10.9±1.6 g/dL; p<0.001) and serum Epo (14.2±9.5, 9.4±4.7 pg/mL; p=0.08) in anemia group. We found higher levels of sFas (3575±1109, 2533±1025 pg/mL; p<0.001), IFNg (7.1±5.9, 5.7±3.2 pg/mL; p=0.09) and iPTH (271±47.3, 110±47.8 pg/mL; p=0.003) in anemia group. Albumin (b = 3.518, 95%CI 1.059-3.873; p<0.001) and sFas (b = -0.252, 95%CI -0.852-0.17; p=0.001) were independently associated with Hb concentration.

Conclusions: This study shows that levels of albumin and sFas were associated with anemia in nondialysis CKD outpatients.

TH-PO254

Serum Soluble-Fas Is a Predictor of Need for Erythropoiesis-Stimulating Agents in Nondialysis CKD

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Background: Erythropoiesis-stimulating agents (ESAs) are commonly used to treat anemia in chronic kidney disease (CKD). Soluble-Fas (sFas) and inflammatory cytokines are associated with renal anemia. **Objective**: To assess predictor factors of need for ESAs in nondialysis CKD patients.

Methods: We retrospectively analyzed and identified 80 nondialysis CKD outpatients with Hb>10g/dl. Thus, CKD outpatients that needed ESA up to 48 months after enrolment in nephrology office were identified. Initiated ESA when Hb values <9.0-10.0 g/dL with iron store replete. Demographic data, ESA use, CKD-EPI, Hb concentration, albumin, iron status, serum sFas, iPTH, inflammatory cytokines and erythropoietin (Epo) levels were recorded. 24 patients needed ESA and 56 patients no needed ESA in this period. We performed comparisons between two groups (ESA and non-ESA). Binary logistic regression was used to determine the impact of factors on ESA need.

Results: The primary causes of CKD were diabetes and hypertension. ACEi were used more in ESA group (46%, 20%; p=0.04). At baseline we observed lower CKD-EPI (42±22, 29±12 mL/min; p=0.01), serum Epo (10.8±1.8, 8.8±2.4 pg/mL; p=0.07) and Hb (13.5±1.7 g/dl, 12±1.8; p=0.09) in ESA group. We found higher levels of serum sFas levels (3537± 578, 2751±1258 pg/mL; p=0.005) in ESA group. We did not observed difference in levels of iPTH, albumin, iron status and inflammatory cytokines. Serum sFas (b = 1.002, 95%CI 1.001-1.004; p=0.01) was independently associated with Hb concentration.

Conclusions: In this study serum sFas was a predictor of need for ESA in nondialysis CKD outpatients within 48 months.

TH-PO255

Estimated Glomerular Filtration Rate (eGFR) and Hemoglobin (Hb) Levels Associated with Anemia Therapy in CKD Patients in a US Commercial Insured/Medicare Advantage Population

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Background: Little is known about the eGFR and Hb levels that trigger initiation of anemia treatment in non-dialysis-dependent CKD patients in the real-world setting. The study objective was to explore Hb and eGFR levels prior to anemia treatment in non-dialysis CKD patients and assess the trigger for anemia treatment based on these test results.

Methods: CKD patients treated for anemia were identified in the HealthCore Integrated Research Database from 1/1/07 to 6/30/15 by the presence of ≥ 1 medical claim each with a CKD and anemia diagnosis. Patients were required to have ≥ 12 months of health plan eligibility prior to their first CKD claim, during which they could not have any claims for CKD or anemia. These patients were 1:1 propensity score matched to CKD patients not treated for anemia. An anemia "at-risk" period was defined as the period between the first CKD diagnosis and anemia treatment date or "pseudo" treatment date assigned to the untreated group. Patients in both groups had an eGFR during the at risk-period and an Hb outpatient result within 90 days prior to treatment/pseudo treatment date. Hb and eGFR levels associated with anemia treatment were evaluated; trigger values were assessed using logistic regression with Youden's J index.

Results: We identified a total of 1724 matched pairs (anemia treated/untreated), with a mean age of 65 years. Anemia treatments included darbepoetin (9.6%), epoetin (24.8%), prescription iron (31.6%) and blood transfusion (60.9%). The mean Hb during the at-risk period was 10.0 and 12.5 g/dL for the anemia treated/untreated cohorts. The mean eGFR during the at-risk period was 41.0 and 52.5 mL/min for the anemia treated/untreated cohorts, with 1/3 of patients in the treated group at stage 4/5 CKD and another 1/3 at stage 3b. The trigger point for anemia treatment was 10.3 g/dL for Hb and 33.3 mL/min/1.73 m^2 for eGFR, with Hb being a stronger predictor of anemia treatment than eGFR. Type of anemia treatment received depended on Hb level.

Conclusions: Two thirds of patients in the anemia-treated group were stage 3b CKD or worse when treatment was initiated, with Hb being the main impetus for therapy. Future research on the interplay among renal function, Hb levels, and anemia treatment initiation is warranted.

Funding: Commercial Support - AstraZeneca LP

TH-PO256

Role of Soluble Transferrin Receptors, Serum Ferritin, and Inflammatory Markers in Assessment of Functional Iron Deficiency in Anemia of CKD

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Background: Anemia in chronic kidney disease (CKD) is multifactorial and functional iron deficiency (FID) is very common. The presence of coexisting inflammation may alter transferrin saturation (TSAT) and serum ferritin (SF) values, thus affecting their utility in assessment of iron stores. Interleukin-6 (IL-6) is the prime mediator of FID through hepcidin induction and has a direct role in the pathogenesis of anemia in CKD. The present study was conducted to explore the role of soluble transferrin receptors (sTfR), SF, IL-6 and high-sensitive C- reactive protein (hsCRP) in anemia of CKD. ESR was measured by Westergren method.

Methods: A total of 77 patients of CKD {Stage 3 (n=31), 4 (n=17) and 5 (n=29)} of either sex, aged >18 years with hemoglobin (Hb) <11 g/dL were studied. Patients with active bleed, chronic infection, systemic disorders, history of recent blood transfusion and those receiving iron supplements were excluded. Hb, serum iron (SI), total iron binding capacity (TIBC) were measured in all the cases and TSAT was calculated. SF, sTfR, hsCRP and IL-6 were measured by ELISA technique.

Results: Taking sTfR/log ferritin (cut-off >1) as gold standard, CKD patients were divided into two groups:- Group-A: Iron deficient erythropoiesis (IDE) (n=31) and Group-B: Non-iron deficient erythropoiesis (NIDE) (n=46). No statistically significant difference was found in the values of Hb, MCV, MCH, MCHC, SI, TIBC, TSAT and SF between the two groups. All patients had raised IL-6 while hsCRP was raised in 60/77 (79.93%) patients. A positive correlation was found between hsCRP and SF (r=0.311, p=0.006) and between ESR and SF (r=0.451, p=0.000); however, no correlation was found with sTfR, indicating that sTfR levels are not affected by inflammation. The criteria i.e. TSAT <20% and SF>100 μg/L showed a sensitivity of only 6.45% in detection of FID. On the other hand, SF levels from 12 to 70 μg/L were able to identify 14/19 (73.7%) cases of FID. Further, sTfR showed significantly higher values in the IDE group (p=0.000).

Conclusions: hsCRP, ESR and IL-6 levels were raised in majority of the patients of CKD with anemia and were not useful in the diagnosis of FID; however, raised sTfR levels and SF values between 12 to 70 μg/L were found to be useful for assessment of IDE (p=0.000).

TH-PO257

Efficient Management of Renal Anemia Is Achieved by Low Ferritin Levels and Moderate Transferrin Saturation Analyzed by Combination of the Hemoglobin Content of Reticulocytes and Iron Markers

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Background: Excessive iron induces negative iron metabolism by production of hepcidin25 (Hep25), but the optimal iron levels for hematopoiesis on hemodialysis (HD) patients is unclear. The hemoglobin content of reticulocytes (CHr) is sensitive indicator of used iron for hematopoiesis. The previous studies indicated CHr level increased by iron therapy in iron deficiency patients, whereas showed no change in iron sufficiency patients. So we investigated the relation among CHr level, iron status, reticulocytes counts and Hep25.

Methods: 181 outpatients on maintenance HD treated with recombinant human erythropoietin were enrolled and examined CHr, serum ferritin(s-ft), transferrin saturation (TSAT), reticulocytes (Ret) counts and Hep 25. The sample was comprised of 115 men with a mean (SD) age of 59.9 (13.8) years, and mean HD duration of 8.6 (6.8) years. CHr and Hep 25 was measured using ADVIA 120 hematology system and LC-MS/MS assay. As management of anemia, the target Hb level was 10–11 g/dL according to the Japanese guidelines. We performed sensitivity analysis using the generalized linear regression model including the interaction term to determine the optimal cut-off values, which correlation coefficients show greatest changes, of s-ft, TSAT and Hep25 for CHr. The correlation between CHr and Ret count was evaluated in four groups classified by iron status.

Results: The optimal cut-off values of s-ft and TSAT for CHr were showed 50 ng/mL (≤50 ng/mL, r=0.47 vs >50 ng/mL, r=0.22; F-statistic, 17.64) and 24% (≤24%, r=0.58 vs >24%, r=0.08; F-statistic, 34.45), respectively. Moreover, two values were suggested for the optimal cut-off of CHr and Hep25. The under and upper values were 20 ng/mL (≤20 ng/mL, r=0.52 vs >20 ng/mL, r=-0.01; F-statistic, 21.12) and 70 ng/mL (≤70 ng/mL, r=0.36 vs >70 ng/mL, r=-0.45; F-statistic, 24.52), respectively. As the Ret count increased, CHr most greatly decrease in the "s-ft ≤50 ng/mL and TSAT ≤ 24%" group, however showed almost no change in the "s-ft >50 ng/mL and TSAT > 24%" group.

Conclusions: This study showed that the iron status of s-ft >50 ng/mL or/and TSAT > 24% had almost no influence on CHr, indicator of used iron for hematopoiesis. However, high level of Hep25 may impair the efficiency of iron use for hematopoiesis.

Funding: NIDDK Support

TH-PO258

Red Blood Cell Volume Is Not Always Decreased in Anemic CKD Patients

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Background: Anemia is defined according to blood hemoglobin concentration ([Hb]), which can be considered a marker of total red blood cell volume (RBCV). However, alterations of plasma volume (PV) may also modify [Hb] without concomitant changes in RBCV. Since anemia and fluid retention are frequent complications of chronic kidney disease (CKD), we hypothesized that anemia during CKD may in part be related to expanded PV without a simultaneous decrease in RBCV.

Methods: To test this hypothesis, we quantified in 50 consecutive stable stage 3-5 CKD outpatients not on dialysis and 7 controls in the same age cathergory: hemoglobin mass, RBCV, PV and total blood volume (BV) using an automated carbon monoxide device. Epo was measured by Elisa. Predicted values for PV, RBCV, and BV were calculated according to nadler's formula for each patient.

Results: CKD patients were divided into anemic and non-anemic patients based on their hemoglobin [Hb] values. While we demonstrated that RBCV was within the predicted range in anemic patients (+8%, p=0.35) but higher than predicted in non-anemic (+14.5%, p=0.02) patients, both BV and PV were higher than predicted values for non-anemic (+15.5% and +19%, p<0.01) and anemic patients (+ 10.5 and +22%, p<0.01), respectively. Anemic patients had a higher PV than controls (p<0.01) whereas their RBCV was not different, whereas non anemic CKD patients had higher RBCV than controls (p<0.01). Thus the cause for anemia in the large majority of the investigated patient population was related mainly to hemodilution and not to a limited erythropoiesis, as also confirmed by the erythropoietin values. [Hb] based anemia over-diagnosed anemia in 20 of the 26 anemic patients.

Conclusions: In conclusion, anemia in CKD as diagnosed by low [Hb] is not necessarily only associated to low RBCV but may also reflect increased plasma volume. This finding could have implications for the treatment of CKD patients and may explain the increased mortality associted to normalization of [Hb] values by rhEpo treatment in the predialysis CKD population.

Funding: Government Support - Non-U.S.

TH-PO259

Estimation of Pre-Dialysis Hemoglobin Concentration Using Intradialytic Crit-Line Monitor Readings

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Background: Anemia is a major complication in hemodialysis (HD) patients. The Crit-Line monitor (CLM) is widely use to determine oxygen saturation, hematocrit and hemoglobin (Hgb) levels. It would be desirable to use CLM to estimate pre-HD Hgb values to reduce blood draws. However, due to hemodilution by the priming fluid, the initial Hgb values at the HD start are consistently lower than pre-HD values. A high initial ultrafiltration rate (UFR) allows rapid removal of the priming fluid while limiting the impact associated with saline extravasation and vascular refill. Our goal was to implements a high initial UFR to evaluate the agreement between the two measurements.

Methods: Prospective, observational study in chronic HD patients. Subjects were studied 3 times. Two pre-HD blood samples were drawn, measured in triplicate by Spectra East Laboratories (Rockleigh, NJ, USA), and the average used for comparison to CLM. Initial UFR was set to 3 L/hr for 8 minutes and then returned to prescribed rate. Hgb was recorded continuously with CLM. Difference of CLM to lab Hgb value was calculated as CLM reading at each time point minus averaged lab value

Results: We included 27 subjects (56.4±15 years, 70% males, 63% African-Americans) and a total of 61 treatments. With rapid ultrafiltration, the difference between CLM and lab values decreased and reached minimal at approximately 6 minutes (Fig.1), and about 75% of subjects had CLM Hgb values that were within ±0.5 g/dL of the corresponding lab reference Hgb

Conclusions: With a high initial UFR, 75% of CLM Hgb values were within ±0.5 g/dL difference of the averaged lab measurement at minute 6. Of note, the lab values are afflicted with some degree of measurement variability contributing to the data spread. Next steps should include development of mixed effects models for prediction of an individualized time point at which to read CLM Hgb, to further increase the agreement between the two methods.

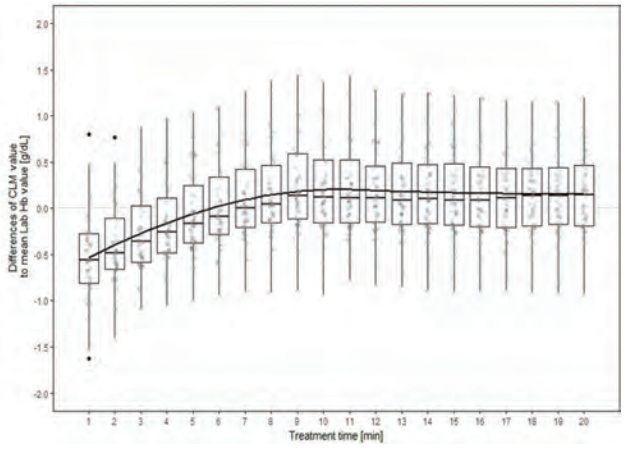

Fig.1. Delta of lab and CLM Hgb values at each time point for the first 20 minutes of HD

TH-PO260

Reduced Hemoglobin Level Increases Risk of Incident Heart Failure and Atherosclerotic Events in CKD: The CRIC Study

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Background: Anemia may exacerbate cardiac ischemia or contribute to abnormal left ventricular remodeling but data regarding the impact of anemia on cardiovascular outcomes in chronic kidney disease (CKD) have been inconsistent.

Methods: We used Cox proportional hazards to examine the association of hemoglobin (Hgb) level (per 1 gm decrease) with incident heart failure, atherosclerotic events (myocardial infarction, stroke, or peripheral artery disease), and all-cause death among participants with CKD in the Chronic Renal Insufficiency Cohort Study.

Results: Among 3,919 participants with CKD (mean age 58 yrs, 45% women, 42% white, 42% black, 13% Hispanic, mean eGFR 45 ml/min/1.73 m^2, median proteinuria 0.19 g/24h, and mean entry Hgb 12.6±1.8), 1,859 (47.4%) participants had anemia (defined using WHO criteria of Hgb <12 g/dL in women and <13 g/dL in men) at study entry. Compared to individuals without anemia, those with anemia were older, more likely to be black or Hispanic, have prior clinical cardiovascular disease, and had a lower mean eGFR at baseline. Over a median follow-up of 8.8 years, we observed 757 heart failure events, 692 atherosclerotic events, and 1148 deaths. In multivariable analyses, lower Hgb was associated with significantly higher rates of heart failure and atherosclerotic events that may be partially explained by subclinical cardiac ischemia.

Conclusions: In a large, diverse CKD cohort, lower Hgb was independently associated with an increased risk for heart failure and atherosclerotic events.

Funding: Other NIH Support - NHLBI K23HL125984

	Heart Failure	Atherosclerotic	All Cause Death
	Hazard Ratio (95% CI) Per 1gm decrease in Hgb concentration		
Model 1 (a)	1.25 (1.19-1.31)	1.18 (1.13-1.24)	1.15 (1.11-1.20)
Model 2 (b)	1.12 (1.06-1.18)	1.10 (1.04-1.16)	1.03 (0.99-1.08)
Model 3 (c)	1.12 (1.06-1.18)	1.10 (1.04-1.16)	1.04 (1.00-1.09)
Model 4 (d)	1.09 (1.04-1.15)	1.08 (1.02-1.14)	1.01 (0.97-1.05)

(a) Adjusted for center, age, sex, race/ethnicity, education, income

(b) Model 1 + cardiovascular disease, systolic BP, HgbA1c, smoking, LDL, eGFR, urine protein, ACE-inhibitor/ARB, aspirin/anti-platelet, statin, erythrocyte stimulating agent

(c) Model 2 plus LVH by ECG

(d) Model 2 plus troponin I.

TH-PO261

Association of Anemia with Clinical Outcomes in Patients with Severe CKD: A Danish Population-Based Study

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Background: Real-world evidence is limited on clinical outcomes associated with anemia in patients with chronic kidney disease (CKD). We investigated the association of anemia with incident dialysis, adverse cardiovascular (CV) outcomes and death in patients with severe CKD.

Methods: We linked laboratory and healthcare databases to identify individuals with stage 4 or 5 CKD (eGFR <30) in Northern Denmark on 1 Jan 2012. We classified patients by anemia grade using lowest hemoglobin (Hb) value in 2011 (grade 1: Hb 10 to <12/<13 g/dL; grade 2+: Hb <10 g/dL). Patients were stratified by dialysis status on 1 Jan 2012 and followed for incident dialysis, first CV event (myocardial infarction, stroke, and heart failure hospitalization) and all-cause death. We computed incidence rates and derived risk curves and adjusted hazard ratios (HRs) through cumulative incidence function and Cox proportional hazards regression.

Results: Of 4,120 patients with severe CKD (median age 77 years), 45% had no anemia, 41% had grade 1 anemia, and 14% had grade 2+ anemia. Incidence rates for dialysis, CV events and death increased with increasing anemia severity (Table). After controlling for baseline differences in age, gender, CV history, other comorbidities, eGFR level and CKD duration, HRs for incident dialysis were increased for patients with grade 1 and particularly with grade 2+ anemia. Moreover, HRs for CV events and death were elevated among both non-dialysis and dialysis patients. A similar risk pattern for CV events and death was observed when non-dialysis patients were censored at dialysis initiation.

Conclusions: In routine clinical care patients with severe CKD, the presence and severity of anemia was associated with increased risks of incident dialysis, CV events and death.

Funding: Commercial Support - AstraZeneca

		Incident dialysis		Cardiovascular event		All-cause death	
Dialysis status at index date	Anemia grade	Incidence rate per 100 person-years (95% CI)	Adjusted hazard ratio (95% CI)	Incidence rate per 100 person-years (95% CI)	Adjusted hazard ratio (95% CI)	Incidence rate per 100 person-years (95% CI)	Adjusted hazard ratio (95% CI)
Non-dialysis	No anemia	1.6 (1.3 - 2.0)	Ref.	7.1 (6.4 - 7.8)	Ref.	10.5 (9.7 - 11.3)	Ref.
	Anemia grade 1	3.4 (2.9 - 4.0)	1.33 (1.03 - 1.70)	9.7 (8.9 - 10.7)	1.28 (1.12 - 1.46)	14.6 (13.6 - 15.6)	1.28 (1.15 - 1.42)
	Anemia grade 2+	4.6 (3.4 - 6.1)	1.41 (0.98 - 2.03)	11.2 (9.3 - 13.5)	1.38 (1.11 - 1.70)	20.7 (18.2 - 23.5)	1.79 (1.54 - 2.07)
Dialysis	No anemia	N/A	N/A	6.4 (3.9 - 9.8)	Ref.	6.4 (4.0 - 9.6)	Ref.
	Anemia grade 1	N/A	N/A	10.7 (7.9 - 14.2)	1.40 (0.79 - 2.48)	13.8 (10.8 - 17.3)	2.15 (1.31 - 3.54)
	Anemia grade 2+	N/A	N/A	13.0 (10.0 - 16.7)	1.74 (0.96 - 3.14)	18.3 (15.1 - 22.1)	3.30 (2.00 - 5.42)

TH-PO262

Delta-He It Is a Novel Biomarker of Mortality in Prevalent Hemodialysis Patients: A Multivariate Regression Predictive Model Development

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Background: Delta-He is a marker of iron availability, which has been suggested as a marker of the inflammation. It is calculated as the difference between the hemoglobin content of reticulocytes (Ret-He) reflects the incorporation of iron into the erythroid progenitor cells over the previous 2–4 days, and the hemoglobin content of erythrocytes (RBC-He). Under normal conditions, Delta-He has a positive value. As iron homeostasis and inflammation are related through the action of Hepcidin, an acute inflammatory response suppresses the availability of iron to erythropoietic progenitor cells and rapidly induces a decrease in Ret-He, leading to a negative value of Delta-He.

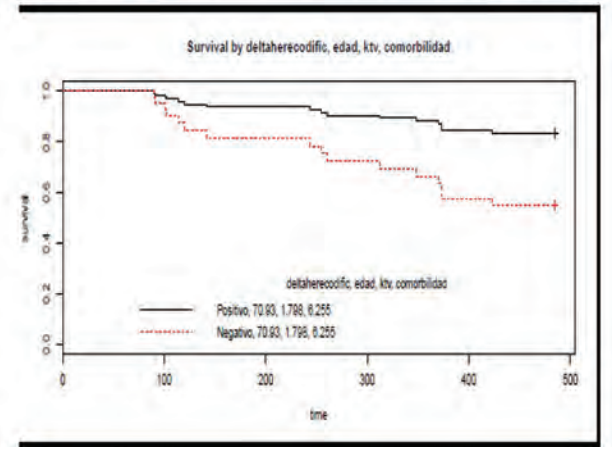
Methods: 78 patients prevalent in Hemodialysis were followed during 1 year. We have analyzed time to the event (mortality from any cause). Has been acknowledged Mortality as Dependente Variable and Delta-He Dicotomized as independent variable. Time in Hemodialysis, KtV, the treatment with erythropoiesis-stimulating agents (ESA) and Fe iv therapy was taken into account, PCR, RET-He and Delta-He. We have realise the determinations through the Sysmex XE 500. A survival study was carried out trougt using Multivariate Regression Cox Model . The predictive model is developed with the regression coefficients. Internal validity was realise by Bootstrap. The model is presented as a nomogram.

Results: 22/78 patients (28.2%) presented exitus. 19/78 patients (24.4%) had Delta-He Negative and require a higher weekly dose of ESA. The delta He has a protective effect against mortality, that is, the greater the value of Delta-He, the less mortality, for each unit that increases Delta He above 0 the mortality decreases by 27%. Discrimination: Index C: 0.74, Calibration: I. Brier: 0.171, R2 Nagelkerke: 0.22.

Conclusions: Delta-He Negative is a predictive factor of all-cause mortality at one year in patients on hemodialysis, associated with inflammation and hypo-responsiveness to ESA.

REGRESION COX MULTIVARIATE. DESARROLLO

	HR				VALOR p
	coef	exp(coef)	se(coef)	z	Pr(>|z|)
deltaherecodific[T.Negativo]	1.16880	3.21813	0.53641	2.179	0.0293
edad	0.08236	1.08585	0.03580	2.300	0.0214
ktv	-0.15132	0.85957	0.24880	-0.608	0.5431
comorbilidad	0.01022	1.01027	0.17594	0.058	0.9537



TH-PO263

The Association of the Difference in Hemoglobin Levels Before and After Hemodialysis with the Risk of 1-Year Mortality in Patients Undergoing Hemodialysis: Results from the Japanese Renal Data Registry

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Background: Few clinical studies have directly examined the associations of hemoglobin (Hb) levels after hemodialysis (HD) and of the difference in Hb levels before and after HD (ΔHb) with patient outcomes. The present study aimed to determine ΔHb and post-HD Hb levels with nationwide data and to examine their associations with all-cause mortality in patients undergoing HD.

Methods: Study Design: Retrospective cohort study Setting and Participants: This study is based on data from 2008 and 2009 recorded in the Japanese Renal Data Registry. Exposures: The ΔHb and the absolute post-HD Hb value. Outcomes: 1-year mortality Analytical Approach: The ΔHb and post-HD Hb level as categorical variables using Cox regression for 1-year mortality, adjusting for potential confounders.

Results: Eligible patients were 38,636 patients. The median ΔHb was 1.0 g/dl (first quartile, 0.4 g/dl; third quartile, 1.5 g/dl), and the median post-HD Hb level was 11.3 g/dl 1.0 g/dl (first quartile, 10.3 g/dl; third quartile, 12.4 g/dl). The median pre-HD Hb level was 10.4 g/dl (first quartile, 9.6 g/dl; third quartile, 11.1 g/dl). The risk of mortality was lower with a ΔHb of 0 to 1.0 g/dl (adjusted hazard ratio [aHR], 0.82; 95% confidence interval [CI], 0.74–0.92) or > 1.0 g/dl (aHR, 0.62; 95% CI, 0.55–0.70) than with a ΔHb < 0 g/dl. The risk for mortality was also lower with a post-HD Hb of 10 to 11 g/dl (aHR, 0.79; 95% CI, 0.71–0.89), 11 to 12 g/dl (aHR, 0.72; 95% CI, 0.64–0.80), or > 12 g/dl (aHR, 0.71; 95% CI, 0.64–0.80) than with a post-HD Hb < 10 g/dl.

Conclusions: Both a low ΔHb and a low post-HD Hb level were associated with a higher risk of 1-year mortality.

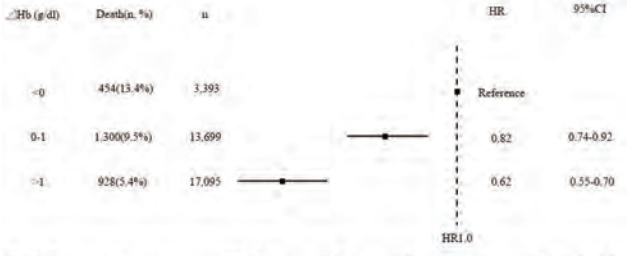

Figure1: The association between categorized △Hb of all patients and all-cause mortality(1-year) in cox proportional hazard model. The model was adjusted with age, gender, dialysis vintage, cause of end stage renal disease, history of cardiovascular disease or amputation, body mass index, serum albumin level, time of dialysis session, blood urea nitro, serum creatinine, serum sodium, serum potassium, adjusted calcium, phosphate, C-reactive protein, PCR, Kt/V, the amount of fluid removal, and type of blood access.

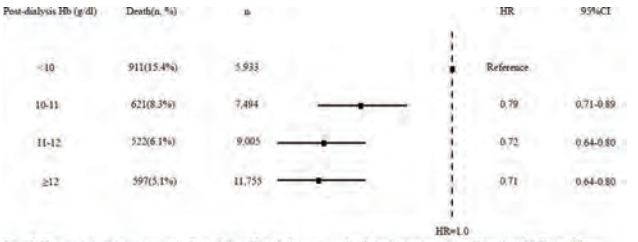

Figure2: The association between categorized post-dialysis Hb and all-cause mortality(1-year) in cox proportional hazard model. The model was adjusted with age, gender, dialysis vintage, cause of end stage renal disease, history of cardiovascular disease or amputation, body mass index, serum albumin level, time of dialysis session, blood urea nitro, serum creatinine, serum sodium, serum potassium, adjusted calcium, phosphate, C-reactive protein, PCR, Kt/V, the amount of fluid removal, and type of blood access. HR, hazard ratio. CI: confident interval, Hb: hemoglobin.

TH-PO264

Differential Effect of Hemoglobin Level on Patient Mortality According to Patient Age in ESRD Patients

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Background: In chronic dialysis patients, achieving an adequate hemoglobin (Hb) concentration is very important because lower than 10 g/dL or higher than 12g/dl can be associated with increased patient mortality. However, it has not been confirmed that it can be applied irrespective of patient age. Therefore, the aim of this study is to investigate the impact of Hb level on the clinical outcomes of dialysis patients according to patient age using the Clinical Research Center registry for end-stage renal disease (CRC-ESRD) data.

Methods: A total of 3,409 patients form CRC-ESRD were included. They were divided into three group by age, age < 40 (n=488), 40<age≤60 (n=1,650), and age >60 (n=1,271). We compared the overall mortality, cardiovascular mortality, all-cause and cardiovascular hospitalization according to mean Hb level.

Results: In age <40 group, Hb ≥12 g/dl group showed higher all-cause mortality (adjusted HR 3.894, 95% CI 1.037-14.624; p=0.044) compared to 10≤Hb <12 g/dl group, whereas HR of cardiovascular hospitalization was higher in Hb < 10g/dl group (adjusted HR 2.268; 95% CI 1.044-4.926, p=0.039). Meanwhile, in age≥60 group, all-cause and cardiovascular mortality was higher in Hb <10 g/dl (adjusted HR 2.098, 95% CI 1.567-2.808, p<0.001 and adjusted HR 2.796, 95% CI 1.669-4.686, p<0.001) compared to 10≤ Hb < 12g/dl group, however the difference between 10≤ Hb < 12g/dl group and Hb ≥ 12g/dl was not significant. In 40<age≤ 60 group, Hb <10g/dl showed higher all-cause mortality (adjusted HR 1.719, 95% CI 1.158-2.252, p=0.007), all-cause hospitalization (adjusted HR 1.572, 95% CI 1.213-2.036, p=0.001) and cardiovascular hospitalization (adjusted HR 1.455, 95% CI 1.037-2.043, p=0.030) compared to 10≤Hb <12 g/dl group, whereas there was no significant difference between 10≤Hb <12 and Hb ≥ 12 g/dl group

Conclusions: Thus, in elderly patient on dialysis, the effect of low or higher hemoglobin level than 10 - 12 g/dL in elderly patients was different from that in young patient.

Funding: Government Support - Non-U.S.

TH-PO265

Measuring Quality of Life in Patients with CKD Anemia – SF36 and KDQOL

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Background: Anemia of chronic kidney disease (CKD) has deleterious impacts on patients' quality of life (QoL). The Standardized Outcomes in Nephrology (SONG) initiative identified QoL components as essential trial outcomes to be reported in hemodialysis and peritoneal dialysis-dependent (DD) patients. Resolving anemia of CKD may lead to more important QoL benefits in non-DD (NDD) patients than in DD patients (Eriksson 2016). QoL is frequently assessed using the 36-item general Short Form (SF-36) and the CKD-targeted Kidney Disease QoL (KDQoL), the latter being preferred in US dialysis clinics (Peipert 2017). It is unclear to which extent QoL tools are used to study anemia of CKD, and specifically in NDD patients. Therefore, we aimed to describe the evidence on treatments for anemia of CKD in which SF-36 and/or KDQoL were used, in both DD and NDD patients.

Methods: Studies included in a broader systematic literature review of treatments for anemia of CKD were reviewed. The Cochrane Library, MEDLINE, EMBASE, NHS EED, and NHS HTA were searched for English publications. Studies published between 1/1/2000-3/17/2017 meeting the following criteria were included: adult patients; focus is anemia of CKD; patients receiving iron, red blood cell transfusions, erythropoiesis-stimulating agents (ESA); results on QoL. Studies that used SF-36 or KDQoL were retained and qualitatively synthesized.

Results: 1,625 publications were identified and 17 met the eligibility criteria. All studies focused on ESA, with or without iron replacement. SF-36 was used more frequently than KDQoL (11/17, 64.7%) across studies. Notably, KDQoL was used more frequently

(vs. SF-36) in studies on DD patients (4 vs. 2) than in studies on NDD patients (1 vs. 8; 2 studies with mixed DD/NDD patients). Both tools showed QoL improvements (SF-36: 8/11, KDQoL: 4/6). QoL domains improved (e.g., vitality, physical/social functioning) and magnitude of results varied widely.

Conclusions: KDQoL was less frequently used in the NDD population than in DD patients (as expected, given CMS guidelines). Findings highlight how QoL treatment benefits are variable, and that there is a lack of standardized use of adapted QoL tools in studies of NDD patients.

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TH-PO266

Associations of Anemia with Quality of Life in CKD Stage 3-5 Patients: Results from CKDopps in the US and Brazil

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Background: The risk of anemia increases with chronic kidney disease (CKD) progression. Some studies suggest that anemia is associated with poorer quality of life (QOL) among non-dialysis CKD patients. Using the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps), we report the associations of anemia with QOL outcomes among CKD patients in the US and Brazil.

Methods: We analyzed CKDopps data on patient characteristics, laboratory measurements and the Kidney Disease QOL-36 (KDQOL-36) survey collected prospectively for stage 3-5 CKD patients (N=1212) at 22 US and 15 Brazilian nephrologist-run clinics from 2014-2018. Hemoglobin (Hgb) levels, reported closest in time to KDQOL-36 completion (median gap: 13 days, IQR: 1-57 days), were modelled separately as continuous and categorical exposures in GEE linear regression models for each QOL outcome, adjusting for country, age, sex, race, smoking history, eGFR, serum albumin, and 13 comorbidities, and accounting for clustering by clinic.

Results: More severe anemia was most strongly associated with poorer scores for QOL domains of general health, physical role, emotional role, burden, effects of kidney disease, as well as the physical and mental component summary scores. Weak to moderate associations were observed with the domains of energy, physical function, and pain.

Conclusions: These findings show moderate associations between anemia and poorer outcomes on several QOL domains in CKD stage 3-5 patients from the US and Brazil, even after accounting for numerous comorbidities. Longitudinal studies would be valuable to understand how patient QOL and well-being are impacted by anemia and its treatment over time.

Funding: NIDDK Support, Commercial Support - This analysis was supported by AstraZeneca. The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects and countries is provided by AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Keryx, Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Proteon, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Dr. Muenz directly., Private Foundation Support, Government Support - Non-U.S.

Table. Association between hemoglobin and QOL outcomes

		Continuous Hgb	Categorical Hgb	
KDQOL-36 Score (Higher = Better)	Observed Score Mean (SD)	β (95% CI) per 1 g/dL lower Hgb	β (95% CI) Hgb <10 vs >12 g/dL	β (95% CI) Hgb 10-12 vs >12 g/dL
Physical component summary	38.5 (11.7)	**-0.3 (-0.6,0.0)**	-1.0 (-3.4,1.4)	-1.1 (-2.5,0.2)
Mental component summary	48.3 (12.2)	**-0.4 (-0.7,-0.0)**	-1.5 (-3.6,0.6)	-0.3 (-1.4,0.7)
General health	43.4 (26.2)	**-1.4 (-2.3,-0.6)**	**-5.3 (-10.3,-0.4)**	-1.6 (-5.6,2.3)
Physical role	51.6 (37.6)	**-1.5 (-2.5,-0.5)**	-6.8 (-14.0,0.5)	**-4.7 (-8.7,-0.7)**
Emotional role	66.5 (36.1)	**-1.3 (-2.4,-0.2)**	-5.7 (-12.8,1.5)	-3.3 (-6.7,0.1)
Burden of disease	69.2 (28.8)	**-1.7 (-2.5,-0.8)**	**-7.8 (-13.8,-1.9)**	**-3.9 (-6.7,-1.0)**
Effects of disease	80.7 (20.6)	**-1.3 (-1.9,-0.6)**	**-6.7 (-11.1,-2.3)**	-1.8 (-3.9,0.2)

β = effect from linear regression

TH-PO267

Relationship Between Anemia Profile and Nutritional Status as Assessed by Subjective Global Assessment in Incident Dialysis Patients

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Background: Anemia is a major complication in patients with end-stage renal disease (ESRD). Subjective global assessment (SGA) is a useful tool assessing nutritional status. We investigated an association with changes of anemia, iron and erythropoietin (ESA) prescription rate, and prescribed ESA dosage after assessing nutritional status using SGA over time in incident ESRD patients.

Methods: The cohort was prospectively collected in 36 centers of the Clinical Research Center for ESRD in Republic of Korea. The incident ESRD patients started hemodialysis or peritoneal dialysis between November 2008 and Feburary 2014. We excluded patients who were younger than 18 years old, or had an underlying liver disease and malignancy. Finally, we included 898 incident ESRD patients in this study. Nutritional status was calssified to well nourished (WN, SGA A) or malnourished (MN, SGA B or C). The patients based on the change of nutritional status was divided into four groups as following: group 1, WN to WN; group 2, WN to MN; group 3, MN to WN; and group 4, MN to MN. Data between baseline and 12 months after dialysis initiation was analyzed.

Results: Serum hemoglobin and hematocrit levels, iron and ESA prescription rate, and ESA dosage were improved in all the patients at 1 year after dialysis commencement (P<0.05 for all). In subgroup analysis based on dialysis modality, serum hemoglobin and hematocrit levels of the hemodialysis patients were ameliorated in all the groups (P<0.001 for all). In addition, iron and ESA prescription rate, and ESA dosage were more definitely reduced in group 1 and 3 than the other groups (P<0.001 for both). However, these trends in the patients with peritoneal dialysis diminished or dissipated in all the groups.

Conclusions: Maintaining proper nutritional status based on SGA improved anemia in the incident dialysis patients, with reducing iron and ESA usage in especially hemodialysis patients.

TH-PO268

Different Effects of Iron Indices on Mortality in Patients with Autosomal Dominant Polycystic Kidney Disease After Long-Term Hemodialysis: A Nationwide Population-Based Study

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Background: Iron supplementation and erythropoietin stimulating agents (ESAs) are essential for maintaining hemoglobin levels in hemodialysis (HD) patients. However, patients with autosomal-dominant polycystic kidney disease (PKD) have higher endogenous erythropoietin levels, so their recommended iron indices for HD patients may be different.

Methods: This cohort study from the Taiwan Renal Registry Data System (TWRDS) enrolled 84,219 HD patients with valid baseline iron profiles. We stratified mortality risk by presence of PKD recorded as underlying disease. The primary outcome was 3-year all-cause mortality. Predictors included time-averaged and baseline serum ferritin levels and transferrin saturation (TSAT, %). Cox regression multivariate analysis adjusting age, comorbidities, important relevant laboratories was used to pursue estimated all-cause hazard ratio (HR) of mortality.

Results: We enrolled 1346 HD patients with PKD and 82,873 HD patients without PKD. Mean ages were 56.2±13.2 and 61.7±13.5 years and follow-up durations were 2.62±0.89 and 2.28±1.04 years, respectively. Mortality risks for ferritin >800 ng/mL (HR=1.32; 95% confidence interval (CI)=1.21-1.43) or TSAT >50% (HR=1.34; 95% CI=1.18-1.52) were significantly higher among patients without PKD than those with normal iron indices. However, a U-shape curve between mortality and Ferritin/TSAT levels was not observed in patients with PKD. In sensitivity test, PKD patients underwent regular ESAs therapy showed no difference with non-ESAs user.

Conclusions: Iron indices affect mortality differently among patients with and without PKD. Iron supplementation, recommended serum ferritin levels, or TSAT should be monitored in HD patients especially without PKD. Clinicians should consider to treat anemia in HD patients individually, especially in PKD.

TH-PO269

C-Reactive Protein Levels Might Affect the Association of Ferritin and Survival in Hemodialysis Patients

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Background: Ferritin is associated with survival in hemodialysis (HD) patients; higher ferritin levels are associated with worse survival. Inflammatory status is also associated with worse survival in the same population. Serum ferritin itself increases in the presence of inflammation. Therefore, we hypothesized that inflammation affects the association between ferritin and survival. We investigated the interaction of C-reactive protein (CRP) and ferritin for dialysis patient survival.

Methods: All patients who were receiving hemodialysis HD treatment thrice a week at Jyoban Hospital, Fukushima, Japan were included in the study. The study period was set as July 2012 through August 2014. Baseline laboratory data including CRP, ferritin, and other clinical indices were collected in July 2012. CRP and ferritin were dichotomized in

the subsequent analysis. The study outcome was set as all-cause mortality. Analyses were conducted using Cox's proportional hazard models. Interaction between CRP and ferritin was also included in the study. Analyses stratified by CRP levels were also conducted.

Results: This study examined 397 patients, 258 of whom were male; 44.6% were diabetic. Their average age was 70.6 years, with an average of 3.6 years using on HDhemodialysis. During the observation period, 73 patients died. Examination of the entire population demonstrated that high CRP (>0.2 mg/dl), but not high ferritin (>200 ng/ml), is associated with worse survival: HR 3.31 (95%CI 1.35–14.5) and HR 0.64 (95%CI 0.15–1.54), respectively. Interaction of CRP and ferritin was also significant. Stratified analysis demonstrated that high ferritin was associated with better survival (HR 0.17, 95%CI 0.01–0.81) only in the low-CRP stratum, but not (HR 2.24, 95%CI 0.94–4.77) in the high-CRP stratum.

Conclusions: Results demonstrated that inflammation status might affect the association between ferritin and survival in hemodialysis HD patients. Iron dosing might be individualized in light of inflammation results.

TH-PO270

Iron Rather than Erythropoietin Mediates the Role of Fibroblast Growth Factor 23 in Renal Anemia in Humans

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Background: Renal anemia is an almost universal complication of chronic kidney disease (CKD). In animal experiments, Fibroblast growth factor 23 (FGF23), a well-known key-player in mineral metabolism, has been causally implicated by suppressing erythropoietin (EPO). We assessed whether FGF23 might contribute to anemia by inducing relative EPO deficiency.

Methods: Hemoglobin, EPO, iron, and mineral metabolism parameters, including both intact (Diasorin) and c-terminal (Immutopics) FGF23 were measured in 225 non-dialysis CKD (stage 1-5, median eGFR 30 ml/min/1.75m^2) patients not on erythrocyte stimulating agent or intravenous iron therapy. To approximate relative EPO deficiency, EPO values from 5483 patients collected at the General Hospital of Vienna with CRP<1 mg/dl and GFR>60 (median eGFR 87) were chosen as reference population for modelling of gender-specific EPO-standard deviation scores (EPO-SDS) stratified to corresponding hemoglobin levels. Analysis was performed by multiple linear regression.

Results: Both intact and c-terminal FGF23 were associated with hemoglobin in univariate analysis but only cFGF23 remained significant after adjustment. Inclusion of EPO-SDS did not alter the association of cFGF23 with hemoglobin. In contrast, iron indices largely displace this interaction.

Conclusions: In patients with predominantly moderate to severe renal function impairment, relative EPO deficiency fails to explain the association of cFGF23 with anemia, which rather seems to be mediated by iron metabolism.

Table 2

	Base model			Iron model				EPO model				Inflammation model			
Marker	Beta	95% CI limits	p	Beta	95% CI limits	p	R^2	Beta	95% CI limits	p	R^2	Beta	95% CI limits	p	R^2
cFGF23 (RU/ml)*	-0.28	-0.44/-0.11	0.001	-0.15	-0.34/0.04	0.126	0.51	-0.32	-0.47/-0.17	<.001	0.58	-0.28	-0.45/-0.11	0.001	0.49
phosphate (mmol/l)*	-0.75	-1.42/-0.07	0.032	-0.76	-1.51/-0.02	0.045	0.51	-0.12	-0.79/0.54	0.712	0.54	-0.76	-1.45/-0.06	0.033	0.46
total calcium (mmol/l)	2.15	0.91/3.39	<.001	1.95	0.65/3.24	0.003	0.53	1.35	0.17/2.54	0.026	0.55	2.11	0.86/3.37	0.001	0.48

Dependent variable:Hemoglobin;Base model:eGFR, gender, albumin, DM II;Iron model:Base PLUS serum iron, hepcidin, transferrin saturation, ferritin, transferrin; EPO model: Base PLUS EPO-SDS; Inflammation model: Base PLUS CRP, interleukin 6

	Unadjusted			Adjusted Base model			
Marker	Beta	95% CI limits	p	Beta	95% CI limits	p	R^2
iFGF23 (RU/ml)*	-0.51	-0.64/-0.39	**<0.001**	-0.14	-0.31/0.02	0.091	0.45
cFGF23 (RU/ml)*	-0.65	-0.78/-0.51	**<0.001**	-0.28	-0.44/-0.11	**0.001**	0.49
Klotho*	1.04	0.39/1.69	**0.002**	0.30	-0.26/0.87	0.289	0.43
total calcium (mmol/l)	4.35	3.09/5.6	**<0.001**	2.15	0.91/3.39	**<0.001**	0.48
phosphate (mmol/l)*	-2.48	-3.11/-1.84	**<0.001**	-0.75	-1.42/-0.07	**0.032**	0.46
PTH (pg/ml)*	-0.65	-0.83/-0.46	**<0.001**	-0.14	-0.36/0.07	0.191	0.46
25(OH) (nmol/l)*	0.46	0.16/0.75	**0.003**	0.06	-0.19/0.30	0.658	0.45
1,25(OH)2D (pmol/l)*	0.89	0.59/1.19	**<0.001**	0.02	-0.29/0.32	0.911	0.45
CRP (mg/dl)*	-0.16	-0.3/-0.02	**0.026**	0.05	-0.07/0.17	0.407	0.45
IL 6 (pg/ml)*	-0.47	-0.64/-0.29	**<0.001**	0	-0.16/0.17	0.961	0.45
serum iron (µg/dl)*	1.41	0.96/1.85	**<0.001**	0.74	0.33/1.16	**<0.001**	0.46
ferritin (µg/L)*	0.09	-0.1/0.28	0.37	0.07	-0.09/0.22	0.404	0.45
transferrin (mg/dl)	0.01	0/0.02	**0.004**	0	-0.01/0.01	0.905	0.42
TRFS (%)*	0.96	0.51/1.41	**<0.001**	0.56	0.18/0.94	**0.004**	0.45
STFR (mg/L)*	0.31	-0.3/0.92	0.321	0.47	0/0.95	0.052	0.43
hepcidin (pg/ml)*	0.03	-0.1/0.15	0.695	0.14	0.04/0.24	**0.007**	0.47
EPO_standard dev score	1.07	0.84/1.3	**<0.001**	0.65	0.45/0.86	**<0.001**	0.54
* binary log transformed							

Table 1

TH-PO271

Iron Overload in Patients on Hemodialysis: Hepatic, Myocardial, and Bone Tissue Deposit

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Background: Anemia is commonly observed among ESRD patients on hemodialysis patients, most of the time requesting intravenous correction of iron deficiency (Fe). However, excessive Fe supplementation leads to increased risk of Fe overload with consequent deposition in organs and tissues such as liver, heart and bone tissue. The objective of the current study was to evaluate this issue in a cross-sectional cohort of ESRD on hemodialysis.

Methods: We included 28 adult patients (16 men), on hemodialysis for at least 3 months, and with serum ferritin levels ≥1,000 mg/l. Serum ferritin, transferrin saturation index (STI), Fe, C reactive protein (CRP), Calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and alkaline phosphatase (AP) levels were recorded. T2* image acquisition of Magnetic Resonance Imaging (MRI) 1,5 Tesla, were used for the assessment of Fe of liver, and heart. R2* were used only of liver. Bone biopsy was also performed

Results: Mean age was was 54±13 years (57% men). Laboratorial values are depicted at the Table 1. T2* [Reference value(RV) > 16 ms] and R2* (RV < 60 s^{-1} ms) MRI of liver showed 6.95 ms [IQR 3.57] and 143.85 s^{-1} ms [IQR 84.52], respectively. MRI T2* of the heart did not show presence of Fe. Bone biopsy revealed that 100% of patients had Fe deposition.

Conclusions: These data detail the Fe distribution throughout the bone and liver but not myocardial in selected high-risk patients on hemodialysis (serum ferritin levels ≥1,000 ng/ml). The impact of Fe deposition on these tissues whether the use of chelation therapy would change this scenario should be evaluated in subsequent studies.

Table 1. Main baseline characteristics of patients

Hemoglobin, g/dl	11.5 ± 3.5
Ferritin, ng/ml	1611 ± 599
Transferrin saturation index, %	42 (25,75)
Fe	100.5 ± 61.5
CRP, mg/L	7.38 ± 6.74
Calcium, mg/dl	9.6 ± 0.7
Phosphorus, mg/dl	5.1 ± 1.7
PTH, pg/ml	589 ± 809
Alkaline Fosfatase, U/L	199 ± 220
Vitamin D, ng/ml	24.45 [9.775]
MRI Heart	
T2*, ms	42.04 [11.33]

TH-PO272

Socio-Demographic Characteristics, Out of Pocket Expenditure and Quality of Life of Hemodialysis Patients in India

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Background: The Dialysis Outcomes in India (DOI) Study is following a cohort of incident dialysis patients to evaluate the impact of socio-demographic and economic factors on clinical outcomes among end stage kidney disease (ESKD) patients initiated on hemodialysis in India. Here we present the baseline socio-demographic and clinical characteristics and Quality of Life (QoL) in the enrolled subjects.

Methods: A total of 1000 subjects were recruited between Nov 2016 & Mar 2018 in 18 facilities across 10 states in India. Routine medical records were utilized for collection of demographic and clinical information. Structured interviews were conducted to collect socio-economic parameters, including out-of-pocket expenses (OoP), with QoL measured using Euroqol-5D-3L®.

Results: Mean age (±standard deviation) of enrolled subjects was 54±16 years, and there were 341 females. Nearly two-thirds of the participants had school education or less (female 73% and males 62%). Over 80% of the female subjects worked within the home and 44% of the males were either retired or not working. A history of hypertension was reported in 64% of subjects (duration 7±6 years) and diabetes in 50% (duration 8±7 years). Mean monthly family income was reported as US$ 602±408. Only one-third of the subjects had health insurance. The mean monthly OoP expenditure was US$ 491±299 for uninsured subjects and US$ 191±103 for insured subjects. Nearly 9% of the subjects had to change their occupation due to kidney disease and treatment schedules. Mean distance travelled to the dialysis unit was 25±15 kms (female 15±9 and males 21±14 km, respectively). Over 16% of the patients reported severe anxiety/depression and 14% reported severe problems related to activities of daily living. Mean QoL Score on the VAS Scale (0-100), was reported at 58 ± 18 (male) and 64 ± 14 (female).

Conclusions: Our study found high dialysis-related OoP expenditure, particularly in those who were uninsured. Low levels of health insurance coverage represents a major challenge for policy makers in mitigating the economic burden of dialysis treatment. High number of participants leaving the workforce highlights the challenges related to maintaining employment for patients undergoing dialysis.

Funding: Commercial Support - Baxter Healthcare Ltd, United Kingdom

TH-PO273

Marginal Cost of Frailty Among Dialysis Patients

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Background: Patients on dialysis incur disproportionately high costs compared to other Medicare beneficiaries, and frail individuals may cost more. We examined the extent to which frailty contributes to higher costs among dialysis patients.

Methods: The ACTIVE/ADIPOSE study enrolled adult hemodialysis patients from June 2009 to August 2011. Individuals utilizing Medicare as the primary payer with active claims were selected for inclusion. Frailty was assessed at baseline and annually for 2 years using Fried's frailty phenotype. Baseline demographic data and costs were derived from linkage with the USRDS and Medicare claims (Part A, B, and D) standard analysis files. We used generalized estimating equations incorporating time-updated frailty to estimate the marginal cost of being frail at the beginning of each year of follow-up, adjusting for age, gender, body mass index (BMI), and comorbid conditions (diabetes, coronary artery disease, and congestive heart failure). All costs were adjusted for inflation to 2017 US dollars and reported per patient per year (pppy).

Results: Among 771 individuals enrolled in the ACTIVE/ADIPOSE study, 345 met inclusion criteria with an average age of 56.1 years and BMI of 29 kg/m^2. 28% of patients were considered frail at baseline, whereas 54% were frail at any time point. Over mean 2.3 years of follow up, frail individuals incurred 23% (95% CI 10-37%) higher costs compared with non-frail individuals ($101,000 pppy, 95% CI $89,000-$116,000, vs $83,000 pppy, 95% CI $75,000 – $91,000). The difference in costs between frail and non-frail patients appears to be driven primarily by higher hospitalization expenditures (26% higher, 95% CI 11%-43%). Neither physician/supplier costs (12% higher, 95% CI 2% lower to 29% higher) nor were expenditures for pharmacy benefits (2% higher, 95% CI 8% lower to 13% higher) statistically different between frail and non-frail individuals.

Conclusions: Frail dialysis patients incur a significantly higher cost relative their non-frail counterparts, primarily driven by higher hospitalization costs. Efforts to address frailty and its association with hospitalizations may lead to a significant reduction in health care expenditure among dialysis patients.

Funding: NIDDK Support

TH-PO274

The Health and Economic Consequences of Missed Dialysis at the Robley Rex Veterans Affairs Medical Center

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Background: Non-adherence to hemodialysis (HD) is associated with increased morbidity and mortality risk, as well as increased health care costs. These patients frequently present to the emergency department (ED) needing urgent HD for volume overload, hyperkalemia, or uremic symptoms. At present, the Robley Rex VAMC does not offer outpatient HD, necessitating full hospital admission for patients who present with urgent need for HD. We hypothesized that offering outpatient HD to patients who missed their scheduled appointments would reduce costs attributed to missed HD hospital admissions, even taking into account increased dialysis nurse overtime utilization.

Methods: We conducted a retrospective analysis of established HD patients evaluated in the ED of the Robley Rex VAMC, between October 2015 and May 2017, for complications secondary to missed dialysis. Individuals that were admitted for any reason other than urgent HD were excluded. The costs for ED evaluation, hospitalization, and dialysis labor costs were obtained. We calculated costs of the full inpatient admission including dialysis and compared those results with the projected cost providing a single outpatient dialysis treatment for each presentation.

Results: There were 92 individual admissions resulting in 209 inpatient dialysis treatments, indicating that patients were often kept for additional HD treatments. The total cost for these admissions was $729,360.93, which roughly equates to $7,927.84 spent per admission. The cost for an outpatient dialysis session (including ED cost) ranges between $1,032.12 and $1,177 accounting for standard labor versus time-and-a-half labor, respectively. Thus, the total expected range for an equivalent 209 HD sessions, if they were to be done as an outpatient, would be between $215,713.08 and $245,993. This results in total savings ranging from $483,367.93 to $513,647.85.

Conclusions: Forming outpatient dialysis capabilities in an acute dialysis unit would help reduce health-care spending in patients being admitted to VA hospitals for missed HD. Further research is still needed in identifying possible reversible barriers in non-adherent patients.

TH-PO275

Fast Track Dialysis: A Novel Triage and Communication Pathway to Reduce Resource Utilization for ESRD Patients Presenting with Missed HD

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Background: Many end stage renal disease (ESRD) patients present to emergency department (ED) with complaints related to missed hemodialysis (HD) or have no established dialysis clinic. Provision of inpatient HD necessitates short stay admission, use of extra resources, coordination between multiple specialties, resulting in substantial cost.

Methods: A multidisciplinary team sought to improve the flow of ESRD patients through the ED by creating a unique triage pathway, Fast Track Dialysis (FTD). FTD care was facilitated with standardized communication between ED, Nephrology, Hospitalist and Nursing. The FTD pathway emphasized use of venous blood gasses for potassium levels, limited telemetry, chest X-ray, and peripheral IV lines. Patients eligible for FTD were identified by ED providers. Exclusions were BP > 200/100, heart rate > 120/ minute, hypoxia requiring oxygen > 4 L/min, potassium > 6.5 mEq/L and clinical concern that would require admission beyond one session of HD, and dialysis access issues requiring immediate intervention. A six-month historical control group (Pre-FTD) was compared with a six-month FTD cohort with hospital stay < 48 hours. The historical group was filtered by admitting diagnosis (ICD-10 codes) related to dialysis conditions, stay < 48 hours, and above exclusion criteria. Outcome measures were time parameters from triage to ED discharge, HD start, and hospital discharge. The estimates of cost were obtained from hospital generated billing.

Results: FTD led to significant reduction in all time parameters studied (Table). The billing cost was lower but reached significance level after excluding 3 outliers who require additional diagnostic testing for head injury, paracentesis and chest pain.

Conclusions: The implementation of a novel patient care pathway intended to identify, triage, and facilitate the care of low risk ESRD patients that required urgent HD led to a reduction in resource utilization.

	Pre-FTD (1/1/17-6/30/17)	95% CI	FTD (9/25/17-3/16/18)	95% CI	p-value
Age, years(SD)	58.6 (13.2)		53.2 (10.1)		<.01
Males, n(%)	44 (53.7)		52 (68.4)		0.23
Triage to ED discharge (Hrs)	7.2	5.90-8.43	4.1	3.34-4.83	<.01
Triage to HD start (Hrs)	12.8	9.15-16.6	5.2	3.52-6.86	<.01
Triage to hospital discharge (Hrs)	26.2	24.28-28.05	14.3	12.4-25.4	0.01
Billing cost (x1000 dollars)	31.51	30.29-32.72	24.15	22.91-25.39	<.01

TH-PO276

Cost Savings Associated with Post-Hospital Medication Therapy Management Program Dialysis Patients

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Background: Dialysis Clinic, Inc. implemented a medication therapy management (MTM) program for End-Stage Renal Disease Seamless Care Organization patients following hospital discharge. Prior results suggested a 56% reduction in readmission rate with MTM compared to no MTM. We determined the potential impact of the MTM process on costs associated with readmision.

Methods: We used a propensity score (PS) to match MTM 1:1 to non-MTM discharges based on clinical characteristics and on the day post-discharge MTM was initiated. Actual readmission costs were obtained from claims data; the percent difference between MTM and non-MTM groups were calculated and used to estimate cost impact if MTM process applied to non-MTM discharges. Readmission rates after MTM completed, or similar time at risk in matched non-MTM patients, was determined. Cost estimates incorporated MTM implementation time (median, interquartile range) and assumed 25%, 50% or 75% of reported MTM program impact on readmission rate.

Results: In the original cohort, there were 162 discharges with 17 readmissions costing $253,652 in the MTM group and 586 discharges with 170 readmissions costing $2,161,163 in the non-MTM group. Median time to complete MTM was 11 days. There were 135 PS matched pairs used, with 26 (19.26%) readmissions in MTM patients and 50 (37.04%) in non-MTM patients (p=0.0002). Readmission costs were $202,659 vs. $580,549, respectively (p<0.001). MTM was associated with 12%, 26%, or 49% cost savings if implemented ≥14 days, ≥11 days or ≥7 days post discharge, respectively. Extrapolating results to the entire non-MTM group, savings ranges from $117,586 to $600,642 (see Table). Cost savings with MTM performed within 11 days of discharge assuming 50% impact approximates $286,020.

Conclusions: MTM process is associated with fewer readmissions and lower inpatient costs. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Savings estimates if MTM process implemented in 586 no-MTM discharges

	≥14 days	≥11 days	≥7 days
25%	$117,586	$143,010	$200,214
50%	$235,172	$286,020	$400,428
75%	$352,758	$429,030	$600,642

TH-PO277

In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey Response and Long-Term Clinical Outcomes

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Background: The In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) survey, introduced into the ESRD Quality Incentive Program, is the only patient-reported outcome measure currently used for value-based reimbursement in dialysis. It is administered twice yearly to assess hemodialysis patient experience. Current response rates are approximately 30%. The relationship between response status and long-term clinical outcomes is unknown.

Methods: All Dialysis Clinic Inc. (DCI) hemodialysis patients age 18 and older treated at their facility for at least 3 months as of August 2012 were eligible for the survey. Covariates included patient demographic, clinical, and treatment related characteristics. Outcomes included mortality, kidney transplantation, and all cause-hospitalization.

Results: Among 10,395 eligible patients who survived the 3-month survey administration, 3,794 (36%) responded to the survey. Over median follow-up of 30 months, 4,178 patients died, 5,336 patients were hospitalized at least once, and 717 patients received a transplant. In multivariable models, survey response was associated with lower mortality (HR 0.80; 95% CI: 0.74-0.85) and hospitalization (HR 0.84; CI: 0.79-0.89) and higher likelihood for kidney transplant (HR 1.15; 95% CI: 0.98-1.35). Sensitivity analyses evaluating the receipt of transplant with competing risk for death, or a composite outcome of death or hospitalization, yielded similar results.

Conclusions: Response to the ICH CAHPS survey is associated with a lower risk for mortality and hospitalization and higher likelihood for kidney transplantation. These findings raise concern about survey result generalizability and use for quality improvement since experiences of high-risk patients are less likely to be captured.

Funding: Other NIH Support - NIH T32 grant-PI Andrew Levey

TH-PO278

Do the Better Medical Results Mean a Higher Costs for the Dialysis Clinic?

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Background: The quality of care for hemodialyzed patients is determined by commonly accepted biochemical parameters controlled periodically. In everyday practice evaluation includes, among other things, the dose of dialysis provided, the control of anemia, the control of calcium-phosphate balance, and the patients' nutrition status. Obtaining good results is related to, among other things, the time of dialysis sessions, water consumption, electricity, prescribed pharmacotherapy. The aim of the study was to retrospectively assess the correlation between the obtained medical results and the costs directly related to the dialysis treatment of patients with chronic renal failure.

Methods: The analysis included 5,500 patients treated in 68 centers in the years 2014-2016. Medical evaluation was based on the percentage of patients achieving the individual target in particular categories: weekly dialysis time > 240 minutes, single-pool kt/v > 1.4, dialysis with arteriovenous fistula, relative overhydration < 13% (female) or <15% (male), Hb concentration in the range of 10-12 g/dl or > 12 g/dl without the use of erythropoiesis stimulating agents (ESA), albumin > 35 g/l, phosphate concentration < 5.5 mmol/l, patient's protection against new HBV infection and the percentage of patients active on the waiting list for kidney transplantation > 7%. For reaching the clinic target in a single category the center was awarded 1 point. The clinic medical result was the sum of points. The assessment was made on a monthly basis. Monthly treatment costs were also assessed. Costs of dialyzers and dialysis lines, electricity, water, concentrates, ESA, iron, anticoagulation, dialysis fluid concentrates, hygiene and dressing agents were included. The medical results were then correlated with the costs incurred in individual months in subsequent years.

Results: The correlation coefficient r between medical results and costs in 2014, 2015 and 2016 was -0.35 ($p < 0.005$), -0.42 ($p < 0.001$) and -0.51 ($p < 0.001$), respectively.

Conclusions: A statistically significant negative correlation between medical results and costs directly related to the treatment of hemodialyzed patients in three consecutive years suggests that better medical results are obtained in centers that better control medical expenses. Better medical care does not necessarily means higher costs for dialysis centers.

TH-PO279

Dialysis Facility Acquisitions and Patient Health Outcomes

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Background: Mergers and acquisitions among healthcare providers are increasingly common. Although dialysis markets have undergone several decades of mergers and acquisitions, their effects on patient health outcomes are unknown.

Methods: We identified patients initiating in-center hemodialysis between 2001 and 2013 from a national ESRD registry and used difference-in-differences (DID) models to estimate the associations among dialysis facility acquisitions, mortality and hospitalization. We used multivariable Cox models and negative binomial models (with predicted marginal effects) to examine mortality and hospital days, respectively. All analyses adjusted for observed differences in patient and geographic characteristics. In addition to examining all facility ownership types, we conducted stratified analyses of facilities that were independently-owned and chain-owned prior to acquisition.

Results: When examining all facility ownership types, dialysis facility acquisitions were independently associated with 0.63 additional hospital days per patient-year (95% CI 0.00 to 1.27; p=0.07). When examining independently-owned facilities, acquisitions led to 2.01 additional adjusted hospitalization days per patient-year (95% CI 0.53 to 3.48) and a nominally significant 13% relative increase in adjusted mortality (95% CI 4% to 22%).

Conclusions: Acquisition of independently-owned dialysis facilities by large dialysis organizations led to higher adjusted mortality and an increase in adjusted hospital days per patient-year.

Funding: NIDDK Support

TH-PO280

The Impact of Debility on Inpatient Mortality and Hospital Costs of ESRD Patients in the United States: A Nationwide Study

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Background: Patients on dialysis often suffer from muscle wasting and reduced exercise tolerance compared with the general population. The impact for this debility on the in-patient dialysis population remains unclear. The purpose of the current study was to determine the inpatient mortality and cost effects of debility between dialysis patients.

Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, end stage renal disease (ESRD) patients with debility were matched with ESRD patients without debility at a 1:1 ratio. We compared inpatient mortality, length of stay and total hospital charges between both groups. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results: Among 1,070,450 hospitalized ESRD patients during 2005 to 2012; only 16,810 (1.57%) were identified with debility. These patients were associated with significantly higher rate of gastrointestinal bleed (2.01 vs 1.77%; p=0.02), obesity (11.92 vs 8.37%), acute CHF (39.12 vs 33.94%; p=0.0001), Atrial fibrillation (23.11 vs 15.06%; p=0.0001) and CAD (41.74 vs 33.99; p=0.0001). Surprisingly, ESRD patients with debility had a significantly lower in-hospital mortality compared with ESRD patients without debility before (4.52 vs 5.09%; p=0.001) and after matching (4.53 vs 6.17%, $p = 0.0001$). Mean length of stay for those with debility was 11.12 days compared with 7.53 days ($p < 0.0001$). Similarly, mean hospital charges were greater for those who had debility compared with control ($69,596 vs $57,752; $p < 0.001$).

Conclusions: Debility in dialysis patients appears to have a lower in hospital mortality compared to more conditioned ESRD patients. It does however increase the costs and length of stay. Interventions to lower debility may help reduce hospital expenditures.

TH-PO281

Can Dialysis Facility Compare (DFC) Star Ratings Inform Patient Choice of Dialysis Facility? Geographic Co-Location of Facilities by Star Rating Category

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Background: Beginning in 2015, Medicare's DFC site implemented a Star Rating system summarizing the selected clinical quality measures reported on DFC. The Star Ratings are intended to provide an easily interpretable summary of dialysis facility's quality performance and to assist consumer decision-making. We hypothesize that patients' choice of dialysis facility might be influenced by the reported Star Ratings, particularly for those whose choice is not limited by distance to a dialysis facility.

Methods: Based on facilities' zip codes and their reported Star Ratings on DFC, we geocoded all 6000+ dialysis facilities in the contiguous U.S.. Facilities with lower star rating performance were defined as those with 1 or 2 Stars; higher star rating performance was defined by 3 to 5 Stars. Distances between two facilities were calculated based on the spherical distance between the centroids of their zip codes using the geosphere package in R.

Results: Fig. 1 shows the locations of dialysis facilities and Star category. A clear geographic pattern for distribution of lower performing facilities is not apparent. Fig. 2 demonstrates that 84% of facilities with lower star rating are within 10 miles of facilities with higher performance.

Conclusions: These results demonstrate that most patients receiving dialysis care in lower star rating facilities have the option to transfer care to higher star rating facilities based on their geographic proximity. Whether the availability of a higher star rating facility in close proximity contributes to the patient's choice of a new or transfer facility remains unanswered by these analyses. Subsequent analyses will stratify lower and higher star rating

facilities to evaluate if patients' choice of dialysis provider is associated with higher rated facilities in close proximity.

Funding: Other U.S. Government Support

Figure 1

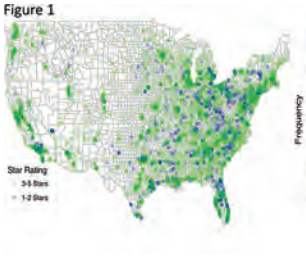
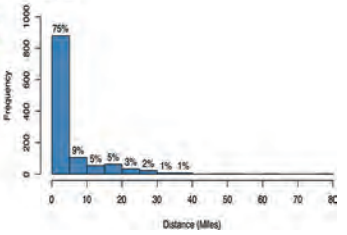


Figure 2



TH-PO282

Medicare Payments for Ambulance Transport Between Skilled Nursing and Dialysis Facilities

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Background: Most dialysis patients receiving care in a skilled nursing facility (SNF) undergo hemodialysis in off-site dialysis facilities and thus require transportation before and after each session. In specific circumstances, Medicare Part B provides coverage for ambulance transport between such facilities. However, Medicare payments to ambulance service providers have been scrutinized by the federal government. By year, we aimed to quantify trends in Medicare expenditures on ambulance transport between SNFs and dialysis facilities.

Methods: We analyzed data from the United States Renal Data System. We searched Medicare Part B claims in payment years 2011-2015 for ambulance transport and retained such claims with an origin/destination code pair that indicated transport between SNF and dialysis facility. We tallied the number of patients with ≥1 ambulance transport between SNF and dialysis facility, the cumulative number of patient-days with ambulance transport, and cumulative Medicare payments for ambulance transport.

Results: Ambulance transport utilization was similar in 2011 and 2012 and subsequently increased to an apex in 2014: 24,327 patients with ≥1 transport between SNF and dialysis facility and 783,786 patient-days with transport (32.2 days per patient). In 2015, utilization fell to 21,601 patients with ≥1 transport between SNF and dialysis facility and 643,808 patient-days with transport (29.8 days per patient). Cumulative Medicare payments for ambulance transport increased from $305.7 million in 2011 to $312.4 million in 2013; thereafter, payments fell to $285.4 million in 2014 and $235.3 million in 2015. In 2015, the Medicare payment rate for ambulance transport was $365 per patient-day, down from $411 per patient-day in 2012. As a share of all Medicare Parts A and B payments among beneficiaries with end-stage renal disease, cumulative Medicare payments for ambulance transport between SNFs and dialysis facilities fell from nearly 1.1% in 2011-2013 to 0.8% in 2015.

Conclusions: Medicare expenditures for ambulance transport between SNFs and dialysis facilities are falling, initially due to lower per-diem payments and later due to lower utilization. Nevertheless, even in 2015, the per-diem Medicare payment for ambulance transport remained more than 50% higher than the base-level Medicare payment ($239) for an outpatient hemodialysis session.

Funding: Commercial Support - NxStage Medical, Inc.

TH-PO283

The 13-Year Experience of Performing In-Center Short Daily Hemodialysis - Who Pays for It?

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Background: Conventional hemodialysis (CHD: 4h3x/wk) has been associated with poor quality of life and high morbidity, hospitalization and mortality rates. An ideal hemodialysis prescription requires ultrapure dialysate, single-use biocompatible membranes, on-line blood monitoring and more frequent and/or longer treatments. Hospitalization represents a significant financial burden, accounting for 40% of total dialysis expenditures. We have successfully run an in-center short daily hemodialysis program (SDHD: 2h6-7x/wk) complying with all requirements for an ideal prescription in the last 13 years. This study aims to demonstrate how we have configured dialysis delivery, improved outcomes and managed resources to achieve an optimal sustainable dialysis practice.

Methods: Operational (productive efficiency, patient compliance and payers coverage), clinical (hospitalization, kidney transplantation and survival rates) and economic (supply dialysis cost, cost-savings and net savings) landscapes were assessed in 176 consecutive unselected private-insured patients (108M/68F; mean age 57.6±19.0 yrs, range 8-97) receiving in-center SDHD treatments (6-7x/wk; lasting 117.2±8.8min, range 105-150; ultrapure dialysate and single-use high-flux dialyzer) from Jun/05 to May/18. Reimbursement has been largely based on patient outcomes and hospitalization rates.

Results: Our in-center SDHD program operates five 2-hour shifts a day (67% higher productivity without increasing fixed costs), the average missed treatment rate was 1.47% and an incremental negotiated approach reached universal insurance coverage for daily regimen. Average hospital stay (2.97 days per patient-year), kidney transplantation rate (7.5%) and mortality rate (7.3%) were better than reported for CHD hospital stay (12 days per patient-year), kidney transplantation rate (4.6%) and mortality rate (19.9%). Daily hemodialysis consumables costs doubled, adding 25% for patient overall cost. Conversely, hospital total length of stay was 75% lower, reducing overall costs by 30% and offseting the additional supply cost.

Conclusions: Our dialysis care redesign has markedly improved patient outcomes and dramatically reduced hospital stays and expenses. With clinical and economic variables combined, it has been possible to sustain a distinctive yet affordable maintenance hemodialysis program.

TH-PO284

Estimated Revenue Gains Associated with Relative Blood Volume Monitoring (RBV-M) in Hemodialysis (HD) Clinics: An Economic Model Using Real-World Data and a Case Size of 12 Medicare Incident Patients

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Background: There are over 100,000 new HD patients (pts) per year (USRDS). For these pts, the first 90 days following HD initiation are associated with elevated hospitalization and mortality rates, along with high healthcare costs. We conducted an economic analysis for incident HD pts using data from a fluid management (FM) quality improvement project (QIP) using RBV-M.

Methods: RBV-M was performed using Crit-Line® Monitors in 9 Renal Research Institute (RRI) Clinics. The QIP was associated with an average of 5.3 fewer hospital days and an estimated reduction of 2.5 missed treatments (txs) per year in incident HD pts (n=1068). Revenue gains from fewer missed txs were calculated using a cost minimization model from a facility level perspective. We assumed that HD clinics continuously served 12 Medicare incident pts with 2 monitors and disposable supplies associated with RBV-M. It was also assumed that pts received HD 3 times per week and HD txs were reimbursed at $350 per patient (i.e. standard Medicare reimbursement amount plus the onset of dialysis adjustment).

Results: Implementing a FM initiative with RBV-M has the potential to generate additional revenue from reducing 2.5 missed txs per year. This translated into gains of $2,048, annually per clinic (with 12 Medicare incident pts) in the implementation year, after accounting for the cost of the monitors and disposable supplies. Once the machines are paid for, either in the second year or if the clinic already owns monitors, annual gains are $6,048, including the cost of disposable supplies. These results do not include potential savings associated with averted hospitalizations or other benefits of the QIP.

Conclusions: RBV-M QI initiatives have the potential to reduce missed txs in incident pts and increase revenue in HD clinics. Assuming a reimbursement of $350 per dialysis treatment and 12 incident pts per clinic, potential revenue gains associated with RBV-M were found to be $2,048 in the start year and $6,048 in the year following implementation (or for clinics who already own monitors). Future cost-effectiveness studies of FM initiatives should consider the additional value gained from including prevalent HD pts who are also likely to benefit from RBV-M.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

TH-PO285

Analytical Methods for Assessing Clinic-Level Outcomes

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Background: Patient outcomes from dialysis units are important indicators of the quality of care provided by each unit. Clinical outcomes for dialysis providers are typically assessed on a per-clinic level. However, the number of patients in each clinic varies greatly, and this can impact the validity of ratings. Different analytical approaches might enhance the estimated ratings.

Methods: Using 2009-2017 data from Dialysis Clinic, Inc. (DCI) clinics, as well as simulated data, we assessed the impact of different estimation approaches (fixed vs. random clinic effects) on ratings based on clinic-level mortality.

Results: Simulations demonstrate that random effects estimates are shrunk towards the overall mean, and have lower standard errors than fixed effects estimates, and that random effects estimates more reliably provide estimates that agree with truth, particularly for smaller clinics. Estimates of mortality from DCI clinics illustrate the degree of shrinkage that is induced through the application of random effects methods (Figure 1).

Conclusions: Random effects approaches are more likely to provide correct rankings of clinics than fixed effects estimates, and might reliably be used to obtain stabilized estimates of mortality rates. However, obtaining estimates in this way may require larger numbers of patients per unit than are often treated within individual clinics. Enhancing information content, either by aggregating across years or by incorporating other data types into an aggregated rating measure, would enable more accurate estimation of clinic performance.

Funding: Clinical Revenue Support

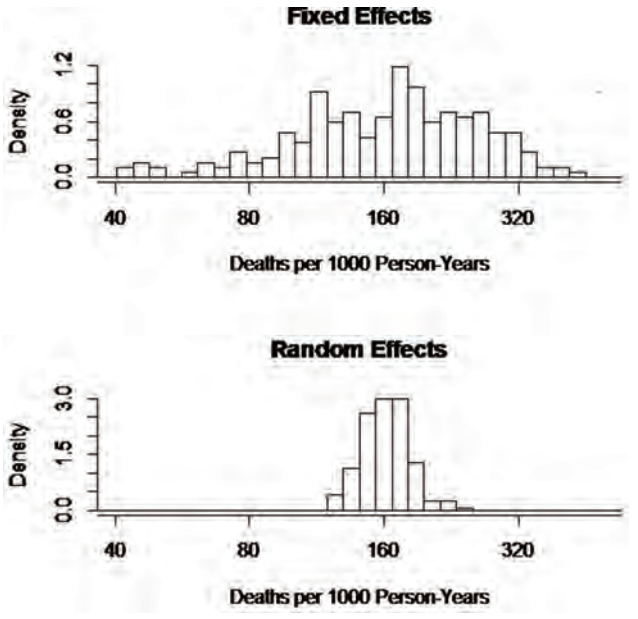

Figure 1. Distribution of unit-specific mortality rates in 2014

TH-PO286

The Centers for Medicare & Medicaid Services ESRD Quality Incentive Program (QIP): Measurement, Monitoring, and Evaluation

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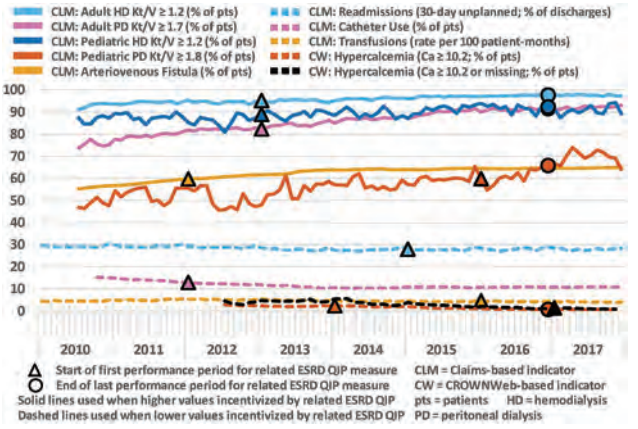
Background: Mandated in 2008, QIP is Medicare's premier value-based purchasing program. Congress designed QIP to link dialysis facility quality with payment. Initially QIP used measures of anemia and hemodialysis adequacy; it now includes a broad set of clinical, safety, and reporting measures. With the recent Meaningful Measures Initiative, CMS is interested in a measure set that reflects the highest priorities for quality measurement and improvement. We describe ongoing monitoring of QIP measures and evaluation of QIP influence on quality, overall and among subgroups of patients and facilities.

Methods: We used Medicare claims, CROWNWeb, and other CMS data to monitor monthly trends in QIP measures during 2010-17.

Results: Performance has improved over time under the QIP for most quality indicators, and has remained relatively stable for the remainder (figure). Smaller recent changes for some indicators may reflect diminishing opportunities for improvement where performance levels are already relatively high (e.g. hemodialysis adequacy, hypercalcemia). Performance was lower for some patient subgroups (e.g. black race, young adults) for some indicators (e.g. fistula use, readmissions, emergency department visits). Many indicators varied by facility characteristics, including ownership, hospital-based vs freestanding, and size. For example, facilities not affiliated with large chains often had consistently lower performance (e.g. peritoneal dialysis adequacy, hospitalizations) or took longer to achieve similar performance levels (e.g. hemodialysis adequacy, fistula use).

Conclusions: In the era of the QIP, overall performance has improved on many indicators of quality of care. Variation in performance on some indicators based on patient and facility characteristics suggests continued opportunities for improvement.

Funding: Other U.S. Government Support



National Trends in QIP Measures, 2010-17

TH-PO287

A Case Study of the Barriers to the Practice of Person-Centered Care within the Context of Hemodialysis Services

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Background: People dependent upon hemodialysis have a high illness and treatment burden. This can be accentuated by care delivery systems that are disease specific, episodic, process focused and fragmented. Person-centered care (PCC) has been shown to provide a number of benefits including: improved health outcomes; increased patient satisfaction; and a reduction in healthcare utilization. Although conceptually PCC is widely supported, its translation into practice is proving to be a challenge. This research explores stakeholder perspectives of how care is provided within hemodialysis services. It particularly focuses on factors that inhibit PCC.

Methods: A case study approach was used that included semi-structured interviews and observation of clinical encounters, including physician rounding. Data was coded inductively and categorized into emergent themes using Nvivo®. Interpretive description was used to analyse the data. A total of 48 people were interviewed: 20 patients, 5 family members, 9 nurses, 6 physicians, 5 managers and 3 social workers. 30 hours of observation were undertaken.

Results: Care was largely limited to the technical aspects of dialysis treatment and whilst there was evidence of PCC, this was episodic and specific to individual clinicians and/or patients. Patients did not perceive their care as individualized, were not involved in decisions regarding it and felt the staff did not have time to listen to their concerns. Nurses described an oppressive and stressful environment with a culture of bullying. The routinization of nursing care and micromanagement, reduced their autonomy and scope of practice. Physician scheduling required reviewing a large number of patients within a short time span; care was often limited to addressing immediate issues and physicians had some concerns regarding continuity. Many of the healthcare professionals alluded to the lack of multi-professional working.

Conclusions: A complex mix of individual, environmental and organizational barriers mitigate against the adoption and practice of PCC within hemodialysis services. In particular, how professionals' practised was often constrained by care processes aimed at meeting demand. This was accentuated by the absence of integrated work practices.

Funding: Other NIH Support - Canadian Institutes for Health Research

TH-PO288

Patient-Nephrologist Prognostic Awareness and Discordance in ESRD on Renal Replacement Therapy

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Background: The one-year mortality rate of patients with ESRD on renal replacement therapy is 20-25%, comparable to many cancers. Several studies have documented that patients with cancer commonly overestimate their likelihood of survival relative to their physicians however it is unclear if this translates into other terminal illnesses.

Methods: Patients with ESRD on RRT age 18 years and older with no cognitive defect were interviewed to evaluate their prognostic estimates at one and five years. Their past medical history and demographic data were abstracted from medical charts. Each patient's nephrologist was then interviewed regarding the prognostic estimate of the patient. Both patient and nephrologist estimates were then compared and a difference of greater than 20% divided the patients into two groups, prognostic concordance or discordance.

Results: 77% of the patients were found to be in prognostic discordance with their nephrologists. This group was older, had more comorbidities, a lower albumin level and a worse prognostic score. The majority of these patients were in disagreement with their nephrologists regarding whether a discussion about prognosis had occurred. The goals of care for 55% of patients was oriented towards an end of life focused on relieving pain and discomfort even if that meant a shorter duration of life.

Conclusions: Communication of prognosis and discussions related to life expectancy and planning for end of life care are lacking in routine care of ESRD patients. ESRD patients therefore tend to overestimate their prognosis, while half of the patients interviewed preferred an end of life care oriented towards symptom control, not longevity, this may lead to overutilization of invasive procedures and higher healthcare costs as well as a delay in palliative or hospice measures.

Table 5: Brief Perception Illness Questionnaire comparison of concordant & discordant patients

Brief Illness Perception Questionnaire: Mean of answers on a scale of 1-10	Concordant Group	Discordant Group	*p* - value
How much does your illness affect your life?	7.40	4.98	0.014
How long do you think your illness will continue?	6.33	7.37	0.200
How much control do you feel you have over your illness?	4.87	5.29	0.833
How much do you think your treatment can help your illness?	7.80	8.49	0.267
How much symptoms do you experience from your illness?	5.60	3.63	0.038
How concerned are you about your illness?	7.73	7.49	0.335
How well do you feel you understand your illness?	8.00	8.50	0.194
How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)	5.07	3.67	0.087

Table 6: Reporting of prognostic discussion discordance

Nephrologist reports having discussion	Patient reports having discussion		
	Yes	No	Total
Yes	13	17	30
No	18	18	33
Total	31	35	66

Table 7: Prognostic awareness comparison of concordant and discordant patients

Prognostic awareness (Patient) frequency and percentage		Concordant Group	Discordant Group	*p*-value
Do you believe that hemodialysis is extending your life?	Yes	15 (100%)	48 (94%)	N/A
	No	0 (0%)	3 (6%)	
Did your physician discuss your prognosis with you?	Yes	6 (40%)	25 (49%)	0.57
	No	9 (60%)	26 (51%)	
Would you like your physician to discuss this with you?	Yes	9 (82%)	18 (51%)	0.09
	No	2 (18%)	17 (49%)	
If you were seriously ill, would you prefer care to: Extend life, even if it meant more pain and discomfort		7 (47%)	22 (45%)	1.00
Relieve pain and discomfort, even it if meant not living as long?		8 (53%)	27 (55%)	
Are you aware that increased weight gain between dialysis sessions affects your prognosis negatively?	Yes	6 (40%)	20 (40%)	1.00
	No	9 (60%)	30 (60%)	
Are you aware that an uncontrolled phosphorus level affects your prognosis negatively?	Yes	3 (20%)	9 (18%)	1.00
	No	12 (80%)	42 (82%)	
Are you aware that a low albumin level affects your prognosis negatively?	Yes	5 (33%)	30 (58%)	0.76
	No	10 (67%)	21 (42%)	
Would you be interested in an educational course or information pamphlet regarding factors that might improve the course of your disease and life expectancy?	Yes	3 (20%)	24 (48%)	0.04
	No	12 (80%)	26 (52%)	
Prognostic awareness (Nephrologist) frequency and percentage				
Would you be surprised if this patient died within the following year?	Yes	11 (73%)	19 (37%)	0.02
	No	4 (27%)	32 (63%)	
Did you have a discussion with this patient regarding his/her prognosis?	Yes	7 (53%)	23 (45%)	1.00
	No	8 (47%)	28 (55%)	

TH-PO289

The Primary Cares Survey of In-Unit Dialysis Patient Primary Care Choices

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Background: The complexity of primary care(PC) management of patients undergoing chronic dialysis often leads to confusion by the patient, nephrologist and traditional PC practitioners regarding the responsibility for the management of their care. In addition to renal failure, dialysis patients have a significant number of co-morbid medical conditions and require numerous medications. Common beliefs regarding PC by patients and their practitioners are not well characterized. Centers for Medicare and Medicaid Services(CMS) has advanced the notion of the patient centered model of care. With the implementation of the ESRD Seamless Care Organizations(ESCO), CMS has placed the dialysis facility and providers as the principal coordinators of patient care, thus implying that PC provisions are incorporated. Ultimately, patients preferences are integral to care delivery and may prove intrinsic to the success or failure of the ESCO model. The objective of the survey is to characterize attitudes amongst dialysis patients regarding PC provisions.

Methods: The PRIMARY CARES (**Primary C**are **A**ttitudes and **Re**nal Replacement **S**election) survey was performed in 7 HD units in the NYC area representing a diverse population of ethnicities, languages (5) and socioeconomic categories with the objective of assessing factors influencing the utilization of PC services.

Results: 832 patients were approached and 511 completed the survey. Of these, 396 (77%) completed the question regarding having someone whom they consider to be their PC provider(PCP) with 44% reporting their PCP was their internist(IM) or family practitioner(FP) vs 45% reporting their nephrologist as their PCP. Regarding which practitioner they would seek for first management of an acute issue, 48% stated their IM/FP vs 38% their nephrologist. Regarding patient preference for PCP, 41% reported their IM/FP vs 44% for nephrologist.

Conclusions: Our results indicate that a significant percentage of dialysis patients identify, utilize and prefer non-nephrology practitioners rather than their nephrologists for acute medical care and PC needs. In the ESCO model, patient preference for, and utilization of, services outside the purview of the dialysis center is likely to have important consequences on the overall success of the program.

TH-PO290

Obstetric Outcomes in Poor CKD Pregnant Women in Mexico

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Background: CKD affects up to 6% of women of childbearing age. Despite that adverse obstetric outcomes are common in CKD pregnant women, the number of successful preganancies has increased over time, especially in high-income countries. We report outcomes in CKD pregnant women, followed at our integrated Obstetric and Renal Clinic.

Methods: Prospective study in CKD pregnant women followed between June 2013-December 2017. CKD was defined as per KDIGO guidelines. Dialysis was initiated when BUN was ≥ 45 mg/dL or when RRT was clinically indicated. Outcomes were compared between patients who required RRT vs conservative treatment.

Results: Table 1

Conclusions: Poor CKD pregnant women have a high rate of adverse obstetric outcomes. However, an integrated nephrological and obstetric prenatal care throughout all stages of CKD, could lead to successful pregancies, even in resource-constrained settings like ours.

Table 1

	All n= 63 (%)	Non-HD n= 43 (%)	HD n= 20	p
Age (y)	23.35 ± 5.8	23.8 ± 6.19	22.3 ± 4.9	0.33
Age < 19 y	14 (22)	9 (21)	5 (25)	0.75
Education < High-School	41 (65)	28 (65)	13 (65)	1.0
Known DM	6 (9.5)	4 (9.3)	2 (10)	1.0
Known HTN	13 (21)	8 (19)	5 (25)	0.73
1st Pregnancy	30 (47.6)	19 (44.2)	11 (55)	0.42
Hgb (g/dL)	10.71 ± 1.8	11.6 ± 1.3	8.8 ± 1.4	0.001
SCr (mg/dL)	2.6 ± 2.6	1.4 ± 0.6	5.2 ± 3.5	0.001
eGFR (ml/min/1.73 m2)	49.7 ± 36.6	63.9 ± 44.6	18.9 ± 16.1	0.001
BMI 25-29.9	12 (21)	7 (19)	5 (25)	0.51
BMI ≥ 30	4 (7.1)	3 (16)	1 (3)	0.10
Known CKD	31 (49)	25 (58)	6 (30)	0.03
on RRT	2 (3.1)	NA	2 (10)	0.07
Referral Pregnancy week	19.1 ± 8.2	19.7 ± 8.9	17.9 ± 0.6	0.42
CKD Stage	x	x	x	
1-2	8 (13)	8 (19)	0 (0)	
3	14 (22)	13 (30)	1 (5)	0.001
4	21 (33)	19 (49)	2 (10)	
5	20 (32	3 (7)	17 (85)	
CKD cause Unkown	33 (55)	20 (50)	13 (65)	
GN	11 (18.3)	10 9 (22.5)	2 (10)	
DM	6 (9.5)	4 (9.3)	2 (10)	0.68
CAKUT	8 (13.3)	4 (10)	4 (20)	
Other	3 (5.0)	3 (7.5)	0 (0)	
SBP (mmHg)	122.1 ± 21.1	121.7 ± 23.1	122.6 ± 16.6	0.87
DBP (mmHg)	78.1 ± 14.4	77.7 ± 14.8	78.8 ± 13.9	0.79
HD time/week (h)			14.63 ± 3.6	NA
URR			61.1 ± 7.9	NA
Kt/v			1.1 ± 0.5	NA
Preeclampsia	13 (21)	10 (23)	3 (15)	0.52
C-Section	48 (77.4)	32 (76)	16 (80)	1.0
Live Birth	56 (92)	39 (95)	17 (85)	0.17
Abortion	2 (3.2)	0 (0)	2 (10)	0.09
Stillbirth	1 (1.6)	0 (0)	1 (5)	0.31
Birth Weight (g)	2231.86±786.3	2281.9 ± 735.7	2119.6 ± 406.9	0.47
BW < 2,500	30 (52)	19 (45)	11 (69)	0.10
VLBW	9 (15.5)	4 (9.5)	5 (31)	0.01
Prematurity	29 (49)	4 (9.5)	13 (76.5)	0.0008
NICU admission	21 (38)	12 (31)	9 (53)	0.11

TH-PO291

Sex- and Age-Associated Differences in the Prevalence of Comorbidities in Dialysis Patients

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Background: In dialysis patients, the presence of non-renal comorbidities is associated with decreased quality of life and poorer outcomes. The prevalence of comorbidities in dialysis may vary by sex and age. We aimed to investigate the prevalence of the common comorbidities in dialysis patients within different age groups for both women and men.

Methods: We analyzed data from all hemodialysis (HD) patients at a large dialysis provider in 2016. Patients were grouped in 14 five-year age categories from 25 years old (y/o) to 95 y/o. For each age-group, we plotted the percent (%) of patients with an active comorbidity of anemia, diabetes (DM), cardiovascular disease (CVD), hyperparathyroidism (HPT), gastrointestinal (GI) bleeding, hypertension (HTN), and infection.

Results: Overall, we studied data from 230,091 patients; 43% were female. When compared to men in the same age group, we observed that: i) Anemia appears to affect a higher % of women 50 y/o and over 65 y/o, ii) Women suffer more infections at younger ages (25 y/o) and >75 y/o, iii) HTN is more prevalent in younger women (30-35 y/o) and in women >65 y/o when compared to men, iv) women show higher or similar prevalence of HPT at all ages, v) DM is more prevalent in women of most ages and, vi) CVD appear similar in men and women with a slight increase in men at age 75-85 y/o. No differences in GI bleeding were noted (Figure 1).

Conclusions: In this analysis we noted that the prevalence of comorbidities in dialysis patients varies by sex and age with a higher percent of women affected by anemia, HTN and DM. Further analyses are needed to elucidate if these differences affect dialysis outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

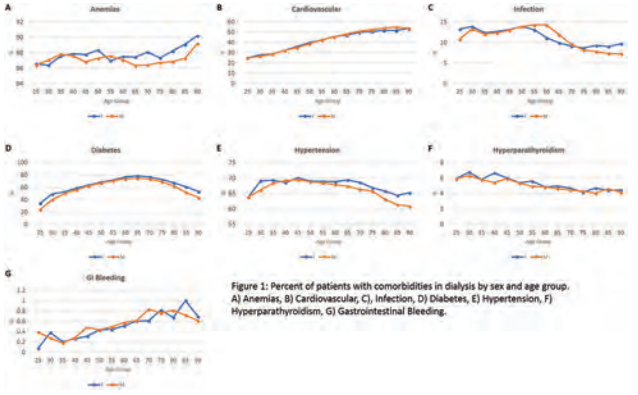

Figure 1: Percent of patients with comorbidities in dialysis by sex and age group. A) Anemias, B) Cardiovascular, C), Infection, D) Diabetes, E) Hypertension, F) Hyperparathyroidism, G) Gastrointestinal Bleeding.

TH-PO292

Gender-Specific Differences Associated with Sociocultural Attributes in Dialysis Patients: A National Cohort Analysis

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Background: Women and men have physiological differences that distinctly affect their health, treatment regimens, and clinical outcomes. Sociocultural factors may also play a significant role on these differences. We investigated whether certain sociocultural and certain clinical factors varied between men and women on dialysis.

Methods: All adult patients from a large dialysis provider who had a comprehensive social worker assessment and/or patient health questionnaire-2 (PHQ2) completed in 2016 were included. The association between sex, age (as of Jan 1, 2016) and sociocultural and clinical attributes noted in Table 1 was investigated. Chi-square and t-tests were used as appropriate.

Results: We included data from 209,378 patients. In both age groups, housing barriers and PHQ2 scores were greater in women, and physical component scores were higher for men. Food security was lower in younger women, but there was no difference by sex in older patients. In both age groups, married and unmarried men tended to rely on their spouse/partner while women tended to rely on a family member other than spouse/partner (Table 1).

Conclusions: Our analysis shows that among dialysis patients, several sociocultural and clinical factors differ between men and women. Further investigation is warranted to elucidate whether these factors influence sex disparities in health outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

Table 1:		18<=Age<55			Age ≥55		
Factors	Question	Female	Male	N P-value	Female	Male	N P-value
Housing	Is the patient's current living situation a barrier to positive treatment outcomes? Yes (%)	2.93	2.58	60,990 0.010	1.90	1.75	143,579 0.035
Depression	PHQ2>=2 (%)	33.93	28.97	49,596 <.0001	28.2	26.2	111,008 <.0001
Physical Function	Physical component score Mean (± std)	39.12 (±10.56)	41.08 (±10.54)	49256 <.0001	35.95 (±10.33)	38.09 (±10.57)	110,226 <.001
Food Security	Is access to food a concern to the patient? Yes (%)	1.91	1.64	60,990 0.013	0.91	0.91	143,579 0.902
Community	When you have a big problem, can you usually rely on:						
	No one but myself (%)	9.0	13.5	48,508 <.0001	7.8	11.0	108,265 <.0001
	Support from my spouse/partner (%)	30.6	35.6		24.4	48.6	
	A member of my family (%)	52.5	42.8		59.2	33.1	
	A friend/neighbor/ health staff/community resource/church (%)	7.9	8.1		8.6	7.4	

TH-PO293

Are Hemoglobin Levels Affected by Sex, Age, and Race in Dialysis Patients?

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Background: In the general population, women have lower reference ranges for hemoglobin (Hgb) levels compared to men, yet no differences are considered for anemia targets in people with chronic kidney disease (CKD). We aimed to explore if differences exist in Hgb levels between men and women initiating dialysis within different age groups and races.

Methods: Data from all incident patients in the United States Renal Data System (USRDS) from 2011-2015 was utilized via the RenDER system. Patients' were separated by sex, race (Asian (ASN), Black (BLK) and White (WHT), and age groups (0-19 years old (y/o), 20-39, 40-55, 56-79 and 80+). Average Hgb levels were obtained from the 2728 Medical Evidence form and compared among categories. The sex gap in Hgb levels $((Female_{Hgb}\text{-}Male_{Hgb})/Male_{Hgb})$ is evaluated for each category.

Results: Data from a total of 481,823 patients was analyzed; 203,804 (42%) were women. Although anemia targets do not differ between men and women with CKD, women tend to have lower levels of Hgb when starting dialysis, and this difference is greater for younger women. Young BLK women show a -4% and a -5.3% difference at ages 0-19 and 20-39, respectively, when compared to men. For young WHT women, Hgb levels differ from men by a -5.3% for the 0-19 y/o group, and a -3.3% for the 20-39 y/o group. However, young ASN women tend to have a smaller gap/difference in Hgb levels when compared to men (between -1 to 1% for 0-19 y/o and 20-39 y/o). The sex gap/difference in Hgb levels becomes less apparent in older age groups of women for the races analyzed (Figure 1).

Conclusions: Findings suggest that there may be differences in Hgb levels between the sexes that vary with age and race, which are most noticeable in WHT and BLK patients. More analyses are necessary to investigate if these sex, age and race dependent differences in Hgb levels affect health outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

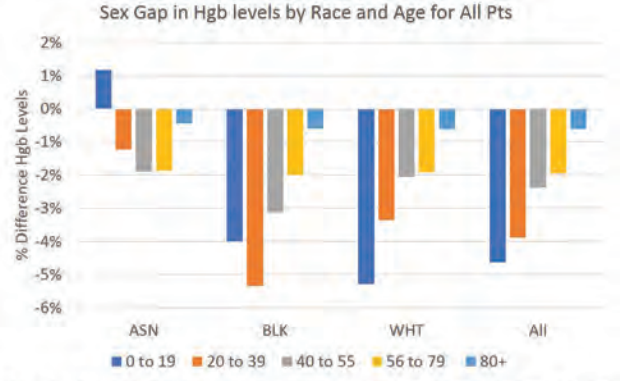

Figure 1: Gap/difference between mean Hgb levels measured in females and males by age and race. Negative values reflect females have a lower mean Hgb levels versus males.

TH-PO294

Evaluation of Diabetes-Related Knowledge Among African American Dialysis Patients

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Background: Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) in the United States, accounting for nearly half of all cases. Although training patients with diabetes on self-management may help improve their health outcomes, the vast majority of U.S. dialysis clinics do not provide diabetes self-management education. As part of a diabetes education program introduction assessment, we examined baseline diabetes-related knowledge and care practices among patients with diabetes at the Emory dialysis clinic. Our overall aim is to introduce diabetes education in the clinic and subsequently assess the impact on clinical outcomes among dialysis patients with diabetes.

Methods: A questionnaire assessing diabetes knowledge and practices was administered on all ESRD patients with diabetes attending the clinic. Data on endocrinology care, most recent HbA1c results and history of amputations were also obtained. Introduction of regular foot checks during dialysis treatment with appropriate referrals to podiatry has now been introduced as a routine clinical practice in the clinic. Review of a diabetes curriculum and recruitment of a specialist diabetes educator is ongoing.

Results: Of the 155 patients, 87 (56%) have a diagnosis of diabetes. 85 (98%) were African Americans, 50 (58%) are males. The mean age was 63 years. The average HbA1C was 6.5%. Only 20 (25%) of the patients were aware of their most recent HbA1C results. About 12 (16%) had a history of limb amputations. A history of vascular studies was documented in 38 (48%) of the patients. Approximately 65 (82%) and 60 (76%) of the patients practiced self-foot and glucose checks respectively. About half of all patients

reported receiving endocrinology care. A total of 17 (20%) patients had abnormal foot examination and were referred for podiatry evaluation

Conclusions: A small proportion of the African American Diabetic ESRD patients were aware of factors that could impact their outcome. Introducing diabetes self-management education at dialysis clinics may help improve patient knowledge and potential clinical outcomes.

TH-PO295

The Impact of Race and Ethnicity upon Health-Related Quality of Life and Mortality in Dialysis Patients

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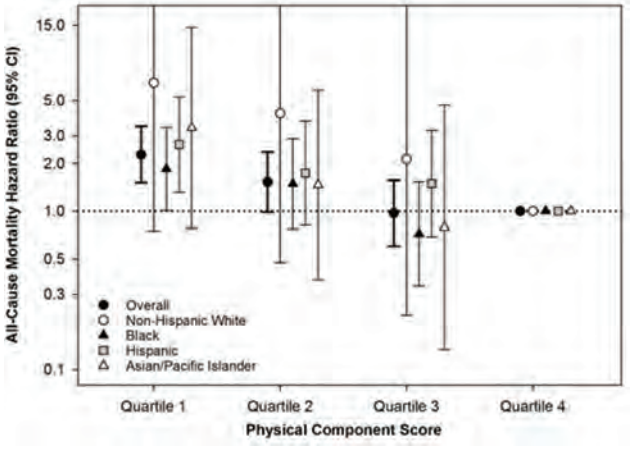
Background: While health-related quality of life (HRQOL) has been increasingly recognized as a strong predictor of mortality among hemodialysis (HD) patients, differences in these associations across diverse racial/ethnic groups have not been thoroughly investigated.

Methods: We examined the relationship between HRQOL and mortality among a prospective cohort of racially/ethnically diverse HD patients recruited across 18 dialysis units over 2011-16. Using Short Form 36 (SF36) surveys administered every 6 months, HRQOL was ascertained by 36 questions summarized as 2 physical and mental health dimension and 8 subscale scores. Associations of time-varying SF36 scores with all-cause mortality were estimated using multivariable Cox models in the overall cohort and within racial/ethnic subgroups.

Results: Among 753 HD patients who met eligibility criteria, the lowest quartiles (Q) of physical and mental health dimension scores were associated with higher mortality in the overall cohort (ref: highest Q): HRs (95% CIs): 2.18 (1.43-3.32) and 1.56 (1.06-2.28), respectively. In analyses stratified by race/ethnicity, among Blacks and Hispanics the lowest Q of physical health dimension scores was significantly associated with higher mortality, whereas in Non-Hispanic Whites and Asian/Pacific Islanders point estimates of the lowest Q suggested higher death risk but did not reach statistical significance. The lowest Q of physical functioning, energy/fatigue, and pain subscale scores were associated with higher mortality in the overall cohort, and were particularly pronounced in Blacks and Hispanics.

Conclusions: Lower self-reported HRQOL scores, particularly related to impaired physical health dimension and subscales, were associated with higher mortality in HD patients, including those of minority background. Further studies are needed to determine whether interventions that augment physical function improve the survival of these diverse populations.

Funding: NIDDK Support



TH-PO296

Quality of Life Reported by Patients with Expanded Hemodialysis by the TheraNova Dialyzer in RTS Colombia

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Background: Patients on hemodialysis have a lower quality of life compared to the general healthy population. Some factors such as restrictions on diet and physical activity, presence of symptoms and time consumed in treatment greatly affect the level of quality of life perceived by patients. The purpose this study was to evaluate changes in quality of life and prevalence of restless legs in the first six months after initiating a change in dialysis therapy from high-flux HD to expanded hemodialysis(HDx) with Theranova dialyzer.

Methods: Cross-sectional study in prevalent hemodialysis patients older than 18 years, enrolled between September 1st and November 30th, 2017, when converted to HDx, in 12 renal clinics of the Renal Therapy Services (RTS) Colombia network. KDQOL ™ 36 and the diagnostic criteria of restless legs were administered 2 times, at baseline and 6 months later. For the analysis, descriptive statistics, ANOVA and Mc Nemar test were used.

Results: 666 patients were evaluated, 61.4% (n =409) were men, the mean age was 59.8 years (SD = 15.3), 60.3%(402) were more than 3 years old in dialysis. We found significant improvements in a large part of the dimensions of quality of life in the time. Details are presented in table 1 In addition, we observed significant reduction of the diagnosis of restless legs. See table 2.

Conclusions: The expanded hemodialysis positively impacts on quality of life and diagnosis of restless legs The results reported by the patients are a valuable intervention that can guide health interventions in search of better clinical results.

Funding: Commercial Support - Baxter Healthcare Corporation

Table 1. KDQOL ™ Quality of Life 36

KDQOL™ 36	Baseline Mean (SD)	Six months Mean (SD)	Difference	P value*
Symptom/problem list	77.75 (16.05)	81.08 (15.07)	3.30	0.0000
Effects of kidney disease	68.90 (22.31)	72.70 (21.89)	3.84	0.0000
Burden of kidney disease	46.48 (27.66)	50.23 (29.74)	3.72	0.0006
SF-12 Physical Health Composite	40.98 (11.24)	41.13 (11.39)	0.14	0.6670
SF-12 Mental Health Composite	51.05 (11.78)	52.10 (11.15)	1.01	0.0348
Table 2. Diagnostic criteria of restless legs				
Diagnostic Criteria of Restless legs	Baseline N (%)	Six months N (%)	Difference %	P value**
Diagnostic Criteria of Restless legs	155 (23.34)	76 (11.46)	11.88	0.0000

*Anova ** McNemar Test

TH-PO297

Impact of Extended Hours Dialysis on Quality of Life Measured by EQ-5D and SF-6D Utility Instruments

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Background: Health economic evaluations often rely on measurements of health utility. Validated health utility assessment tools are available but whether they perform similarly is rarely assessed. We aimed to estimate the effect of extended hours dialysis on utility-based quality of life (QOL) using two multi-attribute utility instruments.

Methods: The ACTIVE Dialysis trial randomised 200 participants to extended hours (≥24 hours/week) or standard hours (≤18 hours/week) haemodialysis for 12 months. Utility-based QOL was assessed every three months by the EuroQOL-5 Dimensions (EQ-5D) and Short Form-6 Dimensions (SF-6D). The mean difference in utility weights between groups was obtained by mixed linear regression. Quality adjusted life years (QALYs), a measure that combines survival and quality of life, were calculated.

Results: Extended dialysis hours did not improve utility-based QOL measured by the EQ-5D (0.036 [95%CI -0.022, 0.093]; p=0.223) but did significantly improve it when measured by the SF-6D (0.027 [95%CI 0.003, 0.052]; p=0.026). There was no significant difference in mean QALYs gained per patient from extended over standard dialysis as measured by the SF-6D (0.015 [95%CI -0.070, 0.041]) or the EQ-5D (0.029 [95%CI -0.108, 0.049]) - equivalent to a mean per patient gain of 5.5 (95%CI -25.6, 15.0) and 10.6 (95%CI -39.4, 17.9) days of perfect health, respectively.

Conclusions: The EQ-5D and SF-6D resulted in distinct interpretations of utility-based QOL differences in extended hours dialysis, although the significant improvement in utility-based QOL found with the SF-6D did not translate into a significant gain in QALYs. These results emphasise the need for a better understanding of the impact of different scoring algorithms and instrument properties on the performance of multi-attribute utility instruments to measure QOL in dialysis patients.

Funding: Commercial Support - Baxter International, Government Support - Non-U.S.

TH-PO298

The Symptom Profile of Hemodialysis Patients in Ontario

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Background: People requiring dialysis reportedly experience a high symptom burden. However, there are few large studies assessing symptoms of this patient population over time. The Ontario Renal Network (ORN) is pilot testing a standardized provincial approach

to symptom screening, assessment, and management using the Edmonton Symptom Assessment System Revised: Renal (ESAS-r:Renal).

Methods: Eight Regional Renal Programs in Ontario were selected to participate in a one year pilot project. Participating programs routinely assess patients undergoing in-facility hemodialysis with ESAS-r:Renal every 4 to 6 weeks. The ESAS-r:Renal questionnaire asks patients to self-report the severity of 12 symptoms between 0 (no symptom) and 10 (worst possible symptom).

Results: Between April 1 and December 31, 2017, there were 5,839 screening attempts by 1,267 patients with 90% of the questionnaires fully completed and 5% partially completed. Forty-two percent of patients were female, 48% had diabetes (Type 1 or 2), and 32% were on dialysis for 5 or more years. Patients frequently reported changes in symptom scores over time. Tiredness was the most common symptom reported (76% of all surveys) and nausea the least reported (26% of all surveys). Scores of 7 or greater were recorded frequently (pain [14%], tiredness [22%], drowsiness [12%], nausea [3%], poor appetite [7%], shortness of breath [6%], depression [7%], anxiety [6%], poor wellbeing [11%], itching [12%], problems sleeping [17%], and restless legs [13%]).

Conclusions: Patients receiving in-facility dialysis frequently have symptoms. The degree to which the symptoms reported through ESAS-r:Renal can be modified and improved requires further research.

Funding: Government Support - Non-U.S.

TH-PO299

What Patients and Caregivers Want in a Personalized Mobile Dialysis Unit

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Background: The Center for Dialysis Innovation (CDI) at the University of Washington (UW) is designing an Ambulatory Kidney to Improve Vitality (AKTIV), a personalized and ambulatory device that will function as an artificial kidney for ESRD patients. Project objectives include developing, testing, and conducting clinical trials demonstrating feasibility of AKTIV to improve the current thrice-weekly hemodialysis treatment. Modern theory of device/product construction calls for user input during conception and design. As we develop the technical aspects of AKTIV, user input is crucial to ensure that engineers and clinicians have target parameters for their final output. Our first set of interviews gathered data from patients and their caregivers and focused on ways to increase the usability of a mobile and self-contained dialysis device.

Methods: At the National Kidney Foundation meeting in Portland in March 2018, we interviewed 26 patients and caregivers with a pre-interview survey and semi-structured interview about their design and feature preferences for a novel, personalized mobile dialysis unit. The 26 participants were between the ages of 24 and 82 years (M = 60.2, SD = 13.9), of which 14 were female, and 19 were patients. Content analysis was performed on the interviews.

Results: Participants chose the belt type for most preferred and the distributed type (parts of the device are separated from each other on the body) for least preferred compared to backpack, vest, and shoulder bag types ($F(4, 124) = 2.80$, $p < 0.05$). Participants reported that the most important features of a wearable dialysis unit were its accuracy and safety, compared to ease of use, comfort, compact, and simplicity to operate ($F(5, 143) = 13.14$, $p < 0.001$). Such preferences varied based on age, gender, and familiarity with wearable devices. Based on this input, we will design up to three different prototypes that were ranked the most preferred.

Conclusions: The interest and motivation of patients and caregivers to be involved in the creation of a personalized and mobile dialysis unit that works essentially as an artificial kidney is extremely high. From qualitative analysis and discussions, the dominant impression we have is patients want the device to be as unobtrusive as possible. We summarize by quoting a patient, "I don't want to be identified as a dialysis patient when I walk into a room."

Funding: Private Foundation Support

TH-PO300

Patient Satisfaction Score in Relation to Hemodialysis Guidelines and Practices: A European Multicenter Analysis

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Background: Understanding patient values and exploring their preferences is critical to caring for the dialysis population. Little is known about the factors that influence patient satisfaction compared with other measured clinical indices of care. We investigated these factors in an international European multicenter descriptive analysis.

Methods: We enrolled 845 HD patients from 13 DaVita centers in Poland (8 centers, n=453) and Portugal (5 centers, n=392). An anonymous patient survey was conducted (14 questions; 5-grade scale: "agree completely" to "disagree") focusing on patient satisfaction with their care at the local facility. Practices, demographic, and laboratory data were analyzed for the same month that the survey was performed and correlated to the survey results at the facility level.

Results: The survey response rate was 81% (range 72-100%). Mean (SD) age was 68 (14) years; 53% were male. Mean Charlson comorbidity index was 7.1 (3.0); 76.3% used AVF, 16.5% used CVC. Mean (SD) Kt/V was 1.8 (0.4), albumin was 39.5 (4.3) g/L, phosphorus was 4.7 (1.3) mg/dL and PTH was 512 (481) pg/mL Mean (SD) patient satisfaction score (0-10) was high 9.1 (1.6) and the net promoter score was 71. High scores (> 90% agree) were observed for all but one of the 14 questions ("*I'm happy with my transportation provider";* 85% agree). Spearman correlation analyses at the facility level showed that patients involved in decision making had higher Kt/V ($p=0.02$). Patients who agreed that their "*chairs and linen were comfortable"* had lower phosphorus ($p=0.02$) and higher Kt/V ($p<0.001$). Patients "*happy with their transportation provider"* had higher Kt/V ($p=0.002$) and lower phosphorus ($p<0.05$) and patients who agreed that their "*treatment started on time"* had higher Kt/V ($p=0.05$). The overall satisfaction score was higher with low Kt/V ($p=0.004$) and high phosphorus ($p<0.05$).

Conclusions: Patient satisfaction surveys provide a critical perspective on the quality of patient-centered healthcare delivery. Information derived from direct evaluation of patient experience of care can be used to identify areas for improvement and support changes in care provision with the aim of improving the overall quality of care for patients.

Funding: Commercial Support - DaVita, Inc

TH-PO301

Assessing a Modified Edmonton Symptom Assessment System as a Patient Report Outcome Measure for Patients on Dialysis in Canada

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Background: Patients with end-stage renal disease (ESRD) often experience heavy symptom burden that is under-recognized in the absence of routine and systematic assessment and management, resulting in poor quality of life. In Canada, British Columbia has implemented a modified Edmonton Symptom Assessment System (mESAS) to monitor symptom burden in patients with ESRD. Completion of the mESAS was voluntary. Implementation started in 2010 and was staggered across facilities. We investigated whether the mESAS functions as a patient-reported outcome measure (PROM) for patients on dialysis, specifically whether the mESAS is feasible to use in routine assessment and is responsive to changes in patient symptoms over time.

Methods: The dataset comprised 3,573 patients from 7 dialysis facilities in British Columbia, 62% of whom had completed at least 1 assessment. Of these, 77% completed more than one assessment that can be used for longitudinal analysis. The dataset included assessments performed between March 2010 and April 2016. We used descriptive statistics to examine mESAS practice and changes in symptom scores over time.

Results: Of the patients with more than 1 mESAS assessment, the majority (69%) of adjacent assessments were completed within a 3 ± 1.5 month timeframe, and an additional 16% were completed within a 6 ± 1.5 month timeframe. For symptoms that were scored within the severe category (between 7 and 10 on the scale), the majority improved to below the severe category in a subsequent assessment. Across years, the proportion of symptom scores in the severe category demonstrated a change to lower scores using the mESAS. The results for improved symptoms scores across centres and years varied between 68 and 93%.

Conclusions: There was sufficient data available for analysis of mESAS scores and changes in scores over time. Serial collection of this data allows a real time opportunity to assess symptom burden at a specific point in time as well as the responsiveness of mESAS over time. There is also important value in collecting PROMs in renal patients to further explore how PROMs can be used to evaluate symptom management strategies and thereby optimize patient quality of life.

TH-PO302

A Multicenter Survey in Toronto of Opinions on Driving Safety in Hemodialysis Patients

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Background: Hemodialysis patients are at an increased risk of adverse health events from operating a motor vehicle and may have their license withdrawn due to safety concerns. However, little is known about the perspectives of nephrology health care practitioners towards driving safety for hemodialysis patients and their awareness of best practice. The purpose of this study was to survey health care practitioners to identify their opinions towards driving practice and safety for hemodialysis patients.

Methods: We developed a 16-item questionnaire about driving safety using a Delphi model with input from 4 nephrologists, 2 nurse practitioners, 2 social workers and 1 nephrology fellow. The questionnaire was distributed amongst the 3 academic hemodialysis centers affiliated with the University of Toronto in Toronto, Canada. All voluntary participants were healthcare professionals caring for dialysis patients. Questionnaires were emailed to participants and their responses were completed on a secure website link.

Results: The survey was distributed to 154 persons with a response rate of 39%. 52% (31) of responders were hemodialysis nurses, 15% (9) were nephrologists and other responders included fellows and other allied healthcare professionals. 60% (36) of responders had greater than 10-years of experience. 88.3% of responders knew of at least one patient who drove regularly. 80% of responders never reported a patient to the provincial

driving authority despite safety concerns. Responses were unchanged despite participants being presented with 3 clinical hypothetical scenarios of unstable patients that drove to hemodialysis sessions. This suggests that participants did not recognize the safety concerns in hypothetical situations where reporting should have occurred. Participants likely did not report patients due to the lack of clear guidelines along with no current mandated reporting requirements. This was further supported by 97% of all responders agreeing that more robust driving guidelines are warranted.

Conclusions: Our preliminary results underscore the lack of clarity, consistency and knowledge with regards to driving safety in hemodialysis patients. Larger national scale surveys will further support the prevalent opinion in Toronto that more comprehensive driving guidelines for hemodialysis patients are warranted.

TH-PO303

Employment 6 Months Prior to and at Dialysis Start: Validation Evidence for CMS-2728 Data

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Background: The CMS-2728 is a unique source of patient employment status 6 months prior and at dialysis start. A USRDS analysis of patients 18-54 initiating in-center hemodialysis (HD) or home dialysis 1996-2013 showed a persistent pattern of job loss in the 6-month pre-dialysis interval (CJASN 2018). The CMS-2728 employment field has not been independently validated, however. We compared incident patients' interview responses obtained approximately 2 months after dialysis start with corresponding employment information from their CMS-2728 report.

Methods: Patients who began in-center HD or home dialysis July 1996-August 1997, English- or Spanish-speaking and without documented cognitive impairment, were recruited for a study of health behaviors/quality of life from 26 dialysis clinics serving the Atlanta GA 23-county area. Participants represented eligible patients in age, race and functional status but the cohort included fewer women. Structured in-person interviews were conducted at a non-dialysis facility location convenient for the patient 67.3 ± 19.5 days after dialysis start. 95/226 study participants were ages 20-54 (median 43) with women 47%; blacks 58%; non-Hispanic whites 35%; and Hispanic, Asian, other 7%. CMS-2728 employment status options include: unemployed, employed full time (FT), employed part time (PT), homemaker, retired (age/preference), retired (disability), medical leave of absence, and student. The patient interview asked: Are you working now (hours/week)? job being held? retired or stopped working; when? keeping house? student (FT, PT)? Using FT, PT, or student to define employment (CJASN 2018), we identified the unadjusted proportion of patients employed 6 months prior and at dialysis start, reported by the CMS-2728 and by patients.

Results: Compared with their CMS-2728 data, 8% more patients reported being employed 6 months prior, while 6% fewer patients reported current employment. Potential job maintenance opportunities were suggested by patients who reported having switched from FT to PT work, said their prior job was "being held," cited a medical leave of absence, or reported being "let go" from their job (in all, 14% of the cohort).

Conclusions: Our study suggests that CMS-2728 employment fields have good validity. Effective interventions are needed to help patients remain in the workforce as they transition to dialysis.

Funding: NIDDK Support

TH-PO304

Reducing Polypharmacy in Dialysis Patients

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Background: Polypharmacy is a freqent problem for patients receiving maintenance dialysis and may increase risk of adverse events and drug interactions. Previous studies have identified 4 drug classes (proton pump inhibitors [PPI], alpha 1 blockers [A1B], diuretics, and statins) in which use may not be necessary in patients receiving maintenance dialysis. This study examined overall medication use and use of 4 non-essential drug classes.

Methods: This study was comprised of 168 patients receiving maintenance dialysis at a single dialysis unit. The mean age was 60.4 (SD 15.8) and median dialysis vintage was 2.4 years with a range of 0.2 to 13.9 years. Overall 49.1% were male. Diabetes mellitus (49.1%) and hypertention (18.0%) were the two main causes of end stage renal disease. The average number of prescribed medications was 11 (SD 5) and ranged from 2-26 medications but was higher among women (11[SD 4]) than among men (10[SD 5]).

Results: Of the 4 non-essential drugs, 51.5% were taking at least one of these drugs, 36.9% were taking at least 2, and 11.5% were taking at least three non-essential medications. Statin use was most common at 56.3% overall and among patients age 70+ years, 75% were using statins. PPI and diuretic use wee noted in 32.5% and 31.7% respectively. A1B use was noted in 8.5% of men with a dialysis vintage of 2.4 years. If the 4 non-essential drugs were eliminated, the average number of medications would decrease to 9 (SD 4) overall, to 9 (SD 5) among men and to 10 (SD 4) for women.

Conclusions: In conclusion, use of non-essential medications is common among patients receiving maintenance dialysis. Elimination of non-essential medications would lead to a reduction of about 1 medication on average. Targeted de-prescribing may help reduce polypharmacy in this patient population.

TH-PO305

Long-Term Follow-Up of Respiratory Function in Maintenance Hemodialysis Patients Following an In - Center Exercise Program for 24 Months

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Background: In spite the well documented benefit of physical exercise on hemodialysis patients (HD) only few reports concern the long-term effect on respiratory function. We designed this study to investigate the effects of continuous moderate-intensity programme applied during hemodialysis sessions by a physiotherapist, on parameters in spirometry.

Methods: We enrolled 60 maintenance HD patients in this study. 44 stable HD patients participated in a 20 – 30 minute exercise program of moderate intensity targeting muscle strengthening and elasticity, articular flexibility in every session for 24 months. 16 HD patients who did not participated served as controls. Spirometry: Forced Vital Capacity (FVC), FVC %, Forced Expiratory Volume in One second (FEV1), FEV1 % and Forced Expiratory Flow over middle half of the FVC – that is, average flow from 25 % of the FVC to 75 % of the FVC during forced expiration (FEF 25 – 75 %) was performed at 0, 12 and 24 months along with biochemical tests: Hct, CRP, Chol, TG, LDL, HDL, TP, Alb, HbA1C and dialysis adequacy (Urr, Kt/V).

Results: Overwhelming acceptance of the program resulted in continuous and constant participation. 7 patients (12 %) were found with undiagnosed COPD in the beginning of the study. Respiratory indices were comparable either the test was performed before or after the HD session. FEV1/FVC index was improved at 12 months and remained improved at 24 months only in the exercising group (76.6 ± 10 v s79.6 ± 8 vs 81.5 ± 7, $p<0.05$).

Conclusions: Adaptation of a thrice weekly exercise program under physiotherapist guidance resulted in the enthusiastic participation of patients and it is one of the longest that have been reported. Patients following the long term exercise improved FEV1/FVC over the follow-up period. Evaluation of respiratory function should be performed in all patients starting dialysis since it reveals latent morbidity. In spite the reports of deterioration of pulmonary function in the long term of maintenance HD the latter remained stable in the control group.

TH-PO306

Aerobic versus Anaerobic Exercise and Oral Nutritional Supplementation Related to Nutritional Status and Physical Function of Adult Haemodialysis Patients: AVANTE Study

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Background: Protein energy wasting affects the nutritional status (NS) and physical function (PF) of dialysis patients. Oral nutritional supplementation (ONS) and resistance exercise (RE) or aerobic exercise (AE), have been shown to be effective for NS and PF. Nevertheless, the combination of RE and AE with ONS has not been completely elucidated. The aim of this study was to assess the effect of a 12-week intradialytic RE or AE program combined with ONS versus ONS without exercise on PF and NS indicators.

Methods: Patients were divided in to three groups: 1) ONS, 2) ONS + RE and 3) ONS + AE. Anthropometrics [body mass index (BMI), body weight (BW), midarm circunference (MAC), arm muscle circumference (AMC) and arm muscle area (AMA)], PF tests [sit to stand, time up and go and six minute walk tests (6 MWT)] and quality of life (QOL) by KDQOL-SF36 were recorded.

Results: All groups had statistical significant increases in BW, BMI, MAC, AMC and AMA ($p<0.05$). All patients significantly improved the three different PF tests and muscle strength; however, groups with AE and RE increased 43 and 42 metres respectively the distance walked in six minutes; while the ONS group increased 11 metres ($p<0.05$). Regarding QOL, the group with ONS + RE shown to have more areas of improvement at the end of the study (sleep, general health and social function, $p<0.05$), followed by the group with ONS + AE (emotional role, $p<0.05$).

Conclusions: The effect of RE or AE combined with ONS versus ONS without exercise improves the PF and NS; however, PF measured with the 6 MWT and QOL was better at the end of the study in both groups with exercise. No statistical significant differences were observed between groups at the end of the study. All interventions have a positive effects on NS and PF.

Funding: Private Foundation Support

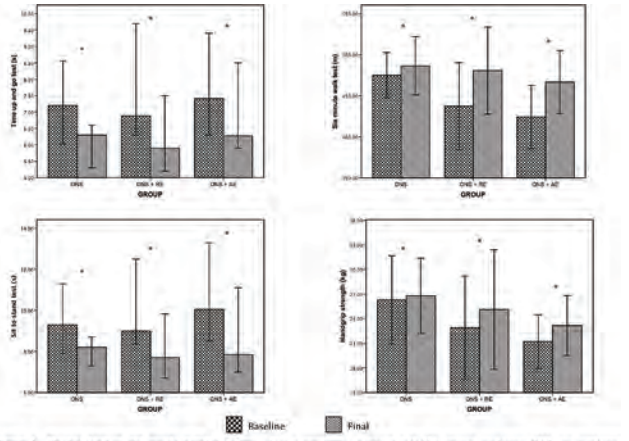

Figure 2. Physical function and muscle strenght changes. Data is represented in median with 95% interval confidence. ONS, oral nutritional supplementation; ONS + RE, oral nutritional supplementation plus resistance exercise; ONS + AE, oral nutritional supplementation plus aerobic exercise. The asterik indicates p<0.05 for the comparison from baseline of each group. No statistical significance difference was observed between groups.

TH-PO307

Dialysis Therapy and Gait Speed: A Repeated Measures Analysis of US Patients on Chronic Dialysis

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Background: Slow gait speed, a patient-centered yet understudied clinical outcome, is a common and independent predictor of future disability, hospitalizations and death among patients with chronic kidney disease. Prior studies have shown that improper fluid management is a likely contributor to physical impairment, but lack of data on the relative importance of the many fluid-related components of dialysis therapy (e.g. baseline fluid overload, blood pressure, and ultrafiltration rate) has limited consensus and evidence-based guideline development. Analyses are needed to understand which managed aspects of dialysis therapy are most associated with functional status declines.

Methods: We measured gait speed at baseline, 12 months, and 24 months, among 652 patients on hemodialysis recruited in the ACTIVE/ADIPOSE cohort study. We used linear mixed effects modeling to examine associations between demographic, comorbid, social, and laboratory data with gait speed trajectory. We then added degree of bioimpedance-measured predialysis volume overload (defined as a fluid state >= 15% relative to extracellular water volume in men and >=13% in women), dialysis treatment time, ultrafiltration rate, and predialysis systolic blood pressure to ascertain whether treatment-related factors were associated with gait speed or its change over time.

Results: Mean gait speed at baseline was 0.94 m/s and declined an average of 0.08 m/s per year. In adjusted analysis, nonwhite race (-0.14 m/s, 95% CI -0.19 to -0.08), female sex (-0.10 m/s, 95% CI -0.13 to -0.06), and BMI > 35 kg/m2 (-0.09 m/s, 95% CI -0.15 to -0.03) were associated with slower gait speeds. Predialysis volume overload was associated with slower gait speed (-0.06 m/s, 95% CI -0.11 to -0.01), but was not a statistically meaningful predictor of future gait speed trajectory. Dialysis treatment time, ultrafiltration rate, and predialysis systolic blood pressure were not independently associated with gait speed.

Conclusions: Certain factors place patients on dialysis at increased risk of slowed gait speed, including a state of predialysis volume overload. Interventions that focus on limiting states of volume overload, compared to other managed aspects of the dialysis treatment, may be more meaningful in limiting gait speed impairment.

Funding: NIDDK Support

TH-PO308

Intradialytic Activities and Health-Related Quality of Life

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Background: Given the time burden and physiologic effects of hemodialysis, patients who spend dialysis time physically or intellectually engaged may have better health-related quality of life (HRQOL). We sought to characterize the association between intradialytic activities and HRQOL and explore patients' interest in performing intradialytic interventions.

Methods: In a prospective cohort study of 431 prevalent hemodialysis patients, an activity score was assigned on a scale of 0-5 points for each active intradialytic task (read, electronic games, puzzles, chat, other-physical/cognitive). We quantified the association between KDQOL components and activity using adjusted linear regression.

Results: The two most common intradialytic activities reported by patients were passive [watching TV (87.9%) and sleeping (72.4%)]. Patients who were female (aOR=1.85, 95%CI:1.28, 2.66; p=0.001), nonfrail (aOR=1.70, 95%CI:1.06-2.70; p=0.03), and nonsmokers (aOR=2.61, 95%CI:1.39, 4.90; p=0.003) had a higher intradialytic activity. Additionally, higher intradialytic activity was associated with better mental HRQOL (+0.83 points, 95%CI: +0.04, +1.62; p=0.04) and kidney disease-specific HRQOL (+1.70 points, 95%CI: +0.47, +2.93; p=0.007), but not physical HRQOL. Each one-point increase in the activity index was associated with a 1.29-fold and 1.25-fold increased odds of interest in intradialytic cognitive training and physical exercise.

Conclusions: Hemodialysis patients with more active intradialytic activities report better mental and kidney disease-specific HRQOL and increased interest in participating in intradialytic interventions. Dialysis providers may consider offering patients with low levels of activity additional support and opportunities to engage in beneficial intradialytic activities.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, Private Foundation Support

	Difference in HRQOL score for each 1- point increase in activity index (95% CI)	P- value
Physical HRQOL	0.52 (-0.27, 1.31)	0.19
Mental HRQOL	0.83 (0.04, 1.62)	0.04
Domains:		
Physical functioning	1.97 (-0.02, 3.95)	0.05
Role limitations due to physical health problems	0.73 (-2.28, 3.75)	0.63
Bodily pain	1.28 (-0.95, 3.52)	0.26
General health	1.27 (-0.60, 3.14)	0.18
Emotional well being	1.33 (0.03, 2.62)	0.04
Role limitations due to emotional problems	1.56 (-1.14, 4.25)	0.26
Social functioning	1.71 (-0.41, 3.83)	0.11
Energy	2.97 (1.10, 4.84)	0.002
Kidney disease-specific HRQOL	1.70 (0.47, 2.93)	0.007
Domains:		
Symptoms	1.32 (0.03, 2.61)	0.046
Effects	2.18 (0.40, 3.96)	0.02
Burden	2.76 (0.35, 5.17)	0.03
Cognitive function	0.18 (-1.29, 1.66)	0.81
Social interaction	1.01 (-0.38, 2.41)	0.16
Sleep	2.66 (0.81, 4.51)	0.005
Social support	1.79 (-0.07, 3.66)	0.06

TH-PO309

The Association Between Handgrip Strength (HGS) and Predialysis Sodium (sNa) in Patients with CKD Stage 5D

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Background: HGS is a useful tool for continuous and systematic assessment of muscle function related to nutritional status. Reduced HGS has been associated with adverse clinical outcomes in patients with stage 5D CKD. In the same patients, low sNa has been associated with malnutrition and mortality. Here, we investigated the role of sNa on muscle mass and function in stage 5D CKD patients.

Methods: We evaluated 73 CKD stage 5D (45 on hemodialysis and 28 on peritoneal dialysis) patients (43 men and 30 women) with HGS, bioimpedance analysis (BIA), anthropometric measurements and malnutrition inflammation score (MIS). According to the diagnostic criteria for sarcopenia established by EWGSOP, patients were diagnosed with reduced HGS, if HGS was below 30 Kg and 20 Kg in men and women, respectively. Predialysis sNa values were defined as the mean of all predialysis measurements available during the preceding 6 months.

Results: Patients with reduced (n=28) as compared to the those with normal HGS (n=45) were older in age (p=0.006), had lower skeletal muscle index (SMI) (p=0.004), mid-arm muscle circumference (MAMC) (p=0.043), sNa (137±2.3 vs. 139.5 ± 2.2 mmol/L; p=0.004), serum albumin (sAlb) (p=0.029) and higher MIS (5.13±2.62 vs. 3.82±2.34; p=0.034). In multivariate logistic analysis, after controlling for age, SMI, MAMC, sAlb and MIS, each increase in sNa by 1 mmol/l was associated with 28 % (OR= 0.72, 95% CI: 0.55-0.94; p <0.05) lower odds of having reduced HGS. sNa was positively associated with HGS (r=0.384; p<0.001) and SMI (r=0.295; p<0.05). In a forward stepwise multivariate (sex, SMI, MAMC, sALB, MIS) model (R^2= 0.499; p<0.001), sNa, along with SMI and sex, emerged as a strong independent predictor of HGS (B=0.791; p<0.05) explaining about 3 % of its variance.

Conclusions: Our results show that a) sNa is strongly associated with both muscle mass and muscle function, b) sNa impacts on muscle strength independently of muscle mass, nutritional status and inflammatory state and c) irrespective of the mechanism(s) underlying the HGS-sNa association, optimizing predialysis sNa may improve HGS and thus clinical outcomes in 5D CKD patients.

TH-PO310

Utility of Regular Management of Physical Activity and Physical Function in Hemodialysis Patients

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Background: Several clinical practice guidelines recommend regular assessment of physical activity and physical function as part of routine care in hemodialysis patients. However, there is no clear evidence to support these recommendations. We investigated whether the proportion of attendance at a regular program for management of physical activity and physical function can predict all-cause mortality and cardiovascular events in hemodialysis patients.

Methods: This retrospective cohort study consisted of 266 hemodialysis patients participating in the management program at least once. Participants were tracked for 3 years after their first attendance at the management program to determine their attendance proportion. The main study outcomes included all-cause mortality and a composite of fatal and nonfatal cardiovascular events.

Results: Median patient age was 64.5 (interquartile range, 56.8–72.0) years, 45% were women, and the median time on hemodialysis was 35.5 (interquartile range, 12.0–114.3) months at baseline. Sixty-five patients died over a median follow-up of 79 months (Figure 1A). The incidence of cardiovascular events was 60 over a median follow-up of 68 months (Figure 1B). Even after adjusting for any of the prognostic models, participants who attended ≦75% of sessions (n=140) had higher risks of mortality (hazard ratio (HR), 1.79 ; 95% confidence interval (CI) : 1.00–3.36 ; P = 0.049) and cardiovascular events (HR, 1.84 ; 95% CI : 1.07–3.48 ; P=0.03) than those attending >75% of sessions (n=126).

Conclusions: Hemodialysis patients in whom physical activity and physical function could be assessed more regularly had better prognosis than those with only intermittent assessment.

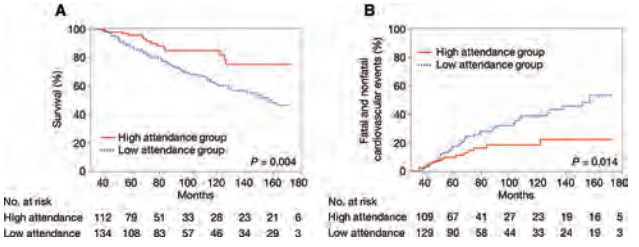

Figure 1. Kaplan–Meier analysis of survival (A) and cardiovascular events (B) in 266 patients undergoing hemodialysis. The High attendance group (attended >75% of all available sessions in the management program) had significantly better survival and lower incidence of cardiovascular disease than the Low attendance group (≤75% attendance).

TH-PO311

A Retrospective Study on the Decline of Muscle Mass in Maintenance Hemodialysis Patients in China

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Background: Sarcopenia is characterized by age-related decline of skeletal muscle plus low muscle strength and/or physical performance. Studys have demonstrated that sarcopenia was associated with adverse health outcomes, such as disability, hospital admission, poorer quality of life and mortality. A high prevalence of sarcopenia is also observed in maintenance hemodialysis (MHD) patients, which need for further investigation. Hence, this study aimed to analyze the risk factors that affect the speed of muscle mass decline in MHD patients.

Methods: The retrospective study was performed in hemodialysis center of Huashan hospital, Fudan university in Shanghai, China. MHD patients suffered muscle mass loss in the past three years were eligible to participate in this study. Patients were divided into low speed group and high speed group according to the speed of muscle mass decline. Univariate linear regression analysis was conducted to assess the associations between muscle mass decline speed and the variables. These variables included age, gender, dialysis vintage, body mass index, normalized protein catabolic rate, serum levels of albumin, hsCRP, 25(OH)D, CO_2-CP. Variables with P≤0.20 were included in the multivariate logistic analysis.

Results: A total of 47 MHD patients were included in this study, of which 23 were male and 24 were female. Mean patient age was 59.30±12.49 years. The mean dialysis duration was 7.24±4.88 years. The low speed group showed shorter dialysis vintage, higher level of serum 25(OH)D and lower Log NT-proBNP, compared with the high speed gruop. There were no significant differences in albumin, prealbumin, cholesterol, nPCR, CO_2-CP, hsCRP, BMI, deltoid skin fold thickness, grip strength and daily steps. Multivariate linear regression analysis showed that dialysis vintage (β=0.309, P=0.017), 25 (OH) D(β=-0.370, P=0.004), Log NT-proBNP (β=0.339,P=0.011) were risk factors associated with muscle mass decline speed in MHD patients.

Conclusions: Risk factors associated with the muscle mass decline speed in maintenance hemodialysis patients include dialysis vintage, 25 (OH)D, and log NT-proBNP. Higher levels of 25 (OH) D contributes to the maintenance of muscle mass.

TH-PO312

Fatigue on Hemodialysis Day Is Associated with Post-Hemodialysis Amino Acids Depletion

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Background: End-stage renal disease (ESRD) patients on maintenance hemodialysis (HD) endure debilitating fatigue. Kidney function is essential for the synthesis, balance, and interorgan exchange of several amino acids (AA) notably aromatic amino acids (AAA) such as phenylalanine, tyrosine, and tryptophan and branched-chain amino acids (BCAA): leucine, isoleucine and valine. Dysregulation of these AA has been implicated in the genesis of fatigue as they may affect neurotransmitters. The relationship of AA with fatigue in HD patients is not known.

Methods: In a cross-sectional study, we examined the relationship between AA and fatigue in a well-characterized cohort of HD patients with T2 diabetes (N=119). The mean±SD age was 54.77±12.76 yr and 48% were female. Mean serum albumin was 3.46±0.38 g/dl, Hgb 11.04±1.43 mg/dl, and HgbA1c 6.93±1.86%. Fatigue on HD day was assessed by the 9-item Brief Fatigue Inventory (BFI) which measures fatigue severity and fatigue impact on daily functioning. BFI has internal consistency coefficient 0.96 and scores range from 0 to 90, lower score = less fatigue. BFI item #3 (Please rate your fatigue that best describes your WORST level of fatigue) was chosen to represent fatigue severity for conceptual simplicity. Free AA in pre- and post-HD plasma were quantified using HPLC-mass spectrometry.

Results: BCAA and AAA levels decreased significantly post HD (p<0.0001 and 0.0009, respectively). Post-HD AA, except for tyrosine, correlated with BFI item #3 and global fatigue scores (mean of all BFI 9 items). On Pearson correlation, post-HD BCAA and AAA levels correlated negatively with worst fatigue (r=–0.24, p=0.015 and r=–0.26, p=0.009, respectively) and global fatigue (r=–0.26, p=0.008 and r=–0.26, p=0.01, respectively). These correlations remained significant after adjustments for HD duration, dialysis shift, and intradialytic changes in body weight and blood pressure. Fatigue intensity, categorized into mild (1-3), moderate (4-6), and severe (≥7) based on BFI item #3 score, inversely related to post-HD AA levels: BCAA (p for trend 0.028) and AAA (p for trend 0.008).

Conclusions: HD procedure depletes BCAA and AAA. Post-HD levels of both BCAA and AAA correlate with fatigue on HD day in ESRD patients. Depleted AA may contribute to impaired neurotransmitters synthesis.

Funding: Private Foundation Support

TH-PO313

Preliminary Analysis of the Effect of Blood Flow Rate Reduction on Post-Dialysis Fatigue

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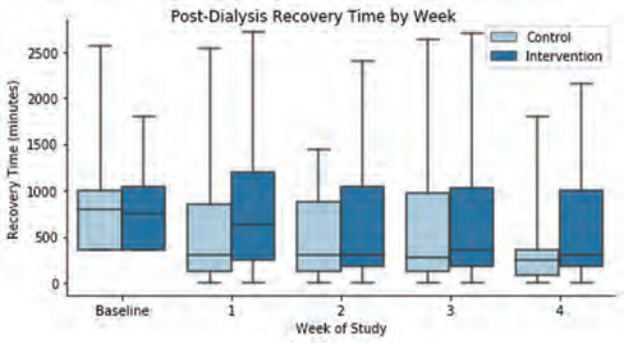
Background: Post-dialysis fatigue is a common complaint among patients undergoing maintenance hemodialysis (HD). It is not known whether hemodialysis blood flow rate (Qb) affects post-dialysis fatigue. We aimed to determine if a reduction in Qb affected the time to recover from HD treatments in patients with significant baseline post-dialysis fatigue.

Methods: We conducted a randomized, controlled trial of patients undergoing maintenance HD ≥3x/week who reported post-dialysis fatigue ≥6 hours at baseline. Preliminary data included 94 subjects randomized to Qb reduction of up to 100 mL/min (minimum Qb 300 mL/min; intervention group, 47 subjects) or to usual care (control group, 47 subjects). Patients with borderline dialysis adequacy were excluded. Subjects were surveyed weekly for 4 weeks regarding their dialysis recovery time (DRT) using the validated question "How long did it take you to recover from dialysis?" Primary outcome was change in DRT.

Results: Mean age was 65.1±12.7 years, 62.8% were men, median vintage was 3.73 years (IQR 2.0–6.7), and 68.1% of subjects had diabetes. Baseline characteristics in post-randomization groups were fairly balanced. Prescribed Qb was reduced from 398±39.8 mL/min to 314±23.1 mL/min in the intervention arm. Prescribed Qb was 389±41.6 mL/min in controls. During the intervention period, median DRTs decreased in both groups (Figure 1). Repeated measures analysis performed on the difference from each time point to baseline did not show a significant difference between intervention and control arms [$F(1,67) = 0.74$, $p = 0.39$].

Conclusions: In maintenance hemodialysis patients with a baseline post-dialysis recovery time of 6 or more hours, we did not observe an effect of Qb reduction of up to 100 mL/min on post-dialysis recovery time.

Funding: Commercial Support - Satellite Healthcare



TH-PO314

Association of Psychosocial Factors with Adherence to Treatment Among Prevalent Dialysis Patients

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Background: Dialysis patients are expected to adhere to dialysis treatments, medications, and dietary and fluid restrictions; these may be complicated by patient psychosocial issues. The aim of this study was to examine the relationship between social worker-assessed psychosocial factors and patients' perceived ease of adherence to treatment among prevalent dialysis patients.

Methods: Data were extracted from the initial comprehensive assessment performed by social workers for patients starting dialysis treatment at three outpatient Emory Dialysis centers. Exposures were social worker-assessed psychosocial factors, primarily depression/anxiety. Outcome was patient-perceived ease of adherence across five categories: ability to come to dialysis, complete dialysis, take medications, follow dietary restrictions, and follow fluid restrictions. Responses were dichotomized as "easy" vs. "not easy." Statistical analysis was performed using ANOVA, *t* test, and Pearson's chi-square.

Results: Of 1334 patients, 205 (15.4%) were reported to have depression/anxiety. Compared to those without depression/anxiety, patients with depression/anxiety were significantly less likely to find adherence across all categories to be easy vs. not easy (Table; $P<0.001$ for all). Daily vs. less frequent social support was associated with greater perceived ease of adherence to coming to (75.5% vs. 65.2%, $P=0.001$) and completing (75.6% vs. 64.3%, $P<0.001$) dialysis. Memory impairment vs. none was associated with lower ease of adherence in the same categories (66.2% vs. 74.4%, $P=0.03$; 64.7% vs. 74.7%, $P=0.01$). History of substance abuse, marital status, living alone, employment, community-dwelling status, and ambulatory assistance were not associated with ease of adherence.

Conclusions: Our results suggest that patients who have depression/anxiety, infrequent social support, or memory impairment are more likely to perceive adherence to various aspects of dialysis treatment as difficult. Further investigation of perceived and actual adherence by these psychosocial factors, which could inform targeted interventions to improve adherence, is warranted.

Table 1. Ease of adherence by presence of depression/anxiety

Category	% of patients reporting "easy" vs. "not easy"	
	Depression/anxiety	No depression/anxiety
Coming to Dialysis Visits (N=1044)	53.4	75.5
Completing dialysis (N=1058)	54.3	75.5
Adherence to Medications (N=1089)	63.9	83.3
Adherence to Diet Restrictions (N=1076)	42.5	65.3
Adherence to Fluid Restrictions (N=1066)	51.0	68.9

TH-PO315

The Psychological Burden Associated with Functional Dependency in Hemodialysis Patients

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Background: Functional dependency is highly prevalent in maintenance hemodialysis (MHD) patients. We investigated associations between functional dependency and the psychological burden reported by MHD patients

Methods: Cross section of 235 MHD patients treated in Salvador, Brazil. Responses to Katz's and Lawton-Brody's functional status questionnaires were used to create 3 groups: highly dependent (n=44), mild dependent (n=109) and independent (n=82). Using KDQOL-SF patients were asked how true was the 4 questions of the kidney disease burden (KDB) scale: 1) disease interferes too much with life, 2) too much time dealing with the disease, 3) feel frustrated with the disease, 4) feel like a burden on my family. Responses varied from definitely true to false; definitive/mostly true defined higher burden. The KDB score (range from 0 to 100) was determined based on patient's responses; higher scores indicate lower burden. Regression models adjusted for age and comorbidities were used to estimate associations of functional status with KDB scores.

Results: Mean age was 51.2±12.4 yr and significantly higher in highly dependent patients ($P<0.001$). The Table shows score differences and the Figure shows the trend in % of responses for each KDB question, by functional status.

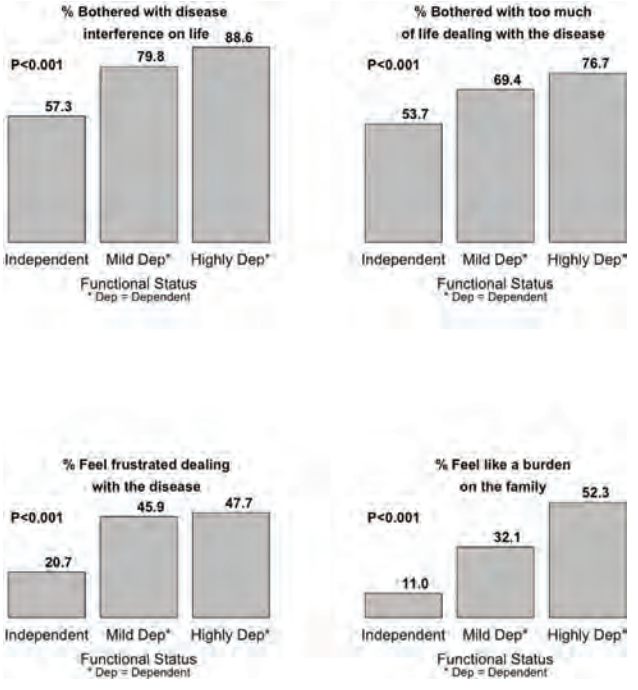
Conclusions: The results indicate that functional dependency represents a strong psychological burden for MHD patients.

Funding: Government Support - Non-U.S.

MEANS AND ADJUSTED DIFFERENCES OF THE KIDNEY DISEASE BURDEN SCORE

FUNCTIONAL STATUS	MEAN KDB SCORE	DIFFERENCE (95% CI)
Independent	64.4±27.2	Reference = 0
Mild Dependent	44.6±26.5	-18.5 (-27.7, -9.36)
Highly Dependent	35.0±25.7	-25.5 (-35.3, -15.7)

KDB = kidney disease burden



Percentages of True or Definitely True Responses for each Item of the Kidney Disease Burden Scale, by Functional Status

TH-PO316

Deep Cerebral Microbleeds Associate with Cognitive Impairment in Dialysis Patients: A Cross-sectional Observational Study

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Background: Cerebral microbleeds (CMBs) are common in dialysis patients, and different location of CMBs resulted from different pathologies. The relationship between CMBs and cognitive impairment (CI) in dialysis patients was controversial. This study aimed to explore whether the distribution of CMBs affects cognitive function in dialysis patients.

Methods: In this cross-sectional study, we enrolled a total of 189 dialysis patients. Patients were divided into 4 groups: without-MBs group, strictly lobar group, strictly deep group, and mixed group. A wide range of cognitive tests were administered to evaluate cognitive function.

Results: In our study, the prevalence of CMBs was 32.8%, 35.2% in HD patients and 29.7% in PD patients. 17 subjects (9.0%) classified as lobar group, 14 subjects (7.4%) as mixed group, and 31 subjects (16.4%) as deep group. Mean arterial pressure (MAP) was significantly associated with the lobar group and deep group. Dialysis vintage was associated with deep group only. Self-reported stroke history and current antiplatelet medication had relevance to the lobar group. There was a significant association between deep CMBs and impaired cognitive function, involving overall cognitive function, memory, language ability and executive function.

Conclusions: Deep CMBs are closely associated with global and specific cognitive impairment in dialysis patients.

Funding: Government Support - Non-U.S.

TH-PO317

Memory Deficit in Hemodialysis Patients: Clinical Characteristics and Cerebral Imaging Findings

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Background: The current study aimed to investigate the characteristics of memory deficit in dialysis patients, as well as using magnetic resonance imaging (MRI) to explore associated cerebral structural and functional changes.

Methods: Sixty patients on maintenance hemodialysis and 60 healthy controls were included. Patients and controls were frequency-matched by age, sex and education. All subjects underwent evaluation of global cognition (The Montreal Cognitive Assessment, MoCA) and episodic memory (Auditory Verbal Learning Test, AVLT). Brain structure and function were evaluated using MRI with 3DT1 and BOLD (blood-oxygen-level dependent) sequences. Voxel-based morphometry (VBM) was used to calculate grey matter volume while ReHo (regional homogeneity) was calculated to assess brain activity.

Results: Compared with controls, patients had significantly lower scores of MoCA and AVLT (learning memory, short delayed recall, long delayed recall). The memory curve plot based on AVLT results demonstrate that patients had a similar memory curve from learning memory to short delayed memory, whereas their memory declined significantly from short delayed recall to long delayed recall while the controls' memory remained stable during this period. Multiple stepwise regression analysis revealed that end-stage renal disease is associated with memory deficit independently. VBM revealed that dialysis patients have significantly reduced grey matter volume in the following area: right cerebellum anterior lobe, bilateral cerebellum posterior lobe, right hippocampus, amygdala, parahippocampus gyrus, left medial frontal gyrus, left fusiform gyrus, bilateral caudate and subcallosal gyrus and left insula. fMRI showed that ReHo declined in dialysis in the left middle and inferior frontal gyrus, as well as in the right supra marginal gyrus. Correlation analysis demonstrated that ReHo of left middle/inferior frontal gyrus correlated with learning memory test score ($r=0.34, p=0.02$).

Conclusions: Our study reveals memory deficit with a special pattern in dialysis patients, as well as that dialysis patients are with diffuse cerebral atrophy and reduced brain functional activity in certain areas. Cerebral functional changes are associated with memory alterations in the patients.

Funding: Government Support - Non-U.S.

TH-PO318

Orthostatic Blood Pressure Decline as a Possible Explanation for Memory Deficit in Dialysis Patients

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Background: Memory deficit is usually ignored by nephrologists but can be detrimental to patients' quality of life as well as prognosis. A better understanding of the mechanisms underlying this condition could improve the care of CKD patients. Here we sought to test the hypothesis that orthostatic blood pressure decline contributes to memory deficit in patients with end-stage renal disease.

Methods: Sixty patients on maintenance hemodialysis and 60 healthy controls (without CKD, cardiovascular diseases or neurologic diseases) were included. Patients and controls were frequency-matched by age, sex and education. The Montreal Cognitive Assessment (MoCA) was used to assess global cognition while the Auditory Verbal Learning Test (AVLT) was used for episodic memory evaluation. Seated and standing blood pressure were measured. Frequency domain heart rate variability (HRV) were recorded and analyzed.

Results: Compared with controls, patients had significantly lower scores of MoCA and AVLT (learning memory, short delayed recall, long delayed recall). They also exhibited rapid blood pressure decline upon standing, with a delayed compensatory rebound following. Correlation analyses showed that orthostatic blood pressure decline was not associated with cognition or memory in the controls, whereas it was correlated significantly to both short recall and delayed recall scores in the patients. Multiple stepwise regression analysis revealed that orthostatic blood pressure decline is an independent predictor for memory deficit (both short recall and delayed recall). The association between orthostatic blood pressure decline and short recall remained significant after adjusting for HRV.

Conclusions: Our study reveals significant memory deficit and overt orthostatic blood pressure decline upon standing in patients receiving maintenance hemodialysis. Orthostatic blood pressure decline is associated independently with memory test scores in a reverse fashion in hemodialysis patients and this association remained significant even after adjusting for heart rate variability, suggesting that orthostatic blood pressure decline possibly induce memory deficit directly, rather than merely a reflection of general cerebral injury.

Funding: Government Support - Non-U.S.

TH-PO319

Improved Thinking Through Dialysis: A Pilot Study Using the BrainCheck Assessment Platform

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Background: It is estimated that 27-67% of the ESRD population is plagued by cognitive dysfunction. This impairment not only decreases QOL and dialysis compliance, but also increases depression and mortality. Drew et al demonstrated that each 1 SD higher executive function score was associated with a 35% lower hazard of mortality. We tested hemodialysis patients with a novel, mobile and digital neurocognitive test, BrainCheck, in an effort to evaluate cognitive improvement after dialysis treatment.

Methods: We prospectively consented and enrolled patients at Dialyspa dialysis center in Houston, TX and administered BrainCheck before and after dialysis. Their performance pre and post-dialysis was shared with the patients in real-time. We also compared the neurocognitive performance of our patients against age-matched controls without ESRD.

Results: We enrolled a total of 29 patients, 17 (58.6%) female. Their ages ranged from 25 to 88, average was 59 years. 11 (37.9%) were African American, 9 (31%) Hispanics, 7 (24.1%) White, and 2 (6.9%) Asians. The educational level breakdown was 12 (41.4%) had some college education, 8 (27.6%) completed high school, 5 (17.2%) had a college degree and 4 (13.8%) a graduate degree. Our findings show that patients who are compliant with dialysis have cognitive function similar to the non-dialysis population. We also found that sharing cognitive performance results with patients could be used as a motivator to increase compliance.

Conclusions: Standard dialysis practice appears to help patients regain cognitive function to levels similar to their non-ESRD counterparts. While more data is needed, this study shows that a brief cognitive test could be used to promote compliance with dialysis treatment. This could translate into QOL gains and decreased mortality in this patient population.

Funding: Private Foundation Support

TH-PO320

Depressive Symptoms as a Function of Race, Gender, and Perceived Social Support in End-Stage Kidney Disease

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Background: Depression negatively impacts physical health and quality of life, and the prevalence of depressive symptoms in individuals receiving maintenance hemodialysis (HD) is 2-3 times higher than in the general population. Further, women and members of minority groups are at an increased risk for depression. Perceived social support (PSS) is found to have protective effects against depression. Yet, the effects of social support, gender, and race on depressive symptoms in HD patients is not well described.

Methods: 117 patients (55% female, 72% self-reported African American (AA)) receiving in-center HD completed questionnaires assessing depressive symptoms and PSS. A 2x2x2 ANOVA was conducted to assess the main effects of PSS, gender, and race on depressive symptoms. Two-way interactions of race x PSS, gender x PSS, and race x gender, as well as the three-way interaction of race, gender, and PSS were also evaluated. Age and self-rated overall health were included as covariates.

Results: Analyses revealed significant main effects of age ($p<.01$), overall health ($p<.01$), and PSS ($p<.01$) on depressive symptoms. There was a significant interaction between PSS and race ($p<.05$), such that AAs had lower levels of depressive symptoms at low levels of PSS and higher levels of depressive symptoms at higher levels of PSS, as compared to whites. Further, there was a significant 3-way interaction among PSS, race, and gender (See Figure 1).

Conclusions: Gender and race are important modifiers of the effects of PSS on depressive symptoms. Patient characteristics such as race and gender should be taken into account when creating tailored, social support-based interventions to treat depression in HD patients.

Funding: NIDDK Support

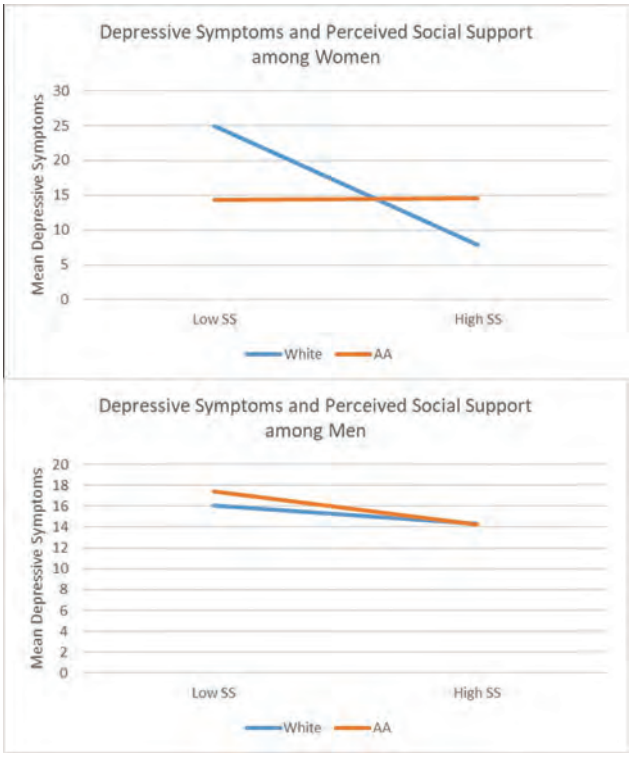

Figure 1. Effect on depressive symptoms of the interaction of PSS, gender, and race.

TH-PO321

Acceptance of Erectile Dysfunction Treatment by Patients on Hemodialysis and Their Renal Providers

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Background: Erectile Dysfunction (ED) is highly prevalent in men receiving chronic hemodialysis (HD). Past studies demonstrate that treatment of ED with phosphodiesterase-5 inhibitors is safe and effective in this population. However, it is unknown whether these medications and other therapies are routinely used. We sought to investigate the acceptance of treatment for ED among men on chronic HD and their renal providers.

Methods: As part of a clinical trial of symptom management in patients on chronic hemodialysis, we assessed erectile dysfunction monthly using the Sexual Health Inventory of Men (SHIM) tool. For men with erectile dysfunction (SHIM score < 22), trained research nurses provided treatment recommendations and if patients and providers accepted them, helped facilitate their implementation. We assessed patients' acceptance of recommendations, reasons for refusal, and providers implementation of therapy. All data was analyzed at the level of monthly assessments.

Results: Of the 101 patients followed for up to 12 months, 46 of 47 (98%) men met criteria for erectile dysfunction. These 46 patients reported ED on 426 monthly assessments. In 49 of the 426 (11.5%) assessments, patients accepted the recommendation for treatment. On 59 assessments (14%) patients were already on treatment or had received a prescription. On 11 monthly assessments (2.5%) patients reported having financial obstacles precluding treatment. On 260 (61%) monthly assessments, patients refused the treatment recommendations. The primary reason patients refused the recommendations was no desire to discuss treatment options (53%) and not interested in being sexually active or not having a partner (38%). In 14 of the 27 assessments (51%) where patients accepted the recommendation, renal providers were unwilling to provide treatment.

Conclusions: Despite the high prevalence of ED in the hemodialysis population, a large majority of patients are not interested in pursuing treatment. For patients interested in treatment, renal providers are commonly unwilling to modify or initiate therapy. Future efforts should focus on identifying patients interested in treatment and improving the provision of therapy for these individuals.

Funding: Veterans Affairs Support

TH-PO322

Management of Uremic Pruritus in Hemodialysis: Effectiveness of a Quality Improvement Treatment Algorithm

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Background: Uremic pruritus (UP) is highly prevalent among dialysis patients and associated with significant morbidity. However, management of UP is inconsistent across centres and many patients remain inadequately treated. The purpose of this study was to analyze the effectiveness of a UP treatment algorithm for chronic dialysis patients.

Methods: We analyzed a cross-section of in-center hemodialysis patients at a tertiary care center and assessed pruritus character (localized or generalized) and severity (0; no itch to 10; worst imagineable itch) using a numerical rating scale (NRS). Those with generalized pruritus rated as moderate to severe (NRS ≥4) were entered into a treatment algorithm consisting of hydrous emollients (all patients) and step-wise use of a topical agent (menthol 0.5%/camphor 0.5% cream), gabapentin (dose increased from 100-300 mg 3X/week) and UV-light. UP severity was recaptured at entry into the algorithm, and assessed at one month after the topical agent and two week intervals after each dose increase of gabapentin.

Results: Overall, 64/196 patients (33%) rated their pruritus as ≥4, and 56/64 entered the algorithm. A total of 39/56 patients (70%) had a persistent pruritus score of ≥4 on reassessment and were prescribed the topical agent; 16/39 patients had a complete response at one month post initiation, 2/39 could not afford the topical, 2/39 developed side effects necessitating discontinuation and 3/39 did not fill the prescription due to other delays. A total of 11 non-responders/non-users of the topical agent received gabapentin; 3/11 patients had a complete and sustained pruritus score of <3 at last follow-up while 3/11 patients failed to respond and were referred for UV light treatment. The remainder had not completed titration of gabapentin or experienced spontaneous remission. Overall, the mean pruritus score fell from 6.5 ± 2.1 to 2.9 ± 1.9 (P<0.001) for those who initiated treatment with the topical agent and had an assessment of their pruritus severity (N=31/39) at four months.

Conclusions: Implementation of a treatment algorithm for UP management effectively reduced UP severity in a cross-section of in-center hemodialysis patients. Future external validation of the algorithm is needed prior to widespread implementation.

TH-PO323

Comparison of Retinal Neurodegenerative Changes in Patients with CKD Undergoing Hemodialysis versus Healthy Controls Assessed by Spectral-Domain Optical Coherence Tomography

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Background: Spectral-domain optical coherence tomography (SD-OCT) represents a reliable tool for retinal layer volume measurement. The aim of this study is to evaluate retinal changes indicating neurodegenerative processes in patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) compared to healthy controls.

Methods: In a prospective observational single center study, we included a total of 70 subjects–32 CKD patients undergoing HD and 38 healthy controls. Circular scans of the optic disc area to determine retinal nerve fiber layer (RNFL) thickness were obtained by SD-OCT and macular retinal layer volumes of both eyes including total retinal volume but also each layer were evaluated.

Results: The group of CKD patients (11 females, 21 males, aged 60.3±15 years) was compared to healthy controls (28 females, 10 males, aged 57.9±10 years). The age- and gender-adjusted temporal superior RNFL sector of the right eye was significantly thinner in HD patients as were several retinal layer volumes such as total retinal volume, ganglion cell layer (GCL), ganglion cell layer + inner plexiform layer (GCL-IPL) and inner retinal layer volume (IRL, comprising RNFL, GCL and IPL) of the right eye and IPL volume of both eyes. To eliminate additive effects of HD and diabetes, we performed a subgroup analysis excluding patients with diabetes mellitus (n=25). The temporal superior RNFL sector was still significantly thinner than in the control group (p=0.021) as were GCL (p=0.014) and GCL-IPL volume of the right eye (p=0.024).

Conclusions: In patients undergoing HD, we observed a decrease in temporal RNFL thickness and retinal layer volumes indicating neurodegenerative retinal alterations in patients with CKD. Thereby, SD-OCT represents a valuable high-resolution imaging technique to explore retinal neurodegenerative changes.

RNFL thickness and retinal volumes

SD-OCT scan	Hemodialysis (n=32)	Healthy controls (n=38)	age-/gender-adjusted p value
Temporal superior right sector of the circular RNFL scan [µm]	122.58±26.73	138.53±20.35	0.016
Total retinal volume right [mm^3]	8.22±0.45	8.51±0.41	0.037
GCL volume right [mm^3]	0.96±0.10	1.05±0.08	0.003
IPL volume right/left [mm^3]	0.83±0.08/0.82±0.07	0.88±0.07/0.88±0.07	0.017/0.044
IRL volume right [mm^3]	6.00±0.43	6.27±0.38	0.042
GCL-IPL volume right [mm^3]	1.79±0.67	1.93±0.15	0.005

TH-PO324

The Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) on Improvement of Mental Health and Clinical Parameters in Hemodialysis Patients – Pilot Study

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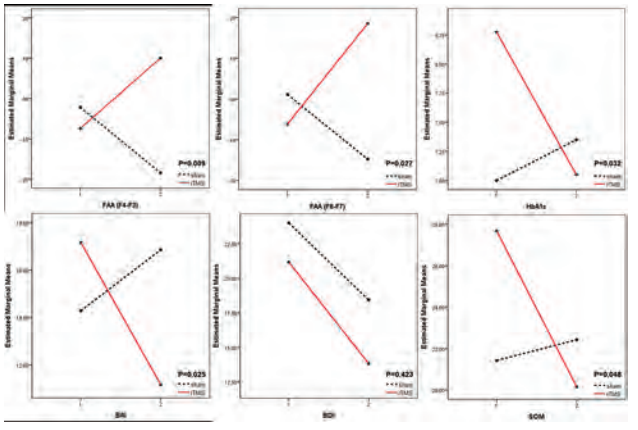
Background: The prevalence of major depressive disorder in patients with ESRD is higher than in diabetes or congestive heart failure. However, it is difficult to prescribe antidepressant treatment because of concern about potential adverse effects in CKD patients. Here, we studied the therapeutic effect of rTMS as a nonpharmacologic treatment in depressed hemodialysis patients.

Methods: The patients with more than 5 points in Patient health Questionnair-9 were randomized to rTMS group and sham group. The rTMS group was stimulated on the left dorsolateral prefrontal cortex for 20 minutes, three times a week. We collected and analyzed the clinical indices before and after TMS treatment, and also collected data of quantitative electroencephalogram (qEEG), and the results of various psychiatric questionnaires (Beck's depression index-II [BDI-II], Beck's anxiety index [BAI] and SCL-90R-Somatization subscales [SCL-90R-SOM]).

Results: In this study, a total of 13 patients were randomized, 7 patients assigned to the sham group and 6 were assigned to the rTMS group. When laboratory findings were compared 1 month after TMS, hemoglobin A1c was significantly improved in rTMS group (8.3% to 7.1%, P=0.046 by pared t-test, P=0.032 by mixed ANOVA). Although there was no statistical significance, serum potassium and intact PTH also showed an improving tendency. The frontal alpha asymmetry (FAA) F4-F3 (P=0.009), and F8-F7 (P=0.027) values in qEEG was significantly improved in the rTMS group than the others. The BDI-II score was improved both with sham (24.0 to 18.4, P=0.009) and rTMS group (21.2 to 13.8, P=0.005), the BAI (rTMS: 11.2±6.1 vs. sham: 16.9±13.0; F 6.7, P=0.025) and SCL-90R-SOM scores (rTMS: 20.2±5.4 vs. sham: 22.4±5.6; F 4.9, P=0.048) showed prominent improvement after rTMS.

Conclusions: In hemodialysis patients, rTMS may improve depression, anxiety, and somatization symptoms, which may lead to improvements in clinical measures.



TH-PO325

Interventions to Improve Sleep Quality in People with CKD: A Cochrane Systematic Review

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Background: Sleep quality is lower for people with chronic kidney disease (CKD). The prevalence of sleep disorder ranges from 45% to 80% in adults with end-stage kidney disease (ESKD) and half of patients with earlier stages of CKD. People with CKD have identified the importance of research focused on better treatments to reduce symptoms of CKD. This Cochrane review evaluates the benefits and harms of interventions to improve sleep quality for adults and children with CKD.

Methods: We searched the Cochrane Kidney Transplant Specialised Register for randomized trials reporting treatment on sleep quality for people with CKD through April 2018. Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was adjudicated using GRADE. Sleep quality was measured by validated sleep scores.

Results: Sixty-seven studies (3427 participants) met review eligibility criteria. Sixty-one studies (3201 participants) involved dialysis patients, three studies involved 104 transplant recipients, and one study involved 45 patients with CKD. Median trial duration was 5 weeks. Mean trial age was 54.3 years. Interventions included acupressure, aromatherapy, benzodiazepine therapy, cognitive-behavioral therapy, dopaminergic agonists, education, exercise, light therapy, massage, melatonin, music therapy, peritoneal dialysis technique, reflexology, relaxation, and telephone support. Methodological reporting was incomplete for most studies. Relaxation had uncertain effects on sleep quality (mean difference [MD] -1.62, 95% confidence interval [CI] -5.03, 1.79; very low certainty evidence). Exercise may provide improvements in sleep quality (standardized MD -1.10, -2.26, 0.05; very low certainty). Acupressure compared to no treatment may improve sleep quality (MD -1.27, -2.13, -0.40; very low certainty) and sleep latency (MD -0.59, -0.92, -0.27; moderate certainty), although effects were smaller than clinically important changes in sleep scores. Effects of other interventions on sleep quality were very uncertain. Evidence in children was absent.

Conclusions: Exercise and acupressure may provide small clinical improvements in sleep quality for people with CKD, although limitations in existing trials reduce the certainty of these findings.

TH-PO326

Association of Self-Reported Sleep Quality with Frailty in Patients on Hemodialysis

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Background: Poor sleep quality is associated with frailty in the elderly, yet the relationship has not been examined in patients on hemodialysis, among whom the prevalence of both poor sleep quality and frailty is higher. We examine the association of sleep quality with frailty in patients on hemodialysis over a two-year period.

Methods: We used ordinal generalized estimating equation analysis to examine the association between self-reported sleep quality and frailty and change in frailty over time in a cohort of 762 hemodialysis patients. Frailty was measured using the Fried frailty phenotype and modeled according to the number of components met. Participants rated sleep quality on a Likert scale in 3 domains: sleep initiation, sleep maintenance, and returning to sleep. A score of 16 or greater on the Center for Epidemiologic Studies-Depression scale indicated depressive symptoms. Measures were conducted at baseline, 12, and 24 mos.

Results: Self-reported difficulty with sleep initiation, sleep maintenance, and trouble returning to sleep were associated with significantly higher odds of being frail in multivariate analysis (table). Impaired sleep maintenance and trouble returning to sleep were also associated with worsening frailty over time. Addition of the inflammatory marker IL-6 did not weaken the association between sleep quality and frailty. The addition of depression to the multivariate model markedly attenuated the association between sleep quality and frailty in all three sleep domains.

Conclusions: Poor sleep quality was associated with higher odds of frailty in patients on hemodialysis, and impaired sleep maintenance and trouble returning to sleep were associated with worsening frailty over time. Our analyses suggest that inflammation does not solely account for these findings and that depression may play a large role in the causal pathway between sleep and frailty.

Funding: NIDDK Support

Odds ratio of higher frailty score and change in frailty over time

Variable	Multivariate‡		Addition of IL-6		Addition of Depression	
	Frailty	Change in Frailty	Frailty	Change in Frailty	Frailty	Change in Frailty
Sleep initiation	1.6* (1.2 - 2.1)	1.2 (0.9 - 1.6)	1.5* (1.2 - 2.0)	1.1 (0.9 - 1.5)	1.1 (0.9 - 1.5)	0.9 (0.7 - 1.2)
Sleep maintenance	1.6* (1.2 - 2.1)	1.5* (1.2 - 1.9)	1.5* (1.2 - 2.0)	1.5* (1.2 - 1.9)	1.2 (1.0 - 1.6)	1.3* (1.0 - 1.6)
Trouble returning to sleep	1.7* (1.3 - 2.2)	1.3* (1.0 - 1.7)	1.7* (1.3 - 2.2)	1.3 (1.0 - 1.6)	1.3 (1.0 - 1.7)	1.1 (0.8 - 1.4)
IL-6, pg/mL	—	—	1.4* (1.2 - 1.5)	—	1.4* (1.2 - 1.5)	—
Depression	—	—	—	—	2.7* (2.2 - 3.3)	—

*p<0.05

‡Adjusted for age, race, ethnicity, sex, BMI, serum albumin, smoking, diabetes, atherosclerotic heart disease, heart failure

TH-PO327

Dialysis After Displacement

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Background: The Syrian war and the influx of approximately 1.5 million refugees into neighboring Lebanon has led to a humanitarian crisis. Refugees have a multitude of chronic medical and psychosocial problems and few resources. End stage renal disease (ESRD) refugees patients have the additional stressor of trying to obtain life-saving therapy under extreme hardship. Here we report on the current experience of ESRD Syrian refugee patients in Lebanon.

Methods: As part of a medical mission through the Syrian American Medical Society (SAMS), four US nephrologists along with ground staff evaluated the dialysis services provided to refugees in Lebanon. The Lebanese government covers dialytic services for their citizens but Syrian refugees depend on Non Government Organizations (NGO) or personal finances to cover their treatments. Two NGOs currently fund the majority of HD treatments for Syrian refugees in Lebanon – Norwegian Aid Committee (NORWAC) and SAMS. Hemodialysis (HD) is the only available dialysis option. Each dialysis session costs approximately $100 per 4 hour treatment session but does not include transportation and oral medications. Patients travel up to 6 hours by bus round-trip to receive HD. Transplantation is not an option due to costs.

Results: There are currently 218 Syrian refugees in Lebanon who require HD, and this number grows by 1-2 monthly. 114 are covered by NORWAC, 37 are covered by SAMS, and 67 patients are on a waiting for list for a sponsored dialysis chair. Waiting list patients wait for NGO coverage, self-pay for an HD session intermittently if they are able to afford it, or die waiting.

Conclusions: The primary obstacle for providing Syrian refugees in need with HD in Lebanon is cost. This vulnerable population mortality risk is high given the limited financial resources available to them and the chronicity of their condition.

Funding: Private Foundation Support

TH-PO328

Vibration Perception Threshold as a Measure of Peripheral Neuropathy in Dialysis Patients: A Pilot Project

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Background: Dialysis patients are at increased risk of fall due to neuropathy and myopathy. Also, significant percentages of dialysis patients are diabetic; making them vulnerable to neuropathy, foot ulcers and fall.

Methods: Vibration perception threshold (VPT) was measured by handheld digital biothesiometer in prevalent dialysis patients. The biothesiometer probe, which vibrates at amplitude proportional to the square of the applied voltage, was applied perpendicular to the test site. VPT value was defined as the voltage level at which subject first felt vibration sense. Measurements were taken at 6 points of plantar aspects of both feet at great toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal, instep and heel. Average of these 6 points was further graded as normal (<15 volts), mild (16-20 volts), moderate (21-25 volts) and severe (>26 volts). All patients were on thrice a week hemodialysis.

Results: Of the 304 subjects, 59.5% were males. Average age was 51.1± 14.1 years and average dialysis vintage was 4.6 ± 3.8 years. 65 % subjects had hypertension, 31.9% had diabetes, 13% subjects had ischemic heart disease. VPT was found to be normal in 41.1%, mild impairment of VPT in 21.3%, moderate in 11.1% and severe impairment in 24.6% of subjects.

Conclusions: Moderate to severe vibration perception threshold impairment was found in 1-in-3 dialysis patients. This calls for quality improvement program to assess prevalence of neuroapthy and to decrease the burden of morbidities and falls.

TH-PO329

Association Between Psychosocial Factors and Receipt of Nocturnal In-Center Hemodialysis Among Prevalent Dialysis Patients

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Background: Compared to traditional in-center hemodialysis (HD), nocturnal dialysis (ND) is characterized by longer sessions and nighttime administration, which may lead to better outcomes for some patients. Given the importance of patient choice in the decision to initiate ND, we explored associations between patients' psychosocial factors and their receipt of ND.

Methods: Among HD patients at a medium-sized dialysis organization, we identified ND patients as those for whom ≥80% of dialysis sessions were ND sessions—starting at 6:30 pm or later and lasting ≥5 hours—over the 3 months (≥20 sessions total) after their first ND session. We extracted dialysis session data from electronic medical records and psychosocial data from social worker assessments typically performed at dialysis start. We performed descriptive analyses of ND and non-ND patients among all HD patients. We also analyzed the subsample of patients whose available psychosocial assessment data were more timely: i.e., patients whose psychosocial assessment was conducted between 1 year before and 1 month after their first ND session (for ND patients) or within the first year of dialysis at the dialysis organization (for non-ND patients). We tested associations of psychosocial factors with ND receipt in logistic regression models.

Results: We identified 64 ND patients in the total sample (5.5% of 1,169 HD patients). ND versus non-ND patients had greater full or part-time employment (26.8% vs. 8.5%, p<0.01), were less likely to require ambulatory assistance (14.1% vs. 41.2%, p<0.01), and were more likely to live alone (33.3% vs. 19.3%, p<0.01). Factors not associated with ND status included being married (26.7% vs. 30.9%, p=0.49) and having daily access to support at home (70.0% vs. 71.6%, p=0.79). For the subsample of 25 ND patients with timely psychosocial data (3.2% of 792 subsample HD patients), the relationships between ND and psychosocial characteristics were similar. Regression results were also qualitatively similar for both samples.

Conclusions: Patient psychosocial characteristics strongly predict receipt of ND care. It may be important to account for differences in psychosocial factors, which are typically unmeasured, when comparing outcomes for ND and non-ND patients.

TH-PO330

Altered Fingerprint Patterns: Revelation of an Unexplored Phenomenon in Patients Receiving Maintenance Hemodialysis

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Background: Epidermal ridge patterns on fingers, commonly known as fingerprints, are not only unique to each individual, but are also thought to remain unchanged over time. As such, they are one of the most commonly used means for identification. In our maintenance hemodialysis [HD] program, an unexpectedly high number of patients reported experiencing difficulty using fingerprints as a biometric for identification. This observation prompted a study to explore whether there are alterations in the papillary ridges in HD population and if so, evaluate its magnitude.

Methods: In this cross-sectional study, a total of 300 subjects including 150 patients receiving HD and an equal number of healthy controls [HC] were enrolled from October 2016 to March 2017. The fingerprints were obtained from all 10 fingers and were analyzed for clarity and pattern. They were classified as intact, partially lost, and completely lost. Based on their occupation, the subjects were categorized into 3 groups: 'Blue-collar' [BC], 'White-collar' [WC], and 'unemployed' [UE]. The patterns of fingerprints (i.e. loops, whorls, and arches) were identified and compared for each group.

Results: The mean age of the HD population and the HC were 46.8 and 47.2 years respectively (72% men in each group). The BC, WC, and UE proportions in the HD group were 70, 30, and 23% respectively, while they were 38, 62, and 20 in the HC. Fingerprint clarity was normal in 76.6 and 98.7% of the HD population and HC respectively (p<0.009). Partially lost fingerprints were detected in 13.3% of the HD group and 1.3% of the HC (p<0.001). While the prints were completely lost in 10% of the HD group, none of the HC was found with found to have lost patterns. Loss of fingerprints was more common in those with BC than WC.

Conclusions: While patients receiving maintenance HD can host a multitude of specific and non-specific skin conditions, to our knowledge, this is the first study on altered fingerprints in this patient population. It shows that compared to HC, a significant number of HD patients lose their fingerprint patterns partially or completely over time. Future studies are needed to confirm these findings, identify the pathophysiology and contributing factors, and explore its potential correlation with common comorbidities in this setting.

TH-PO331

Physician Attribution of Long-Term Catheter Use: A New Way of Looking at Clinical Performance Measures

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Background: Quality metrics in national ESRD programs are traditionally calculated at the dialysis facility level. With the Medicare Quality Payment Program, there is interest in physician-level metrics that could complement existing facility-level measures without increasing provider reporting burden. Our objective was to develop methodology to attribute patient outcomes to either individual physicians or group practices and then compare long-term catheter (LTC) use at the facility and provider-level.

Methods: We used NPI numbers to determine the single provider who received the Monthly Capitated Payment (MCP) from 2016 Medicare physician supplier claims, and identified hemodialysis (HD) patient months from Medicare dialysis facility claims. A group practice arrangement was inferred if multiple practitioners shared a common Tax Identification Number (TIN) and provided MCP services to a specific patient in the year. The percent of total HD patient-months with a LTC from CROWNWeb was then assigned to a practitioner or group practice.

Results: 9307 providers were identified by NPI caring for 338,718 eligible patients. Using NPI alone, 61% of patients were associated with only one MCP practitioner, while using the TIN matching algorithm an additional 33% of patients stayed within a single group practice during 2016 (See Figure). The mean LTC rate of 14.4% at the provider level for 2 of 3 consecutive months was similar to the LTC facility rate of 13.4%. The LTC rate of 9.7% at the provider level for 3 of 3 consecutive months was less sensitive but more specific.

Conclusions: MCP claims can identify the responsible practitioner for a patient's care during a given month. The TIN matching algorithm may allow development of a low-burden patient attribution paradigm for ESRD practitioner quality metrics. This approach yields similar results as the facility-level measure of LTC use and could help align dialysis facility and MCP practitioner quality initiatives.

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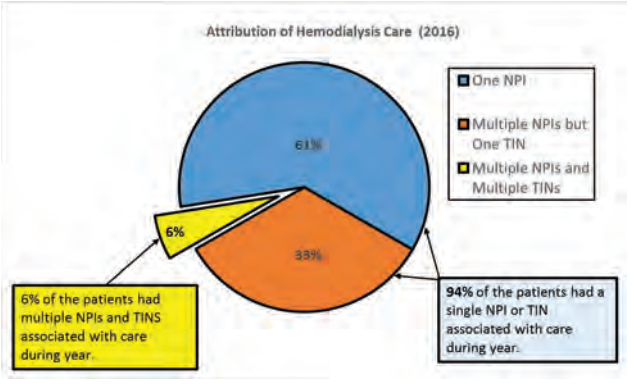

TH-PO332

Dialysate Potassium (K) Concentration and Total Dialysate Volume per Week During More Frequent Hemodialysis (MFHD) Determine Serum K After Transfer from In-Center Hemodialysis (ICHD): Model Predictions

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Background: Low dialysate K concentrations during ICHD induce rapid intradialytic K removal and low postdialysis serum K concentrations; low dialysate K concentrations are also associated with a higher risk of sudden cardiac arrest. Using a mathematical model, we evaluated the effect of the MFHD prescription on predialysis serum K concentration (Kpre), postdialysis serum K concentration (Kpost) and intradialytic decrease in serum K concentration (ΔKintra) after transfer from ICHD.

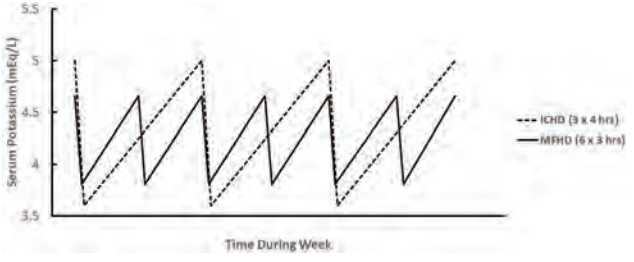
Methods: The mathematical model was modified from one previously published (Agar et al, Hemodial Int 2015) by accounting for colonic K clearance. MFHD prescriptions included treatment frequencies of 3.5, 4, 5 and 6 treatments per week, dialysate volumes of 20-60 L/treatment and treatment durations of 120-240 min. Predialysis serum K concentration during ICHD was assumed between 4.0 and 5.5 mEq/L with a dialysate K concentration of 2 mEq/L.

Results: Model-predicted Kpre, Kpost, and ΔKintra during MFHD were primarily dependent on total dialysate volume per week (TDV) and dialysate K concentration. A schematic weekly profile of serum K during ICHD and MFHD is illustrated in the figure. The range of TDV on MFHD with dialysate K concentrations of 1 and 2 mEq/L required to decrease Kpre, Kpost and ΔKintra below that during ICHD are tabulated.

Conclusions: We conclude that transfer from ICHD to MFHD with low TDV can result in a lower Kpre without reducing Kpost or ΔKintra for dialysate K and MFHD prescriptions typically seen in clinical practice. As with any hemodialysis therapy, additional vigilance is required for patients persistently presenting with hypokalemia or those prescribed high TDV.

Funding: Commercial Support - NxStage Medical

	TDV required to decrease K value below that during ICHD		
MFHD Dialysate K	Kpre	Kpost	ΔKintra
1 mEq/L	80-120 L	120-200 L	>360 L
2 mEq/L	120-175 L	300 L	>360 L



TH-PO333

Effect of Dialysate Potassium (K) Bath During Daily Hemodialysis (DHD) on Serum K Concentration After Transfer from In-Center Hemodialysis (ICHD)

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Background: The choice of the dialysate K bath influences serum K concentration during thrice-weekly ICHD; however, the prescription of the dialysate K bath during DHD has not been extensively studied. We examined the effect of the dialysate K bath during DHD on serum K concentration after transfer from ICHD.

Methods: This post hoc analysis evaluated patients who transferred from ICHD to DHD during the FREEDOM Study (N=345). DHD was performed at low dialysate flow rates; treatment frequency per week and dialysate volume per session were 5.9±0.2 and 22.2±4.0 L, respectively. The change in serum K concentration after transfer from ICHD to DHD (ΔK) was calculated based on the average serum K concentration from the last 3 months of ICHD and the first 3 months of DHD.

Results: ICHD serum K concentration was 5.3±0.7, 4.8±0.6 and 4.4±0.5 mEq/L with ICHD dialysate K bath of 1, 2 and 3 mEq/L, respectively. Mean±SD (N) serum ΔK for combinations of ICHD and DHD dialysate K baths are tabulated. By multiple linear regression, ΔK was inversely associated with both higher ICHD dialysate K bath (P<0.001) and ICHD serum K concentration (P<0.001) when DHD dialysate K bath was 1 mEq/L; no such associations were noted when DHD dialysate K bath was 2 mEq/L.

Conclusions: Transfer from ICHD to DHD at low dialysate flow rates with a dialysate K bath of 1 mEq/L resulted in decreased serum K concentrations, but no changes in serum K concentration occurred with a dialysate K bath of 2 mEq/L. Control of serum K concentration during DHD at low dialysate flow rates is effective; however, the choice of the dialysate K bath can be informed when transfer is from ICHD to DHD.

Funding: Commercial Support - NxStage Medical

	Serum ΔK (mEq/L)	
ICHD Dialysate K Bath (mEq/L)	DHD Dialysate K Bath of 1 mEq/L	DHD Dialysate K Bath of 2 mEq/L
1	-0.42±0.78 (46)*	0.40 (1)
2	-0.47±0.61 (229)*	-0.05±0.43 (11)
3	-0.36±0.74 (49)**	-0.09±0.44 (9)
All	-0.45±0.66 (324)*	-0.04±0.42 (21)

*(P<0.001) & **(P=0.0013) denote different from zero.

TH-PO334

Misclassification of Acid-Base Status Using Serum Bicarbonate in Hemodialysis

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Background: Acid-base status is a potentially modifiable determinant of mortality among ESRD patients. Little is known about how acid-base status changes during hemodialysis, when potential imbalance is directly attributable to treatment. How serum bicarbonate performs in ESRD patients at estimating acid-base status compared to the gold standard – pH – is unknown.

Methods: In a cohort of veterans with ESRD, we prospectively assessed acid-base status monthly at the beginning and end of routine hemodialysis for three months by measuring bicarbonate (as total CO2) and pH. Bias of measured bicarbonate was evaluated with Bland-Altman plots and concordance correlation coefficients comparing measured bicarbonate to that calculated from the Henderson-Hasselbalch equation using pH and pCO2. Categorizing measured bicarbonate and pH, we determined the proportion of pre-dialysis paired samples for which measured bicarbonate misclassified acid-base status (i.e. measured bicarbonate < 24 mmol/L when pH > 7.40, or vice versa).

Results: Among 25 participants, mean pH was 7.41 (± 0.04) pre-dialysis and 7.48 (± 0.05) post-dialysis; 75% of post-dialysis pH measurements were ≥ 7.45. Compared to calculated bicarbonate, measured bicarbonate produced lower estimates of acid-base status both pre-dialysis (mean difference ranged from -1.52 [95% CIs -1.91 to -1.13] to -1.35 [95% CIs -1.69 to -1.00] mmol/L) and post-dialysis (mean difference ranged from -2.70 [95% CIs -3.41 to -1.99] to -0.80 [95% CIs -1.29 to -0.31] mmol/L). There was considerable month-to-month variability in concordance both pre-dialysis (ranging from 0.61 [95% CIs 0.42 to 0.79] to 0.85 [95% CIs 0.76-0.95]) and post-dialysis (0.44 [95% CIs 0.25-0.64] to 0.87 [95% CIs 0.77-0.97]). Compared to pH, 21 of 71 (30%) pre-dialysis bicarbonate samples misclassified acid-base status.

Conclusions: The majority of patients became alkalemic during hemodialysis despite arriving with normal acid base status – a finding currently under recognized in clinical practice. Measured bicarbonate suggested a more acidemic state than was measured by pH. Serum bicarbonate measurements misclassified acid base status in 30% of cases. If confirmed, this observation could impact how physicians prescribe dialysate bicarbonate.

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TH-PO335

Hepatic Response to Cooler Hemodialysis

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Background: Hemodialysis (HD) exerts significant hemodynamic effects on vulnerable vascular beds. The liver has preserved blood flow during dialysis due to its dual blood supply. Even so, its excretory function is lower, despite an increase in toxin-rich portal vein flow. Extracorporeal cooling has a protective effect on multiple organs during dialysis, but its effect on the liver is unknown. We used CT perfusion imaging to examine the effect of cooling on hepatic blood flow and detoxifying function during HD.

Methods: In this pilot randomized cross-over study, 16 HD patients underwent two HD study sessions – one at standard dialysis temperature (36.5 degrees Celsius), and one at cooler dialysis (35 degrees Celsius; order of the sessions was randomly allocated). Participants had dynamic contrast-enhanced CT studies of their liver using a 256-slice GE

scanner pre (baseline), 3 hours into (peak hemodynamic stress), and post HD. Perfusion maps of total liver, hepatic arterial and portal venous blood flow were generated and analyzed by CT Perfusion (GE Healthcare). Furthermore, subjects had non- invasive pulse dye densitometry (Nihon Kohden) measurements of indocyanine green (ICG) clearance as a marker of liver excretory function and serial blood sampling to assess endotoxin levels.

Results: The cohort had an average age of 63years old (range 47-84 years), 37.5% were female and the average dialysis vintage was 66.5 months (range 9-305 months). An increase in portal vein blood flow at peak HD stress compared to baseline was seen in 62.5% (10/16) of subjects with standard HD (118.6±10.0%). Cooler HD prevented this perfusion change in the portal vein (95.7±12.6%, p=0.03). Total liver blood flow and hepatic arterial flow were not statistically different amongst standard vs. cooler HD treatments. Standard HD also resulted in a significant decrease in ICG clearance at peak stress relative to baseline (85.5±10.4%, p=0.02), which was absent in the cooler HD sessions (92.6±12.1%, p=0.25). Cooler HD also had a trend of increased clearance of uremic toxins: indoxyl sulfate, hippuric acid and phenyl sulfate.

Conclusions: In a subgroup of patients, standard HD causes significant increases in toxin-rich portal vein blood flow at peak hemodynamic stress, which can be mitigated by extracorporeal cooling. Cooler HD also preserves the liver detoxifying function, which usually decreases with standard treatment.

TH-PO336

The Effect of Dialysate Sodium Concentration on Intradialytic Hemodynamic Outcomes

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Background: The effects of modest changes in dialysate sodium concentrations on inter-dialytic weight gain (IDWG), blood pressure and intra-dialytic hypotension (IDH) are uncertain. We studied the association between a change in sodium dialysate from 142 to 140 mmol/L and IDWG, blood pressure and IDH in in-centre hemodialysis patients.

Methods: The dialysate sodium concentration was changed from 142 mmol/L to 140 mmol/L in four dialysis units in Hamilton, Canada as part of a policy change. We assessed changes in IDWG, pre- and post- treatment systolic blood pressures, intra-dialytic change in systolic blood pressure, ultrafiltration volume, and frequency of intra-dialytic hypotension (intra-dialytic SBP < 90 mmHg) 8 weeks before and in two 8 week blocks after switching dialysate sodium from 142 to 140 mmol/L. All analyses were done using mixed-effects models in which patients were considered random intercepts and dialysate sodium was considered a fixed effect. All models were adjusted for age and sex.

Results: Analyses included a total of 559 patients. Compared to the 8 weeks before changing the dialysate sodium, 8 to 16 weeks after the change to 140 mmol/L the mean ultrafiltration volume decreased by 0.11 L (95% confidence interval [CI] 0.07 to 0.12, p<0.001), the mean IDWG decreased by 0.10 kg (95% CI 0.02 to 0.18, p=0.01) and the mean pre-dialysis systolic blood pressure fell by 2.8 mmHg (95% CI 2.3 to 2.3, p<0.001). The odds of intra-dialytic hypotension were not significantly different (odds ratio 1.07, 95% CI 0.97 to 1.18, p=0.17).

Conclusions: Decreasing dialysate sodium from 142 to 140 mmol/L was associated with a reduced pre-dialysis SBP and IDWG without increasing the risk of IDH. Large randomized trials to understand the effects of modest changes in dialysate sodium on patient-important outcomes are needed to inform this fundamental component of dialysis care.

TH-PO337

Effects of Ultrafiltration Rate on Decline in Residual Kidney Function Among Patients Receiving Less-Frequent Hemodialysis

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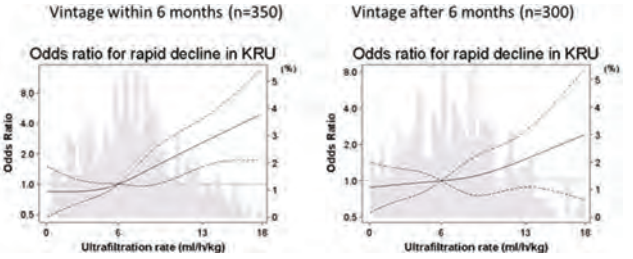
Background: High ultrafiltration rate (UFR) may lead to poor preservation of residual kindey function (RKF) by causing hemodynamic instability. However, there are no data about the association between UFR and decline in RKF in patients receiving less-frequent hemodialysis (HD).

Methods: This study included the patients who started less-frequent HD from 2007 to 2011 and had available UFR and renal urea clearance (KRU) data at baseline and KRU data at 1 year after less-frequent HD initiation. Less-frequent HD was defined as dialysis with a consistent treatment schedule of <3 times per week for 6 or more continuous weeks. Patients were grouped into 4 UFR categories (<6, 6 to <10, 10 to <13, and ≥13 mL/h/kg). We defined rapid decline in RKF as a decline in KRU of more than 20% per year. We explored the association between UFR and rapid decline in RKF using logistic regression models with adjustments for case-mix variables, baseline RKF, and maximal change of blood pressure during dialysis.

Results: Among eligible patients, mean (SD) UFR level was 7.0 (4.7) mL/h/kg. Median (interquartile range) baseline KRU was 5.6 (3.6 – 7.7) mL/min/1.72m^2. In adjusted cubic spline models, we found a nonlinear association between higher UFR and the risk for rapid decline in KRU. In an adjusted logistic regression analysis, UFR ≥13 mL/h/kg had a 2.1-fold higher risk of rapid decline in RKF compared to UFR of 6 to <10 mL/h/kg (odds ratio (OR) and 95% confidence intervals (CI): 2.09 (1.14 – 3.82)). In subgroup analyses based on vintage, the association between UFR and decline of KRU was attenuated in patients who started less-frequent HD more than 6 months after dialysis initiation [Figure 1].

Conclusions: High UFR increased the risk for rapid decline in RKF among patients receiving less-frequent HD.

Funding: NIDDK Support



TH-PO338

Association of Treatment Time and One Year Change in Residual Renal Urea Clearance in Hemodialysis Patients

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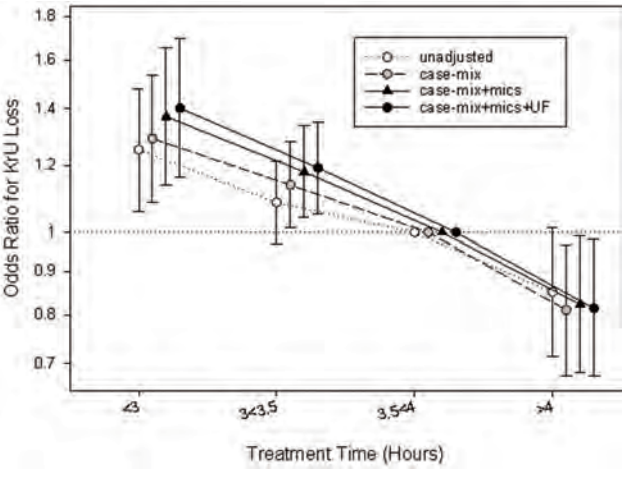
Background: Longer hemodialysis (HD) treatment time has been associated with lower mortality risk. However, there are scant data regarding the effects of increased treatment time with regards to residual renal function (KrU).

Methods: We retrospectively examined associations of baseline (first 91 days of dialysis) HD treatment time and 1-year renal residual urea clearance change in 6,659 patients receiving thrice weekly HD at a large dialysis organization between 2007-2011 and who survived the first year of dialysis and had available KrU data in the first and fifth patient-quarters. Patients were grouped into 4 exposure categories based on average treatment duration during the baseline quarter. Significant KrU loss was defined as a drop ≥20% ([KrU quarter 5 - baseline KrU quarter] / baseline KrU). Logistic regression models were used with covariate adjustment for case-mix, markers of malnutrition and inflammation, and ultrafiltration volume.

Results: The mean age of patients in the cohort was 62±14 years and 35% were female. Treatment duration of <3 hours was associated with higher risk for KrU loss. Longer treatment durations were linearly associated with lower risk of significant KrU loss. These trends persisted across all models of adjustment. In the shortest duration category (<3 hours), the fully adjusted odds ratio (OR) was 1.40 (95% CI, 1.16, 1.69). In the longest duration category (>4 hours), the OR was 0.81 (95% CI, 0.68, 0.98). [Figure]

Conclusions: Among HD patients, shorter treatment duration was found to be associated with higher odds of loss of KrU whereas longer treatment duration was found to be associated with lower odds of KrU loss. Further studies are needed to understand the relationship between treatment time and KrU loss.

Funding: NIDDK Support



TH-PO339

Incremental and Twice Weekly Hemodialysis in Australia and New Zealand

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Background: Most patients with end stage kidney failure starting hemodialysis do so at a standard frequency of three times a week, with occasional patients starting at a twice weekly frequency ("incremental dialysis"). Incremental dialysis may preserve residual kidney function, and has been associated with reduced mortality in dialysis patients. In this study we aimed to report the prevalence of incremental dialysis in an Australian and New Zealand incident dialysis cohort, and outcomes associated with this approach.

Methods: A cohort of incident adult patients starting hemodialysis between 2004 and 2015 was created. We constructed multivariate Cox proportional hazards models with a primary exposure of dialysis frequency at the first survey date. The primary outcome was all-cause mortality with secondary outcomes of cardiovascular and non-cardiovascular mortality.

Results: The cohort comprised 27513 subjects with complete dialysis frequency data, with 970528 patient months of follow up. Of these, 850 started on twice weekly hemodialysis and 783 had complete data for analysis. Compared to patients starting on conventional dialysis, those started on incremental dialysis were older (67 vs 62 years, p<0.001), had a lower BMI (26.1 vs 27.7 kg/m^2, p<0.001), were more likely to be female (45% vs 38%, p<0.001) had a higher eGFR at dialysis start (7.59 vs 6.66ml/min P<0.001) and were less likely to have diabetes (39.2% vs 50.2%, p<0.001). In a multivariate cox model, incremental start dialysis was not associated with reduced hazards for all-cause mortality (HR 1.03, 95% CI 0.92 – 1.16) but in death cause-specific models was associated with an increased risk for non-cardiovascular mortality (HR 1.25, 95% 1.11 – 1.42) but not cardiovascular mortality (HR 0.87, 95% CI 0.71 – 1.07).

Conclusions: In this cohort, incremental dialysis was used infrequently and there was evidence of patient level differences which imply specific selection criteria are used in practice. Outcomes overall were similar, but cause specific mortality risks demonstrated increased non-cardiovascular mortality risks in the incremental cohort, likely reflecting the differences in patient characteristics. A prospective trial to test the safety and efficacy of incremental dialysis should be considered.

TH-PO340

Short Frequent Haemodialysis at Home and Loss of Residual Renal Function

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Background: The importance of preserving residual renal function (RRF) in dialysis patients has long been recognised with benefits in survival, nutrition and biochemical parameters. Frequent nocturnal haemodialysis (FNH) may accelerate loss of RRF but effects of short frequent haemodialysis (SFHD) are less clear. We studied rate of loss of RRF in our cohort of home SFHD patients, comparing to matched thrice-weekly in-centre haemodialysis (ICHD) patients.

Methods: We identified 2 cohorts of patients at our centre both of whom had intermittent measures of residual renal urea clearance (KrU). The SFHD cohort comprised patients initiating SFHD at home between 2009-2017. A separate control historical cohort of ICHD patients was used of those commencing dialysis 1989-2009. Vintage from time of HD initiation was calculated for the SFHD cohort. Each patient was matched against 3 patients in the ICHD control cohort for KrU (±0.5ml/min) at the equivalent vintage (±6 months). Only KrU data after SFHD initiation was used in the SFHD cohort, and from the equivalent vintage time in matched controls. We compared trajectories of KrU decline in both cohorts, correcting for potential confounding variables.

Results: 1073 patients were in the control cohort and 84 patients in the SFHD cohort. 24 patients on SFHD had ≥2 KrU measures following initiation but only 22 patients could be matched with 66 control patients according to the above criteria. KrU at SFHD initiation was 2.3ml/min(IQR 1.3-5.4) in the SFHD group and 1.7(IQR 1.0-4.9) in the control group,p=0.25. Patients in the SFHD group were younger than control patients at the equivalent vintage time (50±SD17 v 64±SD14 years,p<0.001). There was no significant difference in frequency of diabetes, cardiac disease, peripheral vascular disease or gender between SFHD and control ICHD patients. Slope of decline in kidney function was -0.8ml/min/yr(IQR -1.8 to 0.1) in the SFHD group and -0.5(IQR -1.2 to -0.1) in the ICHD control group(p=0.60). Using multiple linear regression to determine predictors of slope of decline in KrU, neither group (SFHD or ICHD) nor age or gender were independent predictors of KrU slope.

Conclusions: We did not find evidence that SFHD at home was associated with an increased rate of decline in RRF. Patients with RRF on home HD might benefit from SFHD rather than FNH, but this needs further exploration.

TH-PO341

Residual Renal Function Loss in Hemodialysis Patients: Is Kidney Stunning the Culprit and Can Dialysate Cooling Help?

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Background: Residual renal function (RRF) declines in patients with ESRD after hemodialysis (HD) initiation, necessitating more aggressive fluid removal in subsequent sessions. It has been postulated that recurrent HD-induced renal ischemic insults lead to RRF decline, while dialysate cooling (DC), a feasible intervention which does not burden patient treatment, has been shown to ameliorate HD-induced circulatory stress in the heart and brain. The purpose of this work was to assess the effects of HD on renal hemodynamics using CT perfusion imaging and to explore DC as a protective intervention against renal intradialytic circulatory stress and RRF decline.

Methods: 26 patients provided written informed consent. All patients received standard (36.5°C) HD and a subgroup of 15 patients were randomized to receive either standard or cooled (35°C) HD first in a 2-visit crossover study design. For each visit, CT perfusion imaging was performed at three timepoints (before, 3 hrs into, and after HD) on a 256-slice CT scanner (GE Healthcare) without interrupting HD treatment. Parametric renal perfusion maps were generated and used to measure kidney blood flow.

Results: Renal perfusion loss ('kidney stunning') was observed in 63% (33/52) of kidneys during standard HD but declined to 50% of kidneys during cooled HD. The drop in renal perfusion at 3 hrs into HD was statistically significant (p<0.05) for the standard HD case but not for the cooled HD case. Figure 1 summarizes the per kidney perfusion measurements.

Conclusions: HD causes an acute drop in renal perfusion, and it may be these recurring ischemic insults over many sessions which result in irreversible renal tissue damage and RRF reduction. However, DC ameliorates these perfusion changes and may help slow RRF decline in HD patients.

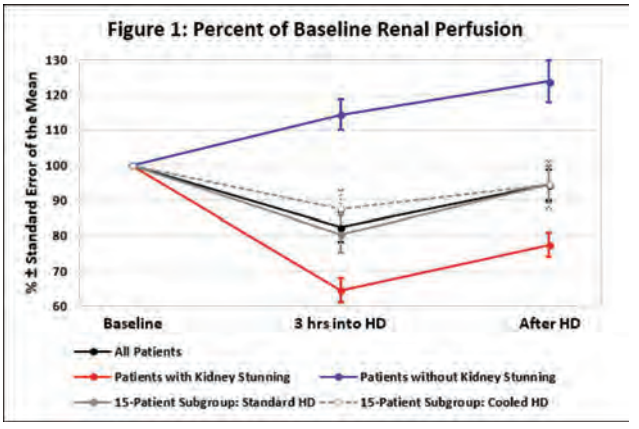

Figure 1: Percent of baseline renal perfusion before, 3 hours into, and after HD. Results are given as average ± standard error of the mean for 26 patients (52 kidneys).

TH-PO342

Allo-Hemodialysis: Intermittent Donation of Kidney Function as a Novel Treatment for Patients with Kidney Failure in Limited Resource Settings

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Background: A global report suggests that 2.2 to 7.1 million people might have died in 2010 prematurely because renal replacement therapy could not be accessed (Liyanage *et al*, Lancet, 2015); the authors noted the largest treatment gaps in low-income countries. Current hemodialysis (HD) is expensive and technically challenging. HD requires a substantial amount of water (300 to 1000 L of tap water per HD, depending on dialysate flow rate, treatment time, and reverse osmosis system rejection rate), a dialyzer, blood lines, and a sophisticated dialysis machine with pumps, heating, and ultrafiltration control systems to safely deliver HD, mostly in-centers. In our research, we systematically questioned long-held paradigms and conceptualized a novel treatment option that may have the potential to increase access to HD and reduce the loss of human life owing to kidney failure.

Methods: We conceptually reduced HD to its essential components, the dialyzer, blood lines, a pump, and ultrafiltration control. While - as in traditional HD - on the dialyzer's blood side the patient's blood flows, the dialysate side is connected to the circulation of a healthy subject ("buddy") and perfused with his/her blood (hence called *allo*HD). Because the "most physiologic dialysate i.e. physiosate" is provided by the buddy, the complexity of HD is substantially reduced. We employed extensive mathematical modeling to explore the feasibility of the *allo*HD.

Results: Our model simulations show that fluid and urea transferred into the buddy are cleared effectively by the buddy's kidneys, while bicarbonate diffuse into the patient. We show that a child can sufficiently be treated by an adult buddy with 3-4 weekly treatments. We show that blood flow rates are a key factor, thus *allo*HD may require catheters or

permanent vascular access in buddy. We also address a host of ethical, societal, biological, and technical questions in our ongoing research.

Conclusions: While dialyzing one human against another may seem unthinkable at first, we challenge the kidney community to rethink pre-conceived notions and reflect on the proposed concept. Prototyping of an *allo*HD device is underway that may be used for bench testing and, ultimately, *in vivo* studies in animals and humans. We believe that *allo*HD holds promise to ease the human burden of kidney disease.

Funding: Commercial Support - Fresenius Medical Care

TH-PO343

Renal Survival in Patients with Multiple Myeloma Requiring Renal Replacement Therapy – A Single Centre Experience

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Background: Renal impairment is a recognised complication of multiple myeloma (MM). The incidence of renal impairment at diagnosis of MM ranges between 20-50%; of these, approximately 10% present with acute kidney injury (AKI) requiring renal replacement therapy (RRT). Advances in MM treatments have improved overall patient survival and can result in complete or partial recovery of renal function. We reviewed outcomes of patients with MM requiring RRT over a 14 year period.

Methods: Patients diagnosed with MM requiring RRT between January 2003 and December 2017 were identified. Patient data was obtained from electronic records.

Results: 38 patients met the inclusion criteria. Median age was 62 years (range 45-86); 53% were male, 76% were Caucasian. Median follow up time was 37 months (range 6–168 months). 55% required RRT at presentation with a new diagnosis of MM. Of the rest, 21% started RRT within a year of diagnosis and 24% started RRT >12 months after diagnosis. Additional factors contributing to initiating RRT included infection (21%), hypercalcaemia (13%) and fluid overload (10%). Median creatinine at start of RRT was 550µmol/l (range 235-1372µmol/l). 37% of all patients had a renal biopsy, which identified cast nephropathy (43%), amyloidosis (43%), light chain deposition disease (7%), and other diagnoses (7%). 44% of patients requiring RRT at presentation recovered sufficient renal function to stop RRT, with a median time to dialysis independence of 1 month (range 1 week - 21 months) and median eGFR 42 mls/minute (range 12-78mls/minute). Only 6% of the cohort who required dialysis later (not at presentation) recovered adequate renal function to stop dialysis. Overall 1 year survival was 93% (N=36), and 5 year survival was 48% (N=21). 47% of all patients had died by the end of 2017; of these, 94% were dialysis-dependent at time of death, with a median time on dialysis of 1 year (range <1 week to 8 years).

Conclusions: In our cohort, more patients (55%) presented with AKI requiring RRT at the time of diagnosis of myeloma than in published literature (10% in Evison et al, British Journal of Haematology 2016); 44% of these patients became dialysis-independent. Our data demonstrates a positive correlation between recovery of renal function and reduced mortality, further reinforcing the importance of prompt treatment of myeloma.

TH-PO344

Effect of Hemofiltration on Anemia, Adequacy, and Bone Mineral Disease in Hemodialysis Patients

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Background: Hemofiltration (HF) is not associated with lower mortality risk compared to standard hemodialysis (HD). However, there are many critical clinical outcomes in dialysis patients in addition to mortality; the impact of HF on these other outcomes is not clear.

Methods: This retrospective study included all patients referred to DaVita clinics in the Kingdom of Saudi Arabia. High-flux HD was the initial modality in all patients. Those who did not achieve adequacy targets or who had poorly controlled phosphorus were switched to post-dilution HF using 18-23L exchange per treatment. Patients dialyzing with a central venous catheter, patients who dialyzed less than 90 days at DaVita, and those with interrupted HF were excluded.

Results: Of the 1115 patients, 215 (19%) were on HF and 900 on high-flux HD; median follow-up was 6 months for all patients. The HF group showed a significant reduction in serum phosphate ($p<0.001$), a significant increase in serum calcium ($p<0.012$) and a significant improvement in Kt/V ($p<0.0001$). The HF group had significantly higher hemoglobin level than the HD group ($p=0.024$), with a significant reduction in weekly erythropoietin (ESA) dose after starting HF ($p<0.001$).

Conclusions: HF improved anemia, ESA dose, dialysis adequacy, and phosphate control in this retrospective analysis of a cohort selected for failure to meet Kt/V and phosphorus targets. Thus, HF can enable achievement of adequate dialysis care in some patients. Randomized-controlled clinical trials are necessary to confirm these findings.

Funding: Commercial Support - DaVita

Comparison of anemia, mineral bone disorder, and adequacy parameters before and after initiation of HF

Parameters	Before HF	After HF	P-value
Serum phosphate, mg/dL, mean ± SD	5.5 ± 1.58	5.15 ± 1.53	<.001
Serum calcium, mg/dL, mean ± SD	8.92 ± 0.82	9.1 ± 0.68	0.01
Kt/V, mean ± SD	1.53 ± 0.36	1.7 ± 0.43	<.001
Hemoglobin, g/dL, mean ± SD	11.15 ± 1.16	11.3 ± 1.08	0.3
PTH, pg/ml, median (IQR)	554 (556-85)	537 (579-55)	0.6
ESA dose, IU/week, median	10000	4000	0.001

TH-PO345

A Bi-National Cross-Sectional Survey of Clinician Attitudes Towards Haemodiafiltration in Australia and New Zealand

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Background: High convection volume hemodiafiltration may improve survival compared to high-flux hemodialysis, however there is significant variation in its use. Clinician attitudes towards hemodiafiltration are poorly understood but may explain differences in practice patterns.

Methods: A 17-question online survey was administered from February 2017 to January 2018. Clinicians involved in the care of hemodialysis patients were invited to participate via the Australian and New Zealand Society of Nephrology. The survey addressed domains of clinician knowledge; hemodiafiltration prescription; perceived benefits, harms, and barriers to use; and indications and contraindications.

Results: Eighty-two responses were received from clinicians affiliated with 49 of 81 hemodialysis units (60% unit response rate). Hemodiafiltration was prescribed by 87% of respondents, but generally to less than 25% of patients. The percentage of respondents prescribing hemodiafiltration to most of their patients was greater for those in privately funded (60%) than publicly funded units (28%). Only 26% of respondents considered the level of evidence supporting the superiority of hemodiafiltration over high-flux hemodialysis to be high. Its key benefits were perceived to be superior middle molecule clearance, hemodynamic stability, phosphate clearance, and amyloid prevention. Common indications included frequent intradialytic symptoms, intradialytic hypotension, and uremic polyneuropathy. Few respondents (14%) agreed hemodiafiltration conveyed harm to patients, however 25% considered frequent circuit clotting to be a relative contraindication. Although most respondents (63%) believed hemodiafiltration was more expensive than high-flux hemodialysis, this was not a barrier to its use. Three-quarters of respondents prescribed post-dilution hemodiafiltration, but only 55% targeted a convection volume greater than 20L.

Conclusions: Most clinicians in Australia and New Zealand prescribe hemodiafiltration, but generally to a small proportion of patients, and high convection volumes are not routinely targeted. Although no specific barriers to its use were identified, the majority of clinicians did not consider the level of evidence supporting its use to be high.

TH-PO346

Effect of Centre and Patient Related Factors on Uptake of Haemodiafiltration in Australia and New Zealand: A Cohort Study Using ANZDATA

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Background: We described the use of haemodiafiltration (HDF) in Australia and New Zealand over time, and any patient or centre-related associations with use of HDF.

Methods: We included all incident patients commencing haemodialysis in Australia and New Zealand between 2000-2014. The primary outcome was commencement of HDF over time, which was evaluated using multivariable logistic regression stratified by country.

Results: Of 27,433 patients starting haemodialysis, 3,339 (14.4%) of 23,194 patients in Australia and 810 (19.1%) of 4,239 in New Zealand received HDF. Uptake increased over time in both countries but was more rapid in New Zealand. In Australia, HDF use was more likely in males (OR 1.13, 95%CI 1.03-1.24, $p=0.009$) with BMI>30 kg/m^2(OR 1.46, 95%CI 1.33-1.61), and less likely in older patients (reference <40 years; 40-54 years OR 0.85, 95% confidence interval [CI] 0.72-0.99; 55-69 years OR 0.79, 95% CI 0.67-0.91; >70 years OR 0.48, 95% CI 0.41-0.56) and those with chronic lung disease (OR 0.84, 95%CI 0.76-0.94, $p<0.001$), cerebrovascular disease (OR 0.76, 95%CI 0.67-0.85, $p<0.001$) or peripheral vascular disease (OR 0.77, 95%CI 0.70-0.85, $p<0.001$). Larger centres (defined by number of new patients/year) were more likely to prescribe HDF: 36-147/year OR 26.75 (95%CI 18.54-38.59); 17-35/year OR 7.51 (95%CI

5.35-10.55); 7-16/year OR 3.00 (95%CI 2.19-4.13; <6/year reference. HDF was used more in private dialysis clinics (public OR 0.13, 95%CI 0.05-0.32). In New Zealand, where there is no private dialysis, HDF use was more likely in Maori and Pacific Islanders (OR 1.32, 95%CI 1.05 – 1.66) compared to Caucasians and less likely in males (OR 0.76, 95%CI 0.62 – 0.94, p=0.01). In both countries, centres with higher HD:PD patient ratios were significantly more likely to prescribe HDF. Centre differences explained 36% of variability in HDF uptake in Australia and 48% in New Zealand.

Conclusions: HDF uptake has increased over time, and was associated with similar centre characteristics, but different patient characteristics in each country.

TH-PO347

The Effect of Frequent Hemodialysis on Phosphate and Fibroblast Growth Factor 23: Results from the Frequent Hemodialysis Network Trials

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Background: Hyperphosphatemia is associated with elevations in fibroblast growth factor 23 (FGF23) and blood pressure in patients with end-stage kidney disease (ESKD). We aimed to ascertain whether reduction in phosphate by frequent hemodialysis is associated with specific changes in biomarker profile amongst patients enrolled in the Frequent Hemodialysis Network (FHN) trials.

Methods: This was a post hoc observational cohort study. We hypothesized that reduction in phosphate is associated with changes in FGF23. We further hypothesized that changes in FGF23 may correlate with variations in blood pressure and markers of collagen turnover.

Results: Among 332 randomized patients, 243 had biomarker data available. Of these, 124 were assigned 3 times a week hemodialysis (94 [Daily Trial] and 30 [Nocturnal Trial]) and 119 patients were assigned to 6 times a week hemodialysis (87 [Daily Trial] and 32 [Nocturnal Trial]). Frequent hemodialysis lowered phosphate, blood pressures, logFGF23 and tissue inhibitors of metalloproteinase (TIMP) - 2 levels. The fall in phosphate correlated to the changes in FGF23 (r = 0.48, p <0.001 [Daily Trial] and r = 0.55, p < 0.001 [Nocturnal Trial]) and trended with changes in systolic blood pressure (r = 0.18, p = 0.057 [Daily Trial] and (r = 0.31, p = 0.04) [Nocturnal Trial].

Conclusions: Reduction of serum phosphate by frequent hemodialysis may modulate FGF23 levels and systolic blood pressure. Frequent hemodialysis may affect pathological mediators of chronic kidney disease – mineral bone-metabolism disorder.

Funding: NIDDK Support

Effect (95% CI) of hemodialysis frequency on phosphate, blood pressure and selected biomarkers

Variables	Daily Trial (3x/week))	Daily Trial (6x/week)	p-value (3x vs. 6x)	Nocturnal (3x/week)	Nocturnal (6x/week)	p-value (3x vs. 6x)
Phosphate (mg/dL)	0.02 (-0.3;0.4)	-0.5 (-0.9; -0.2)*	0.01	0.3 (-0.4; 1.0)	-1.1 (-1.8; -0.4)*	0.004
LogFGF23 (%**)	-14.0 (-38.8; 21.0)	-43.9 (-59.5; -22.5)*	0.051	-9.0 (-50.0; 65.6)	-46.2 (-71.2;0.5)#	0.22
Systolic blood pressure (mmHg)	-2.0 (-6.7; 2.6)	-8.1 (-12.5;-3.7)*	0.038	-3.7 (-10.3; 3.0)	-14.9 (-21.8; -7.9)*	0.019
Diastolic blood pressure (mmHg)	-0.7 (-3.4; 2.0)	-4.5 (-7.0; -1.9)*	0.027	-0.5 (-4.6; 3.6)	-4.7 (-8.9; -0.4)*	0.15
TIMP-2 (pg/ml)	-3888.8 (-11080.2;3302.6)	-14632.5 (-21728.2;-7536.9)*	p<0.0001	-11966.0 (-22090.7;-1841.4)*	-14936.5(-25208.4;-4664.5)*	0.56

* denotes p < 0.05 (within group); # p =0.052 (within group); **expressed as percent difference based on log transformed analysis

TH-PO348

Comparison of the Removal of Uremic Toxins with Medium Cut-Off and High-Flux Dialyzers: A Randomized Clinical Trial

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Background: Accumulation of middle weight toxins (500 Da-60 kDa) in hemodialysis (HD) patients results in increased morbidity and mortality. Conventional high-flux (HF) dialyzers allow efficient removal of beta2 microglobulin (11.8 kDa), but their effect on higher molecular weight molecules is not well established. Whether new generation of medium cut-off (MCO) dialyzer improve removal of middle to high molecular weight uremic toxins remains to be demonstrated.

Methods: Theranova, a randomized, open-label, cross-over study (NCT03211676) was designed to compare MCO-HD to HF-HD on the epuration of middle weight uremic toxins. Forty six patients treated with HF dialyzer Elisio 21H™ for more than 6 months were randomized to either continue on this membrane (n=22) or to receive the Theranova 500™ dialyzer (n=24). After 3 months, patients crossed over to the other dialyzer during 3 other months. Primary outcome was myoglobin (17 kDa) reduction ratio (RR) at 3 months. Secondary outcomes were RR, pre and post dialysis levels of beta2 microglobulin, prolactin, hepcidin, leptin, retinol binding protein, alpha 1 glycoprotein, fibroblast growth factor-23, hyaluronic acid, homocystein and cytokines (IL6, IL1-beta, TNF-alpha) at 3 and 6 months. Nutritional and inflammatory parameters, level of albumin and oxidative stress mediators (8-iso-Prostaglandin, oxidized LDL, superoxide dismutase), anemia parameters and erythropoietin resistance index were also determined.

Results: Forty patients completed the study. Mean age was 76 ± 9 years (male gender 74%). MCO-HD provides higher median RR of myoglobin [59% vs 36%, p<0.0001] whereas beta2 microglobulin RR was similar [77% vs 69%, p=0.7], as compared to HF-HD. Mean pre-dialysis beta2 microglobulin levels [26.9 mg/l vs 28.4 mg/l, p =0.001] and post dialysis myoglobin levels [76 µg/l vs 126 µg/l, p<0.0001] were significantly lower with MCO-HD. Pre and post dialysis albumin levels were significantly lower with MCO-HD [36.9 g/l vs 38.2 g/l, p=0.004] and [40 g/l vs 42.3 g/l, p=0.004].

Conclusions: These preliminary data indicate that MCO-HD provides significant removal of myoglobin and decrease in beta2 microglobulin pre dialysis level, with higher albumin loss than HF-HD. Complete results will be presented during the meeting.

Funding: Commercial Support - BAXTER

TH-PO349

Six Months Evaluation of the Expanded Hemodialysis (Hdx) on Removal Efficiency, Anemia, and Quality of Life

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Background: The High-Flux (HF) dialysers in standard-hemodialysis (HD) allow the removal of a wider spectrum of uremic toxin. However the HD can remove mostly low molecular weight solutes while the HDF can remove solutes around 15kDa, so-called Middle Molecules (MM), improving morbidity and mortality by exchange volumes >15L per session. The new medium cut-off (MCO) filter Theranova® is designed to expand the removal of toxins up to 45kDa in HD compared to HF membranes (HemoDialysis eXpanded, HDx) even with conventional blood flows and without exchange fluid infusion. The aim of this study is to evaluate the performance of HDx and its impact on anemia and quality of life (QoL) in hemodialysis patients (pts).

Methods: 13 stable HD pts were enrolled (M/F 10/3, age 70.8±9) with Qb ≤300 ml/min in a six months' observational case-control study. Each patient was evaluated first with HF filter (T0) and then in HDx for six months. Pre-dialysis (T0-T6) were evaluated: urea, phosphate (P), beta2-microglobulin (B2m), myoglobin (Myo), free light-chains K and λ (FLC-K and FLC-λ), C-Reactive Protein (CRP), hemoglobin (Hb) and albumin. Furthermore Kt/V, dose of EPO, ERI and SF-36 questionnaire were evaluated at the beginning and end of observation. We treat hemodialysis pts according to the KDIGO Guideline for Anemia in CKD. The values have been reported as mean±SD.

Results: HDx (Qb= 275 ± 41 ml/min, TT 215 ± 21 m) shows a significant increase in KT/V (T0 1,31 ± 0,23; T6 1,55 ± 0,17; p= 0.001) with relevant RR of: Urea 69%; P 56%; B2m 63%; Myo 55%; FLC-k 61%; FLC-λ 59%. There is a significant reduction at 6 months for FLC-λ (Tab.1). HDx reduced ERI (T0 9.8 ± 10.5; T6 4.4 ± 5.5; p <0.05) and EPO dose (T0 7692 ± 8518; T6 3615 ± 4464, p <0.05), keeping the Hb unchanged. QoL is significantly improved (ISF: T0 27.3 ± 10.1; T6 40.2 ± 8.4 p= 0.0001) (ISM: T0 43.8 ± 14.2; T6 51.1 ± 9.8 p= 0.001).

Conclusions: HDx effectively removes uremic toxins up to 45kDa, even with Qb <300 ml/min, without reducing serum albumin and with promising results on inflammation. Reduction of ERI and improvement of QoL are encouraging and suggest the use of HDx even in pts who cannot benefit from convective techniques because of vascular access or intolerance to high volumes of exchange.

	Urea (mg/dl)	P (mg/dl)	B2m (mg/l)	Myo (ng/ml)	FLC-k (mg/l)	FLC-λ (mg/l)	PCR (mg/l)	Hb (mg/l)	Albumin (g/dl)
T0	129.9±31.5	4.6±1	28.7±9.2	249.8±81.5	15.9±6.7	86.1±46.0	12.1±13.7	11.6±1.2	3.1±0.4
T6	120.2±28.1	4.3±0.9	25.0±5.4	211.9±77.6	15.0±6.9	33.0±45.5*	5.8±4.7	12.1±0.9	3.2±0.3
p	0.405	0.761	0.125	0.167	0.628	0.004	0.469	0.429	0.746

Tab. 1 Pre-dialytic values of the uremic toxins evaluated during the follow-up.

TH-PO350

Middle Molecules Elimination in Expanded Hemodialysis: Only Convective Transport?

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Background: Hemodialysis using high flux membranes leads to convective transport by internal filtration(IF) [Direct Filtration(DF)/Backfiltration(BF)] and allows middle molecules(MM) elimination. The development of High Retention Onset dialyzers has achieved greater elimination of MM and their depurative capacity could be similar to high convective volumes of online hemodiafiltration. The aim of the study was to assess solute transport mechanisms in expanded hemodialysis(HDx) with Theranova 500(Baxter).

Methods: We analyzed fourteen HDx sessions with similar dialysis conditions: blood flow 400 ml/min, dialysate flow 700 ml/min, dialysate temperature 35.5C and 240 minutes length. Pressures at the inlet and the output of both dialyzer compartments(P_{bi}, P_{bo}, P_{di}, P_{do}) were collected hourly with DBB-EXA monitor(Nikkiso) to estimate convective volume(CV) using different semi-empirical methods previously used to model IF. Blood viscosity data and uremic toxins with various molecular weight were measured pre-dialysis, at 1 hour(pre-filter and post-filter) and post-dialysis to calculate molecules reduction over time and dialyzer *in vivo* clearances.

Results: Ultrafiltration was 1.47±0.9 L and Kt/V 1.74±0.3. Hydrodynamic data (average P_{bi}:259±39, P_{bo}:155±27, P_{di}:271±30, P_{do}:145±29 mmHg, monitor TMP 1.8±4

mmHg, oncotic pressure 20,8±3,4 mmHg, blood viscosity 1,51±0,10 cP) allowed to estimate DF and BF rates and volumes. Models showed a DF flow range from 18.2±4.5 to 29.8±3.1 ml/min and BF flow range from 16.8±1.8 to 26.6±2.3 ml/min. The highest calculated CV was 7160.2±738.9 ml/session. Global, convective and diffusive clearances and molecules RR are summarized in Table. CV was correlated with urea(r:-0.785,p=0.001), creatinine(r:-0.675,p=0.008) and myoglobin(r:0.587,p=0.027) clearances.

Conclusions: Results suggest that diffusive transport is a main mechanism of middle molecules elimination in HDx with Theranova 500. HDx offers a potential advantage achieving efficient depuration of middle molecules without the need for high convective transport volumes.

	MW (Da)	Reduction ratio (%)			Clearances (ml/min) at 60 min		
		[0 – 240 min]	[0 – 60 min]	[60 – 240 min]	Global	Convective*	Diffusive
Urea (mg/dL)	60	84.7 ± 7.4	52.1 ± 8.1	69.2 ± 10.7	341.8 ± 7.2	29.8 ± 3.1	311.9 ± 9.4
Creatinine (mg/dL)	113	77.9 ± 7.9	49.5 ± 6.2	57 ± 11.9	278.3 ± 15.8	29.8 ± 3.1	248.5 ± 18
Phosphate (mg/dL)	96	58.2 ± 15.6	49.1 ± 11.3	17.3 ± 24.2	304.1 ± 27.5	29.8 ± 3.1	274.3 ± 27
β2-microglobulin (mg/L)	11800	79.1 ± 5.8	55.7 ± 6.7	53.1 ± 9.9	147.9 ± 13.9	26.9 ± 2.8	120.9 ± 13
Cystatin C (mg/L)	13300	73.5 ± 5.9	53.3 ± 7.6	43.3 ± 9.4	129.4 ± 8.5	26.2 ± 2.7	103.2 ± 7.8
Myoglobin (ng/mL)	17200	65.4 ± 5.7	46.1 ± 6.7	35.6 ± 9.0	78.1 ± 11.3	23.5 ± 2.4	54.6 ± 10
Prolactin (µg/L)	23000	62.4 ± 10.9	40.5 ± 9.8	37.1 ± 11.3	46.1 ± 30.8	19.9 ± 2.1	26.2 ± 31
Albumin (g/dL)	66200	10.9 ± 5.9	6.5 ± 8.2	5.1 ± 6.2	-9.4 ± 17.1	-	-

* Convective clearances were calculated using the following theoretical sieving coefficients: Sc 0.90 for Beta-2 microglobulin, Sc 0.88 for cystatin C, Sc 0.79 for myoglobin, Sc 0.67 for prolactin, Sc 0.01 for albumin, Sc → 1 for urea, creatinine and phosphates.

TH-PO351

Higher In Vivo β2 Microglobulin Clearance in Expanded Hemodialysis: Preliminary Results of a Cross-Over Trial

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Background: In conventional hemodialysis (HD), β2 microglobulin (β2M), a medium-range molecule (MRM), tend to accumulate in tissues. Online hemodiafiltration (olHDF) increases MRM clearance at expense of more complex dialysis machines. The development of medium cut-off with high albumin retention onset membranes allowed a new therapy, known as expanded hemodialysis (HDx). However, so far, *in vivo* extraction of MRM in this modality is unknown.

Methods: Prospective trial, in which 8 patients switched from HD to olHDF or HDx for 1 month, and then crossed to the other modality for another month, after a washout period of 2 weeks. Pre- and post-dialysis urea, albumin, phosphorus, and β2M were measured in blood and in a sample of homogeneously collected spent dialysate, throughout dialysis procedure. High-flux Diacap™ dialyzers (BBraun, Germany) were used both in HD and in olHDF, while Theranova 400™ dialyzers (Gambro, Germany) in HDx. Ongoing trial is registered at NCT03274518.

Results: Mean age was 48 ± 13 years (75% men), and dialysis duration was 225 ± 12 minutes. Total convection volume in olHDF was 20.3 ± 1.1L. β2M clearance was higher in HDx in comparison to high-flux HD and olHDF (62.2 ± 10.2 *vs.* 36.5 ± 2.6, p = 0.012 and 45.5 ± 18.3 ml/min, p = 0.026 respectively). β2M extraction during dialysis was higher in HDx in comparison to olHDF (196.4 ± 31.3 *vs.* 122.1 ± 43.8 mg, p=0.023). Pre-dialysis serum β2M was not different among the three modalities.

Conclusions: Preliminary results of this trial indicate that *in vivo* clearance and total mass extraction of β2M is higher in HDx in comparison to olHDF.

Laboratorial data from patients, according to dialysis modality

	HD	olHDF	HDx	p
Ultrafiltration (ml)	2625 ± 1233	2775 ± 977	2900 ± 1039	ns
Spent dialysate (L)	182.6 ± 8.8	182.8 ± 9.3	182.9 ± 9.1	ns
Phosphorus (mg/dl)	3.6 ± 1.1	4.8 ± 0.9	4.3 ± 1.9	ns
Phosphorus extraction (mg)	635 ± 344	683 ± 168	775 ± 307	ns
Albumin (g/dl)	3.8 ± 0.3	4.0 ± 0.3	3.7 ± 0.3	ns
Albumin extraction (g)	23.1 ± 1.3	23.1 ± 10.5	18.3 ± 0.9	ns
β2M (ug/ml)	23.7 ± 0.5	23.2 ± 6.9	27.8 ± 5.5	ns
β2M extraction (mg)	136.7 ± 22.9	122.1 ± 43.8†	196.4 ± 31.3†	0.023†
β2M clearance (ml/min)	36.5 ± 2.6*	45.5 ± 18.3†	62.2 ± 10.2*†	0.012*; 0.026†
Urea (mg/dl)	164 ± 29	162 ± 23	161 ± 36	ns
Urea extraction (g)	43 ± 16	42 ± 14	45 ± 18	ns

* HD vs HDx; † olHDF vs HDx

TH-PO352

Medium-Range Molecule Extraction and Intradialytic Hemodynamics: Comparison of Two Convective Dialysis Methods

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Background: Online hemodiafiltration (olHDF) improves intradialytic hemodynamic (IH) stability in comparison to hemodialysis (HD), possibly by lowering dialysate temperature (DT) and increasing medium-range molecule extraction. Using medium cut-off dialyzers in HD machines (HDx) might exert similar effects on IH.

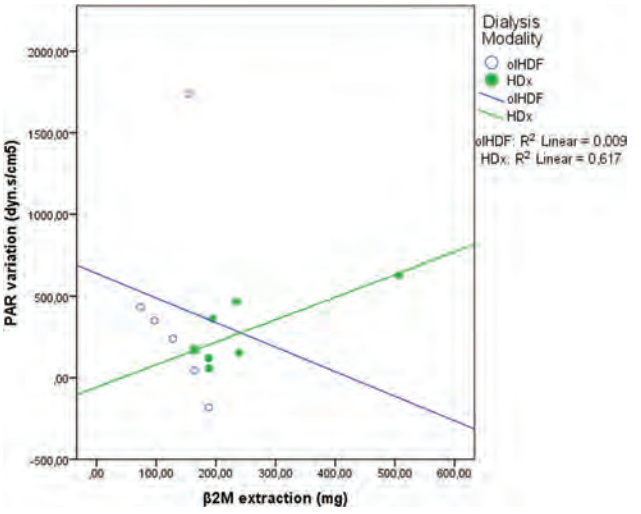
Methods: Prospective trial, in which 8 patients switched from olHDF to HDx. DT was set to 36 °C. Pre-dialysis Beta2 microglobulin (β2M) was measured both in blood and spent dialysate. IH was assessed by Finometer™ during the first and the last 15 minutes of each dialysis session. High-flux Diacap™ dialyzers (BBraun) were used in olHDF, and Theranova 400™ (Gambro) in HDx.

Results: Total convection volume in olHDF was 20.3±1.1L. Post *minus* pre dialysis variation of systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP), stroke volume (ΔSV), cardiac output (ΔCO) and peripheral arterial resistance (ΔPAR) were similar between olHDF and HDx. Positive ΔPAR, indicating increased post-dialysis vascular tonus, was observed both in olHDF and HDx (table), yet correlation between ΔPAR and β2M extraction was observed in HDx (r=0.785, p=0.021), but not in olHDF (r=-0.096, p=0.85).

Conclusions: At a same DT, olHDF and HDx led to similar IH stability. β2M extraction was associated with increased intradialytic PAR only in HDx.

Study data, according to dialysis modality

	olHDF	HDx	p
Ultrafiltration (L)	2.77 ± 0.9	2.90 ± 1.0	ns
β2M (ug/ml)	23.2 ± 6.9	27.8 ± 5.5	ns
β2M extraction (mg)	122.1 ± 43.8	196.4 ± 31.3	0.023
Δsystolic blood pressure (mmHg)	8.7 (-9.9; 18.4)	3.1 (-9.4; 10.1)	ns
Δdiastolic blood pressure (mmHg)	3.1 (-0.8; 11.7)	-4.3 (-3.3; 8.9)	ns
Δstroke volume (ml)	-18.7 (-56.1; -1)	-26.1(-43.7; -22)	ns
Δcardiac output (l/min)	-1.3 (-2.6; -0.5)	-1.4 (-2.2; -1.3)	ns
Δperipheral arterial resistance (dyn.s/cm5)	436 ± 675	252 ± 211	ns



Correlation: β2M extraction vs ΔPAR

TH-PO353

Trial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD): A Safety and Efficacy Study

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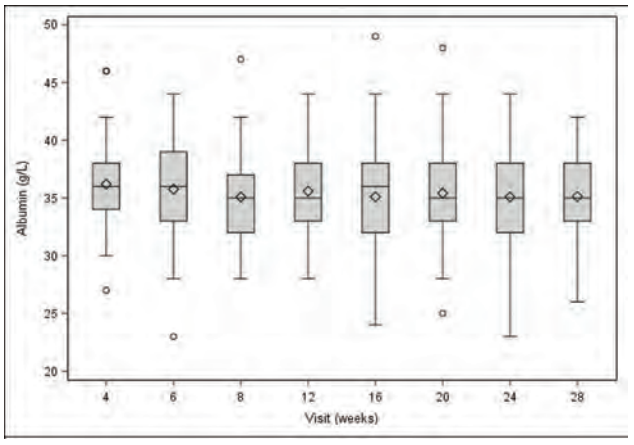
Background: A medium cut-off (MCO) dialyzer is a novel form of hemodialysis (HD) therapy designed to increase clearances of larger middle molecules and uremic toxins but may result in short-term loss of albumin. The safety and efficacy profile following sustained use of this dialyzer has not been established.

Methods: REMOVAL-HD is an investigator led, single-arm, multi-center device study that examined the safety, efficacy and patient-centered outcomes of MCO dialyzer use in chronic HD patients over 6 months. The primary outcome was change in serum albumin between baseline and 6 months. Secondary outcomes included 4-weekly trends in serum albumin, six-minute walk test (6MWT), malnutrition inflammation score (MIS) and symptom burden using restless leg syndrome rating scale and Edmonton Symptom Assessment System Revised (ESAS-R) measured at baseline, 3 and 6 months.

Results: Of 92 enrolled participants, 87 completed the required protocol and were included for analysis. Participants had a mean age of 67± 15 years, 63% were men and 51% were diabetic. The average serum albumin decreased by 1.06 g/L (95% confidence interval [CI] 0.43,1.69], or 2.92%, from baseline. The trend in serum albumin during the intervention period is shown in Figure 1. A sustained, unexplained reduction in serum albumin (>25%) was not observed in any participant. Functional and nutritional assessment using 6MWT (Δ5.7m 95% CI -29.9, 41.3) and MIS (Δ-0.4 95%CI -0.9, 0.1) were stable throughout the treatment period. Similarly, there was no significant change in patient-reported symptom burden.

Conclusions: Regular HD using the MCO dialyzer in a chronic HD population resulted in a small but acceptable reduction in serum albumin. Future randomised controlled trials should now assess the impact of the MCO dialyzer on clinical and long-term patient-centered outcomes.

Funding: Commercial Support - Baxter : Investigator Initiated Research (IIR) Grant



Trend in serum albumin under MCO dialyzer use

TH-PO354

Increasing the Removal of Protein-Bound Uremic Toxins by Hemolipodialysis

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Background: Protein-bound uremic toxins (PBUTs) accumulate at high plasma levels and cause various deleterious effects in ESRD patients because their removal by conventional hemodialysis (HD) is severely limited by their low free-fraction levels in plasma. Here, we assessed the extent to which solute removal can be increased by adding liposomes to the dialysate.

Methods: A reservoir that contained PBUTs and artificial plasma was used for determinating the adsorption capacity of liposomes for p-cresyl sulfate (PCS), indoxyl sulfate (IS) and hippuric acid (HA). The effect of adding liposomes to the dialysate was then quantified and compared with the effect of adding bovine serum albumin (BSA) to the dialysate and dialysate without addition of any sorbent in a rapid equilibrium dialysis (RED) setup and an in vitro closed HD model respectively. Finally, male Sprague-Dawley rats were subjected to 5/6 nephrectomy and fed for 20 weeks to establish the end stage renal failure. They received HD for 240 min at a blood and dialysate flow rate of 1.0 and 5.0 mL/min, respectively. Removal of solutes was determined by reduction ratios (RRs) and total solute removal (TSR) in dialysate.

Results: The uptake of liposomes by direct incubation in vitro showed an obvious dose-response relationship for PCS and IS but not for HA. The percent removal of both PCS and IS but not of HA was gradually increased with the increased concentration of liposomes in the RED setup. In vitro closed HD circulation showed that adding liposomes to the dialysate markedly increased the clearance of PBUTs without greatly altering that of urea and creatinine. The difference was more noticeable for strongly albumin bound compounds. In vivo experiments in uremic rats demonstrated that adding liposomes to the dialysate resulted in higher reduction ratios (RRs) and more total solute removal (TSR) for several PBUTs compared to the conventional dialysate, which was approximately similar to the addition of BSA to the dialysate. There were no significant differences in RRs and TSR of blood urea nitrogen and creatinine with addition of liposomes or BSA to dialysate compared to conventional dialysis.

Conclusions: As an adjunct to conventional hemodialysis, adding liposomes to the conventional dialysate may significantly improve the removal of protein-bound uremic solutes without greatly altering the removal of small, water-soluble solutes.

Funding: Government Support - Non-U.S.

TH-PO355

Bias Between In Vitro and In Vivo Mass-Transfer Coefficient of Urea (KoA) Is Larger in Pediatric Than in Adult Patients on Chronic Hemodialysis

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Background: Hemodialysis (HD) prescription with respect to blood flow (Q_B) dialysate flow (Q_D) and filter KoA significantly differs between pediatric and adult patients. This may explain why urea dialytic clearance (K_D) has been observed to be significantly underpredicted from Q_B, Q_D and KoA in pediatric HD patients using a mechanistic equation. The objective of this analysis was to evaluate factors that could explain this bias, assuming that it results from a bias between reported *in vitro* determined KoA and actual *in vivo* KoA.

Methods: An urea kinetic model previously developed in adult patients was scaled to 923 paediatric and young adult patients aged 1-29 years based on *a priori* physiologic knowledge (inter-compartmental clearance and volumes of distribution; "base model"). Utilizing data from 2676 HD sessions of those patients with pre- and post-HD urea concentration measurements, a mixed effect modelling approach was applied to evaluate the relationship between individual estimates of KoA correction factors (f_{KoA}) required for unbiased prediction of K_D (as indicated by unbiased post-HD urea predictions), and prescription related parameters (Q_B, Q_D, Q_D/Q_B ratio, filter reuse, low/high-flux, ultra-filtration rate, duration of treatment).

Results: Q_D/Q_B ratio was the parameter most strongly associated with individual estimates of f_{KoA} (≈ -10%, 10%, 100% and 200% increased *in vivo* KoA estimated at Q_D/Q_B ratios of 1.5, 2, 5, and 10, respectively; p<0.001), explaining 18% of inter-individual variability (decrease from 42.8 to 35.1%). Inclusion of Q_D/Q_B ratio as a covariate removed bias observed with Q_B and Q_D. A proposed correction equation for Q_B (true Q_B lower than nominal Q_B at rates >200 mL/min) also corrected bias observed at Q_B > 300 mL/min, but did not reduce inter-individual variability. Inclusion of session duration, low-flux filters, and ultra-filtration rate did further improve the model fit, however with small reductions in inter-individual variability.

Conclusions: While *in vivo* KoA has been reported to be *lower* in adult patients than established *in vitro*, the opposite was observed for pediatric patients in the present study. The observed bias could best be explained by high Q_D/Q_B ratios used in pediatric patients indicating that dialyzers require specific characterization under pediatric conditions.

Funding: Private Foundation Support

TH-PO356

Intracellular ATP and Inorganic Phosphate Depletion During Maintenance Hemodialysis

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Background: The origin of depurated phosphate during hemodialysis (HD) remains unknown. Using phosphorus magnetic resonance spectroscopy (^{31}P-MRS), we previously showed in an acute kidney failure model in pig, an increase of intracellular inorganic phosphate (Pi) concentration during hemodialysis associated with a decrease in ATP. This result strongly supports the hypothesis that depurated phosphate could come from the intracellular space. The aim of this study was to measure intracellular Pi in patients during maintenance HD using ^{31}P-MRS.

Methods: Eleven maintenance HD patients were included in the CIPHEMO (Intracellular ATP and Pi Concentrations measurements in HEMOdialysis patients) study, a single-center prospective trial. They underwent a ^{31}P-MRS exam using a 3-Tesla system and a surface coil placed over the calf muscle region for measuring Pi and ATP contents during a standard hemodialysis session (4 hours). ^{31}P-MR spectra were acquired before, during (every 152 seconds) and after the HD session. Phosphatemia, depurated phosphate and calcemia were monitored during HD and parathyroid hormone levels were measured at the beginning and at the end of the session. Calcium balance was also measured.

Results: Intracellular Pi and βATP kinetics can be described in 2 phases. During the first hour of HD, phosphatemia decreased rapidly (-41%, p<0.001) whereas intracellular Pi didn't change (p=0.9) and intracellular βATP decreased (-17%, p=0.038). After 1 hour of HD, phosphatemia decreased slowly, intracellular Pi decreased (p=0.001) and βATP remained constant until the end of the session (p=0.46). Depurated phosphate is nearly constant during the session. Calcemia increased (p<0.01) and parathyroid hormone decreased (p<0.05) during HD. Calcium balance is positive (mean of 17.1 mmol).

Conclusions: This study showed a significant decrease in both intracellular ATP and Pi during hemodialysis. These findings, reported for the first time in HD patients, support the hypothesis that a large part of depurated phosphate could come from the intracellular space in patients on maintenance hemodialysis.

TH-PO357

Removal of Large-Middle Molecules on Expanded Hemodialysis (HDx): A Multicentric Observational Study of 6 Months Follow-Up

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Background: Hemo**D**ialysis e**x**panded (HDx) may potentially represent an innovative way to remove uremic toxins of Large-Medium Molecular weight (LMMs, ≤45 Kda) thanks to the membrane medium cut-off (MCO, Theranova®, Baxter). LMMs are involved in the pathogenic mechanisms of organ dysfunction associated with uremia including inflammation, malnutrition and atherosclerosis. The aim of this study was to evaluate the efficacy of LMMs removal in HDx during an observational multicentric study of 6 months follow-up.

Methods: 41 HD stable patients (age 67,6±13,4) were dialyzed in HDx with Theranova® 400 (1.7 m^2). Each patient was evaluated at baseline with standard HD (T0), 3 months (T3) and 6 months (T6) after HDx. In the first session of the week (for each period), we evaluated the following pre-dialysis parameters: Urea, Creatinine (Creat), Phosphate (P), Beta2-microglobulin (B2m), Myoglobin (Myo), Free Light Chains (FLC-k, FLC-λ),

Hemoglobin (Hb), Albumin and C Reactive Protein (CRP). Data are reported as mean ± standard deviation (SD).

Results: HDx therapy was well tolerated without evidence of major adverse side effects. The main results of the study are summarized in Figure 1. After 3 months of HDx (T3), we observed a significant decrease of pre-dialysis levels of urea (p=0,008), B2m (p=0,003), FLC-k (p=0,026), FLC-λ (p=0,001). No significant differences of the other uremic toxins between the periods (T3 vs. T6) were observed. Albumin levels remained stable during all the study period. A significant decrease of CRP was observed at T3 and T6, suggesting a positive effect of HDx on inflammatory parameters correlated with a worse outcome.

Conclusions: HDx therapy provided high removal of different LMMs, leading to a significant reduction of molecules involved in uremia-associated organ dysfunction in the first 3 months of treatment (T0-T3). Long-term studies with a larger sample size are needed to evaluate the clinical impact of HDx. However, our preliminary data suggest that HDx may improve LMMs removal and inflammatory parameters.

	Urea (mg/dl)	Creat (mg/dl)	P (mg/dl)	B2m (mg/l)	Myo (ng/ml)	FLC-k (mg/l)	FLC-λ (mg/l)	CRP (mg/l)	Hb (mg/l)	Albumin (g/dl)
T0	130.8±41.7	9.8±2.5	4.6±1.4	29.2±7.7	206.6±84.8	111.6±106.5	84.3±72.7	5.09±9.16	10.9±1.3	3.5±0.5
T3	117.1±31.9[a]	9.2±2.1	4.6±1.4	26.6±5.8[a]	206.8±80.3	101.9±95.9[a]	78.1±65.2[a]	3.65±4.52	11.4±1.4	3.4±0.5
T6	120.8±34.1[a]	9.6±2.0	4.8±1.2	26.4±7.2[a]	196.4±85.5	106.6±102.7	79.5±67.8[a]	2.69±3.62	11.3±1.2	3.5±0.4

Figure 1: Pre-dialysis levels of different uremic toxins at study start (T0) and after 3 (T3) and 6 (T6) months of HDx.

TH-PO358

Comparison Between Online Clearance Monitoring (OCM) and Calculated kt/V in Adult Population on Hemodialysis

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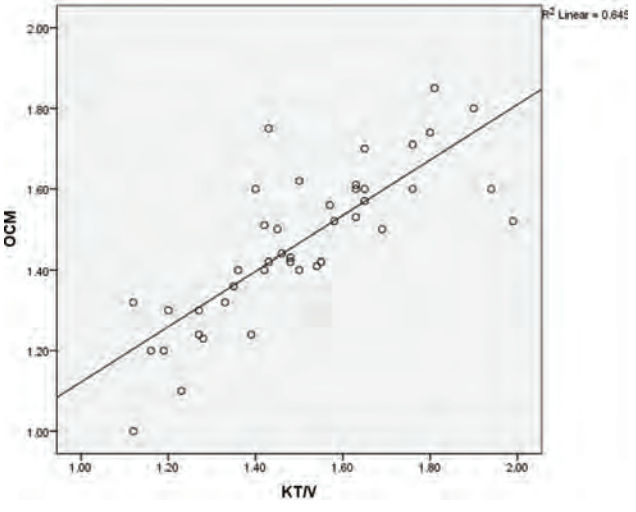
Background: Morbidity and mortality in hemodialysis patients is closely correlated to the delivered dialysis dose. The delivered dose is measured in maintenance hemodialysis patients either by blood samples to calculate Kt/V single pool or by measuring the ionic dialysance in real time using OCM. The aim of this study was to compare the quality of dialysis delivered by calculated kt/V obtained with the formula of lowrie(L) and Daugridas(D) with the results measured by Online Clearance Monitoring(OCM).

Methods: Using Fresenius 4008S machines equipped with OCM, we prospectively studied 42 hemodialysis patients from February 1, 2018 to April 30, 2018. All patients were on hemodialysis for more than three months. Pre and post dialysis urea samples were collected for estimation of Single pool Kt/V and compared with OCM. Patient information was collected and all data analysed using SPSS for windows software package.

Results: The average age of the patients was 56.07 ±13.89 years and the mean duration of dialysis was 28.34 ±34.95 months. Mean blood flow rate was 307.67 ±45.87 mL/min. The mean Kt/V was 1.499 ±0.222 (p=0.000) and the mean OCM was 1.465 ±0.190 (p=0.000). We found a positive correlation between the two parameters i.e a Pearson's Correlation: 0.83 (p=0.000) and an R square value of 0.645. We found that OCM is a good indicator of Kt/V. However, it underestimated Kt/V by 2.07%±8.53%.

Conclusions: Online Kt/V calculated by ionic dialysance is a useful method to estimate dialysis dose without the need of blood samples, however it slightly underestimates Kt/V. In clinical practice Kt/V is done on a monthly basis. Any change in the dialysis prescription would entail repeat labs. OCM can be performed at each dialysis session at no extra cost and in real time. Thus, it can prove to be a helpful tool in the assessment of dialysis adequacy.



TH-PO359

Comparison of Removal Efficiency and Biocompatibility Between Pre- and Post-Dilution On-line Hemodiafiltration

Kenji Sakurai,[1] Takeshi Saito,[1] Hiromi Hosoya,[1] Yoshitaka Kurihara,[1] Daisuke Ishii,[2] Kazunari Yoshida,[3] Kenichi Kokubo,[4] Toru Hyodo.[5] *[1]Hashimoto Clinic, Sagamihara, Japan; [2]Kitasato University Hospital, Sagamihara Kanagawa, Japan; [3]Department of Urology Kitasato University School of Medicine, Sagamihara, Japan; [4]Kitasato University School of Allied Health Sciences, Sagamihara, Japan; [5]Eijin Clinic and Cambodian Association of Nephrology, Hiratsuka, Japan.*

Background: In Japan in late-2016, 329,609 patients received dialysis, 24.2% of whom received hemodiafiltration (HDF). In 79% of HDF, the on-line mode is used, which is mostly performed with the pre-dilution mode (pre-HDF). However, in Europe, all HDF sessions use the post-dilution mode (post-HDF). We previously assessed differences in biocompatibility between pre- and post-HDF based on inflammatory markers and lymphocyte stimulation tests, and reported that pre-HDF is less physically stressful. Here, we used a more biocompatible hemodiafilter to study whether biocompatibility would differ between pre- and post-HDF, and assessed the solute removal efficiency of both modes.

Methods: Eight stable dialysis patients were included in this study. HDF was performed with Fineflux 210S eco (asymmetric triacetate membrane, NIPRO) at a blood flow rate of 250 mL/min and a total dialysate flow rate of 500 mL/min for 4 h/session. The substitution fluid volumes were 60 and 12 L/session for pre- and post-HDF, respectively. To test removal efficiency, urea, creatinine, b_2-microglobulin (MG) (MW:11.8kDa) and a_1-MG (MW:33kDa) levels were measured to determine the reduction rates. Albumin (Alb) leakage was also measured. To test biocompatibility, hs CRP, interleukin (IL)-6, tumor necrosis factor (TNF)-a, pentraxin (PTX)-3, intercellular adhesion molecule (ICAM)-1, and cluster of differentiation 62 platelet (CD62P; a platelet cell surface marker) levels were measured.

Results: Post-HDF was more efficient at removing small-molecular-weight solutes than pre-HDF. The reduction rate of b_2-MG was 81.2±2.6% for both modes. The reduction rates of a_1-MG were 33.1±5.8% for pre-HDF and 37.4±3.9% for post-HDF, showing a significant difference ($p<0.05$). Alb leakages (g/session) were 2.8 for pre-HDF and 3.4 for post-HDF ($p<0.05$). No differences between the two modes were observed in the rates of changes in CRP, IL-6, TNF-a, ICAM-1, and PTX-3 levels. Increases in the expression rates of CD62P were 164.7±24.1% for pre-HDF and 210.7±44.2% for post-HDF ($p<0.05$).

Conclusions: The percent change in the CD62P expression rate was smaller for pre-HDF than for post-HDF; platelets may have been less activated during pre-HDF than during post-HDF under this study's conditions. Post-HDF was more efficient at removing solutes.

Funding: Private Foundation Support

TH-PO360

Using Binding Competitors of Albumin to Promote the Removal of Protein-Bound Uremic Toxins in Hemodialysis: Proof of Concept and Screening of Candidates

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Background: Protein-bound uremic toxins (PBUT) remain a concerning burden as their removal in hemodialysis is limited by their strong interaction with albumin. Despite interesting animal data, the limitation of their intestinal production is disappointing. By enhancing their circulating free-fraction during hemodialysis, the use of binding competitors could be undertaken. The aim of this work was to evaluate the displacing capabilities of some selected solutes and to identify potential candidates for an *in vivo* development.

Methods: Displacement capacity of a fluorescent probe (dansylsarcosine) specific to Sudlow's site II on albumin was tested in spectrofluorimetry. Displacement capacity was then expressed as a concentration displacer/albumin ratio. Short chain fatty acids were provided by Sigma-Aldrich. The selection of potential candidate solutes was realized by an in-silico screening (virtual screening and docking) of 12,055 compounds from Asinex chemotech library. The effect on the free-fraction of indoxyl-sulfate (IS) was tested after an addition of a 1mM solution of octanoic C8 in a solution of bovine serum albumin previously incubated with a solution of IS.

Results: Among the short chain fatty acids tested, C8 and C10 were the more prone to displace dansylsarcosine from site II of albumin (75% for C8 ; displacer/albumin ratio of 5). In silico sreening identify 10 potential candidates among which N-phelyl-glycine and N-phenyl-N-benzenesulfonyl glycine (PBSG) were the best candidates. Indeed, the displacement obtained was roughly 60% for a displacer/albumin ratio between 50 and 250. The addition of a 1mM solution of C8 to a solution of bovine serum albumin permitted an increase of 22% of the free-fraction of IS ($p<0.05$).

Conclusions: C8 permitted a significant increase in the free fraction of IS in vitro. Nevertheless, significant concentrations of short chain fatty acids can lead to a significant hemolysis. Hence, we identified two interesting solutes that could be interesting to promote the removal of PBT: N-phenyl-glycine and PBSG. Those hydrophilic solutes need to prove their safety under physiological conditions and their effects on other compounds bound onto site II of albumin need further investigations.

TH-PO361

A Novel Post-Dilution CVVHDF-RCA with Personalized Initial Calcium Dosing and Fixed Citrate to Blood Flow Ratio

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Background: Regional citrate anticoagulation (RCA) use is limited by concerns of electrolyte complications. We describe a novel approach for post-dilution CVVHDF that minimizes nurse workload, achieves desired circuit anticoagulant activity, and avoids life-threatening hypocalcemia even in patients with fulminant liver failure.

Methods: Post-dilution CVVHDF was performed using Prismaflex machines at one of three blood flow rates 60, 100, or 150ml/min based on patient's body weight. Acid citrate dextrose-A solution (113 mmol/L) was infused into the arterial limb of the extracorporeal circuit at one of three rates 150, 250, 300 ml/h depending on blood flow rate. Equal dialysate/replacement flow rates are determined from a table according to body weight (for 25-30 ml/kg/h total effluent) in those with expected normal citrate metabolism and modified according to weight and circuit plasma flow in those with absent citrate metabolism. Dialysate/replacement fluid electrolyte concentrations were as follows: Na 136-151, K 2-4, Ca 0, and HCO3 25-45 mEq/L, phosphate 0 to 1.36 mmol/L. Initial calcium chloride solution (136 mmol/L) infusion rate was determined according to a dosing table based on effluent rate and daily serum albumin and titrated thereafter according to systemic ionized calcium (iCa) every 6 hours. Circuit iCa was obtained every 12 hours. RCA effectiveness was measured in terms of circuit iCa and filter life. Electrolyte trends for 30 consecutive patients are reported.

Results: The protocol achieves adequate circuit anticoagulation (circuit iCa <0.4 mM in >95% of measured samples). The risk of clinically significant hypocalcemia is less than 1%. The risk of hypernatremia or metabolic alkalosis is abrogated. Clinically significant hypophosphatemia is avoided by spiking commercial solutions with sodium or potassium phosphate.

Conclusions: The approach achieves desired circuit anticoagulant activity, avoids life-threatening hypocalcemia and poses no risks related to RCA.

TH-PO362

Pre-Filter CVVH Results in Longer Filter Life Than CVVHD

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Background: Continuous renal replacement therapy (CRRT) is used to treat severe acute kidney injury (AKI) in hemodynamically unstable patients. The two main CRRT modalities are continuous venovenous hemofiltration (CVVH, convective clearance) and continuous venovenous hemodialysis (CVVHD, diffusive clearance). Filtration fraction, an estimate of hemoconcentration through a filter, is thought to be a major determinant of filter clotting risk in CRRT. In theory, CVVHD produces less hemoconcentration, and therefore less potential for filter clotting, than either pre-filter or post-filter CVVH. However, data to support this claim remain limited. The purpose of this study was to examine filter life in patients treated with either pre-filter CVVH or CVVHD.

Methods: We conducted a retrospective analysis of adult patients initiated on CRRT at the University of Colorado Hospital (UCH) between 2014 and 2016. Filter life was recorded for all filters, which were changed if clinically warranted or after a maximum of 72 hours. Cox regression was used to evaluate time to filter loss in CVVH versus CVVHD, and the model was adjusted for blood flow rate, anticoagulation type, replacement or dialysis fluid flow rate, ultrafiltration rate, and patient weight.

Results: A total of 415 filters from 160 patients were included in the analysis, of which 275 were used in a CVVH circuit and 140 in a CVVHD circuit. The average filter life in those undergoing pre-filter CVVH was 42 hours (SD 25.2) compared to 35 hours (SD 24.3) in CVVHD ($p = 0.01$). Cox regression showed a hazard ratio of 1.3 (CI 1.03 – 1.65, $p=0.028$) for filter loss with CVVHD.

Conclusions: Contrary to out hypothesis, pre-filter CVVH had a longer average filter life than CVVHD, and this pattern remained significant in a Cox regression model. CVVHD results in less hemoconcentration than CVVH, but is not associated with increased filter life. Pre-filter CRRT may be associated with longer filter life through dilution of clotting factors, but further investigation into the mechanism of filter clotting in these CRRT modalities is needed.

Funding: Other NIH Support - T32 DK 007135

TH-PO363

Multipoint Dilution Hemofiltration (MPD-HF): A New Technology for Maximum Convective Clearance

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Background: Convection-based renal replacement therapies (RRT) have the potential to improve patient outcomes when compared to diffusion-based RRT such as hemodialysis (HD), but have limited clearance rates. We propose and characterize Multipoint Dilution HF (MPD-HF), a purely convective blood purification technology which removes the fundamental filtration limit associated with convective RRT. In MPD-HF, filtration of liquid and solutes occurs along the length of the hollow fibers that convey the blood and substitution fluid is pushed into the fibers at multiple points along their length. Since multiple filtration and dilution steps are contained within one pass of the blood through the hollow fiber, the fraction of fluid that can be filtered may be increased to allow a high clearance rate.

Methods: We designed, simulated, fabricated, and tested MPD-HF cartridges comprising commercial Fresenius F200NR hollow fibers passed through 3 filtration and 2 infusion chambers, quantifying clearance of molecules across a range of molecular weights.

Results: Figure 1 shows steady state clearance versus molecular weight for the *in vitro* MPD-HF experiment, a COMSOL model prediction of the MPD-HF, an FX CorDiax 800 HDF dialyzer and an F160 dialyzer. *In vitro* tests yielded an average steady state filtrate fraction of 68%, exceeding commercial HDF cartridge filtrate fractions by a factor of approximately 3 and matching the COMSOL model.

Conclusions: MPD-HF offers substantial increases in the filtrate fraction relative to both HD and HDF. Extrapolating the MPD-HF to 5 or more filtration and dilution chambers allows for a theoretical 100% fluid fraction removal in a single pass, yielding clearance rates higher than HD and HDF.

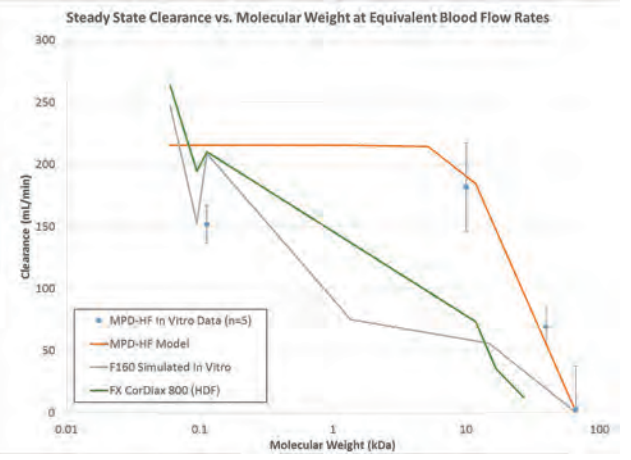

Figure 1. MPD-HF Model and In Vitro Performance

TH-PO364

Measured Dialysate Sodium Deviates Frequently and Sometimes Substantially from Ordered Dialysate Sodium in Acute Care Hemodialysis

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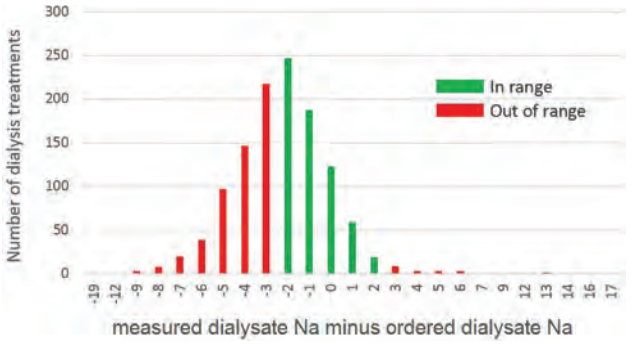
Background: It is unknown if measured dialysate sodium (meas $_D$Na) differs from the ordered $_D$Na (ord $_D$Na) in the acute care setting where hemodialysis (HD) dialysate is created at the point of care via individual acid and bicarbonate concentrates

Methods: We examined HD treatments in an acute care setting where meas $_D$Na was obtained at HD start. An absolute difference between meas $_D$Na and ord $_D$Na >2 mEq/L was considered out of range. Factors in a simple/univariate logistic regression model with random intercept for each dialysis machine included: machine factors (ID#, model, hours of use) and dialysate factors (ord $_D$Na, additives in acid or bicarb jug, dialysate flow rate)

Results: There were 1230 HD treatments on 21 unique Fresenius machines in a 3-mo period. After exclusions (machine ID# unknown, machine <20 HD's), 1196 treatments were analyzed. The difference between meas $_D$Na and ord $_D$Na was close to normally distributed but skewed towards meas $_D$Na <ord $_D$Na; meas $_D$Na was out of range in 46.8% (n=560) of the cases (Fig 1). In the logistic regression analysis, there was a significant effect of machine ID# clustering, with an ICC of 0.20-0.25, on out of range $_D$Na. Other factors (machine model, hours of use, dialysate flow, ord $_D$Na, additives in acid or bicarb jug) were not associated with $_D$Na out of range, when machine clustering was taken into account. In 227 treatments where the meas $_D$Na was out of range (91.5% were <ord $_D$Na), the nurse made a manual $_D$Na adjustment based on the difference between meas $_D$Na and ord $_D$Na. A subsequent meas $_D$Na level was checked during HD. After this adjustment, the meas $_D$Na was within range of the originally ord $_D$Na in 176 (77.5%) of the treatments.

Conclusions: Measured $_D$Na was >2 mEq/L off from ordered $_D$Na in about half of the treatments, with a bias towards a lower level. There appears to be a difference between dialysis machines, with some having a higher % of treatments with out of range $_D$Na, despite consistent and rigorous machine maintenance and testing

Funding: Clinical Revenue Support



TH-PO365

Efficacy and Safety of Oxabact® OC5 in Dialysis Patients with Primary Hyperoxaluria Type 1 (PH1): A Phase II, Prospective, Open-Label Study

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Background: In PH1, endogenous overproduction of oxalate in the liver and, therefore, extremely elevated urinary oxalate excretion lead to early end-stage renal disease with patients requiring dialysis and/or liver (±kidney transplantation). Removal of oxalate via dialysis is insufficient and cannot match the endogenous production. Oxabact®, a formulation of an oxalate-metabolizing bacterium (*Oxalobacter formigenes*), induces active secretion of oxalate in the intestinal lumen and generates reductions in plasma and urinary oxalate (Pox and Uox, respectively) in patients with PH1 at various stages of renal impairment. This Phase II, prospective, open-label study investigated efficacy and safety of an improved Oxabact® formulation, OC5, in patients with PH1 treated with a stable dialysis regimen.

Methods: After a 4-week baseline period, patients received OC5 (one oral capsule containing ≥10^9 CFU lyophilized *O.formigenes*, twice a day) for 6 weeks and were monitored for an additional 4 weeks (initial treatment), before they started an extended treatment at the same dose until transplantation or a maximum of 36 months. Total and free Pox were evaluated monthly. Traditional and Speckle-Tracking Echocardiography were performed at baseline and then every 6 months. Fecal analyses for *O. formigenes* and standard safety assessments were conducted. This is the interim analysis of the study's first 12 months.

Results: To date, 12 subjects have been enrolled and six subjects with a mean (SD) age of 30.5 (14.0) years have received OC5 for up to 12 months. Total Pox (mean at baseline 153.48 µmol/L, maximum mean decrease: 43.52 µmol/L at Week 44) and total:free Pox ratio (mean at baseline 1.468, 1.223 at Week 52; p <0.05) decreased. Cardiac parameters clearly indicated that systemic oxalosis did not worsen under treatment. *O.formigenes* genotype 1 was detectable in all patients. Six subjects reported 52 adverse events; most were mild or moderate (88.5%) and not related (90.4%) to treatment. Two subjects experienced serious adverse events, unrelated to treatment.

Conclusions: A 52-week treatment regimen with OC5 in patients with PH1 undergoing dialysis was safe, reduced Pox, and provided evidence that systemic oxalate deposition was attenuated, which would be of a substantial clinical significance for future transplantation outcome.

Funding: Commercial Support - OxThera AB

TH-PO366

Low Rates of Outpatient Intensified Hemodialysis in Pregnant Women with ESRD

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Background: Pregnancy is a rare event for women on hemodialysis (HD). Observational data suggests that increasing HD hours per week to >20-36hrs and targeting pre-HD BUN<50 during pregnancy improves likelihood of successful delivery. We aimed to characterize pre-delivery HD regimens of pregnant women with ESRD in the US and to identify patient characteristics associated with receipt of intensified HD.

Methods: Deliveries were identified using inpatient claims data from USRDS for all women age 18-44 undergoing HD with Medicare as primary payer in 2012-2015 (n=390). 41 weeks of preceding outpatient HD treatment data in CROWNWeb was examined, including: number of sessions per week, prescribed and delivered HD time, Kt/V, ultrafiltration rate, and pre-HD BUN. We stratified women into "intensified HD" group (5+ sessions per week; INT-HD) vs. "standard HD" (<5 sessions; STD-HD). Comparison of demographic and treatment variables were made for women receiving INT-HD vs. STD-HD using student's t-test.

Results: There was no difference in age, ethnicity, or dialysis vintage of women who received INT-HD vs. STD-HD (Table), nor were there individual patient characteristics which predicted receipt of INT-HD. 39.2% of women in the STD-HD group did not achieve the recommended pre-HD BUN<50 compared to 17.2% of women in the INT-HD group (p<0.0001). Only 12.8% of women were dialyzed at least 5 times per week as outpatients, and less than 5% received ≥20 hrs (1200 minutes) per week. The average total treatment time per week for all delivering women was 745.5 min.

Conclusions: Experts advocate for at least 20 hours (if no residual renal function >36 hours) of HD per week in order to improve pregnancy outcomes. We observed that very few women with ESRD on HD in the US are receiving >20 hrs of HD per week in the outpatient setting and a significant proportion do not achieve the recommended pre-HD BUN.

Funding: NIDDK Support, Other NIH Support - T32 DK007378-38

Variable	Mean (SD) or %		p-value
	INT-HD	STD-HD	
Age (years)	32.4 (5.6)	31.8 (5.4)	0.4303
White race	44.0%	40.3%	0.6196
Black race	48.0%	49.4%	0.8526
Asian race	0.0%	5.0%	<.0001
Other race	8.0%	5.3%	0.5079
Hispanic ethnicity	28.0%	28.2%	0.9725
Dialysis vintage (years)	4.5 (5.5)	5.0 (5.5)	0.5673
Delivered time/week (minutes)	1079 (166)	688 (191)	<.0001
Kt/V	1.48 (0.6)	1.60 (0.3)	0.1789
Ultrafiltration Rate (ml/kg/hour)	5.7 (2.8)	7.9 (3.9)	<.0001
Pre-HD BUN >50	17.2%	39.2%	<.0001

Demographics and Treatment Characteristics in Delivering Women by Group

TH-PO367

Pregnancy Delivery Rates Amongst Women of Child-Bearing Age with ESRD: 2002-2015

Andrea L. Oliverio,[1] Jennifer L. Bragg-Gresham,[1,2] Rajiv Saran,[1,2] Michael Heung.[1,2] *[1]University of Michigan, Ann Arbor, MI; [2]U-M Kidney Epidemiology and Cost Center, Ann Arbor, MI.*

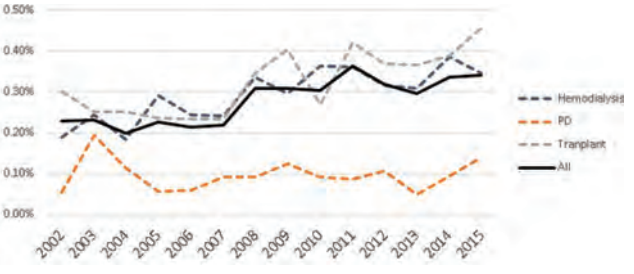
Background: Fertility is depressed in women with advanced CKD and ESRD and improves after transplant. Women with ESRD are at higher risk for pregnancy complications and loss. We sought to identify trends in delivery incidence amongst women with ESRD receiving renal replacement therapy (RRT) in the United States Renal Data System (USRDS).

Methods: We identified deliveries from inpatient claims of all prevalent female ESRD patients aged 18-44 yrs (n=650,282) between 2002-2015. Treatment modality at time of delivery was taken from treatment history files. Modality assignment for non-pregnant women was defined as last modality reported in each year. Rates were expressed as number of delivering women for every woman of child-bearing age receiving that RRT modality within each year. Logistic regression examined associations between patient characteristics and delivery.

Results: 1833 deliveries were observed over the study period. Delivery rates increased overall from 0.23% to 0.34% from 2002-2015 (Figure). Rates were highest for transplant patients, while PD patients had significantly lower rates. Older age was associated with lower odds of delivery (OR=0.91 for each additional year, 95% CI: 0.91-0.92). Black and Hispanic women (compared to White) were more likely to deliver (OR=1.46, 95% CI: 1.29-1.65 and OR=1.44, 95% CI:1.26-1.65, respectively), as were women whose primary cause of ESRD (compared to diabetes) was glomerulonephritis (OR=1.78, 95% CI=1.49-2.13) and hypertension (OR=1.65, 95% CI: 1.35-2.02). For each additional year after ESRD diagnosis, the odds of delivery were lower by 3% (OR=0.98, 95% CI: 0.97-0.99).

Conclusions: The absolute number of deliveries for women of childbearing age with ESRD remains low, but is increasing. The rate of delivery in women receiving HD nearly doubled between 2002 and 2015. Further work is needed to identify factors contributing to this increase. Younger women with shorter ESRD vintage are more likely to deliver and it may be prudent to focus family planning counseling to this subset of patients.

Funding: NIDDK Support, Other NIH Support - T32 DK007378-38



Percentage of delivering women per year amongst prevalent female ESRD patients aged 18-44

TH-PO368

Switching Dialysis Modalities for a Better Outcome: Analysis from the United States Renal Data System (USRDS)

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Background: Since 2011, the prospective payment system dialysis bundle has created more incentive for providers to place patients (pts) on Peritoneal Dialysis (PD) leading

to more pts switching from Hemodialysis (HD) to PD. Previous studies showed that, compared to pts who started with HD, those who started with PD were more likely to be white, younger, non-diabetic, and with less prevalence of obesity and other comorbidities. They were also described to have either better or similar survival. However, patient factors and outcome in those who switch from HD to PD have not been well described. In this study, we compared demographics and survival between pts on HD and those switched from HD to PD.

Methods: Using the USRDS, we analyzed demographics and mortality for 594,872 pts from May 2012 till December 2015. Kidney transplant recipients were excluded. Pts were divided into: HD only, PD only, and HD-to-PD switch groups. Comparison of continuous demographic variables, such as age, BMI, and albumin, was based on t-tests (pooled variances). Comparison of demographic categorical variables, such as sex, race, region, and presence of diabetes, was based on Contingency Analysis. Survival Analyses were performed using Kaplan-Meier curves. A Cox Proportional Hazards model was used to estimate the effects of predictor variables on pts survival as well as on PD modality survival after the switch.

Results: Comparing the HD only (n= 574,606) and switch groups (n= 20,266), we found that switch pts were more likely to be younger at time of 1st ESRD service (5.0 years, $p<0.01$), males, white, non-diabetics, and to have a higher serum albumin (0.05 g/dl, $p<0.01$). Average BMI was surprisingly higher in the switch group (0.4 kg/m^2, $p<0.01$). The switch group had better survival than both the HD only and PD only groups. Among pts who switched, non-diabetics and those with a higher serum albumin had better overall survival as well as PD modality survival. BMI and sex had no significant effect on either.

Conclusions: Demographics in pts who transitioned from HD to PD were similar to those previously reported in pts initiated on PD. Additionally, the HD to PD group had improved survival. These findings provide insight into the demographics influencing the decision to switch pts to PD and the positive impact on survival among those pts.

TH-PO369

Factors Affecting Initial Dialysis Modality in Pediatric ESRD

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Background: Children from minority and immigrant backgrounds are more likely to be placed on hemodialysis (HD) vs. peritoneal dialysis (PD) at onset of end stage renal disease (ESRD). We hypothesize that social determinants of health (SDOH), beyond the effect of race/ethnicity, influence initial dialysis modality.

Methods: We performed a retrospective cohort study of children 1-18 years who started dialysis between 2000-2012 using the US Renal Data System database. Using national census and American community survey data based on the patient's residence zip code, we derived a community level health risk score comprised of 17 items representing the five elements of SDOH defined by Healthy People 2020. (Table 1) Used a multivariable logistic regression model to identify associations between dialysis modality (HD vs. PD) and the health risk score, adjusting for age at incident ESRD, race, sex and ESRD cause.

Results: Among 5,607 patients, 3,472 (61.9%) had HD as their initial modality vs. 2,135 (31.8%) who were started on PD. Patients in the lower quintile for risk score (more favorable community based on the included variables) were more likely to be placed on PD (OR 1.456, p-value 0.000, 95%CI 1.21-1.75) vs those in the highest quintile of risk score (OR 1.267, p-value 0.014, 95% CI 1.049-1.53) when adjusting for age at incident ESRD, race, sex and ESRD cause. In this multivariable model, race was not associated with initial dialysis modality.

Conclusions: Children with highest risk scores were less likely to be placed on PD vs patients in neighborhoods with lower risk. Race was not associated in our model with initial dialysis modality unlike earlier studies looking at similar associations. Our findings suggest that it may be informative to examine SDOH along with race when examining inequities in health care access. Next steps will include differential weighting of variables within the risk score to determine whether there are modifiable factors that impact initial dialysis modality for children.

Funding: NIDDK Support

Neighborhood and the built environment	**Education**
- Vacant housing units	- % High school education
- % Housing overcrowding	- % Non-English speaking
- Assault related deaths	- % Illiteracy
Health and Health care	**Economic Stability**
- % Uninsured	- % Living below poverty level
- % Proportion of pediatricians by population	- % Unemployed
- % Low birth weight	- Food insecurity
- % Obese	- Median household income
Social and community context	
- % Single parent households	
- Voter turnout	
- Average number of people per household	

Variables of Health risk score

TH-PO370

Developing Consensus-Based Outcome Domains for Trials in Peritoneal Dialysis: An International Delphi Survey

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Background: Major inconsistencies in the reporting of outcomes, the omission of patient-reported outcomes, and frequent reporting of surrogate outcomes in trials impedes evidence-informed decision making by patients and their clinicians.

Methods: In an international online 3-round Delphi survey, patients/caregivers and health professionals rated the importance of outcomes using a 9-point Likert scale and provided comments. In rounds 2 and 3, participants re-rated the outcomes after reviewing the scores and comments of other respondents. For each outcome we calculated the mean, median, and proportion rating 7-9 (critically important).

Results: In total, 873 participants (207 [24%] patients/caregivers and 666 [76%] health professionals) from 68 countries completed round 1, and 530 (61%) completed round 3. The top outcomes based on a threshold (mean >8; median ≥8; proportion >85% in both groups) were PD-infection, membrane functioning, PD failure, cardiovascular disease, mortality, catheter complications, and ability to do usual activities. Compared with health professionals, patients/caregivers gave higher priority to 6 outcomes: blood pressure (mean difference of 0.4), fatigue (0.3), membrane functioning (0.3), impact on family/friends (0.1), peritoneal thickening [EPS] (0.1), and usual activities (0.1).

Conclusions: Clinical outcomes were highly prioritised by both stakeholder groups. Patients/caregivers gave higher priority to lifestyle-related outcomes than health professionals. This process will inform a core outcome set to improve the consistency and relevance of outcomes reported in trials in peritoneal dialysis.

TH-PO371

Regional Variation in Peritoneal Dialysis (PD) Time on Therapy (ToT): Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS)

Jeffrey Perl,[1] Junhui Zhao,[2] Bruce M. Robinson,[2] Simon J. Davies,[3] Hideki Kawanishi,[4] David W. Johnson,[5] James A. Sloand,[6] Mauricio Sanabria,[7] Talerngsak Kanjanabuch,[8] Yong-Lim Kim,[9] Jenny I. Shen,[10] Ronald L. Pisoni.[2] *[1]St. Michael's Hospital, Toronto, ON, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Keele University, Stoke-on-Trent, United Kingdom; [4]Tsuchiya General Hospital, Hiroshima, Japan; [5]Princess Alexandra Hospital, Brisbane, QLD, Australia; [6]JAS Renaissance, Chicago, IL; [7]RTS Baxter, Bogota, Colombia; [8]Chulalongkorn University, Bangkok, Thailand; [9]School of Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea; [10]LaBiomed at Harbor-UCLA, Torrance, CA.*

Background: Transition to hemodialysis (HD) carries significant morbidity and reduced quality of life for PD patients. PDOPPS seeks to identify practices aimed at meaningfully prolonging technique survival on PD. Here we describe PD discontinuation and death rate in PDOPPS.

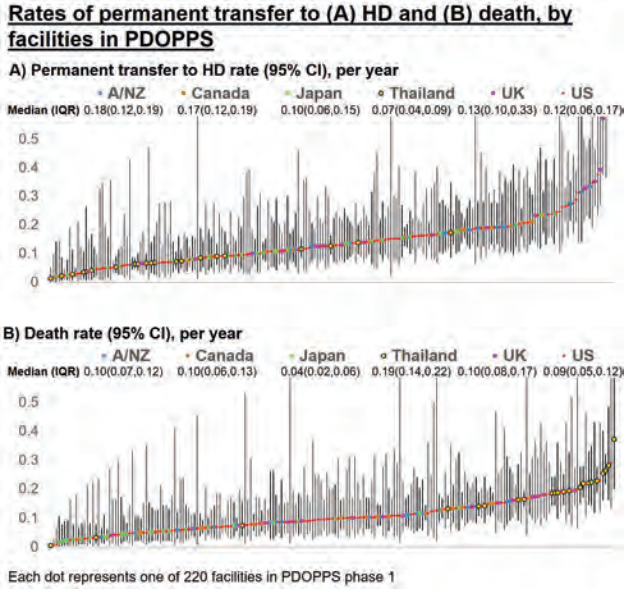
Methods: PDOPPS is a prospective cohort study of randomly selected patients across national samples of PD facilities from Australia/New Zealand (A/NZ), Canada, Japan, Thailand, the UK, and the US. The study population included 20532 patients who were followed until death (on PD) or permanent switch to HD, based on initial designation as a permanent transfer or a temporary transfer with no return at 12 weeks. ToT (from PD start to death or permanent transfer to HD) and hazard ratios (HR) were estimated using Cox models based on PD vintage at study entry (age, sex, and diabetes adjusted).

Results: 16% of patients transferred to HD and 13% of patients died. Median (IQR) ToT was 3.0 (1.3-5.7) years, ranging from 2.3 (1.1-4.4) in the UK to 4.5 (2.3-9.0) in Japan. Relative to the US, HR (95% CI) for transfer to HD were similar in Japan, Canada, and A/NZ, lower in Thailand (0.5, 0.3-0.7), and higher in the UK (1.5, 1.0-2.0). Compared to the US, HR for death was lower in Japan (0.4, 0.3-0.5), higher in Thailand (1.9, 1.4-2.5), and similar in A/NZ, Canada, and the UK. Variation in death, and transfer to HD (was seen across facilities [figure].

Conclusions: In PDOPPS, rates of permanent transfer to HD, and death vary significantly by country and facility. Future work will identify reasons for variation in PD outcomes, and identify practices to reduce the risk of PD attrition.

Funding: Commercial Support - The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects and countries is provided by AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Keryx, Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Proteon, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH)

in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Dr. Perl directly.



TH-PO372

Differing Attitudes Towards Peritoneal Dialysis (PD) Among PD and Hemodialysis (HD) Medical Directors

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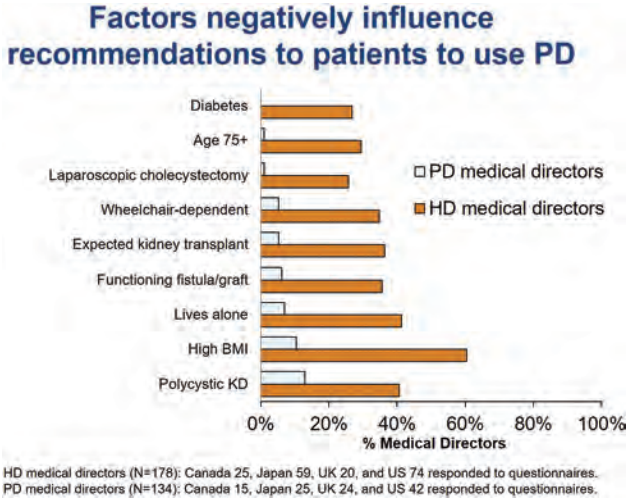
Background: Negative perceptions towards PD may be limiting its use. We compared differences in attitudes towards PD among medical directors in PD vs. HD units.

Methods: PDOPPS and DOPPS are international prospective cohort studies based on national samples of PD and HD patients. From 2014-18 we asked medical directors of dialysis units in Canada, Japan, US, and UK: 1) to rate the level of training and support for PD in their units, 2) whether certain patient factors would influence recommendations to use PD, and 3) to cite potential reasons PD was not more widely used in their program.

Results: 178 (74%) HD and 134 (67%) PD directors responded. PD directors agreed more than HD directors that their nephrologists and nursing staff were well trained in and were enthusiastic about PD (72-96% vs. 59-72%, by country). HD directors were less likely to recommend PD among certain patients (Figure). Among PD medical directors (78%), a leading reason for the lack of PD utilization was due to the myth that "in-center HD would result in the highest quality of care compared to PD" compared to 29% of HD medical directors. Among HD medical directors, leading reasons included patient fears about PD (68%), and comfort with facility HD (75%) as major barriers to PD growth.

Conclusions: Compared to HD medical directors, PD medical directors feel their units have higher levels of trained, enthusiastic staff towards PD, are more likely to recommend PD, and have different opinions regarding drivers of low PD use. Given the majority of patients receive HD, educating HD physicians and staff about PD may lead to consideration of more patients for PD, and greater PD utilization.

Funding: Other U.S. Government Support



TH-PO373

Changes over Time in Outcomes of Incident Peritoneal Dialysis Patients in Southern China

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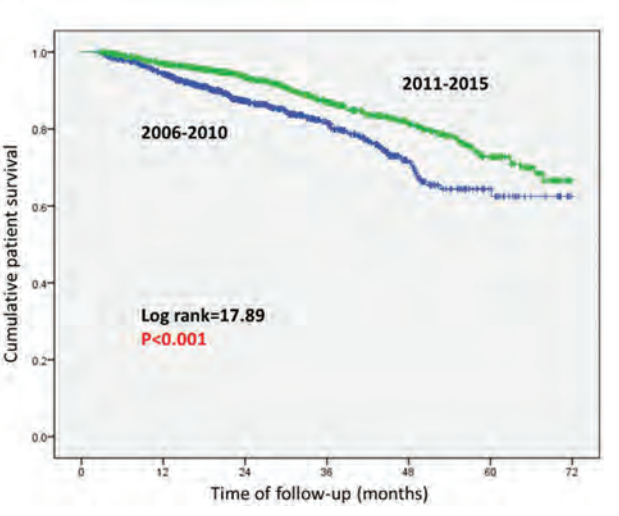
Background: The present study was to investigate the changes in outcomes of incident patients who stated peritoneal dialysis (PD) between 2006-2010 and 2011-2015 in Southern China.

Methods: In this single center retrospective cohort study, incident PD patients from January 1, 2005, to December 31, 2015 at the PD center of The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China were enrolled. Collected baseline data include demographic characteristics and clinical outcomes. Patients initiated PD during 2006-2010 and 2011-2015 were followed-up until December 31, 2011 and December 31, 2016, respectively. The outcomes were compared between the two incident cohorts.

Results: A total of 2021 incident PD patients were enrolled, with mean age 47.2±15.2 years, 40.6% were female. Compared with the 2006–2010 cohort (n=1073), patients initiating PD during 2011-2015(n=948) were younger (46.2±14.8 vs 48.1±15.5 years, p=0.006), had similar baseline eGFR(5.81±2.41 vs. 5.81±2.89 ml/min/1.73m^2, p=0.109) and comparable percentage of diabetes mellitus (24.9% vs 25.7%,p=0.682). The overall peritonitis rate between 2011 and 2015 was lower than 2006-2010 (0.157 vs. 0.160 per patient year, p=0.001). By the end of 1, 3 and 5 years, patients survival rates were 94%, 82% and 63% in 2006-2010 and 97%, 87% and 73% in 2010-2015, respectively (p<0.001); and technique survival rates were 98%, 92% and 85% in 2006-2010 and 98%, 90% and 80% in 2010-2015, respectively (p=0.204). After multivariable-adjusted, patients starting PD in 2011-2015 was associated with lower risk of all-cause mortality (HR 0.76, 95%CI 0.60-0.97, p=0.029).

Conclusions: Peritonitis episodes and patient survival on PD continues to improve, while technical survival remains unchanged. Patients initiating PD between 2010 and 2015 was associated with better patient survival.

Funding: Government Support - Non-U.S.



Cumulative patient survival according to era of PD initiation

TH-PO374

The Effect of Combined Therapy with Peritoneal Dialysis and Hemodialysis: A Prospective Multicenter Study in Japan

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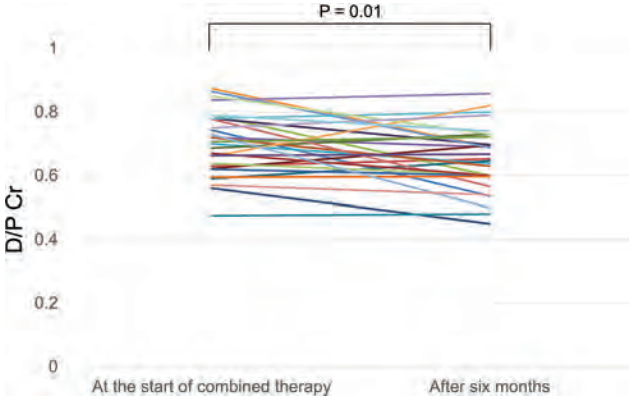
Background: Combined therapy with peritoneal dialysis (PD) and hemodialysis (HD) was widely performed to correct underdialysis and/or overhydration in Japan. However, its clinical result was only reported in retrospective observational studies. We conducted a prospective study to investigate its clinical efficacy in Japan.

Methods: In this prospective multicenter study, we recruited 42 patients started PD from January 1, 2011 to December 31, 2016 (61±9 years, 35 males, and 14 diabetes), and collected clinical information at the start of combined therapy and six months after initiation, prospectively. The changes in parameters between the start of combined therapy and six months later were evaluated using a paired t-test or the Wilcoxon signed-rank test.

Results: Two cases transferred to HD within six months. In the remaining cases, body weight, urine volume, and serum creatinine levels decreased, whereas hemoglobin and serum albumin levels increased. Additionally, dialysate-to-plasma ratio of creatinine (D/P Cr), obtained from a peritoneal equilibration test (PET) decreased significantly from 0.71 ± 0.10 to 0.66 ± 0.10 (P = 0.01) (Figure 1).

Conclusions: In this prospective observational study, both underdialysis and overhydration appear to have been improved by switching from PD alone to combined therapy. Additionally combined therapy could limit further deterioration of the peritoneal membrane. Long-term patient and technical survival will be clarified by the results of ongoing our larger prospective study.



TH-PO375

Peritoneal Dialysis Utilization in US Markets and Associated Hospitalization Rate Ratios for Peritoneal Dialysis versus Hemodialysis

Kristine Kubisiak,[1] Debabrata Ray,[1] Allan J. Collins,[1,2] Eric D. Weinhandl.[1,2] *[1]NxStage Medical, Inc., Victoria, MN; [2]University of Minnesota, Minneapolis, MN.*

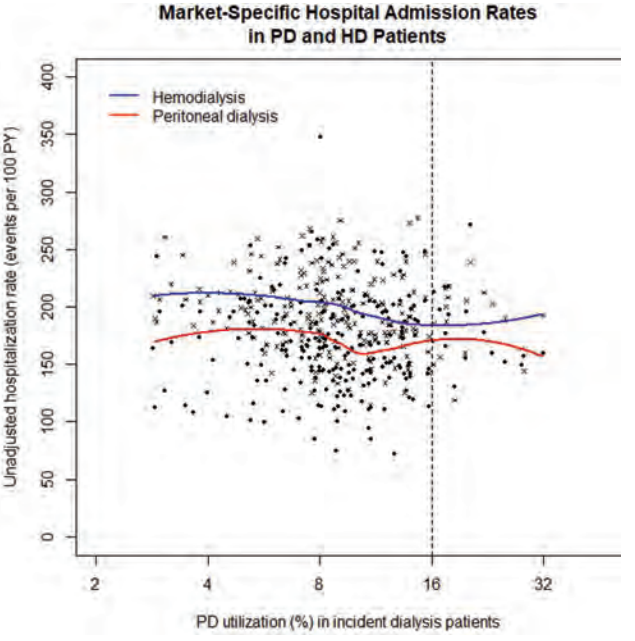
Background: In the United States, peritoneal dialysis (PD) is associated with lower hospitalization risk than in-center hemodialysis (HD) during the first and second years of dialysis. However, increased utilization of PD in a local area may move higher-risk patients from HD to PD, thus attenuating the hospital admission (HA) rate ratio (RR). We assessed the influence of PD utilization in US markets on HA RRs for PD versus HD.

Methods: We analyzed data from the United States Renal Data System. We identified incident dialysis patients in 2006-2013 and retained patients in markets with ≥500 patients. For each area, we calculated the percentage of patients on PD within 3 months of dialysis initiation. Using Poisson regression, we assessed the association of that percentage with the admission rate between 3 and 36 months after dialysis initiation, without censoring for modality change and with fixed effects for markets; only the subset of Medicare patients were included in the model.

Results: The cohort included 323,045 incident dialysis patients in 236 markets. Overall PD utilization was 8.8%. Market-specific HA rates in PD and HD patients are displayed. Market-adjusted HA RRs for PD versus HD were 0.81 with local PD utilization of 2-3% (number of markets, 12), 0.86 with utilization of 4-5% (27), 0.86 with utilization of 6-7% (47), 0.82 with utilization of 8-11% (90), 0.90 with utilization of 12-15% (42), and 0.95 with utilization of ≥16% (18). Compared to the market-adjusted HA RR with local PD utilization of 2-3%, RRs with utilization of ≥12% were significantly different ($P < 0.05$).

Conclusions: Across a gradient of local PD utilization from 2% to 12%, HA RRs for PD versus HD are similar. Local PD utilization ≥12% is associated with attenuated RRs.

Funding: Commercial Support - NxStage Medical, Inc.



TH-PO376

Incremental Peritoneal Dialysis Is Beneficial in Preserving Residual Renal Function, Compared to Full-Dose Peritoneal Dialysis

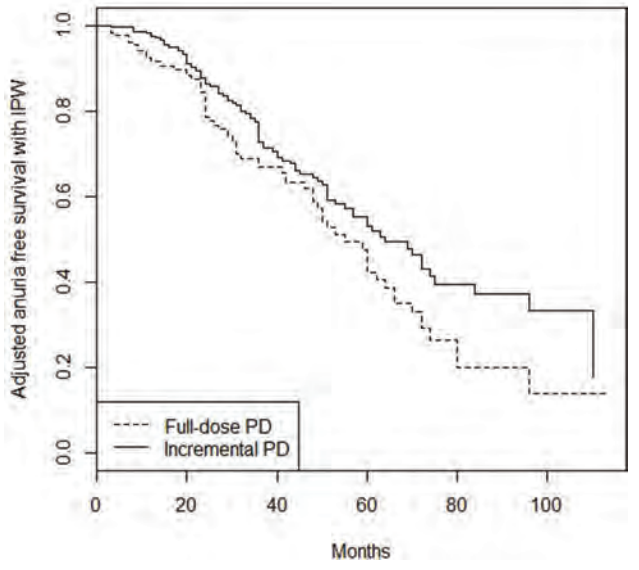
Yeonhee Lee, Seokwoo Park, Seung Seok Han, Hajeong Lee, Dong Ki Kim, Kwon Wook Joo, Curie Ahn, Kook-Hwan Oh. *Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Maintaining residual renal function (RRF) is a crucial issue in peritoneal dialysis (PD). Incremental dialysis is the practice of initiating PD exchanges less than four times a day in consideration of RRF, and increasing dialysis dose step-wisely as the RRF decreases. Effects of incremental PD on the RRF and technique survival have not been widely studied yet. The aim of this study was to compare the outcomes of incremental PD and full-dose PD in terms of RRF preservation and other outcomes.

Methods: Data were extracted from a retrospective PD cohort (16 years of age or older) who started PD between 2007 and 2015 in the PD Unit of Seoul National University Hospital. Full-dose PD was defined as a maximal 4 dwell-times per day for continuous ambulatory peritoneal dialysis (CAPD) and as nightly dialysis sessions for automated peritoneal dialysis (APD). Incremental PD was defined as all other PD except full-dose PD. Outcomes were compared with the use of propensity scores and inverse-probability-weighting (IPW) adjustment to reduce treatment selection bias between incremental and full-dose PD groups. Multivariate time-dependent Cox analyses were performed.

Results: Among 443 included patients, 277 underwent incremental PD and 132 underwent conventional full-dose PD. After IPW adjustment, Incremental PD group exhibited a lower risk of developing anuria (hazard ratio [HR] 0.99; 95% CI, 0.983-0.998). Patient survival, technical survival and peritonitis free survival was similar (Log rank test, $P>0.05$).

Conclusions: In this observational study, incremental PD was beneficial for preserving residual renal function compared to conventional full-dose PD and showed similar patient survival.



Adjusted, weighted anuria free survival curve

TH-PO377

Early Mortality Hazard of Peritoneal Dialysis Is Also Present in Dialysis Modality Converted Patients

Jong Cheol Jeong,[1] Sejoong Kim,[2] Dong-Chan Jin,[3] Ki Young Na.[2] *[1]Ajou University Hospital, Suwon, Republic of Korea; [2]Seoul National University Bundang Hospital, Seongnam, GyeongGi-Do, Republic of Korea; [3]The catholic university of Korea, Suwon, Republic of Korea.*

Background: Peritoneal dialysis showed increased mortality in previous registry reports from east Asian countries. However, hazard pattern according to time have never been investigated. Also, there have been few reports about the outcome of dialysis modality converted patients. We examined 22,210 incident dialysis patients from Korean Society of Nephrology registry.

Methods: We evaluated whether hazard ratio of peritoneal dialysis has time-dependent nature. Survival analysis was performed using a non-proportional hazard fractional polynomial model. Treatment effect of peritoneal dialysis was tested by using inverse probability weighted regression adjustment

Results: During a median follow up of 7.9 years (from 0 to 13.9 years), 13,218/22,210 (59.5%) patients died. Peritoneal dialysis showed significantly elevated hazard ratio till 8 years after dialysis initiation, which has its peak value reaching 1.4 at 3 years. Multivariable analysis adjusted for age at dialysis initiation, sex, and cause of end stage renal disease was conducted. The average treatment effect of peritoneal dialysis showed -0.946 (95% C.I. -1.356 - -0.536, p<0.001) of beta, which is interpreted as -0.946 years less survival in average peritoneal dialysis group. Within those patients who died before 8 years, death related to diabetes was more prevalent in peritoneal dialysis group (35.5% vs 27.8%, p<0.001) For the dialysis modality converted patients, 1,561 patients were analyzed. Peritoneal dialysis converted from hemodialysis showed worse survival with an early bimodal peak of increased hazard ratio.

Conclusions: Peritoneal dialysis showed increased early mortality hazard. Early death within 8 years of peritoneal dialysis might be associated with metabolic risk. This phenomenon was also present for the dialysis modality converted patients.

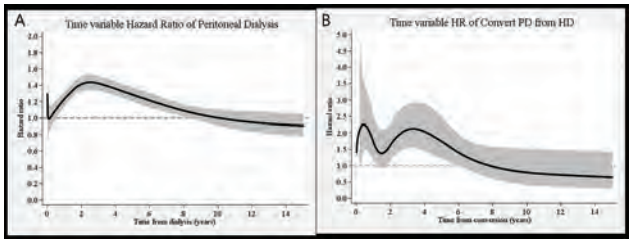


Figure A. Early mortality hazard is elevated in peritoneal dialysis. B. Bimodal peak of early mortality hazard of peritoneal dialysis. HR, hazard ratio; PD, peritoneal dialysis; HD, hemodialysis

TH-PO378

Dialysis Modality and Bleeding Risk

Gurbey Ocak,[1] Alferso C. Abrahams,[1] Maarten B. Rookmaaker,[1] Marianne C. Verhaar,[1] Friedo W. Dekker,[2] Merel Van diepen.[2] *[1]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, Netherlands; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands.*

Background: Bleeding as a manifestation and complication of renal failure was already recognized in the 18th century. However, there is limited information whether bleeding risks are different for peritoneal dialysis patients and hemodialysis patients. From a clinical point of view, there could be a preferred dialysis modality for patients with bleeding problems. Therefore, the aim of this study was to investigate the association between dialysis modality and bleeding risk.

Methods: In total, 1745 incident dialysis patients from the NECOSAD study were prospectively followed for major bleeding events within three years of dialysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for hemodialysis as compared with peritoneal dialysis using Cox proportional hazard analyses. Hazard ratios were adjusted for age, sex, primary kidney disease, antiplatelet drug use, vitamin K antagonist use, EPO use, prior history of bleeding, cardiovascular disease, systolic blood pressure, residual GFR and albumin levels.

Results: Of the 1745 dialysis patients, 1211 started with hemodialysis and 534 started with peritoneal dialysis. A total of 183 patients had a bleeding event during a median follow-up of 2.2 years (interquartile range 1.0-3.0). The bleeding rate was 60.8 per 1000 person-years for hemodialysis patients and 34.6 per 1000 person-years for peritoneal dialysis patients. The crude hazard ratio of bleeding was **1.7 (95% CI 1.2-2.5)** for hemodialysis patients as compared with peritoneal dialysis. Hemodialysis patients as compared with peritoneal dialysis patients had a **1.5-fold (95% CI 1.0-2.2)** increased bleeding risk after adjustment for age, sex, primary kidney disease, prior history of bleeding and cardiovascular disease. After additional adjustment for antiplatelet drug use, vitamin K antagonist use, EPO use, systolic blood pressure, residual GFR and albumin levels, the HR did not change 1.5 (95% CI 1.0-2.4).

Conclusions: In this large prospective cohort of incidence dialysis patients with detailed information, hemodialysis as compared with peritoneal dialysis was associated with an increased bleeding risk. An explanation could be the use of heparin for hemodialysis sessions to prevent clotting of dialysis lines and dialyzers. Future studies should examine whether starting or switching to peritoneal dialysis could be beneficial for patients with bleeding problems.

TH-PO379

Anemia and Mortality in a Mexican PD Cohort

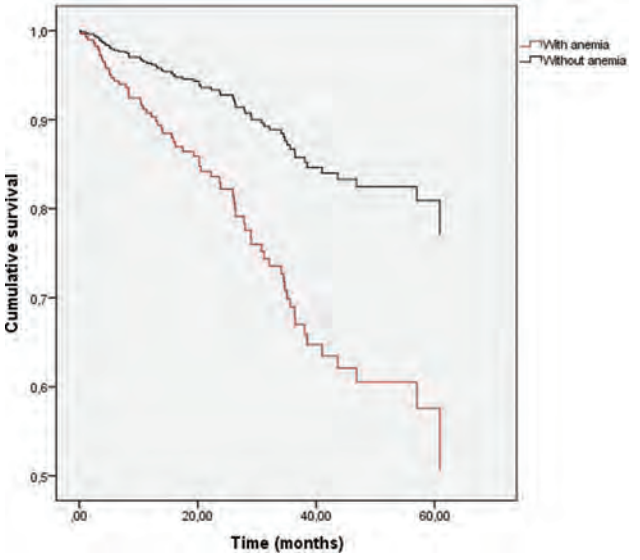
Javier Soto-Vargas, Judith J. Velasco, Renato Parra Michel, Jorge fernando Topete reyes, Leonardo Pazarin-Villaseñor, Mario A. García Cárdenas, Julio A. Gutierrez-Prieto. *Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Especialidad en Nefrologia, Hospital General Regional No 46 del IMSS, GUADALAJARA, Mexico.*

Background: The impact of anemia and its management on mortality is controversial in PD patients, despite of being considered and important part of the adequacy therapeutic plan, and the recommendations are based on evidence derived from HD patients. Thus, our aim was to study the association of anemia in all-cause mortality in a PD cohort.

Methods: During January 2012 to December 2017 we included 802 prevalent PD patients to investigate the impact of anemia (Hgb <10 g/dL) in all-cause mortality. We collected relevant information as demographic characteristics, anthropometric, biochemical, type (i.e. automatized PD or continuous ambulatory PD), dose of dialysis, peritoneal transport rate, as well as residual kidney function and comorbidities, and used them as covariates for a multivariate analysis.

Results: The median follow-up was 23 months (IQR 23-36.4). During the study period, there were 109 (13.6%) deaths. The median age was 47.9 years (IQR 28.3-64.4), 270 (33.7%) were female, and the main etiology of CKD was unknown in 383 (48.7%) patients, and T2D in 336 (42.7%), twenty (4.5%) had a previous kidney transplant, and 71 (14.5%) were initially on HD and then transferred to PD. The prevalence of anemia was 25.2% (202 patients), with a median Hgb level of 11 g/dL (IQR 9.7-12.0). In a binary logistic regression model adjusted for the variables afore mentioned, anemia was associated with all-cause mortality (OR 2.9 CI 95% 1.62-5.25 p<0.001), and this association was confirmed in a multivariate Cox regression (HR 2.5 CI 95% 1.6-4.2 p<0.001).

Conclusions: The presence of anemia is associated with a twofold increased risk for all-cause mortality in PD patients.



Cumulative survival in patients with and without anemia

TH-PO380

Mean Corpuscular Volume and Mortality in Peritoneal Dialysis

Sara S. Kalantar,[1] Carola-Ellen Kleine,[1] Christina Park,[1] Jui-Ting Hsiung,[1] Csaba P. Kovesdy,[2] Elani Streja.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

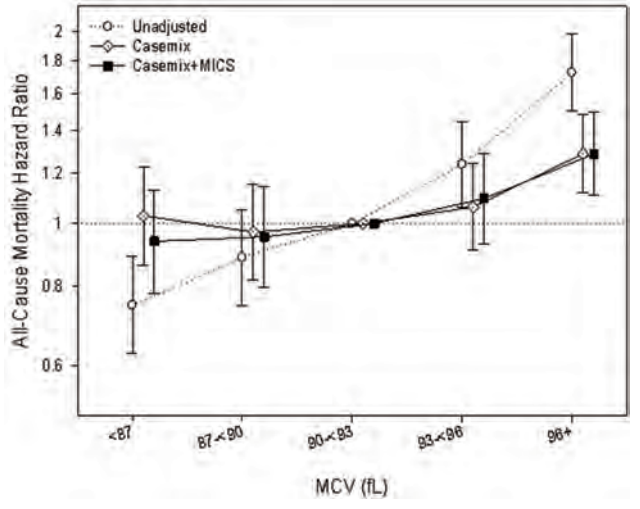
Background: Normocytic and normochromic anemia is a common sequela in chronic kidney disease, however some patients with end-stage renal disease present with macrocytic anemia. In hemodialysis patients abnormal mean corpuscular volume (MCV) was associated with mortality, while so far this association has not been explored in peritoneal dialysis (PD) patients.

Methods: We retrospectively examined a cohort of 14,251 incident PD patients from a large dialysis organization from 2007 to 2011 with MCV measurement within the first 91 days of PD treatment. PD patients were grouped into five *a priori* selected MCV categories. Using Cox models, we explored the association between baseline serum MCV and all-cause death with adjustments for case-mix variables and laboratory markers of malnutrition and inflammation (MICS).

Results: Mean age was 56±16 years and 43% of study participants were women. Higher MCV levels trended towards higher mortality across all levels of adjustment, although the association was attenuated after adjustment of case-mix and MICS variables. The highest MCV category (≥96 fL) was significantly associated with a higher risk of all-cause mortality when compared to the reference group (90-<93 fL) in the fully adjusted model (HR 1.29, 95%Cl 1.11-1.49). Lower MCV categories trended towards lower mortality. [figure1]

Conclusions: In incident PD patients, macrocytosis/higher MCV was associated with higher all-cause mortality risk. The underlying mechanisms of the observed MCV-mortality association remains unclear and should be explored in further studies.

Funding: NIDDK Support



TH-PO381

Renin-Angiotensin System Blockade and Mortality in Peritoneal Dialysis Patients

Godhy E. Hernandez Gonzalez, Javier Soto-Vargas, Denisse Arellano-Mendez, Omar I. Delgado-Ayon, Carlos Daniel Jiménez Mejía, Leonardo Pazarin-Villaseñor, Renato Parra Michel, Julio A. Gutierrez-Prieto. *Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Especialidad en Nefrologia, Hospital General Regional No 46 del IMSS, Guadalajara, Mexico.*

Background: Renin-Angiotensin System (RAS) blockade in Peritoneal dialysis (PD) patients has not been widely examined, however, its use in hemodialysis (HD) patients has been associated with risk reduction in all-cause and cardiovascular mortality. Moreover, mortality in PD patients still represents a challenge for the clinician. Our objective was to determine if RAS blockade improve survival or reduce all-cause mortality in PD patients.

Methods: A total of 248 adult PD patients were prospectively enrolled from January to October 2017. The preliminary findings of 85 patients are presented here. Sixty-four (75%) with RAS blockade and 21 (25%) without it were analysed. The mean follow-up was 13.5±3.4 months. We performed a survival and multivariate analysis adjusted for age, gender and diabetes mellitus, between groups to estimate the all-cause mortality risk.

Results: The median age was 42 years (IQR 27-62) and 64 (74.4%) were male. There were no significant differences in baseline characteristics between groups (e.g. residual renal function, etiology of CKD, comorbidities, type of peritoneal transport and dyslipidemia profile). Four deaths were recorded during follow-up, one (1.6%) in the RAS blockade group and 3 (14.3%) in the control group (p=0.02). Patients with RAS blockade had higher serum potassium (p =0.01) as well as reduced risk for all-cause mortality compared with the group without RAS blockade (OR 0.05, CI 95% 0.03-0.85, p=0.04) in the multivariate analysis.

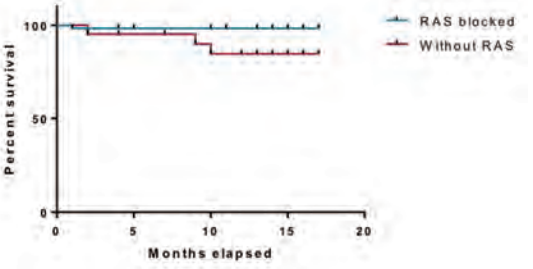
Conclusions: In this prospective cohort of PD patients, the use of RAS blockers was associated with all-cause mortality risk reduction and higher serum potassium.

All-cause mortality Risk according Use of RAS blockade

	Coefficient	P	OR	CI 95%
RAS blockade	-3.05	0.039	0.05	0.03-0.85

Multivariate model adjusted for age, gender and diabetes mellitus.

Survival analysis



Kaplan Meier curve of overall survival according to RAS blockade usage.
Log-rank *p*=0.02

TH-PO382

Baseline Echocardiographic Parameters Predict Mortality in Peritoneal Dialysis Patients

Rodolfo Mario Orihuela,[1,2] Lucino Bahena,[6] Rocio B. Cruz,[7] Ricardo Correa-Rotter,[3] Luis E. Morales-Buenrostro,[5] Abraham Cohen-Bucay.[4] Departamento de Nefrología Hospital Central Militar *[1]Nefrología, Hospital Central Militar, Ciudad de México, Mexico; [2]Nefrología y Metabolismo mineral, Instituto Nacional de Ciencias Medicas y Nutrición, Ciudad de México, Mexico; [3]Institutor Nacional de la Nutricion, Mexico City, Mexico; [4]Boston University Medical Center, Boston, MA; [5]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; [6]Hospital central militar, México, DF, Mexico; [7]Hospital Central Militar, Mexico City, Mexico.*

Background: Patients with end-stage renal disease (ESRD) have high mortality rates and the leading cause of death is CV disease. Multiple baseline factors including age, comorbidities and frailty, have been associated with higher mortality risk. Here we evaluate the prognostic value of baseline echocardiographic structural and functional cardiac abnormalities in incident peritoneal dialysis (PD) patients.

Methods: Prospective cohort study of patients with CKD5 that started PD between 2014 and 2016 at Hospital Central Militar in Mexico City, Mexico. A bi-dimensional transthoracic echocardiogram was performed within 7-14 days before starting PD. The primary objective was to correlate structural and functional echocardiographic parameters with the primary outcome of death by any cause.

Results: We included 138 patients, 44.9% were male, median age 52.3 +/- 15.3, the cause of ESRD was DM in 71%. During a median follow up of 26.8 months 73 patients (52%) died, with a median survival of 30.8 months. In univariate analysis we identified age (p=0.001), DM (p=0.001), residual urine volume (RUV) (p,0.001), serum albumin (p<0.001) and B-type natriuretic peptide (BNP) (p=0.001) as risk factors for mortality. By Kaplan-Meier method we identified the following echocardiographic parameters to be correlated with higher mortality: left atrium volume >20 (p=0.007), mitral insufficiency (p=0.001), LV ejection fraction (EF) <53% (p=0.017), LV hypokinesis (p=0.001) and diastolic dysfunction with a restrictive pattern (p<0.001). Multivariate analysis identified age >50y (OR=2.05, p=0.046), gender (OR=0.53, p=0.010), RUV (OR=0.99, p=0.002), LV EF (OR=0.97, p=0.042), and diastolic dysfunction with a restrictive pattern (OR=3.08, p=0.003) as independent risk factors for mortality.

Conclusions: Baseline echochardiogram (lower LV EF and diastolic dysfunction) at dialysis initiation is a strong predictor of mortality in PD patients, in particular in those with DM. We hereby confirm high mortality rate in patients that start PD, and the previously reported correlation of age, gender, and RUV with mortality.

TH-PO383

A Fast Decline of Residual Renal Function in the First Year Is a Predictor for Early Withdrawal from Peritoneal Dialysis in Non-Diabetic Patients

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Background: Little is known about the relationship of residual renal function (RRF) decline in early period with survival in peritoneal dialysis (PD).

Methods: Total of 567 patients who began PD between January 1, 2005, and June 30, 2013 was investigated. The rate of decline of RRF was determined by the "slope of the trend equation" of serial RRFs. A composite end-point of all-cause mortality and transfer to hemodialysis was used, survival status was censored on June 30, 2016.

Results: The median of "the slope of RRF decline equation" was 0.308 (0.001-2.111) mL/min/1.73 m^2/month. In the median follow-up period of 43 months (12 to 120 months), 65 patients died, 90 patients transferred to HD, and 171 patients underwent kidney transplantation. Male, high baseline RRF, high baseline peritoneal Kt/V urea, low serum albumin and low uric acid were independently associated with the rate of RRF in the first year of PD. RRF decline in the first year remained a predictor of composite end-point (HR, 2.74, *P* =0.001). When the patients were divided into high RRF decline group (>0.308 mL/min/1.73m^2/month) and low RRF decline group (≤0.308 mL/min/1.73m^2/month) at the first three years of PD period, end-point events incidence was higher in high RRF decline group (23.2%) than in low RRF decline group (11.0%) (log-rank test P < 0.001). There were 189 patients in low RRF decline group and 171 patients in high RRF decline group maintaining PD for more than 3 years, in a median follow-up of 54 months (range 37 to 120 months), no significant difference of survival was observed (30.9% in high group vs 46.4% in low group, log-rank test P=0.883). In high RRF decline group, there were 92 patients reaching composited end-point and 112 patients maintaining PD; multivariate Cox regression model showed high peritoneal Kt/V urea after 1 year of PD period and high albumin level were the protective factor for composite end-point (HR, 0.29, P = 0.001; HR, 0.94, P=0.022, respectively), while fast RRF decline remained the risk factor for composite end-point (HR, 3.28, P=0.004).

Conclusions: A faster RRF decline in the first year was a predictor for all-cause mortality and transfer to hemodialysis in non-diabetic PD patients, mainly in the first three year. For patients with faster RRF decline, increase the PD dose was effective to improve survival.

TH-PO384

The Effect of Traditional Chinese Medicine (TCM) Practice on Mortality Risk in a Large Cohort of Patients on Continuous Ambulatory Peritoneal Dialysis (CAPD) from China

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Background: We report mortality risk in a cohort of patients on CAPD from China, comparing outcomes between hospitals classified as TCM hospitals versus conventional ones.

Methods: Data were sourced from the Baxter Healthcare (China) support program database, comprising an inception cohort commencing PD between Jan-2005 and September-2015, followed until death, dropout, loss to follow-up, or November-2015, whichever occurred first. The primary outcome was death. The primary exposure was official classification of the treating hospital as TCM versus conventional, although we separated TCM further according to whether the hospital was affiliated with the China TCM PD Federation (TCM-PDF) or not. We made comparison using Cox proportional hazards models with shared frailty by center, censoring for kidney transplantation and change to HD, adjusting for age, gender, employment, insurance, primary renal disease, size of PD program.

Results: We modelled 100,558 subjects from 1,134 centres over 241,051patient-years. CAPD patients at TCM hospitals were younger, more likely female, with hypertension as kidney disease, urban, unemployed, from larger programs, and treated with < 4 exchanges per day. The modelling results are presented in Table 1.

Conclusions: TCM is associated with better outcomes for PD patients in China. TCM interventions include traditional diet therapy optimizing digestive tract symptoms and therefore nutrition, traditional medications to increase urinary volume and ameliorate the micro-inflammatory state, the use of enemas to reduce accumulation of uremic toxins and maintain bowel habit, and traditional Wu Style Tai Chi Chuan athletics. However, the indentified benefit with TCM appears to be restricted to hospital with an affiliation with the TCM-PDF, and we believe this is due to greater standardization of management, and a greater focus on continuing medical education and scholarly activities in affiliated centers.

Funding: Commercial Support - Baxter Healthcare (China)

Hospital group	Sub-group	n	Hazard ratio for death	95% confidence intervals
Conventional		79,696	Ref	Ref
TCM	All	7,487	0.87	0.76, 0.98
	TCM-PDF	2,484	0.96	0.82, 1.14
	TCM-only	5,003	0.77	0.66, 0.91

TH-PO385

Impact of CMS-Kidney Disease Education Policy on Home Dialysis Rates

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Background: Multiple US and international studies have shown that Kidney disease education (KDE) improves informed selection of home dialysis (HoD) in CKD patients. In 2010, Center for Medicare and Medicaid Services (CMS) approved reimbursement for the KDE services for patients with advanced stage 4 & 5 pre-dialysis CKD. No data is available on the efficacy of this policy change on the patient use of HoD.

Methods: we evaluated the effect of the use of CMS KDE billing code during the pre-dialysis period on the rates of post-ESRD HoD use, and factors associated with HoD use.

Results: Out of 369,938 Medicare enrollees between 2010 and 2014, who were 18 years and older and started dialysis first time after 2010, we identified 3,681 patients (1% of included cohort) in whom KDE services were billed for a total of 6,166 times. KDE services were provided with a median of 218 (25^{th}, 75^{th}:74-462) days prior to the initiation of dialysis therapies. Of the 3,681 KDE recipients, 15% (n=538) used HoD as the initial dialysis modality and 25% (n=903) used HoD at any time after KDE. Twelve percent (n=365) of those initiating dialysis with in-center hemodialysis switched to HoD at a median of 216 (25^{th}, 75^{th}:74-581) days after dialysis initiation. Multivariate logistic regression model showed that younger age, white race, non-diabetes renal disease, employment, absence of congestive heart failure, and atherosclerotic disease, higher MDRD eGFR, albumin>3g/dl, not having a need for assistance with daily activities, prior renal care, and group rather than individual KDE were independently associated with higher odds of HoD therapy. Gender, overall diabetes, cystic kidney disease, BMI, or number of KDE services did not have any impact on the use of HoD therapies.

Conclusions: Despite being recognized by CMS, KDE services are vastly underutilized for the patients with incident ESRD. Use of KDE services is associated with marginal improvements in the HoD rates among incident ESRD patients. A significant proportion of those receiving KDE and using HoD therapy need to initiate with in-center hemodialysis. Better pre-ESRD care coordination may be needed among those who choose HoD but require in-center initiation of dialysis.

TH-PO386

Increased Peritoneal Dialysis as Initial Treatment Modality: A Canadian Costing Analysis

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Background: Kidney failure is increasing in prevalence in Canada. Patients with kidney failure are often treated with dialysis: either hemodialysis (HD) or peritoneal dialysis (PD). There are economic considerations relevant to these therapies, with HD provided in hospital costing over $60,000 and home dialysis (HD or PD) costing between $35,000 and $45,000 per patient annually. Increasing home PD as a modality choice may afford the health care system substantial cost savings.

Methods: We aimed to evaluate the cost-utility of scenarios in which the number of patients offered PD as initial treatment modality is increased to 30% and 40% of incident dialysis starts (baseline Canadian incidence: 20.8%). We accomplished this by performing an incremental cost-utility analysis from the perspective of the Canadian public health payer including all costs related to treating kidney failure with dialysis in the Canadian adult incident dialysis population using data from the Canadian Organ Replacement Register (CORR) between 2004 and 2013. Threshold analysis was performed on the relative risk of infections and hospitalizations from increased PD prescription. Second order Monte Carlo simulations were performed to evaluate parameter uncertainty. Our outcomes were expressed as cost per quality adjusted life years.

Results: Increasing initial uptake of PD to 30% resulted in an average cost savings of $3,132, and increasing uptake to 40% resulted in an average cost savings of $6,529 ($33,970 per new additional PD patient initial therapy over a lifetime horizon). The models were robust to changes in the risk of infection and hospitalization, requiring over 10-fold

increased risk of infection, 7.6-fold increased risk of cardiovascular-related hospitalization, or 2.5-fold increased risk of all-cause hospitalization to reach cost neutrality. Retrospectively applying these findings to the Canadian incident dialysis population for the 10 years between 2004 and 2013 would have resulted in cost savings of $123.1 million and $256.7 million in the 30% and 40% scenarios respectively.

Conclusions: Policy recommendations to increase the initial prescription of home peritoneal dialysis should be considered and are highly cost-effective.

Funding: Commercial Support - Baxter Canada Inc.

TH-PO387

Health-Related Quality of Life: Seeking Novel Targets for Effective Interventions

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Background: Understanding patients' perceived quality of life (QOL) is important in order to provide quality care for chronic kidney disease (CKD) patients. QOL is shaped by several factors including patients' beliefs, symptoms, and behaviours, and yet the interaction between these is not well studied. We studied the interaction between these factors using well-established instruments, to help identify priority targets to meaningfully improve patient care.

Methods: The sample of study were patients with CKD and end-stage renal disease (ESRD). This was a single-phase, cross-sectional survey-based study of adult patients from two centers in London, ON. Patients were recruited in three cohorts: in-center hemodialysis (cHD), CKD (eGFR <30 ml/min), and home dialysis (peritoneal (PD) and home hemodialysis (HHD)). Each set of surveys included the KDQOL-36SF, Illness Intrusiveness Scale (IIS), Dialysis Recovery Time (DRT), Grit Scale, Physical and Emotional Symptom (PES) Questionnaire, BMQ, and PHQ-9. Demographic information was also collected. Surveys were individually scored results from the three cohorts were compared and analyzed using correlation and regression techniques.

Results: Seventy two patients (24 cHD, 24 home dialysis (19 PD, 5 HHD), and 24 CKD) completed the survey package. The cohorts were well balanced with respect to age and comorbidities. There was no difference between the cohorts with respect to any of the surveys except for DRT (cHD=384.63 mins, SD 411.13 versus home dialysis= 142.75 mins, SD 404.46). Physical QOL (pQOL) and mental QOL (mQOL) were not significantly related (R^2=0.045). IIS was significantly associated with decreased pQOL (R^2=0.27, p<0.001). The linear combination of depression, PES, and grit were significantly associated with mQOL (R^2=0.54, p<0.001). While depression (b=-0.31) and PES (b=-0.31) were negatively associated with mQOL, grit (b=0.34) was found to be partially protective.

Conclusions: Using a rigorous series of validated questionnaires, we did not find a significant difference between CKD and ESRD patients on home and in-center dialysis modalities with regards to pQOL or mQOL. We have identified several targets for potential patient education and engagement strategies. Further studies are required to identify how to best integrate this knowledge into practice.

TH-PO388

Development of a Novel Connection Device for Patients on Peritoneal Dialysis (PD)

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Background: The dialysis population has changed significantly with an increasing age, multi morbidity and frailty. At the same time, home care is a major trend in health care systems for clinical and financial reasons.. Overall PD usage is decreasing due to difficulties preparing elderly patients for PD without additional support. A first need finding suggested that there exists the need to develop a novel auto-connect device for PD patients, to overcome current hurdles to PD use. The aim was to understand how such a device could support home care patients and what functionalities would be required to better standardize the therapy.

Methods: The user interface of functional prototypes were tested with more than 30 PD patients, nurses and doctors. Based on the feedback of the test persons, we optimized and iterated the functional prototypes six times over a period of 18 months.

Results: During the tests we identified the following needs for an auto-connect device: (1) a connecting mechanism to accommodate both continuous ambulatory PD (CAPD), as well as automated PD therapy, (2) a therapy guidance that leads the patient through drain, flush, fill, preventing user errors, (3) an antiseptic environment that may better protect the patients from infections, (4) a user interface that was suited for the respective users. After six generations, it was felt that these were merged in a final product design.

Conclusions: The new prototypic device could allow more patients to be treated at home, better protect these patients from infections, further standardize the PD therapy, and support assisted home care models.

Funding: Commercial Support - Peripal AG (start-up), Government Support - Non-U.S.

TH-PO389

Racial and Ethnic Disparities in Treatment Modalities for ESRD Vary by Patient Age

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Background: Black patients present with end-stage renal disease (ESRD) at younger ages than whites, while younger patients are more likely to undergo transplantation (Tx) and to use peritoneal dialysis (PD) or home hemodialysis (HHD) versus in-center hemodialysis (HD). It is unknown whether disparities in treatment modality use across racial/ethnic groups are consistent among all ages.

Methods: We used 2011-2015 USRDS data to identify treatment modalities—Tx, HD, PD, HHD, or Other—at day 90 of therapy (persisting for ≥60 days) for all incident US ESRD patients. We compared use of each modality between racial/ethnic groups (Hispanic, non-Hispanic [NH] Black, NH White, Other) pairwise using t tests, both overall and stratified by age: 22-44, 45-64, 65-74, and 75-99. We computed relative risks (RRs) across groups and tested whether age modified these RRs in multinomial logit models, controlling for patient factors. Missing data, discontinued dialysis/recovered function, and lost follow up (e.g., died before day 90) were excluded.

Results: During 2011-2015, 81.5% of 552,896 patients used HD at day 90, 10.0% used PD, 0.7% used HHD, 2.8% underwent Tx, and 4.9% were classified as Other. NH Blacks and Hispanics were less likely to use PD and Tx and more likely to use HD versus NH Whites (all p<0.01). Tx disparities were greatest among age 22-44 for NH Blacks (RR 0.144) and among age 45-64 for Hispanics (RR 0.318), and were smallest among age 75+ (RRs 0.269 and 0.444, respectively) (all p<0.01; see Table). PD disparities were greatest among age 75+ (RRs 0.476 and 0.625, respectively) and smallest among age 22-44 (RRs 0.691 and 0.825, respectively) (all p<0.01). HHD disparities varied across groups by age. Results were similar in adjusted multinomial logit models.

Conclusions: There are large racial/ethnic disparities in HD, PD, and Tx use by incident ESRD patients. Tx disparities are worse for younger patients, and PD disparities are worse for older patients.

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	Age 22-44 (N=63,038)				Age 45-64 (N=219,723)				Age 65-74 (N=139,703)				Age 75-99 (N=130,432)			
Modality	HD	HHD	PD	Tx	HD	HHD	PD	Tx	HD	HHD	PD	Tx	HD	HHD	PD	Tx
All Patients	74.6%	0.7%	16.8%	6.2%	81.0%	0.7%	11.4%	3.7%	83.2%	0.7%	8.7%	2.1%	84.2%	0.7%	5.9%	0.2%
NH White (ref.)	65.3%	1.1%	19.9%	11.4%	75.8%	1.0%	13.3%	5.9%	80.0%	0.8%	10.0%	2.8%	82.4%	0.7%	6.8%	0.3%
NH Black / NH White (RR)	1.263	0.546	0.691	0.144	1.141	0.568	0.669	0.230	1.104	0.914	0.572	0.267	1.074	1.414	0.476	0.269
Hispanic / NH White (RR)	1.191	0.418	0.825	0.366	1.131	0.385	0.748	0.318	1.104	0.534	0.647	0.372	1.062	1.176	0.625	0.444

Results do not add to 100%: "other" modalities (e.g., center self-hemodialysis, unknown dialysis) excluded.

TH-PO390

Impacts of Medicare Bundled Payment on Utilization of Peritoneal Dialysis and Changes in Treatment Modality

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Background: In 2011, Medicare implemented a new policy that bundled reimbursement for dialysis treatment and ancillary services, removing incentives that made HD a more profitable therapy than PD under the prior payment model. This study examined whether

2011 Medicare ESRD bundled payment (BP) was associated with increased rates of PD utilization and modality switches.

Methods: We used USRDS and Medicare data to identify all US patients with ESRD initiating dialysis (n=619,130) and outpatient dialysis facilities (n=6,433) before (2006-2010) and after (2011-2013) BP. We used logistic models to examine the BP effect on two outcomes of interest observed 90 days after dialysis initiation up to 2 years: any patient utilization of PD and change in treatment modality (HD-PD and PD-HD), adjusting for patient, dialysis provider, and regional characteristics.

Results: Observed **PD utilization** increased from 12.5% in 2006, to 15.0% in 2010 (the year prior to policy change), and to 18.7% in 2013. In adjusted models, BP was associated with increases in PD use in the pre- vs. post-BP era (OR=1.6; 95% CI 1.5,1.6; p<0.0001) and an estimated BP effect of 5 percentage points in PD use between pre and post policy periods (14% pre vs 19% post, for fixed values of covariates). Observed rates of **modality switches** increased from 6.1% in 2006, to 7.5% in 2010 and 9.0% in 2013. Of those initiating HD in the first 90 days, 4.7% switched to PD up to 2 years later in the pre-policy period and 6.3% in the post-policy period. Of those initiating PD in the first 90 days, 24.6% switched to HD in the pre-policy period and 24.1% in post-policy. In adjusted models, BP was associated with higher rates of modality switches for both PD-HD (OR=1.1 95% CI 1.0,1.1; p=0.009) and HD-PD (OR=1.4 95% CI 1.4,1.5; p<0.0001). There was an estimated 0.4 percentage point BP effect on PD-HD switches (18.0% pre vs 18.4% post) and 1.7 percentage points for HD-PD switches (4.4% pre vs 6.1% post).

Conclusions: ESRD bundled payment was associated with increased PD use without a substantial increase in modality failure, achieving a secondary goal of payment reform. More work is needed to determine whether increased use and HD-PD modality switches from payment reform also led to changes in patient characteristics associated with modality use.

Funding: NIDDK Support

TH-PO391

Identification of Factors That Are Associated with Risk of Modality Failure Among Patients Treated with Peritoneal Dialysis

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Background: Treatment with peritoneal dialysis (PD) is associated with better quality of life and clinical outcomes compared to in-center hemodialysis (ICHD). However, a substantial number of patients who initiate PD later fail the modality and switch to ICHD. Identification of factors that are associated with greater risk of modality failure may facilitate targeted interventions to retain patients on PD.

Methods: This retrospective, observational study considered adult patients who, during 2014-2016, were either prevalent on PD or initiated the modality during that time. Data were derived from deidentified electronic health records. The index event was considered as the first of at least 3 consecutive PD treatments (exclusive of training treatments). Follow-up time began on the first day of the calendar month after index and continued until modality failure, or until censoring for study end (31 July 2017) or loss to follow-up. Exposures were time-updated on a monthly basis. In this time to event analysis, Cox regression models (with robust variance estimators) were each tested on a bivariable basis against outcome, followed by joint modeling where multiple potential factors were entered into the model simultaneously. Models were adjusted for age, sex, race, history of congestive heart failure or amputation, and Charlson comorbidity index. Interactions were tested using likelihood ratio testing.

Results: This analysis considered a total of 303,126 patient-months. Factors associated with increased risk of PD modality failure included use of continuous ambulatory PD, total daily exchange volume >12L, indication that the patient needed support for treatment, weight >100kg, change in weight of >2kg, low serum albumin or change in albumin >0.4mg/dL, Kt/V<1.7, hospital admission, and clinical indications of peritonitis. Factors associated with a lower risk of modality failure were receipt of ≥4 retraining sessions, residing >20 miles from the treatment center, albumin>4.0 mg/dL, and treatment in a facility with >150 patients or a facility in which ICHD was not available.

Conclusions: Modifiable factors may contribute to the risk of modality failure among patients treated with PD. Programs targeting these factors may improve time on therapy for patients using this modality.

Funding: Commercial Support - This was a research project conducted by the DaVita Institute for Patient Safety and supported by DaVita Kidney Care

TH-PO392

Trends in the Rate of Conversion from Peritoneal Dialysis to Hemodialysis

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Background: Conversion from peritoneal dialysis (PD) to hemodialysis (HD) is frequently necessitated by medical complications, including peritonitis and ultrafiltration failure. Conversion can be disruptive to the patient, as it usually involves a transition from dialysis in the home to dialysis in a facility and may require placement of a permanent vascular access. In addition, high rates of conversion impose stress on dialysis providers, as high rates necessitate additional training in order to maintain program size. We assessed rates of conversion from PD to HD among US incident patients in 2006-2015.

Methods: We analyzed data from the United States Renal Data System. For each calendar year from 2006 to 2015, we identified all patients that initiated PD within 3 months after dialysis initiation. We retained patients with age between 20 and 99 years and non-missing data regarding race, sex, and primary cause of end-stage renal disease (ESRD). We followed patients from first date of PD until the earliest of conversion to HD (defined as treatment with HD for ≥2 months), death, kidney transplant, or recovery of renal function, but for a maximum of one year. We calculated crude rates of conversion from PD to HD in each per-annum cohort and used Fine-Gray regression to estimate the relative hazard of conversion from PD to HD as a function of PD initiation year, with adjustment for age, race, sex, and primary cause of ESRD.

Results: The number of incident patients on PD reached a nadir of 7924 in the 2008 cohort and monotonically increased thereafter, with 14,273 incident patients on PD in the 2015 cohort. Mean age increased slightly during the study era and reached 59.0 years in the 2015 cohort. The rate of conversion from PD to HD was 20.8 events per 100 patient-years in the 2006 cohort and reached a low of 17.6 events per 100 patient-years in 3 subsequent cohorts: 2010, 2013, and 2015. By Fine-Gray regression, with the 2010-2011 cohorts as referent, the adjusted hazard ratios of conversion from PD to HD were 1.10 ($P < 0.001$) in both the 2006-2007 and 2008-2009 cohorts and 0.99 ($P > 0.5$) in both the 2012-2013 and 2014-2015 cohorts.

Conclusions: Although the number of incident patients on PD grew every year from 2008 to 2015, the rate of conversion from PD to HD during the first year after initiation of PD was essentially unchanged between 2010 and 2015.

Funding: Commercial Support - NxStage Medical, Inc., Clinical Revenue Support

TH-PO393

Prescription Patterns in Dialysis Patients – Differences Between Hemodialysis and Peritoneal Dialysis and Opportunities for Deprescription

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Background: Dialysis patients are at high risk for polypharmacy with many comorbidities and complications from their disease and treatment. The prescribing patterns and burden of polypharmacy in dialysis patients, and specifically the difference between hemodialysis and peritoneal dialysis prescribing, are not well characterized. The objectives of this study were to review prescribing patterns for dialysis patients, to analyse any differences in prescribing patterns between hemodialysis (HD) and peritoneal dialysis (PD), and to identify potential opportunities for deprescription.

Methods: We completed a retrospective analysis of demographic and medication data for patients who were on chronic dialysis from June 3rd 2015 to October 1st 2015. Both prescription and non-prescription medications were collected. Medications were classified by indication - (1) renal complications, (2) cardiovascular (CV), (3) diabetes (DM), or (4) symptom management. Medications were also classified as "Potentially Inappropriate Medications" (PIMs) or not. Ethics approval was granted from the University of British Columbia Research and Ethics Board.

Results: 3017 patients met inclusion/exclusion criteria (2,243 HD, 774 PD). The mean (SD) age was 66.2 (14.8) years. The HD group had more patients over 80 years old (22.1% vs 12.5%) and more patients with DM and CV disease. The mean number (SD) of prescribed medications was 17.71 (5.72) with more medications in the HD group versus the PD group. The mean number of medications increased with dialysis vintage in both groups. HD patients were on more medications for renal complication and symptom management than PD patients. Patients on HD were prescribed more PIMs than patients on PD (5.37 (2.83) vs 4.02 (2.37)).

Conclusions: This is the first study to review and characterize both the prescription and non-prescription medication use in HD and PD patients. Patients in both groups experienced polypharmacy and prescription of PIMs. Patients on HD received more overall medications and more PIMs compared to PD patients. There are opportunities for future systematic and patient informed deprescription initiatives in both patient groups.

TH-PO394

A Peritonitis Surveillance System Developed by a Large Dialysis Organization to Improve the Accuracy and Consistency of Peritonitis Rate Reporting in the United States

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Background: Peritonitis (PTN) remains a major reason for hospitalization of peritoneal dialysis (PD) patients and may result in transfer to in-center hemodialysis. In August 2015, a standardized approach to PTN surveillance was introduced by a large dialysis organization (LDO) to improve the consistency and accuracy of PTN event identification across affiliated programs in the US. The goal of this analysis was to examine the impact of this new surveillance system on the reporting of PTN events since 2015.

Methods: Under the surveillance system, patients with PTN are identified following 6 hierarchical business rules that include the 4 standard diagnostic rules for PTN (based on positive culture, positive cell count, abdominal pain) as well as hospitalization for infection and receipt of intraperitoneal (IP) antibiotics (>8 days, >2 vancomycin doses within 8 days, or >5 doses of non-vancomycin within 8 days). An exemption process exists for PTN events based on the IP antibiotic dosing rule alone. Episodes occurring within 28 days of identification of a prior episode with the same causal organism were considered relapse episodes and were not included in calculations of PTN rates.

Results: During the period August 2015 to December 2017, 10,814 cases of PTN were identified under the surveillance system. Of these, 6280 (58.1%) were identified by standard diagnostic rules, an additional 2793 (25.8%) were identified based on hospitalization, and

a further 1741 (16.1%) were identified based on receipt of IP antibiotics. Exemption filings have remained relatively constant over time. The average time to first PTN event was 19.4 months, with 8.6% of events occurring in the first 90 days on PD. Among PD patients overall, 88% experienced no episodes of PTN, 10% developed 1 episode/year, and 2% were observed to have 2 or more PTN events/year.

Conclusions: A consistent approach to identifying PTN events combining standard criteria with infection-related hospitalizations and IP antibiotic dosing is necessary to compare rates between practices in the US and across LDOs and different countries.

Funding: Commercial Support - DaVita, Inc

TH-PO395

Analysis of After-Hours Oral Antibiotic Protocol for the Treatment of Suspected Peritonitis in Peritoneal Dialysis Patients

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Background: Delays in initiating antibacterial therapy for the treatment of peritonitis may lead to increased risk of peritoneal dialysis (PD) failure. Because intraperitoneal (IP) antibiotic treatment is not available after business hours at most dialysis centers, it is important to have a protocol in place for oral "bridge" therapy until a patient can receive IP treatment. The current analysis was conducted, following FDA fluoroquinolone alert notifications, to evaluate the probability of activity of selected oral antibiotic agents against observed PD infections.

Methods: Causative organisms and oral antibiotic susceptibility were analyzed for all peritonitis cases identified during 2016 among PD patients treated by an LDO. Based on these findings, we determined the probability of activity of selected oral antibiotic agents (cefazolin, cefdinir, ciprofloxacin, trimethoprim/sulfamethoxazole [TMP/SMX]) against infections overall, gram-positive infections, and gram-negative infections.

Results: A total of 4534 cases of peritonitis were analyzed. Causative organisms were: coagulase-negative *Staphylococcus* (41.4%), gram-negative rods (21.2%), *Staphylococcus aureus* (8.1%), *Streptococcus* (9.9%), *Enterococcus* (5.5%), fungal (3.9%), other (12.5%). Assuming this distribution of pathogens for PD infections overall, TMP/SMX was predicted to be the most active agent (57.2% of episodes susceptible), followed by cefdinir (50.6%), ciprofloxacin (42%), and cefazolin (39.4%). Among gram-positive infections alone, 74.3% would be expected to be susceptible to TMP/SMX, and 62.7% to cefdinir. Among gram-negative infections, ciprofloxacin was predicted to be the most active agent (84.3% of episodes susceptible).

Conclusions: Early initiation of treatment for peritonitis is critical to avoid PD failure. Designing a strategy for early therapy administered at home, until a patient can receive IP treatment, can potentially improve outcomes. Based on the current analyses, TMP/SMX and cefdinir are predicted to be the most active oral agents for the treatment of suspected gram-positive infections. Ciprofloxacin should be used only in the case of suspected high-risk, gram-negative infections.

Funding: Commercial Support - DaVita, Inc.

TH-PO396

Serum Galactomannan and (1→3)-β-D-Glucan Testing for Rapid Detection of Fungal Peritonitis

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Background: Fungal peritonitis is one of the most serious complications of peritoneal dialysis. Early detection of the causative organism is a key determining outcome; however, routine culture is time consuming and KOH staining has very low sensitivity. Hence serum (1→3)-β-D-glucan (BG) or galactomannan (GM), both fungal cell wall components, may be candidate biomarkers of fungal peritonitis.

Methods: A comparative multi-centered cross-sectional analysis of paired serum and peritoneal dialysis fluid (PDF) BG (Fungitell, Cape Cod, MA, USA) and GM (Platelia Aspergillus Ag kits, Bio-rad, France) from all PD patients with and without fungal peritonitis (23 cases, 8 cases with bacteria and 23 cases control identified by culture), over a 1 year period, was performed.

Results: PDF and serum of the fungal peritonitis group showed very high GM (2.42±2.15, 1.85±1.22) and BG (410.0±158.3, 355.9±246.9) compared to bacterial peritonitis (0.28±0.12, 0.34±0.14), (7.81±0, 7.81 ±0) and healthy control (0.42±0.16, 0.39±0.10), (7.81 ± 0, 7.81±0), respectively. A GM cut-off value at at 0.5 and BG at 80 pg/ml. showed positive predictive value (PPV) of GM test was 95.45% and negative predictive value (NPV) was 93.75%. The sensitivity and specificity of GM testing in PDF and serum were 91.3% and 96.8% respectively.

Conclusions: BG and GM in peritoneal dialysis fluid and serum with provisional cut-off values were applicable as surrogate biomarkers for the diagnosis of fungal peritonitis in PD patients.

TH-PO397

Smartphone-Based Point-of-Care Diagnostics for Early Detection of Peritonitis

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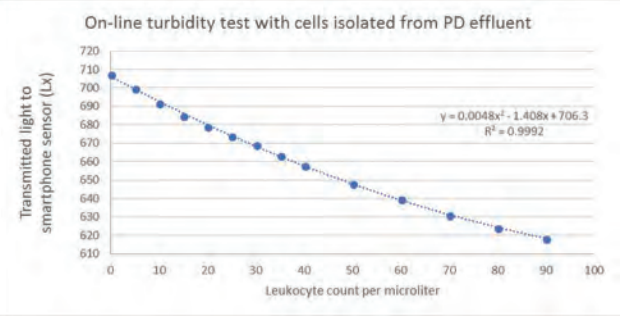
Background: Peritonitis is a serious complication in peritoneal dialysis (PD) and associated with significant morbidity and mortality. Diagnostic criteria include turbid effluent with >100 leukocytes/μl, abdominal pain, and a positive culture. Since accurate diagnosis and a short time-to-treatment are essential for therapy success, we developed a smartphone-based system to measure turbidity in PD fluid. Its use was evaluated in the settings of continuous ambulatory PD (CAPD) and continuous cycling PD (CCPD).

Methods: Total cells of one normal PD effluent were isolated, concentrated, and characterized by count, differential, Wright-Giemsa staining, and flow cytometry. PD effluent was spiked with known amounts of cells isolated from the PD effluent ranging from 5 to 90 leukocytes/μl. Solutions were analyzed in a cuvette (CAPD setup) or pumped through a drain line at 100 ml/min (CCPD setup). Turbidity was measured using the light sensor of a commercially available smartphone. An app (developed in-house) recorded illuminance in real time.

Results: PD effluent contained a total of 159 cells/μl of which 94.4% were red blood cells, 2.5 % leukocytes and 3.1% platelets. The differential showed 7.7% neutrophils, 71% lymphocytes, 18.7% monocytes, 0.8% eosinophils and 1.8% basophils. The PD effluent cell population was confirmed by Wright-Giemsa stain. Flow cytometry showed 20% peritoneal debris. Using the light sensor of the smartphone, a decrease in illuminance was detected with increasing cell concentration. At 90 leukocytes/μl, illuminance was decreased by 15% and 13% in CAPD and CCPD, respectively. The figure exemplifies the tight relationship between cell concentration in the PD effluent and illuminance in the CCPD setting.

Conclusions: A sensitive method to detect an increase of leukocytes in PD effluent was developed. This smartphone-based approach may aid in earlier detection of peritonitis in PD patients since even minor cloudiness can be measured.

Funding: Commercial Support - Fresenius Medical Care North America



Relationship between cell concentration in the PD effluent and illuminance.

TH-PO398

Relative Dialysate White Blood Cell Change Can Predict Treatment Failure in Peritoneal Dialysis-Related Peritonitis: Development and Validation Studies

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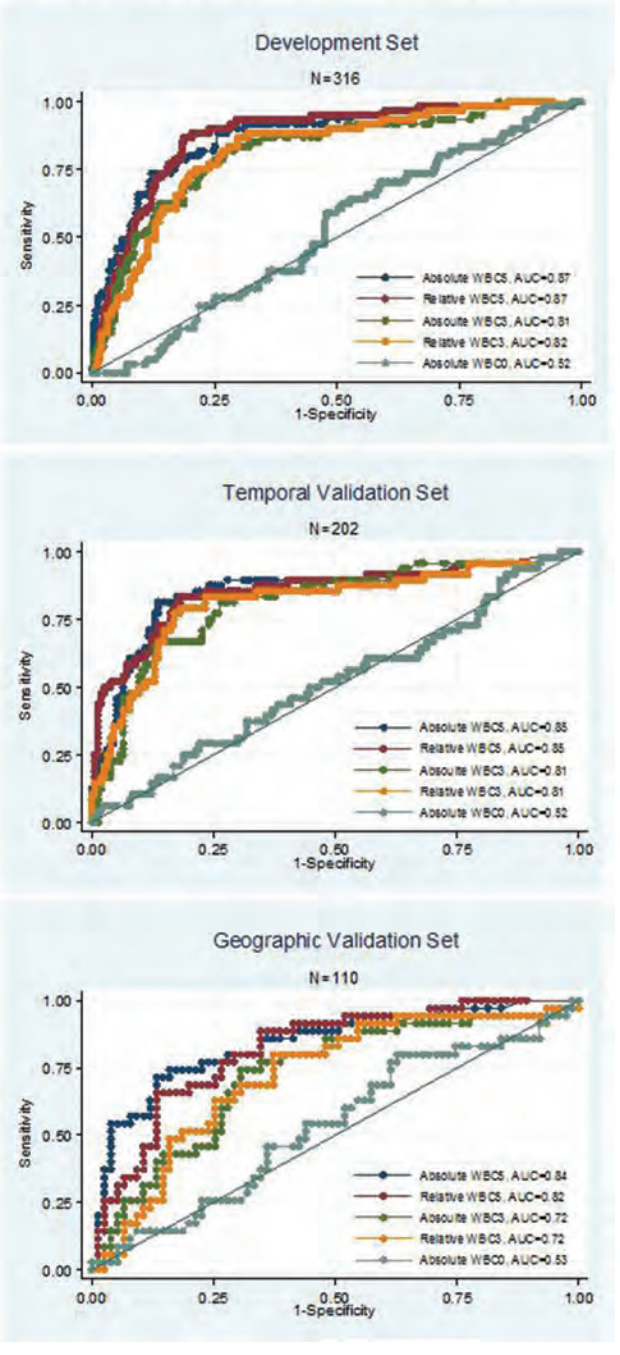
Background: Absolute dialysate white blood cell count (aWBC) can predict treatment failure; however, no study explores predictive ability of relative dialysate white blood cell count (rWBC).

Methods: In this study, there were 3 cohorts. The first (Development set) and second cohorts (Temporal validation set) were conducted in Banphaeo Hospital in different periods. The third cohort (Geographic validation set) was conducted in Kalasin Hospital. Treatment failure was defined as either peritonitis-associated death or transferring to hemodialysis according to physician's judgment. Area under receiving-operating characteristics curve (AUC) of rWBC and aWBC on day 0, 3 and 5 after initial antibiotic treatment were compared. Finally, we defined a cut point of remaining rWBC on day 3 and 5 of ≥33% and ≥15% as a non-response criteria, and compared predictive probability to aWBC criteria (aWBC on day 3 and 5 of ≥1,090 and ≥100 cell/mm^3).

Results: There were 316 (cohort 1), 202 (cohort 2) and 110 (cohort 3) episodes of PD-related peritonitis included for analysis. The majority of initial antibiotic regimens in all cohorts were intraperitoneal Cefazolin and Ceftazidime. Overall treatment failure rate was 19%, 24% and 32%, respectively. Discriminative ability showed similar AUC of rWBC and aWBC on day 3 and day 5 (Figure 1). Baseline WBC had poor AUC. Using a defined cut-off criteria, rWBC ≥15% on day 5 had a better predictive ability comparing to aWBC ≥100 cell/mm^3 in the development set (52% *vs* 44%) and in two validation sets (61% *vs* 55% and 57% *vs* 51%).

Conclusions: rWBC ≥15% on day 5 showed a good predictive probability. We suggest to use this pattern as an alternative criteria to predict treatment failure in PD-related peritonitis.

Figure 1. Receiving-operating characteristics curve



TH-PO399

Association Between Serum Diamine Oxidase, D-Lactic Acid, and Peritoneal Dialysis Related Peritonitis

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Background: Abdominal infection is one of serious complications of peritoneal dialysis patients. Studies have shown dysfunctional intestinal barrier seriously affects the efficacy of peritoneal dialysis, and increases serum diamine oxidase(DAO) and D-lactic acid(DLA) levels.

Methods: To investigate the changes of DAO and DLA in patients with peritoneal dialysis-associated abdominal infection, and to find predictable indicators of abdominal infection. We collected 45 peritoneal dialysis patients from January 2017 to January 2018. They include 30 patients without abdominal infection and 15 patients with abdominal infection. We observe the serum levels of DAO, DLA, albumin(ALB), hemoglobin(Hb), interleukin-6(IL-6), and tumor necrosis Factorα(TNFα).

Results: 1. In the patients with abdominal infection, the levels of DAO 18.7±4.9(U/L), DLA 40.1±10.2(mg/L), IL-6 12.8±3.5(pg/ml), TNFα18.9±6.7 (pg/ml)(P<0.05) after abdominal infection were significantly higher than those before abdominal infection. 2. In the patients without infection, the levels of DAO 2±0.5 (U/L), DLA 10±2 (mg/L), IL-6 2.8±2.1 (pg/ml) and TNFα4.2±3.4 (pg/ml) (P<0.05) were obviously lower than those of pre-infection indicators in patients with abdominal infection.3. In patients with abodminal infection, pre-infection serum ALB 25.1±5.6 (g/L), Hb 90±10.7 (g/L) (P<0.05) decreased compared with the data in non-infection group. 4. According to the medical histories we found that in the 15 cases of abdominal infection, 10 cases had a history of diarrhea. Among them, 3 cases of patients had taken drugs regulating intestinal flora;In contrast to patients without drugs, the interval of abdominal infection were prolonged from 1.5 ± 2 months to 10±5.3 months (P>0.05), the levels of DAO, DLA, IL-6 and TNFα were decreased(P<0.05), and ALB and Hb levels were decreased(P>0.05).

Conclusions: Serum DAO, DLA levels may be predictors of peritoneal dialysis abdominal infection;Intestinal barrier disorders induces elevated DAO and DLA which induce the increase of inflammatory cytokines IL-6 and TNFα, affect the nutritional status of patients, decrease ALB and Hb level and promote the abdominal infection; drugs regulating intestinal bacteria prolong the period of infection but the data are not statistically significant. Large sample studies are needed. The mechanism how intestinal barrier dysfunction induced abdominal infection needs further study.

Funding: Private Foundation Support

TH-PO400

A New Initiative to Measure the Provincial Rate of Peritoneal Dialysis Related Peritonitis in Ontario

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Background: Peritonitis is an important complication of peritoneal dialysis (PD), as it is the most common cause of PD technique failure. In April 2016, the Ontario Renal Network (ORN, which funds dialysis in Ontario) launched a provincial quality improvement (QI) initiative with the aim to shift from local monitoring of peritonitis rates to a province-wide standardized tracking system. The initiative was launched with the objectives of defining a provincial average rate of peritonitis, and an individualized rate for each of the Regional Renal Programs (RRP), comparing provincial rates against the ISPD benchmark of 0.67 cases per annualized patient and sharing provincial data and developing program-level QI plans to help minimize peritonitis risk.

Methods: All 26 RRPs in Ontario collected and reported data from May 2016 – December 2017 using a tracking tool incorporating indicator methodology developed by an expert panel. Reported peritonitis events formed the numerator for the rate calculation, while the denominator was derived from the Ontario Renal Reporting System database (ORRS) to calculate person-time on PD. The peritonitis rate is expressed as number of infections per year at risk, combining patient-time from all PD patients at each RRP.

Results: Over a period of 20 months (May 2016 to December 2017), 888 unique peritonitis cases were reported over a total of 1,426,243 patient days (3908 annualized patients). Program-level peritonitis rates ranged from 0.10 – 0.44 and the provincial average was 0.23 episodes/365 PD catheter-days. Quarterly reports were shared with the programs for data validation, comparison and monitoring purposes. The initiative enabled consistent measurement and reporting of peritonitis that allowed programs to benchmark themselves against their peers, and design local quality improvement plans.

Conclusions: The risk of peritonitis is deemed to be relatively low in Ontario, and consistently below ISPD targets. This initiative has produced a sustainable system of data collection for monitoring the risk of peritonitis, and is part of a larger strategy to ensure that all patients receiving dialysis therapy experience as few complications as possible for safe and individualized dialysis access.

Funding: Government Support - Non-U.S.

TH-PO401

Significant Decrease in PD Peritonitis Rate Using FMC Multiple Tubing Segment Set with Stay Safe Pin Technology Compared to Baxter MiniCap Extended Life PD Transfer Set

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Background: Peritoneal Dialysis Peritonitis (PDP) is a common and serious complication of Peritoneal Dialysis (PD) resulting in structural & functional alteration in membrane function and membrane failure. Reporting PDP rates varies by country. As of 2016, ISPD recommends a rate < 0.5 episodes/year at risk. Any measures to reduce PDP rate is of utmost importance. We analyzed our PDP data retrospectively, comparing Baxter to FMC transfer sets for PDP. Our center has one of the lowest PDP rates compared to ISPD's 2016 PDP recommendation.

Methods: PD data from Davita Home Dialysis Center, Columbus GA was retrospectively analyzed from Aug. 2013 to Dec. 2017. During this period a total of 111 PD patient data was available for analysis. Baxter transfer sets were used initially from Aug. 2013, and then transitioned to FMC transfer set from 2016 onwards. During this period (53

months) there were 39 PDP episodes; of these 32 were single episode. PDP rate per year and per month was calculated for overall study group and between Baxter and FMC Sets.

Results: Total of 111 patients, mean age is 57.82 ± 1.89 yrs, 68(61%) male, 66 (59.5%) used Baxter & 45(40.5%) used FMC transfer set. Mean BMI was 32.15, nPR 0.727, Albumin 3.41 g/dL, HB 10.25 g/dL, PTH 465.93, with a mean K^+ of 4.35 mmol/dL. 21 PDP episodes (53.8%) were due to Staph species. For a total of 159.67 PD years, overall PDP rate in the cohort was 0.244/year, and 1 PDP in every 4.304 years or 1 in every 51.65 months. First PDP occurred at a mean of 465.2 days from the start of PD. Baxter patient had higher KTV at 2.101 ± 0.11, versus FMC 1.746 ± 0.11 (p=0.035).

Conclusions: Data from our center indicates our PDP rate is significantly lower in comparison to ISPD data, suggesting both Baxter and FMC transfer sets are equally effective in achieving such a low PDP rate. Baxter's higher KTV rate correlates to higher PDP rate. Between the two, the FMC transfer set was more effective in reducing PDP, with the lowest rate and more delayed occurrence of PDP. We recommend a large prospective study to validate our data.

Data	Over All (n=111)	Baxter (n=68)		FMC (n=45)		
			SEM		*SEM*	*p-Values*
1 PDP in # Years	4.304	3.661	0.16	5.765	0.14	*P<0.0001*
1 PDP in # Months	51.649	43.639	1.92	68.182	1.64	*P<0.0001*
PDP % Occurence	15.45%	16.51%	3.3	5.38%	3.4	*P<0.0468*
PDP per 1 Year*	0.224	0.275		0.1734		
PDP per 1 Month	0.021	0.023		0.0144		
KTV	1.98	2.101	0.11	1.746	0.11	*p = 0.035*
* ISPD PDP Data = <0.5 per year at risk						

TH-PO402

Apartment vs Single Family Home and Its Effect on Peritonitis Among Peritoneal Dialysis Patients, A Single Center Study in an Urban Population

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Background: Peritonitis is a significant complication among patients undergoing Peritoneal Dialysis (PD). It can lead to significant morbidity, loss of ultrafiltration, permanent membrane damage, and treatment failure. Social aspects including geographical location and educational status have been implicated in the risk of developing peritonitis however no studies have assessed the impact of living space on peritonitis risk. We hypothesize that nephrologists may not offer PD to patients with small living quarters due to a perceived increased risk of peritonitis. This issue is exacerbated in urban populations where most patients live in apartments and not single family homes. Our aim was to determine if home size has any impact on PD peritonitis.

Methods: A retrospective review of prevalent patients undergoing Peritoneal Dialysis between 1998 and 2005 in a single center in an urban population. Inclusion Criteria were all adult patients with complete follow up and housing information for the duration of PD treatment. Data collected for each individual patient included Race, Gender, Age at time of initiation of PD, Presence of Diabetes, BMI, Type of living quarters (House vs Apartment), occurence of Peritonitis and time to first peritonitis or PD discontinuation.

Results: A total of 85 patients met the inclusion criteria and had 35 individual episodes of PD peritonitis. A Univariate Logistic Regression between type of living quarters and Peritonitis had an Odds Ratio 0.53, 95% Confidence Interval, 0.22 to 1.27, p=0.158. We then performed a multivariate logistic regression to control for known independent risk factors for peritonitis including, age, gender, race, diabetes, BMI and residual renal function and found an Odds Ratio 0.48, 95% confidence interval, 0.18 to 1.28. p=0.144. A Cox Regression analysis was then performed to assess the time to peritonitis in relation to living in an apartment with a Hazard Ratio 0.65, 95% confidence interval 0.33 to 1.24, p= 0.186.

Conclusions: To our knowledge this is the first study to examine the effect of living quarters on PD peritonitis in an urban population. Our data suggests that there is no increased risk of peritonitis based on living quarters and should not be a contraindication for PD.

TH-PO403

Development of Risk Prediction Model for Infection-Related Mortality in Peritoneal Dialysis Patients

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Background: The risk assessment for infection-related mortality remains limited in patients on peritoneal dialysis (PD). The aim of this study was to develop a risk model to predict the 2-year infection-related mortality risks in PD patients.

Methods: A total of 606 patients who started and continued PD over 90 days from Fukuoka PD Registry Study in Japan were enrolled into the study. Participants were enrolled from January 1, 2006 to December 31, 2016 and followed up until December 31, 2017. To create a prediction rule, the score for each variable was weighted by the regression coefficients calculated using a Cox proportional hazards adjusted by the risk factors for infection-related mortality, including demographic, comorbidities and laboratory data.

Results: During a follow-up period (median, 2.2 years), a total of 138 patients died; 58 of these patients died of infectious disease. The final model for infection-related mortality consisted of six factors, including age, sex, serum albumin, serum creatinine, total cholesterol and renal Kt/V. The incidence of infection-related mortality increased linearly with an increase in the total risk score (P for trend <0.001). Furthermore, the prediction model showed adequate discrimination [c-statistic=0.73 (0.67–0.79)] and calibration (Hosmer-Lemeshow test, P=0.66).

Conclusions: In this study, we developed a new prediction model using clinical measures for infection-related mortality in PD patients.

TH-PO404

Peritonitis Before Peritoneal Dialysis Training: A Single Center Experience

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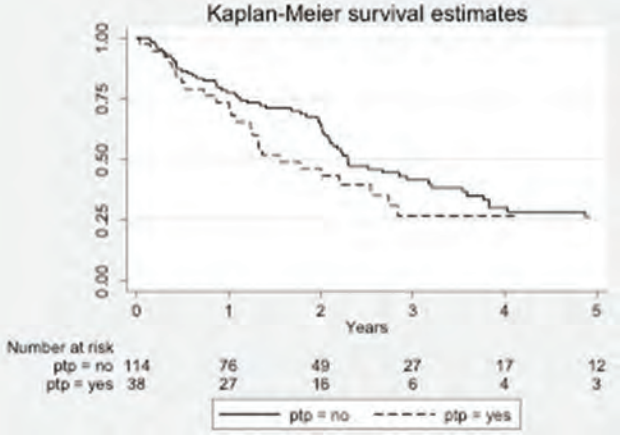
Background: Peritoneal dialysis (PD)-related peritonitis is an important risk factor for death and technique failure in PD patients. The predictors and outcomes of peritonitis prior to commencing PD (pre-training peritonitis [PTP]) are poorly understood. The aim of this study was to examine risk factors and long-term patient outcomes in those who experience PTP.

Methods: This single-center, matched case-control study included patients commencing PD from 1January 2005 to 31December 2015. PTP patients were matched 1:3 with those who developed peritonitis after PD training, based on tertiles of age and diabetic status. We examined risk factors for PTP, immediate and long-term outcomes, including technique and patient survival.

Results: Thirty-eight patients with PTP were identified and matched to 114 control patients. Compared to controls, PTP patients were significantly more likely to have history of hypertension (100% vs 89%, p=0.04), late nephrologist referral (21% vs 9%,p=0.04), open surgical PD catheter insertion (82% vs 44%,p<0.001), and pre-training exit site infection (34% vs 2%,p<0.001). PTP patients experienced comparable rates of peritonitis cure (58% vs 65%, p=0.50), temporary haemodialysis transfer (13% vs 11%,p=0.77), technique survival (HR 1.47, 95% CI 0.94-2.29,p=0.09) and patient survival (HR 1.35, 95% CI 0.52-3.49,p=0.54). There was a significant two-way interaction between history of ischaemic heart disease (IHD) and PTP status (p=0.02), such that technique failure risk was increased in PTP patients with IHD (HR 2.82, 95% CI 1.37-5.84,p=0.005) but not those without IHD (HR 0.88, 95% CI 0.41-1.92,p=0.75).

Conclusions: The risk of PTP was increased by factors relating to patient, catheter insertion approach and clinical events. Patient outcomes were comparable between PTP and post-training peritonitis, except for a greater risk of technique failure in patients with PTP and IHD.



Technique survival for PTP group compared with non-PTP group

TH-PO405

Feasibility of Resuming Peritoneal Dialysis After Catheter Removal Due to Severe Peritonitis

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Background: The resumption of peritoneal dialysis (PD) after a peritonitis requiring peritoneal catheter (PC) removal is unlikely and remains poorly studied. We analyzed the characteristics and outcomes of patients resuming PD after peritonitis.

Methods: We reviewed all episodes of peritonitis between 1996 and 2017 and identified the cases in which the catheter was removed. We compared the data of patients who restarted PD after PC removal (Group 1) with those who did not (Group 2) and identified the causes.

Results: Of 483 peritonitis episodes, PC was removed in 48 patients (16.9%). Of these, 18 (37.5%) resumed PD and 30 (62.5%) did not. The median duration of PD before catheter removal was 24.5 months (range 14.2-40) and the number of previous peritonitis episodes was 2 (range 1-3). The indications for catheter removal were: refractory and relapsing peritonitis; fungal, mycobacterial and polymicrobial peritonitis. The organisms identified were: S. aureus 20.8% (n=10), Candida sp 18.8% (n=9), P. aeruginosa 14.6% (n=7), other Gram-negative bacilli 20.8% (n=10), mixed growth 8.3% (n=4), Mycobacterium sp 6.3% (n=3), other Gram-positive 4.2% (n=2) and no growth 6.3% (n=3). Group 1 (n=18): 89.9% (n=16) were male, median age was 53 years (range 44 – 64) and Charlson Index was 4 (range 2 – 6). PD was resumed successfully in all with a median duration of PD afterwards of 14.1 months (range 4-69). Group 2 (n=30): 60% (n=18) were male, median age was 64 years (range 48 – 76) and Charlson Index was 6 (range 4 – 8). Causes of no reinsertion were: death due to peritonitis 16.7% (n = 5), transplantation 6.7% (n = 2) and transfer to hemodialysis (HD) 76.6% (n = 23). HD- switch was due to non- medical reasons in 47.8% (n = 11), including fear of peritonitis 10.4% (n=5), family decision 36.3% (n = 4) and social dependence in 18.2% (n = 2). Group 1 was younger (p = 0.041), had a higher proportion of men (p = 0.049) and a lower Charlson index (p = 0.045). No other statistically significant difference was found between both groups.

Conclusions: Resuming PD after PC removal is feasible. A high proportion of patients do not restart PD for non-medical reasons, mostly fear of peritonitis and family decision.

TH-PO406

Linoleic Acid Co-Treatment Inhibits Bacterial Biofilm Formation in Continuous Ambulatory Peritoneal Dialysis (CAPD) Catheter

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Background: Peritonitis is a serious complication in patients receiving PD responsible for significant morbidity and technical failure. Biofilm formation of catheter is considered as an underlying mechanism for relapsing, recurrent and intractable peritonitis. However, little has been known to prevent it. Here we aimed to investigate the protective effect of linoleic acid (LA) on catheter biofilm formation, which is one of the elements of ginger extract demonstrated an inhibitory effect on biofilm of industrial and environmental settings such as water pipes system.

Methods: Biofilm was formed by overnight culture of S.aureus and P. aeruginosa (PA 14) with and without treatment of LA, and quantified by measurement of OD at 595nm after staining of crystal violet. The amount of extracellular polymeric substance (EPS) attached to biofilm was also examined. Additive therapeutic effect of LA on biofilm formation was examined by co-treatment of antibiotics (cefazolin(CF) for S.aureus and tobramycin(TM) for P.aeruginosa) with LA. Intracellular cyclic digulanylate (c-di-GMP) and related gene activity under LA treatment were also examined. Cellular and functional toxicity of LA was assessed using human mesothelial cells and mice.

Results: LA treatment reduced biofilm formation (0, 10 and 100nM: 1.41±0.17, 0.95±0.11, 0.64±0.07, p<0.001, respectively), and EPS production was also markedly decreased. After LA treatment, reduction of c-di-GMP, secondary messenger of microorganism, and related gene activities were observed. Bacterial biofilm inhibitory effect was synergistically increased by co-treatment of LA (25nM) with antibiotics (CF *vs.* CF+LA: 0.60±0.03 *vs.* 0.13±0.19, TM *vs.* TM+LA 0.18±0.05 *vs.* 0.06±0.04). Cytotoxicity measured by LDH and MTS assay was not increased, and liver and renal functional and histologic abnormalities were not observed in mice after LA treatment.

Conclusions: Co-treatment of LA with antibiotics was effective to inhibit bacterial biofilm formation in catheter. It should be studied further as a therapeutic strategy to reduce recurrent peritonitis.

TH-PO407

Predictive Values of Different Blood Pressure Measurements for Left Ventricular Diastolic Dysfunction in Peritoneal Dialysis Patients

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Background: Cardiovascular diseases (CVDs) are main causes of death in end stage renal disease (ESRD) patients and one of the CVDs, left ventricular diastolic dysfunction is suggested to be associated with increased mortality in these patients. Hypertension is known to be implicated in the pathogenesis of diastolic dysfunction and an important modifiable risk factor for diastolic heart failure. In this study, we compared different methods of blood pressure (BP) measurement and evaluated comparative values of BP measurement for predicting diastolic heart dysfunction in patients on peritoneal dialysis (PD).

Methods: A total of 52 prevalent PD patients were enrolled. We measured ambulatory BP, office BP, home BP, and central BP. The ambulatory BP was recorded for 24 hours, office BP was measured at least in two visits, and home BP was measured for one week. The central BP was estimated using radial artery tonometry. Patients underwent transthoracic echocardiography and the presence of diastolic dysfunction was determined according to 2016 American Society of Echocardiography and European Association of Cardiovascular imaging (ASE/EACVI) guideline.

Results: Left ventricular diastolic dysfunction was best predicted by ambulatory systolic BP (area under the curve (AUC), 0.845; 95% CI, 0.726-0.964). The office systolic BP (AUC, 0.661; 95% CI, 0.457-0.866), home systolic BP (AUC, 0.661; 95% CI, 0.481-0.842), and central systolic BP (AUC, 0.623; 95% CI, 0.441-0.805) were inferior to ambulatory systolic BP monitoring in predicting diastolic dysfunction. In multivariate analysis adjusted for age, sex, PD vintage, diabetes and coronary artery disease, only ambulatory systolic BP had significantly increased OR for diastolic dysfunction (OR, 1.094; 95% CI 1.004-1.192). The other adjusted ORs of office, home, and central systolic BP for diastolic dysfunction were not statistically significant.

Conclusions: Ambulatory systolic BP was the strongest predictor of left ventricular diastolic dysfunction in comparison with the other BP measurements including office, home, and central systolic BP, in ESRD patients on PD.

TH-PO408

A Machine Learning Model to Predict Patient Risk of Peritonitis Episodes

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Background: Peritonitis infections are one of the primary complications in the use of peritoneal dialysis. Predicting what patients are at a higher risk of peritonitis is of great interest so that cases of peritonitis can be caught early, or patients can be given additional training to prevent peritonitis infections altogether.

Methods: We analyzed data of 36,329 peritoneal dialysis patients who were treated by a large dialysis provider from 2016-2017. We had 10,522 cases of peritonitis over this period. We trained a machine learning model (XGBoost boosted tree model) to predict which patients will be diagnosed with a peritonitis infection in the next month based on patients' history of peritonitis, symptoms noted by nurses during assessments, routine clinical laboratory values, and demographic data.

Results: Our machine learning model achieved an area under the ROC curve of 0.736. The features that were found to be most important for prediction were: whether the patient has had a previous peritoneal infection, how long the patient has been on peritoneal dialysis days since previous infection, changes in potassium levels, and albumin levels (Table 1).

Conclusions: We built a machine learning model that was able to predict which patients will have a peritonitis infection in the next month. This model can be used to allocate resources to try to catch infections early or prevent them. Future work can expand the features the model has access to in order to improve the model performance.

Funding: Commercial Support - Fresenius Medical Care

Variable	Mean value for peritonitis	Mean value for uninfected
Vintage	647 days	621 days
Previous infection	32%	13%
Days since infection	102	153
Change in potassium	.052	.028
Albumin	3.34	3.48

TH-PO409

Short Patient and Technique Survival Following First Peritonitis in Peritoneal Dialysis Patients: Does Timing of First Peritonitis Matter?

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Background: To investigate whether patient and technique survival in peritoneal dialysis (PD) are related to timing of first peritonitis.

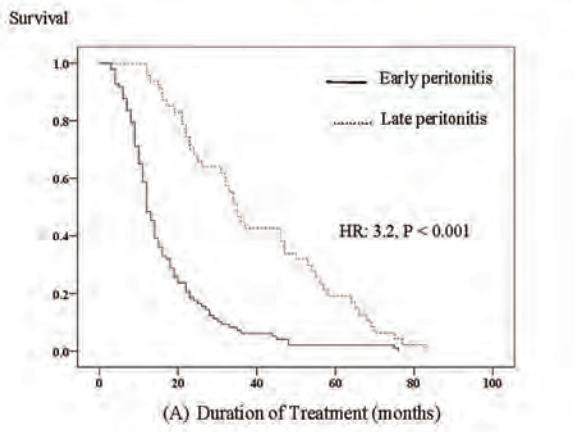
Methods: In this retrospective study, 144 patients on peritoneal dialysis who were 18 years of age and older and had at least one episode of peritonitis between 2004 and 2016 were included. They were divided into early peritonitis (EP) group (n = 97) which included patients who had their first peritonitis within 12 months from start of PD therapy, and late peritonitis (LP) group (n = 47) which included patients who had their first peritonitis after 12 months from start of PD therapy. Technique and patient survival of both groups were compared in terms of time following first incident peritonitis using Cox proportional hazard model.

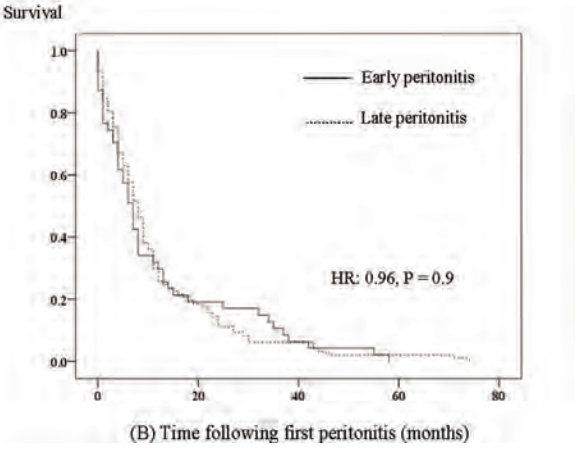
Results: EP group had shorter time on PD therapy compared to LP group (median 16.7 ± 13.1 vs 39.8 ± 20.1 months respectively, p < 0.001). However, EP and LP groups had similar patient survival in relation to time following first incident peritonitis (16 % vs 19 % at 24 months, HR: 0.96, CI 95%: 0.84 – 1.23, p = 0.9) and similar technique survival (16% for both groups at 24 months, HR: 1, CI 95%: .96 – 1.04, p = 0.7). There was no difference in causal microorganisms between both groups (p = 0.45).

Conclusions: Incident first peritonitis is associated with short patient and technique survival independently of time taken to develop the event.

Funding: Government Support - Non-U.S.

Fig 2. Patient survival following peritonitis in early peritonitis and late peritonitis according to (A) duration of treatment and (B) time following first peritonitis





TH-PO410

Exit-Site Infection Associated with Baseline Body Mass Index in Patients Initiating Peritoneal Dialysis

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Background: The International Society for Peritoneal Dialysis (PD) guidelines recommend the monitoring of PD-related infections as well as the incidence of peritonitis. However, the incidence rate of PD-related infections or the associated clinical factors have not been well investigated.

Methods: Forty-seven patients who initiated PD between 2012 and 2017 were retrospectively reviewed. The clinical data were compared between the patients developing exit-site infection (ESI) and those who did not during the initial 60 days after initiating PD. Kaplan–Meier analysis and Cox proportional hazards model were used to identify the factors associated with ESIs using the time to initial ESI from data in the cohort. An ESI was defined as the presence of purulent drainage with positive culture results, and was counted as one occurrence when the infection lasted for <4 weeks.

Results: The number of annual ESI events and their annual incidence rates between 2012 and 2017 were 1, 6, 18, 32, 20, and 36 and 0.83, 0.86, 1.36, 1.09, and 1.59 (per patient-years), respectively. The body mass index (BMI) in patients who developed ESIs before the initial 60 days (25.9 ± 4.4 kg/m^2) was significantly higher than that of patients who did not develop ESIs (21.7 ± 2.8 kg/m^2); the occurrence of diabetes mellitus (DM) was also significantly higher (9/16 vs. 7/31) and the D/P Cr was significantly lower (0.57 ± 0.08 vs. 0.66 ± 0.10) in patients with ESIs than in those without ESIs. There were no significant differences in variables, such as age, sex, stepwise PD initiation, presence of caregiver, and serum albumin, between the two groups. Kaplan–Meier revealed that the high BMI group divided by the median value and the occurrence of DM indicated a higher rate of ESI (Log-Rank: p = 0.006 and 0.026, respectively) compared with the group with low BMI and that without DM. The Cox proportional hazards model revealed that ESI events during the 2 years were significantly affected by the patients' BMI [hazard ratio (HR), 1.236; 95% confidence interval (95% CI), 1.07–1.41; p = 0.002] but not by the presence of DM (HR, 0.952; 95% CI, 0.29–3.03; p = 0.934).

Conclusions: Our findings suggest that ESIs are associated with baseline BMI of patients initiating PD in our study population. Body weight control at the time of PD initiation can potentially diminish the risk of ESI.

TH-PO411

Estimating Residual Kidney Function in Dialysis Patients Without Urine Collection

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Background: Measurement of RKF is recommended for adjustment of the dialysis prescription, but timed urine collections are difficult and prone to errors. Few equations to estimate RKF in dialysis patients using serum concentrations of low molecular weight proteins (LMWP) have been externally validated (Shafi T et al, Kidney Int 2016).

Methods: We developed RKF estimating equations using linear regression analysis in 823 peritoneal dialysis patients in the Guangzhou PD Study. The reference tests were measured clearance of urea nitrogen (UN) (mCl_{UN}, ml/min) and average clearance of UN and creatinine (mCl_{UN-cr}, ml/min/1.73 m^2). The index tests were estimated clearance (eCl) using UN and creatinine (eCl_{UN-cr}), beta-trace-protein (eCl_{BTP}), beta-2-microglobulin (eCl_{B2M}), cystatin C (eCl_{cys}) and combinations. Equations were then externally validated in 826 hemo- and peritoneal dialysis patients in the NECOSAD study and also compared to published validated equations.

Results: In external validation, bias was within ±1.0 (Table). Precision and accuracy were significantly better for eCl_{BTP}, eCl_{B2M} and $eCl_{BTP\text{-}B2M}$ than $eCl_{UN\text{-}cr}$. The area-under-the-curve for predicting mCl_{UN} >2.0 ml/min for eCl_{B2M} and $eCl_{BTP\text{-}B2M}$ was 0.853 and 0.848, respectively (Figure). Results were similar to other validated equations.

Conclusions: These results confirm the validity and extend the generalizability of estimation of RKF from serum concentrations of LMWPs without urine collection.

Funding: Commercial Support - Siemens, Dialysis Clinic Inc., Private Foundation Support

Table: Performance of estimating equations in the NECOSAD cohort (n=826)

	Guangzhou PD Study equations				Shafi et al equations
Variables	RMSE (95%-CI)[a]	Bias (95%-CI)[b]	Precision (95%-CI)[c]	Accuracy (95%-CI)[d]	Accuracy (95%-CI)[d]
Equations to estimate mCl_{UN}	ml/min	ml/min	ml/min	%	%
UN-Creatinine	0.71 (0.66, 0.76)	0.82 (0.71, 0.91)*	2.06 (1.90, 2.24)	71.9 (69.8, 74.6)	74.6 (71.5, 77.5)*
BTP	0.62 (0.58, 0.67)	0.36 (0.28, 0.44)**	1.77 (1.63, 1.90)**	77.6 (74.7, 80.4)**	80.4 (77.6, 82.2)*
B2M	0.59 (0.55, 0.62)	0.74 (0.67, 0.85)*	1.66 (1.51, 1.78)**	79.8 (77.1, 82.7)**	79.0 (76.2, 81.5)
Cystatin C	0.67 (0.62, 0.72)	-0.32 (-0.43, -0.17)**	1.99 (1.81, 2.17)**	75.3 (72.5, 78.4)	79.0 (76.2, 81.5)*
BTP-B2M	0.51 (0.48, 0.54)	0.59 (0.50, 0.65)**	1.51 (1.39, 1.75)**	81.5 (78.8, 84.1)**	81.1 (78.2, 83.6)
Equations to estimate mCl_{UN-cr}	ml/min/1.73 m^2	ml/min/1.73 m^2	ml/min/1.73 m^2	%	%
UN-Creatinine	0.61 (0.57, 0.64)	0.74 (0.60, 0.85)*	2.21 (1.96, 2.43)*	68.2 (65.0, 71.4)	68.3 (65.0, 71.5)
BTP	0.55 (0.52, 0.58)	0.24 (0.12, 0.43)**	2.15 (1.91, 2.33)**	72.4 (69.3, 75.4)*	70.8 (67.7, 74.0)
B2M	0.51 (0.48, 0.54)	0.53 (0.42, 0.62)**	1.84 (1.66, 2.02)**	77.6 (74.7, 80.4)**	68.9 (65.6, 72.0)*
Cystatin C	0.57 (0.54, 0.61)	-0.25 (-0.38, -0.13)**	2.26 (2.09, 2.52)**	71.4 (68.4, 74.5)	71.4 (68.3, 74.7)
BTP-B2M	0.51 (0.48, 0.54)	0.24 (0.12, 0.39)**	1.80 (1.63, 1.97)**	79.2 (76.5, 81.9)**	74.4 (71.5, 77.2)*

All associations between filtration marker and outcome are linear except for B2M (two-slope polynomial model, breakpoint for B2M at 23 mg/l). UN-Creatinine equations also contain age and sex as co-variables. Of note, equation developed by Shafi et al contained in part different variables.
Abbreviations: RMSE=root-mean-square-error; CI=confidence interval; mCl_{UN}= clearance of urea nitrogen in ml/min; UN=urea nitrogen; BTP=beta-trace-protein; B2M=beta-2-microglobulin; mCl_{UN-cr}=average clearance of urea nitrogen and creatinine in ml/min/1.73 m^2.
[a] RMSE defined as the standard deviation of mean difference between measured and estimated clearance.
[b] Bias is defined as the median difference between measured and estimated total clearance.
[c] Precision is defined as the interquartile range of the median differences between measured and estimated total clearance.
[d] Accuracy is defined as the % of estimated clearances within ±2 units of measured clearances.
* p<0.05, ** p<0.001 for difference between the corresponding equation and UN-cr equation within each metric.
# p<0.05, ## p<0.01 for difference between the corresponding equation and the corresponding Guangzhou PD study equation (i.e. same row).

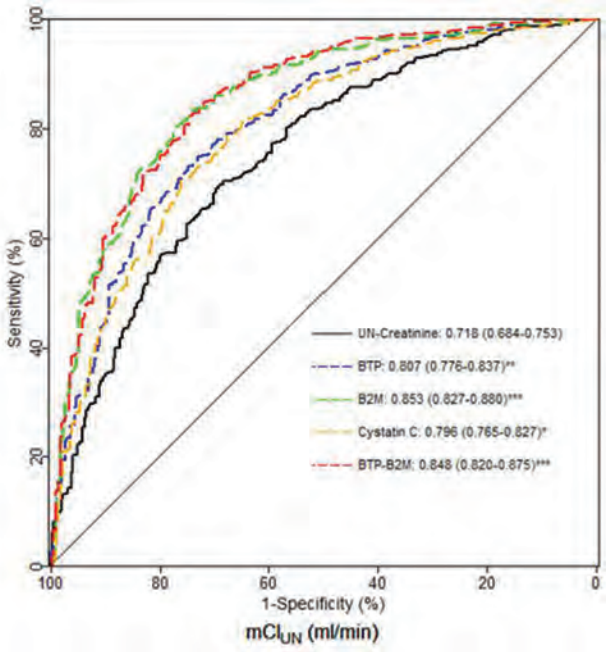


Figure: Receiver-operating-characteristics curves for the diagnostic accuracy of estimating equations to detect an urea nitrogen clearance (mCl$_{UN}$) >2.0 ml/min in the NECOSAD dataset (n=826). Equations can be identified by the markers that were used. The area under the curve result for every equation is presented with confidence intervals. All associations between filtration marker and outcome are linear except for B2M (two-slope polynomial model, breakpoint at 23 mg/l). Abbreviations: UN=urea nitrogen; BTP=Beta-trace-protein; B2M=Beta-2-microglobulin; Cl$_{UN}$=clearance of urea in ml/min; * p<0.05, ** p<0.01, *** p<0.001 for difference to UN-Creatinine equation

TH-PO412

Lipid Level and Its Impact on Cardiovascular Mortality in Peritoneal Dialysis Patients

Yong kyu Lee, Elani Streja, Hamid Moradi, Kamyar Kalantar-Zadeh. *Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA.*

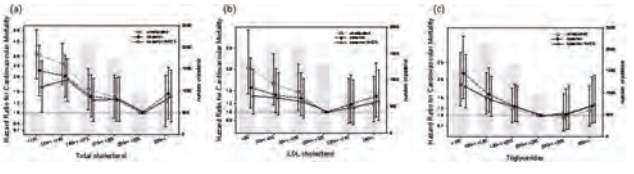
Background: Peritoneal dialysis (PD) patients show different characteristics in terms of lipid profile and qualitative function compared to hemodialysis (HD) patients, however there are limited large-scale studies regarding the influence of lipid level on cardiovascular mortality in PD patients. The guideline for lipid control, which is focused on cardiovascular mortality in HD patients, needs validation with respect to its application in PD patients.

Methods: 7,543 PD patients were selected from a national cohort of patients treated by a large dialysis organization during 2007-2011. We sought to verify the relationship between lipid levels—including total cholesterol, LDL cholesterol, and triglyceride levels—and cardiovascular mortality. Lipid levels were divided into 6 strata and 3 different hierarchical adjustment models were applied to observe the change in relationship after adjustment.

Results: Total cholesterol, LDL cholesterol, and triglyceride showed a consistent trend, whereby patients in the lowest stratum were observed to have highest cardiovascular mortality: hazard ratios were 2.183 (1.634-2.916), 1.513 (1.166-1.963), and 1.788 (1.348-2.373), respectively in case-mix adjusted models. Cardiovascular mortality risk showed a reversed J-shaped association with inflection at a total cholesterol level of 200-230mg/dL, LDL cholesterol level of 100-120mg/dL, and triglyceride level of 200-250mg/dL.

Conclusions: In contrast to conventional belief, PD patients with low total cholesterol, LDL cholesterol, and triglyceride levels showed higher cardiovascular mortality.

Funding: NIDDK Support



TH-PO413

HDL Cholesterol Level and Its Impact on Cardiovascular Mortality in Peritoneal Dialysis Patients

Yong kyu Lee, Elani Streja, Kamyar Kalantar-Zadeh, Hamid Moradi. *Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA.*

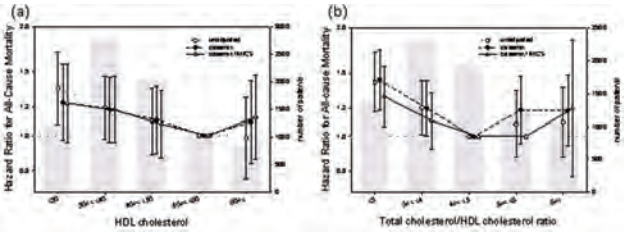
Background: HDL cholesterol is traditionally believed to be beneficial in preventing cardiovascular mortality by reverse cholesterol transport and restricting LDL cholesterol oxidation. However, in ESRD patients, the effect of HDL cholesterol was shown to deviate due to its qualitative and quantitative alteration.

Methods: 7,839 peritoneal dialysis (PD) patients were selected from a national cohort of patients treated at a large dialysis organization during 2007~2011. We sought to verify the relationship between HDL cholesterol and total cholesterol/HDL cholesterol ratio and all-cause mortality. Each exposure parameter was divided into 6 strata and 3 different hierarchical adjustment models were applied to observe the change in relationship after adjustment.

Results: Although patients with low HDL cholesterol showed higher all-cause mortality risk in the unadjusted model, the risk was attenuated after adjustment, with a hazard ratio of 1.235 (0.970-1.573) in the case-mix adjusted model. However, patients with low total cholesterol/HDL ratio showed higher all-cause mortality risk which was robust even after adjustment for case-mix and markers of malnutrition/inflammation (MICS), with a hazard ratio of 1.433 (1.183-1.736) in the case-mix adjusted model. Both showed a reversed J-shaped association with the inflection point at 50-60mg/dL for HDL cholesterol and 4-5 for total cholesterol:HDL cholesterol ratio. The highest HDL cholesterol level group showed a mortality risk of 1.090 (0.836-1.421) and the highest total cholesterol:HDL cholesterol ratio group showed a mortality risk of 1.178 (0.940-1.477).

Conclusions: PD patients with low HDL cholesterol and total cholesterol:HDL cholesterol ratio showed higher all-cause mortality. However, higher HDL cholesterol and total cholesterol:HDL cholesterol ratios showed neither the beneficial effect observed in the general population nor the deleterious effect observed in HD patients.

Funding: NIDDK Support



TH-PO414

Serum Osteopontin Level Is Positively Associated with Central Arterial Stiffness in Patients with Peritoneal Dialysis

Wei-Chen Lin, Bang-Gee Hsu. *Buddhist Tzu Chi General Hospital, Hualien, Taiwan.*

Background: Osteopontin (OPN) is generally regarded as a proinflammatory and proatherogenic molecule and is associated with atherosclerosis. The aim of this study was to evaluate the relationship between serum OPN on central arterial stiffness by measuring of carotid-femoral pulse wave velocity (cfPWV) values in patients with peritoneal dialysis (PD).

Methods: Fasting blood samples were obtained from 70 PD participates in the study. Carotid-femoral pulse wave velocity was measured by a validated tonometry system. cfPWV values of > 10 m/s were used to define the high central arterial stiffness group, while values ≤ 10 m/s were regarded as the control group, according to the ESH-ESC 2013 guidelines. Serum OPN levels were measured using a commercial enzyme-linked immunosorbent assay kit.

Results: Twenty-two patients (31.4%) had high central arterial stiffness and were of older age (P = 0.001) and had longer PD vintage (P = 0.024), higher C-reactive protein (P = 0.005) and OPN levels (p < 0.001) compared to subjects with control group. Multivariate logistic regression analysis of the factors significantly associated with central arterial stiffness revealed that OPN (odds ratio: 1.044, 95% confidence interval: 1.020–1.069, P < 0.001) and PD vintage (odds ratio: 1.027, 95% confidence interval: 1.007–1.047, P = 0.009) were the independent predictors of central arterial stiffness in PD patients. Multivariate forward stepwise linear regression analysis also showed that OPN level (β = 0.477, adjusted R^2 change = 0.269, P = 0.001) was positively associated with cfPWV values in PD patients.

Conclusions: In this study, serum OPN level was positively associated with cfPWV values in PD patients and was the independent predictors of central arterial stiffness in PD patients.

TH-PO415

Serum Osteoprotegerin Level Is Positively Associated with Peripheral Artery Disease in Patients with Peritoneal Dialysis

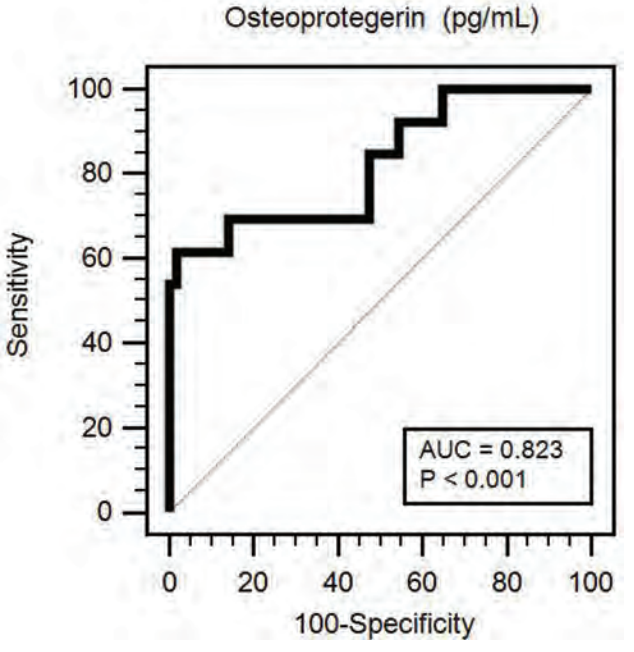
Wei-Chen Lin,[2] Bang-Gee Hsu.[1] *[1]Division of Nephrology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan; [2]Buddhist Tzu Chi General Hospital, Hualien, Taiwan.*

Background: Osteoprotegerin (OPG) levels may be a potential biomarker of complications and severity of cardiovascular disease. Peripheral arterial disease (PAD) is associated with an increased risk of death in peritoneal dialysis (PD) patients. Our aim was to evaluate the relationship between serum OPG levels and PAD by ankle-brachial index (ABI) among PD patients.

Methods: Fasting blood samples were obtained from 70 PD patients. The ABI values were measured using an ABI-form device (VaSera VS-1000). Serum OPG levels were measured using a commercial enzyme-linked immunosorbent assay kit. Left or right ABI values that were < 0.9 were included in the low ABI group.

Results: Among 70 PD patients, 13 patients (18.6%) were in the low ABI group. Compared with patients in the normal ABI group, patients in the low ABI group had higher prevalence of diabetes (p = 0.044), higher serum C reactive protein (CRP) (P < 0.001), and higher serum OPG level (P < 0.001), while lower serum creatinine level (P = 0.013) and peritoneal Kt/V (P = 0.048). According to the multivariate logistic regression analysis, OPG (Odds ratio [OR]: 1.027, 95% confidence interval [CI]: 1.010-1.045, P = 0.002) and CRP (each increase of 0.1 mg/dL, OR: 1.102, 95% CI: 1.006-1.207, P = 0.037) were the independent predictors of PAD in PD patients. The area under the receiver operating characteristic (ROC) curve (AUC) indicates the diagnostic power of OPG at predicting PAD of PD patients was 0.823 (95% CI: 0.714-0.904, P < 0.001).

Conclusions: In this study, serum OPG level was proved to be involved in the pathogenetic process of PAD in PD patients.



TH-PO416

Relationship Between Hypomagnesemia and Abdominal Calcification Index in Peritoneal Dialysis Patients: A Cross-Sectional Study

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Background: Several previous reports have reported that hypomagnesemia was associated with high mortality in hemodialysis (HD) patients. However, the influence of hypomagnesemia on the prognosis of peritoneal dialysis (PD) remains unclear. We investigated relationship between abdominal calcification index (ACI) and cardiovascular risk factors in PD patients.

Methods: A total of 184 PD patients were included in the current study. ACI was calculated calculated as average calcification area of consecutive 20 slices of abdominal aorta measured by abdominal plain CT (computerized tomography). We evaluated relationships between ACI and cardiovascular risk factors, including serum phospahte, serum calcium, whole parathyroid hormone, serum agnesium, lipid status, Hemoglobin A1c (HbA1c), blood pressure (BP), peritoneal function, echocardiographic findings.

Results: The overall, mean age was 64.9 years old, male/female was 132/52, average PD vintage was 12 months. Median value of magnesium was 1.92±0.3 mg/dl. We deviated participants into two groups; low magnesium (Mg<1.9) group and high magnesium (Mg≥2) group. Low magnesium group had a lower HbA1c and higher ACI. There was no difference in age, sex, ejection fraction, BP, peritoneal function, past history of cardiovascular disease between two groups. In the multiple regression analysis, hypomagnesemia was an independent predictor for high ACI (β=-2.73, P<0.007).

Conclusions: Hypomagnesemia at initiation of PD was strongly correlated with high ACI and its relationship did not change even after adjusting by plausible cardiovascular risk factors, hypomagnesemia was an independent predictor for high ACI. These results suggest that hypomagnesemia might be involved in calcification progression in PD patients.

TH-PO417

Concentric Left Ventricular Hypertrophy at Peritoneal Dialysis Initiation May Predict Death and Cardiovascular Disease in Patients Using Neutral-pH Solution

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Background: Left ventricular hypertrophy (LVH) is known as one of the risk factors of mortality and cardiovascular disease (CVD) in the patients undergoing peritoneal dialysis (PD). Concentric LVH (cLVH) is the most frequent left ventricular geometry model in dialysis patients. The relationship between cLVH at PD initiation and prognosis is not well known. We investigated whether cLVH at PD initiation is associated with mortality and incidence of CVD in PD patients.

Methods: The data from patients who started PD at The University of Tokyo Hospital were collected retrospectively. Clinical parameters measured at PD initiation were obtained. The definition of cLVH was as follows; left ventricular mass index is ≧115 g/m^2 and relative wall thickness is ≧0.42. All patients were divided into two groups with and without cLVH. Morality, incidence of CVD, technique survival rate were compared between two groups. We also investigated the relationship between clinical parameters and cLVH at PD initiation.

Results: A total of 126 patients was included and mean follow-up period was 44 months. The mean age was 58.5±11.8 y.o., male was 76%, and automated PD was selected in more than 90% patients. All patients were treated using neutral-pH PD solution. Twenty-six patients (21%) had cLVH at PD initiation. Kaplan-Meier analysis revealed that cLVH group had significant higher mortality, higher incidence of CVD, and lower technique survival rate compared with non-cLVH group (Log rank: p < 0.01, = 0.02, and < 0.01, respectively). The result of Cox proportional hazards model demonstrated that age and cLVH were independent predictors of mortality (hazard ratio, 1.08 and 3.67; 95%CI, 1.04 to 1.14 and 1.18 to 11.46; p < 0.01 and = 0.02; respectively). Age, hemoglobin, and geriatric nutrition risk index (GNRI) were independently correlated with cLVH (odds ratio [95% confidence interval]: 1.07 [1.02-1.11], 0.53 [0.30-0.93], and 0.92 [0.86-0.99], respectively).

Conclusions: Concentric LVH at PD initiation may be a possible predictor of mortality and CVD in patients using neutral-pH PD solution.

TH-PO418

Peritoneal Ultrafiltration on Refractory Heart Failure

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Background: Fluid Overload (FO) in Heart Failure (HF) is a major risk factor for morbidity and mortality.

Methods: The primary outcome of this study was to evaluate the safety and efficacy of Icodextrin for peritoneal ultrafiltration in Refractory HF (RHF) patients with FO and to assess the change in New York Heart Association (NHYA) Class, body composition measurement by electrical bio-impedance, length of hospital stay (LHS) and hospital costs (HC) in a 1 year follow up.

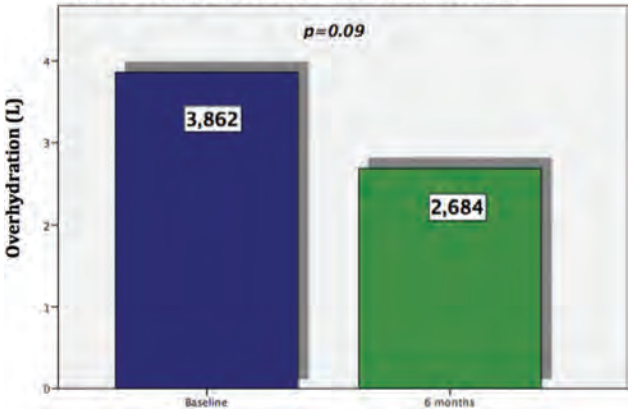
Results: we included a total of 6 patients with RHF and FO, table 1 shows baseline and post-intervention characteristics of participants. During the follow up we registered 1 episode of peritonitis and 1 mechanical dysfunction of peritoneal catheter. The median of LHS in one year previous treatment was 35 (RIC 23-50) vs 3 (RIC 2-25) days in 1 year follow-up (p 0.07). Also, a 1 year HC pre-intervention was $6,804.82 (RIC $4,308.62 - 11,579.14) vs $676.56 (RIC $420.69 –4,093.65) US dollars (p 0.06). At 6 months follow up we registered 2 deaths (34%).

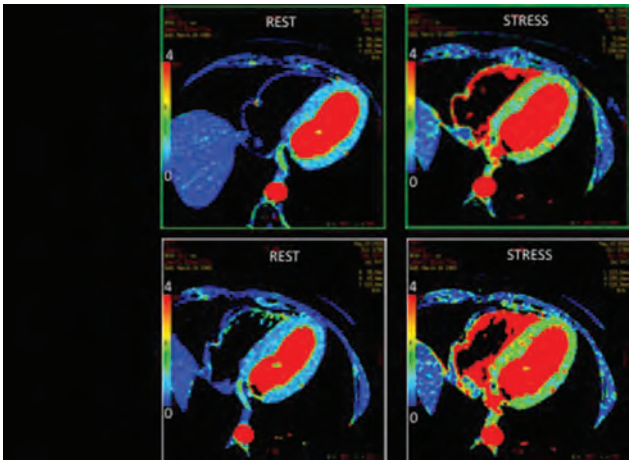
Conclusions: we observed a better FO control and an improvement of symptoms (NYHA class), also a decrease of LHS and HC. The limitation of this study is the sample size but with a tendency towards statistical significance.

Baseline and Post-intervention characteristics

Patients characteristics (n=6)	Baseline	6 months
Female n (%)	3 (50)	
Age (yr)	62 ± 6.4	
Primary Cause of HF Ischemic Cardiomyopathy n (%) Valvulopathy n (%)	4 (67) 5 (83)	
Major co-morbidities Pulmonary Hypertension n (%) DM2 n (%) Arterial Hypertension n (%) Liver Failure n (%)	3 (50) 1 (17) 1 (17) 2 (34)	
Diuresis (mL/day)	920 ± 259	
NT-Pro Brain Natriuretic Peptide (pg/mL)	14359 ± 10313	
Left Ventricular Ejection Fraction (%)	45 ±17	
NYHA Class II n (%) III n (%) IV n (%)	0 0 0 6 (100)	(p=0.01) 4 (67) 2 (33)
Glomerular Filtration Rate - CKD Epi (mL/min/1.73 m2)	22.6 ± 13.4	34.5 ± 23.3
Laboratory: Blood Urine Nitrogen (mg/dL) Potassium (mEq/L) Albumin (g/dL)	55.4 ± 28 4.1 ± 0.4 3.9 ± 0.6	48 ± 14.3 4.4 ± 0.8 3.5 ± 0.3
Overhydration (L)	3.9 ± 1.3	2.7 ± 1.4 (p 0.09)

Figure 1. Change in Overhydration post intervention





TH-PO419

Pilot Study to Determine Whether Cooled Peritoneal Dialysis Confers Cardioprotective Effect

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Background: Despite lack of dialysis induced ischema (characteristic of hemodialysis), patients receiving peritoneal dialysis (PD) also suffer excess cardiac morbidity and mortality- driven by high rates of heart failure and sudden cardiac death. Currently there are no effective primary prevention therapies. Moderate hypothermia is well established in animal models to provide protection against demand ischemia. Furthermore, perfusion heterogeneity disrupts the passage of myocardial depolarization increasing the risk of ventricular re-entrant circuits. The aim of this study was to explore PD as a method of delivering a cooling intervention and test whether or not it could reduce segmental or global stress induced cardiac ischemia.

Methods: We studied 6 patients at 2 study visits. Myocardial perfusion was measured using high resolution 256 slice CT scanning at rest and with adenosine stress. The first visit was done on patients' usual PD regimen, second visit utilised peritoneal dialyzate cooled to 32-33 ^{0} C, to reduce body temperature by 0.5 ^{0} C. Myocardial Perfusion was assessed using the American Heart Association segmentation model with ANOVA test, and perfusion pattern heterogeneity was measured by standard deviation of segmental perfusion.

Results: Cooled dialysate was tolerated well by all patients. No symptoms of cold or drain pain were reported. Cooling significantly decreased rest and trended towards decreased stress global and segmental cardiac perfusion (mean values being 75.53 to 165.83 mL/min/100g). Pharmacological stress was associated with an increase in perfusion heterogeneity (mean increase in SD from 10.87 to 21.09). However, cooling the dialysate significantly reduced this effect by 25%.

Conclusions: Moderate hypothermia can be safely delivered using PD. It provides significant reduction in a potential key risk factor for cardiac sudden death and warrants further investigation to reduce cardiovascular attrition in PD patients.

TH-PO420

Lower Risk of Hospitalizations in Cardiorenal Patients Using Once-Nightly Icodextrin Peritoneal Exchanges

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Background: The purpose of this study is to investigate the benefits of using a nightly icodextrin peritoneal dialysis (PD) solution in the cardiorenal (diuretic-resistant congestive heart failure) patient. Icodextrin is a glucose polymer that has been used as a replacement for the glucose traditionally used in the PD long dwells, as the oncotic pressure gradient can be maintained at adequate ultrafiltration (UF) values for 8-12 hours during sleep. Icodextrin-based solutions (ICO) are well tolerated, lack the metabolic side effects of glucose, and enhance the clearance of small and middle-sized molecules as a consequence of increased convective flow. Patients using one exchange nightly lead a more "normal" life when compared to patients using continuous cycling peritoneal dialysis (CCPD) with glucose solutions, as CCPD requires a nightly cycler apparatus which restricts the patient ability to ambulate at night.

Methods: This study provides data from a sample size of 11 individuals (9 males and 2 females) currently on once-nightly icodextrin peritoneal exchanges. Hospital admissions over an equal date range before and after starting extraneal dialysis treatment were compared.

Results: In our study, we observed that patients using once-nightly icodextrin exchange had fewer hospitalizations (p=0.0149), and reported an overall better quality of life after initiation of icodextrin peritoneal dialysis with decreased hospital admissions for CHF and progressive chronic kidney disease.

Conclusions: By augmenting UF in the cardiorenal patient with recurrent episodes of decompensated heart failure through once-nightly icodextrin exchanges, patients receive adequate clearance with preserved residual renal function as well as fewer hospitalizations. In addition, patients report more restful sleep and a better quality of life as a result of not being attached to a machine at night. They also enjoy being able to travel with their solutions delivered to their destination without having to carry a cycler.

TH-PO421

Association Between Use of Alpha-Blockers in Older Adults and Hypotension and Hypotension-Related Clinical Events

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Background: Alpha- blockers (AB) are effective and commonly prescribed medications as part of a multi-drug regiment in the management of hypertension. Little is known regarding the risk of hypotension and hypotension-related clinical outcomes in older adults with ongoing AB use. We set out to assess the risk of hypotension and related adverse events with AB use compared to other anti-hypertensives in the older adults.

Methods: A population-based, retrospective cohort study of 933,033 older adults (≥ 66 years) prescribed an anti-hypertensive medication between 1995 and 2015 in Ontario, Canada. A high dimensional propensity score was used to match the dispensing of AB compared to other anti-hypertensives. AB exposure was modeled as a time-varying and cumulative covariate using extended, conditional Cox proportional hazards to examine the association with outcomes. Study outcomes were hospital admissions or emergency room visits for hypotension, related events (syncope, fractures, falls), major adverse

cardiovascular events (MACE) and all-cause mortality. We examined subgroups of age, total number of anti-hypertensives and concurrent beta-blocker use.

Results: Among 69,092 matched patients prescribed AB (mean age 75.1 SD 6.5 years) with a median follow up 3.7 (IQR 1.4 to 9.5) years, the incident rate of hypotension and related events were significantly higher compared to other anti-hypertensives (hypotension 1.15 vs. 0.39, syncope 1.47 vs. 0.46, falls 4.37 vs. 1.37, fractures 2.23 vs. 0.69 per 100 person-years of follow-up). In time-varying exposure models with additional adjustment for the total number of anti-hypertensives, the higher risk persisted (hypotension HR 1.34 95%CI 1.26-1.43, syncope HR 1.49 95%CI 1.41-1.57, falls HR 1.27 95%CI 1.23-1.32, HR fractures 1.41 95%CI 1.34-1.48). Secondary outcomes of MACE and all-cause mortality were higher or similar among AB users (MACE IR 7.03 vs. 2.31, mortality 6.54 vs 6.37 per 100 person-years follow-up).

Conclusions: Treatment of hypertension in older adults with AB is associated with a higher risk of hypotension, hypotension-related events and MACE. Our findings suggest that AB should be used with caution, even as add on therapy for hypertension in older adults.

TH-PO422

Beta Blocker (BB) Use Patterns at ESRD Transition and Mortality Outcomes Among Congestive Heart Failure (CHF) Patients Starting Hemodialysis (HD)

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Background: While BB have demonstrated benefit in CHF, there is uncertainty among HD pts. Comparative BB outcomes (beta selective, dialyzability, lipophilic) in the ESRD transition period are lacking; while studies on newly initiated BB after ESRD are conflicting and overall sparse. Among CHF patients on BB at ESRD transition, we evaluated BB use patterns and 1-year mortality.

Methods: A retrospective cohort study (1/1/2007-6/30/2016) within Kaiser Permanente Southern California (an integrated health system) of CKD patients with CHF who transitioned to HD while on BB. BB use and type [dialyzable (D) vs non dialyzable (ND)] were evaluated. Multivariable regressions were used to estimate 1-year mortality HR based on post ESRD transition BB use and type.

Results: A total of 2756 pts w CHF on BB transitioned to HD (age 68 yrs, 57% males, 31% whites, 23% blacks, and 34% Hispanics). Within 120 days post transition, 25% of pts discontinued BB, 38% were on D BB, and 24% were on ND BB. Post ESRD transition, 6.5% switched their BB dialyzable types (similar both directions). Mean blood pressure w/ in 120days post transition was 130/65mmHg but lowest among ND BB pts. Mortality rates were 126.5 (per 1000 person-yrs), 205.7, and 223.2 for D BB, ND BB, and pts off BB, respectively. 1-yr mortality HR's were 1.37 (1.07-1.74) and 1.66 (1.32-2.09) for ND BB and off BB compared to D BB pts. Carvedilol (ND) pts had a mortality HR of 1.32 (1.00-1.73) vs metoprolol (D).

Conclusions: Among CHF pts on BB who transitioned to HD, 25% discontinued BB while 6.5% switched BB dialyzability types. The highest short-term mortality were observed in pts off BB followed by ND BB compared to D BB. Given the vulnerable state of ESRD transition and the high-risk CHF ESRD population, BB use may be an area of focus to help improve ESRD transition outcomes.

Funding: NIDDK Support

All-cause mortality

	Death/1,000 person-years	Crude HR (95% CI)	Adjusted HR (95% CI)*
HD-dialyzable BB^	126.5	Reference	Reference
Non-dialyzable BB^	205.7	1.62 (1.28-2.05)	1.37 (1.07-1.74)
BB discontinued	223.2	1.76 (1.40-2.21)	1.66 (1.32-2.09)

* Adjusted for age, sex, race, Afib, mean SBP<110 w/in 120days post ESRD, CCI, & cause of ESRD

^HD-dialyzable BB: atenolol, metoprolol, nadolol, sotalol; HD-nondialyzable BB: bisoprolol, carvedilol, labetalol, propranolol.

TH-PO423

Use of Calcium Channel Blockers Before Dialysis until Dialysis Initiation Is Associated with All-Cause Mortality During Maintenance Dialysis

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Background: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are reno-protective renin-angiotensin system blockade agents (RASBs) that are recommended for patients with chronic kidney disease (CKD), especially for diabetic nephropathy. However, a meta-analysis of CKD patients including those on dialysis demonstrated no significant difference in mortality between those on RASBs or calcium channel blockers (CCBs). Therefore, we examined whether the use of CCBs was associated with all-cause mortality and cardiovascular (CV) events in patients with incident dialysis.

Methods: The subjects were patients in 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis between October 2011 and September 2013. We enrolled 1,520 subjects in the study. Baseline was defined as the time at which dialysis was initiated. Survival prognosis and incidence of CV events as of September 30, 2016, were determined from medical records. We classified patients into two groups according to the use of CCBs at the time of dialysis initiation: those who received CCBs (CCB group; n = 1,199) and those did not receive CCBs (non-CCB group; n = 321). Study outcomes included mortality and the incidence of CV events in the two groups. Factors contributing to all-cause mortality were examined using multivariate Cox proportional hazards regression analysis. In addition, we compared all-cause mortality stratified by use of RASBs.

Results: A log-rank test showed significant differences in all-cause mortality and the incidence of CV events between the two groups (p = 0.001 and p = 0.003, respectively). Multivariate stepwise Cox proportional hazards analysis revealed that all-cause mortality and the incidence of CV events were significantly lower in the CCB group than in the non-CCB group (hazard ratio [HR] = 0.62, 95% confidence interval [CI]: 0.46 – 0.85, p = 0.003 and HR = 0.74, 95% CI = 0.56 – 0.98, p = 0.037) (Table). All-cause mortality rates were significantly lower in the CCB group than in the non-CCB group among patients who did not receive RASBs (HR = 0.70, 95% CI: 0.52 – 0.95, p = 0.021).

Conclusions: The use of CCBs in patients before dialysis initiation was associated with reduction in all-cause mortality and CV events during maintenance dialysis.

TH-PO424

Effect of Aspirin on Cardiovascular Disease Outcomes in ALLHAT Participants with and Without CKD

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Background: Those with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD), as well as increased CVD-related and all-cause mortality. In the general population, aspirin is effective in the secondary prevention of CVD, for those at high risk of occlusive vascular events. For patients with CKD, however, it remains unclear whether aspirin is useful in either the primary or secondary prevention of CVD.

Methods: We performed a secondary analysis of the randomized controlled trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) to assess the effect of baseline aspirin use on the initial primary endpoint, nonfatal myocardial infarction (MI), or fatal coronary heart disease (CHD) and secondary end points, all-cause mortality and stroke. Differences in baseline characteristics between subjects with and without aspirin use were examined and then used to generate a propensity-matched analysis population. Using conditional logistic regression models, we estimated the effect of aspirin on the outcomes. We created additional models testing for differences in the effect of aspirin across 3 levels of kidney function (eGFR $\geq$ 90, 60-89, and <60).

Results: The ALLHAT trial (n=33,537) contained 11,250 participants with complete data who reported using aspirin at baseline. There were significant differences in the race, sex, and cardiovascular disease history of aspirin versus non-aspirin users. The propensity-matched dataset included 6,894 non-aspirin users matched with replacement to aspirin users and achieved an analysis population (n=22,500) with balance across possible confounders. The risk of the primary study endpoint (OR = 0.98, 95% CI = 0.90-1.06) and stroke (OR = 0.92, 95% CI = 0.82-1.03), was not significantly different between aspirin users/non-users. Aspirin users were at significantly lower risk of all-cause mortality compared to non-users (OR = 0.75, 95% CI = 0.70-0.80). There were no significant interactions between aspirin and baseline eGFR kidney function for these three endpoints.

Conclusions: Aspirin use is not associated with decreased odds of non-fatal MI, fatal CHD or stroke but is associated with decreased odds of all-cause mortality for participants in the ALLHAT trial. These results are consistent across baseline eGFR.

Funding: Veterans Affairs Support

TH-PO425

Association of Hyperuricemia and Serum Uric Acid Lowering Medication with Mortality in Hemodialysis Patients

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Background: In the general population hyperuricemia is associated with increased cardiovascular risk and mortality. It is unknown whether this association exists in hemodialysis patients as well and whether this population benefits from serum uric acid (SUA) lowering medication.

Methods: We performed a retrospective analysis of 601 patients on chronic hemodialysis therapy in five dialysis outpatient centers for a maximum follow-up of 100 months (mean follow-up 41 months). Death was defined as primary endpoint. Hyper- and normouricemic subjects differed in age. Therefore a Cox regression analysis adjusted for age was performed in addition to Kaplan Meier survival analyses.

Results: Kaplan Meier survival curves showed a higher cumulative survival rate for those subjects with a higher than median SUA concentration both based on mean annual SUA concentrations and baseline SUA concentrations (three months after the initiation of dialysis, p<0.05 each). Groups showed no significant difference in survival anymore after adjustment for age in Cox regression analyses (p>0.05 each). SUA lowering therapy (allopurinol or febuxostat) revealed no effect on cumulative survival, neither in Kaplan Meier nor in Cox regression analysis (p>0.05 each). Body mass index had no impact on

survival rates. There were 22 symptomatic gout attacks during the follow-up corresponding to an incidence of 1/93.3 patient years. Among those with prior symptomatic hyperuricemia (10.1% of overall population) 47.5% continued on medication, 52.5% discontinued. Only 6 subjects with prior symptomatic hyperuricemia developed additional gout attacks after the initiation of hemodialysis (1/342.2 patient years), all of them despite medication.

Conclusions: The present analysis shows that – in contrast to the general population – hyperuricemia is not associated with increased mortality in patients undergoing hemodialysis. A "reversed epidemiology phenomenon" of better survival with higher SUA concentrations disappears after adjustment for age. SUA lowering therapy is neither associated with a survival benefit nor a significant reduction of gout free patient years. These data indicate that SUA lowering medication might be dispensable after the initiation of dialysis.

TH-PO426

Association Between Warfarin Use and Clinical Outcomes in Late-Stage CKD Patients with Atrial Fibrillation

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Background: The effect of warfarin on clinical outcomes in late-stage chronic kidney disease (CKD) patients with atrial fibrillation (AF) is unclear.

Methods: We examined a national cohort of 23,201 US veterans with incident end stage renal disease (ESRD) who developed incident AF prior to initiating renal replacement therapy. We examined the association of warfarin therapy following the diagnosis of AF with cerebrovascular accidents (CVA) (ischemic stroke or transient ischemic attack), hemorrhagic strokes, post-dialysis fatal bleeding and all-cause mortality in multivariable adjusted time dependent Cox models adjusting for demographic characteristics and comorbidities.

Results: Patients were 77±9 year old, 95% male, 13% African-American, 99% hypertensive, 79% diabetic, and 88%, 88% and 64% had histories of ischemic heart disease, congestive heart failure and CVA, respectively. 5,632 (24.3%) patients received treatment with warfarin during the study period. As shown in the Table, the risk of all outcomes except all-cause mortality were higher in those exposed to warfarin when compared to those not exposed to warfarin. These differences in outcomes remained significant even after multivariable adjustment, except fatal bleeding events, which showed no significant associaiton (Table).

Conclusions: Warfarin use in advanced CKD is associated with higher risk of ischemic and hemorrhagic CVA, but lower risk of mortality after ESRD transition. Randomized controlled trials are needed to determine the risks and benefit of warfarin therapy in patients with incident AF and advanced CKD.

Funding: NIDDK Support, Veterans Affairs Support

	Overall (1000 patient years [95% CI])	No-Warfarin Exposure (1000 patient years [95% CI])	Warfarin Exposure (1000 patient years [95% CI])	Adjusted Hazard Ratio for Warfarin Exposure (95% CI)
All-cause mortality	469.7 [463.0-476.4]	496.2 [487.9-504.6]	416.3 [405.6- 427.4]	0.93 [0.90- 0.96]
Ischemic CVA	65.5 [64.3- 66.8]	61.6 [60.3-62.9]	97.7 [93.1-102.4]	1.39 [1.31- 1.48]
Hemorrhagic Stroke	8.6 [8.2 – 9.1]	7.6 [7.2-8.0]	15.5 [14.1-17.1]	1.52 [1.32- 1.75]
Fatal Bleeding Event	7.4 [6.6- 8.3]	8.1 [7.1-9.3]	6.1 [4.9-7.6]	0.86 [0.62 – 1.19]

TH-PO427

Hyperkalemia and Renin-Angiotensin Aldosterone System Inhibitor (RAASi) Therapy in CKD: A General Practice-Based, Observational Study

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Background: Data on hyperkalemia frequency among chronic kidney disease (CKD) patients receiving RAASis and its impact on subsequent RAASi treatment are limited. We sought to assess the incidence of clinically significant hyperkalemia in CKD patients who were prescribed a RAASi and the proportion of patients with RAASi medication change after experiencing incident hyperkalemia.

Methods: We conducted a retrospective, population-based cohort study (1 January 2013-30 June 2017) using Australian national general practice data from the NPS MedicineWise's MedicineInsight program. The study included adults aged ≥18 years who received ≥1 RAASi prescription during the study period and had CKD (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m^2). Study outcomes included incident clinically significant hyperkalemia (serum potassium >6 mmol/L or a record of hyperkalemia diagnosis) and among patients who experienced incident hyperkalemia, the proportion who had RAASi medication changes (cessation or dose reduction during the 210-day period after the incident hyperkalemia event).

Results: Among 20,184 CKD patients with a median follow-up of 3.9 years, 1,992 (9.9%) patients experienced an episode of hyperkalemia. The overall incidence rate was 3.1 (95% CI: 2.9-3.2) per 100 person-years. Rates progressively increased with worsening eGFR (e.g. 3.5-fold increase in patients with eGFR <15 vs. 45-59 ml/min/1.73m^2). Among patients who experienced incident hyperkalemia, 47% had changes made to their RAASi treatment regimen following the first occurrence of hyperkalemia (discontinuation: 37% and dose reduction: 10%). In the full multivariable model, higher levels of serum potassium at the time of the hyperkalemia event was significantly associated with a greater likelihood of medication change (per 0.1 mmol/L increase: odds ratio [OR] 1.05, 95% CI: 1.02-1.08).

Conclusions: In this analysis of adult RAASi users with CKD, hyperkalemia and subsequent RAASi treatment changes were common. Further assessment of strategies for hyperkalemia management and optimal RAASi use among people with CKD are warranted.

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TH-PO428

The Feasibility of Interventions to Increase Potassium Intake for Hypertension: A Systematic Review of the Evidence

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Background: Increased potassium (K) intake has been reported to decrease blood pressure (BP) in animal studies as well as clinical trials. On this basis, major organizations including the American Heart Association recommend increasing K intake, preferably by diet, as a non pharmacological mean of reducing BP. However, it is not clear if the interventions for efficaciously increasing K intake are reproducible or feasible for translation into public health. Hence, we conducted a systematic review of the evidence to review this from randomized controlled trials (RCTs).

Methods: We conducted a literature search using an information specialist of MEDLINE, EMBASE and Cochrane CENTRAL till November 2017. Two reviewers selected RCTs that were in adults, with an intervention aimed at increasing K intake, with blood pressure as an outcome. From RCTs which reported both a significant change in BP and K using 24 hour urine K, we evaluated the interventions for ease of reproducibility and feasibility based on prespecified criteria.

Results: The initial search retrieved 1199 non-duplicate citations. After applying eligibility criteria, 90 studies were selected for inclusion. In 31 studies, the change in BP or K was not significant. Of the remaining 59 studies which reported a significant change in K and BP, 47 reported a change in K based on 24 hour urinary K measurement. 32/47 studies used a K supplement, with details provided on dose and administration to make it both reproducible and feasible. 15/47 studies used a dietary intervention, of which in 4, the intervention was not described in sufficient detail to be reproducible. The remaining 11 studies were feeding trials, with intervention consisting of provision of prepared meals, or of food items on a daily basis to make them unfeasible for routine clinical practice.

Conclusions: Dietary potassium interventions from trials in which there was a significant change in K based on 24 hour urine, and a significant change in BP, and which describe methods insufficient detail to be reproduced, are not feasible for routine clinical practice.

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TH-PO429

Variation in Use of Antihypertensive Medications After Kidney Transplant and Associated Outcomes: A National Study

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Background: Hypertension is a common comorbidity in kidney transplant (KTx) recipients. Impact of antihypertensive medication (AHM) regimen on patient and graft outcomes is not clear.

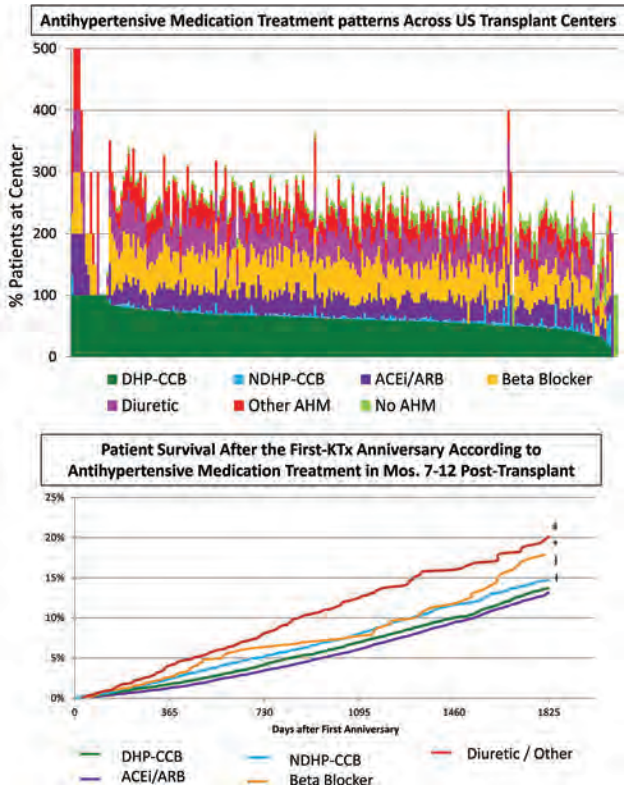
Methods: A novel database linking SRTR registry data for 54,153 KTx recipients with AHM fill records from a large pharmaceutical claims warehouse (2008-2015) was used. Mutually exclusive regimens were defined hierarchically as based in: Angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEi/ARB), dihydropyridine calcium channel blockers (DHP-CCB), beta blockers (BB) and vasodilators/others. Associations (adjusted hazard ratio, $_{95\%\ LCL}$ aHR $_{95\%\ UCL}$) of AHM regimen 7-12 months post-transplant with patient and graft survival over 5 years were quantified by multivariate Cox regression with adjustment for recipient, donor and transplant factors, and clustering for center.

Results: The most common AHM post-transplant was DHP-CCB, followed by BB, ACEi/ARB, and diuretics. Regimen patterns varied by transplant centers (**Fig 1**). In bi-level hierarchical modeling, compared to DHP-CCB-based treatment, ACEi/ARB use was more common in those with diabetes, obesity, and mTORi-based immunosuppression.

Unadjusted survival varied with AHM treatment (**Fig 2**). Compared to DHP-CCB reference, adjusted mortality was higher in those on NDHP-CCB (aHR $_{1.11}1.24_{1.37)}$ and 'other' agents (aHR $_{1.11}1.24_{1.37}$, but lower in those on ACEi/ARB (aHR $_{1.44}1.69_{1.99}$).

Conclusions: While associations may in part reflect unobserved selection factors, controlled studies are needed to determine optimal AHM regimens after KTx, reduce unjustified practice variation, and inform evidence-based best practices.

Funding: NIDDK Support



TH-PO430

Effect of Vitamin D Repletion on Cardiorenal Biomarkers and Vascular Function in a High-Risk African American Cohort

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Background: African Americans (AAs) suffer disproportionately from cardiovascular disease and chronic kidney disease (CKD), and eighty percent of AAs are vitamin D deficient. The effects of vitamin D on vascular and renal health in patients with CKD have been contradictory in part due to different study designs. We previously showed that vitamin D repletion significantly decreased markers of inflammation and oxidative stress in a high-risk cohort of AAs with controlled hypertension and preserved renal function. In this study, we examined the effect of vitamin D on c-terminal fibroblast growth factor-23 (cFGF23), plasminogen activator inhibitor-1 (PAI-1), and vascular and renal function in a subset of the cohort.

Methods: We performed a randomized, placebo-controlled study of high-risk AAs (N=65) with vitamin D deficiency treated with 100,000 IU vitamin D3 or placebo every 4 weeks for 12 weeks. We measured eGFR (MDRD) albumin-to-creatinine ratio (ACR), and quantified plasma cardiorenal biomarkers (cFGF23 and PAI-1 by ELISA) and determinants of vascular function (pulse wave velocity, augmentation index, ambulatory systolic and diastolic blood pressure). We performed multiple regression analysis controlling for the placebo-treated group to understand the relationship between FGF23 and PAI-1 with cardiovascular and renal risk factors.

Results: Vitamin D3 levels increased (p<0.0001) and iPTH levels decreased (p=0.0060) with vitamin D3 repletion. There was no change in systolic/diastolic blood pressure and no correlation between vitamin D3 repletion and levels of cFGF23 or PAI-1. However, logPAI-1 was associated with improved augmentation index (p=0.045) and a trend for improved ACR (p=0.074), and reduced PAI-1 levels were associated with improved eGFR (p<0.0300). There was a trend for reduced FGF23 with improved augmentation index (p=0.078); and for logcFGF23 with improved pulse wave velocity (p<0.069).

Conclusions: Vitamin D3 repletion may modulate vascular and renal function in AAs with controlled hypertension and vitamin D3 deficiency. Further study may provide a better understanding of the genetic predisposition of vitamin D repletion on vascular and renal function in high-risk AAs with vitamin D deficiency.

Funding: Other NIH Support - NIMHD

TH-PO431

Clinical Factors Associated with Choice of Oral P2Y12 Inhibitors (P2Y) in Chronic Dialysis

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Background: Due to systematic exclusion of patients on chronic dialysis in P2Y clinical trials, risk factors associated with their choice remain unknown.

Methods: Using U.S. Renal Data System data, we identified dialysis patients who received new P2Y prescriptions, and analyzed trends in P2Y use and clinical risk factors associated with their choice using regression models.

Results: From 2011 to 2014, 36,590 ESRD patients received P2Y (95% clopidogrel, 3% prasugrel and 2% ticagrelor) with a proportional decrease in clopidogrel use, no change in prasugrel use and a proportional increase in ticagrelor use (p-for trend <0.0001, 0.61 and <0.0001). Median age was 64.0 years, 18% were ≥75 years, 54% men, 36% African American, 19% Hispanic and 93% on hemodialysis. History of atherosclerotic heart disease (ASHD) and thrombotic cardiovascular (CV) events were associated with choice of ticagrelor over clopidogrel [adjusted OR 5.43 (3.23, 9.15) and 2.13 (1.73, 2.62)] and prasugrel over clopidogrel [10.24 (6.66, 15.74) and 1.88 (1.63, 2.16)]. Severity of comorbidities and presence of diabetes mellitus were not associated with P2Y choice. Of the clinical events occuring 90-days prior to the index date of P2Y, percutaneous coronary intervention was the strongest independent factor favoring ticagrelor over others, adjusted OR 10.21 (8.09, 12.89) and 1.75 (1.32, 2.30).

Conclusions: Ticagrelor has gained popularity while prasugrel use remained unchanged in dialysis patients. In the absence of outcomes data in dialysis patients, clinicians favored use of ticagrelor over other P2Ys when patients had history of ASHD or CV events or were undergoing coronary revascularization. These findings suggest presence of channeling bias in prescribing P2Y to this patient population.

Funding: Private Foundation Support

Figure 1

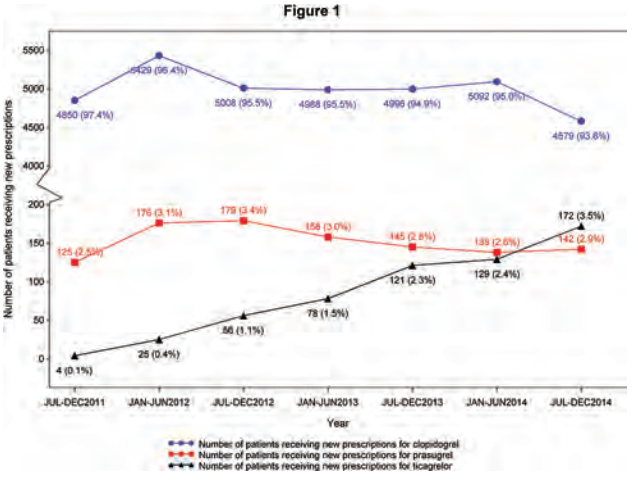

Figure showing semiannual trend in dialysis patients receiving new prescriptions for P2Y from July 2011 to December 2014

TH-PO432

48-Hour Ambulatory BP (ABPM) Monitoring and the Estimated Risk of Death in the Hemodialysis Population: A Multicenter, International Study

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Background: ABPM extended to 44h or 48h has been proposed by consensus documents by the ASN and the ESH and the ERA-EDTA (EURECAm) as the ideal metric for estimating the BP-related health burden in ESRD but information on the relationship between this metric and the risk of death is still restricted to a limited number of single center studies.

Methods: We investigated the relationship between 48h ABPM and the probability of death as estimated by the ARO risk score in a cohort of 278 hemodialysis patients in 7 centers in 3 European countries. The ARO risk score is a well-validated instrument based on 14 risk factors for death specific to the hemodialysis population (KI 87, 996–1008, 2015).

Results: Average 48h diastolic BP robustly correlated in an inverse fashion with the estimated risk of death at 1 year (r=-0.350, P<0.001) and at 2 years (r=-0.331, P<0.001) and these associations were confirmed in separate analyses of day-time and night-time average values (P<0.001). Furthermore, 48h pulse pressure was a direct predictor of the estimated death risk at 1 year (r=0.330, P<0.001) and at 2 years (r=0.293, P<0.001) and again this metric predicted the estimated risk of death in separate analyses of day and night time recordings.

Conclusions: In a multicenter study in 3 countries 48h diastolic and Pulse Pressure correlated strongly with the estimated risk of death and this was true for both average daytime and night-time values. Extended ABPM recordings reflect the health burden of BP in the hemodialysis population. *Torino C, Sarafidis PA, Ekart R, Loutradis C, Karpetas A, Raptis V, Bikos A, Papagianni A, Balafa O, Siamopoulos K, Pisani G, Morosetti M, Del Giudice A, Aucella F, Di Lullo L, Battaglia G, Tripepi R, Tripepi G, London G, Zoccali C.

TH-PO433

Ambulatory Blood Pressure Monitoring: Assessing Capacity and Practice Patterns of the Improving Renal Outcomes Collaborative (IROC)

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Background: Ambulatory Blood Pressure Monitoring (ABPM) is recommended for assessment of hypertension in patients with a kidney transplant (KTx) and/or chronic kidney disease (CKD). IROC is a multicenter learning health system comprised of patients and families, clinicians, and researchers from 23 pediatric nephrology centers, working together to improve health of patients with kidney disease.

Methods: 23 IROC centers were surveyed from July to December 2017 and asked to report the number of transplant and CKD patients under their care, their center's protocol for ABPM, ABPM unit availability vs need, ABPM return mechanism, challenges and barriers to performing ABPM.

Results: All centers responded to the survey and cumulatively care for approximately 4256 CKD and 2497 KTx patients. There were an average (std dev) of 109 (+/- 51) KTx and 224 (+/- 114) CKD patients at each center. 17 (74%) centers report intending to use the IROC protocol: yearly if last ABPM was abnormal OR every 3 years if last ABPM was normal for patients ≥ 7 years old and 1 year post-transplant. One center reported once a year screening regardless of last ABPM result. Five centers reported using other protocols. With regard to ABPM device needs, 16 (70%) of centers report a shortage of units, 1 center reports just enough units, and 6 (26%) of centers report excess units. The majority of centers (20/23, 87%) report ABPM devices are returned by the patient or through courier/postal service. The main barriers to performing ABPM per protocol are insurance approval, workflow, and shortage of ABPMs.

Conclusions: Three-quarters of IROC centers plan to use the recommended IROC ABPM protocol, however many centers report a shortage of ABPM units for the number of patients cared for. In order to decrease the negative impact of barriers to performing ABPM according to recommendations and standards, structured quality improvement is underway to optimize workflow and utilization of existing ABPM units.

TH-PO434

Magnitude of the Difference Between Clinic and ABPM BPs Predicts Mortality Risk

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Background: Ambulatory blood pressure (ABP) monitoring is recommended for the detection of masked and white coat hypertension in patients with CKD. Our objective was to determine whether the magnitude of the difference between ambulatory and clinic BP's has prognostic implications.

Methods: We examined data from 610 participants of the African American Study of Kidney Disease and Hypertension (AASK) Cohort Study, who had completed the AASK Trial and had both clinic BP and ABP performed at Cohort entry. We performed multivariable Cox proportional hazards models to determine the association between absolute systolic BP (SBP) difference between clinic and awake ABPs with death.

Results: Mean age was 61 years, 38% were female, and mean eGFR was 39. During median follow-up of 10 years, 33% died; 30% developed ESRD. The association between the clinic-awake SBP difference and risk of death is shown in Figure1 and Table1. Higher clinic-versus-awake SBP (white coat phenomenon) was associated with higher mortality risk compared to 0-5mm Hg clinic-awake SBP difference. A ≤ -5 mmHg lower clinic-versus-awake SBP (masked phenomenon) was also associated with higher mortality. Additonal adjustment for clinic SBP or ambulatory SBP did not change these findings.

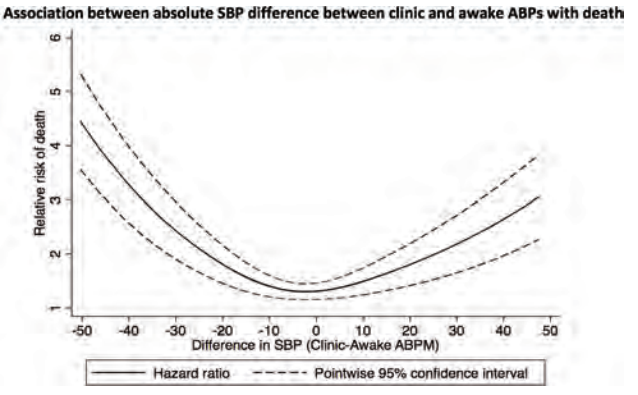
Conclusions: Our data revealed a U-shaped, independent association between the magnitude of the difference between clinic and ambulatory SBP and mortality in black patients with CKD. Further studies are needed to examine whether interventions to lower clinic-ABP differences will improve patient outcomes.

Funding: NIDDK Support

Difference between clinic and mean awake ABP and long-term risk of death

Absolute SBP difference between clinic BP and awake ABP	N	Unadjusted Model	Adjusted Model*
"White Coat Effect"			
≥ 10 mm Hg	104	2.30 (1.27-4.18)	2.31 (1.27-4.22)
5 to <10 mm Hg	58	2.07 (1.07-4.02)	1.84 (0.94-3.56)
0 to <5 mm Hg	77	Reference	Reference
"Masked Effect"			
-5 to <0 mm Hg	91	1.04 (0.54-2.02)	1.15 (0.59-2.24)
≤ -5 mm Hg	280	1.82 (1.06-3.13)	1.82 (1.05-3.15)

*Adjusted for age, sex, heart disease, proteinuria, and eGFR at entry



TH-PO435

Office Blood Pressure Measurement (OBPM) in Children: The SPA Project

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Background: If blood pressure (BP) measurement still remains challenging in adults, it is even more in children. Current guidelines suggest to measure office BP with three readings and average them when the first BP is elevated otherwise to perform only one BP reading (AAP 2017) or to measure BP 3 times every 3 min using the average of the last two (ESH 2016).

Methods: Since 2010, we regularly perform unattended multiple OBPM (mOBPM) with a validated (OMRON M3) device: after 5 min rest, at least 10 automated readings are taken every 3 min on the non-dominant arm. Readings <5th or >95th centile and mOBPM with coefficient of variation (CV)>15% are discarded.

Results: 286 healthy, non-obese children (141 females; median BMI 15.4 Kg/m2 IQR 14.5-16.4), median age 5.7 (IQR 5.3-6.1) years, were analyzed. The median CVs of included mOBPMs were 7% (IQR 5-9) for systolic and 4% (IQR 3-6) for diastolic BP. The readings #1-10 were compared with the mean of all 10 measurements (Wilcoxon matched-paired-signed-rank-test, significance assigned at $p<0.01$). The first 3 measurements were significantly different from the mean, while the readings #4-10 were not. Based on the mean, only 11 subjects had a systolic or diastolic BP >90th centile (n=5 >95th c.le) while single measurement significantly over-estimated high BP (Fig.1).

Conclusions: Although most guidelines advice ≥2 BP readings, these findings suggest that mOBPM should include ideally 10, but at least 4 repeated measurements.

Acknowledgements:F.Argirò,P.Bardelli,A.Bianchi,T.Bollani,M.Bonvissuto,G.Bosetti,R.Cambria,G.Capobianco,G.Casani,G.Catanese,C.Cauda,P.Cinquepalmi,S.Coletta,E.Dardi,A.Daverio,M.DiPietro,L.Filippucci,A.Fornaro,S.Francario,V.Gandini,S.Genoni,L.Loguercio,A.Manolo,P.Marchetto,R.Marinello,L.Martignoni,A.Mezzopane,A.Monolo,M.Morelli,M.Musetti,S.Paparone,G.Pastorelli,M.Picca,C.Poletti,M.Scarazatti,L.Simionato,A.Spalla,F.Tel,V.Valdambrini,M.Vinciguerra.

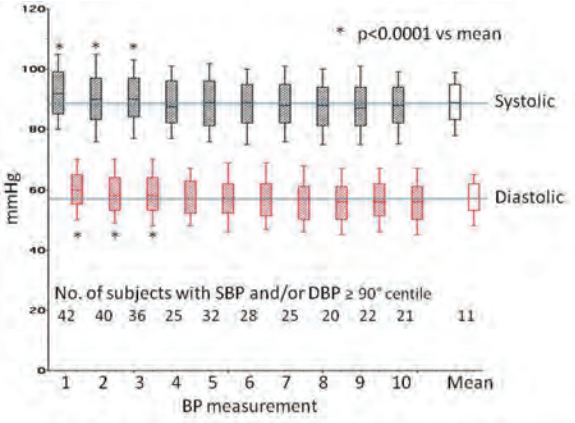

Figure 1: mOBPM in 286 children. Differences between each BP reading and the mean of all 10 measurements (blue line) are depicted.

TH-PO436

Multiple Spot Urine Sampling Is More Precise, Accurate, and Simpler Compared to 24-Hours Collection for Estimating Sodium Excretion

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Background: The estimate of Sodium (Na) intake is of important for monitoring hypertensive patients on Na restriction. 24 hours urinary collection (24-hrsUC) is inaccurate because of errors in time and/or volume measuring. In addition, the urinary collection is unpractical and often done during weekends thus is not representative of the usual Na intake. Since spot urine sampling (SUS) is not affected by any of the above mentioned sources of error, we hypothesized that the mean urinary Sodium-to-urinary Creatinine ratio (uNa-to-uCrR) of multiple SUS, collected in different days, is more precise and accurate for estimating the average Na excretion compared to 24-hrsUC.

Methods: A total of 301 urine samples (1 for each voiding) and the related 52 24-hrsUC performed in different days in 10 heathy subjects (age range 3-65, 6 females, up to 11 voidings per day) were collected. For the purpose of comparison, uNa excretion in mEq/Kg/day from each sample was derived multiplying by 2 each uNa-to-uCrR (the mean conversion constant obtained from all ratios as determined from 24-hrsUCs). We calculated Lin's correlation coefficient, mean bias, and 95% limits of agreement (LOA), of uNa for: 1) The single 24-hrsUC, using the individual overall 24-hrsUC average as reference; 2) 1000 random samples of means of 4 spot urine samples (1 per subject in 4 different days) using the individual overall 24-hrsUC average as reference. Statistical analysis was performed using Stata 15.

Results: 1) The single 24-hrs-UC urine collections showed a Lin's coefficient of 0.78, with 95% limits of agreement (LOA) of +1.39 mq/Kg/die (difference between upper and lower LOA: 2.78). 2) In the 1000 random samples the average Lin's coefficient was 0.82. Difference between upper and lower LOA was smaller than 2.78 in 58.2% of samples.

Conclusions: Sodium excretion can be estimated, on average, more precisely, accurately and practically, as the mean of 4 uNa-to-uCrR in different days, then with a single 24-hrsUC. In details the mean of 4 spot samples (expressed as mean ((uNa-to-uCr) x 2) will provide a more reliable estimate (in mEq/kg/day) in as many as 58% of determinations.

TH-PO437

Evaluating Blood Pressure Control in a VA Renal Clinic: A Performance Improvement (PI) Initiative

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Background: The suboptimal control of hypertension in adult Americans highlights a major need for performance improvement activities at the practice level to achieve better blood pressure (BP) control and meet national benchmarks. We evaluated factors associated with poor BP control among hypertensives referred to our Veterans Administration Renal Clinic with the goal of defining potential correctable characteristics of the persistently hypertensive patient. This abstract presents the data of our baseline assessment - the essential first step in a PI initiative.

Methods: *Study cohort*: Veterans followed at the Renal Clinic in September 2017, including new consults and follow-up appointments. *Site:* VA Health Care System, Minneapolis, Minnesota *Study Type:* Retrospective, as a part of PI initiative *Methodology*: Manual review of medical records beginning September 2017. Patient follow-up: 3 months *Data recorded*: Demography, co-morbidities and medications control of BP defined by JNC 8 guidelines as a core clinical metric, unless a different goal was documented by the provider. *Statistics*: Chi-square analysis for unadjusted comparisons of patients by BP control and logistic regression for odds ratio (OR) calculations.

Results: A total of 105 veterans were included in the final study cohort. Compared to those not achieving goal BP (n = 55), those achieving BP goal (n = 50) had an average BP of 129/75 mmHg (vs. 151/82 mmHg) with a mean age of 68.2 years (vs. 69.8 years). The average medication number was 3.1 (vs. 2.4). Those not achieving BP goal during follow-up period were less likely to receive any intervention (43.6% vs. 68%; OR 0.36) and more likely to remain uncontrolled on subsequent clinic follow up (81.8% vs. 40%; OR 6.67). No significant differences by comorbidity or individual provider were observed.

Conclusions: Veterans not achieving BP goals in Renal Clinic were less likely to receive any intervention, a finding that did not vary by comorbidity. This data signifies a preliminary step to design future quality improvement interventions to identify high-risk groups and direct efforts to improve our population-level cardiovascular outcomes.

TH-PO438

What New Guideline Brought to Turkish Hypertension Profile?

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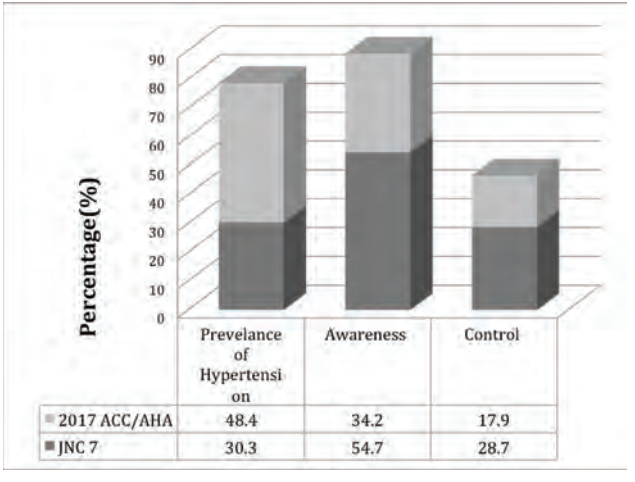
Background: 2017 ACC/AHA guideline lowered the numbers for the diagnosis of HT to 130/80 mmHg for adult population with the aim for the early diagnosis of life threatening complications of HT such as heart attack and/ or stroke. Turkey is a developing Euroasian country with the population of 82 million and has dominance of relatively younger age. Although, young population is predominating, cardiovascular disease is still major public health concern in Turkey. In 2003, the first large sample sized (n=4910) epidemiological study (PatenT study) showed the prevalence of HT as 31.8% in Turkey. After nine years, PatenT 2 trial showed prevalence of hypertension as 30.3 %.This study aimed to determine to assess current epidemiology of hypertension including, prevalence, awareness and control rates among Turkish adults, using criteria from the 2017 ACC/AHA guideline and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).

Methods: We analyzed data from PatenT 2 study (n= 5437). Blood pressure measurements were performed three times and awareness and treatment were assessed by self-reporting and control was defined as SBP/DBP less than 140/90 mmHg.

Results: According to the 2017 ACC/AHA and JNC7 guidelines, the crude prevalence of hypertension among Turkish adults was 48.4% and 30.3%, respectively and the awareness rate of the hypertension diagnosis was 34.2 % and 54.7 %, respectively. The control rate in hypertensives was 28.7 % according to the JNC 7, 17.9 % according to the 2017 ACC/AHA guideline.

Conclusions: Compared with the JNC7 guideline, the 2017 ACC/ AHA guideline results in a considerable increase in the prevalence of hypertension and substantial decrease in control rates and awareness of hypertension in Turkish adults.

Funding: Private Foundation Support



TH-PO439

New Guidelines Shift Prevalence of Elevated Blood Pressure (BP) Among US Adults Both with and Without CKD

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Background: In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) published guidelines that redefine criteria for hypertension (HTN) using a lower threshold of BP. We sought to determine the number of individuals reclassified as having HTN by prior treatment with antihypertensive medication (Rx) and presence or absence of CKD.

Methods: We used National Health and Nutrition Examination Survey data (1999-2014) to estimate the total number of non-pregnant adults aged ≥20 years who would have been reclassified from having pre-HTN (systolic BP [SBP] 120-139 mmHg) per the 2003 Seventh Report of the Joint National Committee (JNC7) BP guidelines to having elevated BP (SBP 120-129 mmHg) or stage 1 HTN (SBP 130-139 mmHg) per 2017 ACC/AHA definitions. BP measures were averaged from three readings taken during medical examination, and medication use was obtained from the household interview. We further examined the number of people with and without CKD having HTN status reclassified. CKD was defined as having an estimated glomerular filtration rate (eGFR) between 15-59 ml/min/1.73m^2 or eGFR ≥60 mL/min/1.73m^2 with urine albumin to creatinine ratio ≥30 mg/g.

Results: About two-thirds of people initially defined as having pre-HTN in the JNC7 were reclassified to stage 1 HTN according to the ACC/AHA guidelines. The proportion was similar among individuals with and without CKD; among those receiving and not receiving pharmacologic treatment for HTN; and over time. This represents approximately one-quarter to one-third of all adults with CKD (28 M; 16 M on Rx) or without CKD (173 M; 36 M on Rx).

Conclusions: According to the latest guidelines, during the period 1999-2014, a large proportion of people would have been reclassified from pre-HTN to stage 1 HTN. In addition, these results suggest that the new guidelines may stimulate intensification of therapy for individuals already being treated for HTN, whether or not they have CKD.

Funding: Other U.S. Government Support

Pre-HTN Reclassified by New BP Guideline n (% of 201M U.S. adults)

Survey Years	Treated with Rx		Not Treated with Rx	
1999-2014	Elevated BP	Stage 1 HTN	Elevated BP	Stage 1 HTN
CKD	2 M (14.7)	4 M (28.5)	2 M (14.5)	4 M (29.5)
No CKD	6 M (17.6)	12 M (34.2)	22 M (15.9)	32 M (23.1)

M=million

TH-PO440

Applying the New Intensive Blood Pressure Categories to Non-Dialysis CKD Population from PATRIOTIC Survey

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Background: The 2017 high blood pressure clinical practice guideline reported by the American College of Cardiology/American Heart Association put forward new categories of blood pressure (BP). This study aimed to assess the applicability of the new guideline in non-dialysis chronic kidney disease (CKD) population.

Methods: This is a nationwide, multicenter, cross-sectional study with a large sample. A total of 8927 non-dialysis CKD patients in 61 tertiary hospitals in all 31 provinces, municipalities, and autonomous regions of China (except Hong Kong, Macao, and Taiwan) were analyzed. The categories of BP were defined as normal BP (<120/80 mmHg), elevated BP (systolic BP 120–130 mmHg and diastolic BP <80 mmHg), and stages 1 (systolic BP 130–139 mmHg or diastolic BP 80–89 mmHg) and stage 2 (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) hypertension. The prevalence and control of hypertension were estimated using a new definition, and the association between the main target organs' injury and new categories of BP was analyzed.

Results: The prevalence, awareness, and treatment of hypertension in non-dialysis CKD patients were 79.8%, 72.4%, and 68.3%, respectively. Approximately 11.9% had BP <130/80 mmHg, and 6.6% had BP <120/80 mmHg. Subgroups via categories of BP had significant difference in age, sex, body mass index (BMI) categories, primary causes, and CKD stages (P <0.001). After multivariable adjustment, only stage 2 hypertension was associated with decreased renal function (odds ratio [OR] 2.4, 95% confidence interval [CI] 1.9–3.0, P<0.001), cardiovascular disease (OR 2.0, 95% CI 1.3–3.1, P=0.001), and cerebrovascular disease (OR 2.7, 95% CI 1.2–5.8, P=0.015).

Conclusions: Using the new definition of hypertension, the higher prevalence and lower control of hypertension were shown in non-dialysis CKD participants. More studies are necessary to confirm the applicability of new categories of BP in CKD population because only stage 2 hypertension showed statistical association with the main target organs' injury.

TH-PO441

Screening and Management of Albuminuria in a Large Integrated Health System

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Background: Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend albuminuria screening in patients with hypertension or diabetes for appropriate risk stratification. Little is known about factors associated with adherence to KDIGO-recommended treatment goals for patients with albuminuria.

Methods: We used data from 212,068 adults ≥ 18 years of age with eGFR ≥ 15 ml/min/1.73m^2, who were seen by a primary care provider between 2015-2016 in a large, integrated health system. Patients were categorized as having severely increased albuminuria per KDIGO guidelines (ACR 300+ mg/g, PCR 500+ mg/g, or urine dipstick 1+), using quantitative tests if available. We then examined associations between sociodemographic and clinical factors with attainment of KDIGO-recommended goals [renin-angiotensin-aldosterone system (RAAS) inhibition, blood pressure (BP) goal <130/80, and statin treatment] in patients with severely increased albuminuria.

Results: Mean age was 55.2 years, 55.7% were female, 19% were current smokers, and 13.0% had baseline eGFR < 60 ml/min/1.73m^2. Among 87193 patients with hypertension, 70.5% were screened using any method, 41.3% were screened with ACR or PCR, and 9.9% had severely increased albuminuria. Among 33655 patients with diabetes, 91.3% were screened using any method, 82.9% were screened with ACR or PCR, and 10.4% had severely increased albuminuria. Of the 22153 patients with 1+ or greater protein on dipstick, only 40.2% also completed an ACR or PCR. Adherence to KDIGO-recommended goals was low in severely albuminuric patients (30.8% taking RAAS inhibitors, 33.8% taking statins, 48.2% with clinic BP <130/80); only 7.8% achieved all 3 goals. Factors associated with attainment of all 3 KDIGO-recommended goals in severely albuminuric patients included older age, cardiovascular risk factors, cardiovascular disease, and quantitative protein testing (Table). CKD was not associated with attainment of these goals.

Conclusions: Adherence to KDIGO guidelines for albuminuria remains suboptimal. Future research is needed to improve screening and management of albuminuria.

Funding: NIDDK Support

Factors associated with Achievement of KDIGO-recommended Goals (RAAS inhibition, statins, clinic BP < 130/80) in 17,121 patients with severely increased albuminuria

	Adjusted odds ratio (95% confidence interval)	p-value
Male	1.11 (0.98-1.25)	0.10
Age 60 years or older	1.58 (1.36-1.84)	<0.01
Current or former smoker (compared to never smoker)	1.14 (1.00-1.29)	0.04
Hypertension	4.39 (3.49-5.52)	<0.01
Diabetes	1.45 (1.24-1.70)	<0.01
Dyslipidemia	4.77 (3.83-5.93)	<0.01
Myocardial infarction	1.53 (1.24-1.88)	<0.01
Stroke	1.25 (1.05-1.49)	0.01
Congestive heart failure	1.21 (1.03-1.43)	0.02
eGFR less than 60 ml/min/1.73 m^2 at baseline	1.04 (0.88-1.22)	0.43
Any protein quantification (ACR or PCR)	1.21 (1.03-1.42)	0.02

TH-PO442

CKD Screening Rate and Blood Pressure (BP) Control in Veterans with Hypertension

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Background: Hypertension (HTN) control is a key strategy to prevent CKD progression. Earlier recognition of CKD (by eGFR and albuminuria) and volume optimization using diuretics are important to achieve adequate BP control. Prevalence of CKD is a third higher in Veterans; however, CKD screening rate in hypertensive Veterans, HTN control and utilization of diuretics in Veterans with CKD is unclear.

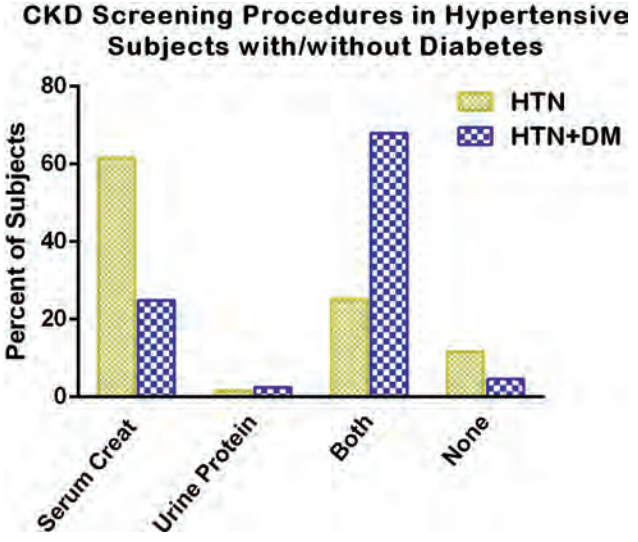
Methods: We analyzed Veterans Integrated Service Network corporate Data Warehouse for Veterans seen at least twice in primary clinics with ICD-9 codes for HTN and diabetes. The Final cohort of 241,235 subjects was examined for serum creatinine/eGFR reported at least twice 90 days apart, urine protein and ICD-9 for CKD. BP readings from last two clinic visits were averaged to evaluate the HTN control.

Results: Ten percent of final cohort did not have any CKD screening procedures. Figure 1 shows the percentage of hypertensive subjects with (N=92,129) or without diabetes (N=128,099) with available serum creatinine or urine protein measurements or both. CKD (eGFR<60 ml/min and/or ACR>30mg/g) was present in 27.2% subjects but only 6% had CKD ICD-9 code in the chart. Table 1 demonstrates the HTN control and baseline characteristics in these 27.2% subjects.

Conclusions: While hypertensive Veterans get eGFR checked, identification of albuminuria is suboptimal and despite screening procedures the recognition of CKD is low. Only one third CKD Veterans had BP <130/80 mmHg and 29% were on diuretics. These results warrant exploration of factors responsible for these low rates and design interventions to address those factors to improve HTN control.

Funding: Veterans Affairs Support

	BP<130/80 mmHg N=22013 (37.5%)	BP 130-140/80-90 mmHg N=17839 (30.4%)	BP>140/90 mmHg N=18915 (32.2%)	p value
SBP/DBP mmHg	118.02 ± 9.38/66.13 ± 7.30	133.71 ± 4.7/74.28 ± 8.13	153.00 ± 12.46/79.78 ± 10.53	
Age (Yr)	70.46 ± 11.00	68.51 ± 11.19	68.91 ± 11.38	<.001
Race (%):	–	–	–	
Hispanic	10.3	11.6	12.3	
Black	29.8	19.7	23	<.001
White	59.24	64.3	49.8	
Asian	0.17	0.17	0.21	
Medications (%):	–	–	–	
ACEI/ARB	62.8	64.8	69.7	
Diuretics	32.6	25.1	29.7	
Beta Blocker	51.0	45.7	51.5	<.001
CaCh Blocker	34	51.4	63.4	
Alpha Blocker	17.9	17.9	15.5	
Others	7.49	12.2	21.8	



TH-PO443

Prediction Model for Cardiovascular Death Including Proteinuria and Estimated Glomerular Filtration Rate in a General Population

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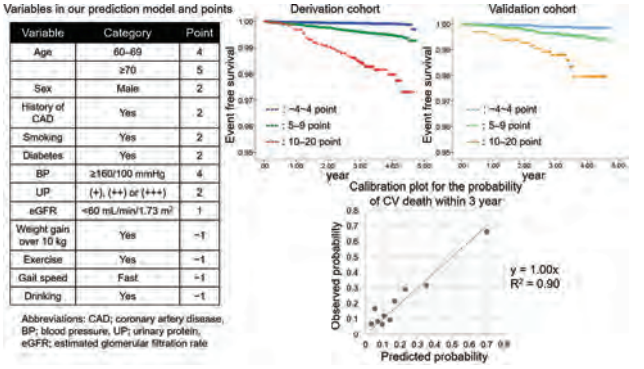
Background: There are several prediction models for coronary or cardiovascular (CV) events, some of which include estimated glomerular filtration rate (eGFR). However, there has been no prediction model for CV death that includes proteinuria and eGFR.

Methods: This was a longitudinal cohort study. Inclusion criteria was subjects aged 40–74 years in a Japanese nationwide Specific Health Checkup database in 2008. Exclusion criteria were subjects with missing data. The exposures of interest were demographics, comorbidities, blood pressure, laboratory data, and lifestyle factors. Outcome variable was CV death. Subjects were randomly assigned to derivation and validation cohorts by 2:1 ratio. Points for prediction model were determined based on regression coefficients derived from the Cox proportional hazards model in the derivation cohort. The model was validated by Kaplan-Meier curves and calibration plot in the validation cohort.

Results: Among 295,297 subjects, data for 120,823 were available for analysis (80,549 and 40,274 in the derivation and validation cohorts, respectively). During a mean follow-up of 3.6 years, there were 204 and 106 CV deaths in the derivation and validation cohorts, respectively. Proteinuria and eGFR were significantly associated with CV death and were included in the model. Other variables included in our prediction model were shown in the figure. Kaplan-Meier curves of 3 risk groups defined by points in the prediction model were matched between the derivation and the validation cohorts, and calibration plot was well calibrated ($y = 1.00x$, $R^2 = 0.90$).

Conclusions: Our prediction model for CV death including proteinuria and eGFR was well calibrated. External validation in another cohort is required before clinical use.



TH-PO444

Prevalence of Cardiovascular Risk Factors and Association with CKD in sub-Saharan Africa

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Background: Cardiovascular disease (CVD) risk factors are also risk factors for initiation and progression of CKD. The epidemiology of CVD risk factors and their associations with CKD have not been defined in a well-characterized cohort of patients with CKD in sub-Saharan Africa which may differ from high income countries.

Methods: We studied 919 patients with CKD from diabetes, hypertension, sickle cell disease, HIV, and unknown causes compared with 3504 healthy participants with no CKD from the H3Africa Kidney Disease Research Network. We determined the prevalence of self-reported hypertension, diabetes, smoking, and dyslipidaemia in sub-Saharan African population, and their relationship with CKD risk. Multivariate logistic regression method was used to determine association between the risk factors and CKD.

Results: The mean age was 45.7±15.5years and 59.4%% were females. Patients with CKD were older (48.9±15.8years) than the control participants (45.6±14.9years), p=0.001; they have lower BMI (25.3±5.4kg/m^2 versus 26.4±6.1kg/m^2, p=0.001), lower hemoglobin, (11.3±2.1g/dL versus 13.3±1.7g/dL, p=0.001) and higher Albumin-Creatinine Ratio (65.1±37.6mg/g versus 6.2±4.1mg/g, p=0.001). Compared with the control participants, patients with CKD have higher prevalence of hypertension (68.87% versus 31.44%, p=0.001); diabetes (28.61% versus 18.46%, p=0.001), dyslipidaemia (11.42% versus 5.96%, p=0.001); and smoking (7.39% versus 3.11%, p=0.001). Table 1 shows the odds of each CVD risk factor and having CKD.

Conclusions: Traditional CVD risk factors are prevalent and consistently associated with CKD especially hypertension in middle aged adults in sub-Saharan Africa. Prevention and optimal treatment of these risk factors may reduce CKD progression in sub-Saharan Africa.

Funding: Other NIH Support - National Human Genome Research Institute (1U54-HG006939-01)

Table 1: Association of self-reported cardiovascular risk factors with CKD in Sub-Saharan Africa

CVD risk factors	Unadjusted Odd ratio (95% CI)	*Adjusted Odd ratio (95% CI)	P value
Hypertension	4.74 (4.04-5.57)	5.18 (4.34-6.19)	0.001
Diabetes	1.47 (1.44-2.02)	1.47 (1.22-1.76)	0.001
Dyslipidemia	1.99 (1.55-2.54)	2.12 (1.62-2.74)	0.001
Smoking	2.39 (1.74-3.25)	1.51 (1.09-2.10)	0.001
Age	1.01 (1.01-1.02)	1.01 (1.00-1.01)	0.052

*Each CVD risk factor was adjusted for others

TH-PO445

Arterial Stiffness and Kidney Function Decline in SPRINT

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Background: Arterial stiffness increases with advancing age and chronic kidney disease. Arterial stiffness may contribute to a decline in kidney function; however, evidence is inconsistent. We hypothesized that greater baseline arterial stiffness was independently associated with rapid decline in kidney function over the longitudinal follow-up period in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: 538 adults who participated in an ancillary study of SPRINT which measured arterial stiffness (aortic pulse-wave velocity [aPWV]) were included in this analysis. Multivariable logistic regression was used to examine the association between baseline aPWV and rapid decline in kidney function (estimated glomerular filtration [eGFR] decline >3 ml/min/1.73m^2/yr) over the follow-up period (median of 3.7 yrs).

Results: Mean age was 72±3 years with a mean baseline aPWV of 10.6±2.6 m/sec and eGFR of 67±21 ml/min/1.73 m^2. 109 participants had rapid decline in renal function over the follow-up period. After adjustment demographics, randomization group, co-morbid conditions, smoking, body-mass index, estimated glomerular filtration rate, urinary albumin to creatinine ratio, antihypertensive medications, systolic blood pressure, and heart rate, baseline aPWV was not associated with increased odds of rapid decline in kidney function (OR: 1.03, 95% CI: 0.93-1.13 per unit increase in aPWV). In the fully adjusted model, baseline aPWV above the median also did not associate with rapid decline in kidney function (OR: 0.92, 95% CI: 0.56-1.51).

Conclusions: Among adults at high risk for cardiovascular events, greater arterial stiffness is not associated with rapid decline in kidney function.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA

TH-PO446

Plasma Sodium Is Associated with Arterial Stiffness in SPRINT

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Background: High dietary sodium may induce small yet physiologically relevant increases in plasma sodium concentrations, which associates with increased systolic blood pressure. Cellular data suggests this is mediated by increased endothelial cell stiffnes, as measured by atomic force microscopy. We hypothesized that higher plasma sodium levels were associated with greater arterial stiffness in participants in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: 8,004 adults who participated in SPRINT were included in the analysis of the association of plasma sodium level with pulse pressure (PP), a surrogate measure of arterial stiffness. 542 adults who participated in an ancillary study of SPRINT which measured aortic pulse-wave velocity (aPWV) were included in the analysis of the association of plasma sodium with aPWV. Multivariable linear regression was used to examine the association between baseline plasma sodium levels and a) PP and b) aPWV.

Results: Mean age was 68±9 years with a mean serum sodium level of 140±3 mmol/L. In the PP analysis, after adjustment for demographics, randomization group, co-morbid conditions, smoking, body-mass index, estimated glomerular filtration rate, urinary albumin to creatinine ratio, antihypertensive medications, and heart rate, higher plasma sodium was associated with increased baseline PP (tertile 3 [≥141 mmol] vs. tertile 2 [139-141 mmol]; β: 1.11, 95% CI: 0.49-1.73). In the ancillary study, higher plasma sodium was associated with increased baseline aPWV in the unadjusted analysis (tertile 3 vs. tertile 2; β: 0.53, 95% CI: 0.02-1.03). However, in the fully adjusted model, this association was no longer significant (β: 0.39, 95% CI: -0.10-0.88).

Conclusions: Among adults at high risk for cardiovascular events, higher plasma sodium was independently associated with baseline arterial stiffness as measured by PP, but not by aPWV. The latter analysis may have been limited in power due to a smaller samples size.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA

TH-PO447

Impact of Cardiovascular Events on Mortality and Decline of Renal Function in Patients with CKD

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Background: CVEs are common and significant complications amongst patients with CKD. The association of CKD and CVE is well publicised. However, the impact of CVE on subsequent kidney survival is not well described. We aimed to study the impact of new cardiovascular events (CVE) on mortality and deterioration of kidney function in a prevalent chronic kidney disease (CKD) patient cohort.

Methods: A retrospective cohort study of 1,123 patients of a tertiary teaching hospital, registered in the CKD.QLD registry between January 2011 and August 2017 and with a minimum of 2 years follow up time. CVE data (ischaemic heart disease (IHD), stroke and peripheral vascular disease (PVD)), renal function (eGFR CKD-EPI) and mortality events were extracted from integrated medical records. Subjects who progressed to end stage kidney disease were imputed an eGFR 8mL/min/1.73m^2 at the date of kidney replacement therapy (KRT). Delta eGFR (mL/min/1.73 m^2/year, (CKD-EPI)was calculated as the difference between latest eGFR compared to at time of incident CVE.

Results: 222 patients had at least one incident CVE which included IHD (n=144), stroke (n=51) or PVD (n=40). CVE events had a significant ($p<0.05$) impact on mortality, even after adjusting for age, gender and/or history of prior IHD, stroke and/or PVD. Kaplan-Meier analysis showed survival was reduced by 700 days (2867 (SE=67) vs 2167 (SE=61)) in the CVE cohort ($p<0.01$). There was no significant change in the absolute mean delta eGFR in subjects with and without CVE, adjusted for age (2.6mL/min/1.73 m^2/year (SE=0.4) vs 1.7mL/min/1.73 m^2/year (SE=0.2); p=0.2). Nor was there a significant different in progression to KRT, adjusting for age, gender and previous IHD, stroke and PVD (CVE 11.5% vs no CVE 10.4%; p=0.6).

Conclusions: New cardiovascular events are a flag for premature mortality in the CKD cohort as they are for the general population. However, patients with the shortest survival could have been excluded due to the exclusion criteria of the study. Moreover, incident CVE do not seem to have a significant association with accelerated progression of renal dysfunction or transition to KRT in CKD patients.

TH-PO448

Association of Blood Pressure with Urinary Sodium, Potassium, and Sodium/Potassium Ratio in CKD - The French CKD-REIN Cohort Study

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Background: The urinary sodium-to-potassium ratio (uNa/K) has been repeatedly shown to be more closely linked to blood pressure (BP) than urinary sodium or potassium excretion alone, both in general population and in patients with arterial hypertension. Whether this is also true for patients with CKD is unknown.

Methods: We assessed associations of BP with spot urine sodium/creatinine (uNa/Cr), potassium/creatinine (uK/Cr), and uNa/K in 1658 patients with CKD stages 3 or 4 under nephrology care. We used the mean of 2 office BP readings for analyses. Urinary Na, K, and creatinine concentrations were measured in second-void urine samples and expressed in mmol/L. Associations of BP with uNa/Cr, uK/Cr, and uNa/K modeled by 4-knot splines were assessed using generalized linear models adjusted for age, gender, eGFR, albuminuria, diabetes, heart failure, dyslipidemia, body mass index, and number of antihypertensive drugs.

Results: Median (IQR) age was 68 (59-76) years; most patients were men (65.3%), had CKD stage 3 (54.9%), and albuminuria (71.7%). Mean systolic (SBP) and diastolic (DBP) BP were 141 and 78 mm Hg, respectively. More than 90% of the patients had a history of arterial hypertension, and only 34% among them had controlled BP <140/90 mmHg. Median (IQR) uNa/Cr, uK/Cr, and uNa/K were 11.6 (7.9-16.3), 5.3 (4.1-7.0), and 2.2 (1.5-3.1), respectively. Spot uNa/Cr and uNa/K were positively associated with SBP (p 0.004 for both urinary indices) and with pulse pressure (p 0.002 and 0.019, respectively). The mean difference (β) in SBP between the highest and the lowest quartile (Q4-Q1) was 4.48 (95%CI 1.81-7.16) mmHg for uNa/Cr and 4.47 (95%CI 1.91-7.03) mmHg for uNa/K. Spot uK/Cr was not associated with any of the BP indices. The higher the quartile of uNa/K, but not of uNa/Cr, the higher the likelihood of uncontrolled (p 0.066) or apparently treatment resistant hypertension (p 0.033).

Conclusions: The positive association of urinary sodium, but not potassium, excretion with SBP and pulse pressure suggests a predominant role of sodium intake in determining BP level in many patients with CKD stages 3-4. In contrast with the general population, spot uNa/K does not appear to be more informative than uNa/Cr in such patients.

TH-PO449

Renal Impairment Modifies the Association Between Sodium Intake and Risk of Stroke – An Analysis of INTERSTROKE

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Background: Stroke is the second most common cause of death and the third most common cause of disability worldwide (1). Excess sodium intake, and renal impairment, are associated with an increased risk of stroke. We performed an analysis of the INTERSTROKE case-control study to investigate the relationship between estimated urinary sodium excretion (used as a surrogate for intake) and stroke.

Methods: INTERSTROKE was a standardized international case-control study that recruited 26,919 participants in 32 countries (2). We included participants with urine samples collected and measurement of spot urine sodium, potassium, and creatinine. 24-hour urinary sodium excretion was estimated using the Kawasaki, Intersalt, and Tanaka equations (7–9). Multivariable unconditional logistic regression was performed to compare the risk of stroke across four quartiles (<3.2 g/day, 3.2–4.4 g/day, 4.4–5.8 g/day, >5.8 g/day) of estimated 24-hour urinary sodium excretion using 3.2–4.4g/day as the reference quartile, as this was the category with lowest risk.

Results: Of the 26,945 participants, 13,483 were cases and 13,462 were controls. 23,258 participants had urine collected and processed. Mean eGFR (CKD-EPI) was 79.83 (23.49) ml/min/1.73m^2. Mean 24-hour estimated sodium excretion was 3.56 (1.95) g/day

for cases and 3.43 (1.56) g/day for controls (p<0.001). After adjustment for age, sex, hypertension, diabetes, ethnicity, and region, <3.2 g/day (OR 1.38 [1.28-1.48]) and >5.8 g/day (OR 1.67 [1.55-1.79]) of sodium excretion were both associated with increased odds of stroke (ischaemic stroke and intracerebral hemorrhage). 4.4 – 5.8 g/day was not significant (OR 1.05 [0.97-1.13]). The pattern of association across quartiles was consistent with 24-hour sodium excretion estimated with Intersalt and Tanaka equations. The magnitude of association increases across each CKD stage (Table 1).

Conclusions: Our data report that renal function amplifies the association of sodium intake with stroke, and suggest that moderate stroke intake is associated with lowest stroke risk in all stages of renal impairment.

Risk of stroke by 24hr estimated sodium excretion (Tanaka) and CKD stage (CKD-EPI)				
CKD Stage (Participants)	24 hr Estimated Sodium Excretion (Tanaka)			
	<3.2 g/day	3.2–4.4 g/day	4.4–5.8 g/day	>5.8 g/day
>90 (7690)	1.36 [1.18-1.56]	Ref.	0.94 [0.82-1.07]	1.76 [1.55-2.00]
60-90 (9098)	1.32 [1.18-1.49]	Ref.	1.14 [1.02-1.29]	1.72 [1.52-1.94]
45-60 (2772)	1.45 [1.18-1.78]	Ref.	1.31 [1.06-1.63]	1.78 [1.41-2.25]
30-45 (1079)	1.31 [0.94-1.83]	Ref.	1.45 [0.97-2.15]	2.45 [1.64-3.69]
<30 (482)	1.66 [0.96-2.88]	Ref.	2.10 [1.08-4.17]	2.45 [1.28-4.78]

TH-PO450

Age, Tissue Sodium, and Blood Pressure Associations in Healthy, Hypertensive, and Hemodialysis Subjects

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Background: Sodium magnetic resonance imaging (^{23}Na MRI) can non-invasively quantify sodium (Na) concentrations in tissues such as the skin and muscle. However, previous tissue Na studies in healthy subjects and hemodialysis patients reported only one lower leg concentration. We used ^{23}Na MRI to quantify tissue Na in the anterior (AT) and posterior (PT) muscle regions of the leg in healthy, hypertensive (HTN), and HD subjects. We also examined group differences in tissue Na concentrations and the association of tissue Na to age and blood pressure (BP).

Methods: We recruited 22 subjects (45±18 years, 26.0±3.7 kg/m^2, 50% male, 64% white, 50% HTN, 27% HD) from the University of Illinois and a dialysis clinic in central Illinois. ^{23}Na MRI was performed on a Siemens TIM Trio/Prisma II 3T system (birdcage head coil). We conducted ^{23}Na MRI region of interest (ROI) analysis in a double-randomized and blinded manner for tissue Na concentrations. We also collected height, weight, and standardized BP.

Results: Across groups, Na concentration was significantly different (p<0.05) and lower in AT compared to PT (AT 18.6±5.1 mM, PT 26.0±4.9 mM; p< 0.05). PT Na was correlated both with age (R=0.64, p<0.01) and SBP (R=0.57, p<0.01). AT Na was also correlated with age (R=0.68, p<0.01), SBP (R=0.70, p<0.01), and with PT Na (R=0.62, p<0.01). Regression analysis demonstrated a significant relation between both age and SBP with both AT Na and PT Na (Table 1).

Conclusions: Na concentration in the calf differs depending on the site of quantification, with AT having a lower concentration than PT. This was a consistent finding across subject groups, despite differing Na concentrations by group. AT and PT are correlated with each other as well as age and SBP. Lower leg Na concentrations could differ due to muscle fiber type differences or because the AT region is smaller muscle group, thus more difficult to quantify than the PT region.

Age and BP Regression by Tissue Sodium

	Model A: AT Tissue Na, mM			Model B: PT Tissue Na, mM		
	Beta	P-value	Adj. R^2	Beta	P-value	Adj. R^2
Model 1:						
Age, years	0.18	<.01	0.43	0.16	<.01	0.40
Model 2:						
BP, mmHg	0.16	<.01	0.46	0.13	<.01	0.29

TH-PO451

Estimating the Association Between Urinary Cadmium and Hypertension: Bias Introduced by Missing Data on Renal Function

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Background: Cadmium exposure is associated with hypertension and ultimately all-cause mortality. Reduced renal function leads to decreased urinary cadmium excretion, and is aside from smoking an important confounder of the causal relationship of urinary cadmium and hypertension. The current project aimed to demonstrate an easily applicable method to overcome missing data to establish an unbiased association between urinary cadmium and hypertension in a large U.S. cohort of postmenopausal women sampled between 1993-1998.

Methods: Data were derived from the Women's health Initiative. Filtered urinary cadmium was measured by Inductively Coupled Mass Spectrometry and normalized to urine creatinine (μg/g). Hypertension was defined as a systolic blood pressure (SBP) >140 mmHg or a diastolic BP (DBP) > 90 mmHg or use of antihypertensive medication. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. We estimated the odds of having hypertension in relation to log-transformed urinary cadmium adjusted for age, ethnicity/race, education, U.S. region, smoking, body mass index, and anemia (hemoglobin<12g/dL). Because of 76% missing data on eGFR, we performed analysis (1) unadjusted for eGFR, (2) adjusted for eGFR but restricted to a complete sample, and (3) adjusted for eGFR with imputed eGFR values. We performed multiple imputation (SAS 9.4. Proc MI) using a Monte-Carlo-Chain method (100 iterations) and estimated variance with Rubin's formula.

Results: In 1460 women aged 63(±7) years, the mean urinary cadmium was 0.61(±46)μg/g and 44% had hypertension. Eight percent were current, 37% were past, and 54% were never smokers. The unadjusted odds ratio (OR) for prevalent hypertension was 0.84 (95% CI 0.73 – 0.96). The OR for model 1 was 0.92 (95% CI 0.78-1.07), whereas in model 2 restricted to complete sample on eGFR OR was 0.63 (95% CI 0.42-0.94). After imputation for eGFR (model 3), the OR was 0.91 (95% CI 0.77-1.07), which is similar to estimates obtained in model 1. Assumptions of missing out of randomness and normal distribution were met for the imputation.

Conclusions: Our example demonstrates that using a study sample without missing data may provide biased estimates of association, and imputation of important confounders and covariates can be used if missing is random.

Funding: Other NIH Support - NIEHS

TH-PO452

Relationship Between Ankle Brachial Blood Index (ABI) and Cardiac Ankle Vascular Index (CAVI) and Prognosis in Maintenance Hemodialysis Patients

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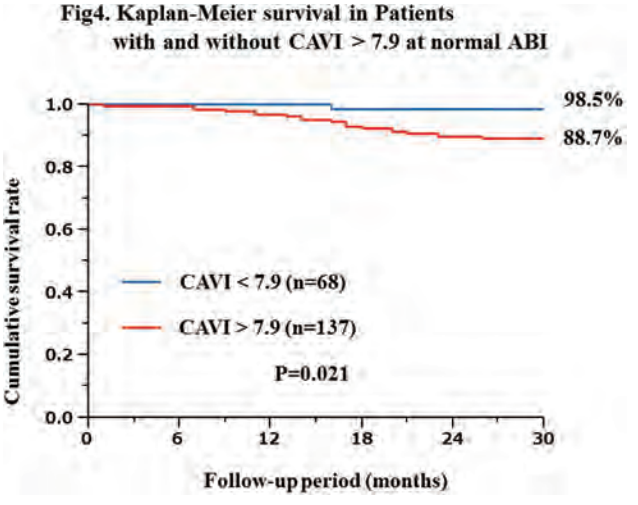
Background: Ankle brachial blood index (ABI) and cardiac ankle vascular index (CAVI) are both indicators of systemic atherosclerosis. We investigate the relationship between ABI and CAVI in maintenance hemodialysis patients and their prognosis.

Methods: We measured ABI and CAVI for 297 patients undergoing maintenance hemodialysis treatment at Masuko memorial hospital. The cut-off value of CAVI was calculated by ROC analysis.

Results: During the observation period (median 28 months), 47 cases (15.8%) died. In 2-year survival rate, the ABI abnormal group (<0.9, n = 92) was significantly lower than in the normal group (> 0.9, n = 205) (67.7% vs. 92.6%, p <0.0001, adjusted hazard ratio 2.18). There was no difference in the survival rate between the CAVI abnormal group (> 9.0, n = 91) and the normal group (<9.0, n = 114) in the ABI normal group (91.1% vs. 93.6%, p = 0.74). However, when a new cut-off value (7.9) by ROC analysis was used, 2-year survival rate in the CAVI abnormality group (n = 137) was significantly lower than that in the normal group (n = 68) (88.7% vs. 98.5%, p = 0.021).

Conclusions: CAVI as a prognostic indicator should have a lower Cut-off value in maintenance hemodialysis patients with increased arteriosclerosis than the Cut-off value used by general population. In addition, it was suggested that even with normal ABI patients, it is possible to stratify prognostic risk by measuring CAVI.



TH-PO453

Clinical Features of Dialysis Patients at Risk of Lower Limb Amputation

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Background: Dialysis patients are at elevated risk for peripheral artery disease (PAD), lower extremity ulcers, and lower limb amputations (LLA) (Garimella et al, 2017). As part

of a quality improvement project for the current foot check process, a large dialysis provider piloted a Limb Preservation Project (LPP) capturing clinical features of patients' limbs at risk for amputation to streamline processes for specialist referral. We analyzed what features were more common in patients with LLA.

Methods: LPP was deployed at 9 dialysis clinics during Sept 2017 to Jan 2018. Dialysis clinics received a monthly list of patients considered high risk for foot ulcer who then received screening for dermatologic, mechanical and vascular changes in lower extremities.

Results: Among 571 patients considered high risk, there were 458 remarkable features documented. In those without a prior amputation (n=496), there were 356 features documented, and for those with a prior amputation (n=75), 102 were features documented. Patients with a prior amputation most frequently had bandaged wound on their non-amputated limb (23.53%), an open wound/ulcer on their amputated limb (18.63%), and abnormal nails (11.76%). Patients without a prior amputation most frequently had abnormal nails (36.25%), skin cracks/fissures (16.01%), and a bandaged wound (10.11%).

Conclusions: Results suggest that regardless of amputation status, the presence of abnormal nails and bandaged wounds may be a common clinical feature in dialysis patients at risk of lower extremity vascular disease.

Figure 1: Clinical Features	# of Features for Patients without Amputation	% of Features for Patients without Amputation	# of Features for Patients with Amputation	% of Features for Patients with Amputation	Odds Ratio
Skin cracks/fissures on amputated limb(s)	0	0.00%	9	8.82%	0
Vascular insufficiency with skin and/or temperature changes on amputated limb(s)	0	0.00%	6	5.88%	0
Open wound/ulcer on amputated limb(s)	0	0.00%	19	18.63%	0
Abnormal nails/nail care needed	130	36.52%	12	11.76%	3.11
Poorly fitting shoes	4	1.12%	0	0.00%	Infinity
Skin cracks/fissures	57	16.01%	10	9.80%	1.64
Change in foot/leg skin color	34	9.55%	6	5.88%	1.62
Temperature difference between calves and feet or between the left and right foot	17	4.78%	3	2.94%	1.62
Vascular-related pain on walking/claudication	25	7.02%	0	0.00%	Infinity
Open wound/ulcer	35	9.83%	11	10.78%	0.91
Red, hot, swollen midfoot or ankle	5	1.40%	1	0.98%	1.42
Dry or wet gangrene	6	1.69%	1	0.98%	1.72
Inflammation over a corn, callus, bunion, hammertoe or bony prominence	7	1.97%	0	0.00%	Infinity
Bandage/dressing in place over an active wound	36	10.11%	24	23.53%	0.43

TH-PO454

Interarm Difference in Blood Pressure: Prevalence, Risk Factors, and Relevance for Diagnosis of Disease of the Aorta Among Patients Referred to Specialized Regional Hypertension Center

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Background: Initial evaluation of hypertension (HTN) should include assessment of blood pressure (BP) in both arms. The prevalence of high interarm BP difference ranges from 3% in the general adult population to about 10% in the patients with HTN. However, we lack proper estimates of its prevalence, and existing practice of follow up for these patients in a referred population.

Methods: We performed a retrospective chart review of all prevalent patients followed at the Hypertension Center at the Ottawa Hospital. BP data from the first visit were used for assessment for interarm BP difference. We considered interarm difference in either systolic or diastolic BP in excess of 10 mmHg for casual BP by mercury sphygmomanometry to be clinically significant.

Results: 493 patients of 580 patients were included in this study based on available data. The prevalence of clinically significant interarm difference in systolic or diastolic BP was 16.2% and was similar among men and women. These patients were more likely to be smokers (current or previous; 53.5% vs 36.8%) with peripheral arterial disease (PAD, 15% vs 8%). None of these patients had undergone further investigations of ascending aorta/aortic arch.

Conclusions: A significant proportion of referred patients have a high interarm difference in systolic or diastolic BP. No clinical investigations were ordered to evaluate for ascending aorta/aortic arch disease reflecting the physicians' lack of understanding of its clinical relevance. The association with smoking and PAD suggests underlying aortic/large vessel disease as a potential mechanism in some patients.

Demographics	All patients in Hypertension clinic included in study	Patients with interarm SBP or DBP difference ≥10mmg	Patients without interarm SBP or DBP difference ≥10mmg
Total N	493	80 (16.2%)	413 (83.8%)
Men	256 (51.9%)	40 (50.0%)	216 (52.3%)
Age	59.39 ± 16.81	61.23 ± 15.54	59.04 ± 17.04
BMI	31.0 ± 10.8	32.1 ± 21.4	30.8 ± 7.2
Waist Circumference	104.5 ± 17.2 cm	104.5 ± 16.9 cm	104.5 ± 17.2 cm
Smoking status:			
Current smokers	119 (24.1%)	10 (12.5%)	109 (26.4%)
Ex-smokers	76 (18.4%)	33 (41.3%)	43 (10.4%)
Diabetes mellitus:			
T1DM	5 (1.0%)	0 (0%)	5 (6.3%)
T2DM	144 (29.2%)	20 (25%)	124 (30.0%)
CAD	71 (14.4%)	13 (16.2%)	58 (14.0%)
PVD	48 (9.7%)	12 (15.0%)	36 (8.7%)
CVD	53 (10.8%)	6 (7.5%)	47 (11.4%)
A.fib	23 (4.7%)	3 (3.8%)	20 (4.8%)
CHF	18 (3.7%)	2 (2.5%)	16 (3.9%)
Systemic inflammatory disease	32 (6.5%)	6 (7.5%)	26 (6.3%)
Creatinine	95.9 ± 37.1	97.7 ± 38.8	95.5 ± 36.8
LDL	2.53 ± 1.10	2.27 ± 1.05	2.58 ± 1.10
Proteinuria	192 (38.9%)	32 (40%)	160 (38.7%)
Hypertension meds:	2.85 ± 1.50	2.81 ± 1.41	2.85 ± 1.52
Thiazide diuretic	254 (51.5%)	40 (50.0%)	214 (51.8%)
ACEI	207 (42.0%)	27 (33.8%)	180 (43.6%)
ARB	180 (36.5%)	37 (46.3%)	143 (34.6%)
Long-acting CCB	318 (64.5%)	53 (66.3%)	265 (64.2%)
Alpha blocker	45 (9.1%)	5 (6.3%)	40 (9.7%)
K-sparing diuretic	64 (13.0%)	5 (6.3%)	59 (14.3%)
Beta blocker	229 (46.5%)	33 (41.3%)	196 (47.5%)
Loop diuretic	37 (7.5%)	4 (5.0%)	33 (8.0%)
Other	77 (15.6%)	23 (28.8%)	54 (13.1%)
Lipid lowering therapy	247 (50.1%)	41 (51.3%)	206 (49.9%)

All figures as mean ± standard deviation or N (%)

TH-PO455

Association of Vascular Calcification with Brain Atrophy in Patients with CKD: Cross-Sectional and Longitudinal Analyses

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Background: It has been reported that brain atrophy (BA) progresses rapidly in chronic kidney disease (CKD) patients, especially in patients on hemodialysis (HD). We previously demonstrated that BA progressed more rapidly in patients on peritoneal dialysis (PD) compared with patients with non-dialysis dependent CKD (ND) (Tsuruya K, et al. AJKD, 2015). Vascular calcification (VC) has been considered to be an independent risk factor for cardiovascular disease including cerebrovascular disease; however, it remains unclear whether VC affects BA. Thus, we examined the association between VC and BA by cross-sectional and longitudinal analyses among CKD patients.

Methods: In the present study, 157 CKD (90 ND, 42 PD, and 25 HD) patients aged 62 (mean) ± 10 (SD) years (men 91, diabetes 46) were recruited and underwent MRI scanning at baseline and after two years. T1-weighted MRI images were analyzed with statistical parametric mapping software. Total gray matter (GM), total white matter (WM), and cerebrospinal fluid (CSF) were segmented and each volume was quantified using MRI voxel-based morphometry. GM ratio (GMR), calculated by normalization of GM volume to intracranial volume determined by summation of GM, WM, and CSF volume, and annual reduction rate of GMR (ARR-GMR) were used to evaluate BA. At baseline, all participants underwent multidetector computed tomography to assess coronary artery calcification score (CACS) and the values were transformed into the square root values (SR-CACS) to reduce the skewed distribution. We examined the associations of SR-CACS with GMR and ARR-GMR using multiple regression analysis.

Results: The mean GMR significantly decreased from 40.0% at baseline to 39.2% after 2 years, and the mean ARR-GMR was 0.38 percentage-point. SR-CACS was significantly negatively associated with GMR and positively associated with ARR-GMR. The association with GMR remained significant even after adjustment for age, sex, diabetes, systolic blood pressure, hemoglobin, dialysis status (ND, PD, or HD), current smoking, and regular drinking (Model-1), and the association with ARR-GMR also remained significant even after adjustment for Model-1 and baseline GMR (Model-2).

Conclusions: CACS was significantly associated with rapid progression of BA in CKD patients. This study suggests that VC might affect BA.

TH-PO456

Prevalence of Abdominal Aortic Calcifications in CKD Patients in the Arabian Gulf Region

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Background: Abdominal aortic calcification (AAC) is an important risk factor for cardiovascular disease (CVD). CVD is the commones complication of chronic kidney disease (CKD). In the Arabian Gulf, few studies were conducted on CKD patients. Aim was to determine AAC prevalence in dialysis and non-dialysis CKD patients and determine relevant predictive factors.

Methods: We performed a multi-center, multi-national chart review of 546 adult CKD patients who have had a plain abdominal x-ray within 6 months prior to study entry. We collected data about patients' demographics, CKD stage, medical history and comorbidities, lipid profile, current medications and reviewed X-rays for AAC presence.

Results: A total of 544 CKD patients were eligible for analysis including 325 (59.7%) dialysis patients and 219 (40.3%) non-dialysis patients. 290 (53.3%) patients were males and 369 (67.8%) were diabetics. Mean age was 57.98 years (SD ± 15.39). Table 1 describes the distribution of patients according to CKD stage and AAC prevalence in each stage. Overall, AAC was reported in 203 (37.3%, 95% CI=33.2%: 41.4%) patients. AAC prevalence among dialysis patients (126 patients, 38.8%) did not differ significantly from that among non-dialysis patients (77 patients, 35.2%) (p=0.393). Higher risk of AAC development was associated with age, as mean age for AAC group was 66 for non AAC group was 53 (p< 0.001); diabetes, as 45.3% of diabetics developed AAC, compared to 20.6% of non-diabetics developing AAC (p< 0.001), with diabetic patients 2.1 times more likely to have AAC than non-diabetic patients; and longer dialysis vintage, which was 1.92 years in AAC group compared to 1.18 years in non AAC group (p= 0.003). Gender, hypertension and CVD had no associations with AAC.

Conclusions: Our study shows that AAC is present in more than one third of CKD patients in the Arabian Gulf. Risk is higher with older age, diabetes, and longer dialysis vintage.

Funding: Commercial Support - Sanofi

AAC Prevalence

CKD Stage	Number of patients	Patients with AAC
Non Dialysis	219 40.3% of all	77 35.2% of non dialysis
CKD 2	29 13.2% % of non dialysis	5 17.2% % of Corresponding CKD stage
CKD 3	81 37%	33 40.7%
CKD 4	45 24.7%	22 40.7%
CKD 5	55 25.1%	17 30.9%
Dialysis	325 59.7% of total	126 38.8% of all dialysis
Total	544	203 37.3% of total

TH-PO457

Thyroid Status and Coronary Artery Calcification in a Prospective Hemodialysis Cohort

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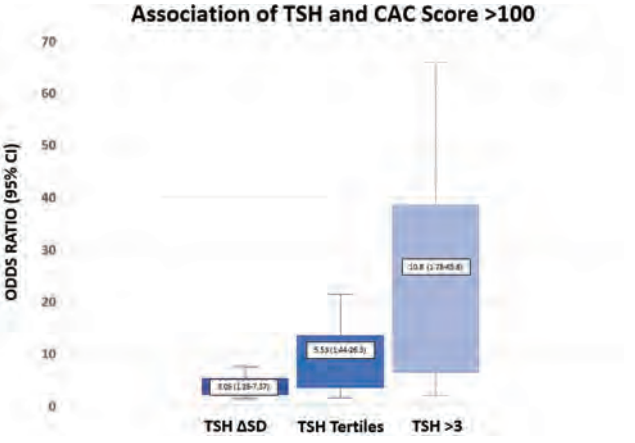
Background: In the general population, hypothyroidism is a known risk factor for coronary heart disease (CHD) and death. Experimental data suggest that low levels of circulating thyroid hormone (e.g., triiodothyronine [T3]) are causally associated with vascular calcification via downregulation of matrix Gla and klotho (i.e., vascular calcification inhibitors), and human studies suggest that low T3 levels are associated with higher risk of coronary artery calcification (CAC). However, little is known about the association of thyroid status, defined by serum thyrotropin (TSH) as the most sensitive and specific biochemical metric of thyroid function, with risk of CAC in the hemodialysis population.

Methods: In a secondary analysis of 104 patients from the Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID) trial, we examined the association of serum TSH levels with total Agatston CAC score. Cross-sectional associations of thyroid status with CAC score (total Agatston score >100, threshold for which moderate non-obstructive coronary artery disease highly likely) were estimated using logistic regression models adjusted for age, sex, and race.

Results: We observed that increasingly higher increments of serum TSH (defined as change in 1 standard deviation = 1.9mIU/L) were associated with a 3-fold higher risk of higher CAC score: OR (95%CI) 3.05 (1.26-7.37). When categorized as tertiles, the highest TSH tertile was also associated with a higher risk of higher CAC burden (ref: lowest tertile): OR (95%CI) 5.53 (1.44-26.3). Similarly TSH levels >3mIU/L were associated with a higher risk of higher CAC score (ref: ≤3mIU/L): OR (95%CI) 10.82 (1.78-65.8).

Conclusions: These data indicate that higher serum TSH levels are associated with higher risk of CAC in hemodialysis patients. Further studies are needed to determine of thyroid hormone supplementation ameliorates CHD burden in this population.

Funding: NIDDK Support



TH-PO458

Repeat Intravascular Ultrasound Guided Renal Artery Angioplasty in a Patient with Fibromuscular Dysplasia

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Introduction: Fibromuscular dysplasia (FMD) is one of the etiologies of renal artery stenosis (RAS) and secondary hypertension. Balloon angioplasty has emerged is emerging as a mainsstay of treatment in patients with FMD usually show substantial clinical response to renal angioplasty without stenting.

Case Description: We report a case of 32 -year-old male case of secondary hypertension from RAS due to with repeat intravascular ultrasound guided renal artery angioplasty. Her blood pressure (BP) was 165/95 with heart rate of 89 bts/min on presentation with chronic headaches. Her physcial exam was within normal limits. Labs revealed sodium of 138, potassium of 4.6, chloride of 97 and bicarbonate of 23 mmol/l respectively. BUN was 13 and creatinine was 0.87 mg/dl respectively. Secondary hypertension workup was negative except borderline elevated renin level. Doppler renal ultrasound showed increased velocity in the proximal portion of left renal artery concerning for left RAS. Patient's medications were adjusted including maximum dose of lisinopril without improvement in home blood pressure readings. Renal angiography was performed which revealed classic beaded appearance of bilateral renal artery showing FMD. Therefore, percutaneous transluminal angioplasty of bilateral renal arteries was performed. BP improved temporarily for a month after the procedure but slowly started to go up with average BP being 150's systolic and 100's diastolic. Doppler renal ultrasound showed increased velocities in bilateral renal arteries. Therefore percutaneous transluminal angioplasty of bilateral renal arteries was performed again. BP improved after the second balloon angioplasty and was now sustained. 3 months after follow up her BP improved to systolic 110-120 and diastolic of 70-80 mm hg without requiring any antihypertensives.

Discussion: This is the only case reported in medical literature to the best of our knowledge where repeat balloon angioplasty was attempted with successful and sustained BP control. Through this case we propose that repeat intravascular ultrasound guided renal artery angioplasty can be considered in patients with bilateral RAS due to FMD in whom the first attempt fails to control BP without stent placement. Further studies are needed to study the long term benefits of this procedure on BP control and kidney function.

TH-PO459

Impact of Ageing and Cardiovascular Risk Factors on Retinal Neurodegeneration Assessed by Spectral-Domain Optical Coherence Tomography

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Background: Spectral-domain optical coherence tomography (SD-OCT) has become a reliable imaging technique for the evaluation of retinal layer volumes. The aim of this study is to characterize age-related neuroretinal alterations and thereby identify risk factors for the process of retinal ageing.

Methods: This was a prospective observational single center study including 62 healthy subjects–25 young (aged<40 years) and 37 elderly healthy individuals (aged≥40 years). Macular retinal layer volumes of both eyes were evaluated by SD-OCT, comprising total retinal volume and each layer separately.

Results: In the group of young subjects (12 females/13 males, aged 25.1±3.5years) fasting plasma glucose (FPG) and HbA1c were significantly lower than in elderly subjects (28 females/9 males, aged 58.2±10years). There were no significant differences in systolic (SBP) and diastolic blood pressure (DBP). Gender-adjusted retinal layer volumes of both eyes including total retinal, RNFL, ganglion cell layer (GCL), inner plexiform layer (IPL), GCL-IPL, inner retinal layer (IRL, comprising RNFL, GCL-IPL) and outer nuclear layer

(ONL) volume were lower in the group of elderly subjects compared to young individuals. Additionally, partial correlation analysis revealed a significant negative correlation between retinal layer volumes and age (r range: -0.633 to -0.272, p range: <0.001-0.032), SBP (r range: -0.319 to -0.266, p range: 0.014-0.036), DBP (r range: -0.386 to -0.275, p range: 0.004-0.035), FPG (r range: -0.448 to -0.297, p range: 0.001-0.036) and HbA1c (r range: -0.433 to -0.286, p range: 0.002-0.044).

Conclusions: In this study, we detected significant differences in retinal layer volumes indicating age-related retinal neurodegenerative processes and identified risk factors for retinal ageing such as hypertension and a dysregulated glucose metabolism.

Retinal layer volumes

Retinal layer volume [mm^3]	Young subjects Right eye / left eye	Elderly subjects Right eye / left eye	Gender-adjusted p value Right eye / left eye
Total retina	8.86±0.40 / 8.80±0.37	8.47±0.35 / 8.46±0.35	< 0.001 / 0.001
Retinal nerve fiber layer (RNFL)	1.00±0.14 / 0.93±0.08	0.91±0.11 / 0.86±0.12	0.007 / 0.005
Ganglion cell layer (GCL)	1.14±0.07 / 1.13±0.07	1.04±0.07 /1.04±0.09	< 0.001
Inner plexiform layer (IPL)	0.91±0.06 / 0.92±0.05	0.80±0.06 / 0.88±0.07	0.007 / 0.003
GCL-IPL	2.05±0.13 / 2.05±0.12	1.92±0.13 / 1.91±0.16	< 0.001
Inner retinal layer	6.59±0.30 / 6.56±0.33	6.23±0.31 / 6.20±0.33	< 0.001
Outer nuclear layer	1.81±0.25 / 1.83±0.24	1.65±0.19 / 1.68±0.18	0.020 / 0.018

TH-PO460

Serum Magnesium Levels and Subsequent Risk of Peripheral Artery Disease

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Background: Hypomagnesemia has been associated with increased risk of several cardiovascular phenotypes presumably through its interaction with calcium and phosphate, but its relation to peripheral artery disease (PAD) is not well established. Magnesium (Mg) homeostasis is tightly regulated by the kidney, and thus the relationship between Mg and PAD may be weaker in CKD.

Methods: Using data from the Atherosclerosis Risk in Communities (ARIC) Study, we investigated the association of serum Mg with incident PAD in 14,293 participants free of prevalent PAD at baseline (mean age 54.6 years [SD 5.7], 26.2% black, 1.2% with GFR<60 mL/min/1.73m^2, 9.5% with DM). We used multivariable Cox models to quantify the association of Mg (< vs. ≥ the median value of 1.6 mEq/L) with incident PAD accounting for potential confounders. We further evaluated these associations, stratified by GFR above and below 60 mL/min/1.73m^2.

Results: Over a median follow-up time of 25.9 years, a total of 620 cases of incident PAD were observed. In fully adjusted models, the association between higher Mg and PAD was significant (HR=0.80, 95% CI: 0.67 – 0.95) (Table). Modeled continuously, the risk of PAD decreased significantly with every 0.1 mEq/L increase in Mg (HR 0.49, 95% CI: 0.30 – 0.82). In stratified analysis, this association persisted for participants with GFR above 60 mL/min/1.73m^2 but not for those with GFR<60. The interaction between Mg and GFR for PAD risk was significant (p=0.01). Among other electrolytes, higher calcium trended towards lower risk of PAD (HR=0.86, 95% CI: 0.72 – 1.01).

Conclusions: Higher serum Mg is independently associated with a lower hazard of incident PAD, though this association was not seen in individuals with reduced GFR. Our results suggest potential contribution of low serum Mg levels in the development of PAD independent of other calcium-phosphate metabolism.

Funding: Other NIH Support - The project described was supported by Grant Number T32 HL007024 from the National Heart, Lung, and Blood Institute, National Institutes of Health

Multivariable Cox Proportional Hazards Models for Incident PAD

	OVERALL (N=14,293)		GFR<60 (N=167)		GFR≥60 (N=14,126)	
Variable	HR	P	HR	P	HR	P
Serum Mg	0.80 (0.67, 0.95)	0.01	1.48 (0.65, 3.39)	0.35	0.79 (0.66, 0.94)	0.01
Serum Ca	0.86 (0.72, 1.01)	0.07	0.84 (0.33, 2.19)	0.73	0.90 (0.75, 1.07)	0.23
Serum P	1.09 (0.92, 1.29)	0.32	0.74 (0.29, 1.86)	0.53	1.09 (0.91, 1.29)	0.36

Adjusted for age, sex, race, education, smoking status, drinking status, HTN, DM, prevalent coronary heart disease, total cholesterol, HDL cholesterol, serum electrolytes (potassium, calcium, phosphate), and eGFR.

TH-PO461

Dialysis Modality and Risk of Atrial Fibrillation: A Systematic Review and Meta-Analysis

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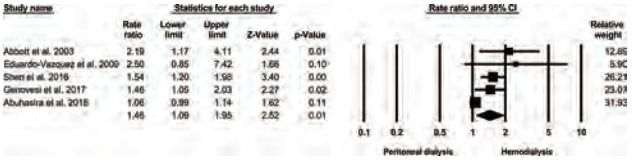
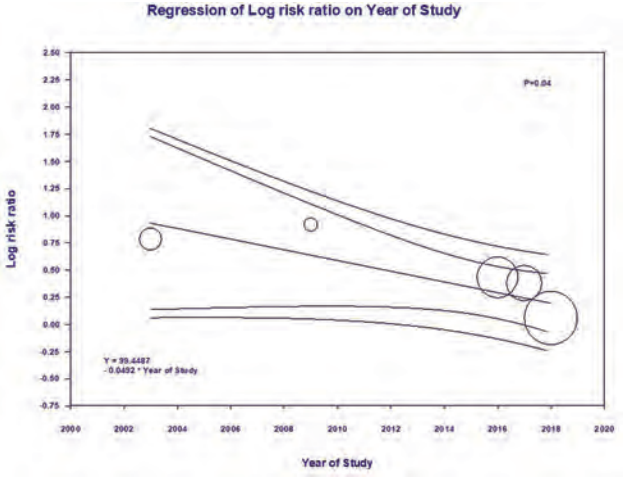
Background: Several studies have demonstrated that end- stage renal disease (ESRD) patients on dialysis are at higher risk for atrial fibrillation, which can be associated with stroke and increased mortality. However, the risk of atrial fibrillation in patients on different renal replacement modality remains unclear. We performed this meta-analysis to assess the risks of atrial fibrillation in ESRD patients on hemodialysis (HD) compared to peritoneal dialysis (PD).

Methods: A systematic review was conducted in MEDLINE, EMBASE, Cochrane databases from inception through April 2018 to identify studies that evaluated the risk of atrial fibrillation of patients on different dialysis modalities. Effect estimates from the individual study were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird.

Results: 5 observational studies with a total of 22,779 dialysis patients (19,623 on HD and 3,156 on PD) were enrolled. Compared with PD, HD was associated with significantly increased risk of atrial fibrillation with pooled rate ratio of 1.46 (95% CI, 1.09-1.95). Meta-regression showed significant negative correlations between risk of AF among HD patients and year of study (slopes = -0.049, P = 0.04).

Conclusions: HD status is associated with 46% higher risk of atrial fibrillation compared to PD. However, compared to those on PD, there are potential reductions in the risk of atrial fibrillation among ESRD patients on HD overtime.





TH-PO462

Sex Disparities in Cardiovascular Events in Incident Dialysis Patients

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Background: Cardiovascular events remains the leading cause of mortality in patients with end stage renal disease (ESRD) and the risk of cardiovascular events is 10 to 20 times higher in ESRD as compared to general population. Sex disparities in the major cardiovascular events in dialysis patients have not been studied.

Methods: We evaluated 96,729 patients who initiated dialysis between 1/1/2007 and 12/31/2008 from the United States Renal Data System with linked claims for Medicare Part A and Part B or Medicare Primary Other as the primary payer for the entire one year post dialysis initiation. Using ICD-9 codes, we identified hospitalizations for major adverse cardiovascular events (MACE), defined by unstable angina, acute myocardial infarction (MI), congestive heart failure (CHF), and stroke. Using case mix adjusted logistic regression models, we examined the impact of sex on MACE as the primary outcome.

Results: The mean age was 70±12 years. In the study cohort, 45.2% were women and 61.4% were white patients. All cause one-year mortality was 43.3%. Overall, women had higher frequency of MACE as compared to men (41.8% vs. 38.3%, p value<0.0001). Additionally, women had higher incidence of acute hospitalizations with CHF (36.7% vs. 33.1%, p value<0.0001), and stroke (5.8% vs. 4.5%, p value < 0.001) as compared to men. The frequency of unstable angina (7.3% vs. 7.5%, p value = 0.20) and acute MI (2.6% vs. 2.5%, p value = 0.26) was comparable between women and men. In the adjusted analyses, women had higher odds of MACE as compared to men (OR, 1.16; 95% CI, 1.13-1.19). As compared to men, women also had higher adjusted odds of CHF (OR, 1.17; 95% CI, 1.14-1.21) and stroke (OR, 1.28; 95% CI, 1.20-1.35). Odds of acute MI (OR, 1.08; 95% CI, 1.00-1.18) and angina (OR, 0.99; 95% CI, 0.94-1.04) did not differ significantly between men and women.

Conclusions: Women are 16% more likely to have acute hospitalizations with MACE as compared to men in the first year after incident ESRD. Additionally, women experience 17% higher rates of hospitalization with CHF and 28% higher rates of hospitalization with stroke. Further studies are needed to better delineate the factors associated with this sex disparity in the risk of MACE, and its treatment approaches.

TH-PO463

The Cut-Off Value of NT-Pro BNP to Diagnose Cardiac Insufficiency with Both Decreased and Preserved Ejection Fraction Value in Patients with Stage 3 to 5D CKD

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Background: BNP and NT-Pro-BNP are widely used in clinical work for the diagnosis of heart failure even in patients with chronic kidney disease(CKD). Previous research focused on the heart failure with decreased ejection fraction (EF). However, heart failure/ insufficiency with preserved EF occurs in a large amout CKD patients especially in the early period. This research is to explore the diagnosis cut-off value of NT-Pro BNP for cardiac insufficiency in CKD patients with stage 3 to 5D, and to analyze its probable influential factors.

Methods: CKD patients with 3 to 5D stages who were hospitalized in the department of nephrology, which belongs to an affiliated hospital of our university, from April 2016 to April 2017 were enrolled. All the patients measured plasma NT-Pro BNP and completed echocardiography within 1 month. Criteria for heart insufficiency included both the patients' symptoms, the 2013 ACCF/AHA heart failure guideline and recommendations and the American Society of Echocardiography as well. Informations of age, sex, weight, height, BMI, blood pressure, NT-ProBNP, GFR, serum electrolytes, index of echocardiography were collected. According to GFR, the patients are divided into three groups: CKD3, CKD4, CKD5 (non-dialysis, hemodialysis, and peritoneal dialysis). SPSS software is used for data analysis.

Results: (1) A total of 396 patients met our inclusion crtieria. NT-Pro BNP was negatively correlated with GFR, EF, sodium, potassium or chloride and positively correlated with E/A, LV, LA, RV, RA, IVS, LVPW, EDD, ESD, EDV, ESV and CKD stages ($p<0.05$). (2) Linear correlation analysis showed ESV, EF, ESD, EDV, E/A, NT-Pro BNP, LV, LA, E/e' correlated with heart failure; multi-factor logistic regression analysis showed that the factors affecting heart failure included E/A, ESV and NT-pro BNP. The diagnostic cut-point value of NT-pro BNP for heart insufficiency increased with the increase of CKD stage (CKD stage 3: 3654.0pg/ml; CKD stage 4: 7584.5pg/ml; CKD stage 5 non-dialysis: 9465.5pg/ml; peritoneal dialysis: 18667.5pg/ml; hemodialysis: 29362.0pg/ml).

Conclusions: NT-Pro BNP cut-off values for cardiac insufficiency should be established according to different CKD stages and considering both decreased and preserved EF value in order to improve early diagnosis and treatment of heart insufficiency.

TH-PO464

N-Terminal Pro-B-Type Natriuretic Peptide and Cardiac Troponin T for Detection of Left Ventricular Hypertrophy in Non-Dialysis CKD Patients

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Background: The mortality of cardiovascular disease (CVD) in the patients with chronic kidney disease (CKD) is significantly higher than in the general population. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT) have been shown to be powerful predictors of cardiovascular mortality. In subjects with albuminuria or impaired renal function, the use of these cardiac biomarkers has been debated. In this cross-section study, we tried to investigate whether these two biomarkers could predict left ventricular hypertrophy (LVH) in subjects with CKD patients and the prediction power of both.

Methods: A total of 1320 pre-dialysis CKD patients were recruited in this study. NT-pro-BNP and cTnT were all measured on the Roche cobas E602 (Roche Diagnostics). Left ventricular mass index (LVMI) were determined by an echocardiographic examination.

Results: Participants in high NT-proBNP group, as well as participants in high cTnT group, had a worse cardiovascular risk profile and had more LVH. Participants with high cardiac biomarkers had also more often a lower eGFR and higher proteinuria. Multivariable-adjusted association of NT-proBNP level and LVH was OR 1.233(95%CI 1.131 to 1.345) for per 1000pg/ml increase. Multivariable-adjusted association of cTnT level and LVH was OR 1.005(95%CI 1.001 to 1.010)for per 100ng/L increase. Then we identified optimal threshold value for NT-ProBNP and cTnT. The 90th percentile of NT-proBNP had moderately high positive likehood ratios for detecting LVH, 50th percentile of NT-proBNP had moderately low negtive likehood ratios for detecting LVH. The 90th percentile and 50th percentile of cTnT had optimal positive likehood ratios and negtive likehood ratios separately for detecting LVH.

Conclusions: NT-proBNP and cTnT both are independent factors associated with the echocardiographic parameters of LVH in CKD patients. The diagnostic performance of NT-proBNP is significantly superior than cTnT.

Association of NT-proBNP and cTnT with LVH

Variables	NT-proBNP(per 1000pg/ml)	cTnT(per 100ng/L)
Demographic-adjusted	1.373(1.262-1.495)**	1.014(1.009-1.020)**
Multivariate-adjusted	1.233(1.131-1.345)**	1.005(1.001-1.010)*

Data are presented as OR (95% CI).*P<0.05, **P<0.001.

Left ventricular hypertrophy was defined as LVM/height2.7 >47 g/m2.7 for women and >50 g/m2.7 for men.

TH-PO465

ADAM17 as a Predictor of CV Events in CKD Patients

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Background: Previous studies have demonstrated a positive correlation between ADAM17 and TNFα in cardiovascular (CV) disease. Increased expression of TNFα and ADAM17 has important implications in advanced cardiac dysfunction. We studied the relationship between baseline circulating ADAM17 activity, cardiovascular events and mortality in CKD patients from the NEFRONA study after 48 months of follow-up.

Methods: 2,570 patients without history of previous CV disease from the observational and multicenter NEFRONA study were divided into three groups: non-dialysis CKD stage 3-5 patients (CKD3-5, n=1,463), hemodialysis or peritoneal dialysis patients (CKD5D, n=538) and control patients (CONT, n=569). Baseline circulating ADAM17 activity was analyzed using a fluorimetric assay in plasma samples. Survival was analyzed by Kaplan-Meier curves for the following events: CV event, CV mortality, non-CV mortality and all mortality causes according to ADAM17 activity, diabetes, age, smoking and dialysis requirement. Cox regression analyses were used to identify risk factors for these events.

Results: Circulating ADAM17 activity was higher in patients with CV events and in patients with CV mortality, non-CV mortality and all-cause mortality ($p<0.05$). In the unadjusted Cox model, circulating ADAM17 activity was a risk factor for CV events, CV mortality and all-cause mortality in CKD patients. However, circulating ADAM17 was not a risk factor for non-CV mortality. In the multivariate Cox regression model, circulating ADAM17 activity, older age, male sex, diabetes and dialysis were identified as independent risk factors for CV events.

Conclusions: Higher levels of circulating ADAM17 activity correlated with a worst survival rate in patients with CV events, CV death and all mortality causes. Circulating ADAM17 activity could be an independent predictor for CV events in CKD patients without previous history of CV disease.

Funding: Government Support - Non-U.S.

CV events				
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
sADAM17 median(≥14.9)	1.89(1.38-2.59)	**0.000**	1.71(1.22-2.40)	**0.002**
Sex (male)	1.59(1.15-2.20)	**0.005**	1.53(1.10-2.12)	**0.011**
Diabetes	2.31(1.72-3.10)	**0.000**	2.15(1.58-2.91	**0.000**
Hypertension	1.01(0.84-1.22)	0.921	1.18(0.70-2.02)	0.548
Age(≥65 years)	1.75(1.29-2.37)	**0.000**	1.65(1.20-2.26)	**0.002**
CKD stages CKD3-5 Dialysis	2.69(1.98-3.67)	**0.000**	2.60(1.87-3.61)	**0.000**
Smoking	1.25(0.88-1.77)	0.205	1.30(0.91-1.86)	0.148

TH-PO466

α-Adducin Polymorphism's Influence on Ischemic Strokes

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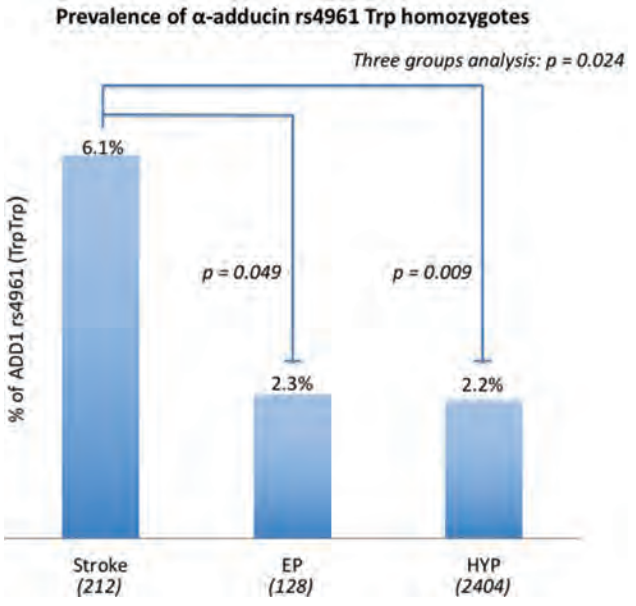
Background: rs4961 Gly460Trp variant of the alpha Adducin gene (ADD1) has been associated with renal sodium retention and salt sensitive hypertension. Previous studies indicated ADD1 Gly460Trp as associated to higher risk of cardiovascular diseases. The aim of this study is to assess whether there is a correlation between this ADD1 variant and the development of ischemic strokes

Methods: 212 patients with ischemic stroke (IS) were recruited from San Raffaele Hospital in Milan and divided into four categories according to Oxford Classification. These patients were compared to a cohort of elder general population (EGP, 128 patients) and a cohort of hypertensive patients (HYP, 2404 patients), both with no history of strokes.

Results: In IS group mean age at strokes' diagnosis was 72.34±11.9, 61% men, 39% women. The incidence of CV risk factors was: hypertension 66%, diabetes 22%, hypercholesterolemia 40% and hypertriglyceridemia 13%, previous stroke 14%, CKD 16%. Two comparable populations were selected with similar age (71.28±6.9 years for EGP) and with the same incidence of risk factors (for HYP population). Notably, the presence of subjects homozygous for ADD1 mutated allele (rs4961 TrpTrp) is more than double in patients bearing ischemic stroke than in the two others (6.1% IS vs. 2.3% EP, $p=0.049$; 6.1% IS vs. 2.2 HYP, $p = 0.009$; fig.1). There was no statistically difference among the various types of stroke.

Conclusions: These data suggest a correlation between mutated alpha-Adducin and the increased incidence of all types of ischemic stroke. No correlation was found with the other hypertension-related genes analysed (as ADD2, ADD3). rs4961 alpha-Adducin polymorphism should be considered as an independent risk factor for ischemic strokes, even if these events donot appear directly linked to hypertension. Finally, alpha-Adducin polymorphism itself might be a candidate gene in the pathogenesis of stroke.



TH-PO467

APOL1 Genotypes and Vascular and Endothelial Function in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: The *APOL1* high-risk genotypes, present in 13% of U.S. blacks, are associated with an increased risk for hypertension-attributed kidney disease. Biopsy studies show differences in kidney vasculature by *APOL1* status, but less is known about the variants' associations with systemic vascular and endothelial function.

Methods: Using a recessive genetic model, we examined the cross-sectional associations of *APOL1* risk genotypes (high=2 risk alleles; low=0-1 risk allele) with subclinical measures of vascular and endothelial function in MESA. Outcomes included measures of vascular (small and large arterial elasticity [SAE, LAE] by HDI PulseWave CR-2000 and ascending aortic distensibility [AAD] by magnetic resonance imaging) and endothelial (by brachial artery Doppler flow-mediated dilation [FMD]) function. We constructed linear regression models, adjusting for age, sex, and genetic global ancestry.

Results: We included African-American MESA participants with available *APOL1* genotyping and measurements of SAE (n=1586), LAE (n=1586), AAD (n=985), and FMD (n= 777) at Exam 1 (2000-2002). Mean age was 62 years, 54% were female, 59% had hypertension, mean systolic blood pressure was 131 ± 22 mmHg, and mean $eGFR_{CysC}$ was 90 ± 20 ml/min/1.73 m^2. Mean (SD) SAE, LAE, AAD, and FMD were 4.2 (2.5) ml/mmHg*100, 13.5 (5.8) ml/mmHg*100, 1.7 (1.3) 1/mmHg*1000, and 0.2 (0.1) mm, respectively. In linear regression models, the *APOL1* high-risk genotypes were not associated with SAE, LAE, AAD, or FMD, though there was a trend of lower AAD among *APOL1* high- vs. low-risk individuals (Table).

Conclusions: Among African Americans in MESA, the *APOL1* high-risk genotypes were not associated with subclinical measures of vascular or endothelial function. Further studies are needed to clarify the potential role of *APOL1* in vascular changes.

Funding: NIDDK Support

Table: Association of *APOL1* with subclinical measures of vascular and endothelial function at MESA Exam 1 (2000-2002).

	Small Arterial Elasticity (SAE)		
	N	**Mean (SD)**	**β (95% CI)**
***APOL1* low-risk**	1393	4.20 (2.55)	1.00 (ref)
***APOL1* high-risk**	193	4.01 (2.30)	-0.11 (-0.47, 0.24)
p-value		0.33	0.54
	Large Arterial Elasticity (LAE)		
	N	**Mean (SD)**	**β (95% CI)**
***APOL1* low-risk**	1393	13.49 (5.88)	1.00 (ref)
***APOL1* high-risk**	193	13.41 (2.10)	-0.05 (-0.88, 0.78)
p-value		0.85	0.91
	Ascending Aortic Distensibility (AAD)		
	N	**Mean (SD)**	**β (95% CI)**
***APOL1* low-risk**	863	1.69 (1.31)	1.00 (ref)
***APOL1* high-risk**	122	1.55 (0.75)	-0.21 (-0.46, 0.03)
p-value		0.09	0.09
	Flow-mediated Dilation (FMD)		
	N	**Mean (SD)**	**β (95% CI)**
***APOL1* low-risk**	692	0.15 (0.10)	1.00 (ref)
***APOL1* high-risk**	85	0.16 (0.09)	0.01 (-0.02, 0.03)
p-value		0.58	0.56

*Models adjusted for age, sex, and genetic global ancestry.

TH-PO468

Plasma Sphingolipid and Mortality Risk in Incident Hemodialysis Patients

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Background: ESRD patients receiving hemodialysis (HD) are at high risk of mortality, particularly cardiovascular (CVD) mortality. Plasma sphingolipids have been identified as predictors of CVD mortality in the general population. Despite the high prevalence of dyslipidemia in HD, no studies have examined the associations of sphingolipids with mortality risk in this population.

Methods: This study included 368 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study. Plasma sphingolipid (ceramides, glucosylceramides and lactosylceramides) levels were measured at baseline by liquid chromatography-tandem mass spectrometry. Proportional hazards regression was used to examine the association of sphingolipids with CVD mortality and all-cause mortality.

Results: At baseline, mean age was 55 years, 39% were female, 72% were African American, 58% had diabetes, and the mean comorbidity index was 5.2. Over a median 2.5 years (IQR: 1.4-3.5 years) of follow-up, there were 78 deaths from all causes, of which 33 were from CVD. The highest tertile of glucosylceramide C16GC (0.81-5.88 μM) was associated with increased risk of all-cause (HR: 1.81; 95%CI: 1.02-3.22) and CVD mortality (HR: 2.63, 95%CI: 1.08-6.55) as compared to the lowest tertile (0.03-0.40 μM) after adjusting for demographics and comorbidity.[Figure] There was no evidence of association between other sphingolipids and risk of all-cause or CVD mortality.

Conclusions: Glucosylceramide C16GC was associated with CVD and all-cause mortality among adults incident to HD. These results suggest that glycosphingolipid imbalance may contribute to increased mortality risk in ESRD. Further studies are needed to confirm these new and important findings.

Funding: NIDDK Support

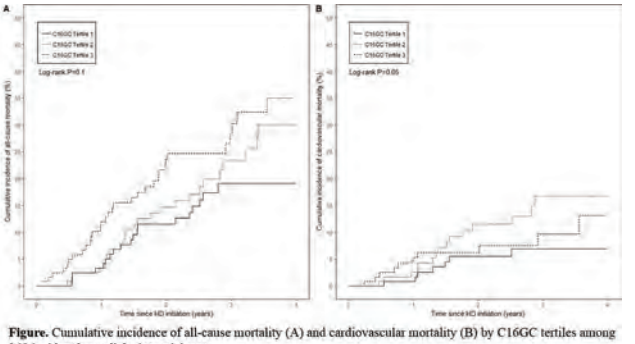

Figure. Cumulative incidence of all-cause mortality (A) and cardiovascular mortality (B) by C16GC tertiles among 368 incident hemodialysis participants

TH-PO469

Plasma Sphingolipids and Cardiovascular Disease Risk in Incident Hemodialysis Patients

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Background: Risk of cardiovascular (CVD) morbidity is high in adults with ESRD undergoing hemodialysis (HD). Many CVD risk factors are prevalent in ESRD, including dyslipidemia. Recent studies identified plasma sphingolipids as independent predictors of CVD in the general population; however, no studies have examined this association in HD patients.

Methods: This study included 368 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) study. At baseline, plasma sphingolipid (ceramides, glucosylceramides and lactosylceramides) levels were measured by liquid chromatography-tandem mass spectrometry. We examined the cross-sectional association of sphingolipids with intermediate CVD outcomes (uncontrolled hypertension [SBP ≥140 mm Hg or DBP ≥90 mm Hg], left ventricular hypertrophy [left ventricular mass index >51 g/m$^{2.7}$], and low ejection fraction [ejection fraction <55%]) using multiple logistic regression.

Results: At baseline, mean age was 55 years, 39% were female, 72% were African American, 58% had diabetes, 36% had coronary artery disease, and 41% had congestive heart failure. Higher glucosylceramide C16GC was consistently associated with higher odds of uncontrolled hypertension, left ventricular hypertrophy, and low ejection fraction independent of demographic, CVD, and dialysis factors.[Table] No other sphingolipid was consistently associated with these intermediate CVD outcomes.

Conclusions: Glucosylceramide C16GC was consistently associated with intermediate CVD outcomes. These results suggest that abnormal glycosphingolipid metabolism may contribute to increased CVD risk in ESRD. Additional studies in other dialysis cohorts are needed to confirm our results.

Funding: NIDDK Support

Table. Associations of glucosylceramide with intermediate CVD outcomes in incident hemodialysis patients

	Per 1 log μM higher Glucosylceramide C16GC	
	OR (95% CI)	P-Value
Uncontrolled hypertension		
Unadjusted	1.39 (1.07-1.81)	0.01
Adjusted [a]	1.34 (1.01-1.76)	0.04
Left ventricular hypertrophy		
Unadjusted	1.35 (1.02-1.79)	0.04
Adjusted [b]	1.53 (1.11-2.13)	0.01
Reduced ejection fraction		
Unadjusted	1.53 (1.09-2.14)	0.01
Adjusted [b]	1.06 (1.01-1.12)	0.03

[a] Model adjusted for age, sex, race, comorbidity index, BMI, and non-HDL lipid concentration
[b] Model *a* and additionally for systolic and diastolic blood pressure, number of antihypertensive medications, serum parathyroid hormone concentration, and serum C-reactive protein concentration

TH-PO470

FGF-23, Hypertension, and Dyslipidemia in Glomerular Disease

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Background: Fibroblast growth factor-23 (FGF-23) has direct effects on vasculature and myocardium and is a risk factor for cardiovascular disease (CVD); however, the impact on CVD in glomerular disease (GD) has not been addressed.

Methods: Plasma intact FGF-23, casual blood pressure (BP) and serum lipids were measured cross-sectionally in Nephrotic Syndrome Study Network (NEPTUNE) participants. Multiple regression analyzed the association of FGF-23 with BP and lipids adjusted for age, sex, black race, glomerular diagnosis, estimated glomerular filtration rate (eGFR), urine protein:creatinine (UPC), obesity and phosphorus (+ height in BP models). FGF-23 was divided into tertiles (<100,≥170 pg/ml). Hypertension (HTN) was defined as BP ≥130/80 mmHg for adults and per established definitions in children (Flynn 2017). BP index (BPi) was calculated as BP÷130/80 for adults and 95th %tile for children. Dyslipidemia (DLP) was defined as abnormal triglycerides, HDL or non-HDL for age (AHA 2013, Daniels 2011).

Results: 204 adults (46±16 yr, 60% M, 23% black) and 93 children (9.6±5 yr, 59% M, 42% black) with median eGFR of 78.4 (IQR 50,104.9) ml/min/1.73m^2 and UPC 1.83 (IQR 0.57,3.8) were evaluated. Diagnoses included membranous 17%, minimal change 24%, FSGS 33% and IgA 14%. Median FGF-23 was 73 (IQR 50,110) pg/ml, PTH 38 (IQR 26,59) pg/ml and phosphorus 3.9 (IQR 3.4,4.4) mg/dl. HTN was present in 68% and DLP in 75%; mean SBPi was 0.83±0.15 and DBPi 0.94±0.18. The highest tertile of FGF-23 was associated with HTN, SBP, DBP, SBPi and DBPi, vs. the lowest tertile in adjusted models (Table 1). FGF-23 was not associated with DLP.

Conclusions: In NEPTUNE, FGF-23 was directly associated with HTN and BP. Further study of FGF-23 as a therapeutic target for reducing CVD in GD is warranted.

Funding: Other NIH Support - NCAS, Private Foundation Support

Table 1. Association of FGF-23 with BP and Lipids (adjusted models)

	FGF-23 Highest compared to Lowest Tertile	P value
	OR (95% CI)	
Hypertension	7.33 (1.27, 42.4)	**0.03**
Dyslipidemia	0.85 (0.26, 2.8)	0.79
	β (95% CI)	
SBP	8.97 (0.99- 16.95)	**0.03**
DBP	6.56 (0.99- 12.12)	**0.02**
SBPi	0.06 (0.006- 0.12)	**0.03**
DBPi	0.1 (0.02- 0.18)	**0.01**
Total Cholesterol	20.1 (-20.4, 60.6)	0.33
LDL	15.8 (-17.5, 49.1)	0.35
HDL	0.96 (-11.4, 13.3)	0.88
Triglycerides	16.7 (-42.2, 75.5)	0.58

TH-PO471

Clinical Characteristics Enhancing the Predictive Ability of C-Reactive Protein on Incident Hypertension

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Background: Previous studies have demonstrated that the elevated CRP predicts the development of cardiovascular disease. However, it is still argued whether elevated CRP was independently associated with the elevation of blood pressure. This study was to investigate the predictability of CRP level on incident hypertension according to the clinical characteristics in normotensive general Korean population.

Methods: We examined 7,481 normotensive subjects from Korean Genome and Epidemiology Study (KoGES). They were stratified into 4 groups by quintiles of their baseline CRP levels, and followed-up for 10 years to monitor the incident hypertension. Cox proportional hazards model was used to calculate the hazard ratios (HRs) and 95% confidential interval (CI) for hypertension according to quintiles of CRP level. Additionally, subgroup analysis was performed by gender, obesity/non-obesity, dysglycemia/normal glycemia and middle (40-54 years) /old age (55-69 years).

Results: In all participants, compared to group of quintile 1, adjusted HRs for hypertension significantly increased in group of quintile 4 (1.22 [95% CI 1.04-1.43]). In subgroup analyses, women, obese and middle-aged subgroup showed the statistically significant HRs for hypertension at quintile 4 (women subgroup: 1.37 [95% CI 1.09-1.72]; obese subgroup: 1.33 [95% CI 1.07-1.66]; middle-aged subgroup: 1.31 [95% CI 1.07-1.59]), and dysglycemic subgroup had the statistically significant HRs for T2DM at both quintile 3 (1.33 [95% CI 1.04-1.71]) and quintile 4 (1.34 [95% CI 1.04-1.73]).

Conclusions: Our results suggest that the predictability of CRP on hypertension is enhanced in clinical conditions including women, obesity, dysglycemia and middle age.

TH-PO472

Hypertension and Dyslipidemia in Childhood Nephrotic Syndrome

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Background: Children with nephrotic syndrome (NS) often have hypertension (HTN) and dyslipidemia (DLP). However, these CVD risk factors have not been well described over time and in relation to renal outcomes in NS.

Methods: Longitudinal analysis of children with new onset NS in the Nephrotic Syndrome Study Network (NEPTUNE) was conducted. HTN and DLP were defined as per established definitions (Flynn 2017, Daniels 2011). BP was indexed (BPi) to the 95%. Generalized Estimating Equation models compared HTN and DLP among those reaching complete remission (CR) (urine protein:creatinine [UPC] <0.3) vs. no CR. Regression models examined the association of baseline BP and lipids with outcomes of CR, 40% eGFR drop, eGFR <90 ml/min/1.73m^2 at last follow up and eGFR slope adjusted for age, sex, race, follow up, medications, eGFR and obesity.

Results: 81 children (4.3±2.3 yr, 63% M, 24% black) with mean baseline eGFR 112±48 ml/min/1.73m^2 and UPC 4.5±9.2 were evaluated. At baseline, 58% had HTN and 81% had DLP (Table). Among CR, DLP decreased over time (*Q*10.8, p=0.01) but HTN did not change (*Q*10.8, p=0.39). For no CR, HTN and DLP did not change over time. In adjusted models, no CR had greater odds of HTN (OR 3.4 CI1.16-10.8) and greater LDL

(β 35 CI 2.9,68) over time. For outcomes, baseline elevated total cholesterol (HR 1.01 CI 1.00-1.01), greater LDL (HR 1.01 CI1.0-1.02) and triglycerides (HR 1.01 CI 1.001-1.01) were associated with increased risk of 40% eGFR drop. Baseline BP and lipids were not associated with other outcomes.

Conclusions: In NEPTUNE, HTN and DLP were prevalent in children with new onset NS and were worse over time in those with no CR. In addition, baseline lipids were found to independently predict poorer renal outcomes.

Funding: Other NIH Support - NCAS

Table. Clinical Characteristics at Baseline

Mean±SD or N(%)	No remission N = 25	Complete remission N = 56	p value
Demographics			
Age at enrollment, years	3.08±1.80	4.79±2.91	<0.01
Follow up, months	8.96±5.99	15.32±7.49	<0.01
BMI percentile	82.53±17.20	74±24.98	0.18
NS Characteristics:			
eGFR (ml/min/1.73m²)	119.11 ± 43.18	110.61±50.57	0.56
UPC	10.43±9.14	3.50±8.99	0.09
Blood Pressure			
HTN	11/18 (61.1)	27/48 (56.3)	0.72
SBP index	0.97±0.11	0.99±0.07	0.39
DBP index	1.01±0.15	0.99±0.17	0.74
Lipids			
Dyslipidemia	13/15 (86.7)	31/39 (82.1)	0.66
Total Cholesterol (mg/dL)	326±124	301±94	0.42
Triglycerides (mg/dL)	240±118	197±121	0.26
HDL (mg/dL)	65±23	78±25	0.09
LDL (mg/dL)	213±97	183±85	0.27
Outcomes			
40% decrease in eGFR	4 (16)	9 (16.1)	0.99
eGFR <90 ml/min/1.73m²	4 (16)	15 (26.8)	0.34
eGFR slope, months	2.3±7.7	-0.92±4	0.15

TH-PO473

Pericytes Detachment and Peritubular Capillaries Injury in Malignant Hypertensive Nephrosclerosis Patients

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Background: Peritubular capillary (PTC) injury contributes to the progression of various kidney disease. However, its impact on renal prognosis has not been well reported in malignant hypertensive nephrosclerosis (MHN) patients. The disintegration of interstitial pericytes may cause PTC loss and expansion of interstitium. This study investigated the role of PTC loss and pericytes distribution in MHN patients.

Methods: One hundred patients with essential MHN confirmed by renal biopsy from Jan. 2003 to Jun. 2016 in Peking Union Medical College Hospital were recruited. Clinical data and pathologic findings carefully reviewed. IHC and immunofluorescence staining of CD34 and PDGFRβ were used to evaluate PTC loss and pericytes distribution. The primary end point was defined as renal replacement therapy, kidney transplant as well as death. Cox regression was used to identify factors related to prognosis.

Results: The patients were mostly young males (male 88%; age 34.9±8.5ys) with significantly elevated blood pressure (225.2±26.4/152.0±25.0 mmHg), decreased eGFR (22.1±15.2 mL/min/1.73 m²) and proteinuria (median 1.4 g/d). Remarkable tubular atrophy (62.8±19.1%) and interstitial fibrosis (65.0±17.8%) were observed. PTC loss evaluated by CD34 staining was more significant in MHN patients (n=70), compared with benign hypertensive nephrosclerosis (n=17, P=0.025) and glomerular minimal lesion patients (n=17, P=0.001). PTC area correlated well with eGFR (r=0.496, P<0.001) and proteinuria (r=-0.351, P=0.006). Tubulointerstitial PDGFRβ expression (n=36) was higher than BHN (n=15, P=0.035) and GML patients (n=10, P=0.01). Immunofluorescence double staining of CD34 and PDGFRβ showed detachment of pericytes from PTC in tubulointerstitium. After 60.5±38.7 months' follow up of 92 eligible subjects, the cumulative renal survival rate at 1, 3, 5, and 10 years was 94.6%, 84.1%, and 69.2%, and 31.2%, respectively. Multivariate COX regression indicated PTC injury, inadequate blood pressure control and proteinuria>1g/d are associated with poor renal prognosis.

Conclusions: PTC injury predicted the long-term renal outcome in patients with MHN. Detachment of pericytes from endothelial cells might play a role of the PTC injury.

TH-PO474

Hypertensive Epidemiology and Potential Blood Pressure Goals in IgA Nephropathy

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Background: IgA nephropathy is the most prevalent form of primary glomerulonephritis worldwide. Hypertension is one of the most important risk factors in the progression of kidney disease. Our aim was to identify the epidemiology of hypertension in IgA nephropathy.

Methods: This was a nationwide, multi-center, cross-sectional study. We analyzed 1055 patients with IgA nephropathy from 61 tertiary hospitals in China (except Hong Kong, Macao, and Taiwan). Hypertension was defined as blood pressure (BP) ≥ 140/90 mmHg. Three BP goals were used to assess BP control: < 140/90 mmHg, < 130/80 mmHg, and < 125/75 mmHg. The outcomes included factors associated with hypertension, decreased renal function, and potential BP range goals for IgA nephropathy, which were analyzed based on 24-hour proteinuria levels of <1 g/d or ≥ 1 g/d.

Results: We found that 63.3% of our participants with IgA nephropathy had hypertension. Blood pressures were controlled under 140/90 mmHg in 49.1% of participants, 34.3% of patients with proteinuria <1 g/d reached the goal of BP <130/80 mmHg, and only 12.9% of patients with proteinuria >1 g/d achieved BP <125/75 mmHg. With proteinuria <1 g/d, the odds ratios (95% confidence interval) [ORs (95% CI)] of decreased renal function with BPs < 140/90 mmHg, < 130/80 mmHg, and < 125/75 mmHg were 0.9 (0.5 - 1.6), 1.0 (0.5 - 1.8), and 1.0 (0.5 - 2.0), respectively (P > 0.05). With proteinuria ≥1 g/d, the ORs of target BPs < 140/90 mmHg, < 130/80 mmHg, and < 125/75 mmHg were 0.4 (0.2 - 0.6), 0.2 (0.1 - 0.4), and 0.3 (0.1 - 0.5), respectively (P < 0.05).

Conclusions: Hypertension was prevalent in IgA nephropathy and hypertensive control was suboptimal. It might be rational to keep BP < 140/90 mmHg in patients with proteinuria <1 g/d, and < 130/80 mmHg in patients with proteinuria ≥1 g/d, respectively. Randomized clinical trials in IgA nephropathy are needed to evaluate BP range goals.

TH-PO475

Anxious Adolescents and Diastolic Hypertension

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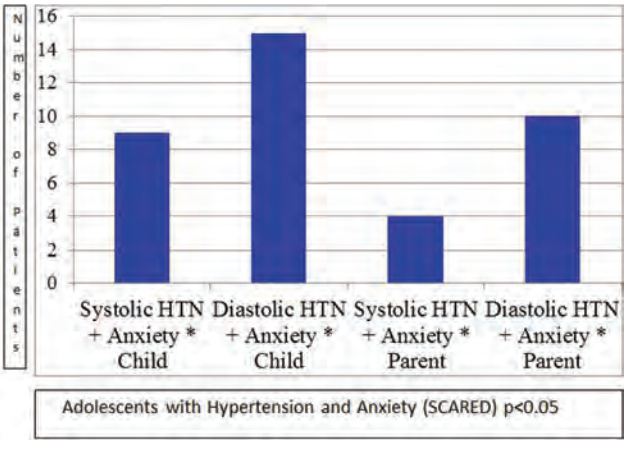
Background: Anxiety is prevalent in 15-20% of children, often negatively affecting health and quality of life. Pediatric hypertension (HTN) is on the rise, affecting 5% of all children. While anxiety correlates with elevated blood pressure (BP) in adults, this has not been studied in children. The primary objective of this study was to examine the relationship between anxiety and HTN in adolescents.

Methods: We screened Adolescents aged 12-18 years in a pediatric nephrology clinic for anxiety. Adolescents and their parents were asked to complete the generalized anxiety subset of the Screen for Child Anxiety Related Disorders (SCARED) questionnaire in regards to the adolescent. A score of ≥ 9 out of 18 was labeled as a positive screen for anxiety. BP was measured at the same visit. Hypertension was defined as systolic or diastolic BP > 95th percentile for age, height, and gender.

Results: Ninety-nine adolescents and their parents completed the questionnaire. The median age was 15 years with 54% of the responders being male. Sixty-two percent had either elevated blood pressures in the office or had diagnosis of hypertension. Nine percent had history of anxiety and 37% screened positive on the SCARED questionnaire. Adolescent's anxiety score correlated with parental rating of adolescent's anxiety (r = 0.4, p <0.01). Parents who perceive their children as anxious had a greater proportion of diastolic HTN compared to non-anxious children 53% vs 29% (p < 0.05) but not systolic hypertension 21% vs 26%, (p = 0.6). Anxious children had higher diastolic HTN (p < 0.05).

Conclusions: Parental perception of child's underlying anxiety level may predict higher diastolic BP measurement at office visit. Future studies should include larger cohort size, and use of ambulatory BP monitoring, and assessment of anxiety score in different subsets of HTN (primary vs secondary). Screening for anxiety may play an important role in the evaluation of patients with hypertension.



TH-PO476

High Prevalence of Significant Structural Heart Disease by Echocardiography in Patients Undergoing Evaluation for Kidney Transplantation

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Background: Although the deleterious effect of structural heart disease in patients with advanced kidney disease is well known, the specific contribution of valvular abnormalities

has been less well characterized. Detailed echocardiographic criteria have been proposed by the Acute Dialysis Quality Initiative XI Workgroup to identify dialysis patients with underlying structural heart disease. We sought to determine the prevalence of structural heart disease, including valvular disease, in a single center cohort of dialysis patients referred for kidney transplant evaluation.

Methods: We performed a retrospective analysis of single center echocardiographic data obtained from patients undergoing kidney transplant evaluation from 2006 to 2018. Studies that took place at least six months after initiating dialysis were included. Analyses were performed with SAS using Chi square, ANOVA, or Fisher's exact test.

Results: Patients undergoing initial kidney transplant evaluation at the University of Virginia were evaluated by echocardiography, n = 461. They were 58.6% men, and median age was 58 years, interquartile range (IQR) 48 - 66. Median duration of dialysis was 29 months, IQR 17 - 50. Comorbidities included hypertension (89.6%), diabetes (55.8%), and coronary disease (21.7%). The table below shows the frequency of cardiac disease by transplant status at the time of data collection. There were no cases of significant mitral or tricuspid stenosis, and no significant pulmonic valve pathology.

Conclusions: Prevalence of structural heart disease in patients referred for kidney transplant evaluation is high. Patients who ultimately underwent kidney transplant had significantly lower prevalence of structural heart disease, including mitral regurgitation, aortic stenosis, and tricuspid regurgitation, compared to non-transplanted patients.

Echocardiographic Parameter	Overall Cohort (n=461)	Transplanted Patients (n=266)	Actively Listed (n=106)	Expired (n=62)	Inactive (n=27)	P value
Left ventricular dysfunction (EF ≤ 45%) (%)	17.57	6.02	15.09	56.45	51.85	< 0.0001
Right ventricular dysfunction (mild or worse) (%)	15.58	3.81	22.86	41.94	29.63	< 0.0001
Mitral regurgitation (moderate or worse) (%)	4.3	1.61	2.86	16.13	7.41	< 0.0001
Aortic stenosis (moderate or worse) (%)	3.09	0.55	4.12	11.32	0	0.0016
Aortic regurgitation (moderate or worse) (%)	0.51	0.48	0	0	3.7	0.2168
Tricuspid regurgitation (moderate or worse) (%)	7.05	2.04	6.6	27.42	7.41	< 0.0001
Pulmonary hypertension (estimated PASP ≥ 50 mm Hg) (%)	8.24	1.13	14.15	24.19	18.52	< 0.0001
Left ventricular hypertrophy (IVS or PWD ≥ 1.2 cm)	53.8	58.65	48.11	50	37.04	0.0628

TH-PO477

Association Between Post-Dialysis Blood Pressure and Extracellular Volume Status in Hemodialysis Patients

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Background: Volume status and hypertension are closely associated with cardiovascular outcome in receiving hemodialysis (HD) patients. New noninvasive bedside tools, such as bioimpedance analysis (BIA) has been reported to assess objective fluid status. Aim of the study was to ascertain the association between hydration status measured by BIA and postdialysis blood pressure in HD patients.

Methods: We conducted a cross-sectional multi-center study. All patients underwent a postdialysis BIA to assess hydration status which was calculated by the ratio of extracellular water (ECW) to total body water(TBW). Patients were divided into three groups, those in whom the blood pressure decreased during dialysis by≥20mm Hg (PDHYPO), those in whom the SBP increased by≥10mmHg (PDHYPER), and in whom the SBP did not meet the definitions of intradialytic hypotension or hypertension, termed as PDSTABLE group. DeltaSBP was calculated by SBP difference between before and after HD. Laboratory data including dialysate sodium as well as serum sodium level was collected and subjective global assessment (SGA) was used for assessing nutritional status.

Results: A total of 254 prevalent HD patients were included in this study. Fifty-four patients (21.3 %) had PDHYPO and seventy-four patients (39.2%) had PDHYPER. Age, SBP after dialysis (SBP_{post}), and deltaSBP were significantly higher, while hemoglobin, serum albumin and sodium and SGA were lower in the PDHYPER group than in PDHYPO and PDSTABLE group. The PDHYPER group showed higher ECW/TBW than in PDHYPO and PDSTABLE group. (0.414 ± 0.011 *vs.* 0.402 ± 0.012, 0.406 ± 0.02, $p<0.001$). In spearman correlation coefficient, deltaSBP ($r=+0.231$, $p<0.001$) and phase angle ($r=-0.804$, $p<0.001$) showed a significant correlation with ECW/TBW. In multiple logistic regression analysis, older age, lower SGA, lower albumin, and higher ECW/TBW were the independent risk factors affecting PDHYPER.

Conclusions: Our data support that increased ECW/TBW is significantly associated with postdialysis blood pressure in HD patients.

TH-PO478

Normal Body Mass Index with Non-Alcoholic Fatty Liver Disease Is Associated with Coronary Calcification in Patients with CKD

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Background: Increased coronary artery calcification (CAC) for assessing the burden of coronary atherosclerosis has been reported in patients with chronic kidney disease (CKD). Although non-alcoholic fatty liver disease (NAFLD) is associated with obesity and metabolic syndrome, it may also present in lean individuals. This study aimed to investigate whether normal body mass index (BMI) with NAFLD is associated with coronary artery calcification (CAC) in the patients with CKD.

Methods: Data from a total of 1,479 patients with CKD with normal BMI were provided from 2005 through 2017. CAC score was measured with computed tomography. BMI was considered to be normal if it was less than 25 kg/m^2. To assess the central obesity, waist-to-hip ratio (WHR) was also obtained. NAFLD was diagnosed in patients with evidence of liver steatosis at ultrasonography.

Results: Six hundred ninety-nine (47.2%) patients had CAC in CKD with NAFLD. The CAC was significantly higher in the CKD patients with NAFLD than the CKD patients without NAFLD (66.2±238.9 vs. 39.8±158.2, $p<0.001$). After adjusting for age, gender, hypertension, diabetes, dyslipidemia, WHR, estimated glomerular filtration rate, fasting plasma glucose, total cholesterol, NAFLD was significantly associated with increased risk of CAC in CKD patients with normal BMI (OR=1.754, $P<0.001$).

Conclusions: Our study showed that NAFLD was significantly associated with CAC in the non-obese patients with CKD with normal BMI

TH-PO479

Obesity in Glomerular Disease

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Background: Obesity is a risk factor for cardiovascular disease (CVD) and contributes to the development and progression of kidney disease. The impact of obesity on glomerular disease has not been well-described.

Methods: Longitudinal data were from 488 participants in the Nephrotic Syndrome Study Network (NEPTUNE). Obesity was defined as body mass index (BMI) ≥30 kg/m^2 for adults and ≥95% for children. Blood pressure (BP), lipids, complete remission ever (urine protein:creatinine [UPC] <0.3) and composite endpoint (ESRD or 40% decrease in eGFR) were compared in obese vs. non-obese. Generalized estimating equations examined obesity with outcomes, adjusted for age, sex, black race, glomerular diagnosis, follow-up, edema, UPC, eGFR, steroids, calcineurin inhibitors (CNI), renin angiotensin blockade (RAAS), SBP and obesityxedema.

Results: 322 adults (46.5±16 yr, 62% M, 21% black) and 166 children (9.6±5 yr, 57% M, 42% black) with baseline median eGFR 83 (IQR 53,105) ml/min/1.73m^2 and UPC 2(IQR 0.7,4.3) were evaluated. 43% of adults and 38% of children were obese (35% and 34% in non-edematous, respectively). The proportion with obesity did not change during mean 35±20 months of follow-up (Q=11.9, p=0.29). See Table 1. In adjusted models, obesity was associated with hypertension (HTN) (OR1.61 CI 1.14-2.28), greater SBP (β5.73 CI 0.15-11.3) and lower HDL (β-8.1 CI-12.17– -4.03) in adults. For children, obese had greater DBP index (0.03 CI 0.001– 0.07), greater triglycerides (β29.3 CI 1.91–56.7) and lower HDL (β-6.87 CI -12.07- -1.68), as well as increased odds of HTN (OR2.14 CI 1.26–3.65), dyslipidemia (OR1.61 CI 1.04–2.5) and high HDL (OR2.24 CI 1.31–3.81) compared with non-obese. Obesity was not associated with renal outcomes.

Conclusions: In NEPTUNE, obesity is common and associated with CVD risk when compared to non-obese participants.

Funding: NIDDK Support

Table 1. Clinical characteristics at baseline

N (%) or Mean (SD)	Adult obese N = 138	Adult non-obese N = 184	p-value	Pediatric obese N = 63	Pediatric non-obese N = 103	p-value
BMI (kg/m^2)	36.5±6.6	25.1±3.1	**<0.0001**	27.5±8	19.3±3.6	**<0.0001**
BMI percentile	-	-		98.2±1.4	65±29.8	**<0.0001**
Cohort: MCD	39 (28.3)	12 (6.5)	**<0.01**	29 (46)	53 (51.5)	0.41
MN	38 (27.5)	41 (22.3)		1 (1.6)	0 (0)	
FSGS	53 (38.4)	52 (28.3)		23 (36.5)	20 (19.4)	
IgA	32 (23.2)	16 (8.7)		4 (6.3)	5 (4.9)	
Disease Duration (months)	2.3±5.23	2.5±5.8	0.81	1.9±2.4	1.3±2.3	0.12
Edema	76 (55.1)	71 (38.6)	**<0.01**	26 (41.3)	32 (31.1)	0.18
RAAS use	96 (69.6)	86 (46.7)	0.07	19 (30.2)	32 (31.1)	0.9
Steroid use	27 (19.6)	36 (19.6)	1.0	34 (54)	59 (57.3)	0.68
CNI use	2 (1.4)	6 (3.3)	0.3	17 (27)	14 (13.6)	**0.03**
Hypertension	112 (81.2)	120 (65.2)	**<0.01**	33 (52.4)	45 (43.7)	0.28
SBP (mmHg) for adults/SBP index for children*	128.2±17.0	124.1±17.8	**0.04**	0.96±0.12	0.93±0.1	0.05
DBP (mmHg) for adults/DBP index for children*	77.91±10.8	76.4±11.8	0.24	0.94±0.18	0.91±0.16	0.33
Dyslipidemia	114 (82.6)	131 (71.2)	**0.01**	51 (81)	67 (65)	0.09
Total Cholesterol (mg/dl)	252±96	270±103	0.13	275±135	308±141	0.16
HDL (mg/dl)	60±26	72±30	**<0.0001**	70±31	82±26	**<0.01**
LDL (mg/dl)	146±79	161±87	0.11	161±106	192±113	0.11
Triglycerides (mg/dl)	232±161	182±128	**0.002**	217±190	172±130	0.11
Composite Endpoint	40 (28.9)	42 (22.8)	0.21	14 (22.2)	19 (18.4)	0.55
Complete Remission Ever	57 (41.3)	94 (51.1)	0.08	43 (68.3)	76 (73.8)	0.44
eGR slope (months)	-0.34±0.69	-0.29±0.77	0.57	-0.41±1.9	-0.13±1.3	0.32

*BP index = BP divided by 95%tile BP for age, sex, height

TH-PO480

Renal Transplantation Improves Cardiovascular Autonomic Efficiency and Decreases Stroke Volume Variability in Chronic Hemodialysis Patients

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Background: Renal transplantation (TX) was shown to enhance autonomic function and its cardiovascular efficiency (CvE), but its effect on stroke volume (SV) variability (sdSV), a measure of myocardial responsiveness consistency and poor prognostic significance was not defined.

Methods: Beat-to-beat systolic blood pressure (SBP) and interbeat intervals (IBI) monitoring was performed in 72 non-diabetic chronic hemodialysis (HD) patients (pts.), in 41 pts. after TX and in 27 healthy controls (C). The power spectral densities of IBI and SBP in the low frequency (LF) range were calculated from Finometer recordings of SBP and IBI spontaneous variations. SV and total peripheral resistance (TPR) were assessed using the ModelFlow method. The standard deviations (sd) of the above indices were considered to represent their variabilities. Differences in variability indices between SBP periods, 10% above (high) or below (low) the mean SBP were considered representative of CvE.

Results: : Table 1 (see below) lists hemodynamic data and SBP and IBI variability indices during low-high SBP periods. These periods were associated with increased SV and TPR in all groups and decreased sdSV in HD. SBP and IBI variability changes between low-high periods were blunted in HD and restored in TX. Overall sdSV was significantly increased in HD (p=0.025 and 0.001 vs C and TX). Overall LFIBI was lower in HD (p=0.001 vs C). LF SBP decreased after TX (p=0.001 vs HD).

Conclusions: In HD, increased LF SBP, decreased LF IBI and the attenuated variation between low-high SBP episodes are consistent with sympatheric overactivity and suppressed overall autonomic function. Renal TX improves CvE and decreases sdSV,suggesting enhanced myocardial responsiveness.These effects may contribute to the improved survival after TX.

Table 1. (median and interquartile ranges).

	C		HD		TX	
	Low-High SBP	p	Low-High SBP	p	Low-High SBP	p
SBP (mmHg)	104 (20) 137 (24)	0.001	113 (24) 155 (30)	0.001	108 (22) 141 (29)	0.001
sdSBP (mmHg)	5.03 (3.50) 7.23 (2.80)	0.001	6.87 (2.70) 6.94 (2.40)	NS	5.12 (2.20) 7.05 (2.70)	0.001
IBI (ms)	798 (116) 758 (110)	0.001	815 (168) 828(174)	0.044	828 (188) 802 (205)	0.004
sdIBI (ms)	39 (25) 42 (21)	0.013	24 (17) 23 (18)	NS	21 (19) 31 (24)	0.001
LF SBP (mm Hg^2 /Hz)	52 (96) 138 (108)	0.003	123 (114) 114 (138)	NS	53 (52) 108 (87)	0.001
LF IBI (ms^2/Hz)	4467 (6005) 4076 (5154)	NS	1250 (2366) 1174 (2822)	NS	1059 (2544) 2465 (6282)	0.001
SV (ml)	75 (30) 79 (22)	0.001	81 (36) 86 (36)	0.001	81 (41) 84 (38)	0.0326
sdSV (ml)	4.51 (2.07) 5.66 (3.06)	NS	7.25 (3.27) 6.21 (2.73)	0.001	5.36 (3.22) 4.98 (3.18)	NS
TPR (mmHg.s/ml)	0.852 (0.240) 0.942 (0.220)	0.013	0.842 (0.360) 1.021 (0.440)	0.001	0.800 (0.580) 0.893 (0.490)	0.001

TH-PO481

HIFs in the Renal Medulla Regulate Natriuresis and Blood Pressure Through COX2

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Background: Hypoxia inducible factors (HIFs) are essential for the maintenance of cellular oxygen homeostasis. In response to hypoxia, stabilized HIFs initiate the expression of genes that alleviate hypoxic stress. HIFs are now important therapeutic targets for CKD anemia. In the phase 2 clinical trial of FG4592(a kind of HIFs stabilizers) in our center, we found that this drug not only corrected anemia but also downregulated blood pressure. Cyclooxygenase 2 (COX2) in the renal medulla was reported to promote natriuresis and decrease blood pressure. HIFs could induce COX2 in some tumors. In the present study we investigated the mechanism underlying the blood pressure lowering effect of HIFs.

Methods: We used mice metabolic cages to measure daily sodium balance. The mice were fed with the same amount of gel food. To capture transient changes in the urine Na+ excretion prior to attainment of a new steady state, daily 8-hour urine were collected after the administration of the drugs. The urinary volume and urinary sodium concentration were measured.

Results: In the clinical trial of FG4592 in our center, patients' mean blood pressure decreased about 5mmHg compared with basal condition(91.5±1.5mmHg vs. 96.5±1mmHg, $P < 0.05$,n=10) after 8-week treatment. The administration of FG4592 significantly increased the daily urinary volume and urinary sodium excretion of the mice on high salt diet (8%NaCl). The cumulative sodium excretion of consecutive 4 days was higher in the FG4592 group than the control group(3.77±0.36mmol vs. 2.82±0.25mmol, $P < 0.05$,n=8). The expression of COX2 in the medulla was increased in the FG4592 group. When we used COX2 inhibitor celecoxib together with FG4592, the natriuresis effect of the latter one was abolished.

Conclusions: HIFs in the renal medulla lower blood pressure through upregulating COX2 and promoting natriuresis.

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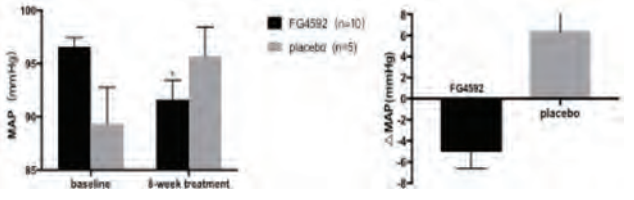

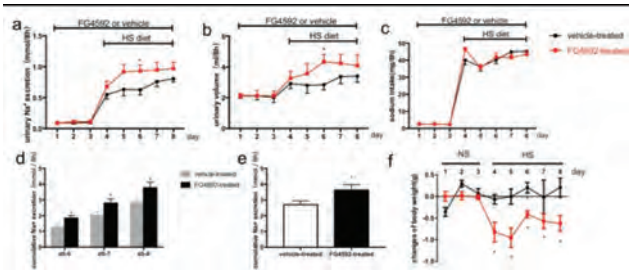

TH-PO482

Cilia Disruption May Regulate the Renal Inner Medulla NOS Pathway

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Background: Primary cilia act as flow-mediated mechanosensors, signaling via intraflagellar transport (IFT). We previously reported that NO synthase 1 (NOS1) is the major isoform contributing to flow-induced nitric oxide (NO) production in the inner-medullary collecting duct (IMCD) and contributes to natriuretic responses. In this study, we hypothesized that functional ciliary IFT contributes to IMCD NOS1 abundance and activation.

Methods: Mouse IMCD cells were studied under static or flow (10 dynes/cm^2) conditions for 1-hr to assess NO production (HPLC) and ciliary marker expression (western blot). Inner medullary (IM) NOS isoform abundance and urinary NO excretion were measured in 2 models of cilia disruption, PCK rats and conditional IFT88 knockout mice.

Results: Exposure to flow significantly increased IMCD NO production (static: 168±18, flow: 312±26 pmol/mg pr/hr; n=6/group, p<0.05) and ciliary marker expression, IFT88 (static: 1.0±0.3, flow: 1.7±0.1 RDU/b-actin; n=6/group, p=0.02) and acetylated-α-tubulin (static: 1.0±0.2, flow: 1.9±0.2 RDU/b-actin; n=6/group, p=0.01) compared to static controls. IM NOS1α abundance was not elevated in PCK rats (SD: 1.00±0.1, PCK: 1.22±0.1 RDU/b-actin; n=4/group, p>0.05), but NOS1β abundance was increased compared Sprague Dawley (SD) control rats (SD: 1.0±0.2, PCK: 3.9±0.2 RDU/b-actin; n=4/group, p<0.01). NOS3 abundance was similar between SD and PCK rats (1.0±0.1 and 0.9±0.1 RDU/b-actin, respectively; n=4/group, p>0.05). However, pNOS3 Thr495 expression, a NOS3 inhibitory phosphorylation site, was significantly higher in PCK rats (SD: 1.0±0.3, PCK 3.1±0.5 RDU/total NOS3; n=4/group, p<0.01). Similarly, NOS1β expression in IFT88KO mice trended to be higher compared to controls (Cre-: 1.0±0.4,

Cre+ 3.0±0.6 RDU/b-actin; n=3/group, p=0.06). No significant changes in NOS3 abundance were observed (Cre-: 1.0±0.1, Cre+ 1.2±0.2 RDU/b-actin; n=3/group, p>0.05). Urinary NO excretion was similar in SD and PCK rats (SD: 6.1±2.2, PCK 10.0±0.4 umol/day; ßΔn=4-5/group, p>0.05) as well as Cre- and Cre+ IFT88KO mice (Cre-: 211±61, Cre+ 220±13 nmol/day; n=3/group, p>0.05) on normal salt diet. These data suggest that ciliary disruption influences NOS isoform abundance in the renal IM.

Conclusions: In conclusion, functional cilia may contribute to acute flow-induced NO production and NOS isoform abundance.

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TH-PO483

Regulation of ABCG2 Transporter and Uric Acid Metabolism in a Model of Hyperuricemia

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Background: Hyperuricemia is one of the most frequent complications in chronic kidney disease (CKD). Previously, we showed that the gene expression of the urate transporter ATP-binding cassette subfamily G member 2 (ABCG2) is upregulated in the ileum in the rat remnant kidney model (Yano et al. Clin Exp Nephrol 2014), indicating that the intestine may participate in uric acid metabolism in CKD. However, the role of each part of the intestinal tract in uric acid metabolism in normal and hyperuricemic states have not been clarified. In this study, uric acid concentrations and ABCG2 expression in the different part of intestine were evaluated in normal and hyperuricemia model rats.

Methods: Using Sprague-Dawley rats, we evaluated ABCG2 expression in each part of the intestinal tract by immunofluorescent study. Uric acid concentrations in the serum and in the tissue homogenates were measured by LC/MS. We also evaluated the ABCG2 levels in the intestine of hyperuricemia rats. Hyperuricemia was induced by feeding a diet containing 5% oxonic acid, the uricase inhibitor.

Results: In the intestinal tract of normal rats, the concentration of tissue uric acid (in μg/g tissue) was 5-10 times higher in duodenum and jejunum than in ileum and transverse colon (duodenum 102 ± 16; jejunum 112 ± 16; ileum 17 ± 8.2; transverse colon 7 ± 4). Co-staining of ABCG2 and villin revealed that ABCG2 was highly present in the villus and crypt of the duodenum. Administration of oxonic acid increased serum uric acid levels by 2.1 fold ($P < 0.05$). Comparison of the ABCG2 staining between control and hyperuricemic rats indicated that ABCG2 was upregulated in the ileum by hyperuricemia.

Conclusions: ABCG2 is highly expressed in the duodenum and jejunum at basal condition. However, Hyperuricemia upregulates ABCG2 in the ileum. These data are consistent with our previous studies showing the upregulation of ABCG2 in the ileum in the rat remnant kidney model, and suggest a compensatory role of ileum in hyperuricemic states.

TH-PO484

Insulin: Genetic and Physiological Influences on Human Uric Acid Homeostasis

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Background: Insulin plays a key role in hyperuricemia. In particular, hyperinsulinemia in metabolic syndrome is inversely correlated with urinary uric acid (UA) excretion and insulin infusion in humans reduces urinary fractional excretion of UA.

Methods: An existing GWAS cohort was analyzed, testing for association between genetic variants in the insulin and insulin receptor genes with serum UA (SUA). HEK 293T cells, human PTC5 proximal tubule cells, and *Xenopus* oocytes were probed with antibodies to UA transporters, the insulin receptor, downstream kinases, and the relevant phospho-kinases. ^{14}C-UA transport was assayed in these cell lines and in oocytes expressing individual transporters.

Results: Variants in the human insulin and insulin receptor genes demonstrated significance for association with variation in SUA, at $p<10^{-4}$ and $p<10^{-7}$, respectively. HEK293T and PTC5 proximal tubular cells express several endogenous UA transporter proteins, including GLUT9, OAT10, and URAT1. Insulin activates PI3 kinase/Akt and MEK/ERK signaling pathways through the insulin receptor in HEK 293T and PTC5 cells, as detected with phospho-kinase antibodies, with activation of endogenous ^{14}C-UA transport. The stimulatory effect of insulin on UA uptake is abrogated by uricosurics and by inhibition of protein tyrosine kinase (genistein), PI3 kinase (LY295002), and MEK/ERK (PD98059). UA transport mediated by GLUT9a, GLUT9b, OAT10, OAT3, OAT1, NPT1 and ABCG2, expressed separately in *Xenopus* oocytes, is also activated by insulin, with equivalent activation of signaling pathways and differential effects of signaling inhibitors on insulin-stimulated UA transport. Insulin has no effect on URAT1, OAT4, and the SMCT1/2 nicotinate transporters, when expressed in oocytes. GLUT9a is the basolateral exit pathway in reabsorption of filtered UA by the proximal tubule; given much greater absolute UA transport rates mediated by GLUT9 isoforms, much of the anti-uricosuric effect of *in vivo* insulin infusion is likely due to activation of GLUT9a.

Conclusions: Variation in the human insulin and insulin receptor genes affects SUA. Insulin and associated signaling pathways also activate multiple UA transporters, indicating a pivotal physiological role for insulin in UA homeostasis. We postulate that basolateral GLUT9a in the proximal tubule is the dominant post-translational target of insulin in the regulation of renal UA transport.

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TH-PO485

Claudin-10a Confers Chloride Permeability to the Tight Junctions of the Proximal Tubule

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Background: In the renal proximal tubule (PT) part of the bulk reabsorption of water and electrolytes takes place via the paracellular pathway. This paracellular pathway is regulated by the tight junction (TJ) complex which consists of a belt like structure around the apical pole of the epithelial cells. In contrast to most other epithelia where this belt is composed of multiple strands forming a meshwork, the PT shows only between one and five strands reflecting its high paracellular permeability. The selectivity of the TJ is mainly determined by the claudin composition of the TJ.

Methods: Micro-dissected PTs of claudin-10a specific knock-out animals (KO) and of wild-type controls (WT) were investigated in a double-barreled perfusion system. Diffusion potentials (DPs) were generated by either replacing the basolateral solution by an isosmotic 30 mM NaCl solution or by replacing Cl^- with HCO_3^-. DP were used to calculate relative permeability (P) ratios for Na^+, Cl^- and HCO_3^-. Immunofluorescence against claudin-10, claudin-2 and claudin-3 was performed on single isolated tubules.

Results: In WT, the early convoluted part of the proximal tubule (early PCT) showed anion selectivity (P_{Cl}/P_{Na} = 1.52 ± 0.07), the last straight part (PST) showed cation selectivity (P_{Na}/P_{Cl} = 1.26 ± 0.06) and the convoluted segments in between showed intermediate selectivity. PT TJ showed higher permeability for Cl^- than for HCO_3^- with the highest P_{Cl}/P_{HCO3} (1.86 ± 0.25) in late PCT. In PCT, claudin-10a expression was dominant in the TJ, in PST claudin-2 expression predominated. In addition, in this last segment of the PT, the tightening claudin-3 was expressed and co-localized to the TJ. In KO early PCT, claudin-2 moved to the TJ. Consequently, the early PCT lost anion selectivity completely and displayed high cation selectivity (P_{Na}/P_{Cl} = 2.86 ± 0.45). In KO late PCT, P_{Cl} was lower than P_{HCO3} (P_{Cl}/P_{HCO3} = 0.88 ± 0.15). In KO PST differences were less pronounced but qualitatively similar (P_{Na}/P_{Cl} = 2.00 ± 0.14; P_{Cl}/P_{HCO3} = 1.05 ± 0.06).

Conclusions: In summary, PT TJ selectivity changes along its axis from anion to cation selectivity. The anion selectivity is further characterized by preference of Cl^- over HCO_3^- and is claudin-10a dependent.

TH-PO486

Functional Proteomics of Isolated Perfused Cortical Collecting Ducts

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Background: In renal physiology and pathophysiology large-scale omic data sets are generally generated from bulk samples, e.g. the complete kidney or cortex vs. medulla. It is therefore difficult to predict implications for functional changes taking place in the individual, highly specialized and very distinct nephron segments. In the context of hypertension it is of high clinical relevance to understand regulation of salt transport in the collecting duct and the phenomenon of salt-sensitivity. The aim of this study was to establish a method to correlate measured electrophysiological properties of individual, isolated perfused cortical collecting ducts (CCD) with respective proteomic data.

Methods: For the electrophysiological properties, freshly isolated CCDs of 6-8 week old C57Bl6 mice were investigated in a double-barreled perfusion system. Transepithelial voltage (V_{te}) was recorded and transepithelial resistance as well as amiloride sensitive equivalent short-circuit current ($\Delta I'_{sc}$) were calculated. After these measurements every single tubule was recovered, processed and ultrasensitive mass spectrometry was performed.

Results: In manually collected CCD segments we were able to identify more than 4000 distinct proteins. In the perfusion experiments, protein expression patterns typical for intercalated cells or, principal cells, respectively, showed negative correlation in the proteome. V_{te} varied between -8.5 and -32.5 mV and correlated with the regulator protein NEDD4. $\Delta I'_{sc}$ as a measure of electrogenic sodium reabsorption was reflected by the expression level of the b-subunit of the epithelial sodium channel.

Conclusions: We could show that functional proteomics on a single nephron segment is possible and allows function-proteome correlations. This unique data acquisition approach will allow conclusions on physiological or pathophysiological outcomes based on omics data at the level of functional units rather than total organ samples.

TH-PO487

mTORC1 Regulates Renal Proximal Tubular Megalin Function

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Background: Renal proximal tubular cells constantly recycle nutrients to ensure minimal loss of essential substrates into the urine. Thus, endocytosis is a hallmark of the

proximal tubule. Protein uptake is mediated by the scavenger receptors megalin and cubilin, followed by internalization of the ligand-receptor complex via the clathrin-mediated pathway. The mTORC1 complex is a principle regulator of proximal tubular function, including endocytosis. However, the effect of mTORC1 on megalin function remains unknown.

Methods: Tubular deletion of mTORC1 was created by crossbreeding Raptor$^{fl/fl}$ with Pax8rt-TA and TetOCre mice. Phosphoproteomics were performed to analyze the phosphorylation of megalin in the renal cortex. Endocytosis was detected in proximal tubules using Alexa555-labelled lactoglobulin. *In vitro*, we induced mTORC1 activity through transient transfection with Rheb, used megalin minireceptor 2 (MMR2) to introduce mutations in the respective phosphosite S4577A, S4577D, S4577E, and followed endocytosis through Alexa555-labelled albumin.

Results: mTORC1-deficient mice showed normal megalin expression and distribution within proximal tubules compared to wildtype mice. Interestingly, receptor-mediated endocytosis of Alexa555-labelled lactoglobulin was blocked in mTORC1-deficient mice. Phosphoproteomics of mTORC1 deficient mice revealed a strongly reduced phosphorylation at S4577 of the C-terminus of megalin, which was confirmed by transient transfection of MDCKII cells with Rheb stimulating mTORC1 activity. Transfection of wildtype or mutated MMR2 in MDCKII cells caused no difference in megalin expression and its cellular distribution. However, endocytosis was increased in the presence of S4577D mutant compared to megalin wildtype

Conclusions: mTORC1 complex is an important regulator of proximal tubular function and phosphorylates megalin to influence megalin function.

Funding: Private Foundation Support

TH-PO488

Proximal Tubule-Specific Regulation of NPT2a by NHERF1

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Background: NHERF1 (Na-H Exchanger Regulator Factor 1), a PDZ protein that expresses an Ezrin binding domain (EBD), regulates proximal tubule BBM expression of NPT2a (Na-phosphate cotransporter), a critical determinant of phosphate homeostasis, through interactions with NPT2a and Ezrin (an actin cytoskeleton linking protein). Knockout of NHERF1 or Ezrin results in aberrant trafficking and diminished BBM expression of NPT2a. Additionally, knockout of NHERF1 decreases association of NPT2a with Ezrin. We hypothesize that NHERF1 regulates NPT2a trafficking through PDZ interactions and NPT2a anchoring through EBD interactions.

Methods: To test our hypothesis, we generated cDNA constructs encoding: NPT2a full-length (FL); NPT2a PDZ1-deficient (TRL-); NPT2a/NHERF1 chimera wherein the EBD of NHERF1 replaces the TRL motif of NPT2a (Chimera); NHERF1 full-length (FL); and NHERF1 EBD deficient (EBD-). We transfected HEK293 cells, which express Ezrin but not NPT2a or NHERF1, with wild-type and mutant NPT2a and NHERF1 constructs and assessed their expression and function with ^{32}P-phosphate uptake, immunofluorescence microscopy, and differential centrifugation/western blot experiments.

Results: HEK293 cells expressing NPT2a FL, NPT2a TRL-, or NPT2 Chimera constructs all exhibited 2.5-fold greater phosphate uptake versus sham- or vector-only transfections. Co-transfection with NHERF1 FL or NHERF1 EBD- constructs did not enhance phosphate uptake. Contrary to the diminished NPT2a membrane expression observed in proximal tubule cells lacking NHERF1 or transfected with NPT2a TRL-, immunofluorescence of HEK293 cells transfected with wild type and mutant NPT2a constructs demonstrated plasma membrane localization in the absence or presence of NHERF1. Wild type and mutant NHERF1 constructs exhibited global expression throughout the cell, even at the lowest transfection level (75 ng/ul). Differential centrifugation/Western blotting of transfected cells revealed wild type and mutant NPT2a expression in only the organelle and plasma membrane compartments, while wild type and mutant NHERF1 construct expression was observed in organelle, plasma membrane, and cytosol compartments.

Conclusions: These studies suggest that 1) NHERF1 regulation of NPT2a is proximal tubule specific; and 2) unidentified accessory protein(s) are essential for the BBM trafficking, localization, and function of NPT2a in proximal tubule.

Funding: Veterans Affairs Support

TH-PO489

Dissecting the Na/K-ATPase Signaling Complex in Renal Proximal Tubule: A Cross-Linking Approach

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Background: The Na/K-ATPase α1 subunit and c-Src have been shown to form a signaling complex. Activation this signaling cascade regulates sodium handling in proximal tubule, systemic oxidative stress, and uremic cardiomyopathy. The present study is to investigate the formation of the Na/K-ATPase signaling complex, especially the binding of the α1 subunit and c-Src under native condition in live cells.

Methods: Crosslinking studies were performed in live LLC-PK1 cells with sulfhydryle-sulfhydryle crosslinkers BMH (non-cleavable) and DTME (cleavable). SDS-PAGE and WES system were used to determine the crosslinking efficiency and molecular weight shifts under denatured condition. Blue Native gel electrophoresis (BN-PAGE) was used to identify the molecular weight of the complex under native condition. A BN-PAGE/SDS-PAGE 2D system was used to separate and identify the components of the Na/K-ATPase complex by silver staining and Western blot.

Results: (1) Both BMH and DTMH effectively crosslink the α1 subunit and c-Src, demonstrated by Western blot analysis in both SDS-PAGE and WES system. (2) In BN-PAGE system, like in control, both BMH and DTME-treated samples showed protein bands closer to marker of 720 kDa (between 480 and 720 kDa markers). Western blot analysis showed co-existence of the α1 subunit, β1 subunit, c-Src, and caveolin-1. (3) In WES system, like seen in control, there is a clear crosslinking between the α1 subunit and c-Src, by comparing the data amongst BMH and DTME crosslinking treatments, combined with or without DTT/SDS cleavage. (4) In the BN-PAGE/SDS-PAGE 2D system, preliminary data showed that the complex contains the α1 subunit, c-Src, and caveolin-1. (5) Interestingly, pretreatment with pNaKtide (a peptide derived from the α1 subunit), an antagonist of the Na/K-ATPase signaling, increases ouabain-sensitive 86Rb+ uptake in LLC-PK1 cells. Moreover, pNaKtide also co-exists with the Na/K-ATPase complex.

Conclusions: Our data indicated that the Na/K-ATPase signaling complex contains the Na/K-ATPase α1 subunit, c-Src, and caveolin-1. Further studies with mass spectrometry need to be performed to confirm the findings, and might be able to find more component(s) of the complex.

Funding: Other NIH Support - Jiang Liu, Government Support - Non-U.S.

TH-PO490

Osmotic Diuresis by SGLT2 Inhibition Is Associated with Increased Renal Solute-Free Water Reabsorption and AQP2 Expression in Diabetic Rats

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Background: Most of the filtered glucose is reabsorbed in the early proximal tubule by the sodium-glucose cotransporter SGLT2. The glycosuric effect of the SGLT2 inhibitor ipragliflozin is associated with a sustained diuretic and natriuretic tone that activates compensatory increases in fluid and food intake to stabilize body fluid volume (Am J Physiol Renal Physiol 2018, May 23. doi: 10.1152/ajprenal.00143.2018). However, the compensatory mechanisms that are activated on the level of renal tubules remain unclear.

Methods: Non-obese type 2 diabetic Goto-Kakizaki (GK) rats were treated with vehicle (Veh) or 0.01% (in diet) ipragliflozin (Ipra) (n= 4-5) with free access to food and water. After 8 weeks, GK rats were placed in metabolic cages for 24h urine collection. Blood was collected by cardiac puncture and whole kidneys for western blot were harvested under terminal isoflurane anesthesia.

Results: Body weight (365±10 vs. 353±5 g) and serum glucose (303±46 vs. 312±25 mg/dL) were similar between Veh and Ipra. Ipragliflozin increased food and fluid intake (food: 19.5±1.5 vs. 27.8±0.9 g/24h*, fluid: 37.0±7.0 vs. 87.0±5.9 mL/24h*, *P<0.05 vs Veh), urine volume (25.7±3.9 vs. 64.2±4.9 mL/24h*), urinary glucose excretion (1.0±0.6 vs. 5.9±0.4 g/24h*), urinary Na^+ excretion (2.2±0.2 vs. 3.2±0.3 mEq/24h*), renal osmolar clearance (128±17 vs. 265±13 mL/24h*) and solute-free water reabsorption (102±14 vs. 201±9 mL/24h*). The renal membrane protein expression of SGLT2 and AQP2 was increased, whereas NKCC2 expression was decreased in the Ipra vs Veh group. The expression of SGLT1, NHE3, phosphorylated NHE3 (S605 and S552), AQP1 and ENaC (aENaC, bENaC and gENaC) was similar between the groups.

Conclusions: The SGLT2 inhibitor ipragliflozin induced a sustained glycosuria, diuresis, and natriuresis, and increased solute-free water reabsorption in the kidneys of diabetic rats. The latter was associated with an increase in renal AQP2 expression. These results suggest that the osmotic diuresis induced by SGLT2 inhibition stimulates compensatory fluid reabsorption in the collecting duct.

Funding: Government Support - Non-U.S.

TH-PO491

Acidosis Stimulates SDF/CXCR4 Expression and Antimicrobial Responses via HIF-1α in Mouse Collecting Duct (M-1) Cells

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Background: Intercalated cells (ICs) mediate H^+ and HCO_3 secretion in the kidney collecting duct (CD), We reported that IC adaptation to metabolic acidosis is mediated by SDF1 signaling via CXCR4 (JCI 125:4365, 2015), and that metabolic acidosis stimulates expression of the antimicrobial peptide (AMP) cathelicidin in rabbit urine (AJP 313: F1061, 2017).

Methods: We used M-1 cell line (ATCC CRL-2038), from mouse l (CD), as an *ex vivo* model. M-1 cells were cultured in normal (25mM $NaHCO_3$) and acidic (10mM $NaHCO_3$, 10uM EIPA) medium±HIF-1α stabilizer (IOX2,100uM), HIF-1α inhibitor PX-478 (60uM), LPS (200ng/ml), and Arginine (5mM) for 24hr. Total RNA was isolated and antimicrobial peptides, cathelicidin (Camp) and beta-defensin 2 (BD2)) and SDF1/CXCR4 mRNA abundance determined by real-time qRT-PCR and the ΔΔCt method. Uropathogenic *E. coli* (UPEC) were incubated (5 MOI) with M-1 cells for 90min; unbound bacteria removed by washing, intracellular infection of M-1 cells was determined by gentamicin (100ug/ml) treatment, prior to lysis. Dilutions of cell lysates were plated on agar to determine UPEC burden.

Results: Acidosis induced Camp (2.1 fold±0.20, n=3, p< 0.001), BD 2 (2.83 fold±0.26, n=3, p< 0.01), SDF1 (2.44 fold±0.28, n=3, p<0.01), and CXCR4 mRNA (3.1 fold±0.29, n=3, p<0.01); Prior exposure to acid media decreased by 35% the UPEC burden (mean CFU/ml: Normal=$1.12\pm0.07x10^6$; Acidosis= $7.37\pm0.03x10^5$, p<0.01). IOX2 increased Camp (2.81 fold±0.31, n=6, p< 0.05) and BD2 mRNA abundance (3.80 fold±0.36, n=6, p< 0.01),

and PX-478 reduced M-1 cell resistance to infection conferred by acid-medium by 12% (mean CFU/ml: Acidosis=4.5±0.45x10⁴; Acidosis+PX-478=5.3±0.6x10⁴, p<0.05). M-1 cells treated by combination of IOX2, LPS, and Arginine were substantially more resistant to infection (mean CFU/ml: Untreated=6.7±0.55x10⁴; IOX2, LPS,Arg=2.8±0.35x10⁴, p< 0.01), a 58.2% decrease in UPEC burden. LPS induced SDF1 and CXCR4 mRNA in normal (SDF1: 2.67±0.33, n=3, p< 0.01; CXCR4: 2.94±0.38, n=3, p<0.01) or acidic (SDF1: 4.68±0.61, n=3, p< 0.01; CXCR4: 6.47±0.29, n=3, p<0.01) medium.

Conclusions: Acidosis, via activation of HIF-1α, stimulates expression and function of innate immune defense peptides as well as SD1 and CXCR4 in kidney collecting duct cells.

TH-PO492

Metabolic Acidosis Increases Susceptibility of Mice to Uropathogenic E. coli (UPEC)-Induced Pyelonephritis (PN)

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Background: Carbonic anhydrase 2-deficient mice show metabolic acidosis with deficient urine acidification, and are more susceptible to UPEC-induced PN (Hains, AJP 307:F869, 2014). Whether the susceptibility to PN is due to H^+ transport abnormalities or acidosis is unclear. In this study we examined the impact of acidosis on susceptibility of refluxing C3H-HEouJ mice to PN.

Methods: Metabolic acidosis was induced in C3H-HEouJ mice via NH_4Cl (2% w/w) supplementation of food±I.P. administration of acetazolamide (ACZ 100 mg/kg). Acid-base state was assessed by blood gas using an iSTAT® G3+ and pH of urine collected under water-saturated mineral oil in metabolic cages housing 2-4 mice. Collecting duct (CD) fragments were enriched from collagenase-digested mouse kidney by DBA-lectin magnetic sorting. Relative abundance of SDF1 and antimicrobial peptide (AMP) mRNAs (cathelicidin [Camp]; beta defensin-2 [BD2]) in CDs was determined by qRT-PCR via ΔΔCt. Female C3H-HEouJ mice were infected with UPEC strain CFT073 @ 10^7 cfu/50 µl via transurethral inoculation. Bacterial burden (cfu/g) in bladder and kidney was determined by culture of tissue homogenates. Statistical significance utilized T-test or Mann-Whitney Test.

Results: NH_4Cl-fed mice were acidotic (s[HCO3] 18.2±0.65*, Ur pH 5.8±0.02*; N=8) compared to normal (NL) (s[HCO3] 22.2±0.68; Ur pH 6.8±0.01, *p<0.05, N=24); co-administration of ACZ resulted in severe acidosis and reduced urine acidification (s[HCO3] 12.8±0.7**; Ur pH 6.9±0.05, p<0.001 versus NL, N=5-9). UPEC infection alone did not induce SDF1 mRNA; however acidosis+UPEC infection induced SDF1 expression 3.5±0.4 fold over NL (p<0.01). Severe acidosis (NH_4Cl+ACZ) increased Camp (2.1±0.11) and BD2 (2.3±0.36) mRNA, whereas expression of SDF-1 mRNA was induced 10.5±1.0 compared to NL (p<0.01). Acidotic mice were more susceptible to PN than NL (kidney mean cfu/g: NL $4.1x10^3$; Acidosis $2.6x10^8$, p<0.001; N=7-8). UPEC burden was also higher in bladders from acidotic mice compared to normal (mean cfu/g: NL $6.8x10^5$; Acidosis $8.6x10^8$, p<0.001).

Conclusions: Metabolic acidosis increases the susceptibility of C3H-HEouJ mice to PN. Increases in AMP expression with acidosis do not compensate for an apparent loss of barrier function, manifested as increased production of SDF1, a key mediator of the kidney response to metabolic stress (e.g. hypoxia, acidosis).

TH-PO493

Monophosphoryl Lipid A (MPLA) Prevents LPS-Induced Inhibition of HCO3- Absorption in Medullary Thick Ascending Limb Through Negative Regulation of Interleukin-1 Receptor-Associated Kinase-1 (IRAK-1)

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Background: LPS inhibits HCO_3^- absorption in the MTAL through activation of a basolateral TLR4-MyD88-ERK pathway that is upregulated by sepsis. Recently we showed that pretreatment with the nontoxic immunomodulator MPLA prevents inhibition of HCO_3^- absorption by LPS through activation of a TLR4-TRIF-PI3K pathway that prevents LPS-induced ERK activation. Here, we examined molecular mechanisms that underlie the protective inhibitory interaction between the MPLA-PI3K and LPS-ERK signaling pathways.

Methods:

Results: We first examined IRAK-1, a critical mediator of LPS signaling downstream of TLR4 that is downregulated in LPS tolerant cells. Treatment of mouse MTALs with LPS for 15 min in vitro increased IRAK-1 phosphorylation 1.5-fold. The effect of LPS to activate ERK in the MTAL was prevented by a selective IRAK-1 inhibitor, establishing IRAK-1 as the upstream mediator of ERK activation in the LPS pathway. Pretreatment of MTALs with MPLA for 2 h in vitro prevented LPS-induced IRAK-1 activation. This effect of MPLA was eliminated by a PI3K inhibitor. Toll-interacting protein (Tollip) is an intracellular protein that is induced in LPS tolerant cells and negatively regulates LPS signaling by suppressing IRAK-1 activity. To assess whether Tollip may be involved in MPLA's actions in the MTAL, mice were pretreated with MPLA or vehicle 48 h prior to sham or cecal ligation and puncture (CLP) sepsis surgery. MPLA pretreatment increased Tollip expression in microdissected MTALs and inner stripe of outer medulla from sham and CLP mice. In addition, treatment with MPLA for 2-3 h in vitro increased Tollip expression in inner stripe of control mice.

Conclusions: We conclude that MPLA activates a PI3K-dependent pathway that inhibits LPS stimulation of IRAK-1 in the MTAL, thereby preventing LPS-induced ERK activation that inhibits HCO_3^- absorption. These protective effects of MPLA likely are mediated through the induction of Tollip, an immunomodulatory protein that negatively regulates IRAK-1. These results provide new evidence that renal tubule epithelial cells are capable of undergoing immune reprogramming that affords resistance to LPS and identify IRAK-1 as a key molecular target through which MPLA prevents LPS impairment of HCO_3^- absorption in the MTAL.

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TH-PO494

Secretin-Stimulated Urinary HCO3- Excretion: A Function of CFTR and Pendrin

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Background: The gastro-intestinal hormone secretin (SCT), the first hormone ever discovered (Bayliss and Starling, ca. 1905), is able to acutely increase the amount of HCO_3^- in the urine, but the underlying mechanism remains enigmatic. The actions of secretin are well understood in gastro-intestinal physiology; among many functions it acts as an important activator of pancreatic HCO_3^- secretion. Intriguingly, the SCT receptor is also expressed in the collecting duct (CD) of the kidney.

Methods: Real time monitoring of urine flow and urinary pH was allowed by bladder catheterization and insertion of micro pH-electrodes in the outflow of the catheter in i.v. anaesthetized mice.

Results: Here, we show that SCT elicits acute urinary alkalisation, increases urinary [HCO_3^-] and urinary HCO_3^- excretion rate in anaesthetized mice. This effect is present in multiple mouse strains corroborating data from older studies in healthy humans. Importantly, we identified that the SCT effect is completely absent in mice lacking the apical Cl^-/HCO_3^- exchanger pendrin, which, in the kidney, is exclusively expressed in the apical membrane of β-IC of the CNT/CD. Moreover, we found that the SCT effect on urinary pH is dramatically diminished in mice with either global knock-out of CFTR or renal tubule-specific knock-out of CFTR. The effect on urinary [HCO_3^-] and urinary HCO_3^- excretion is completely abolished in both CF animal models, corroborating early data from children suffering from cystic fibrosis. Noteworthy, CFTR expression has been shown to be several folds higher in β-IC cells compared to α-IC and principal cells.

Conclusions: In conclusion, this study has defined the molecular mechanism of SCT-induced urinary HCO_3^- excretion as a function of the specific activation of the β-IC of the CD. Thus, in close similarity to the established mechanism of SCT-induced HCO_3^- excretion in the exocrine pancreas, an analogous mechanism was identified in the kidney.

Funding: Government Support - Non-U.S.

TH-PO495

MAGE-D2 Promotes Expression and Stability of Pendrin Protein

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Background: We recently showed that mutations in *MAGE-D2* cause polyhydramnios with preterm delivery of the affected baby and a severe but transient form of antenatal Bartter's syndrome (tBS). Although reduced total and apical expression of the sodium–chloride transporters NKCC2 and NCC was shown in vivo and in vitro, which explains massive salt losing (Laghmani et al, N Engl J Med. 2016), additional transporters may also be impaired. One potential candidate is Pendrin, because its loss increases salt losing and because it is expressed in the distal tubule as MAGE-D2. Consequently, the aim of the present study was to investigate the potential role of MAGE-D2 in Pendrin biogenesis.

Methods: Pendrin protein expression was monitored in transiently transfected HEK293 cells by immunoblotting, which allows the detection of both the immature (core-glycosylated) and mature Pendrin protein. Stability of Pendrin protein was assessed by cycloheximide chase assay. We studied the effects of wild type MAGE-D2 and mutant R446CMAGE-D2 on Pendrin expression. In addition, the role of endogenously expressed MAGE-D2 role was investigated by small interfering RNA. To assess the specificity of our findings, we also analyzed the effects of MAGE-D2 overexpression on NHE3 biogenesis.

Results: MAGE-D2 co-expression robustly increased expression of immature and total cellular Pendrin protein in a dose dependent manner. Cycloheximide chase assays (CHX) showed that in cells over expressing MAGE-D2, stability of immature Pendrin is increased. In contrast to MAGE-D2 wild type, R446CMAGE-D2, a missense mutation identified in a tBS patient, co-expression significantly decreases Pendrin stability. Analogous to R446CMAGE-D2, knockdown of endogenous MAGE-D2 by small interfering RNA also decreases Pendrin stability. In contrast to Pendrin, our preliminary data did not reveal an effect of MAGED2 on the expression of total NHE3.

Conclusions: Our findings show that MAGED2 specifically promotes the expression of Pendrin. Importantly, our data indicate that MAGED2 affects multiple salt transporters in the distal tubule, thus explaining the severe phenotype.

TH-PO496

Transcriptome Profiling in Pendrin Deficient Mice Provides New Insight into the Role of Pendrin in Kidney Physiology

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Background: Slc26a4 (Pendrin) is a Cl^-/HCO_3^- exchanger that is primarily expressed on the apical membrane of B-intercalated cells in the kidney connecting tubules/cortical collecting ducts and plays a critical role in salt absorption and bicarbonate secretion.

Methods: To gain better insight into the role of pendrin in kidney function, RNA-Seq analysis was performed on kidney cortices of wild type and pendrin KO mice and results verified by Northern hybridization and/or immunofluorescence labeling.

Results: The most dramatic changes in the expression of solute transporters belonged to the families of organic anion and cation transporters and their collaborating partners, which are primarily expressed in the proximal tubule. The expression of the basolateral organic anion transporters, OAT1 and OAT3 (Slc22a6 and a8), along with their interacting partner NaDC-3 (Slc13a3), was significantly increased and paralleled a robust enhancement in the expression of the apical voltage driven urate efflux transporter Npt4 (Slc17a3). Likewise, the expression of the basolateral organic cation transporter, Oct2 (Slc22a2) increased and was matched by the enhanced expression of MATE1 (SLC47A1) and NHE-8 (Slc9a8) on the apical membrane. The activation of NHE-8 is likely to provide the necessary luminal proton for MATE1, an organic cation/H^+ exchanger on the apical membrane of the proximal tubule. In addition, the Na^+-Sulfate cotransporter (Slc13a1) which is expressed on the apical membrane of proximal tubules and mediates sulfate absorption showed significant up-regulation.

Conclusions: In conclusion, deletion of Slc26a4 is associated with enhanced expression of organic anion and cation transporters on the basolateral and apical membranes of the proximal tubule. We propose that the coordinated regulation of organic anion and cation transporters in the kidney proximal tubule of pendrin KO mice supports an important role for pendrin in the excretion of endogenous and exogenous organic cations (such as creatinine, guanidine, metformin, cisplatinum, etc), endogenous and exogenous organic anions (uric acid, prostaglandins, uremic toxins, penicillin, methotrexate, linezolid, etc), and inorganic anions such as sulfate.

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TH-PO497

NBCe1A Regulates Citrate Excretion During Hypokalemia Through NaDC1 Expression-Dependent and Independent Mechanisms

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Background: Urinary citrate is an alkali equivalent and chelates calcium, thus is critical to acid-base homeostasis and prevention of calcium nephrolithiasis. Hypokalemia causes hypocitraturia; proximal tubule NaDC1 mediates citrate reabsorption and is thought to be the major regulator of citrate excretion. However, whether NaDC1 protein expression changes in hypokalemia and the signaling pathways involved are unknown.

Methods: Mice were fed either a K-control diet for 2 days or K-control diet for 2 days then K-free diet for 4 days. Urinary citrate was measured using ^{1}H-NMR. We determined NaDC1 expression in the proximal convoluted tubule (PCT), proximal straight tubule in the medullary ray (PST-MR) and outer medulla (PST-OM) using quantitative immunohistochemistry. To determine the role of NBCe1-A in the signaling pathway regulating NaDC1 expression, we compared mice with NBCe1-A deletion (KO) with wild-type (WT) littermates.

Results: While on K-control diet, urinary citrate excretion did not differ between WT and NBCe1-A KO mice. However, KO mice had significantly less NaDC1 immunolabel than WT mice in the PCT and PST-MR. A K-free diet for 4 days decreased citrate excretion significantly in both genotypes, but the decrease was significantly blunted in KO mice compared to WT mice (WT, 95±3% decrease; KO, 83±6% decrease; $P<0.05$). In WT mice, K-free diet increased PCT and PST-MR NaDC1 immunolabel significantly compared to K-control. In contrast, in NBCe1-A KO mice NaDC1 expression did not differ significantly between K-control and K-free mice in any proximal tubule segment, PCT, PST-MR or PST-OM.

Conclusions: (1) K-free diet decreases citrate excretion by increasing NaDC1 expression in the PCT and PST-MR through a mechanism that involves signaling through the basolateral membrane protein NBCe1-A; (2) In NBCe1-A KO mice fed K-control diet, either alternative citrate transporters or NaDC1 regulation through a mechanism other than steady-state protein expression enables similar rates of citrate reabsorption despite less total NaDC1 expression than WT; and, (3) In the absence of NBCe1-A a K-free diet acts through NBCe1-A-independent signaling pathways to increase citrate reabsorption through a mechanism that does not involve altered NaDC1 protein expression.

Funding: NIDDK Support

TH-PO498

Proximal Tubule NBCe1-A-Dependent Regulation of Ammonia and Potassium Metabolism During Hypokalemia

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Background: Dietary potassium restriction is associated with increased ammonia excretion, but neither the specific proteins that signal this response nor the functional role of increased ammonia excretion are known. This study's purpose was to determine NBCe1-A's role in the effect of dietary potassium restriction on ammonia metabolism and potassium homeostasis.

Methods: Mice were fed either a K-control diet for 2 days or K-control diet for 2 days followed by K-free diet for 4 days. To determine NBCe1-A's role we compared mice with NBCe1-A deletion (KO) with wild-type (WT) littermates. All studies included both male and female mice and inclusion of sex in statistical analyses did not change any conclusions.

Results: Urinary ammonia excretion increased during each day of K restriction in WT mice. In KO mice the increase in ammonia excretion was significantly less on each day than in WT mice. Compared to WT, NBCe1-A KO had significantly lower cortical expression of key ammoniagenic proteins, phosphoenolpyruvate carboxykinase and phosphate-dependent glutaminase, and greater expression of the ammonia-recycling protein, glutamine synthetase. NBCe1-A deletion also altered renal K handling during K-free diet. After 4 days of K-free diet, hypokalemia was significantly more severe in KO mice than in WT (KO, 2.5±0.2; WT, 3.5±0.2 mM, $P<0.001$). Despite more severe hypokalemia, urinary K was significantly greater in KO than WT during dietary potassium restriction. Total NCC and phospho-NCC expression, which decrease renal K excretion, were significantly lower in hypokalemic KO than WT mice. Hypokalemia normally decreases ROMK expression; however, despite more severe hypokalemia in KO mice, ROMK expression did not differ significantly between WT and KO. This suggests abnormal ROMK regulation in NBCe1-A KO mice contributed to the more severe hypokalemia.

Conclusions: 1) NBCe1-A is essential to the signaling pathway that increases ammonia excretion in response to dietary potassium restriction; 2) Hypokalemia induced by a K-free diet appears to regulate distal K transport through a proximal tubule-dependent mechanism involving NBCe1-A, signaling through DCT NCC phosphorylation, and regulating ROMK expression.

Funding: NIDDK Support

TH-PO499

Renal H+/K+ ATPases Mediate Benzamil-Inhibited Urinary H+ Excretion

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Background: Acute inhibition of ENaC causes a marked urinary alkalization. It was previously assumed that the so-called "voltage hypothesis" explains this urinary pH effect. The "voltage hypothesis" states that the lumen-negative ENaC-dependent transepithelial voltage provides the driving force for H^+ secretion via the vacuolar H^+ ATPase in neighbouring α-intercalated cells of the CD. In two preceding studies, we have contested the "voltage hypothesis". This, therefore, calls for an alternative explanation of the mechanism of ENaC blocker-mediated urinary alkalisation. Here we present data that strongly supports the involvement of renal H^+/K^+ ATPases, which are also located in the apical membrane of the α-IC.

Methods: In vivo studies in anesthetized mice were conducted to continuously measure urine output, urine electrolytes and urine pH.

Results: Application of benzamil acutely alkalized the urine (delta pH: 0.33±0.07). In parallel, the ambient luminal $[K^+]$ dropped markedly. In animals fed a low K^+ diet, the benzamil-induced urinary alkalisation was greatly enhanced (delta pH: 0.74±0.12) and a significantly lower urine $[K^+]$ nadir was reached. In double knock out mice lack both isoforms of the H^+/K^+ ATPases the benzamil effect was completely absent.

Conclusions: These data support the following explanation. ENaC inhibitors elicit their effect indirectly via their marked K^+ sparing property. They induced a strong drop of the ambient luminal $[K^+]$ concentration with impedes H^+/K^+ ATPases function and thus tubular H^+ secretion. Thus, we postulate that the lack of substrate (K^+) causes the luminal alkalisation by benzamil.

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TH-PO500

Muc1 Deficiency Causes Urinary Acidification Defects in Mice

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Background: Mucin 1 (human MUC1, mouse Muc1) is expressed on the apical surface of most epithelial cells, including the thick ascending limb (TAL) and distal nephron segments. Proximal tubular expression of Muc1 is induced in ischemia-reperfusion injury, where it stabilizes HIF-1a and b-catenin and plays a protective role. A frame-shift mutation in MUC1 causes autosomal dominant tubulointerstitial kidney disease. However, there is

limited information regarding its functional role in normal kidney. Muc1 knockout mice have no clear phenotype in the absence of stressors (e.g. bacterial infection). The TRPV5 Ca^{2+} channel was reported to be stabilized on the cell surface by galectin-dependent cross-linking to MUC1, providing a novel mechanism for regulation of this ion channel. We observed robust Muc1 apical and sub-apical staining in type A and type B intercalated cells (ICs). In Type A ICs, Muc1 co-localizes with the vacuolar H^+ ATPase (V-ATPase), a protein complex that mediates apical ATP-driven H^+ secretion. V-ATPase subcellular localization regulates H^+ secretion, while defects in V-ATPase function can cause renal tubular acidosis. As Muc1 and the V-ATPase are highly expressed in ICs, we tested the hypothesis that Muc1 regulates V-ATPase expression and function.

Methods: Muc1 KO ($Muc1^{-/-}$), Muc1 heterozygous ($Muc1^{+/-}$) and control mice were given 2.5% sucrose with or without 0.28 M NH_4Cl in drinking water for 7 days. Plasma electrolytes, urine pH and NH_4^+ were measured. Kidneys were processed for immunoblotting and confocal immunofluorescence (IF) microscopy.

Results: IF staining of fixed mouse kidney slices revealed that Muc1 co-localizes with luminal V-ATPase in ICs. Moreover, V-ATPase moved from the cytosol to the apical surface when WT mice were subjected to an acid load. In contrast, V-ATPase remained cytosolic in $Muc1^{-/-}$ mice. In response to acid-loading, both $Muc1^{-/-}$ and $Muc1^{+/-}$ mice exhibited impaired urinary acidification while only Muc1 KO mice exhibited greater metabolic acidosis. The IC-specific a4-subunit of V-ATPase co-immunoprecipitated with Muc1 in extracts of mouse kidney, suggesting that they are components of a protein complex.

Conclusions: These results suggest that Muc1 interacts with the V-ATPase and influences its cell surface localization in type A ICs, and is necessary for a normal renal response to an acid load.

Funding: NIDDK Support

TH-PO501

AKAPs-PKA Disruptors Robustly Increase AQP2 Activity Independently of Vasopressin

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Background: Congenital nephrogenic diabetes insipidus (NDI) is characterized by the inability of the kidney to concentrate urine. Congenital NDI is mainly caused by loss-of-function mutations in the vasopressin type 2 receptor (V2R), leading to impaired aquaporin-2 (AQP2) water channel activity. So far, treatment options of congenital NDI either by rescuing mutant V2R with chemical chaperones or by elevating cyclic adenosine monophosphate (cAMP) levels have failed to yield effective therapies. In this study, we focused on direct activators of PKA as novel therapeutic targets of congenital NDI. The intracellular distribution and activity of PKA are largely controlled by A-kinase anchoring proteins (AKAPs). We examined the effects of AKAPs-PKA disruptors, which dissociate the binding of AKAPs and PKA.

Methods: The effects of AKAPs-PKA disruptors, FMP-API-1 and its derivatives, were examined by mouse cortical collecting duct (mpkCCD) cell lines, isolated tubule microperfusion experiments, and V2R-inhibited NDI mouse model.

Results: FMP-API-1 increased PKA/AQP2 activity in mpkCCD cells. In microperfusion experiments, FMP-API-1 increased osmotic water permeability to the same extent as vasopressin. We then synthesized derivatives of FMP-API-1 to obtain greater pharmacological potency. *In vivo*, FMP-API-1/27 phosphorylated AQP2 at S256 and S269 more strongly than vasopressin and increased urine osmolality in V2R-inhibited NDI mouse model.

Conclusions: FMP-API-1 is a promising lead compound for the treatment of congenital NDI caused by V2R mutations.

TH-PO502

Empagliflozin Contributes to Polyuria via Transcriptional and Post-translational Control of Aquaporin-2 in Diabetic Rat Kidneys

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Background: It has been suggested that one of the most possible mechanisms for the positive cardiovascular and renal outcomes observed with empagliflozin, a selective sodium-glucose contransporter type 2 (SGLT2) inhibitor, would be related to effects on osmotic diuresis and natriuresis. However, the natriuretic effect of SGLT2 inhibitors has been reported to be transient, and long-term data related to diuretic change are sparse.

Methods: This study investigated the effect of a 12-week treatment with empagliflozin (3 mg/kg) on renal sodium transporters and water channels in diabetic OLETF rats by comparing it with other antihyperglycemic agents that included lixisenatide (10 μg/kg), a glucagon-like peptide receptor-1 agonist, and voglibose (0.6 mg/kg), an α-glucosidase inhibitor.

Results: At 12 weeks of treatment, the serum sodium level and fractional excretion of sodium were not significantly different between empagliflozin-treated and control diabetic rats. Empagliflozin-treated diabetic rats produced slightly decreased, but still high, urine volume and glycosuria, and showed significantly higher electrolyte-free water clearance than diabetic rats treated with other agents. In empagliflozin-treated rats, renal protein expressions of Na^+-K^+-$2Cl^-$ cotransporter and epithelial Na^+ channel were decreased, and Na^+-Cl^- cotransporter expression was unaltered compared with control diabetic rats. Empagliflozin increased the expression of aquaporin (AQP)7 but did not affect AQP1 and AQP3 protein expressions in diabetic kidneys. Despite the increased expression in vasopressin V2 receptor, protein and mRNA levels of AQP2 in kidneys of empagliflozin-treated diabetic rats were significantly decreased compared to control diabetic rats. In addition, empagliflozin increased the phosphorylation of AQP2 at S261 through the activation of p38- mitogen-activated protein kinase, protein phosphatase 2B and glycogen synthase kinase 3α, and cyclin-dependent kinases 1 and 5.

Conclusions: The collective results indicate that the long-term use of empagliflozin may promote diuresis associated with downregulation of AQP2 as well as its sustained natriuretic ability.

Funding: Government Support - Non-U.S.

TH-PO503

Epithelial Depolarization Induces AQP2 Up-regulation via Non-Canonical Ser-269 Phospho-Regulation Independently of Any Hormonal and Chemical Stimulation

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Background: Aquaporin-2 (AQP2) has multiple vasopressin-sensitive phosphorylation sites in its C-terminal region. We previously examined how pS256-positive AQP2 is catalyzed by vasopressin or forskolin stimulation using a phospho-specific AQP2 immuno-isolation technique, and identified a combined phospho-regulation: pS256-pS261-AQP2 changed to pS256-pS261-pS269-AQP2, and then transformed to pS256-pS269-AQP2 in both MDCK cells and mouse kidney. This cascade translocates pS256-positive AQP2 to the apical plasma membrane. We defined this phospho-regulation as canonical in this study. We next applied phospho-specific AQP2 immuno-isolation to quantify phospho-AQP2 in the total-AQP2 population. In the process of assay establishment, we hypothesized that cell polarization status affects AQP2 phosphorylation.

Methods: In this study, we divided MDCK cells stably expressing rat-AQP2 into two groups: cells were grown to confluence for 3 days and 1) their medium was just replaced with fresh normal DMEM without trypsinization (polarized group), or 2) they were trypsinized and re-plated with the same DMEM (depolarized group). Cells were lysed 24 h later without any hormonal or chemical stimulation and subjected to western blotting.

Results: Wild-type AQP2 significantly increased in the depolarized group. Ser-256 and Ser-261 phosphorylation was not changed, whereas Ser-269 phosphorylation significantly increased in the depolarized group. In S269A-AQP2 cells, depolarization-induced AQP2 upregulation did not occur. Interestingly, S256A-AQP2 was significantly upregulated in the depolarized group with a significant increase of Ser-269 phosphorylation.

Conclusions: These results demonstrate the existence of polarity-induced and hormone-independent AQP2 regulation, indicating a novel rationale for AQP2 function, i.e. in wound healing, tubular regeneration, cyst formation. In addition, we identified non-canonical AQP2 Ser-269 phospho-regulation, which is independent of prior Ser-256 phosphorylation and is not accompanied by subsequent Ser-261 dephosphorylation. These findings provide a basis for subsequent studies to investigate multi-functional roles of AQP2 beyond the categorical flame of apical water channel in polarized epithelial cells.

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TH-PO504

AQP11 Plays a Role in Water Homeostasis in Concert with AQP4 in the Brain

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Background: Water transport in the brain is tightly controlled by blood-brain-barrier (BBB) composed of endothelial cells (AQP1, 11) and glial foot processes (AQP4) where AQP4 regulates brain edema. Here we examined AQPs mRNA expression in acute hyponatremic or hypernatremic mice models of wild type and AQP11-null mice as AQP11-null mice suffer from renal failure which precludes chronic models.

Methods: By intraperitoneal injection, hypo- and hyper-natremic models were produced with water+desmopressin or 2M NaCl solution four or six hours before sacrifice, respectively. The expression of AQP1, 4 and 11 mRNA were quantified by RT-real-time PCR of whole brain RNA. Brain water content was calculated with 4-day-dried weight in 80 C oven and extravascular leakage by biotin permeability assay.

Results: In the control state, AQP11-null brain showed half AQP4 expression without AQP1 change as compared with wild mice (Na 153.3 vs. 150.7 mEq/L), whereas brain water content was similar (78.98 vs 78.61%). Acute hyponatremia (123.6 vs. 126.0 mEq/L) enhanced AQP4 expression in AQP11-null to the level of the wild mice with no change of AQP1, whereas it did not change AQP1, 4, nor 11 in wild mice. Brain water content was similar (79.93 vs. 79.8%) with expanded perivascular space, Virchow–Robin space. On the other hand, acute hypernatremia (199.5 vs. 208.0 mEq/L) increased AQP4 to the level of wild mice in AQP11-null with half AQP1 expression, whereas it decreased AQP1 and AQP11 by half without change in AQP4 in wild mice. Brain water content was significantly lower in AQP11-null than wild mice (75.34 vs. 76.65%) which was also documented histologically by cellular shrinkage in the brain cortex. Biotin permeability assay revealed no leakage in hypo- and hyper-natremic states. The results suggested that AQP4 expression was downregulated to match the decreased water transport at the endothelium in AQP11-null but may be enhanced to compensate for AQP11-null with osmotic changes although acute hypernatremia produced more water loss in AQP11-null brain.

Conclusions: We conclude that AQP11 may play a role in water homeostasis in concert with AQP4 at BBB with compensating enhanced AQP4 expression in AQP11-null with osmotic challenge. The results set a stage for examining the role of AQP11 in disease states such as brain edema. We are currently studying middle cerebral artery hemi-infarction model in AQP11 null mice.

Funding: Government Support - Non-U.S.

TH-PO505

Lithium and Gsk3α Inhibition Reduces Aquaporin-2 Expression in Primary Cultured Inner Medullary Collecting Duct Cells Due to Independent Mechanisms

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Background: Lithium is a widely used drug for the treatment of bipolar disorders. However, it has severe side effects and up to 40 % of the treated patients develop a diabetes insipidus. Lithium affects also the activity of the glycogen synthase kinase 3 (Gsk3) and mice deficient for Gsk3β isoform in the renal collecting duct showed severe urine concentration abilities. The respective cellular and molecular mechanisms are still not fully understood.

Methods: We used primary cultured inner medullary collecting duct cells to analyze the underlying mechanisms. The cells were treated for different time points and with different concentrations of lithium, the pharmacological inhibitor of the Gsk3α/β (SB216763) or the Gsk3β specific Inhibitor TWS119. The cells were additionally incubated with inhibitors of the lysosomal (using bafilomycin) or proteasomal pathways (using MG132) alone or together with the above mentioned drugs. The expression of Aqp2 was analyzed on the mRNA level by qPCR and on the protein level by Western blot and immunofluorescence analysis.

Results: The qPCR experiments showed that only lithium induced a down regulation of Aqp2 mRNA expression while Gsk3 inhibition by SB216763 had no effect and surprisingly TWS119 led to increased expression. While inhibition of the proteasome with MG132 did not prevent the lithium or SB216763 mediated down regulation of Aqp2, the inhibition of the lysosomal activity with bafilomycin or chloroquine prevented lithium and SB216763 mediated down regulation of Aqp2 on the protein level. On the mRNA level lithium still induced down regulation of Aqp2. The treatment with bafilomycin and chloroquine induced accumulation of Aqp2 in lysosomal structures, which was prevented when the cells were treated with dbcAMP which led to phosphorylation and membrane localization of Aqp2. While down regulation of Aqp2 was also evident when lithium was applied together with dbcAMP, dbcAMP prevented the SB216763 induced down regulation of Aqp2. Interestingly the use of TWS119 induced the expression of Aqp2 on protein and mRNA level.

Conclusions: We showed that lithium and the Gsk3α/β inhibition by SB216763 induces down regulation of Aqp2 on different levels. The exclusive Gsk3β inhibitor TWS119 had the opposite effect indicating that Gsk3α inhibition is involved in Aqp2 down regulation.

Funding: Government Support - Non-U.S.

TH-PO506

Inhibition of Polo-Like Kinase 1 (PLK1), a Cell Cycle Regulator, Prevents the Dysregulation of AQP2, AQP3, and NKCC2 in Obstructive Nephropathy

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Background: Obstructive kidney disease is accompanied by the dysregulation of water channels and sodium transporters, which could account for the water/sodium disorders after obstruction release. PLK1 is known as a key modulator of cell cycle progression. Recently, cell cycle-associated mechanism was shown to contribute to the renal tubular injury. Here we proposed that the inhibition of PLK1 may preserve the water channels and sodium transporters of renal tubules in obstructive nephropathy.

Methods: Male C57BL/6 mice were subjected to unilateral ureteral obstruction (UUO) surgery or sham operation. On day 4 and day 6 after UUO surgery, mice received i.p injection of specific PLK1 inhibitor BI6727(15mg/kg). On day 7 after UUO surgery, animals were sacrificed and kidney samples were collected for analysis.

Results: qRT-PCR analysis detected that the marked reduction of AQP2, AQP3, and NKCC2 (40-60%) in obstructed kidneys were largely normalized by BI6727 treatment at mRNA levels. By immunohistochemistry and Western blotting, we further confirmed that post therapy (day 4 and day 6 after kidney obstruction) by BI6727 entirely restored the reduction of AQP2 and NKCC2 proteins to the normal levels. Due to the known role of PGE2 cascade in regulating water channels and sodium transporters in obstructed kidney, we measured COX-1, COX-2 and mPGES-1 and observed 3-8 folds increments of these components of PGE2-generating cascade. However, BI6727 therapy did not affect the upregulation of COXs and mPGES-1, suggesting that inihbition of PLK1 prevserved AQP2, AQP3, and NKCC2 possibly through a prostaglandin-independent mechanism.

Conclusions: Inhibition of PLK1 restored the downregulation of AQP2, AQP3, and NKCC2 in obstructed kidneys, suggesting a novel role of tubular cell cycle progression in dysregulating water channels and sodium transporters independently of prostaglandin-associated mechanism in obstructive nephropathy.

TH-PO507

Phosphorylation of Ser261 and Dephosphorylation of Ser269 Is Important for Urinary Excretion of AQP2

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Background: AQP2 a key membrane protein which determines water permeability of collecting ducts. AQP2 is regulated by phosphorylation at S256, S261 and S269. As a short-term regulation of vasopressin, intracellular amount S261 phosphorylated-AQP2 (261-P) decreases whereas 269-P increases with relatively stable 256-P. The decrease in 261-P can be explained by dephosphorylation, degradation, or even extrusion out of the cell. In this sence, it is intriguing whether phoshorylation is involved in the urinary excretion of exosomal AQP2 and if so, which phosphorylation site is critical.

Methods: Human urine samples were obtained from a central diabetes insipidus patient (CDI, 45 years old, female). DDAVP 0.25ug was administered to the nasal mucosa after 24 h withdrawal. Urine samples were collected pre and after the administration until 3 h. Urine exosomes were obtained by the differential centrifugation, and analyzed by Western blot using a usual and 256-P, 261-P and 269-P-specific antibodies. Endogenously AQP2-expressing cells (mpkCCD) and stably rat AQP2-transfected MDCK cells (AQP2-MDCK) were cultured on the permeable support and the culture medium in the apical side were analyzed

Results: 1) In a CDI patient, DDAVP administration evoked a steady increase in urine osmolality until 3 h. Western blots of urine exosomal AQP2 excretion corrected for creatinine showed that total AQP2 rapidly increased until 1 h (8.5 times compared to the pre), then gradually increased until 3 h. 256-P progressively increased until 3 h. On the other hand, 261-P reached its peak increase at 0.5 h (2.4 times), and then, surprisingly decreased to the pre level at 2 h. 269-P was hardly visible throughout the study periods. 2) Western blots of apical culture medium of mpkCCD and AQP2-MDCK after vasopressin/forskolin stimulation, total, 256-P and 261-P were observed, but 269-P was minimally visible, although all these phosphorylated forms were observed in the cell lysates. 3) The LC-MS/MS phosphoproteomic analysis of human urine confirmed the presence of phosphorylation at S256 and S261, but not at S269.

Conclusions: These results indicate the importance of phoshorylation at S261 and dephoshphorylation at S269 in exosomal excretion of AQP2, highlighting the significant role of the endocytosis-exosome pathway in AQP2 metabolism in collecting ducts.

Funding: Government Support - Non-U.S.

TH-PO508

Level of ENaC Activity Drives Hypertension from Chronic Activation of Vasopressin V2 Receptors

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Background: Vasopressin can contribute to sodium homeostasis and blood pressure regulation by stimulating the epithelial sodium channel (ENaC) through activation of vasopressin V2 receptors (V2R) in principal cells of the distal nephron. However, a direct link between chronic activation of V2R, high ENaC activity, and high blood pressure remains to be established *in vivo*.

Methods: We asked whether an isolated increase in V2R-mediated ENaC activity can lead to high blood pressure. We tested the blood pressure effects of chronic activation of V2R in mice with varying levels of ENaC activity. We infused dDAVP (100 ng/hr), a specific V2R agonist, for two weeks into Liddle (beta-ENaC-R566X), Pseudohypoaldosteronism Type 1 (PHA) mice, or wild type (WT) littermates and used radiotelemetry to compare blood pressure responses. We fed all mice normal sodium chow because they have similar blood pressures at this level of dietary sodium.

Results: We found that infusion of dDAVP into WT mice increased baseline blood pressure (systolic (SBP) by 4.3±0.47 mmHg and mean arterial pressure (MAP) by 3.7±0.45 mmHg, $P<0.05$); infusion of dDAVP into Liddle mice increased baseline blood pressure to a greater extent (SBP increase by 7.3±1.16 mmHg and MAP increase by 7.0 mmHg±1.57, $P<0.05$). Infusion of dDAVP into PHA1 mice induced no rise in baseline blood pressure. Blood pressure was highest in dDAVP-infused Liddle mice compared to dDAVP-infused WT or PHA mice (SBP 146±5.75 mmHg (Liddle) vs 135 or 137 mmHg; MAP 127±4.16 mmHg (Liddle) vs 119 or 120 mmHg). We also found that administration of benzamil, a specific ENaC inhibitor, only restored blood pressures of dDAVP-infused Liddle mice (SBP decrease by 4.86±1.31 mmHg and MAP decrease by 4.9±1.21 mmHg, $P<0.05$).

Conclusions: Our findings demonstrate that a specific increase in V2R-mediated ENaC activity in Liddle mice is sufficient to raise blood pressure. Since infusion of dDAVP can raise blood pressure in Liddle mice, our findings also suggest that the Liddle (beta-ENaC-R566X) mutation and V2R can stimulate ENaC through distinct pathways. Finally, since V2R-mediated increase in blood pressure in WT mice is not sensitive to benzamil inhibition, chronic activation of V2R is also sufficient to raise blood pressure through ENaC-independent pathways.

Funding: NIDDK Support

TH-PO509

Loss-of-Function Mutation in the Epithelial Na+ Channel Alpha Subunit Reduces Salt/Aldosterone-Induced Hypertension in Mice

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Background: Epithelial Na^+ channels (ENaC) have an important role in regulating blood pressure and extracellular [K^+]. We previously identified a point mutation in mouse ENaC alpha subunit (H283R) that significantly enhanced Na^+ self-inhibition, reflecting a reduced open probability specifically due to extracellular Na^+. Its homologous human variant

(H255R) has similar effects. In this study, we investigated whether the loss-of-function mutation H283R would protect mice from salt and aldosterone-induced hypertension.

Methods: H283R was introduced into the exon 2 of gene Scnn1a (encoding alpha ENaC) in C57/BL6J mice using CRISPR/Cas9-mediated gene editing method. Six homozygous H283R mice and six littermates were implanted with radio telemeters to record blood pressure, heart rate and activity level. Following seven days recording under normal salt (0.5% NaCl) diet, mice were fed with a high salt (4% NaCl) diet and implanted with minipumps for aldosterone infusion. Data recording continued for four additional weeks.

Results: There were no significant differences in pulse, systolic, diastolic and mean arterial pressures, heart rates, activity and blood electrolytes under normal Na^+ diet conditions, except for a modest difference in blood [Na^+]. Blood pressures displayed normal diurnal variation. Blood pressures gradually increased in all mice after switching to high salt diet plus aldosterone infusion. However, H283R mice displayed significantly lower systolic, diastolic and mean arterial pressures than wild type mice on multiple days ($p < 0.05$). Both day and night blood pressures showed significant differences between the two groups. Heart rate and activity were similar in the two groups. Plasma aldosterone levels measured at the end of the experiment were not significantly different. We did not observe significant differences in Na^+ and K^+ concentrations in blood and urine samples in these mice.

Conclusions: The Na^+ self-inhibition enhancing mutation H283R in ENaC alpha subunit protects mice from high salt and aldosterone-induced hypertension. Our observations suggest that certain loss-of-function human ENaC variants like H255R may protect individuals from the development of salt-sensitive hypertension.

Funding: NIDDK Support

TH-PO510

Interleukin 6 plus High Salt Increases Functional Epithelial Sodium Channel Activity

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Background: Hypertension (HTN) is characterized by increased sodium (Na^+) reabsorption, and increased cytokines such as interleukin 6 (IL6). Our data suggests that IL6 infusion increases blood pressure (BP) and distal nephron Na^+ transporter expression/activity, with an early reduction in urinary Na^+ excretion (U_{Na}). However, whether this reduction in U_{Na} is mediated by epithelial sodium channel (ENaC) activity is unknown. We hypothesize that IL6 increases ENaC activity.

Methods: Mice were treated with IL-6 (16ng/hr, 0.1%BSA) or vehicle via osmotic minipump, and fed high salt (HS, 4%) diet for 1 or 3 days (1D, 3D). ENaC open probability (P_o), functional expression (fN) and functional activity (fNP_o) were assessed in split open tubules (cortical collecting duct, CCD) from IL6-treated (IL6+HS) and vehicle (HS) mice. Data are expressed as mean±SEM, where SEM is patch number in at least 3 mice per group.

Results: We observed a trending increase in ENaC fN in CCD from IL6+HS after only 1D, reaching significance by 3D (0.94±0.14, n=44 *vs.*0.63±0.08, n=63, $p<0.05$), compared to HS only. Although open probability (P_o) was not increased, fNP_o was almost doubled in IL6+HS treated mice after 1D (0.24±0.08, n=51 *vs.* 0.12±0.04, n=62), and significantly increased after 3D (0.28±0.07, n=44 *vs.* 0.13±0.04, n=63, $p<0.05$).

Conclusions: Here, we show that increased IL6 causes trending increases in ENaC fN and fNP_o, after only 1D. These data correlate with our data showing U_{Na} is reduced in the first 24 hours. Continued IL6+HS treatment significantly increased both fN and fNP_o by day 3, also correlating with increases in ENaCα/γ expression and BP (by D3). We later see increased U_{Na}, indicating pressure natriuresis. These data suggest that, remarkably, IL6 may activate distal nephron Na^+reabsorption, even with increased dietary salt. These data reveal a novel role for IL6-mediated changes in U_{Na} excretion, leading to salt-sensitive HTN.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

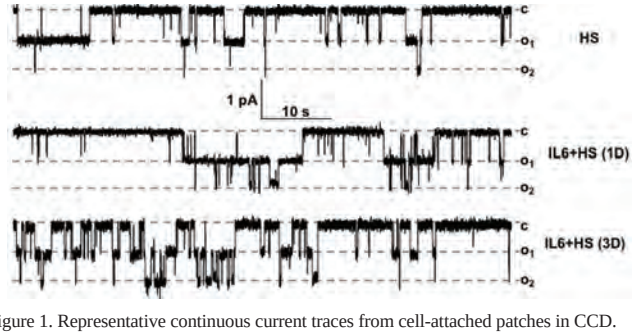

Figure 1. Representative continuous current traces from cell-attached patches in CCD.

TH-PO511

Role for Collecting-Duct ET-1 in the Response to High-Salt Diet plus Mineralocorticoid Treatment

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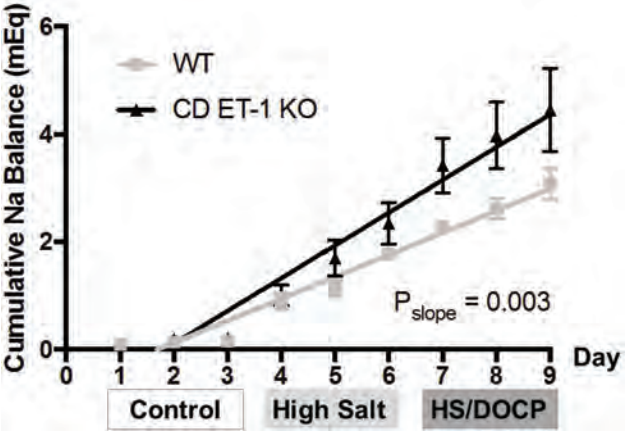
Background: Mice lacking the circadian clock protein Per1 exhibit a reduced night:day ratio in urinary Na excretion during the acute response to a high salt (HS, 4% NaCl) diet plus mineralocorticoid (DOCP) treatment. New results indicate that 24 hr urinary Endothelin-1 (ET-1) peptide is increased in male kidney-specific Per1 KO mice compared to control mice under these conditions. ET-1 is a known circadian clock target gene. These data led us to hypothesize that ET-1 action is important for maintaining the normal night:day ratio in renal Na excretion in response to HS/DOCP.

Methods: We generated renal collecting duct-specific ET-1 KO mice using Aqp2-Cre. Male CD ET-1 KO (n=5) mice and age-matched littermate controls (WT)(n=6) were acclimated to metabolic cages. Urine collections (24 hr) were made over 3 days of control diet and 3 days of HS. Mice were then treated with 75 µg/g BW DOCP. Urine collections (12 hr) were made for 3 days of HS/DOCP. Cumulative Na balance was calculated. Genotype effects were assessed during the HS and HS/DOCP interval using linear regression. Genotype and treatment effects were assessed by 2-way repeated measured ANOVA. Night:day urine Na excretion ratios were compared by t-test.

Results: Contrary to our hypothesis, CD-specific KO of ET-1 did not alter the night:day ratio in urine Na excretion in response to HS/DOCP (KO 5.6±1.4, WT 3.8±0.7, $p=>0.05$). The rate of increase in cumulative Na balance was significantly greater in CD ET-1 KO mice vs. WT.

Conclusions: Under the conditions tested, CD ET-1 does not appear to be necessary to maintain night:day differences in urinary Na handling. However, consistent with the known natriuretic role for ET-1 in the CD, CD ET-1 mice do retain significantly more Na in response to HS/DOCP compared to WT. These data demonstrate that CD ET-1 is necessary for the natriuretic response to a high salt diet plus mineralocorticoid.



TH-PO512

Detection of Na+ Stores in the Myocardium and Skeletal Muscle of DOCA Treated Mice Using 23Na-MRI

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Background: Disturbances in Na^+ homeostasis with accumulation of Na^+ in tissue are present in salt sensitive hypertension. Tissue Na^+ distribution could be recently visualized in vivo by ^{23}Na-MRI. If Na^+ accumulation occurs also in organs of the cardiovascular system is unknown. We hypothesized that the myocardium is able to absorb significant amounts of Na^+ that could be detected by ^{23}Na-MRI.

Methods: DOCA-pellets were implanted in 10 male FVB mice while a sham procedure was performed on 10 FVB mice. Subsequently, both groups received 1% NaCl water for 2 weeks. ^{23}Na-MRI at 7Tesla was used to quantify Na^+ in heart and skeletal muscle. Furthermore, electrolytes were determined chemically in both tissues. In a fraction of mice intracellular Na^+ of the myocardium was measured by electron beam microscopy. Echocardiography was performed and blood pressure determined.

Results: Compared to control mice DOCA treated mice showed a significantly higher Na^+ content in skeletal muscle (27.0 ± 5.7 vs. 46.6 ± 8.9 mmol/l, p<0.001) and in heart muscle (61.6 ± 9.1 vs. 73.7 ± 11.7, p<0.05, figure 1). The fraction of bound Na^+ was increased in DOCA skeletal muscle (6.4 ± 0.8 vs. 13.0 ± 4.3 a.u., p<0.05) suggesting intracellular Na^+ accumulation. Electron beam microscopy of heart muscle also detected a higher intracellular Na^+ amount in DOCA animals compared to controls (0.12 ± 0.03 (n=4) vs. 0.29 ± 0.01 a.u. (n=3), p<0.001). Chemical electrolyte analysis confirmed Na^+ accumulation in both tissues. A reduced ejection fraction (74 ± 4 vs. 46 ± 15%, p<0.05) and hypertension was found in DOCA animals.

Conclusions: Na^+ accumulation occurs intracellularly in skeletal muscle and in heart muscle in vivo upon DOCA salt treatment indicating Na^+ uptake rather than extracellular accumulation. Increased Na^+ content of the myocardium might directly contribute to cardiac dysfunction.

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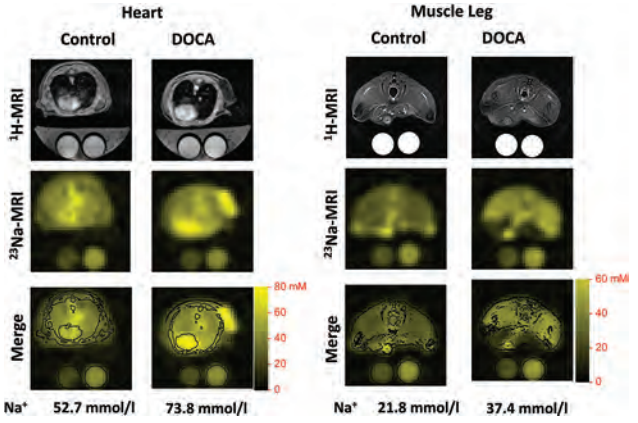

Figure 1, representative MR images.

TH-PO513

Response of WNK-1 Intercalated Cell (IC) Knock-out Mice to a High K+ Diet

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Background: In the cortical collecting duct (CCD), IC BK channels mediate flow-induced K+ secretion (FIKS) and contribute to the renal adaptation to dietary K+ intake. IC BK channel apical expression and activity are enhanced by a high K+ diet. In HEK cells, L-WNK1 also stimulates BK channel expression and activity. The observation that L-WNK1 expression is enhanced in the CCD of rabbits on a high K+ (HK) diet suggests that L-WNK1 contributes to modulation of the BK channel by dietary K+. We asked whether IC L-WNK1 expression is necessary for enhanced BK activity and renal adaptation to a HK diet.

Methods: We generated mice with IC-specific deletion of L-WNK1 (IC-WNK1-KO) by crossing floxed L-WNK1 mice with V-ATPase Cre mice. KO and floxed control mice were placed on a HK diet for 10 days to maximally stimulate BK channel expression.

Results: Perforated whole-cell recordings of ICs in CCDs from IC-WNK1-KO mice revealed significant reduction in charybdotoxin (CbTX)-sensitive K+ currents vs. controls (440 +/- 64 pA vs. 703 +/- 92 pA, respectively; N = 4 and 4; p =0.003). IC-WNK1-KO mice also exhibited higher blood [K+] vs. controls (5.6 +/- 1.0 vs. 5.0 +/- 0.9 mEq/L; N = 21 and 19; p = 0.048). Despite the increased blood [K+] in the IC-WNK1-KO mice, urinary K+ excretion in response to an intra-peritoneal bolus of 10% vol/wt 0.9% saline was similar in KOs and controls (4.5 +/- 9.0 vs. 4.6 +/- 7.0 mcmol/hr/g; N = 9 and 7).

Conclusions: The observations that IC-WNK1-KO mice have higher blood [K+] and reduced CbTX-sensitive currents in CCD ICs indicate that these mice have a defect in urinary K+ secretion, highlighting the importance of L-WNK1 in ICs for adaptation to a HK diet. The retained capacity for K secretion in response to a saline load suggests upregulation of other K+ secretory processes.

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TH-PO514

Novel KLHL3-Binding Motif of WNK4 and Its Potential Role in Familiar Hyperkalemic Hypertension

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Background: Gene mutations in with-no-lysine [K] kinase 4 (WNK4), and in kelch like 3 (KLHL3), have been found in patients with familiar hyperkalemic hypertension (FHHt, also known as pseudohypoaldosteronism type 2, PHAII). The level of WNK4 protein is controlled by KLHL3, which is the substrate adaptor in the cullin-RING ubiquitin E3 ligase complex for the degradation of WNK4. Mutations in either the acidic motif of WNK4 or the Kelch domain of KLHL3 impair their binding and raise the protein level of WNK4. The increased WNK4 protein abundance and total kinase activity stimulates the activity of sodium-chloride cotransporters (NCC) via SPAK/OSR1, and ultimately results in FHHt. Currently the acidic motif in WNK4 is recognized as the only binding motif for KLHL3. Our aim of this study is to determine whether additional KLHL3 binding site exists in WNK4, if so, whether it is relevant to FHHt.

Methods: WNK4 deletion constructs and KLHL3 FHHt mutants were made by PCR-based mutagenesis approaches. The constructs were expressed in *Xenopus laevis* oocytes. Western blotting and GST pull-down approaches were used to evaluate the interaction and degradation of WNK4 constructs.

Results: In addition to the region containing acidic motif, the WNK4 C-terminal region (amino-acids 1046-1243) was capable of pulling down KLHL3, indicating that there is a new KLHL3-binding motif in this region. Using deletion constructs, the new binding motif was narrowed down to a 30 amino-acid stretch (amino-acids 1051-1080). WNK4 lacking either the acidic motif or the novel motif was rapidly degraded in the presence of KLHL3; however, WNK4 protein was stable when both motifs were deleted. Similar to the acidic motif, the new motif is also rich in Asp/Glu residues. Since the Kelch domain of KLHL3 has a positive surface electrostatic potential, similar to the acidic motif, the negatively charged residues in the new motif are likely important for the electrostatic interactions. Indeed, FHHt mutations in the Kelch domain of KLHL3 impaired the degradation of WNK4 lacking the acidic motif, and this effect was more pronounced for the FHHt mutations at the surface of the Kelch domain.

Conclusions: A new KLHL3-binding motif was identified in the C-terminal region of WNK4. The new motif is likely involved in the pathogenesis of FHHt.

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TH-PO515

WNK1 and WNK4 Form Heteromultimer to Regulate NCC In Vivo

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Background: Sodium reabsorption via the sodium-chloride cotransporter (NCC) in distal convoluted tubule (DCT) plays an important role in total body sodium homeostasis. In vitro, with-no-lysine (WNK) kinases WNK1 and WNK4 both activate NCC through intermediate STE20/SPS1-related proline- and alanine-rich kinase (SPAK) and related oxidative stress-responsive 1 (OSR1). It has been reported that WNK1 and 4 interact in vitro. Yet, it is believed that in vivo WNK4 is the main regulator of NCC, in part based on findings that Wnk4-null mice have a nearly complete loss of NCC activity. In addition, WNK4 is essential for stimulation of NCC by low dietary potassium intake through lowering the intracellular chloride concentration. The role of WNK1 in the regulation of NCC in vivo remains poorly understood.

Methods: Global Wnk1-null mice are embryonic lethal, due to loss of WNK1-OSR1/SPAK signaling in the vascular endothelium. To study the role of WNK1 in kidney, we generated a mouse model that expresses constitutive-active SPAK in a variety of tissues including vascular endothelium, but with virtually no expression in the kidney. This approach creates a viable mouse model with functionally kidney Wnk1-null.

Results: Kidney Wnk1-null mice exhibit renal sodium wasting and little NCC activity compared to wildtype mice as assayed by thiazide-sensitive urinary Na excretion and phospho-NCC western blotting. Reciprocal co-immunoprecipitation experiments reveal that WNK1 and WNK4 form complexes in the kidney. Wnk4-null mice have minimal NCC activity and NCC activity is not stimulated by low dietary potassium intake. Unlike that in Wnk4-null mice, low dietary potassium intake stimulates NCC activity in kidney Wnk1-null mice.

Conclusions: Our results provide evidence supporting the notion that WNK1 and WNK4 form heteromultimers in vivo to regulate NCC. WNK4 is more sensitive than WNK1 to inhibition by intracellular chloride.

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TH-PO516

WNK1-SPAK-NCC Signaling Cascade Is Involved in Salt Sensitive Hypertension Induced by Aristolochic Acid Nephropathy

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Background: Increased salt sensitivity is one of the major reasons for resistant hypertension in chronic kidney disease (CKD). Recent evidence suggests that not only reduced glomerular filtration but also aberrant sodium handling in renal tubules contribute to salt sensitivity. We previously demonstrated with-no-lysine kinase (WNK) - oxidative

stress-responsive gene 1 (OSR1)/Ste20-related proline-alanine-rich kinase (SPAK) - NaCl cotransporter (NCC) signaling cascade is essential for sodium handling in the distal nephron and its inappropriate activation leads to salt sensitive hypertension. However, WNK signaling in CKD has not been evaluated. In the present study, we investigated the role of WNK signaling in the development of salt sensitive hypertension induced by aristolochic acid nephropathy (AAN).

Methods: C57BL6/J or SPAK$^{-/-}$mice were administered aristolochic acid I (AA-I) intraperitoneally twice a week for 6 weeks followed by 6 week disease development time. After the treatment, sodium transporter protein expression was assessed and the effect of high salt diet (HSD) on blood pressure was examined.

Results: AAN mice showed salt sensitive hypertension (systolic blood pressure after HSD, mean±SE: 112.5±2.6 mmHg in AAN and 102±1.0 mmHg in control, $p<0.05$, unpaired t test). In the AAN model, protein levels of WNK1, phosphorylated SPAK and phosphorylated NCC were significantly increased. Immunofluorescent study revealed increased expression of WNK1 and phosphorylated SPAK at distal convoluted tubules. Even after mice were fed a HSD, expression level of WNK signal remained increased. Increased phosphorylation of NCC was not observed in AA-I treated SPAK$^{-/-}$mice, indicating NCC was activated through WNK1-SPAK phosphorylation cascade. As tumor necrosis factor α (TNFα) mRNA expression level was elevated in AAN mice kidney, we next evaluated the effect of TNFα on WNK signaling. We found that increased expression of WNK1, phosphorylated SPAK and phosphorylated NCC were attenuated in AAN mice treated with TNFα inhibitor etanercept.

Conclusions: NCC is activated through WNK1-SPAK signaling cascade in AAN mice and could contribute to salt sensitive hypertension. TNFα is involved in WNK signal activation induced by AAN.

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TH-PO517

Vacuolated Podocytopathy: A Novel Injury with the Use of BRAF Inhibitors

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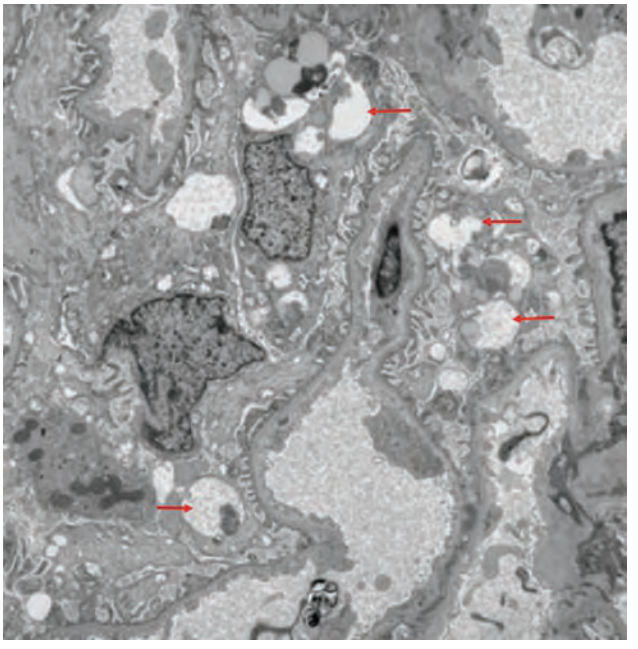
Introduction: With expanded use of BRAF inhibitors, nephrotoxicities including acute interstitial nephritis (AIN) and nephrotic syndrome (NS) have been described in recent literature. We present a novel case of vacuolated podocytopathy with sub-nephrotic range proteinuria associated with BRAF inhibition.

Case Description: A 64-year-old woman with non-small-cell lung cancer on dual BRAF/MEK inhibition with Vemurafenib and Trametinib, was referred for AKI evaluation. Her serum creatinine (SCr) was 2.1 mg/dL, increased from 1.0 mg/dL 2 months prior. Urine protein/creatinine ratio was between 0.4 – 0.7. Urinalysis was otherwise non-contributory. BRAF inhibition was held due to presumed AIN, but renal function only improved to 1.4 mg/dL. Treatment was restarted due to lack of therapy options with increase in SCr to 2.0 mg/dL. A renal biopsy was performed for definitive diagnosis. Pathology surprisingly showed a minimal interstitial infiltrate but extensive podocyte injury with cytoplasmic vacuolization and nearly global foot process effacement (FPE) was seen on electron microscopy. Given stable renal function, treatment was continued. Her SCr remained around 2.0-2.2 mg/dL and proteinuria remained < 1g until her death from septic shock few months later.

Discussion: BRAF inhibitors are linked with AIN and NS with diffuse FPE. We describe a novel finding of podocyte vacuolization and FPE with sub-nephrotic proteinuria. We recommend renal biopsy for patients on BRAF inhibitors with AKI of undetermined etiology to allow precise identification of the renal lesion. Our patient continued on BRAF inhibitors with stable CKD and proteinuria, suggesting that drug withdrawal is not necessary for all patients, particularly those with limited treatment options.



EM with podocyte vacuolization (arrow) and FPE

TH-PO518

LECT2 Amyloidosis in a Pediatric Renal Allograft

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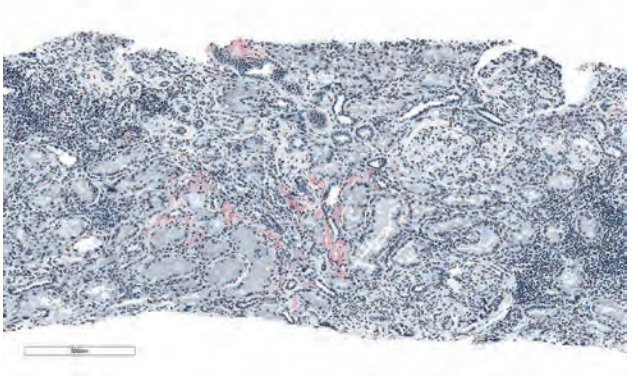
Introduction: LECT2 amyloidosis is a common form of systemic amyloidosis. We present, to our knowledge, the first case of ALECT2 in a pediatric renal allograft.

Case Description: A 19 y/o Hispanic male with ESRD from posterior urethral valves, s/p living unrelated kidney transplant (2002, age 4), presented with a sCr of 2.4mg/dl (baseline 1.9mg/dl) and 3.6g/day proteinuria. He received daclizumab induction and was maintained on tacrolimus/MMF/sirolimus/prednisone. Past history was notable for episodes of ACR and C4d+AMR treated with thymoglobulin, IVIg, OKT3 and rituximab; de-novo C1q nephropathy; and ultimately transplant-glomerulopathy. Current biopsy showed Type1B ACR and chronic active AMR (C4d+). During low power ultrastructural analysis, unusual electron-lucent material was noticed in interstitial areas. Closer examination revealed disorganized fibrils measuring 8-12nm in diameter. Subsequent Congo Red staining confirmed scant interstitial amyloid deposits. Routine amyloid typing stains were negative, therefore mass spectrometry was performed, confirming ALECT2. Treatment with thymoglobulin, IVIg and rituximab stabilized the sCr at 1.9mg/dl. Follow-up biopsy showed resolution of the ACR. No further treatment changes were made. At last follow-up renal function was stable.

Discussion: ALECT2 is more common in elder Hispanic patients. ALECT2 can occur as a de-novo or recurrent process in renal transplants. Here we hypothesize that chronic inflammation from repeated episodes of rejection coupled with ethnic predilection resulted in ALECT2. Unexplained proteinuria in Hispanic patients and unusual patterns of amyloid distribution are clues to the diagnosis of ALECT. Detailed ultrastructural analysis could help to discover small amounts of amyloid not discernable by light microsopy. Mass spectrometry helps in cases that cannot be classified by stains. Awareness of ALECT2 in young patients is important due to prognostic implications and recurrence in subsequent allografts. There is no treatment for ALECT2.



Congo Red

TH-PO519

Leukocyte Chemotactic Factor 2 Amyloidosis with Concurrent Post-Infectious Glomerulonephritis and Diabetic Nephropathy

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Introduction: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a form of amyloidosis that manifests with progressive renal failure. Biopsies typically exhibit congophilic deposits that are most prominent in the interstitium. ALECT2 is the third most common form of amyloidosis with strong ethnic bias, affecting mainly Hispanics with chronic renal insufficiency. Significant proteinuria is rarely associated with ALECT2 unless a second concurrent glomerulopathy is present. We report a case of ALECT2 with nephrotic syndrome due to concurrent post-infectious glomerulonephritis and diabetic nephropathy.

Case Description: A 50-year-old Hispanic female with no significant medical history admitted for anasarca, was found to have bilateral pleural effusions and newly diagnosed type 2 diabetes mellitus. Laboratory values were significant for HgbA1c of 13.2%, normal renal function, albumin of 2.5 g/dL and 4.5 grams of proteinuria. Serological workup showed positive ANA with decreased C3 and C4. HIV, hepatitis, SPEP and serum free light chains were negative. Although diabetic nephropathy (DN) can cause nephrotic range proteinuria, it rarely presents with nephrotic syndrome. Thus, renal biopsy was performed which showed multiple glomerular abnormalities including glomerulonephritis (GN) with dominant C3 staining along with predominat mesangial deposits and nodular diabetic glomerulosclerosis. Congo red was performed which showed scattered positive staining in the interstitium, consistent with amyloid. Mass spectroscopy further characterized the amyloid type as ALECT2. The patient was discharged with insulin therapy and started on an ACE-inhibitor. The differential diagnosis for her C3-dominant GN included post-infectious GN and C3 GN. At 6 weeks clinic follow up, her C3 level normalized favoring the diagnosis of post-infectious GN.

Discussion: ALECT2 is one of the more recently recognized amyloid proteins to affect the kidney and fairly prevalent however it is still under recognized. Concurrent glomerular disease is not uncommon in patients with ALECT2, with DN being most frequent. Coexistence of three disease processes (post-infectious GN, DN and ALECT2) makes our case exceptional. This case also illustrates the significance of renal biopsy in patients with atypical presentations of common renal diseases.

TH-PO520

Fibrillary GN vs Amyloidosis on Renal Biopsy: Dilemma on How to Treat

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Introduction: Glomerular disease may be associated with fibrillary deposits on glomerular basement membrane or mesangium. Frequently there is a clear distinction between Amyloidosis and non-amyloid fibrillary deposits based on the fibril size on electron microscopy and reaction to Congo red stain. But occasionally we see overlapping patterns. Here we present a unique case of glomerular deposition disease with an overlapping pattern, where the kidney biopsy showed Congo red positivity, but the fibril sizes were larger than as expected in amyloidosis. Patient presented with acute kidney injury (AKI) and clinical evidence of glomerulonephritis (GN).

Case Description: A 58 y/o male with medical history of hepatitis C status post treatment with Harvoni in 2015 with negative viral PCR (9/2016), well controlled type 2 DM (HbA1C 5.2), well controlled HTN, Chronic kidney disease stage III A presented as an outpatient consult for worsening serum creatinine. The serum creatinine rose from a baseline of 1.1 mg/dl to 3.2mg/dl in a period of 3 months. 24hr urine showed significant proteinuria measured at 2682 mg. His urine sediment showed microscopic hematuria, but no dysmorphic features. Serologic studies showed elevated kappa/lambda ratio at 2.52 but normal serum and urine protein electrophoresis, normal C3 and C4 complement levels, and negative anti neutrophil cytoplasmic antibody. Patient underwent renal biopsy, which showed glomerulopathy - mesangioproliferative pattern, with mesangial and subendothelial fibrillary deposits. The fibrils measured 14.8 nm in diameter, and these deposits were congo red positive, and were reactive for IgG (predominant IgG4) and C3. The stain for protein A was negative. In addition, there were advanced chronic changes noted in the parenchyma, including global and segmental glomerulosclerosis (52% of glomeruli) and significant tubulointerstital fibrosis (60% of the cortex). Considering atypical findings on renal biopsy and underlying significant tubulointerstital fibrosis, we decided to treat him with mycophenolate and prednisone instead of more aggressive chemotherapy for amyloidosis. He responded well as his serum creatinine trended down from 3.2 mg/dl to 1.5 mg /dl in 6 months.

Discussion: We believe this is the first case of glomerular deposition disease with overlapping features of amyloidosis and fibrillary GN, who responded well to a rather conservative regimen of MMF with steroid.

TH-PO521

Unwanted Deposits: A Rare Cause of AA Amyloidosis

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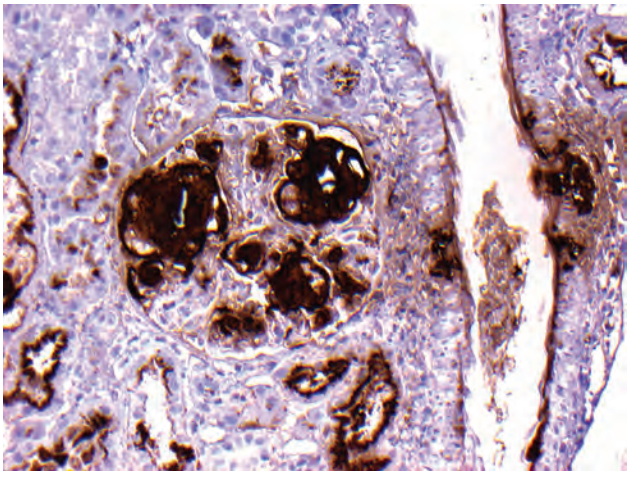
Introduction: Amyloidosis is a disorder resulting from pathologic deposition of protein subunits in multiple organ systems, often including the kidneys. It is divided into two major subgroups: AL amyloidosis due to overproliferation of light chains from a monoclonal plasma cell population, and AA amyloidosis resulting from chronic inflammatory states including a variety of autoimmune diseases, infections, and malignancies. Identification of the associated disorder can direct therapy to minimize further organ damage. We describe a case of AA amyloidosis secondary to Castleman's disease (CD).

Case Description: A 37 year old woman with a history of anemia was referred to clinic for nephrotic-range proteinuria. Laboratory evaluation showed a urine protein:creatinine of 10.3, a serum creatinine of 0.83 mg/dL and albumin of 2 g/dL. A kidney biopsy showed glomerular amyloid deposits. Serum protein electrophoresis and serum free immunoglobulins did not show evidence of a monoclonal gammopathy. Evaluation for secondary causes of AA amyloidosis was notable for a 5 cm pararenal mass and abnormal lymph nodes on PET scan. A biopsy of the mass revealed lymph node tissue with amyloid deposits and morphologic features consistent with CD. HHV-8 and HIV testing were negative. She was started on siltuximab, a monoclonal interleukin-6 (IL-6) antibody, with reduction in her urine protein:creatinine to 2.1, improvement in albumin to 3 g/dL and an increase in her hemoglobin from 6.2 g/dL to 15.6 g/dL.

Discussion: Amyloidosis carries tremendous morbidity to affected individuals with limited, non-curative therapy available. Identification of the patient's CD as the underlying trigger of her AA amyloidosis allowed for directed treatment that resulted in dramatic improvement in her proteinuria and resolution of her anemia. Excess IL-6 is hypothesized to play a role in CD, particularly HIV and HHV-8 negative cases. This case provides additional support for the role of IL-6 inhibitors in the treatment of idiopathic CD.



TH-PO522

Amyloid Nephropathy in the Setting of Rosai-Dorfman Disease

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Introduction: Rosai-Dorfman disease is a non-neoplastic histiocytic disorder characterized by massive lymphadenopathy secondary to infiltration and dilation of the lymph node sinuses by large histiocytes. Massive cervical lymphadenopathy is the hallmark, but extranodal involvement has been described in 43% of cases. It can affect most organs, with about 4% of cases affecting the kidneys.

Case Description: A 64-year-old Hispanic man with diabetes mellitus and hypertension was diagnosed with Rosai-Dorfman disease 9 years ago. He was treated initially with surgical debulking, rituximab, cyclophosphamide, vincristine and prednisone. Rituximab was used intermittently since, with the last dose given 4 years ago. On current presentation, he has dysphagia and progressive cervical, hilar, mediastinal and retroperitoneal lymphadenopathy. Creatinine was elevated at 2 mg/dL from a baseline of 1.17 mg/dL. Imaging and urological studies showed no evidence of obstruction. Diagnostic work-up revealed dysmorphic RBCs, proteinuria of 14 g/day, hypocomplementemia, and positive ANA and anti-RNP70. Hepatitis panel, HIV, PR3, and MPO were negative. There was an abnormal monoclonal protein in the gamma region but kappa/lambda ratio was normal. He was empirically treated with rituximab (375mg/m2 weekly for 4 doses) and dexamethasone 40 mg daily for disease recurrence. However, the kidney function continued to deteriorate, so a kidney biopsy was performed. Widespread amyloid was noted predominantly in the interstitium, with only focal glomerular and vascular involvement. Immunofluorescence showed weak IgG without light chain restriction and corresponded to scattered subepithelial immune deposits.

Discussion: There have been few reports of amyloidosis with Rosai-Dorfman Disease, one with generalized AA amyloidosis. We postulate that cytokine production by histiocytic cells, subsequently induced synthesis of precursor proteins facilitating amyloidogenesis in this patient. Amyloid can be found anywhere in the kidney, but glomerular deposition typically predominates in most forms. This report highlights a rare association of this histiocytic disorder and renal amyloidosis, predominantly with interstitial deposition.

TH-PO523

Apolipoprotein A-IV Amyloidosis: An Unusual Cause of Renal Amyloidosis and CKD

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Introduction: Apolipoprotein A-IV associated amyloidosis (AApoAIV amyloidosis) is a rare cause of amyloidosis with only few reported cases in the literature. Renal AApoAIV amyloidosis histologically exhibits medullary involvement with sparing of the cortex. The diagnosis of renal AApoAIV amyloidosis requires a high degree of suspicion and examination of the renal medulla on renal biopsy. The definitive diagnosis is best established by mass spectrometry. Here we present two patients with renal AApoAIV amyloidosis.

Case Description: Case 1 Fifty-three-year-old white male with past medical history of well-controlled type 1 diabetes mellitus and hypertension presented with a 10-year history of slowly declining renal function (Serum creatinine 1.1 mg/dl 10 years ago and 1.7 mg/dl in 2018). Urinalysis was unremarkable and 24-hour urine collection showed 240 mg of protein. He was found to have a positive serum immunofixation with IgA kappa monoclonal protein and was diagnosed with IgA kappa smoldering myeloma by bone marrow biopsy. Subsequent renal biopsy showed multifocal, medullary deposition of amyloid of amyloid material. No similar deposits were seen within the renal cortex. Mass spectrometry surprisingly identified apolipoprotein A-IV amyloid deposition and no peptides were identified for any other types of amyloid. The smoldering myeloma was thought to be unrelated to the amyloid. Case2 Sixty-Eight-year-old white female has had stage 3 CKD since 2009, when her serum creatinine was 1.4. Creatinine increased to 1.6 in 2016 and she underwent renal biopsy which showed a focal area of amyloid deposits in the medulla. Mass spectrometry identified the amyloid as Apolipoprotein A-IV. The patient's renal function has remained stable over the last 2 years. Neither patient had extra-renal manifestations of amyloidosis or family history of amyloidosis.

Discussion: Apolipoprotein A-IV amyloidosis is a rare type of amyloidosis that seems to have a predilection for the kidney and is limited to the renal medulla. The limitations of the amyloid to the medulla correlates with the clinical findings of slow decline of renal function, unremarkable urinalysis, and no significant proteinuria. The pathogenesis of apolipoprotein A-IV amyloid formation is unknown. There are no known treatment options at this time and management is conservative.

TH-PO524

Podocytic Infolding Glomerulopathy in a Patient with Systemic Lupus Erythematous

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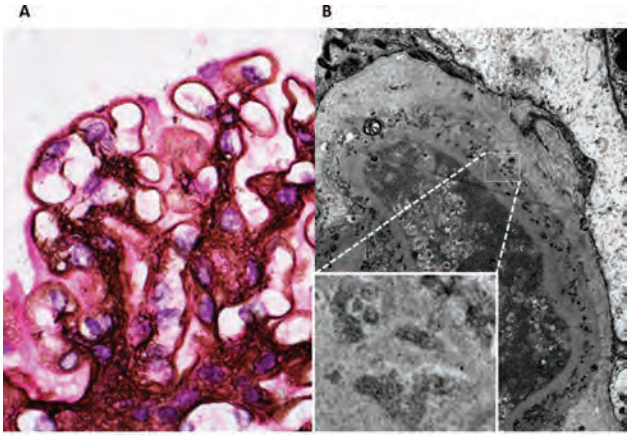
Introduction: Podocytic infolding glomerulopathy (PIG) has been proposed as a new disease entity. This is first case of PIG reported in a woman patient of African American ancestry. Five case reports of PIG complicated by focal segmental glomerulosclerosis (FSGS).

Case Description: A 35-year-old African American woman with a history of systemic lupus erythematous and autoimmune enteritic ganglionitis presents with new acute kidney injury with serum creatinine 1.6 mg/dL (baseline 0.8 mg/dL) and nephrotic range proteinuria. Urinalysis was positive for 3 red blood cells, 5 white blood cells per high power field and no red blood cell casts. Urine protein/creatinine ratio was 19 g/g. C3 and C4 levels were 90 and 30 mg/dL, respectively. Anti-DNA screen, anti-PLA2 receptor antibody, HIV and hepatitis panel was negative. Renal sonogram showed normal sized kidneys with minimally increased echogenicity and unchanged mild bilateral hydronephrosis. Kidney biopsy demonstrated significant FSGS with collapsing features. Under periodic acid methenamine silver (PAMS) staining, the glomeruli had a diffuse moth-eaten appearance along glomerular capillary loops (Figure A). On ultrastructural examination there were numerous electron dense intramembranous membrane bound structures and microspheres entrapped in the glomerular basement membrane (GBM) of capillary loops (Figure B and Inset) consistent with PIG. Despite treatment with various immunosuppressive therapies the patient still progressed to end stage renal disease.

Discussion: In PIG, microspheres or microtubular structures, or both, are associated with the infolding of cytoplasmic processes of podocytes into the GBM as a consequence of capillary wall remodeling. The mechanism of PIG is unknown and has been reported in predominantly in Asian and in the setting of connective tissue diseases.



TH-PO525

Collagen Glomerulopathy – A Rare Entity

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Introduction: Collagen glomerulopathy (CG) is a rare, non-immunoglobulin deposition disease of unknown etiology, first reported by Arakawa et al in 1979. CG is characterized by agglomeration of atypical type III collagen fibrils in mesangial matrix and subendothelial space. CG is a rare entity, with most of the cases reported from Japan. We describe one such rare case of CG seen in a pediatric patient and emphasize its clinical significance.

Case Description: A 7-year-old Hispanic girl presented with intermittent hematuria and foamy urine since few weeks. She had no family history of renal disease. Patient was normotensive with mild pedal edema and specifically no nail or patellar dysplasia. Labs revealed serum creatinine of 0.44 mg/dl, albumin of 3.3 g/dl, hyperlipidemia and normal complement levels. Urinalysis confirmed hematuria with 2.6 gm of proteinuria on quantification. Renal ultrasound was unremarkable. A diagnostic renal biopsy conducted revealed widespread foot process effacement and nodular mesangial deposits suggestive of collagen III glomerulopathy. She was managed conservatively with angiotensin converting enzyme inhibitors with partial remission of proteinuria.

Discussion: Type III collagen is a structural protein that is normally absent in the glomerulus. Abnormal accumulation of type III collagen in the mesangium and subendothelial space leads to proteinuria. Electron microscopy showing mesangial deposits of large (43-65 nm) whorled fibrils is essential for definitive diagnosis. This is distinguished from nail-patella syndrome by the absence of collagen III accumulation in lamina densa of basement membranes. CG typically presents with hypertension, edema, proteinuria and progressive kidney disease. Familial occurrence with autosomal recessive inheritance has been described. The etiopathogenesis remains elusive, but is associated with factor H deficiency and Hemolytic uremic syndrome. Supportive therapy with control of hypertension and edema is recommended. Role of corticosteroids is unclear. Among patients who received a transplant, none have shown disease recurrence. Our case represents only the second case of CG published from the US. Clinicians should be cognizant of this rare entity and differentiate it from other fibrillary disorders as treatment is supportive rather than the toxic immunosuppressive therapy.

TH-PO526

A Case of Sporadic Glomerulopathy with Fibronectin Deposits with a Mutation in FN1

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Introduction: Glomerulopathy with fibronectin deposits (GFND) is a rare renal disease with massive mesangial, and subendothelial fibronectin deposits. It presents proteinuria, often in the nephrotic range in the third to fourth decade, and slow progression to end-stage renal disease. Here we describe a case with GFND from a genetic mutation.

Case Description: A 52-year-old lady presented with edema and 2-year-history of hypertension. Since 6 years ago, mild proteinuria and microscopic hematuria have been detected by regular health check-up. Family history was negative for any kidney diseases. She was diagnosed as having nephrotic syndrome (massive proteinuria, 7.7 g/gCr, hypoalbuminemia, 2.6 g/dl, normal level of creatinine of 0.42 mg/dl). A renal biopsy showed lobular appearance and membranoproliferative glomerulonephritis-like lesions on light microscopy. Electron microscopy revealed homogeneous granular fine fibers. In a case with micro-fibrillar deposits in glomeruli, it is necessary to rule out an amyloidosis and a glomerulopathy derived from immunoglobulins. In this case, Direct Fast Scarlet staining and immunofluorescence were all negative. Following the above results, we suspected her of GFND. Next, we carried out mass spectrometry to identify the origin of deposits in laser micro-dissected glomeruli. Majority of detected proteins was fibronectin. Furthermore, immunohistochemistry of the fibronectin showed intense staining in the mesangium and subendothelium. Thus, she was diagnosed as having GFND. We performed

genetic analysis to identify mutations of fibronectin 1 gene (FN1) and found heterozygous deletional mutation (p.Pro1472del).

Discussion: Clinically, it has been difficult to identify the origin of glomerular deposition especially in a case with micro-fibrillar deposits. However, laser micro-dissection and mass spectrometry could accurately identify the major protein of deposits, leading to a diagnosis with GFND. GFND is a rare inherited autosomal dominant disease and 60% of the cases have mutations in the FN1. Recently, 11 pathogenic variations (10 exonic and one intonic) in the FN1 have been reported. In exonic variants, only one is in the integrin-binding domain, the others are in the heparin-binding domain. In this case we detected deletional mutation in the integrin-binding domain (p.Pro1472del) which was consistent with those reported by others.

TH-PO527

A Unique Case of Lipoprotein Glomerulopathy

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Introduction: Lipoprotein Glomerulopathy has recently been recognized as a unique type of glomerular injury characterized by lipid accumulation in the glomerular capillaries. It has been mainly reported in Asian patients, and linked with rare APOE gene mutations resulting in a structurally abnormal Apolipoprotein E (ApoE).

Case Description: A 47-year-old Filipino male presented to the renal clinic with nephrotic-range proteinuria. Past Medical history was significant for hypertension treated with irbesartan and carvedilol. Physical exam was unremarkable. Labs showed serum creatinine of 1.47mg/dl (unclear baseline). Urine microscopy revealed several red blood cells. Urine protein to creatinine ratio was 5.1 g/g with a urine albumin to creatinine ratio of 3.7 g/g. Renal Ultrasound was unremarkable. Further workup, including ANA, ANCA, HIV, Anti-GBM antibody, serum and urine protein electrophoresis, was negative. Hemoglobin A1C was 5.1. Total cholesterol was 221mg/dL with triglycerides of 180 mg/dL, HDL cholesterol of 55mg/dL, VLDL cholesterol of 36mg/dL and LDL cholesterol of 142mg/dL. Patient underwent kidney biopsy for definitive diagnosis. Light microscopy showed 32 glomeruli, many with dilated capillary lumina filled with very pale, mesh-like lipoprotein "thrombi". Five glomeruli were globally sclerosed. Oil red O stain highlighted glomerular capillary lumina thrombi. There was evidence of focal areas of interstitial fibrosis and mononuclear inflammatory infiltration. Immunofluorescence did not reveal any immune-complex deposits. Electron microscopy showed remodeling of the glomerular basement membranes and capillary loops were distended and occluded by lipid-like material containing vacuoles of different sizes and with lamellation. His genetic testing showed both APOE alleles to be E3.

Discussion: Approximately 95% of individuals with type III hyperlipoproteinemia have the E2/E2 genotype. The remainder have rare mutations in one copy of the APOE gene some of which are not detectable by the APOE genotype test. Lipoprotein thrombi in the glomerulus should prompt consideration for Lipoprotein glomerulopathy. Based on clinical information and renal biopsy results, this patient has lipoprotein glomerulopathy in the absence of APOE E2/E2 genotype.

TH-PO528

A Case of Successful Treatment of Collapsing FSGS Secondary to Parvovirus B19

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Introduction: Parvovirus B19 is a rare cause of collapsing glomerulopathy. The clinical course of collapsing glomerulopathy is characterized by proteinuria and progressive renal failure. This case discusses the first immunocompetent patient with biopsy proven collapsing glomerulopathy secondary to Parvovirus B19 successfully treated with Intravenous Immunoglobulin (IVIG).

Case Description: A 38 year old African American man presented to our ED with three days of fatigue, poor appetite, fever, chills, night sweats, and joint pain with swelling. At time of our evaluation his vital signs were within normal limits and physical exam was unremarkable. Laboratory data upon admission was notable for elevated creatinine (1.6mg/dL) and proteinuria (7.2 g/g). The patient's IgG, IgM and PCR for Parvovirus were positive. Kidney biopsy revealed collapsing glomerulopathy with acute tubular injury and minimal interstitial fibrosis. The patient's PCR titer was elevated to 542,000 IU/ml on hospital day 5. Intravenous immunoglobulin (IVIg) was started on day 6 at a dose of 400 mg/kg/day for a total dose of 150 grams over five days. On day 8, his repeat parvovirus PCR began to trend down. The patient's creatinine peaked at 2.29 mg/dL on hospital day 6 however then it began to trend down with treatment as well. The patient was discharged in stable condition on hospital day 11. Three weeks after discharge all his symptoms had abated and his serum creatinine improved to 1.38 mg/dL with proteinuria of 1.1g/g. Patient's parvovirus PCR titer notably decreased to 3,400 IU/ml with this treatment.

Discussion: Collapsing glomerulopathy is prevalaent in patients with human immunodeficiency virus (HIV) and more recently, there have been several cases showing an association with Parvovirus B19. Optimal treatment for Parvovirus associated collapsing glomerulopathy is unknown. We were able to diagnose Parvovirus B19 early by elevated viral PCR and initiated treatment for our patient quickly preventing further progressive renal damage. In addition to strict blood pressure control, the patient was treated with IVIG at a dose of 400mg/kg for five days. The patient was not placed on any corticosteriod therapy. The patient's Parvovirus viral PCR, serum creatinine and proteinuria trended downward. This is the first patient with successful corticosteriod-free treatment of parvovirus induced FSGS with intravenous immunoglobulin.

TH-PO529

A Unique Treatment Strategy in Collapsing Glomerulopathy in a Native Kidney

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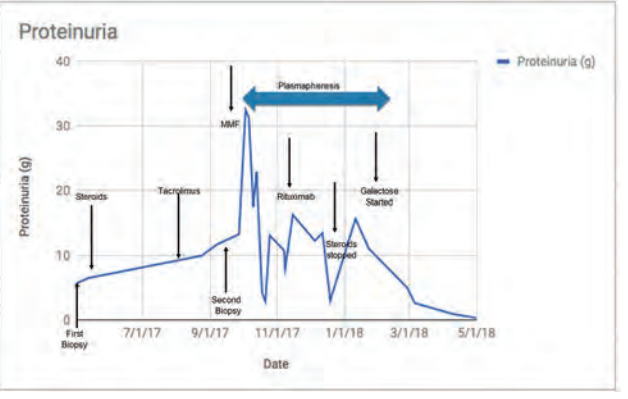
Introduction: Collapsing glomerulopathy (CGP) is a fast progressive glomerular disease. We present a unique case of CGP in a native kidney that responded to multi-drug therapy, which included therapeutic plasma exchange (TPE) leading to complete remission.

Case Description: A 62 year old Indian male presented in June 2017 with AKI (2.65 mg/dl), and nephrotic syndrome (5.6g/24hours). His initial presentation prompted a kidney biopsy which revealed CGP with minimal fibrosis. The patient was started on steroid therapy and ARB therapy. The patient however continued to progress and tacrolimus was added to the regimen. His proteinuria worsened to 32.5g. The patient was subsequently re-biopsied. The biopsy revealed CGP with minimal IFTA. All of his secondary work-up for autoimmune, viral and cancer causes was negative. A combination therapy approach was used and the patient was then initiated on TPE, MMF and continued to tacrolimus (Figure). Steroids were tapered off. Interestingly, with only a few sessions of TPE, his proteinuria improved to <3gm. When TPE was halted, proteinuria returned. This prompted re-initiation of TPE. The patient subsequently had a progressive decrease in proteinuria down to <2gm over 2-3 months. He was maintained on MMF and tacrolimus. In an attempt to come off TPE, he was given a dose of rituximab 1gm and then started on supplemental powder of galactose 0.2 g/kg orally two times per day. After 2 months of therapy he is off TPE and his creatinine stable at 1.2mg/dl with 0.3g proteinuria.

Discussion: This case report suggests that administration of a multimodality approach as used in kidney transplant patients with recurrent CGP might be useful in native kidney idiopathic CGP. This novel case report findings support the performance of randomized clinical trials to assess the efficacy of the use of multi-modal approach to idiopathic CGP.



Proteinuria trend with reference to various treatments used

TH-PO530

Adrenocorticotropic Hormone (ACTH) in the Treatment of Refractory Childhood Nephrotic Syndrome (NS)

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Introduction: Treatment resistance or failure to respond to conventional therapies in NS is associated with poor prognosis. ACTH is recognized as therapy for podocytopathies, though these data are based on small observational studies in adults. There are no published data on the use of ACTH therapy in the pediatric population. We report a case of steroid-resistant NS in a 10 year-old boy who failed multiple secondary therapies but showed a partial response to ACTH injection (ACTHAR) therapy.

Case Description: A 10-year-old Hispanic boy who was diagnosed with NS at the age of 2. He was initially steroid sensitive but frequently relapsing. Cyclosporine A (CsA) was initiated as a steroid-sparing agent and he achieved a 5-year period of stability. However, he eventually began to relapse while on CsA. Tacrolimus and mycophenolate mofetil (MMF) were also ineffective. During this time he became steroid resistant. Triple therapy with steroids, tacrolimus and MMF was unable to induce even a partial remission. A renal biopsy showed early focal segmental glomerulosclerosis (FSGS). Whole exome sequencing showed only a heterozygous variant in PLCE1. He became dependent on twice weekly albumin infusions due to anasarca and persistent hypoalbuminemia (less than 1.2g/dl). Urine protein/creatinine (UPC) ratios were persistently in the nephrotic range. Over 18 months he persisted in uncontrolled relapse, complicated with 5 episodes of acute kidney injury. His creatinine plateaued at 0.7-0.8 mg/dl, whereas in remission it had been 0.3-0.4 mg/dL. We initiated ACTHAR as a last resort given concerns for progressive renal impairment. Initial therapeutic response was minimal with dose of 40 units biweekly. After increment to 80 units biweekly, he demonstrated significant improvement. His serum creatinine improved to his baseline of 0.30 mg/dl and UPCs decreased by more than 50%. Serum albumin improved spontaneously to 1.9-2.0g/dl, resulting in discontinuation of scheduled albumin infusions.

Discussion: This case highlights that ACTHAR may be a viable therapeutic alternative for children who are resistant to other therapies for NS. Additionally, the role of his PLCE1 mutation is unclear but we suspect a compound heterozygous state for another unidentified pathogenic mutation and/or epigenetic modifications may be playing a role in his refractory NS.

TH-PO531

Treatment of Nephrotic-Range Proteinuria with Tacrolimus in Mitochondrial Trifunctional Protein Deficiency

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Introduction: Mitochondrial trifunctional protein (MTP) deficiency is a rare autosomal recessive disorder of long-chain fatty acid oxidation that leads to lactic acidosis, recurrent rhabdomyolysis, cardiomyopathy, and hepatic dysfunction.

Case Description: A 7-month old girl, with known MTP deficiency, presented with poor oral intake and lethargy. Laboratory analysis revealed a low corrected serum calcium level of 6.6 mg/dl, elevated CK level of 14,080 U/L, and nephrotic range proteinuria with a urine protein to creatinine ratio (uPCR) of 7.6 mg/mg. Serum albumin was low at 2.8 g/dl and urine beta-2-microglobulin was mildly elevated at 556 mcg/g creatinine (nl <300 mcg/g). The patient was treated for primary hypoparathyroidism and rhabdomyolysis, known complications of MTP deficiency. Despite resolution of her rhabdomyolysis, she continued to have nephrotic range proteinuria and underwent a renal biopsy that demonstrated minimal change disease and foot process fusion. She was started on tacrolimus and her uPCR gradually normalized 8 months after treatment. She has continued to have normal renal function and uPCR values at the time of this report (2 years of age). The patient has an older sister with the same heterozygous deletion in the HADHB gene (c.1059delT), which is predicted to cause truncation and loss of long-chain-3-hydroxyacyl CoA dehydrogenase function, leading to MTP deficiency. This sister was diagnosed with nephrotic syndrome and focal segmental glomerulosclerosis at 18 months of age, and developed end stage renal disease at 20 months of age.

Discussion: Renal involvement has been reported in only 1 patient with MTP deficiency to date, the sister of our patient. The pathogenesis of proteinuria in the 2 siblings remains elusive. Given that other mitochondrial disorders, such as coenzyme Q10 deficiency, have been associated with nephrotic syndrome, the proteinuria may be related to their mitochondrial dysfunction. Calcineurin inhibitors have been reported to reduce proteinuria by stabilizing the podocyte actin cytoskeleton. Tacrolimus was an effective treatment for our patient, who has maintained normal renal function, unlike her sister. Further investigation will be needed to determine the role of calcineurin inhibitors in the treatment of nephrotic syndrome associated with mitochondrial disorders.

TH-PO532

Hepatitis B and C Dual Infection and Collapsing Glomerulopathy: Report of a Rare Association

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Introduction: Collapsing Glomerulopathy (CG) is marked by severe hypertension and proteinuria, poor response to corticosteroids, and a rapid progression to end-stage renal disease. Many viral illnesses, including HIV, have been implicated in the pathogenesis of this disease. However, the association between CG and Hepatitis C virus (HCV) or Hepatitis B virus (HBV) remains less clear.

Case Description: A 55 y/o man with a history of HTN, Hepatitis B and C, and liver cirrhosis presented with altered mental status. He was hemodynamically stable, however, had significant laboratory derangements including a Cr of 19 mg/dl (recent baseline was 0.9), K of 7.3, CO2 11, and pH of 7.14. His lactic acid, coagulation panel and bilirubin levels were within normal limits. Urine microscopy showed muddy brown casts and no hematuria. He was also found to have nephrotic range proteinuria. HIV and Parvovirus B19 IgM antibodies were negative. Dialysis had to be initiated for uremia, hyperkalemia and acidemia. By light microscopy, the renal biopsy showed segmental glomerulosclerosis in 10/17 viable glomeruli with 3 glomeruli showing a collapsing pattern and podocyte hyperplasia. Severe interstitial fibrosis and tubular atrophy (IFTA) was noted. Immunofluorescence and electron microscopy showed tubulo-reticular inclusions (TRIs) within the endothelial cytoplasm. Patient's mental status, electrolytes and acidemia improved with dialysis. However, he remained dialysis dependent and given the severity of his kidney disease on presentation and the degree of IFTA, renal injury was deemed unlikely to recover.

Discussion: The uncommon association of CG and HCV infection in HIV-negative patients has been reported, mainly in patients treated with interferon. There has been only one reported case of CG associated with HBV infection. As our patient was HIV-negative and was not treated with interferon, the occurrence of CG was attributed to his dual infection with HBV and HCV, especially since TRIs were found on electron microscopy. It is possible that a synergistic action during this dual infection led to the development of CG, a glomerular lesion that rarely occurs with either viral infection alone. This case highlights the need for further research to elucidate the pathogenetic role HBV and HCV may play in the development of CG.

TH-PO533

An Infantile Nephrotic Syndrome Case Caused by COQ6 Gene Defects Revealed by Pair Analysis and Custom Array CGH

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Introduction: Comprehensive genetic analysis using next-generation sequencer (NGS) of causative genes for steroid resistant nephrotic syndrome (SRNS) have been established all over the world currently. It enables us to treat some kinds of monogenic SRNS patients with specific therapies and improve the renal prognosis; Coenzyme Q10 (CoQ10) supplementation for patients with CoQ10 deficiency related gene variants, such as *COQ6*, *PDSS2*, *COQ2*, and *ADCK4*. In this study, we conducted NGS analysis for the infantile SRNS patient, and to detect a copy number variation (CNV), we performed NGS data-based pair analysis and custom array CGH.

Case Description: Patient was a 1-year-old boy. He was diagnosed with SRNS and performed a renal biopsy. Electron microscopic examination revealed abnormal mitochondria (dysmorphic mitochondria, lacking cristae or abnormal proliferation) in podocytes. We conducted targeted panel sequencing analysis using NGS and detected only one *COQ6* monoallelic reported variant on maternal allele (c.782C>T, p.Pro261Leu). Next, we conducted CNV analysis with pair analysis using the NGS analysis data and custom array CGH. Both analysis successfully detected the same copy number changes in exons 1–2 of the *COQ6* gene on paternal allele. He was thus started supplementation of CoQ10, and remission was achieved.

Discussion: Comprehensive gene screening system with NGS were effective method to detect causative gene variants in SRNS. In addition, conducting pair analysis and custom array CGH were remarkably useful to detect CNVs. Specific therapy of CoQ10 for the patient carrying *COQ6* mutations was very effective when it was started in the early stages, so try not to miss the opportunity for the cases with CoQ10 glomerulopathies starting supplementation.

TH-PO534

Identification of Novel Mutations and Phenotype in the Steroid Resistant Nephrotic Syndrome Gene NUP93

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Introduction: In 11-30% of steroid-resistant nephrotic syndrome (SRNS), a known gene mutation can be detected. *NUP93* is a widely expressed gene that encodes a highly conserved nuclear pore protein that has been shown to cause non-syndromic autosomal recessive focal segmental glomerulosclerosis (FSGS). Here we describe a case of novel *NUP93* mutations in a child with a syndromic SRNS phenotype.

Case Description: We identified compound heterozygous mutations of *NUP93* gene using whole exome sequencing (WES) in a patient presented with syndromic SRNS and progressed to ESRD in her first decade of life. An African American and Hispanic 5-year-old girl presented with nephrotic syndrome, including nephrotic-range proteinuria (UPC of >29 mg/mg), edema, and hypoalbuminemia. She was clinically fluid overloaded, hypertensive, and quickly became anuric and required renal replacement therapy. She had signs of chronic kidney disease including hyperparathyroidism, anemia, and short stature. A urinalysis 1 year prior showed 3+ proteinuria that was not quantified. In addition to her kidney involvement, she had developmental delay with autistic features; including delays in expressive language, fine motor, social communication and repetitive hand movements. Additionally, she had two episodes of heart failure requiring inotropic support after having adequate dialysis for more than a month. Her echo showed systolic and diastolic dysfunction (ejection fraction as low as 35%) and dilated cardiomyopathy features of unclear etiology that did improve with aggressive nutritional support and blood pressure management.

Discussion: We detected compound heterozygous mutations in *NUP93* a maternal missense mutation (ch16:56855426 A>G) c.206A>G, p.Y69C and a paternal nonsense mutation (ch16:56868107 C>G) c.1236C>G, p.Y412X. The mutations were highly conserved through phylogeny and had high pathogenicity prediction scores. We describe in this case novel mutations in the SRNS gene *NUP93* resulting in a syndromic phenotype with neurologic and cardiac features. It remains unclear the degree to which *NUP93* contributed to her cardiomyopathy, as this gene has also been described as localizing to cilia as well as the nucleoporin. WES is the ideal test for patients with SRNS as a conclusive molecular diagnosis does influence therapeutic choices.

TH-PO535

A Patient with PLA2R Membranous Nephropathy and "Non-Depletion" After Rituximab

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Introduction: Rituximab failure in patients with membranous nephropathy with nephrotic syndrome has been described in the literature. We present a case of PLA2R membranous nephropathy who progressed immunologically and did not show evidence of B cell depletion despite use of rituximab.

Case Description: A 62 year-old man with history of hyperlipidemia and hypertension presented with sudden onset lower extremity edema. Labs revealed sCr 1.1 mg/dL, albumin 2.9 g/dL, total cholesterol 235 mg/dL, triglycerides 116 mg/dL, and LDL 132 mg/dL. He had 12.5 grams of protein/24 hour urine collection. ANA, C3, C4, hepatitis panel, serum and urine electrophoresis were all negative/ unremarkable. A renal biopsy was performed which revealed membranous nephropathy that stained positive for PLA2R. Proteinuria and renal function deteriorated despite maximal ARB therapy for >3 months. He was given rituximab infusion 1 g IV every 2 weeks x 2 doses in November 2017. PLA2R antibody titers, CD19 count, sAlb, and sCr were obtained after 2, 4, and 5 months from rituximab therapy as shown in Table 1. Unfortunately given the extent of immunologic progression, we considered treatment failure in this patient and decided against additional rituximab infusions.

Discussion: We present a case with a rare and relatively severe phenotype of PLA2R membranous nephropathy who did not show evidence of B cell depletion and had persistent PLA2R titer progression despite treatment with rituximab. In patients PLA2R membranous nephropathy with nephrotic phenotypes, the use of immunologic biomarkers to ascertain early response is critical in deciding whether to continue or to consider alternative treatments. Novel therapeutic targets such as newer generation anti-CD 20 agents (ie ofatumumab) and plasma cell targets may be helpful in patients with relapsing or rituximab resistant disease. Furthermore, additional biomarkers (eg long-lived plasma cell markers, CD38 and CD138) may be useful while assessing response.

Table 1

	1/2018	3/2018	4/2018
CD19 count (71-567/μL, 5-25 %)	8 (1%)	59 (3%)	49 (3%)
PLA2R Ab titer	1:320	1:640	1:5120
sAlb (g/dL)	1.9	1.2	1.7
sCr (mg/dL)	2.6	3.2	3.5

TH-PO536

A Case of Anti-PLA2R Antibody Positive Membranous Nephropathy Diagnosed in Pregnancy with Antibody Transfer to Infant

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Introduction: Phospholipase A2 receptor (PLA2R) antibody is a pathogenic agent found in 70-80% of patients with primary membranous nephropathy (MN). Whether anti-PLA2R Ab is transmitted from maternal to fetal circulation remains unknown. We report a case of nephrotic syndrome during pregnancy with elevated anti-PLA2R Ab level in maternal serum, and subsequent detection of high levels of antibody in the infant, suggesting that anti-PLA2R Ab likely crosses the placenta.

Case Description: A 33 year old woman was transferred to our medical center at 28 weeks of gestation for ongoing management of pregnancy complicated by nephrotic syndrome. The patient had been diagnosed with the nephrotic syndrome at approximately 16 weeks of gestation based on edema, hypoalbuminemia (0.9g/dL), and 6g of protein on 24 hour urine collection. She had no known history of kidney disease. On arrival to our institution, serum creatinine (Cr) was at her baseline of 0.6 mg/dL with albumin 0.4g/dL. Anti-PLA2R Ab levels were found to be elevated at 479.6 RU/mL. A presumptive diagnosis of primary MN was made and renal biopsy was deferred due to her advanced gestation. Pt remained in the hospital for the duration of her pregnancy and underwent successful diuresis documented by 80 pound weight loss and significant improvement in her edema. She had successful delivery of a male baby at 34 weeks 3 days of gestation. 24 hour urine collection from the patient immediately following delivery showed 12g proteinuria. Cr remained stable throughout the admission. Anti-PLA2R Ab was measured in both mother and baby immediately post-delivery with values of 405.1 and 43.1 RU/mL, respectively.

Discussion: This case suggests that anti-PLA2R Ab crosses the placenta to reach fetal circulation. Whether this results in renal disease in the baby is unclear, though there are case reports of fetal morbidity associated with maternal neutral endopeptidase deficiency leading to congenital membranous nephropathy. Children of mothers with primary MN during pregnancy should be monitored pre- and post-natally for signs of renal disease mediated by Anti-PLA2R Ab.

TH-PO537

PLA2R-AB Positive Malignancy-Associated Membranous Nephropathy: A Case Report

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Introduction: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults and the most frequent paraneoplastic glomerular disease associated with solid tumors. MN is either idiopathic (iMN) or secondary to malignancy (M-MN), infections, autoimmune diseases or drugs. Features such as the presence of the M-type Phospholipase A2 Receptor (PLA2R) antibodies and IgG subclass have been suggested to help distinguish idiopathic from secondary MN. However, 15-17% of cases of M-MN are anti PLA2R antibody positive, raising question about the specificity of these antibodies for the diagnosis of iMN. This is of importance as the treatment of this disease centers upon whether the disease is determined to be primary or secondary.

Case Description: We present here a case of a 78-year-old African female with pancreatic adenocarcinoma who was referred for lower extremity swelling and evaluation for proteinuria. A 24hr urine collection demonstrated 8.3 g of proteinuria and serum albumin of 1.3 g/dl. Her glomerular filtration rate was estimated to be 96 ml/min per 1.73/m2. Monoclonal gammopathy was not detected. Serum anti-PLA2R Antibodies were severely elevated, greater than 1500 RU/ml. A kidney biopsy revealed a prominent glomerular basement membrane and subepithelial deposits on electron microscopy. Anti-PLA2R AB was strongly positive on immunofluorescence. Features of paraneoplastic glomerulopathy were also present (near full-house pattern on IF, Kappa chain co-dominance, equivalent IgG4, IgG1 and IgG3 isotypes). The patient was empirically started on high dose corticosteroids given the preliminary result of proliferative glomerular disease and a near full-house pattern. She received capecitabine and radiotherapy with significant reduction in tumor size. Repeat Anti-PLA2R AB titers was 4 RU/ml

Discussion: This case highlights the complexity in trying to identify iMN from M-MN and the challenges facing the nephrologist in the treatment of this disease. The normalization of Anti-PLA2R AB in the setting of treating her malignancy suggests direct involvement of Anti-PLA2R AB in the mechanism of M-MN. Future studies are needed to evaluate the importance of anti PLA2R Antibodies in M-MN

TH-PO538

THSD7A Associated Membranous Glomerulonephritis Due to Antibody Produced by Lymph Node around Metastasis of the Thymoma

Wei Han,[1] Tomo Suzuki,[1] Shiika Watanabe,[1] Mayumi Nakata,[1] Daisuke Ichikawa,[1] Atsuko Ikemori,[2] Junki Koike,[3] Yugo Shibagaki.[1] *[1]Nephrology, St.Marianna university school of medicine, Kawasaki, Japan; [2]St. Marianna University School, Kawasaki, Kanagawa, Japan; [3]St.Marianna University, Kawasaki, Japan.*

Introduction: Membranous glomerulonephritis (MGN) are known to be associated with malignant tumor and tumor resection can lead to remission of MGN. MGN with thrombospondin type-1 domain-containing 7A (THSD7A), which is one of the transmembrane protein antigen to podocyte, have been recently reported to be also associated to malignancy. We present a first case of THSD7A-associated MGN with thymoma that was later diagnosed with lymphatic metastasis.

Case Description: A 61-year-old woman with past medical history of asthma was referred to our clinic for bilateral edema in lower extremities and proteinuria. Her labs showed nephrotic syndrome and kidney biopsy was done. Although there was no proliferative nor spike lesions in glomeruli on light microscopy, IgG and THSD7A were stained strongly positive along glomerular capillary on immunofluorescence and subepithelial deposits on electron microscopy. Thus, she was diagnosed as THSD7A-associated MGN and subsequently found to have thymoma. She underwent extended thymectomy and postoperative radiation since thymoma type B3 was confirmed pathologically. However, proteinuria persisted in spite of steroid administration for asthma. Three years later, positron emission tomography (PET) revealed a tumor of right subclavian space, in which biopsy specimen showed histology similar to that of thymoma, thus diagnosis of metastatic recurrence was made. She underwent another course of radiation, followed by a PET confirming the complete disappearance of the metastasis, and proteinuria decreasedto less than 1 g/gCr in a year. Additional investigation revealed that, although anti-THSD7A antibody was negative in thymoma itself and in metastatic lesion, it stained strongly positive in the cells of the lymphatic node around the metastatic lesion just as staining in the glomeruli.

Discussion: We report a first case as far as we know showing the THSD7A-associated MGN with metastatic thymoma. It is intriguing that thymectomy itself could not result in remission of her proteinuria presumably due to continued exposure to THSD7A antibody produced by the lymph node around the metastasis. We need to keep in mind of searching for metastasis or remnant tumor in cases which proteinuria does not respond well to tumor resection in THSD7A associated MGN complicated in malignancy.

TH-PO539

Secondary Membranous Nephropathy Was Induced by Gastrointestinal Stromal Tumor in Patient with Idiopathic Membranous Nephropathy

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Introduction: The membranous nephropathy (MN) is a major cause of nephrotic syndrome. The major causes of secondary MN are malignancy, autoimmune disease, infection, and drug toxicity. However, gastrointenstinal stromal tumor (GIST) rarely induces secondary MN. We report here a biopsied case with onset of secondary MN accompanied by GIST on idiopathic MN successfully treated by the resection of GIST.

Case Description: A 77-year-old man was diagnosed as the idiopathic MN at 60-year-old, and treated by oral corticosteroid, resulted in incomplete remission. From age of 71, serum levels of CA19-9 had increased at 1278 U/mL, however, any malignancy was not detected. He was hospitalized because of exacerbation of urinary protein (5.1g/gCr) at 77-year-old. Although steroid pulse therapy was initiated, level of urinary protein was not improved. To rule out complication with other glomerular injuries, we performed renal biopsy. Light microscopic finding indicated MN, but not other glomerulonephritis. Immunofluorescence analysis of IgG subclass showed IgG1 and IgG2 dominant, despite IgG4 deposits were dominant in previous renal biopsy specimens. Furthermore, serum anti-PLA2R antibody was negative. We thus diagnosed as the secondary membranous changes on idiopathic MN. We further surveyed complication of malignant disease and could find GIST by PET-CT. After 1 month from resection of GIST, serum CA19-9 decreased within normal range, and the level of proteinuria also improved to 1.4 g/gCr.

Discussion: This is the novel case with onset of secondary MN on idiopathic MN. Moreover, GIST typically does not show increased levels of serum CA19-9 and rarely induced secondary MN.

TH-PO540

Diffuse Lymphadenopathy as Red Herring for Secondary Membranous Nephropathy

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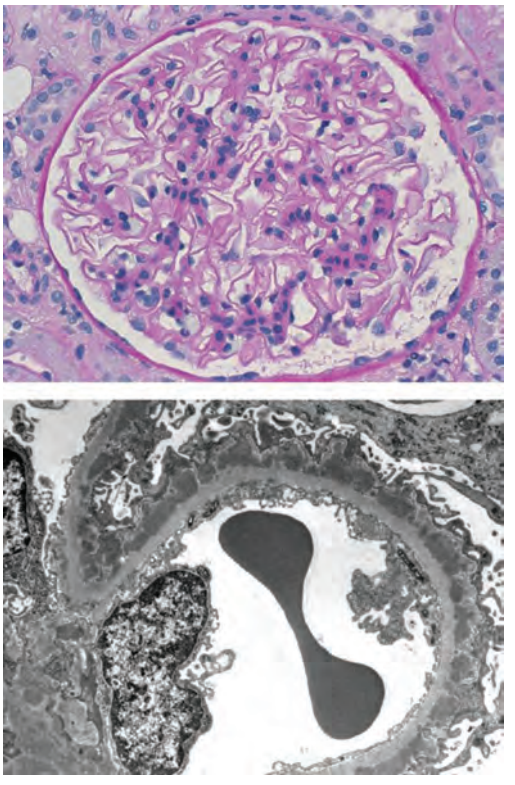
Introduction: Membranous nephropathy (MN) is associated with a high risk of thromboembolism. We describe a patient who presented with multiple thromboemboli with delayed diagnosis of secondary MN due to diffuse lymphadenopathy suspicious for malignancy.

Case Description: A 26-year-old African American female presented with dyspnea, pleuritic chest pain, and edema. CTA revealed multiple segmental PEs and a left renal vein thrombosis. Imaging also found diffuse mediastinal and axillary lymphadenopathy with a prominent hilar mass compressing the right lower lobe pulmonary artery, all of which were FDG avid on PET. Radiology findings was suspicious for lymphoma, however an axillary node biopsy was negative for cancer. Infectious workup was negative. Laboratories were significant for creatinine of 0.6mg/dl, albumin <1 gm/dl, and 7.3 grams proteinuria. Serologies were positive for ANA, anti-Smith, anti-dsDNA, and anti-U1RNP. Kidney biopsy showed widespread IgG-dominant subepithelial deposits consistent with MN. A secondary cause of MN was suggested by mesangial widening with deposits, tubuloreticular inclusions, and lack of PLA2R staining. Based on serologies, arthritis, and renal involvement, the patient was diagnosed with systemic lupus erythematosus (SLE). She was started on high dose prednisone, mycophenolate and anticoagulation. Resolution of proteinuria and edema was seen after six months. Followup physical exam and chest X-ray showed no lymphadenopathy.

Discussion: Diffuse lymphadenopathy, though less common nowadays, may be a prominent presenting feature of SLE and was highlighted in our case. Initial delays in kidney biopsy occurred due to malignancy evaluation and this atypical SLE presentation. Our case was ultimately diagnosed to be SLE with hypercoagulability due to nephrotic syndrome from MN.



TH-PO541

Biallelic CUBN Variants as a Cause of Isolated Proteinuria - Challenging the Investigative Paradigm

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Introduction: Proteinuria is a common kidney presentation. Historically, diagnostic workup of patients with isolated proteinuria involved thorough urinalysis, imaging and blood sampling before potentially proceeding to renal biopsy. However recent advances have resulted in reduced cost and increased availability of genomic sequencing for establishing clinical diagnoses.

Case Description: An 8year old boy was referred with an incidental finding of persistent proteinuria during investigation for nonspecific abdominal pain. He had no haematuria and had normal serum albumin. All other investigations including blood analysis for haematological, biochemical and immunological parameters, renal ultrasound, ophthalmology and audiology assessment were unremarkable. Further assessment revealed consanguineous family history and a brother also with isolated proteinuria. Renal biopsy demonstrated normal light microscopy and global uniform thinning of the glomerular basement membrane on electron microscopy. Chromosomal microarray revealed long continuous stretches of homozygosity (LCSH) representing ~4.5% of the genome. Shared regions of LCSH between the brothers were identified using the Genomic Oligoarray and single nucleotide polymorphism (SNP) Evaluation tool. Examination of these regions implicated *CUBN*, on chromosome 10p12.31. Research whole genome sequencing of both affected individuals was performed with informed consent (HREC/15/QRCH/126). This revealed a homozygous stop-gain variant in *CUBN* (NM_001081.3, c.4689_4690delTAinsAT, p.(CysIle1263*), ACMG Class 5).

Discussion: *CUBN* mutations have been implicated as a hereditary cause of megaloblastic anaemia and variable proteinuria. This is the second reported family with isolated proteinuria due to biallelic *CUBN* variants in the absence of megaloblastic anaemia, demonstrating the utility of genomics to identify single gene causes of nephropathy, and in doing so, to expand the associated phenotypic spectrum. Therefore, genomic sequencing, undertaken earlier in the diagnostic workup, has the potential to reduce the need for invasive investigations and to reduce the time to definitive diagnosis for patients and families.

TH-PO542

Thymic Disease-Associated Nephropathy: A Report of 21 Cases from a Single Institution

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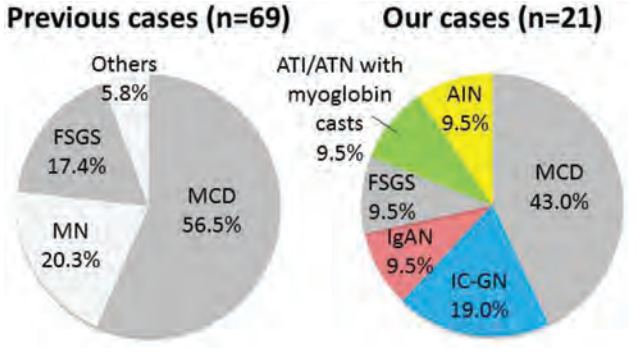
Introduction: Nephropathy in patients with thymic diseases such as thymoma and myasthenia gravis (MG) is rare. Previously, 69 cases have been reported from multiple institutions, and of these, common diseases are minimal change disease (MCD; 56.5%), membranous nephropathy (MN; 20.3%), and focal segmental glomerulosclerosis (FSGS; 17.4%). Here we characterize the spectrum of new 21 renal disease cases associated with thymic disease from a single hospital.

Case Description: Total 36,562 renal biopsy cases from 2005 through mid 2018 were reviewed at Cedars-Sinai Medical Center. 21 cases (0.057%) of patients have history of thymoma and/or MG. Pathological diagnoses are following: MCD (9 cases; 42.9%), Immune complex-mediated glomerulonephritis (IC-GN; 4 cases; 19.0%), FSGS (2 cases; 9.5%), IgA nephropathy (IgAN; 2 cases; 9.5%), acute tubular injury/necrosis (ATI/ATN) with myoglobin casts (2 cases; 9.5%), and acute interstitial nephritis (AIN; 2 cases; 9.5%).

Discussion: Consistent to the previous reports, MCD is the most common renal lesion in patients with thymic diseases. However, we did not observed MN, the second most common disease in the reports. We, instead, observed 4 cases of IC-GN that did not fit to MN: 2 showed mild IC-GN superimposing on MCD; 1 showed lupus nephritis-like GN (ISN/RPS CLASS II) without proliferative features; and 1 showed lupus nephritis-like GN (CLASS II) with segmental membranous change. We also experienced kidney diseases that haven't been reported before as an association with thymic disease: IgAN, ATI/ATN with myoglobin casts, and AIN. 2 cases of IgAN were low-grade without hypercellularity (endocapillary hypercellularity or crescents). 2 cases of ATI/ATN with myoglobin casts showed multiple myoglobin-positive tubular casts. Of AIN cases, one showed mild tubulitis with mild immune complex deposits both in mesangium and along tubular basement membranes. Another case showed granulomatous AIN. In conclusion, this is the largest and unique case series of nephropathy in patients with thymic disease from a single institution.



Summary

TH-PO543

Spontaneous Tumor Lysis Syndrome in Renal Solid Tumor: Case Report

Bruno N. Cesar,[1] Nilo E. Nunes,[4] Erica L. Reghine,[2] Cicero rodrigo M. Alves,[3] Renato D. Foresto,[2] Maria A. Hazin,[3] Marcelino S. Durao.[2] *[1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil; [2]Universidade Federal de Sao Paulo, São Paulo, Brazil; [3]Universidade Federal de Sao Paulo, São Paulo, Brazil; [4]Universidade Federal de Sao Paulo, São Paulo, Brazil.*

Introduction: Tumor Lysis Syndrome (TLS) results from a large release of intracellular material from malignant cells death, especially after chemotherapy. Spontaneous TLS (STLS) is commonly associated with aggressive hematological malignancies and rarely observed in solid tumors.

Case Description: A 67-year- old male presented to the hospital with progressive dyspnea, weakness and oliguria in the last two days. His medical records were hypertension, diabetes, coronary heart disease and a recently diagnosed renal mass. Blood tests showed creatinine: 8.8 mg/dL, urea: 272mg/dL; potassium: 6.4 mEq/L; serum uric acid: 15.9 mg/dL; phosphate: 7.6 mg/dL; ionic calcium: 1.07mmol/L. Two months before, creatinine level was 1.0 mg/dL. Abdominal and renal doppler ultrasound were performed and showed normal sized kidneys with a hypoechoic image on the left side, without signs of thrombosis. Abdominal CT scan showed a Bosniak-III left expansive kidney lesion. According to the clinical and laboratory findings, STLS diagnosis was performed. Due to a lack of response to conservative measures, hemodialysis was initiated and after three sessions kidney function improved and dialysis was discontinued. The patient underwent left nephrectomy. Histological analysis showed a clear cell renal cell carcinoma Fuhrman 3, stage T3a, with recent evidences of hemorrhage and tumor necrosis. The disease was restricted to kidney tissue. The patient was discharged from the hospital on the 5th post-operative day. At this time, blood tests showed creatinine was 1.6mg/dL, potassium 5 mEq/L, phosphate: 5.8 mg/dL, ionic calcium: 1.2 mmol/L and uric acid: 4 mg/dL.

Discussion: STLS is a serious event that affects patients with cancer. There are few reports of its association with solid tumors, especially in the case of renal cell carcinomas. In this report, the diagnosis of STLS was performed using the Cairo-Bishop criteria and was classified as grade 4. In most reported cases, larger masses with metastases prevailed and the patient died immediately after diagnosis. Physicians should be aware of the diagnosis since it requires prompt actions to improve outcomes.

TH-PO544

A Case of Intravascular Large B-Cell Lymphoma Diagnosed by Renal Biopsy

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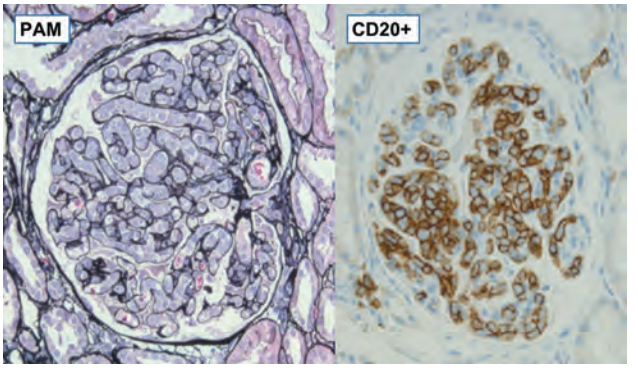
Introduction: Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large-cell lymphoma characterized by the proliferation of lymphoma cells within small vessels. In general, patients with IVLBCL exhibit aggressive clinical courses and most cases are diagnosed at autopsy. Although recent advancements in chemotherapy have markedly improved patient prognosis, an early diagnosis by biopsy remains critical. Therefore, random skin biopsy or bone marrow biopsy is performed in most cases. To date, some case reports have mentioned IVLBCL diagnosis by liver, lung, and brain biopsies. Here, we report a rare case of IVLBCL diagnosed by renal biopsy in a patient with the clinical phenotype of persistent proteinuria together with an elevated serum titer of proteinase-3-anti-neutrophil cytoplasmic antibody (PR3-ANCA).

Case Description: The patient was a 66-year-old woman with a history of bilateral leg edema, erythema, and pruritis. Laboratory data revealed high serum PR3-ANCA titer (92.6 U/ml), and chest computed tomography revealed lung nodules. Four months after the first presentation, the patient developed rapidly progressing dyspnea and persistent proteinuria (1.22 g/day) without hematuria. Renal biopsy revealed intraglomerular infiltration of enlarged atypical lymphocytes. Immunofluorescent staining showed that these cells were characterized as CD3-, CD5-, CD20+, CD79a+, CD10-, bcl-6+, and MUM1+. On the basis of these findings, the patient was eventually diagnosed with IVLBCL. After several cycles of chemotherapy, her proteinuria decreased (0.04 g/day) and PR3-ANCA titer declined (11.3 U/ml).

Discussion: We report a rare case of IVLBCL accompanied with persistent proteinuria and an elevated serum PR3-ANCA titer. In this case, identification of large lymphoma cells within the small vessels of the kidney was a key factor for early diagnosis and successful treatment.



TH-PO545

Primary Bilateral Renal T-Cell Lymphoma Presenting as Rapidly Progressive Glomerulonephritis

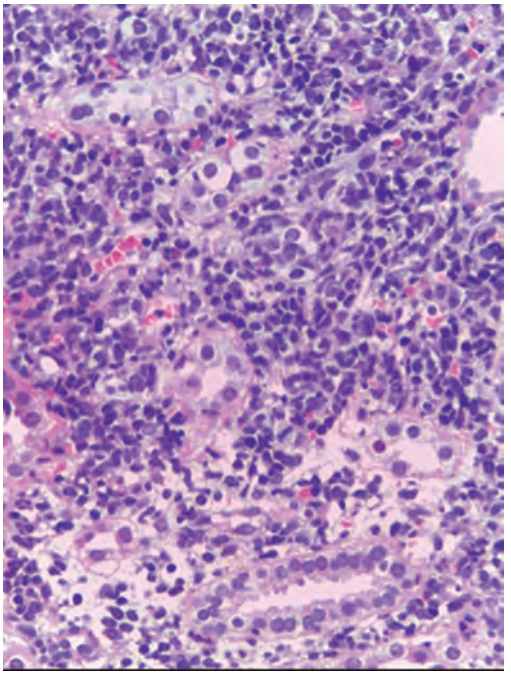
Maria Carolina R. Coêlho, Camila B. Oliveira, Denise M. Costa, Gisele Vajgel, Luis H. Sette, Marcelo Souto maior, Maria Alina G. Cavalcante, Lucila Maria Valente. *Hospital das Clínicas HC - UFPE, Recife, Brazil.*

Introduction: Primary renal lymphoma (PRL) is a extremely rare disease defined as a non-Hodgkin's lymphoma (NHL) involving the kidney in the absence of primarily extrarenal lymphatic disease. Acute kidney injury (AKI) as the initial presentation of lymphoma is even more uncommom.

Case Description: A 43 y/o man presented with edema, weight loss, asthenia and exertional dyspnea for 1 month. Urinalysis and renal function were normal (SCr 1.0mg/dL). After 2 weeks, SCr was 3.6mg/dl and he was hospitalized. He presented microscopic hematuria and mild proteinuria (486mg/24h) with progressive oliguric AKI (SCr 4.2) requiring dialysis. US showed discrete bilateral enlarged kidneys. He received methylprednisolone IV and oral prednisone 1mg/kg/day for the clinical diagnosis of rapidly progressive glomerulonephritis. Kidney biopsy showed diffuse lymphoid intersticial infiltration and immunohistochemistry was compatible with T-Cell lymphoma (CD 3 + / Bcl 2 + / CD 20 - / CD 10 - / CD 5 + / CD 23 - / Ki 67 90%). CT of the thorax, abdomen and pelvis confirmed enlarged kidneys and excluded infiltration in other organs. Before a specific treatment, the patient had a poor outcome, dying with septic shock days after.

Discussion: Despite its rarity, PRL should be kept in mind in the differential diagnosis of AKI with bilateral enlarged kidneys. Clinical manifestations are often nonspecific, with flank pain, hematuria, and weight loss predominating. Lymphomatous infiltration causing

AKI is a uncommon presenting finding and prognosis is poor. Although B-cell NHL are more commom, T-cell NHL have been described as a cause of PRL.



Intersticial lymphocytic infiltration (HE stain; magnification X 400)

TH-PO546

Renal Mucormycosis Presenting as Rapidly Progressive Renal Failure

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Introduction: Mucormycosis is an invasive fungal infection with high mortality (~95% if disseminated). Caused by filamentous fungi in the Zygomycetes class, this infection has become increasingly frequent among immunosuppressed patients. The most common form of invasive mucormycosis is rhino-cerebral, with renal involvement being the rarest. Identification of mucormycosis as the cause of renal failure can be missed due to difficulty of successfully culturing mucorales. We describe a patient with chronic lymphocytic leukemia (CLL) and rapidly progressive renal failure (RPRF) with suspected Richter transformation who was diagnosed with angioinvasive mucormycosis based on renal biopsy specimen.

Case Description: 70-year-old Caucasian man with relapsed CLL presented with fevers up to 102°F daily and night sweats. Creatinine (Cr) increased from baseline 1.1 mg/dL to 3.65 on admission. He had been maintained on rituximab/revlimid for the past half-year. He was recently hospitalized for dyspnea and cough, for which he received voriconazole for suspicion of pulmonary aspergillus. PET scan revealed a new metabolically active retroperitoneal mass, while kidneys were unremarkable. Urine sediment showed RBCs, WBCs, and no casts. ANCA was negative. Despite IV fluids and suspension of nephrotoxic drugs, he progressed within one week to anuric renal failure necessitating hemodialysis. CT-guided renal biopsy was performed. Light microscopy showed necrotizing granulomas with multinucleated giant cells and pleomorphic, PAS-positive fungal forms that were interstitial and intra-arterial. Fungi were broad, non-septate, and thick-walled with irregularly spaced branching hyphae typical of mucor. He was immediately treated with liposomal amphotericin-B and IVIG, then isavuconazole for maintenance therapy. He defervesced after initiation of amphotericin-B but remains dialysis-dependent.

Discussion: This is a unique presentation of mucormycosis in a patient with underlying hematological malignancy and RPRF. This biopsy specimen drastically changed management. Manifestation of renal mucormycosis includes hematuria, pyuria and acute renal failure that can mimic RPRF. As mucorales are notoriously difficult to culture and radiologic imaging is nonspecific, histological diagnosis is required. This case speaks to the importance of early biopsy in renal failure of unclear etiology in immunocompromised patients.

TH-PO547

Mastocytosis of the Kidney: A Rare Manifestation of Systemic Mastocytosis

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Introduction: Systemic mastocytosis (SM), a rare, progressive myeloproliferative neoplasm, is characterized by clonal mast cell infiltration into tissues. Renal involvement of SM is unusual, with only three case reports currently described in the literature, and carries a grim prognosis.

Case Description: A 71 year old male with a history of hypertension, presented with a one year history of fatigue, 60 lb. weight loss, and increasing abdominal distention. Physical exam was notable for a frail, cachectic male with hepatosplenomegaly and peripheral edema. Laboratory analysis revealed acute kidney injury, decreased hepatic synthetic function, and pancytopenia. Urinalysis displayed grade 1 proteinuria and granular casts. Abdominal ultrasound showed increased echogenicity of the kidneys, ascites, and hepatic cirrhosis. The patient had no known risk factors for liver disease and underwent liver biopsy demonstrating diffuse mast cell infiltration with pericentral hepatocyte necrosis. Serum tryptase levels were elevated: 203 ng/ml (normal <11.5). Ensuing bone marrow biopsy showed 100% cellularity with 30-40% mast cells, confirming the diagnosis of SM. The kidney injury, initially managed as hepatorenal syndrome with albumin, midodrine, and octreotide, rapidly progressed requiring hemodialysis. Kidney biopsy revealed tubular injury and mast cell interstitial nephritis (Image 1). Midostaurin, a multikinase inhibitor, was initiated as disease directed therapy. The patient was eventually discharged but remained dialysis dependent.

Discussion: SM is associated with mutations in the receptor tyrosine kinase KIT (CD117). SM subtypes and median survival range from indolent (16 years) to mastocytoma (2 months). Renal involvement may occur even with indolent SM and has been reported as MPGN, interstitial nephritis, and light chain deposition disease. In each case, the kidney injury was progressive, requiring hemodialysis, and survival was worse than expected despite KIT directed therapy.

Image 2: Kidney biopsy CD117 stain highlighting increased interstitial mast cells

TH-PO548

Something Amiss with Cannabis: AKI Associated with Cannabidiol Ingestion

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Introduction: Cannabidiol (CBD) is a nonpsychoactive phytocannabinoid that is a popular dietary supplement with proposed medicinal properties. Although synthetic cannabinoids (SCs) such as K2/Spice have been implicated in kidney injury in over 20 case reports, CBD's renal effects are not as well documented.

Case Description: A 58 year old female with diabetes, hypertension and two weeks of abdominal pain and diarrhea presented with one day of emesis, anuria and CT imaging concerning for mild colitis. Medications were omeprazole, losartan, carvedilol, metformin and Insulin. She had started ingesting commercial, hemp-derived CBD Oil three months earlier but denied drug use, including Spice, K2 or marijuana. She had tachycardia and mild abdominal tenderness on physical examination. Initial lab tests showed renal failure, with a serum Cr 7.1 mg/dL (baseline 1.0), BUN 49 mg/dL, and potassium 7.1 mmol/L. The patient received emergent hemodialysis for refractory hyperkalemia. Urine output improved and gastrointestinal symptoms resolved in 24 hours. Urinalysis was negative for casts but urine protein/Cr and microalbumin/Cr ratios were 15 g/g and 4.4 g/g, respectively. Autoimmune and viral workups were unremarkable, as were SPEP, UPEP and free light chain assay. Renal biopsy showed extensive isometric cytoplasmic vacuolization of tubular cells. Under electron microscopy, these vacuoles were seen to be membrane-bound and corresponded to dilated endoplasmic reticulum. This disease pattern suggested toxic tubular injury and occurred on a background of diabetic glomerulosclerosis with mild TA/IF. Urine studies demonstrated evidence of a proximal tubulopathy with elevated 24h fractional excretion of phosphorous (68.4%) and Uric Acid (7.8%). The patient's renal function improved over the next week and she was discharged with a Cr of 3.1 mg/dL.

Five weeks after discharge, her serum Cr and proteinuria had improved to 1.4mg/dL and 215 mg/g, respectively.

Discussion: The mechanism for SC-associated kidney injury is unknown but tubular vacuolization has been documented in several cases. Although CBD differs from SCs in that it has little activity on the Cannabinoid 1 and 2 receptors, it has >65 molecular targets and could share a common mechanism for renal injury. This is the first reported case of renal injury associated with CBD use.

TH-PO549

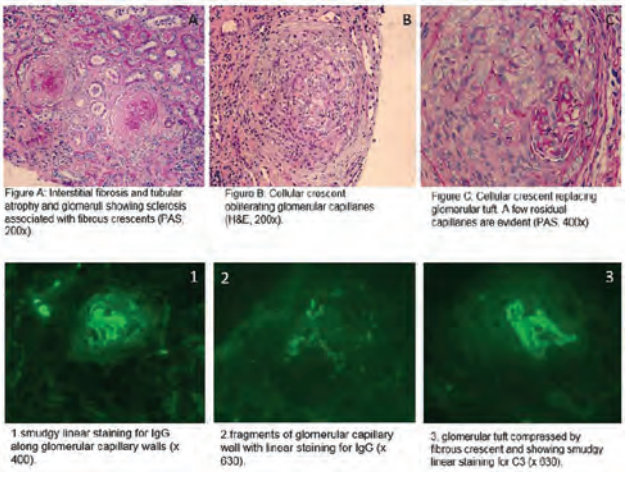
ESRD Secondary to Anti-Glomerular Basement Membrane Disease in a Child with Common Variable Immunodeficiency

Sai Sudha Mannemuddhu, Kiran K. Upadhyay. *Pediatric Nephrology, UF Shands, Gainesville, FL.*

Introduction: Anti- glomerular basement membrane (GBM) disease is an uncommon autoimmune disorder that is characterized by rapidly progressive glomerulonephritis (GN) caused by autoantibodies against the α3-chain of type IV collagen in the GBM. Commom variable immunodeficiency (CVID) is a primary immunodeficiency manifested by hypogammaglobulinemia, inability to make functional antibody, and recurrent infections. We report an interesting association of anti-GBM disease with CVID.

Case Description: A 15-year-old Caucasian female with prior normal renal function presented with 2 weeks of nephrotic proteinuria, oliguria, AKI, and was found to have serum anti-GBM antibody. She had been diagnosed with CVID and West Nile meningoencephalitis at 3 and 12 yrs of age respectively. Her renal biopsy showed crescentic GN with at least 50% global glomerulosclerosis and immunofluorescence showed linear staining for IgG along the glomerular capillary wall. There was no clinical or radiological evidence of pulmonary hemorrhage. She was treated with pulse IV steroids, Cyclophosphamide, Rituximab and several sessions of plasmapheresis. Her serum anti-GBM antibody level decreased from 194 U/mL at presentation to 0 U/mL post therapy. However, she progressed to ESRD within weeks and required dialysis. Her clinical course was complicated by hypertensive encephalopathy, CMV meningoencephalitis, CMV viremia, status epilepticus, and she passed away a few months later from lower respiratory infection related complications.

Discussion: Anti-GBM disease is a rare autoimmune condition, which has not been reported in association with a primary immunodeficiency syndrome. ESRD secondary to anti-GBM disease in a patient with CVID is an interesting association and supports role of immune dysregulation in systemic autoimmune disease.



Kidney Biopsy images- Anti GBM disease

TH-PO550

Renal Injuries Induced by Castleman's Disease

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Introduction: Castleman's disease is a benign lymphoproliferative disorder in which interleukin-6 (IL-6) is thought to play a pathogenetic role. Although renal involvement in Castleman's disease were reported, etiology of renal injuries is currently unknown, due to lack of data from renal biopsy. Here, we report two renal biopsied Castleman's disease in which successfully treated with the tocilizumab, a humanized anti-IL-6 receptor antibody.

Case Description: < *Case 1* > A 30-year-old man presented swelling of systemic lymph node. Pathological analysis of cervical lymph node biopsy showed plasmacyte infiltration, and ruled out malignant lymphoma and IgG4-related disease. Laboratory data indicated anemic state, hypoalbuminemia, polyclonal hypergammaglobulinemia, high levels of CRP (9.1 mg/dl), IL-6 (20.6 pg/ml) and VEGF (513 pg/mL). Taken together, he was diagnosed as multicentric Castleman's disease. The eGFR was 110.8 ml/min/1.73m^2, however, 0.6 g/day proteinuria and microscopic hematuria were detected. Then kidney biopsy was performed. The pathological findings of kidney biopsy specimen showed mild proliferation of mesangial cell. No immune deposits were detected by immunofluorescence analysis. < *Case 2* > A 49-year-old man was detected anemia and swelling of systemic lymph node. Cervical lymph node was biopsied, and laboratory investigation showed anemic state, hypoalbuminemia, polyclonal hypergammaglobulinemia and high level of CRP (8.7 mg/dl), IL-6 (43.0 pg/ml) and VEGF (1250 pg/ml). Taken together, he was diagnosed as multicentric Castleman's disease. The eGFR was 56.8 ml/min/1.73m^2, and 0.6g/day proteinuria and microscopic hematuria were detected at the time of renal biopsy. The pathological findings showed mild mesangial cell proliferation and global sclerosis in 10% of total glomerulus. Immunofluorescence analysis did not show any immune deposits.

Discussion: We present cases of kidney injury induced by Castleman's disease. In both cases, significant infiltration of plasmacyte and IL-6 positive cells were not detected in kidney biopsy specimens. Importantly, tocilizumab, but not corticosteroid successfully improved urinary abnormality. Although the mechanism and clinical course of renal involvement in Castleman's disease is unclear, these cases suggested that kidney injury in patients of Castleman's disease is induced by systemic overproduced IL-6 which proliferate mesangial cells.

TH-PO551

Prominent Swelling of Glomerular Endocapillary Cells in Two Cases of TAFRO Syndrome

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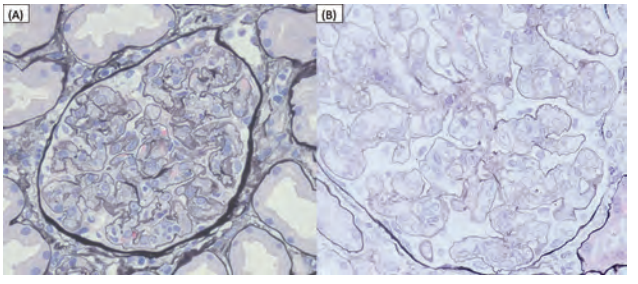
Introduction: TAFRO syndrome, which is characterized by thrombocytopenia (T), anasarca (A), fevers (F), reticulin myelofibrosis/renal disorder (R), and organomegaly (O), is sometimes a fatal systemic inflammatory disease. The histopathological findings remain unclear because it is often difficult to perform renal biopsy due to severe thrombocytopenia. We herein report the histopathological findings of two cases of TAFRO syndrome in which renal biopsies were performed.

Case Description: Case 1: A 51-year-old male was admitted due to fever, fatigue, high CRP value, thrombocytopenia, and resistance to antibiotic drug treatment of two weeks' duration. He showed anasarca and multiple lymph node enlargement. He was diagnosed with TAFRO syndrome. Even though intensive care, including administration of corticosteroids, tocilizumab, and hemodialysis were continued, he died on the 24th day of hospitalization due to multiple organ dysfunction. Renal biopsy revealed marked swelling of glomerular endocapillary cells. Case 2: A 34-year-old man was referred due to fatigue, pretibial pitting edema, urinary protein, and urinary occult blood of one-month duration. He was admitted to the hospital for renal dysfunction and heightened inflammatory response. Hepatosplenomegaly, ascites, and thrombocytopenia was observed. He was diagnosed with TAFRO syndrome due to elevated VEGF and IL-6 levels. Prednisolone was administered and the heightened inflammatory response and proteinuria were ameliorated. Renal biopsy revealed endocapillary hypercellularity, endothelial cell enlargement, mesangiolysis, and duplication of basement membrane. These findings were compatible with thrombotic microangiopathy.

Discussion: The findings suggest that endothelial dysfunction is consistent with the characteristics of TAFRO syndrome, which was observed in this case as a membranous proliferative glomerulonephritis (MPGN)-like glomerular lesion. Renal impairment in TAFRO syndrome may be caused by secondary MPGN due to endothelial cell disorder.



TH-PO552

A Case of Multicentric Castleman Disease – TAFRO Variant, Presenting with Renal TMA

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Introduction: Castleman's disease is a rare systemic lymphoproliferative disorder in which immune cells become activated to produce excess cytokines, particularly IL-6. A subset of cases are related to HIV or HHV-8. There is a wide heterogeneity of symptoms in the disease, ranging from asymptomatic to multisystem organ dysfunction. TAFRO syndrome is a unique clinicopathologic variant of multicentric Castleman's disease first described in 2010 in Japan by Takai et al. It includes thrombocytopenia, anasarca, microcytic anemia, fever, reticulin fibrosis, renal dysfunction, and organomegaly. To our knowledge, this syndrome has yet to be reported in the U.S.

Case Description: 20 y.o. male with previous normal kidney function, presented with AKI, lymphadenopathy, anasarca, and diarrhea after 2 month history of myalgia, malaise, back pain, diarrhea, vomiting, low grade fevers, and night sweats. He endorsed large amounts of NSAIDs use for myalgias. He presented with serum creatinine of 2.4 mg/dL which continued to rise despite conservative therapy with isotonic volume expansion and peaked at 4.7 mg/dL. The urinalysis was bland and urine protein-to-creatinine ratio was

0.1 g/g. Extensive workup including serologies for hepatitis and autoimmune disease were negative. Noncontrast CT was obtained which revealed prominent axillary, retroperitoneal, mesenteric, and inguinal lymphadenopathy. A renal biopsy revealed thrombotic microangiopathy (TMA) with mostly arterial changes, and evidence of mesangiolysis. Further workup for hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura was negative. An excisional left axillary lymph node biopsy revealed classic findings of Castleman's disease. PCR for CMV, EBV, HIV, HHV-6, and HHV-8 were all negative. He was started on oral steroids, as well as IL-6 inhibitor (siltuximab) and developed hyperkalemia which was refractory to medical management, and required correction via conventional hemodialysis. He was continued on prednisone and received situximab infusion every 3 weeks with full recovery of renal function.

Discussion: Specific targeting of pathogenic mechanism of Castlaman's associated TMA with siltuximab in our case resulted in complete recovery of dialysis dependent renal TMA. To our knowledge, this is the first case of extremely favorable outcome of Castlaman's disease associated TMA treated with IL-6 inhibitor.

TH-PO553

Double Trouble or a Separate Entity: AKI Secondary to ANCA Vasculitis with IgG4 Nephropathy

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Introduction: Antineutrophil Cytoplasmic Antibody-Associated (ANCA) vasculitis is reported to be associated with tissue infiltration by IgG4 cells and IgG4-related disease (IgG4-RD) is associated with elevated ANCA titers. IgG4-RD diagnosis is considered with caution in a patient with ANCA vasculitis as JSN criteria, one of widely used criteria for diagnosis, suggests that IgG4-RD is an unlikely diagnosis in patient with vasculitis. However, there is growing evidence of possible overlap between IgG4-RD and ANCA vasculitis, especially granulomatosis with polyangiitis, GPA. Few case reports showed histological evidence of both disease in the same organ. We present a case of GPA disease with concurrent histological evidence suggestive of IGg4 disease involving the kidney. These patients when treated with rituximab had good disease outcome

Case Description: A 61 year old woman with multiple co-morbidities including hypertension, chronic obstructive lung disease and chronic kidney disease was admitted for evaluation of shortness of breath and dysuria. she developed acute kidney injury during the first week of hospitalization along with purpuric rash on legs. no ocular, thyroid, salivary or oral manifestation by history or examination. urine analysis showed no dysmorphic RBCs. UPC was of 1.5. Serology for ANA, Anti-dsDNA, hepatitis panel and HIV was negative. PR3-ANCA was + and C3&4 were low. Renal biopsy was performed with finding of acute focal segmental necrotizing pauci-immune glomerulonephritis, active tubulointerstitial nephritis with interstitial and tubular basement membrane immune complex deposits, area of storiform fibrosis, and area of abundant IgG4 (20 cells/HPF). Serum IgG4 subclass level was elevated. These findings are suggestive of IgG4-RD. A CT of abdomen/pelvis did not reveal any other organ involvement. she was started on prednisone and rituximab with improvement of renal function back to baseline

Discussion: Clinical & histological evidence suggestive of IgG4-RD and ANCA vasculitis can co-exist in the same organ, including the kidney. Our findings support the growing evidence of possible association between IgG4-RD and GPA vasculitis. Understanding this association might help us have better understanding of underlying pathophysiology of both diseases. Rituximab was observed to be effective for treatment of IgG4-RD overlapping with ANCA vasculitis

TH-PO554

IgG4 Nephritis, When Rising Creatinine Is Not a Progression of CKD

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Introduction: Immunoglobulin G4 (IgG4) is a rare disease with a diagnosis dependent on high clinical suspicion, specially when a single organ is affected. We present a case of IgG4 tubulointerstitial nephritis (TIN) and discuss when to suspect this disorder.

Case Description: A 64-year-old male with history of type 1 diabetes and chronic kidney disease with a creatinine (Cr) baseline of 1.2mg/dL, was referred to clinc after having an increase of Cr to 3.3mg/dL over 4 months. There were no recent changes in medications or sickness. Blood pressure and diabetes were under control with an HBA1C of 7.3% and microalbuminuria of 33mcg. Urinalysis (UA) showed 2-4 red blood cells and a protein/cr ratio of 800mg/g. Due to the unlikelihood of rapid progression of diabetic nephropathy, investigation for acute kidney injury with serology and renal ultrasound were pursued. Results were significant for low C3 and C4 and a rising Cr of 3.5mg/dL. Consequently, a kidney biopsy was done, revealling diffuse TIN with a dense plasma cell infiltrate with a high proportion of IgG4 cells and tubular basement membrane immunocomplex deposits. IgG4 levels were 683.5 mg/dL. With the diagnosis of IgG4 TIN, patient was started on prednisone 40 mg daily. After 1 month, the patient's Cr was 2.3mg/dL and after 4 months, 1.9mg/dL with IgG4 levels of 118 mg/dL. Patient is currently off prednisone and is being monitored for recurrence.

Discussion: IgG4-related kidney disease has higher prevalence among older men and it is usually related to extra renal disease, with sole renal impairment in 2-12% of cases. The pattern of intrinsic disease is most commonly TIN but can also be membranous. Patients can present with worsening of baseline CKD, making it important to add IgG4 disease in your differential. Igg4 disease should be suspected in patients with rising Cr and signs of tubular injury, but no white blood cells on UA neither obvious pharmacological or infectious etiology. Low complement levels and normal ESR/CRP are suggestive of IgG4 disease, however, to fit the diagnosis, biopsy findings of TIN with >10 igG4positive plasma cells/hpf in addition to one of the clinical criteria of elevated igG4 and igG levels, specific imaging findings or extra renal disease must be present. Steroids are first line treatment and remission is achieved in 82% of cases. Rituximab is indicated in refractory cases. Patients with higher GFRs tend to respond well to treatment.

TH-PO555

Rare Case of IgG4-Related Kidney Pseudotumor

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Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibroinflammatory condition that can involve one or multiple organs in the body. It is characterized by tissue lymphoplasmacytic infiltration with IgG4+ plasma cells, storiform fibrosis, and possibly elevated serum IgG4 levels. Renal involvement by IgG4-RD is rare and can be confused with kidney neoplasms as it has the tendency to form pseudotumor.

Case Description: A 40-year-old woman complained of abdominal pain for three months. Abdominal CT and MRI scan revealed an enhancing lesion in the lower pole cortex of the left kidney measuring 2.7 x 2.4 x 2.2 cm. The lesion showed central necrosis with thick enhancing wall and it was minimally exophytic without violation of Gerota's fascia. There were also stable borderline and enlarged retroperitoneal lymph nodes. Kidney function tests including eGFR, BUN, and serum creatinine were normal. The patient's preliminary diagnosis was renal cell carcinoma and partial nephrectomy was performed. Gross examination showed a 2 X 2 X 1.3 cm white, firm poorly circumscribed irregular lesion with no evidence of necrosis or hemorrhage. Microscopic examination showed large areas of storiform fibrosis with intense lymphoplasmacytic infiltrate and vascular involvement. Immunohistochemical stains showed increased IgG4+ plasma cells (>25 cells/HPF). The IgG4+: IgG+ plasma cell ratio was 50%.

Discussion: IgG4-RKD is the term used to describe multiple kidney lesions including tubulointerstitial nephritis, renal pyelitis, or renal insufficiency as a result of retroperitoneal fibrosis. CT scan of patients with IgG4 tubulointerstitial nephritis usually reveals multiple low density parenchymal lesions. The presence of a solitary lesion with exophytic appearance is rare. In these circumstances, it is usually very difficult to rule out a neoplastic process based on imaging alone. Steroids are the first-line treatment in most patients. A high clinical suspicion, serum IgG4, and a representative biopsy are usually sufficient to make the diagnosis in most cases. Awareness about the unusual instances where imaging studies are worrisome for malignancy can help avoid unnecessary surgery.

TH-PO556

A Case of IgG4 Related Disease (IgG4-RD) Presented with Membranous Nephropathy (MGN) Several Years Before Other IgG4 Manifestations

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Introduction: IgG4-RD is a systemic immune mediated condition that is characterized by mass-forming inflammatory lesions and lymphoplasmacytic infiltration with increased IgG4 positive plasma cells in affected tissue. Tubulointerstitial nephritis is the most common form of renal involvement in IgG4-RD. MGN can be secondary to IgG4-RD ("IgG4-related MGN"), usually identifiable as such due to concurrent or previous other organ involvement by IgG4-RD.

Case Description: A 67 year old man initially presented with nephrotic syndrome with 7.8 g/day proteinuria. He underwent a renal biopsy which revealed by immunofluorescence global granular glomerular basement membrane staining with IgG, C3, and kappa and lambda light chains typical of MGN. The patient failed treatment with mycophenolate mofetil and subsequently was switched to oral cyclophosphamide which induced a remission. 3 Years later, at age 70, he developed chronic sinusitis that was resistant to medical treatment. At age 73, he developed bilateral large parotid glands. On further evaluation, serum IgG4 subclass was markedly elevated at 2180 mg/dL. A parotid fine needle aspiration was done which revealed a polytypic plasma cell infiltrate with increased numbers of IgG4-positive plasma cells consistent with IgG4-RD. He also underwent prostatic biopsy for enlarged prostate which revealed increased number of IgG4-positive plasma cells, consistent with involvement by IgG4-RD. The kidney disease remained in remission at the time of IgG4-RD diagnosis. Serum anti-PLA2R antibodies checked at the time of IgG4-RD diagnosis were negative.

Discussion: In this case a patient was diagnosed with IgG4-RD 7 years after initial diagnosis of MGN. PLA2R serum testing was not available at the time of initial presentation with proteinuria. The patient's MGN could have represented primary (PLA2R-associated) MGN that was treated and was in remission; alternatively, the MGN may have represented an early manifestation of IgG4-RD, which would provide a unifying diagnosis of the immune-mediated conditions. Teaching point: Clinicians should maintain high a suspicion for development of IgG4-RD years after initial diagnosis of MGN in the right

clinical setting. Serum PLA2R testing may be contributory, as reported IgG4-related MGN cases are negative for PLA2R.

TH-PO557

Tubulointerstitial Nephritis as the Initial Presentation of IgG4-Related Disease

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Introduction: IgG4 related disease (IgG4-RD) is a systemic, autoimune fibrosing condition that was recently recognized, initially as autoimmune pancreatitis, less than 15 years ago. Since then, it has been shown to involve other organs, manifesting as cholangitis, retroperitoneal fibrosis, aortitis, pneumonitis and nephritis. While membraonus glomerulonephritis has been described, tubulointerstitial nephritis (TIN) is the most common for m of IgG-4 related kidney disease (IgG4-RKD). It is marked by IgG4 positive lymphoplasmocytic infiltrate.

Case Description: A 40 y/o caucasian male with a history of Asthma and Graves disease presented for evaluation of elevated creatinine, which was 1 mg/dl at baseline and on evaluation was 1.99 mg/dL. His creatinine increased over the next 6 months to a peak of 3.5. Urinalysis showed mild proteinuria and a bland sediment. He was referred for renal biopsy which showed significant plasma cell infiltrate with more than 50 IgG4 positive cells per HPF, as well as lymphocytic tubulitis. Intrestingly, eosinophils were seen on the biopsy. The clinical significance of this is as yet unclear. He was shown to have leveated total IgG as well as elevated IgG4. He subsequently developed respiratory symtoms and CT imging of his chest showed a nodule, with surrounding ground glass changes. Steroid therapy was initiated and he has had resolutionof the chest findings and improvement in creatinine.

Discussion: This case adds to our body of knowledge and supports proposed diagnostic criteria which combines histology, imaging and serology. It also supports the notion that renal involvement may precede systemic findings. Diagnosis of this condition warrants awareness and vigilance as specific immune staining is required and may need to be requested to make the diagnosis.

TH-PO558

Lysozyme-Induced Nephropathy as a Cause of Interstitial Nephritis in Sarcoidosis

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Introduction: Sarcoidosis manifests interstitial nephritis of an unknown etiology. We report a case series of interstitial nephritis in patients with sarcoidosis, that could be associated with lysozyme-induced tubular injury.

Case Description: Kidney biopsy specimens of four cases of sarcoidosis, four cases of other interstitial nephritis such as drug-induced, IgG4-related and Sjogren syndrome, and one case of chronic myelomonocytic leukemia induced interstitial nephritis were analyzed retrospectively by immunohistochemistry and electron microscopy. All four patients with sarcoidosis showed interstitial nephritis in the kidney. Specimens were stained with anti-lysozyme antibody and showed positive staining in proximal tubular cells, whereas negative immunostainings in the other three cases of interstitial nephritis. Strong lysozyme staining was also present in interstitial nephritis caused by chronic myelomonocytic leukemia, the mechanism of which is known as a lysozyme-induced tubular injury. The serum lysozyme level increased slightly in sarcoidosis and was markedly elevated in chronic myelomonocytic leukemia. Electron microscopy revealed increased number and size of lysosomes in proximal tubules of sarcoidosis and chronic myelomonocytic leukemia, those of which were associated with serum lysozyme levels.

Discussion: Underlying mechanisms of interstitial nephritis in sarcoidosis could be associated with proximal tubular absorption of lysozyme. We suggest that tubular injury of both sarcoidosis and chronic myelomonocytic leukemia could be categorized into lysosome-induced nephropathy. Chronic myelomonocytic leukemia induces acute kidney injury with overloaded lysozyme to the proximal tubules. On the other hand, chronic tubular injury of sarcoidosis may be associated with above average lysozyme stress on the tubules.

TH-PO559

ANCA Vasculitis Presenting with Chronic Active Interstitial Nephritis Without Glomerular Involvement

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Introduction: ANCA-associated vasculitis (AAV) with renal involvement typically causes pauci-immune glomerulonephritis. We present a rare case of chronic active interstitial nephritis as the sole renal lesion, without glomerulonephritis, in a patient with MPO AAV.

Case Description: A 45-year-old female with a history of Crohn's disease, GERD with Barrett's esophagus, endometriosis, and polyarthralgias was evaluated in nephrology clinic in 2018. Acute interstitial nephritis was initially diagnosed in 2011 on renal biopsy. There was no evidence of glomerulonephritis. p-ANCA was positive with MPO titer of >100 units/mL. She lacked systemic symptoms of AAV. Serum creatinine peaked at 2.1 mg/dL and improved to 0.9 mg/dL with prednisone and azathioprine. Repeat biopsy in 2013 for worsening renal function again showed acute interstitial nephritis and no vasculitic glomerular involvement. Prednisone and cyclosporine were started, with improvement in serum creatinine from 1.9 to 1.2-1.4 mg/dL. Crohn's disease was diagnosed in 2014 and adalimumab was started in 2016. Acute interstitial nephritis was attributed to Crohn's and cyclosporine was stopped in 2016. Her gastrointestinal symptoms improved with adalimumab, but renal function and abnormal urine sediment did not. Attempt was made to switch omeprazole to an H2-blocker but this was not tolerated. Repeat renal biopsy in 2/2018 showed chronic active interstitial nephritis with severe interstitial fibrosis and tubular atrophy and no active glomerular disease. MPO titers remained high at 132 units in 3/2018. She was started on mycophenolic acid and prednisone without significant response, followed by rituximab induction therapy for AAV-associated active interstitial nephritis. Serum creatinine continued to worsen to 5.5-5.7 mg/dL and preparations are being made to start peritoneal dialysis.

Discussion: AAV may present with isolated interstitial nephritis without glomerular involvement. The rarity of this presentation may contribute to delay in diagnosis and appropriate management. Alternate explanations for interstitial nephritis, such as Crohn's disease or PPI use, should be considered with caution in the setting of high-titer ANCA positivity.

TH-PO560

Anaplasmosis Induced Acute Interstitial Nephritis (AIN) Following Tick Bite: A Rare Association

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Introduction: AIN usually results from immune mediated tubulointerstitial injury initiated by medications and infections. We present a rare case of kidney biopsy proven AIN associated with Anaplasmosis following a tick bite.

Case Description: 82 year old Caucasian woman with HTN, HLD presented with fever, tremors, myalgia and fatigue following a camping trip in Catskills where had significant outdoor exposure to the woods. She was found to have AKI, thrombocytopenia and transaminitis. She had serum creatinine(Scr) of 6.62 on admission which peaked at 6.78 during hospitalization. Four months prior, her Scr was 0.9.She denied use of herbal supplements or antibiotics, however had used NSAIDs in the week before hospitalization. Urinalysis showed microscopic hematuria with 10-25 RBCs. Kidney ultrasound was negative for obstructive uropathy. Serological work up for glomerulonephritis was negative. Peripheral smear showed intracellular inclusions suggestive of morulae concerning for Anaplasmosis, and she was initiated on treatment with Doxycycline. Kidney biopsy was performed that revealed moderate AIN, along with 13% glomerulosclerosis, 10% interstitial fibrosis and tubular atrophy, and severe arterial and arteriolar sclerosis. AKI, transaminitis and thrombocytopenia started improving with initiation of Doxycycline. She did not require corticosteroid therapy. Although a tick was not noticed specifically, and work up including Anaplasma antibody, Ehrlicia PCR and Lyme's titres were negative, she was continued on treatment for Anaplasmosis due to high clinical suspicion of the disease. She completed 10 day course of Doxycycline. AKI resolved and Scr decreased to 1.16mg/dl 5 weeks after initial presentation.

Discussion: AIN mediated by various systemic bacterial, viral and parasitic infections is well known. However, association of AIN following anaplasmosis from a tick bite has not been well documented in the literature. To our knowledge, we report the first case of AIN in association with Anaplasmosis. Nephrologists, Infectious disease specialists and Internists should to be aware of this rare cause of AIN. Corticosteroids have no role in infection associated AIN as they are contraindicated in setting of active infection. AKI usually is reversible as infection is treated. Our patient regained baseline kidney function with antimicrobial therapy.

TH-PO561

AKI Associated with Suspected Yersinia Infection in Spring 2017

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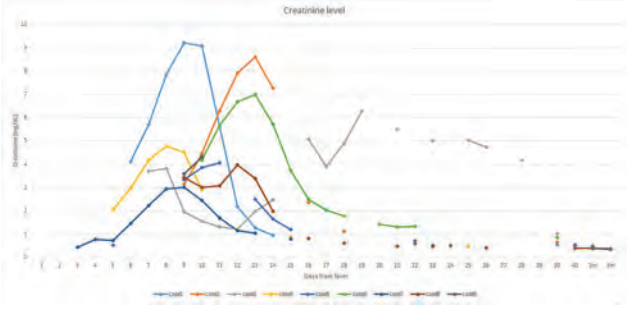
Introduction: *Yersinia pseudotuberculosis*, a zoonotic pathogen is known to cause fever, acute gastroenteritis, mesenteric lymphadenitis, or acute kidney injury (AKI). There have been frequent *Yersinia* infection outbreaks associated with contaminated food and unsterile water ingestion in the past. While it was considered practically eradicated with improvement of public health including control of mountain water cleanness, we experienced several cases with suspected *Yersinia* infection in 2017.

Case Description: There were 9 cases suspected of *Yersinia* infection (Male:Female 6:3, mean age 7.57 years (range 3.01 - 12.18)). Six cases occurred in May and 8 resided in metropolitan Seoul area. Three cases had history of drinking mountain water. All the cases first presented with fever for median 13 days (range 6 - 20), and gastrointestinal symptoms and oliguria followed. Imaging studies revealed mesenteric lymphadenitis, terminal ileum wall thickening, and increased parenchymal echogenicity of kidney. Creatinine levels

increased to 3.03 - 9.22 mg/dL. Their urinalysis revealed sterile pyuria, proteinuria, and glycosuria, suggesting interstitial nephritis. Oliguria continued for 4-17 days and one patient required hemodialysis, however, all of them completely recovered from AKI. Rash developed later in four cases, and desquamation was noted in three. Mean disease duration from the onset of fever to discharge was 11.9 days (range 6 - 24). In the diagnostic work-up, *Yersinia pseudotubuerculosis* was isolated in stool culture in one patient. Anti-*Yersinia* IgA and IgG were found positivein six patients within three months after the onset of disease, suggesting recent *Yersinia* infection.

Discussion: *Yersinia pseudotubuerculosis* infection is a well-known cause of interstitial nephritis presenting with AKI. When a patient present fever, acute gastroenteritis, fever and AKI, clinician should suspect *Yersinia* infection. Furthermore, diagnosis of such a case warrants surveillance to identify the infection source and prevent an outbreak.



TH-PO562

A Unique Case of Tubulointerstitial Nephritis with Late-Onset Uveitis and Thrombotic Microangiopathy Induced AKI, Withdrawal from Hemodialysis, and Relapse

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Introduction: Tubulointerstitial nephritis and uveitis syndrome (TINU) was first described in 1975 and there have been three hundred reported cases throughout the world since.

Case Description: A 37-year-old man presented with malignant hypertension (MHT) due to obstructive sleep apnea-hypopnea syndrome, acute kidney failure, and tubular dysfunction. Only hypertensive retinopathy was found. Renal biopsy showed TMA induced renal injury (possibly due to MHT)) with acute interstitial nephritis (AIN, Fig. 1-3). He had been taking pseudo-genseng lately. He was treated with hemodialysis, ACEI for MHT, oral prednisone for AIN (30mg/d for 6 weeks and then tapered to 5mg/d). His renal function improved 5 months post biopsy. Hemodialysis was withdrawn and steroid was stopped. Kidney injury recurred 3 months thereafter. Bilateral uveitis (Fig. 5-7) was found and TINU was confirmed. Prednisone of 15mg/d was reinitiated and renal and tubular recovery were observed within 6 weeks. He is under follow-up. Anti-mCRP antibody assay and Hazardous genotype were sent for tests.

Discussion: It is a unique case with severe AKI due to MHT induced TMA together with TINU. It is important to note that at the time of renal biopsy, with the history of pseudo-genseng use, and ocular tests, he was misdiagnosed as drug-induced AIN and therefore prescribed a relatively short course of prednisone. His recurrent kidney injury with concomitant uveitis after prednisone withdrawal strongly suggested the needs for long-term follow up and elongated prednisone therapy for TINU. Another issue is that routinely ocular examination is critical, as here uveitis can be completely asymptomatic. In this case both TMA and AIN contributed to AKI, which requires further investigation.

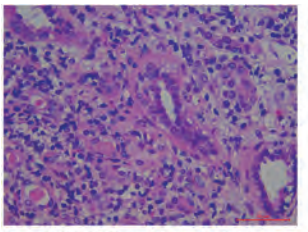
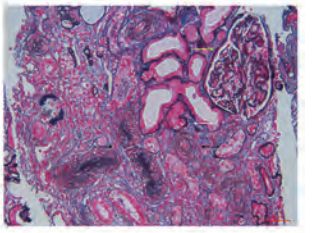


Figure 1. HE, tubulointerstitial infiltration of inflammatory cells

Figure 2. PASM+Masson, glomerular ischemia (yellow arrow), tubular atrophy with protein cast (white arrow), mucoid intimal thickening and onion peel like hyperplasia (black arrows).



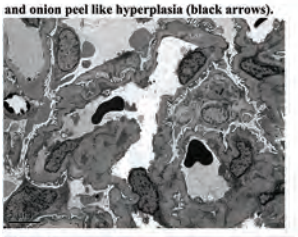


Figure 3. Electron microscope. Wrinkled glomerular basement membrane, atrophic tubules as well as interstitial infiltration of lymphocytes and monocytes were demonstrated, and there are no dense deposits.

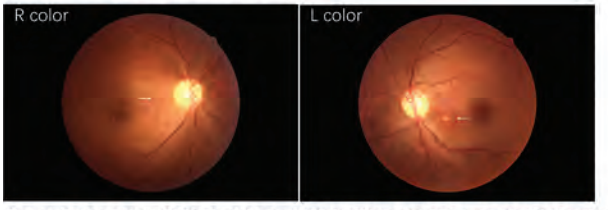


Figure 4. Fundus photograph Multifocal chorioretinal lesions (shown by white arrows, right side heavier)

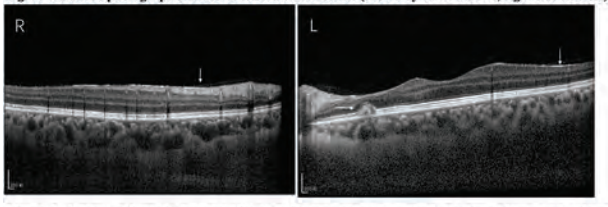


Figure 5. Optical coherence tomography of both eyes showed marked macular edema and epiretinal membrane, and focal lesion with high reflectivity (white arrows)

TH-PO563

Karyomegalic Interstitial Nephritis: A Genetic Form of Renal Disease

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Introduction: Karyomegalic interstitial nephritis is a rare systemic disease mainly manifested as progressive renal disease

Case Description: A 34 years-old man from Burkina Faso presented to the nephrology clinic for evaluation of CKD. He moved to the USA 1 year before presentation. On the initial visit to our clinic he had no acute complaints. He was seen by a nephrologist 6 years ago at his home town and was told that he had an elevated serum creatinine of 1.62 mg/dL. His medical history included untreated hepatitis B, frequent upper tract respiratory infections and unilateral gynecomastia. Family and social history were non-contributory. His current laboratory exams revealed a normal cell count, creatinine of 1.6 mg/dL, BUN of 13 mg/dL, a protein/creatinine ratio of 0.45 mg/g and a ALT and AST of 53 and 42 U/L respectively with normal bilirubin and mild elevation of alkaline phosphatase, hepatitis b viral load was 15428 IU/mL. Urinalysis showed trace glucose, protein and blood with normal appearing RBC and few granular casts on the sediment. Further work up including ANA, ANCA, SPEP, RF, hemoglobin A1C, hepatitis C, complement levels and immunoglobulin levels, were all unremarkable. A renal biopsy was performed which showed a primary tubulointerstitial disease with enlarged tubular epithelial nuclei, suggestive of karyomegalic interstitial nephritis (KIN).

Discussion: KIN was first reported in 1974 on a 22 years-old woman who died from hepatic carcinoma and a fungal respiratory infection, autopsy showed extreme dysplasia in the renal tubular cells. There have been around 40 more case reports, most include young patients with CKD progressing to ESRD in early adulthood, recurrent respiratory infections and abnormal LFTs. Our patient had this classic features in addition to hepatitis B and gynecomastia, which are of unclear relevance. It was initially hypothesized that KIN was triggered by a virus or toxin causing transient LFT elevations, but recently mutations in FAN1, a gene coding for a nuclease involved in DNA repair, have been identified. There is no specific treatment, our patient is currently being evaluated for breast biopsy and treatment of hepatitis B, ACE inhibitor was started for renal protection. This case adds to

the short list of case reports and brings to clinicians an interesting differential diagnosis of chronic tubulointerstitial disease.

TH-PO564

HIV Infection Associated with Plasma Cell-Rich Acute Interstitial Nephritis: A Case Report

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Introduction: Acute interstitial nephritis (AIN) in HIV infected patients is usually attributable to drugs, opportunistic infections, and immune syndromes (e.g. immune reconstitution syndrome and diffuse infiltrative lymphocytosis syndrome). Whether HIV itself causes AIN is uncertain.

Case Description: A 59-year-old African female with a past history of hypertension was admitted with generalized weakness. Medications included lisinopril and nifedepine, and she denied NSAID, herbal, or illicit drugs. Physical exam disclosed no evidence of sicca syndrome. Laboratory evaluation was remarkable for serum creatinine of 12.9 mg/dl and blood urea nitrogen 149 mg/dl (baseline 3 months prior was 1.1mg/dl and 23 mg/dl respectively), hemoglobin 8.2g/dl, platelets 67 cells/mm^3, 2+ schistocytes in peripheral smear, and LDH of 365 U/L. Urine microscopy showed innumerable WBCs/hpf, but no RBCs or casts. Spot urine protein–to-creatinine ratio was 1.7g/g. Given the suspicion for microangiopathic hemolytic anemia, she received empirical plasma exchange for 8 sessions, with no improvement of hematological parameters. Subsequent HIV-1 antibody test was positive, with viral load of >715,000 copies/ml, and CD4+ count of 20 cells/mm^3. ADAMTS-13 activity was normal. Renal biopsy showed normal appearing glomeruli and tubulointerstitial nephritis with numerous CD138+ plasma cells. No granulomas or features of thrombotic microangiopathy were seen. Immunofluorescence exam was negative, and no electron dense deposits or endothelial cell tubuloreticular inclusions were seen. Extensive infectious disease work up was negative. Bone marrow biopsy revealed hypercellular marrow, polyclonal plasmacytosis with CD138+ plasma cells (20%), and no evidence for malignancy or infections. Antiretroviral therapy (ART) regimen was started, with subsequent improvement in hematological parameters. Serum creatinine improved to 2.5mg/dl and proteinuria resolved.

Discussion: To our knowledge, there are only 2 previous case reports where AIN was thought to be a direct complication of HIV infection, both of which also showed a plasma cell-rich tubulointerstitial infiltrate. The exclusion of common causes of AIN and response to ART therapy in our case suggest that HIV infection itself may occasionally present with acute kidney injury and AIN.

TH-PO565

Taming Nephrogenic Ascites by Living Kidney Transplant in a Developing Country

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Introduction: Nephrogenic ascites is a diagnosis of exclusion and describes the refractory ascites in patients with renal failure before or after the initiation of dialysis. It's a rare and devastating condition with an inconsistently reported incidence that is as low as 0.7%. Renal transplant is considered the most effective management and has been described predominantly in deceased donor transplants from the high income countries. In low and middle income countries, nephrogenic ascites is still a visible problem but successful management with living kidney donation is not well reported.

Case Description: 45 years old male known case of ESRD was on twice weekly maintenance hemodialysis schedule since June 2010 via left brachiocephalic arterio-venous fistula, His Hypertension for the same time period was being managed by Losartan and Carvedilol. He presented with gradual abdominal swelling for last 6 months in the year 2016. There was no history of current or preceding fever, abdominal pain, altered bowel habits, jaundice, weight loss, body aches or missed dialysis sessions. He was being dialyzed twice weekly with blood flow of 300 ml/min and dialysate flow rate of 500-600 ml/min. His average Inter-dialytic weight gain had been around 2.5 kg. Examination and work up demonstrated a serum albumin of 3.7mg/dl, low SAAG and exudative lymphocytic ascites and a normal peritoneal biopsy in a well-nourished man. After exhaustive work up; cardiac, hepato-billiary, infective and other causes of ascites were appropriately excluded. Intensification of hemodialysis and ultrafiltration with intermittent paracentesis did not improve his ascites. He underwent renal transplantation by donation from his spouse with paracentesis prior to transplantation. Instant graft function and uneventful post-transplant period resulted in gradual resolution and disappearance of ascites over 2 months.

Discussion: Not all patients completely fit the usual profile for nephrogenic ascites. Our patient developed nephrogenic ascites despite adequate nutritional status, normal serum albumin, ACE inhibitors and strict compliance with the dialysis schedule. Meticulous work up is required to exclude the direct causative pathologies. Lliving kidney transplant is an effective management strategy and can be carried out with only a fractional increase in work up related cost even in low and middle income countries.

TH-PO566

A Unique Case of Oliguric Renal Failure in the Immediate Post-Transplant Period

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Introduction: Vascular complications are a well-recognized cause of renal allograft failure in the immediate post-op period. Renal allograft torsion is a rare cause of vascular compromise leading to graft injury that is associated with significant morbidity. We present a case illustrating the unique challenges of recognizing and treating this condition.

Case Description: 69yo F with history of end-stage renal disease secondary to polycystic kidneys on hemodialysis presented for deceased donor kidney transplantation. She had excellent urine output (UOP) and a transplant ultrasound with normal flow dynamics in the immediate post-op period; however, on post-op day #1 there was a significant decline in UOP which did not improve with intravenous fluid administration. Ultrasound of the graft demonstrated "abnormal waveforms throughout the transplanted kidney with tardus parvus waveforms and reversed diastolic flow" concerning for either renal artery stenosis or main renal vein thrombosis. She was taken emergently to the operating room for exploration. It was revealed that the graft had rotated 180 degrees about the axis of the artery and vein with the lower pole pointing toward the right flank. It appeared that the inferior aspect of her native right polycystic kidney may have abutted the upper pole of the allograft causing it to rotate medially. Upon reversal of the rotation there was immediate restoration of normal color, turgor and palpable pulse to the renal parenchyma and Doppler ultrasound confirmed excellent venous and arterial flows; a nephropexy was performed prior to closure. The patient had excellent post-op UOP and creatinine began downtrending in the next week and had stabilized at 0.8mg/dL by 1 month post-transplant.

Discussion: Fewer than 20 cases of allograft torsion have been reported in the literature as a cause of graft failure; over 50% of these grafts were lost. Most cases (15/16 in one review) occurred in simultaneous pancreas kidney (SPK) transplant recipients (13/16) or pediatric recipients (2/16). We present a rare case of a non-SPK allograft recipient who experienced allograft torsion and the first reported implicating native polycystic kidneys as a risk factor. While a rare complication, allograft torsion is associated with a high rate of graft loss and non-specific ultrasound findings; a high index of suspicion and surgical exploration are needed to salvage the organ.

TH-PO567

An Atypical Cause of Autoimmune Hemolytic Anemia in a Post Kidney Transplant Patient

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Introduction: Autoimmune hemolytic anemia (AIHA) is a rare but devastating consequence of solid organ transplantation. Commonly AIHA can be attributed to immunosuppression with calcineurin inhibitors or viral infection. Here we describe a unique cause of AIHA due to Coombs negative IgA associated AIHA that was refractory to both steroid therapy and adjustments in immunosuppression.

Case Description: 23-year-old Hispanic female with history of deceased donor kidney transplant in October 2016 (on tacrolimus, sirolimus, prednisone) presented with fatigue, sclera icterus, and jaundice. Recently she was given clindamycin for dental procedure. On lab Hgb low to 4 gm/dL (baseline 12). Work up revealed elevated LDH, low haptoglobin, elevated retic count, and indirect hyperbilirubinemia consistent with hemolytic anemia. Parvovirus B19 was negative. G6PD level was elevated. Peripheral blood smear revealed marked spherocytosis, anisocytosis, and schistocytes. High sensitivity Coombs test was negative. No splenomegaly on abdomen ultrasound. After transfusion Hgb improved to 8.6, and she was discharged on Prednisone 60mg daily. However she was readmitted a week later with Hgb low to 4.8. Cr uptrended to 1.48 mg/dL (baseline 1.2). Tacrolimus was discontinued. PNH flow cytometry and SPEP were unremarkable. Bone marrow biopsy revealed increased erythropoiesis, supportive of peripheral red blood cell destruction. After transfusion Hgb improved to 8. Pt was continued on 60mg Prednisone along with initiation of azathioprine. But one week later, Hgb again low to 4.9. Sirolimus was then stopped. Negative coombs hemolytic panel and a drug induced antibody panel were sent. Negative coombs hemolytic panel detected an IgA autoantibody against red blood cells. Rituximab was initiated (375mg/m^2 weekly). One month later, Hgb stabilized in range 13-14 with return of Cr to baseline. Sirolimus was restarted.

Discussion: This case illustrates an extremely rare autoimmune hemolytic process that is Coombs negative, non-drug induced, and steroid refractory in a kidney transplant patient. Splenectomy is usually considered as the first line therapeutic option for steroid refractory IgA associated AIHA, but in a post transplant patient there is the significant increase in infection risk that must be considered. Rituximab therapy though second line was the better choice in this patient who has achieved complete response to therapy.

TH-PO568

AKI from Orthostatic Renal Graft Compression Following Weight Gain

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Introduction: We present the first reported case of orthostatic renal graft compression from central adiposity resulting in acute kidney injury.

Case Description: A 61 year old man with a cadaveric transplant presented with hypertension and acute kidney injury with a creatinine rise from 80 to 210 μmol/L. His

past medical history included controlled diabetes, hypertension, ischaemic heart disease, and obesity requiring gastric sleeve with subsequent weight gain from 90 to 110kg. Renal biopsy was consistent with acute tubular necrosis without significant interstitial inflammation or signs of rejection. Serial renovascular duplex studies of the transplant graft were abnormal. Initial scanning showed severely reduced diastolic flow normalising towards the upper pole (RI0.78). The renal vein flow had normal phasicity and renal artery velocity was 336cm/s. Repeat scanning showed absence of diastolic flow and reduced perfusion despite a patent renal transplant artery and vein. Raising the fatty apron cephalad normalised renal blood flow with resistive indices between 0.76-0.79 throughout the kidney. Subsequent laparascopy ruled out adhesional obstruction and CO2 angiogram confirmed normal transplant vessels, anastomotic sites and intra-renal branches. Following initial empiric pre-biopsy pulsed steroids for presumed rejection, he was treated with bedrest and his creatinine was130µmol/L on discharge. Whilst advising weight loss, he was treated with an abdominal support belt.

Discussion: Our case highlights the potential growing problems of increasing obesity and inadequate assessment tools to assess abdominal weight gain in transplant patients. Transplant physicians and surgeons need to be aware of renal graft compression from an enlarged bulky omentum and fatty apron. Diagnosis requires positional prone doppler sonography. Aside from weight loss, optimal treatment is not known.

TH-PO569

Transplant Renal Artery Thrombosis: Uncommon Complication of Acute Rejection

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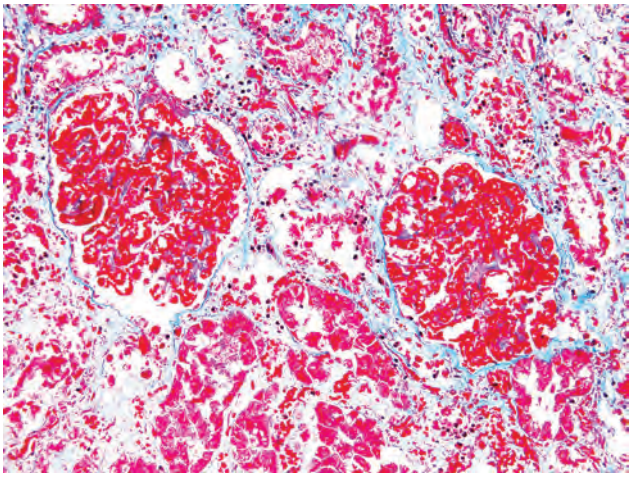
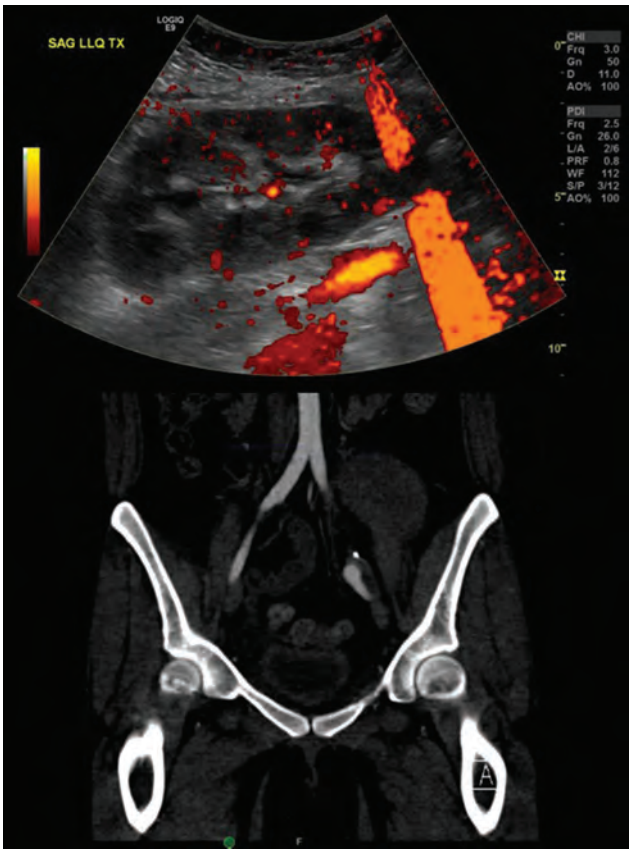
Introduction: Acute transplant renal artery thrombosis is rare, primarily seen in the immediate post-transplant setting related to surgical complication. We present a case of acute transplant renal artery thrombosis in a patient receiving treatment for acute cellular and antibody mediated rejection.

Case Description: 21 year old female with a stable renal transplant for 3 years (baseline creatinine 0.8 mg/dl) was admitted for acute kidney injury (creatinine 7.41) after not taking her immunosuppression due to gastroenteritis. She began empiric pulse dose methylprednisolone on presentation. Allograft biopsy on hospital day 3 showed acute cellular and antibody mediated rejection. She was started on thymoglobulin and plasma pheresis with initial improved renal function (creatinine 3.39). On hospital day 7, she began to have a progressive decline in urine output and kidney function. Doppler ultrasound revealed minimal perfusion to the transplant [Fig 1a]. Repeat kidney biopsy had near total renal infarction [Fig 2]. Confirmatory CT angiogram [Fig 1b] revealed no flow in the transplant renal artery. She re-initiated hemodialysis.

Discussion: Acute transplant renal artery thrombosis should be considered if anuria develops while being treated for allograft rejection. Prompt diagnosis and intervention is essential to prevent graft loss, unfortunately the most common outcome.





TH-PO570

Delayed Graft Failure Secondary to Renal Vein Thrombosis in a Patient with a Permanent IVC Filter

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Introduction: Transplanted renal vein thrombosis (RVT) is a rare cause of delayed graft failure in renal transplant patients. The estimated prevalence of graft vein thrombosis is 0.1% to 4.2%, mostly occurring in the early transplant period. The associated morbidity is devastating, given the high risk of permanent graft failure. Patient and donor related factors, along with multiple perioperative events, and immunosuppressive agents are incriminated for venous thrombosis in the early transplant period. We describe herein, an unusual case of RVT leading to severe graft failure after ten years of transplantation.

Case Description: A 53-year-old male with a deceased donor renal transplant 10 years prior, for suspected glomerulonephritis, was admitted to the hospital with progressive bilateral lower extremity swelling, decreased urine output and weakness. One week prior, he was treated for suspected urinary tract infection at an outside facility. His graft function had been stable with a baseline creatinine 1.3-1.5 mg/dl on tacrolimus and mycophenolate. On evaluation, with help of ultrasonography and computed tomography, he was noted to have bilateral venous thromboses of iliac and popliteal veins with an extension into the transplanted renal vein. He was also noted to have a filter in his inferior vena cava, inserted in 2002. The patient was managed by catheter directed thrombolysis with help of tissue plasminogen activator (tPA), as well as systemic heparin therapy. His hospital course was complicated by acute severe graft dysfunction needing initiation of renal replacement therapy, and development of an anticoagulation related rectus sheath hematoma. His RVT showed partial resolution along with recovery of graft function in the ensuing two weeks. He was discharged on oral anticoagulation and off dialysis. Recent infection, obesity, a retained IVC filter, and possible undiagnosed hypercoagulable states were considered to have played roles in the thrombosis in this case.

Discussion: This case describes an atypically late presentation of transplanted renal vein thrombosis years after renal transplant. This case exemplifies both the risks associated with RVT, and the need for astute clinical vigilance for the early detection and timely initiation of appropriate therapy to salvage the precious graft in transplanted patients.

TH-PO571

Unusual Bilateral Renal Parenchymal Urine Leak After Pediatric En Bloc Kidney Transplantation

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Introduction: Use of en bloc kidney transplantation (EBKT) has not been universally accepted due to risk of technical difficulties and concerns related to inadequate nephron mass. We report an unusual case of renal parenchymal urine leak after EBKT that ultimately led to removal of both renal moieties.

Case Description: We transplanted pediatric en bloc deceased donor kidneys to a 49 year male with ESRD. Caudal ends of donor inferior vena cava and aorta were anastomosed to recipient's external iliac vein & artery. On POD 6, there was increased output of clear fluid in wound drain. CT-cystogram performed at this time showed mild caliectases of both transplant kidneys but no anastomotic bladder leak. Surgical re-exploration on POD 8 revealed necrotic area on infero-lateral pole of lateral kidney leaking urine. Parenchymal leakage was repaired, but drain output remained high. On POD 31, patient was readmitted for abdominal pain. Renal scan revealed tracer accumulation originating from lower pole of lateral kidney confirming persistence of urine leak. Exploration confirmed recurrent lateral kidney urine leak at site of previous repair but other kidney showed a necrotic area at lower pole. Both kidneys were removed. Patient was relisted for transplantation.

Discussion: Early onset of urine leak from a necrotic area points towards vascular injury. Interestingly, pediatric recipient of liver from same donor as en bloc kidneys developed portal vein thrombosis. Another possible mechanism of urine leak could be thermal injury if Argon beam coagulation is used for superficial hemostasis on the thin cortex of pediatric kidneys after reperfusion. It could be speculated that prolonged surgical drainage along with bladder decompression could have salvaged en bloc kidneys. However, this patient continued to have abdominal pain despite presence of surgical drain. The second kidney were removed due to concern for impending infection at vascular anastomosis.

Strategies to prevent complications after EBKT

Avoid very small pediatric donors with history of severe hypotension
Ensure good flushing of pediatric kidneys in donor
Preserve perinephric abd periureteric fat
Avoid vascular injuries during backbench preparation
Use pediatric ureteric stents
Avoid recipients with uncontrolled hypertension
Consider perioperative anti-coagulation

TH-PO572

Choriocarcinoma Related to Kidney Transplantation

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Introduction: Malignancy related to solid-organ transplantation (Tx) due to immunosuppression is widely discussed and appears as one of the most common causes of graft failure and death. Cancer in the donated organ is rare, however, and its prognosis uncertain.

Case Description: A 58 year-old (y/o) male, on hemodialysis for the past 5 years due to hypertensive nephrosclerosis, was admitted for kidney Tx. His serologies and Panel Reactive Antibodies were negative. The donor was a 41 y/o female whose cause of death was subarachnoid hemorrhage. Her creatinine was 0.6mg/dL and 2 previous spontaneous abortions were the only reported significant medical history. Tx proceeded with a 31-hour cold ischemia time, a 0.86 KDRI and 36% KDPI. We followed institutional protocols for surgery and immunossupression, with no apparent complications. The patient presented delayed graft function, assessed by kidney ultrasound, CT scan and biopsy. The diagnosis of acute BANFF IIB rejection was established and treatment with Thymoglobulin® initiated, however no graft function improvement was observed. He developed infectious complications thereafter, followed by transplantectomy due to the possibility of pyelonephritis. Anatomopathological analysis of the graft revealed metastatic choriocarcinoma to the kidney. Similar findings were reported in other recipients of organs from the same donor. The heart recipient presented normal graft function and no signs of metastasis despite abnormal levels of serum beta-HCG (45mUI/mL). The contralateral kidney recipient evolved with normal graft function in spite of ascending serum beta-HCG (48.450mUI/mL). Shortly after, she presented pulmonary metastasis and death after refusing transplantectomy and an unsuccessful attempt of chemotherapy. The liver transplant in another recipient was initially successful, however ascending beta-HCG and hepatic nodules were identified. This patient is currently under chemotherapy. Our patient has presented full recovery following transplantectomy, with no signs of metastasis on PET-CT scan and normal serum levels of beta-HCG (1mUI/mL).

Discussion: To our knowledge, this is the second report of kidney graft with choriocarcinoma metastasis, however the first to compare outcomes between kidney graft preservation and transplantectomy, and its metastatic implications to different grafts.

TH-PO573

PML-IRIS in a Patient with Kidney Transplant

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Introduction: Progressive multifocal leukoencephalopathy (PML) is a degenerative disease involving the central nervous system. It is caused by the John Cunningham virus (JCV) which commonly affects immunocompromised patients. We present the first case of PML complicated by immune reconstitution inflammatory syndrome (IRIS) described in a kidney transplanted patient.

Case Description: A 60 year old female with a history of kidney transplant in 2009 and native kidney failure due to IgA nephropathy who presented to the clinic with partial expressive aphasia and loss of executive function. Patient was on tacrolimus (FK) and mycophenolate (MMF) as maintenance therapy. Physical exam does not show any facial droops or motor weakness. MRI brain finding was concerning for PML. Lumbar puncture had positive PCR for JC virus in spinal fluid. Serum JCV viral load was positive. Remaining serology and metabolic panel were normal. MMF and subsequently FK were both removed from the regimen. Patient then developed aphasia and right sided weakness. MRI showed new mass effect. Brain biopsy was consistent with PML-IRIS. Patient was started on dexamethasone with a slow prednisone taper. She exhibited a good neurological improvement two weeks into the treatment.

Discussion: PML is a severe opportunistic infection commonly affecting patients with immunosuppressed state. Manifestations of PML include motor deficit, dysarthria, dysphasia but most commonly weakness. MRI shows hyperintense lesion on T2 at the subcortical white matter. IRIS occurs due to exaggerated T cell response in patient who was previously immunocompromised. Symptom can occur one week to few months after treatment of primary disease. PML-IRIS is well documented clinical entity in human immunodeficiency virus infection, however, there is scant data and little awareness about the presentation in transplant patients. In patient with kidney transplant, post-transplant lymphoproliferative disease is also highly on the differentials as it is common complication for all solid organ recipients. The re-activation of immune system in our patient was likely due to discontinuation of immunosuppressant in fear of progression of PML. Diagnosis would be challenging without biopsy. Take home points: This is the first case of PML-IRIS described in patients with kidney transplant. Patient had dramatic neurological recovery after prednisone taper, but patient is at high risk for chronic allograft rejection.

TH-PO574

Breaking the Rules on PTLD

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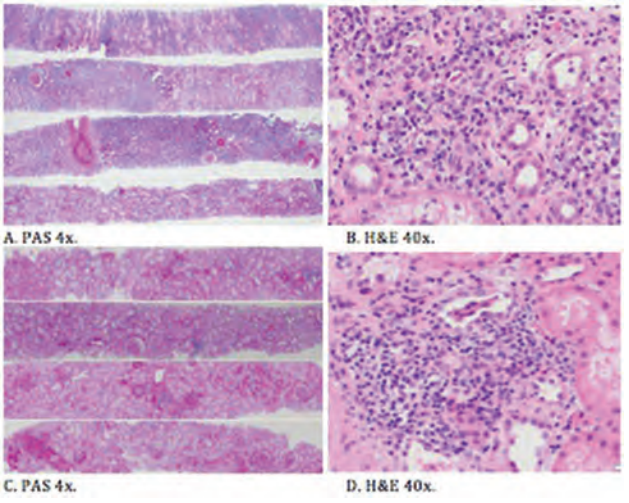
Introduction: Early post-transplant lymphoproliferative disorder (PTLD) is mostly, but not invariably, associated with Epstein-Barr virus (EBV) infection. Most EBV-negative PTLDs occur more than a year post-transplant (median 50 months versus 10 for EBV-positive) with the majority being monomorphic (67% versus 42% of EBV-positive). They are also more aggressive and more likely to require anti-neoplastic therapy along with reduced immunosuppression. Moreover, most PTLDs are B or T-cell clonal neoplasms and rarely plasma cell-rich entities.

Case Description: We present a unique case of a 53-year-old male with end-stage renal disease due to hypertensive nephrosclerosis who underwent deceased donor renal transplant with nadir serum creatinine (SCr) 1.6mg/dl. Perioperative course was uneventful. We used alemtuzumab induction with tacrolimus, mycophenolate mofetil, and corticosteroid maintenance therapy. Both donor and recipient were EBV seropositive. After the first month, patient underwent renal biopsy for suboptimal renal function, which showed nonspecific changes. At month two, he developed BK viremia, so immunosuppression was reduced. SCr then increased to 2.2mg/dl, prompting another biopsy, which showed a clonal plasma cell neoplasm (A, B) with lambda light chain predominance (kappa/lambda 1:10) and a negative EBV-encoded RNA in situ hybridization (EBER). Bone marrow biopsy showed no sign of plasma cell disorder. Patient was diagnosed with renal-limited polymorphic PTLD and treated with further immunosuppression reduction only. Biopsy six weeks later showed normal kappa/lambda and near complete resolution of PTLD (C, D).

Discussion: This is a very unusual case in that our patient was EBER-negative with a plasma cell-rich PTLD, yet presented early post-transplant with a polymorphic PTLD and an excellent response to reduced immunosuppression alone.



Diffuse interstitial inflammation (A) with many plasma cells (B). Focal interstitial inflammation (C) with few plasma cells (D).

TH-PO575

Recurrent Monoclonal Ig Associated C3GN Post Transplant

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Introduction: C3 glomerulopathy (C3GN) is one type of renal injury characterized by the predominant staining for C3 with absent or minimal staining for other immunoglobulin (Ig). Although the optimal treatment is unknown, success has been reported with B cell targeted chemotherapy. We describe a case of monoclonal Ig-associated C3GN recurring soon after transplant.

Case Description: A young woman with ESRD attributed to hypertension on hemodialysis for 7 years underwent a deceased donor kidney transplant in 2017. Creatinine (Cr) was 1.1 mg/dL with proteinuria of 0.35g/g at 1 week post-transplant. Within several weeks of transplant, she developed clinical nephrotic syndrome with Cr 2.5 mg/dL and proteinuria 4.3g/g. Renal allograft biopsy demonstrated a membranoproliferative glomerulonephritis (MPGN) on light microscopy. Immunofluorescence (IF) showed 2+ staining for C3. There was weak staining for IgM and C1q. Electron microscopy showed rare subendothelial electron dense deposits. Serum and urine were positive for a monoclonal IgG kappa with M spike of 0.64 g/dL. Records retrieved included a kidney biopsy in 2009 which showed MPGN. IF showed IgG2+, C3 2+, C1q 2+, and kappa 1+. A monoclonal IgG kappa was detected, but a bone marrow biopsy was negative for a plasma cell dyscrasia. On reaching ESRD in 2010, she transferred care and records were not forwarded for transplant evaluation. Our patient underwent a second bone marrow biopsy that confirmed the presence of monoclonal plasma cells (0.2% of total). Workup for multiple myeloma was negative. She was commenced on cyclophosphamide, bortezomib, and dexamethasone. With treatment, proteinuria has improved to 2.2 g/g and renal function stabilized with a last follow-up Cr of 1.8.

Discussion: Our patient had a monoclonal gammopathy of renal significance (MGRS) which remained indolent for many years but caused recurrent disease rapidly after transplant. Successful treatment of monoclonal Ig associated C3GN in native kidney disease with chemotherapy has been described, but reports of treatment for recurrent disease post-transplant have been scant. In addition to chemotherapy, use of eculizumab has been reported to be successful. Following chemotherapy, our patient will be evaluated for an autologous stem cell transplant. Our case adds to the limited literature and awareness surrounding the diagnosis and treatment of this rare disease.

TH-PO576

New Pathogenic Mutations of Complement Factor H Causing Early Recurrence of C3 Glomerulonephritis After Kidney Transplantation

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Introduction: C3 glomerulonephritis (C3GN) is a rare group of kidney disorders caused by over-activation of the alternative complement pathway. C3GN usually recurs between 3 to 6 months post-transplant. Here we report two likely pathogenic heterozygous variants in complement factor H (CFH), not previously described, involved in early recurrence of C3GN.

Case Description: A 24 year old female with history of left nephrectomy (vesicoureteral reflux) and ESRD with a kidney biopsy showing C3GN (MPGN with C3 deposition and microangiopathy (TMA)) received a deceased donor kidney transplant (KDPI 54%). She was on hemodialysis for 3 years with 2 vascular access thrombotic events. Her cPRA was 0% and received steroids-basiliximab for induction. She developed early post-transplant renal vein thrombosis (day 1) with no urinary flow. A thrombectomy was performed and heparin was started. Thymoglobulin was initiated. The patient evolved with delayed graft function, with scintigraphy (MAG3) compatible with acute tubular necrosis (ATN), and was discharged on dialysis with tacrolimus, mycophenolate and prednisone. Three weeks later her creatinine clearance was 11 ml/min/1.73m^2. A kidney graft biopsy was performed showing signs of ATN but also arteriolar acute TMA and extensive C3 deposition, with negative C4d. Anti-HLA antibodies were negative. The patient developed recurrent allograft infections and loss of kidney function. Therefore, a transplant nephrectomy was performed 3 months after transplantation. A genetic study was performed by NGS for *CFH, CFI, CFB, C3, MCP, THBD, DGKE*, and MLPA for *CFH-CFHR1* hybrid gene and *CFHR1-CFHR3* deletion. Levels of CFH were slightly low 111.8 mg/L (NV 156-572). We found two variants in the N-terminal end of CFH: a new one in SCR1 domain (p.G60R) and a rare one in SCR4 domain (p.P260S) not previously reported.

Discussion: Several modeling software predicted that both mutations are probably pathogenic. In both cases the substitution induces the change of a hydrophobic amino-acid for an hydrophilic one, potentially affecting structure and function of CFH. We report these two new CFH mutations as a potential cause for both fluid phase and cell-surface complement activation, accounting for the original disease and the early recurrence after transplant.

TH-PO577

Short Eculizumab Administration in the Treatment of De Novo Thrombotic Microangiopathy (TMA) in Kidney Transplant: Case Series

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Introduction: De novo TMA adversely affects kidney transplant recipient and allograft survival. It remains unknown why only a relatively small percentage of the renal transplant recipients develop TMA. Complement activation is the common denominator in this condition. Eculizumab, a humanized monoclonal antibody targeted against complement C5, has been showed to be effective in the treatment of de novo TMA. How long the treatment have to be maintained is debated. We report the description of a prospective cohort of 10 patients primary treated with eculizumab (1 or 2 infusion) for de novo TMA after transplantation.

Case Description: All the recipients were transplanted with compatible ABO. The cohort were homogenous for age, sex, cold ischemic storage, inductive and mantainance imunosuppresive therapies. Diagnosis of de novo TMA was established by the founding of the triad: microangiopathic hemolytic anemia, thrombocytopenia and worsening of kidney function, excluding other potential secondary causes, as suggested in the literature. We performed kidney biopsies in 3 cases (**Figure 1**). All the subjects developed de novo TMA in the first week after transplantation. Eculizumab (600 mg) was administered once or twice based on lab findings at 1 week after infusion. TMA remission and impoved of kindey function were obtained in 9 patients (**Figure 2**).

Discussion: Eculizumab can be used to safely treat de novo TMA and also with efficacy, even if ceased in the short term.

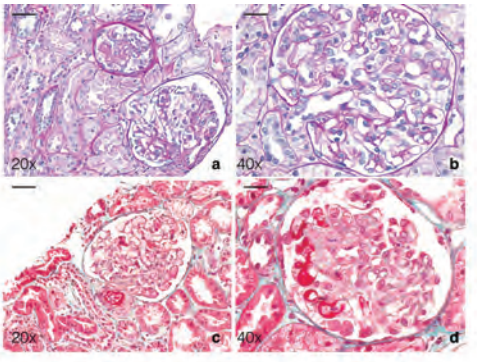

Figure 1. Representative images of a patients with acute thrombotic angiopathy; glomerular abnormalities; arterial and arteriolar lesions. (a), (b) Periodic acid-methenamine-silver stain; (c), (d) Masson trichrome stain.

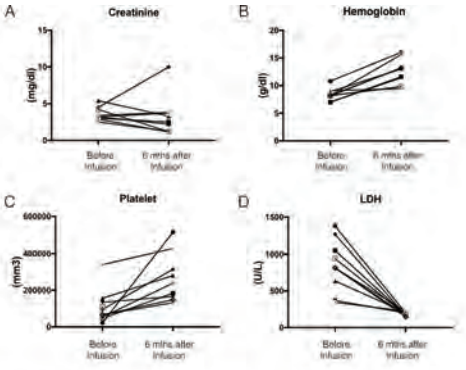

Figure 2. Individual outcome of the hematological and kidney parameters of the patients treated with aculizumab after the kidney transplantation at time points: Immediately before infusion and 6 months of follow up. A: creatinine; B: Hemoglobin; C: platelets; D: LDH (lactate dehydrogenase).

TH-PO578

Allograft Membranous Nephropathy of Donor Origin – Response to the Immunological Environment of the Recipient

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Introduction: Primary membranous nephropathy (MN) is the common cause of nephrotic syndromes in adults. The exact mechanism of kidney injury remained elusive until discovery of the podocyte antigen PLA_2R and its IgG antibodies. We report a unique case of MN in the transplanted kidney.

Case Description: 59-year-old Caucasian female with history of HTN, DM and ESRD on hemodialysis for 6 years underwent the deceased donor renal transplant (DDRT) (HLA A24:68/B35:57/DR18:11 to A2:2/B35:39/DR4:14) with DGF. She required hemodialysis four times post DDRT. The kidney frozen section obtained before transplantation show 135 glomeruli, 4% glomerulosclerosis, mild fibrosis and acute tubular necrosis. Eighteen days post DDRT, urine protein/creatinine ratio 34.2gm/gm was noted and SCr was 1.73 mg/dL on standard therapy (tacrolimus, mycophenolate mofetil, prednisone). Allograft biopsy done 40 days post-transplant show thickened glomerular basement membranes with strong positivity for IgG, C3 and PLA_2R1. Electron microscopy show subepithelial deposits along the basement membranes with spikes in between them. The original allograft biopsy performed at the time of transplant was stained with Jones silver and positive for PLA_2R1, confirming that MN was of donor origin. The recipient's serum PLA_2R antibody was negative for 4 times over 8 months. Her serum albumin plummeted from 4.6g/dL to 2.4g/dL within 2 months after DDRT, but gradually improved to 4g/dL in 6 months. Proteinuria decreased to 1gm/24 hour and SCr remained 1.5-2.0mg/dL. Immunosuppression stays the same. We plan to repeat the allograft biopsy one year after DDRT to follow the expected histological recovery of the donor derived MN.

Discussion: This unique case of donor derived MN and subsequent clinical disease resolution after transplantation further supports the notion that PLA_2R antibody is critical for the pathogenesis of MN. It is possible that immune mediated GN may eventually clear from the transplanted kidney with no adverse effect on allograft function after kidney is removed from the donor auto-antigenicity environment. Thus, the future allograft biopsy should show disappearance of PLA_2R immune complex in the transplanted kidney.

TH-PO579

Secondary Focal Segmental Glomerulosclerosis in Pregnancy: A Risk for Renal Transplant Patients

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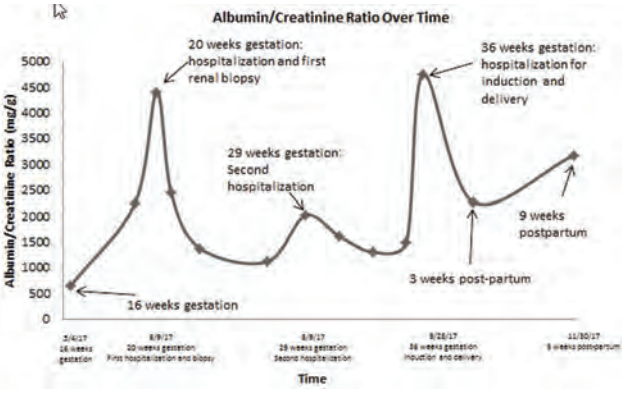
Introduction: Pre/eclampsia is usually the cause of worsening hypertension and proteinuria in pregnancy; however, these findings in a renal transplant patient lead to a wider differential. We present a case of focal segmental glomerulosclerosis (FSGS) in a pregnant patient 16 years post renal transplant.

Case Description: A 39 year old female with end stage renal disease secondary to lupus nephritis status/post living related kidney transplant, obesity, and hypertension presented with marked proteinuria and worsening hypertension at 14 weeks gestation. Her post-transplant course had been uncomplicated by proteinuria. At presentation, she developed worsening hypertension and 24h total protein was 3.2 g. With strict blood pressure control, urine albumin-to-creatinine ratio (ACR) decreased to 641 mg/g (figure). At 20 weeks, ACR increased to 4399 in the setting of worsening hypertension. She was admitted to the hospital, and urinalysis showed no hematuria and C3/C4, dsDNA and other serologic workup was negative. Kidney biopsy revealed cellular FSGS with glomerulomegaly and 70% foot process effacement, concerning for hyperfiltration injury vs *de novo* primary FSGS. Proteinuria initially improved with strict blood pressure control; however she developed worsening hypertension, proteinuria, and edema at 36 weeks gestation due to pre-eclampsia and underwent cesarean section. She continued to have nephrotic range proteinuria, and renal biopsy at 11 weeks post-partum demonstrated features of secondary FSGS.

Discussion: The differential for proteinuria and hypertension in pregnant renal transplant patients includes pre/eclampsia, rejection, transplant glomerulopathy, and recurrent or *de novo* glomerular disease. Pregnancy creates a physiologic state of hyperfiltration due to increased fluid retention and blood flow. While allografts generally adapt to these changes, patients with obesity and uncontrolled hypertension are at risk for hyperfiltration-induced renal injury and FSGS, which in this case, was unmasked by pregnancy.



TH-PO580

A Novel Approach to Successfully Prevent Membranoproliferative Glomerulonephritis Recurrence in a High-Risk Transplant Patient

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Introduction: Membranoproliferative glomerulonephritis (MPGN) is a particularly challenging primary pathology in kidney transplant patients due to its high rates of recurrence and graft loss. Aggressive or crescentic disease at presentation, low complement levels pre-transplantation, monoclonal gammopathy, live-related transplantation and certain HLA-associated risk factors are predictive of recurrence risk in the allograft. Various strategies have been used to manage such recurrence, but data is limited on pre-emptive management.

Case Description: We report the case of a 63-year-old woman with immune-complex-mediated idiopathic MPGN who had several risk factors for allograft recurrence, receiving a second renal transplant following early recurrence in her first transplant. Rising creatinine and new proteinuria led to biopsy confirmed recurrent disease in her first transplant at Day 76, with return to long term haemodialysis at day 86 despite maximal medical therapy to salvage the graft. 10 years later, she received a second, well matched transplant. Induction immunosuppression included anti-thymocyte globulin at day 0,1,2; plasma exchange at day 3 and rituximab at day 5 and 18. Protocol biopsy at day 79 demonstrated minimal tubulitis and no recurrent primary disease. Another biopsy performed at day 197 due to elevated creatinine following clostridium difficile infection, again demonstrated no recurrent disease. She remains on prednisolone, mycophenolate mofetil and tacrolimus with stable graft function at 7 months.

Discussion: The optimal management of patients with idiopathic MPGN at the time of transplantation is unknown. We demonstrate a new approach with rituximab and plasma exchange for pre-emptive management of a patient with idiopathic MPGN and multiple risk factors for early recurrence. This strategy has been successful in maintaining recurrence-free graft function at 7 months post transplantation

TH-PO581

Renal Replacement Lipomatosis in Transplanted Kidney

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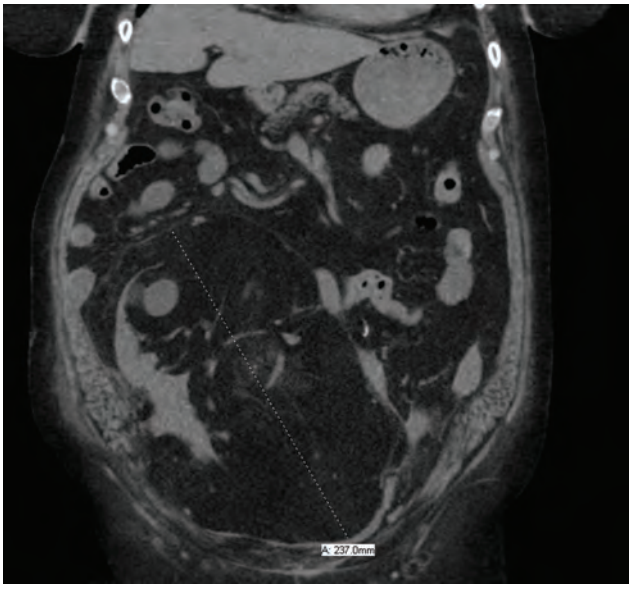
Introduction: Renal sinus lipomatosis (RSL) is a rare disorder where fatty tissue proliferate within the renal sinus and hilum. Renal replacement lipomatosis (RRL) is a severe form of RSL.

Case Description: A 63-year-old female with a history of end stage renal disease due to chronic glomerulonephritis underwent deceased donor renal transplant in February,1997. She has been diagnosed with chronic allograft dysfunction since 2002 with baseline S Cr 1.7-2 mg/dL. Immunosuppression has been maintained with Cyclosporine A, Mycophenolate mofetil and Prednisone. She experienced recurrent urinary tract infections since her kidney transplantation. She presented to emergency department with abdominal pain. On examination, a large right lower quadrant mass could be palpated. S Cr was at her baseline. CT scan of the abdomen and pelvis revealed a 24 cm large fatty mass centered in the hilum of the right lower quadrant renal transplant with splayed transplant parenchyma and collecting system. CT scan reading suggested the possibility of well differentiated liposarcoma. CT guided biopsy of the mass was performed. Pathology demonstrated mature adipose tissue with chronic inflammation.

Discussion: Renal replacement lipomatosis (RRL) is a rare condition, characterized by excessive fatty proliferation of the renal sinus with atrophy of the renal tissue. Aging, obesity and calculus disease are possible risk factors for RRL. Recurrent urinary tract infections has been described in most cases of RRL. The period between renal transplant

and RRL diagnosis has been variable in the literature, ranging from 6 months to 8 years. Our case was diagnosed after 21 years from her renal transplant. RRL is a very rare disease in kidney transplant. It should be differentiated from other fat containing tumors like liposarcoma and angiomyolipoma.



TH-PO582

A Case of a Kidney Transplant Recipient with Severe Throat Pain

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Introduction: Deceased donor renal transplants have a 5-year graft survival rate around 90% at our center. However, combination immunosupressive therapy increases susceptibilty to infections. Here we report the case of a patient with a history of multiple bacterial, viral and fungal infections who presented with throat pain.

Case Description: This 50-year-old woman had chronic kidney disease secondary to lupus nephritis; she received a renal transplant from a deceased donor after a failed transplant from a live donor. She was managed with thymoglobulin-based induction and maintained on mycophenolate mofetil, prednisone, and belatacept, which was switched to tacrolimus four weeks after transplantation. Her course was complicated by ganciclovir-resistant CMV disease of the GI tract, recurrent ESBL E coli bacteremia, RSV bronchiolitis requiring prolonged intubation, Pneumocystic jiroveci pneumonia and probable pulmonary aspergillosis, requiring tracheostomy for ventilator weaning. Four months after being weaned from the ventilator, she presented with severe right neck pain, throat pain, and dysphagia. MRI revealed a rim enhancing collection in the left laryngeal tissue abutting the left lateral thyroid cartilage. Following percutaneous drainage, cultures grew no bacteria; she was treated with meropenem and vancomycin. Her throat pain and dysphagia worsened and she was started on voriconazole empirically. Left neck exploration revealed a severely remodeled, necrotic and fibrous sternothyroid muscle. Extensive debridement of the deep strap layer was performed and a subperichondrial abscess drained. Pathology revealed necrotic cartilage with septate fungal hyphae, compatible with a diagnosis of Aspergillus laryngeal abscess. Due to progression of the fungal infection on empiric voriconazole, the patient was switched to posaconazole. Her pain and dysphagia improved and she was discharged on day 23 with posaconazole. After 3 months of treatment, her throat pain resolved.

Discussion: We report a rare case of an Aspergillus abscess of the larynx causing neck and throat pain and dysphagia. Differential diagnosis for throat pain in immunosuppressed kidney transplant recipients needs to include bacterial, viral, and fungal pathogens.

TH-PO583

A Case of Biopsy Proven Histoplasmosis in a Renal Allograft

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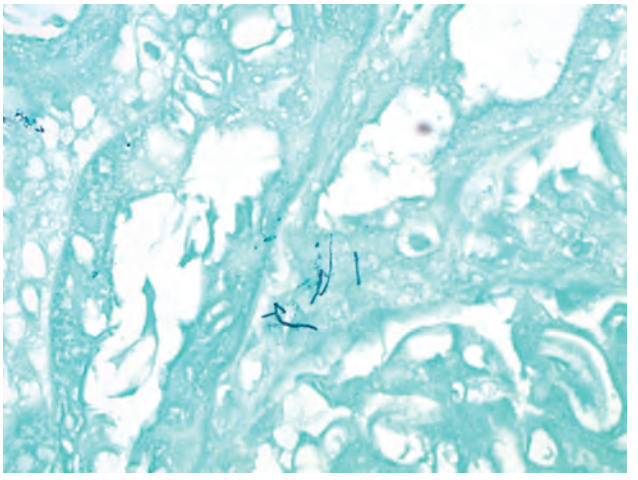
Introduction: Fungal infections in immunocompromised hosts are well described. However, histoplasma capsulatum is not known to directly infect the allograft in kidney transplant (KT) patients. We report a case of disseminated histoplasmosis infecting the renal allograft.

Case Description: A 52 year old male with ESRD from IgA nephropathy, status post deceased donor KT in 2007, presented in 2017 with constitutional symptoms, dry cough and AKI for 3 weeks. His transplant course was complicated by an early Banff 1A rejection and was maintained on tacrolimus (FK), mycophenolate (MMF) & prednisone. Of note, he had recently been renovating a house in southern Ohio. CT chest & abdomen showed bilateral lung opacities, mediastinal/hilar lymphadenopathy & perinephric fat stranding around the allograft. Due to the unexplained AKI, a renal biopsy was done, showing focal granulomatous interstitial inflammation with silver positive organisms and glomerulitis with macrophages containing histoplasma. A transbronchial lung biopsy confirmed granulomatous pneumonia with histoplasma, meeting criteria for disseminated histoplasmosis. Histoplasma urinary antigen also resulted positive later. He was discharged on itraconazole and MMF was held. He was re-admitted a week later with diffuse morbiliform rash concerning for cutaneous histoplasmosis, but skin biopsy was consistent with drug reaction. Due to amphotericin B intolerance, he was switched to oral fluconazole, with a goal of 12 months treatment. At 3, 6 & 9 months follow up, he continued to do well with his creatinine stabilizing at baseline. His MMF was resumed after 6 months of antifungal treatment.

Discussion: We present a unique case of a biopsy proven disseminated histoplasmosis involving renal allograft in a KT patient who has done well with treatment. Our case underscores the importance of a broad differential and thorough history when evaluating immunocompromised patients.



GMS stain showing both yeast and hyphae in the interstitium, consistent with histoplasmosis.

TH-PO584

Isolated Intrarenal Mucormycosis Due to Rhizopus Species in a Pediatric Renal Transplant Recipient

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Introduction: Mucormycosis (MM) is an unusual but well-known complication of solid organ transplant, which disseminates aggressively with a high mortality rate. Our patient may be the first reported child with isolated renal allograft MM.

Case Description: 3-y.o. female, with ESRD due to hypoplastic/dysplastic kidneys, received a cadaveric renal transplant after basiliximab induction, with subsequent pred, tac, and MMF. 4 weeks post Tx she developed fatigue, tachypnea, and increase in SCr to 1.7 from baseline of 0.4. UA revealed moderate LE, + nitrites, many WBCs and RBCs, and moderate bacteria. Renal US showed mildly distended ureter and renal pelvis with collecting system debris. She received broad-spectrum antibiotics. Renal biopsy showed tac toxicity. She stabilized and was discharged on reduced tac. Antibiotics discontinued as urine culture was negative. 5 weeks post-discharge, she redeveloped fever, pyuria, and rising SCr. US showed thickened ureter and renal pelvis. Parenteral antibiotics were resumed. Urine culture was negative. Repeat UA showed less but persistent pyuria. Antibiotics broadened on hospital day (HD) 2 due to unremitting fever. Steroid pulse on HD 3 for possible rejection. Fever abated on HD 4, and steroids tapered after no rejection on biopsy (HD 6). Tachycardia, new fever (HD 7) and tachypnea (HD 8) developed with progressive abdominal distention. US showed fluid collections within allograft. *Rhizopus* sp. was identified from intrarenal fluid aspirate, and amphotericin and posaconazole were begun. Transplant nephrectomy occurred the next day. CNS, chest, abdomen, and pelvis imaging were negative for disseminated MM. After nephrectomy, catheterized UA was benign. 10 days post-op, she developed new fever. Laparotomy showed no disease spread. Other organ recipients from same donor did not develop MM. She received a 3-month posaconazole course with clinical improvement. She was discharged after 2-month hospitalization. She has been off antifungal therapy for >1 month, and is doing well on outpatient hemodialysis.

Discussion: MM is a rare, usually disseminated complication of renal transplant with mortality reported as >50% when graft involvement occurs. MM isolated to the renal allograft is unusual. Clinicians should consider the possibility of intrarenal allograft MM with bacteriologic culture negative patients with pyuria.

TH-PO585

A Case Report of Pulmonary Alveolar Proteinosis in a Renal Transplant Recipient

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Introduction: Pulmonary alveolar proteinosis (PAP) is a diffuse lung disease characterised by accumulation of surfactant. Clearance of surfactant by alveolar macrophages is regulated by granulocyte macrophage colony stimulating factor (GM-CSF). Autoimmune PAP due to GM-CSF antibodies is the most common cause of PAP

in adults. Secondary causes include dust exposure, haematological malignancy and immunosuppressive medications.

Case Description: A 52 year old man developed progressive shortness of breath, hypoxia and productive cough one year post living unrelated renal transplant for polycystic kidney disease. This is in the context of BK virus nephropathy at three months post-transplant requiring a change in immunosuppressants from tacrolimus and mycophenolate to cyclosporine and leflunomide. A high resolution computed tomography (HRCT) of the chest demonstrated bilateral peri-hilar ground glass opacities. Pneumocystis jiroveci pneumonia (PJP) treatment was commenced with no clinical improvement. Bronchoscopy with bronchoalveolar lavage was inconclusive. The patient underwent a transbronchial biopsy which was positive for periodic acid-Schiff (PAS) proteinaceous material confirming the diagnosis of pulmonary alveolar proteinosis. There was no evidence of haematological malignancy clinically and on bone marrow biopsy. Immunosuppression was changed to tacrolimus and mycophenolate with no improvement in respiratory symptoms. Serum GM-CSF antibodies subsequently returned positive with titres rising from 0.50 to 0.66 suggestive of autoimmune PAP. Rituximab, intravenous immunoglobulin and plasma exchange were considered however patient responded clinically and radiologically after a total lung lavage.

Discussion: Pulmonary alveolar proteinosis is a rare but important differential diagnosis to consider in patients with subacute onset of dyspnoea and hypoxia with the typical radiological changes of ground glass opacity and interlobular and intralobular septal thickening. Importantly PJP can mimic PAP and must be excluded in an immunosuppressed patient. Primary PAP due to GM-CSF antibodies accounts for the vast majority of adult PAP with whole lung lavage as the gold standard of treatment. Secondary PAP due to haematological malignancy, dust exposure and immunosuppressants must be considered and excluded.

TH-PO586

Belatacept Recovers Renal Allograft Function Despite Extensive Fibrosis

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Introduction: Prolonging kidney allograft lifespan is a complex problem despite advances in the field. Histological findings of fibrosis indicate irreversible injury, that increases with severity, ultimately resulting in graft loss. Good renal function despite severe fibrosis is a goal of therapy. We present 2 patients whose renal function improved with Belatacept in presence of substantial chronic damage.

Case Description: Patient 1: 46 year old male recipient of a deceased donor kidney. Received thymoglobulin induction and maintained on Tacrolimus, Mycophenolate Mofetil and Prednisone. Biopsy 1 week post transplant for poor renal function, showed significant fibrosis(Table1). Belatacept was substituted for Tacrolimus.He was liberated from dialysis 4 months later. Renal function continued to slowly improve over the years. Patient 2: 35 year old lady received a living donor kidney. Immunosuppression similar to that of Patient 1. Three years post transplant, she was noted to have worsening renal function. Biopsy showed extensive chronic changes(Table1). Conversion to Belatacept led to gradual improvement in renal function.

Discussion: Belatcept's renal sparing abilities improve renal function and can extend allograft survival despite severe chronic injury. The improvement is gradual occurring over several months to years, indicating a mechanism beyond the initial mitigation of the vasoconstrictive effects of Tacrolimus.

Table 1

Time to Biopsy Post transplant(CrCl)	Banff Criteria
Patient 1:	
Time 0 (4ml/min)	g0, i0,t0, v0, cg0, ci1, ct1, cv3, mm0, ah2, ptc0, ti0
1 week (7ml/min-Belatacept initiated pos-transplant day 16)	g0, i0, t0, v0, cg0, ci3, ct3, cv3, mm0, ah3, ptc0, ti1, C4d0
1 year (38ml/min)	g0, i0,t0, v0, cg0, ci1, ct1, cv3, mm0, ah2, ptc0, ti0, C4d0
4 year (50.3ml/min)	g0, i0, t0, v0, cg0, ci1, ct1, cv3, mm0, ah2; ptc0, ti0, C4d0
Patient 2	
Time 0 (24ml/min)	g0, i0, t0, v0, cg0, ci0, ct0, cv2, mm0,ah0, ptc0, ti0
1 year (87ml/min)	g0, i0, t0, v0, cg0, ci1, ct1, cv1, mm0, ah0, ptc0, ti0, C4d0
3 year (47ml/min- Belatacept initiated)	g0, i0, t0,v0, cg0, ci2, ct2, cv1, mm0,ah2, ptc0, ti2, C4d0
5 year (61ml/min)	g0, i0, t0, v0, cg0, ci2, ct2, cv1, mm0, ah2; ptc0, ti1, C4d0

Crcl: Creatinine Clearance in ml/min

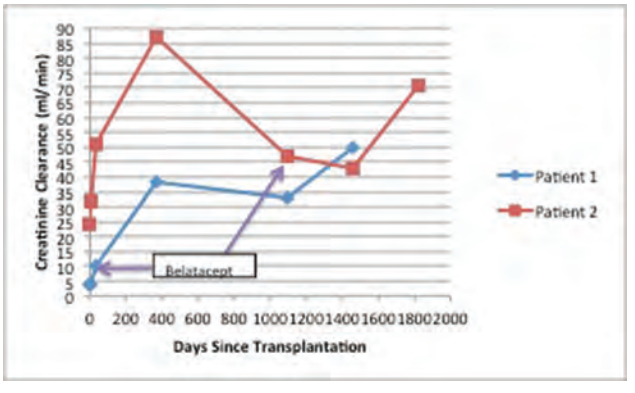

Fig 1

TH-PO587

TCR NGS Based Evidence for Differential Diagnosis and Personalized Therapy in BKV Nephropathy

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Introduction: BKV nephropathy (BKVAN) is a disease in 10% of renal transplant recipients which might lead loss of the graft in up to 80% of the cases. Current the diagnosis is based on assessment of BKV viral load in serum with assessment of inclusion bodies by kidney biopsy for definitive diagnosis. In case of identified BKVAN, the principle treatment is to decrease or alter the immunosuppressive regimen. However, the pathological features of BKVAN overlap with those of acute cellular rejection, where decrease of immunosuppression is detrimental.

Case Description: We were presented with a German male, transplanted with a kidney from a close living relative. The patient had a high BKV load (432500 copies/ml), but histological findings demonstrated borderline rejection according to BANFF, and SV40 negative findings. Faced with the vexing question of increasing or decreasing immunosuppression we obtained blood and a biopsy from the patient. By way of magnetic bead enrichment of activated T-cells we isolated T-cells reactive to BKV and donor cells in a direct and indirect fashion. Together with the fresh renal tissue, the activated T-cells were prepared for next-generation sequencing (NGS) of the T-cell receptor (TCR). We isolated T-cells in all three activation modi, which indicates an expansion of virus as well as donor specific T-cells in the patient, and underpins the complexity of diagnosis. When we compared the TCR repertoires of activated peripheral T-cells to those in the biopsy, we observed a distinct and strong presence of BKV specific T-cells in the transplant. This clearly excluded acute cellular rejection and allowed confident decrease of the immunosuppressive regimen. The graft function improved and the patient shows no signs of BKV infection nor graft rejection.

Discussion: TCR NGS profiling is a novel, but labor insensitive technique. The turnaround time is about 5 days and donor derived cells are required for optimal results. Identification of the specificity of tissue infiltrating T-cells by TCR NGS is nonetheless a valuable technique for differential diagnosis and personalized therapy.

TH-PO588

The Conundrum of a Peculiar Skin Lesion on the Face of a Renal Transplant Recipient

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Introduction: Parasitic infections may be challenging to diagnose especially in transplant population. We present a rare case of cutaneous larva migrans (CLM) at an unusual site in a renal transplant recipient.

Case Description: 64 year African American female with a medical history of Autosomal Dominant Polycystic Kidney Disease, who received a cadaveric transplant 3 months ago presented for routine follow up. She had no complaints except that of a disfiguring skin lesion on her forehead associated with itching. She denied fever, cough, other skin involvement, recent travel or exposure to sand beaches or contaminated soil. She does not have any pets. Physical exam revealed an expanding serpiginous papule on her forehead which was extremely pruritic. Home medications were not suggestive of any correlation. All routine labs were normal. She tried some over the counter topical and oral anti-allergic meds with no benefit. Although, a very unusual location but with telling clinical presentation a diagnosis of CLM was made and she was treated with oral Ivermectin. Patient reported complete resolution of her rash 5 days post treatment.

Discussion: Transplant population is prone to myriad of infections including parasitic infestations, incidence of which may be as high as 2.4%. The most common parasitic infection once reported was Strongyloids. Intestinal parasitic infestations are more common in Solid Organ Transplant recepients especially in developing countries. A parasitic infection should always be in the list of differential diagnosis, if clinically suggestive so as to avoid the diagnostic delay and further potential complications. CLM is rarely reported in transplant patients and the lesion on forehead is exceptionally rare. We present successful outpatient management of a rare clinical presentation of CLM.

Face lesion

TH-PO589

Diffuse Alveolar Hemorrhage with Respiratory Failure: A Case of Strongyloides Hyperinfection Post Renal Transplantation

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Introduction: Strongyloides Stercoralis is an intestinal nematode which infects millions of people. It is endemic in South Asia, Latin America, Sub Saharan Africa and South Eastern United States. The infection usually is asymptomatic but can be serious in the immunocompromised Host.

Case Description: We present 60 y.o.African American Male an Army Veteran 2 months post Deceased Donor Renal Transplant on Immunosuppression. He presented with 10 days of severe fatigue, weight loss, cough, and multiple loose stools every day. He was born in Central Texas and lived most of his life in this area. He had no travel to Asia or the Middle East. Visited Mexico and Florida a few times in the remote past. Initial imaging was consistent with pulmonary infiltrates. Progressive Anemia with pulmonary infiltrates prompted Bronchoscopy with BAL which revealed Diffuse Alveolar Hemorrhage. Started on high dose pulse steroids, plasmapheresis. Intubated for Respiratory failure.. ANCA, APS, Anti-GBM, ANA profile was negative and kidney biopsy showed no evidence of vasculitis. Repeat BAL was positive for the larval forms of Strongyloides. Diffuse purpuric rash on abdomen, punch Biopsy revealed Strongyloides larvae. Stool O&P returned positive for the Strongyloides, but ELISA was negative.. He was started on subcutaneous Ivermectin and albendazole but showed no improvement. Irreversible septic shock ensued resulting in death. His pre transplant serum returned negative for Strongyloides antibody. Donor serum returned positive for Strongyloides. liver and lung tissues showed larval forms on autopsy.

Discussion: The global burden caused by Strongyloides stercoralis is not completely known. Humans become infected when filariform larva penetrates the skin or mucosa. Hyperinfection happens in immunocompromised hosts when reduced immunosurveillance leads to unrestricted proliferation of the worms. In hyperinfection, enteric bacteria can be carried by larvae which results in fatal septicemia. The American Society for Transplantation guidelines recommend screening for Strongyloides in recipients from endemic areas with no mention of donor screening Increased suspicion, surveillance, and screening of the donors and recipients from the endemic areas is needed to avoid any fatal effects of the superinfection in transplant recipients.

TH-PO590

APRT Deficiency Related Crystalline Nephropathy Causing Acute Renal Allograft Dysfunction: A Case Report

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Introduction: APRT(Adenine Phosphoribosyl Transferase) deficiency is an AR metabolic disorder that leads to accumulation of insoluble purine dihydroxyadenine (DHA) in the kidney. It results in crystalluria & urinary stones leading to renal colic, hematuria, UTI & renal failure. Age at presentation can range from 5 months to late adulthood. Upto 50% of patients may be asymptomatic. Prevalence is largely unknown. Lack of awareness, inadequate evaluation of stones & confusion of DHA crystals with uric acid or calcium oxalate contribute to diagnosis being missed. We report here a case of acute renal allograft dysfunction secondary to APRT deficiency related crystalline nephropathy, a relatively rare entity.

Case Description: A 51 year-old male was evaluated for acute allograft dysfunction. His past history was significant for ESRD secondary to nephrolithiasis. No stone biochemical analysis or genetic studies were performed. He underwent living unrelated kidney transplantation (donor wife) 3 months back. Post-operative period was uneventful with nadir S.Crt of 1.2mg/dl. Basiliximab for induction and tacrolimus, MMF& prednisolone were used for maintenance immunosuppression. On routine labs he was found to have S.Crt of 2.3mg/dL. USG allograft was unremarkable. Renal allograft biopsy was performed and showed 0/5 glomeruli being sclerosed. Tubulopathic changes in form of tubular epithelial simplification and intraluminal polarizable crystals were noted. No evidence of rejection was found. A histopathological diagnosis of acute tubular injury with tubular crystallization was made.24hUr oxalate level was 55.6mg/d(N<45) & Pl. Oxalate was 3.34µmol/L(N< 3.0). Genetic analysis revealed a previously unreported homozygous nonsense mutation in exon 3 of APRT gene. Hence a clinical diagnosis of APRT deficiency related renal disease was made. He was started on Allopurinol 100mgBID with low purine diet & increased fluid intake. S.Crt gradually improved to 1.2 and has remained stable for last 1 year.

Discussion: Initial presentation of APRT deficiency can be insidious onset of renal dysfunction due to crystalline tubulopathy or interstitial nephritis without urolithiasis. High index of suspicion, correct identification of DHA crystals, renal biopsy & genetic testing are needed to clinch the diagnosis. Treatment with allopurinol, low purine diet and increased fluid intake is simple & effective.

TH-PO591

Clinical Tolerance - A Rare but Highly Deserved State of the Post-Transplant Patient

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Introduction: Graft tolerance is a clinical situation defined as stable graft function without clinical features of chronic rejection, and in the absence of any immunosuppressive drugs, usually for longer than 1 year's duration. This is observed more frequently in liver transplant patients but spontaneous graft tolerance has also been rarely reported in kidney allograft recipients. Many of these patients with presumed tolerance, in fact, are detected when they report to the treating physician with near normal graft function, but in the absence of immunosuppression. We present a case of immune tolerance following kidney transplant in an individual with normal graft function who had gone 10+ years without any immunosuppression.

Case Description: 62-year-old male with the history of DM II, hypertension, renal stone, past deceased donor kidney transplant (2002) presented with chief complaint of abdominal pain, fever, and diarrhea for one week. His CT of the abdomen and pelvis showed a perforated appendix and was treated with antibiotics and the abscess was drained. He recovered from his current illness and his discharge creatinine was 1.07 mg/dL with eGFR 75 ml/min. He received an HLA-matched deceased donor kidney transplant on 2002. His postoperative course was uncomplicated and creatinine improved from 5 mg/dL to 2 mg/dL at discharge. He was discharged on tacrolimus, mycophenolate, and prednisone. He gradually lost follow-up and stopped taking all of his medications, including his immunosuppressants, for more than 10 years on his own accord. He preserved his renal function for all these years without any immunosuppressive medications. His chimerism study from buccal mucosal cells was negative but could not exclude microchimerism. He was subsequently discharged and maintained off immunosuppressive medications.

Discussion: The evolution of tolerance to donor alloantigen in vivo is a dynamic process involving many mechanisms that contribute at different stages. The clinical characteristics of tolerance patients are limited due to its rare occurrence. Our patient gradually discontinued his immunosuppressive over the course of months by himself. The possible mechanisms for his immune tolerance could be central (intrathymic) deletion, peripheral deletion, anergy, ignorance and/or microchimerism, either alone or in combinations. He still maintains a good graft function without any immunosuppressant.

TH-PO592

Graft-versus-Host Disease After Kidney Transplant

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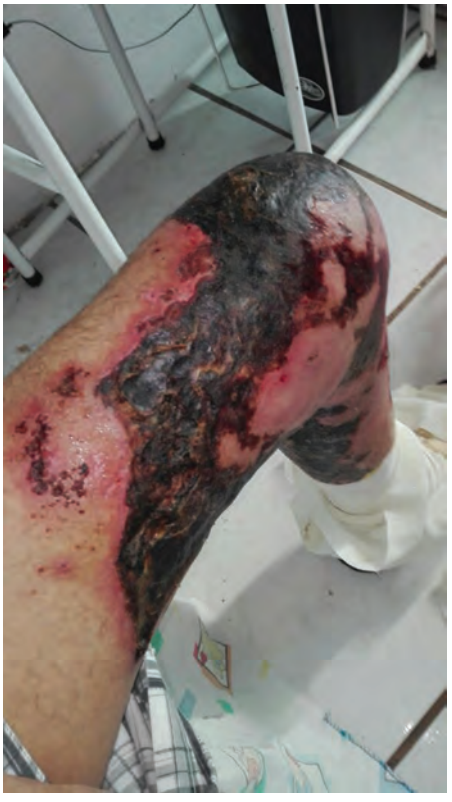
Introduction: Graft-versus-host disease is an uncommon complication after solid organ transplantation. Few cases of graft-versus-host disease after kidney transplantation have been reported.

Case Description: A 32-year-old man was admitted to our hospital in August 2017 due to cellulitis of the right leg. He received ceftriaxone and clindamycin. His past medical history included end-stage renal failure at the age of 19 years old. It was necessary to start peritoneal dialysis until he received a renal transplant in 2007 from a related donor (his father, 41-years-old at the time), he had matching HLA (A, B and DR) antigens. The recipient received induction therapy with rabbit-antithymocyte globulin and a triple immunosuppressive regimen. In February 2018 he developed bullous lesions burning pain on the back of the left leg. Skin lesions then coalesced and became hemorrhagic, spreading to the rest of the leg and thigh. They eventually turned into crusts in a month. A Dermatology evaluation was requested, and a skin biopsy was performed. Biopsy reported: epidermal

acanthosis and mild spongiosis of the basal layer; upper dermis showed blood vessels with lymphocytic infiltrate (without vasculitis). There was proliferation, thickening and homogenization of collagen tissue fibers and deep perifollicular fibrosis with a suggestive diagnosis of sclerodermiform dermatosis chronic variant of graft-versus-host disease.

Discussion: The main risk factors include donor HLA homozygosity, peri-organ lymphoid tissue transfer and the relationship between recipient immunogenicity and the immunosuppressive drug regimen. Diagnosis is made by specific tests which detect macrochimerism, single-tandem repeat and DNA analysis which quantifies relative amounts of different DNA.



TH-PO593

Blood in a Urine Collection...Is It an Infection or Rejection? Adenovirus Is Our Selection!

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Introduction: Adenovirus-induced granulomatous interstitial nephritis (AGIN) is rare and has a high risk of graft loss in renal transplant patients. Diagnosis can be made with quantitative urine and blood PCRs and biopsy. We present a case of hemorrhagic cystitis, AGIN, admixed with rejection.

Case Description: 53 year old male with a history of ESRD secondary to ADPKD had a DDRT in 2010 with no notable post-transplant complications. His baseline SCr was 1.6 mg/dl, and he was maintained on tacrolimus, MPA, and prednisone, with goal tacrolimus troughs between 5-8 ng/ml. He had presented to an urgent care with dysuria, hematuria, and AKI (Scr to 1.9 mg/dl) and treated with ciprofloxacin for 10 days. He came to our facility one week later with diarrhea, fevers, and AKI (SCr of 2.9 mg/dl) that did not improve with IV fluids and antibiotics. In light of hematuria, urine and serum adenovirus PCR were sent which resulted as greater than 2,000,000 and 72,698 copies respectively. Transplant kidney biopsy showed ACR Banff IB, suspicious for chronic, active ABMR with severe glomerulitis, moderate pertitubular capillaritis, and mild transplant glomerulopathy. Light microscopy showed severe tubulointerstitial inflammation with lymphohistiocytic proliferation, numerous monocytes and lymphocytes with areas of interstitial hemorrhage, epithelial cell necrosis, rupture of basement membranes, and rare tubular epithelial cells with enlarged nuclei with a smudgy, glassy appearance. Occasional vague necrotizing granulomas were identified. Electron microscopy showed 30-40% foot process effacement with segmental duplication of capillary walls. SCr peaked at 3.2 mg/dl; he received IVIG for AGIN. Dose of prednisone was increased to 10 mg, and tacrolimus level ran between 5-8 ng/ml with MPA at 360 mg bid. He was unable to tolerate further IVIG secondary to headaches. Serum adenovirus PCR one week after IVIG dosing had detectable viral loads but less than 500 copies. Discussion with Transplant ID colleagues led to the decision to hold cidofovir secondary to potential nephrotoxicity. His renal function remains stable at SCr of 1.8 mg/dl.

Discussion: We identified and properly treated a rare cause of AKI due to AGIN admixed with ACR. Prompt diagnosis and treatment led to resolution of viremia as well as improvement in renal function with graft salvage.

TH-PO594

A Case of Hereditary Diffuse Gastric Cancer in a Renal Transplant Patient

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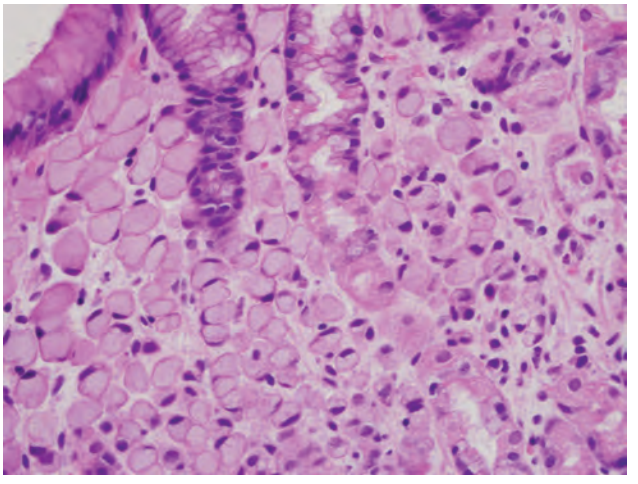
Introduction: Hereditary diffuse gastric cancer is a highly invasive malignancy which is usually advanced at the time of presentation and associated with a poor prognosis. We report a case diagnosed less than one year after kidney transplantation.

Case Description: A 33-year-old woman with end stage renal disease due to renal agenesis post kidney transplant 8 months ago was admitted with a 5-month history of post-prandial abdominal pain and a 20-pound weight loss. An abdominal CT scan and ultrasound prior to admission were unrevealing. An endoscopy 2 months ago showed gastritis, at which time she started pantoprazole and sucralfate, with no improvement. She was also on tacrolimus, mycophenolate sodium and prednisone. Her family history was significant for stomach cancer in her father who died at age 33 as a result. She had normal vital signs and exam except for a low blood pressure of 99/64. An upper endoscopy showed a localized area of gastritis in the posterior body of stomach which was biopsied. CT scan of the abdomen and pelvis showed mild ascites and a small bowel obstruction. Posterior wall biopsy result came back showing diffuse type adenocarcinoma with signet ring cells. Diagnostic paracentesis showed malignant cells. Genetic testing identified a mutation in CDH1. Patient's functional status was too poor for chemotherapy and she passed away 2 months from diagnosis.

Discussion: Hereditary diffuse gastric cancer is associated with mutations in a tumor suppressor gene (CDH1) which encodes E-cadherin. Affected individuals develop gastric cancer at a young age. Diffuse gastric cancer in first or second degree relatives under the age of 40 is an indication for genetic testing. Prophylactic gastrectomy is recommended between the age of 20 and 30 in mutation carriers because of the extremely high risk of cancer.



Pathology result showing signet cell adenocarcinoma

TH-PO595

Successful Treatment and Five Years Disease-Free Survival in a Donor Transmitted Metastatic Melanoma with Ipilimumab Therapy

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Introduction: Approximately 7% of deceased donors have unknown cancer at the time of organ procurement. More than 50% of these have no apparent contraindication to organ donation. The commonest transmitted malignancy is renal cell cancer (19%), followed by melanoma (17%). Donor transmission of melanoma is often fatal as it is commonly metastatic at the time of diagnosis. Cases with remission following transplant nephrectomy and withdrawal of immunosuppression are few. To our knowledge this is only the second case of donor-derived melanoma that was successfully treated with Ipilimumab. Our patient has the longest disease-free survival (five years) reported in the literature till date.

Case Description: 66-year-old female, status post deceased donor Kidney transplant in December 2012 for diabetic nephropathy received a 5/6 HLA-mismatched kidney, underwent induction with basiliximab and glucocorticoid followed by maintenance with tacrolimus and mycophenolate. In March 2013, she developed acute deterioration of allograft function. MRI abdomen/pelvis was suspicious for neoplastic involvement of the allograft with metastases to spleen and bone marrow. Biopsy of the posterior iliac spine and sacrum was positive for metastatic melanoma. Explantation of the allograft on 3/15/2013 showed metastatic involvement. Immunosuppressants were discontinued, and she was initiated on dialysis. Her melanoma was BRAF V600E mutation favorable. Staging studies confirmed widespread metastases involving the bone, liver, spleen, and lungs (TxNxM1c stage IV, allograft-associated). On 4/2013, she was started on vemurafenib (960 mg bid) but was discontinued in August 2013 due to several cutaneous lesions. She was then treated with four cycles of Ipilimumab (3 mg/kg, every three weeks, 8/13/13-10/15/13) without significant side-effects. Quality of life improved. No further progression of cancer was evident on serial imaging and she has been in remission for five years.

Discussion: Despite careful donor selection, cancer transmission to the recipient is inevitable. Early diagnosis, cessation of immunosuppression to allow rejection of the allograft and transplanted cancer cells, transplant nephrectomy, and treatment with chemotherapy/immunotherapy can improve survival. The role of HLA mismatch in prognosis is unclear and a topic for future research.

TH-PO596

A Rapid Onset of De-Novo Allograft Nephrolithiasis

Amita Maibam, Ana L. Castellanos. *University of Kentucky, Lexington, KY.*

Introduction: De-novo renal allograft nephrolithiasis is a rare condition with incidence of approximately 1 %. Persistent hyperparathyroidism (HPT) after kidney transplant occurs in 15-50% cases but rarely causes renal calculi. Mean duration to diagnosis is 28±22 months. Here we report a case of allograft nephrolithiasis soon after transplantation with underlying tertiary HPT on cinacalcet.

Case Description: A 47-year-old Caucasian male with history of biopsy proven IgA nephropathy, hypertension, ESRD on peritoneal dialysis for 4 years underwent a deceased donor kidney transplant. He received thymoglobulin induction and was started on mycophenolate, tacrolimus, and prednisone for maintenance immunosuppression. After 2 weeks of surgery, cinacalcet was started for hypercalcemia (11 mg/dl). At 6 weeks post transplantation, ureteral J stent was found to be severely encrusted. The stent was removed with subsequent passage of several small stones. Analysis showed 100% brushite stones. A CT stone protocol revealed transplanted kidney with multiple calculi within the collecting system with evidence of obstruction. It was treated with stenting, lithotripsy, and percutaneous nephrostomy placement. Intact parathyroid hormone (iPTH) was 455 pg/ml with serum ionized calcium 6.1 mg/dl and phosphorus of 2.2 mg/dl. Renal function remained stable with serum creatinine of 1.3 mg/dl to 1.4 mg/dl. Patient underwent near-total parathyroidectomy after a nuclear scan showed enlarged parathyroid glands. Histopathology reported hyperplastic glands. One year post parathyroidectomy, there has been no new stone formation with normalization of calcium and iPTH.

Discussion: The most striking aspect of our case was asymptomatic de-novo nephrolithiasis, which presented within 6 weeks after transplantation. It emphasizes the need to remain vigilant of this possible complication during the early post-transplant period in patients with persistent hypercalcemia and HPT. Close monitoring of calcium, phosphorus, and iPTH levels along with necessary imaging can lead to timely diagnosis of this potentially allograft threatening complication. Parathyroidectomy can be performed with excellent outcomes.

TH-PO597

A Gigantic Renal Cyst Mimicking Ascites

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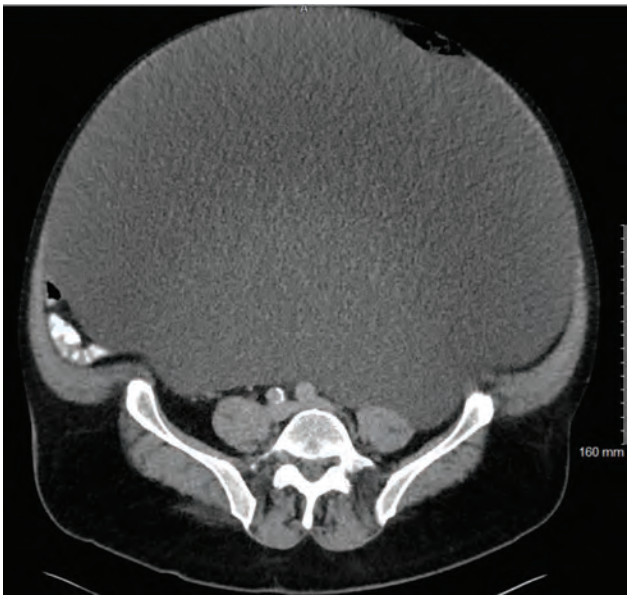
Introduction: The incidence of renal cyst increases with age above 50 years. Majority of the cyst are < 2cm and the reports of size >15cm are extremely rare. Here we present a peculiar case of a 75-year-old male with an exceptionally massive renal cyst, but unremarkable symptoms.

Case Description: A 74-year-old Caucasian male with history of type 2 diabetes mellitus and hypertension who was admitted to the hospital for evaluation of chest pain of cardiac origin. Incidentally on exam, he was found to have a protuberant abdomen with fluid wave concerning for ascites. He has no known history of liver disease and he reported gradual increase in abdominal girth for last 15 years. He was further evaluated with CT abdomen and pelvis which demonstrated numerous fairly simple appearing cysts noted to arise from both kidneys. The largest arises from the lower pole of the left kidney and measures 40 x 27 x 30 cm. He denies any family history of polycystic kidney disease. Patient underwent continuous percutaneous catheter placement in largest cyst with 20L of serous fluid removed over 2 days with negative microbiology, and with significant improvement in abdominal distention thereafter.

Discussion: Renal cyst should be considered as one of the differentials in patients with progressive distension of abdomen. To the best of our knowledge, this case represents the largest reported renal cyst. Our findings highlight the fact that benign renal cyst can grow over several years while remaining relatively asymptomatic, can mimic ascites and can pose diagnostic and therapeutic dilemma.



Computed tomography of abdomen showing bilateral renal cysts with the largest measuring 40 x 27 x 30 cm on the left kidney.

TH-PO598

CMV Nephritis with Glomerular Involvement

Mohammad Y. Alsawah. *Nephrology, St John Hospital & Medical Center, Detorit, MI.*

Introduction: Cytomegalovirus (CMV) infection is common in kidney transplant recipients, but infection related pathologic changes of the renal allograft are uncommon. Histologically, it presents with viral inclusions in tubular epithelial cells and interstitial inflammation. We describe a case of CMV nephritis with inclusions in glomerular endothelial cells without associated interstitial infiltrate or epithelial cell inclusions.

Case Description: A 17 year old African American male with history of ESRD from focal segmental glomerulosclerosis received a preemptive living kidney allograft from his mother. Both donor and recipient were CMV seropositive. Post-operatively, creatinine level plateaued at 2 mg/dL without significant proteinuria on serial monitoring. An allograft biopsy was performed for elevated creatinine level 5 weeks post-transplant showed no evidence of rejection or recurrence of the primary disease. Staining for both SV40 and CMV was negative. Three months postoperatively, the patient developed abdominal pain and weight loss. Abdominal CT scan showed no abnormalities. Gastric endoscopy showed mild gastritis. A peripheral blood quantitative CMV viral load by PCR was >3 million copies / ml. The patient's creatinine level increased to 2.5 mg/dL. A repeat allograft biopsy showed enlarged endothelial cells with cytoplasmic inclusion that stained positive for CMV. There was no evidence of capillary thrombosis, interstitial inflammation or tubular epithelial cell inclusions. Peripheral blood CMV viral load was elevated over 3 million IU/ml despite receiving maintenance valganciclovir post-transplant prophylaxis. CMV viral resistance pattern revealed a UL97 mutation. Viremia ultimately responded to increasing valganciclovir dose over a 5 months period of follow-up.

Discussion: CMV induced cell inclusions in kidney allograft recipients with CMV disease is uncommon and usually involves epithelial tubular cells. Bhadauria et al described CMV infection in 74 of 521 live donor kidney recipients (1). Only 4 cases developed histologically confirmed CMV allograft disease. In another review of 2900 kidney allograft indication biopsies only 4 cases of glomerular endothelial cells were described(2). Ganciclovir resistance occur in 2-4% of CMV infections (3), but there are no reports of association of this resistance with any specific pathologic findings on kidney biopsy.

TH-PO599

Everything Comes Down to Poo

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Introduction: Use of immunosuppressive agents can predispose transplant recipients to a variety of side effects like malignancies, infections, anemia. Anemia in post transplant period can be from several causes including delayed graft function, blood loss, infections. Here we present a case of anemia from Hemphophagocytic lymphocytosis (HLH) caused by Cytomegalovirus (CMV) colitis in a patient with negative CMV viremia

Case Description: A 54 yom was admitted for symptomatic anemia without active source of bleeding. He had a history of deceased donor renal transplant, CMV Donor negative/Recipient positive and EBV Donor positive/Recipient positive, complicated by delayed graft function. He had a history of chronic anemia, unresponsive to Epogen therapy. Bone marrow biopsy was done which demonstrated hemophagocytosis and atypical erythroblasts possibly related to viral infection. Immunostains for Parvovirus, EBV, CMV were negative. Due to RBC hypo-proliferation as well as development of diarrhea,

he was empirically started on IV ganciclovir for possible CMV colitis. He underwent colonoscopy with colon biopsy demonstrating distortion, increased chronic inflammatory cells, crypt atrophy, focal crypt abscess. Immunoperoxidase staining was positive for CMV. The etiology of patient's hemophagocytosis was from non-disseminated CMV. He was discharged home on oral valgancyclovir as well as outpatient clinic follow up

Discussion: Post transplant anemia can be due to medication side effects, frequent phlebotomy tests, slow graft function, viral infection. HLH is a syndrome of excessive inflammation and tissue destruction due to exaggerated immune response. Primary HLH is caused by a genetic mutation and secondary HLH occurs in autoinflammatory and autoimmune disease, lymphoma, viremia, iatrogenic immunosuppression. It is diagnosed if there is a mutation in a known causative gene or if at least 5 of 8 diagnostic criteria are met: fever, splenomegaly, cytopenia involving > 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, biopsy proven hemophagocytosis, low or absent natural killer cell activity, elevated serum ferritin, elevated CD25 levels. The pathogenesis of HLH is not well understood. Impairment of Natural killer-cell (NK-cell) function caused by viral infections can lead to persistent activation of macrophages and production of cytokines. When HLH is triggered by a viral infection, treatment of the underlying viremia is recommended

TH-PO600

Spontaneous, Non-Traumatic Renal Hemorrhage: An Under-Recognized Entity

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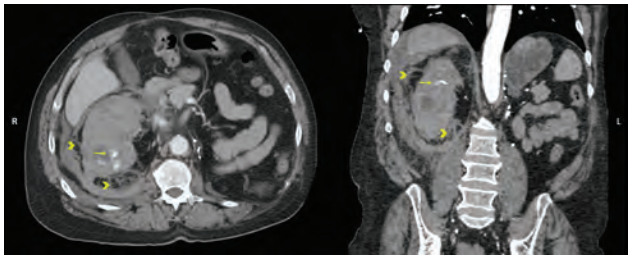
Introduction: We present a case of spontaneous, non-traumatic renal hemorrhage in a patient with end-stage renal disease (ESRD), also known as Wunderlich syndrome.

Case Description: A 61-year-old man with ESRD, on hemodialysis for two years, left renal cell carcinoma status post nephrectomy 20 years ago, hypertension and 40 pack-years smoking history presented to our institution for sudden-onset right flank pain radiating to the right leg. His blood pressure at presentation was 130/90 mmHg, pulse 98 bpm and physical examination was significant for tenderness over the right flank without signs of peritonitis. Laboratory testing was significant for a drop in hemoglobin to 7.9 g/dL from a baseline value of ~11 g/dL. Platelet count and international normalized ratio were within normal limits. A computed tomography (CT) scan of the abdomen demonstrated acute hemorrhage throughout the right kidney extending into the anterior and posterior pararenal spaces. In addition, there was extravasation of contrast at the upper pole, indicating active bleeding [Figure 1]. There was no obvious underlying renal mass or evidence for acquired cystic kidney disease. He underwent renal artery angiogram and embolization using lipiodol-ethanol mixture and gelfoam. His blood count subsequently stabilized and was discharged in stable condition.

Discussion: Wunderlich syndrome, first described in 1856 is a rare condition characterized by acute spontaneous, non-traumatic renal hemorrhage into the subcapsular and perirenal spaces. Patients may present with the classic 'Lenk's triad' of symptoms consisting of acute flank or abdominal pain, a palpable flank mass, and hypovolemia but the presentation is variable and non-specific in most cases. CT scan is the imaging modality of choice and treatment often includes renal artery embolization or nephrectomy, depending on the severity. It is important to note that ESRD patients are predisposed to bleeding diathesis in the setting of uremic platelet dysfunction, anemia, increases in nitric monoxide, irregularities in von Willebrand factor and impaired platelet-vessel wall interaction.



TH-PO601

Young African American Male with Mild Bilateral Hydronephrosis and Kidney Failure

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Introduction: Retroperitoneal fibrosis (RPF) is a rare condition that requires high clinical suspicion for prompt diagnosis as routine imaging studies may be nondiagnostic.

Case Description: A 27-year old African American man presents with a 4-week history of constant aching pain of abdomen and back without associated consitutional symptoms. Past history: unprovoked deep venous thrombosis of right leg and a recent episode of scotal swelling/ejaculation difficulty Medication: apixaban Exam: ill-appearing, blood pressure 130/75 mmHg Unremarkable cardiopulmonary exam, minimally tender abdomen, bilateral costovertebral angle tenderness, trace bilateral lower leg edema Labs: Na 133, K 5.0, total CO_2 25 meq/l, blood urea nitrogen 57 mg/dl, creatinine 12.55 mg/dl Urinalysis bland Renal ultrasound: mild hydronephrosis Abdominal/pelvis CT without contrast: mild bilateral hydroureteronephrosis with inflammatory changes, no obvious mass/lymphadenopathy. At the insistence of the renal team to rule out RPF, a CT urogram was performed which revealed an infiltrative mass encasing aorta, inferior vena cava, and commmon iliac vessels. Evaluation for infectious, malignant, and vasculitic etiologies was negative. Laparoscopic biopsy revealed dense fibroadipose tissue, lymphocytic aggregates, focal scattered IgG4-positive plasma cells, and fibrin deposition. IgG4-related disease criteria not met. Patient underwent bilateral nephrostomy placement with resolution of kidney failure with plan to initiate corticosteroids for presumed idiopathic RPF.

Discussion: RPF is a relatively rare condition that involves chronic inflammatory and fibrotic changes in the retroperitoneum that can lead to encasement and compression of retroperitoneal structures. Implicated etiologic factors including drugs, malignancy, infections, radiation, and trauma may be present in 30% of cases and idiopathic in all others. Prompt diagnosis relies on recognition of a classic clinical presentation (Figure) as initial imaging studies (non-contrast CT or ultrasound) may be falsely negative for significant obstruction.

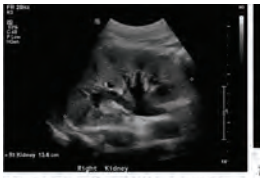

Figure 1. Renal ultrasound shows increased renal cortical echogenicity and mild hydronephrosis

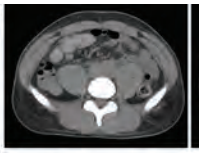

Figure 2. Abdomen/pelvis CT without contrast. Ill-defined, infiltrative soft tissue mass encasing both aorta and inferior vena cava. (Initially read as negative for mass or lymphadenopathy)

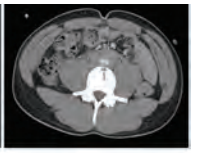

Figure 3. Abdomen/pelvis CT with contrast. 7.2cm mass encasing the aorta and inferior vena cava.

Clinical presentation of retroperitoneal fibrosis:
Typically affects patients between the ages of 40 and 60 years; Male predominance 2:1 to 3:1
Symptoms: generalized malaise, weight loss, nausea, oliguria, anuria; constant dull pain involving lower back and/or flank with radiation to groin or lower abdomen; testicular pain; deep venous thrombosis and lower extremity edema (compression of inferior vena cava); leg claudication (arterial compression); mesenteric ischemia (compression of mesenteric arteries)

TH-PO602

Rhabdomyosarcoma: A Frightening Differential for Bladder Outlet Obstruction (BOO) in Children

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Introduction: Posterior urethral valves (PUV) are the most common cause of bladder outlet obstruction (BOO) in children. While many children are diagnosed prenatally on ultrasound, a few children may occasionally present outside of the neonatal period. In toddlers, bladder outlet obstruction can present with history of dribbling or weak urinary stream, and more often, following a febrile urinary tract infection. While PUV remains the most common cause of BOO in male children beyond the neonatal period, other etiologies for BOO must be considered, including urethral strictures, ureteroceles, bladder diverticula, and masses. We describe a case of rhabdomyosarcoma presenting with bladder outlet obstruction.

Case Description: 13month old previously healthy full term Caucasian male presented with two weeks of constipation, decreased appetite, decreased urine output, and concern for dehydration. On exam, he had hypertension, a distended, tender abdomen, and normal external genitalia. Labs were notable for CO2 of 10mEq/dL, BUN 83mg/dL, creatinine 1.4mg/dL, and WBC 17.6 $x10^9$/L. Abdominal Xray was unremarkable. Ultrasound revealed a distended bladder and bilateral hydronephrosis consistent with BOO. Pt experienced significant clinical improvement following urethral catheter placement; his creatinine improved to 0.2mg/dL. On voiding cystourethrogram (VCUG) for evaluation of posterior urethral valves, he was found to have a 2.9 x 2.8cm lobulated prostatic mass with invasion into the bladder. Biopsy revealed embryonal rhabdomyosarcoma. At this time, he continues on chemotherapy and radiation therapy.

Discussion: Rhabdomyosarcoma is the most common pediatric soft tissue sarcoma and accounts for 7-8% of all solid malignant tumors in children. It has a bimodal age distribution, affecting children less than two years old and adolescents. 15-20% arise from genitourinary sites. Bladder and prostate rhabdomyosarcoma can present with symptoms of bladder outlet obstruction, as in this patient. Prognosis and morbidity is dependent on staging, histology, age, and the extent of bladder sparing interventions. Rhabdomyosarcoma remains a rare, but important cause of bladder outlet obstruction in infants and toddlers. In children presenting with new onset obstructive uropathy, a broad differential including malignancy must be considered as prompt diagnosis allows for definitive therapy.

TH-PO603

Rare Type of Pyelonephritis

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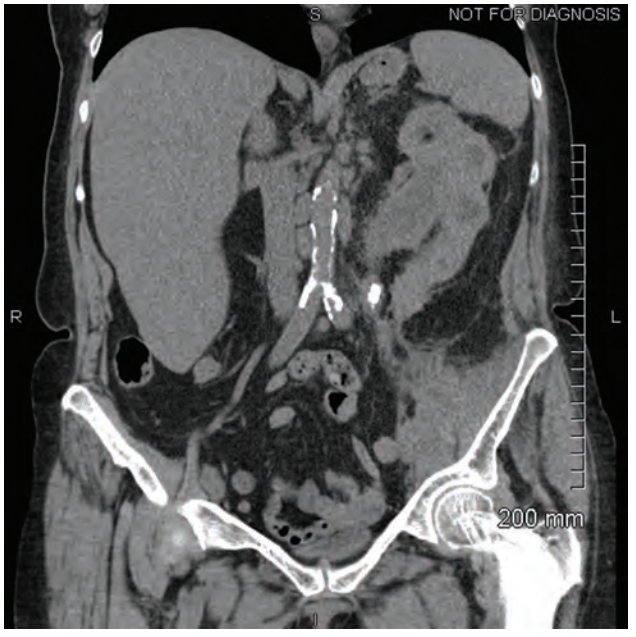
Introduction: Xanthogranulomatous pyelonephritis (XGP) is a rare chronic destructive granulomatous inflammatory process of renal parenchyma accounting for 0.6% of histologic cases of chronic pyelonephritis. Exact etiology is unknown however this process is associated with long term obstruction and infection. The aim of this case report is to enhance awareness of this rare condition in an effort to prevent delayed treatment and adverse outcomes.

Case Description: A 69 year old woman presented with left hip and flank pain of 3 weeks duration. Vital signs were as follows: temp 98.5, 104 HR, 16 RR, BP 133/64. Physical exam revealed left costovertebral angle tenderness. Labs were notable for leukocytosis WBC 16.5, hemoglobin 8.4, hematocrit 26.9, MCV 83.5, creatinine 1.7, BUN 18 mg/dL. Urinalysis revealed >100 WBCs, positive nitrite, moderate leukocyte esterase. She

underwent CT scan of the abdomen pelvis which revealed severe cystic replacement of left renal parenchyma, perinephric inflammatory changes, left ureteral calculus distal to the left UPJ, and left psoas muscle fluid collection (figure). IV antibiotics and pain medication were given. A nephrostomy tube and drain was placed with cultures showing E coli. She remained afebrile and had satisfactory drain outputs. She underwent left radical open nephrectomy and adequate postoperative recovery. Specimens showed no distinct corticomedullary junctions, granulomatous inflammation and cholesterol clefts.

Discussion: Clinical presentation of XGP may be vague. Its diffuse or advanced stage typically requires nephrectomy. Antibiotics may be used for treatment of focal or bilateral XGP. In summary, this case highlights many features characteristic for a rare type of chronic pyelonephritis with associated psoas abscess complication. Maintaining a high index of suspicion for this condition leading to an accurate and earlier diagnosis may influence prognosis.



TH-PO604

Encrusted Pyelitis in a Patient with Solitary Functional Kidney

Meghana Chalasani, Bruce Horowitz, Josephine Abraham. *University of Utah, Salt Lake City, UT.*

Introduction: Encrusted pyelitis is a rare infectious disease affecting the urothelium and is usually caused by *Corynebacterium urealyticum*, a non-hemolytic gram-positive bacillus.

Case Description: A 79-year old woman with a history of urothelial carcinoma and atrophic left kidney was found on a surveillance abdominal CT scan to have linear calcifications within the collecting system of the right kidney with bilateral urothelial thickening concerning for encrusted pyelitis. Patient was diagnosed with urothelial carcinoma after a CT scan done for evaluation of painless hematuria showed severe left hydronephrosis with a focal enhancing mass at the left uretero-vesicular junction. She did not have evidence of metastases and underwent radical cystectomy with ileal conduit. Scan two months later showed resolution of left hydronephrosis, atrophic left kidney, and normal right kidney. CT scan three months later showed diffuse atrophy of the left kidney with minimal enhancement of the left renal artery, consistent with chronic ischemia and right-sided alkaline encrusted pyelitis. Patient reported urinary discoloration but no fever or dysuria. Serum creatinine remained unchanged. Urine culture was obtained and patient was started on ciprofloxacin. Urine culture was negative. Patient stopped taking the antibiotic due to shoulder pain. Urinalysis one month later showed a pH of 7.5, 5-10 red blood cells and 5-10 white blood cells per high power field, and a large leukocyte esterase. Culture was again negative. CT scan 2 months later showed progression of calcifications. A 24-hour urine stone risk profile is being considered.

Discussion: Encrusted pyelitis is a consequence of lithiasis due to urea-splitting organisms, particularly *Corynebacterium urealyticum*. Urea is hydrolyzed via urease to ammonium thereby alkalinizing the urine and promoting the formation of magnesium ammonium phosphate stones. Risk factors include endourological procedures, renal transplant, immunosuppression, and prolonged broad-spectrum antibiotics. Complications are ureteral stenosis, renal abscesses, and obstructive uropathy with resultant end-stage renal disease. Diagnosis is suggested by urine culture isolation of a culprit organism and unenhanced imaging which classically shows calcified encrustations in the wall of the urinary tract. Treatment involves antibiotic therapy for at least fourteen days and acidification of the urine.

TH-PO605

Changes in Gene Expression of Hypothalamic Neuropeptides Controlling Feeding Regulation in Bilaterally Nephrectomized Rats

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Background: Anorexia is one of the most widespread eating disorders that appears to contribute to malnutrition in patients with advanced renal dysfunction. While several mechanisms underlying uremic anorexia have been proposed, the hypothalamic neuropeptides that regulate feeding in the hypothalamus of uremic patients are poorly understood. These neuropeptides act both on the hypothalamus and other appetite-regulating centers throughout the brain.

Methods: We evaluated the gene expression of hypothalamic feeding-regulating neuropeptides after bilateral nephrectomy, a model of acute renal dysfunction. Adult male rats received bilateral nephrectomy or a sham operation. The rats were decapitated at 6, 12, and 24 h after treatment. The brains were removed immediately, frozen on dry ice. The brains were then cut into 12-μm-thick sections using a cryostat and the locations of the hypothalamic areas, including the paraventricular nucleus (PVN), arcuate nucleus, and lateral hypothalamic area, were determined according to the coordinates of a mouse brain atlas. The gene expression of corticotrophin-releasing hormone (CRH) in the PVN; propiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript, neuropeptide Y, agouti-related peptide in the ARC; and melanin-concentrating hormone and orexin in the LHA, were quantified by in situ hybridization histochemistry. After treatment, cumulative food intake, water intake, and body weight were measured.

Results: The mRNA levels of *POMC* and *CRH*, which suppress feeding behavior, were significantly increased after bilateral nephrectomy compared with sham-operated rats. The food intake of nephrectomized rats decreased compared with sham-operated rats, but there was no difference in body weight and water intake between both groups.

Conclusions: The results suggest that *POMC* and *CRH* in the hypothalamus may be involved in the development of anorexia in bilateral nephrectomized rats. This report may provide new insights into the physiological mechanism underlying anorexia in patients with renal dysfunction.

TH-PO606

CD147/Basigin Is Involved in the Pathogenesis of Hepato-Renal Disease Under the Status of Satiation and Starvation

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Background: Gluconeogenesis from lactic acids and ketogenesis from fatty acids are critical for maintaining energy homeostasis and physiological activity during starvation in mammals. Besides ATP production necessary for substance transport by themselves, the kidneys are constantly complementing energy production of the liver which is a critical regulator in this setting. Therefore, excessive accumulation of glycogen and fat in metabolic syndrome causes chronic kidney disease and non-alcoholic fatty liver disease (NAFLD). CD147/Basigin (Bsg), a glycosylated transmembrane protein, is involved in glycolysis-lactate metabolism on carcinogenesis. We therefore investigated on physiologic functions of Bsg in energy metabolism under the status of satiation and starvation.

Methods: Two independent mice models were performed using wild-type ($Bsg^{+/+}$) or Bsg-deficient ($Bsg^{-/-}$) mice treated with high fat diet (HFD) or starvation (free drinking water), respectively.

Results: Levels of blood glucose (BS) and liver ATP in standard diet-fed $Bsg^{-/-}$ mice were lower than those of $Bsg^{+/+}$ mice. Alternatively, activation of β-oxidation and autophagy were observed in the kidneys and liver of $Bsg^{-/-}$ mice. AMPK activation was also found in $Bsg^{-/-}$ liver. BS suppression in tolerance tests for pyruvate or alanine was exhibited, indicating that $Bsg^{-/-}$ mice showed a reduction of gluconeogenesis. In accordance with these findings, HFD-fed $Bsg^{-/-}$ mice ameliorated tubulointerstitial injury showing vacuolar formation, disease activity of NAFLD, and insulin resistance. Of note, starved $Bsg^{-/-}$ mice became NAFLD as well. This phenomenon might be caused by autophagic activation leading to the accumulation of triglyceride. Regardless of lower ATP values in $Bsg^{-/-}$ mice, surprisingly, life survival of $Bsg^{-/-}$ mice was similar with that of $Bsg^{+/+}$ mice. The kidneys may compensate for energy shortage of $Bsg^{-/-}$ mice by activation of ketogenesis. Indeed, HMGCS2 that catalyzes the first reaction of ketogenesis was induced in $Bsg^{-/-}$ kidneys, but not liver.

Conclusions: CD147/Basigin is involved in the pathogenesis of hepato-renal disease through the regulation of autophagy, gluconeogenesis and ketogenesis under the status of satiation and starvation.

TH-PO607

Defining the Renoprotective Mechanism of Deiodinase 3 in Podocytes

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Background: Deiodinase 3 (D3) is a membrane-bound enzyme that reduces local thyroid hormone signaling in most cell types. By preventing the bioavailability of tri-iodothyronine

(T3), the metabolically active thyroid hormone, D3 efficiently regulates thyroid signaling in tissues to modulate vital processes such as metabolism. While deiodinases have been studied in several endocrine tissues, the role of D3 in controlling T3 in renal tissue has not been addressed, despite emerging studies demonstrating overlapping complications of kidney disease and thyroid hormone dysfunction. As numerous glomerulopathies can stem from energetic dysfunction of podocytes, which have mechanisms that respond to both glomeruli derived and circulating changes in hormone levels, we aimed to determine the significance of D3 dysfunction in podocyte derived kidney disease.

Methods: D3 expression was measured via qRT-PCR, Western blot and confocal analysis. Regulatory capacity of D3 was analyzed via a T3 cleavage assay. The role of D3 in podocyte derived kidney disease was evaluated *in vitro* by inducing injury to cultured podocytes and *in vivo* using podocyte specific D3 KO mice challenged with LPS. Renal dysfunction was assessed by urine Albumin:Creatinine ratio and by quantifying effacement (processes/ GBM length). Cytoskeletal, metabolic and protein trafficking markers were measured in lentiviral-driven D3 knockdown podocytes to determine the renoprotective mechanism of D3. Glomerular D3 expression was measured in renal biopsies from kidney disease patients by immunofluorescence intensity.

Results: D3 is highly expressed in podocytes and downregulated in injury models, resulting in compartmentalization of D3 in the golgi and nuclear region where metabolically active T3 resides. Podocyte specific D3 KO mice responded poorly to LPS-induced kidney injury, resulting in heavy proteinuria and foot process effacement compared to control. Biomarkers of metabolic stress and impaired protein trafficking were upregulated in D3 deficient podocytes. D3 expression in glomeruli of kidney disease patients suffering from minimal change disease, diabetic nephropathy, or focal segmental glomerulosclerosis showed unique profiles amongst diseases.

Conclusions: D3 plays a renoprotective role against thyroid hormone associated kidney disease in podocytes. We propose D3 reduces energy expenditure to prevent podocyte exhaustion and death.

TH-PO608

Caloric Restriction Improves Established Proteinuria in Adriamycin-Induced Nephropathy

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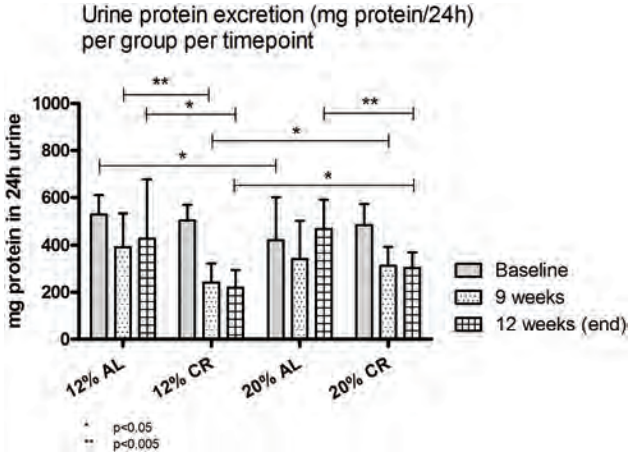
Background: Reduction of proteinuria is an important strategy to prevent loss of kidney function. Preclinical studies suggest that caloric restriction (CR), induced at young age, protects against age-related proteinuria. None of these studies investigated the effect of CR in established renal disease. We hypothesized that CR in established proteinuria reduces urinary protein excretion (UPE).

Methods: Male Wistar rats (n= 56; age 12± 2 wk) were intravenously injected with 2.1mg/kg Adriamycin. At 6 wks after injection, baseline UPE was measured. At 7 wks after injection rats were randomly assigned to 4 groups: An ad libitum (AL) and a CR group (60% of AL food intake) fed with a 12% protein diet (12%AL, 12%CR) and an AL and a CR group fed with a 20% protein diet (20%AL, 20%CR). All groups were treated for 12 wks. UPE was measured at wk 9 and 12 and mean arterial blood pressure (BP) at the end of the study.

Results: Baseline UPE was similar in all groups (p>0.20) with a median value of 495 and an interquartile range of 127mg/24h. After 12 wks of diet, all animals exposed to CR had a 20.3% lower UPE (p=0.003) compared to AL fed animals. At wk 9 this effect was only seen in the 12%CR group. BP in animals exposed to CR was -21.2% lower (p<0.0001) compared to AL fed animals.

Conclusions: Caloric restriction lowers UPE and BP in rats with established proteinuria. Protein restriction was effective if applied in combination with CR. These results may guide future intervention studies in patients with proteinuric and obesity-related nephropathy.



TH-PO609

Renal Adverse Effects of Long Term Whey Supplementation with Resistance Training in Rats

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Background: The usage of whey protein is already widespread; as resistance trainers and in-patients use whey protein alike. There is reliable evidence against other supplements, it is lacking for whey protein. The aim of the study was to identify the adverse effects of whey protein usage on kidneys.

Methods: 48 young male albino wistar rats are divided into 6 (n=8); Normal (20%) Protein(NP)-Sedentary(NPS), NP-Resistance training(NPRT), High(45%)Protein(HP) Sedentary(HPS), HP-Resistance Training(HPRT), Abuse(70% Protein)(A)-Sedentary(AS), and Abuse-Resistance Training(ART) groups. The rats were fed ad libitum. Training was maintained by resistance protocol in a motorised treadmill. On days 1 and 90 12 hour urine and blood samples were collected. Urea, microalbuminuria and pH were detected in the urine. Blood analysis included: Albumin, Blood Urea, Creatinine, CRP and NGAL. Rats were killed and histopathologically analyzed. Tissue samples were fixed with 10% formalin and stained with H&E, Kongo Red stains. Statistics were done by Kruskal Wallis test.

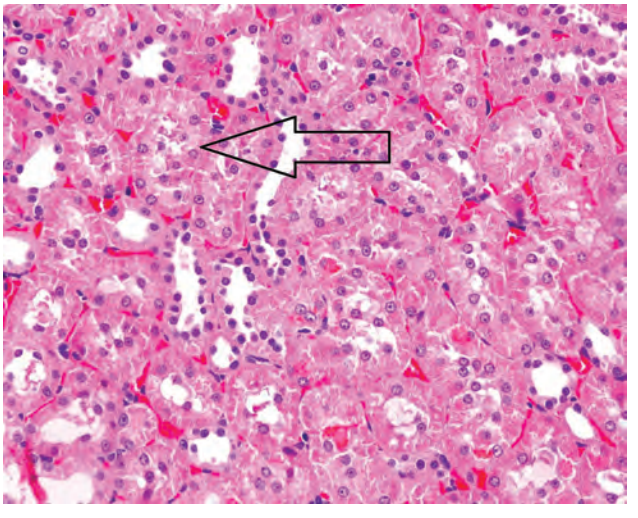
Results: Results are shown in Table 1. Histopathological examination shows congestion and tubular damage on HP-RT, A-RT, and HP-S groups. There was no sclerosis or glomerular damage present in any of the groups.

Conclusions: Whey protein intake created a dose-response in causing significant microalbuminuria and tubular destruction in our study. This supports the suggestion that long-term intakes of protein at the upper limits from whole protein sources may compromise renal health.

Funding: Clinical Revenue Support

Table 1

	Blood Albumin (g/dl)			Blood Urea (mg/dl)			Creatinine (mg/dl)			CRP (mg/dl)			NGAL (pg/ml)			Urinary Urea (mg/dl)			Microalbuminuria (mg/dl)			Urinary pH		
	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value	Day 1	Day 90	p value
NP-S	3.03 ± 0.09	3.15 ± 0.12	p=0.195	80.00 ± 5.51	86.5 ± 8.03	p>0.05	0.46 ± 0.02	0.50 ± 0.03	p>0.05	0.18 ± 0.04	0.15 ± 0.03	p>0.05	508.73 ± 117.62	298.6 ± 71.5	p<0.05	4096.25 ± 424.67	7752 ± 1789	p=0.05	12.64 ± 4.71	17.11 ± 6.5	p<0.05	6.75 ± 0.71	7.09 ± 0.32	p>0.05
NP-RT	3.05 ± 0.15	2.93 ± 0.12	p>0.05	83.625 ± 3.93	97.10 ± 2.36	p<0.05	0.49875 ± 0.02	0.57 ± 0.02	p>0.05	1.98 ± 0.66	2.14 ± 0.67	p>0.05	238.13 ± 154.29	266.2 ± 160.18	p>0.05	8317.50 ± 740.54	7542 ± 6.39	p=0.05	18.86 ± 9.51	28.12 ± 17.8	p<0.05	7.38 ± 0.99	8.19 ± 0.37	p>0.05
HP-S	3.04 ± 0.05	2.65 ± 0.20	p<0.05	79.88 ± 8.16	41.3 ± 6.39	p<0.05	0.41 ± 0.03	0.26 ± 0.03	p<0.05	0.80 ± 0.90	0.77 ± 0.09	p>0.05	186.56 ± 98.14	453.6 ± 262.9	p>0.05	9547.50 ± 1274.58	9829 ± 323	p>0.05	14.89 ± 3.33	20.43 ± 0.31	p<0.05	6.69 ± 0.53	7.88 ± 0.74	p>0.05
HP-RT	2.98 ± 0.09	2.87 ± 0.13	p>0.05	86.5 ± 7.86	57.5 ± 1.93	p<0.05	0.44 ± 0.02	0.53 ± 0.03	p<0.05	1.03 ± 0.71	1.87 ± 0.68	p>0.05	175.63 ± 55.95	536.3 ± 725.1	p>0.05	10255.00 ± 759.49	10490 ± 602	p>0.05	30.93 ± 9.08	37.6 ± 10.5	p<0.05	7.75 ± 0.85	8.0 ± 0.46	p>0.05
A-S	2.90 ± 0.12	2.99 ± 0.04	p>0.05	91.88 ± 9.01	58.0 ± 7.91	p<0.05	0.43 ± 0.02	0.56 ± 0.02	p<0.05	1.23 ± 0.54	1.40 ± 0.52	p>0.05	388.9 ± 141.8	980.86 ± 224.42	p>0.05	5958.75 ± 981.70	9351 ± 866	p=0.05	19.81 ± 7.94	57.8 ± 60.09	p<0.05	7.06 ± 0.56	8.13 ± 0.73	p>0.05
A-RT	3.09 ± 0.10	2.65 ± 0.12	p<0.05	100.38 ± 10.64	62.0 ± 8.52	p<0.05	0.44 ± 0.02	0.58 ± 0.06	p<0.05	1.76 ± 0.92	1.88 ± 0.67	p>0.05	276.3 ± 183.06	199.7 ± 26.11	p>0.05	11228.75 ± 1051.68	9675 ± 1059	p=0.05	29.03 ± 5.29	28.9 ± 4.1	p>0.05	7.38 ± 0.59	7.69 ± 0.65	p>0.05



A-RT rat with tubular desquamation.

TH-PO610

The Effects of Whey Protein Intake on Bone Mineral Metabolism in Rats

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Background: High protein intake affects the blood and urine phosphate levels. Phosphate is shown to be correlated with FGF-23. The aim of the study is to investigate the the effects of Whey Protein intake on the whole cascade of bone mineral metabolism.

Methods: 48 young male albino wistar rats are divided into 6 (n=8); Normal (20%) Protein(NP)-Sedentary(NPS), NP-Resistance training(NPRT), High(45%)Protein(HP) Sedentary(HPS), HP-Resistance Training(HPRT), Abuse(70% Protein)(A)-Sedentary(AS), and Abuse-Resistance Training(ART) groups. The rats were fed ad libitum. Training was maintained by resistance protocol in a motorised treadmill. On days 1,30, 60 and 90 a 12 hour urine sample and a blood samples were collected from each animal. Calcium, phospate were detected in the urine. The blood analysis included: LDH, Albumin, calcium, phosphate. FGF-23 and vit-D was analysed by ELISA.

Results: Results are shown in Table1.

Conclusions: Whey Protein intake negatively affected the the bone mineral metabolism and created a dose-response while training has an alleviating positive effect. Serum, urine phosphate and FGF-23 were shown to be significantly correlated and supports such studies.

Funding: Clinical Revenue Support

Table1

		Normal Whey Protein				High Whey Protein				Abuse Whey Protein				p values		
		Sedentary		Exercise		Sedentary		Exercise		Sedentary		Exercise		Diet Effect	Training Effect	Dose Effect
	Days	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Serum Albumin (mg/dl)	30	3.63	0.46	3.46	0.92	3.57	0.16	3.39	0.07	3.56	0.12	3.31	0.64	p<0.05	p<0.05	p>0.05
	60	3.24	0.15	3.44	0.92	3.13	0.07	3.41	0.64	3.15	0.12	3.23	0.11	p<0.05	p<0.05	p>0.05
	90	3.10	0.12	2.90	0.12	2.60	0.20	2.88	0.13	2.99	0.35	2.65	0.12	p<0.05	p<0.05	p>0.05
Serum LDH (U/L)	30	858.25	273.95	963.38	200.61	1019.14	209.61	1348.29	267.75	1586.25	213.35	1717.88	551.35	p>0.05	p>0.05	p>0.05
	60	1466.38	248.73	1021.25	331.64	1358.50	419.08	1195.13	196.6	1472.13	387.00	1471.75	416.49	p>0.05	p>0.05	p>0.05
	90	2561.00	319.02	711.13	338.30	2108.50	484.40	732.50	278.59	1897.63	181.05	1462.75	564.04	p>0.05	p>0.05	p>0.05
Serum Calcium (mg/dl)	30	10.85	0.30	10.66	0.32	11.08	0.26	10.66	0.15	10.96	0.24	10.93	0.39	p>0.05	p>0.05	p>0.05
	60	10.38	0.30	10.28	0.25	10.08	0.27	10.28	0.16	10.44	0.29	10.26	0.27	p>0.05	p>0.05	p>0.05
	90	10.18	0.31	9.93	0.13	9.84	0.13	10.23	0.74	10.01	0.10	10.64	0.71	p>0.05	p>0.05	p>0.05
Serum Phosphate (mg/dl)	30	6.68	0.35	5.76	0.31	6.01	0.64	5.31	0.48	5.86	0.49	5.31	0.47	p<0.05	p<0.05	p>0.05
	60	5.61	0.60	5.49	0.29	4.79	0.85	6.03	0.42	5.15	0.34	5.91	0.35	p<0.05	p<0.05	p>0.05
	90	8.89	1.42	6.20	0.84	8.62	0.82	7.21	1.54	7.02	0.63	7.24	0.74	p>0.05	p<0.05	p>0.05
FGF-23 (mg/dl)	30	720.43	134.30	626.00	153.76	711.97	155.49	647.38	198.23	692.77	272.55	754.80	171.91	p>0.05	p>0.05	p>0.05
	60	773.29	135.32	857.89	134.12	750.39	181.18	818.26	288.27	850.83	83.66	891.77	60.14	p>0.05	p>0.05	p>0.05
	90	913.90	74.73	636.31	203.60	942.23	73.09	889.61	93.74	865.88	136.73	806.95	120.85	p>0.05	p<0.05	p>0.05
Vitamin D (picogram/dl)	30	4.35	0.90	4.19	0.76	4.14	1.56	5.29	1.69	4.28	0.94	5.91	1.63	p<0.05	p<0.05	p>0.05
	60	4.07	1.90	4.27	0.90	2.95	0.38	5.89	1.50	3.53	0.92	6.16	2.82	p>0.05	p<0.05	p>0.05
	90	7.17	4.66	7.51	2.77	6.73	3.15	5.97	2.42	8.78	2.89	11.50	3.50	p>0.05	p>0.05	p>0.05
Urine Phosphate	30	80.64	35.13	137.25	42.80	38.14	24.98	55.68	14.44	16.95	16.43	48.04	22.42	p>0.05	p>0.05	p>0.05
	60	75.88	40.80	88.20	35.03	47.56	29.70	48.80	25.78	66.71	32.50	55.80	34.90	p>0.05	p>0.05	p>0.05

TH-PO611

Monounsaturated Fatty Acids Protect Proximal Tubules from Lipotoxicity

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Background: A disrupted glomerular filtration barrier, such as in nephrotic syndrome, causes loss of serum albumin into the urine. As albumin is an important carrier of fatty acids (FAs), the increased exposure of the tubular nephron to FAs may contribute to disease progression. This is particularly the case for FAs such as palmitic acid (PA) as their saturated acyl chains are known to damage the endoplasmic reticulum (ER) and mitochondria. To cope with excess lipids, FAs can be esterified with glycerol and deposited as triglycerides in cytoplasmic lipid droplets (LD). Here, we addressed the question in how far lipid unsaturation promotes lipid storage and thereby prevents lipotoxicity in proximal tubular cells.

Methods: *in vitro* experiments with PA and oleic acid (OA) were performed on iREC (induced renal tubular epithelial cells) and HK-2 cells. The inducible conditional knockout mouse of *Nphs2* was used as an *in vivo* model of nephrotic syndrome. Mice were maintained on MUFA (monounsaturated fatty acids) or SFA (saturated fatty acids) diets two weeks before Cre induction until death.

Results: To mimic the overexposure of proximal tubules to albumin that takes place during nephrotic syndrome, iRECs were treated with different doses of albumin-FAs. While the treatment with PA-BSA resulted in the upregulation of ER stress markers and decreased cell survival, the additional treatment with OA-BSA completely rescued the phenotypes. To assess the capacity of OA to sequester saturated FAs into LDs, we analyzed lipid droplet formation. In contrast to PA, OA increased LD formation, which occurred in a DGAT1/2 dependent manner. Moreover, lipid trafficking studies with the fluorescent analog of a saturated fatty acid BODIPY-C12 showed that co-treatment with OA shifted BODIPY-C12 from the ER into LDs. Finally, our preliminary *in vivo* data suggest that Nphs2 KO mice live longer with MUFA diet compared to SFA diet.

Conclusions: Collectively, our work shows that OA protects renal tubular cells from lipotoxicity by channeling PA into LDs. Our findings suggest that promotion of unsaturation and, thereby, lipid storage can improve the homeostasis of PTs during nephrotic syndrome and, thus, ameliorate the progression of the disease.

Funding: Private Foundation Support

TH-PO612

GCN5-Like Protein 1 Controls Lipotoxicity in Proximal Tubule Cells by Regulating Fatty Acid Oxidation via Mitochondrial Enzyme Acetylation

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Background: Lipotoxicity termed as the accumulation of satuarated nonesterified fatty acid (NEFA) and their metabolites playS a vital role during the progression of chronic kidney disease (CKD). NEFA catabolism is mainly through the b-oxidation in mitochondria. Due to a high energy demand and relatively little glycolytic capacity, fatty acid oxidation (FAO) is particularly important for the proximal tubule cells. However, the upstream mechanisms remain unclear. Lysine acetylation is a reversible post-translational modification, and is particularly important in the regulation of mitochondrial metabolic enzymes. However, the effects of acetylation status on the NEFA b-oxidation and lipotoxicity in the proximal tubule cells remains unclear. In this study, we aimed to investigate how FAO rate in the tubule cells is controlled by mitochondrial acetylation status and how these changes affect lipotoxicity.

Methods: Human proximal tubular epithelial cells (HK-2) were stimulated with palmitic acid (PA) and C57BL/6 mice were received a high-fat diet (HFD) for 18 weeks. The expression of acetylated-lysine and GCN5-like Protein 1 (GCN5L1) were detected by both immunohistochemistry and western blot. The immunoprecipitation assay was used to evaluate the acetylation levels of long-chain acyl-CoA dehydrogenases (LCAD) and 3-hydroxyacyl-CoA dehydrogenase (β-HAD). Fatty acid β-oxidation rate, triglyceride content, ac-CoA, and the activity of LCAD and β-HAD were assessed by appropriate kits.

Results: The expression of total lysine acetylation was increased in palmictic acid (PA) cultured HK-2 cells and high-fat feeding mice kidneys. PA induced LCAD and β-HAD hyperacetylation and reduced enzymatic activity along with decreased fatty acid oxidation rate and ac-CoA contents. Interestingly, GCN5L1 was upregulated in vivo and vitro high fat conditions. Finally, the silence of GCN5L1 in HK-2 cells led to the deacetylation of LCAD and β-HAD and accelerated FAO rate, which eventually attenuated lipid deposition.

Conclusions: The acetylation of mitochondrial proteins supressed FAO in renal proximal tubule cells. GCN5L1 suppression attenuates lipotoxicity by upregulating FAO via reversible mitochondrial enzyme LCAD and β-HAD acetylation. The manipulation of acetylation status might act as a promising therapeutic intervention for lipotoxicity in CKD.

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TH-PO613

Effect of Exogenous Supplementation with Alpha Lipoic Acid on Nuclear Reduced Glutathione Levels in Rat Kidney Cortex and Medulla

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Background: Dietary supplementation with the antioxidant alpha lipoic acid has been found to increase reduced glutathione (GSH) levels in mitochondria from kidney and heart tissue in old rats. GSH is the major antioxidant inside cells and provides protection against damage by free radicals produced as a consequence of oxidative metabolism. The purpose of this study was to investigate the effect of dietary supplementation with alpha lipoic acid on GSH levels in the nucleus of rat kidney cells.

Methods: Old female Experimental Lewis rats (22 months of age; n = 4) received alpha lipoic acid (100 mg/Kg of body wt) via i.p. injection for one week. Age-matched Control rats (n = 4) did not receive any supplementation. The kidneys were harvested from anesthetized rats and the cortex and medulla were separated and homogenized. The nuclear fractions were isolated using differential centrifugation. The GSH and total glutathione (Tot GLUT; GSH plus oxidized GSH) were measured using a spectrophotometric assay. GSSG (oxidized GSH) levels were estimated from the difference between Tot GLUT and GSH levels and then divided by 2. Comparisons were done using a Student' s T Test.

Results: There were significant increases in GSH and Tot GLUT levels in both the kidney cortex and medulla with dietary supplementation.

Conclusions: These findings suggest that dietary supplementation with alpha lipoic acid may also be beneficial to cell nuclei in rat kidney by increasing the GSH levels and thus, providing protection against free radical damage.

Effect of Alpha Lipoic Acid on Nuclear GSH Levels in the Rat Kidney

	GSH - nmol/ g kid wet wt		GSSG - nmol/ g kid wet wt		Tot GLUT - nmol/ g kid wet wt	
	Control	Experimental	Control	Experimental	Control	Experimental
Cortex	112 ± 17	245 ± 44 *	2.1 ± 0.2	5.5 ± 1.5	116 ± 16	258 ± 41 *
Medulla	99 ± 10	219 ± 42 *	2.9 ± 0.5	11.7 ± 5.6	105 ± 9	310 ± 50 *

All data shown as X +/- SEM; * Significantly different from Control at $p < 0.05$

TH-PO614

Inhibiting Na/K-ATPase Oxidant Amplification Loop Regulates Aging in C57B16 Old Mice

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Background: Aging is driven by accumulation of oxidative damage; Na/K-ATPase signaling amplifies oxidants and is linked to several oxidation-related diseases. The progressive decline of physiological integrity, manifests as: loss of cell division, oxidative stress, DNA damage and overexpression of senescence genes. Oxidant stress causes cellular and DNA damage contributing to impaired physiological function, disease development, and life span reduction. As we identified, the Na/K-ATPase amplifies oxidant signaling and we speculate that a peptide inhibiting this pathway, pNaKtide, may be effective to regulate cellular senescence, thus delaying and/or reversing aging by attenuating oxidative stress.

Methods: Using human fibroblasts we evaluated levels of senescence markers, cell injury, apoptosis, and Na/K-ATPase signaling activation, with and without pNaKtide. C57Bl6 male mice, young (4 months) and old (17 months) were fed normal chow diet or Western Diet (WD). They were randomly divided into 6 groups: (1) Young Control, (2) Young+pNaKtide (3) Old+Control, (4) Old+pNaKtide (5) Old+WD, (6) Old+WD+pNaKtide. After 8 weeks of control or WD diet, groups 2, 4 and 6 were injected with pNaKtide, (intraperitoneal dose of 25-mg/kg, every 7 days for 8 weeks). Tissues from liver, kidney, and heart were evaluated markers of aging and Na/K-ATPase signaling activation.

Results: Fibroblasts exposed to oxidative stress underwent oxidation-induced senescence and had increased levels of senescence markers, cell injury, apoptosis, and

Na/K-ATPase signaling activation. Treatment with pNaKtide significantly reversed those levels. Levels of aging markers and oxidant stress in old mice were higher than those of young mice. Among cardiac and adipose tissues, senescence, apoptosis and oxidant stress were exacerbated in old mice and even more so when fed WD. pNaKtide treatment significantly reversed levels of aging markers in old mice regardless of diet.

Conclusions: These data show that Na/K-ATPase signaling is intimately involved in the aging process and may serve as a target for anti-aging interventions. pNaKtide inhibited amplification of the oxidant signalling via blocking the Na/K-ATPase pump thus alleviating genetic and phenotypic attributes of aging. pNaKtide holds potential as a novel drug for treating cellular damage that contributes to manifestations of aging and WD.

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TH-PO615

Effects of Gemfibrozil on Fatty Acid Induced Insulin Resistance in Adipocytes

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Background: Hyperlipidemia, specifically hypertriglyceridemia has been incriminated in contributing to insulin resistance in diabetes. However it is unclear if correcting hypertriglyceriemia improves insulin sensitivity and prevent diabetes in the context of metabolic syndrome. We hypothesized that reduction of lipid uptake by adipocytes using gemfibrozil would improve insulin signaling and facilitate glucose transport.

Methods: Mouse 3T3-L1 preadipocytes were differentiated into adipocytes by commercial differentiation cocktail and were stimulated with fatty acids 1 mM of palmitate (C16:0), oleate (C18:1), and linoleate (C18:2) for 24 hrs on 8th day of differentiation. The fatty acid treated adipocytes were labeled as obese while the fatty acid untreated cells were labelled as lean. The obese cells were further treated with Gemfibrozil (10 μM, 25 μM, 50 μM and 100 μM) for 72 hrs. Triglyceride assay and Oil red O staining were performed to determine lipid droplet accumulation. Cell lysates were used to study expression of insulin signaling proteins by western blot analysis. For determining the expression of GLUT4, membrane fraction was separated from the cytosolic fraction.

Results: Upon incubation with fatty acid mixture, the lipid content in adipocytes significantly increased (obese cells) compared to untreated cells (lean cells). Gemfibrozil treatment decreased triglyceride content in the obese cells in a dose dependent manner with a significant change even at the lowest concentration of 25 μM. This data was further supported by reduction in lipid droplet accumulation in the obese cells as observed by Oil Red O staining. Western blot data revealed that gemfibrozil at 25 μM decreased IRS-1 phosphorylation at Ser 307 which is significantly increased in obesity and insulin resistance. Gemfibrozil also increased Akt phosphorylation which was decreased in the obese cells. GLUT 4 expression in whole cell lysate remain unchanged but increased in the membrane fraction of treated obese cells. Moreover investigation of upstream signaling showed that gemfibrozil reduced phosphorylation of IKK-β but not JNK.

Conclusions: We conclude that Gemfibrozil reversed insulin resistance in obese adipocytes by modulating phosphorylation of IRS-1, Akt and IKK-β and thereby facilitated insulin signaling.These observations may have implications for prevention and treatment of diabtetes in metabolic syndrome.

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TH-PO616

ATP-Citrate Lyase Is an Epigenetic Regulator to Promote Renal Injury in Metabolic Syndrome

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Background: Metabolic syndrome, characterized by obesity and type 2 diabetes, is a leading cause of chronic kidney disease. Obesity-related renal injury, characterized by ectopic lipid accumulation in the kidney, has increased dramatically in recent years. Hyperglycemia and hyperlipidemia, key features of metabolic syndrome, drive excess nutrient flows into kidney cells; as a result, enhanced cell metabolism increases intracellular acetyl-CoA concentration, which provides the substrate for de novo lipid synthesis as well as for histone acetylation. Here we tested the hypothesis that ATP-citrate lyase (Acly), an enzyme that converts citrate to acetyl-CoA, functions as an epigenetic regulator of renal injury by promoting ectopic lipid synthesis and histone acetylation.

Methods: Acly, lipogenic and fibrogenic genes in the kidney of ob/ob BTBR mice and mesangial cells were quantified by qRT-PCR and Western blotting. Kidney sections were analyzed by H&E, PAS and oil red O staining. Histone acetylation in gene promoters was assessed by ChIP assays.

Results: Ob/ob BTBR mice developed glomerulomegaly, glomerulosclerosis and ectopic lipid accumulation in the kidney compared with ob/+ controls, accompanied by increases in total lipids, triglyceride and cholesterol contents in the renal cortex. Acly, lipogenic (ACC, FAS, HMGCR) and fibrogenic (TGF-β1, FN) genes were markedly up-regulated in the kidney of ob/ob BTBR mice, so was histone acetylation at the H3K9/14 and H3K27 sites. Inhibition of Acly activity by SB-204990 not only blocked histone acetylation but also suppressed the expression of the lipogenic and fibrogenic genes in the ob/ob BTBR kidneys. ChIP assays confirmed that these gene promoters were hyperacetylated at the H3K9/14 and H3K27 sites. Exposing mesangial cells to a combination of high glucose, sodium palmitate and TNF-α synergistically stimulated Acly expression and enzymatic activity, increased H3K4/19 and H3K27 acetylation, up-regulated the lipogenic and fibrogenic genes and promoted histone acetylation in these gene promoters. Blockage of Acly by SB-204990 or siRNA attenuated these regulatory processes, whereas Acly overexpression enhanced these regulations.

Conclusions: These observations strongly suggest that Acly is a critical epigenetic regulator to promote renal injury via epigenetic mechanisms in obesity

TH-PO617

Investigating the Sex-Specific Progression of CKD: Sex Hormones and Sex of the Cell in Human Kidney Metabolism

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Background: Male sex predisposes to chronic kidney disease (CKD). We hypothesized that the effector androgen dihydrotestosterone (DHT) would induce key molecular alterations in human renal proximal tubular epithelial cells (PTECs). We quantified the proteome of DHT- vs. estradiol(EST)-treated PTECs, and uncovered androgen-induced perturbations in renal metabolism that may be directly responsible for the faster CKD progression in men. Our goal is to characterize sex- and sex hormone-specific alterations in the PTEC metabolic function, and relate them to hypertrophy, oxidative stress, and inflammation.

Methods: PTECs from 2 male vs. 2 female donors were stimulated with Control, DHT (100nM), or EST (100nM) for 16h or 24h. We employed a Seahorse analyzer to monitor glycolysis (as extracellular acidification rate, ECAR) and oxygen consumption rate (OCR). Changes in ECAR and OCR were related to the extracellular glucose levels, intracellular ATP, oxidative stress (O_2^-), apoptosis (phosphatidilserine, PS) and cell diameter (n=4-6/group). Secreted levels of 15 chemokines/cytokines were quantified through a Multiplex Bead-Based Assay.

Results: Male PTECs showed significantly increased ECAR and OCR, ATP-linked respiration, maximal glycolitic and respiratory capacity, O_2^- and PS levels than female PTECs. In male PTECs, ECAR was increased after DHT stimulation, whereas OCR was increased by DHT and EST at baseline and in response to mitochondrial stress. In male PTECs, glucose concentration in the media was reduced by DHT treatment and glucose reduction was prevented by androgen receptor inhibitors. In turn, ATP, O_2^-,PS levels, cell diameter and secretion of cytokines IL-6 and MCP1 were increased by DHT. DHT also augmented ATP levels in female PTECs. Interestingly, both DHT and EST increased ECAR and OCR in the PTECs from only one of the female donors.

Conclusions: DHT-induced proteome alterations are linked to a more glycolytic and oxidative phenotype in the human renal cell, and to higher glucose consumption, oxidative stress, apoptosis, IL-6/MCP1 secretion, and hypetrophy. Moreover, the metabolic function of PTECs and their susceptibility to sex hormones vary depending on the sex of the donor. Thus, not only hormonal but also (epi)genetic factors may contribute to a sex dimorphism in human renal metabolism.

TH-PO618

Renal Cortical Mitochondrial Dynamics and Elimination During the Normoalbuminuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the normoalbuminuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria (Clin Sci 124:543-52, 2013). Because accumulation of damaged mitochondria can contribute to renal dysfunction, we aimed to determine if oxidative stress in DM triggers renal cortical mitochondrial fission, fusion and elimination through mitochondria-selective autophagy (mitophagy).

Methods: Rats receiving i.p. injection of streptozotocin (STZ, 65 mg/kg) or vehicle (Sham) were either left untreated or treated with telmisartan (TLM, an angiotensin receptor blocker; 10 mg/kg/d). Two weeks later, blood glucose concentration (BG), blood pressure (BP), glomerular filtration rate (GFR), and urinary excretion of albumin and *N*-acetyl-β-D-glucosaminidase (NAG) were measured. Renal cortical 3-nitrotyrosine (3-NT; an oxidative stress marker) was detected by HPLC. Fission-, fusion-, and mitophagy-related proteins were quantified in renal cortical homogenates by Western blot and localized by immunohistochemistry.

Results: STZ rats displayed hyperglycemia that was unaffected by TLM. BP, albumin excretion, and NAG excretion were similar in all groups. Compared with Sham rats, GFR and renal cortical 3-NT levels were increased in STZ rats, and both changes were prevented by TLM. Renal cortex from STZ rats displayed TLM-sensitive increases in the mitophagy-related proteins LC3-II and PINK1 (all $P<0.05$). Renal cortical Drp1 levels were 3-fold higher in STZ than in Sham rats, with STZ+TLM rats exhibiting intermediate levels of this fission marker. In contrast, levels of the fusion marker Mfn2, and mitophagy-related proteins BNIP3 (dimer) and p62 levels did not differ among groups. Immunohistochemical staining confirmed that the mitophagy-related proteins in STZ were located at renal tubular sites.

Conclusions: These data suggest that fission, but not fusion, of renal cortical damaged mitochondria is enhanced by in DM. TLM-sensitive accumulation of PINK 1 and LC3-II the tubular epithelium during DM suggests that oxidative stress activates the PINK1-parkin pathway, in which PINK1 binding to LC3-II (an established marker for autophagosome formation) results in mitochondrial elimination via autophagy.

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TH-PO619

Preliminary Analyses on Dietary Inflammatory Index Among Participants in the Palm Tocotrienols in Chronic Hemodialysis (PATCH, USA) Study

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Background: Inflammation is a predictor of mortality in hemodialysis (HD) patients. The dietary inflammatory index (DII) assesses the potential effect of diet on systemic inflammation. The aim of this preliminary analysis was to evaluate the use of DII and examine the associations between DII, diet composition and key anthropometry.

Methods: Dietary 24 hr recalls were collected at baseline from HD patients participating in the PATCH clinical trial (NCT02358967), an ongoing one year double-blind intervention (300 mg tocotrienols or placebo, daily) which includes quarterly anthropometric measures. Data was analyzed using Food Processor ESHA Research. After accounting for under reporters, the DII score was calculated from 85 patients (Age 62 ± 12 yrs., 67% men, 95% African American). Handgrip strength (HGS) was measured using a Jamar dynamometer for 48 of the subjects. A z-score transformation was applied to mean baseline HGS scores using normative grip strength data and these standard scores were compared with clinical and demographic characteristics collected from medical records.

Results: DII showed a significant positive correlation with percent calories from saturated fatty acids (r = 0.38) and significant negative correlations with dietary monounsaturated (r = -0.38) and polyunsaturated fatty acids (r = -0.37), vitamin E tocopherol (r = -0.69), the vitamin E to linoleic acid ratio (r = -0.23), and the phosphorus to protein ratio (r=-0.43). When subjects were divided into tertiles based on DII score, significant decreasing trends were observed for HGS and significant increasing trends for serum phosphorus. Weaker grip strengths were significantly and positively correlated with serum ferritin levels between 800 and 1200 ng/ml for a sub-set of the population (n = 18; r = -0.54).

Conclusions: Inflammation may be implicated in CKD induced muscle loss. The restrictive nature of the renal diet, though controlling serum phosphorus, was proinflammatory for this study group. Thus, DII may be a useful tool for exploring the role of specific dietary fatty acids and antioxidants to the contribution of inflammation in the African American HD population. (Supported by the Malaysian Palm Oil Board, Government of Malaysia)

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TH-PO620

Impact of the Gene Encoding Canonical Transient Receptor Potential 1 Channel (TRPC1) on Glucose Intolerance and Liver Steatosis Is Condition-Specific: Role of Hyperphagia, Obesity, and High Fat Diet (HFD)

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Background: We recently noted spontaneous development of metabolic syndrome (MetS) in TRPC1 null mice vs wild type (wt). We now studied the impact of gene dosage, role of adipokines, & responses to a HFD (45%) vs. normal (N) (10-13%) FD x 4 m.

Methods: We did metabolic studies in ♂ littermates of all 3 genotypes, using standard chemical techniques & ELISA for insulin, leptin, & adiponectin

Results: On normal chow, from 4th-5th to 30th week, null mice ate & weighed more than +/- & wt. After 30 weeks, intake & weight gains in null became similar to +/- & wt. At 2 m, null mice had hyperglycemia & hypercholesterolemia. Their livers were 36% heavier & triglyceride content (TGC) 47% higher. Liver echogenicity was elevated by 50-150 % at 7, 11, & 22 m, corroborated by 140% higher liver TGC. At 12 m, only null mice had hyperlipidemia (30% higher blood total cholesterol, 60% higher LDL, & 200% higher TG). In +/- & wt, blood lipids, liver density at 12 & 19 m, & liver TGC at 19 m were all normal. Fasting glucose was elevated only in null (up 20% at 1 m, 23% at 3.5 m & 13% at 15.5 m). Thus on a normal diet, 1 TRPC1 gene allele could prevent hyperphagia, obesity, MetS & hepatic steatosis. As expected, HFD vs. NFD stimulated leptin & insulin, comparably in all 3 genotypes, without affecting adiponectin or weight gains. Contrary to a normal diet, HFD increased liver density in +/- & wt, but unexpectedly & inexplicably, not in null. On NFD, HOMA-IR was similar among all 3 genotypes, but HFD induced the highest HOMA-IR in wt (3.1 vs 1.3 in +/-) & the largest liver TGC hike in wt (3.3 x vs 2 x in +/- vs 1.6 x in null). During glucose tolerance test, the area under the curve for plasma glucose vs time was again paradoxically the highest in wt vs null.

Conclusions: We conclude: 1. Normally, TRPC1 helps maintain glucose & lipid homeostasis, presumably by preventing hyperphagia & obesity seen in diploid deficiency, which renders hypothalamic neurons relatively resistant to anorexigenic effects of lepin. 2. When stressed by a HFD, the wt TRPC1 gene dose-dependently predisposes the mice to glucose intolerance & steatosis. 3. Mechanisms for these diverse effects are unknown but unrelated to changes in insulin, leptin or adiponectin.

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TH-PO621

Daily Oscillation of the Plasma Inorganic Phosphate Concentration: Impact of Nampt Deficient Mice

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Background: Circulating inorganic phosphate (Pi) exhibits a remarkable daily oscillation based on food intake. In humans and rodents, the daily oscillation in response to food intake may be coordinated to control the intestinal absorption, renal excretion, cellular shifts, and extracellular concentration of Pi. Hyperphosphatemia is linked to vascular calcification with chronic kidney disease (CKD) and is an independent risk factor for cardiovascular mortality in hemodialysis patients. Despite the circadian variations, it is the fasting morning serum Pi concentration that is linked to cardiovascular events and mortality in most epidemiologic studies. However, mechanisms regulating the resulting oscillation are unknown. Here we investigated the roles of the sodium Pi cotransporter SLC34 (Npt2) family and nicotinamide phosphoribosyltransferase (Nampt) in the daily oscillation of plasma Pi levels.

Methods: We used $Npt2^{-/-}$ mice, liver-specific $Nampt^{-/-}$ and $Nampt^{+/-}$ mice to reveal the mechanisms of daily oscillation of the plasma Pi concentration.

Results: The daily oscillation of the plasma Pi concentration is roughly linked to urinary Pi excretion. The expression of renal Npt2a and Npt2c, and intestinal Npt2b proteins also exhibit a dynamic daily oscillation. Analyses of $Npt2a^{-/-}$ and $Npt2c^{-/-}$ revealed the importance of renal Pi reabsorption and cellular Pi shifts in the daily oscillation. In $Npt2a^{+/+}$ and $Npt2a^{-/-}$, fasting significantly increases plasma Pi concentration and disappeared completely daily oscillation compared with the feeding group. The administration of nicotinamide (vitamin B3) and a specific Nampt inhibitor (FK866) in the active and rest phases revealed that the Nampt/NAD system is involved in renal Pi excretion. Additionally, for cellular shifts, liver-specific Nampt deletion disturbed the daily oscillation of plasma Pi during the rest but not the active phase. In systemic $Nampt^{+/-}$ mice, NAD levels were significantly reduced in the liver, kidney, and intestine, and the daily oscillation of the plasma Pi concentration was attenuated.

Conclusions: The findings of the present study suggest that the Nampt/NAD^+ system, together with the kidney and soft tissues, plays an important role in generating the daily oscillation of plasma Pi levels. It may enhance our understanding of the changes in plasma Pi levels in CKD patients.

TH-PO622

Microbiota Dysbiosis Contributes to Liver Injury in Apolipoprotein Knockout Mice Through the Disruption of Cholesterol Homeostasis

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Background: Our previous studies demonstrated that cholesterol accumulation in liver contributes to the progression of nonalcoholic fatty liver disease (NAFLD). The exact mechanisms of this process have not been completely explained. This study aimed to investigate the effects of gut microbiota on cholesterol homeostasis of liver in NAFLD.

Methods: Broad-spectrum antibiotics were used to eliminate gut microbiota in high-fat diet (HFD) induced apolipoprotein E knockout mice. Feces were collected and proportions of microbiota were analyzed by 16S rRNA gene sequencing. Serum lipids were examined by automatic analyzer. Cholesterol accumulation in liver was detected by Oil red O staining, Filipin staining, and intracellular free cholesterol quantitative assay. The expressions of molecules involved in cholesterol homeostasis were measured by immunohistochemical staining and Western blotting.

Results: As demonstrated by 16S rRNA gene sequencing,the abundance of *Desulfovibrio* was significantly increased in HFD mice while the abundance of *Bacteroidetes, Ruminococcaceae,* and *Lactobacillus* decreased when compared with the control. Antibiotics treatment effectively depleted gut microbiota in HFD mice. Interestingly, depletion of gut microbiota significantly decreased total cholesterol(TC) and low density lipoprotein(LDL) in the plasma and lipid accumulation in livers of HFD fed mice. Immunohistochemical staining and Western blotting further demonstrated that the expressions of LDL receptor (LDLR) and 3-hydroxy-3-methyl-glutaryl-CoA reductase(HMGR) were downregulated in antibiotics delpleted HFD fed mice.

Conclusions: Our findings demonstrated that gut microbiota dysbiosis may be responsible for the liver injury in NAFLD by disrupting cholesterol homeostasis. This study provides more evidence for that modification of gut microbita dysbiosis is suggested to be a potential target for NAFLD therapy.

TH-PO623

Arginine Bioavailability Correlates with Cardiac Remodeling in Mice with CKD

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Background: Nitric oxide (NO) is critical for vascular homeostasis. Arginine (Arg), the sole nitrogen donor for NO synthesis, is the common substrate for NO synthase & arginase

enzymes (Fig 1). Global arginine bioavailability ratio (GABR) has been proposed to reflect substrate availability for NO synthesis by accounting for Arg concentration relative to its catabolic products ornithine (Orn) & citrulline (Cit). Low GABR has been associated with increased mortality in adults with heart failure & coronary artery disease. This study aimed to determine the relationship between GABR & measures of cardiac structure & function in mice with CKD.

Methods: CKD was established in male 129X1/SvJ mice via 2-stage partial nephrectomy. Plasma was collected at 8 & 16 wks post surgery & Arg, Orn & Cit were measured by LC/MS/MS. GABR was calculated as [Arg]/([Orn]+[Cit]). Echos were performed at 8 & 16 wks. Relative wall thickness (RWT) was calculated using M-mode parasternal long-axis measurements (IVS;d+LVPW;d)/LVID;d & myocardial performance index (MPI) as (IVCT+IVRT/ET) on trans-mitral Doppler. In a separate experiment, CKD mice received diet supplemented with Arg or alanine (nitrogen control) for 12 wks to determine effect on myocardial function.

Results: GABR was significantly reduced in mice with CKD compared to controls at both 8 wks [median (IQR) 0.56 (0.52-0.61) vs 0.74 (0.72-0.78); *p=0.01*] & 16 wks [0.41 (0.36-0.49) vs 0.64 (0.55-0.68); *p=0.03*]. There was a significant association between GABR & LVH (RWT; r=-0.39, p=0.02) & diastolic dysfunction (E/A ratio; r=0.37, p=0.04). At 12 wks, CKD mice on Arg supplementation compared to mice on control diet showed improved LVH (RWT 0.47±0.08 vs 0.58±0.06; *p=0.01*) & MPI (0.81±0.12 vs 1.05±0.11; *p<0.01*).

Conclusions: GABR is decreased in mice with CKD & correlates with worsening structural (RWT) & functional (E/A ratio) cardiac changes. Interestingly, Arg supplementation improved LVH & MPI at 12 wks. Additional studies are underway to determine underlying etiology of reduced GABR in CKD.

Funding: NIDDK Support

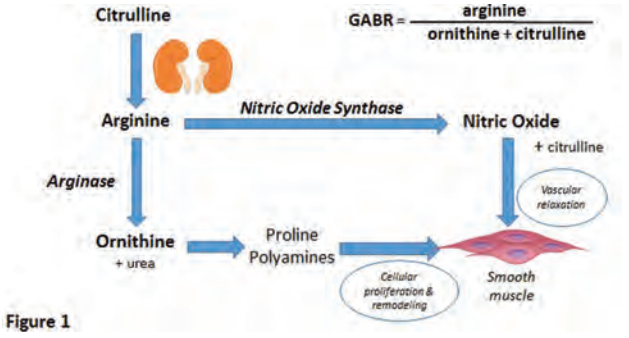

Figure 1

TH-PO624

Eliminating SIRPα Prevents Elevations in Blood Pressure, Suppresses Aldosterone and Cardiac Fibrosis in CKD

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Background: A major consequence of chronic kidney disease (CKD) is uremic cardiomyopathy characterized by cardiac dysfunction and fibrosis. Potential mechanism for the development of CKD-induced cardiomyopathy is increased aldosterone and impairment of intracellular insulin signaling (i.e., dephosphorylation of IRS1 and the insulin receptor) mediated by SIRPα. We reported that SIRPα is activated by inflammation and found that SIRPα is increased in cardiac muscles of mice with CKD. Here we examine the influences of SIRPα on systolic blood pressure (BP), aldosterone and cardiac fibrosis.

Methods: We used a global KO of SIRPα (SIRPα Mt) mice and compared them with wild type (WT) mice ± CKD (subtotal nephrectomy). At 8 weeks following CKD, we examined mice for cardiac fibrosis by picrosirius red staining plus systolic BP. To determine if over-expression of SIRPα, affects fibrosis directly we transfected myotubes with a plasmid expressing SIRPα vs. GFP. Finally, we immunoblotted myotubes to evaluate levels of SIRPα, αSMA, pSMAD3, and GAPDH.

Results: Systolic BP levels in WT mice with CKD was higher compared to values in WT control mice. These results mirror increases in aldosterone (2.3-fold higher) vs. WT control mice. Interestingly, SIRPα Mt control mice had lower systolic blood pressures; aldosterone levels were also significantly lower vs. WT control. Additionally, WT mice with CKD displayed 5.2-fold higher levels of aldosterone vs. SIRPα Mt with CKD. Next, we stained for fibrosis markers in WT CKD and SIRPα Mt mice with CKD. Picrosirius red staining revealed a significant reduction in cardiac fibrosis found in SIRPα Mt with CKD compared to values in WT mice with CKD. Myoblasts that had been transfected to overexpress SIRPα vs. GFP plasmids. We determined that fibrosis markers (i.e. αSMA) were significantly increased in myotubes overexpressing SIRPα. Finally, intracellular signaling of TGFß, pSmad3 was significantly stimulated.

Conclusions: Since cardiac fibroblasts express high affinity corticoid receptors for aldosterone, our results suggest that SIRPα contributes to the accumulation of collagen within the myocardial interstitium, leading to cardiac fibrosis and failure in CKD. Thus, suppression of SIRPα undoubtedly plays a critical role in blocking aldosterone secretion and elevations in systolic blood pressure to prevent cardiac fibrosis in CKD.

Funding: Veterans Affairs Support

TH-PO625

Voluntary Physical Activity Improves Physical Function and Disease Outcomes in a Rat Model of CKD

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Background: Chronic kidney disease (CKD) progression is associated with reduced muscle size, strength and overall mobility. Previous studies using exercise as an intervention for CKD have been inconclusive. We hypothesized that physical activity would attenuate musculoskeletal dysfunction and CKD-related outcomes.

Methods: Four groups of rats were used: 1) CKD, 2) CKD + voluntary wheel running, 3) Normal littermates (NL) and 4) NL with voluntary wheel running (N=12/gr). Wheels were freely accessible in animal cages. Data collection began at 25 weeks (~CKD stage 2-3) and ended at 35 weeks of age (~stage 5 CKD). Muscle strength (i.e. maximal voluntary grip), maximal aerobic capacity (VO2 max), were tested at 25 and 35 weeks; serum biochemistries were assessed at 35 weeks. Data was analyzed via one-way ANOVA with post-hoc comparisons.

Results: CKD rats performed the same average wheel distance/day and speed as NL animals indicating exercise tolerability. Wheel running had negligible effects in NL animals. In contrast, wheel running significantly improved multiple outcomes in CKD rats: 1) significantly reduced phosphorous, PTH and FGF23 (Table 1); 2) reduced kidney weight and left ventricular mass index (-12%, p<0.05; -8.5%, p<0.01, respectively); 3) reduced serum oxidative stress marker 8-OHdG by (-45%, p<0.05); 4) improved grip strength by 16% compared to 10% reduction in CKD alone (p<0.05); and 5) Increased time to fatigue (min) during VO2 testing (12.6 min, 8.5 min, p<0.001) but did not change maximal oxygen capacity.

Conclusions: In a progressive rat model of CKD, voluntary wheel running had significant improvement of the biochemistry, tissue weights, oxidative stress and physical function. The results suggest that physical activity may have beneficial effects in CKD.

Funding: NIDDK Support

Table 1. Biochemistry of CKD and CKD Wheel at 35 weeks of age

	BUN		Ca++		Phosphorous		PTH		FGF23	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CKD	44.4	7.8	9.45	1.5	6.1	1.1	803	539	3644	2757
CKD+Wheel	39.5*	5.4	8.17	1.8	5.2*	1.3	522*	197	1912*	1337

*p<0.05, CKD vs. CKD Wheel n=10-14 rats each group

*p<0.05, CKD vs. CKD Wheel n=10-14 rats each group

TH-PO626

Chondroitin Sulfate Supplement Alleviates Nephrocalcinosis in Hyperoxaluric Rats

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Background: Nephrocalcinosis and nephrolithiasis are common features of primary hyperoxaluria that contributes to end stage renal disease. We observed low urinary chondroitin sulfate (CS) and high hyaluronic acid (HA) excretion in hyperoxaluric nephrolithiasis patients and considered these were risks of nephrocalcinosis. This study aimed to investigate the effect of CS and HA supplement in hyperoxaluric rats.

Methods: Hyperoxaluric Wistar rats induced by ethylene glycol and vitamin D intraperitoneal injection was supplemented with CS (40 mg/kg/day) and/or HA (10 mg/kg/day). Urinary CS and HA excretion were measured. Histopathology of kidney tissue was reported.

Results: All hyperoxaluric rats developed moderate to severe nephrocalcinosis in 15 days. CS supplement entirely inhibited calcium deposition in renal tissue in all rats (p < 0.05). HA supplement had no effect on nephrocalcinosis formation, however, combination of CS and HA supplement can lessen the degree of nephrocalcinosis, but not as effective as giving CS alone.

Conclusions: CS supplement in hyperoxaluric patients could be beneficial in prevention of nephrocalcinosis. Besides, HA supplement might have detrimental effect in interrupt the CS activity.

Severity score of nephrocalcinosis in hyperoxaluric rats

Group	Nephrocalcinosis grade (Median, IQR)	Tubular obstruction	Tubulo-interstitial fibrosis
Control	0 (0)	0	0
Hyperoxaluria	4 (2-4)	0	0
CS supplement	0 (0)*	0	0
HA supplement	2.5 (1-4)	0	0
CS & HA supplement	0.5 (0-2)*	0	0

Nephrocalcinosis grading score: 0, no deposit; 1, 1-2 deposits/section; 2, 3-5 deposit/section; 3, 5-10 deposits/section; 4, >10 deposits/section. Tubular obstruction score: 0, no obstruction; 1, tubular obstruction present. Tubulo-interstitial fibrosis: 0, no fibrosis; 1, fibrosis present. *p < 0.05 compared with Hyperoxaluria group.

TH-PO627

An Oral Absorbent, Surface-Deacetylated Chitin Nano-Fiber Ameliorates Renal Injury and Oxidative Stress in 5/6 Nephrectomized Rats

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Background: We recently prepared surface-deacetylated chitin nanofibers (SDACNFs) by the mechanical treatment of the exoskeletons of crabs, followed by partial deacetylation of the amide groups on the surface of the resulting chitin nanofibers. SDACNFs have attracted considerable interest in medical fields, because of their various bioactivities. For example, SDACNFs were reported to suppress increases in body weight and serum leptin levels in a model of obesity that was induced by feeding a high fat diet. These results indicate that SDACNFs are work as potent functional foods that could be used in the treatment of various diseases.

Methods: The rats were divided into four groups as follows: (a) untreated nephrectomized group (N=5). The rats received only standard rat chow. (b), (c), and (d) deacetylated chitin powder (DAC), SDACNFs and AST-120 treated nephrectomized group, respectively. These rats received standard rat chow and the above samples at a daily dosage of 40 mg/kg of body wt for a period of 4 weeks, respectively (n=5). After 0 and 4 weeks of treatment, plasma samples obtained from each of the rats were immediately frozen and stored at -80 °C until used for analysis.

Results: An oral administration of low doses of SDACNFs (40 mg/kg/day) over a 4 week period resulted in a significant decrease in serum indoxyl sulfate (IS), creatinine and urea nitrogen levels, compared with a similar treatment with DAC or AST-120. The SDACNFs treatment also resulted in an increase in antioxidant potential, compared with that for DAC or AST-120. Immunohistochemical analyses also demonstrated that SDACNFs treated CRF rats showed a decrease in the amount of accumulated 8-OHdG compared with the CRF group.

Conclusions: The findings reported here indicate that a lower dose of SDACNFs than that of DAC has the potential to reduce the levels of uremic toxins (such as IS) that induce the production of free radicals in the intestinal tract, thereby inhibiting the subsequent occurrence of oxidative stress in the systemic circulation in CRF model rats. Thus, the removal of such substances from the systemic circulation could lead, not only to a reduction in oxidative stress, but also to the prevention of cardiovascular disease in CRF (Anraku et al., Carbohydrate Polymers, 2017).

TH-PO628

Xenogeneic Kidney Generation with Human Nephron Progenitor Cells in Zebrafish

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Background: Generating human stem cell-based tissue in animals may provide replacement human organs, establish novel disease models, and aid in drug development through toxicity screening and therapeutic testing. Human nephron progenitor cells (hNPCs) derived from human pluripotent stem cells (hPSCs) are attractive sources for human kidney generation in animals; however, techniques to replace host kidney tissue with hNPCs are yet to be developed. Here we employ transparent zebrafish (Casper) to enable real-time monitoring of xenotransplanted, fluorescent hNPCs and visualize human nephron formation.

Methods: hNPCs were differentiated from hPSCs by our previously established protocol. Cas9 mRNA and gRNAs targeting Lhx1a or Wt1b, essential transcriptional factors for kidney development in zebrafish, were injected into single cell stage embryos. Cell Tracker- or GFP-labeled hNPCs were transplanted to blastoderm stage embryos and nephrogenesis visualized overtime. Nephrons were evaluated by qPCR with human-specific primers and immunostaining for human solute transporters and segment-specific proteins.

Results: Zebrafish with targeted disruption of either Lhx1a or Wt1b died by 24 days post treatment (dpt), while transplantation of hNPCs rescued 14.5% of similarly treated zebrafish ($p<0.00001$). All zebrafish that underwent gRNA treatment exhibited renal insufficiency with evidence of edema at 3 dpt, however, hNPC transplantation resolved renal insufficiency by 20 dpt. Transplanted hNPCs migrated to the pronephric area, expressed human SIX2 in early nephrogenesis (9 dpt), and formed glomerular and tubular structures that connected to DBA^+ zebrafish collecting ducts at a later stage (26 dpt). Notably, hNPCs contributed to $Podocalyxin^+$ cells in membrane-enclosed structures that contained human $CD31^+$ capillary loops, indicating human glomerular development in zebrafish. qPCR using human-specific primers validated human nephron formation in zebrafish.

Conclusions: We developed novel methods for generating human kidney tissue in animals. After eliminating NPCs in early zebrafish embryos using CRISPR/Cas9 genome editing, xenotransplantation of hNPCs generated human nephron structures in zebrafish. Our results serve as a proof-of-concept that isogenic patient-specific kidney tissue may be generated in animals for translational applications.

Funding: Private Foundation Support

TH-PO629

Developmental Trajectories Inform the Derivation of Podocytes in-a-Dish

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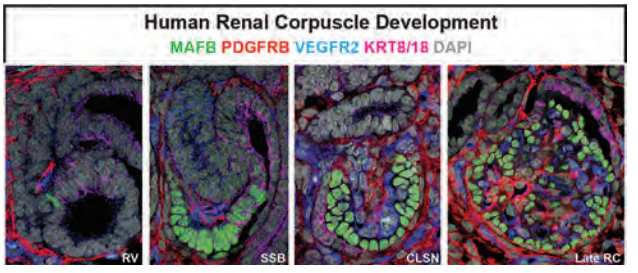
Background: In the renal corpuscle, podocytes, mesangial cells and vascular endothelial cells form a highly organized filtration device that enables plasma fluid to pass from the circulatory system into the epithelail network of the nephron. The derivation of podocyte-like cells from differentiating pluripotent stem cells has been reported by a number of groups through a variety of approaches. Before moving to disease modeling and drug discovery, an evaluation of the properties of *in vitro* derived cells to their *in vivo* counterparts is important.

Methods: In this study, we used *in vivo* studies, single-cell RNA sequencing and bioinformatics to explore the developmental trajectory of the human podocyte. Employing a fluorescently labeled hESC line to visualize and isolate *in vitro* derived podocyte-like cells, we performed a comparative analysis of these cells with their human embryonic counterparts.

Results: Through high-resolution microscopy, chromatin structure profiling, single-cell and bulk transcriptional profiling, we identified transcriptional landmarks during *in vivo* and *in vitro* podocyte development.

Conclusions: We found that hESC-derived podocytes shared molecular signatures with normal human podocytes, including the ability to form intricate interactions with their neighbors and attract blood vessels. A substantial podocyte profile is generated without accompanying interactions with mesangial or endothelial cell types. Our analyses also identified distinct transcriptional signatures between *in vitro* and *in vivo*-derived cells that point to opportunities to improve podocyte production in culture.

Funding: NIDDK Support



TH-PO630

Brain Derived Neurotrophic Factor (BDNF) Inhibition Dramatically Reduces Off-Target Cells in Kidney Organoid

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Background: Kidney organoids differentiated from pluripotent stem cells hold great promise for disease modeling and ultimately as a source of replacement tissue, however we have shown that all protocols also generate substantial off-target cell types, primarily neurons. To eliminate off-target cells without altering kidney cell maturation, we performed single cell RNA-seq and analyzed ligand - receptor pairs expressed exclusively within the neuronal lineages. We identified 19 receptors with 24 cognate ligands, and determined that the neuron survival factor BDNF and its receptor NTRK2 was expressed exclusively in the neuronal lineage. We tested whethyer inhibition of BDNF-NTRK2 signaling during organoid differentiation would reduce neuronal populations without altering kidney differentiation.

Methods: A range of doses of the NTRK2 inhibitor K252a was screened as well as different time schedules during organoid differentiation from human induced pluripotent stem cells. We assessed marker expression by qPCR and immunofluorescence, as well as scRNA-seq on control and K252a-treated organoids. We sequenced 3,314 cells to a final read depth of 50K mapped reads/cell with 3,056 transcripts and 1,524 unique genes detected per cell.

Results: Out of 16 different dosing and timing protocols tested, we found that 250 nM, of K252a added at day 12 did not alter nephron formation according to marker expression by qPCR and immunofluorescence. By contrast, neuronal markers were reduced by almost ten-fold. scRNA-Seq of control vs. K252a-treated organoids showed that all major kidney cell types remained present with K252a treatment, but the neuronal lineage was reduced by over 90%, from 29.8% of total organoid cells before treatment to 2.1% after treatment.

Conclusions: We employed a rational approach based on organoid scRNA-seq to identify BDNF signaling as a potential neuronal survival pathway contributing to the growth of off-target cells in during kidney organoid differentiation. Inhibition of this pathway reduced off-target cells by more than an order of magnitude without affecting kidney differentiation, illustrating the power of scRNA-seq to improve organoid differentiation protocols.

Funding: NIDDK Support

TH-PO631

Generation and Validation of a Novel Primary Renal Interstitial Cell Line

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Background: The renal interstitium is indispensable for proper nephrogenesis during mammalian kidney development. Interstitial cells also play a central role in the adult kidney fibrotic response. Despite the clinical significance, limited reagents are available to examine the signaling mechanisms that govern interstitial cell biology. To this end, we have generated an immortalized primary renal interstitial cell (PRIC) line. Canonical WNT signaling drives cellular proliferation in a number of developmental and disease contexts. Furthermore, *in vivo* deletion of Wnt7b from the collecting duct or β-catenin from interstitial cell precursors leads to medullary hypoplasia, suggesting a role for paracrine WNT signaling on interstitial cell maintenance. Biochemical analysis with our validated PRIC line confirmed that WNT drives renal interstitial cell proliferation.

Methods: A novel isolation method was utilized to purify PRICs from postnatal mice. Cells were then transduced with a mCherry-tagged SV40T temperature sensitive lentivirus construct to produce a heterogeneous population termed "bulk" SV40T PRICs. Clonal lines were isolated and expanded from single cells and screened for expression of postnatal interstitial zone markers. The transfection efficiency of isolated clones was evaluated with a GFP-expressing construct. The affects of treatment with the WNT agonist CHIR and the TCF/LEF1 inhibitor Fh535 on proliferation was measured by EdU labeling and ClickIt chemistry.

Results: As expected, "bulk" SV40T PRICs showed expression of SV40T at 33°C which was lost when cultured at 37°C. Clone 3-1 was selected for further characterization based on its transcriptional profile and expression of the common interstitial markers Pdgfrβ, α-SMA, Meis1, fibronectin and vimentin. The transfection efficiency of clone 3-1 was determined to be approximately 40%. Treatment of clone 3-1 with CHIR produced a time-dependent increase in the feedback pathway reporters *Axin2* and *Lef1*. In addition, clone 3-1 exhibited a dose-dependent increase in proliferation in response to CHIR. Finally, co-treatment with Fh535 abrogated the mitotic response observed with CHIR alone.

Conclusions: These experiments confirm that clone 3-1 is a viable *in vitro* model to study interstitial cell biology and that canonical WNT signaling through TCF/LEF1 drives renal interstitial cell proliferation.

Funding: NIDDK Support

TH-PO632

Directed Differentiation of Functional Kidney Cells from Human Induced Pluripotent Stem Cells

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Background: Many diseases and drugs affect kidney function by damaging the glomeruli, which serve as the functional units of the kidney and the center for blood filtration. An *in vitro* model of human glomerulus could facilitate therapeutic discovery and illuminate kidney disease mechanisms. Efforts to develop such models are hindered by the lack of functional human podocytes, the specialized epithelial cells that regulate selective permeability in the glomerulus. Human pluripotent stem (hPS) cells have a remarkable capacity to self-renew indefinitely and differentiate into almost any cell type under appropriate conditions. Thus, hPS cells could potentially serve as an unlimited source of podocytes; however, a method for directing their differentiation into glomerular podocytes remains elusive.

Methods: We hypothesized that a systematic investigation of multiple factors within the cellular microenvironment -- including cell-cell interactions, soluble signaling molecules, and mechanical properties of the extracellular matrix (ECM) -- could yield an effective method for podocyte differentiation.

Results: By following this principle, we developed a highly efficient method for differentiation of hPS cells into podocytes. The hPS-derived podocytes express markers consistent with mature phenotype and exhibit primary and secondary foot processes. By using Organ Chip microfluidic devices, we developed an *in vitro* model of the human glomerular capillary wall that supports podocyte differentiation and recapitulate the normal tissue-tissue interface and selective permeability of the glomerulus.

Conclusions: Our results demonstrate the feasibility of generating mature podocytes in a robust manner, providing an opportunity to engineer a functional human kidney model. These results could facilitate investigations to illuminate developmentally regulated events in kidney pathophysiology, and provide a low cost alternative to animal models for the development of therapeutics for human kidney disease. As podocytes are unable to undergo regenerative proliferation *in vivo*, these results also provide opportunities for cell therapy and regenerative medicine.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

TH-PO633

A Simple Bioreactor-Based Method to Generate Kidney Organoids from Pluripotent Stem Cells

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Background: Kidney organoids generated from human pluripotent stem cells have the potential to revolutionize how kidney development and injury are studied. Current protocols are technically complex and suffer from poor reproducibility and high reagent costs restricting scalability.

Methods: To overcome these issues, we have established a simple, inexpensive and robust method to grow kidney organoids in bulk from human induced pluripotent stem cells.

Results: Our organoids develop tubular structures by day (d) 8 and show optimal tissue morphology at d14. A comparison with fetal human kidney suggests that d14 organoid renal structures most closely resemble 'capillary loop' stage nephrons. We show that deletion of *HNF1B*, a transcription factor linked to congenital kidney defects, interferes with tubulogenesis, validating our experimental system for studying renal developmental biology.

Conclusions: Taken together, our protocol provides a fast, efficient and cost-effective method for generating large quantities of human fetal kidney tissue, enabling the study of normal and aberrant human renal development.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO634

Generation of Induced-Pluripotent Stem Cells and Kidney Organoids from Pediatric Urine Specimens

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Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are the leading cause of renal failure in children worldwide. Mouse models are widely used to explore underlying mechanisms in CAKUT, but important differences exist between human and murine renal development. Induced-pluripotent stem cells (iPSCs) and kidney organoids generated from actual CAKUT-patients, and closely related, healthy controls, can serve as complementary tools to study processes as nephrogenesis. **Objective:** Generate patient-specific iPSCs and kidney organoids in an efficient, non-invasive manner.

Methods: Previously published protocols (Zhou et al., *Nat Protoc*, 2012; Takasato et al., *Nat Protoc*, 2016) were adapted. Urine cells (UCs) were grown from remnant urine samples routinely obtained in a nephrology outpatient clinic (incl. bag-collected urine). UCs were reprogrammed to urinary iPSCs (UiPSCs) using non-integrating episomal reprogramming vectors (Oct4/Sox2/Lin28/L-Myc/Klf4). UiPSC pluripotency was confirmed by qRT-PCR, immunostaining and embryoid body assays, and euploidy by karyotyping. Kidney organoids were generated from UiPSCs and control blood-derived iPSCs (BiPSCs).

Results: Remnant urine specimens were obtained from 17 patients (1mo-17yr old). UC cultures were established in 71% (12/17) of single urine collections (urine bag: 4/7, 57%, p=0.59 vs. mid-stream specimens) with median urine volume 26ml (range 10-75ml). Sufficient UC numbers for reprogramming were obtained within 16-25 days. Bacterial contamination was not observed. Episome-free UiPSC clones were obtained within 2-3 passages after reprogramming three UC cultures. Differentiated UiPSCs showed mRNA expression patterns (HOXD11/GATA3) matching those of differentiated BiPSCs and published data of differentiated fibroblast iPSCs. Organoids generated from UiPSCs closely resembled BiPSC-kidney organoid morphology and mRNA/protein expression of glomerular, tubular and stromal markers.

Conclusions: A rapid and non-invasive protocol was established to generate iPSCs/kidney organoids from pediatric urine samples. These results provide a readily applicable new platform for CAKUT-research with a low threshold for participation of patients (including infants) and indispensable, patient-specific controls.

Funding: Government Support - Non-U.S.

TH-PO635

Development and Characterization of Kidney Micro-Organoids from PSCs to Facilitate Kidney Cell Scale-Up

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Background: The directed differentiation of human pluripotent stem cells (hPSCs) has enabled the generation of kidney organoids with potential applications in disease modelling, drug screening and regenerative medicine. The approach is expensive and faces limitations to long-term culture. As a result, novel cost-effective techniques are needed to enable scale-up of kidney cells types *in vitro* and facilitate higher throughput screening approaches.

Methods: To generate kidney micro-organoids, hPSCs were differentiated to intermediate mesoderm using 7uM CHIR for 4 days and FGF9 until 7 days in 2D monolayer culture. On day 7 cells were dissociated using EDTA and allowed to form cell aggregates via low-speed swirling using an E6 media containing a cocktail of growth factors. Within 24hr, cell aggregates were transformed into cell aggregates which, after a further 12 to 18 days in suspension culture, formed complex kidney micro-organoids within a single culture flask.

Results: Mature kidney micro-organoids revealed the presence of intact nephron segments, including podocytes (NPHS1+), proximal (LTL+) and distal (ECAD+) nephron epithelium and collecting duct (ECAD+GATA3+) segments with distinct lumens. Each micro-organoid contains only 6-10 nephrons. As a result, imaging through an entire organoid is feasible. 10x Chromium single-cell RNA sequencing analysis identified the

presence of 11 distinct kidney cell types, both confirming the presence of anticipated renal cell types and revealing a reduced level of surrounding stroma compared to our previously described protocol (Takasato et al, 2015). With this novel method, a starting population of 4.5 million cells (D7+0) was expanded to 150-200 million kidney cells (40 fold) within 20 days, providing a platform for the economical production of kidney cells for various biological applications. Treatment of organoids with Adriamycin induced podocyte cell death and decreased podocyte specific gene expression.

Conclusions: This is a cost-effective method for the generation of large numbers of hPSC-derived kidney cells. As a result, this technique will improve the feasibility of drug toxicity screening and regenerative cell therapy.

TH-PO636

Fluorescent Reporters in Kidney Organoids Generated with Cheap Mini-Bioreactors for High-Throughput Modeling of Kidney Fibrosis

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Background: Kidney organoids from human pluripotent stem cells (hPSCs) provide a unique opportunity to study human kidney development and kidney diseases. Current protocols are low throughput, generate immature and off-target cell types, and are costly. We tested the ability of spinning bioreactors to overcome these limitations.

Methods: We 3D-printed spinning mini-bioreactors that fit onto 12-well plates, as described (Qian et.al. Cell, 2016). We adapted the Takasato organoid differentiation protocol to the spinning mini-bioreactors by initially differentiating hPSC in a mono-layer for 7 days, followed by low-attachment plate culturing to generate spheroids for another 5 days, and then transferring the spheroids to a mini-bioreactor for maturation for 7- 42 days. We optimized the throughput and characterized resulting kidney organoids by qPCR, immunofluorescence and single cell RNA-seq (scRNA-seq). Finally, we generated and validated three novel fluorescent reporter hPSC lines relevant to the study of fibrosis in kidney organoids (Fibronectin1-GFP, Col1a1-GFP and Gli1-turboGFP).

Results: One 12-well plate could generate 200-600 kidney organoids, representing a more than 100 – fold increase compared to the original Takasato protocol. scRNA-seq analysis revealed that when compared to the standard organoid protocol using a transwell plate, the kidney organoids generated with the mini-bioreactor exhibit more mature nephron structures (including ureteric bud), and more closely resemble the adult human kidney by Pearson correlation. We validated that Fibronectin1-GFP, CollA1-GFP and Gli1-turboGFP all express in the correct stromal cell type in mini-bioreactor-derived organoids. Furthermore, kidney organoids generated by the mini-bioreactor method mount a fibrotic response when treated with 20 μM cisplatin for 2 days by using RPMI medium for organoid differentiation.

Conclusions: We used a 3D-printed spinning mini-bioreactor to increase kidney organoid throughput by at least 100-fold. The protocol is cheaper and results in better differentiation of nephron structures when compared to the standard protocol using a transwell plate. We have generated and validated novel fluorescent reporter hPSC lines relevant to studying fibrosis. This work will accelerate adoption of kidney organoid protocols for the research community.

Funding: NIDDK Support

TH-PO637

Mesenchymal Stem Cells Derived from Induced Pluripotent Stem Cells and Bone Marrow Are Equally Effective in Ameliorating Lipotoxicity-Induced Kidney Injury

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Background: Human induced pluripotent stem cell-derived mesenchymal stem cells (iPS-MSCs) are promising as an alternative to bone marrow-derived mesenchymal stem cells (BM-MSCs) for cell-based therapy. Lipotoxicity is an important pathogenetic factor leading to chronic kidney injury. This study aims to compare the therapeutic effects of iPS-MSCs and BM-MSCs in ameliorating lipotoxicity-induced kidney lesions.

Methods: Mice (C57BL/6J) fed normal diet (ND; 10 kcal%) or high-fat diet (HFD; 60 kcal%) for 12 weeks were randomly divided into vehicle control, iPS-MSC and BM-MSC subgroups (n=8 in each group), followed by infusion of saline or MSCs via tail vein and fed for further 8 weeks before sacrifice. Body weight, blood glucose and urine albumin were monitored throughout the experiment. Renal histological changes were assessed by Periodic acid-Schiff staining. Renal endoplasmic reticulum (ER) stress, inflammation and apoptosis were evaluated by real-time quantitative PCR, Western blot and TUNEL assay.

Results: Compared to ND group, mice fed HFD had significantly increased (1) body weight, blood glucose and urine albumin; (2) tubular injury score (tubular vacuolation and tubular glycogenated nuclei), glomerular size and mesangial expansion; (3) expression of markers for ER stress (BiP, p-eIF2α, ATF4, p-IRE1α, CHOP) and related phosphorylated signaling molecules (p-NF-κB, p-ERK, p-JNK); (4) expression of pro-inflammation mediators (IL-6, Cxcl1, Cxcl2) and (5) apoptosis (Bax/Bcl2 ratio and number of renal TUNEL-positive apoptotic cells). All these events were significantly attenuated by infusion with iPS-MSCs or BM-MSCs to the HFD-fed mice. Notably, iPS-MSCs and BM-MSCs infusion to HFD-fed mice have equivalent efficacy in ameliorating all the above-mentioned readouts in HFD-induced kidney injury.

Conclusions: Our study suggests comparable capability of iPS-MSCs and BM-MSCs in ameliorating lipotoxicity-induced kidney injury, supporting iPS-MSCs as a valuable alterative source to BM-MSCs for therapeutic application. (*Funding:* Health and Medical Research Fund Advance Medical Research Ref. #03143726 and Mrs. Rita T. Liu SBS of L & T Charitable Foundation Ltd)

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TH-PO638

Adipose-Derived Regenerative Cells: Therapeutic Potential

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Background: Studies in our hybrid rat model of transplantation/ischemic reperfusion injury (IRI) have demonstrated improvement in kidney function post injection of adipose-derived regenerative cells (ADRCs) into the renal artery. This technique has translational value in human transplant surgery as ADRCs provide a robust supply of cells from accessible tissue, do not require culturing, and can be generated/delivered at point of care during the time of transplant. The mechanism on how these cells establish regenerative conditions during IRI remains elusive.

Methods: Flow cytometric analysis was performed on rat ADRCs extracted from inguinal tissue (n=14). Cells were surveyed for markers that identify viability, immune cells, immune cell subsets, epithelial cells, pericytes, and mesenchymal stem cells. Rat ADRC RNA expression for angiogenic, anti-oxidant, and anti-/inflammatory markers were measured by real-time PCR. Whole body imaging and histology was performed to track DiR labelled ADRCs. Protein isolated from the kidney at 1 hour 24, and 48 hours post injection were surveyed with a proteome profile array and through western blotting.

Results: ADRCs appear to be a pleomorphic cell suspension with multiple potential active subsets including T-cells, macrophages and mesenchymal stem cells. RNA expression from whole rat ADRCs indicate production of growth and repair factors, and notably- angiogenin and matrix metallopeptidase-2; and chemokine, CXCL1. ADRCs accumulate in clustered regions of the corpuscle 1 and 24-hours post injection of ADRCs. Gene expression studies performed on the kidneys at 1, 24, and 48 hours post injection identified an upregulation of angiogenic factors VEGFa and angiogenin; anti-oxidant HO-1; and inflammatory factors IFN-gamma and IL-6 when compared to sham-injected control. Protein profiling indicated an upregulation of TIMP-1 and of ligands important in leukocyte trafficking.

Conclusions: Data in the context of our model, suggest they serve as a vehicle for discrete administration of angiogenic and anti-oxidant factors. Counterintuitively, data also suggests that concomitant to secreting repair factors, at early timepoints, factors are secreted which attract inflammatory-related immune cells. Collectively, changes in RNA and protein levels of leukocyte trafficking-related factors suggest a major role for leukocytes in early IRI repair.

Funding: Government Support - Non-U.S.

TH-PO639

Kidney Organoids for Improved Prediction of Human Nephrotoxicity

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Background: Nephrotoxicity accounts for only 2% of drug development failures in pre-clinical studies which rises to 19% of drug attrition during phase 3 clinical trials, highlighting the need for improved pre-clinical predictive tools. The poor predictability stems either from inter-species differences or from an inability to distinguish drug-specific versus generalized toxicity due to poor expression of drug transporters (TPs), such as Organic Cation Transporters (OCTs) and Organic Anion Transporters (OATs) in primary cells, and limited availability of co-culturing models recapitulating cell-cell interactions *in vitro*. Here we demonstrate the utility of human pluripotent stem cell-derived kidney organoids for pre-clinical nephrotoxic assessment.

Methods: Kidney organoids were generated following a 6-step directed differentiation protocol. Using qPCR and immunostaining, drug TP expression was characterized overtime from differentiation day 8 - 50. The following known nephrotoxicants were tested: cisplatin (an OCT-mediated tubular toxicant), aristolochic acid and tenofovir (OAT-mediated tubular toxicants), and puromycin aminonucleoside (a Plasma Monoamine Transporters [PMAT]-mediated podocyte toxicant). Injury responses were assessed by immunostaining, qPCR and biomarker assays. Cimetidine and probenecid, inhibitors of OCTs and OATs respectively, were employed to assess drug TP-mediated nephrotoxicity in tubules.

Results: Drug TPs, OAT1, OAT3, OCT2 and PMAT, were expressed in kidney organoids with maturity. Cisplatin 5 μM induced KIM-1 and γH2AX expression in LTL^+ tubules which was partially reversed by cimetidine, indicating TP-mediated injury. Cisplatin at 50 μM resulted in widespread injury to all nephron compartments with increased levels of MCP-1 and TNFR1 in culture media, representing generalized toxicity responses. Aristolochic acid and tenofovir also caused LTL^+ tubular injury at a low concentration, and probenecid suppressed injury responses. Puromycin aminonucleoside induced loss of foot processes and podocyte apoptosis without evidence of tubular injury.

Conclusions: Kidney organoids replicated drug TP-mediated nephrotoxicity in a segment-specific manner, serving as a novel pre-clinical tool to assess nephrotoxicity with the ability to distinguish between drug-specific and generalized toxicity responses.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

TH-PO640

Stem Cell-Derived Podocytes from Blacks with FSGS and High Risk ApoL1 Expressed More ApoL1 Protein and Reduced Viability in Response to Interferon γ

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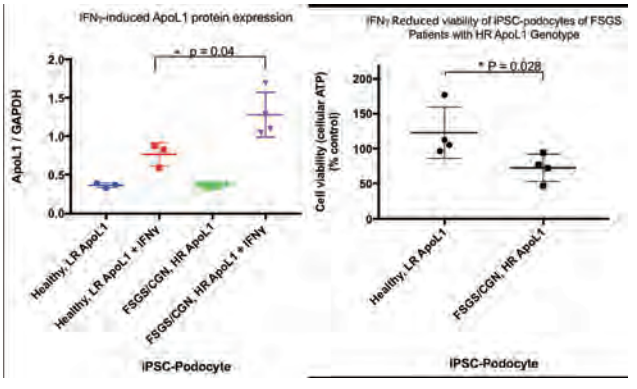
Background: Podocyte injury/loss is the cellular hallmark of ApoL1-nephropathies. Blacks with high risk (HR) ApoL1 alleles (G1G1, G2G2, or G1G2) have 7-10-fold increased risk of Focal segmental glomerulosclerosis (FSGS). HR ApoL1 is sensitive but not specific for FSGS. Estimated 20% of carriers of HR ApoL1 develop ApoL1-nephropathy. There is need for functional assay to identify truly at-risk blacks. Lack of disease-relevant podocyte model has stalled research progress. Our goal is to utilize stem-cell derived podocytes as tools for determining an individual's risk of ApoL1-nephropathy.

Methods: We recruited blacks with biopsy-proven FSGS (cases) and healthy controls with normal GFR and no proteinuria. ApoL1 was genotyped by sanger sequencing. Induced pluripotent stem cells (iPSCs) generated from PBMCs were differentiated into markers-confirmed podocytes based on published protocol. Podocytes were treated/not with interferon γ (IFNγ). Cell viability, comparative transcriptome, and protein expression were determined by cellular ATP content, RNA-seq and immunoblotting, respectively.

Results: 81.8% (9 of 11) cases have HR ApoL1 allele versus 16.7% (1 of 6) of controls. IFNγ induced higher ApoL1 protein expression in podocytes derived from cases despite similar intergroup ApoL1 mRNA levels. IFNγ reduced the viability of podocytes derived from cases with HR ApoL1 but not of controls, including control with HR ApoL1 genotype. Transcriptome analysis shows that IFNγ differentially upregulated genes involved in endocytic recycling, PI3K-mediated signaling, and actin filament-based movement in podocytes derived from cases.

Conclusions: iPSC- podocytes of blacks with ApoL1-nephropathies have a distinct cellular/molecular response to IFNγ which could be harnessed for Identification of blacks most at risk to develop ApoL1-nephropathy in future.

Funding: Private Foundation Support



IFNγ induces higher ApoL1 protein & reduces viability of iPSC-podocytes of blacks with HR ApoL1 & FSGS/collapsing GN, CGN. Not applicable, NA

TH-PO641

Modelling APOL1 Nephropathy Using Kidney Organoids

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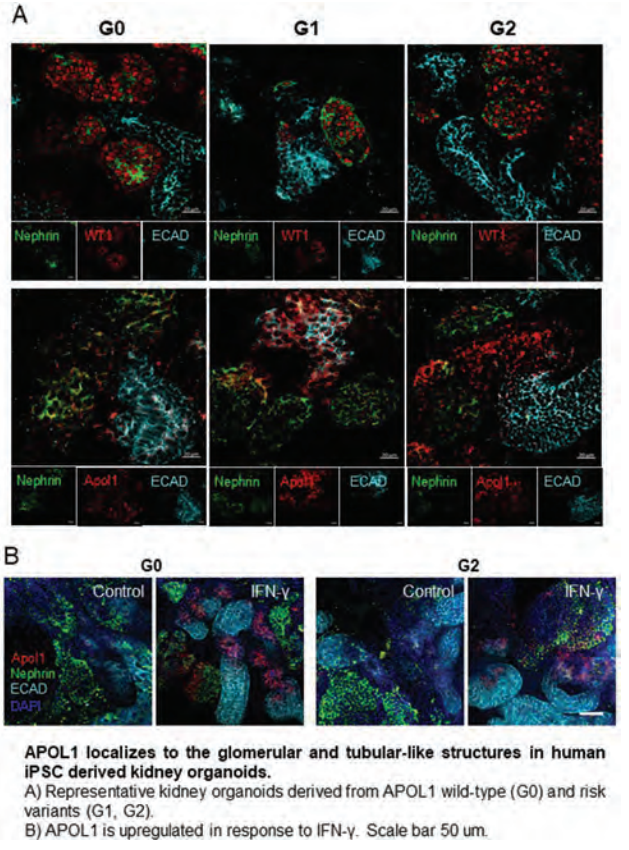
Background: Apolipoprotein L1 (APOL1) is a gene expressed only in humans and some primates. Its genetic variants (G1 and G2) are strongly associated with kidney diseases including non-diabetic kidney disease, FSGS, and HIVAN. The mechanism leading to APOL1 nephropathy remains unclear partly due to inadequate animal models that can recapitulate the events leading to human disease.

Methods: We generated non-isogenic and isogenic iPSC lines for wild type APOL1 (G0) and risk variants (G1, G2) using dermal fibroblasts reprogrammed with Sendai virus. Kidney organoids were generated using the protocol established by Takasato et al. (Nat Protoc. 2016, 11:1681-92). RNA-sequencing was performed on differentiated kidney organoids day 28 with and without interferon (IFN)-gamma. After QC and adaptor trimming, reads were mapped to the reference genome with STAR aligner and then analyzed in EdgeR. Network analysis was performed with Metacore.

Results: As expected, iPSCs from different sources had variable characteristics in terms of rate of cell division, ability to differentiate and to form kidney organoids but we were able to select representative, comparable iPSC lines for the generation of kidney organoids. Our APOL1 kidney organoid model demonstrated expected localization of APOL1 to podocytes and proximal tubules and appropriately upregulate interferon stimulated genes when treated with IFN-gamma. APOL1 was equally expressed across the genotype groups. Gene enrichment analysis was notable for transcription changes in HIF1 targets in the risk variants compared with the wild type group.

Conclusions: Our human iPSC derived model for APOL1 nephropathy will be used to further characterize the APOL1 genetic variants. We now have a robust model that will serve as a platform for understanding the mechanisms that lead to disease, drug testing and potential cell therapies.

Funding: Other NIH Support - NIMHD, Commercial Support - Vertex Pharmaceuticals, Government Support - Non-U.S.



APOL1 localizes to the glomerular and tubular-like structures in human iPSC derived kidney organoids.
A) Representative kidney organoids derived from APOL1 wild-type (G0) and risk variants (G1, G2).
B) APOL1 is upregulated in response to IFN-γ. Scale bar 50 um.

TH-PO642

Identification of Nephron Progenitor Cell (NPC) Markers Derived from Human Embryonic Stem Cells (hESCs) by Single-Cell RNA Sequencing

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Background: The steady rise of chronic kidney diseases has caused a major burden for the healthcare systems worldwide. Yet, most of their molecular pathomechanisms are understudied due to the lack of functional model systems. In vitro modeling of kidney diseases and nephrotoxicity drug testing mainly employ immortalized kidney cell lines that do not truly represent their in vivo counterparts, or rely on limited sources of mouse and human primary kidney cells that de-differentiate in culture. hESC-derived NPCs, in contrast, may provide unlimited cell source for the generation of functional kidney disease models. Most current protocols differentiate pluripotent cells to various kidney cell types that aggregate into kidney organoids. These systems utilize undefined matrices and xenogenic products with high variability, making it difficult to study molecular disease mechanisms. The objective of this study was to generate a pure population of NPCs from hESCs in a chemically defined system through the identification of NPC markers.

Methods: hESCs were differentiated on human recombinant laminin toward mesoderm, metanephric mesenchyme and NPC lineage in the presence of relevant Wnt signaling molecule.

Results: By day 30, we observed 82% $WT1^+$ in total cell population via FACS analysis. Quantitative RT-PCR showed significant increases in mRNA expression of kidney lineage markers, in particular those of podocytes (OSR1, WT1, SYNPO, and NPHS1), and significant decreases in early metanephric mesenchymal markers from day 6 to day 30 (CD133 and CD24). We performed single-cell RNA sequencing on hESC-derived cells at different time points to establish signature surface markers that could allow us to purify and enrich for NPC population. From the analysis of the single-cell transcriptome, we have identified a set of genes whose gene expression profiles are highly correlated with those of podocyte lineage genes. Among those, we have selected potential surface markers for NPC enrichment, such as CD83, PLP2, and TM7SF2.

Conclusions: Our highly reproducible protocol allows efficient production of hESC-derived NPCs in monolayer in a chemically defined, xeno-free culture. These cells promise to provide an unlimited source to construct kidney disease models for analyzing drug clearance and toxicity, and for studying molecular disease mechanisms.

Funding: Government Support - Non-U.S.

TH-PO643

Identification of ROBO2 and Integrin B4 as Potential Surface Markers for the Isolation of Live Nephrogenic Cells from Human Fetal Kidneys

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Background: In the developing kidney, the formation of new nephrons relies on a small population of self-renewing nephrogenic progenitors (NP) characterized by co-expression of SIX2 and CITED1. Despite their essential role in renal formation and maturation, identification of surface markers that can facilitate their isolation has not yet been successful. We report here the isolation of a live cell population with NP traits from human fetal kidneys (hFK) using a novel combination of surface markers.

Methods: We have previously reported the isolation of NP cells from hFK cells using RNA probes. Based on our RNA-seq performed on these cells we have identified ROBO2 and Integrin B4 as potential surface markers for direct isolation of NP of human origin. ROBO2+IntegrinB4+ cells were isolated using FACS and RNAseq analysis was immediately performed to characterize their gene expression and evaluate their genetic profile. Data were compared with the SIX2+CITED1+ cells isolated by RNA-probe. Dissociation/reaggregation assays were performed to confirm their nephrogenic traits. Potential for long term expansion was also explored.

Results: Expression of ROBO2 and IntegrinB4 was histologically confirmed within the cap mesenchyme during development in 17-week hFK. FACS of ROBO2+IntegrinB4+ cells from hFK confirmed enriched expression of SIX2 and CITED1 in more than 90% of the cells. RNASeq analysis confirmed expression of genes including SIX2, CITED1, SIX1, PHF19, OSR1 and EYA1 suggesting a nephrogenic signature. Expression of human NP markers was validated by flow cytometry. NP showed the ability to integrate in developing renal structures expressing nephrogenic markers when co-cultured with dissociated/re-aggregated hFK. Optimal culture conditions for long-term expansion without loss of NP traits were also successfully established.

Conclusions: Our preliminary results suggest that ROBO2 and IntegrinB4 are potential candidates as surface markers for the direct isolation of cells with nephrogenic characteristics, including the expression of SIX2 and CITED1, from hFK without the use of any genetic manipulation. This system represents a novel method of isolating a pool of NP that can be applied towards studies of renal cell specification, thus increasing our knowledge of human renal development

Funding: Private Foundation Support

TH-PO644

BMSCs Labeled with Sialyl Lewis X Had Higher Homing Rate to the Kidney of AKI Rats

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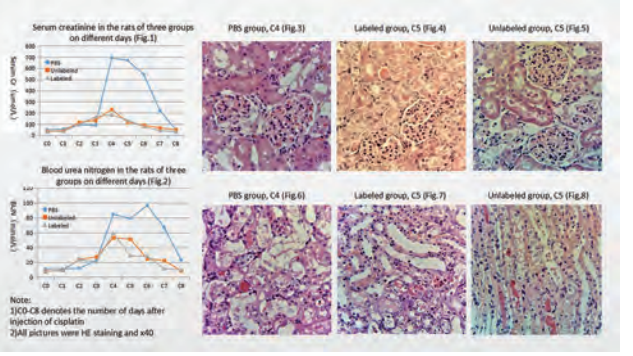
Background: Bone marrow mesenchymal stem cells (BMSCs) were applied to treat various diseases. After transplantation, BMSCs could migrate to the injured organ which is called homing. To enhance homing, a new technology has been developed, in which biotin-streptavidin is used to attach sialyl LewisX, the ligand of adhesion molecule to BMSCs surface.

Methods: BMSCs from male SD rats were isolated, amplified, and labeled with sialyl LewisX by biotin-streptavidin system. The acute kidney injury(AKI) rat model was induced by cisplatin in female SD rats. Forty-eight AKI rats were divided into three groups: PBS, labeled BMSCs, and unlabeled BMSCs. After application of cisplatin, rats were transplanted with BMSCs or PBS.

Results: BMSCs significantly improved the renal function of AKI rats. Serum creatinine and blood urea nitrogen in BMSCs groups were statistically significantly lower than those of PBS group on 4-7 days after cisplatin injection (Fig. 1,2). Unfortunately the differences of renal function between the labeled and unlabeled groups were not statistically significant. There were more cells exuded in renal glomeruli and interstitium in the labeled group than in the unlabeled or PBS group, suggesting that the BMSCs labeling may increase BMSCs' homing to the kidney of AKI rats (Fig. 3-5). BMSCs reduced renal tubular and interstitial lesions to some extent, such as renal tubular dilatation, epithelial cell detachment, basement membrane exposure, intra-luminal cellular cast, interstitial edema and cell infiltration. The regeneration of renal tubular epithelium in transplanted groups were slightly higher (Fig. 6-8).

Conclusions: BMSCs labeled with sialyl LewisX had higher homing rate to the kidney of AKI rats. BMSCs transplantation significantly improved the renal function of AKI rats, and to some extent, reduced renal tubular and interstitial lesions.

Funding: Government Support - Non-U.S.



TH-PO645

Hypoxia-Preconditioned Mesenchymal Stem Cells Attenuate Renal Fibrosis by Upregulating Renal M2 Macrophage Polarization

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Background: Tubulointerstitial fibrosis is the final common pathway of all kidney diseases and also represents the major determinant of renal function decline. Infiltrating renal macrophages critically govern the homeostasis of renal fibrogenesis and the extent of renal interstitial fibrosis. M1 macrophages release pro-inflammatory cytokines and result in tissue destruction; conversely, M2 macrophages secrete anti-inflammatory cytokines and promote tissue repair. Mesenchymal stem cells (MSCs) are promising cell-based therapy and previously we have shown hypoxia-preconditioned MSCs (HMSCs) exhibited better anti-inflammatory and anti-apoptotic effects. Nonetheless, whether HMSCs attenuate renal interstitial fibrosis through modulating the phenotype of infiltrating macrophages remains unclear.

Methods: Male C57BL/6J mice undergoing unilateral ureteral obstruction (UUO) were administered either phosphate-buffered saline, normoxic MSCs or HMSCs. Histology, fibrosis content, inflammation markers and macrophage phenotypes were analyzed in the obstructed kidney tissue. In vitro, we also determined the phenotypic change and inflammatory gene expression in M1 macrophages after coculture either with normoxic MSCs or HMSCs.

Results: The extent of fibrosis in UUO-injured kidney was significantly decreased by HMSCs treatment as compared with normoxic MSCs or phosphate-buffered saline. Interestingly, HMSCs significantly decreased the number of inducible nitric oxide synthase (iNOS)-positive M1 macrophages and contributed to early expression of arginase (Arg)-1-positive M2 macrophages in obstructed kidney than normoxic MSCs, suggesting that HMSCs facilitated an M1-to-M2 phenotypic transition in obstructed kidneys. Flow cytometry, immunoblotting and real-time polymerase chain reaction analysis also demonstrated that HMSCs downregulated STAT-1, iNOS expression and upregulating mannose receptor and Arg-1 expression. Furthermore, HMSCs treatment resulted in more anti-inflammatory M2c macrophages and less pro-fibrotic M2a macrophages infiltration in obstructive kidneys.

Conclusions: HMSCs treatment reduced renal fibrosis and facilitated an early M1-to-M2 phenotypic change of renal macrophages in mice UUO, predominantly upregulating M2c macrophages. HMSCs can be a promising therapeutic approach for the inflammatory fibrotic kidney diseases.

Funding: Government Support - Non-U.S.

TH-PO646

Adult Renal Stem/Progenitor Cells Exert Immunomodulatory Activity on T Regulatory Cells and Double Negative T Cells

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Background: Several studies show the active role of Adult Renal Stem/Progenitor Cells (ARPCs) in kidney repair processes during acute or chronic injury. However, little is known about their immunomodulatory properties and their capacity to regulate specific T cell subpopulations. The aim of our study was to investigate the immunomodulatory properties of ARPCs on human T cells.

Methods: Human Peripheral Blood Mononuclear Cells (PBMCs) of healthy subjects were activated through incubation with Concanavalin A for 24h. ARPCs were activated by triggering TLR2 for 24h with Lipoteichoic acid (LTA) and co-cultured with T cells. Cell proliferation was measured by MTT cell viability assay. Phenotypic characterization of T cells was performed by flow cytometry. The relative expression levels of 36 cytokines of T cells and ARPCs, alone and in co-culture, were determined by Human Cytokine Proteome Array.

Results: TLR2-activated-ARPCs were able to decrease T cell proliferation after 24h of co-culture (p=0.017). In order to investigate changes in subset of T cell populations, we co-cultured PBMCs with activated ARPCs for short (5 days) and long period (15 days) of time. ARPCs did not affect CD3+CD8+ nor CD3+CD4+ T cells. Instead, we observed a significant decrease of Tregs (p<0.001) and CD3+CD4-CD8- DN T cell (p<0.0001) subpopulations after 5 and 15 days. Not significant effects were shown when T cells were co-cultured with renal proximal epithelial cells. Finally, by proteome array we identified cytokines secreted by ARPCs responsible for the immunomodulatory effect. SERPIN-E1, MIF, IL-8 and IL-6 were significantly up-regulated in the supernatant of T cells cocultured for 24h with TLR2-activated ARPCs, while were not present in supernatant of T cells alone.

Conclusions: Our data showed that ARPCs can regulate immune response by inducing T cell modulation through the TLR2 engagement. Interestingly, ARPCs lead to down-regulation of Tregs and DN T cells, which are involved in the balance between immune tolerance and autoimmunity. Moreover, we identified four cytokines with a key role in this system. These findings can help to clarify the role of ARPCs in immunomodulation and could be translated to potential clinical treatment.

Funding: Government Support - Non-U.S.

TH-PO647

Using the T30H Mouse to Investigate the Role of Myocardin in Obstructive Uropathy

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Background: Obstructive uropathies account for 20% of paediatric end stage renal failure. Irreparable damage often occurs to the kidneys before surgical correction of obstruction is possible. There are few in vivo models of this process. T30H mice were generated many years ago and have a balanced, heritable chromosomal translocation between chromosomes 2 and 11. The exact translocation point was previously unknown. They die soon after birth with large non-emptying bladders, hydronephrosis and reduced nephron numbers, despite there being no physical obstruction. Nevertheless, they are still a useful model for many features of obstructive uropathy.

Methods: We have utilised next generation sequencing, histology, RT-PCR and cell culture to examine gene expression and the bladder phenotype.

Results: We have investigated the T30H genome and discovered the exact translocation point, it does not span recognised genes, but is upstream of myocardin, a master regulator of smooth muscle. In the bladder, markers such as α SMA and Calponin are absent or expression is severely reduced. Urothelial markers such as Uroplakin 3a are unchanged. The translocation has no effect on all other systems involving smooth muscle, organs such as the heart and gut appear normal. The splice variants of myocardin present in wild type and T30H mice at birth are similar, suggesting expression levels of these splice variants are more important than whether or not they are expressed. Quantitative PCR will be required to confirm this hypothesis. We have isolated smooth muscle cells from wild type bladders at E14, then transfected them with lentivirus containing myocardin shRNA. This gene knockdown causes both reduced growth and expression of smooth muscle specific genes, including αSMA, consistent with the bladder phenotype *in vivo*. We are investigating the bladder phenotype in utero; the defect is identifiable using ultrasound from E16. In future we will uncover the developmental point when the defect is instigated, and whether the defect arises as a failure of muscle development, or whether the muscle grows and then is not maintained.

Conclusions: Understanding bladder smooth muscle regulation will better our knowledge of urinary tract development, and enable us to develop improved therapies for treating smooth muscle complications arising from urinary tract malformations.

Funding: Private Foundation Support

TH-PO648

Impact of Obesity on Mesenchymal Stem Cell Senescence

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Background: Obesity induces inflammation and contributes to the pathogenesis of kidney disease. Endogenous mesenchymal stem/stromal cells (MSC) mediate tissue repair, and show promise as exogenous therapy of kidney injury. However, chronic inflammation may impair the regenerative potential of MSC. We hypothesized that in human adipose tissue-derived MSC, obesity induces senescence, a growth-arrest program that transitions cells to a pro-inflammatory state.

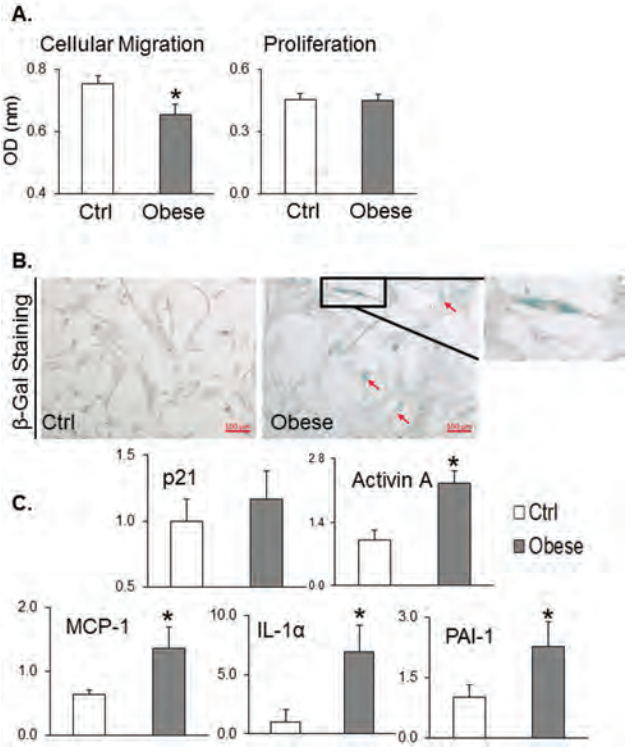
Methods: MSC proliferation and migration were studied in MSC harvested from subcutaneous abdominal fat from obese (n=6, BMI ≥35 kg/m^2) and age-matched lean controls (n=6, BMI <30 kg/m^2) during bariatric or kidney donation surgeries. Cellular senescence was evaluated by senescence-associated β-galactosidase (SA-β-gal) activity (staining), and by expression of cell cycle arrest (p21) and senescent-associated secretory phenotype (SASP) (MCP-1, IL-1α, and PAI-1) markers (quantitative PCR).

Results: Among all subjects, mean age was 59±8 years, eGFR 64.8±15.3 mL/min/1.73m^2, and 66% were females. Obese-MSC exhibited similar proliferation capacity as Control-MSC, but their migratory potential was lower, suggesting MSC dysfunction (Fig A). Senescence burden as per SA-β-gal staining, p21 and SASP markers expression was elevated in Obese-MSC (Figs B-C).

Conclusions: Human obesity induces senescence in adipose tissue-derived MSC. This impairment in endogenous cellular repair systems may permit development of kidney lesions that are inadequately repaired in subjects with obesity, and limit delivery of autologous MSC to the subjects kidneys'.

Funding: NIDDK Support

ASN Abstract 2018
Date:05/30/2018



TH-PO649

The Metabolic Syndrome Alters the Transcriptome and Proteome of Swine Mesenchymal Stem Cells

Aditya S. Pawar, Alfonso Eirin, Xiang yang Zhu, Lilach O. Lerman. *Mayo Clinic, Rochester, MN*.

Background: Mesenchymal stem cells (MSCs) possess endogenous reparative properties & have been proposed as an exogenous therapeutic intervention in patients with chronic kidney disease (CKD). The metabolic syndrome (MetS) often coexists with and aggravates CKD, but whether MetS interferes with the reparative capacity of MSC remains unknown. We hypothesized that integrated comparison of the mRNA, microRNA, and protein content of MSCs isolated from Lean and MetS pigs would reveal pathways impacted in MSC by MetS.

Methods: Domestic pigs were fed a Lean or MetS diet (n=4 each) for 16 weeks. MSC were harvested from subcutaneous abdominal fat, and expression profiles of microRNAs, mRNAs, and proteins obtained by high throughput sequencing and LC-MS/MS proteomic analysis. TargetScan and ComiR were used to predict target genes of microRNAs (that often inhibit gene and protein expression) altered in MetS-MSCs. Functional annotation analysis was performed using DAVID 6.7 database.

Results: Differential expression analysis revealed 12 microRNAs upregulated in MetS-MSCs (fold change >1.4, p<0.05), which may target 7,728 genes, whereas 33 mRNAs and 78 proteins were downregulated (fold change <0.7, p<0.05). Integrated analysis showed that microRNAs upregulated in MetS-MSCs may target 33% of mRNAs and 45% of proteins downregulated in MetS-MSCs (Fig. 1A), and functional analysis showed that targeted proteins are mainly involved in apoptosis (e.g. CASP9, LAPTM5, LRG1) (Fig. 1B), angiogenesis (e.g. FGF1, AKT2) (Fig. 1C), and insulin signaling (e.g. AKT2, PP2CB) (Fig 1D).

Conclusions: MetS alters the transcriptome and proteome of swine adipose tissue-derived MSCs, via post-transcriptional regulation of genes and proteins involved in apoptosis, angiogenesis, and insulin signaling. MetS-induced changes in the MSC transcriptome and proteome may limit their use as an autologous cell-based regenerative therapy in CKD

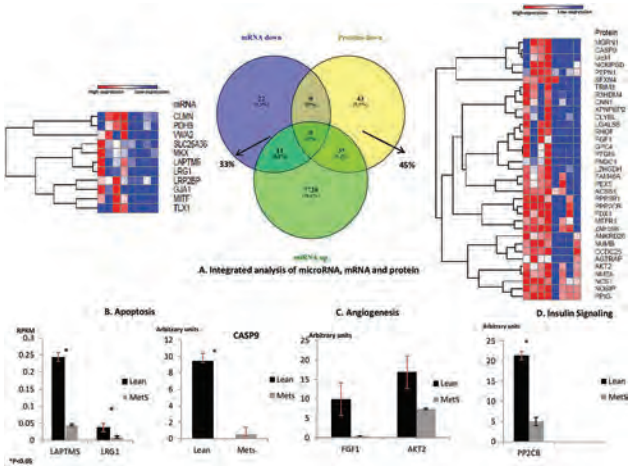


Figure 1

TH-PO650

Metabolic Syndrome and Renal Artery Stenosis Induce Mitochondrial Damage in Swine Scattered Tubular Cells

Arash Aghajani Nargesi, Xiang yang Zhu, Ishran M. Saadiq, Amir Lerman, Lilach O. Lerman, Alfonso Eirin. *Mayo Clinic Rochester MN, Rochester, MN.*

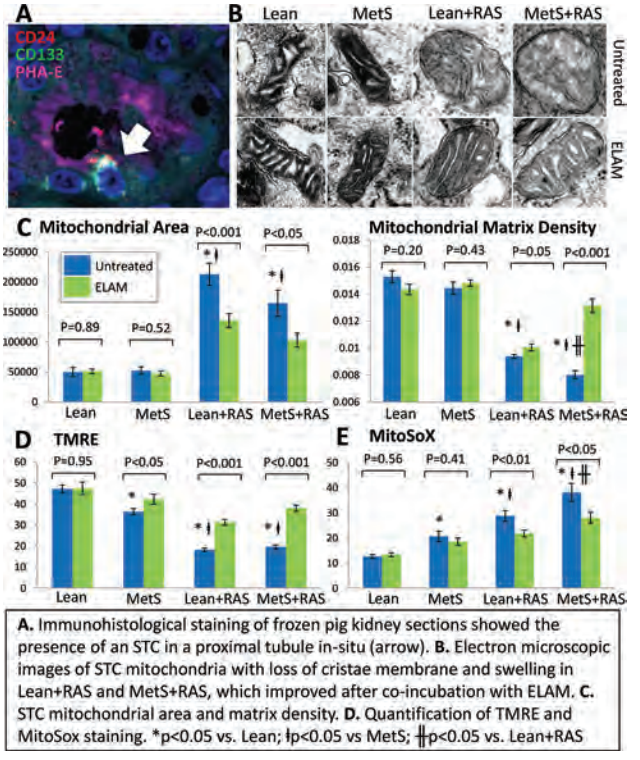
Background: Scattered tubular cells (STC) are considered to contribute to repair neighboring injured renal tubular epithelial cells. Mitochondria mediate STC biology and function, by producing energy and modulating redox status. We hypothesized that kidney injury due to coexisting metabolic syndrome (MetS) and renal artery stenosis (RAS) in swine impairs STC mitochondrial structure and function, which can be attenuated with mitoprotection.

Methods: CD24+/CD133+ STC (Fig. A) were isolated from pig kidneys after 16wks of MetS or Lean diet with or without RAS (n=7 each). Mitochondrial structure (electron microscopy), membrane potential (TMRE staining), and oxidative stress (Mito-SOX staining) were assessed in STC untreated or incubated with the mitoprotective drug elamipretide (ELAM, 1nM for 6hrs).

Results: Mitochondrial area increased and matrix density decreased in Lean+RAS- and MetS+RAS-STC compared to Lean- and MetS-STC, but both were restored in ELAM-treated pigs (Fig. B-C). Mitochondrial membrane potential diminished and mitochondrial production of reactive oxygen species increased in MetS-, Lean+RAS-, and MetS+RAS-STC, but reversed after treatment with ELAM (Fig. D-E).

Conclusions: Coexisting MetS and RAS induce structural and functional alterations in swine STC mitochondria, which might limit their regenerative potential. These observations suggest a potential role for mitoprotection in preserving the renal reparative capacity of STC.

Funding: NIDDK Support, Commercial Support - Stealth Biotherapeutics Inc



A. Immunohistological staining of frozen pig kidney sections showed the presence of an STC in a proximal tubule in-situ (arrow). **B.** Electron microscopic images of STC mitochondria with loss of cristae membrane and swelling in Lean+RAS and MetS+RAS, which improved after co-incubation with ELAM. **C.** STC mitochondrial area and matrix density. **D.** Quantification of TMRE and MitoSox staining. *p<0.05 vs. Lean; ŧp<0.05 vs MetS; ǂp<0.05 vs. Lean+RAS

TH-PO651

Mechanisms Involved in the Disturbances in Renal Development in Pups from Vitamin D Deficient Dams

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Background: Vitamin D_3 (Vit.D_3) has been related with cellular proliferation, differentiation and apoptose and with the regulation of renin gene, which are important events in renal development. Pups from dams submitted to a Vit.D_3 deficient diet during nephrogenesis (gestation and lactation), present changes in renal development that can persist in adult life. This study investigates the influence of Vit.D_3 deficiency on changes in renal development, the mechanisms involved and its consequences in adult life.

Methods: Offspring (Hannover rats) from mothers fed with normal (control group, CG) or vitamin D restricted (VitD-) diets were used in this study. Body weight (BW) was evaluated at birth, during lactation and at 3 months and 6 months of age. Systolic blood pressure (SBP) was measured monthly using a tail-cuff plethysmography. Blood and urine samples were collected to quantify Vit.D3, creatinine, Na^+, K^+, Ca^{+2}, angiotensin II (ANGII) and albuminuria levels. The kidneys were removed for histological, morphometric and immunohistochemical studies 3 and 6 months after birth.

Results: Vit.D deficient pups presented decreased BW at the end of lactation and increase in adult life compared to CG ($p< 0.05$). These animals showed higher SBP and plasma ANGII levels in the adult life compared to CG ($p< 0.05$). These pups also presented a significant decrease in urine osmolality, sodium and potassium fractional excretion and increase in water intake and urinary volume ($p< 0.05$). Decreased expressions of JG12 (a marker of endothelial cells) in renal cortex and glomerulus, and of synaptopodin (a marker of filtration barrier) in glomerulus were observed in VitD- compared to CG ($p< 0.05$). These animals also presented decreased glomerular area and increased fractional mesangial area compared to CG ($p< 0.05$). However, there was no difference in serum calcium levels, glomerular filtration rate, and albuminuria between the groups.

Conclusions: The current findings showed that the renal development is impaired in pups from dams VitD restricted with consequences in their adult life. These alterations can be at least in part provoked by the disturbances in the renal angiogenesis induced by the renin angiotensin system upregulation in pups with Vit.D deficiency

Funding: Government Support - Non-U.S.

TH-PO652

Autologous Mesenchymal Stromal Cell Paracrine Function in Diabetics with and Without Kidney Disease

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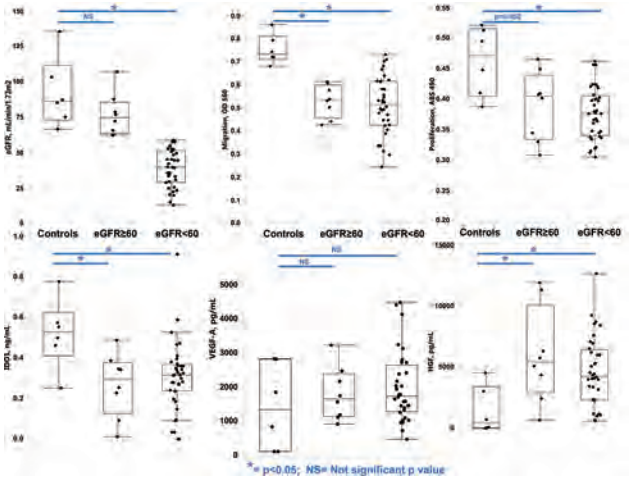
Background: Cell-based therapy applying autologous mesenchymal stromal cells (MSCs) is a promising treatment option for diabetic kidney disease (DKD). MSC provide immunomodulatory, antioxidant, anti-fibrotic, and pro-angiogenic effects in the diseased kidney, but *the diabetic and/or uremic milieu may diminish their regenerative capacity in humans*. To test the relative contributions of these milieus, we studied MSC paracrine function in patients with diabetes with and without reduced kidney function.

Methods: MSCs were harvested from subcutaneous abdominal fat tissue of **DKD subjects** (**n=44**) and **Controls** (**n=6** kidney donors). Levels of secreted cytokines [VEGF, hepatocyte growth factor (HGF; angiogenesis), indoleamine 2,3-dioxygenase (IDO; immunomodulation)] were measured in conditioned media from 3rd passage MSC. MSC functional capacity was measured by migration and proliferation assays.

Results: DKD subjects were older (67±7 vs 47±22 years), had higher BMI (35±6 vs 30±4 kg/m^2), and lower eGFR (46±20 vs 92±24 mL/min/1.73m2; all p<0.05), while sex (females 41% vs 67%) and race (whites 84% vs 100%; all p>0.2) were similar to controls. eGFR was <60 in 36 (82%) DKD subjects. DKD-MSC **migration** and **proliferation** were reduced compared to Control-MSC (**Figure**) and their **IDO** secretion was lower. Yet, **VEGF** secretion was similar and **HGF** was increased in DKD-MSC. Most study differences between DKD-MSC and Control-MSC were independent of kidney function.

Conclusions: Diabetes blunts the migration and proliferation capacity of human MSC in vitro, with little further contribution by a fall in kidney function. Nonetheless, angiogenic cytokines important for kidney regeneration are relatively intact, supporting MSC suitability for autologous cell-based therapy in DKD patients.

Funding: NIDDK Support, Private Foundation Support



MSC Function and Paracrine Activity in Diabetes Subjects (eGFR≥60; eGFR<60 mL/ min/1.73m^2) and Controls

TH-PO653

Low Circulating CD34+ Cell Count Is a Significant Predictor of Cardiovascular Death Among Chronic Hemodialysis Patients

Ahmad B. Kaihan,[1] Yoshinari Yasuda,[2] Takahiro Imaizumi,[3] Masaki Okazaki,[3] Naotake Tsuboi,[3] Shoichi Maruyama.[3] *[1]Department of Nephrology/CKD, Nagoya University Graduate School of Medicine, Nagoya city, Japan; [2]Nagoya University Graduate School of Medicine, Nagoya, Aichi-ken, Japan, Nagoya, Japan; [3]Nagoya University Graduate School of Medicine, Nagoya, Japan.*

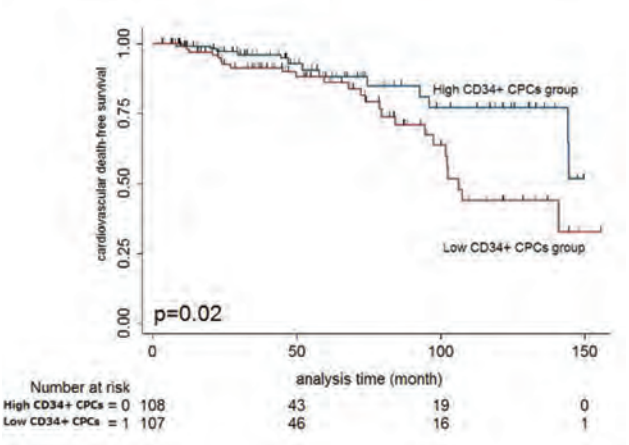
Background: Circulating CD34-positive (CD34+) cells play an essential role in neo-angiogenesis and in maintaining vascular endothelial function. A reduced CD34+ cell count was reported that associated with cardiovascular events and all-cause mortality. In this study, we aimed to validate association of low CD34+ cell count with cardiovascular death and all-cause mortality among chronic hemodialysis patients with longer follow up period.

Methods: In this prospective cohort study, 216 CKD patients on chronic hemodialysis enrolled from Mar 2005 to May 2005 and followed by the end of 2017 at Nagoya Kyoritsu Hospital. A cutoff number (0.41 cells/μl) for circulating CD34+ cells was determined by dividing all patients into two equal group of low CD34+ CPCs group (n=108) vs high CD34+ CPCs group (n=108) to predict cardiovascular death in the future, and the number of circulating CD34+ cells determined by flow cytometry at the time of enrollment. The primary outcome was cardiovascular death and all-cause mortality.

Results: During an average 59 months of follow-up, of 139 (64.7%) deaths, 38 (17.7%) cardiovascular deaths occurred. Cumulative cardiovascular death-free survival was significantly less in the low numbers of circulating CD34+ cells group. By multivariate analyses, age, DM, current smoking, history of CVD, and GNRI were significantly associated with all-cause mortalities, whereas, low numbers of circulating CD34+ cells (HR;1.98, p=0.037), GNRI (HR;0.95,p=0.042), and history of CVD (HR;2.92; p=0.031) were significant predictors for cardiovascular deaths.

Conclusions: This study revealed that a low number of circulating CD34$^+$ cells is significantly associated with risk of cardiovascular deaths, but not with all-cause mortalities in patients on chronic hemodialysis.

Funding: Commercial Support - MSD, Dainippon-Sumitomo, Kowa,Chugai,Nippon-Boehringer, Kirin, Mochida,Nippon Boehringer Ingelheim



TH-PO654

Differentiation Efficiency of Human Induced Pluripotent Stem Cell (iPSC) to Endothelial Cells in Patients with ESRD

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Background: Human induced pluripotent stem cell-derived endothelial cells (hiPSC-ECs) could be promising for treatment of renal disease. However, it is unclear whether hiPSC could be differentiated to endothelial cell (EC) in ESRD patients. Therefore, we first sought to generate hiPSC from peripheral blood mononuclear cell (PBMC) of ESRD patient, then compared the efficiency of hiPSC lines differentiating into ECs with healthy control.

Methods: The hiPSC-ECs were generated from differentiation of hiPSCs using vascular endothelial growth factor (VEGF) and bone morphogenetic protein-4 (BMP-4). At first, the expression of iPSC markers (NANOG, SSEA-4, and TRA-1-81) were assessed with confocal laser scanning microscopy, then hiPSC-ECs were purified based on positive expression of CD31. Subsequently, expression of endothelial markers (CD31, CD 34, and CD 133) were assessed with flow cytometric analysis. After 6 days in cell culture, stain with pluripotency markers (NANOG, SSEA-4, and TRA-1-81) on confocal image revealed iPSC were successfully generated in both healthy control and ESRD patient.

Results: Upon magnetic purification based on CD31+ expression, the hiPSC-EC population was observed to display typical endothelial surface markers in both groups (CD31, CD34, CD133, vWF, and Flt). However, hiPSC-ECs from ESRD patient showed much lower colonies of co-expression of CD31/CD34, CD31/CD133, and CD34/CD133 in FACS, compared to normal control. This was consistent with that the percentage of CD31 expression cell or co-expression of CD31/CD34 cells to total cells were much lower in ESRD group compared to that of healthy control.

Conclusions: In conclusion, the efficiency of hiPSC differentiating into ECs in ESRD patient were diminished compared to healthy control.

TH-PO655

Prevalence Estimates of Polycystic Kidney and Liver Disease by Population Whole Genome Sequencing

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Background: Estimating the prevalence of Autosomal Dominant Polycystic Kidney Disease (ADPKD) is challenging due to age-dependent penetrance and incomplete clinical ascertainment. ADPKD has an estimated lifetime risk of ~1 in 1000, while recent epidemiologic studies report a point prevalence of 3-5/10,000. Severe Autosomal Dominant Polycystic Liver Disease (ADPLD) is rare (<1 in 100,000), but milder forms may be clinically unrecognized. Quantity of functional polycystin-1 is a common genetic link between ADPKD and ADPLD. Using two large population sequencing databases, we estimated the lifetime prevalence of cystic kidney and liver diseases using stringent criteria for defining pathogenic variants.

Methods: Rare variants identified in genes involved in ADPKD (*PKD1, PKD2),* ADPLD (*SEC63, PRKCSH, GANAB, ALG8, SEC61B, LRP5*) and potential cystic disease

modifiers (*PKHD1, DZIP1L, UMOD, REN, MUC1, TSC1, TSC2, HNF1B, VHL, COL4A1, COL4A3, COL4A4, COL4A5)* were obtained from whole genome and exome sequencing from gnomAD ($n_{genomes}$=15,496, n_{exomes}=123,136) and BRAVO ($n_{genomes}$=62,784). Variants were evaluated for quality and annotation, compared with the Mayo PKD mutation database, and evaluated by bioinformatic prediction.

Results: High confidence pathogenic mutations in whole genome sequencing provides a lower bound lifetime ADPKD prevalence of 9.3/10,000 (95% confidence interval, 7.2 to 11.5). Estimates from whole genome and exome data were not statistically different. No significant differences in prevalence were observed between ethnicities. Protein truncating mutations in ADPLD genes and potential cyst modifier genes were found in 20.2/10,000 (95% confidence interval, 18.2 to 22.1) and 124.8/10,000 (95% CI, 119.4 to 129.1), respectively.

Conclusions: Population whole genome and exome sequencing supports a lower bound lifetime prevalence of ADPKD of about 1 in 1000. Truncation mutations in genes causative of ADPLD are surprisingly common, found in about 1 in 500. Individually rare variants in other cystic genes are cumulatively common and have the potential to modify the phenotype of ADPKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO656

Diverse Disease-Causing Genes in Clinical Diagnosed Autosomal Dominant Polycystic Kidney Disease in Taiwan

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Background: To study the disease-causing mutations of autosomal dominant polycystic kidney disease (ADPKD) in Taiwan; we examined a total of 10 genes related to kidney and liver cysts. We collected a total of 153 ADPKD families and 40 cystic kidney disease individuals. The diagnosis of ADPKD were established by clinical and image studies from nephrology investigators. The study was approved by the institutional review board of the Kaohsiung Medical University Hospital.

Methods: We examined our cohort by study the disease-causing genes of ADPKD (*PKD1*, *PKD2*, *GANAB*, and *DNAJB11*), ARPKD (*PKHD1*), and ADPLD (*PRKCSH*, *ALG8*, *LRP5*, *SEC61B*, and *SEC63*). Long-range PCR primers were designed for *PKD1* exon1 to 33 and *PKD2* genes to avoid the amplification of *PKD1* pseudogenes. Primer pool 1 contained a total of 60 primer pairs for PKD1 exon 1 to 33 and the primer pool 2 contained 287 primer pairs for PKD1 exon 34-46 and other genes. Multiplex microfluidic PCR system (Fluidigm Access Array) was used, followed by barcoding PCR with next-generation sequencing on Illumina MiSeq or MiniSeq. Fastq files were loaded into CLCbio Genomic Workbench for bioinformatic analysis. Five microsatellites markers (D4S1534, D4S1542, D4S1563, D4S1544, D4S414) were used to analyze families with *PKD2* R803* mutation.

Results: We identified mutations in 74.5% (114/153) of the ADPKD families in Taiwan. PKD1 and PKD2 represented 65.8% and 34% of diagnosed families, respectively. More than half of PKD2 mutations (22/39) were *PKD2* R803* mutation. Marker D4S1563 differentiated those *PKD2* R803* families into two groups. Heterozygous mutations of *GANAB*, *ALG8*, *LRP5*, *SEC63*, and *PKHD1* were identified in our ADPKD cohort. Three missense PKD1 mutations were found in the non-ADPKD individuals.

Conclusions: Our study showed clinical diagnosed ADPKD is a genetic heterogeneous disease with different genes and variable clinical spectrum. De novo and compound heterozygous *PKD1* mutations were found in individuals presented with severe disease. Microsatellite analysis indicated two different but closely related founders leading to the high prevalence of *PKD2* R803* mutation in Taiwan. Furthermore, disease-causing ADPLD genes can be found in ADPKD families and *PKD1* mutations can be found in individuals diagnosed as simple kidney cysts.

Funding: Government Support - Non-U.S.

TH-PO657

Development of Strategies for Genetic Diagnosis of Hereditary Glomerulopathies, Tubulopathies, and Cystic Kidney Diseases by the Sequencing Sets of Genes

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Background: Accurate clinical diagnosis in hereditary renal pathologies, especially glomerular and tubular disease, has proven to be difficult, as different pathologies may appear as clinical phenocopies. Genetic studies have the advantage of ensuring an accurate diagnosis and anticipate the disease. The implementation of NGS technology into routine genetic diagnostic practices allows the screening of large sets of genes in a single test.

Methods: Our group, based on the clinical classification, generated different panels for the sequence of renal disease genes in single tests: (1) panel for cystic kidney disease (up to 72 genes) (2) panel for glomerular disease (26 genes) and (3) panel for tubular disease (36 genes). Also, our group solved one of the limitations of conventional pre-designed NGS kits for target enrichment in regions with high homology pseudogenes (such as the *PKD1* gene) by developing particular primers to amplify specifically the replicated region of *PKD1* gene (exons 1-34).

Results: By analyzing a cohort of 291 families with PKD clinical diagnosis, we identified the causal mutation in 88% (n=255) of the families. In 94% (n=240) of these cases the clinical and genetic diagnosis were concordant. Of the 71 patients with a clinical diagnosis of glomerular disease and 31 with tubular disease subjected to genetic analysis, we identified the causal mutation in 62% (n=44) and 52% (n=16) of the cases, respectively. The concordance between genetic and clinical diagnosis was 66% (n=29) for the glomerular cohort and 69% (n=11) for tubular cohort. Most cases of misdiagnosis were associated with syndromic diseases with very similar phenotypes, such as Gitelman and Bartter syndromes.

Conclusions: The strategy of grouping genes by phenotype for genetic testing probed to be efficient in finding the causal mutation. Our results make clear the need of a genetic test to avoid misdiagnosis of certain renal pathologies.

TH-PO658

Whole Exome Sequencing Identifies Several Patients with Undiagnosed Autosomal Dominant Polycystic Kidney Disease in an Unselected Cohort

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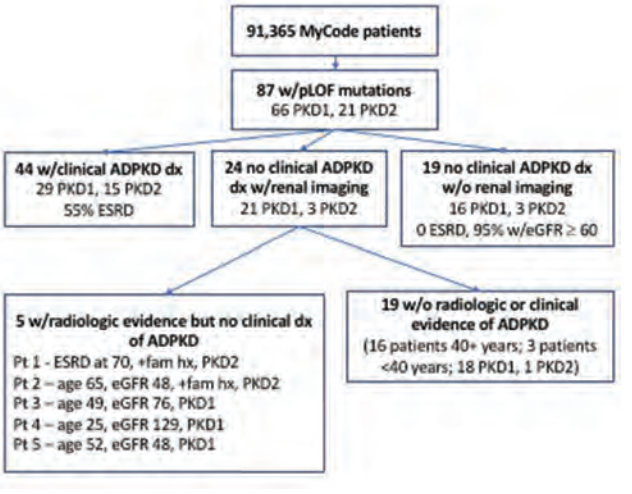
Background: The utility of whole exome sequencing (WES) to identify genetic causes of end-stage renal disease (ESRD) such as autosomal dominant polycystic kidney disease (ADPKD) is uncertain.

Methods: We used WES data from the Geisinger-Regeneron DiscovEHR cohort, an ongoing health system-based genetics study, to identify patients with putative loss of function (pLOF) *PKD1* and *PKD2* mutations. Clinical evidence of ADPKD was ascertained using electronic health record data [diagnosis codes, estimated glomerular filtration rate (eGFR), family history], and confirmed by chart review. We considered ADPKD to be undiagnosed if there was no mention of the diagnosis in clinic notes.

Results: Out of 91,365 adults with WES data, we identified 87 (66 *PKD1*, 21 *PKD2*) patients with pLOF mutations. A total of 44 (29 *PKD1*, 15 *PKD2*) patients had previously been diagnosed with ADPKD, including 24 (21 *PKD1*, 3 *PKD2)* patients with ESRD **(Figure)**. Of the remaining 43 patients without existing ADPKD clinical diagnoses, 24 had imaging data available, and 5 had radiologic findings suggesting ADPKD (3 with multiple renal and liver cysts, 2 with multiple bilateral renal cysts). One of the 5 patients with undiagnosed ADPKD had *PKD2* pLOF mutation, ESRD at the age of 70 attributed to hypertension and diabetes and a brother with ESRD attributed to diabetes. The remaining 4 patients with radiologic findings suggesting ADPKD but no clinical diagnosis had eGFR ranging from 48 to 129 ml/min/1.73m^2). There were 19 patients with renal imaging (18 *PKD1*, 1 *PKD2*) who had no renal cysts.

Conclusions: Population-based WES may provide an opportunity to identify previously undiagnosed ADPKD patients who could benefit from targeted treatment and family counseling. Additional targeted sequencing will be needed to confirm WES results for PKD1 mutations.

Funding: NIDDK Support



TH-PO659

A Genotype-First Approach Identifies Atypical PKD in DNAJB11 Mutation Carriers

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Background: Approximately 7-8% of autosomal dominant polycystic kidney disease (ADPKD) cases remain genetically unresolved. Mutations in *DNAJB11*, an ER co-chaperone molecule with a significant role in polycystin-1 maturation and trafficking, were recently identified in ADPKD patients with non-enlarged, cystic kidneys in the absence of PKD1/2 mutations. Little is known about the association between putative loss of function (pLOF) *DNAJB11* mutations with ADPKD in an unselected population.

Methods: We used whole exome sequencing (WES) from 91,365 patients in the Geisinger-Regeneron DiscovEHR cohort to identify patients with pLOF *DNAJB11* mutations (early-termination, frameshifts and start-loss mutations). Electronic health record data (diagnostic billing codes, eGFR, imaging) were examined to determine clinical phenotype. Evidence for the presence of renal and liver cysts was determined using natural language processing and manual review of imaging reports.

Results: We found 7 *DNAJB11* pLOF variants in 10 patients (median eGFR 60 mL/min/1.73m2) in our cohort, of whom 9 had renal imaging. Of the 2 younger patients (age 26 and 28) with renal imaging, 1 had a unilateral renal cyst, and 1 had bilateral hydronephrosis and right nephrolithiasis. Of the 7 older patients (age 49-72) with renal imaging, 3 had multiple, bilateral renal cysts, and 1 had multiple, unilateral renal cysts. One patient was diagnosed with ESRD at age 59. Two of the 7 patients were sisters carrying the same early termination mutation: a 61yo presenting with bilateral renal cysts, and a 55yo with multiple left renal cysts. Three patients carried rare *PKD1* missense variants (MAF 0.01%-0.15%), all of which are classified as *Likely Neutral* in the Mayo PKDB. Three patients presented with nephrolithiasis. Only one patient was hypertensive.

Conclusions: Using WES in an unselected population, our findings provide further evidence that loss of function mutations in *DNAJB11* could lead to normal-sized cystic kidneys and ESRD. Furthermore, we show the utility of a large-scale exome sequencing study combined with detailed EHR data in identifying rare genetic causes of kidney disease.

Funding: NIDDK Support

TH-PO660

PKD1 Duplicated Regions Limit Clinical Utility of Whole Exome Sequencing for Genetic Diagnosis of ADPKD

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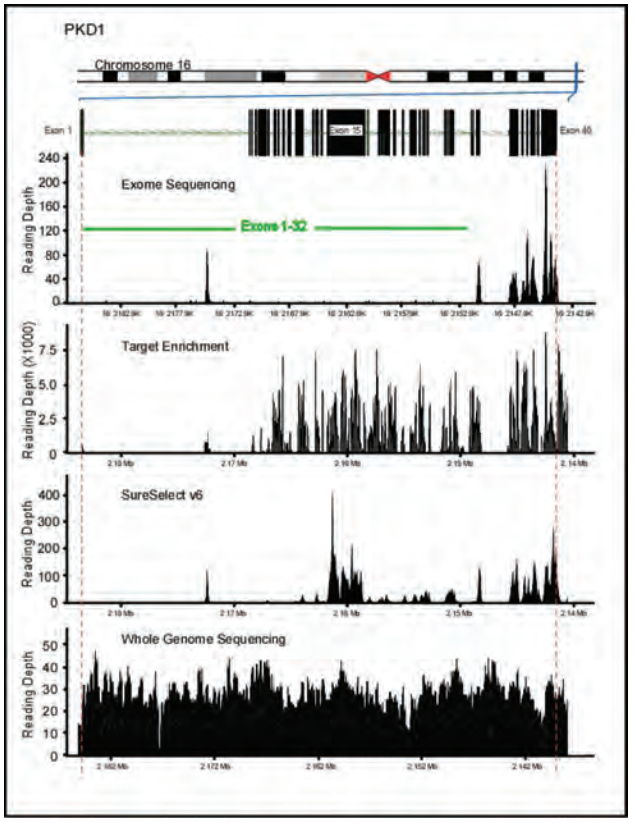
Background: Genetic diagnosis of ADPKD is complicated by the existence of *PKD1* pseudogenes located proximal to the original gene. The ability of NGS platforms in identification of ADPKD mutations, especially in the duplicated regions of *PKD1*, is important for potential utilization of such technologies in diagnostic applications.

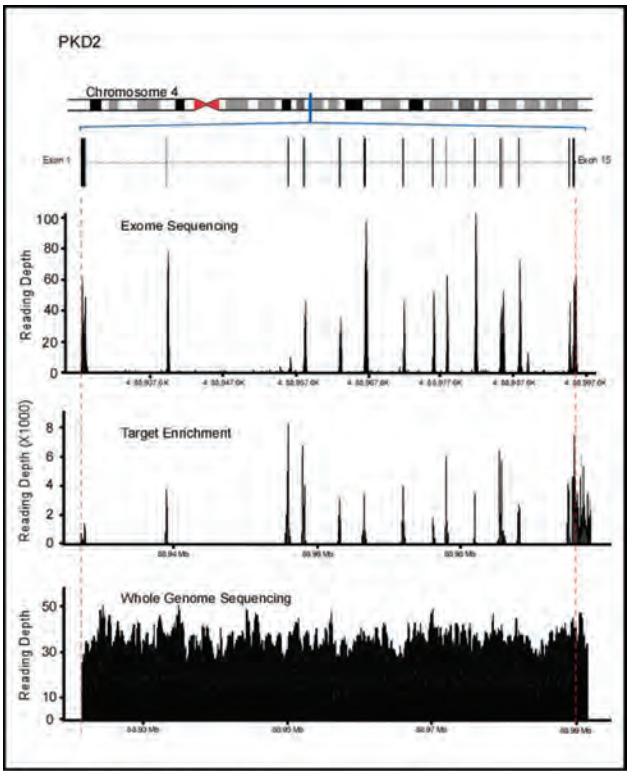
Methods: We evaluate the efficiency of WES, WGS & Targeted enrichment in sequencing *PKD1* and *PKD2* for the detection of ADPKD mutations in patients who were clinically evaluated by ultrasonography and RFT.

Results: WES had a 50% sensitivity in detection of *PKD1* mutations as the reading depth and sequencing quality were low over the duplicated regions of *PKD1*.

Conclusions: Our investigation highlights a major limitation of WES platform in ADPKD genetic diagnosis.



***WES and Target enrichment coverage map of* PKD1.** *WES of exons 1 to 32 of* PKD1 *showed low coverage while PKD2 coverage showed proper depth of all exons. Target Enrichment showed proper coverage for coding regions of PKD1 and PKD2. SureSelect v6 improved the coverage of* PKD1 *but in comparison to WES but exons 1 to 14 remained poorly covered. WGS showed proper covering of the entire* PKD1.



***WES, Target enrichment coverage map and WGS of* PKD2.** PKD2 *was covered properly using all methods.*

TH-PO661

The Genetic Complexity of ADPKD Is Illustrated in the HALT PKD Clinical Trial Cohort

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Background: The HALT PKD clinical trials consisted of hypertensive ADPKD patients, 15-49y with an eGFR >60 ml/min/1.73m^2 (Study A; n=558) or 18-64y with an eGFR 25-60 ml/min/1.73m^2 (Study B; n=486), but without total kidney volume requirements for recruitment. Hence, this population represents the cross-section of ADPKD seen by nephrologists and so provides an opportunity to characterize the genetics of a "typical" renal clinic population.

Methods: DNA samples were available from 970 patients from Study A and B that were screened by Sanger sequencing and MLPA for the *PKD1* and *PKD2* genes. Genetically unresolved cases were screened on a next generation sequencing (NGS) panel containing 65 known or candidate PKD genes. In some cases, further family analysis was performed to test segregation.

Results: Likely pathogenic mutations were detected in 95.1% of cases, 506 (52.2%) and 266 (27.4%), *PKD1* truncating or *PKD1* non-truncating, respectively, with 166 (15.2%) *PKD2.* The NGS revealed 23 mutations missed by the Sanger screen (21 *PKD1*, 2 *PKD2*), some due to allele drop out, with two others still being evaluated. A GANAB and a DNAJB11 family were identified, plus one with *PKD2* and *COL4A1* mutations. Five patients were *PKD1* mosaics, detected due to family analysis (2x), MLPA (1x), or NGS (2x), with the mutant allele at ~20-40% of the wildtype level. One patient was digenic for a *PKD1* (2 codon, inframe deletion) and a *PKD2* (nonsense) mutation, with ESRD=43y. Two *PKD1* mutations were likely gene conversions with the *PKD1* pseudogenes, and in three other cases the pathogenic allele consisted of three weak *PKD1* variants in cis shown in vitro to have additive effects. Two PKD2 patients co-inheriting hypomorphic *PKD1* variants had move severe disease than expected.

Conclusions: While the majority of HALT PKD patients have ADPKD due to a monoallelic mutation to one of the two common genes, a total of five causative genes have now been identified. Mosaicism or complex inheritance were also characterized in >1% patients, likely an underestimate of the true complexity due to difficulty of detection and interpretation, in this "typical" ADPKD population.

Funding: NIDDK Support, Other NIH Support - Mayo Translational PKD Center

TH-PO662

Performance of Targeted Cystogene Next Generation Sequencing in an ADPKD Population with CKD

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Background: Next generation sequencing (NGS) panels containing all genes in a disease category can provide high throughput, comprehensive coverage with a single screen, be cost effective, have high diagnostic efficiency, and provide information about possible disease modifiers. Mutation data in ADPKD is increasingly being recognized for its diagnostic and prognostic value. However, screening ADPKD populations is complicated by genic and extreme allelic heterogeneity, segmental duplication of *PKD1* with six pseudogenes sharing >97% sequence similarity with *PKD1*, and several GC rich regions.

Methods: The screened ADPKD patients had impaired renal function but without ESRD. Samples were screened using an NGS panel containing 136 known or candidate renal cystic or ciliopathy genes. Read alignment and variant calling were performed using the Genome Analysis Toolkit, and LOG2 ratio data was generated to assess for large deletions or duplications. Variant mining was performed with Golden Helix SNP & Variation Suite. Predicted pathogenic base pair variants were confirmed by Sanger sequencing with Multiplex Ligation-dependent Probe Amplification (MLPA) employed to confirm large rearrangements.

Results: A >40x read depth was obtained for 96.80 ± 0.14% (95% CI) of the 683kb target region, although lower coverage of particularly GC rich regions of *PKD1* was found. Of 384 cases with complete analysis, 187 (48.7%) were *PKD1* truncating, 98 (25.5%) *PKD1* non-truncating, and 63 (16.4%) *PKD2*. The pathogenic variants included 11 large deletions (8 in *PKD1* and 3 in *PKD2*) and 2 large duplications (*PKD1*) detected by CNV analysis. The 36 (9.4%) unresolved cases, including some with *PKD1* and *PKD2* variants of uncertain significance, are being rescreened by the conventional LR-PCR/Sanger approach to determine if specific mutations were missed. Genic and allelic complexity is also being assessed in these cases.

Conclusions: Targeted NGS identifies *PKD1* and *PKD2* pathogenic variants nearly as effectively as cumbersome LR-PCR/Sanger approaches. Detailed analysis of negative cases will detect screening deficiencies and highlight possible improvements to the panel design.

Funding: NIDDK Support, Other NIH Support - Mayo Translational PKD Center

TH-PO663

PKD1 Truncating Mutations with Mild Kidney Disease Is Underrecognized

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Background: Renal disease is highly variable in autosomal dominant polycystic kidney disease (ADPKD). Multiple studies have shown that *PKD1* protein truncating (PT) mutations are associated with the most severe disease with larger TKV and earlier onset of renal failure among all mutation classes. In the Extended Toronto Genetic Epidemiology Study of Polycystic Kidney Disease (eTGESP), we sought to determine whether *PKD1* PT mutations were uniformly associated with severe kidney disease.

Methods: The study cohort comprised 1279 patients from 555 families recruited in Toronto between 2006 and 2017. All recruited families were comprehensively screened for *PKD1* and *PKD2* mutations; Mayo Clinic Imaging Classification (MCIC) was performed in 430 patients with TKV by MRI. Kidney function and MCIC were used to assess disease severity.

Results: We studied 430 patients with TKV and mutation results for their renal disease severity. Among 146 patients with *PKD1* PT mutations and TKV, 31 (21%) from 28 families were found to have mild renal disease (MCIC 1A or 1B; most with normal eGFR) which is comparaible to patients with PKD2 mutations (Table 1). Three families displayed concordance with mild renal disease among affected family members; 13 families displayed discordance with both mild and severe disease among affected family members. Their *PKD1* PT mutations were distributed across all exons and included 16 frameshift, 10 nonsense, and 2 canonical splice site mutations. No patients had atypical kidney imaging patterns.

Conclusions: We found mild kidney disease comparable to that associated with *PKD2* mutations in 21% of patients with *PKD1* PT mutations. The presence of a positive familiy history of ADPKD in many of these patients makes somatic mosaicism an unlikely explanation. Rather, our data suggest a favorable modifier effect due to as yet unidentified genetic and/or environmental factors. Future research to identify factors underpinning this modifier effect can provide insight into disease mechanism and improve patient care.

	PKD1 PT Mayo 1A-1B n=31	PKD1 PT Mayo 1C-1D-1E n=115	PKD2 n=107
Age at MRI (years) - mean (SD)	35.7 (11.6)	37.4 (10.7)	44 (12.3)*
Gender (M/F)	11/20	50/65	43/64
ht-TKV (ml/m) - median [IQR]	342 [270-383]	902 [662-1319]*	707 [335-1133]*
eGFR (ml/min/1.73m2- CKD-EPI) - median [IQR]	96 [85.5-107]	79.7 [50-107]*	85.2 [62.2-99.6]
CKD stages (n, %) Stage 1-2 Stage 3 Stage 4-5	27 (87) 4 (13) 0	77 (67) 27 (25.5) 11 (9.5)	76 (81) 16 (17) 2 (2)

* p<0.05

TH-PO664

Molecular Genetic Analysis in Patients with Severe Polycystic Kidney Disease

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a severe form of chronic kidney disease, frequently diagnosed prenatally. ARPKD is primaly caused by mutations in the PKHD1 gene, nevertheless, phenotype of polycystic kidneys with early onset is present as a part of several syndromes caused by mutations in number of other genes, such as HNF1β, PKD1, PKD2, NPHP etc. Thus, the molecular genetic analysis can be very useful in differential diagnosis of polycystic kidneys in young patients. The results of complex molecular genetic analysis of 42 patients with very early onset PKD are presented.

Methods: The molecular analysis was carried out using next-generation sequencing (NGS) method with capture-based library preparation. The panel of about 80 genes associated with the formation of polycystic kidneys was analyzed. Sequencing data were analyzed with an in-house bioinformatic pipeline designed for detection of single nucleotide variants, small indels and CNV (copy-number variation). Due to the existence of pseudogenes, the PKD1 gene was simultaneously analyzed by NGS with amplicon-based library using long-range PCR. The group of patients comprised 39 young patients with polycystic kidneys (16.6±13.4) and three prenatally diagnosed fetuses. All patients had phenotype compatible with ARPKD, early onset ADPKD or polycystic kidneys in combination with additional abnormities in various organs.

Results: The panel of 80 genes was analyzed in all 42 patients. Thirteen patients harbored mutations in genes PKHD1 or PKD1. In one child combination of one PKHD1 and one TMEM237 mutation was found (p.I2957T and p.A18X, respectively). Such a finding could explain phenotype of polycystic kidneys arising in a young age of this patient. But mutations in other genes were also found in 13 patients: TMEM67, NPHP4, OFD1, BBS1, BBS12, PEX6. These genes with detected mutations are associated with nephronophthisis and developmental abnormalities of kidneys. These heterogeneous findings mirror variable and unclear phenotype of young patients with polycystic kidneys.

Conclusions: Because of an etiologic heterogeneity of polycystic kidney disease phenotype, especially in patients with polycystic kidneys arising prenatally or in a very early age, the complex mutational analysis of several genes is needed for reliable diagnosis. Supported by the grant projects *GAUK 1015* and *PROGRES- Q25/LF1*

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TH-PO665

Rare Deleterious Collagen IV Gene Variants Are Overrepresented in "No Mutation Detected" ADPKD Patients

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Background: Genetic investigation of autosomal dominant polycystic kidney disease (ADPKD) cohorts yields the underlying *PKD1* (77%) or *PKD2* mutation (15% cases); 8% cases have no mutation detected (NMD) in these genes. This NMD group may include ADPKD phenocopies. Type IV collagen, an integral component of the basement membrane exists mainly as α1α1α2 and α3α4α5 heterotrimers in the kidney. Mutations in genes encoding these α-chain isoforms are linked to Alport syndrome (*COL4A3*, *COL4A4*, *COL4A5*), Thin GBM disease (*COL4A3*, *COL4A4*) and HANAC (hereditary angiopathy, nephropathy, aneurysms, muscle cramps) (*COL4A1*). Bilateral kidney cysts are reported with heterozygous *COL4A1* mutations as part of HANAC syndrome and also sporadically in few patients with thin GBM disease.

Methods: A clinically and radiologically defined ADPKD cohort (N=178) constituting patients with *PKD1* or *PKD2* mutation (N=161) and those with NMD (N=17) in *PKD1, PKD2* or other genes known to associate with polycystic kidneys (*GANAB, DNAJB11* or Polycystic Liver Disease genes) was investigated using whole exome sequencing for rare (minor allele frequency $<5x10^{-5}$) variants meeting deleteriousness criteria using bioinformatics scores.

Results: Analysis of NMD patients (N=17) identified pathogenic heterozygous type IV collagen variants in four patients. These included HANAC causing *COL4A1* variants in 3 patients, of which 2 had missense variants each and one patient was compound heterozygous for a *COL4A1* truncating variant and a *COL4A3* missense variant. One patient had a splice site *COL4A4* variant that we confirmed to cause complete skipping of exon 28 by a minigene splice assay. Collagen IV variants of similar deleteriousness assessed in 161 patients with a *PKD1* or *PKD2* mutation revealed a significantly lower burden as compared to NMD patients (*COL4A1;* p-value 0.009); (*COL4A3* and *COL4A4*; p-value 0.029). Clinical and imaging review of NMD patients with collagen IV variants showed fewer or atypical appearing cysts.

Conclusions: Rare deleterious mutations in *COL4A1*, *COL4A3*, *COL4A4* are overrepresented in the 'no mutation detected' ADPKD cohort. Characterization of predicted deleteriousness of type IV collagen variants using bioinformatics scoring and splice assay is useful. The causation link, if any, between the type IV collagen genes and cystic kidneys is however elusive.

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TH-PO666

Correlation of Gene Mutation and Prognosis in Japanese ADPKD Patients

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most prevalent hereditary renal disorder. PKD1 mutation is one of the risk factors of worse renal prognosis. Recently, the prognostic classification(Mayo classification), based on height-adjusted total kidney volume and age, has been proposed to predict renal outcomes. It is still unclear, however, whether PKD 1 mutation is definitive risk factor in Japanese patients due to the lack of relevant studies. The aim of this study is to examine whether known risk factors of ESRD are valid to predict renal prognosis in Japanese ADPKD patients.

Methods: Study design: retrospective cohort study. Primary outcome : Event-free survival rate; more than 30% decline in eGFR and initiation of renal replacement therapy were defined as event. We enrolled patients who visited our hospitals during 2006-2016. Gene analysis to detect PKD1 or PKD2 mutation was performed in all participants. Patients were classified into 1A~1E according to height-adjusted TKV (HtTKV) and age according to the Mayo classification. Cox proportional hazard model was used to estimate hazard ratios for renal event.

Results: We identified 255 patients with ADPKD. Among them, 191 patients (74.9%) had PKD1 mutation, 50 patients (19.6%) had PKD2 mutation, and in 14 patients (5.5%), we could not detect the mutations. In PKD1 group, larger proportion of patients were classified into 1C~1E of Mayo classification [1A: 6 (3.1%), 1B: 44 (23.0%), 1C: 76 (39.8%), 1D: 38 (19.9%), 1E: 27 (14.1%) vs 1A: 5(10%), 1B: 17(34.0%), 1C: 18 (36.0%), 1D: 9 (18.0%), 1E: 1 (2.0%)], which indicated worse prognosis in PKD1 group compared with PKD2 group at the baseline. The hazard ratio for renal event among PKD1 group, compared with PKD2 group was 2.45 (95% CI: 1.14-6.40; *P=0.0196*). The event free survival rates in patients with PKD1 truncating mutation and those with non-truncating mutation were 34.6% and 29.8%, respectively, but their difference was not statistically significant (Hazard ratio 1.1, 95% CI: 0.65-1.84; P=0.70).

Conclusions: This is the one of the largest cohort studies of ADPKD patients with gene analysis in JAPAN. In Japanese ADPKD, patients with PKD1 mutation had significantly worse renal prognosis than those with PKD2 mutation, as reported in American and European population.

TH-PO667

Quality Control of Polycystin 2 Missense Mutants in the Endoplasmic Reticulum

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder and is a leading cause of end-stage renal disease. ADPKD arises from mutations in the *PKD1* and *PKD2* genes, encoding the primary ciliary proteins polycystin 1 (PC1) and polycystin 2 (PC2), respectively. Myriad mutations have been documented throughout the *PKD* loci, ultimately resulting in aberrant signaling, cell proliferation, and fluid secretion. In addition to the primary cilium, PC2 also localizes to the endoplasmic reticulum (ER). Given PC2's large size, topological complexity, and localization, we hypothesize that PC2 missense mutants may misfold and be turned over by the endoplasmic reticulum-associated degradation (ERAD) pathway. ERAD triages newly synthesized aberrant proteins and directs misfolded or misassembled confomers for degradation via the ubiquitin proteasome system. Due to an incomplete understanding of the factors that influence early events during PC2 maturation, we investigated PC2 biogenesis in the genetically-tractable model system, *S. cerevisiae*.

Methods: We have established a yeast expression system for 3XHA-PC2 to study the early biosynthetic decisions that mediate the folding, maturation, and degradation of PC2 missense mutants. Disease-causing PC2 variants were generated by site-directed mutagenesis, expressed in *S. cerevisiae*, and their metabolism was examined using cycloheximide chase analysis. Results from the yeast model were further confirmed via transient transfection of GFP-PC2 into HEK293 cells.

Results: Our preliminary data indicate that select PC2 missense mutants are more rapidly degraded in both yeast and HEK293 cells relative to wild type PC2. Moreover, unstable PC2 mutants are more highly poly-ubiquitinated than wild type PC2. In addition, following treatment with the proteasome inhibitor MG132, the level of polyubiquitinated protein increases to a greater extent for PC2 missense variants, suggesting selective turnover by the proteasome.

Conclusions: The findings support our hypothesis that PC2 missense mutants are ERAD substrates. Given recent interest in the development of protein folding modulators for other ERAD-related diseases, our data provide a promising hint that the maturation of some PC2 missense mutants may be amenable to pharmacological correction. Funded by NIDDK101584 to CJG and NIDDK079307 to JLB.

Funding: NIDDK Support

TH-PO668

HDAC6 Controls Polycystin-2 Expression in Pkd1-Null Cells

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Background: ADPKD is a hereditary disorder that affects 1:1000 to 1:500 people and is characterized by fluid-filled cysts that arise from renal tubules. ADPKD results from mutations in either the PKD1 or PKD2 gene, which encode the gene products polycystin 1 (PC1) and polycystin 2 (PC2), respectively. Although PC1 and PC2 have been studied intensively, information on how they function is still emerging. It has been previously shown that PC2 is degraded via proteasome in MDCK cells. We have shown that overexpression of PC1 accelerates PC2 degradation via the autophagy in MDCK cells. It is unknown how PC2 is degraded in *Pkd1*-null cells. Here we proposed to determine degradation pattern of PC2 and whether HDAC6 alters PC2 expression in *Pkd1*-null cells.

Methods: To determine PC2 degradation pattern we have treated *Pkd1*-null and control cells with cycloheximide to block translation and then inhibited autophagy with bafilomycin and proteasome with MG132, and examined PC2 expression. Next, we inhibited HDAC6 activity with TSA and examined PC2 expression.

Results: Inhibition of proteasome with MG132 prevented degradation of PC2 in control cells, suggesting that PC2 is degraded via proteasome when PC1 is expressed. Inhibition of autophagy with bafilomycin prevented degradation of PC2 in *Pkd1*-null cells, suggesting that PC2 is degraded via autophagy when PC1 is absent. In immunoprecipitation assay PC2 had higher affinity for p97/VCP, a proteasome substrate, in control cells than in *Pkd1*-null cells, indicating that PC2 is degraded via proteasome when PC1 is expressed, but not in *Pkd1*-null cells. Inhibition of HDAC6 activity with TSA decreased PC2 expression in both *Pkd1*-null and control cells suggesting that HDAC6 regulates PC2 expression.

Conclusions: PC2 is mainly degraded via autophagy in *Pkd1*-null cells and via proteasome in control cells. HDAC6 regulates PC2 expression in both *Pkd1*-null and control cells. Further studies will have to determine whether HDAC6 controls PC2 trafficking in *Pkd1*-null cells.

Funding: NIDDK Support

TH-PO669

Human-Specific Abnormal Alternative Splicing of the Wild-Type PKD1 Gene Induces Premature Termination of Polycystin–1

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Background: Human *PKD1* is unusual in that it contains two long polypyrimidine tracts in introns 21 and 22 (2.5kb and 602bp, respectively, 97% C+T), whereas the mouse and other species lack these C+T rich regions. Western blot analysis of polycystin-1 (PC1), using a monoclonal antibody to the extreme N—terminus indicates that humans, but not mice, have a smaller EndoH sensitive product, termed Trunc_PC1. Here we show that Trunc_PC1 is the product of differential splicing across introns 21 and 22 and that 28.8-61.5% of human transcripts undergo splicing events that lead to premature translational termination. Thus, the presence of these polypyrimidine tracts leads to decreased levels of full length functional PC1 reducing the level of PC1 signaling from normal alleles and in the context of a mutant allele may force signaling below a critical 'cystogenic' threshold.

Methods: We used RT-PCR from exons 20-24 to quantify the number of splice forms terminating early using NanoPore sequencing. We also compared the number of copies PC1 mRNA per mg total RNA at the 5' and 3' end of the human transcript and compared this with the copy number from normal mouse kidneys. We also created a stable cell line that produces a C-terminally FLAG tagged PC1 cDNA that terminates after exon-20, the region where Trunc_PC1 is predicted to end.

Results: Assaying seven adult kidneys showed that 62.2±12.6% of PC1 transcripts read through and had the accepted sequence while the remainder mis-spliced and truncated. We measured the PC1 mRNA copy number in nine adult human kidneys. For the 5' probe (exon 15) and 3' (exon 34) probes, there were $7.38\pm3.47x10^5$ and $1.03\pm0.354x10^6$ copies/µg, respectively --- about 22--31 copies per cell. Mice had a similar number of total transcripts $9.59\pm2.30x10^5$ copies/mg. The synthetic cDNA had an identical mass to Trunc_PC1 showing that they are the same species.

Conclusions: About 40% of human *PKD1* transcripts terminate early producing Trunc_PC1 implying that humans are dosage hypomorphs when compared to mice. Furthermore, the presence of an ER resident truncated form of the PC1 protein may interfere with the assembly of the polycystin complex.

Funding: NIDDK Support

TH-PO670

Species-Specific Differences in Pkhd1 Transcriptional Regulation: The Role of Cystin, the Cys1 Gene Product

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Background: ARPKD (MIM 263200) typically results from mutations in *PKHD1*, which encodes a set of secreted and membrane-bound isoforms, referred to as FPC (Onuchic, 2002). Our previous studies showed: 1) mouse *Pkhd1* is transcriptionally complex (Boddu, 2014); 2) cystin, the protein disrupted in the *Cys1*^{cpk} mouse, interacts with Srsf5, a pre-mRNA *splicing* factor (Watts, 2016); 3) *Pkhd1* exon 51 contains a functional Srsf5 binding site. In the current study, we compared *Pkhd1/PKHD1* and cystin

in mouse, rat and human; assessed whether cystin is a transcriptional regulator of *Pkhd1*; and examined consanguineous families with genetically unresolved hepato-renal fibrocystic disease (HRFD) for *CYS1* mutations.

Methods: We performed RT-PCR and comparative informatic analyses for mouse, rat and human *Pkhd1/PKHD1* and cystin, respectively. For minigene splicing assays, we transfected a mouse *Pkhd1* exon 6, 7, 51 construct into TERT-immortalized $Cys1^{wt}$ (wt) and $Cys1^{cpk}$ (*cpk*) stable cell lines, and wt and *cpk* primary collecting duct cells. Whole exome sequencing was performed in 258 consanguineous HRFD families.

Results: Comparative RT-PCR showed that mouse *Pkhd1* encodes multiple isoforms; rat *Pkhd1* and human *PKHD1* have minimal transcriptional complexity. There is limited inter-species *PKHD1/Pkhd1* homology (72%, human-mouse; 71%, human-rat; 86%, mouse-rat). In contrast, cystin is identical in mouse and rat, but rodent-human identities are limited (58%, human-mouse; 59%, human-rat). Quantitative minigene assays revealed differential splicing of the *Pkhd1* construct in wt and *cpk* cell lines. Preliminary Iso-Seq analyses of wt and *cpk* kidneys support differential *Pkhd1* splicing. Finally, we identified a 5 yo HRFD boy with a homozygous *CYS1* variant, c.318+5G>A, that is predicted to disrupt the exon 1 donor site.

Conclusions: Our data demonstrate that: 1) the transcriptional regulation of mouse *Pkhd1* is distinct from its rat and human orthologues; 2) cystin is highly conserved among rodents, but there is limited rodent-human homology; 3) cystin is a transcriptional regulator of mouse *Pkhd1*; and 4) *CYS1* mutations are a rare cause of human HRFD. Our data suggest that in $Cys1^{cpk/cpk}$ mice, loss of cystin function may contribute to renal cystogenesis due in part to alterations in *Pkhd1* transcriptional regulation.

TH-PO671

Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing

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Background: Severe PLD (sPLD) is a rare and poorly understood phenotype seen in both ADPKD and ADPLD. Mutations of *SEC61*, *SEC63*, *PRKCSH*, *GANAB*, and *ALG8* have been shown to cause PLD by impairing the maturation and transit of polycystin-1 (PC1) through the endoplasmic reticulum protein-processing (ER-PP) pathway. We hypothesize that rare mutations including ER-PP pathway genes that segregate in multiple families may modify PLD in patients with ADPKD and ADPLD.

Methods: We performed whole exome sequencing (WES) using Illumina HiSeq2000/2500 with SSV4/5 capture kit in 203 patients from Canada, U.S., Belgium, and the Netherlands, including 23 affected discordant sib-pairs and 16 affected concordant sib-pairs for sPLD from 39 families (matched by gender and age) and 125 sporadic cases. All patients with sPLD had a cystic liver of >4x normal volume. We performed a focused analysis on 168 genes involved in ER-PP pathway. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF ≤1%) deleterious variants of high and moderate impact as predicted by PolyPhen-2, SIFT, PROVEN, Mutation Tester, Mutation Assessor, Mammalian and Vertebrate nucleotide-level conservation, and Combined Annotation Dependent Depletion.

Results: Overall, we achieved a mean target coverage of 99X with 90% of the targeted exomes having >30X read depth. We identified 123 ER genes with rare deleterious variants and among them, we found 9 ER genes (i.e. *UGGT1*, *UGGT2*, *SEC31B*, *SEC24D*, *SEC23B*, *ALG8*, *ALG6*, *PRKN* and *ATF6B*) with rare high and/or moderate impact variant(s) present in more than 6 subjects and each segregated with PLD disease severity in 1 to 4 families and 4-10 sporadic sPLD cases.

Conclusions: Our results suggest extensive genetic heterogeneity with no one single gene accounting for a large proportion of severe PLD cases. Future in-vitro and/or in-vivo functional studies will be needed to define the potential pathogenicity of the most promising candidate genes. Identification of genetic modifiers of severe PLD has the potential to improve risk prediction and treatment of this unusual complication.

Funding: Private Foundation Support

TH-PO672

Disruption of the EF-Hand Domain of Polycystin-2 Ameliorates Cystic Disease Caused by Polycystin-1 Deficiency

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Background: Polycystin-2 (PC2/TRPP2), the product of one of the genes mutated in ADPKD, is expressed in the endoplasmic reticulum (ER) and ciliary membranes. The COOH-terminal tail of PC2 contains a potential Ca^{2+} binding EF-hand motif. A mouse model termed $Pkd2^{TEAA}$, in which critical residues at the EF-hand were substituted with alanine (T769A, E772A) to inactivate the Ca^{2+}-binding properties of PC2-EF, was generated via CRISPR/Cas9 methodology [ASN2017, TH-PO597]. The $Pkd2^{TEAA}$ mutant does not result in loss of PC2 function as evidenced by the lack of cysts in $Pkd2^{TEAA/TEAA}$ animals. In this study we assessed the impact of the $Pkd2^{TEAA}$ allele on *Pkd1* derived cysts.

Methods: The $Pkd1^{R2220W}$ human REJ mutant ($Pkd1^{RW}$) is a representative candidate of a PC1 hypomorphic missense mutation as it leads to a clear yet partial defect in PC1 biogenesis and cleavage. Mutant alleles were further modified by insertion of a V5 epitope tag in-frame at the C-terminus to detect the mutant proteins ($Pkd1^{RW}$-*V5* and $Pkd2^{TEAA}$-V5). The $Pkd2^{TEAA}$ mouse was crossed onto a $Pkd1^{RW/flox}$ background under the control of *Pkhd1-Cre* (collecting duct-specific). The kidneys were examined by histological and morphological parameters.

Results: Compared to $Pkd1^{RW/flox}$*; Pkhd1-Cre* mice, the kidneys at P24 from $Pkd1^{RW/flox}$*;* $Pkd2^{TEAA/+}$*; Pkhd1-Cre* mice displayed a decreased KW/BW ratio (0.16 ± 0.02 vs 0.067 ± 0.04, ***p<0.001) and BUN (mg/dL: 93.6 ± 24.97 vs. 38.6 ± 19.54, **p<0.0013). We observed a marked increase in apoptosis specifically in cyst-lining epithelia expressing $Pkd2^{TEAA}$. No significant difference in the protein levels of PC1 or PC2 proteins could be detected between the different genotypes.

Conclusions: Inactivation of the Ca^{2+}-binding properties of PC2 EF-hand on a partially PC1 deficient background results in improved cystic phenotype possibly via specific apoptosis of PC1 mutant cyst-lining epithelial cells. Modulators of PC2 EF-hand function may alter PC2 function *in vivo* to slow cyst progression in the setting of some PC1 missense mutations.

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TH-PO673

Loss of the Master Regulator of Mitochondrial Fusion Opa1 in Renal Tubules Is Not Sufficient to Drive Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder. The most commonly mutated gene, *PKD1*, encodes for polycystin-1 (PC1). We showed enhanced glycolysis and reduced mitochondrial-derived ATP in *Pkd1* mutant cells and kidneys (Rowe et al. 2013). A direct role of PC1 on mitochondrial regulation has been recently shown, either at the mitochondria-associated membranes, MAMs (Padovano et al. 2017), or by direct translocation of the PC1 C-terminal tail (CTT) in the mitochondrial matrix (Lin et al. 2018). We wondered whether mitochondrial dysfunction is a driver, or else a modifier, in PKD.

Methods: Transmission electron microscopy (TEM) on kidney sections, Seahorse XFe96 Analyzer for mitochondrial oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), mitochondrial network morphology by mt-DsRFP live imaging, genetic ablation of *Opa1* using Ksp-Cre line.

Results: We detected alterations in mitochondrial network morphology, in OCR, and in ECAR in $Pkd1^{-/-}$ cells. We found decreased number of mitochondria, many with aberrant cristae, mitochondrial fragmentation, and decreased mitochondrial respiration in the cystic epithelia of $Pkd1^{fl/-}$*:Ksp-Cre* kidneys at P4. At the molecular level we identified decreased mitochondrial pro-fusion protein Opa1, and increased fission regulator Drp1 in the cystic kidneys. To determine the contribution of reduced Opa1 and the consequent mitochondrial alterations in renal epithelia, we generated $Opa1^{fl/fl}$*:Ksp-Cre* mice. Animals are born at the expected mendelian ratio and die within the first three months of life. At sacrifice gross kidney enlargement was observed, and this is mostly due to expansion of DBA positive tubules. Decreased mitochondrial respiration was observed, but cells maintained a cuboidal shape. Despite the increase in the kidney volume over time, we detected only mild tubule dilation at P60, and no overt cyst formation.

Conclusions: Our data indicate that deletion of PC1 in the kidney epithelium results in alteration in mitochondrial structure and fitness. Surprisingly, decreasing mitochondrial proficiency by means of Opa1 ablation is not sufficient *per se* to drive cystogenesis. We are currently verifying if crossing $Opa1^{fl/+}$ *with* $Pkd1^{fl/-}$*:Ksp-Cre* accelerates disease progression and/or other molecular players are involved in PKD.

Funding: Private Foundation Support

TH-PO674

Rescue of Suppressed Autophagy in Polycystic Kidney Disease

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Background: Autophagy maintains proteostasis by sequestering damaged organelles and proteins into autophagosomes for delivery to the lysosome where cargo is degraded and recycled. Several treatments that have been shown to ameliorate PKD in mice are potent activators of autophagy. The aims of the study were to determine the effects of several autophagy inducers on autophagy, apoptosis, and proliferation markers in PKD kidneys and to determine whether kidney-specific autophagy knockout results in a cystic phenotype.

Methods: Mice were treated with 2-deoxyglucose (2DG), trehalose (TRE), or metformin (MET) followed by bafilomycin (BAF) to measure autophagic flux. p62 (autophagy-specific tag for degradation & marker of autophagy inhibition), LC3-II (marker of autophagosomes), Atg12-5 (marker of autophagosome elongation), cleaved caspase 3 (marker of apoptosis), and AMBRA1 (Activating molecule in Beclin1-regulated autophagy) that links autophagy to cell proliferation by promoting dephosphorylation and degradation of cMyc (transcription factor that activates pro-proliferative genes) were measured by immunoblot. Kidney-specific Atg7-/-mice received MRIs at 180D of age to precisely measure cyst volume and number.

Results: PKD kidneys had significantly reduced autophagic flux compared to WT, which was rescued by 2DG. Further, PKD kidneys had less Atg12-5 complex vs WT, an effect blocked by TRE. PKD kidneys had more cleaved caspase 3, a marker of apoptosis,

compared to WT, which was decreased by MET, 2DG, and TRE. cMyc phosphorylation was greater in PKD compared to WT, an effect blocked by 2DG. Trehalose increased AMBRA expression in PKD kidneys (Table 1, *p<0.05). On MRI scan, mean number of cysts (0.5mm) in 180 day old Atg7-/- mice was 5±2 vs. 1±0.5 in WT (p<0.05). One Atg7-/- kidney was massively cystic.

Conclusions: In summary, 2DG restored autophagic flux in PKD kidneys. Autophagy inducers increased expression of autophagy-related proteins and decreased apoptosis and proliferation markers. Kidney-specific knockout of autophagy in 180 day old mice resulted in a cystic phenotype.

Funding: Other U.S. Government Support

Table 1

	FLUX	Atg12-5	p cMyc	AMBRA	CC3
WT VEH	0.4±0.05*	0.4±0.05*	0.8±0.1*	0.7±0.1	1.0±0.05*
PKD VEH	0.1±0.03	0.2±0.02	1.3±0.1	0.7±0.1	1.6±0.09
PKD 2DG	0.3±0.06*	0.2±0.08	0.9±0.1*	1.3±0.1	1.0±0.15*
PKD TRE	0.1±0.08	0.3±0.07	1.2±0.2	1.2±0.1*	0.6±0.1*
PKD MET	0.1±0.07	0.2±0.02			0.9±0.08*

TH-PO675

Head-to-Head Study of Sirolimus and an mTOR Kinase Inhibitor (TORK) in a Hypomorphic Model of Polycystic Kidney Disease

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Background: Sirolimus indirectly inhibits mTORC1 and reduces but does not completely inhibit cyst growth in rodent models of autosomal dominant polycystic kidney disease (ADPKD). Sirolimus was not effective in human PKD and was associated with side effects. The novel ATP competitive mTOR kinase inhibitors (TORKs) e.g. Torin2 directly inhibit mTOR kinase that results in inhibition of both mTORC1 and 2. TORKs, which increase liver enzymes, have a different side effect profile to sirolimus, which causes mucositis. We report a head-to-head comparison of Torin2 versus sirolimus in a hypomorphic mouse model of PKD.

Methods: C57Bl/6 *Pkd1* p.R3277C (PKD) mice were treated with 0.5mg/kg sirolimus (SIR) or 10mg/kg Torin2 (TORK) daily from 50 to 120 days of age. Serum BUN was analyzed using an enzymatic assay. Cyst area was quantified from H&E stained kidneys. Kidneys were immunoblotted for mTORC1 substrates, pS6 and p4E-BP1 (S65), mTORC2 substrate, pAkt (S473), LC3-II (autophagosome marker), and p62 (autophagy-specific ubiquitin-binding protein). Autophagic flux was defined as the difference between LC3-II before and after administration of the lysosomal inhibitor bafilomycin.

Results: Kidney weight and serum BUN were significantly decreased in TORK- and SIR-treated mice compared to vehicle (VEH). CVD showed a tendency to decrease with both TORK and SIR. pAKT was decreased in both TORK and SIR treatments. pS6 was significantly decreased in SIR-treated mice only. TORK significantly increased autophagic flux (FLUX). No side effects were noted on gross examination in either treatment group.

Conclusions: For the first time, we have shown in a head-to-head study that the TORK, Torin2, is as effective as sirolimus in decreasing kidney size and serum BUN in a hypomorphic ADPKD mouse model. Both drugs inhibited pAKT. SIR had a better effect on pS6 than TORK. Interestingly, TORK resulted in a significant increase in autophagic flux. As Torin2 has a short half-life (~1 hr), further studies are warranted to determine whether more frequent dosing of Torin2 will be more effective than sirolimus.

Funding: Other U.S. Government Support

Table 1

	KW/BW(%)	BUN (mg/dL)	pAKT	pS6	FLUX	p62	Cyst area,%	p4EBP1
PKD VEH	2.6±0.1	63±2	0.8±0.2	1.3±0.1	0.02±0.1	1.03±0.05	31.6±3.2	0.7±0.1
PKD TORK	2.1±0.2*	41±4*	0.3±0.1*	1.0±0.2	0.82±0.2*	0.88±0.02	22.1±4.8	0.4±0.1
PKD SIR	2.3±0.02*	39±4*	0.2±0.1*	0.7±0.04*	0.10±0.2	0.86±0.01	20.2±3.2	0.4±0.1

*p<0.05 vs VEH,

n=4

TH-PO676

The Role of LKB1-AMPK Signaling on Renal mTOR and Cyst Progression in ADPKD

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Background: In ADPKD, the mTOR pathway is thought to contribute to cyst epithelial cell proliferation and cyst growth. Downstream components of the mTOR pathway, i.e. ribosomal protein S6, are aberrantly phosphorylated in cyst-lining cells. Fluid accumulation within the cyst cavity is driven by Cl^- secretion via apical CFTR Cl^- channels. AMP Kinase (AMPK) is an important negative regulator of both mTOR and CFTR. Liver Kinase B1 (LKB1), a well-known tumor suppressor, directly phosphorylates and activates AMPK. Previously, we showed that BIT-11, a novel small molecule LKB1 activator, increased P-AMPK and decreased P-S6 in human ADPKD cells. BIT-11 decreased ADPKD cell proliferation, Cl^- secretion and *in vitro* cyst growth and blocked cyst-like tubule dilations in *Pkd1*$^{-/-}$ mouse kidneys in metanephric organ culture. Our hypothesis is that the LKB1-AMPK pathway regulates mTOR-mediated cell proliferation and CFTR-dependent fluid secretion by cystic cells and modulates ADPKD progression.

Methods: An inducible LKB1 knockout cell line was generated from *Lkb1*$^{flox/flox}$*:ROSA26-Cre*^{ERT2} mouse kidneys. To determine if the loss of LKB1 is sufficient to induce cystic disease, we crossed *Lkb1*$^{flox/flox}$ and *Pkhd1-Cre* mice to knock out LKB1 selectively in collecting ducts (CDs). To test the effect of direct LKB1 activation, BIT-11 was delivered by daily gavage from 5 to 20 weeks to *Pkd1*$^{RC/RC}$*:Pkd2*$^{+/-}$ mice, an ADPKD model that develops a renal cystic disease by 5 weeks of age and a progressive decline in renal function.

Results: *Lkb1*$^{flox/flox}$*:ROSA26-Cre*^{ERT2} renal cells were treated with tamoxifen to delete LKB1 expression. The loss of LKB1 significantly decreased P-AMPK, but had no effect on mTOR signaling. CD-specific knockout of LKB1 in otherwise normal mice resulted in hydronephrosis; however, renal cyst formation was not observed. On the other hand, treatment with BIT-11 caused a significant decrease in kidney weight (percent body weight), blood urea nitrogen and interstitial fibrosis in *Pkd1*$^{RC/RC}$*:Pkd2*$^{+/-}$ mice.

Conclusions: The LKB1-AMPK pathway does not appear to regulate basal mTOR activity in the adult kidney; however, direct activation of this pathway using a novel LKB1 activator decreased mTOR-mediated cell proliferation and the decline in renal function in ADPKD mice, suggesting that this may be a potential therapeutic approach for the treatment of ADPKD.

Funding: NIDDK Support, Private Foundation Support

TH-PO677

Renal Stones in Mice Compound-Heterozygous for Hypomorphic Pkd1V and Pkd1RC Alleles

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Background: Disease severity in orthologous mouse models of ADPKD is determined in part by the nature of the *Pkd1* mutation. While null mutations cause *in utero* cyst formation and embryonic lethality, hypomorphic mutations *Pkd1*$^{V/V}$ and *Pkd1*$^{RC/RC}$ are sufficient for embryonic survival. *Pkd1*$^{V/V}$ mice express a mutant form of polycystin-1 that fails to undergo autocatalytic cleavage at its G-protein coupled receptor proteolysis site and develop renal cystic disease postnatally and die between 2-6 weeks of age. *Pkd1*$^{RC/RC}$ mice express a temperature-sensitive folding mutant with reduced levels of mature protein and can live over a year with mild, slowly progressive cystic disease. The phenotypic consequences of these two distinct hypomorphic *Pkd1* mutations together are not known.

Methods: *Pkd1*$^{V/+}$ and *Pkd1*$^{RC/+}$ mice on a C57 background were crossed to produce compound-heterozygous *Pkd1*$^{V/RC}$ mice. Mice were maintained on breeder diet from birth, and sacrificed at 3 or 26 weeks of age and kidneys analyzed. Presence of renal stones in 26 week old adult mice was determined by micro computed tomography (μCT) analysis of kidneys following euthanasia.

Results: Three week old *Pkd1*$^{V/RC}$ mice had elevated kidney weight to body weight ratios (15.3 ±0.87) and their kidneys were obviously cystic by visual inspection. To determine the long-term consequences of disease we maintained a cohort of mice to 26 weeks of age. The majority of the mice thrived throughout the duration of the study and had significantly lower kidney weight to body weight ratios compared to 3 week old mice. Visual inspection of kidneys from adult mice revealed the presence of numerous large, white masses immediately underneath the renal surface. Analysis of these kidneys by μCT determined that the masses were mineralized deposits of ~0.5mm diameter present throughout the renal cortex but absent from the medulla.

Conclusions: *Pkd1*$^{V/RC}$ mice are severely cystic by 3 weeks of age. However, these cystic kidneys retain sufficient function to maintain survival up to 26 weeks of age and presumably beyond. Kidneys from adult mice had mineralized deposits throughout the renal cortex. To our knowledge this is the first known instance of renal stones in a mouse model of ADPKD.

Funding: NIDDK Support

TH-PO678

The Role of Interferon Regulatory Factor-5 in Acceleration of Cystogenesis in Polycystic Kidney Disease

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Background: In mouse models of polycystic kidney disease (PKD), unilateral nephrectomy (UNx: 1K) accelerates kidney cyst growth compared to non-nephrectomized (2K) mice. Analysis of RNA sequencing data revealed that 1K compared to 2K *Pkd1* deficient mice have enrichment of genes associated with inflammation, phagocytosis, and macrophages. Previous studies showed that macrophages promote cystogenesis in mouse models of PKD; however, transcription factors that control cytokine production by macrophages in cystic disease have not been identified. Herein, we study the role of interferon regulatory factor-5 (IRF5), a transcription factor involved in macrophage activation and cytokine release, during cyst progression in 2K vs 1K *Pkd1* deficient mice.

Methods: Adult *Pkd1*$^{flox/flox}$ mice with or without CAGG-cre were administered tamoxifen for global knockout of the *Pkd1* gene. Three weeks after cre induction, mice underwent sham surgery or UNx to accelerate cyst formation. Kidneys were harvested at 3 (early stage) or 6 (late stage) weeks after UNx and kidney immune cells were analyzed by flow cytometry. Some mice were treated with weekly injection of IRF5 antisense oligonucleotide (40mg/kg/wk: Ionis Pharma) or scrambled ASO for a total of 3 or 6 weeks after UNx and kidney was harvested for kidney immune cells/cytokine and histology.

Results: *Pkd1* deficient mice had increased kidney IRF5 mRNA levels compared to control mice. 1K *Pkd1* mice increased inflammatory cytokine production, cyst growth and infiltrating ($CD11b^{hi}$, $F4/80^{lo}$) and resident macrophage ($CD11b^{lo}$, $F4/80^{hi}$) numbers compared to 2K *Pkd1* deficient mice. Preliminary results indicate that treatment with IRF5 ASO (total 3 and 6 weeks) in 1K *Pkd1* mice had no effect on kidney macrophage numbers, but significantly decreased kidney T cell accumulation, inflammatory cytokine production and cyst growth. Further comparison of male and female mice shows that 1K female mice had higher kidney IRF5 levels compared to male mice and a better response to IRF5 ASO treatment.

Conclusions: UNx in *Pkd1* mice increases the number of kidney macrophages, inflammatory cytokine and cyst growth. IRF5 ASO treatment suppressed kidney IRF5 levels/reduced inflammation and attenuated the acceleration of cytogenesis in *Pkd1* mice.

Funding: NIDDK Support

TH-PO679

AMP-Activated Protein Kinase (AMPK) Drug Re-Purposing for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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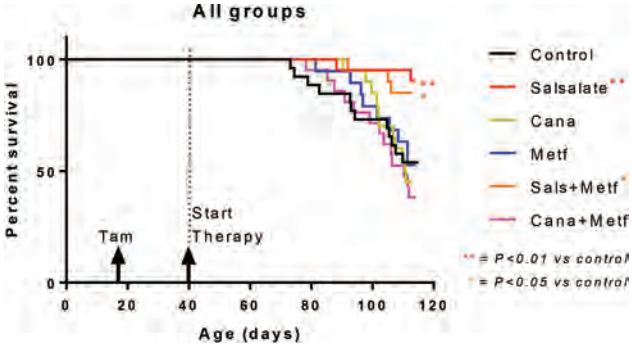
Background: ADPKD is an important cause of end stage renal disease (ESRD). Multiple studies have highlighted AMPK as a potential therapeutic target for ADPKD. Notably, metformin (MET) attenuated cystic kidney disease in an aggressive PKD model. MET and canagliflozin (CAN) are indirect AMPK inducers, while salsalate (SAL) is a direct AMPK activator; all have excellent safety profiles for clinical use.

Methods: We tested the efficacy of MET, CAN, SAL, MET+CAN or MET+SAL in a tamoxifen-inducible Pkd1(iKsp-Pkd1del) conditional knock-out mouse model. Tamoxifen was used on days p18 and p19 to induce adult onset PKD (n=20 male mice/group). AMPK drug treatments were then started from p40 using dosages expected to yield serum levels similar to those observed in the clinical settings. Blood Urea (BU) levels were monitored weekly and mice with ESRD (BU >20 mmol/L) were sacrificed. The experiment continued until 50% of the untreated mutant mice reached ESRD.

Results: Compared to the untreated mutant mice, SAL alone ($p<0.01$) or SAL+MET ($p<0.05$) improved kidney survival and reduced kidney weights (Figure). MET, CAN, or MET+CAN did not have any effect. At the end of the study, 91% and 85% of the SAL and SAL+MET groups were free of ESRD versus 38%-58% in the other groups. SAL+MET did not differ from SAL suggesting a lack of synergism. Molecular analyses (systems biology and protein analyses) are currently in process to understand the mechanisms of action.

Conclusions: SAL is a promising re-purposed drug which may be readily translated to the clinical setting for treatment of ADPKD. MET at the dosage used in the usual clinical setting had no therapeutic effect in our model. *Equal contribution of first two authors and last two authors.

Funding: Private Foundation Support



Improved survival free of ESRD in the Salsalate and Salsalate+Metformin groups compared to the untreated mutant mice and other treatment groups.

TH-PO680

Inhibition of Wnt/β-Catenin Signaling Slowed Cystogenesis in Postnatal Mouse Model of ADPKD

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Background: The Wnt signaling pathway has an important role for nephron development and elevated expression of β-catenin, master regulator of the Wnt signaling pathway, is shown to correlate with cystogenesis in autosomal dominant polycystic kidney disease (ADPKD). Here we provide further evidence that inhibition of Wnt/β-catenin pathway slowed cystogenesis in a postnatal model of ADPKD using *Ksp-CreER^{T2}; Pkd1$^{flox/flox}$* mice.

Methods: To understand the pathological contribution of Wnt signaling in ADPKD, we measured expression of Wnt gene and β-catenin expression *in vivo* using two murine models of ADPKD where postnatal cystogenesis could be observed. We also tested the effect on cyst formation of small molecule inhibitors of β-catenin interaction with either CBP or p300.

Results: We observed increased expression of Wnt genes in and higher levels of β-catenin in cystic kidneys of both *Hoxb7-Cre-IRES-eGFP;Pkd1$^{flox/flox}$* mice and *Ksp-CreER^{T2};Pkd1$^{flox/flox}$* mice. Although the overall pattern differed between these models, Wnt7a was consistently over-expressed in both models of ADPKD. To test whether canonical Wnt signaling was required for cystogensis, we inactivated one copy of the *Ctnnb1* gene, encoding β-catenin, in *Ksp-CreER^{T2};Pkd1$^{flox/flox}$* mice. Reduced progression of cyst enlargement was observed in *Ksp-CreER^{T2};Pkd1$^{flox/flox}$:Ctnnb1$^{flox/+}$* mice. Furthermore, treatment of *Ksp-CreER^{T2};Pkd1$^{flox/flox}$* mice with a small molecule, ICG-001, that blocks the interaction of β-catenin with CBP slowed the progression of cyst formation and mice showed reduced kidney:weight to body weight ratio. In contrast, a small molecule, IQ-1, which blocked the interaction of β-catenin with p300 had no effect in cyst progression.

Conclusions: Our study demonstrates that the canonical Wnt signaling pathway has an important role in cystogenesis and inhibition of the β-catenin-CBP complex by ICG-001 may serve as a new therapeutic target to decrease cyst formation.

Funding: NIDDK Support

TH-PO681

COX2 Inhibition Slows Disease Progression and Improves the Altered Renal Lipid Mediator Profile in the Pkd2WS25/- Mouse Model of ADPKD

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Background: Oxylipins are bioactive lipid mediators formed by oxygenation of polyunsaturated fatty acids via cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) monooxygenases. We have shown that the earliest and most consistent alteration in the oxylipin profile in diverse models of cystic kidney diseases is increased levels of COX derived prostanoids. Several of these, such as PGD_2 and PGE_2 have been shown to mediate renal cyst formation by increasing intracellular cAMP production, a known abnormality in various forms of cystic kidney diseases. Further, inhibition of COX oxylipin formation reduces disease progression in a model of nephronophthisis, as well as in some non-cystic renal diseases. The present study was carried out to determine whether a selective COX2 inhibitor would reduce disease progression and ameliorate the altered renal oxylipin profile in the Pkd2 orthologous mouse model of autosomal dominant polycystic kidney disease 2 (ADPKD2).

Methods: Weanling male $Pkd2^{WS25/-}$ mice were provided a standard laboratory rodent diet (AIN-93G) with or without 50 mg celecoxib per kg body weight per day, for 13 weeks. Renal cysts were analyzed histomorphometrically and serum BUN and creatinine levels were determined. Targeted lipidomic analysis of renal oxylipins was performed by HPLC-tandem mass spectrometry.

Results: Diseased animals had significant cyst involvement and reduced renal function as indicated by elevated BUN. Consistent with our previous studies, 8 of 11 COX derived prostanoids were higher in diseased kidneys. In addition, 24 of 33 LOX oxylipins and 7 of 16 CYP oxylipins were lower in diseased kidneys. Drug treatment reduced cyst area by 50%, cyst volume by 70%, and serum creatinine and BUN by 10-20%. With respect to lipid mediators, drug treatment reduced 5 of the 8 elevated COX derived prostanoids and increased 5 of the 24 LOX and 5 of the 7 CYP oxylipins that were reduced by disease.

Conclusions: Selective COX2 inhibition significantly ameliorates disease progression and improves renal function in Pkd2 mice. Further studies on dose, potential risks, and long-term effects of COX2 inhibition are needed to determine whether this is a viable therapeutic option to treat ADPKD. Supported by the Natural Sciences and Engineering Research Council of Canada

Funding: Veterans Affairs Support, Government Support - Non-U.S.

TH-PO682

A Strategy for Reducing Cysts in Autosomal Dominant Polycystic Kidney Disease with a CFTR Corrector

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Background: ADPKD is associated with progressive enlargement of cysts. Mutations in *pkd1 and pkd2* induce growth-related pathways, including heat shock proteins raising the prospect that pharmacological interventions that target these pathways might alleviate or prevent ADPKD. The purpose of our study was to demonstrate a role for VX-809, a corrector of cystic fibrosis transmembrane conductance regulator (CFTR), in reducing cyst growth.

Methods: We used the *Pkd1$^{fl/fl}$; Pax8^{rtTA}; TetO-cre* mouse model which, when treated with doxycycline, allows for the ablation of PC1. These mice, where injected IP with doxycycline (4 µg of doxycycline/g body weight) on postnatal days (PND)11, PND12, and PND13, to induce multiple large cysts and large polycystic kidneys at approximately 3 weeks of age. Kidneys were harvested, sectioned and analyzed.

Results: Mice injected daily with VX-809 (30 mg/kg) from PND10 to PND20 showed significantly less cyst growth (see Fig 1). VX-809 improved renal function, as evidenced by a lower blood urea nitrogen (BUN) and creatinine. In proximal tubule-derived, *Pkd1*-knockout cells and in cystic kidneys, VX-809 reduced both basal and forskolin-activated cAMP levels, inhibited cyst growth and reduced levels of the heat shock proteins Hsp27, 70, and 90 which are upregulated in cystic kidneys. In the cystic mice, VX-809 decreased an ER stress marker, the GADD153 protein, cell proliferation, and apoptosis. Importantly

in proximal tubule-derived, cultured *Pkd1*-knockout cells, VX-809 increased the activity of the sodium proton exchanger, NHE3 which is down regulated in these cells.

Conclusions: VX-809 reduces the ability of cysts to grow by reducing the levels of HSPs and restore the NHE3 activity in proximal tubule cells. VX-809 could potentially be a new way to treat patients with ADPKD.

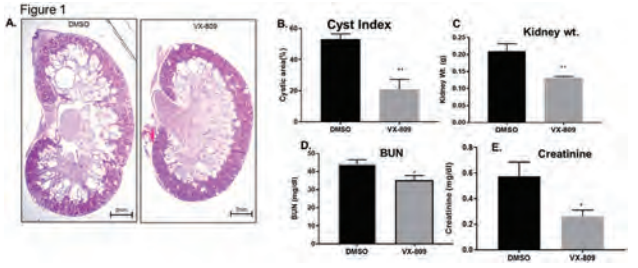

Fig. 1: Cystic mice kidneys before and after treatment with VX-809. See text for details.

TH-PO683

Ketogenic Dietary Interventions Ameliorate Disease Progression in a Rat Model of Polycystic Kidney Disease

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Background: PKD cells have recently been shown to have an altered metabolism favoring aerobic glycolysis similar to the Warburg effect in cancer. Possible glucose dependency may provide an opportunity for the treatment of PKD by dietary interventions. We and others recently showed that a mild reduction in food intake strongly inhibits disease progression in PKD mouse models. Here we tested the hypothesis that these beneficial effects are due to ketosis caused by intermittent starvation rather than caloric restriction per se.

Methods: The Han:SPRD rat model of PKD was utilized to test the effects of time restricted feeding and a ketogenic diet, respectively, and on the progression of PKD. For time-restricted feeding, animals were given access to normal chow *ad libitum* for 8 hours per day. A ketogenic diet consisting of ~80% dietary fat administered *ad libitum* without time-restriction.

Results: Animals treated with either a ketogenic diet or a time-restricted feeding regime consumed comparable calories to *ad libitum* controls and showed a significant decrease in markers of disease progression including a decrease in fibrosis, 2-kidney to bodyweight, cystic index, markers of proliferation, and mTOR activity.

Conclusions: Dietary interventions that lead to ketogenesis significantly attenuate disease progression in the Han:SPRD rat model of PKD. Mechanistically, this may be due to the lack of glucose availability in ketosis. Alternatively, or in addition, the ketone body beta-hydroxybutyrate (BHB) is known to regulate several signaling pathways involved in PKD, including mTOR, and may directly influence cell growth and proliferation of cystic cells. These data taken together suggest that safe and feasible dietary interventions may be effective PKD patients.

Funding: Private Foundation Support

TH-PO684

Glucose Metabolic Profiles in Renal Tissue of an Orthologous PCK Rat Model of Human PKD Using Metabolic and Proteomic Analyses

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Background: Polycystic kidney disease (PKD) is an inherited disorder characterized by excessive cellular proliferation and fluid secretion of the tubular epithelial cells due to genetic mutation. To detect altered renal metabolic and enzymatic activities, we performed metabolic and proteomic analyses in the PCK rat, an orthologous model of human autosomal recessive PKD.

Methods: In renal tissue of 20-week-old PCK and age-matched normal rats, metabolic products were analyzed by using capillary electrophoresis time-of-flight mass spectrometry and MasterHands metabolome analysis software; proteomic products were analyzed using Orbitrap mass spectrometry and Proteome Discoverer™ software.

Results: Metabolic analysis revealed a 1.8-fold increase in cAMP content in PCK cystic kidneys compared with normal kidneys, the same trend seen from our previous study using radioimmunoassay. Upstream glycolysis metabolites were decreased as follows: glucose 1-phosphate (0.5-fold), glucose 6-phosphate (0.5-fold) and fructose 6-phosphate (F6P, 0.6-fold); and downstream, 3-phosphoglyceric acid (3-PG, 4.2-fold) was increased in PCK samples. 2-Phosphoglyceric acid and phosphoenolpyruvate were detected in only PCK kidneys, not in normal kidneys. On proteomic analysis, increased fructose-bisphosphate aldolase A, an enzyme that converts F6P to 3-PG, was seen in PCK rats (3.6-fold). Tricarboxylic acid (TCA) cycle metabolites were increased as follows: citric acid (23-fold), *cis*-aconitic acid (8.5-fold), isocitric acid (32-fold), succinic acid (1.6-fold), fumaric acid (1.7-fold), and malic acid (2.1-fold) in PCK kidneys; 2-oxoglutarate was detected in only PCK kidneys. Citrate synthase, which converts acetyl CoA (2.0-fold) to citric acid, was increased (7.5-fold) in PCK kidneys. In the non-oxidative phase of the pentose phosphate pathway, increased ribose 5-phosphate (R5P) was detected in only PCK kidneys. Increased transaldolase (3.0-fold), which converts sedoheptulose 7-phosphate (S7P, 0.6-fold) to F6P, was found in PCK kidneys. Also, transketolase (2.4-fold), which converts S7P to R5P, was increased in PCK cystic kidneys.

Conclusions: These findings suggest that increased activity of pentose phosphate pathway as well as glycolysis and TCA cycle may play important roles in promoting PKD progression.

Funding: Government Support - Non-U.S.

TH-PO685

Discovery and Preclinical Characterization of RGLS4326 for the Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Edmund Lee,[1] Tania M. Valencia,[1] Annelie E. Schairer,[1] Kara Kersjes,[1] Jian Li,[1] Andrea N. Flaten,[2] Vishal Patel.[2] *[1]Regulus Therapeutics, San Diego, CA; [2]University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in the *PKD1* or *PKD2* genes, is among the most common human monogenetic disorders and a leading genetic cause of end-stage renal disease (ESRD). MicroRNAs (miRs) are non-coding RNAs that play central roles in cell differentiation, proliferation and survival by binding to complementary target mRNAs, resulting in repression of translation and eventual degradation of the targeted mRNAs. We have previously demonstrated that miR-17 promotes ADPKD progression, and inhibiting miR-17 is a promising strategy for the treatment of ADPKD.

Methods: RGLS4326 was discovered through screening a chemically-diverse library of >100 oligonucleotides for their ability to inhibit miR-17 in a miR-17 luciferase sensor assay. RGLS4326 was extensively profiled in multiple safety assays, including biochemical, ex-vivo tissues slices and in vivo studies. Preclinical efficacy of RGLS4326 was studied in both Pkd2-KO and Pcy mouse models of PKD.

Results: In preclinical studies, RGLS4326 potently inhibited miR-17 activity, displaced miR-17 from the translationally active high molecular weight polysomes, and de-repressed multiple miR-17 target genes in different mouse kidney cell lines. RGLS4326 shows favorable pharmacokinetic profiles in both normal and PKD mouse models, where preferential distribution to kidney compare to other tissues was evident. Most importantly, we have demonstrated that RGLS4326 confers efficacy in two mouse models of PKD following subcutaneous administrations.

Conclusions: Our preclinical data support the clinical development of RGLS4326 for the treatment of ADPDK. RGLS4326 is currently being studied in Phase I clinical studies.

Funding: Commercial Support - Regulus Therapeutics

TH-PO686

Efficacy of RGLS4326 in Human Primary ADPKD 3D-Cyst Cultured Cells

Annelie E. Schairer,[1] Tania M. Valencia,[1] Steven Lockton,[1] Sole Gatto,[1] Michael Kim,[1] Darren P. Wallace,[2] Edmund Lee.[1] *[1]Regulus Therapeutics, San Diego, CA; [2]University of Kansas Medical Center, Kansas City, KS.*

Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in the *PKD1* or *PKD2* gene, is among the most common monogenetic disorders and a leading genetic cause of end-stage renal disease. Kidney-specific overexpression of miR-17~92 produce kidney cysts in mice, whereas genetic knockdown of miR-17~92 attenuates disease progression in multiple mouse models of PKD. RGLS4326 is designed to specifically bind to miR-17 family of microRNAs, antagonize miR-17 activity and reduce disease progression in mouse models of PKD. In this study, we investigate the effect of RGLS4326 treatment on 3D growth of human primary ADPKD cyst cells derived from ADPKD donor nephrectomy samples.

Methods: Primary human ADPKD cyst cells (HuADPKD) were transfected with RGLS4326 or control oligo at 20nM, 100nM or 300nM for 24h. RNA samples were harvested for confirmation of miR-17 inhibition by measuring de-repression of a selected set of direct miR-17 target genes (PD-Sig) and RNA sequencing. Cells following 24h transfection were then seeded and further cultured in 3D cyst formation assay for 8 additional days.

Results: Functional inhibition of miR-17 in HuADPKD following RGLS4326 treatment was confirmed by PD-Sig. At the end of 8 additional days of 3D culturing, RGLS4326 consistently reduced growth of HuADPKD derived from multiple donors, decreasing cyst count and proliferation. Kolmogorov-Smironov test statistics on RNA sequencing data comparing log2FC cumulative distribution indicated significant upregulation (i.e. de-repression) of predicted miR-17 target genes after RGL4326 treatment. De-repression of selected direct miR-17 target genes were confirmed by qPCR and their implication on RGLS4326's mechanism of action in conferring efficacy were investigated.

Conclusions: RGLS4326 inhibits 3D cyst formation and growth of HuADPKD cells *in vitro* compared to oligo control. Our preclinical data supports the clinical development of RGLS4326 which is currently in Phase 1 for the treatment of ADPKD.

Funding: Commercial Support - Regulus Therapeutics

TH-PO687

RGLS4326 Confers Efficacy and Modulate Aberrant Signaling and Metabolic Pathways in PKD Mouse Models

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Background: Autosomal dominant polycystic kidney disease (*ADPKD)* is caused by mutations in *PKD1* and *PKD2* genes, where expansion of fluid-filled cysts and renal fibrosis often leads to end-stage renal disease. MicroRNAs are short non-coding RNAs that modulate several biological processes. We have previously shown that aberrant expression of miR-17 family of microRNAs is involved in human ADPKD pathogenesis. RGLS4326 is a chemically-modified oligonucleotide designed to sterically inhibit miR-17 functions and has been shown to reduce cyst growth *in vitro* and *in vivo*. The goal of this study was to determine the signaling pathways modulated by RGLS4326 treatment in PKD mouse models

Methods: RGLS4326 is efficacious in the *Pkd2-KO* and Pcy mouse models of PKD. We performed RNA sequencing and metabolite profiling using kidney samples from both mouse models following RGLS4326 treatment. Ingenuity Pathway Analysis was used to provide novel insights into signaling pathways modulated by RGLS4326 treatment.

Results: Through RNA sequencing, we identified >10000 differentially expressed genes in the PKD kidney samples compared to their age- and strain-matched normal controls. Comparative pathway analysis identified several dysregulated signaling pathways in the two PKD mouse models, including the Pparα, WNT/ β-catenin and cell cycle signaling, that were in turn modulated following RGLS4326 treatment. Next, we performed global metabolite profiling comparing *Pkd2-KO* and normal kidneys, and identified several biochemical alterations in the *Pkd2-KO* model, including substantial changes in lipid metabolism. In particular, decrease in β-fatty acid oxidation pathway was observed in the *Pkd2-KO* kidneys, which corroborates with previously observed Pparα-dysregulation in PKD mouse models. Importantly, modulation in lipid metabolites were also observed following RGLS4326 treatment.

Conclusions: Our results indicate that RGLS4326 confers efficacy and modulate aberrant PKD signaling and metabolic pathways. RGLS4326 is currently in Phase I clinical studies for the treatment of ADPKD.

Funding: Commercial Support - Regulus Therapeutics

TH-PO688

Effects of Pharmacologic Galectin-3 Inhibition on the Cardiac Phenotype and Survival of Pkd1-Deficient Mice

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Background: Myocardial abnormalities are a significant phenotype in ADPKD. We have previously shown that *Pkd1*-deficient mice develop cardiac dysfunction, a phenotype significantly rescued by galectin-3 (Gal-3) knockout.

Methods: In this scenario, we investigated the effects of 2 Gal-3 inhibitors on the cardiac phenotype of a *Pkd1*$^{+/-}$ noncystic mouse (HT) and on survival of a severely cystic mouse homozygous for a *Pkd1*-knockin allele that prevents polycystin-1 cleavage (VV). GR-MD-02 (GR, 60mg/kg), a Gal-3 extracellular inhibitor, or FTS (10mg/kg), an intracellular inhibitor of Gal-3/Ras interaction, was administered intraperitoneally 3x/week, starting at P1. Echocardiographic and protein expression analyses were performed in HT and wild-type (WT) mice at 5-6 weeks while survival was assessed in VVs.

Results: Left ventricular (LV) ejection fraction and shortening fraction were decreased in HTs compared to WTs [43.1% (35.8-54.2) *vs* 59.2% (52.8-66.0), p<0.01; and 23.3% (22.9-25.1) *vs* 31.2% (25.2-39.4), p<0.01; respectively], parameters partially rescued by FTS [52.3% (48.8-57.1) and 27.0% (22.5-29.3) *vs* untreated WT, NS], but not by GR. Interventricular septum diameter, on the other hand, was increased by GR in HTs [0.75 (0.71-0.81) *vs* 0.63mm (0.55-0.68), p<0.01), with only a trend for FTS (p=0.09). GR was also followed by trends of increase in LV mass/BW (p=0.12) and LV posterior wall diameter (p=0.08) in HTs. GR increased P-ERK2 expression in HT and WT hearts [1.70 (1.19-2.46) *vs* 1.29 AU (0.82-1.32), p<0.05; and 1.65 (1.03-3.49) *vs* 1.01 AU (0.94-1.07), p<0.05; respectively], while FTS increased P-ERK2 only in WTs [1.98 AU (1.52-2.51), p<0.01]. GR and FTS did not modify expression of P-GSK3β and P-PKCα and δ in HT and WT hearts, and did not improve survival in VVs.

Conclusions: Our findings revealed that intracellular inhibition of Gal-3 partially rescued systolic function parameters in HTs while its extracellular inhibition induced cardiac hypertrophy without rescuing the systolic phenotype. Differences between effects of pharmacologic inhibition and genetic Gal-3 KO are likely based on their distinct timings of Gal-3 activity suppression, levels of suppression and action site profiles. Our data suggest that pharmacologic Gal-3 inhibition may lead to beneficial effects on the ADPKD cardiac phenotype under specific circumstances.

Funding: Government Support - Non-U.S.

TH-PO689

PS-341 Attenuates the Progression of Autosomal Dominate Polycystic Kidney Disease

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Background: The proteasome, which is a key component of the ubiquitin-proteasome pathway, has emerged as an important cancer therapeutic target. PS-341 (also called Bortezomib or Velcade) is the first proteasome inhibitor approved for multiple myeloma and has been tested in many clinical trials against other types of cancers. One of the mechanisms by which PS-341 exerts its anticancer effect is inactivation of nuclear factor-kB (NF-kB) through prevention of IkBa degradation.

Methods: Pkd1 conditional knock out mice were injected intraperitonealy with ps-341 0.3mg/kg twice a week from postnatal 15th day. Then cacrificed at postnatal 32th day. Serum was collected to test the BUN and creatinine levels. We use IHC to measure protein levels of NF-kB pathways and PCNA, TUNEL and Flow cytometry to detect apoptosis, MTT to test proliferation.

Results: In this study, we showed that PS-341 can effectively inhibited cyst growth in Pkd1 conditional knock out mice. PS-341 attenuates the progression of PKD through alleviating the BUN and serum creatinine levels in Pkd1 conditional knock out mice as well as improving the survival rate. However we didn't found a decreased level of NF-kB which reveals that PS-341 may not retard disease progression through NF-kB pathway. However we found that PS-341 inhibits renal epithelial cells proliferation and promotes renal epithelial cells apoptosis in vivo and in vitro.

Conclusions: Collectively, these findings suggest that PS-341 inhibits renal epithelial cells proliferation and promotes apoptosis which provides a new strategy for treating and preventing the progression of ADPKD in the future.

Funding: Government Support - Non-U.S.

TH-PO690

Novel Screen to Identify Kinase Drug Targets for Autosomal Dominant Polycystic Kidney Disease

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Background: Activation of kinases and the downstream signaling pathways they activate is central to the pathogenesis of cyst growth in ADPKD. However, while the human kinome consists of more than 500 kinases, only a fraction of these kinases have been tested to determine if they play a role in ADPKD pathogenesis. As a result, there are likely many kinases that are more active in ADPKD kidneys that play prominent roles in disease that are yet-to-be discovered and may be good therapeutic targets. We have now adapted a novel approach to broadly screen PKD kidneys in an unbiased manner for kinases that are more active in PKD kidneys compared with wild type kidneys.

Methods: Active kinases were affinity captured by passing wild type and PKD kidney lysates through columns containing multiplexed kinase inhibitor beads. Bound kinases were then identified by LC separation followed by tandem mass spectrometry. Increase in kinase expression and/or activity was validated by Western Blot and the specific kidney cells expressing the kinase was determined by Immunohistochemistry. The relevance of a kinase to cyst growth *in vivo* was assessed by treating PKD mutant mice with specific kinase inhibitors and/or genetically by generating kinase knockouts using CRISPR/Cas9.

Results: We identified a number of both known and unknown kinases specifically upregulated or downregulated in mouse PKD kidneys. Focal adhesion Kinase (FAK) is one of the promising kinase identified in the screen. We found that FAK and phospho-FAK expression was upregulated in cyst lining epithelium in PKD kidneys. Consistent with FAK playing an important role in cyst growth, treatment of *Pkhd1-Cre;Pkd1*$^{fl/fl}$ mice with the FAK inhibitor VS-4718 slowed cyst growth, preserved renal function, and prolonged survival. VS-4718 treatment led to the inhibition of multiple signaling pathways that could account for the therapeutic benefit including paxillin, p130cas, AKT and Stat3.

Conclusions: This is the first time PKD kidneys have been probed proteomically in an unbiased manner to identify the full range of kinases that are more active in PKD kidneys with the goal of identifying new therapeutic targets. So far we have identified FAK as a potential drug target that can slow cyst growth and preserve renal function and are currently in the process of working up several other promising kinases

Funding: Private Foundation Support

TH-PO691

A Novel Zebrafish Drug-Screening Model for Cystic Kidney Disease

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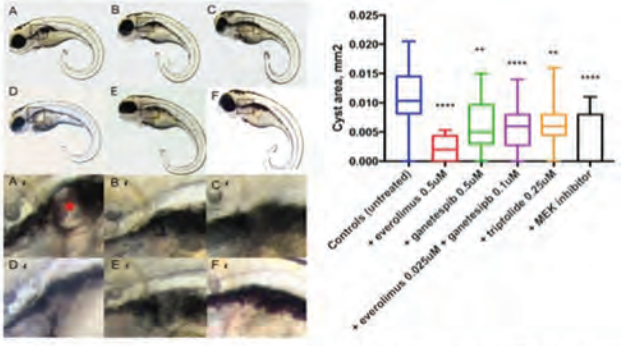
Background: Cystic kidney disease affects millions of people worldwide, and is most commonly associated with dysfunction of cilia. Ciliopathies are a highly heterogeneous disease group, continually expanding with the discovery of new genes and availability of genetic diagnostics. However, treatment options for ciliopathy lag far behind. We are using zebrafish to understand the genetic basis of ciliopathies and we have identified a new zebrafish model of ciliopathy that manifests cysts in the pronephric kidney of the zebrafish embryo and have developed this model for drug discovery.

Methods: In a forward genetic approach, mutagenesis of the zebrafish genome was carried out using an alkylating agent to cause random mutations, followed by screening over several generations to select for phenotypes of interest; which included body curvature and organ laterality defects. Further phenotypic characterisation of one mutant line revealed pronephric cysts. RNA sequencing was conducted to find a missense mutation in the highly conserved WD-40 domain of the Intraflagellar Transport protein - Ift144. This ciliopathy model was then used to screen selected drugs with known effect on kidney cysts. Zebrafish were dechorionated at 24 hours post fertilisation and exposed to treatment (drug in DMSO solvent, in E3 media) at 28°C until 4 days post fertilisation, and assessed under brightfield microscopy.

Results: The cyst area of *ift144* -/- embryos was measured repeatedly across three independent experiments to ensure both experimental and biological repeats. We observed significant reduction of cyst size compared to control, by Student's t-test for all treatment groups (see figure).

Conclusions: We present a novel zebrafish model for ciliopathy with a mutation in the ciliary gene *ift144*, which consistently presents with kidney cysts that can be rescued with drugs that are known to ameliorate cyst size. This model has significant advantages for use as a high throughput drug-screening system.



Drug effect on cyst size (black box and inset, cyst marked with asterisk) in ift144 -/- mutants according to treatment group. A: DMSO 'un-treated' control B: Everolimus (0.025μM) and ganetispib (0.1μM) C: Triptolide (0.25μM) D: Everolimus (0.5 μM) E: MEK inhibitor PD98059 (0.5μM) F: Ganetespib (0.5μM)

Results

succumb to disease within seven years of life. Thus, cats are a useful model to investigate genetic modifiers that influence disease progression and severity. Also, because of the consistent genetic background of the breed and the solitary causal mutation, drug trials can be more accurately interpreted as to success and failure, without complications of genetic heterogeneity of either the patient or the causal gene mutation.

Methods: Two normal and eleven Persian-derived cats heterozygous for the *PKD1* c.10063C>A variant were evaluated by ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). Glomerular filtration rate (GFR), complete blood count, serum chemistries, symmetric dimethylarginine (SDMA), and urine analyses were determined.

Results: Ten clinically normal cats had multiple bilateral cysts and classified as feline chronic kidney disease (CKD) stage 1. Most cysts were located in the cortex or at the corticomedullary junction, with far fewer in the medulla. The oldest cat, 8.1 yrs, had slightly elevated SDMA at 15 and creatinine at 16 and a slightly lowered urine specific gravity of 1.028, and tentatively classified as CKD stage 2. Three cats had GFRs below 2.5. CT-based fractional cyst volume (FCV in mls) ranged from 0.63 – 28.22% and increased with age (r = 0.94). One cat had fast progression when considering cystic development and age with 1.08 FCV/mo at 19 mo. The stage 2 cat had the highest FCV of 28.22% but its FCV/mo was 0.29 ml/mo.

Conclusions: CT and MRI modalities are sufficient in cats to determine TKV and FCV. TKV is not a prognostic indicator of disease in cats. FCV is highly correlated with age. Fast progressing cats can be identified and used for the analysis of genetic variants that modify disease progression. Whole genome sequencing of slow and fast progressing cats is underway to elucidate the modifying variants.

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TH-PO692

Hearing Impairment, a Novel Functional Readout, in Pkd2 Mutant Zebrafish

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Background: Zebrafish have been a valuable model for studies of PKD, with conservation of phenotypes and signaling pathways. Phenotypic readouts have consisted mainly of pronephric cysts and body curvature. The only method for assessing kidney function in embryos is dye clearance, which is affected by many factors and, therefore, is not a reliable indicator. Hair cells of the ear and zebrafish lateral line share many features in common with renal epithelial cells and are responsible for hearing. We have identified hearing assays as a novel approach for assessing pkd2 function.

Methods: We assayed hearing using a standard acoustic startle response (ASR) in 6-7 day old zebrafish. 100 or 400 Hz stimuli were delivered using MATLAB, and responses were recorded using a video camera. Startle responses consisted of a sudden change in swimming velocity or direction in response to the tone and were scored as 1 or 0 for presence or absence, respectively.

Results: The ASR assay was validated using neomycin to ablate lateral line hair cells by established methods. After one hour in neomycin no hair cells were visible using yo-pro-1 or daspei vital dyes and the frequency of response to a 400 Hz tone was reduced 50% compared to untreated sibling controls (0.5±0.2 vs 0.24±0.2, $p<0.04$, n=24 fish/group from 3 clutches). The response of hi4166 pkd2$^{-/-}$ zebrafish to a 400 Hz tone was reduced 35% compared to wild-type sibling controls (0.50±0.2 vs. 0.17±0.2, $p<0.03$, n=56 fish/group from 7 clutches). This population of fish also responded 30% less frequently to a 100 Hz tone (0.83±0.1 vs 0.24±0.1, $p<0.0001$). Our ASR assay was additionally validated using a novel transposon mutant line, spinner. This line develops ventral body curvature, pronephric cysts, and fails to develop hair cell kinocilia analogous to the central cilium, as determined by acetylated alpha tubulin labeling. Spinner mutants show profound hearing loss at both 400 and 100 Hz (0.88±0 vs 0.04±0 and 0.93±0.1 vs 0.12±0.1, $p<0.001$, n=16-24 fish/group from 2-3 clutches).

Conclusions: These data show that the established hi4166 pkd2 mutant zebrafish line have hearing loss, suggesting hearing can be used as an alternative to dye clearing assays for pkd2 function in zebrafish. They further suggest the relevance of hair cells as a model for studies of PKD.

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TH-PO693

Feline Autosomal Dominant Polycystic Kidney Disease Model to Elucidate Genetic Modifiers of Cyst Progression

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease in domestic cats. The feline *PKD1* mutation (c.10063C>A) causes a stop codon in exon 29 (C3284X) and is the only known variant causing ADPKD in cats, specifically Persians and related-breeds. Many ADPKD cats remain subclinical though some show rapid disease progression, develop chronic kidney disease (CKD) and

TH-PO694

Early Imaging Biomarkers of ADPKD: Longitudinal Study of Quantitative MRI and Texture Analysis in a Murine Model

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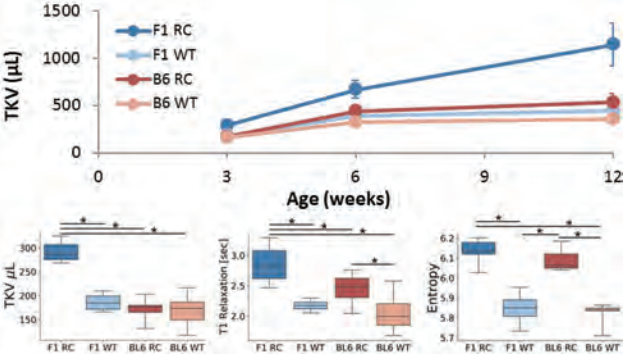
Background: Currently, only a fraction of the wealth of information that could be disclosed by radiological imaging is used to assess disease status and follow progression of ADPKD. Advanced MR imaging techniques can be used to measure renal structural and functional properties. We hypothesized that advanced MRI acquisitions and image analysis methods detect renal tissue alterations preceding changes in TKV in the *Pkd1*$^{RC/RC}$ mouse model in different backgrounds.

Methods: *Pkd1*$^{RC/RC}$ model mice (C57BL/6 and *C57Bl6 x 129s6Svev/Tac* 'F1' background, n=7 each), as well as wild-type (C57BL/6 and 'F1' background, n=5 each) were imaged at 3, 6, and 12-weeks of age. Mice imaging was performed under anesthesia with a 16.4T NMR spectrometer. TKV and texture were measured on T2-weighted images, and T1 relaxation maps were calculated and measured within the kidneys. Regions-of-interest were drawn to cover cortical and medullary regions.

Results: Figure 1 shows TKV progression for the four phenotypic groups, as well as the 3-week means of TKV, T1 relaxation, and entropy texture feature (a measure of tissue heterogeneity). The fast progressing group ('F1') exhibited a significant increase in TKV compared to wild-type, whereas the C57BL/6 model did not. In contrast, T1 relaxation and texture properties were found to clearly differentiate the model mice from corresponding wild-type.

Conclusions: Quantitative MR parameters and texture features can serve as early biomarkers of PKD. These parameters could be useful for pre-screening in trials as they inform on early disease. Moreover, they may afford more parameters to evaluate treatment benefits, which may be detectable over shorter study durations.

Funding: NIDDK Support



Top panel – volume progression of the four groups in this study. Bottom panel – boxplot comparisons of TKV (left), T1 relaxation (middle), and Entropy texture feature (right) at three-week time point.

TH-PO695

Deletion of miR-214 Skews Macrophage Polarization to Promote Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by fluid-filled cysts that arise from kidney tubules and compress functioning nephrons leading to kidney failure. MicroRNAs (miRs) are small non-coding RNAs that can regulate gene expression. Our understanding of the role microRNAs in ADPKD is limited. The goal of this study was to understand the role of miR-214 in ADPKD.

Methods: Q-PCR and in situ hybridization were performed to analyze the expression of miR-214 and its host lncRNA transcript, *Dnm3os* (Dynamin 3 opposite strand), in mouse and human ADPKD. Next, we genetically deleted miR-214 expression in *Pkhd1/Cre*; *Pkd2*$^{F/F}$ (*Pkd2*-KO) mice and *Pkd1*$^{RC/RC}$ mice, two genetic models of ADPKD. Kidney mRNA sequencing and pathway analysis was performed to elucidate the differential gene expression pattern between *Pkd2*-KO and *Pkd2*-miR-214$^{-/-}$ double KO mice. *In vitro*, mIMCD3 and RAW264.7 cells were treated with miR-214 mimics.

Results: Q-PCR showed that miR-214 and *Dnm3os* expression was upregulated in mouse and human ADPKD kidneys. In situ hybridization revealed that miR-214 and *Dnm3os* are expressed in both the cyst epithelium and interstitium. miR-214$^{-/-}$ mice displayed no phenotypic abnormalities. Deletion of miR-214 in *Pkd2*-KO mice increased kidney weight/body weight ratio, raised serum BUN and shortened survival. Pathway analysis of differentially expressed genes revealed that miR-214 deletion results in a shift in the type of inflammation present in *Pkd2*-KO kidneys. Accordingly, further molecular and histological analysis revealed an increase in M2-like macrophages in *Pkd2-miR-214*-KO kidneys. Conversely, miR-214 mimics reduced expression of M2 markers and cytokines in RAW264.7 and mIMCD3 cells. Deleting miR-214 in a second long-lived, slowly-progressing mouse model, the *Pkd1*$^{RC/RC}$ mouse, also led to increased total kidney volumes as measured by serial MRI and an increase in M2-like macrophages.

Conclusions: miR-214 expression is increased in mouse and human ADPKD kidneys. Deletion of miR-214 aggravates cyst growth and shortens survival. miR-214 may suppress cyst growth by inhibiting M2-like polarization of macrophages. Our studies suggest that augmenting miR-214 may be a potential novel therapeutic approach for ADPKD.

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TH-PO696

miR-210-3p Inhibition Decreases Fibrosis and Improves Renal Function in Murine ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cystic enlargement. In *mcwPkd1*$^{(nl/nl)}$ hypomorphic mice, peri-cystic areas are hypoxic early in the disease course. These hypoxic areas are markedly positive for hypoxia inducible factor-1α (HIF-1α). These areas develop fibrosis with disease progression. miR-210-3p is HIF-1α inducible and increases in response to hypoxia. We hypothesize that peri-cystic hypoxia initiates a repair response via HIF-1α and miR-210-3p which contributes to interstitial fibrosis.

Methods: Cystic kidneys at weekly intervals starting at postnatal (PN) day 21, were sectioned and stained with trichrome and PCNA. RNA extracted from laser capture micro-dissection (LCM) trichrome (TC) positive peri-cystic regions at PN28, & 42 was examined for expression of miRNA 210-3p. PN21 peri-cystic regions negative for trichrome stain was used as a control. Anti-miR-210-3p was injected IP starting at PN21 Q 4 days till PN42. Untreated cystic kidneys were used as control. RNA was extracted from both cystic treated and untreated kidneys at PN42. Serum obtained at harvest was used to assess renal function.

Results: 1. In LCM captured peri-cystic regions, miRNA-210-3p is upregulated 6-fold at PN28 and 5-fold at PN42 compared with PN21. 2. Anti-miR-210-3p treated cystic kidneys at PN42 compared with age-matched untreated cystic kidneys has: (a) 35% reduction in serum creatinine; (b) 75% decrease in trichrome positive/fibrotic areas; (c) proliferation (PCNA) is restricted to tubular epithelia vs both tubular epithelia and peri-cystic regions in untreated controls; (d) up-regulation of anti-fibrotic mRNA's Hgf (19.22-fold), IFNg (7.95-fold), Il10 (523.68-fold), Il13ra2 (31.99-fold) and down-regulation of pro-fibrotic mRNA's Ctgf (-10.79) and Il5 (-4.31) and ECM component Col1a2 (-94.86).

Conclusions: Conclusions- 1. We demonstrate that expression of miR-210-3p increases in hypoxic peri-cystic regions with disease progression at PN28 and PN42. 2. *In vivo* inhibition of miR-210-3p: improves kidney function; decreases interstitial fibrosis; reduces proliferation in peri-cystic regions; increases expression of anti-fibrotic mRNAs (Hgf, IFNg, Il10, Il13ra2) and decreases profibrotic (Ctgf, Il5) and ECM matrix component (Col1a2).

TH-PO697

Long Noncoding RNA Hoxb3os Is Dysregulated in Autosomal Dominant Polycystic Kidney Disease and Regulates mTOR Signaling In Vivo

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is primarily caused by mutations in *PKD1* and *PKD2*. Mutations of *PKD1* and *PKD2* produce abnormalities in multiple intracellular signaling pathways, including activation of the mTOR pathway. Long noncoding RNAs (lncRNAs) are single-stranded RNA molecules over 200 nucleotides in length and lacking a long open-reading-frame. lncRNAs play important roles as epigenetic regulators of development and disease, but their involvement in PKD has not been previously described.

Methods: We have recently identified a kidney-specific lncRNA, called *Hoxb3os*, which is downregulated in kidney-specific *Pkd1* and *Pkd2* mutant mice and in cystic kidneys from ADPKD patients.

Results: Deletion of *Hoxb3os* in mIMCD3 mouse kidney epithelial cells resulted in activation of the mTOR pathway and increased oxidative phosphorylation (Aboudehen K, et al. J Biol Chem, 2018, in press). Consistent with activation of mTORC1 signaling, *Hoxb3os*-deficient cells displayed increased cell proliferation and defective autophagy. To identify the role of *Hoxb3os* in vivo, we used CRISPR-based gene editing to delete the genomic DNA encoding *Hoxb3os* in mouse zygotes. PCR analysis of genomic DNA and qRT-PCR analysis of kidney RNA demonstrated successful ablation of *Hoxb3os* in multiple independent founders. Mice lacking *Hoxb3os* were viable and had grossly normal kidney morphology up to age post-natal day P28. Immunoblot analysis of mutant kidney lysates showed increased phosphorylation of mTOR and downstream targets of mTORC1 but not mTORC2. *Hoxb3os* mutant kidneys also showed increased cell proliferation and defective autophagy. Co-immunoprecipitation experiments revealed that *Hoxb3os* was found in a complex with phosphorylated mTOR but not dephosphorylated mTOR in mouse kidney lysates.

Conclusions: Collectively, these findings identify *Hoxb3os* as a kidney-specific lncRNA that binds to mTORC1 and directly inhibits its downstream activity. Suppression of *Hoxb3os*may contribute to the activation of the mTOR pathway in ADPKD, and restoration of *Hoxb3os*may have therapeutic benefit.

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TH-PO698

Actin and Intermediate Filament Protein LAD1 (Ladinin1) Is Dysregulated in ADPKD Mouse Model

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Background: There have been reports that Polycystin1 (PC1) co-localizes with actin/intermediate filament and could have functional roles in its organization, but much remains poorly understood. We have previously reported the transcriptomics of an orthologous ADPKD mouse model using 80 kidneys from *Pkd1*cko;Tg(Cre/Esr1) 102-210 days-old mice, in which *Pkd1* knockout was induced at P40. We found *Lad1* (Ladinin-1), a poorly characterized intermediate-filament protein, was one of the top differentially expressed genes. Here we focus on characterizing *Lad1* expression and function as a candidate regulator of cytoskeleton dynamics in ADPKD.

Methods: 16 kidneys (8 WT, 8 KO) were used for qPCR and 12 (6 WT, 6 KO) for immunoblotting. *Lad1* mRNA and protein expression levels were evaluated by qPCR and immunoblot in a pair of DBA and LTL cell lines derived from *Pkd1*$^{CKO/CKO}$ mouse, with corresponding mutant derived after Cre-expression. Mouse and humand Lad1 were cloned with various epitope tags to ease detection. A human keratinocyte cell line with high levels of endogenous LAD1, HaCat, and an MDCK cell line expressing recombinant, HA-tagged human PC1 were used for characterizing LAD1 and actin dynamics.

Results: *Lad1* mRNA and protein levels were 58.8% (exon1-2; 50.0% exon4-5) and 67% lower, respectively, in *Pkd1*mutant kidneys ($p<0.01$ for each analysis). In the cell lines, *Lad1* mRNA and protein levels were 46.0% (n=3, p=0.16) and 67.7% (n=3, $p<0.01$) lower in mutants compared to the paired WT cells. In characterizing Lad1 protein, we found that both endogenous and recombinant Lad1 migrates at ~72Kda, not at the size of 59kDa predicted by both its MW and companies that sell Lad1 antibodies. Using the HaCat cell line to better characterize LAD1 function, we found that LAD1 levels increased with cell confluency. Confocal studies determined that LAD1 generally co-localizes with actin in stress fibers and in a cortical "rim" pattern at the cell edge, which is decreased at cell-cell junctions. This pattern was also seen in the MDCK and DBA renal epithelial cell lines.

Conclusions: LAD1 is a poorly understood cytoskeletal protein whose expression increases with cell density but whose level is down-regulated in cystic kidney. Further study will be required to determine whether the downregulation observed in cystic kidney reflects altered cell-cell sensing.

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TH-PO699

Gene Expression Profile of Pkd1 Null Endothelial Cells During Embryonic Development

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Background: Polycystins (PCs) play a critical role in vascular development. *Pkd1/2* null embryos die in mid gestation with polyhydramnios, subcutaneous edema and focal hemorrhage. A subset of these phenotypes are recapitulated by deleting *Pkd1* or *Pkd2* in endothelial cells. At the cellular level, we have shown that *Pkd* deficient endothelial cells exhibit aberrant branching morphogenesis and altered directional migration. The specific signaling pathways regulated by polycystins in endothelial cells, however, are unknown. To understand the functional consequences of polycystin deficiency in endothelial cells we performed RNA sequencing (RNA-seq) in *Pkd1*$^{-/-}$ endothelial cells at two embryonic time points.

Methods: We harvested *Pkd1*$^{-/-}$ and littermate control embryos at E13.5 and E14.5 (N=36 total) and isolated endothelial cells using anti-CD31^{+} (specific marker for endothelial cells) coated magnetic beads. RNA was extracted and sequenced independently using 50bp single-end reads. Data was processed using Cutadapt and gene expression quantified using Salmon and R. Differential gene expression analysis was performed using DESeq2 package and enriched pathways were identified using clusterProfiler package.

Results: We identified more than 200 genes that were differentially expressed (Log2 (FC)≤ ± 0.25 and a corrected p-value of <0.05) at each time point. At E13.5 functional clustering revealed an enrichment of genes expressing extracellular matrix components and genes involved in the innate immune response among top ranked. At E14.5, we found upregulation of genes related to cell migration, cell proliferation and angiogenesis probably as a mechanism to compensate the aberrantly developed embryonic vasculature. We found that the *ATPase, H+ transporting, lysosomal V0 subunit C (Atp6v0c*, Gene ID11984) was the most highly downregulated gene at both developmental stages analyzed, (Log2 FC= -1.61 and -1.50 respectively, and q= 0.00E+00 for both). Silencing of this gene was shown to effectively suppress migration and invasion of prostate cancer cells (PC-3M-1E8), which is relevant in the context of the migration defects we observe in *Pkd* mutant endothelial cells.

Conclusions: Our study revealed extensive transcriptional changes in *Pkd1* mutant endothelial cells supporting the importance of polycystin signaling in endothelial cells and in vascular morphogenesis.

Funding: NIDDK Support

TH-PO700

Exome-Wide Association Study Identifies Candidate Susceptibility Genes for Congenital Obstructive Uropathy

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Background: Congenital Obstructive Uropathy (COU) is a cause of kidney failure in children. Monogenic forms of disease account for a small portion of cases. Rare variant association tests are promising approaches to identify novel disease genes.

Methods: We conducted exome sequencing in 292 COU cases and 8541 controls. Following diagnostic variant annotation in genes implicated in congenital anomalies of the kidney and urinary tract (CAKUT) using ACMG criteria, we searched for novel susceptibility COU genes using case-control exome-wide collapsing analyses for rare functional variants. We tested gene-level dominant and recessive models via fisher-exact statistics. Qualifying variants were selected using computational scores based on conservation and location in intolerant exons or conserved domains. We analyzed gene-set enrichment using 299 OMIM genes implicated in CAKUT in comparison to a control set of 857 olfactory genes. Finally, we cross-annotated suggestive signals with results from a GWAS for common variants consisting 398 cases and 8197 controls.

Results: ACMG-based variant prioritization revealed pathogenic mutations in 11(3.7%) COU cases. Gene-level collapsing showed 20 genes with p<5x10-4 for dominant model (MAF<0.0005) and 2 genes for the recessive model (MAF<0.01), although no exome-wide significant signals (<2.5x10-6) were attained. Two candidate genes were particularly interesting: 1.*MAZ* (dominant missense model; p=3.58x10-5), a gene demonstrated to regulate urogenital development in a mouse model, and 2.*FLNA* (recessive model; p=4.25x10-5), a gene implicated in Otopalatodigital Spectrum Disorders, where hydronephrosis and megaureter were reported. Cross-annotation with GWAS signals revealed evidence for association of common variants to *MAZ* (p=7.06x10-3– 6.96x10-4). Gene set analysis for genes involved in kidney function showed enrichment for rare functional variant (χ2 = 9.12; p=2.5x10-3) compared to olfactory control genes (χ2=0.15; p=0.70) in cases versus controls.

Conclusions: This study addresses the contribution of rare and common variants under various genetic models to solve the etiology of COU. Preliminary results implicate both rare and common variants in *MAZ* as novel risk factors for COU.

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TH-PO701

Analysis of De-Novo Coding Mutations Identifies New Candidate Genes for Kidney Malformations

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Background: Renal hypodysplasia (RHD) is one of the most common cause of pediatric kidney failure. Although multiple causative genes have been identified, they only account for 10-15% of cases. A search for de-novo "mutations" (DNMs), has led to the identification of numerous novel genes for congenital heart defects and neurodevelopmental disorders. We hypothesized that de-novo analysis can similarly identify new RHD-causing genes.

Methods: Whole-exome sequencing was performed on 88 RHD trios. The sequences were annotated using an in-house software, ATAV, and DNMs were identified. Potential enrichment for DNMs was analyzed with the denovolyzer package in R. Exploratory gene-set enrichment analysis was performed with the Molecular Signatures Database (MSigDB).

Results: We identified a significant 1.5-fold enrichment for DNMs in cases compared to expectations ($p= 1.7x10^{-4}$). The enrichment mostly originated from probands with renal agenesis or renal hypoplasia, and not from those with multicystic dysplastic kidneys. Globally, the DNM signal was mainly driven by genes that are highly expressed during murine kidney development. De-novo loss-of function mutations were detected only in two genes known to be associated with kidney disorders (*PAX2* and *TSC2*) but none of the missense DNMs occurred in known RHD genes. In pathway analysis, we observed a 11.8-fold enrichment for missenses in genes targeted by NF1 ($p= 7.9x10^{-5}$), a 4-fold enrichment for DNMs in the CHEK2 network ($p= 2.8x10^{-4}$) and a 6.4-fold enrichment for DNMs in genes potentially regulated by PAX4 ($p= 1.3x10^{-4}$). We did not find independent DNMs in the same gene, confirming heterogeneity of disease.

Conclusions: Despite limited sample size, we detected an excess of de-novo mutations in RHD, identifying an important mechanism of disease. Gene-set analysis may help to pinpoint which genes are driving this enrichment. Analysis of larger cohorts is likely to identify genes with recurrent de-novo variants, enabling identification of causal genes.

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TH-PO702

Mutations in PIK3C2A Cause Syndromic Short Stature Associated with Eye, Skeletal, and Renal Involvement

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Background: PIK3C2A is a member of the phosphoinositide 3-kinase (PI3K) family that catalyzes the phosphorylation of phosphatidylinositol (PI). Class II PI3Ks has been attributed a wide-range of biological functions including, angiogenesis, cellular signaling, endosomal trafficking, exocytosis as well as ciliary formation and function. However, its function is still poorly understood. Identifying the genetic basis of Mendelian diseases provide insight into gene function, susceptibility to disease and can improve clinical care.

Methods: We performed whole exome sequencing in three independent consanguineous families to identify the underlying single-gene disease-causing mutation. We then obtained dermal fibroblasts from skin biopsies of the affected individual and healthy controls for molecular studies.

Results: We identified three homozygous protein-truncating mutations in the gene *PIK3C2A* in five children from independent consanguineous families. The affected individuals show a considerable overlapping phenotype including cataract, skeletal abnormalities, hearing loss and renal involvement among other features. Molecular data of patient-derived fibroblasts were consistent with loss of *PIK3C2A* function as evidenced by the lack of PIK3C2A protein. In addition we demonstrate that the PIK3C2A deficiency caused impaired cilia formation, decreased levels of PI in primary cilia, and altered the phosphorylation status of Akt, GSK3beta as well as the expression level of *AXIN2*.

Conclusions: We demonstrate that loss-of-function mutations in *PIK3C2A* resulting in a novel syndrome consisting of short stature, cataracts, hearing loss, skeletal abnormalities and renal involvement. This discovery, together with studies of other disorders of PI metabolism, will enable future studies to discover the pathophysiological mechanism basis of this syndrome to better understand the role of PIK3C2A.

TH-PO703

ZMYM2 Mutations Cause Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) with Syndromic Features

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the most common cause (45%) of chronic kidney disease in the first three decades of life. CAKUT can present as an isolated renal condition or as part of a clinical syndrome. First insights into the pathogenesis of CAKUT came from identification of ~40 single-gene causes of isolated CAKUT and ~179 single-gene causes of syndromic CAKUT.

Methods: We performed whole exome sequencing (WES) to identify novel monogenic causes in a worldwide cohort of 600 individuals with CAKUT.

Results: We identified 13 different dominant heterozygous mutations in *ZMYM2* (*MYM-type zinc fingers type 2*) in 15 unrelated families; p.Val61del, p.Glu126Ala, p.G257fs p.Ile387Val, p.Gln398*, p.Cys536Leufs*13, p.Arg540ins*, p.Lys649Arg, p.Tyr763His, p.Gly775Glu, p.Asp997del, p.Pro1002Ser, p.Glu1031Lys. *ZMYM2*, a transcriptional regulator, contains 10 tandem zinc fingers called myeloproliferative and mental retardation (MYM)-type zinc fingers. *ZMYM2* is expressed in the urothelial cells and renal tubules in human cells and in the bladder and genital tubercle of the developing mouse. The encoded protein acts as a transcriptional co-repressor as part of the BHC histone deacetylase complex and through interaction with SUMO-2. Affected individuals exhibited a broad spectrum of CAKUT phenotypes. In addition, there were genito-urinary tract pathologies including imperforate hymen and cryptorchidism. Interestingly, patients carrying missense alleles had an isolated CAKUT phenotype, whereas patients carrying truncating alleles exhibited syndromic features such as facial dysmorphsim, developmental delay, hypotonia, and autism spectrum disorder.

Conclusions: We here discovered *ZMYM2* mutations as a novel cause of autosomal dominant CAKUT. Furthermore, we found evidence of an allelic genotype-phenotype correlation, in which null mutations in *ZMYM2* (e.g., protein truncating) cause syndromic CAKUT phenotypes, whereas hypomorphic mutations (e.g., missense) cause isolated CAKUT phenotypes.

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TH-PO704

COL4A1 Mutations as a Potential Novel Cause of Autosomal-Dominant CAKUT in Humans

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease <30 years of age. While the genetic locus containing *COL4A1* (13q33-34) has been implicated in vesicoureteral reflux (VUR), the role of *COL4A1* in isolated kidney disease is unclear (Vats *JASN* 17:1158, 2006). We hypothesized that mutations in *COL4A1* can cause abnormal kidney development in humans.

Methods: We performed whole exome sequencing in a cohort of 638 families (258 families with nephronophthisis (NPHP) and 380 families with CAKUT). Genetic variants were analyzed assessing evolutionary conservation, in-silico prediction programs, and minor allele frequency in public databases (gnomAD, EVS, 1000 Genomes), as previously described (Braun *Nat Genet* 49:1529, 2017).

Results: We identified eight different heterozygous mutations in *COL4A1* in eight unrelated families with CAKUT, while no *COL4A1* mutations were present in the NPHP negative control cohort. All eight individuals had heterozygous only missense variants in *COL4A1* (D928H, G1392S, G1450S L1235R, M838V, P603S, P816L, P1224L) with an isolated CAKUT phenotype. Affected individuals exhibited a spectrum of CAKUT phenotypes ranging from renal agenesis, small echogenic dysplastic kidneys, multicystic dysplastic kidney, left ectopic dysplastic kidney, hydronephrosis, to VUR. VUR was the predominant phenotype (5/8 families). Three patients had extra-renal features (facial dysmorphism, low set ears, hypotelorism, hearing loss, and uterus unicornis). *COL4A1* demonstrates extreme loss-of-function intolerance (pLI = 1), supporting autosomal dominant inheritance.

Conclusions: We identified heterozygous *COL4A1* mutations as a potential novel autosomal dominant cause of CAKUT. The observation that some patients exhibit an extra-renal phenotype, while others have isolated CAKUT, suggests the possibility of allelism.

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TH-PO705

Exome Sequencing in Human Bladder Exstrophy and Knockdown Studies in Zebrafish Implicate SLC20A1 as Candidate Gene and Major Regulator of Urinary Tract Development

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Background: Bladder exstrophy-epispadias complex (BEEC) represents the severe end of human congenital anomalies of the kidney and urinary tract (CAKUT). Exome and Sanger sequencing in BEEC patients identified two novel *de novo* variants (p.G237R; p.V298A) and one novel maternally transmitted variant (p.K441Q) from an affected mother in *SLC20A1*. All three variants were predicted to be disease causing. *SLC20A1* encodes for a Na^+/PO_4 cotransporter known to play a role in proliferation and TNF-induced apoptosis. We investigated the developmental function of *slc20a1a* in developing zebrafish larvae (zfl) performing Morpholino (MO) knockdown (KD) experiments. The urinary tract in zfl consists of two pronephric ducts, similar in segmentation to human nephrons, that fuse at the cloaca. *Slc20a1a* is frequently used as pronephric in situ hybridization (ISH) marker.

Methods: *Slc20a1a* KD was done by injecting ATG-binding MOs in 1-2 cell staged eggs, blocking the gene's translation. Specificity was shown by Western Blot and rescue experiments by co-injection of human mRNA transcripts of *SLC20A1*. For phenotype characterization different assays were used such as sulforhodamine 101 excretion, ISH, immunohistochemistry (IHC) on paraffin sections and the transgenic zf reporter line *Tg(wt1b:GFP)*.

Results: MO KD of *slc20a1a* in zfl results in a severe lethal phenotype affecting multiple organ systems. Focusing on urinary tract, we see formation of pronephric cysts and disorganization of the cloaca. Excretion assay uncovers severe opening defects of the cloaca for the intestine, similar to our index patient with cloacal exstrophy and an imperforate anus. Yolk endocytosis defects resemble abdominal wall fusion deficiencies. IHC shows defects in proliferation and apoptosis.

Conclusions: Our data suggests *slc20a1a* as major player in urinary tract development of zf. Mild MO phenotypes present with urinary tract abnormalities. Severe MO phenotypes present with a high lethality among zfl - underlining the overall importance of *slc20a1a* during embryonic development. In conclusion, exome sequencing in human bladder exstrophy and developmental biology studies in zfl implicate *SLC20A1 a*s disease gene for human BEEC and therefore CAKUT and as major regulator of urinary tract development.

TH-PO706

A Genome-Wide Association Study Provides Insight into the Etiology of Congenital Obstructive Uropathy

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Background: Congenital Obstructive Uropathy (COU) is a frequent anomaly of the urinary tract. Human genetic and clinical data suggest that both rare and common genetic variants might be involved in the pathogenesis of COU.

Methods: We conducted SNP genotyping in 398 COU cases and 8197 controls on different Illumina platforms. Genome-wide association study (GWAS) was performed on two Caucasian cohorts of 280 cases (cohort 1) and 118 cases (cohort 2), divided based on platform. After standard QC we retained 444614 and 632574 markers in cohort 1 and cohort 2, respectively. We imputed these marker sets separately using the HRC1.1 panel. The results were meta-analyzed with METAL. Suggestive signals were cross-annotated with results from our exome-wide collapsing analysis for rare variants in 292 COU cases and 8541 controls.

Results: Meta-analysis of the two cohorts (398 cases, 8197 controls and 7503796 markers) revealed 3 suggestive associations. The 1st was on chr4q26 (rs4833590; p=3.01x10^{-7}) in *SEC24D*. A disruption of this gene causes embryonic lethality in mice, and mutations in humans are implicated in the Cole-Carpenter Syndrome-2 with no known urinary tract involvement. Other genes within 250Kb of this variant are *CEP170P1*, *LOC729218*, *METTL14* and *SYNPO2*. The 2nd was on chr12q21 (rs10777060; p=9.98x10^{-6}), 105.8kb upstream of *BBS10*, implicated in Bardet-Biedl syndrome, a ciliopathy with renal and urinary tract involvement. Neighboring genes are *OSBPL8* and *NAP1L1*. A 3rd suggestive signal was on chr4q32 (rs6536312;p=9.70x10^{-6}), 231.1kb upstream of *ETFDH*, a gene implicated in glutaric acidemia IIC, which features urogenital defects. Neighboring genes are *TMEM144*, *RXFP1*, *C4orf46* and *PPID*. Cross-annotation with exome-wide collapsing analysis in 292 COU cases and 8541 controls showed evidence for enrichment in rare variants in *BBS10* (p=3.2x10^{-3}) and *TMEM144* (p=1.2x10^{-2}).

Conclusions: We present preliminary GWAS findings based on a relatively small sample size of 398 COU cases and identified 3 candidate loci. Integration with rare variants from an exome-wide association study permitted locus refinement and identification of novel susceptibility genes for follow-up studies in larger cohorts.

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TH-PO707

A Mutation Identified in Patients with Congenital Anomalies of the Kidney and Urinary Tract Interrupts ROBO2-SLIT2 Association and Signaling Pathway

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) is a major cause of kidney failure in children and young adults. ROBO2 is a receptor for ligand SLIT2. ROBO2 and SLIT2 plays key roles in early ureteric bud outgrowth during kidney development and nervous system formation. There are approximately 30 *ROBO2* missense mutations identified in CAKUT patients. However, functional significances of these mutations are remained to be characterized. To elucidate if these mutations would structurally disrupt ROBO2-SLIT2 interaction and functionally compromise its signaling pathway, we have analyzed a missense mutation of *ROBO2*, p.G98W (c.292G>T), located in the ROBO2 first Ig domain that serves as the ligand binding site for SLIT2.

Methods: Site-directed mutagenesis was used to introduce c.292G>T point mutation into a human ROBO2 cDNA. Calcium phosphate transfection strategy was used to express ROBO2 in HEK cells. Protein expression was confirmed by Western blot analysis and ROBO2-SLIT2 interaction was analyzed using the ForteBio Bio-Layer Interferometry (BLI) system Octet RED96e. Postnatal anterior subventricular zone (SVZa) neuronal migration assay was performed to examine the functional impact of the mutation on ROBO2-SLIT2 signaling pathway.

Results: BLI binding assay showed a positive interaction between ROBO2 and SLIT2, however, the p.G98W mutation in ROBO2 first Ig domain hinders this binding compared with its wild type control. Functional assay indicates that the extracellular portion of ROBO2, a 153 residue peptide containing the binding domain for SLIT2, is able to block ROBO2-SLIT2 signaling pathway that repels neuronal migration. In contrast, after the p.G98W mutation was introduced, the mutated ROBO2 peptide reduces this functional blocking activity on neuronal migration.

Conclusions: Our results provide molecular mechanistic evidence that p.G98W in ROBO2 first Ig domain interrupts the ROBO2-SLIT2 receptor-ligand association, which may in turn disrupt their signaling pathway during early kidney development and result in CAKUT phenotypes in patients carrying this mutation.

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TH-PO708

Mutations in BNC2 Lead to Autosomal-Dominant Lower Urinary Tract Obstruction (LUTO)

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Background: Congenital "lower urinary tract obstruction" (LUTO) is defined by a decrease in the free passage of urine through the urethra. About three out of 10,000 pregnancies are affected; the etiology is so far unknown.

Methods: Whole exome sequencing (WES) in a family with 4 affected from 3 generations was performed. 258 LUTO patients were screened for further variants in the identified candidate gene *BNC2* using Sanger sequencing. Functional studies comprised in situ hybridization (ISH) studies in mouse embryos, translational knock-down (KD) in developing zebrafish larvae (zfl) using Morpholino oligonucleotides (MO) and 'rescue' experiments by co-injection of human *BNC2* mRNA with the *bnc2*-MO in zfl as well as overexpression of *BNC2* mRNA in zfl.

Results: Filtering of WES Data revealed a nonsense mutation (c.2554C>T; p.Arg852*) in *BNC2* (basonuclin 2). Out of 258 LUTO patients one additional family (affected father and son) carrying a novel missense mutation (c.2663A>G, p.H888R) in *BNC2* could be identified. Affected members in both families presented with anatomical obstruction of the urethra due to posterior urethral valves (PUV), requiring surgical removal, and urethral stenosis with fetal presentation, requiring surgical reconstruction. Functional characterization of *Bnc2* using ISH showed expression at E13.5 in developing mouse urethra. KD of bnc2 by injection MO in zfl caused cloacal obstruction with formation of a vesicle at the distal end of pronephric duct in 11% of zfl and cystic dilated deformed glomeruli and dilated pronephric ducts in 50%. Co-injection of human *BNC2* mRNA with *bnc2*-MO in zfl showed rescue of the phenotype only at an amount of 100pg of mRNA. Already slight overexpression of human *BNC2* mRNA in zfl lead to the same phenotype as KD, confirming the specificity of the *bnc2*-MO suggesting that the observed phenotypes in fish and human are the result of gene dosage imbalance of *BNC2*.

Conclusions: Human genetic and developmental biology models suggest BNC2 mutations as the first monogenic cause of LUTO.

TH-PO709

Tackling Undetermined ESRD by Whole Nephrome Sequencing in Adult Patients Waiting for Kidney Transplantation

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Background: End-stage renal disease (ERSD) of undetermined etiology constitutes a significant clinical challenge, notably in kidney transplantation (KT). In absence of renal histology, genetic analysis may further elucidate ESRD etiology. To date, hereditary kidney disease is thought to represent < 10% of ESRD patients, mainly attributed to ADPKD. In recent years, however, a multitude of additional rare genetic ESRD conditions have been discovered without being yet systematically considered in clinical routine. To tackle the issue of undetermined ESRD prior to KT, we aimed to broadly analyze for genetic causes in patients on the waitlist.

Methods: Patients on the local KT-waitlist (n=134) were stratified based on their presumed etiologies: i) non- hereditary (n=56); ii) hereditary, including clinically diagnosed ADPKD (n=29); iii) undetermined, including biopsy-proven FSGS (n=49). The latter patients were analyzed by whole "*nephrome*" sequencing, comprising more than 290 ESRD-associated OMIM-genes.

Results: An undetermined etiology was found in 36% of individuals (49/134) on the waitlist, 40% of whom reported a positive family history. We detected a robust genetic diagnosis in 24% (12/49). The genes COL4A3/5 were found most frequently mutated in undetermined ESRD. Taken together, hereditary nephropathies, including ADPKD, were identified in 31% (41/134) of the overall cohort. By significantly increasing the proportion of hereditary diagnoses (from n=29 to n=41, p<0,05), the rate of undetermined ESRD went down from n=49 to n=37 (p<0,05).

Conclusions: By this pilot study, we demonstrate the beneficial use of whole "nephrome" sequencing to significantly reduce the proportion of undetermined ESRD prior to KT. In absence of renal histology or unspecific histological conditions, such as FSGS or TMA, genetic analysis may not only provide a robust diagnosis but helps differentiating recurrent from non-recurrent etiologies, thereby contributing to personalized KT management and adequate evaluation of potential living donors.

TH-PO710

Outcomes of Patients with Genetic Renal Disease in Regional Australia

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Background: Genetic aetiology comprises a significant proportion of adults with chronic kidney disease (CKD) who develop end-stage kidney disease (ESKD) and experience an excess of morbidity and mortality. Our aim was to evaluate the outcomes patients with genetic renal disease (GRD) in Tasmania, Australia.

Methods: Individuals with GRD in Tasmania were identified from AUDIT4 (renal unit clinical database, n=2407) and ANZDATA (Australia and New Zealand Dialysis and Transplantation Registry, n=361) from 1st January 2012 until 1st May 2018. After discarding duplicates, 2434 individuals referred to tertiary renal services were reviewed.

Results: In Tasmania, GRD comprised 8.5% of the CKD population (208/2434). GRD patients were younger than non-GRD patients (mean 52y vs. 64y, p <0.001). There was no significant difference in gender or mean eGFR (in non-dialysis patients) between cohorts. Since 2012, GRD patients have more commonly developed ESKD, commenced renal replacement therapy (RRT) or received transplants than non-GRD patients (40% vs. 17%, p<0.001; 39.4% vs. 12.3% p<0.001; 30.3% vs. 5% p<0.001). Furthermore, GRD patients commenced RRT at a younger age (mean 46y vs 55y, p<0.001). Of the GRD cohort, there was no significant difference in gender. Cystic kidney disease was the most common GRD (48%), followed by Congenital Abnormalities of the Kidneys and Urinary Tract (CAKUT) (37%). Patients with CAKUT started RRT younger than those with cystic disease (mean 39y vs. 55y, p<0.001). Those who received transplants did so earlier (mean 36y vs. 52y, p<0.001). Patients with glomerular, tubular/metabolic or other uncommon GRDs were more likely to be older males. Very few of the people with GRD were known to the Tasmanian Clinical Genetics Service, had received genetic testing or counselling.

Conclusions: Patients with GRD in Tasmania experience earlier morbidity, including the need for RRT and transplant. This data supports the development of a tailored genetic renal service to improve outcomes in affected individuals in Regional Australia.

TH-PO711

Yield of Atypical Hemolytic Uremic Syndrome (aHUS) Genetic Susceptibility Panel Testing

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Background: Hemolytic uremic syndrome (HUS) is characterized by hemolytic anemia, thrombocytopenia and renal failure secondary to thrombotic microangiopathy (TMA). 90% of HUS cases are associated with infection by Shiga toxin-producing E.coli. About 10% of HUS cases are associated with genetic or acquired defects in the regulation of the alternative complement pathway. In about 60% of individuals affected with aHUS, a specific genetic susceptibility variant may be identified. Clinical genetic testing in patients with aHUS not only informs their disease process but also provides therapeutic and prognostic insight for their management.

Methods: The Genetics and Genomics Laboratory at Cincinnati Children's Hospital has developed an aHUS genetic susceptibility panel which includes 10 aHUS associated genes. We reviewed the orders we received for this panel over the last two years (June 2016- May 2018) to assess the yield of this genetic test. We also assessed the proportion of pathogenic variants identified in each individual gene on this panel.

Results: Over the last two years, we have tested 338 patients suspected with genetic aHUS through our aHUS genetic susceptibility panel. 29.6% of the patients were heterozygous for the CFHR3-CFHR1 deletion, which is similar to its frequency in the general population. The CFHR3-CFHR1 deletion in the heterozygous state does not confer risk of developing aHUS. 8.3% of the patients were homozygous for the CFHR3-CFHR1 deletion, which is associated with increased risk of developing aHUS. 10.1% of the patients had pathogenic or likely pathogenic sequence variants in one or more of the ten genes on the panel. Two of the patients were homozygous for the CFHR3-CFHR1 deletion in addition to pathogenic sequence variants. Three of the patients had pathogenic sequence variants in two different genes. Overall, about 16.9% of the patients with suspected genetic aHUS were found to carry genetic variations that conferred them increased risk of developing aHUS. The proportion of pathogenic variants identified in each individual gene on this panel are *C3* (1.6%), *CFB* (1.6%), *CFH* (16.13%), *CFHR1* (4.8%), *CFHR3* (11.3%), *CFHR3- CFHR1* homozygous deletion (45.2%), *CFHR5* (3.2%), *CFI* (14.5%), *DGKE* (3.2%), *CD46* (6.5%) and *THBD* (1.6%).

Conclusions: This study emphasizes the significance of genetic analysis in patients with suspected aHUS.

TH-PO712

Whole-Exome Sequencings Reveal Additional Extracellular Matrix Gene Mutations in Atypical Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease caused by uncontrolled activation of the alternative pathway of complement and induces microangiopathic hemolytic anemia, thrombocytopenia, acute kidney failure and extrarenal manifestations. Most of studies revealed aHUS with pathogenic loss-of-function of complement or gain-of-function regulators of complement. Whether patients with aHUS may have additional extracellular matrix gene mutations is not known at present, we did this study to explore this possibility.

Methods: This study used whole-exome sequencing(WES) to screen our six adult patients, five of them responded to anti-C5 therapy while one patient did not receive anti-C5 treatment due to financial issue. After completing the whole-genome sequencing analyses, we used functional protein association network -STRING for correlation evaluation.

Results: The whole-exome sequencing analysis revealed all six patients were with loss-of-function of complement or gain-of-function regulators of complement (table 1). WES revealed a novel heterozygous mutation in AEBP1 in three aHUS patients, a novel heterozygous mutation in SCUBE1 in two aHUS patients, and a novel heterozygous mutation in WNT2B in two aHUS patients. In addition, one patient had both SCUBE1 and AEBP1 mutations. The STRING network revealed these mutation genes participated in extracellular matrix environment molecule pathways.

Conclusions: Our results demonstrate aHUS patients from Taiwan have additional mutations in extracellular matrix genes (e.g. AEBP1, SCUBE1, and WNT2B). The additional extracellular matrix gene mutations may play a role in the disease severity. We will further clarify the functional molecular interactions between alternative complement pathway and extracellular matrix genes.

Table 1

Patients	Complement related gene mutation	Extracellular Matrix Genes mutation
Case 1	CFH, CFHR1, CFHR3, CFI, C3, THBD	AEBP1
Case 2	CFH, CFHR1, CFHR3, CFI, C3, THBD, CFB	AEBP1
Case 3	CFH, CFHR1, CFHR3, CFI, C3, CD46, THBD, CFB	AEBP1, SCUBE1
Case 4	CFH, CFHR1, CFHR3, CFI, C3, CFB	SCUBE1
Case 5	CFH, CFHR1, CFHR3, CFI, C3	WNT2B
Case 6	CFH, CFHR1, CFHR3, CFI, C3, CD46, THBD, CFB	WNT2B

TH-PO713

Additional Genes Associated with Atypical Hemolytic Uremic Syndrome

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Background: Atypical hemolytic uremic syndrome (aHUS) is a life-threatening, ultra-rare thrombotic microangiopathy. This partially penetrant genetic disease, featuring a characteristic triad of hemolytic anemia, thrombocytopenia and renal failure, is caused by complement overactivation. 50 to 80% of aHUS patients have a detectable genetic mutation in one of several genes that may lead to overactivation of complement. All aHUS sequencing assays cover a core group of complement genes: CFH, CFI, CFB, C3, MCP/CD46. Additionally, sequencing of CFHR5, THBD, DGKE, as well as copy number to detect the homozygous deletion of CFHR1-CFHR3 or CFHR1-CFHR4 (but not single nucleotide variants within CFHR1, CFHR3 or CFHR4 alone), are often included. More rarely, PLG is sequenced; its inclusion is based on findings from a single publication (Bu (2014) J Am Soc Nephrol 25, 1) where they found several aHUS patients harboring known, rare pathogenic PLG variants.

Methods: Genomic DNA was extracted from patient whole blood and sequenced using an aHUS genetic panel. This panel comprised twelve genes (CFH, CFI, CFB, C3, MCP/CD46, CFHR1, CFHR3, CFHR4, CFHR5, THBD, DGKE and PLG) and was sequenced using targeted next generation sequencing. Variants were confirmed by Sanger sequencing as needed.

Results: Here we describe multiple instances where we detected suspicious variants within PLG and CFHR3 in patients where the aHUS Genetic Panel was ordered by their physician. Some of the suspicious variants we found in PLG (eight cases with p.Lys38Glu and one case with p.Arg253His) were the same variants seen previously by Bu et al; both variants are also associated with plasminogen deficiency. The suspicious CFHR3 variants we observed were severe (splice site, nonsense, frameshift) and either exceedingly rare or novel.

Conclusions: These results 1) replicate the finding by Bu et al of PLG having a role in aHUS, and 2) suggest a potential novel contribution from CFHR3. CFHR3 has previously only been implicated in aHUS as part of a large homozygous deletion that also removes the neighboring gene CFHR1. Furthermore, it is thought that in the case of this large homozygous deletion, it is the absence of CFHR1 that is causitive while CFHR3 is incidental. These results hint at the possibility that rare, dominant negative variants in CFHR3 may also lead to aHUS.

TH-PO714

Safety and Effectiveness of Eculizumab for Adult Patients with Atypical Hemolytic-Uremic Syndrome in Japan: Interim Analysis of Post-Marketing Surveillance

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Background: Eculizumab has been available for the treatment of atypical hemolytic–uremic syndrome (aHUS) in Japan since 2013. To assess safety and effectiveness of eculizumab in adult aHUS patients in the real-life setting, we performed interim analysis of a post-marketing surveillance mandated by Japanese regulations.

Methods: This study enrolled any patient diagnosed with TMA excluding Shiga toxin-producing Escherichia coli-HUS or thrombotic thrombocytopenic purpura based on Japanese clinical guideline published in 2013 as inclusion criteria and treated with eculizumab. According to the guideline revised in 2016, the enrolled patients were with aHUS (complement-mediated HUS) and secondary TMA.

Results: Thirty-three patients with aHUS and 27 patients with secondary TMA were enrolled. Median treatment duration of aHUS was 24weeks. Complement genes variants were detected in 11 of 18 aHUS patients who underwent genetic analysis (61.1%). Among the 29 aHUS patients with available baseline data, platelet count (PLT), lactic dehydrogenase and serum creatinine (SCr) improved within 1-month after eculizumab initiation. TMA event–free status, complete TMA response, PLT normalization, and SCr decrease were achieved in 67.9% (19/28), 27.8% (5/18), 56.5% (13/23), and 57.1% (16/28) of patients, respectively. Thirty-three adverse reactions, i.e., hypertension, hyperuricemia, nasopharyngitis and edema, were observed in 13 of 33 aHUS patients.

Conclusions: This interim analysis confirmed the acceptable safety profile and effectiveness of eculizumab for Japanese adult aHUS patients in real-world settings.

Funding: Commercial Support - Alexion Pharma GK

TH-PO715

Genetic Analysis and Genotype-Phenotype Studies of a Cystinuria Cohort

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Background: Cystinuria is an inherited kidney stone disorder caused by mutations to the *SLC3A1* and *SLC7A9* genes. While most cases are due to biallelic mutations to either gene, monoallelic and digenic families have been described, with overall considerable disease variability. Nevertheless, clear genotype/phenotype correlations have not been described to date.

Methods: A next generation sequencing (NGS) panel consisting of 90 known and candidate kidney stone genes was developed and validated. A total of 49 unrelated, genetically unscreened individuals with a clinical diagnosis of cystinuria were analyzed using this panel. Preliminary correlations with phenotype were made with the genic groups.

Results: The baseline mean (SD) characteristics of the cohort were: age at diagnosis = 19.6y (12.5), number of stones = 5.8 (6.6), cystine excretion = 939.9mg (323.6), eGFR = 82.1ml/min/1.73m^2 (24.5), with age at last follow up = 43.8y (14). A total of 34 patients (69.4%) had biallelic *SLC3A1* and 11 (22.4%) biallelic *SLC7A9* mutations. One *SLC3A1* and two *SLC7A9* cases had a single detected mutation, and one case had no mutations detected. Large rearrangements, detected by LOG2 ratio analysis of the sequence data and confirmed by Multiplex Ligation-dependent Probe Amplification (MLPA), accounted for 31.9% of all *SLC3A1* mutations, mainly the common ex5-9 duplication. Other common mutations were the *SLC3A1* missense change p.Met467Thr (21.7% alleles) and the nonsense mutation p.Arg270* (18.8%), while for *SLC7A9* the missense mutation p.Gly105Arg accounted for 29.2% of pathogenic alleles. Ten novel mutations were identified for each gene. The only detected correlation with genotype was with baseline mean stone number, *SLC3A1* = 7.1 (7.1), *SLC7A9* = 2.0 (2.1; p=0.05) in this cohort.

Conclusions: This analysis shows the utility of a panel-based NGS approach in cystinuria populations and more broadly in patients with suspected monogenic stone disease. Other genetic and/or environmental factors likely also contribute to the observed phenotypic variability.

Funding: NIDDK Support

TH-PO716

A Custom Next Generation Sequencing (NGS) Panel for Kidney Stone Disease Resolves Diagnosis in Mutation Negative Patients Clinically Diagnosed with Dent Disease

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Background: Dent disease is an X-linked disorder characterized by low molecular weight proteinuria, nephrolithiasis/nephrocalcinosis and CKD. We previously performed molecular screening of suspected Dent patients by Sanger sequencing of the known genes: *CLCN5* and *OCRL*. The majority of cases were genetically resolved, but there remained a cohort with no mutations detected (NMD), which we analyze here employing a NGS panel.

Methods: A NGS panel consisting of 90 known and candidate genes related to urinary stone risk was developed and 61 NMD suspected Dent families screened. The phenotype of resolved patients was compared to the implicated gene.

Results: Likely pathogenic mutations consistent, or in one case divergent, with the presenting phenotype were detected in 5 (8%) of the 61 NMD families (Table). Two cases with *SLC34A3* mutations were detected, one with a missense, an inframe deletion and a splicing mutation and a second homozygous for a novel frameshifting duplication. *SLC12A1* biallelic missense mutations were found in a patient with a typical Bartter phenotype. A patient with a *KCNJ1* frameshifting duplication and missense mutation had nephrocalcinosis, proteinuria, and CKD, but lacked the typical electrolyte abnormalities of Barrter. One subject was homozygous for a previously described *CLDN16* missense mutation. An additional patient was found to have two large chromosomal duplications, confirmed by MLPA and microarray analysis, which we have categorized as possibly pathogenic. Three additional patients with weaker biallelic variants in candidate genes are being further assessed.

Conclusions: This analysis demonstrates the utility of a panel-based NGS approach in unresolved patients with suspected monogenic causes of nephrocalcinosis or urinary stone disease and is valuable since the phenotypes of these disorders can demonstrate significant divergence and overlap.

Funding: NIDDK Support

Gene	Age of Presentation	Sex	Affected Family Members	Nephrocalcinosis	Hypercalciuria	Proteinuria (>1g)	LMWP	CKD
SLC34A3	17	F	Y	Y	Y	Y	Y	Y
SLC34A3	8	M	Y	Y	Y	N	U	Y
SLC12A1	3	M	N	Y	Y	Y	Y	N
KCNJ1	55	M	Y	Y	Y	Y	Y	Y
CLDN16	2	M	U	Y	Y	Y	U	Y

TH-PO717

SRNS-Associated MYO1E Mutations Have Differential Effects on Myo1e Activity and Stability

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Background: Mutations in the *MYO1E* gene, encoding myosin 1e (Myo1e), are associated with steroid resistant nephrotic syndrome (SRNS). We set out to characterize novel *MYO1E* mutations identified in SRNS patients (Sadowski et al., JASN, 2015, **26**(6): 1279-89).

Methods: Using adenoviral transduction of EGFP-Myo1e constructs into cultured podocytes, we compared steady-state expression levels, protein turnover rates, and localization of the wild type (wt) Myo1e and several Myo1e mutants, including mutants with point mutations in the motor domain and a frame shift mutant d3094-7 lacking the C-terminal SH3 domain.

Results: We found that two mutants, the T119I motor domain mutant and the d3094-7 frame shift mutant, had low expression levels and high turnover rates and did not localize to cell-cell junctions, where Myo1e is thought to aid in the assembly of the slit diaphragm complexes. In an attempt to restore Myo1e protein stability, we treated cells expressing these mutants with a proteasome inhibitor and observed accumulation of the mutant proteins. The restoration of protein expression in cells expressing the d3094-7 mutant resulted in a partial recovery of the junctional localization and dynamics of this protein. In contrast, an increase in the protein level of the T119I mutant achieved using proteasome inhibition was accompanied by formation of random, seemingly insoluble, aggregates (as determined using fluorescence recovery after photobleaching (FRAP)). Further investigating the properties of those Myo1e mutants that did not exhibit decreased protein stability, we found that the dynamics of one of the motor domain mutants at the junctions was decreased compared to the wt Myo1e. Using FRAP, we found that the mobile fraction of this mutant was lower than that of the wt Myo1e while the half time of fluorescence recovery was higher.

Conclusions: Overall, our findings indicate that while some SRNS-associated mutations affect Myo1e stability and folding, others may have more specific effects on motor domain activity. Furthermore, proteasome inhibition needs to be further examined as a potential therapeutic approach for alleviating the effects of those mutations that affect Myo1e stability without disrupting its motor function.

Funding: NIDDK Support, Private Foundation Support

TH-PO718

Quantification of Urinary 2,8-Dihydroxyadenine Excretion in Patients with APRT Deficiency

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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a rare disorder that results in renal excretion of 2,8-dihydroxyadenine (DHA) in large amounts, leading to kidney stones and chronic kidney disease. We have recently developed a high-throughput ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) assay for quantification of urinary DHA. The purpose of this study was to assess 24-h urinary DHA excretion in APRTd patients, heterozygotes and healthy subjects, and the effect of varied purine intake in patients.

Methods: Nineteen patients in the APRT Deficiency Registry of the Rare Kidney Stone Consortium, 4 heterozygotes and 10 healthy volunteers not taking medications affecting the metabolism or excretion of purines, participated in the study. The effect of varied dietary purine intake was assessed in 4 patients not receiving drug treatment. Urinary DHA excretion was measured in 24-h urine specimens and single void urine samples, expressed as mg/24 h and DHA/Cr ratio (mg/mmol), respectively. Associations were examined using Spearman's correlation coefficient.

Results: The median (range) urinary DHA excretion in 28 samples from 19 patients with APRTd was 138.1 (63.8-291.5) mg/24 h. No DHA was detected in any 24-h urine samples from 4 heterozygotes and 10 healthy individuals. The DHA/Cr ratio in 42 random void urine samples from 19 patients was 13.1 (3.8-37.2) mg/mmol. No correlation was found between urinary DHA excretion and kidney function (r=0.04, p=0.816). The correlation between the first morning void urine DHA/Cr and the 24-h urinary DHA excretion in samples obtained in the same 24-h period was high (r=0.84, p<0.001). The urine DHA excretion was 128.6 (107.2-160.1), 135.8 (114.4-188.4) and 133.5 (102.6-159.6) mg/24 h on self-selected, purine enriched and purine restricted diets, respectively.

Conclusions: Patients with APRTd excrete large amounts of DHA in their urine, while DHA is undetectable in both heterozygotes and healthy subjects. Timed urine samples can be replaced with DHA/Cr ratio in first morning void urine specimens for monitoring of DHA excretion. Short-term changes in purine intake do not seem to affect DHA excretion.

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TH-PO719

Diagnosis of Adenine Phosphoribosyltransferase Deficiency by ATR-FTIR Spectroscopy

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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a rare inherited disorder of purine metabolism characterized by renal excretion of large amounts of crystalline 2,8 dihydroxyadenine (DHA). Affected individuals develop kidney stones and progressive CKD, and eventual ESRD, secondary to renal parenchymal DHA crystal deposition; diagnosis is often missed and its true prevalence is uncertain. Currently, the primary method leading to diagnosis is the detection of DHA crystals by urine microscopy; however, several urinary crystalline species can easily be confused with DHA. Therefore, it is crucial to develop a rapid and sensitive point-of-care method for identification of DHA in human urine samples.

Methods: Fourier-transform infrared (FTIR) spectroscopy has been shown to be a straightforward and reliable technique for the diagnosis of a variety of kidney stones. We assessed attenuated total reflection (ATR) FTIR spectroscopy as a means of detecting DHA in urine.

Results: An optimal method for accurate detection and quantitation of DHA in a dried urine pellet was developed. Urine samples from untreated APRTd patients in whom the presence of DHA had been confirmed by ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS-MS) were assessed using ATR-FTIR. Insoluble DHA was detected in 17 of the 20 urine samples with concentrations ranging from 1.4 - 24.8 μM. In 3 samples, ATR-FTIR indicated the presence of a different insoluble component related to a form of uric acid or its salts, possibly in combination with other compounds. Hence, this method may be useful in routine clinical screening to identify cases of APRTd. In addition, IR analysis of pure DHA revealed a second physical form of DHA, probably an amorphous state, which has not been reported before. It is unclear whether amorphous DHA may be involved in disease pathogenesis and/or if the lack of recognition of amorphous DHA contributes to under-diagnosis of APRTd.

Conclusions: In conclusion, ATR-FTIR may be a useful and rapid 'point-of-care' screening tool for early diagnosis of APRTd. Both the method and instrumentation can be adapted easily and cheaply for clinical use. The clinical significance of the newly identified amorphous DHA remains to be established.

Funding: Private Foundation Support

TH-PO720

Development of a 2D-UPLC-MS/MS Assay for Therapeutic Monitoring in Patients with APRT Deficiency

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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a rare hereditary purine metabolism disorder resulting in accumulation and renal excretion of 2,8-dihydroxyadenine (DHA), causing kidney stones and chronic kidney disease (CKD). The drugs allopurinol and febuxostat reduce urinary DHA excretion and ameliorate the disease manifestations. We developed a two-dimensional ultra-performance liquid chromatography tandem mass spectrometry (2D-UPLC-MS/MS) assay for simultaneous measurement of DHA and the pharmacological agents allopurinol, its active metabolite oxypurinol, and febuxostat in human plasma for monitoring of pharmacotherapy.

Methods: A design of experiments was used to define the optimum 2D-UPLC-MS/MS conditions based on the minimum number of experiments. Experimental screening of the variables was performed by D-optimal design to identify factors influencing retention time, peak height and peak area for all compounds. Variables were optimized with central composite face design and related to sensitivity and retention time using partial least square regression. Protein precipitation was carried out with 1% formic acid in methanol as a crash solvent. Plasma samples from APRTd patients and control specimens from laboratory personnel were used for the study.

Results: The plasma concentration of DHA, allopurinol, oxypurinol, and febuxostat was reliably achieved with the 2D-UPLC-MS/MS assay. The DHA concentrations in plasma from 3 APRTd patients were 456, 459 and 741 ng/mL off drug treatment and 130, 61 and 27 ng/mL while on allopurinol or febuxostat therapy. By contrast, DHA was not detected in plasma from healthy controls. The plasma allopurinol and oxypurinol concentration during drug treatment in the 3 patients was 802, 2391, 5089 and 6810, 7076 and 12,510 ng/mL, respectively, and the febuxostat concentration was 1276 ng/mL in 1 patient.

Conclusions: Our data suggest that the 2D-UPLC-MS/MS assay may be used to monitor the efficacy of pharmacotherapy and treatment adherence among APRTd patients. This method may prove useful in determining the plasma DHA concentration that must be attained in order to prevent new kidney stone growth and CKD progression in these patients.

Funding: NIDDK Support, Other NIH Support - Rare Kidney Stone Consortium (U54KD083908), part of the Rare Diseases Clinical Research Network (RDCRN), which is an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS).

TH-PO721

Safety and Efficacy Study of Lumasiran (ALN-GO1), an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Primary Hyperoxaluria Type 1

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Background: In Primary Hyperoxaluria Type 1 (PH1), defective alanine:glyoxylate aminotransferase leads to excessive hepatic oxalate production, leading to progressive renal impairment and multi-organ damage from systemic oxalosis. Lumasiran, an investigational RNAi therapeutic suppresses hepatic glycolate oxidase, decreases the conversion of glycolate to glyoxylate, and results in reduced oxalate production.

Methods: ALN-GO1-001 is a randomized, placebo-controlled, single-blind, multicenter trial, evaluating lumasiran in patients with PH1 ≥6 years of age with urinary oxalate (UOx) ≥0.7 mmol/1.73m^2/day and eGFR >45 mL/min/1.73m^2. One of four patients in each dosing cohort was randomized to placebo prior to subcutaneous lumasiran. Cohorts 1 & 2 received 3 monthly doses of 1 mg/kg or 3 mg/kg, respectively; cohort 3 received 2 quarterly doses of 3 mg/kg lumasiran. An additional 4 patients received lumasiran in expansions of each of the first 2 cohorts. The primary endpoint is safety; secondary endpoints include change in 24-hour UOx from baseline. Eligible patients may continue dosing in the open-label extension (OLE) study.

Results: Patients in cohorts 1-3 had a mean age of 13.1 years (range 6-43), 7 (58%) female, and baseline UOx was 1.58 mmol/1.73m^2/day (range 0.63-2.37). Lumasiran has demonstrated acceptable preliminary safety and tolerability with no treatment related serious adverse events or discontinuations; majority of adverse events were mild/moderate and unrelated to study drug. All patients treated with lumasiran in cohorts 1-3 experienced UOx lowering below 0.7 mmol/1.73m^2/day, with a mean maximal decrease of 65%. Data available 85 days after initial dosing in the first 3 cohorts (n=9) showed a mean UOx reduction of 63% (range 49-73%). Data from patients in all cohorts (n=20), including quarterly dosing, expansions and OLE will be presented.

Conclusions: Preliminary results demonstrate acceptable safety data and lowering of UOx in patients with PH1 supporting the continued development of lumasiran as a potential therapeutic to alleviate pathologic overproduction and consequences of excess oxalate in this devastating disease.

Funding: Commercial Support - Alnylam Pharmaceuticals

TH-PO722

Endogenous Pentraxin 3 Inhibits Nephrocalcinosis and Protects from Hyperoxaluria-Induced CKD

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Background: Patients with primary hyperoxaluria type 1 have an elevated oxalate production leading to intrarenal calcium oxalate crystal deposition (nephrocalcinosis) and CKD progressing to ESRD. Pentraxin 3 (PTX3) exerts a variety of regulatory functions in acute and chronic tissue inflammation. Also, PTX3 acts as an opsonin for a variety of pathogens and endogenous particles. We hypothesized, that PTX3 would exhibit opsonin-like functions on calcium oxalate crystals and inhibiting crystal growth and nephrocalcinosis.

Methods: Direct effects of PTX3 on calcium oxalate crystals were investigated in chemico using standard imaging techniques. To study the role of PTX3 in vivo, we used a murine model of hyperoxaluria induced nephrocalcinosis where *Ptx3*-deficient B6;129-mice or their *PTX3*-competent littermates were fed with a high-oxalate diet for 21 days. PTX3 expression was assessed by Western blot and immunohistochemistry. Phenotype analysis included histochemistry, flow cytometry and GFR measurement.

Results: Adding PTX3 to supersaturated calcium and oxalate in-chemico dose-dependently inhibited crystal growth, while an isomolar albumin control did not (A). PTX3 protein was undetectable in the urine of healthy wildtype mice but increased within 3 weeks of oxalate feeding. Immunhistochemistry of kidney sections indicated that urinary PTX3 originated from tubular epithelial cells. Testing the role of PTX3 in vivo we induced hyperoxaluria in *Ptx3*-deficient mice and their wildtype littermates. In this particular background, lack of PTX3 induced profound nephrocalcinosis associated with interstitial inflammation and fibrosis as well as a linear decline in GFR, whereas *Ptx3*+/+ littermates where protected (B-D).

Conclusions: Thus, PTX3 is an endogenous inhibitor of calcium oxalate crystallization even in profound hyperoxaluria. It will be interesting to look into the precise mechanism

of action and to develop therapeutic strategies to exploit this novel found function of PTX3 to prevent nephrocalcinosis in primary hyperoxaluria, a disease with currently very few treatment options.

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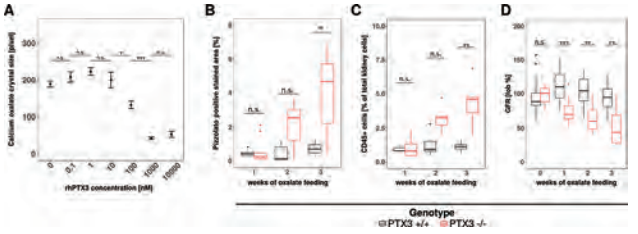

TH-PO723

Cardiac Oxalosis in Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH) is an inherited disease characterized by increased hepatic production of oxalate (ox). Renal excretion of excess ox causes kidney stones, nephrocalcinosis, and renal damage. As GFR declines plasma ox (Pox) increases and can cause systemic calcium oxalate deposits (oxalosis). Cardiac involvement results in conduction abnormalities and infiltrative cardiomyopathy. However, epidemiology of cardiac oxalosis in PH is not well defined.

Methods: The PH registry of the Rare Kidney Stone Consortium was queried for information regarding cardiac function. Among 128 PH subjects with Pox available prior to transplant, 101 had type 1 (PH1), 14 PH2, and 13 PH3. ECG studies (n=433 from 52 subjects), echocardiograms (n= 92 from 40), Pox (nl < 1.6 umol/L), and urine ox (Uox, nl < 0.46 mmol/24 hrs) at initial evaluation and during follow-up were analyzed. E/e' was used for diastolic function (nl <13). LV strain nl < -18%.

Results: At diagnosis mean (median) age was 18.6 (11.5) yrs, eGFR 75 (65) ml/min/1.73m^2, urine oxalate (Uox) 1.9 (1.7) mmol/1.73m^2/day, and Pox 21.3 (6.1) umol/L. At diagnosis 1/52 ECGs were abnormal, with atrial fibrillation (afib) in a subject with eGFR 66. Subjects were followed for 14.1 (11.4) yrs. Pox increased as eGFR declined (p<0.0001) as expected. Overall 14/52 PH subjects had 48 abnormal ECGs showing 1st degree or variable AV block (n=6), bundle branch block (3), afib (5), and LVH (4). Abnormal ECG studies did not differ across eGFR groups (p=0.22). Table 1 shows clinical characteristics and echo at last followup.

Conclusions: Using standard clinical tests, most PH subjects demonstrate good cardiac function, even at eGFR < 30 when Pox increases significantly. Whether more sensitive monitoring tools will demonstrate earlier manifestions of cardiac oxalosis remains to be established.

Funding: NIDDK Support, Commercial Support - OxThera, Private Foundation Support

Clinical findings at last follow-up

	eGFR <29, ESRD	eGFR 30-59	eGFR 60-89	eGFR > 90	Total	p value
	n=52	n=19	n=31	n=26	n=128	
eGFR, mean (SD)	10.5 (6.3)	46.8 (7.8)	72.08 (7.8)	227 (436)	76 (211)	<0.0001
Age follow-up (yrs)	35.5 (19.4)	38.3 (21.2)	30.1 (16.4)	25.8 (14.5)	32.6 (18.4)	0.08
Years follow-up	11.4 (13.3)	12.8 (12.8)	15.3 (12.0)	19.1 (12.4)	14.1 (13.0)	0.01
Pox, umol/L	58.6 (50.2)	13.9 (26.7)	4.0 (3.3)	3.8 (6.8)	26.9 (41.9)	<0.0001
LV EF, %	59 (6)	60 (6)	57 (9)	54 (2)	58 (7)	0.10
Diastolic function, E/e'	10.5 (4.6)	9.6 (2.4)	11.6 (3.7)	8.8 (2.5)	10.6 (3.8)	0.10
LV Strain, %	-20.6 (0.8)	-19 (2.1)	-18.9 (2.0)	-17.8 (1.9)	-19.2 (1.9)	0.06

TH-PO724

Blood Pressure and Biological Phenotype in Healthy-Carrier Relatives of Patients with Gitelman Syndrome

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Background: Gitelman syndrome (GS) is the most frequent salt-losing tubulopathy caused by loss of function mutations in the SLC12A3 gene, encoding for the thiazide-sensitive NaCl cotransporter. Depending on the country, 1 to 4 % of the population is heterozygous carrier of pathogenic variant. Consequence of this status remains debated. The aim of this study was to evaluate the impact of SLC12A3 heterozygous mutations on blood pressure (primary outcome) and on electrolyte and glucose homeostasis.

Methods: This cross-sectional study included 239 subjects, both sex, 18-75 years old: 81 heterozygous carriers (HC) of class 4-5 variants (ACMG 2015), 81 non-carrier normotensive subjects (NC) matched to HC on age, sex and BMI and 77 patients with genetically proven GS. Home blood pressure (HBP) measurements were done the 3 consecutive days before admission in hospital for blood and urine sampling and oral glucose tolerance test (OGTT).

Results: As compared to NC, HC had similar HBP, blood and urine concentrations of electrolytes (Na, K, Cl, tCO_2 Mg, Ca), and values of PTH, vitamin D, renin, aldosterone and markers of bone remodeling as well as response to OGTT (all p>0.05, paired t test NC vs HC). Systolic BP increased similarly with age in both groups. GS had renal hypokalemia, hypomagnesemia and low urinary calcium excretion. Ten patients had known hypertension. GS had however lower SBP than the other groups (mean difference 4.5 (CI95 1.18; 7.78), p 0.0087 and 4.1 mmHg (CI95 0.20; 8.07), p 0.0410; NN and HC vs GS) and higher cardiac frequency (mean difference 4.5 (CI95 -7.4; -1.5), p 0.0040 and -3.7 bpm (CI95 -7.0; -0.5), p 0.0271; NC and HC vs GS). The increase in SBP with age was blunted in GS patients. GS had significant higher basal glycaemia and insulin concentrations and HOMA-IR (homeostatic model assessment for insulin resistance) than the other groups independently of BMI. OGTT showed a prediabetes status in 14% of GS patients compared with 4 and 5% in HC and NC.

Conclusions: In conclusion, we found no difference between heterozygous carriers and age- and sex-paired healthy controls. GS patients have a risk to develop type 2 diabetes pointing out the importance of body weight control in GS patients.

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TH-PO725

Markers of Potassium Homeostasis and Quality of Life in Salt Losing Tubulopathies

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Background: Gitelman and Barter Syndrome are the most frequent genetically inherited salt losing tubulopathies (SLT) with limited treatment options and quality of life (QOL) is reduced. Treatment options include supplementation of potassium (K+) and magnesium, potassium sparing diuretics. However evidence from randomized controlled trials indicate low efficacy of current treatments in terms of increasing K+. Morover K+ may not reflect the magnitude of the concommittant secondary hyperaldosteronism in those patients. Optimal endpoints for treatment trials should include QOL however little is known of optimal clinical cut-offs of laboratory values and their relation in SLT. The trans-tubular potassium gradient (TTKG) has been shown to be an accurate surrogate for hyperaldosteronism and of excellent use in other entities related to hyperaldosteronism like liver cirrhosis.

Methods: In this prospective cross-sectional study we included 11 patients with SLT. We measured laboratory parameters (K+, Mg++, Ca++, TTKG, Aldosteron) and their relation with QOL assessed by the RAND SF-36. The primary hypothesis was that TTKG may reflect QOL more accurately than K+ and serve as an end-point in future treatment trials. Secondary endpoints were the presence of cardiac arrhythmia in 24h ECG and cardiac abnormalities via ultrasound (US).

Results: The cohort consisted of mainly females with a median age of 29 years. The median K+ was 3.3 mmol/l and median TTKG 9.5. While there was a positive correlation of K+ and TTKG, we did not observe a significant correlation of TTKG with serum aldosterone. Comparing QOL domains we observed that TTKG showed a trend for better physical functioning while K+ was significantly related to emotional wellbeing and trend for energy and general health. Aldosterone was significantly related to role limitations emotional and physical. Urinary potassium with a threshold >20 mmol/l was inversely related with energy/fatigue and general health and a trend for emotional wellbeing while TTKG <10 or K+>3 mmol/l were not related to QOL. No relevant abnormalities were observed in either 24h ECG or cardiac US.

Conclusions: TTKG is not a suitable marker for hyperaldosteronism in SLT and K+ and TTKG are not sufficient endpoints for treatment trials for SLT in relation to QOL. Future treatment trials in SLT should include QOL assessment as well urinary parameters.

TH-PO726

MAP17 and SGLT2 Interaction in Cellular Models and Human Kidney Specimen

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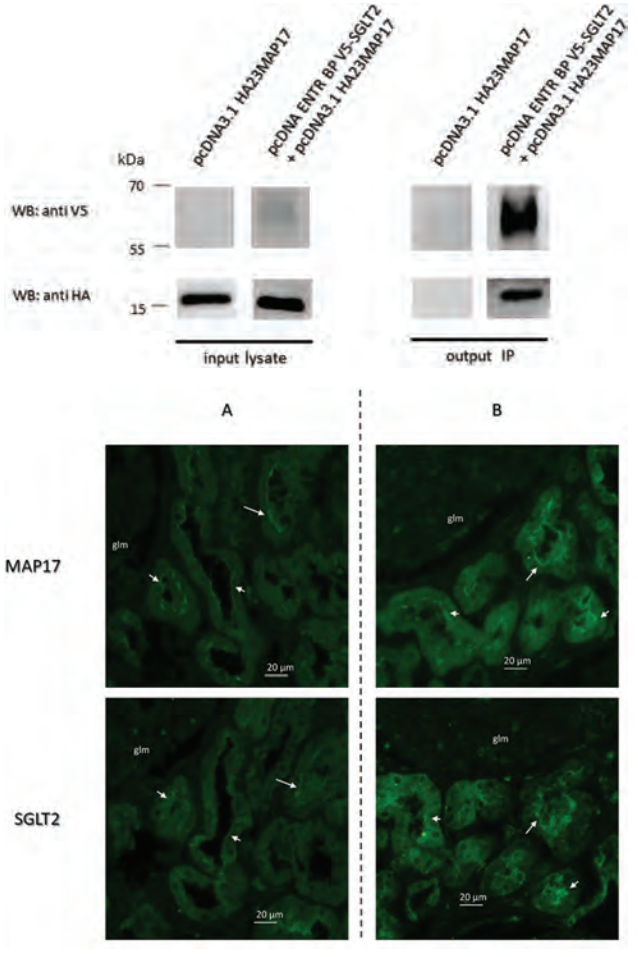
Background: Mutations in SGLT2, a Na/coupled glucose transporter of the early proximal tubule, are responsible for Familial Renal Glucosuria (FRG), and SGLT2 pharmacological inhibition has become a promising new therapy in type 2 Diabetes Mellitus. MAP17 was recently identified by means of expression cloning as an accessory protein for SGLT2 activity and mutations in MAP17 coding gene were found in a SGLT2 negative FRG individual. However, the way MAP17 promotes SGLT2 activity is unknown. In this work we investigated the hypothesis that MAP17 is a binding partner for SGLT2 and that both proteins interact and dimerize.

Methods: We engineered a N-terminal V5 tagged SGLT2 plasmid and coexpressed together with a HA tagged MAP17 construct in HEK293 cells. We assayed the interaction of both proteins in vitro by immunofluorescence and immunochemistry techniques. In

addition, we performed histological examination and immunofluorescence observations in human normal kidney sections to evaluate MAP17 and SGLT2 expression in the kidney.

Results: In HEK293 cells cotransfected with both constructs, MAP17 and SGLT2 were shown to colocalize in a perinuclear and cytoplasmic vesicular staining. In addition, MAP17 coimmunoprecipitated with anti V5 goat antibody only in the presence of V5-SGLT2 construct (fig.1). Finally, SGLT2 and MAP17 largely overlap in their abundance at the brush border of proximal tubule epithelial cells (fig. 2).

Conclusions: We have shown that SGLT2 and MAP17, when overexpressed, interact in vitro and, likewise, under constitutive expression in the kidney, they also overlap their abundance in the proximal tubule. This interaction provides the biochemical foundation for the physiological observation that MAP17 is a necessary activator of SGLT2.



TH-PO727

Renal Ablation of GLUT2 Leads to Intracellular Glycogen Accumulation and Recapitulates the Fanconi Bickel Syndrome

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Background: Fanconi-Bickel syndrome, also known as glycogenosis type XI, is characterized by hepatic glycogen accumulation and proximal renal tubular dysfunction. Patients mainly suffer for a typical renal Fanconi syndrome associated with fasting hypoglycaemia. Currently, there is no causative therapy beside fluid and electrolyte supplementation. Loss of function mutations of *SLC2A2,* encoding for GLUT2, causes FBS. Impairment of GLUT2 alters glucose metabolism in hepatocytes and increases glycogen accumulation. Since the cells of the proximal tubules share a similar glucose metabolism as hepatocytes, a similar mechanism could be hypothesized, but no evidences so far has been provided

Methods: In order to generate an experimental model of FBS, we selectively knock-out GLUT2 expression in PAX8 expressing cells by mean of a Cre-Lox recombination strategy. This approach results in an efficient ablation of GLUT2 in the renal cortex

Results: GLUT2 cKO mice recapitulate the renal phenotype of FBS patients. They present with normo-glycaemic glycosuria and no signs of altered glucose metabolism when challenged with a glucose load. Glycosuria decreases, but is still detectable after fasting. GLUT2 cKO mice present an osmotic driven polyuria that improves by reducing theosmotic load. cKO mice present low molecular weight proteinuria and phosphaturia. This latter is sustained by a downregulation of Napi2a abundance in the cortex of GLUT2 cKO mice. When challenged with a sodium bicarbonate load, at serum level of bicarbonate equal as control mice, they excrete a double amount of bicarbonate, showing that GLUT2 ablation lead to proximal renal tubular acidosis. At histology, the proximal tubule cells appear hypertrophic compared with littermate controls. Quantification of renal cortical glycogen content shows a three fold increase abundance in cKO mice, suggesting that GLUT2 ablation alters significantly the intracellular glucose metabolism

Conclusions: We generate a mouse model cKO for GLUT2 recapitulating FBS. We show that GLUT2 is crucial for intracellular glucose metabolism in the proximal tubule cells since its ablation leads to a severe glycogen accumulation and loos of function. This model is suitable for testing novel pharmacologic approach to rescue FBS

TH-PO728

A Unique Mutation in the MODY1 Gene HNF4A Causes Fanconi Syndrome by Shifting Lipid Catabolism to Anabolism

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Background: Renal proximal tubular cells (PTCs) have the task to reabsorb most of water, solutes and proteins filtered by the glomerulus. To cope with their high energy demand, PTCs exclusively rely on fatty acid oxidation. However, lipid metabolism needs to be finely regulated in this tissue as recent evidence has suggested that renal lipid accumulation and lipotoxicity may lead to kidney dysfunction. Here, we focus on the function of the nuclear hormone receptor HNF4A whose mutations cause MODY1, a monogenic type of diabetes in humans. Only one mutation (p.R85W) in the DNA binding domain leads to additional PTC dysfunction (also known as Fanconi syndrome), but the reason for this is unclear.

Methods: To address the role of HNF4A in lipid metabolism and to illuminate the pathogenetic mechanisms underlying the R85W mutation, we made use of the *Drosophila* model. In particular, we utilized fly nephrocytes as a simplified cell model for PTCs.

Results: We show that HNF4A controls a genetic program that regulates lipid metabolism in nephrocytes. Silencing HNF4A causes an increase in lipid droplet size and number, while the overexpression of HNF4A causes depletion of lipid stores through brummer/ATGL-mediated neutral lipolysis. Interestingly, very high expression levels of HNF4A or the expression of the R85W mutation behave in a dominant-negative fashion by triggering a shift from lipid catabolism to lipid anabolism. In addition to a lipolysis block, this involves the increased DGAT1-dependent formation of lipid droplets. In both conditions, the lack of lipolysis leads to mitochondrial depolarization, possibly due to the decreased availability of free fatty acids and lack of ATP production. The mitochondrial damage is accompanied by the accumulation of ER fragmentation, p62- and PDI-positive protein aggregates and a strong induction of autophagy. Collectively, these organellar injuries eventually lead to nephrocyte loss and shorten the life span of flies.

Conclusions: Altogether, our data describe a novel pathogenetic mechanism for Fanconi syndrome with important implications for the general understanding of lipid metabolism in PTCs. Moreover, targeting HNF4A or one of its downstream partners could represent a very useful therapeutic strategy in situations with lipid overload in the PTCs.

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TH-PO729

Congenital Renal Glycosuria Is Associated with Healthier Weight at Adolescence: Nationwide Cross Sectional Study of 2.38 Million Examinees

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Background: Glucose filtered in the glomeruli is normally reabsorbed by the sodium coupled glucose transporters (SGLTs), mostly the SGLT2, located in the renal tubules. Mutations in the genes coding for these transporters were shown to cause renal glycosuria. It was shown recently in various studies that pharmacological inhibition of SGLT2 causing renal glycosuria is an effective treatment for diabetic patients. Among the desirable effects of these medications is weight lost and reduction of blood pressure. The aim of the current study is to investigate whether adolescents with renal glycosuria are less likely to be overweight or obese

Methods: Medical and socio-demographic data on 2,385,093 adolescents examined for medical fitness prior to military service from 1977 to 2016 were retrieved from the Israeli Defense Forces conscription center database. We conducted a cross sectional study to evaluate the association between renal glycosucria diagnosed in the conscription center and the overweight (85-95 BMI percentiles) and obesity (>95 bmi percentiles). Multinomial regression model were used.

Results: The final study cohort comprised of 2,388,163 conscripts of whom 1069 (0.045%) were assigned with numerical code meaning renal glycosuria not related to diabetes. The adjusted OR for overweight and obesity was 0.69 (95% CI, 0.54-0.89) and 0.60 (95% CI, 0.42-0.85), respectively.

Conclusions: Congenital Glycosuria may is associated with healthier metabolic profile, specifically less overweight and obesity, and this effect is already seen at adolescence

TH-PO730

Genetic and Functional Characterization of PHEX Gene Variants in 42 Children with X-Linked Hypophosphatemic Rickets

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Background: X-linked hypophosphatemia, a disorder of renal phosphate wasting and the most common heritable form of rickets, is caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homolog (PHEX). The aim of this study was to explore the molecular basis of 42 children with HR in the Chinese population.

Methods: All patients were analyzed for the PHEX gene by direct sequencing. When no mutations were detected in PHEX gene, multiplex ligation-dependent probe amplification (MLPA) analysis was performed. PHEX non-truncating mutation and two truncated mutations were characterized in vitro by assessing their effects on PHEX expression, subcellular localization and glycosylation pattern.

Results: Among 42 patients, 40 patients (95%) harbored mutations in the PHEX gene. In particular, we detected 35 different mutations, including eleven indel mutations including nine frameshift mutations resulting from small deletions or insertions and one 3bp deletion mutation (31.4%), seven missense (20%), seven splice sites mutations(20%), five nonsense (14.2%), and five exonic deletion (14.2%). Among these mutations, 21 mutations have not been previously described in the literature or entered in PHEXdb and HGMD. Clinical presentation and disease severity did not show an evident correlation between the truncating and non-truncating mutation type. Like the nonsense mutaion R567X and Q714X, five of the six non-truncating mutation detected in our cohort also led to retention of the PHEX protein in endoplasmic reticulum, in an immature form, as determined by glycosylation pattern and proteasomal degradation analysis and immunofluorescence.

Conclusions: Our findings expand the mutation spectrum of PHEX, confirm that mutations in PHEX are the most frequent cause of HR, and truncating mutations is the most often mutation type in Chinese patients. Our clinical and experimental evidence also showed no correlation between the degree of disease severity and the PHEX genotypes.

TH-PO731

Human Gout Risk Variant ABCG2 Q141K Results in Profound Hyperuricemia and Significant Changes to Kidney Function in a New Mouse Model

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Background: Gout is the most common inflammatory arthritic disease and is a consequence of having elevated circulating urate (UA) levels (hyperuricemia). GWAS studies have identified a number of key urate transporter genes that contribute to gout risk and are expressed in the kidney and the intestines. Yet recent work from others has shown individuals carrying the most common gout risk variant, Q141K ABCG2, have no measureable difference in their renal fractional excretion of urate (FEUA). These data beg the question of whether or not ABCG2 has a role in the renal urate excretion pathway.

Methods: We have made a new mouse knock-in model of the human gout risk variant, Q141K ABCG2 (in mice, Q140K) on a C57BL6J mouse background using CRISPR Cas9 gene editing techniques, and have used biochemical, Immunofluorescence, and renal physiological measurements to described the renal phenotypes of a human risk variant carried by 500 million individuals world-wide.

Results: We first confirmed and localized the ABCG2 protein in the mouse and human tubule, confirming unambiguously that ABCG2 expression in apical membrane of the human proximal tubule is robust. The Q140K ABCG2 mutant male mice proved to be profoundly hyperuricemic, and although the mutant mice displayed both a slight decrease in renal protein abundance and a decrease in FEUA, it was significantly less than observed in the intestines, with female mice showing no defect at all. In addition to the decrease in FEUA, the male mutant mice exhibited other hallmarks of declining renal function including, reduced eGFR, signs of metabolic acidosis, impaired ammonium secretion, and evidence of more wide spread metabolic alterations, including increased blood glucose and insulin levels.

Conclusions: Our new mouse model of the common human gout risk variant, Q141K ABCG2, shows that a single loss of function point mutation in a single urate transporter has significant phenotypic effects on mammalian physiology, and this work provides evidence that alterations in urate homeostasis alone can effect kidney function, consistent with the hypothesized causal role of urate in renal and metabolic diseases.

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TH-PO732

Urinary MicroRNAs in Fabry Disease Patients with Mild Nephropathy

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Background: Analyze the urinary excretion profile of microRNAs (UEPmiR) regulated by TGF-β-SMAD. Fibrotic: miR-21;miR-192;miR-433. Anti Fibrotic: miR-29;miR-200)

Methods: microRNAs extraction from urinary cell pellet was achieved. RNAU6 was endogenous control. Relative miR expression levels were calculated with ΔΔCt method. Dependent variable: UEPmiR. Independent variables: age, gender, α-galA activity, genotype, CKD stage and proteinuria.

Results: Healthy subjets: 8p (4m/4f); age: 25.9±15.2ys; eGFR: 120.7±18.7 ml/min/1.73m^2. All nonalbuminuric patients. FD population: 24p (7m/17f); age: 23.7±17.3ys; decreased α-galA: 100% males/13.3% females; eGFR: 137.3±37.2 ml/min/1.73m^2; microalbuminuria: 16.7% (1/7) males/35.3% (6/17) females. There were no statistically significant differences in age (p=0.741), eGFR (p= 0.239) and ACR (p=0.204) between healthy subjects and FD patients. microRNA expression in FD patients according to age, gender, genotype, α-galA activity, eGFR, and ACR: significant differences were found between sexes and normal or decreased α-galA only in miR-29 (p=0.041;0.041) and miR-200 (p=0.048;0.048), respectively. FD patients with normal α-galA, without clinical criteria to start enzyme replacement therapy (ERT)(A1 group), did not present differences in UEPmiR compared to healthy subjects. FD patients with more severe phenotype and received ERT (A2 group) did not present differences in UEPmiR compared with healthy subjects neither A1 group. FD patients with normal α-galA and without clinical criteria to start ERT (B1 group), presented a UEPmiR indicative of renal fibrosis (decrease of miR-29 and miR-200). FD patients with decreased α-galA and clinical criteria to start ERT had a different UEPmiR than B1 group, finding that miR-29, in B2 group, behaves similar to healthy subjects.

Conclusions: FD males have a profibrotic UEPmiR. UEPmiR was similar between healthy subjects and two groups of FD patients, i) patients with mild FD phenotype and normal α-galA activity and ii) patients with normal α-galA but with a more severe phenotype receiving ERT. In FD patients with low α-galA activity without ERT, a profibrotic UEPmiR was found; compared with FD patients with low α-galA activity and severe phenotype with ERT, an increase of miR-29 was observed. A probable effect of ERT should be evaluated in longitudinal studies.

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TH-PO733

The Prevalence of Fabry Disease in Patients Undergoing Hemodialysis in the Northernmost Region in Japan

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Background: Fabry disease, an X-linked, progressive and life-threatening genetic disease, is caused by abnormalities in the α-galactosidase A (α-Gal A) gene. Several studies in Japan reported 2-3% of males suffering from left ventricular hypertrophy were affected with Fabry disease, however, the prevalence of Fabry disease in patients undergoing hemodialysis is still unknown.

Methods: In this prospective, multicenter study, we screened 1,476 patients receiving dialysis from multicenter of the northernmost prefecture in Japan. Patients with a low α-Gal A activity were assessed using dried blood spots on filter paper, and a genetic study of the α-Gal A gene was performed for these patients.

Results: A total of 1,476 patients (66% male, median age 67.0 years) underwent screening and 52 had low α-Gal A activity; of these, two males had α-Gal A mutations. A 64-year-old man had the genetic mutation of p.M187V in exon 4. Another 55-year-old man had the genetic mutation of c.908-928del21 in exon 7, which is a new mutation not described before in the literature, but potentially pathogenic. Both patients had severe left ventricular hypertrophy and had diagnosed as having chronic glomerulonephritis without renal biopsy. The prevalence of Fabry disease is 0.14% in patients undergoing hemodialysis in the northernmost region in Japan.

Conclusions: Dried blood spot screening was considered as a simple and effective method for detecting the underlying patients with Fabry disease. Clinicians should be aware of Fabry disease as a potential cause of hemodialysis, especially in hemodialysis patients with severe left ventricular hypertrophy without renal biopsy.

TH-PO734

Bedside Assessment of the Microcirculation in Patients with Fabry Disease

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Background: Fabry disease is a hereditary lysosomal storage disease with a loss of α-galaktosidase A activity, in which accumulation of glycosphingolipids leads to cellular damage in endothelial cells and other cell types. The endothelial surface layer (ESL) with the glycocalyx is important for endothelial cell function. We, therefore, assessed the ESL as well as circulating components of the ESL in Fabry patients. Visualization of the microcirculation can lead to a better understanding of its contribution to the pathophysiological changes in Fabry disease.

Methods: 29 patients with Fabry disease and 33 healthy age- and gender-matched controls were analysed by intravital microscopy with the GlycoCheck™ technology (Micro Vascular Health Solutions) to measure ESL thickness (perfused boundary region), red blood cell filling velocity, and microvascular density. Circulating ESL components (syndecan-4, thrombomodulin), cytokines (MCP-1), and regulatory molecules (ADAM-17, VEGF-R1) were measured in plasma using ELISA. Patients were clinically characterized by organ involvement (heart, kidney, brain).

Results: Perfused boundary region was significantly decreased in patients with Fabry disease (1.96 ± 0.28, vs. 2.36 ± 0.27, p = 0.001). Circulating markers of the ESL were not different between groups. Microvascular density was significantly lower in Fabry patients compared to controls (median 284.50 vs. 580.83 μm/mm^2, p = 0.001). The alterations in microcirculation were independent of the degree of organ involvement. MCP-1 concentration was significantly increased in Fabry patients (346.19 ± 91.82 pg/ml

vs. 288.13 ± 95.22 pg/ml, p = 0.018) which was pronounced in patients with cardiac involvement.

Conclusions: Our data suggest an increase in ESL density, and no change in glycocalyx breakdown in patients with Fabry disease. In addition, a rarefication of microvessels was observed. Our findings suggest pathophysiological changes in the microvascular structure of patients with Fabry disease. The enhanced inflammation is not directly related to the microvascular changes.

TH-PO735

Fabry Nephropathy: Transcriptome Sequencing of Microdissected Renal Compartments from Archival Kidney Biopsies at Baseline, and After 5 and 10 Years of Enzyme Replacement Therapy

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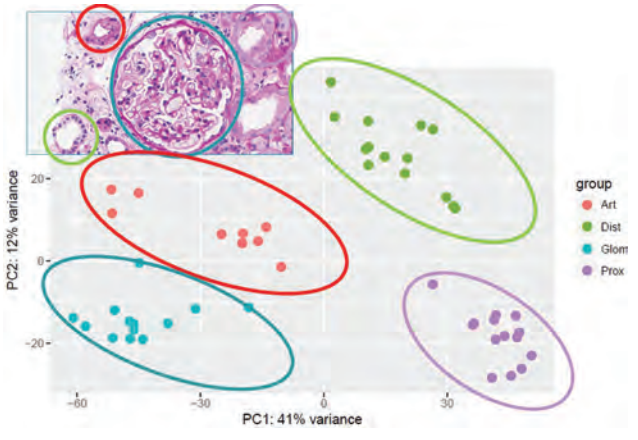
Background: The present study exploited next generation mRNA sequencing from kidney biopsies of Fabry patients with a classical phenotype

Methods: Kidney biopsies (n=15) were obtained with a 16G needle from Fabry patients (n=5) from 2003-2014. Median patient age at baseline biopsy was 18 years (7-30 y). Control biopsies from peri-tumorous tissue of renal cancer patients (n=32). Formalin-fixed, paraffin-embedded (FFPE) kidney biopsies were obtained: a) baseline prior to enzyme replacement therapy (ERT; n=5), b) after 5y of ERT (n=5), and c) 8-10y of ERT (n=5). Total RNA was extracted from laser-captured, microdissected glomerular, proximal tubular, distal tubular and arterial cross-sections (High Pure FFPET RNA extraction kit; Roche). cDNA libraries were prepared using the TruSeq RNA Access Library Prep Kit® (Illumina) and sequenced on an Illumina HiSeq 2500/HiSeq 4000 instrument

Results: We present the results of the first 42 samples of a larger ongoing series. Several hundred mRNAs were differentially expressed (p-value <0.05, abs. fold change >2) between normal controls and Fabry baseline samples, and between the baseline samples and the two different treatment time points. The samples segregated completely within their own compartment (Fig. 1) in principle component analysis. Gene Set Enrichment Analysis in the glomerular compartment demonstrated enriched gene sets of extracellular matrix, EMT, fibrosis, and immune response in the 10 year biopsies compared to baseline (p<0.05) despite ERT. Several key regulatory inflammatory genes were found to be upregulated in all compartments

Conclusions: NGS is feasible in archival Fabry disease kidney biopsies, expanding the potential utility of kidney biopsies to detect markers of Fabry nephropathy, chronic kidney disease and therapeutic targets

Funding: Commercial Support - Sanofi Genzyme, Shire, Government Support - Non-U.S.



TH-PO736

Implications of Renal Impairment on Dosing of Delayed-Release Cysteamine Bitartrate

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Background: Delayed Release Cysteamine Bitartrate(DRCys) is used to treat nephropathic cystinosis (NC) in order to prolong native kidney function and ameliorate other systemic effects of NC. A biomarker, WBC cystine levels (WBCCys) guides optimal cystine reduction. To date, there are no studies on the effects of impaired renal function, including hemodialysis (HD) on DRCys elimination, and Study RP103-16001 was designed to address these missing data.

Methods: Subjects (all without NC) with mild, moderate, or severe renal impairment, or ESRD requiring hemodialysis, (HD) (8 each; NKF classification based on eGFR) and 32 matched healthy controls were studied. HD subjects received a single 200 mg dose of DRCys twice: 3hr before or 2hr after HD on different days. All remaining subjects received one 200 mg DRCys dose. Blood was sampled for 24h after each dose to detemine cysteamine concentrations. Pharmacokinetic analysis was conducted using mixed-effects (population) methods with NONMEM software (ICON Development Solutions, Hanover MD).

Results: Table 1 reports drug clearance relative to healthy controls. For subjects with renal impairment except those on maintenance HD, the effect on DRCys clearance is small, within ±20% of the values in the controls. In HD subjects, clearance fluctuates between successive HD treatments, being maximal post HD and then decreasing.

Conclusions: Although increasing renal impairment is associated with a decrease in the apparent clearance of DRCys, the magnitude is relatively small, and unlikely to necessitate dose reduction However, the decrease in clearance between HD sessions may cause DRCys efficacy to vary over that time frame. Therefore, biomarker WBCCys results should be interpreted in the context of when patients had the WBCCys sampled relative to HD. Mechanisms for HD-associated clearance changes are unknown but may involve HD improving CYP function.

Funding: Commercial Support - Horizon Pharmaceuticals Inc.

Factors for apparent clearance of DRCys related to residual renal function (eGFR) compared to healthy controls

Degree of impairment	eGFR (ml/min/1.73m2)	Factor
Mild	>90	1.192
Moderate	60-89	0.849
Severe	30-69	0.801
ESRD	Maintenance HD	
Concurrent HD		0.602
Post-HD		0.803

TH-PO737

MAGED2 (Re)wires G-Protein Coupled Receptor Signaling in Renal Collecting Duct Cells

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Background: Recently mutations in MAGED2 were identified as a genetic cause of very severe X-linked polyhydramnios and transient antenatal Bartter syndrome. Since MAGED2 does not code for a transmembrane protein, the molecular mechanisms that contribute to the antenatal Bartter syndrome remain elusive. First results suggest that MAGED2 acts indirectly on ion channels and transporter expression in the kidney tubule system.

Methods: The role of MAGED2 in renal cell culture systems was studied by analyzing the proteome and phospho-proteome after MAGED2 depletion and by analyzing the influence of MAGED2 on vasopressin induced signaling in mouse collecting duct cells using Western Blot, qPCR and proteomic analyses.

Results: We show that MAGED2 ablation in HEK293T cells induced large effects on the phosphoproteome, without affecting protein levels. Since MAGED2 is expressed during development in collecting duct cells of newborn mice, we analyzed the effects of MAGED2 knockdown on vasopressin-dependent signaling in renal collecting duct cells. We found that MAGED2 knockdown altered V2R-induced cAMP-generation kinetics, phosphoproteome rewiring, and blunted phosphorylation on downstream nodes such as phosphorylated CREB. V2R induced ERK inhibition and aquaporin-2 phosphorylation were not affected. Interestingly, these alterations resulted in a marked increase in aquaporin-2 abundance during long-term V2R activation, that was mediated transcriptionally, potentially through the mediator complex.

Conclusions: In conclusion, we show that MAGED2 is a novel modulator of G-protein coupled signaling, that might control important signaling events involved in ion transport and nephron plasticity in the distal nephron. The relevance of these findings needs to be recapitulated in vivo.

TH-PO738

Model of Megalin Trafficking in Differentiated Proximal Tubule Cells and Its Application in Dent Disease

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Background: The polarized epithelial cells that comprise the proximal tubule (PT) have a specialized, high capacity apical endocytic pathway necessary to maintain a protein-free urine. The multiligand receptor megalin plays an essential role in the binding and uptake of proteins in the ultrafiltrate. The molecular identities of the compartments involved in sorting of ligands and recycling of receptors in PT cells and the kinetics of megalin trafficking through them are unknown. Dysfunctional PT endocytosis results in tubular proteinuria that can progress to renal failure, as is commonly observed in Dent disease, an X-linked disorder caused by mutations in the Cl^-/H^+ exchanger CLC-5. Reduced endocytic uptake in Dent disease is likely due to decreased expression of megalin receptors (without altered mRNA levels); however, the mechanism by which this occurs is unclear.

Methods: We previously discovered that OK cells cultured under continuous fluid shear stress develop morphological and functional features similar to that of the PT *in vivo*, including high apical endocytic capacity and increased megalin expression. Using

biochemical techniques, we have estimated endocytic and recycling rates and the half-life of surface megalin. These data were used to construct a model of megalin trafficking in differentiated PT cells. To study megalin trafficking in a Dent disease cell model, we knocked-down CLC-5 expression in these cells using siRNA. Typical knockdown efficiency was ~70%.

Results: We present an ordinary differential equation model of megalin trafficking describing surface and internalized pools of megalin with estimated kinetic parameters. The model is capable of achieving a steady-state with a much larger pool of internalized megalin compared to surface within a range of realistic parameters; this is consistent with observations made by our biochemical assays and by indirect immunofluorescence of endogenous megalin. In our Dent disease cell model, we observed decreased megalin expression as observed *in vivo*, and we are quantifying megalin trafficking kinetics in these cells to identify the affected step(s).

Conclusions: Our new PT cell culture model provides an ideal system in which to determine the organization of the apical endocytic pathway and to delineate the mechanistic basis of genetic diseases that cause tubular proteinuria.

Funding: NIDDK Support

TH-PO739

Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) Associated with a Mutation in GNAS

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Background: NSIAD refers to a genetic form of urinary concentration independent of anti-diuretic hormone (ADH). So far, it has only been shown in association with gain-of-function mutations in AVPR2. Here, we present 2 unrelated boys with a novel syndrome including NSIAD.

Methods: Clinical and genetic investigations in 2 patients. The identified mutation was further studied *in vitro*.

Results: Both boys presented in the neonatal period with hyponatremia, initially treated with sodium supplementation and additional fludrocortisone, which was complicated by hypertension. Detailed investigations in one patient at the age of 3 years revealed clinical euvolemia, a persistently elevated urine osmolality (796-1006 mosm/kg) with suppressed copeptin (<3.6 pmol/l) and unresponsiveness to a tolvaptan challenge. Salt and mineralocorticoid supplementation was discontinued with normalization of blood pressure and maintenance of normonatremia with spontaneous reduction in fluid intake (30ml/kg/d). A subsequent transient episode of hyponatremia (128 mmol/l) was associated with increased weight and blood pressure, suppressed copeptin and a urine osmolality of 1038 mosm/kg. Both patients also had complex endocrine abnormalities, including elevated serum PTH concentrations (66-454 pg/l), hypocalciuria (0.06-0.09 mol/mol) and gonadotropin-independent precocious puberty. Molecular analysis revealed a de novo variant in *GNAS* c.1126T>G; p.(F376V) on the maternally inherited allele in both patients. In vitro studies of mutant Gαs-F376V revealed agonist-independent activation of AVPR2, LHCGR and PTH1R.

Conclusions: We show a novel form of NSIAD associated with an activating mutation in *GNAS*, encoding the stimulatory G protein Gαs. In the collecting duct, Gαs associates with AVPR2 and activates adenyl cyclase to initiate urinary concentration. Our data indicate that mutant Gαs-F376V can activate independent of ADH signalling. Different mutations in *GNAS* have been previously associated with disease, including McCune-Albright Syndrome and Pseudohypoparathyroidism. The unique phenotype associated with this mutation can be explained by the differential impact on signalling with the various associated receptors, as well as the effect of imprinting on tissue-specific expression.

Funding: Government Support - Non-U.S.

TH-PO740

Whole Exome Sequencing Reveals Mutations in the Purinergic Receptors P2RX2 and P2RX7 as Novel Causes of Neurogenic Bladder and CKD

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Background: Neurogenic bladder is caused by disruption of the normal neural pathways that regulate bladder relaxation and contraction. In severe cases, neurogenic bladder can lead to vesicoureteral reflux, recurrent urinary tract infections, and even chronic kidney disease and renal failure. Animal models of bladder dysfunction suggest that neurogenic bladder can be caused by single gene mutations. However, to date, no mutations have been identified in humans.

Methods: To identify monogenic causes of neurogenic bladder, we applied homozygosity mapping with whole exome sequencing (WES) to our worldwide cohort of families with congenital anomalies of the kidneys and urinary tract (CAKUT).

Results: We identified a homozygous missense mutation (p.Gly322Arg) in the gene *P2RX2* and a compound heterozygous missense mutation (p.Leu320Pro, p.Pro582Leu) in the gene *P2RX7* in two families with neurogenic bladder. Both families also have secondary vesicoureteral reflux and chronic kidney disease. The mutations identified are well-conserved evolutionarily, rare in the general population, and have deleterious in silico prediction scores. P2RX2 and P2RX7 belong to the purinergic family of receptors, which are ATP-gated cation channels, and both are expressed in the urothelium and bladder smooth muscle. Additionally, *P2rx2* knockout mice have impaired bladder reflexes (Cockayne J Physiol 567:621, 2005), which mimics the phenotype of our patients.

Conclusions: We identified recessive missense mutations in two purinergic receptors, *P2RX2* and *P2RX7*, in families with neurogenic bladder. Purinergic signaling has been reported to play an important role in bladder contractility, and we therefore propose that mutations in these genes may be novel monogenic causes of neurogenic bladder in humans.

Funding: NIDDK Support

TH-PO741

Clinical Utility of Secondary Genetic Findings in CKD

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Background: Whole-exome sequencing (WES) is increasing utilized in nephrology. In addition to providing a specific etiology for nephropathy, genome-wide testing can detect other variants of potential clinical relevance. However, neither the prevalence of such secondary findings among patients with kidney disease nor their clinical implications, including for nephrologic care, has been assessed.

Methods: 2,187 patients with all-cause chronic kidney disease (CKD) underwent WES at the Columbia Institute of Genomic Medicine. 87% were adults (aged >21y) and 49% self-identified as non-European. We analyzed WES data for variants diagnostic for 850 medically actionable monogenic diseases, using American College of Medical Genetics clinical sequence interpretation criteria. The clinical implications of secondary genetic diagnoses were assessed via their capacity to initiate extra-nephrologic subspecialty referrals and to inform key aspects of nephrologic management, such as dialysis care and choice of therapy.

Results: 149 (7%) patients had a secondary genetic diagnosis. Yield did not differ significantly between pediatric and adult cases (OR=0.70 [0.37, 1.23], P=0.25) nor between self-identified Europeans and non-Europeans (OR=0.83 [0.59, 1.18], P=0.31). The secondary genetic diagnoses spanned 78 medically actionable monogenic disorders and would initiate extra-nephrologic referral involving 19 different specialties. Moreover, in 76 (51%) of the 149 cases, the disorders found could be mistaken as secondary CKD comorbidities and would require disease-specific treatment. Strikingly, in each case, the secondary genetic diagnosis had meaningful implications for nephrologic care. For example, the inherited cancers found in 79 patients would inform type and dose of immunosuppression for renal transplantation, and, in the 45 with glomerulopathy, therapy for their primary renal disease as well. Similarly, the hereditary cardiac conditions noted in 40 patients would impact dialysis and/or choice of anti-hypertensive agent.

Conclusions: WES of a large all-cause CKD cohort yielded secondary genetic diagnoses in 7%, with meaningful implications for nephrologic care. Our findings reveal a novel utility of genome-wide testing in nephrology and the associated need for multidisciplinary management.

Funding: NIDDK Support

TH-PO742

Enhance Utility of Family-Centered Diagnostic Exome Sequencing in Children with CKD: A Comparison of 497 Families in Trios and Singleton

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Background: The utility of family centered whole exome sequencing (WES) for the diagnosis of children with chronic kidney disease (CKD) has not been adequately studied.

Methods: Patients with CKD identified according to KDIGO guidelines were grouped into five phenotype categories-nephrosis, nephritis, proteinuria(non-nephrotic), congenital abnormalities of the kidney and urinary(CAKUT), CKD2-5 stage of unknown cause and miscellaneous. WES data from Chinese Children Genetic kidney Disease Database (CCGKDD) including 10 different renal centers in CHINA were analyzed. Singleton WES was performed as a first-tier sequencing test. Family-based exome sequencing included trio whole exome sequencing followed by family inheritance–based model filtering, comprehensive medical review, familial segregation analysis, and analysis of novel genes.

Results: Of 497 enrolled children with CKD, 330 received genetic diagnosis through singleton WES compared with 167 who underwent trios-WES. A molecular diagnosis was reported for 171 families (34.4%) with 78.3% of the diagnostic mutations not previously reported. A positive or likely positive result in a known disease causing gene was identified in 29.0%(89/330) of patients in singleton vs. 49.1% (82/167) of families in trios. Genetic diagnosis rates for each phenotypic category were 33.3% for nephrosis group, 26.6% for nephritis group, 43.4% for proteinuria group, 349.3% for CAKUT group, 36.6% for CKD 2-5 stage of unknown cause group and 32.5% for miscellaneous group (Fig.1). Novel gene findings were identified in 4.2%(4/167) of patients in trios.

Conclusions: The multicenter cohort of WES cases demonstrate the utility of family-based exome sequencing and analysis to obtain the highest reported detection rate in children with CKD.

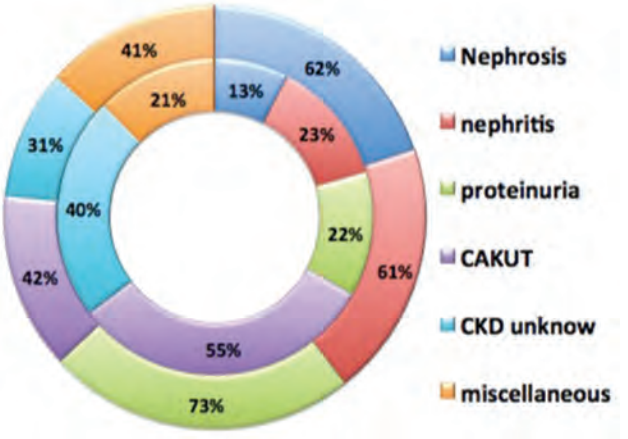

Fig.1 Genetic diagnosis rates for each phenotypic category in children with CKD comparing in singleton and trios-WES (Singleton: inner ring;Trios: outer ring)

TH-PO743

Novel Diagnostic and Therapeutic Approaches for Kidney Diseases: Potential Applications of Noncoding RNAs Associated with Regulation of NOTCH2 and TP53

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Background: The NOTCH2 and TP53 genes are linked to many diseases including kidney diseases. In humans NOTCH2 associated with kidney developmental abnormalities and Alagille Syndrome. In addition to the known function of TP53 in limiting cell proliferation, TP53 involved in regulation of self-renewal and maintenance of the nephron progenitor pool. Previous studies showed excessive expression linkup NOTCH2 and TP53 to kidney diseases. We hypothesized that long noncoding RNA (lncRNA) which are tissue-specific regulators of gene expression are involved in cross-talk for tight control of expression of genes associated with kidney diseases, for example, the NOTCH2 and TP53. The genomic regions of the two genes host characterized and uncharacterized lncRNA. We aimed to investigate the potential interaction and cross-talk between the WRAP53 WD repeat containing antisense to TP53 and the uncharacterized lncRNA genes convergently or divergently configured to the protein-coding gene NOTCH2 in the regulation of both genes.

Methods: The search for unreported miRNA sequences in the WRAP53 WD repeat containing antisense to TP53 and predicted uncharacterized lncRNA LOC105378939, LOC111776218, LOC101929178 and LOC105378940 ncRNAs loci analyzed by the miRBase search tool. The microRNA recognition elements (MRE) in the NOTCH2 and TP53 mRNAs, identified by RNA22 v2 microRNA target detection tool. The miR binds to the target MRE.

Results: The lncRNAs loci are the source of various types of miRNAs. The analysis of the WRAP53 WD repeat containing antisense to TP53 and LOC105378939, LOC111776218, LOC101929178, and LOC105378940 detected several types of miRs. The discovered miRs bind to the target MRE of the mRNAs of the NOTCH2 and TP53. The miRs from WRAP53 WD repeat containing antisense to TP53 bind the MRE targets of NOTCH2. The miR sequences are comparable but not similar to the human (Homo sapiens) hsa-miR, for example, hsa-miR-6743-3p, hsa-miR-6510-5p, hsa-miR-1285-3p, and hsa-miR-519b-3p.

Conclusions: The detected miRNAs from the investigated lncRNAs may provide novel approaches to delineate the complex mechanisms associated with NOTCH2 and TP53 in kidney diseases. The lncRNAs can act as diagnostic biomarkers and suggest therapeutic opportunities for the treatment of kidney diseases.

TH-PO744

Kidney Disease Associated Variants of ApoL1 Show Gain-of-Function in the pH-regulated Cation Channel Activity

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Background: Variants in the protein ApoL1 are largely responsible for the increased risk of progressive kidney disease in people of African ancestry. ApoL1 is an amphitropic membrane protein that inserts into membranes a low pH where it confers anion-selective permeability. After titration to neutral pH, the anion permeability is suppressed and a non-selective cation permeability is activated. We used vesicle based ion flux and membrane association assays to assess for functional difference among variants.

Methods: Recombinant ApoL1 isoforms were expressed in E. coli. KCl-loaded phospholipid vesicles were mixed with protein and assayed for efflux in presence of a large KCl gradient. Efflux was initiated by addition of selective ionophore (valinomycin to assess Cl permeability, or Cl ionophore 1 to assess K permeability), and detected with a chloride selective electrode. The initial rate of efflux after addition of ionophore minus the rate with control vesicles is taken as the ApoL1-dependent ion permeability. To assess membrane association, vesicles and protein were mixed at pH 6, then titrated to pH 7.5, stripped of peripherally bound protein, separated by flotation through a sucrose cushion and detected by western blotting.

Results: All variants show Cl-selective permease activity at low pH that is essentially identical. In contrast, the K-permeability of the disease-associated variants G_1 and G_2 is substantially higher than the WT (G_0). All three variants were purified simultaneously, with assays performed on the same day with the same reagents. Three independent sets of purified protein showed the same pattern of activity. Combining data from the three sets, G_1 and G_2 showed 2.08 ± 0.17 and 2.03 ± 0.28 fold greater activity than G_0 (mean ± SEM, P<0.001 for each). Membrane association experiments demonstrated consistently increased membrane binding by G_1 and G_2 compare to G_0 with 3.02 ± 0.49 and 3.30 ± 0.36 fold more binding than G_0, respectively (P<0.001 for each).

Conclusions: Kidney disease associated variants of ApoL1 show consistently greater cation channel activity and greater membrane insertion than the wild type protein. The data suggest increased membrane insertion and hence greater channel activity in kidney cells could be a mechanism contributing to disease progression.

TH-PO745

A Quantitative 23Na-MRI Protocol to Assess Muscle Na Concentrations: Protocol Reliability and Na Level Heterogeneity Between the Anterolateral and Superficial Posterior Compartments of the Lower Leg

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Background: Previous sodium magnetic resonance imaging (^{23}Na-MRI) studies demonstrated that sodium (Na) can be stored in muscle without thoroughly describing the image quantification methodology. ^{23}Na-MRI image region of interest (ROI) analysis is a subjective process that depends on user experience. We sought to develop a reliable protocol to quantify Na concentrations in two lower leg muscle compartments. The intra- and inter-rater reliability of our quantification protocol and the heterogeneity of Na level between two assessed muscle compartments were also examined.

Methods: Twenty-five ^{23}Na-MRI (3T system) images from 21 subjects (16 healthy subjects/5 hemodialysis patients) were quantified for muscle Na concentrations. We de-identified and randomized all images into two sets for ROI analysis by two trained researchers. Two ROIs were designated as the anterolateral (AL) and superficial posterior (SP) lower leg muscle compartments. We calculated Intraclass correlation coefficient (ICC) estimates based on 2-way mixed-effects models to determine the intra- and inter-rater reliability of our protocol on muscle Na concentrations of AL and SP compartments. Simple linear regression (SLR) analysis was used to investigate the relationship between the average muscle Na concentration of AL and SP (AL-SP mean) and the difference between AL and SP muscle Na concentrations (AL-SP difference).

Results: The ICCs of inter and intra-rater reliability for muscle Na concentrations of AL and SP compartments were all above 0.97, indicating excellent reliability. SP compartment muscle Na was higher than in the AL compartment (SP=20.32±8.69 mM, AL=15.57±5.92 mM, p=0.001). However, Na concentrations of the two compartments were strongly correlated (r=0.697, p<0.01). Linear regression of the AL-SP mean versus the AL-SP difference was significant (β1=-0.444, p=0.013; R2=0.232).

Conclusions: The reliability of our ^{23}Na-MRI image analysis protocol in the measurement of Na concentrations in lower leg muscular compartments was high. Muscle Na concentrations varied between muscle compartments, suggesting a heterogenous Na distribution among different muscle groups. The variance of muscle Na concentrations between compartments increased as the total muscle Na level elevated.

Funding: Private Foundation Support

TH-PO746

Determination of Renal Blood Flow Based on PET/CT-Rubidium-82-Technology in Healthy Subjects

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Background: Changes in Renal Blood Flow (RBF) play an important patophysiological role in the widespread diseases hypertension and kidney disease. However present methods for RBF-determination in humans have several disadvantages. Myocardial blood flow is routinely assessed with PET/CT and the perfusion tracer rubidium-82 (Rb-82). Renal PET with Rb-82 has shown great promise regarding determination of RBF. The purpose of the study is to develop a new and reliable method for determination of RBF based on PET/CT and Rb-82 using a 1-tissue compartment model. To minimize radiation exposure, the input function in the model and the kidneys have to be in the same field of view. Therefore we examined whether the abdominal aorta (AA) is a valid alternative as input function instead of the left ventricular blood pool (LVBP) which is routinely used.

Methods: 10 healthy subjects underwent dynamic PET/CT-scans with Rb-82 as perfusion tracer in two different bed positions. Rb-82 was given as bolus injections. Volumes of interest were placed in the kidneys, LVBP and AA and time activity curves were generated. An input function was derived from both the LVBP and AA. A 1-tissue compartment model was used for estimation of RBF. The K1-parameter represents RBF. K1-values derived from the two different input functions were compared.

Results: The mean K1-value derived from LVBP was 2.14 ± 0.52 ml/min/g and 2.11 ± 0.57 ml/min/g for the right and left kidney respectively. The mean K1-value derived from AA was 2.69 ± 0.40 ml/min/g and 2.77 ± 0.77 ml/min/g for the right and left kidney respectively. For both input functions, the mean K1-value for the right kidney was not

significantly different from the mean K1-value for the left kidney. For LVBP the intra-assay variation coefficient was 14.7% for the right kidney and 12.2% for the left kidney. For AA the intra-assay variation coefficient was 12.7% and 13.2% for the right and left kidney respectively.

Conclusions: Our preliminary results show that the PET-Rb-82 method is feasible for determination of RBF. Use of AA-activity as input function seems to be physiologically most valid because of the direct input to the renal arteries and the derived K1-values are significantly higher than K1-values obtained using activity from LVBP.

Funding: Government Support - Non-U.S.

TH-PO747

Evaluation of Renal Fibrosis Using Elastic Scattering Spectrophotometry (ESS)

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Background: Interstitial fibrosis and tubular atrophy (IFTA) are hallmarks of progressive CKD. The standard method of assessment requires one or more biopsy cores and semiquantitative measurement by histology using stains such as Masson's trichrome. The method is invasive, labor intensive and fraught with potential sampling error due to the patchy nature of IFTA. We propose an alternative, quantitative, minimally invasive method of fine-needle sampling at several sites using Elastic-Scattering Spectroscopy (ESS). ESS is a broadly applicable method that measures wavelength-dependence of optical scattering probability of tissue and is sensitive to the amount of fibrosis.

Methods: ESS was performed using three animal models (n=5 per model) of renal fibrosis (adenine-induced CKD, unilateral ureteral obstruction (UUO) and a remnant kidney model). The ESS spectrum was obtained using a fiberoptic probe with a 150 μm illumination fiber and a 100μm collection fiber, with measurements recorded from several points in the cortex and the medulla of the kidneys. The spectra were normalized at 650 nm to facilitate comparison of the spectral shapes to the ESS spectra obtained from time = 0 (untreated controls). The ESS spectra were correlated with the amount of fibrosis measured by trichrome staining.

Results: All three models were associated with a rise of BUN and an increase in IFTA. Adenine-induced fibrotic kidneys showed a distinct spectral trend of increased scattering intensity in the ultraviolet region (300-400 nm) compared to normal kidneys. Similar spectral changes were observed in the UUO model, with the degree of spectral change dependent on the time after ligation. A linear correlation was observed between fibrosis as assessed by Trichrome stain and the ESS spectral feature.

Conclusions: The linear correlation for even this small data set is encouraging and bodes well for ESS as a quantitative measure of IFTA. Collectively, these data support further studies to explore ESS as a viable point-of-care technique to detect renal fibrosis quickly, offering the potential for a rapid, quantitative and objective assessment of fibrotic status, overcoming some of the limitations of the current method.

TH-PO748

Stiffness Imaging in Native Kidneys by Magnetic Resonance Elastography: A Feasibility Study

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Background: Development of kidney fibrosis results in loss of kidney function among patients with chronic kidney disease (CKD). Kidney biopsy is the standard method for fibrosis detection in native or transplanted kidneys and there is not currently a non-invasive technique to detect kidney fibrosis. We undertook a pilot study in healthy individuals of different ages to explore the feasibility of performing magnetic resonance elastography (MRE) to determine the range of stiffness in healthy kidneys.

Methods: Six healthy subjects with eGFR > 60 ml/min/1.73m^2 were included in the study. Kidney imaging was performed on a Siemens 3T MR scanner. Following acquisition of scout images for location of the kidneys, MRE was performed with patients in the prone position using 60Hz frequency with 2 different driver positions. In method 1 driver was placed in the midline overlying the spine just below the ribs and one image of both kidneys at the level of the hilum in the axial plane and one image through the long axis of each kidney obtained in the sagittal plane (3 images). In method 2 the driver was placed off midline on the flank to acquire images in the axial and sagittal planes a total of 4 images. MRE images were processed with multiple regions of interest in analysis for each kidney.

Results: Two male and 4 female subjects with age range 32 – 66 years were included. Kidney stiffness was heterogeneous across both kidneys and between individuals (Table 1). The overall mean stiffness measure for both kidneys together did not differ significantly between method 1 and method 2 (P = 0.4).

Conclusions: MRE of native kidneys was feasible and tolerated by all subjects. Kidney stiffness was heterogeneous across both kidneys. Stiffness measured by either method yielded similar results. However, method 1 requires acquisition of fewer images and does not require repositioning of the driver position thereby shortening scan time.

Funding: Private Foundation Support

Kidney Stiffness

Table 1	Left Kid.kPA	Left Kid. kPa	Rt. Kid. kPa	Rt. Kid. kPA	Both Kid. kPa
Method	Mean (SD.)	Range	Mean (SD.)	Range	Mean (SD.)
1.	5.25 (0.95)	3.90 - 6.60	5.19 (1.30)	4.32 - 7.52	5.22 (1.08)
2.	5.30 (0.95)	4.36 - 6.17	5.64 (0.61)	4.67 - 6.41	5.66 (0.63)

TH-PO749

Understanding the Effects of Haemodialysis on Blood Flow: An Imaging-Mathematical Modeling Study

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Background: Haemodialysis (HD) is a circulatory stress to organs. The clinical assessment of blood flow (BF) during HD is challenging. We are developing *in silico* tools to permit patient specific prediction of HD effects on BF, to accelerate translation. This study aimed to test the feasibility of creating imaging informed, patient specific simulations of multi-organ perfusion under the stress of HD.

Methods: We reconstructed 3D liver and kidney BF using CT images from a previous study, under both standard and cooled dialysate (DC). Ten patient data sets were analysed. Volumes of each organ were calculated. A binned histogram of blood flow distribution was computed for each case. Patient specific mathematical models of blood flow (Kharche *et al.* Front. Physiol. 2018) based on observed organ shape and BF distributions, known blood vessel morphometry, autoregulation mechanisms, and mathematically optimized spatial BF distribution were successfully generated for further study. Novel texture analysis based on fractal dimension was implemented to quantify BF heterogeneity in the images as well as models.

Results: One 3D reconstructed aorta-liver-kidney composite is shown in Figure 1,A. Histograms of BF (Figure 1, B) show that DC altered BF. In all cases, portal hepatic BF increased markedly due to DC. The volumes of organs were also affected by both dialysis and DC.

Conclusions: The development of patient specific *in silico* models of the multi-organ blood flow consequences of HD appears to be feasible and warrants further study to accurately predict individual treatment responses and optimize treatment parameters.

Funding: Private Foundation Support, Clinical Revenue Support

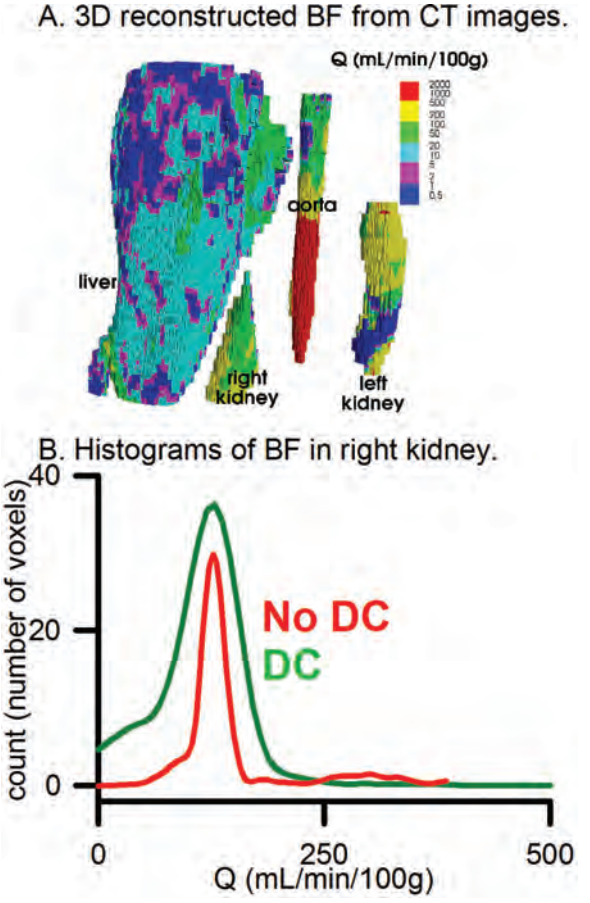

Figure 1. A. Reconstructed BF maps of aorta, liver, and kidneys. B. Histogram of BF in right kidney before (red) and after (green) cooling.

TH-PO750

Quantification of the Effects of a Haemodialysis Patient's Cardiac Ejection Fraction: Towards Patient Specific Risk Prediction

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Background: Hemodialysis (HD) patient hearts suffer chronic ischemia and uremia, leading to contractile dysfunction and arrhythmia risk. Although 2D echocardiography is advanced, image quality is a limiting factor. The black box nature of commercial software is a further challenge. To address these concerns, image analysis-computational tools were developed to produce patient specific structural and functional cardiac models to assist therapy individualisation.

Methods: Echo images from 7 patients were acquired from a previous study. The endocardial and epicardial borders were automatically segmented using our new computer codes. Using the endocardial border, 3D left ventricle chambers were reconstructed for each frame using the modified Simpson's rule. Normalised chamber volumes were computed from the 3D geometry. Patient specific geometries were encoded into low parameter oblate spheroid structures to permit future assessment of arrhythmia risk of the uremic hearts.

Results: 3D geometry reconstruction was successfully implemented in all data sets. A 3D endocardial surface encompassing the left ventricle chamber is shown in Fig. 1, A. The variation of left ventricle volume over one heart beat in one patient is shown in Fig. 1, B. HD reduced ejection fractions (avg. 50% to 44%).

Conclusions: Development of our own codes will permit us to customised analysis on a echocardiographic instrument vendor independent basis. The patient specific structural geometries will provide the essential basis for patient specific contractile and arrhythmia simulated assessment as a next generation tool for dialysis therapy optimisation.

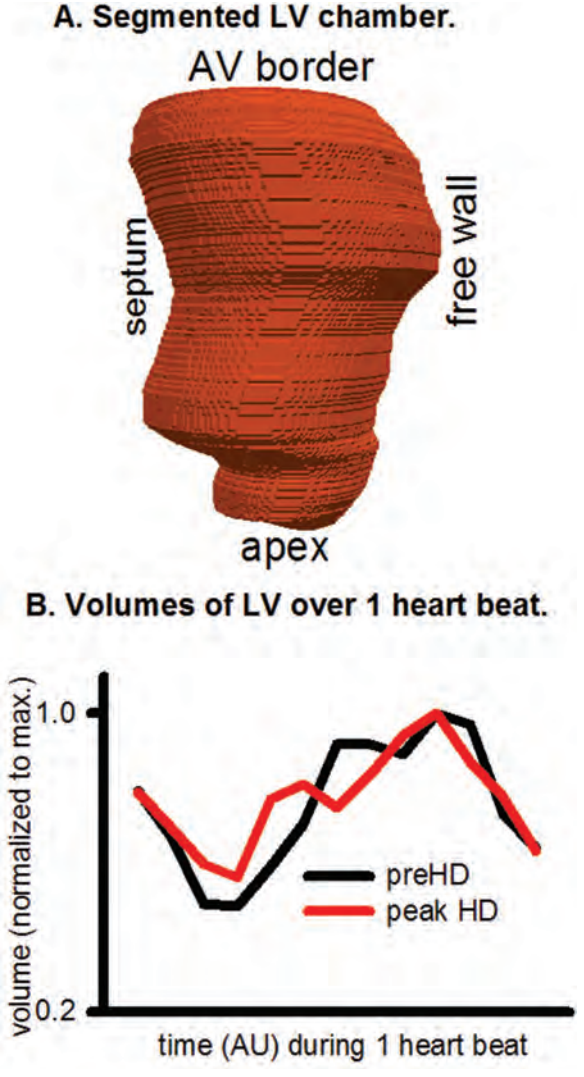

Figure 1. A. Reconstructed 3D LV chamber based on an echo frame. B. LV chamber volume during one heart beat.

TH-PO751

Preliminary In Vitro Biocompatibility Test on a New Wearable/Portable Device for Extracorporeal Blood Ultrafiltration

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Italy; [3]Ospedale "S. Bortolo" AZ. ULSS 6, Vicenza, Italy; [4]IRRIV, Vicenza, Italy; [5]Università degli Studi di Padova, Vicenza, Italy; [6]Free University of Bolzano-Bozen, Bolzano, Italy; [7]University of Padova, Vicenza, Italy.

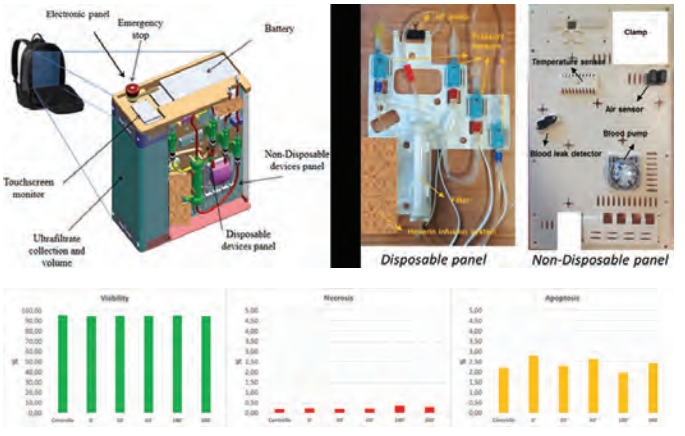
Background: Development of a portable/wearable device for extracorporeal blood ultrafiltration (UF) would lead to impressive clinical, social and economic benefits for patients suffering of chronic kidney disease. This work presents a new prototype of a wearable device for blood UF, named RAP, able to remove excess fluids from fluid overload patients with chronic kidney disease, and a preliminary *in vitro* test of potential induced cytotoxicity by measuring apoptosis and necrosis in monocytes cell line due to indirect contact with the device.

Methods: The RAP has been developed as a backpack/trolley configuration. This original layout guarantees the best compromise between miniaturization and ergonomics, introducing an original positioning of many components in 3 independent panels:(a) disposable components,(b) non-disposable devices and (c) electronics. The device has been equipped with a power-bank able to last almost 6 hours and a device for remote monitoring. Cytotoxicity test was performed by circulating, through the RAP, complete RPMI medium. Monocytes were incubated for 24h in samples taken after 0', 30', 60'. 180' and 360'.

Results: RAP and its design are shown in Figure 1, where also the non-disposable panel and the disposable one, manufactured with addictive technology, are shown. As shown in Figure 2, no inductions of increased necrosis or apoptosis on monocytes with respect to control appeared during a 6h-treatment.

Conclusions: RAP is a new, innovative wearable device for blood ultrafiltration. Arrangement of components can simplify the preparation of the device. Cytotoxic tests demonstrate no induction of cells necrosis or apoptosis. RAP is now ready for human trial.

Funding: Private Foundation Support



TH-PO752

Quantification of Internal Filtration in Hollow Fiber Hemodialyzers with Medium Cut-Off Membrane

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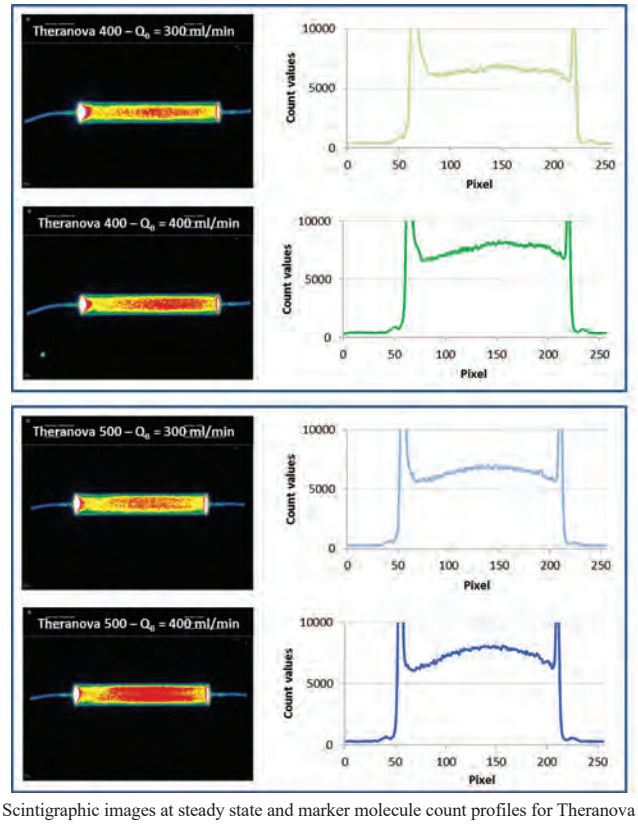
Background: Inadequate removal of molecules between 5 and 50KDa may cause long term complication in chronic hemodialysis. Medium Cut-off (MCO) is a new class of membranes with enhanced sieving properties and negligible albumin loss. MCO membrane allows to perform expanded hemodialysis (HDx), a technique based on high internal filtration (IF). The present study is designed to quantify IF in two MCO dialyzers (Theranova 400 and 500, Baxter, Deerfield, USA) using a nuclear imaging technique previously validated.

Methods: Blood and dialysate compartment pressure drop along with transmembrane pressure, were measured in a closed *in vitro* circuit with human blood (blood flow (Q_B)=300 and 400ml/min; dialysate flow 500ml/min; net ultrafiltration rate 0ml/min). A non-diffusible marker molecule (albumin macro-aggregates labelled with ^{99}Tc metastable) was injected in the blood compartment and nuclear emission was recorded by a gamma camera. Relative variations in concentration of the marker molecule along the length of the filter were used to calculate local cross filtration.

Results: Based on marker concentration profiles, IF was estimated (Figure 1). For Theranova 400, IF were 29.7 and 41.6ml/min for Q_B of 300 and 400ml/min. For Theranova 500, IF were 31.6 and 53.1ml/min for Q_B of 300 and 400ml/min respectively.

Conclusions: MCO membrane provides significant amounts of IF due to the particular combination between hydraulic permeability of the membrane and reduced inner diameter of the fibers. High IF combined with enhanced sieving profile of MCO membrane, leads to improved removal of a wider spectrum of uremia retention molecules in HDx, without requiring complex equipment.



Scintigraphic images at steady state and marker molecule count profiles for Theranova 400 and Theranova 500.

TH-PO753

Direct Hemoperfusion of Protein-Bound Uremic Toxins Using Activated Carbon

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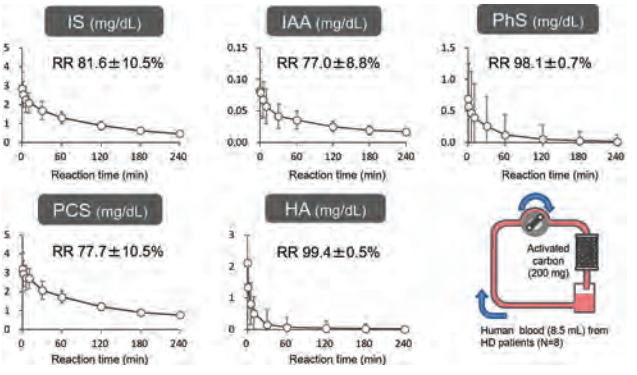
Background: Accumulation of protein-bound uremic toxins (PBUTs) is associated with mortality due to various systemic disorders in patients with CKD, especially those undergoing dialysis. The clinical outcomes of such patients could be improved by removing sufficient quantities of PBUTs; however, conventional dialysis lacks this ability. We examined the efficacy of activated carbon in adsorbing circulating PBUTs via direct hemoperfusion *in vitro*.

Methods: An *in vitro* blood circulating system composed of 6.5-8.5 mL blood circulating around a column containing activated carbon (50, 100, or 200 mg) was constructed. Bovine blood containing PBUTs at the same concentration as that found in the blood of dialysis patients, as well as blood from hemodialysis patients (n = 8) were used. After circulation for the designated amount of time, sera were collected and the levels of PBUTs, such as indoxyl sulfate (IS), p-crecyl sulfate (PCS), indole acetic acid (IAA), phenyl sulfate (PhS), and hippuric acid (HA), were analyzed with mass spectrometry.

Results: Activated carbon decreased bovine blood PBUT level in a dose and time dependent manner (ex. reduction rate: IS 66.4%, 80.1%, and 93.8% following 60-minute circulation in columns containing 50, 100, and 200 mg of activated carbon, respectively). All tested PBUTs were dramatically adsorbed by activated carbon from the blood of patients undergoing hemodialysis [pre vs post 4-hour circulation: IS median 3.01 (IQR: 2.58-3.38) vs 0.43 (0.41-0.51) mg/dL, PCS 3.34 (0.38-5.15) vs. 0.96 (0.12-1.18) mg/dL, IAA 0.073 (0.057-0.080) vs. 0.018 (0.016-0.019) mg/dL, PhS 0.452 (0.240-0.651) vs. 0.008 (0.004-0.012) mg/dL and HA 1.368 (0.874-1.881) vs. 0.006 (0.004-0.013) mg/dL] (Figure).

Conclusions: Activated carbon effectively adsorbed blood PBUTs *in vitro*. Direct hemoperfusion with activated carbon could be a promising strategy to remove circulating PBUTs from the blood of patients with CKD.



TH-PO754

Evaluation of Biocompatibility and Cytotoxic Effects of New Sorbent Cartridges for Blood Hemoperfusion

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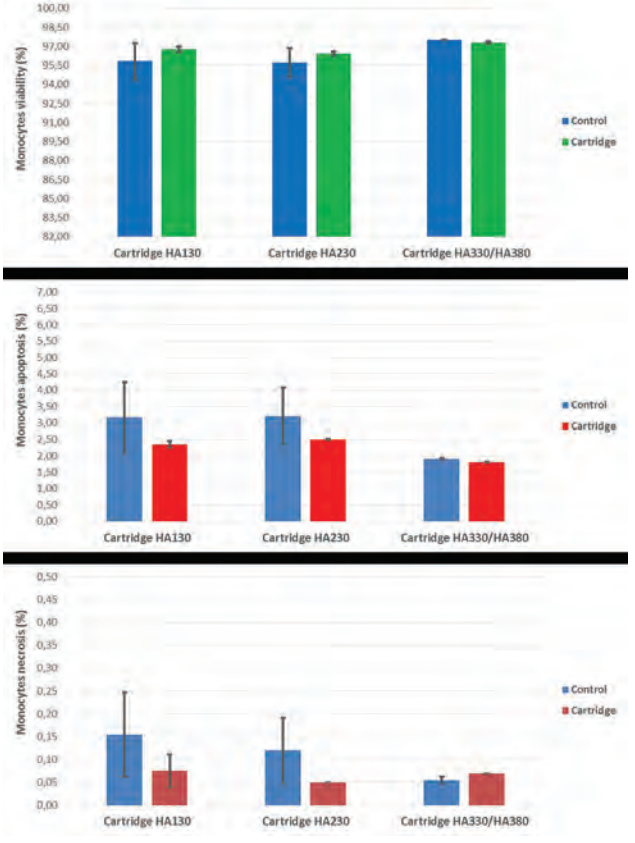
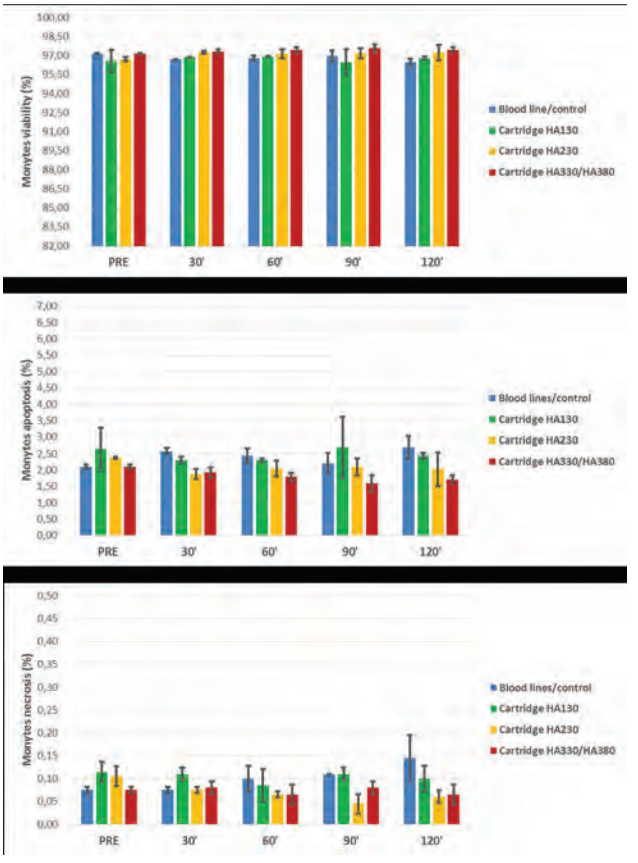
Background: Adsorption cartridges applied in extracorporeal purification therapies, involve direct contact of blood with the sorbent material. The potential induced cytotoxicity is an important issue. The aim of this study was to investigate potential *in vitro* cytotoxic effects of sorbent cartridges HA130, HA230, HA330/380 (Jafron, China) on U937 monocytes.

Methods: Monocytes were exposed to the sorbent material in static and dynamic manners. In static test, cell medium samples were collected after 24 hrs of incubation in the cartridges. In dynamic test, hemoperfusion modality has been carried out and samples at 30, 60, 90 and 120 min were collected.

Results: Compared to control samples, the viability remained the same and there was no evidence of increased necrosis or apoptosis in monocytes exposed to the cartridges in the static tests (fig.1). Similarly, there was no remarkable difference in the viability, apoptosis and necrosis of U937 between each sample and the controls during the dynamic test (fig.2).

Conclusions: Our in vitro testing suggests that HA130, HA230, HA330/380 cartridges possess an optimal level of biocompatibility and their use in HP is not associated with adverse reactions or signs of cytotoxicity.





TH-PO755

Immunomodulation Therapy Improves Cardiac Function in Chronic Heart Failure (CHF)

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Background: Cardiovascular disease is the leading cause of mortality in the US, accounting for 45% of all deaths. CHF and cardiorenal syndrome (CRS) are now understood to be multi-system disease processes involving not only the cardiovascular system but also the renal, neuroendocrine and immune systems. No effective therapy is currently available to treat the most severe subset of CHF patients that have progressed to acute decompensated HF. The **Selective Cytopheric Device (SCD)** is an immuno-regulating, extracorporeal, membrane device targeted to modulate the cardio-depressant effects that are associated with CHF. SCD is a platform technology focused on immunomodulation of the acute and chronic inflammation associated with acute and chronic organ dysfunction. SCD polysulfone fibers selectively sequester and immunomodulate activated systemic leukocytes as they flow through the fiber casing via an extracorporeal circuit and are subsequently released back to the systemic circulation.

Methods: 12 dogs with advanced CHF (ejection fraction (EF) <35%) were used: 5 dogs received sham therapy (No Rx) and 7 dogs received SCD Rx sessions. 6-hour Rx sessions were administered every 48-72 hours for a total of 3 times over a 1-week period. Cardiac parameters were measured at 48 hours, 2 and 4-weeks post. Samples were taken to evaluate of systemic cytokines, leukocyte immune state, spleen density, and macrophage distribution in heart tissue and peritoneal lavage.

Results: EF% significantly increased in SCD Rx animals from 34.0±0.8 to 38.7±1.2% ($p<0.01$) measured at 48 hours post Rx and sustained through 4 weeks at 39.3±1.5% ($p<0.005$). EF% correlated with significant increases in stroke volume, end systolic volume and overall cardiac output. Changes were not observed in control animals. Changes in cardiac parameters correlated to a decrease in systemic leukocyte activation as measured by CD11b, decrease in macrophage density in heart, less pro-inflammatory macrophages in peritoneal lavage, and normalization of spleen cell density.

Conclusions: Pre-clinical study results show SCD Rx for CHF to have clinically relevant therapeutic benefit that was sustained over the 4-week follow-up period. A pilot clinical study is planned to evaluate this approach in severe CRS.

Funding: Other NIH Support - HL118792

TH-PO756

Mussel-Inspired Approach Towards Heparin-Immobilized Cellulose Hydrogel for Selective Removal of Low Density Lipoprotein from Whole Blood

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Background: Cardiovascular disease is the leading cause of death in most countries and is responsible for a significant economic and health care burden. To date, it has been well established that the elevated low density lipoprotein (LDL) level in serum is associated with the development and progression of coronary artery disease, stroke, heart failure and peripheral arterial disease. Although statins exhibit excellent efficacy of lowering LDL in most occasions, they fail to improve the outcomes of patients with familial hypercholesterolemia without LDL apheresis. Dextran sulfate adsorption and heparin-induced extracorporeal LDL precipitation are commercially available at present in the US. However, both of them require initial separation of plasma, making it impossible to remove LDL from whole blood. Therefore, it is of great importance to develop a new LDL absorbent to overcome the drawbacks of the existing techniques.

Methods: Heparin-immobilized cellulose (HeTaCe) hydrogels were fabricated through a mussel-inspired approach. Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, thermo-gravimetric analysis were used to characterize the chemical compositions of the hydrogels. The contact activation, complement activation, hemolysis ratio and clotting times of the hydrogels were performed to investigate the blood compatibility. Moreover, we conducted both statical adsorption test and dynamic simplified simulative column adsorption test to evaluate the adsorption clearance, capacity and selectivity of LDL from whole blood *in vitro*.

Results: Characterization of the hydrogels confirmed the successful synthesis of the new absorbent. HeTaCe hydrogels exhibited low hemolysis ratio (<1%), suppressed complement activation and contact activation, mild impact on whole blood and prolonged clotting times. *In vitro*, an ideal adsorption capacity of 79.1 mg/g with a significant clearance of 48.3% from 14.77 to 7.64mmol/L towards LDL was achieved and the dynamic adsorption test further demonstrated a selective adsorption of LDL without a significant reduction of HDL level in a simulative system.

Conclusions: HeTaCe hydrogels may have great potential application in safe and efficient LDL adsorption from whole blood, making it possible to improve the outcomes of patients with high cardiovasular risk.

TH-PO757

Arteriovenous Mock Circulation Loop for Enhanced In Vitro Testing of an Implantable Bioartificial Kidney

Parsa Taheri-Tehrani,[1] Jarrett Moyer,[1] William H. Fissell,[2] Sukhveer S. Sandhu,[1] Shuvo Roy.[1] *[1]University of California San Francisco, San Francisco, CA; [2]Vanderbilt University, Nashville, TN.*

Background: Arterial mock circulation loops (MCL) are recognized as an appropriate *in vitro* alternative to cumbersome and cost-intensive animal studies for the development of blood-contacting mechanical circulatory assist devices. In contrast to an arterial pump, a silicon nanopore membrane (SNM)-based bioartificial kidney (BAK) is dependent upon arteriovenous (AV) implantation of a mechanically robust and biocompatible hemofilter. An MCL that mimics arteriovenous shunt physiology (pressure, flow rate and pressure-time curve) is an essential tool for *in vitro* refinement of the BAK. Here, we describe an AV-MCL and a corresponding bond graph mathematical model used to refine physiologic parameters of the physical setup.

Methods: An AV-MCL was prototyped using commercial off-the-shelf pneumatic and hydraulic components. Two check valves (mimicking heart valves), two vertical chambers (mimicking atrium and ventricle), and a pneumatic solenoid valve (mimicking the AV node) were used to reproduce cardiac function. Flow resistors, a compliance chamber, and venous reservoir were used to reproduce the circulatory system. BAK prototypes were mounted in the AV MCL, and surgically implanted in an adult Yucatan pig in separate experiments. The bond graph model was used to adjust the AV-MCL parameters to reproduce the AV physiologic parameters obtained experimentally in the animal.

Results: *In vivo* arterial, graft and venous pressures (mmHg) were 110/69 (mean 86), 78/60 (72), and 13/6 (9), respectively. The MCL yielded arterial, graft, and venous pressures of 110/67 (mean 81), 79/48 (58), and 13/10 (11). The BAK hemofilter blood flow *in vivo* was 1032 mL/min, compared to 940 mL/min in the MCL. The pressure waveforms measured from the AV-MCL were well predicted by the mathematical model.

Conclusions: An AV-MCL was developed with a corresponding bond graph mathematical model, and successfully replicated *in vivo* AV pressure and flow conditions through BAK prototypes. The bond graph model facilitates further refinement of AV-MCL physiologic parameters, such as pressure-time waveforms. Moreover, the MCL is portable, adjustable and reusable, allowing rapid iterative *in vitro* testing of BAK prototypes. This system offers device feedback and refinement of BAK design prior to animal trials.

Funding: Other NIH Support - NIH Funding

TH-PO758

Unveiling Protein-Protein Interaction of Maleic Acid-Induced AKI Using a Newly Developed Probe

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Background: Protein-Protein Interactions (PPIs) are important regulators of cellular metabolism and functions in physiology and pathology. However, it is challenging to decipher this complex interaction network of proteins in cells. Maleic acid (MA), an industrial raw material, was found to be illegally added as an emulsifier to starch-based food products by manufacturers in Taiwan in 2013. MA has been associated with renal dysfunction in many animal experiments. The goal of this study was to create a chemical probe that could detect MA-associated proteins in human renal proximal tubular cells that might be used for future detection and therapeutic targeting purposes.

Methods: Chemical probes were developed to investigate protein–protein interactions between MA and renal proteins. In the fabrication of these MA probes, we used silicon dioxide (SiO_2) modified with a silanized linker (3-aminopropyl triethoxyslane, APTES) to generate MA with APTES–SiO_2 particles. The probes were then incubated with the cell lysates of normal human kidney cell lines (HK-2) and subjected to MS/MS to identify several MA-related proteins. STITCH database was utilized to create a schematic illustration of the relationship among proteins associated with MA.

Results: We found nucleophosmin, neutral alpha-glucosidase AB, translocon-associated protein subunit alpha, elongation factor 1-gamma, 60S acidic ribosomal protein P0-like, and heat shock protein (HSP 90-alpha and beta) to be MA-associated proteins. These findings suggest that MA-induced acute kidney injury may come about as a result of regulation of protein transportation, cell processing, endoplasmic reticulum stress, ribosomal modulation and protein folding and unfolding.

Conclusions: The probes developed for this study can potentially be used to identify and detect the target proteins and help characterize a network of MA PPIs.

TH-PO759

Glomerular Disease Augments Kidney Accumulation of Synthetic Polymers

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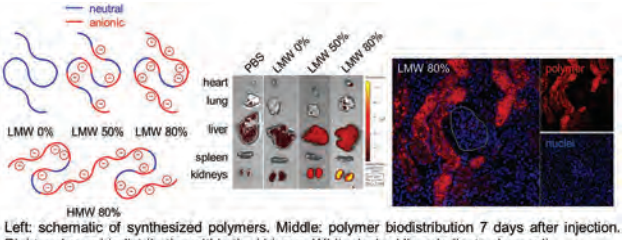
Background: Targeted polymeric drug carriers can significantly improve the solubility and therapeutic profiles of their drug cargoes, while minimizing side effects and toxicity. Physicochemical properties of the carriers drive organ accumulation and are therefore important in the design process. However, carrier properties such as polymer size and charge that are important for kidney targeting are not well understood or reported. To answer some of these questions, here we tested the effects of polymer charge and molecular weight (MW) on kidney distribution.

Methods: A panel of low-MW (LMW) polymers with fixed MW (~25 kDa) and increasing anionic content (0, 50, 80%) was intravenously injected into mice, and tissue accumulation was quantified after 7 days. A high-MW (HMW), highly anionic (47 kDa, 80% anionic) polymer as well as mice with experimental glomerular disease were used to test the effects of MW and loss of filtration selectivity on polymer distribution.

Results: LMW polymers exhibited increasing kidney accumulation with increasing anionic content, and this trend was statistically significant (p-value < 0.0001). Confocal imaging of kidney sections revealed that polymers accumulated mostly in proximal tubules. Glomerular disease significantly augmented kidney accumulation of LMW 80%, but not HMW 80%, polymers. *In vitro*, LMW 80% polymers did not cause significant changes in viability in cultured proximal tubule cells, and were shown to be uptaken by active endocytosis. Dextran sulfate, a competitor of scavenger receptors, significantly reduced polymer uptake (p-value < 0.0001).

Conclusions: This study revealed important features of polymers that drive kidney accumulation: highly anionic polymers with MW ~25 kDa preferentially accumulate in the kidneys and specifically in proximal tubules, and glomerular disease enhances accumulation. Importantly, these polymers were not cytotoxic *in vitro*, and were uptaken by endocytosis and/or anionic scavenger receptors. These findings establish an important foundation in developing targeted drug carriers for kidney disease applications.

Funding: Other U.S. Government Support



Left: schematic of synthesized polymers. Middle: polymer biodistribution 7 days after injection. Right: polymer biodistribution within the kidneys. White dashed lines indicate glomeruli.

TH-PO760

Small-Sized Cationic miRi-PCNPs Selectively Target the Kidney for High-Efficiency Anti-Fibrosis Treatment

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Background: MicroRNA perhaps become an innovative and effective target in the clinical treatment of renal fibrosis. However, the poor stability *in vivo*, low transfection efficacy, inappropriate bio-distribution and rapid renal clearance of miRNA greatly limits its clinical applications. In this study, we produced small-sized cationic miRi-PCNPs with excellent biocompatibility, high cellular uptake efficiency, selectively kidney targeting capacity and high efficiency anti-fibrosis treatment.

Methods: The encapsulation efficiency and drug loading efficiency of miRi was evaluated through measuring UV-vis absorption peak intensity of the bottom solution. The conjugation and stability of the miRi in PCNPs were evaluated through agarose gel electrophoresis. Biocompatibility was assessed using cell counting kit-8, ELISA Kits and HE staining. Transfection efficiency of miRi-PCNPs *in vitro* was evaluated by fluorescence microscopy and flow cytometry. *In-* and *ex-vivo* fluorescence imaging software was used to assess the bio-distribution of PCNPs. Western blot, pathological staining and real-time PCR analyses showed that therapeutic efficiency of miRi-PCNPs on kidney fibrosis in unilateral ureteral obstruction mice.

Results: The image of agarose gel electrophoresis showed that easily degraded miRi was encapsulated in PCNPs and thus prevented from degradation by ribonuclease. Cytotoxicity, immunotoxicity and systemic toxicity assays suggested that PCNPs had excellent biocompatibility. Flow cytometric assessment revealed that high transfection efficacy of miRi-PCNPs. *Ex vivo* fluorescence imaging indicated that PCNPs had kidney-targeting ability. Western blot, pathological staining and real-time PCR analyses showed that therapeutic efficiency of miRi-PCNPs on kidney fibrosis was much higher than bare miRi.

Conclusions: The miRi-PCNPs possessed excellent biocompatibility, high gene transfection efficacy and specific kidney targeting capacity. Therefore, small-sized cationic PCNPs would be a promising drug deliver for RNA, which represents an innovative avenue of designing and developing targeting therapy system for renal fibrosis or other diseases.

TH-PO761

Substrate Elasticity Governs Differentiation of Renal Tubule Cells in Prolonged Culture

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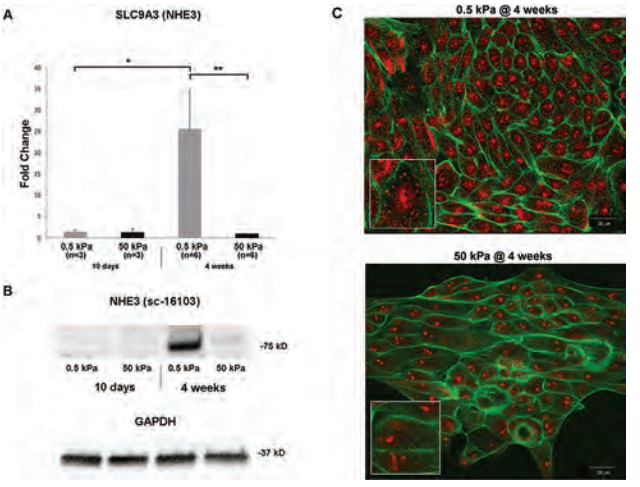
Background: Primary tubule epithelial cells rapidly dedifferentiate in culture and form a flattened epithelium lacking the brush border essential to apicobasal transport. This dedifferentiation undermines the use of cultured cells for drug screening and cell-based therapies. We hypothesized that substrate mechanical properties have a strong influence on differentiation in primary renal cell culture.

Methods: We cultured primary renal tubule cells on polyacrylamide hydrogels of varying elasticity for 2 and 4 weeks. We measured expression of key transporter proteins essential to renal tubule cell function at the transcript and protein level.

Results: Primary tubule cells cultured on soft substrates for two weeks did not show marked differences in transcript or protein levels for NHE3 or AQP1, but after 4 weeks in culture, NHE3 and AQP-1 were increased on 0.5kPa gels compared with 50 kPa gels. Smad2 phosphorylation increased with increasing substrate stiffness, suggesting a role for TGF-β signaling. Indeed, addition of TGF-β to cell culture media abolished the elasticity-dependent increase in NHE3.

Conclusions: These data support the hypothesis that scaffold elasticity is a critical factor in differentiation of renal tubule cells in culture.

Funding: Other NIH Support - NIBIB



NHE3 figure. (A): Expression levels of SLC9A3 (NHE3) were determined by qPCR in primary HREC cultured on soft (0.5 kPa), and stiff (50 kPa) hydrogels. Cells were harvested at short (10 days) and long (28 days) time points. (B): NHE3 protein levels were determined by Western Blot analysis. (C): NHE3 (Red) and F-actin (Green) staining of HREC cells cultured on soft (0.5 kPa) and stiff (50 kPa) hydrogels for 4 weeks. * p=0.003, ** p=0.00002.

TH-PO762

Gentamycin Induced Nephrotoxicity in an Artificial System of the Renal Proximal Tubule

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Background: Mimicking proximal tubular physiology within cell-based artificial model systems might help to investigate pathophysiology of nephrotoxic drugs such as gentamycin commonly leading to acute kidney injury. We present a model system for transport processes along the proximal tubular barrier (TB).

Methods: Immortalized proximal tubule cells (RPTEC) and blood outgrowth endothelial cells (BOEC) were seeded on a transwell membrane (TW) to build a TB. Barrier function was measured by transepithelial electrical resistance (TEER) of the cellular layers on a daily basis. Gentamycin, moxifloxacin and vehicle control (CTRL) were added over the whole experiment (21 days) to investigate their nephrotoxic potential and disturb TB. The treatment influence on glucose transport through the TB was determined by adding fluorescent d-glucose analog (2-NBDG) to the medium above the RPTEC layer. Fluorescence intensity was measured after 90 min at the opposite TW side. Moreover the inhibition of SGLT2 by dapagliflocin (dapa) and canagliflocin (cana) and vehicle control (contr) during antibiotic treatment was studied.

Results: Moxifloxacin treatment increased TEER (median: 153 Ωcm² vs control 115 Ωcm²), while gentamycin lowered TEER (median: 73 Ωcm²). 2-NBDG concentration increased in the gentamycin treated group (0.79 µg/ml ±0.08 vs control 0.48 µg/ml ±0.07). No differences were found due to moxifloxacin. In CTRLs SGLT2 inhibition led to a reduction of 2-NBDG concentration in BOEC medium (CTRL: 0.5±0.07 µg/ml; ddapa: 0.3 ± 0.03 µg/ml; cana: 0.3 ± 0.06 µg/ml)). In cell systems treated with gentamycin 2-NDBG concentration was reduced following SGLT2 inhibition (contr: 0.8 ±0.09 µg/ml; dapa: 0.5 ±0.02 µg/ml; cana: 0,4 ±0.06 µg/ml). Moxifloxacin had no effect.

Conclusions: In the present study a functional renal proximal tubule cell culture model suitable for drug testing assays was established. TEER and direct 2-NDGB transport were suitable to identify nephrotoxic effects on the TB in vitro. In a next step, this system will be integrated in our established microfluidic system.

TH-PO763

Genome Engineering of Renal Epithelial Cells with Improved Function for an Implantable Artificial Kidney

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Background: Development of an implantable artificial kidney (IAK) will require renal epithelial cells capable of reabsorption of salt and water. We used genome engineering to bioengineer cells for improved Na^+/H^+ exchange and H_20 reabsorption. The non-viral *piggyBac* transposon system enables genome engineering cells to stably overexpress one or more transgenes simultaneously. The CRISPR/Cas9 system (dCas9-VP64) enables selective endogenous gene upregulation in human cells.

Methods: We generated epitope tagged human sodium hydrogen exchanger 3 (NHE3) and aquaporin-1 (AQP1) cDNA expressing *piggyBac* transposon vectors. *piggyBac* transposase expression enabled stable transposon integration and overexpression of NHE3

or AQP1 in cultured renal epithelial cells. The transposon system was also used to integrate dCas9-VP64 into human kidney cells.

Results: As a proof-of-principle, we generated renal epithelial (MDCK) cells stably expressing a cumate inducible NHE3 and confirmed induced overexpression via Western blot and immunofluorescence analysis. We also generated MDCK cells stably overexpressing AQP1. Cell surface delivery of NHE3 and AQP1 was confirmed using cell surface biotinylation assays. Importantly, MDCK cells expressing AQP1 and cumate inducible NHE3 demonstrated increased cellular transport. We subsequently used a high-throughput flow cytometry analysis to generate a library of MDCK clones with varying expression of AQP1 and NHE3 to determine the best ratios for optimized transport function. We tested and validated various guide RNAs (gRNAs) for targeted upregulation of endogenous AQP1 and NHE3 in human kidney cells at both the mRNA and protein level.

Conclusions: Our results reveal that genome engineering can enable improved cellular transport via stable overexpression of AQP1 and NHE3 in polarized kidney epithelial cells. We are currently attempting to extend these studies to human renal proximal tubular epithelial (RPTEC) cells. Additionally, the dCas9-VP64 system enables upregulation of endogenous AQP1 and NHE3 in human kidney cells. These studies will allow us to determine the optimal genome engineering approach and renal epithelial cell type for maximal function in the IAK.

Funding: Other NIH Support - NIBIB

TH-PO764

Pathophysiology of Proteinuria: Human Serum Increases Proliferation and Markers of AKI in an Ex Vivo Model of the Human Proximal Tubule

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Background: Proteinuria is a pathological cause for progressive kidney damage. Prolonged exposure to excess glomerular filtered protein may create tubulointerstitial lesions via activation of proinflammatory, proapoptotic, and profibrotic pathways in renal proximal tubular cells[1]. Thus the proximal tubule likely plays an important role in propagating the decline of renal function in proteinuric kidney disease[2].

Methods: Here, we exposed a 3D microphysiological system (MPS) of the human kidney proximal tubule developed in our lab[3] to human serum to explore key functional and structural events that may eventually lead to progressive tubulointerstitial damage. This is a bioengineered platform containing a tubular collagen scaffold that houses human proximal tubule cells. Perfusion setup allows for the delivery of media and experimental solutions, as well as physiological shear stress applied to the cellular tubule.

Results: Treatment with 0.5%, 1%, and 2% human serum for 48 hours led to an increase in kidney injury molecule 1 (KIM-1) concentrations measured from MPS effluents, with an average 3.55 fold increase in the 2% human serum group. The percent of cells expressing the proliferation marker Ki67 dramatically increased with ascending concentrations of human serum (8% in control vs 38% in 2 percent human serum).

Conclusions: These data demonstrate that proximal tubule cells exposed to proteins contained in human serum shed KIM-1 (a urinary biomarker of acute kidney injury) and undergo a burst of proliferation, perhaps as a compensatory mechanism or as an initiative to begin tubular wound healing. Future efforts will include prolonging exposure times, quantifying injury-associated microRNAs, and performing transcriptomic profiling with RNA sequencing to reveal novel biomarkers or pathways involved in proteinuric pathophysiology.

Funding: Other NIH Support - NCATS - National Center for Advancing Translational Science/CASIS - Center for the Advancement of Science in Space

TH-PO765

An In Vivo Vascularization Model for the Implantation of Embryonic Kidneys

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Background: A major obstacle to implantation of *ex vivo* engineered 3D tissues is the incorporation of a functional vascular supply in order to minimize the ischemic injury and support the growth of the new tissue. This may be overcome in an *in vivo* vascularization model where the engineered tissues can be implanted into a pre-vascularized chamber. The main goal of our present study is to design such a vascularization chamber and test its applicability for the implantation of embryonic kidneys.

Methods: The chamber was composed of three polydimethylsiloxane (PDMS) layers: a base layer holding the chamber, a center layer containing the vascularization chamber with an opening on one side to allow the in-growth of blood vessels, and a top layer that closes the chamber. Pre-vascularization of the chamber was achieved by first loading the chamber with collagen I (C), matrigel (M) or matrigel+VEGF (MV), followed by implantation of the chamber between the abdominal aorta and vena cava in a mouse. After the chamber was pre-vascularized, mouse embryonic kidneys were placed onto the chamber. The growth and development of the embryonic kidneys were monitored and analyzed.

Results: We found that endothelial cells and developing vascular networks were detected in the chamber as early as 48h after implantation. Filling the chamber with MV significantly shortened the time required for pre-vascularizaion: 7 days for C loaded chambers, 5 days for M loaded chambers, and 2 days for MV loaded chambers. As compared to non-vascularized chambers, implantation of E12.5 mouse embryonic kidneys to pre-vascularized chambers showed significant increase in size and ureteric branching after 7 days.

Conclusions: We demonstrate in our present study that the *in vivo* vascularization model by using pre-vascularized chamber could be useful for the implantation of embryonic kidneys. Further studies are going on to optimize our system and examine the development and vascularization of the implanted embryonic kidneys.

Funding: Private Foundation Support

TH-PO766

In Silico Pharmacological Assessment of Nifedipine and Mibefradil in Modulating Action Potential in Guinea Pig Ureter Smooth Muscle Cells

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Background: Urinary stones with higher diameter are unlikely to pass in the ureter in most situations. Activation of muscarinic and adrenergic receptors increases the amplitude of ureter smooth muscle (USM) contractions. Understanding the drug effects with respect to various ion channels offers several possibilities for safety pharmacological assessment. Here our overarching objective is to utilize the computational model to simulate the effects of nifedipine and mibefradil on the USM cell action potential (AP).

Methods: The USM cell is described as an equivalent electrical circuit with a number of variable conductances representing two voltage-gated Ca^{2+} (T - type and L- type) channels, two voltage-gated potassium channels, three calcium-dependent potassium channels. A drug model for nifedipine and mibefradil were simulated by multiplying the maximal conductance of L-type and T-type Ca^{2+} channels with a scaling factor between 0 and 1 to mimic the drug concentration. The maximum conductance value of the L-type and T-type Ca^{2+} channels were set to 0.00006 and 0.00002 mho/cm^2 respectively.

Results: The resting membrane potential (RMP) was set at — 50mV. A current pulse of 2 nA for 50 ms was injected to evoke the AP. The peak amplitude of AP and total inward current were substantially reduced after adding nifedipine by 50% and 100 % of it's control value. Adding mibefradil by 50% of it's control value reduced the peak amplitude of AP and inward current. However, the addition of mibefradil by 100% resulted no AP and zero inward current. The results showed that both L-type and T-type Ca^{2+} channels play important roles in generating APs, although L-type calcium channel is the major contributor to the total inward current. This simulation showed that the activation of more T-type Ca^{2+} channels will cause higher excitability of the USM cell.

Conclusions: Our approach provides a "virtual workbench" for simulating USM cell AP with maximal objectivity and faithfulness with regard to recordings in experiments. This in silico assessment showed that while inhibition of L-type Ca^{2+} channel suppresses or eliminates APs, the RMP is left unaffected. Complete inhibition of T-type Ca^{2+} channel also reduced USM cell excitability. A compound of nifedipine and mibefradil may form a new pharmacological maneuver towards USM cell contraction of high amplitude.

TH-PO767

Extracellular Matrix Stiffening by Sugars: Implications for Diabetic Nephropathy

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Background: Stiffening of the extracellular matrix (ECM) contributes to a number of diseases including cancer and organ fibrosis. Diabetes leads to formation of advanced glycation end products (AGEs) that crosslink the ECM and may lead to increased matrix stiffness. The pathological consequences of ECM stiffening in diabetes are not fully understood and may be a mechanism by which AGEs contribute to disease progression is diabetic nephropathy. The goal of this work was to evaluate the effectiveness of AGE inhibitors in mitigating sugar-induced ECM stiffening of decellularized kidney ECM. AGEs are known to elicit receptor-mediated pathogenic effects that are independent of ECM stiffening. In order to evaluate the specific effects of ECM stiffening, we developed a novel ex vivo model to alter the mechanical properties of the ECM to evaluate effects on tubular epithelial cell function.

Methods: To evaluate the effects of sugar exposure on ECM stiffness, porcine kidney cortex was detergent decellularized and incubated in reducing sugars (glucose and ribose). The elastic modulus of sugar-modified ECM was measured by compression testing in the presence and absence of the AGE inhibitors pyridoxamine and DTPA. To evaluate cellular response to ECM stiffening, decellularized kidney cortical ECM was crosslinked with genipin. Tubular epithelial cells were cultured on genipin stiffened ECM and matrix and growth factor gene expression were analyzed by qRT-PCR.

Results: Sugar incubation resulted in a concentration-dependent increase in ECM stiffness in the presence of both glucose and ribose. Both PM and DTPA reduced ECM stiffening by glucose and ribose, but were most effective in the presence of glucose. Genipin modification of decellularized ECM resulted in a dose-dependent increase in stiffness that was similar to that induced by sugar modification. Tubular epithelial cells grown on genipin modified ECM showed upregulation of collagen IV and connective tissue growth factor gene expression.

Conclusions: These data show that inhibiting AGE formation mitigates sugar-induced ECM stiffening ex vivo. We introduce a method of evaluating cellular response to ECM stiffening by genipin modification of decellularized kidney ECM and show that kidney cells had increased expression of pro-fibrotic genes. These preliminary studies suggest that ECM stiffening may have pathological consequences in diabetic nephropathy.

Funding: NIDDK Support, Private Foundation Support

TH-PO768

Cyclosporine Induces Fenestral Injury in Bioengineered Human Kidney Microvessels

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Background: The use of cyclosporine A (CsA), a potent calcineurin inhibitor and immunosuppressant drug, has greatly improved the survival of patients receiving organ transplants, but also frequently results in significant nephrotoxicity. Transplant patients treated with CsA have developed acute kidney injury with arteriolopathy, thrombotic microangiopathy (TMA) and tubulopathy. However, the mechanisms underlying human kidney-specific toxicological sensitivity to CsA are still poorly understood. Thus, there is a need to build human kidney-specific biomimetic models capable of replicating clinical patterns of CsA-induced kidney injury.

Methods: Here, using 2-D culture and bioengineered 3-D microvessels containing human kidney peritubular microvascular endothelial cells (HKMECs), we show CsA exposure at as little as 1 h at 1 µg/mL leads to endothelial injury not observed using human umbilical vein microvascular endothelial cells (HUVECs). We then analyzed clinical biopsies of patients who recieived CsA and expressed TMA for the presence of peritubular capillary dysfunction.

Results: CsA induced dysfunction in HKMECs characterized by the loss of fenestrae, shear stress-related changes in cell morphology, signs of vascular inflammation, erythrocyte adhesion to the luminal surface of the endothelium and extravasation of erythrocytes into the interstitial space, whereas HUVECs were unaffected. CsA disrupted the formation of the fenestral diaphragm protein, PV-1. Vascular endothelial growth factor (VEGF) signaling, which is known to be integral to support fenestrae, was also blocked by CsA, whereas adding VEGF partially protected HKMECs from CsA-induced morphologic changes. Integrated genome regulatory analyses identified key distinctions in the landscapes of HKMECs compared to HUVECs, particularly around genes related to formation and maintenance of fenestrae. Kidney transplant biopsies from patients experiencing CsA toxicity showed a loss of PV-1 and evidence of erythrocyte extravasation which are consistent with changes in our bioengineered kidney 3-D microvessels.

Conclusions: These data demonstrate that CsA directly targets human kidney microvascular endothelial cells, disrupting their fenestral structure and function, and provides novel insights into kidney-specific organotypic mechanisms of CsA-induced microvascular injury.

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TH-PO769

Platelet Accumulated Stress Modeling Predicts Platelet Activation and Thrombosis

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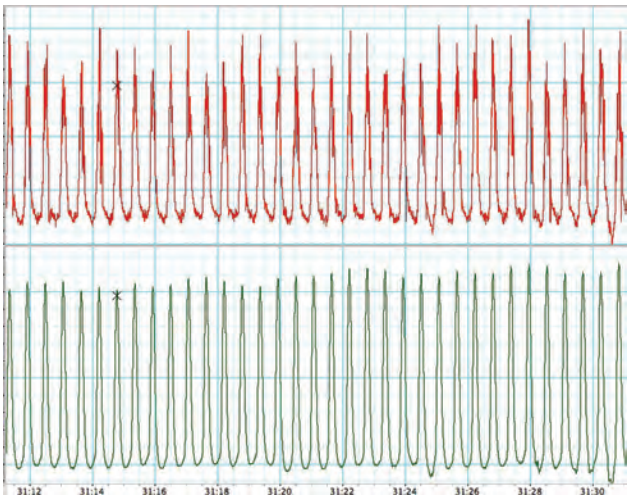
Background: Thrombosis is a dreaded complication in blood-contacting medical devices including implantable artificial kidneys (IAK). Fluid shear stress primes platelets to initiate thrombosis. We compared computational predictions of platelet accumulated stress (PAS), biochemichemical assays of platelet activation, and in vivo thrombosis between two different implanted hemofilter designs.

Methods: Platelet accumulated stress distributions under unsteady flow in two candidate blood conduit designs were predicted using computational fluid dynamics (CFD) tools. Hemofilter catrtridges were machined from polycarbonate and implanted in Class A dogs for 2-7 days without anticoagulation. Platelet activation was measured using a modified prothrombinase assay. Thrombosis was assessed by measuring cyclic variation in blood velocity downstream of a controlled femoral artery lesion.

Results: The two different hemofilter designs gave rise to two distinct histograms of PAS. In some animals, the hemofilter with the larger PAS (A) thombosed almost immediately while the other hemofilter (B) did not. In animals where both cartridges remained patent, platelet stress as measured by prothrombinase activity agreed with CFD predictions. Femoral artery flow was disrupted to a greater extent in animals implanted with hemofilter A than Hemofilter B.

Conclusions: We showed that CFD predicted biochemical measures of platelet activation and propensity to thrombosis in an animal model of an implanted hemofilter. Platelet stress is a useful tool to predict thromboembolic complications in blood contacting medical devices.

Funding: Other NIH Support - NIBIB



Pulsatile flow was comapred between a femoral artery with a standarized trauma (red) and a contralateral control artery (green). Cyclic variations in flow distinct from respiration arise from transient thrombosis at the arterial trauma.

TH-PO770

Patient-Friendly Kidney Function Monitoring

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Background: Chronic Kidney Disease was ranked the 13th leading cause of Death in 2013. Measuring the creatinine level in blood became an important biomarker to evaluate the kidney performance by filtering the wastes. The objective is to develop an easy low-cost monitoring method of the level of creatinine in blood without visiting a medical facility. It is an alert for individuals to check their kidney functions and communicate with a nephrologist when they suspect a kidney failure in the early stages.

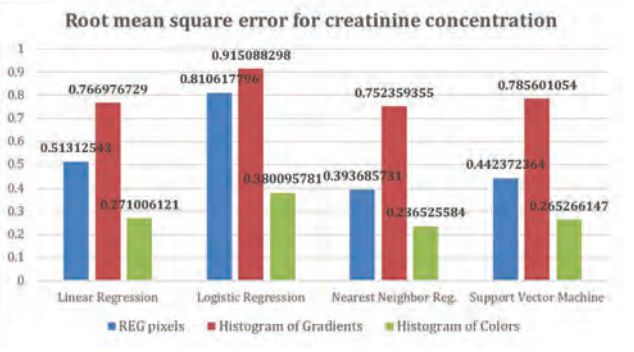
Methods: The project is based on using paper microfluidics technology. A paper strip with alkaline picrate solution produces a colorimetric response upon applying a creatinine sample. 65 different creatinine concentrations were tested to detect the colorimetry change and images were captured using a smart-phone camera inside a light-box. The color intensity feature was extracted using different technqiues. The features extracted were used to train the several machine learning models for testing.

Results: The results show that the best machine learning models that gives the best accurate results and the lowest root mean square error is Nearest Neighbor regression model using the histogram of colors extraction technique.

Conclusions: We proved the feasibility and the reliability of our proposed technique. We are providing individuals with an affordable, reliable, and remote technology to allow rapid and frequent testing of kidney health. Individuals will be able to monitor their kidney functions without visiting a medical facility. So, we can imagine how this method would help patients to get early treatment, adjust medication dose, or monitor the performance of the transplanted kidney. Our approach is using a smart-phone for detection due to the accessibility of a smart-phone to any individual.

Root-mean square error for creatinine concentration prediction 0-4 (mg/dl)

	Linear Regression	Logistic Regression	Nearest Neighbor Regression	Support Vector Machine
REG pixels	0.51312543	0.8106177963	0.3936857306	0.4423723639
Histogram of Gradients	0.766976729	0.9150882978	0.7523593551	0.7856010536
Histogram of Colors	0.2710061214	0.380095781	0.2365255844	0.265266147



Root-mean square error for creatinine prediction concentration 0-4 (mg/dl).

TH-PO771

Exercise Games to Improve Balance and Mobility in Diabetic Patients Undergoing Hemodialysis: A Randomized Controlled Trial

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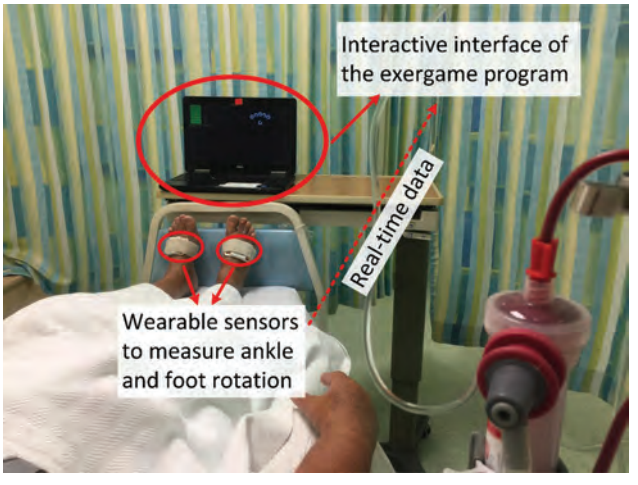
Background: Poor balance and mobility are serious problems for older adults undergoing hemodialysis (HD). Patients visit HD clinics multiple times a week which provides an optimal opportunity for intervention. We have developed an interactive foot and ankle exercise game (exergame) that can be played during HD to improve mobility and balance.

Methods: Sixty diabetic subjects receiving HD were recruited and randomized into an intervention group (IG: n=29, age=63.3±8years, BMI=31.2±6kg/m2, female=41%) or control group (CG: n=31, age=66.5±10years, BMI=32.3±8kg/m2, female=55%). Both groups underwent a 4-week ankle and foot exercise program (30-min per session, 2 sessions per week) during HD. The IG received exercise via the exergame program (Fig. 1). The CG received foot and ankle exercise without any technology. Balance and mobility were examined at baseline and conclusion of the program.

Results: All IG subjects achieved to complete all exercise tasks. No adverse event were reported. None of the subjects in the IG was dropped out. In balance exam under eyes-open condition, the IG had higher improvement in ankle stability, hip stability, and center of mass sway in response to exercise, when compared with the CG (58% vs. 3%, 47% vs -1%, and 59% vs. -8%, respectively, $p<0.05$). Similar between-group difference was also observed under eyes-closed condition. From mobility standpoint, results suggested 5% reduction in sedentary behavior ($p=0.049$, Cohen's effect size $d=0.70$) and 53% more vigorous activities in the IG compared to the CG in response to exercise.

Conclusions: This study demonstrated feasibility and effectiveness of an innovative game-therapy program to improve balance and mobility in HD patients. The key innovation of this intervention is its practicality to be done during HD, which could address the limitations of prior exercise interventions in HD patients.

Funding: Government Support - Non-U.S.



TH-PO772

Augmented Foam Sclerotherapy with Laser Treatment for Cystic Disease from In Vitro Sclerosant Screening Platform

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Background: Sclerotherapy has been empirically used in cyst ablation as managemental treatment of polycystic kidney. However valid, clinical reports and research mostly rely on the ex-vivo platform and desultory treatment methods. To standardize the sclerotherapy and minimize the complication of usage of sclerotherapy treatment to cystic disease, in vitro platform from which the sclerosing solution be tested and enhanced sclerosing treatment methods for cyst ablation must be studied.

Methods: The transwell system and collagen embedded cells were used in this study as the in vitro platform. The cellular membrane-disrupting effect was quantitatively measured in vitro by LDH assays which have been not tried before to our knowledge. Screening of sclerosing solution was conducted by measuring LDH level on this system. Photochemical tissue bonding from foam-delivered rose Bengal stains was carried out using 532nm green laser and two-photon laser. Sclerosing effect and degree of inflammation from the augmented foam sclerosant was studied in vivo.

Results: We found that the suggested in vitro platform reflect differential sclerosing properties from different sclerosing material than conventional cell analysis. In this study, we obtained the improved sclerosing foam with greater sclerosing and retention properties. This sclerosant was optimized with polidocanol, glycerol and rose bengal sufficient for cyst ablation and laser-assisted photochemical tissue bonding of the cystic membrane.

Conclusions: To our knowledge, our study is the first in suggesting sclerotherapy with photochemical tissue bonding combined treatment methods, along with the suggested foam sclerosant screening platform. We believe our research would extend possible treatment option for cyst management in polycystic kidney, as well as the promoting the development of safer, better sclerosing materials.

TH-PO773

Prognosis of C1q Nephropathy Is Not Different According to the Presence of Segmental Sclerosis or Nephrotic Proteinuria

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Background: C1q nephropathy is pathologically defined, however, clinical characteristics and prognosis of it remain poorly understood.

Methods: We collected the clinical and pathologic findings of 6413 adult patients with renal biopsy since 2000. We selected 29 patients followed more than 3 months after renal biopsy among 34 patients diagnosed as C1q nephropathy. We matched age and gender to the patients with FSGS and MCD and analyzed the incidence of ESRD.

Results: In patients with C1q nephropathy, estimated GFR was 83.2± 34.7 (20.1-126.9) ml/min/1.73 m^2 and UPCR was 3.30 ± 4.08 (0.05-18.53) g/g creatinine. Glomerular segmental sclerosis (SS) was present in 14 (48.3 %) patients. Patients with SS had higher level of systolic blood pressure and lower level of eGFR compared to patients without SS (127.0 ± 9.8 vs 114.5 ± 13.0 mmHg, p=0.010, and 67.4± 31.8 vs 98.0 ± 31.3 ml/min/1.73 m^2, p=0.016, respectively). Other findings such as UPCR and pathologic findings except amount of SS were not different between groups. The levels of eGFR and UPCR at 6 months after renal biopsy was not different in C1q patients according to the presence of SS. There were 17.2 % (5/29) incidence of ESRD during 94.2 ± 48.6 months. The most important prognostic factors were the amount of glomerular global sclerosis by Cox's hazard proportional model adjusted by age, gender, eGFR, and pathologic findings. The presence of SS or the level of UPCR at renal biopsy were not the independent risk factors to renal outcome. The renal outcome was worse in C1q nephropathy compared to MCD (0/28), but, similar between C1q nephropathy and FSGS (6/28) (p=0.008 by Log-rank test).

Conclusions: Glomerular global sclerosis is the most important risk factor to the renal outcome rather than glomerular segmental sclerosis or UPCR in C1q nephropathy. The prognosis of C1q nephropathy was similar to that of FSGS and worse than that of MCD.

TH-PO774

Histopathologic and Clinical Outcomes in Idiopathic and Diabetic Nodular Glomerulosclerosis

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Background: Idiopathic nodular glomerulosclerosis (ING) is a rare form of glomerulopathy with an unclear pathogenesis. The hallmark of this entity is mesangial nodularity in the absence of diabetes mellitus or specific immune deposits on immunofluorescence. We hypothesized that ING and diabetic nephropathy (DN) have distinct histopathological features that explain their pathogenesis.

Methods: From Jan 2001 to Dec 2016, native renal biopsy interpretations were queried from Indiana University Health's electronic database. Natural language processing followed by manual adjudication confirmed 49 cases of ING. Histopathologic features were compared between individuals with ING(N=49) and DN (N=770). Clinical and histopathological features of ING cohort were studied in detail and compared with previous cohorts.

Results: The mean age of ING cohort was 68 y with a Caucasian (73%) and male (55%) predominance. Clinical findings at presentation included renal insufficiency (81%) and nephrotic range proteinuria (53%). 94% had hypertension while 68% had a smoking history. All 49 patients had prominent diffuse mesangial sclerosis with focal or global nodularity. Interstitial fibrosis, tubular atrophy, and arteriosclerosis were present in >90% of patients. Among cases with follow up (N=25, median 616 days), 60% progressed to ESRD, 67% had declining renal function (creatinine increase of 0.5 mg/dL), and 38% died. Between the ING and DN cohorts, the only significant differences in histological findings were the degree of arteriosclerosis and podocyte foot process effacement, which were more prevalent and severe in the diabetic cohort (P<0.001).

Conclusions: In our cohort of ING, we confirmed the close association of hypertension, hyperlipidemia, and smoking observed in prior studies. We found minimal histologic differences reported between patients diagnosed with ING and DN. The histologic similarity of ING and DN glomerular lesions suggests there may be a common pathogenic process that is distinct from the presence or absence of diabetes mellitus. Future longitudinal studies are required to determine the pathogenesis of nodule formation in ING.

TH-PO775

Glomerular Basement Membrane Composition Controls Podocyte Morphology and Downstream Signaling

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Background: Type IV collagen α3,4,5 networks are specific to the basement membranes in the eye, ear and the kidney. Absence of the heterotrimer leads to Alport syndrome, characterized by basement membrane defects and in the glomerulus by podocyte foot process effacement and detachment. Previous studies have shown that podocytes in Alport syndrome are exposed to ectopic matrix ligands as type IV collagen α1,1,2. Here, we investigated how exposure of podocytes to distinct matrix ligands influences molecular signaling events.

Methods: Human podocytes were spread on type IV collagen or laminins (511 or 521), and cellular morphology was assayed using light microscopy. Podocyte adhesion complexes were isolated and we analysed global protein levels on the different ligands using mass spectrometry-based proteomics. We used laser-based micropatterning to restrict cellular morphology and dissect the links between cell geometry and matrix ligand signalling and to determine how these factors regulate intracellular signaling in time and space.

Results: Matrix ligands determined distinct podocyte morphologies: podocytes on type IV collagen were rounded, compared to podocytes on laminin isoforms, which were more elongated. Proteomic analysis revealed ligand-dependent adhesion complex composition, with upregulation of PKCa in laminin-spread podocytes. Ratiometric imaging revealed increased focal adhesion signaling in podocytes spread on type IV collagen, associated with increased Rac1 signaling. Interestingly, when podocytes were restricted to micropatterned laminin circles or collagen IV lines, there was a partial rescue of the focal adhesion-signaling phenotype.

Conclusions: We show that exposure to different basement membrane ligands results in altered downstream signaling and podocyte morphology. Furthermore, we suggest that podocyte morphology controls downstream signaling independently of the basement membrane ligand. Loss of the mature type IV collagen α3,4,5 network exposes podocytes to a range of different matrix ligands. Our data suggest that altered basement membrane composition may contribute to podocyte effacement in Alport syndrome through changes in podocyte morphology and signaling. Rescuing these defects in podocyte morphology could represent a new therapeutic strategy.

TH-PO776

Podocytic Infolding Glomerulopathy: An Indian Case Series

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Background: Several cases of Podocytic infolding glomerulopathy (PIG) has been reported from Japan as a new disease entity since 2008. It is a rare glomerular abnormality seen predominantly among women in associaciation with membranous nephropathy and autoimmune diseases involving glomerular basement membrane (GBM) bubbling visualised by light microscopy (LM), invagination of the podocyte membrane, and the presence of microspheres viewable by electron microscopy (EM). The clinical features and pathogenesis of this condition are still unclear. We reviewed clinical, biochemical, and pathological features of cases of PIG at our institute.

Methods: We retrospectively analysed cases of PIG as per the diagnostic criteria during preceding two years

Results: Seven cases of PIG have been reported from our institute. The mean age of the patients was 48, (43-65) years, and all were men. Both hypertension and diabetes were seen in five, one each had hypertension and diabetes. Four patients had nephrotic range proteinuria and two had insignificant proteinuria. All had increased creatinine with a mean of 4.3mg%. Autoimmune workup and viral markers were negative in all. LM showed diabetic nephropathy (DN) in 5 cases and hypertensive changes in 1 case and secondary FSGS in 1 case. Microspheres were present in all but podocyte infolding was present in 1 and cluster formation of microspheres was found in 3 cases.

Conclusions: PIG in our case series differs from that of Japan in male preponderance and is associated with diabetic nephropathy. The clinical significance of PIG in south Indian population is yet to be elucidated

TH-PO777

Characterizing Renal Involvement in Hermansky-Pudlak Syndrome in a Zebrafish Model

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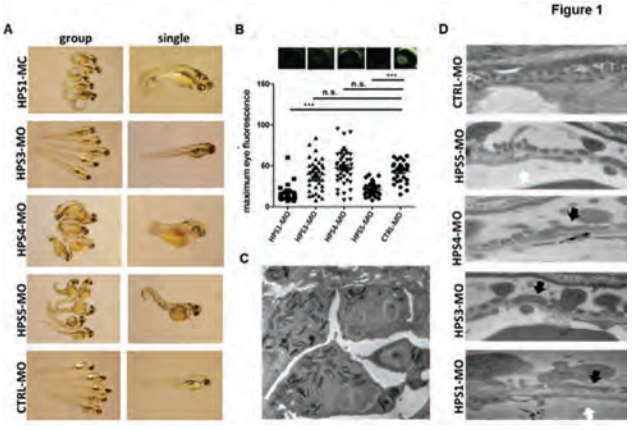
Background: Hermansky-Pudlak Syndrome (HPS) is an autosomal recessive genetic disorder, which is characterized by oculo-cutaneous albinism, a platelet storage pool deficiency as well as a lysosomal accumulation of ceroid lipofuscin. Impaired renal function and proteinuric kidney disease has been reported in some studies but we hypothesize that renal involvement in HPS is underestimated.

Methods: To evaluate proteinuric kidney disease in HPS we used the transgenic zebrafish line Tg(l-fabp:eGFP-DBP). These zebrafish express a fabp-promoter regulated enhanced GFP-labeled vitamin-D-binding-protein that resembles the size of human albumin. The loss of eGFP-DBP from the circulation indicates a dysfunction of the glomerular filtration barrier and can easily be assessed in the eye of the fish. We performed morpholino injection of different HPS isoforms at one to four cell stage of the zebrafish.

Results: Pericardial effusion and yolk sac edema were seen after knockdown of HPS-1, -4 and -5. Knockdown HPS-1 and -5 induced significant of proteinuria at 96 hour post fertilization. To determine whether edema and proteinuria resulted from glomerular defects, we used transmission electron microscopy of the zebrafish pronephros. Intracellular inclusion bodies were mainly seen in podocytes indicating that podocytes are the dominant glomerular cell type effected in HPS. Moreover, podocyte effacement could be detected after knockdown of different HPS isoforms (figure 1).

Conclusions: We established the first animal model to investigate glomerular damage in HPS. Understanding the renal involvement in HPS may allow the use of already existing therapeutic options and could prolong the life expectancy of affected patients.

Figure 1



(figure 1)

TH-PO778

A High-Power View of Renal Pathology of Sickle Cell Disease In Vivo

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Background: Sickle cell disease (SCD) is commonly associated with chronic kidney disease. In SCD a mutation of the β-globin chain of hemoglobin (Hbb) causes the sickling of red blood cells (RBC). The complexity of renal histopathology in SCD is well recognized, however its pathogenesis is not fully understood. The purpose of this study was to improve the mechanistic understanding of the renal pathology development of SCD by establishing an intravital imaging model of the SCD kidney for the comprehensive, high-power quantitative visualization of renal morphology and function at the single cell and nephron level.

Methods: C57BL/6;129 female mice (5-8 weeks old) homozygous for both $Hbb^{tm2(HBG1,HBB)Tow}$ and $Hba^{tm1(HBA)Tow}$ mutations were used as a model of SCD. High resolution intravital multiphoton microscopy (MPM) of the intact living kidney was performed either in single-session or serial imaging.

Results: Compared to healthy control C57BL/6 mice, SCD mice displayed numerous enlarged superficial glomeruli with robust hyperdynamic vascular pathology and inflammation. Metabolites of hemoglobin degradation typical of the SCD environment (likely bilirubin) were readily detectable as green autofluorescence in the circulating plasma, and accumulated intracellularly in the glomerular mesangium and in tubular segments. Among the normally 'doughnut' shaped RBCs, sickled variants were also visible. Glomerular hyperfiltration was manifested by robustly increased glomerular diameter, and expanded Bowman's space and tubular lumen. However, RBC velocity was decreased in glomerular capillaries, likely due to sickling and the observed numerous microthrombi, and the glomerulus-specific homing of different immune cell populations ($CD3^+$ and $CD44^+$). Albumin-Alexa594 uptake was visible in endothelial cells, podocytes, and proximal tubule cells. Over time, glomerular filtration barrier permeability increased progressively as evidenced by the robust filtration of albumin and 500 kDa dextran to the Bowman's space by 8 weeks of age.

Conclusions: This study successfully performed in vivo MPM imaging of the SCD kidney, and directly visualized the impaired glomerular hemodynamics, endothelial and tubular injury, and chronic inflammation characteristic to SCD. MPM imaging of novel cellular and molecular mechanisms will help to improve our understanding of SCD kidney disease and to identify new targets for future therapeutic development.

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TH-PO779

Toll Like Receptor 4 Expression in Kidney Biopsies with Adaptive FSGS

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Background: Adaptive focal segmental glomerulosclerosis (FSGS) is characterized histologically by glomerulosclerosis with progressive interstitial fibrosis and tubular atrophy (IFTA). This is an important cause of kidney failure in native as well as transplanted kidneys.

Any injury to the native or the transplanted kidney from factors such as chronic reflux, obesity, viral infections, rejection lead to progressive kidney failure which is histologically characterized by adaptive FSGS. Pathogenesis of progressive renal dysfunction in adaptive FSGS remains unclear and hence therapies remain ineffective at present. Toll like receptors are innate immune receptors that recognize molecular patterns of tissue injury termed as damage associated molecular proteins (DAMPs). The activation of this pathway leads to recruitment of inflammatory cells to the areas of injury leading to progressive fibrosis. Since adaptive FSGS is initiated by chronic injury we propose that DAMPs released from the injured kidneys lead to TLR activation and activate sterile inflammation and fibrosis leading to progressive disease.

Methods: Retrospective chart review was performed to identify patients with adaptive FSGS and clinical characteristics were obtained. Archived kidney biopsy slides of these cases were stained for TLR4 utilizing immunohistochemistry

Results: We analyzed expression of TLR4 in the native and transplant kidney biopsies of 8 patients with adaptive FSGS. 3 of the 8 biopsies showed tubular epithelial cell expression of TLR4. Mean Serum Creatinine at the time of biopsy and IFTA scores were higher in the group with TLR4 positive stain compared to the group with negative stain (Serum creatinine 3.7 mg/dl vs 1.16 mg/dl respectively) (IFTA 41% vs 21%).

Conclusions: This study identifies role of TLR4 activation in adaptive FSGS. Biopsies with advanced renal dysfunction expressed TLR4 and TLR4 expression was absent when the renal disease was not advanced. Findings of this study need to be verified in a large sample size.

TH-PO780

Identification of Disease-Relevant MicroRNA-Target Gene Interactions

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Background: We previously determined that deletion of the miR-21 gene accentuates TGF-β induced, diabetic and aging-associated glomerular disease in mice. Because miRNA-target gene interactions are cell-type and context specific, we used independent methods to identify relevant *in vivo* target gene interactions for miR-21.

Methods: Candidate microRNA target gene interactions for miR-21 were identified by Pearson correlation between mRNA and microRNA abundance in micro-dissected glomeruli from patients undergoing nephrectomy at Michigan Medicine using Affymetrix ST2.1 arrays and small-RNA Illumina-truseq (n=39). Genes differentially expressed in kidney cortex of miR-21 deficient and wildtype mice were determined using Affymetrix ST2.1 arrays (n=8). Presence of microRNA target genes in the RNA-induced silencing complex (RISC) were experimentally identified using PAR-CLIP (photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation) and further validated using Bru-seq (bromouridine sequencing) in cultured human podocyte and HK2 cells. Retained candidate miR-21 target genes were further validated in kidney cortex of aged miR-21 deficient and wildtype mice (age 24-28 months; n=24) using qRT-PCR. The relevance of these genes for human pathology and phenotype was determined by association with clinical as well as glomerular and tubulointerstitial morphometric parameters as assessed through routine and immunohistochemical stains and quantitative image analysis in FFPE sections.

Results: 1761 and 1309 genes exhibited significant correlation with miR-21-5p or miR-21-3p ($p<0.05$; FDR<0.05: 10 and 1, respectively). 1728 genes were significantly different between miR-21 WT and KO mouse kidney cortex ($p<0.05$). PAR-CLIP identified 752 and 687 cross-linked binding sites for miR-21-5p and miR-21-3p in 517 and 367 unique genes, respectively. Some genes, including Smad7, exhibited differential targeting by miR-21 in podocytes and HK2-cells, and after exposure to TGF-β. Of these miR-21 target genes, 15 exhibited statistically significant correlation with clinical and morphometric parameters in nephrectomies and two exhibited significant differential expression in kidney cortex of aged miR-21 mutant mice ($p<0.05$).

Conclusions: MicroRNA-target gene interactions are cell-type and context specific and require careful further investigations.

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TH-PO781

Insertions and Deletions (InDels) in the Non-Translated Human Genome Upstream of ZHX2 Alter ZHX2 mRNA Expression in MCD and FSGS

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Background: ZHX proteins, especially ZHX2, play a critical role as transcriptional regulators of human and experimental podocyte disease. Multiple groups conducting whole exome sequencing were unable to find significant mutations in these genes in human glomerular disease. We sequenced the genome upstream of ZHX2 and the intronic sequence looking for insertions and deletions that may induce DNA conformational changes, resulting in altered ZHX2 expression.

Methods: The 1.3 million bp region between the beginning of the immediate upstream gene HAS2 and the end of ZHX2 was sequenced in 28 patients with nephrotic syndrome (8 MCD, 2 FSGS tip lesion, 8 FSGS with mutations in slit diaphragm genes, 4 recurrent FSGS,2 recurrent non-HIV collapsing glomerulopathy, and 4 Hodgkin disease with nephrotic syndrome) and 27 healthy controls using Agilent Custom capture and high throughput Illumina sequencing to obtain about 8 million sequences per sample. The Qiagen Biomedical Genomics Workbench software was used to identify InDels > 3 bp and > 20 sequences present exclusively in the patient population. One of the InDels identified was replicated in cultured podocytes using CRISPR Cas9 technology to study changes in ZHX2 expression.

Results: We identified 5 InDels (size range 6 to 67) shared by than one patient and 40 others (size range 4 to 133) present in a single patient. These InDels were absent in controls and the 1000 genomes project. Patients with MCD and FSGS tip lesion had a high percentage of deletions (approximately 80%), whereas those with other forms of FSGS had mostly insertions (approximately 66%). Significance of these indels was verified by inserting one of these indels upstream of ZHX2 in single cell derived immortalized human podocytes by CRISPR-Cas9 approach. Podocytes carrying this InDel developed reduced ZHX2 expression.

Conclusions: Insertions and deletions upstream of the ZHX2 gene are commonly present in patients with MCD and FSGS patients and alter ZHX2 mRNA expression.

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TH-PO782

Proteoglycans Play a Major Role in the Charge Selectivity of the Glomerular Barrier

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Background: The loss of ability to retain macromolecules is a critical step during kidney disease progression. The luminal surface layer of the glomerular capillary endothelium (ESL) is an understudied part of the filtration barrier. The ESL consist of a glycocalyx and an endothelial cell coat, which together form a stagnant mucosal layer – an additional barrier to prevent a leakage of high molecular weight proteins such as albumin.

Methods: In this study, we were guided by basic principles of ion exchange chromatography. In order to elute highly negatively charged proteoglycans of the ESL, we used 1 M NaCl solution (HS). 1 M mannitol (HO) was included to evaluate osmotic effects. A control fraction was eluted with normal saline solution (0,15 M NaCl) (NS). Solutions were introduced intraarterially to rat kidneys under anesthesia *in vivo.* Venous effluent was collected and analyzed using proteomics and mass spectrometry. Immunohistochemistry was used to confirm the presence of identified PGs and the thickness of the glomerular ESL was evaluated using intralipid droplets.

Results: We identified 9 PGs in ESL, for their contribution to the glomerular barrier function (presented in the order of high to low abundance): lumican, glypican-1, syndecan-4, perlecan, podocan, decorin, serglycan, agrin and biglycan. In general, PGs were more abundant in HS samples compare to NS and HO. TEM demonstrated that the glomerular ESL thickness was significantly reduced in HS perfused rats – 28% ($p<0.05$) compared to rats perfused with NS.

Conclusions: ESL itself is formed by PGs, glycosaminoglycans, glycoproteins and soluble proteins and represents a dynamic structure with significant molecular turnover. As a part of molecular sieving system, PGs support the characteristic permselective properties in kidneys by balancing the level of mentioned molecules. Thus molecular composition of the ESL may have a significant impact on local charge alterations which can lead to severe interruptions of the filtration system and, as a result, macromolecular leakage. These findings might be essential for understanding kidney pathology development and protein leakage at a molecular level as well as result in new possible targets for treatment of proteinuria.

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TH-PO783

The Role of DDR1 in Podocyte Lipotoxicity and Progression of Alport Syndrome

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Background: The glomerular basement membrane (GBM) is primarily composed of laminin and Collagen type IV. *De novo* production of the α1 chain of collagen type I (Col I) has been observed mouse models of Alport Syndrome (AS, Col4a3KO). Discoidin domain receptor 1 (DDR1) is a unique receptor tyrosine kinase that is activated by collagens. Deletion of the DDR1 in Col4a3KO mice was shown to improve survival and renal function. However, how DDR1 activation by aberrant collagen production contributes to podocyte injury and proteinuria is poorly understood. I test the hypothesis that aberrant Col I induced podocyte injury via DDR1-dependent lipotoxicity.

Methods: Differentiated human podocytes were serum starved, followed by 18hrs treatment with 50ug/mL Col I (Corning). Following collagen treatments, podocyte lipid content was determined by BODIPY 493/503 and Cell Mask Blue staining. Free Fatty acid (FFA) uptake assessed using a fluorometric free fatty acid uptake kit (abcam). Mice in which exon 5 of a3 chain of collagen type IV is deleted (Col4a3KO), a model for AS, were obtained from the Jackson Laboratory for the determination of kidney cortex DDR1 phosphorylation

Results: DDR1 phosphorylation was increased in kidney cortex from Col4a3KO mice and the degree of DDR1 phosphorylation correlated with blood urine nitrogen (BUN, $R^2=0.7$, $p<0.01$). *In vitro*, DDR1 was phosphorylated by collagen type I (50μg/mL, 18hr) in cultured human podocytes. Increased intracellular lipid accumulation ($p<0.05$), Free fatty acid (FFA) uptake ($p<0.01$) and intracellular triglyceride level ($p<0.01$) were also observed in Col I treated podocytes. DDR1 dominant active (DA) transfected HEK293 cells showed increased expression of CD36, a protein involved in FA uptake, and increased FFA uptake compared to cells transfected with DDR1 WT and dominant negative (DN, $p<0.05$). siRNA knock down of CD36 reduced FFA uptake when compared to scramble siRNA control ($p<0.05$). Col I induced DDR1 activation is associated with podocyte lipotoxicity, FFA

uptake and intracellular lipid droplet deposition. Glomeruli isolated from Col4a3KO mice showed increased lipid content and increased expression of CD36.

Conclusions: Our data suggest that Col I-induced/DDR1-mediated lipotoxicity may represent a novel mechanism leading to podocyte injury in AS.

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TH-PO784

Novel Parietal Epithelial Cell Subpopulations in FSGS and the Origin of the Glomerular Tip Lesion

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Background: Beside the classical flat PECs, proximal tubular epithelial like cells extend onto Bowman's capsule (termed columnar PECs). In addition, a third intermediate PEC subgroup is identified at the junction between the flat and columnar PEC subgroups. Here, we have investigated the potential relevance of these PEC subgroups in focal segmental glomerulosclerosis (FSGS) for the first time.

Methods: The previously described transgenic mouse line PEC-rtTA labeled all three PEC subgroups. To allow lineage-tracing experiments, we identified the inducible Pax8-rtTA mouse line, which labeled specifically the two novel subgroups, columnar and intermediate PECs, but not flat PECs.

Results: In aging Pax8rtTA mice, cell fate mapping showed no evidence for significant transdifferentiation from flat PECs to columnar or intermediate PECs or vice versa. In glomerular disease (rapidly progressive glomerulonephritis, and FSGS), columnar PECs transitioned in part into the intermediate PEC phenotype. Intermediate PECs preferentially expressed activation markers CD44 and Ki-67, suggesting that this subgroup of PECs is activated more easily than the classical flat PECs. In murine FSGS, columnar and intermediate PECs formed sclerotic lesions contributing more than half of the cells. In FSGS patients, cells forming the tip lesions expressed markers of intermediate PECs.

Conclusions: In summary, columnar PECs acquire a transient phenotype termed intermediate PECs, which is more prone to cellular activation and proliferation compared to the classical flat PECs. Both novel PEC subgroups showed the capacity to form sclerotic lesions. We propose that in human FSGS patients tip lesions originate from this novel subgroup of PECs, which is located close to the tubular outlet.

TH-PO785

Isolation of Functional Podocytes from Urine of Alport Patients and Establishment of a Kidney Glomerulus Chip

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Background: Alport syndrome (AS) is a genetic disorder characterized by mutations in genes of collagen IV α3α4α5 network. In AS patients, podocyte loss starts at birth and results in progressive reduction in podocyte number per glomerulus with time, correlating with renal damage. However, data on the phenotypic characteristics of human AS podocytes are currently limited. Our goal was to set up a novel human *in vitro* model representing the functional and molecular alterations typical of human AS glomerulus.

Methods: We generated conditionally immortalized podocytes from urine of three different patients (aged 16.5 ± 5.5 years) with Alport syndrome (AS podocytes). Patient 1 showed mutation in Col4α3 gene, while Patient 2 and Patient 3 were mutated in Col4α5 gene in heterozygosity and in hemizygosity, respectively. AS podocytes were analyzed for specific podocyte markers by RT-PCR and Western Blot and release of collagen IV chains by ELISA. Podocyte motility was tested in a wound-healing assay. We generated a kidney glomerulus chip using primary human glomerular endothelial cells and control or AS podocytes using a millifluidic device for continuous perfusion of co-culture. Passage of FITC-labeled albumin and inulin was measured by fluorimeter.

Results: Podocytes were immortalized with temperature-sensitive SV40T and telomerase reverse transcriptase. Cell showed growth at 33°C (permissive condition) and differentiation at 37°C, with expression of typical podocyte markers. Levels of nephrin, but not of podocin or synaptopodin, were significantly reduced in respect to control podocytes. Significant reduction of specific collagen IV chains were detected, confirm specific functional alterations. AS podocytes had significantly reduced motility in respect to control podocytes. Moreover, when co-cultured with human glomerular endothelial cells in an organ-on-a-chip millifluidic device, AS podocytes presented increased permeability.

Conclusions: In conclusion, we generated Alport podocytes and identified specific molecular and functional alterations. Moreover, we developed a human Alport glomerulus-on-a-chip that replicates kidney disease phenotype in vitro. This will be pivotal to test pharmacological approaches for glomerular alterations in Alport disease.

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TH-PO786

β2-Adrenergic Receptor Stimulation Accelerates Podocyte Recovery from Injury Through Increased Mitochondrial Biogenesis

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Background: Mitochondrial biogenesis (MB) is an adaptive response required to meet the metabolic and energy demand during acute injury to various organs, including kidney suggesting that MB plays a central role in cellular recovery from injury. In this report, we demonstrate that β2-AR mediated MB accelerates the recovery of podocytes from injury.

Methods: RNA-Sequencing of inured podocytes was performed to identify differential gene expression of mitochondrial genes. Oxygen consumption rate in response to β2-AR activation was measured using sea-horse approach. Effect of β2-AR agonist formoterol on restoring injury-induced loss of actin cytoskeleton organization and localization of slit-diaphragm protein Neph1 was analyzed using confocal microscopy. Additionally, formoterol was used to stimulate β2-AR in mice and determine its ability to restore the loss of glomerular filtration function. The histological, ultrastructural and immunostaining analysis of kidney sections was performed to assess structural and molecular changes in treated mice kidneys. MtDNA copy number was estimated through the qPCR analysis.

Results: Injury induced significant upregulation of β2-AR along with PGC-1α and several key components of the mitochondrial ETC. The activation of β2-AR by formoterol showed remarkable restoration of injury-induced changes in actin cytoskeleton organization and loss of Neph1 at the podocyte cell membrane. Importantly, in a mouse model of NTS-induced glomerulonephritis, post NTS-injury when glomerular dysfunction was established, treatment with β2-AR agonist formoterol accelerated the recovery of glomerular function by reducing proteinuria and restoring kidney pathology. Immunoblotting and qPCR analysis showed that multiple proteins of the ETC were elevated and glomerular expression of the MB marker PGC-1α was restored. mtDNA copy number was significantly higher in mice treated with β2-AR agonist formoterol. Additionally, β2-AR knockdown in cultured podocytes significantly reduced mtDNA copy number and increased podocytes susceptibility to glomerular injury.

Conclusions: Overall, these results reveal β2-AR stimulation as a critical event required for podocyte recovery and identifies β2-AR agonist as a novel therapeutic target for treating podocytopathies.

Funding: NIDDK Support

TH-PO787

MAD2B-Medicated Cell Cycle Re-Entry of Podocytes Is Involved in the Pathogenesis of FSGS

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Background: Mitotic spindle assembly checkpoint protein 2 (MAD2B), an APC/C inhibitor, plays a pivotal role in cell cycle control. Previously, we reported that upregulation of MAD2B is involved in several renal diseases. However, the role and mechanism of MAD2B in the pathogenesis of focal segmental glomerulosclerosis (FSGS) is not known. In this study, we aimed to explore the role and mechanism of MAD2B in regulation podocyte cell cycle re-entry during FSGS.

Methods: Mouse FSGS model and conditionally immortalized human podocytes (HPCs) under puromycin aminonucleoside (PAN) treatment was utilized. Expression of MAD2B, APC/C complex regulatory molecules Cdh1, as well as its substrates cyclinB1, skp2, p27 and cyclinE1 was detected by western blot and immunohistochemistry. The cell cycle was analyzed by flow cytometry. Ki-67 and p-H3 expression was assessed by western blot and immunofluorescence. Knockdown of MAD2B was carried out by lentiviral shRNA transfection. Ku55933, a specific inhibitor of ATM kinase, was utilized. And PYR-41 was applied to interfere ubiquitination. CoIP was performed to assess the interaction between ATM and MAD2B.

Results: Comparing to control mice, the level of MAD2B in the glomeruli of FSGS mice is elevated dramatically. In PAN-treated HPCs, MAD2B deficiency attenuated the upregulation of p-H3, cyclinB1 and reversed Cdh1 reduction, which was companied by less cells staying in S-stage. Furthermore, pharmacological interference of ATM kinase activity in vitro ameliorated the accumulation of MAD2B with the less expression of p-H3 and Ki67 and the preservation of podocyte function presenting as increased podocin and CD2AP abundance. Finally, by using inhibitor targeting ubiquitinaton abolished the ATM kinase-mediated MAD2B regulation and subsequent cell cycle re-entry of podocytes, both in vitro and in vivo.

Conclusions: Overexpression of MAD2B is involved in the cell cycle re-entry and podocyte injury during FSGS, while ATM kinase-mediated posttranslational modification, especially ubiquitination is the potential upstream mechanism for MAD2B regulation.

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TH-PO788

Characterizing Podocyte Cell Cultures and Genetic Markers of Podocyte Maturity

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Background: Podocytes are terminally differentiated cells that are vital to kidney function. Injury and loss of these cells leads to the presence of protein in the urine, scarring of the kidney, and ultimately renal failure. Conditionally-immortalized differentiated podocytes provide an in vitro model to test hypotheses regarding mechanisms of disease and responses to treatment. However, podocytes in culture lack slit diaphragms and may lack expression of certain podocyte-specific proteins, leading to doubts about maturation of cultured podocytes. Objective: To assess cultured podocytes for maturity, we characterized transcriptomic changes of podocyte differentiation at the single-cell resolution.

Methods: Undifferentiated and differentiated mouse podocytes were disassociated, prepped with a methanol fixation protocol (10X Genomics), and sequenced on an Illumina HiSeq machine (26x40). To assess transcriptomic changes associated with differentiation and passage number, cells were clustered with principal component analysis (PCA) and visualized with t-Distributed Stochastic Neighbor Embedding (tSNE). Cell clusters were labeled by visual inspection of expression of published cell-type specific markers. We leveraged publicly-available scRNAseq data of mouse kidney to identify differentially expressed genes associated with podocyte maturation and to infer the trajectory of differentiation along the podocyte lineage.

Results: We analyzed 1.8e9 reads in 17467 cells, identifying marker genes expressed in differentiated mouse podocytes. Differentiated podocytes in culture expressed markers of S-shaped bodies/early podocytes (Col4a1, Col4a2, Col4a5, Pax2) as well as markers of mature podocytes (Synpo, Podxl, Nupr1, Plce1, Foxd1). Other markers of mature podocytes were not expressed in cultured podocytes (Wt1, Nphs1, Nphs2, Col4a3, Col4a4).

Conclusions: Though differentiated podocytes in culture share transcriptomic signatures with mature podocytes in vivo, important differences remain. Future work will continue to differentiate mature mouse podocytes in culture as well as mature podocytes in human kidney organoids. Podocytes are critical to healthy kidney function. A robust in vitro model of mature podocytes is vital to assessing mechanisms of kidney disease and responses to treatment.

Funding: Commercial Support - Goldfinch Bio

TH-PO789

Involvement of Alpha-Actinin-4 in Focal Adhesion Signaling in Podocytes

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Background: Podocytes are specialized epithelial cells that cover the outer surfaces of glomerular capillaries. They adhere tightly to the glomerular basement membrane and elaborate foot processes to form slit diaphragm for plasma ultrafiltration. Previously, we found that alpha-actinin-4 facilities the recruitment of Shp2 at focal adhesions (FA) that promotes RhoA/ROCK signaling for actomyosin contractility in cells response to matrix rigidity. In this study, we aim to investigate the role of alpha-actinin-4 in controlling cellular tension by focal adhesion signaling in podocytes.

Methods: A mouse temperature-inducible podocyte line was used as a cell model, and the alpha-actinin-4 gene, ACTN4, was knockout by CRISPR/Cas9 method to study its role in the regulation of Shp2 and ROCKII activation.

Results: Differentiated podocytes exhibited matured FAs and stress fibers accompany with hyperactivation of Shp2 and ROCKII that were sensitive to the puromycin aminonucleside-induced podocyte injury. We found that ACTN4 deficiency abolished adhesion-mediated Shp2 and ROCKII activation in podocytes. By Shp2 FRET biosensor, we also demonstrated that alpha-actinin-4 is important for Shp2 activation. Inhibition of Shp2 activity significantly reduced ROCKII activation, FA and stress fiber formation that resulted in protein leakage during filtration.

Conclusions: Our results suggest that alpha-actinin-4 is required for adhesion-mediated Shp2 activation. It facilitates ROCK-mediated actomyosin contractility for strengthening cell adhesion and cytoskeletal architecture those are crucial for podocyte filtration function.

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TH-PO790

Gut Microbial Metabolite Butyrate Protects Podocytes from Damage Through Epigenetic-Mediated Mechanisms

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Background: Chronic Kidney Disease (CKD) is characterized by gradual impairment of renal function over a period of months or years leading to permanent kidney failure. The damages or loss of podocytes, specialized cells involved on filtration process, stand as one of the most important causes that lead to a CKD. The literature comprises a large number of experimental attempts that focus on mitigating the damage to the podocytes. In recent years, many studies point to the gut microbiota as a modulator of intestinal and extraintestinal diseases through the generation of short chain fatty acids (SCFA). It is already known that chronic kidney patients have an imbalanced gut microbiota and lower production of SCFA. Thus, we have explored the protective role of butyrate, an AGCC able to regulate epigenetic processes during the progression of experimental glomerulopathy induced by doxorubicin.

Methods: Wild type mice were induced to develop glomerulopathy by a single dose of doxorubicin and treated with butyrate.

Results: Wild type mice treated with butyrate showed improvement of renal function, associated to a preserved podocyte layer in the glomerular basement membrane and reduction of pro-inflammatory and pro-fibrotic markers in the kidneys. Particularly, butyrate modulated the activity of enzymes involved on epigenetic modifications in the kidneys and changed the levels of histone markers (H3K9Ac, H3K4me3 and H3K9me3) in the promoter region of the genes encoding synaptopodin, podocin and NEPH-1 in podocytes. Concomitantly, treatment with butyrate was associated with the regulations of small GTPases activity Rac1 and Cdc42 and maintenance of the organization of actin filaments in the podocytes grown *in vitro*.

Conclusions: Our results demonstrate that butyrate exerts relevant effects on podocyte homeostasis during experimental nephropathy through epigenetic mediated mechanisms.

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TH-PO791

Anti-PLA2R Modulation of Human Podocytes: An In Vitro Model to Investigate the Glomerular Basement Membrane (GBM) in Membranous Nephropathy (MN)

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Background: 80% of MN patients have IgG autoantibodies to the phospholipase A2 receptor (PLA2R) expressed on podocytes. IgG-PLA2R immune complexes (IC) deposit in the GBM which over time shows expansion with associated proteinuria and consequent nephrotic syndrome. “Spikes” seen on silver stained sections represent formation of new GBM matrix between the deposits. How anti-PLA2R modulates podocyte, IC accumulation in the GBM and the molecular processes that control this GBM dysregulation remain unclear. **Hypothesis:** Anti-PLA2R treatment of podocytes *in vitro* will alter cell signaling and matrix composition/deposition.

Methods: In order to identify pathways involved in extracellular matrix (ECM) compositional changes in MN, we performed RNA sequencing and mass spectrometry (MS) analysis. Differentiated human podocytes over-expressing PLA2R were treated with protein G purified human anti-PLA2R from 10min up to 24h. Total RNA was sequenced and differential gene expression analysis was performed between the treated and control groups ($P<0.05$). For the MS experiment, podocytes were daily challenged with anti-PLA2R over 7 days. Cells were denuded and the deposited matrix analysed. Identified proteins were integrated with the human matrisome database and peptides quantified using Maxquant software.

Results: TGFβ and Hippo signaling pathways were upregulated in the treated podocytes. EGR1, a transcription regulator of target genes involved in inflammatory and tissue damage processes was significantly increased (11fold) 1 hour post treatment. CTGF and CYR61 genes were also upregulated (6 and 3fold) suggesting activation of the YAP/TAZ pathway, component of the Hippo cascade. This pathway maintains podocytes homeostasis, integrity of the GBM and increases expression of matrix genes. Preliminary MS data of the treated podocytes ECM revealed a decrease in laminin and collagen proteins and an increase in ECM regulators and proteoglycans.

Conclusions: Anti-PLA2R can modulate podocyte matrix production *in vitro*. Our study revealed an early activation of YAP/TAZ pathway in cultured podocytes when treated with anti-PLA2R and a decrease in the main proteins of the GBM at a later stage. Candidate pathways will need to be further validated in order to decipher the mechanism of GBM organisation and remodelling in MN.

Funding: Private Foundation Support

TH-PO792

Single Glomerular Proteomes Connect Morphology and Function in Proteinuric Kidney Disease

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Background: Kidney diseases are frequently heterogenous and affect different glomeruli to different extents.

Methods: We use ultrasensitive sample preparation combined with quantitative targeted and untargeted proteomics of single glomeruli to unravel functional co-expression modules in glomerular populations. We analyze microdissected glomeruli of three animal models

Results: In single glomeruli from three different rodent models of sclerotic glomerular disease, we identified a coherent protein expression module consisting of extracellular matrix protein deposition (reflecting glomerular sclerosis), glomerular albumin (reflecting proteinuria) and LAMP1, a lysosomal protein. This module was associated with a loss of podocyte marker proteins while genetic ablation of LAMP1-correlated lysosomal proteases could ameliorate glomerular damage in vivo. Furthermore, proteomic analyses of individual glomeruli from patients with genetic sclerotic and non-sclerotic proteinuric diseases revealed increased abundance of lysosomal proteins, in combination with a decreased abundance of mutated gene products.

Conclusions: Single glomerular proteomes connect morphology and function in proteinuric kidney disease. Altered protein homeostasis (proteostasis) is a conserved key mechanism in proteinuric kidney diseases. Moreover, our technology can capture intra-individual variability in diseases of the kidney and other tissues at a sub-biopsy scale.

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TH-PO793

A Multi-layered Quantitative In Vivo Expression Atlas of the Podocyte Unravels Kidney Disease Candidate Genes

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Background: Damage to and loss of glomerular podocytes has been identified as the culprit lesion in progressive kidney diseases. The molecular identity of podocytes is currently not known.

Methods: We combine deep mass spectrometry-based proteomics with mRNA sequencing, bioinformatics, and hypothesis-driven studies to provide a comprehensive and quantitative map of mammalian podocytes

Results: The analyses identified unanticipated signaling pathways in podocytes. Comparison of the in vivo datasets with proteomics data from podocyte cell cultures showed a limited value of available cell culture models. Moreover, in vivo stable isotope labeling by amino acids uncovered surprisingly rapid synthesis of mitochondrial proteins under steady-state conditions that was perturbed under autophagy-deficient, disease-susceptible conditions. Integration of acquired omics dimensions suggested FARP1 as a candidate essential for podocyte function, which could be substantiated by genetic analysis in humans and knockdown experiments in zebrafish. FARP1 is a potentially mechanosensitive proteins that links the actin cytoskeleton to the membrane.

Conclusions: This work exemplifies how the integration of multi-omics datasets can identify a framework of cell-type-specific features relevant for organ health and disease.

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TH-PO794

Integrative Computational Characterization of Membranous Nephropathy from Genome-Wide Transcriptome Profiles

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Background: Genome-wide expression data from kidney tissue of patients with nephrotic syndrome provide an opportunity to elucidate mechanisms of injury specific to membranous nephropathy (MN). NEPTUNE and ERCB are prospective, multicenter cohort studies of patients with kidney disease profiled for whole-genome transcriptomes from microdissected biopsy tissue. These datasets provide rich, complementary resources to study the molecular characteristics of MN.

Methods: We examine whole-genome expression profiles of patients with MN and with other causes of nephrotic syndrome (e.g. FSGS, MCD, IgAN) from the NEPTUNE and ERCB cohorts. We construct machine learning classifiers to distinguish patients with each disease based on gene expression and evaluate performance using five-fold crossvalidation. Using Significance Analysis of Microarrays, we identify genes differentially expressed in MN and common to both cohorts. To identify functional modules within the MN-specific gene set, we perform community clustering of these genes in a kidney functional network which integrates thousands of transcriptome-wide assays using tissue-specific regularized Bayesian integration (Greene et al. 2015; Krishnan et al. 2016).

Results: We find that glomerular gene expression can separate patients with MN from other nephrotic patients with high accuracy (AUC=0.9). The genes most predictive of MN diagnosis in NEPTUNE are also differentially expressed in MN patients in the independent ERCB cohort. We identify 220 genes differentially expressed in MN patients common to both cohorts. These genes are enriched in multiple Gene Ontology terms, including anatomical structure morphogenesis, biological adhesion, and basement membrane, and also significantly enriched in homologs of mouse podocyte markers (Park et al. 2018). Clustering the MN-specific genes in a kidney functional network uncovers multiple modules, including gene clusters enriched in ion transport and the extracellular matrix.

Conclusions: This work identifies an expression profile specific to MN patients, enriched in podocyte-specific genes, and shared across patients in two independent cohorts. Such work may facilitate transcriptome-based disease classification, insight into disease pathophysiology, and targeted therapeutics.

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TH-PO795

Urinary Lipidomics: A New Biomarker in FSGS

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Background: Primary focal segmental glomerulosclerosis (FSGS) is the most common glomerular pathology leading to end-stage renal disease in pediatric patient population. The refractory nature of FSGS and a more than 30% recurrence rate after kidney transplantation renders treatment of FSGS as one of the most difficult challenges in pediatric nephrology. A significant knowledge gap in understanding the mechanism of progression in FSGS hampers the development and implementation of successful treatment strategies. We reported an increase in urinary fatty acid (FA) and lysophosphatidylcholine (LPC) levels in patients with FSGS in comparison to patients with minimal change disease (MCD). **We hypothesize that phospholipase A2 (PLA2) metabolizes phosphotidylcholine (PC) leading to LPC and FA accumulation causing cellular toxicity in proximal tubule epithelial cells and podocytes contributes to progression in FSGS.**

Methods: Mouse model of FSGS was induced by mutation of Fyn and Cd2ap(Fyn$^{-/-}$ Cd2ap$^{+/-}$) in podocytes. Untrageted lipidomics of urine and kidney lysates of FSGS mice was analyzed by CSH-QTOF MS/MS. Cytosolic PLA2 expression in podocytes and proximal tubule epithelial cells was investigated by RNA sequencing. Western blotting and immunoflurescence staining was utilized to examine cPLA2 and PLA2 receptor expression in FSGS mice and human kidney biopsy sections with MCD and FSGS.

Results: Untargeted lipidomics of FSGS mice urine demonstrated increased FA and LPC levels reminiscent of human urine samples. Lipidomic analysis of kidney lysate of FSGS mice revealed increased LPC levels. Cytosolic PLA2 and PLA2 receptor expression was increased in the proximal tubule epithelial cells and podocytes by western blotting, immunofluorecence and RNA sequencing in FSGS mice. Human kidney biopsy sections with FSGS revealed increased cPLA2 and PLA2 receptor expression in proximal tubule epithelial cells and podocytes in comparison to MCD.

Conclusions: We concluded that PLA2 activity is increased in proximal tubule epithelial cells and podocytes in mouse and human FSGS. Moreover urinary detection of PLA2 by products, LPC and FA, renders urinary lipidomics a novel tool for predicting the diagnosis and prognosis of FSGS. We propose that increased levels of circulating PLA2 and cellular levels of cPLA2 leads to accumulation of toxic lipid metabolites and contributes to progression by inducing apoptosis and inflammation in FSGS.

Funding: NIDDK Support

TH-PO796

Nebulette Is a Novel Actin-Associated Protein That Stabilizes Foot Process Architecture in Kidney Podocytes

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Background: Nebulette (*Nebl*) is a mechanosensitive actin-associated protein belonging to the nebulin family that stabilizes sarcomeric structures. It has been associated with dilated cardiomyopathy, and it is thought to be cardiac-specific. Its role in kidney function is unknown. Using isobaric tagged glomarular proteomics in the puromycin-induced rat nephropathy model, we identified nebulette as the most significant glomerular protein whose expression negatively correlated with proteinuria. We hypothesized that nebulette plays a critical role in cytoskeletal stability of kidney podocytes.

Methods: We used the NephroSeq database and immunohistochemistry to check for transcript and protein expression levels of nebulette in human kidneys. Primary podocytes isolated from global nebulette knockout mice (*Nebl*-KO) and their wild-type littermates (WT) were used to define the role of nebulette in podocyte physiology. We used high-content microscopy, live-cell imaging, and atomic force microscopy to quantify morphological characteristics, cell motility, calcium dynamics, and cytoskeletal integrity. We evaluated nebulette's functional role *in vivo* using the adriamycin-induced nephropathy model in WT and *Nebl*-KO mice.

Results: NephroSeq database revealed that nebulette expression was enriched in healthy glomeruli and decreased significantly in DN and FSGS patients. Immunohistochemistry and immunogold electron microscopy showed localization of nebulette in human podocytes, specifically in foot processes. Morphologically, *Nebl*-KO podocytes showed significantly smaller spreading area, nuclear size and lower number of focal adhesions. Further, *Nebl*-KO podocytes exhibited significantly altered cellular motility and calcium dynamics. *In vivo*, there was significantly higher albuminuria and foot process effacement in Nebl-KO mice treated with adriamycin at two weeks.

Conclusions: Nebulette is a novel actin-associated protein that localizes to the foot processes of kidney podocytes, and it is associated with glomerular disease in humans. It plays a key role in podocyte physiology by stabilizing the cytoskeletal integrity and regulating focal adhesion dynamics.

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TH-PO797

Gadolinium-Based Contrast Agents Are Metabolic Disruptors in the Kidney and Exacerbate Obesity- and Diabetes-Induced Kidney Injury

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Background: Obesity-related renal injury and diabetic kidney disease are characterized by activation of glomerular mesangial cells and podocyte damage with alteration of lipid metabolism/lipid accumulation in both cell types resulting in matrix accumulation and eventual progression to glomerulosclerosis with loss of renal function. We examined the consequences of gadolinium-based contrast agent (GBCA) treatment in the kidney from mice with normal kidney function and the potential interplay between obese and diabetic states and GBCA exposure.

Methods: GBCA was administered for 4 weeks (as previously described); Metabolomics was by Metabolon. Obesity and diabetes (T1D) were induced by high fat diet (HFD, 60% kcal saturated fat) or streptozoticin, respectively (22 week durations of each condition). Obese and T1D mice in the GBCA groups were treated for 4 weeks prior to sacrifice.

Results: GBCA caused renal fibrotic lesions and podocyte injury that correlate with metabolic disorders as evidenced by increased serum triglyceride/cholesterol levels and insulin resistance. GBCA also induced expression of fatty acid translocase FAT/CD36—an indicator of fatty acid uptake—and lipogenic enzymes ATP citrate lyase (ACLY) and fatty acid synthase (FASN), indicators of *de novo* lipid synthesis. Metabolomic analysis indicated that renal lipid metabolism and metabolic markers of collagen turnover were significantly altered by GBCA. HFD- and T1D-induced fibrotic and podocyte injuries are worsened by GBCA. GBCA exacerbated 1) HFD-mediated hyperlipidemia, 2) CD36/ACLY/FASN upregulation, and 3) lipid metabolism as assessed by metabolomics.

Conclusions: Our work provides the first evidence that GBCA causes significant metabolic disorders and kidney injury in mice without renal insufficiency. These injurious actions of GBCA are amplified in obese and T1D. The understanding of the functional interplay between GBCA and diabetes/obesity will allow the development of therapeutic interventions or the establishment of effective preventive measures to reduce GBCA- and diabetes/obesity-mediated renal pathologies. This will help break the vicious cycle in which GBCA exposure in patients with normal kidney function or in obese or diabetic patients that may be more susceptible to GBCA-mediated renal pathologies.

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TH-PO798

KLF15 Suppress Mesangial Cell Proliferation via Increasing the Sumoylation of P53

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Background: Mesangial cell proliferation is a key pathological feature in a number of common human renal diseases including IgA and diabetic nephropathies. Knowledge of MCs response to pathological stimuli is crucial to the understanding of these disease processes. Our previous study demonstrated Krüppel-like factor 15 (KLF15), a kidney-enriched zinc finger transcription factor, is required for inhibiting the proliferation of mesangial cell. This study aims to clarify the direct target gene and the downstream mechanism of KLF15 regulating mesangial proliferation.

Methods: DNA of primary human glomeruli mesangial cells (HMCs) was purified for sequencing after the chromatin immunoprecipitation with anti-KLF15 antibody. Differential expression protein of cells overexpressed KLF15 were assayed by SILAC/HPLC/MS-MS. We screened out small ubiquitin-related modifier 1 (SUMO1) as the direct transcriptional target of KLF15 and validated with ChIP-PCR or Luciferase assay. Finally, we interpreted whether SUMO1 was able to sumolyate p53 then block cell cycle and inhibit cell proliferation using co-IP and EDU assay in vitro. Also demonstrated these mechanisms on the anti-thy1 rat model.

Results: We showed that in vitro treatment with PDGF BB or high glucose induced a rapid decrease of KLF15 and SUMO1 expression in HMC with proliferation, also decreased in the renal cortex of anti-thy 1 model at the proliferated periods. SUMO1 was screened out and validated as one of the direct target proteins of KLF15. SUMOs are a group of post-translational modification proteins and participate in transcriptional regulation, protein stabilization, and the cell cycle. Furthermore we demonstrated overexpress KLF15 or SUMO1 enhanced the stability of P53 (Sumolyation-p53 expression increased) that functioned to block the cell cycle of HMCs, therefore obliterate the cell proliferation. Conversely, knockdown of SUMO1, even if cultured with PDGF BB, HMCs proliferation rates declined along with less sumolyation-P53. Finally, results showed the level of sumolyation-P53 in the kidney cortex from anti-thy 1 rat model decreased at proliferation periods.

Conclusions: These studies manipulate the critical mechanism of KLF15 targeting SUMO1 in mediating the proliferation of mesangial cells. It will be a potential target for IgAN or diabetic nephropahty's therapy.

TH-PO799

Gender Differences in the Development of Glomerulopathy in Mice with an EGFR Gain-of-Function Mutation

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Background: The epidermal growth factor receptor (EGFR) is widely expressed in the kidney in both glomeruli and tubules. Under pathological conditions, persistent and dysregulated EGFR activation mediates progressive glomerular and tubulointerstitial injury in progressive kidney diseases. Although gender differences mediating predisposition to kidney injury are well known, no previous studies have investigated the potential role of EGFR in these differences.

Methods: *Dsk5* mice have a Leu863Gln mutation within a region of the kinase domain that stabilizes the receptor activation loop, producing a gain-of-function allele that increases basal EGFR kinase activity. Both male and female heterozygous *Dsk5* mice on the 129 background were used. *Dsk5* mice were oopherectomized or castrated before puberty to investigate the effect of sex hormones on EGFR expression and glomerulopathy.

Results: In male *Dsk5* mice constitutive EGFR activation was confirmed by intense phospho-EGFR immunostaining not seen in wild type mice. At 15 weeks of age, male *Dsk5* mice exhibited glomerulopathy, with mesangial proliferation and segmental and global sclerosis. They also had increased albuminuria, loss of podocytes and increased tubulointerstitial fibrosis as indicated by Sirius red and Masson's trichrome staining. Kidneys had increased mRNA and protein levels of profibrotic and fibrotic components, including TGF-β, α-smooth muscle actin, connective tissue growth factor, fibronectin, collagens I, III, IV and increased immune cell infiltration and proinflammatory cytokines/chemokines, such as MCP-1, TNF-α, IL-6, and IL-1α. Unexpectedly, there was minimal kidney injury in female *Dsk5* mice at up to 30 weeks of age. Renal mRNA and protein EGFR levels were significantly lower in age-matched females than males. Oopherectomy had no effect on renal EGFR levels and injury in female *Dsk5* mice, while castration protected against the kidney injury seen in intact male *Dsk5* mice, in association with a reduction in EGFR expression to levels seen in female mice.

Conclusions: These studies indicate that constitutive EGFR activation promotes glomerular and tubulointerstitial injury in male mice, but not in female mice, and this gender difference may be at least in part due to androgen-dependent higher basal levels of EGFR expression.

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TH-PO800

Extracellular Vesicles Derived from Amniotic Fluid Stem Cells as Potential Therapy for CKD

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Background: The crosstalk between podocytes and glomerular endothelial cells (GEC) is vital for the maintenance of glomerular function. VEGF signaling plays a key role in the progression of chronic kidney disease (CKD). The discovery of safe therapeutics designed to specifically target the glomerular crosstalk, specifically VEGF signaling, is ground-breaking. We propose that extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) can restore glomerular crosstalk and delay disease progression in Alport Syndrome, a model of CKD.

Methods: GEC were isolated from (Tek-Cre driven) tdT AS and WT mice along disease progression, characterized by WB and RNA-seq with specific focus on VEGF signaling and endothelial damage. EVs were isolated from AFSC, characterized and injected in vivo using our established protocols. Histology and kidney function were evaluated in injected and control mice.

Results: Glomeruli and GEC present with upregulated VEGF signaling before high level of proteinuria. RNA-seq data showed, for the first time, that AS-GEC present with modulation of genes involved in GBM deposition (collagen and laminin) and regulation (MMPs), glycocalyx component (syndecan, perlecan ect), and endothelial markers (VCAM1, ICAM), before the onset of proteinuria. Administration of EVs, at early stage, restore VEGF levels to normal by trapping excessive VEGF (EVs present VEGFR1 and VEGFR2 on the surface) and improve kidney function in AS mice. In light of clinical translation of EVs for CKD, we characterized EVs from human AFSC. We developed specific identity, purity and potency assays that generate EV lots with very similar characteristics between harvests. EVs of human origin present reno-protective activity in vivo in AS mice as well as capability of modulating glomerular VEGF signaling.

Conclusions: Our data suggest that VEGF-induced GEC damage might play a key role in the pathogenesis of AS and its progression and that administration of EVs can delay disease progression by preventing endothelial injury and by restoring to normal VEGF signaling. In sum, our work possibly will facilitate the discovery of new potential glomerulus-specific targeted intervention, thus possibly minimizing disease progression and ameliorating the life of patients affected by CKD.

Funding: Private Foundation Support

TH-PO801

ICOSL in Non-Immune Cells Functions as an Inducible Potent αvβ3 Integrin-Selective Antagonist to Prevent Early Kidney Disease

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Background: ICOSL, the ligand for the inducible co-stimulator (ICOS), was the third member of the B7 superfamily discovered, is mainly expressed by antigen presenting cells (APCs), and functions in regulating T cell mediated immune responses. ICOSL has traditionally been assigned the fundamental role as an exclusive ligand for ICOS and was thought to be restricted to the immune system. As such, its potential function in non-hematopoietic cells under disease conditions remains completely unexplored.

Methods: *In vitro* and *in vivo* approaches were used to conduct the following analyses: qPCR, immunohistochemistry, surface plasmon resonance, cellular adhesion assays, ACR and BUN level measurements, electron microscopy, and bone marrow transplantations. Available on-line databases were used for 3D-modeled homology structure analysis. Rescue experiments involved injection of recombinant ICOSL into ICOSL KO mice.

Results: We find that unlike other B7 co-stimulatory molecules, ICOSL contains a known integrin-binding motif: arginine-glycine-aspartic (RGD), and selectively binds to αvβ3 but not to α3β1 integrin. Indeed, this binding depends on the activation state of αvβ3 integrin and is largely inhibited by the presence of synthetic RGD peptide, a selective antagonist of αvβ3. We also find that the RGD motif present in ICOSL is functionally active and modulates the αvβ3 integrin-dependent adhesion of podocytes. Consistent with the rapid induction of podocyte ICOSL expression by inflammatory stimuli, glomerular ICOSL expression is greatly increased at early stages of human proteinuric kidney diseases such as focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy (DN). Furthermore, ICOSL deficiency results in an increased susceptibility to kidney injury and severe proteinuria in mice, and can be rescued by recombinant ICOSL injection.

Conclusions: Here we report a novel, renoprotective role for ICOSL in early kidney disease through its selective binding to active αvβ3 integrin. Our work identifies a novel role for ICOSL: protecting the kidney filter from injury by serving as a potent αvβ3-selective antagonist, and provides new insights into various pathological diseases associated with aberrant αvβ3 activation.

Funding: NIDDK Support

TH-PO802

High Activity of Tissue Remodeling Cell Signaling Cascades in the Macula Densa

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Background: The macula densa (MD), a plaque of 15-20 specialized cells, sits at the vascular pole of the glomerulus and plays a traditional role in maintaining renal hemodynamics and the renin-angiotensin system. However, the new tissue remodeling function of MD cells is emerging. The present study aimed to examine the activity and role of major cell signaling pathways in MD cells, and to test if augmenting these pathways specifically in MD cells would alter renal tissue remodeling.

Methods: RNA seq and gene profiling was used to establish and analyze the gene profile of mouse MD cells under control and stimulating low dietary salt conditions. To confirm MD specificity of top gene candidates, immunohistochemistry (IHC) was performed on mouse and human kidney sections for Wnt/β-catenin, mTOR, PI3K, and MAPK signaling pathways that are known to regulate cell biology and tissue remodeling. To test for cell proliferation and rate of protein synthesis, EdU staining and a O-propargyl-puromycin incorporation-based assay were performed, respectively, in kidney sections of control WT mice and in a new genetic model of inducible MD-specific Wnt gain-of-function (*gof*).

Results: Combined gene profiling and IHC identified the highest activity of Wnt, mTOR, PI3K, and MAPK signaling in MD cells in the mouse and human kidney cortex. A TCF/Lef:H2B-GFP Wnt signaling reporter mouse model and activated β-catenin IHC showed the strongest labeling in MD cells. In MD-Wnt(*gof*) mice after 5 weeks of induction, a robust increase in MD cell proliferation, nucleus-to-cell volume ratio, and protein synthesis were found compared to WT control. MD-Wnt(*gof*) mice also featured enlarged glomeruli, increased PDGFRβ+ mesangial expansion and angiogenesis. Treatment with lithium (GSK3β inhibitor for Wnt stimulation) for 2 weeks had similar effects on MD cell morphology, cell biology, glomerular size and cell composition.

Conclusions: In summary, the renal cell type with the strongest Wnt, mTOR, PI3K, and MAPK activity is the MD, which is a chief sensor and effector of the local tissue environment. Wnt signaling is an important regulator of MD morphology, cell biology, and new function in tissue remodeling, which can be augmented in new developing regenerative therapeutic strategies.

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TH-PO803

Investigating Basement Membrane Assembly

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Background: The glomerular basement membrane (GBM) is a specialised condensed network of extracellular matrix. Monocultures of podocytes and endothelial cells synthesise and organise a complex matrix *in vitro* and this has significant overlap with the components of the GBM *in vivo*. Whilst these cultures assemble type IV collagen this is predominantly the α1α1α2 network and not the mature α3α4α5 network, which is required for the long-term integrity of the GBM. We hypothesised that the combination of glomerular cell coculture and flow would alter the composition of matrix and lead to a more mature phenotype with greater similarity to the GBM *in vivo*.

Methods: To generate flow we utilised the QV600 bioreactor (Kirkstall) and a custom-designed bioreactor constructed with the silicone-based polymer PDMS. Detachable podocyte and endothelial cell sheets were engineered and assembled into the bioreactors to create cocultures without the need for an intervening material for support. Cells and matrix were examined in static and flow conditions using light and electron microscopy and mass spectrometry (MS)-based proteomics. The function of this coculture system as a semi-permeable filtration barrier was examined using fluorescently labelled dextrans.

Results: Endothelial cells and podocytes readily formed cell sheets and could be assembled as cocultures into bioreactors. Both cell types were viable in coculture and in static and flow conditions. Electron microscopy revealed the presence of basement membrane-like structures between cocultured cells and functional analysis confirmed intact barrier function. Proteomic analysis of cells under flow conditions demonstrated an upregulation of basement membrane proteins including altered laminin and collagen IV isoforms compared to static conditions.

Conclusions: Podocyte and endothelial cells are viable in direct contact and under flow conditions and flow influences both the composition and assembly of matrix in our system suggesting roles for both cell-cell cross-talk and fluid flow in the assembly of basement membranes. This system has utility for understanding the basic biology of GBM formation and glomerular cell interaction with the GBM in addition to testing compounds that could repair a damaged GBM in the context of glomerular disease.

Funding: Commercial Support - GlaxoSmithKline

TH-PO804

Podocyte Development/Function Depends on Primary Cilia and the Exocyst

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Background: Diseases affecting podocytes are leading causes of ESRD. Until recently, podocytes were thought not to have primary cilia, as cilia are not seen on adult podocytes; however, primary cilia were reported on developing podocytes in 2010. In 2014, a mutation in ciliary protein IFT139 was found in patients with FSGS, suggesting cilia involvement in GN. Our mRNA profiling of injured podocytes showed downregulation of the highly-conserved 8 protein exocyst trafficking complex. We previously showed that the exocyst is necessary for ciliogenesis in kidney tubule cells, zebrafish, and mice. Exocyst members were also mutated in families with ciliopathies affecting the kidney. Thus, we hypothesized that the exocyst is critical for podocyte development/function.

Methods: We generated podocyte-specific Exoc5 knockout (KO) mice, by crossing Podocin-Cre and Exoc5 fl/fl mice, and studied patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Results: Podocyte-specific Exoc5 KO mice showed massive proteinuria and died within 5 weeks of birth. Importantly, isolated glomeruli stained with acetylated alpha tubulin showed primary cilia in wild-type, but not Exoc5 KO, mouse glomeruli. Histological analysis showed severe defects with increased fibrosis, proteinaceous casts, effaced podocytes, and slit diaphragm loss in Exoc5 KO mice; while IF showed significant mislocalization of slit diaphragm proteins Neph1 and Nephrin. Podocyte-specific Exoc5 KO mice phenocopied Cdc42, an exocyst regulator, KO mice reported by others. Mapping and Western blot analyses showed upregulation of canonical and non-canonical arms of the TGFβ pathway, including ERK and SMAD3 activation, in Exoc5 knockdown podocytes, and Exoc5 KO glomeruli. We next examined copy number variation (CNV) data derived from genome-wide SNP arrays from 256 patients with nephrotic syndrome enrolled in NEPTUNE. This dataset identified CNV that were greater than 100kb, overlapped a gene, and were ultra-rare or absent in control populations. Within, we identified two patients with qualifying CNV affecting exocyst component, *EXOC4*: a male toddler of Asian ancestry with steroid resistant minimal change, and an African-American female in her third decade with collapsing FSGS.

Conclusions: Our data implicate exocyst-based ciliogenic mechanisms in podocyte development/function, and suggest a novel target for intervention.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-PO805

A Novel Interaction Between Synaptojanin-1 and ZO-1 Indicates Clathrin-Mediated Turnover at the Slit-Diaphragm

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Background: The importance of clathrin-mediated endocytosis (CME) for podocyte health has long been established. Deletion of Synaptojanin 1 (Synj1), which is involved in the uncoating of clathrin-coated vesicles (CCV), resulted in severe albuminuria and foot process effacement in mice. The aim of this study is to further understand the underlying mechanism and role of Synj1 at the slit-diaphragm (SD).

Methods: We created a mouse monoclonal antibody specific for the Synj1 isoform expressed in podocytes. Mass Spectrometry analysis following immunoprecipitation (IP) of podocyte lysate revealed tight junction protein, Zonula occludens 1 (ZO-1) as a binding partner. To further identify the binding domains, we transfected Cos7 cells with various tagged truncated ZO-1 and Synj1 plasmids and performed IP. We analyzed through live imaging, the temporal and spatial relationship between ZO-1 and clathrin in isolated control podocytes. Immunofluorescence (IF) staining with ZO-1 and clathrin light-chain antibodies on wild-type and *Synj1* KO mouse podocytes was performed to determine ZO-1 localization.

Results: The association of Synj1 with ZO-1 was confirmed by IP in Cos7 cells overexpressing Synj1 and ZO-1. Binding between the SH3 domain of ZO-1 and proline-rich domains of Synj1 was observed. IF staining of wild-type mouse podocytes demonstrated ZO-1 co-localized with clathrin-coated pits. Live cell imaging further revealed CME of ZO-1. However, Synj1 KO podocytes displayed ZO-1 mislocalization in the cytosol when compared to wild-type.

Conclusions: We identified a novel binding partner of Synj1, the slit-diaphragm protein ZO-1, which indicates clathrin-mediated turnover of ZO-1 similar to Nephrin likely occurs. IF images and live cell imaging further corroborated these findings. Furthermore, inhibiting uncoating of CCV in Synj1 KO podocytes resulted in mislocalization of ZO-1. These findings illustrate the importance of clathrin-mediated recycling of slit-diaphragm proteins during podocyte health and disease.

Funding: NIDDK Support

TH-PO806

Correlation Between Endocapillary Proliferative and Nephrotic-Range Proteinuria in Children with Henoch-Schönlein Purpura Nephritis

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Background: The endocapillary proliferative (EP) lesion is not included in ISKDC pathological classification of HSPN. The main objective of the study was to determine the

pathological importance of EP in the development of proteinuria in children with Henoch-Schönlein purpura nephritis (HSPN).

Methods: The pathological features of 148 HSPN children with nephrotic-range proteinuria were investigated retrospectively. 24-hour proteinuria was measured by pyrogallol red-molybdate. Urinary IgG, transferrin and albumin levels were measured by immunonephelometry. The correlations between EP lesion and 24-hour proteinuria, urinary IgG, urinary transferrin and urinary albumin were analyzed. Renal biopsy specimens were immunohistochemically stained for nephrin and podocalyxin.

Results: Of total 581 cases of children with HSPN who underwent renal biopsy, 148 cases (25.5%) presented with nephrotic-range proteinuria. The pathological types of HSPN with nephrotic-range proteinuria were categorized as IIb, IIIa, IIIb, IIIb with EP, IVb, and pure EP type. Among these types, pure EP type accounted for 7.4%. The levels of 24-hour proteinuria and urinary albumin were the highest in EP type among all pathological types, and the percentage of EP correlated with 24-hour proteinuria and urinary albumin levels. 24-hour proteinuria was significantly higher in pure EP type relative to HSPN IIb type, and significantly higher in IIIb with EP, compared with HSPN IIIb. Nephrin, but not podocalyxin, was downregulated in EP segment.

Conclusions: In addition to mesangial proliferation and crescent formation, EP is an independent pathogenic factor in HSPN with nephrotic-range proteinuria. Downregulation of nephrin in EP segment is a potential molecular mechanism of nephrotic-range proteinuria. Albumin is the major urinary protein component in HSPN with EP.

TH-PO807

Immune Response to Tonsillar Microbiome Are Perturbed in the Development of IgA Nephropathy

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Background: The aberrant immune response in palatine tonsils against commensal bacteria has been estimated to be involved in the development of IgA nephropathy (IgAN). To elucidate these mechanisms, we focused on the relationship between the expression of TNFSF13 (APRIL) and galactose-deficient IgA1 (Gd-IgA1) and the composition of bacteria in tonsillar crypts.

Methods: We enrolled 57 patients with IgAN and 27 with recurrent tonsillitis (RT) who were undergone tonsillectomy. Genomic DNA were extracted from the excised tissues of tonsillar crypts in each patient and V4 regions of the 16S-ribosomal RNA gene sequence were applied to assess the relative abundance of bacteria. These tissues were also solubilized with a lysis buffer and the concentration of extracted proteins were quantified with BCA methods. The levels of APRIL and Gd-IgA1 in tonsils or serum were measured by ELISA, and the degree of Gd-IgA1 deposition in glomerulus were evaluated by immunohistochemical analysis. We analyzed the correlations between the levels of APRIL, Gd-IgA1 and bacterial abundance, as well as the grade of glomerular injury.

Results: Immunohistochemical analysis revealed that Gd-IgA1 was localized in germinal center of tonsils and the degree of its stained area was correlated with tonsillar Gd-IgA1 levels. The degree of Gd-IgA1 deposition in glomerulus was significantly correlated with tonsillar Gd-IgA1 levels. The levels of Gd-IgA1 in tonsil were significantly higher in IgAN patients with more extended glomerular damage, while tonsillar Gd-IgA1 levels in IgAN patients did not differ from those in RT patients. Tonsillar APRIL levels were significantly higher in IgAN patients than in RT patients ($P < 0.01$). The levels of tonsillar APRIL in RT were positively correlated with the relative abundance of *Prevotella* genus in tonsils, however, the upregulated levels of tonsillar APRIL in IgAN did not show any robust associations with 16S microbiota in tonsils.

Conclusions: Gd-IgA1 and increased APRIL expression in tonsils could be involved in the development of IgAN. Further analysis is needed to reveal the role of microbiome on the mucosal immunity in tonsils of patients with IgAN.

TH-PO808

Deposition of IgA and C3 on the Glomerular Loop Significantly Correlates with Urinary Protein in Immunoglobulin A Vasculitis with Nephritis (Henoch-Schonlein Purpura Nephritis)

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Background: Immunoglobulin A vasculitis with nephritis (IgAVN) is considered to be systemic form of IgA nephropathy (IgAN). Both IgAN and IgAVN are defined by the presence of IgA dominant glomerular deposits. However, the pathological significance of the difference in glomerular location of IgA and other immunogrobulin deposits is remain unclear. In this study, we investigated which clinical findings and renal prognosis correlate with immunostaining findings in IgAVN.

Methods: We conducted a retrospective study of 33 adult patients of biopsy-proven IgAVN and analyzed these cases in terms of clinicopathological feature and renal prognosis. Especially, we evaluated renal biopsy specimens of IgAV in detail by immunostaining.

Results: 33 adults IgAVN patients (male:21, female:12) were analyzed. Averege age was 41.12±14.7 years old at the renal biopsy. Localization of glomeruli of IgA, IgG, IgM as immunoglobulin, C3, C4d, C1q as complement factor, and fibrin, fibrinogen, kappa chain, lambda chain as others were examined by immunostaining. IgA deposition was observed on glomerular loop (capillary wall) of 10 patients (30%). The average proteinuria was 3.60±2.61 g/day in the IgA deposited on glomerular loop group and 1.53 ±1.63 g/day in the group with no IgA deposition on glomerular loop group. (P=0.0047) Furthermore, C3 deposition was also observed on glomerular loop of 10 patients (30%). The average urine protein was 4.04±2.64 g/day in the C3 deposited on glomerular loop group and 1.34±1.28 g/day in the group with no C3 deposition. (P<0.001) From these results, we revealed that the deposit of IgA and C3 on glomerular loop in immunostaining findings was positively correlated with the amount of the proteinuria. However, renal prognosis was no significant difference in both group in one year after treatment.

Conclusions: The deposition of IgA and C3 in the glomerular loop were significantly correlated with the amount of puroteinuria. These results suggested that these deposition may play a key role in the pathogenesis of IgAVN, and also suggested that the selection of therapy for IgAVN might be affected.

TH-PO809

GWAS-Follow-Up Study Identified Abnormal LIF Signaling Network Involving STAT1 and Src Family Protein-Tyrosine Kinases in IgA1-Secreting Cells from Patients with IgA Nephropathy

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Background: Genome-wide association studies (GWAS) in IgA nephropathy (IgAN) provide insight into disease pathobiology by identifying genetic loci and mapping the associated molecular pathways. A GWAS locus on chr. 22q12 encompasses genes that include *LIF* that encodes leukemia inhibitory factor, an IL-6-related cytokine implicated in mucosal immunity and inflammation. In this study, we characterized LIF signaling pathways leading to overproduction of galactose-deficient IgA1 (Gd-IgA1), using IgA1-secreting cell lines derived from peripheral blood of patients with IgAN and healthy controls (HC).

Methods: IgA1 was determined by ELISA, Gd-IgA1 lectin ELISA with *Helix aspersa* lectin. To assess LIF signaling pathways, we used global protein-tyrosine kinases (PTKs) activity profiling, immunoblotting, siRNA knock-down, and a JAK2 inhibitor.

Results: LIF activated STAT1 phosphorylation (Y701) to a greater level in IgA1-secreting cells from patients with IgAN (n=5) compared with those from HC (n=5) ($p<0.01$). LIF-mediated increase in Gd-IgA1 production by IgA1-secreting cells from patients with IgAN were reduced by siRNA *STAT1* knock-down ($p<0.05$). Use of a JAK2 inhibitor revealed that this enhanced phosphorylation of STAT1 in IgA1-secreting cells from patients with IgAN was not mediated by JAK2. PTK activity profiling indicated that LIF signaling activated Src family of PTKs, based on highest kinase statistics (Kstat) and specificity.

Conclusions: LIF induced abnormal STAT1 signaling and enhanced production of Gd-IgA1 in IgA1-secreting cells from patients with IgAN, providing possible explanation for the phenotype associated with a GWAS locus encompassing *LIF*. Moreover, our exploratory data indicate involvement of Src family PTKs in LIF signaling that needs to be further explored.

Funding: NIDDK Support

TH-PO810

Nasal-Associated Lymphoid Tissue Is the Major Induction Site for Nephritogenic IgA in Murine IgA Nephropathy

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Background: The pathogenesis of IgA nephropathy (IgAN) is closely associated with dysregulation of mucosal immune system, which manifests as mesangial IgA deposition leading renal impairment. Several papers reported that Toll-like receptor 9 (TLR9) activated by exogenous pathogens is suspected in aggravation of renal injury in IgAN. However, it is unclear which gut-associated lymphatic tissue (GALT) or nasal-associated lymphoid tissue (NALT) is more involved in the pathogenesis of IgAN. Although the origin of nephritogenic IgA has been obscure, several studies demonstrated the efficacy of tonsillectomy and corticosteroid therapy, whereas the novel targeted-release formulation of budesonide targeting intestinal mucosal immunity reduced proteinuria in IgAN patients. In present study, we focused on the role of NALT and GALT using IgAN-prone ddY mice.

Methods: Levels of aberrantly glycosylated IgA and IgG-IgA immune complexes (IC) in serum and supernatant from cultured cells from NALT, Mesenteric lymph node (MLN) and spleen were measured using IgAN onset and quiescent ddY mice (each n=16) with or without TLR9 ligand (CPG-ODN) stimulation. Level of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin (SNA) and Ricinus communis agglutinin I (RCA).

Results: In IgAN onset ddY mice, serum levels of aberrantly glycosylated IgA and IC were significantly higher than those in quiescent ddY mice. However, there were no significant differences in the levels of aberrantly glycosylated IgA and IC produced by MLN between IgAN onset and quiescent mice. Serum levels of aberrantly glycosylated IgA and IC correlated with those in culture supernatant of splenocytes, but SNA and RCA assay revealed that the sugar component of IgA from MLN was different from that in circulatory IgA in IgAN onset ddY mice. The levels of aberrantly glycosylated IgA and IC in NALT and splenocytes were significantly increased by CpG-ODN, however those in MLN were not increased.

Conclusions: Aberrant glycosylation of IgA leading to IC formation was found in cell supernatant from NALT but not in MLN/GALT. The present study suggest that the NALT has a key role in the pathogenesis of murine IgAN

TH-PO811

Patients with Immunoglobulin A Nephropathy Is Associated with Elevated Urinary Mitochondrial DNA Copy Number

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Background: Urinary mitochondrial DNA (mtDNA) levels are considered to reflect mitochondrial injury in kidney. However, mitochondrial injury in IgA nephropathy (IgAN) remains unknown. We hypothesized that IgAN would be associated with increased urinary mtDNA copy numbers.

Methods: We prospectively enrolled age-sex matched healthy volunteers (HV) and biopsy-proven IgAN (n=30 each). Urinary copy number of the mtDNA genes cytochrome-c oxidase-3 (COX3) and nicotinamide adenine dinucleotide dehydrogenase subunit-1 (ND1) were measured by quantitative polymerase chain reaction. We measured also urinary ND-1 and COX3 3 months after medical treatment in IgAN (n=12).

Results: The mean estimated glomerular filtration rate (eGFR) was significantly lower in IgAN compared with HV (75.2±28.8 vs 107.2±12.1 mL/min/1.73m^2, respectively, p<0.001). $\log_{10}$ND1/nDNA and $\log_{10}$COX3/nDNA were significantly higher in IgAN compared with HV (5.70±0.36 vs 5.14±0.34, 5.68±0.37 vs 5.15±0.33 copies/μl of urine/nDNA, respectively, both p<0.001). There was no significant relation between urinary mtDNA copy numbers and tranditional prognostic markers at presentation in IgAN such as mean arterial pressure, eGFR, and the amount of proteinuria. In the M score of the Oxford classification, $\log_{10}$ND1/nDNA and $\log_{10}$COX3/nDNA were significantly lower in IgAN patients with mesangial hypercellularity (5.61±0.39 vs 5.89±0.20, p=0.014, 5.60±0.41 vs 5.85±0.16 copies/μl of urine/nDNA, p=0.022, respectively). Medical treatment did not reduced urinary mtDNA copy numbers.

Conclusions: Urinary mtDNA copy numbers were elevated in patients with IgAN. This suggests mitochondrial damage would be a pathogenesis in IgAN.

Relation between urinary mtDNA levels and clinical variables in patients with immunoglobulin A nephropathy

Variables	Mean arterial pressure	Estimated glomerular filtration rate	Proteinuria
log $_{10}$ND1/nDNA level	r = -0.072, P = 0.706	r = 0.147, P = 0.438	r = -0.073, P = 0.701
log $_{10}$COX3/nDNA level	r = -0.047, P = 0.805	r = 0.125, P = 0.511	r = -0.010, P = 0.957

Data were analyzed by Spearman's rank correlation coefficient.

COX3, cytochrome-c oxidase-3; mtDNA, mitochondrial DNA; ND1, nicotinamide adenine dinucleotide dehydrogenase subunit-1.

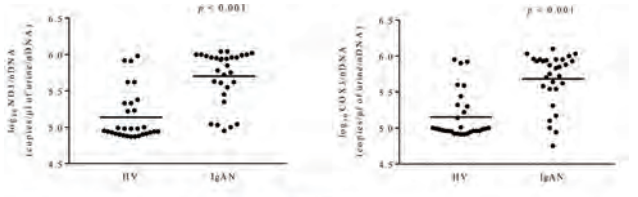

Figure. Urinary mtDNA copy number of patients with IgAN and HV.
COX3, cytochrome-c oxidase-3; HV, healthy volunteers; IgAN, immunoglobulin A nephropathy; mtDNA, mitochondrial DNA; ND1, nicotinamide adenine dinucleotide dehydrogenase subunit-1.

TH-PO812

Plasma Galactose-Deficient IgA1/C3 Ratio Is Strongly Associated with Disease Progression in IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) and C3 mesangial codeposition is a hallmark of IgA nephropathy (IgAN). In this large cohort study, we aim to evaluate Gd-IgA1/C3 ratio in the progression of IgAN.

Methods: In this study, we included 1157 IgAN patients with a median follow-up period of 42 months. Plasma Gd-IgA1 was measured at the time of diagnosis using a lectin-based ELISA. The composite kidney failure event was defined by 50% decline in eGFR or ESRD and renal survival was modeled using the Cox proportional hazards method and restricted cubic splines.

Results: Although high plasma Gd-IgA1 levels were associated with the risk of kidney progression events, the association was not in a linear relationship. While the correlation between plasma Gd-IgA1/C3 ratio and risk of kidney failure was a linear relationship. After adjusted for traditional risk factors, higher levels of Gd-IgA1/C3 ratio was independently associated with a greater risk of deterioration in renal function with a HR of 2.15 (95% CI=1.21–3.81, P=0.008) per ln(Gd-IgA1/C3). In reference to the first quartile, the risk of kidney progression event increased such that the HR for the second quartile was 1.84 (95% CI=1.05–3.24, P=0.034), 1.79 (95% CI=1.02–3.12, P=0.041) for the third, and 2.08 (95% CI=1.22–3.54, P=0.007) for the fourth quartile of the Gd-IgA1/C3 ratio.

Conclusions: Plasma Gd-IgA1/C3 ratio was an independent risk factor for kidney progression events.

Cox regression model associations of baseline plasma Gd-IgA1/C3 levels with incidence of composite end point.

	HR (95% CI) and P value			
	Unadjusted	Model 1	Model 2	Model 3
Per ln(Gd-IgA1/C3)	3.00 (1.73-5.21)	3.02 (1.74-5.24)	2.68 (1.59-4.53)	2.15 (1.21-3.81)
P value	8.9×10^{-5}	8.1×10^{-5}	2.2×10^{-4}	0.008
Gd-IgA1/C3 quartiles				
1	Reference	Reference	Reference	Reference
2	1.68 (0.99-2.85)	1.61 (0.94-2.76)	1.63 (0.95-2.80)	1.84 (1.05-3.24)
P value	0.055	0.082	0.076	0.034
3	1.97 (1.17-3.31)	1.90 (1.13-3.22)	2.10 (1.24-3.55)	1.79 (1.02-3.12)
P value	0.010	0.016	0.006	0.041
4	2.49 (1.51-4.12)	2.47 (1.49-4.07)	2.29 (1.39-3.80)	2.08 (1.22-3.54)
P value	3.5×10^{-4}	4.3×10^{-4}	0.001	0.007

Model 1 was adjusted for sex and age. Model 2 was adjusted for covariates in model 1 plus eGFR, proteinuria, and mean arterial blood pressure. Model 3 was adjusted for covariates in model 2 plus Oxford MESTC scores and steroids or other immunosuppressive agents.

TH-PO813

Collectin-11 Is a Recognition Molecule in Glomerular Activation of Lectin Pathway in IgA Nephropathy

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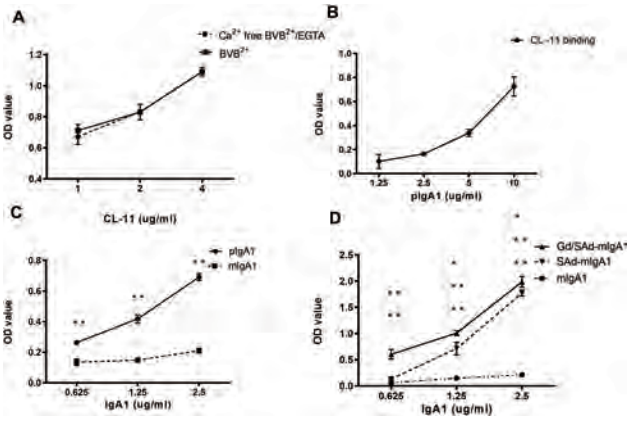
Background: Glomerular activation of lectin pathway (LP) was reported in IgA nephropathy (IgAN), and further associated with disease severity and therapy. Besides mannose-binding lectin (MBL) and ficolin, which could recognize glycans of IgA1 and lead to LP complement activation in IgAN, collectin-11 (CL-11) is a newly identified recognition molecule in LP. Here we explored the involvement of CL-11 in complement activation of IgAN.

Methods: We enrolled 60 IgAN patients for Immunofluorescence staining of CL-11, MBL, ficolin, MASP2, MASP1/3, C4d, C3c and C5b-9 in renal biopsy specimens. Additionally, plasma samples from 10 patients with IgAN were collected for IgA1 purification. Using jacalin affinity chromatography, Sephrcryl S300 and glycosyl hydrolysis treatment, monomeric IgA1 (mIgA1), polymeric IgA1 (pIgA1), as well as sialic acid deficient IgA1 (SAd-IgA1) and sialic acid/galactose deficient IgA1 molecules (Gd/SAd-IgA1) were prepared and their binding with CL-11 were detected by ELISA.

Results: In our IgAN patients, 36.7% (22/60) had mesangial CL11 deposition. Among them, 14 also had MBL and ficolin deposition, 1 had MBL without ficolin, 4 had ficolin without MBL, while 3 without MBL or ficolin. All of the 22 IgAN patients with mesangial CL-11 deposition, presented with MASP (MASP2 or MASP1/3), C4d, C3 and MAC deposition, which co-localized with CL-11. In vitro, pIgA1 showed a Ca^{2+}-independent binding with CL-11, and the binding was in a dose-dependent manner. Between concentrations of 0.625-2.5 ug/ml, pIgA1 showed significantly higher binding to CL-11 than mIgA1, while Gd/SAd-IgA1 had significantly higher binding to CL-11 than SAd-IgA1 and IgA1.

Conclusions: Our results suggested collectin-11 as a recognition molecule in LP in IgAN. Collectin-11 prone to bind with aberrant glycosylated polymeric IgA1, which might contribute to the glomerular complement activation of LP in IgAN.

Funding: Government Support - Non-U.S.



TH-PO814

VIS649 Reduces Serum IgA Levels in NHPs Dose Dependently: PK/PD Exposure-Response Modeling for Translation to Treatment of IgA Nephropathy

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Background: VIS649 is a humanized IgG2 monoclonal antibody that targets A PRoliferation-Inducing Ligand (APRIL), a cytokine that is implicated in IgA nephropathy

(IgAN) pathogenesis. Targeting APRIL activity to reduce levels of aberrantly glycosylated circulating IgA_1 may alter IgAN disease progression.

Methods: Cynomolgus monkeys (NHP; n=4/grp) were IV administered vehicle or VIS649 (0.5, 2.5 and 10 mg/kg) once weekly for 4 weeks, and followed for 8 weeks without treatment. Study endpoints included serum VIS649 and immunoglobulin (Ig) levels and peripheral lymphocytes (flow cytometry). Temporal changes in IgA concentration after VIS649 administration were described with a population pharmacokinetic/pharmacodynamic (popPK/PD) model using an indirect response model.

Results: At the 0.5 and 2.5 mg/kg dose levels there was a ~50% reduction in serum IgA levels. VIS649 administration at 10 mg/kg levels resulted in a ~70% serum IgA reduction. This maximal effect of ~70% reduction was confirmed in parallel studies at doses of up to 100 mg/kg and indicates that additional mechanisms support basal levels of IgA production. The effect of VIS649 on reducing IgA levels was reversible and observed after discontinuation of VIS649 treatment during the no-dose period with dose-dependent time to recovery. There was a lesser effect on serum IgG/IgM levels and peripheral lymphocytes were not affected. In a parallel study, a reduction in IgA+ mononuclear cells in GALT and tonsil tissues was observed, consistent with APRILs effect on Ig class switching and plasma cell survival in the mucosal compartment. These data were used to develop a popPK/PD model. Model simulation of single dose VIS649 in humans, in the range of 1-3 mg/kg, predicts a maximal (~70%) reduction in IgA levels followed by a dose-dependent return to baseline. Model simulation of repeated monthly doses suggest dose levels in the 0.3 to 3 mg/kg range will maintain a reduction in IgA levels below 50% of baseline.

Conclusions: VIS649 treatment reduces serum IgA levels in NHPs in a dose proportional manner. These data point to a clear potential therapeutic use of VIS649 in humans with IgAN.

Funding: Commercial Support - Visterra, Inc.

TH-PO815

Comparison of IgA1 Hinge-Region O-Glycoforms Between Patients with IgA Nephropathy and Healthy Subjects

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Background: IgA1 with galactose (Gal)-deficient hinge-region (HR) *O*-glycans (Gd-IgA1) plays a key role in the pathogenesis of IgA nephropathy (IgAN). Monoclonal antibody (mAb) specific for Gd-IgA1 developed for detection of Gd-IgA1 was used in ELISA to confirm elevated serum Gd-IgA1 levels in IgAN patients. An earlier study found that IgAN glomerular immunodeposits were enriched for Gd-IgA1, supporting a key role of Gd-IgA1 in IgAN pathogenesis. To identify potentially disease-specific IgA1 HR *O*-glycoforms, we profiled serum IgA1 HR glycopeptides using specimens from Japanese IgAN patients and healthy controls (HC) of different races.

Methods: IgA1 from sera of 20 Japanese IgAN patients and 50 HC, recruited from Caucasian, Black, Hispanic, Asian, and Japanese populations, was purified by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 HR glycosylation heterogeneity was analyzed by liquid chromatography-high-resolution mass spectrometry (LC-MS). Area under the peaks of extracted ion chromatogram (XIC) of identified IgA1 HR *O*-glycopeptides was calculated and expressed as relative abundance (RA) for each glycopeptide as percentage of all HR glycopeptides. The amount of each glycopeptide was then calculated by multiplying serum IgA concentration (mg/dL) by RA for the specific glycopeptide.

Results: Approximately 60% of HR *O*-glycoforms contained one to three Gal-deficient *O*-glycans in IgA1 from IgAN patients as well as healthy subjects. The amount of Gal-deficient HR variants was increased in IgA1 from IgAN patients compared to that of HC (P =0.043, IgAN *vs.* all HC; P =0.011, IgAN *vs.* Japanese HC). IgA1 with single Gal-deficient *O*-glycan was notably increased in patients with IgAN compared to HC (P =0.043, IgAN *vs.* all HC; P =0.009, IgAN *vs.* Japanese HC).

Conclusions: Profiling of IgA1 HR *O*-glycoforms of IgAN patients and HC indicated that Gd-IgA1 glycoform with single Gal-deficient *O*-glycan was elevated in Japanese IgAN patients compared to HC. Future analysis of IgA1 HR *O*-glycoforms in the glomerular immunodeposits will allow comparison with nephritogenic Gd-IgA1 glycoforms in sera of IgAN patients.

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TH-PO816

Disease Specific Profile of Fecal Microbiome in IgA Nephropathy

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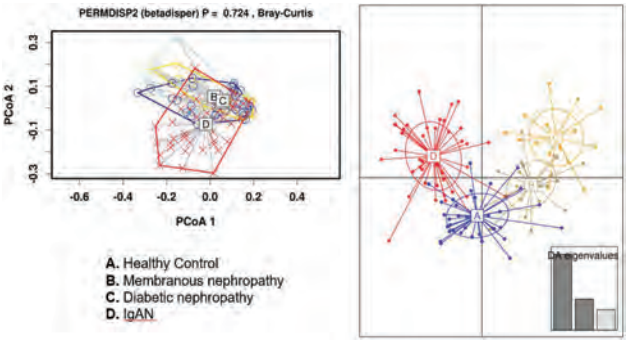
Background: The mucosal immune system plays a role in the pathogenesis of Immunoglobulin A nephropathy (IgAN). Previously, the gut microbiota was proved to be essential to develop the IgAN in mice model. However, little has been known about the relationship between IgAN and the intestinal microbiome in human.

Methods: We enrolled 41 biopsy-proven IgAN patients at 3 centers and collected fecal specimens at the time of renal biopsy. Feces from 36 patients with biopsy-proven membranous nephropathy (MN) or diabetic nephropathy (DMN) were used as disease control (DC) and from 35 healthy volunteers as healthy control (HC). The composition of the microbiota was analyzed using extracted metagenomic DNA from the feces by Illumina MiSeq system.

Results: The estimated glomerular filtration rates (eGFR), which represents the renal function, were 106, 74 and 71 mL/min/1.73m^2 for HC, DC, and IgAN group, respectively. The Shannon diversity index did not differ among the 3 groups. Beta-diversity were plotted using principal coordinate analysis, which showed separation of IgAN from HC and DC groups. At phylum level, the relative abundances of Firmicutes and Acinetobacteria were higher, whereas those of Bacteroidetes and Proteobacteria were lower in IgAN patients than HC, DC groups. When we divided DC group into 21 patients with MN and 15 patients with DMN, the results from a comparison of 4 groups still showed IgAN specific character. At genus level, the number of the significantly different genus was 7 between HC and DC, 24 between HC and IgAN, and 28 between DC and IgAN. When IgAN patients were divided into two groups on the basis of eGFR 60 mL/min/1.73m^2 or 3g/day of proteinuria, the bacterial composition did not differ between groups.

Conclusions: The fecal microbiota of IgAN differed from those of healthy and disease control. We could tell the microbial difference of IgAN was not due to renal function but the IgAN-specific factor. For further investigation, shotgun metagenomic DNA sequencing is undergoing to characterize the functional genes of microbiota.



TH-PO817

The Differences in Podocyte Injury Between IgA Nephropathy and Membranous Nephropathy Based on Proteomics Analysis

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Background: IgA nephropathy (IgAN) is the most common primary glomerular nephritis worldwide. Currently, the diagnosis has to depend on renal biopsy which is an invasive practice. The developing proteomics can provide new ideas for exploring the potential biomarkers and pathogenesis of IgAN.

Methods: The renal tissue of 59 patients with IgAN was obtained and screened for differential protein expression (DEPs) profile by a high throughput method liquid chromatography-mass (LC-MS). The results in IgAN were compared to those in 9 patients with membranous nephropathy (MN) and 19 cases of adjacent normal tissues from renal cell carcinoma. Specific proteins in IgAN and MN were selected. Histochemical stain and double-labelling immunofluorescence stain were used to locate the proteins expressed in IgAN and MN. siRNA and stimulus were used to establish the gene expression cell models, and genes and proteins were detected by RT-PCR and western blot.

Results: (1) An overall sum of 6636 proteins were identified in IgAN, MN and normal tissue. There were 1086 DEPs in IgAN and 392 specific DEPs in IgAN when compared with MN. (2) Samples from patients with IgAN and MN were clearly distinguishable from normal controls. (3) Specific podocyte marker proteins such as nephrin and podocin were down-regulated both in IgAN and MN. Specific DEP CD151, which is a membrane protein of podocyte, was down-regulated in IgAN and has no expression change in MN. Histochemical stain and double-labing IF stain showed CD151 was located in IgAN and its expression was lower and weaker than that in MN and normal tissue. Specific DEP PLA2R1, which is a specific podocyte membrane protein, was significantly up-regulated in MN and has no expression change in IgAN. Histochemical stain showed PLA2R1 was higher and stronger expressed in the podocyte of MN. (4) TNFα could suppress CD151 expression and VEGFA could upregulate PLA2R1 expression in human primary podocyte, and down regulation of VEGFA in podocyte by siRNA could suppress the expression of PLA2R1.

Conclusions: Our study identified the differential expression of proteins in IgAN and MN tissues based on the proteomics analysis and detected the specific proteins CD151 and PLA2R1. TNFα-induced CD151 down-expression and VEGFA-induced PLA2R1 activation in podocyte might be one of the mechanisms in IgAN and MN that cause podocyte injury.

TH-PO818

Understanding the Nature of IgA Deposits in Secondary Glomerular Diseases

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Background: Galactose-deficient IgA1 (Gd-IgA1) is important to the pathogenesis of primary IgA nephropathy (IgAN) and Gd-IgA1 is found in the glomeruli of IgAN. Other glomerular diseases mimic IgAN and feature significant glomerular IgA deposits, but it is not clear if the IgA in these kidneys is galactose-deficient. This study was done to qualitatively assess IgA in the glomerular deposits of patients with Staphylococcal infection-associated IgAN (IA-IgAN) and cirrhosis-associated IgAN (CA-IgAN).

Methods: Double immunofluorescence staining was done on paraffin-embedded kidney biopsies with anti-human IgA and with the monoclonal antibody KM55, which specifically recognizes Gd-IgA1. Kidney biopsies were from United State (US) and Argentine cohorts, and included patients with primary IgAN (n=9) as positive controls, lupus nephritis (LN, n=11) as negative controls, IA-IgAN (n=6) and CA-IgAN (n=5). The Argentine cohort also included 5 additional patients who had proliferative LN with dominant IgA deposits before and after treatment. IgA and Gd-IgA1 were graded semi-quantitatively based on an intensity scale of 0-3.

Results: Gd-IgA1 staining was robust in patients with primary IgAN as expected, and minimal in patients with LN (Table). In patients with CA-IgAN and IA-IgAN staining for Gd-IgA1 was positive but at about half the intensity of primary IgAN (Table). LN patients who had significant glomerular IgA deposits pre- and post-treatment did have detectable Gd-IgA1 at an intensity about half of Argentine primary IgAN. Gd-IgA1 intensity in primary IgAN was less in Argentine patients than US patients.

Conclusions: Galactose-deficient IgA is present in secondary glomerular diseases with IgA-dominant immune complexes. It is not clear if galactose-deficiency is acquired or if the systemic process unmasks intrinsic defects in IgA.

Funding: Clinical Revenue Support

Cohort	Gd-IgA1 Intensity
Primary IgAN-US	2.6±0.4
LN-US	0.4±0.4
CA-IgAN-US	1.3±0.9
IA-IgAN-US	1.7±1.2
Primary IgAN-Argentina	1.6±1.0
LN+dominant IgA-Argentina	0.7±0.3

TH-PO819

Activation of Toll Like Receptors 7/8 Altered IgA1 O-Glycosylation via Regulating Expression of O-Glycosyltransferases in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is featured with O-glycosylation deficiency of IgA1 antibody, but the underlying mechanism of production of Gd-IgA1 was unknown.

Methods: The expression levels of TLRs were analyzed by real-time PCR. The secretion of IgA1 molecules and their O-glycan after TLR activiation were meansured by ELISA. The expression of O-glycosyltransferases was analyzed by Western blot.

Results: We found that gene expression levels of TLR7 and TLR8 were significantly increased in peripheral blood mononuclear cells (PBMCs) of IgAN patients (Figure 1A). *Ex-vivo* activation of TLR7/8 in PBMCs led to more IgA1 antibody production and higher O-glycan deficiency of IgA1 antibody in IgAN patients as compared with healthy donors (Figure 1B). Meanwhile, activation of TLR7/8 resulted in decreased expression C1GalT1 and increased GalNAcT2 expression in B cells of IgAN patients (Figure 2).

Conclusions: Thus, activation of TLR7/8 play important role in pathogenesis of IgA nephropathy by regulating the expression of O-glycosyltransferase and later the galactose deficiency of IgA molecules.

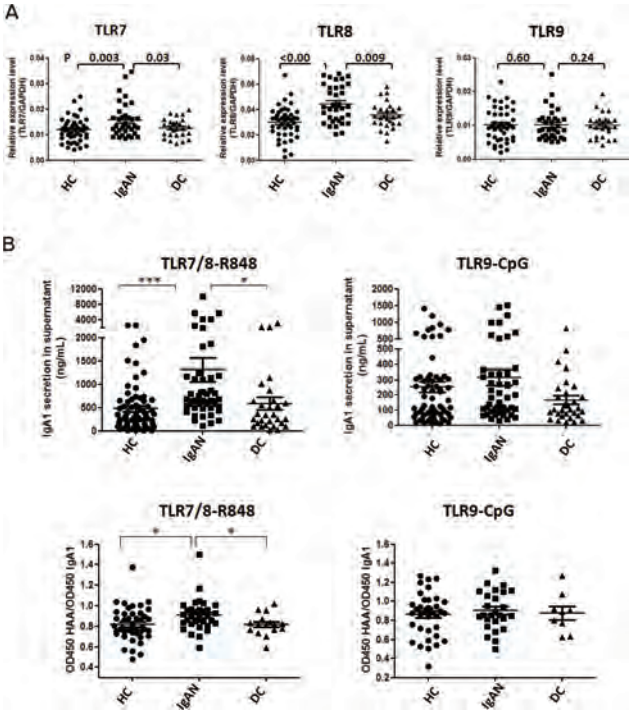

Figure 1-TLR7/8 activation led to augmented IgA1 secretion and galactose deficiency

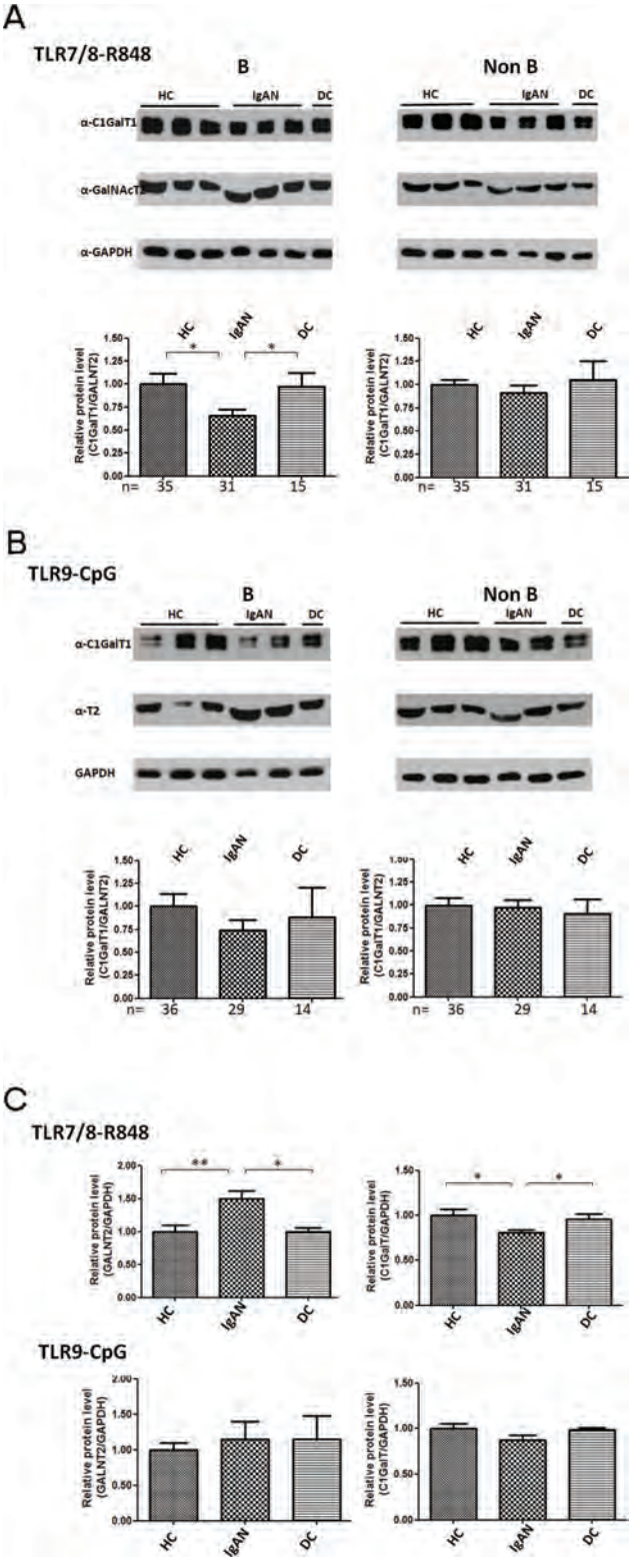

Figure 2-TLR7/8 activation regulates expression of O-glycosyltransferases.

TH-PO820

TLR9 Activation Is Involved in Aberrant IgA Glycosylation via APRIL- and IL-6-Mediated Pathways in IgA Nephropathy

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Background: Toll-like receptors (TLRs) play a key role in the pathogenesis of IgA nephropathy (IgAN). Galactose-deficient IgA1 (Gd-IgA1) is involved in development of the disease. However, the mechanisms driving Gd-IgA1 production have not been fully elucidated. Although previous reports indicated a proliferation-inducing ligand (APRIL) and IL-6 may be involved in Gd-IgA1 synthesis in IgAN, the mechanisms leading to the overproduction of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs are still unclear.

Methods: IgAN prone ddY mice were divided into two groups with CpG-ODN (TLR9 ligand) immunization (n=18) or without (n=18). CpG-ODN was injected intraperitoneally 3 times a week for 12 weeks. Renal pathology and serum levels of aberrantly glycosylated IgA, IgG-IgA ICs, APRIL and IL-6 were evaluated after 12 weeks. We also examined the mechanisms of production of Gd-IgA1 in human IgA1-secreting cells.

Results: Injection of ddY mice with CpG-ODN increased production of aberrantly glycosylated IgA and IgG-IgA ICs, resulting in exacerbated kidney injury ($P<0.05$). Serum levels of APRIL correlated with serum levels of aberrantly glycosylated IgA and IgG-IgA IC ($P<0.05$). CpG-ODN stimulation induced production of aberrantly glycosylated IgA in splenocytes of ddY mice through increase of APRIL and IL-6. In human IgA1-secreting cells, TLR9 activation enhanced Gd-IgA1 production *via* increase of APRIL and IL-6. Production of Gd-IgA1 was partly reduced by siRNA for *APRIL* and/or anti-IL-6.

Conclusions: TLR9 stimulation enhanced synthesis of nephritogenic IgA through overproduction of APRIL and IL-6 in IgAN. Moreover, the present study clarified the crosstalk between APRIL and IL-6, of note APRIL and IL-6 independently promote the production of aberrantly glycosylated IgA.

TH-PO821

T-Follicular Like Helper Cells Enhance IgA Secretion in IgA Nephropathy

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Background: Dysregulated IgA1 response is a central defect in the development of IgA Nephropathy (IgAN), but is it not clear if the altered IgA1 response is attributed to excessive self-proliferation of IgA+ B-cells or an imbalance in the B-cell-T-cell interactions. We investigated the mechanism of IgA production, focusing on the function of T-follicular helper (Tfh) cells, which have recently been shown to play an essential role in antibody response.

Methods: We studied 15 IgAN patients and 20 healthy controls (HC). IgA antibody secreting cells (ASC) were measured by flow cytometry. Naive B-cells, Naïve CD4+ T-cells and T-follicular like helper cells were sorted from the PBMC of patients, and IgA was measured from the B-cell-T-cell co-cultures.

Results: We detected a 3.6 fold increase in IgA ASC numbers and 1.6-fold increase in Tfh like cells in the peripheral blood of IgAN patients compared to HC. Both IgA ASC and Tfh like cell numbers were strongly correlated with the increased IgA and IgA1 levels in the plasma. To distinguish whether enhanced IgA production is dependent on B-cells or Tfh like cells, we performed co-culture experiments. Autologous co-culture experiments of Tfh like cells with naïve B-cells resulted in significantly increased IgA production in cells derived from IgAN patients (172.9 ± 60.9 ng/ml), compared to HC (58.4 ± 13.3 ng/ml). Next, we performed co-culture experiments with cells derived from two pairs of monozygotic twins who are discordant for IgAN. Co-culture of Tfh like- and naïve B-cells from monozygotic twins with IgAN and one self-declared healthy control, and as expected yielded significantly higher IgA production compared to co-culture of cells from their corresponding healthy twins. In addition, Tfh like cells from the IgAN twins significantly increased IgA production from the naïve B-cells from the healthy twins (169.5 ± 31.9 ng/ml) but Tfh like cells from the one healthy twin only elicited baseline IgA production from naïve B-cells from the IgAN twins (59.3 ng/ml).

Conclusions: Our data demonstrate an independent role of T-follicular like helper cells in enhanced generation of IgA in IgAN, identifying a new important step in IgAN pathogenesis. Future studies will be directed towards identification of molecular programs leading to enhanced Tfh like cell count and activity in IgAN.

Funding: NIDDK Support

TH-PO822

Urinary Galactose-Deficient IgA1 Represent a Disease-Specific Marker of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is an autoimmune disease characterized by IgA1-containing immune deposits in mesangium. Galactose-deficient IgA1 (Gd-IgA1) is recognized by anti-glycan autoantibodies, resulting in formation of pathogenic immune complexes. These immune complexes deposit in the kidney, activate mesangial cells, and induce glomerular injury. We recently elucidated that glomerular Gd-IgA1 was specifically detected in IgAN, but not in the other renal diseases by immunohistochemistry using Gd-IgA1 monoclonal antibody (KM55 mAb). We hypothesized that a fraction of Gd-IgA1 from

the glomerular deposits may be excreted into the urine and thus represent a disease-specific marker.

Methods: We recruited biopsy proven 129 patients with IgAN and 79 patients with other renal diseases (control) hospitalized from 2015 to 2017. Serum and urine samples collected at the time of renal biopsy were used to measure Gd-IgA1. Serum and urinary Gd-IgA1 were determined by KM55 mAb. Moreover, consecutive urinary Gd-IgA1 were measured during the course of therapy in 51 patients with IgAN.

Results: Urinary Gd-IgA1 levels were significantly higher in patients with IgAN compared with control (P<0.01). Even in patients with IgAN revealed trace proteinuria (less than 0.3g/gCr), urinary Gd-IgA1 were definitely detected. Moreover, urinary Gd-IgA1 decreased response to therapy (P<0.001). Urinary Gd-IgA1 levels were well correlated with proteinuria in patients with IgAN (P<0.001), but not in control.

Conclusions: Urinary Gd-IgA1 was elevated in patients with IgAN. The fraction of Gd-IgA1 from the glomerular deposits may be excreted into the urine, as serum levels of Gd-IgA1 did not correlate with urinary Gd-IgA1. Importantly, urinary Gd-IgA1 may be an early biomarker compared with proteinuria in patients with IgAN. U rinary Gd-IgA1 is also useful to determine disease activity. Urinary Gd-IgA1 may thus represent a disease-specific biomarker of IgAN.

Funding: Government Support - Non-U.S.

TH-PO823

Circulating Autoantibodies in Lupus Nephritis Patients Target the Cytoskeleton Linking Protein, Moesin, and Disrupt Podocyte Actin Cytoskeleton

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Background: The pathogenesis of lupus nephritis (LN) is characterized by glomerular deposition of immune complexes (IC) containing nucleosomes and anti-nuclear autoantibodies. However, proteomic studies in LN and other glomerular diseases identified a number of autoantibodies against tissue proteins. We used a targeted proteomic approach combining immunoblot analysis of human podocyte membrane proteins using sera from LN patients with high performance MS to identify moesin as a candidate target protein. We showed that autoantibodies against moesin were present in the sera of patients with proliferative LN and glomeruli in renal biopsies from those patients showed increased expression of moesin. This study tested the hypothesis that autoantibodies to moesin participated in IC formation in LN.

Methods: Frozen remnant kidney biopsy samples from patients with proliferative LN were cut into 4-6 μm sections (n= 5) and incubated with anti-moesin antibody at 1:50 overnight followed by sequential incubation with: 1) fluorescent secondary antibody at 1:200 2) fluorescent conjugated anti-human IgG at 1:200. Images were obtained on confocal microscopy. A human-derived podocyte cell line was cultured on collagen-coated glass bottom dishes at 37°C for 8-10 days. Cells were serum starved with 0.5% FBS medium 24 h before anti-moesin antibody, IgG controls, or vehicle was added for 24 h. Actin organization was detected by staining with rhodamine-phalloidin for 30 minutes. Rhodamine staining on confocal microscopy images was analyzed visually and for actin anisotropy by FibrilTool.

Results: To determine if moesin was contained in IC, renal biopsies from patients with proliferative LN were examined for co-localization of moesin and IgG. Confocal images showed minimal co-localization, indicating anti-moesin autoantibodies were not participating in IC formation. As moesin is a cytoskeletal linking protein, the ability of anti-moesin to disrupt podocyte actin organization was tested. Podocytes cultivated with anti-moesin antibodies, but not control IgG or vehicle, showed loss of actin cytoskeletal organization and decreased anisotropy.

Conclusions: We conclude that autoantibodies against moesin may participate in glomerular injury in LN by disruption of podocyte cytoskeletal organization.

Funding: NIDDK Support

TH-PO824

A Humanized Mouse Model of SLE and LN

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Background: Lupus Nephritis (LN) is a common complication of systemic lupus erythematosus (SLE) with unclear etiology and limited treatment options. Single Nucleotide Polymorphisms (SNPs) in ITGAM (which codes for CD11b) strongly associate with disease pathogenesis. Yet, the role of these mutations in disease pathobiology is unclear, primarily because of a lack of experimental models. Additionally, while available spontaneous or induced mouse models of SLE have advanced our understanding of lupus, none of them replicate human disease very well. Here, we present a novel humanized mouse model of SLE and LN that better mimics the human disease and, we hope, will greatly improve our understanding of the cellular and genetic determinants driving lupus and aid in the development of novel therapeutics.

Methods: Peripheral blood mononuclear cells (PBMCs) were transferred from healthy donors or SLE patients into NSG mice (Healthy-NSG and SLE-NSG). Weekly blood and urine samples were collected and humanized mice were monitored for lupus symptoms until end-point at 6-weeks post engraftment when they were sacrificed and tissues, serum and blood were harvested for further analysis.

Results: Using our optimized protocol, the engraftment of healthy and SLE PBMCs was 100% successful in the NSG mice. We observed an average of 78% human CD45+ cells in the spleens at 6 weeks post engraftment. Interestingly, mouse CD11b+Gr1+ cells and human CD14+ cells were significantly elevated *in vivo* in SLE-NSG mice as compared to healthy-NSG mice. Within 1 week, SLE-NSG mice also lost whiskers and developed alopecia. Histopathological analysis of nasal dermis showed increased epidermal thickness and leukocyte density. Similar to human PBMC donors that displayed renal decline, SLE-NSG mice also showed significantly elevated levels of serum anti-dsDNA and suPAR, and significantly reduced kidney function, as indicated by elevated levels of proteinuria, renal leukocyte infiltration, renal fibrosis and glomerular damage.

Conclusions: This novel humanized SLE/LN model exhibits several clinical manifestations of human lupus and is an important tool to test therapies.

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TH-PO825

Clinical Associations with Serum Syndecan-1 Level in Patients with Lupus Nephritis

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Background: Cardiovascular disease is an important long-term complication in patients with lupus nephritis. The endothelial glycocalyx regulates the adhesiveness of circulating cells to vascular endothelial cells and vascular permeability. Syndecan-1 is a component of the endothelial glycocalyx, and syndecan-1 shedding occurs in endothelial cell activation or injury.

Methods: Serial serum samples from patients with biopsy-proven Class III/IV lupus nephritis were obtained at intervals of 3-4 months over two years. In addition, paired samples with one obtained during flare and the other during remission were included. Sera from age- and sex-matched patients with IgA nephropathy (IgAN), SLE patients without nephritis, and healthy subjects were included as controls (n=25 for each group). Serum syndecan-1 level was determined by ELISA.

Results: Four hundred and sixty sera from 29 lupus nephritis patients (20 females and 9 males; age 39.0±10.2 years; disease duration 7.6±8.6 years) were studied. Serum syndecan-1 level was significantly higher during active lupus nephritis compared with remission, and also the IgAN, non-renal lupus, and healthy control groups (P<0.001, for all). Syndecan-1 level correlated with SLEDAI (r=0.535, P<0.001), anti-dsDNA antibody level (r=0.407, P=0.003), serum creatinine level (r=0.262, P=0.05), proteinuria (r=0.571, P<0.001), and inversely correlated with serum C3 (r=-0.443, P=0.001) and albumin levels (r=-0.568, P<0.001). Circulating syndecan-1 level showed a temporal relationship with disease activity and changes in anti-dsDNA antibody and C3 levels. ROC curve analysis showed that serum syndecan-1 level distinguished active lupus nephritis from healthy subjects with sensitivity and specificity rates of 96.3% and 96.0% respectively, from IgAN patients with respective rates of 85.2% and 91.3%, and from non-renal lupus patients with respective rates of 85.7% and 70.4% (P<0.0001, for all).

Conclusions: Active lupus nephritis is associated with increased circulating syndecan-1 level, and thus may contribute towards the pathogenesis of cardiovascular complications in patients with lupus nephritis.

Funding: Government Support - Non-U.S.

TH-PO826

Complement Activation in Renal Thrombotic Microangiopathy Associated to Systemic Lupus Erythematosus: An Exploratory Analysis

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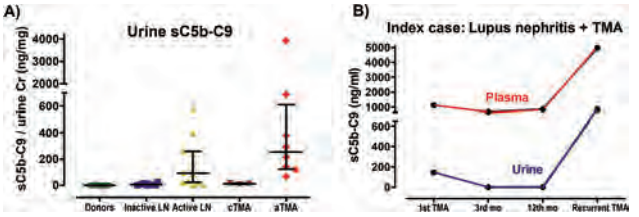
Background: Renal thrombotic microangiopathy (TMA) in SLE is a rare and severe manifestation with dismal prognosis. While complement participation in lupus nephritis (LN) has been studied, its role in SLE renal TMA remains lesser explored.

Methods: To study complement proteins we included patients with SLE-renal TMA (n=12), active biopsy-proven LN (n=12), inactive SLE patients (n=9) and living kidney donors (n=5). Renal TMA patients were divided into acute TMA (aTMA) or chronic TMA (cTMA) according to histopathology. Terminal complement pathway activation was evaluated by a soluble C5b-C9 ELISA. Alternative pathway urine C3d fragment was evaluated with a specific monoclonal antibody. Groups were compared by Kruskal-Wallis test and correlations obtained by Spearman's rho.

Results: Of 12 patients with SLE renal TMA, 3 (25%) had positivity for aPL antibodies and 9 corresponded to aHUS. Renal TMA patients presented with higher arterial pressure, serum creatinine and dsDNA titers; while hemoglobin, platelets and haptoglobin levels were lower than in active LN. Notably, renal TMA patients had few systemic manifestations of microangiopathic hemolytic anemia. Renal TMA biopsies showed higher global sclerosis, interstitial fibrosis and tubular atrophy. Plasma and urine sC5b-C9 titers in both renal TMA and active LN groups were higher than in inactive LN and kidney donors. Urine sC5b-C9 titers were higher in renal aTMA compared to cTMA (Figure A). In the Figure B we present the case of a patient with SLE and 2 renal TMA episodes. As shown, urine and plasma sC5b-C9 titers rose during the acute event and diminished after treatment. There was a trend for higher urine C3d fragment in aTMA compared to cTMA and active LN. There was a correlation between urine sC5b-C9 titers and serum creatinine (r=0.308, p=0.017) and proteinuria (r=0.686, p<0.001).

Conclusions: There is activation of complement pathway in renal TMA evidenced by the elevation of complement protein's fragments. It should be further explored if these tests may be of use to follow-up the course of the disease.



TH-PO827

Hepcidin Modulates Macrophage Iron Metabolism to Attenuate Lupus Nephritis

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Background: Lupus nephritis (LN) is an end-organ manifestation of systemic lupus erythematosus (SLE) mostly affecting the female population. Renal inflammation, macrophage recruitment and proliferation are associated with worse outcome in LN. Hepcidin is a primary regulatory of macrophage iron metabolism and phenotype. The role of Hepcidin or iron transport has not been investigated in lupus. We hypothesized that hepcidin would mitigate LN by targeting macrophage responses.

Methods: 8-week-old femaleMRL/*lpr* mice (a spontaneous model of SLE) were treated twice a week with saline or 50 µg of hepcidin (i.p) for 10 weeks, following which outcomes like microalbuminuria, histopathology, and other markers of macrophage inflammation and proliferation were examined. In-vitro, macrophages (J774A) were treated with Hepcidin and stimulated with Polyinosinic-polycytidylic acid (Poly (I:C)) or M-CSF1 to evaluate inflammatory and proliferative response.

Results: Saline-treated mice developed severe LN by 18 weeks of age as indicated by high microalbuminuria, fibrosis, renal Cox-2, IL-6, CXCL-1 and M-CSF transcripts, immune complex deposits, iron accumulation and an infiltration of F4/80+ve macrophages. Hepcidin treatment significantly reduced all these manifestations of LN. There was an increase in renal H-ferritin and a concomitant decrease Rrm-1 and Rrm-2, iron dependent enzymes required for DNA synthesis. This was associated with a reduction in Ki-67 positive macrophages and other cells within the kidney. In-vitro hepcidin induced H-ferritin in macrophages and reduced their labile iron (Fe^{2+}) content. H-ferritin^{hi}macrophages secreted less IL-1bfollowing Poly (I:C) stimulation and proliferated less in response to M-CSF1.

Conclusions: We demonstrate a novel protective effect of hepcidinagainst LN which could open new therapeutic approaches to treat LN. Hepcidin induces H-ferritin that lowers labile iron and reduces inflammatory response and macrophage proliferation, two cardinal features of LN. Renal iron accumulation and increased Cox-2 suggest involvement of Ferroptosis in the pathogenesis of SLE. Further studies are required to investigate whether hepcidin also targets renal parenchymal cells or other immune effectors.

Funding: NIDDK Support

TH-PO828

Urinary Galectin-3 Binding Protein as a Predictive Marker for Lupus Nephritis Flare

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Background: Identifying predictive markers of lupus nephritis (LN) flare has been elusive but is necessary to improve outcomes. Serum galectin-3 binding protein (G3BP) is correlated with interferon signature in active SLE. We aimed to define the specificity of urine G3BP (*u*G3BP) as marker of LN flare and determine its ability to predict flare and response to treatment.

Methods: *u*G3BP protein expression was measured from urine collected at the time of kidney biopsy and compared across multiple glomerular diseases including active LN (n=97), IgA nephropathy (n=27), diabetic nephropathy (n=10), primary membranous nephropathy (n=10), ANCA-associated vasculitis (n=4) and healthy controls (n=20). Additionally, active LN expression was compared to LN remission (n=52). *u*G3BP levels were normalized for urinary creatinine (Cr). To examine uG3BP expression longitudinally, urine from the Ohio SLE cohort study (OSS) of 27 LN patients (44 flares) was measured by ELISA at 5 different time points; -4, -2, flare, +2, and +4 months post flare. *u*G3BP expression was compared between each time point to understand if *u*G3BP is a sensitive marker to predict the development and resolution of inflammation in LN.

Results: *u*G3BP expression was significantly increased in all tested kidney diseases, except ANCA compared to healthy controls ($p<0.0001$). The highest concentration of *u*G3BP was found in active LN (423.79±32.06 ng G3BP/mg Cr). *u*G3BP expression was significantly greater at LN flare compared to controls (423.79±32.06 vs 44.8 ng G3BP/mg cr, $p<0.0001$), IgA nephropathy (423.79±32.06 vs 138 ng G3BP/mg Cr, $p<0.0001$) and remisison LN (423.79±32.06 vs127.5 ng G3BP/mg Cr, $p<0.0001$). *u*G3BP expression increased incrementally from 4 months pre-flare to flare, peaked 2 months post-flare ($p=0.02$ compared to flare levels) and significantly decreased 4 months post-flare ($p=0.01$).

Conclusions: *u*G3BP, while not specific, is highly expressed at LN flare reflecting interferon activation. *u*G3BP expression may predict LN flare but due to limited samples size data are currently inconclusive. Further investigation is warranted. *u*G3BP expression may be a predictive marker of treatment response.

Funding: Commercial Support - Merck KGaA, Germany

TH-PO829

Molecular Profiling of the Kidney in Lupus Nephritis (LN) to Identify Heterogeneity in Different Races and Ethnicities

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Background: Black and Hispanic LN patients have worse kidney outcomes than white patients. Beyond socioeconomic status, we postulated that differential activation/inactivation of molecular pathways during LN flare may contribute to this racial and ethnic difference. To test this hypothesis we examined the intrarenal transcript profiles of African American (AA), Caucasian (Cau) and Caucasian Hispanic (H) patients at their first "induction naïve" LN flare

Methods: Kidney biopsies were done at the first episode of class III or IV LN in 13 AA, 11 Cau, and 8 H patients. Glomeruli were isolated by laser capture microdissection. RNA was analyzed using Nanostring technology. The expression of 579 genes was compared between groups. Transcripts with at least a 2-fold change and $p<0.01$ were considered differentially expressed

Results: Eight transcripts differentiated AA from Cau, one was upregulated. The expression of HLADRA was 2-fold higher and the immune-modulator HLADOB was 2-fold lower in AA compared to Cau. IL-4, a Th2 pathway gene was downregulated in AA compared to Cau. One hundred transcripts differentiated Cau from H. Thirty-three of these were upregulated in Cau compared to H. The top 3 upregulated transcripts were: fibronectin (FN1, fold change (FC) =34.82; p=1.8x10-12), osteopontin (SPP1, FC= 24.43; p=1.27x10-07) and FCER1G (FC 17.68; p=5.28x10-09). Pathway analysis revealed downregulation of INF (A1, A2 and B1) and Th2 signaling in Cau compared to H. Hundred and nine transcripts were downregulated in AA compared to H. The main pathways affected were T helper cell differentiation, Th1 and Th2 activation and T/B cell signaling.

Conclusions: Molecular signatures appear to be different for the same histologic class of LN in different races and ethnicities. The differences in HLA, IL4 and T/B cell signaling genes suggest a greater propensity toward immune activation and inflammation in AA compared to Cau. This may partly explain why AA LN patients have more severe kidney injury. The molecular signature of Cau compared to H suggests more inflammatory disease in Cau but more T cell-mediated immune activation in H

Funding: NIDDK Support

TH-PO830

Podocyte Autophagy Could Protect Renal Injury in Lupus and Might Be a Therapeutic Target

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Background: More recent studies suggested that defects in autophagy contribute to the pathogenesis of SLE, especially in adaptive immunity. Occurrence and progression of lupus nephritis (LN) is the end result of complex interactions between regulation of immune responses and pathological process by renal resident cells, but there is still a lot of missing information for an establishment on the role of autophagy in pathogenesis of LN and as a therapy target.

Methods: Systemic and organ specific etiologies of autophagy were firsly evaluated by autophagy protein quantification in tissue homogenates in MRL$^{lpr/lpr}$ lupus prone and female C57BL mice. Analysis of gene expression was also adopted in human blood and urine sediments. Then, some key mediators of the disease, including complement inactivated serum, IgG from patients with LN (IgG-LN) and IFN-α were chosen to induce podocyte autophagy. Podocyte injuries including apoptosis, podocin derangement, albumin filtration, and wound healing were monitered simultaneously with autophagy steady-state and flux.

Results: Elevated LC3B in kidney homogenates and increased autophagosomes in podocyte from MRL$^{lpr/lpr}$ were observed. In humans, mRNA levels of some key autophagy genes were increased in blood and urinary sediments, and podocyte autophagosomes were observed in renal biopsies from patients with LN. Complement inactivated serum, IgG-LN and IFN-α could induce podocyte autophagy in a time and dosage dependent manner, and by reactive oxygen species production and mTORC1 inhibition, respectively. Autophagy inhibition aggravated podocyte damage whereas its inducer relieved the injury.

Conclusions: Podocyte autophagy could protect renal injury in lupus and might be a therapeutic target.

Funding: Government Support - Non-U.S.

TH-PO831

Urine IP-10 Increased Sensitivity in Lupus Nephritis Detection

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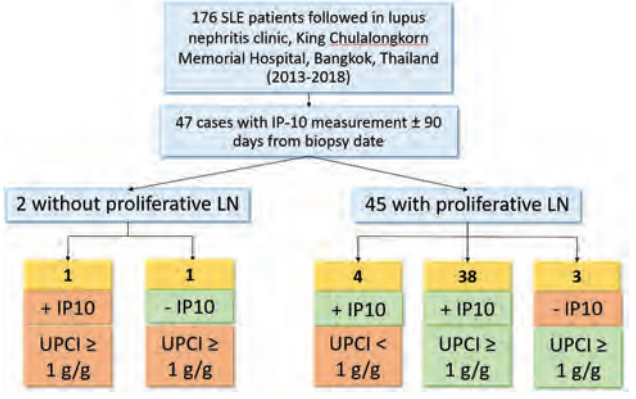
Background: Interferon γ-inducible protein(IP-10) is an important T-helper1 chemokine expressed locally in the kidney of lupus patients. Non-invasive test for urine IP-10 may improve the detection of active lupus nephritis(LN).

Methods: Since 2013, urine IP-10 has been measured in all SLE patients with clinical suspicion of LN at the specialized LN clinic in a tertiary care hospital in Thailand. We retrospectively reviewed the case records of those who underwent renal biopsy from October 2013 to February 2018 and had urine IP-10 measurement within 90 days from date of renal biopsy.

Results: Of 176 SLE patients followed at LN clinic, 47 had renal biopsy with urine IP-10 measurement within the certain period. Urine IP-10 was positive (> 2 log copies number) in 42 out of 45 patients(93%) with biopsy-proven proliferative LN, while proteinuria was found (UPCI > 1) in 41 patients (91%). Two patients who had only renal scarring on biopsy had proteinuria, while urine IP-10 was negative in 1 patient(Figure 1). Four patients with proliferative LN who had positive urine IP-10 without proteinuria were noted for focal podocyte foot process effacement (Table 1). All of them had stable renal function and normalization of C3 without proteinuric flare after 6-month of induction therapy. There were 8 patients who had serial urine IP-10 measurement prior to renal biopsy. In 6 patients, urine IP-10 was positive before proteinuric flare (median 6 months), whereas 2 patients were simultaneously positive for proteinuria and IP-10.

Conclusions: Urine IP-10 enhances sensitivity of LN detection, especially in those without proteinuria. Its levels even increased prior to proteinuric flare in most cases. Combined use of urine IP-10 and conventional markers may increase early detection of LN and ultimately improve renal outcomes

Funding: Government Support - Non-U.S.



Clinical and laboratory characteristics of patients with biopsy-proven proliferative lupus nephritis who had 1) positive urine IP-10 without proteinuria and 2) proteinuria with negative urine IP-10

Subject	ISN/RPS class	Foot process effacement	eGFR	Alb	UA WBC	UA RBC	UPCR	Anti-dsDNA	C3	C4	Indications for renal biopsy
Positive urine IP-10, UPCI <1 g/g											
1	3	Focal	0.62	3.4	20	50	0.97	202.96	46.4	12.3	Active urinary sediment and low complement
2	3	Focal	0.36	3.8	20	5	0.5	800	30	3.44	Active urinary sediment and low complement
3	4	NA	1.24	3.1	20	5	0.59	800	42.3	8.6	Increased creatinine
4	4	NA	0.76	4.3	1	0	0.21	NA	80.9	NA	Unexplained cysts
Negative urine IP-10, UPCI ≥1 g/g											
5	3+5	Diffuse	0.87	3.2	5	20	7.2	151.94	36.1	8.9	Proteinuria
6	3	Diffuse	2.63	NA	20	180	1.62	800	58	10.4	Proteinuria
7	3	NA	3.42	3.7	1	5	9.77	0	39.6	4.84	Proteinuria

TH-PO832

Angiotensin-II Type 1 Receptor Agonist Antibodies Are Prevalent in Lupus Nephritis Patients But May Have Limited Clinical Impact

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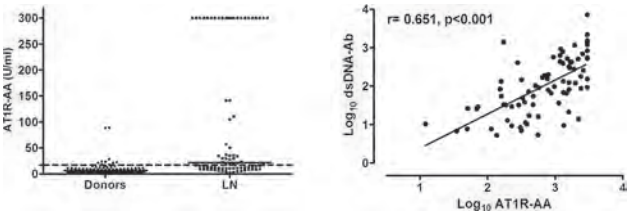
Background: Angiotensin II type 1 receptor agonist antibodies (AT1R-AA) have been associated with hypertension, atherosclerosis and vascular inflamation in human diseases.

Methods: The aim of the study was to evaluate the prevalence of AT1R-AA in lupus nephritis (LN) and their association to hypertension and vascular damage. Eighty LN patients were evaluated by ambulatory blood pressure monitoring (ABPM), carotid Doppler ultrasound and renal biopsy vessel morphometry. AT1R-AA were evaluated in 112 kidney donors as a control group. AT1R-AA response to induction to remission therapy was followed for 6 months. Variables were compared by Fisher exact test or Kruskal-Wallis test. For correlations, serological titers were log-transformed and evaluated by Pearson test.

Results: Plasma AT1R-AA were positive in 45 (56.3%) and 23 (28.8%) had titers >250u/ml (Figure 1). AT1R-AA titers correlated with double-strand DNA antibodies' (dsDNA-Ab) titer (r=+0.651,p<0.001, Figure 1) and serum complement fragments C3 (r=-0.289,p=0.009) and C4 (r=-0.451,p<0.001). 77% of patients had an abnormal ABPM result, with 58% and 23% manifesting a diminished or absent dipping respectively. There was no association between AT1R-AA and ABPM blood pressure levels. Abnormal carotid intima-media thickness was found in 7.8%, with a trend for a greater CIMT in patients with the highest AT1R-AA titers. Subintimal fibrosis >10% was found in 46.3% of kidney biopsies. There was no association between AT1-AA titers and subintimal fibrosis. AT1R-AA response to treatment was evaluated in 40 patients. AT1R-AA titers course followed that of the dsDNA-Ab but was not associated with the response to treatment.

Conclusions: AT1R-AA are highly prevalent in lupus nephritis patients and closely correlate with serological activity but their pathogenic role is questionable. AT1R-AA cannot be recommended to be measured routinely.

Funding: Government Support - Non-U.S.



A) AT1R-AA in kidney donors and LN patients. B) Correlation between AT1R-AA and dsDNA antibodies.

TH-PO833

B Cell Subsets and Signatures in Lupus Nephritis Patients Receiving Mycophenolate or Azathioprine Maintenance

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Background: Mycophenolate mofetil (MMF) and azathioprine (AZA) are standard maintenance agents for lupus nephritis (LN), and recent data suggested that MMF confers lower long-term flare risk. Aberrant B cell profiles have been implicated in LN pathogenesis, but the effect of MMF and AZA on B cell subsets and related signatures has not been investigated.

Methods: We measured the B cell subsets and serum and intracellular levels of relevant B cell signatures (miRNA148a, BACH1, BACH2 and PAX5) in stable LN patients receiving MMF or AZA (n=10 in each group), combined with low-dose prednisolone, as maintenance immunosuppression.

Results: The MMF group showed higher % of circulating naïve B cells and lower % of plasma cells (4.8±5.2% and 0.2±0.3% respectively, compared with 0.9±1.5% and 0.8±0.9% in AZA group, p=0.029 and 0.043), but had no difference in circulating memory B cells (p=0.97). The MMF group also showed lower plasma cell/naïve B and memory B/naïve B ratios (0.1±0.2 and 1.3±2.1 respectively, compared with 1.7±1.4 and 1.7±1.1 in AZA group, p=0.003 and 0.023). The MMF group showed numerically higher intracellular BACH1, BACH2 and PAX5 in naïve B cells (relative expression (RQ): 1.2±0.5, 1.4±0.2 and 2.6±1.7 respectively compared with AZA group; p>0.05, for all) (Figure 1A) and in plasma cells (RQ: 1.3±0.1, 1.4±0.3 and 1.3±0.6 respectively compared with AZA group; p>0.05, for all) (Figure 1B), but showed no difference in serum and intracellular miRNA148a.

Conclusions: The alterations in B cell subsets and related signatures might contribute to the differential risk of relapse in patients receiving MMF or AZA maintenance.

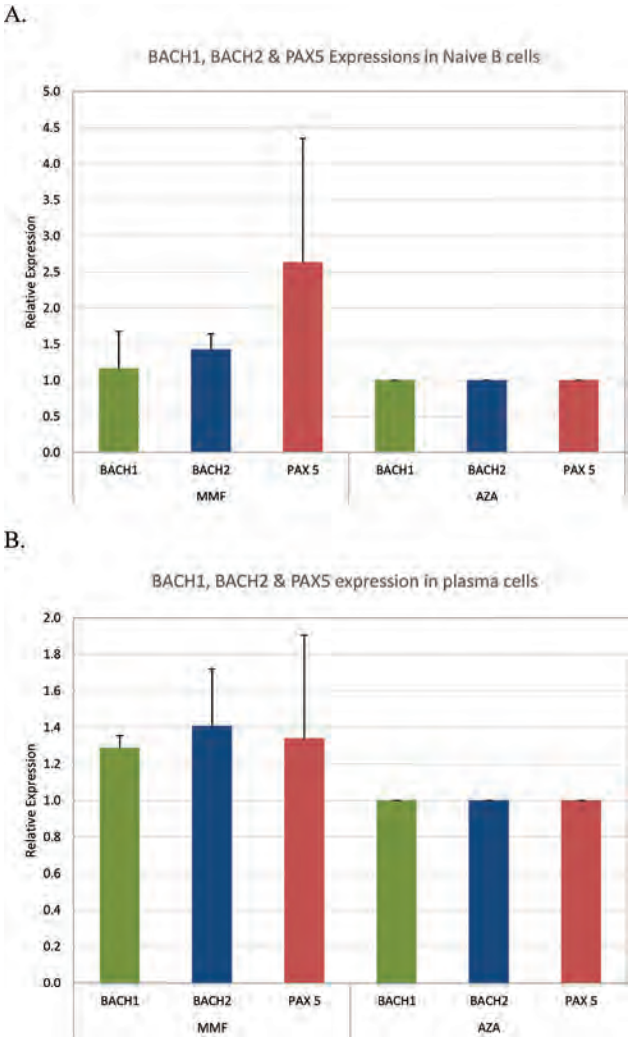

Figure 1. Intracellular BACH1, BACH2 and PAX5 expression in (A) naïve B cells and (B) plasma cells of patients receiving mycophenolate or azathioprine maintenance.

TH-PO834

Histologic vs Clinical Remission in Proliferative Lupus Nephritis at 6 Months - An Experience from a State Run Tertiary Care Centre in Southern India

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Background: Aim and objective of this study is to describe the renal histology of the second biopsy and correlate histopathological remission with clinical remission at 6 months.

Methods: The study conducted in Department of Nephrology, Institute of Nephro-Urology, Victoria Hospital Campus Bangalore, India between Oct 2015 and Nov 2017. A total of 50 consecutive patients with biopsy proven Proliferative Lupus Nephritis were included in the study. Clinical response was defined as complete (CRR), partial (PRR) or non-response (NRR) according to recent definitions. Histological response (HR) was defined as Class I, II or III/IV-C on repeat biopsies.

Results: 1/3 rd cases who were achieved complete remission clinically failed to achieve histological remission. Out of 19 patients 12(63%) had transformation to favorable class in CRR group. Out of 19 patients 12(63%) in PPR group and out of 12 patients 8(66%) in NRR group had unfavorable class at 6 months. Though Chronicity Index increased in all clinical subgroups, non responders had statistically significant increased CI.

Conclusions: The protocol renal biopsies performed at six months demonstrated an increase in chronicity, especially within the same histological class. 1/3rd patients with complete remission group had active lesions at the end of induction treatment, questioning the current induction therapy of 6 months which may not be sufficient. More RCTs are needed to test whether repeated biopsies should be considered as a part of the evaluation of treatment response in LN.

TH-PO835

The Composition of the Human Nasal Microbiome in Granulomatosis with Polyangiitis: A Pilot Study

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Background: Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is a multi-system disease predominantly affecting the ear, nose and throat (ENT) tract, the lower respiratory tract and the kidneys. A role for *Staphylococcus aureus* nasal colonization in GPA has been proposed and thus we undertook a study to determine the role of the nasal microbiome in GPA.

Methods: We investigated the nasal microbiome by culture, bacterial 16S rRNA profiling, and shotgun metagenomic sequencing in patients with either active or inactive GPA, disease controls (microscopic polyangiitis or eosinophilic GPA), healthy healthcare professionals and healthy household controls.

Results: Presence of *S. aureus* as assessed by nasal culture could be detected in eight out of 12 active GPA patients (66.7%), which was more frequent compared to inactive patients (34.1%). Beta-diversity analysis revealed significant differences in the abundance of staphylococcal species between active GPA and healthy controls (p=0.0007) and disease controls (p=0.0023), while a correlation between *S. aureus* and active disease (p=0.0075) could be observed by Spearman correlation analysis. The presence of *Staphylococcus epidermidis* was associated with healthy controls (p=0.042). *Staphylococcus pseudintermedius*, generally assumed to be a dog- and cat-pathogen, showed an abundance of 13.01% among Staphylococci.

Conclusions: Our study offered new insights into the complex nasal microbiome of patients with GPA. We observed an association between active disease and *S. aureus*. Longitudinal studies are necessary to investigate the potential relationship of microbiome changes on the relapse rate of patients with GPA.

TH-PO836

Plasma Calprotectin Is a Marker of Stable Remission in ANCA Vasculitis

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Background: In ANCA vasculitis, an increase in serum calprotectin (S100A8/9) was implicated as a marker of relapse and inflammation, but levels did not normalize during remission. Serum may not allow sensitive measurement of S100A8/9. We sought to determine if S100A8/9 is best measured in plasma or serum and if it is a marker of disease activity and remission in ANCA vasculitis.

Methods: S100A8/9 was measured by ELISA (BioLegend) in 16 paired serum and plasma samples. Plasma levels were also tested in 31 patients during active (BVAS>3, 15 MPO, 16 PR3) and remitting disease and in 14 age/gender matched healthy subjects. Additionally, 8 patients (4 MPO, 4 PR3) in long term remission off therapy (LTROT) for ≥5 years were evaluated and compared to healthy subjects.

Results: Serum measures of S100A8/9 averaged 2.90 μg/mL higher and had a higher standard deviation than plasma measures (4.29 vs 4.02 respectively). Thus, plasma measures were used for all analyses.

Conclusions: Plasma S100A8/9 levels were elevated during active disease. Levels decreased during remission, but remained higher than in healthy controls. Patients in LTROT, however, had plasma S100A8/9 levels similar to healthy subjects. These findings suggest S100A8/9 is elevated during active disease and decreases, but remains slightly elevated, during remission, possibly due to subclinical inflammation. Levels may continue to decrease and normalize in long term remission off therapy. Prior studies may have observed artificially elevated levels of S100A8/9 due to measurements obtained in serum rather than plasma.

Funding: NIDDK Support

Measurement of plasma S100A8/9 (ug/mL) in ANCA vasculitis patients and healthy subjects

Groups		Active Disease	Disease Remission	Healthy Subjects	P Value Paired Act vs Rem*	P Value Remission vs Healthy Subjects**
All paired patients	N Median (IQR)	31 2.56 (1.90, 5.31)	31 1.60 (1.13, 2.00)	14 0.86 (0.77, 1.26)	<.0001	0.009
MPO patients	N Median (IQR)	15 2.99 (1.99, 5.26)	15 1.60 (1.23,1.98)	14 0.86 (0.77, 1.26)	0.002	0.005
PR3 patients	N Median (IQR)	16 2.54 (1.82, 6.66)	16 1.58 (0.86, 2.28)	14 0.86 (0.77, 1.26)	0.018	0.085
LTROT patients	N Median (IQR)		8 1.10 (0.77, 1.44)	14 0.86 (0.77, 1.26)		0.517

*P value was calculated by signed rank paired test. ** P value was calculated by Wilcoxon two sample test.

TH-PO837

Myeloperoxidase-ANCA-Positive Granulomatosis with Polyangiitis Is a Distinct Subset of ANCA-Associated Vasculitis: A Retrospective Analysis Of 455 Patients from a Single Center in China

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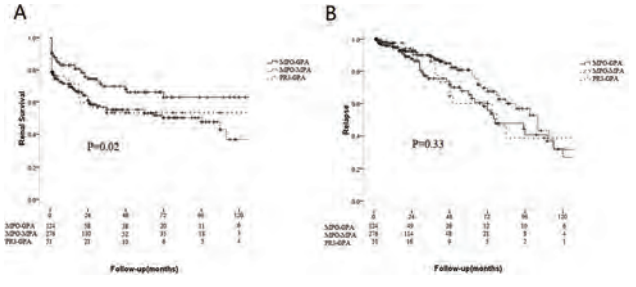
Background: Antineutrophil cytoplasmic antibody (ANCA) directed to proteinase 3 (PR3) used to be considered the serologic marker for granulomatosis with polyangiitis (GPA). However, patients with myeloperoxidase (MPO)-ANCA positive GPA have been increasingly reported. The aim of this study was to analyze the clinical and pathological characteristics and outcome of Chinese patients with MPO-ANCA positive GPA.

Methods: The clinical and renal histology data, renal outcomes, response to treatment, relapse and mortality were compared between patients with MPO-ANCA positive GPA and MPO-ANCA positive microscopic polyangiitis (MPA) as well as proteinase 3 (PR3)-ANCA positive GPA.

Results: 455 patients with ANCA-associated vasculitis (AAV) were recruited in this study. 276/455 patients were classified as MPO-ANCA positive MPA, 4/455 patients were classified as PR3-ANCA positive MPA,124/455 were MPO-ANCA positive GPA and 51/455 were PR3-ANCA positive GPA. Compared with MPO-ANCA positive MPA patients, MPO-ANCA positive GPA patients had significantly higher BVAS score and milder renal lesion at diagnosis. The probability of developing ESRD was significantly higher in patients with MPO-ANCA positive MPA than MPO-ANCA positive GPA. MPO-ANCA positive GPA patients were likely to have relapse than MPO-ANCA positive MPA patients. Compared with PR3-ANCA positive GPA patients, MPO-ANCA positive GPA patients had significantly higher proportion of female, less constitutional symptoms and milder renal lesion at diagnosis.

Conclusions: Patients with MPO-ANCA positive GPA should be regarded as a unique subset of AAV. This subset of AAV patients had relatively milder renal injury. Although ANCA specificities play an important role in differentiating AAV, taking the disease type together to classify AAV may be more rational.

Funding: Government Support - Non-U.S.



(A) Renal survival of the three subsets of patients. (B) Relapse of the three subsets of patients.

TH-PO838

A Staphylococcal Plasmid Encoded Peptide Induces Anti-Myeloperoxidase Nephritogenic Autoimmunity

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Background: Loss of tolerance to MPO in ANCA-associated glomerulonephritis (GN) is poorly understood. It is unknown whether molecular mimicry plays any role in this process. We tested whether microbial peptides homologous to a dominant pathogenic MPO CD4+ T cell epitope ($MPO_{409-428}$), relevant to several MHCII and lying within an MPO epitope hot spot, would induce anti-MPO autoimmunity.

Methods: Immunity to MPO and $MPO_{409-428}$ was studied in microbial peptide immunized C57BL/6 (B/6, I-A^b), BALB/c (I-A^d/E^d) and HLA-DR15 transgenic mice (proliferation, IFN-γ and IL-17A ELISPOT). Anti-MPO GN and anti-MPO immunity in response to peptides, proteins (MPO/ovalbumin as positive/negative controls) and *S.aureus* strains with/without plasmids carrying the relevant 6-phosphogluconate dehydrogenase (6PGD) sequence were studied in B/6 mice (I-A^b/$MPO_{415-428}$ tetramers, cytokines, MPO-ANCA IIF/ELISA, neutrophil ROS production, MPO-ANCA transfer). Anti-6PGD antibodies (Ab) were measured in sera of healthy humans and patients.

Results: The 4 most homologous microbial peptides were immunogenic but did not induce anti-MPO autoreactivity. However, a plasmid-derived peptide from 6PGD (6PGDp) with similar critical binding residues for $MPO_{409-428}$ in B/6, BALB/c and DR15+ mice, found in some *S.aureus* strains, induced expansion of $MPO_{415-428}$ tetramer+CD4+ cells, anti-MPO T cell autoimmunity (to $MPO_{408-428}$ and whole MPO) and bioactive MPO-ANCA in B/6 mice. 6PGDp induced anti-MPO autoreactivity in mice with different MHCII (I-A^d/E^d and DR15). Related 6PGD sequences from other *S.aureus* strains did not induce anti-MPO responses. Healthy human and vasculitis patient sera contained anti-6PGD Ab, demonstrating its immunogenicity in humans. 6PGDp-immunized mice developed GN when MPO was deposited in glomeruli by anti-basement membrane globulin. Immunization with *S.aureus* containing a plasmid with the mimic 6PGD sequence, or another *S.aureus* strain transformed with a different plasmid expressing the 6PGD mimotope, also induced anti-MPO GN with anti-MPO cellular and humoral autoimmunity, showing that plasmids with this sequence induce nephritogenic anti-MPO autoimmunity.

Conclusions: A microbial plasmid encoded peptide induces anti-MPO autoimmunity via molecular mimicry implicating plasmids, as bacterial replicons capable of horizontal gene transfer, in autoimmune disease.

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TH-PO839

Integrated Proteomics and DNA Analysis of Pathogenic IgG from Patients with Anti-GBM Nephritis

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Background: Anti-glomerular basement membrane (anti-GBM) nephritis (Goodpasture's disease) is marked by immune destruction of kidneys and lungs triggered by IgG autoantibodies that bind the NC1 domain of the α3 chain of collagen IV. Current therapy consists of toxic immunosuppression. Selective therapeutic targeting of pathogenic IgG and B cells is highly desirable, but precluded by the lack of information about their structural basis.

Methods: To address this problem, we used an innovative approach validated in vaccine biology. $F(ab')_2$ fragments were isolated by pepsin digestion from circulating IgG of two patients with active anti-GBM nephritis and purified on α3(IV)NC1 affinity columns. Antigen-binding (Ag+) and non-binding (NB) flow-through $F(ab')_2$ were trypsin digested and evaluated by liquid chromatography-tandem mass spectrometry. Peptide spectra were analyzed using a reference library generated from productively rearranged Ig heavy chains (n=11903) in the International ImMunoGeneTics database and formatted for use by the Mascot search engine.

Results: 826 unique spectral matches were identified. 41 peptides were identified in both patients' Ag+ $F(ab')_2$ and absent in NB flow-through $F(ab')_2$. All Ag+ matches aligned to Ig heavy chain variable region (VH) genes, primarily in conserved framework regions. Notably, 32% aligned to alleles of a VH gene with an unusual highly hydrophobic heavy chain complementarity determining region 2 (HCDR2) that was previously associated with autoreactivity and reported to encode a human anti-α3(IV)NC1 collagen monoclonal Ig derived from a humanized immune system mouse.

Conclusions: We find evidence of shared and biased gene use among pathogenic IgG that bind α3(IV)NC1 collagen in patients with anti-GBM nephritis. This suggests that patients' GBM-binding IgG contain unusual targetable motifs in their Ag binding sites. Future interrogation of the spectra using patient-specific Ig DNA reference libraries, generated from patients' lymphocytes, will permit identification of non-genomic-DNA-templated peptide sequences that are found within HCDR3, a unique region of the Ag binding site created in B cells during VH-DH-JH gene recombination and for which sequences are not present in public databases. Rare motifs will provide additional therapeutic targets for personalized disease management.

Funding: NIDDK Support, Other NIH Support - NIH National Center for Advancing Translational Sciences (NCATS) and NIEHS, Veterans Affairs Support

TH-PO840

Modulation of Immune Response in Kidney Lymph Node During Crescentic Glomerulonephritis

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Background: Crescentic glomerulonephritis (GN) is an inflammatory condition characterized by a rapid deterioration of renal function. Previous studies of crescentic GN have focused on immune activation in the kidney. However, the role of fibroblastic reticular cells (FRCs), the prominent cells comprising the stromal compartment of the kidney lymph node (KLN), has not been studied in this condition.

Methods: We induced nephrotoxic serum nephritis (NTN), a classic experimental model of crescentic GN, in mice. We investigated the contribution of FRCs in the KLN to the activation of the immune response in crescentic GN using flow cytometry, RT-PCR, hematoxylin and eosin (H&E) staining, and immunofluorescence staining.

Results: Investigation of the microarchitecture of the KLN during NTN revealed an increase in the deposition of extracellular matrix fibers by FRCs, associated with the propagation of specialized blood vessels known as high endothelial venules, through which lymphocytes traffic into the lymph node, as well as the expansion of the lymphatic vasculature. The KLN contained an expanding population of pro-inflammatory $CD4^+$ effector memory T cells and Th17 cells. Removal of the KLN, depletion of FRCs, and treatment with anti-podoplanin antibody each resulted in a reduction of renal injury.

Conclusions: The pro-inflammatory activity of FRCs in the KLN is crucial to the propagation of the immune response in crescentic GN. Our findings can serve as a basis for the development of immunosuppressive therapy for crescentic GN directed towards modulating the activity of FRCs.

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TH-PO841

Targeting Neutrophil Serine Proteases in ANCA-Associated Vasculitis

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Background: ANCA-activated neutrophils and monocytes cause necrotizing vasculitis. Enzymatically active neutrophil serine proteases (NSPs) contribute to the injury. NSPs include neutrophil elastase (NE), cathepsin G (CatG), and proteinase 3 (PR3) that also provides a major ANCA antigen. NSPs are generated from inactive zymogens by cathepsin C (CatC) during neutrophil maturation in the bone marrow. CatC loss-of-function mutations prevent NSP maturation leading to zymogen degradation. We characterized NSPs in humans and mice and tested the hypothesis that pharmacological CatC inhibition eliminates NSPs in a neutrophil differentiation model and reduces PR3-ANCA induced respiratory burst as well as neutrophil-mediated endothelial injury.

Methods: We prepared highly purified human and murine neutrophils and monocytes. We assessed NSP proteins by immunoblotting and flow cytometry, and proteolytic activity using specific FRET substrates. We employed a reversible cyclopropyl nitrile CatC inhibitor (IcatC) to reduce NSPs in neutrophils differentiated from $CD34^+$ HSC *in vitro*. We assessed superoxide production by ferricytochrome C reduction and endothelial injury by phalloidin staining.

Results: Human and murine neutrophils and monocytes expressed PR3, NE, and CG by immunoblotting and flow cytometry. All three NSPs were enzymatically active by FRET assays. Protein amounts and proteolytic activity were significantly higher in neutrophils compared to monocytes. *In vitro* differentiated human neutrophils progressively expressed active NSPs during maturation. IcatC significantly reduced NSP proteins and enzymatic activity. PR3 surface protein decreased by 79%±10% ($p<0.01$), cellular protein by 82%±4% ($p<0.001$) and PR3 enzymatic activity by 98%±1% ($p<0.001$). Anti-PR3 antibodies provoked less superoxide release (46%±6% of control, $p<0.01$) in neutrophils differentiated in the presence of IcatC compared to buffer control (n=4). In addition, supernatants from neutrophils that were differentiated in the presence of IcatC caused less cytoskeletal damage in HUVECs.

Conclusions: Pharmacological CatC inhibition down-regulates NSPs, abrogates PR3-ANCA induced respiratory burst in an *in vitro* neutrophil differentiation model, and reduced neutrophil-mediated endothelial damage. CatC inhibition may provide a future treatment strategy in ANCA vasculitis.

Funding: Government Support - Non-U.S.

TH-PO842

Spleen Tyrosine Kinase Expression and Function in Human Neutrophils in ANCA-Associated Vasculitis

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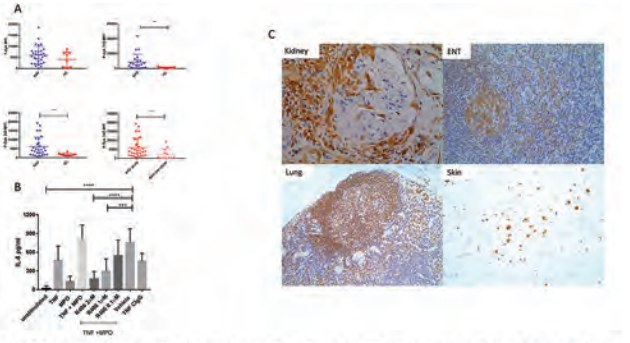
Background: Syk is a cytoplasmic tyrosine kinase which plays an important role in immunoreceptor signalling. Syk is phosphorylated following ANCA-induced neutrophil activation, and we have previously shown that a Syk inhibitor is an effective treatment in experimental autoimmune vasculitis. This study aimed to investigate neutrophil SYK function in patients with AAV.

Methods: Neutrophils were isolated from healthy donors (n=10) and patients with AAV (acute presentation n=21; relapse n=10; remission n=12). Intracellular staining for total (T-Syk) and phosphorylated (P-Syk) was analysed using flow cytometry. Neutrophils were primed with TNFα 2ng/ml and stimulated with 100 μg/ml MPO-ANCA IgG (or control IgG). R406, a small molecule Syk inhibitor, or vehicle was added prior to addition of IgG. RNAscope for Syk mRNA was performed on kidney sections, and IHC for T-Syk on extra-renal AAV tissues including ENT, lung and skin.

Results: There were similar levels of T-Syk present in neutrophils from HC and those with AAV. There was increased Syk phosphorylation at both the 319 and 348 residues in patients with active AAV compared to HC or patients in remission (Figure 1A). When TNFα primed neutrophils were stimulated with MPO-ANCA IgG there was significant IL-8 release, that was inhibited by R406 in a dose dependent manner (Figure 1B). There was evidence of T-Syk in infiltrating inflammatory cells in non-renal sites of AAV (Figure 1C). There was also evidence of Syk mRNA in infiltrating leucocytes in glomeruli from patients with crescentic AAV but not in patients with sclerotic lesions.

Conclusions: Syk is phosphorylated to a greater degree in patients with than in healthy controls indicating greater neutrophil Syk activity in patients with AAV. Syk plays a role in cytokine production from neutrophils which may be pathogenic, and Syk mRNA and protein can be identified at sites of tissue inflammation. These results suggest there may be a role for Syk inhibition in decreasing neutrophil mediated damage in patients with AAV.



A. T-Syk and P-Syk expression in neutrophils from healthy controls (HC) and patients with AAV. Statistical analysis carried out using Mann-Whitney U test: **p<0.01 **B.** IL-8 production by human neutrophils following stimulation with TNFα and MPO-ANCA IgG. Statistical analysis carried out using one way ANOVA with Dunnetts post hoc correction for multiple comparisons. ****p<0.0001, ***p<0.001 **C.** T-Syk expression in vasculitis.

TH-PO843

P2X7 Knockout Does Not Protect from Experimental Glomerulonephritis and Vasculitis

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Background: P2X7 is an ionotropic receptor for extracellular ATP previously shown to be important in inflammation and fibrosis. It may also play a role in autoimmunity. Both strains of P2X7 deficient mice are incomplete knockouts and have generated conflicting results. Therefore we have assessed the importance of P2X7 in autoimmunity and glomerulonephritis (GN) using a novel P2X7 knockout (KO) rat & a small molecule P2X7 inhibitor.

Methods: Three in vivo models, nephrotoxic nephritis (NTN), experimental autoimmune GN (EAG) and experimental autoimmune vasculitis (EAV) were used to induce disease in P2X7 KO and WKY wild type (WT) rats. P2X7 antagonist (A438079) or vehicle (sterile water) was administered twice daily for 6 days after induction of NTN. Disease severity and development of autoimmunity were assessed in each model (NTN- day 7 and 28, EAG- day 28, EAV- day 42).

Results: P2X7 KO rats were not protected from disease in NTN, EAG or EAV models. P2X7 KO and WKY WT rats had similar renal function, urinary abnormalities, histological disease severity, lung injury and circulating and deposited antibody. Figure 1 shows a representative EAG experiment. However, when P2X7 antagonist (A438079) was administered to rats with NTN from day 0-6 both WT and P2X7 KO rats were protected from disease with marked improvement in urinary abnormalities, renal function and histological disease severity (Figure 2).

Conclusions: P2X7 KO rats are not protected from 3 distinct models of glomerular disease. However, the P2X7 antagonist had a marked protective effect from renal injury in both P2X7 KO and WKY WT rats, suggesting that its effect is unrelated to P2X7 and is off-target.

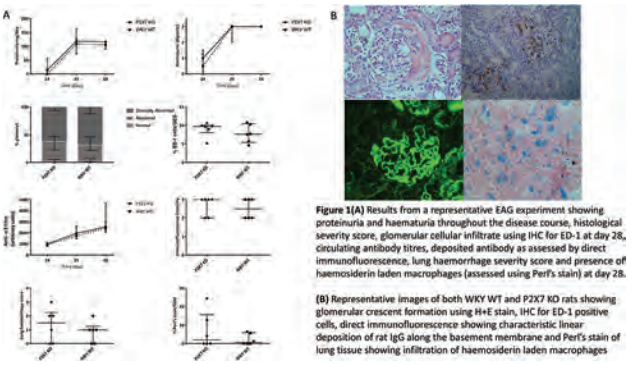

Figure 1(A) Results from a representative EAG experiment showing proteinuria and haematuria throughout the disease course, histological severity score, glomerular cellular infiltrate using IHC for ED-1 at day 28, circulating antibody titres, deposited antibody as assessed by direct immunofluorescence, lung haemorrhage severity score and presence of haemosiderin laden macrophages (assessed using Perl's stain) at day 28.

(B) Representative images of both WKY WT and P2X7 KO rats showing glomerular crescent formation using H+E stain, IHC for ED-1 positive cells, direct immunofluorescence showing characteristic linear deposition of rat IgG along the basement membrane and Perl's stain of lung tissue showing infiltration of haemosiderin laden macrophages

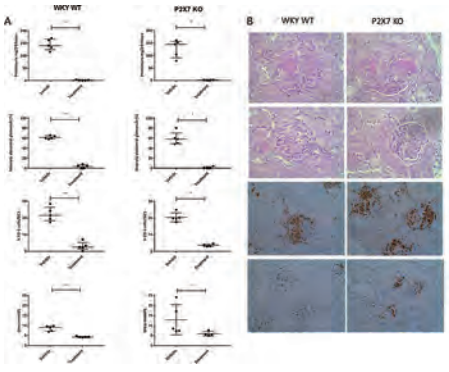

Figure 2(A) Day 7 NTN in P2X7 KO and WKY WT rats treated with P2X7 antagonist or vehicle. Antagonist treated rats in both the P2X7 KO and WKY WT groups have decreased proteinuria, markedly decreased severity of glomerular injury, decreased infiltrating ED-1 positive cells and improved renal function when compared to vehicle treated rats. Statistical analysis performed using Mann-Whitney U test. **p<0.01, *p<0.05

(B) Representative histology showing severe glomerular injury in vehicle treated rats on row 1 and near normal glomeruli in antagonist treated rats on row 2. IHC for ED-1 positive cells with profound cellular infiltrate in vehicle treated rats on row 3 and minimal infiltrate in antagonist treated rats on row 4.

TH-PO844

Critical MPO Epitopes Drive the Adaptive Immune Response in MPO-ANCA Vasculitis

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Background: Autoimmune diseases, including ANCA vasculitis, rely on broad immunosuppression to treat disease. However, research to understand the interactions between human leukocyte antigen (HLA), autoantigen, and effector immune cells, would permit the development of targeted therapies to revolutionize treatment.

Methods: HLA was determined by sequence typing and peptide-HLA interactions were predicted and confirmed by *in silico* and *in vitro* binding studies. Class II tetramers were utilized to identify circulating autoreactive T cells. The clonality of anti-myeloperoxidase (MPO) T cells was determined by TCR sequencing. ELISA studies examined the temporal B cell response to MPO peptides.

Results: Patients with HLA-DPB1*04:01 and/or HLA-DRB4*01:01 exhibit CD4+ T cell reactivity to specific epitopes of MPO contained in tetramers. Autoreactive T cells are enriched for memory T cells as indicated by expression of CD25, CD45RO and CCR7. Additionally, autoreactive cells produce IL-17A upon stimulation. Tetramer positive cells are clonally restricted as evidenced by loss of TCR diversity when compared to naïve and memory T cell populations. Furthermore, this region of MPO is targeted by patient ANCA, and specific antibody reactivity is most detectable at onset of disease. These T and B cell epitopes are contained in a region of MPO that is buried and immune system recognition is dependent on secondary structure.

Conclusions: These data define the specific interactions between the autoantigen, MPO, and the adaptive immune system within ANCA vasculitis. Collectively, this study informs the development of new antigen-specific therapies in ANCA vasculitis and autoimmune disease.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Award Number TL1TR001110

TH-PO845

Identification of PR3-ANCA MPA and MPO-ANCA GPA as Different Subsets of ANCA Disease

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Background: Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are two major clinicopathologic variants of ANCA vasculitis. Typically, MPA and GPA have been associated with MPO-ANCA and PR3-ANCA, respectively. In this study, we detailed the characteristics of the less common subsets PR3-ANCA MPA and MPO-ANCA GPA.

Methods: Patients from the Glomerular Disease Collaborative Network (GDCN) inception cohort were analyzed. Clinicopathologic phenotype was established according to the Chapel Hill Consensus Conference nomenclature. Baseline manifestations, relapses, ESRD, and survival were studied. Fisher's exact test and Wilcoxon rank sum test were used for comparisons. Proportional hazards models were used to evaluate multivariable time to relapse, ESRD, and death for specificity controlling for age, sex, lung and ear, nose, and throat (ENT) involvement, creatinine at diagnosis and induction with cyclophosphamide. Because the GDCN is primarily composed of nephrologist thus resulting in a cohort where biopsy-proven renal involvement was present in almost all patients, prevalence of kidney disease was not compared between groups.

Results: See Table 1. *MPO-ANCA MPA vs PR3-ANCA MPA*: MPA patients with MPO-positivity were older and had lower prevalence of ENT and musculoskeletal manifestations. *MPO-ANCA GPA vs PR3-ANCA GPA*: Patients with MPO-ANCA were older, more likely female, and had lower prevalence of ENT and nervous system involvement. In the proportional hazards models, ANCA serotype was not predictive of relapse, ESRD, or death neither in MPA nor in GPA (Table 1).

Conclusions: PR3-ANCA MPA and MPO-ANCA GPA represent particular subsets of ANCA disease with distinct organ involvement. The impact of these differences on the clinical management warrants further evaluation.

Funding: Other NIH Support - *

TABLE 1. BASELINE CLINICAL MANIFESTATIONS AND OUTCOME OF SPECIFIC ANCA SUBSETS

	MPO-ANCA MPA (n=176)	PR3-ANCA MPA (n= 119)	*P* value	MPO-ANCA GPA (n=39)	PR3-ANCA GPA (n= 105)	*P* value
Demographics						
Age at diagnosis, median (IQR), years	63 (50, 71)	53 (39, 64)	**<0.001**	60 (44, 70)	46 (30, 60)	**0.006**
Female, no. (%)	91 (52)	50 (42)	0.097	23 (59)	39 (34)	**0.012**
Follow-up, months, median (IQR)	36 (12, 73)	37 (10, 87)	0.743	44 (17, 106)	53 (23, 125)	0.1182
Clinical manifestations at disease onset						
Lung involvement, no. (%)	102 (58)	69 (58)	1.00	31 (79)	84 (80)	1.00
ENT involvement, no. (%)	49 (28)	53 (44.5)	**0.004**	21 (54)	81 (77)	**0.012**
Musculoskeletal involvement, no. (%)	70 (40)	67 (56)	**0.006**	16 (41)	59 (56)	0.133
Gastrointestinal involvement, no. (%)	22 (12.5)	14 (12)	1.00	6 (15)	8 (8)	0.205
Nervous system involvement, no. (%)	23 (13)	22 (18)	0.248	2 (5)	25 (24)	**0.008**
Skin involvement, no. (%)	45 (26)	33 (28)	0.788	8 (20.5)	35 (33)	0.155
Eye involvement, no. (%)	8 (4.5)	10 (8)	0.217	5 (13)	15 (15)	0.797
Initial induction therapy						
Methylprednisolone bolus, no. (%)	124 (70)	81 (68)	0.700	30 (77)	66 (63)	0.163
Prednisone & cyclophosphamide, no. (%)	171 (97)	115 (97)	1.00	38 (97)	105 (100)	0.270
Plasma exchange, no. (%)	40 (23)	31 (26)	0.579	10 (26)	20 (19)	0.488
Rituximab, no. (%)	13 (7)	4 (3)	0.203	2 (5)	17 (16)	0.100
Outcome			Hazards Ratio (95% CI)*			Hazards Ratio (95% CI)*
Relapse, no (%)	67 (38)	58 (49)	1.29 (0.87, 1.91)	21 (54)	74 (70)	1.77 (0.98, 3.28)
ESRD, no (%)	51 (29)	36 (30)	0.98 (0.62, 1.54)	17 (44)	24 (23)	0.60 (0.30, 1.21)
Dead, no. (%)	88 (50)	46 (39)	0.92 (0.64, 1.33)	13 (33)	29 (27)	1.20 (0.56, 2.55)

ENT ear, nose and throat; ESRD=end-stage renal disease; Eye involvement= iritis/uveitis
* p-value for HR (95% CI) was not significant

TH-PO846

The Role of MPO, Plasma Cell, and CD20 in the Pathogenesis of Human MPO-ANCA-Associated Glomerulonephritis

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Background: Myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-associated glomerulonephritis (GN) is characterized by pauci-immune necrotizing glomerulonephritis. We reported that MPO and immune complexes composed of MPO-anti MPO antibody may play some direct roles in the pathogenesis of glomerular capillary injuries in the early phase of the disease. Previous studies have suggested involvement of infiltrated macrophages and lymphocytes. Here we investigated a possible role of MPO-positive cells, plasma cells, CD20-positive B-lymphocytes in the development of MPO-ANCA- associated GN.

Methods: Patients with ANCA-associated vasculitis (AAV) were diagnosed according to the definition of the 2012 Chapel Hill Consensus Conference and the 1990 American College of Rheumatology classification criteria. Using renal biopsy specimen including more than 10 glomeruli that were obtained from 20 patients with MPO-ANCA-associated GN, we analyzed the extent of glomerular infiltration of CD20-positive cells and plasma cells as well as extracellular and cellular deposition of MPO by immunohistochemistry. The colocalization of MPO and plasma cells / CD20 cells was also examined by double staining for MPO and CD20 using immunofluorescence.

Results: CD20-positive cells were found only in 5 of the 151 glomeruli (0.67%) and mainly located in the peritubular capillaries around the glomeruli with active lesions. In contrast, plasma cells were frequently observed in 124/151 glomeruli (82.1%) of the early phase and located mainly in the endocapillary proliferative lesions and extra-capillary crescentic lesions. MPO exists along the glomerular capillary walls near the infiltrated MPO-positive neutrophils in the early phase. No colocalization of CD20-positive cells with MPO-positive cells / MPO deposition was observed, but MPO was occasionally stained in plasma cells.

Conclusions: These results suggest that plasma cells, rather than CD-20 positive cells, may play some roles possibly through MPO in the pathogenesis of human MPO-ANCA-associated glomerulonephritis.

TH-PO847

Chemokine Receptor 8 in Peripheral Blood Mononuclear Cells Can Be a Novel Diagnostic Biomarker for ANCA-Negative ANCA-Associated Vasculitis

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Background: Diagnosis of antineutrophil cytoplasmic autoantibodies associated vasculitis (ANCA-associated vasculitis; AAV) is based on clinical and histologic features with elevated serum ANCA levels, however, not all cases show ANCA positive. In such cases, diagnosis of AAV without histological examination is quite difficult. We have found that the chemokine receptor 8 (CCR8) level in peripheral blood mononuclear cells correlates with activity of MPO-ANCA positive AAV; CCR8 is upregulated both in mRNA

and protein levels, which was reported in the previous meeting. In this study, we extended our research of CCR8 levels in ANCA-negative AAV.

Methods: Peripheral blood mononuclear cells were collected from 81 patients representing rapidly progressive glomerulonephritis on their initial visit. Participants were categorized as ANCA-positive AAV, immune complex small vessel vasculitis, vasculitis associated with systemic disease, and ANCA-negative AAV according to Chapel Hill consensus conference criteria. CCR8 gene expression levels in each group were assessed retrospectively.

Results: CCR8 gene expression levels were significantly higher in patients with ANCA-negative AAV compared to those in healthy controls. The area under the ROC curve was 0.92 (95% CI: 0.76-1.00) with a sensitivity of 91.7% and a specificity of 100%. CCR8 levels in patients with ANCA-positive AAV also showed a higher value with statistical significance. The area under the ROC curve was 0.83 (95% CI: 0.79-0.96) with a sensitivity of 75.6% and a specificity of 100%. Immune complex small vessel vasculitis and vasculitis associated with systemic disease did not show the CCR8 elevation. These data indicate that CCR8 is upregulated in pauci-immune glomerulonephritis regardless of serum ANCA levels.

Conclusions: CCR8 could be a useful biomarker in diagnosis of ANCA-negative AAV representing rapidly progressive glomerulonephritis.

TH-PO848

The Emergence of Goodpasture's Disease Following Hematopoietic Stem Cell Transplant: Clues to Disease Etiology?

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Introduction: Goodpasture's disease is an autoimmune disorder caused by autoantibodies against collagen IV in the glomerular and alveolar basement membranes. It has been postulated that a conformational change of the native autoantigen, the α345NC1 hexamer of collagen IV, is imperative for the development of disease. Perturbation of the quaternary structure causes dissociation of the hexamer, which elicits autoantibodies against subunits, but not the native hexamer. This contrasts with Alport's post-transplant nephritis, where the pathogenic alloantibody binds directly to native NC1 hexamer.

Case Description: We studied a patient who developed anti-GBM disease following allogeneic haematopoietic stem cell transplant. Autoantibody specificity was analysed by ELISA including binding to individual NC1 monomers of collagen IV (α1-α6), immunodominant epitopes of α3 chain, and native versus dissociated NC1 hexamers from glomerular basement membrane. Binding of autoantibody from patient serum to normal kidney GBM was also assessed. Anti-GBM antibodies were directed against the α3 NC1 domain of collagen IV and developed rapidly reaching peak level in patient serum within 5 weeks. They targeted predominantly the E_A epitope of α3 NC1. Antibody binding to native α345NC1 hexamer was minimal; however, binding was greatly increased upon hexamer dissociation. None of the polymorphic genetic differences between donor and recipient collagen IV genes would be predicted to cause a significant NC1 conformational change or to provide a target for antibody binding. Both patient and donor possessed the Goodpasture's susceptibility HLA-allele *DRB1*1501*.

Discussion: This is the first report of Goodpasture's disease occurring post-HSCT where the pathogenesis has been studied from onset to recovery. The specificity and binding properties of the antibodies along with sequencing results indicate that this is a post-transplant autoimmune rather than alloimmune phenomenon. This case also demonstrated the rapidity, in a matter of weeks, of high titres of pathogenic antibody production highlighting the nature of emergent Goodpasture's disease. Our findings demonstrate the importance for early diagnosis of Goodpasture's disease and timely treatment for preserving kidney function.

TH-PO849

High Glucose Promotes Macrophage Switching to M1 Phenotype via Down-regulating STAT-3-Mediated Autophagy

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Background: Imbalance of M1/M2 macrophages phenotype activation is a key point in diabetic nephropathy (DN). Macrophages mainly exhibit M1 phenotype, whcih contribute to the inflammation and fibrosis in DN. Studies indicate that autophage plays an important role in M1/M2 activation. However, the mechanism of autophage regulating macrophage M1/M2 phenotype in DN is unknown. Thus, the aim of this study is to explore whether high glucose induced macrophage switch to M1 phenotype via down-regulating STAT-3-mediated autophagy.

Methods: In vivo, DN model rats were established by intraperitoneal injection with streptozocin (STZ). Rats were sacrificed respectively at 18w for histological and molecular analysis. In vitro, RAW264.7 cells were cultured with 30mM glucose with or without autophagy regulator and STAT-3 regulator intervention. Meanwhile, the classical activation models of M1 and M2 macrophages were established as control group. The expressions of autophagy-related proteins (LC3, Beclin-1, p62), M1 markers (iNOS, TNF-α) and M2 markers (MR, Arg-1) were detected by immunofluorescence and Western Blot.

Results: In vivo, macrophages were exhibited to M1 phenotype in DN and displayed a lower level of autophagy. Additionally, iNOS expression was negative correlated with LC3 (r=-0.619, P<0.05) and pSTAT-3 (r=-0.951, P<0.05). In vitro, electronic microscope analysis showed intact autophagy (Fig.1). RAW264.7 macrophages switched to M1 phenotype under high glucose conditions. Autophagy was downregulated in such high glucose induced M1 macrophages. The expression of LC3 (autophagy maker) increased by STAT-3 activator. Meanwhile, both the STAT-3 activator and autophagy activator (rapamycin) promoted glucose-induced M1 macrophage translating to M2 macrophage. However, after inhibition of STAT-3 expression with STAT-3 siRNA, autophagy activator contributes to the reduction of the conversion of macrophages from M1 into M2 phenotype in high glucose-induced macrophage.

Conclusions: High glucose promotes macrophage switching to M1 phenotype via down-regulating STAT-3-mediated autophagy.

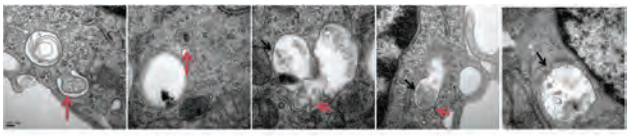

Fig.1 The intact autophagy is observed in vitro.
A:The isolation film formation and extension; B: Autophagosome; C: Lysosome chemotaxis to autophagosome; D: Fusion; E: autophagolysosome. Autophagosome (Red); Lysosome (Black), Scale bar = 100nm.

TH-PO850

Active Vitamin D Regulates Macrophage M1/M2 Phenotypes via the STAT-1-TREM-1 Pathway in Diabetic Nephropathy

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Background: Imbalance of M1/M2 macrophages phenotype activation is a key point in diabetic nephropathy (DN). TREM-1(Triggering Receptor Expressed On Myeloid Cells 1) is essential for macrophage function regulation. Signal transducer and activator of transcription (STAT) is a key factor that regulates the activation of macrophage M1/M2 phenotypes. Our previous studies indicated that active vitamin D (VD) has renoprotective role. This study aimed to investigate whether VD suppresses macrophage transition to the M1 phenotype via inhibiting the high glucose-induced STAT-1 phosphorylation to reduce TREM-1 expression.

Methods: Pathological changes in kidney tissue were detected and the expression of CD68 TREM-1, STAT-1, M1 makers and M2 makers were acquired in renal tissue of DN patients and 18w DN rats. In vitro, RAW 264.7 cells were treated by high glucose with or without VD. TREM-1 siRNA, STAT-1 siRNA and high expression plasmid of TREM-1 and STAT-1 were explored to elucidate the underlying mechanism. The expression of TREM-1 and STAT-1 and the changes of macrophage phenotype were examined separately by Western Blot, immunofluorescence stain.

Results: (1) In DN patients, the expression of M1 markers (iNOS, TNF-α) and TREM-1, pSTAT-1 were increased in comparation with NC group(P<0.05). Additionally, iNOS expression was positive correlated with the TREM-1 expression (r=0.757, P<0.05), pSTAT-1 (r=0.808, P<0.05). (2) In DN rats, the enlargement of glomerular surface area, expansion of glomerular mesangial matrix, the expression of CD68, TREM-1, pSTAT-1 and M1 markers (iNOS) were significantly increased compared with NC group (P<0.05), while above changes were markedly decreased in DN+VD group (P<0.05). (3) In vitro, VD significantly decreased high glucose induced CD68, TREM-1, pSTAT-1 and M1 markers (iNOS) expression. However, above effects from VD were abolished when TREM-1 or STAT-1 expression was overexpressed by TREM-1 or STAT-1 plasmid. Inhibition of STAT-1 expression with STAT-1 siRNA decreased TREM-1 expression, while, TREM-1 regulation by TREM-1 siRNA or TREM-1 overexpression techniques did not affect STAT-1 expression.

Conclusions: VD can inhibit macrophage transition to the M1 phenotype through the STAT-1/TREM-1 pathway under high glucose condition.

TH-PO851

Serum Amyloid A and Clinical Outcomes in Early Diabetic Kidney Disease

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Background: Risk of end-stage renal disease (ESRD) and death is increased by higher systemic levels of serum amyloid A (SAA) in patients with advanced diabetic kidney disease (DKD), but not among those with early or no DKD. The study aim was to determine relationships between indicators of locally-produced SAA and clinical outcomes in these patients.

Methods: In Pima Indians with type 2 diabetes, SAA protein was measured in urine (enzyme-linked immunosorbent assay, n=159) and SAA mRNA was quantified (microarray, n=46) in kidney tissue from research biopsies. Cox-proportional hazard models tested

whether urinary SAA forecasted future ESRD and all-cause death. Linear regression models tested for cross-sectional associations of SAA mRNA in kidney tissue with urine albumin-to-creatinine ratio (UACR) or estimated glomerular filtration rate (eGFR; CKD-EPI-creatinine). Urine and blood samples for these analyses were collected within 6 months of the biopsies.

Results: Baseline characteristics included: age 47±11 (mean±SD) years, women (117/159; 74%), hemoglobin A1c 9.1±2.3%, diabetes duration 17±7 years, body mass index 36±8 kg/m^2, renin angiotensin system inhibitor use (64/159; 40%), systolic blood pressure 124±16 mm Hg, UACR 39,14-209 mg/g (median, interquartile range), eGFR 103, 91-114 mL/min/1.73m^2. During a median of 12.5 years, 25 participants developed ESRD and 53 died. SAA-positive urine forecasted ESRD (hazards ratio [HR] 3.73, 95% confidence interval [CI] 1.11–12.53, p=0.022), but not death (HR 1.71, 95% CI 0.53– 5.50). In kidney tissue, tubulointersitial SAA mRNA was associated with a 6.3 mL/min/1.73m^2 lower eGFR (p<0.001) and a 0.80 log-fold increase in UACR per log-fold change in SAA mRNA (p<0.001). Glomerular SAA mRNA was associated with a 4.5 mL/min/1.73m^2 lower eGFR (p<0.001) and a 0.58 log-fold increase in UACR per log-fold change in SAA mRNA (p<0.001).

Conclusions: Urinary SAA forecasted ESRD and higher levels of SAA mRNA in kidney tissue correlated with lower eGFR and higher UACR. Associations between indicators of locally-produced SAA and clinical outcomes point to a candidate mechanism for DKD onset and progression in diabetic patients with early or no DKD.

TH-PO852

Sodium Glucose Cotransporter 2 Inhibition with Dapagliflozin Confers Renoprotection by Downregulating Megalin in Proximal Convoluted Tubules

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Background: Megalin is an endocytic receptor expressed in the proximal tubules. We found that megalin mediates the endocytosis of glomerular-filtered nephrotoxic proteins, causing high-fat diet (HFD)-induced kidney disease in mice (JASN 2016). Thus, we speculate that appropriate suppression of renal megalin function may delay the development and progression of DKD. Sodium glucose transporter 2 (SGLT2) inhibitors are known to exert renoprotective actions and increase β_2-microglobulin, an endocytic ligand of megalin, in urine of patients with type 2 diabetes. Therefore, we studied the effect of dapagliflozin, a widely used SGLT2 inhibitor, on megalin expression in proximal tubular epithelial cells (PTECs).

Methods: Eleven-week-old male C57BL/6J mice, fed a normal fat diet (NFD), were administered 1mg/kg dapagliflozin or vehicle via oral gavage for 7 days; or eight-week-old mice were fed an HFD and administered 1mg/kg dapagliflozin or vehicle for 4 weeks. The effect of dapagliflozin on renal megalin expression was investigated by immunoblotting, quantitative PCR, and immunohistochemistry. Cultured immortalized rat PTECs (IRPTCs) transfected with human SGLT2 cDNA (S-IRPTCs) were treated with 20 μM dapagliflozin or vehicle and evaluated for 2-deoxy-D-glucose uptake and megalin expression.

Results: Dapagliflozin suppressed megalin expression transcriptionally in mice fed either an NFD or HFD. Megalin expression was decreased in the proximal convoluted tubules, but not in the proximal straight tubules. In HFD-fed mice, no difference was noted in blood glucose levels between dapagliflozin and vehicle treatments. Urinary albumin and α_1-microglobulin, endocytic ligands of megalin, were increased in dapagliflozin administered mice. In S-IRPTCs treated with dapagliflozin, the expression of both megalin protein and mRNA was decreased in association with decreased glucose uptake.

Conclusions: The renoprotective effect of SGLT2 inhibitors may be at least partly due to megalin downregulation, which would have impacts on the therapeutic strategies with SGLT2 inhibitors including the interpretation of megalin-associated urinary biomarkers in diabetes.

TH-PO853

SGLT2 Inhibition Relieves High Glucose-Induced Metabolic Disorders in Tubular Epithelial Cells Through Regulation of HIF-1α Pathway

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Background: SGLT2 inhibitor (SGLT2i) has been proved to be renoprotective by reducing hyperperfusion, hyperfiltration and hypertension in glomeruli of diabetic kidney. However, high concentration of glucose reabsorbed into proximal tubular cells induced consequence abnormalities in glucose and lipid metabolism seems to be detrimental in diabetic kidney disease (DKD). In this study, we examined whether SGLT2i dapagliflozin may rectify metabolic disorders and explore the possible mechanism.

Methods: Diabetic model was induced by streptozotocin injection. Losartan was used as hemodynamic control. Dapagliflozin and losartan were given by oral gavage for 12 weeks. Mice were randomly assigned into six groups as follows: control + vehicle, control + dapagliflozin (5mg/kg), control + losartan (10mg/kg), diabetes + vehicle, diabetes + dapagliflozin (5mg/kg), diabetes + losartan (10mg/kg). High glucose-incubated primary tubular cells (PTCs) were treated with or without dapagliflozin for indicated time periods.

Results: In both diabetic kidney and glucose-treated PTCs, metabolic abnormalities were notable as demonstrated by increased lactate level and lipid accumulation accompanied with increased expression of enzymes for glycolysis and decreased expression of enzymes for fatty acid oxidation. Dapagliflozin treatment decreased blood glucose level, attenuated the increase of kidney/body weight ratio, albuminuria excretion rate, urinary NGAL level and tubulointerstitial fibrosis. Furthermore, dapagliflozin treatment relieved the increase of lactate level and accumulation of lipid droplet in tubular cells. The increased expression of glycolytic enzymes and decreased expression of fatty acid enzymes were rectified by dapagliflozin. These metabolic benefits were not observed in losartan-treated group. Moreover, expression of HIF-1α, the regulator of metabolism was increased, which suggested the stabilization of HIF-1α in diabetic kidney. Nevertheless, dapapagliflozin treatment inhibited HIF-1α stabilization. HIF-1α stabilizer BAY85-3934 blocked the protective role of dapagliflozin on metabolism in high glucose-treated PTCs.

Conclusions: We suggested that SGLT2 inhibitor protects against metabolic abnormalities and relieves tubular damage in diabetes through HIF-1α pathway.

Funding: Government Support - Non-U.S.

TH-PO854

Renal SGLT2 mRNA Expression in Diabetic and Non-Diabetic Kidney Disease in Humans

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Background: In the setting of diabetes, intraglomerular hypertension is associated with chronic kidney disease (CKD) progression, in part through sodium-glucose cotransporter 2 (SGLT2)-mediated suppression of tubuloglomerular feedback (TGF). Pharmacological inhibition of SGLT2 activates TGF and reduces CKD progression in the setting of diabetes, and is being examined as a renal protection strategy in non-diabetic CKD trials. Despite interest in this field and ongoing trials, levels of renal SGLT2 mRNA expression in human health and disease have not yet been fully examined. Our aim was to quantify human renal SGLT2 mRNA expression in healthy controls (HC), in glomerulonephritis subtypes (GN) and in patients with diabetic kidney disease (DKD).

Methods: SGLT2 mRNA expression was quantified and compared in HC vs. GN vs. DKD in the European Renal cDNA Bank (ERCB). Second, renal SGLT2 mRNA expression from the Nephrotic Syndrome Study Network (NEPTUNE) was analyzed using biopsies from patients with membranous nephropathy (MN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN). mRNA was obtained by microdissection of tubulointerstitial compartments from adult renal biopsies and processed using a microarray platform.

Results: In ERCB (n=166), SGLT2 mRNA expression was 9.42±0.50, 9.19±0.50 and 8.85±0.64 in HC, GN and DKD respectively (p=0.0044). SGLT2 mRNA expression was higher in HC vs. DKD and GN vs. DKD (p<0.05 for both). In NEPTUNE (n=121), there were no mRNA expression differences across GN subtypes (MN vs. MCD vs. FSGS vs. IgAN). In NEPTUNE patients with GN, eGFR (r= 0.32, p<0.001) was positively correlated with SGLT2 mRNA expression and interstitial fibrosis was negatively correlated with SGLT2 expression (r=-0.23, p<0.01). No relationships were seen with proteinuria.

Conclusions: SGLT2 mRNA expression is lower in patients with DKD compared to HC or GN, and is related to the degree of interstitial fibrosis in GN patients. In light of protective effects on DKD outcomes in clinical trials despite apparently having the lowest SGLT2 mRNA expression, further studies are required to better understand the relationship between SGLT2 protein levels and/or activity and CKD outcomes in humans.

TH-PO855

Early B Cell Factor 1 Plays a Role in the Maintenance of Glomerular Filtration Barrier Integrity

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) and organ failure worldwide. Current therapies are inadequate and at best slow progression but do not arrest or reverse it. Proteinuria is associated with DKD progression and reflects loss of integrity of the glomerular filtration barrier (GFB). Defining the mechanisms underlying a compromised GFB during the progression of DKD is key to developing effective therapeutic strategies. We identified *EBF1* as associated with macroalbuminuria and ESRD by our GWAS analysis in a case (n=2,861 individuals with T1DM) vs control (n=12,418 individuals with T1DM and no evidence of renal disease 15 years post-diagnosis) approach. Here we investigate the contribution of EBF1 to proteinuria associated with DKD using a zebrafish model of GFB integrity and elaborate on its role in maintaining a functional GFB.

Methods: To investigate a possible causative role for EBF1 in loss of GFB integrity with resulting proteinuria Tg(l-fabp:DBP:EGFP) zebrafish embryos were injected with

control or EBF1 morpholinos. Morpholinos targeting the podocyte gene *CD2AP* were used as a positive control. Tg(l-fabp:DBP:EGFP) transgenic zebrafish express a fluorescent plasma protein with a molecular weight equivalent to human albumin. Compromised GFB integrity leading to loss of the fusion protein from the circulation can be quantified by fluorescence imaging of the retinal plexus. The ultrastructure of GFB was visualised using electron microscopy. While RNA sequencing analysis was used to map the transcriptome of EBF1 knockdown fish vs control.

Results: EBF1 knockdown led to a significant loss of retinal fluorescence compared to control and equivalent to that of CD2AP at 96hpf. Knockdown also caused generalised edema compared to control, further supporting a role for this gene in kidney function. EM analysis revealed loss of EBF1 caused pronounced podocyte foot process effacement and screening of a cohort of cell lines confirmed high levels of expression of EBF1 in podocytes. RNA sequencing analysis combined with Ingenuity Pathway Analysis revealed desregulated transcripts and key pathways affected by EBF1 knockdown which were validated by real time PCR.

Conclusions: These findings suggest that EBF1 plays a key role in maintaining GFB integrity.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO856

Microangiography Reveals the Protective Role of Liraglutide on Renal Microvascular Impairment in Rats with Metabolic Syndrome

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Background: Progressive renal impairment associated with metabolic syndrome remains a significant cause of morbidity and mortality. We investigated whether chronic high dose liraglutide (LIRA, GLP-1 agonist) treatment affects the metabolic profile and extent of renal inflammation and renal endothelial function in lean fa/+ and obese fa/fa (ZFDM) rats.

Methods: 8-week old lean fa/+ and obese fa/fa ZFDM rats were treated with vehicle or LIRA (1mg/kg/day, subcutaneous) for 8 weeks. Systolic blood pressure (SBP) was monitored in ZFDM rats at 0, 4 and 8 weeks using tail-cuff method. Glomerular filtration rate (GFR) was measured in conscious rats at 0, 4 and 8 weeks using the fluorescein isothiocyanate sinistrin method. X-ray microangiography was then used to investigate renal vascular function (vessels 70-350 μm diameter). Further, renal function parameters including urinary albumin, creatinine and albumin creatinine ratio were measured.

Results: We found that in comparison to the saline treated obese fa/fa rats, LIRA treated rats had significantly lower SBP, and restored GFR (Fig. 1A-B) due in part to an increase in nitric oxide-mediated vasodilation in small renal arteries and arterioles (<200 μm diameter) (Fig. 1C-F). Further, vessel internal diameter, visible vessel number and caliber (%) increased after LIRA treatment compared to vehicle-treated rats (Fig. 1G-I). Moreover, the high dose LIRA treatment largely prevented the decline in renal function seen in vehicle treated obese fa/fa rats (elevated urinary albumin and depressed creatinine).

Conclusions: These results strongly suggest that high dose LIRA treatment significantly improved the endothelial function of microvessels in the renal circulation, and greatly improved renal function.

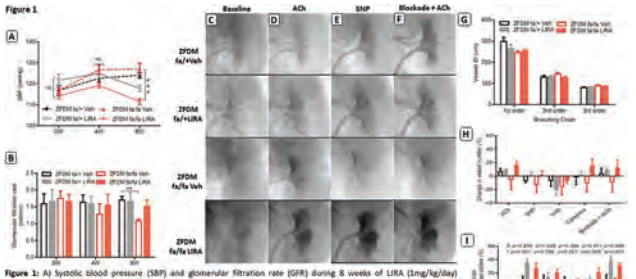

Figure 1: A) Systolic blood pressure (SBP) and glomerular filtration rate (GFR) during 8 weeks of LIRA (1mg/kg/day) treatment in lean fa/+ and obese fa/fa ZFDM rats. **Representative X-ray micro angiograms of the renal vasculature in ZFDM rats after 8 weeks of LIRA treatment.** (C-F) Images during baseline, and infusions of acetylcholine (ACh), sodium nitroprusside (SNP) and ACh following blockade of gap junctions (carbenoxelone), prostaglandins (indomethacin) and endothelium derived hyperpolarization factors (charabydotoxin, apamin). Calibration wire = 50 μm. (G) Vessel internal diameter categorized by branching order during baseline lactate infusions. (H) LIRA treatment shown greater vessel number recruitment after blockade compared to vehicle treated rats. (I) Mean change in 2nd order vessel diameter from baseline ± SEM. The significance of group differences was determined by ANOVA for factors of strain (S) and drug treatment (T).

TH-PO857

Possible Role of Ketone Body Metabolism in SGLT2 Inhibitor-Mediated Renoprotection in High Fat Diet-Fed ApoE-Knockout Mice

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Background: A recent study showed that empagliflozin, a SGLT2 inhibitor, slowed renal function decline rate in diabetic patients regardless of proteinuria stage, suggesting that the treatment has a renoprotective property in diabetes. This animal study was aimed at revealing the renoprotective action of empagliflozin on atherosclerosis-related renal injury in diabetes, and a possible role of ketone body production in its renoprotective mechanism.

Methods: Study 1 examined the effect of oral administration of empagliflozin (30mg/kg) for 8 weeks on atherosclerosis and renoprotection in high fat diet (HFD)-fed ApoE knockout (ApoE$^{-/-}$) mice, an animal model for atherosclerosis. Study 2 examined the effect of oral administration of 1,3-butanediol, a ketone body precursor, for 8 weeks on atherosclerosis and renoprotection in HFD-ApoE$^{-/-}$ mice.

Results: In Study 1, empagliflozin treatment significantly improved atherosclerosis in HFD-fed ApoE$^{-/-}$ mice. HFD-ApoE$^{-/-}$ mice showed significant increases in serum cystatin C levels without albuminuria, and F4/80-positive macrophage infiltration and fibronectin deposition in renal interstitium. These renal alterations were all significantly improved by the empagliflozin treatment, which was accompanied by significant increases in serum β-hydroxybutyric acid (β-OHB) levels. In study 2, although the 1,3-BD treatment did not improved atherosclerosis in HFD-fed apoE$^{-/-}$ mice, similarly to the results from the empagliflozin study, the 1,3-BD treatment significantly improved serum cystatin C, and renal F4/80-positive macrophage infiltration and fibronectin deposition along with maintaining renal ATP contents in HFD-ApoE$^{-/-}$ mice. Finally, we confirmed that β-OHB supplementation inhibited apoptosis in the cultured proximal tubular cells stimulated with high glucose, saturated fatty acids and hypoxia.

Conclusions: Ketone body-derived energy supply to the hypoxic kidney could be a promising therapy for preventing renal dysfunction in diabetic kidney disease.

TH-PO858

Association Between MYH9 and APOL1 Gene Polymorphisms and the Risk of Diabetic Kidney Disease in Patients with Type 2 Diabetes in a Chinese Han Population

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Background: Single nucleotide polymorphisms (SNPs) in MYH9-APOL1 gene regions have been reported to be associated with diabetic kidney disease (DKD) in the American population. The susceptibility of MYH9 and APOL1 polymorphisms with DKD in Chinese populations has not been well studied. In this study, we examined the association of MYH9 rs3752462 (T>C) and APOL1 rs136161 (C>G) with DKD in a Chinese Han population.

Methods: MYH9 rs3752462 (T>C) and APOL1 rs136161 (C>G) were genotyped in 303 DKD patients and 364 type 2 diabetes mellitus (T2DM) patients without kidney disease using the TaqMan SNP genotyping assay. Chi-squared test and multivariate logistic regression were used to evaluate the association.

Results: We observed that only MYH9 rs3752462 was associated with DKD (genotype, P= 0.004; allele, P= 0.002). Genetic model analysis revealed that rs3752462 was associated with increased risk of DKD under a dominant model adjusted by age and sex (adjusted Odds ratio [aOR], 1.675; 95% CI 1.225-2.289; P= 0.001) and an additive model (TC vs TT: aOR, 1.649; 95% CI 1.187-2.290; CC vs TT: aOR, 1.817; 95% CI 0.980-3.367; P= 0.005). The combined effect of rs3752462 TC + rs136161 CC genotype showed a association of DKD adjusted by age and sex (aOR, 1.732; 95% CI 1.128-2.660; P= 0.012). After a Holm-Bonferonni correction for multiple tests, the C allele frequencies of the rs3752462 and the TC + CC genotype in dominant model were considered statistically significant with a markedly increased risk of DKD (P<0.00208; P<0.002).

Conclusions: Our results suggest that MYH9 rs3752462 is significantly associated with an increased risk of DKD in Chinese Han individuals.

Funding: NIDDK Support

TH-PO859

Genome-Wide Association Study of Urinary and Plasma KIM-1 Levels in Type 1 Diabetic Subjects with Diabetic Kidney Disease

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Background: Kidney injury molecule 1 (KIM-1) is a transmembrane protein primarily expressed at the apical membrane of proximal tubular cells following kidney damage. Urinary and plasma levels of this biomarker are increased in patients with non-diabetic chronic kidney disease and diabetic kidney disease. Here, we performed a genome-wide association study (GWAS) to investigate whether genetic factors influence urinary and plasma KIM-1 levels in type 1 diabetes.

Methods: KIM-1 levels were measured in 688 baseline urine specimens and 826 plasma specimens from participants with type 1 diabetes enrolled in the Joslin Kidney Study. Genotyping was performed using Illumina's HumanCoreExome BeadArray. Imputation of additional variants across the KIM-1 locus was performed using IMPUTE2 and 1000 Genomes Phase 3 data. Association analyses between KIM-1 levels and single nucleotide polymorphism (SNP) data were calculated using linear regression implemented in Plink.

Results: The strongest GWAS SNP associated with urinary KIM-1 levels was a missense variant (rs12522248; Thr207Ala; P=6.3x10^{-6}) located in exon 3 of the *KIM1* gene. The most strongly associated GWAS SNP with plasma KIM-1 levels was rs2436424 (P=5.0x10^{-6}), located 230kb downstream of *KIM1*. Using imputed SNPs to fine-map this locus, we identified 45 SNPs with P<1.0x10^{-5}, including 2 variants approximately 50kb downstream of *KIM1* with P<1x10^{-7}.

Conclusions: Using a GWAS and imputation analysis of urinary and plasma KIM-1 levels, we identified strong associations in the KIM1 gene that suggests that genetic variants at this locus impact KIM-1 levels in response to kidney injury. Further investigation is needed to fully understand the role of genetic variation on KIM-1 levels and how these

potentially impact the utility of this biomarker in patients with or at risk of diabetic kidney disease.

Funding: Private Foundation Support

TH-PO860

Prevalence of Angiotensin Type II Receptor (ATTR) Gene Polymorphism in Patients with Type 2 Diabetes with Nephropathy in India and Its Effect on the Antiproteinuric Efficacy of ACE Inhibitor Therapy

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Background: Involvement of renin angiotensin system has been implicated in the etiopathogenesis of diabetic nephropathy (DN). Angiotensin converting enzyme inhibitor (ACEI) drugs are commonly prescribed for reno-protection in patients with DN; however, response to ACEI therapy is not uniform in all patients. Aim of this study was to investigate the prevalence of ATTR A1166C gene polymorphism in North Indian patients with DN and its role on the anti-proteinuric efficacy of ACEI therapy.

Methods: In the present study, 270 patients having Type 2 diabetes mellitus for ≥ 5 years with nephropathy aged between 30 to 65 (mean 52.23±6.01) years were enrolled and treated with ACE inhibitor (ramipril) and subsequently followed at regular intervals for 2 years for assessment of urinary albumin/creatinine ratio (ACR) and estimated GFR. Patients were classified as responders if they had a decrease in urinary ACR by ≥50% at the end of 2 years follow up. Genotyping of ATTR A1166C gene polymorphism was performed by primer specific polymerase chain reaction and RFLP technique.

Results: Out of 270 patients, 231 completed the follow up of 24 months. 151(65%) patients with DN were found to be responders following ACE inhibitor therapy. Median urinary ACR values declined from the baseline value of 109.9 mg/g creatinine to 47.3 mg/g creatinine ($p<0.001$). At the end of 24 months, increase in serum creatinine above the baseline (0.28±0.3 v/s 0.61±0.2) ($p=0.269$) and decline in eGFR-MDRD (8.40±16.0 v/s 12.84±15.0 mL/min/1.73m^2) ($p=0.058$) between responders and non-responders respectively were not significantly different. All subjects displayed wild type allele (A) of this polymorphism and showed no genotypic variation; hence polymorphism of ATTR A1166C gene does not appear to have any role on the variability of anti-proteinuric effect following ACEI therapy.

Conclusions: In patients with Type 2 diabetes mellitus with nephropathy, approximately two third patients were found to have significant anti-proteinuric response following ACEI therapy. ATTR A1166C gene polymorphism is extremely rare in Northern India and does not appear to play any role in influencing the variation in anti-proteinuric effect following ACEI therapy.

Funding: Government Support - Non-U.S.

TH-PO861

XORs in the Genetic Susceptibility of Diabetic Kidney Disease in Mice

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Background: Diabetic kidney disease (DKD) is the leading single cause of ESRD in the United States. Approximately 30% of diabetic patients develop DKD even with comparable blood glucose levels, indicating a significant genetic component for disease susceptibility. Differential susceptibilities to DKD have also been observed in well-defined strains of inbred mice. The underlying mechanisms that contribute to differential susceptibility to DKD are still poorly understood in both patients and rodent models. The glomerulus is the primary site of injury with glomerular hypertrophy and podocyte depletion being the hallmarks for progressive DKD. Our work has demonstrated that ROS and mitochondrial oxidative stress damage accumulation, particularly in glomerular endothelial cells (GECs), leads to podocyte loss via endothelial-to-podocyte crosstalk in experimental mouse models of DKD and focal segmental glomerulosclerosis.

Methods: We used the BXD recombinant inbred panel to map genetic loci (QTL) associated with number of podocytes after long-term diabetes (6 months). We used parent strains inbred DBA/2J (D2) mice as susceptible, and C57BL/6J (B6) mice as resistant to diabetes-induced podocyte depletion associated with DKD susceptibility. Genetic mapping identified a cis-acting regulatory of the Xdh gene encoding xanthine dehydrogenase XDH/XO (xanthine oxidoreductase (XOR)). XORs catalyze the oxidation of purine substrates, xanthine and hypoxanthine, producing uric acid (UA) and are a major enzymatic source of cellular ROS. Both products have been demonstrated to be risk factors for cardiovascular diseases and DKD.

Results: Xdh expression in glomeruli and XO activity in serum were significantly increased in diabetic D2 mice, but not B6 resistant mice. XOR inhibition resulted in significantly reduced albuminuria, prevention of podocyte loss, as well as a reduction in DNA oxidation damage in the glomeruli of diabetic D2 mice. Using a luciferase reporter assay we examined if the two nucleotide variant could influence XOR activity. Our results show increased XOR activity of 293T cells when treated with high glucose (30mM) compared to controls. We have now generated mice with knock-in variants using CRISPR/Cas9 to determine their functional role in DKD susceptibility.

Conclusions: These data suggest that the identified promoter variant regulates XOR activity potentially linked to genetic susceptibility to DKD.

Funding: NIDDK Support

TH-PO862

Tubular and Injury Marker Expression Across Nephron Subsegments in Diabetic Nephropathy

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Background: Laser Microdissection (LMD) allows precise separation of nephron structures under immunofluorescence (IF). Several markers have been identified in the literature that are associated with specific subsegments of a nephron. Here, we examine the expression of known tubular and injury markers in kidney tissue of diabetic nephropathy (DN) biopsies and healthy nephrectomies.

Methods: Kidney biopsies from subjects with DN as well as a wedge biopsy from a healthy donor kidney were obtained. Tissue was preserved in OCT for 4 years at -80° C and sectioned into 12 µm thick sections on LMD PPS-membrane slides. Each slide was subjected to a rapid staining protocol, using DAPI, FITC-Phalloidin and Na/K channel antibody. Each slide underwent identical antibody staining and LMD, followed by RNA isolation, and sequencing. Transcriptomics data were obtained using RNAseq methodology on Illumina platform, and analyzed using R Studio.

Results: This study revealed that LMD methodology successfully allows for accurate identification of specific sub segments of a nephron, as shown by presence of markers associated with those structures and the absence of markers associated with other regions: NPHS1 and NPHS2 for the glomerulus, CUBN and SLC34A1 for the S1 and S2 proximal tubule, LRP2 for the S3 proximal tubule, and AQP2 and SCCN1G for the collecting duct. In addition, the transcriptomic analysis revealed differential expression of tubular injury markers like LCN2 (NGAL) expressed in the S1 and S2 subsegment. In contrast, HAVCR1 (KIM1) and TIMP2 expression was increased in the S3 subsegment.

Conclusions: LMD is an important tool that allows for accurate identification and isolation of tubular subsegments within renal tissue and subsequent RNA analysis. An increased expression of injury markers associated with different tubules was observed in the diseased kidney tissue samples. This suggests that specific regions of the nephron may respond to injury in different ways, which may further contribute to the pathogenesis and progression of DN.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO863

Intraglomerular Cross-Talk Between Mesangial Cells and Podocytes Inhibits Normal ER-Associated Degradation Processes and Induces Podocyte Injury in Diabetic Nephropathy

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Background: We previously reported that endoplasmic reticulum (ER) stress induced by glucolipotoxicity and homeostatic inflammation through intraglomerular cellular crosstalk may play an important role in the progression of diabetic nephropathy. However, involvement with these consequences in podocyte injury still remains unclear.

Methods: Cluster analyses were performed using cDNA microarray data set of isolated glomeruli from two distinct diabetic mouse models. ER stress and apoptotic responses were evaluated in cultured mouse podocytes MPC5 stimulated with mesangial cell-cultured medium (MC-sup) under high- and low-glucose conditions (HG, LG). The effects of an ER-associated degradation (ERAD) inhibitor Eeyarestatin I (EerI) in MPC5 and db/db mice were also examined.

Results: Commonly increased or decreased genes in both DM models were associated with apoptosis (enrichment score 3.03), inflammation (3.03), and energy metabolism (1.24), suggesting ER stress as a potential factor. Pathway-focused PCR array analysis revealed that ERAD pathway was suppressed, but apoptotic pathway was enhanced in podocytes stimulated with HG MC-sup. Besides, these responses were also observed in isolated diabetic glomeruli. In vitro, IRE1α and spliced XBP1 were suppressed in podocytes by HG MC-sup, although apoptosis evaluated by TUNEL-staining, Bax, ATF6 and CHOP was markedly increased. These results were augmented by HG MC-sup compared to LG MC-sup. Other types of cells, such as proximal tubular cells or macrophages, did not show any similar responses. Of note, treatment with EerI recapitulated these results in podocytes, and exacerbated albuminuria in db/db mice.

Conclusions: It is recently reported that ERAD pathway may play important roles in the maintenance of podocytes to avoid ER stress in several glomerular diseases including diabetic nephropathy. In the present study, we firstly reveal that intraglomerular crosstalk between mesangial cells and podocytes inhibits normal ERAD processes, potentially causing podocyte injury in diabetic conditions.

TH-PO864

Irisin, a Myokine, Ameliorates Diabetic Nephropathy by Restoring Autophagy in Podocytes

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Background: Moderate exercises have been demonstrated to ameliorate diabetic nephropathy in some clinical studies. However, the mechanism remains unknown. Skeletal muscle could excrete many myokines while exercises. Irisin is one of the myokines which could mediate the communication between muscle and other organs. Therefore, we hypothesis that exercised muscle-excreted irisin protects kidneys from diabetes mellitus.

Methods: We crossbred muscle-specific PGC-1α overexpression of mice (an animal model mimicking exercise) with db/m mice to get mPGC-1α-db/db mice. The urine albumin creatinine ratio (uACR) and pathologic change of kidneys were examined. Besides, recombinant irisin had been administrated to twelve-week-old db/db mice and their db/m littermates. The renal function and pathologic change were accessed to evaluate the protection effect of Irisin. Conditionally immortalized human podocyte cells were used for in vitro study to investigate how irisin protect podocytes from injury of high glucose (30mmol/l).

Results: There were significant accumulation of mesangial matrix, fusion of podocytes foot processes, widen of GBM as well as decrease of autophagy in the kidney of db/db mice. However, these kidney pathological injuries were remarkably improved in mPGC-1α-db/db mice. Meanwhile, the mice also showed significant alleviation of the excretion of uACR than db/db mice without mPGC-1α. These results indicate that mPGC-1α could alleviate kidney injury induced by diabetes. Irisin was found as one of the significantly increased myokines in the skeletal muscles of mPGC-1α mice, then we treated db/db mice with irisin for eight weeks. After peritoneal injection of irisin, the kidney pathologic change and microalbuminuria of db/db mice were all alleviated when compared to those db/db mice without irisin injection. Furthermore, Irisin treatment significantly restored autophagy in podocytes of db/db mice. Meanwhile, in vitro study, irisin improved the expression of autophagy related proteins and autophagy flux in high glucose cultured podocytes.

Conclusions: Our results indicate that the myokine, irisin, prevents the progression of diabetic nephropathy by restoring autophagy in podocytes. Irisin is one of the myokines that mediate the effect of exercised-muscle prevents diabetic nephropathy, which may become a new strategy to protect the kidney from diabetes.

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TH-PO865

Astaxanthin Attenuates Diabetic Kidney Injury Through Up-Regulation of Autophagy

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Background: The aim of this study was to investigate effects of astaxanthin (ATX) on renal injury in diabetic mice and its underlined renal protective mechanism.

Methods: Rats were randomly divided into five groups: normal, high fat diet, high fat + DM, high fat + ATX treatment, high fat + DM + ATX treatment. Fasting blood glucose, Urinary protein / Crea were measured. Renal pathological changes were evaluated with HE and PAS staining. In vitro, HTECs, HMCs and Podocytes were treated with ATX in the presence or absence of 30 mmol/L D-glucose or autophagy inducer.

Results: Diabetic rats treated with ATX had reduced 24h urinary protein excretion, blood glucose and lipids level as compared with those in vehicle-treated rats. The same as Glomerulus mesangial matrix expansion and renal tubular epithelial cell injury(Fig1,2). Moreover, ATX treatment markedly reduced protein levels of p62, α-SMA, FN and collagen IV in the kidney of diabetic rats(Fig3). In vitro, high glucose was shown to inhibit expression LC3-II and increase expression of p62 as compared with normal glucose while these changes were reversed with ATX treatment. ATX treatment also inhibited expression of α-SMA, collagen IV and FN in cultured kidney cells(Fig4,5).

Conclusions: The current study shows that ATX attenuates diabetes-induced kidney injury probably through upregulation of autophagic activity in kidney cells and anti-fibrosis effects.

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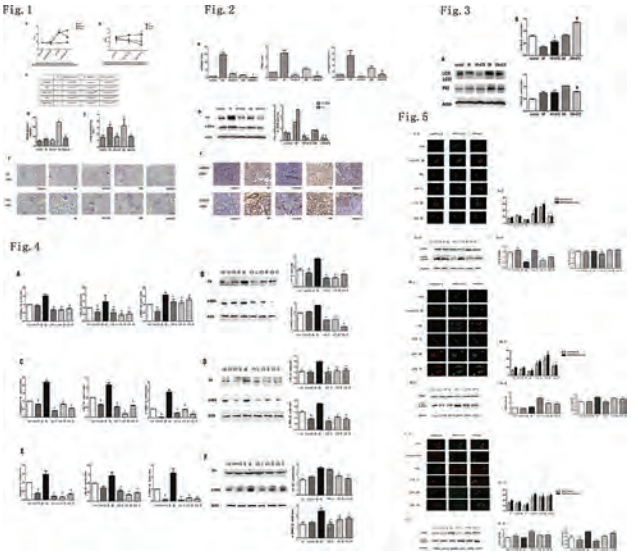

Figure 1. ATX treatment decrease serum glucose and urinary protein in diabetic rats. Fasting blood glucose, Urinary protein / Crea, H&E and PAS staining were measured. **Figure 2.** ATX reduces the expression of α-SMA, FN and collagen IV in the renal of diabetic rats.**Figure 3.** ATX induces autophagy in the renal of diabetic rats. Protein expression of α-SMA and FN in renal was determined by WB. **Figure 4.** ATX reduce renal fibrosis factors of HTECs, HMCs and Podocytes.**Figure 5.** ATX induces autophagy in HTECs **A.**, HMCs **B.**, Podocytess **C.**.

TH-PO866

Apelinergic System in the Kidney: Implications for Diabetic Kidney Disease

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Background: The bioactive peptides of the apelinergic system and its receptor APJ may play a protective role in cardiovascular and diabetic kidney disease (DKD). We examined the glomerular localization of APJ in the db/db mice and the effect of hyperglycemia and Angiotensin II on APJ mRNA in cultured podocytes. The impact of AT1R blockade on APJ expression was also studied in db/db mice.

Methods: Obese db/db mice of 8wk of age were used as a model of type 2 diabetes and their littermates db/m served as non diabetic controls. mRNA for APJ and propreapelin was measured by real time PCR; protein expression for APJ was studied by western blot on kidney lysates. Immunohistochemistry and immunofluorescence microscopy was used to localize APJ in the kidney.

Results: APJ co-localized with podocyte but not endothelial cell markers. In podocytes stimulated with *Pyr*[1]Apelin-13 a change in the phosphorylation status of the signaling proteins, AKT, ERK and p70S6K, was observed with an increase 15 min after stimulation. Apelin-13 decreased activity of Caspase-3 in podocytes after high glucose exposure reflecting an anti-apoptotic effect of APJ stimulation. In podocytes, APJ mRNA was down regulated in high glucose, and exposure to angiotensin II led to a further significant decrease in APJ mRNA. APJ and propreapelin mRNA in kidneys from *db/db* mice were decreased when compared to *db/m* controls; treatment with the specific AT1R blocker Telmisartan significantly increased APJ mRNA and propreapelin levels.

Conclusions: APJ is mainly localized in podocytes and in this cell type its activation by Apelin-13 abolishes the proapoptic effect of high glucose, suggesting a potential therapeutic role of apelin and emerging agonists with extended half- life in DKD. In addition, AT1 blockade with Telmisartan resulted in an increase in APJ mRNA and propreapelin levels in db/db mice suggesting a link of the apelinergic system and the AT1 receptor

Funding: NIDDK Support

TH-PO867

Effects of Ang-(1-7) and Its Receptor Regulating Bradykinin System on Podocyte Injury Induced by High Glucose

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Background: The mechanisms of diabetic nephropathy are still enigmatic. We hypothesized that RAS component Ang-(1-7) and its Mas receptor (MasR) and bradykinin (BK) system may play a protective role in podocyte injury induced by high glucose.

Methods: The Podocytes cultured in vitro were respectively interfered with low glucose (5mM, LG), high glucose (30mM, HG), HG+Ang-(1-7), HG+HOE140 (BKB2R antagonist), HG+ des[Arg(9)]BK (BKB1R agonist), HG+Ang-(1-7)+A779 [Ang-(1-7) antagonist], HG+ Ang-(1-7)+HOE140 and HG+ Ang-(1-7)+des[Arg(9)]BK. The CCK8 method detected the activity of podocytes and the flow cytometry detected the apoptosis of podocytes. The mRNA and proteinic expression of AT1R, MasR, BKB1R, BKB2R and podocyte-specific proteins (nephrin, podocin, WT-1) was examined by q-PCR and Western blot. The podocytes were also interfered with inhibitor of ERK and JNK, the expression of pERK/ERK, pJNK/JNK in podocytes was semi-quantificated by Western blot to investigate the signaling passway involved in the regulation.

Results: The CCK8 and flow cytometry results showed that the descent of podocyte activity and podocyte apoptosis induced by HG was rescued by Ang-(1-7) and HOE140. The effect presented concentration dependency. des[Arg(9)]BK and A779 displayed antagonistic action against Ang-(1-7), which aggrated the podocyte apoptosis and the descent of cell activity, moreover, the effect was most obviously at 10uM concentration. The results of q-PCR and Western blot indicated that HG stimulation up-regulated the expression of AT1R, BKB1R, BKB2R and down-regulated MasR, Nephrin, Podocin and WT-1. Ang-(1-7) and HOE140 could relieve the action of HG but A779 and des[Arg(9)]BK was the converse of Ang-(1-7) in some extent. The synergetic protective effect of HOE140 and Ang-(1-7) was more significantly. HG and des[Arg (9)]BK activated the MAPKs signaling passway yet Ang-(1-7) and HOE140 inhibited it. The inhibitor of MAPKs further decreased the podocyte apoptosis induced by HG.

Conclusions: Ang-(1-7)/MasR may decrease the up-regulation of BKB1R and BKB2R induced by HG, antagonist Ang II- ACE-AT1R axis, and then inhibit the activation of MAPKs and podocyte apoptosis. The synergistic reaction of Ang-(1-7)/MasR and BK system could protect podocyte from injury induced by HG.

Funding: Private Foundation Support

TH-PO868

Diabetic Conditions Enhance the Phosphorylation of PACSIN2/Syndapin II in Podocytes

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Background: We previously found that PACSIN2/syndapin II, which regulates endocytosis and intracellular trafficking, is elevated in glomeruli of Zucker Diabetic Fatty (ZDF) rats showing aberrant localization of nephrin and severe albuminuria. We also showed *in vitro* that PACSIN2 overexpression reduces nephrin insertion at the plasma membrane. PACSIN2 can be phosphorylated at serine 313 (pS313-PACSIN2) by Protein Kinase C alpha (PKCα), which in turn regulates the endocytic activity of PACSIN2. Importantly, PKCα is elevated in diabetes and associated with loss of nephrin expression. The aim of this study was to evaluate the phosphorylation status of PACSIN2 in glomeruli in diabetes. We also assessed the regulation of pS313-PACSIN2 and the presence of nephrin at the plasma membrane after treating cultured podocytes with palmitate, elevated in patients with diabetes.

Methods: PKCα, total PACSIN2 and pS313-PACSIN2 levels were assessed by Western blotting. On-Cell Western, a 96-well plate -based surface labeling assay, was used to determine the insertion of nephrin at the plasma membrane. Glomeruli were isolated from lean and obese ZDF rats by graded sieving. Cultured podocytes were incubated with palmitic acid or with sera from patients with T2D having normo- or microalbuminuria.

Results: PKCα, total PACSIN2 and pS313-PACSIN2 were elevated in glomeruli of obese and diabetic ZDF rats compared to lean controls. Also, the level of free fatty acids was increased in the sera of obese ZDF rats. Increased pS313-PACSIN2 and a trend for an increase of total PACSIN2 were observed when human podocytes were incubated with sera from patients with T2D with microalbuminuria compared to normoalbuminuric patients. Treating podocytes with palmitic acid resulted in the time-dependent phosphorylation of PACSIN2 on S313. Palmitic acid treatment also resulted in the reduction of nephrin inserted at the plasma membrane.

Conclusions: Our results indicate that PACSIN2 and its phosphorylation at serine 313 are elevated in glomeruli in a rat model of diabetes and diabetic kidney disease. This could be a consequence of elevated circulating palmitate and result in the reduction of nephrin at the plasma membrane, causing the destabilization of the slit diaphragm and albuminuria.

Funding: Private Foundation Support

TH-PO869

Knockout of Heterogeneous Nuclear Ribonucleoprotein F (hnRNP F) in Podocytes Aggravates Podocyte Loss in Streptozotocin-Induced Diabetic Mice Through Alternative Splicing of Insulin Receptor Gene

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Background: Insulin receptor (INSR) signaling is important for podocyte integrity. The INSR gene encodes two isoforms via alternative splicing: INSR-A (excluding exon 11) and INSR-B (including exon 11). In pancreatic beta cells, INSR-A renders beta cells vulnerable to programmed cell death, whereas INSR-B is protective. In the present study, we investigated whether deletion of heterogeneous nuclear ribonuclear protein F (hnRNP F) in podocytes would aggravate podocyte injury in streptozotocin (STZ)-induced diabetic mice through modulating the alternative splicing of INSR isoforms.

Methods: Podocyte-specific hnRNP F knockout (KO) mice were generated by crossbreeding podocin (Pod)-Cre mice with floxed hnRNP F mice. Diabetes was induced in male 12-week old Pod-hnRNP F KO mice and control littermates with streptozotocin (STZ) (i.p., 50 mg/kg/day) for five consecutive days. Mice were euthanized 8 weeks after the STZ injections. Urinary ACR was assessed at 4 and 8 weeks after STZ-administration. Kidneys were processed for histology. Podocyte numbers were counted by p57 staining. Mouse renal cortex, isolated glomeruli and primary cultured podocytes were subjected to RT-PCR to assess INSR-A and INSR-B mRNA expression. Podocytes from control littermates and Pod-hnRNP F KO mice cultured in normal and high glucose media were also studied.

Results: INSR-A and INSR-B mRNA were equally expressed in the glomeruli of non-diabetic WT mice. STZ-induced diabetes aggravated kidney injury and podocyte loss in Pod-hnRNP F KO mice as compared with diabetic control littermates. Diabetic Pod-hnRNP F KO mice exhibited lower INSR-B/A mRNA ratio in isolated glomeruli and primary cultured podocytes as compared to diabetic control mice. *In vitro*, in high glucose media, more cultured podocytes from Pod-hnRNP F KO were detached as compared to those from control littermates.

Conclusions: Deficiency of hnRNP F in podocytes aggravates podocyte loss and kidney injury in STZ-diabetic mice through modulation of the alternative splicing of INSR mRNA resulting in lower INSR-B/A mRNA ratio.

Funding: Government Support - Non-U.S.

TH-PO870

ABCA1 Mediated Mitochondrial Dysfunction Contributes to Podocyte Injury in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is characterized by podocyte loss, altered mitochondrial oxidative phosphorylation complexes (OXPHOS), and glomerular lipid accumulation. We have shown that ATP Binding Cassette A1 (ABCA1)-mediated cholesterol efflux is impaired in clinical and experimental DKD. Here, we test the hypothesis that ABCA1 deficiency causes mitochondrial dysfunction in podocytes and contributes to injury in DKD.

Methods: Sera were obtained from Pima Indian patients with diabetes and progressive DKD (P, n=15) and non-progressive DKD (NP, n=16) as assessed by changes in measured GFR over a 10 year period. Scrambled control (siCO) and siRNA *ABCA1* podocytes (siABCA1p) were treated with patient sera. ABCA1 expression, cholesterol efflux, mitochondrial OXPHOS complexes, cardiolipin (mitochondrial specific phospholipid) content and cytotoxicity were measured. Elamipretide (cardiolipin peroxidase inhibitor) was utilized for selected *in vitro* and *in vivo* experiments. $BTBR^{ob/ob}$ (ob/ob) mice with podocyte specific ABCA1 deficiency (DKO) were generated and analyzed.

Results: P sera treated podocytes show reduced ABCA1 mRNA expression, and cholesterol efflux and increased cytotoxicity compared to NP. siABCA1p are more susceptible to NP and P sera induced cytotoxicity when compared to siCO. siABCA1p show decreased basal OCR, cardiolipin accumulation, and alterations in OXPHOS complexes. Elamipretide treated siABCA1p are protected from NP and P sera mediated cytotoxicity compared to siCO. DKO mice have increased albuminuria, mesangial expansion, podocyte loss, FPE and mitochondrial damage as compared to ob/ob mice. Treatment with Elamipretide of db/db mice is sufficient to reduce albuminuria, mesangial expansion, BUN and podocyte loss.

Conclusions: Our data indicate that a reduction of *ABCA1* expression in podocytes is a susceptibility factor for DKD progression. These data also indicate that ABCA1 deficiency results in cardiolipin accumulation and mitochondrial dysfunction. Inhibition of cardiolipin oxidation prevents podocyte loss and DKD in diabetic mice. Treatment strategies to restore ABCA1 function may be beneficial in DKD.

Funding: NIDDK Support, Private Foundation Support

TH-PO871

DESI-MSI Based Spatial Metabolomics and METASPACE Indicates RNA and Mitochondrial Dysfunction in Renal Proximal Tubules of Mice with Diabetes

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Background: Diabetic kidney disease (DKD) remains the largest contributor to end stage renal disease and insightful biomarkers are required for identifying pathways to target for prognosis and therapeutics. Knowledge about the spatial distribution of metabolites in kidney tissues of DKD patients/animals will enhance the cellular contribution of biomarkers.

Methods: In the current study, we employed an ambient desorption electrospray ionization - mass spectrometry imaging (DESI-MSI) approach to characterize the metabolome in kidney tissue sections in a model of DKD. The data output was coupled to a novel bioinformatics platform (METASPACE). DESI-MSI was performed for spatial

untargeted metabolomics analysis in kidneys of mouse models (F1 C57BL/6J-Ins2Akita male mice at 17 weeks of age) of type 1 diabetes (T1D, n = 5) and heathy controls (n = 6). MetaboAnalyst 3.0 was employed for statistical analysis, metabolic pathway analysis, and biomarker analysis.

Results: Mice with DKD had increased relative abundances of pseudouridine, accumulation of free polyunsaturated fatty acids (PUFAs), and decreased relative abundances of phospholipids in cortical proximal tubules when compared with healthy controls. In the biomarker analysis, a five-metabolite biomarker set (i.e., phosphatidylglycerol (PG) 32:0, pseudouridine, hexose, phosphatidylserine (PS) 34:1, and diphenyl disulfide) was developed for diagnosing DKD. The AUC for the ROC curve is 0.994 (95% CI, 0.981-1; Empirical $P < 0.001$), which indicates that the biomarker set has excellent diagnostic ability for DKD in mice.

Conclusions: In summary, this new study demonstrates that DESI-MSI can be successfully used to distinguish cortical proximal tubules in healthy and diabetic tissues based on altered relative abundance of lipid profiles. DESI-MSI technology coupled with the METASPACE will serve as a powerful tool to shed new light on fundamental pathways in DKD.

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TH-PO872

Carrier Specific miRNA Distribution and Function in Diabetic Nephropathy: A Novel Concept for Monitoring Microvascular Injury

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Background: We previously demonstrated an association between total plasma levels of specific microRNAs (miRs) and microvascular injury in patients with diabetic nephropathy (DN). However, circulating miRs are carried in exosomes, the RNA-binding protein Argonaute2 (AGO-2) or high-density lipoprotein (HDL). Therefore, identification of the carrier specificity of selected miRs could improve their biomarker potential while carrier-specific transfer of miRs to vascular cells could affect vascular integrity.

Methods: We assessed the plasma carrier distribution of miRs in DN (n=21), diabetes mellitus (DM; n=15; eGFR of ≥ 30 mL/min) patients and healthy controls (n=15). Exosomes, HDL and AGO-2 were isolated using size exclusion chromatography, KBr density gradient ultracentrifugation and immunoprecipitation, respectively. MiR expression was determined and validated using TaqMan® miRNA Arrays and correlated to markers of vascular injury, including angiopoietin-2 (Ang2), soluble thrombomodulin (sTM) and capillary tortuosity. *In vitro* studies were performed to assess transfer and function of specific miRNA-carrier complexes.

Results: Specific miR-carrier complexes associated with DN and vascular injury. Most notably, we found exosome-miR-21 and AGO-2-miR-660 levels to display a significant increase in both DM and DN groups compared to healthy controls and correlated with capillary tortuosity and Ang2, respectively. Furthermore, exosome-miR-126 levels increased while HDL-miR-132 levels decreased in DN and correlated with levels of Ang2. Mechanistically, *in vitro* studies demonstrated that HDL-miR-132 and exosome-miR-21 and -126 transferred to endothelial cells, repress validated target genes and ultimately affect angiogenic capacity and barrier function.

Conclusions: Our data suggest that carrier specific miRs have improved sensitivity as biomarkers for vascular injury in DN and are not just by-products of disease progression but can play an active, and modifiable role in the regulation of vascular integrity.

TH-PO873

Transcriptome of Extracellular Vesicles Derived from In-Vitro Podocytes, Proximal Tubule, and Mesangial Cells

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Background: Extracellular vesicles (EVs) are lipid-bilayer structures of variable sizes (30-1000nm) secreted by all cell types. They show a characteristic vesicle surface consisting of a variety of proteins and lipids while the intracellular content is a rich array of proteins and distinct RNA species. These reflect accurately the physiological state of their cells of origin. In diabetes, development of renal insulin resistance has a major role in end-organ complications like Diabetic Kidney Disease (DKD). Little is still known of the secreted EV repertoire of especially podocytes. Here our objective was to characterize EVs secreted by DKD target cells, podocytes, proximal tubular cells and mesangial cells using the Hydrostatic Filtration Dialysis (HFD) for EV harvesting.

Methods: We used cell culture media from podocytes, proximal tubule and mesangial cells in four conditions; 1) Basal 2) Insulin resistant 3) Insulin receptor transfected 4) Insulin receptor transfected and insulin resistant. EVs were isolated from 50ml of cell culture media, respectively using the recently described HFD. Quality of EV yield was analyzed by negative-staining EM and by Western blotting. Vesicle concentration was determined by Nanoparticle Tracking Analysis (NTA). Isolated RNAs were profiled with Bioanalyzer Pico kit and subjected to RNAseq after cDNA library preparation using QIAseq miRNA Library Kit. RNAseq was performed using HiSeq 3000 (Illumina) Paired-end (2X150) protocol.

Results: The isolated EVs appeared typical at EM and were positive for the EV-marker TSG101 in Western blotting. RNA yield was of high quantity and quality and thus suitable for RNAseq. Different treatments had distinct effect on vesiculation of the investigated cells. Ninety-six EV miRNAs could clearly discriminate between cell types and engineered cells. There were distinct EV miRNAs to reflect treatment effect within each of the individual cell types studied.

Conclusions: EV analysis provides a novel approach to reveal valuable pathophysiology, pathway and signaling information of cultured target cells. Changes in EV miRNAs may give insight into insulin resistance on DKD target cells and on diabetic nephropathy.

TH-PO874

Long Noncoding RNA DLX6-AS1: A Novel Biomarker of Diabetic Kidney Disease

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Background: A growing body of evidence suggests that lncRNAs act as competing endogenous RNAs or natural microRNA sponges and are involved in diverse human diseases including diabetic kidney disease (DKD). Our previous study showed that LncRNA DLX6-AS1 expression was increased in kidney biopsy specimens from DKD patients. However, whether LncRNA DLX6-AS1 expression is associated with albuminuria in DKD remains unknown and was explored in this study.

Methods: A total of 22 type II diabetic patients without albuminuria (diabetes mellitus group), 43 patients with DKD (microalbuminuria group=20,macroalbuminuria group=23) and 32 healthy controls were enrolled in this study. Blood samples were collected. The levels of LncRNA DLX6-AS1 was estimated by RT-qPCR. The correlation between LncRNA DLX6-AS1 levels and clinical variables was assessed by Spearman correlation analysis. Linear regression was applied to model the relationship between urine albumin/creatinine ratio as the dependent variable and other parameters. ROC analysis was performed and the area under the curve (AUC) was estimated to evaluate the power of LncRNA DLX6-AS1 for predicting DKD.

Results: The four groups were comparable in sex, age and triglyceride levels. No significant difference was noted in duration of diabetes and incidence of diabetic retinopathy among subgroups of diabetes. Compared with healthy controls, the serum levels of lncRNA DLX6-AS1 was decreased in diabetic mellitus group ($P<0.05$), but was increased in DKD patients ($P<0.05$). This difference remained statistically different after adjustment for eGFR or HDL-C, as shown by linear regression analysis. In addition, serum LncRNA DLX6-AS1 levels were found to positively correlate with urine albumin/creatinine ratios(rs=0.626,$P<0.001$), but negatively correlate with eGFR(rs=-0.289,$P=0.020$). Receiver operating characteristic (ROC) curve analysis was conducted to determine the ability of serum LncRNA DLX6-AS1 levels to serve as biomarkers for predicting DKD. The area under the ROC curve (AUC) was estimated to be 0.879 (95% CI = 0.798 to 0.961), suggestive of an excellent sensitivity and specificity of serum LncRNA DLX6-AS1 levels in predicting DKD.

Conclusions: Serum levels of LncRNA DLX6-AS1 correlate with albuminuria in patients with diabetic kidney disease and may serve as a biomarker for predicting DKD.

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TH-PO875

The Leptin Receptor in Mouse Kidney: Gene Expression of Splice Variants and a Potential Anti-Albuminuric Role in Podocytes

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Background: Leptin regulates food intake and metabolism primarily through leptin receptor splice variant B (LEPRB) in brain and liver. Little is known about LEPR splice variants in the kidney or their function.

Methods: A) Urinary albumin to creatinine ratios (UACR) and mRNA expression of renal LEPR splice variants LEPRA, LEPRB & LEPRC (by RT-qPCR, norm. to b-actin) were determined in non-diabetic mice (nd) and in obese/hyperglycemic mice lacking endogenous leptin (ob/ob) ± leptin substitution for 6 days (osmotic minipump: 4.7 μg/day s.c.) (all mice ~4 months of age & BTBR background)(n=5-8/group). B) C57BL6 mice with knockdown of LEPRs in podocytes (podocin-Cre) were generated to determine GFR (by plasma elimination kinetics of FITC-sinistrin in conscious mice) and UACR (n=8/group).

Results: A) Leptin substitution restored plasma leptin levels in ob/ob (4.3±0.3 vs 4.6±0.7 ng/ml in nd mice) and reduced hyperglycemia (275±29 vs 573±17 mg/dl in vehicle-treated ob/ob; $P<0.05$). In all 3 groups, the renal mRNA expression was higher for LEPRA vs LEPRB or LEPRC, and the expression of all 3 variants was higher in medulla vs cortex. The cortical expression of all 3 variants was lower in ob/ob vs nd, and not significantly affected by leptin substitution. Medullary expression was more variable. The transcription factor Atf3 is a newly discovered mediator of brain LEPRB. Atf3 mRNA was increased in kidney cortex & medulla in ob/ob vs nd and not altered by leptin substitution. The latter, however, reduced UACR in ob/ob (pre to post: 650±145 to 167±45 μg/mg; $P<0.05$) whereas vehicle was ineffective (632±283 to 819±217 μg/mg). B) Ten week old male mice with LEPR knockdown in podocytes had similar blood glucose

(129±5 vs 117±3 mg/dl) and GFR (436±16 vs 443±18 μl/min) but enhanced UACR vs wild-type littermates (20.5±7.4 vs 8.8±1.5 μg/mg; P<0.05).

Conclusions: On mRNA level, LEPRA is the dominant renal splice variant of the LEPR, and LEPR splice variants are higher expressed in medulla vs cortex. Absence of leptin did not upregulate mRNA expression of LEPR splice variants in cortex or medulla, but enhanced mRNA of the LEPRB target gene Atf3. Functional studies were consistent with an anti-albuminuric effect of leptin, potentially via LEPR in podocytes.

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TH-PO876

Photoacoustic Ultrasound Can Non-Invasively Detect Kidney Fibrosis

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Background: Fibrosis is a key manifestation and driver of chronic kidney injury. Despite its importance, the options for measuring fibrosis are limited. The only available test is a needle biopsy, a time-consuming, invasive procedure that at best samples < 1% of one kidney, leading to the potential for sampling bias. Unlike biopsy, ultrasound can quickly and non-invasively image the entire kidney. While historically limited to the imaging of gross abnormalities, the recent combination of laser technology with ultrasound ("photoacoustic (PA) ultrasound") has dramatically expanded its capabilities. Based on the principle that each molecule has its own unique light absorption spectrum, PA ultrasound can be used to non-invasively image specific molecules. We have previously demonstrated that PA ultrasound can specifically detect extracellular matrix in a model of ischemia-reperfusion injury (doi: 10.1117/12.2291199). Our goal was to test whether PA ultrasound could detect milder degrees of fibrosis in a clinically relevant model of diabetic nephropathy.

Methods: Diabetes was induced in renin-overexpressing, hypertensive TTRhRen mice using a low dose STZ injection protocol (Ren-STZ mice, n=7). Ren-STZ mice develop hypertension, hyperglycemia, albuminuria, and renal fibrosis (Thibodeau et al, PLoS ONE 2014). Kidneys were imaged in vivo using a VevoLAZR system at 21 MHz by Photoacoustic (PA) spectral sweep from 680 to 970 nm at 0 and 20 wks post-STZ, and compared with wild-type littermates injected with citrate (WT-citrate, n=9). 20 wks post-injection, kidneys were assessed by picrosirius red (PSR) staining to quantify fibrosis.

Results: Ren-STZ mice developed hypertension (138±7vs. 98±5 mmHg) and hyperglycemia (28.0±2.6 vs. 9.7±0.3 mmol/L) compared to WT-citrate mice 20 wks post-STZ injection. As expected, Ren-STZ kidneys were more fibrotic than WT-citrate controls (PSR intensity: 5.4±0.1 vs. 2.8±0.1). Prior to STZ injection, the photoacoustic spectra of Ren-STZ and WT-citrate kidneys were similar. However, 20 wks post-STZ, Ren-STZ kidneys demonstrated significantly different photoacoustic spectra compared to their WT-citrate counterparts, in line with the fibrosis observed histologically.

Conclusions: Our data suggest that photoacoustic ultrasound may enable the non-invasive, whole organ imaging of kidney fibrosis.

Funding: Private Foundation Support

TH-PO877

ROCK2 Inhibitors for the Treatment of CKD

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Background: The Rho Associated Coiled-Coil Containing Protein Kinase (ROCK) serine/threonine kinases, ROCK1 and ROCK2, are central signalling proteins that regulate a range of cellular responses such as cell migration, contraction, proliferation, cytokine and growth factor expression, and integrin-mediated cell-to-cell adhesions. These processes are central to the aberrant wound healing response that can progress to chronic injury and organ fibrosis. Small molecule pan-ROCK inhibitors have been shown to be anti-fibrotic in a range of animal models including: bleomycin induced lung fibrosis, high fat diet induced liver fibrosis and models of kidney fibrosis. However, ROCK signalling is also involved in regulating vascular tone and pan-ROCK inhibitors have been shown to cause hyperaemia and hypotension, limiting their use in patients. There is significant homology between the ROCK1 and ROCK2 isoforms however there is evidence that ROCK2 has additional roles distinct from ROCK1 in both inflammation and wound healing. For example, ROCK2 is upregulated in diabetic kidney disease and in the diseased vascular network of patients at risk of chronic kidney disease (CKD).

Methods: Redx have developed a series of potent ROCK2 inhibitors, that are highly selective against ROCK1 and a panel of 468 kinases.

Results: Redx ROCK2 selective compounds potently suppress the release of pro-fibrotic factors from kidney mesangial cells, cultured in high glucose. In a model of acute kidney injury, our selective ROCK2 tool compound reduced podocyte damage, and the expression of inflammatory and profibrotic genes in the kidney. In addition, in a telemetered rat study, no significant reduction in blood pressure or increase in heart rate was recorded, indicating that a selective ROCK2 inhibitor could avoid these side-effects typically observed with pan-ROCK inhibitors and increase the safety window at efficacious doses.

Conclusions: Highly selective ROCK2 inhibitors, therefore, could provide a novel and effective therapy for patients with progressive kidney fibrosis who currently have few and largely ineffective therapy options.

Funding: Commercial Support - Redx Pharma

TH-PO878

Hyperoside Alleviates the Early Glomerular Pathological Changes in Diabetic Kidney Disease by Inhibiting Akt/mTOR/p70S6K Signaling Activity

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Background: Hyperoside (HYP), a bioactive component of *Abelmoschus manihot*, has been widely applied to clinical therapy in the early diabetic kidney disease (DKD) patients. However, it remains elusive whether HYP can ameliorate inchoate glomerular injuries in hyperglycemia. Recently the activation of phosphatidylinositol-3-kinase (PI3K)/serine-threonine kinase (Akt)/mammalian target of rapamycin (mTOR) signaling and its downstream regulator, 70-kDa ribosomal protein S6 kinase (p70S6K), play important roles in the early glomerular pathological changes of DKD including glomerular hypertrophy, glomerular basement membrane (GBM) thickening and mild mesangial expansion. This study aimed to clarify therapeutic effects of HYP during the initial phase of DKD and its underlying mechanisms.

Methods: Fifteen rats were randomly divided into 3 groups: the normal, the model and the HYP groups. The early DKD model rats were induced by unilateral nephrectomy combined with intraperitoneal injection of streptozotocin, and administered with either HYP suspension or vehicle after modeling and for a period of 4 weeks. Changes in incipient glomerular lesions-related parameters in urine and blood were analyzed. Kidneys were isolated for histomorphometry, immunohistochemistry, immunofluorescence and Western blotting (WB) at sacrifice. In vitro, murine mesangial cells (MCs) were used to investigate inhibitory actions of HYP, on cellular hypertrophy-associated signaling pathway by WB, compared with rapamycin (RAP).

Results: For the early DKD model rats, HYP ameliorated micro-urinary albumin, body weight and serum albumin, but had no significant effects on renal function and liver enzymes; HYP improved renal shape, kidney weight and kidney hypertrophy index; HYP attenuated glomerular hypertrophy, GBM thickening and mild mesangial expansion; HYP inhibited phosphorylation of Akt, mTOR and p70S6K, and protein over-expression of transforming growth factor-β1 in kidneys. *In vitro*, phosphorylation of PI3K, Akt, mTOR and p70S6K in MCs induced by high-glucose was abrogated by treatment of HYP or RAP.

Conclusions: This study demonstrated HYP alleviates the early glomerular pathological changes of DKD, likely by inhibiting Akt/mTOR/p70S6K signaling activity *in vivo* and *in vitro*, and provided the first evidence that HYP directly contributes to the prevention of the early DKD.

Funding: Government Support - Non-U.S.

TH-PO879

Identification and Validation of Differentially Expressed Urinary Exosomal MicroRNAs in Type 2 Diabetic Kidney Disease

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Background: There is a need for improved biomarkers for the early detection of diabetic kidney disease (DKD). MicroRNAs (miRNAs) are short, non-coding regulatory RNA molecules commonly found in urinary exosomes that may be differentially expressed during renal dysfunction. We evaluated urinary exosomal miRNA expression in type 2 DKD (T2DKD).

Methods: 87 previously reported human urinary exosomal miRNAs were profiled (Qiagen Human Urine Exosome Focus miRNA Panel) to identify differentially expressed miRNAs in a discovery cohort of patients with T2DKD (n= 14) and individuals with T2D and normal renal function, matched by age and gender (n= 15). Differentially expressed target miRNAs were validated in a second cohort of patients with T2DKD (n= 22) or no diabetes and poor renal function (n=18), and control subjects with T2D and normal renal function (n= 22).

Results: Quantitative expression profiles were normalised according to the NormFinder algorithm. Urinary miR-21-5p, let-7e-5p and miR-23b-3p were significantly upregulated in T2DKD cases compared to T2D controls with good renal function (P<0.05). Conversely, miR-30b-5p and miR-125b-5p expression were significantly lower in T2DKD cases compared to T2D controls (P<0.05). In a logistic regression analysis adjusted for age, sex and mean arterial blood pressure, only miR-21-5p remained significantly associated with T2DKD (odds ratio=3.28, confidence intervals: 1.14 – 9.43; P=0.03). Independent validation in the replication cohort confirmed up-regulation of miR-21-5p expression in T2DKD (2.13-fold, p<0.01) and also in patients without diabetes and poor renal function (1.73-fold, p<0.05). In contrast, miR-30b-5p was downregulated in T2DKD (1.22-fold, p<0.01) and in patients without diabetes and poor renal function (1.52-fold, p<0.005).

Conclusions: Our data identified differential expression of miR-21-5p and miR-30b-5p in individuals with poor renal function, although further clarification to determine if these are associated with general mechanisms of renal dysfunction is required.

Funding: Government Support - Non-U.S.

TH-PO880

Soluble cMet Levels in Urine Are a Significant Prognostic Biomarker for Diabetic Nephropathy

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Background: Hepatocyte growth factor (HGF) and its receptor, cMet, activate biological pathways necessary for repair and regeneration following kidney injury. Here, we evaluated the clinical role of urinary cMet as prognostic biomarker in diabetic nephropathy (DN).

Methods: A total of 218 patients with DN were enrolled in this study. We examined the association of urine cMet levels and long-term outcomes in patients with DN.

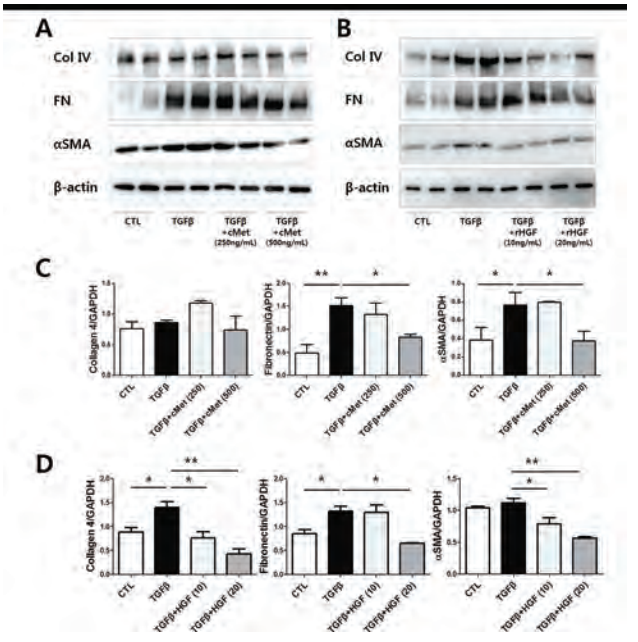
Results: The levels of urinary cMet were higher in patients with decreased renal function than in patients with relatively preserved renal function (5.17 ± 9.56 ng/ml versus 1.86 ± 4.85 ng/ml, P = 0.001). A fully adjusted model revealed that a urinary cMet cutoff of 2.9 ng/mL was associated with a hazard ratio for end-stage renal disease of 2.50 (95% confidence interval 1.18–4.53, P = 0.007). The addition of urinary cMet to serum creatinine and proteinuria provided the highest net reclassification improvement. We found that in primary cultured human glomerular endothelial cells, TGFβ treatment induced fibrosis, and the protein expression levels of collagen IV, fibronectin, and αSMA were decreased after administration of an agonistic cMet antibody.

Conclusions: In conclusion, elevated levels of urinary cMet at the time of initial diagnosis could predict renal outcomes in patients with DN.

Comparison of the ROC curve, IDI and category-free NRI of the Cr vs. Cr, UPCR vs. Cr, UPCR, cMet/Cr in predicting ESRD

	AUC (95% CI)	DeLong test P-value	IDI P-value	(95% CI)	category-free NRI P-value	(95% CI)
ESRD						
Cr	0.858 (0.808, 0.907)	Reference	Reference		Reference	
cMet/Cr	0.694 (0.623, 0.765)	<.0001	<.0001	6.52% (3.18%, 9.87%)	<.0001	88.31% (65.02%, 111.61%)
Cr+UPCR	0.889 (0.846, 0.931)	0.0369	0.0001	6.76% (3.38%, 10.15%)	<.0001	82.64% (59.07%, 106.22%)
Cr+UPCR+cMet/Cr	0.890 (0.848, 0.933)	0.0295	0.0001		<.0001	
Death						
Cr	0.644 (0.569, 0.720)	Reference	Reference		Reference	
cMet/Cr	0.620 (0.536, 0.704)	0.5943	0.0748	0.32% (-0.53%, 1.17%)	0.1726	11.95% (-15.42%, 39.31%)
Cr+UPCR	0.633 (0.556, 0.710)	0.5717	0.4641	2.76% (0.16%, 5.35%)	0.3923	2.82% (-31.11%, 25.47%)
Cr+UPCR+cMet/Cr	0.641 (0.558, 0.724)	0.9138	0.0372		0.8453	
Composite						
Cr	0.865 (0.818, 0.911)	Reference	Reference		Reference	
cMet/Cr	0.694 (0.626, 0.761)	<.0001	<.0001	2.86% (0.46%, 5.27%)	<.0001	81.06% (57.53%, 104.59%)
Cr+UPCR	0.878 (0.835, 0.922)	0.1490	0.0196	4.78% (2.10%, 7.46%)	<.0001	74.21% (50.30%, 98.12%)
Cr+UPCR+cMet/Cr	0.886 (0.844, 0.928)	0.0555	0.0005		<.0001	

Cr, creatinine; UPCR, urine protein-to-creatinine ratio; ESRD, end stage renal disease; CI, confidence interval; IDI, integrated discriminatory improvement; NRI, net reclassification improvement



TH-PO881

Urinary Peptidomic Analysis Reveals Bioactive Uromodulin Peptides Associated with Early Type 1 Diabetes

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Background: Diabetic nephropathy is the leading cause of kidney disease worldwide. Yet, current treatments cannot prevent the progressive nature of the disease, exposing our limited understanding of the early kidney response to chronic hyperglycemia. In this study, we compared the urinary peptidomes of youths with type 1 diabetes without evidence of nephropathy and age/sex-matched healthy controls, in order to determine early changes in protein processing in the hyperglycemic kidney.

Methods: The study population comprises two separate cohorts: a discovery cohort (N = 30) and an internal validation cohort (N = 30). Urines were normalized to creatinine and underwent 10kDa-filter centrifugation to isolate naturally occurring peptides. In the discovery phase, filtered peptides were then fractionated and then injected on a Q-Exactive mass spectrometer. For the validation phase, parallel reaction monitoring (PRM) assays were developed on a Q-Exactive HFX instrument. MaxQuant and Skyline were used for peptide identification and quantification. Proteasix was used to predict proteases responsible for generating differentially excreted peptides.

Results: A total of 6349 urinary peptides from 750 proteins were quantified. Of the 15 differentially excreted peptides (P < 0.05), five remained significant after Benjamini-Hochberg adjustment (q < 0.05). Seven of these top 15 peptides derive from the C-terminal region of uromodulin, which regulates uromodulin polymerization. Out of the twelve predicted proteases, hepsin, granzyme A, kallikrein-6, and plasminogen were shortlisted because they were detected in healthy kidney tissues (Human Protein Atlas) and were altered at the level of gene expression in diabetic nephropathy (Nephroseq v5 database). Differential excretion of six uromodulin peptides was validated by PRM. Two of the validated uromodulin peptides induced NF-κB signaling in HK-2 cells, suggesting a potential role in mediating inflammation in kidney cells.

Conclusions: Differences between youths with type 1 diabetes and healthy controls are reflected in the urinary peptidome before the development of microalbuminuria. Uromodulin peptides we discovered may play a significant role in the early injury in a diabetic kidney and may represent a therapeutic target.

TH-PO882

Pirfenidone May Protect Against Diabetic Kidney Disease by Reducing Fumarate

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Background: Recent studies suggest that Pirfenidone (PFD) has anti-fibrotic effect in various diseases including diabetic kidney disease (DKD). We previously demonstrated that in type 2 diabetic animal models PFD significantly reduces the expansion of mesangial matrix. Furthermore, in a placebo-cotrolled clinical study we found that PFD treatment for 54 weeks significantly improved eGFR with a low dose. In the current study we aim

to identify predictive metabolite biomarkers and potential mechanisms associated with renoprotective effects of PFD and also tested a longer acting and better tolerated version.

Methods: 1) Two types of PFD (short acting and long acting) were administered to 16 week db/db and db/m control mice (n=8 each). After 4 weeks, 24 hr urine was collected and 70 urinary metabolites were quantified using GC-MS/MS. 2) Urine and plasma from our prior clincal trial was assessed for metabolite markers from samples collected every 3 months. Fumarate in human urines was also assessed with a specific fumarate assay kit.

Results: Significant changes in metabolites were observed between the db/mand db/db, and PCA plot clustered the two groups into well-defined spaces. The db/db mice treated with PFD were in closer proximity to the db/db cluster with a slight trend toward the db/m cluster. Untreated Db/db mice had lower levels of succinate, citrate, 3-methyl crotonyl glycine, 2 hydroxyglutarate, and uracil, but PFD treated db/db mice had the levels restored either partially or completely back to the levels of db/m. Interestingly, the db/db mice had three fold increase in fumarate as compared to the db/m mice ($p<0.0001$), while long acting PFD treatment significantly reduced the fumarate levels below that of db/m mice ($p<0.0001$). In the human study, the baseline urine fumarate level of placebo treated patients showed negative correlation with the rate of change in GFR at 12 months ($r=-0.89$, $p<=0.05$). The correlation was not observed in subjects treated with PFD.

Conclusions: The anti-fibrotic effects of PFD in kidney has effects on several urinay metabolites identified to be regulated in human diabetic kidney disease. Fumarate may be a useful biomarker in the mouse model of diabetic kidney disease and may be a potential marker for anti-fibrotic therapies.

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TH-PO883

Urinary Baseline AQP5 Is Independently Associated with eGFR Decline in Patients with Type 2 Diabetes and Nephropathy

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Background: Water channel AQP5 has been shown to be upregulated in kidney biopsies from patients with diabetic nephropathy, and may serve as a biomarker for tubular damage. Here we investigate whether urinary baseline water channel AQP5 is independently associated with eGFR decline in patients with type 2 diabetes and nephropathy.

Methods: Baseline urine samples (n=997) were used from the SUN-Macro randomized placebo controlled double blind clinical trial, which evaluated the renoprotective effects of sulodexide in patients with type 2 diabetes and nephropathy. Human AQP5-specific enzyme-linked immunosorbent assay was measured in baseline urine. Pearson correlation and multiple linear regression between baseline AQP5 with eGFR slope (calculated by ≥3 serum creatinine during follow-up) was performed, and association with fast renal function decline, defined as eGFR slope less than 3.0 mL/min/1.73m^2/year, was determined by logistic regression.

Results: Follow-up eGFR data over 1.4 years from n=700 were available for analysis. AQP5 was undetectable in 138 patients. Tertiles of baseline AQP5 were 0.4 [0 – 2.2], 7.3 [5.9 – 9.1], and 16.0 [13.0 – 21.6] (ng/mL), respectively (p-value <0.01). Patients in the highest tertile of AQP5 had significantly higher total cholesterol, lower baseline eGFR, and higher levels of albuminuria compared to the lowest tertile. Baseline AQP5 was inversely correlated with eGFR slope (Pearson's r = -0.12, p-value = 0.001), and independent of clinical risk factors age, sex, race, and baseline: SBP, DBP, HbA1c, Tot. Cholesterol, eGFR, and UACR (β = -0.05, p-value = 0.004). Furthermore, baseline AQP5 was significantly associated with fast eGFR decline (OR = 1.03 (95%CI 1.003 – 1.06), p-value = 0.03).

Conclusions: Our data suggest that baseline AQP5, a possible marker of tubular dysfunction, is independently associated with the progression of eGFR decline in patients with type 2 diabetes and nephropathy. Validation of these findings in an external cohort is necessary.

Funding: NIDDK Support

TH-PO884

PI3 Kinase/Akt Node Acts as a Driver for High Glucose-Induced miR-214 Expression to Induce a Positive Feedback Loop via PTEN for Matrix Protein Expression in Proximal Tubular Epithelial Cells (PTECs)

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Background: We have recently shown that high glucose (HG) increased the expression of miR-214 to regulate renal fibrosis by directly targeting the 3' UTR of PTEN tumor suppressor protein (Am J Physio Cell Physiol 313: C430, 2017). The mechanism by which HG regulates miR-214 expression is not known. We hypothesized involvement of PI 3 kinase (PI 3 K)/Akt cascade in this process.

Methods: Human PTECs, activation-specific phospho-antibodies, shRNA, dominant negative kinases, real time qRT-PCR and immunoblotting were employed.

Results: In human PTECs, HG increased the expression of miR-214. To address the role of PI 3 K, we used its inhibitor Ly294002 (Ly). Ly significantly inhibited the HG-stimulated expression of miR-214. Similarly, expression of dominant negative PI 3 K markedly blocked the miR-214 expression in response to HG. Inhibition of Akt, the downstream kinase of PI 3 K, by MK2206 significantly suppressed the HG-induced miR-214 expression. In diabetic renal pathology a significant role of mechanistic target of rapamycin complex 1 (mTORC1) has been established. Rapamycin significantly attenuated the miR-214 expression by HG. Furthermore, shRNA against raptor, required for mTORC1 activation, blocked the HG stimulated miR-214 expression, similar to rapamycin. Since miR-214 downregulates PTEN to drive tubular matrix protein expression, we examined the role of PI 3 K/Akt in PTEN protein expression. Downregulation of PTEN by HG was reversed by dominant negative PI 3 K or Akt, which led to inhibition of mTORC1 activity as judged by phosphorylation of its substrate S6 kinase at Thr-389. Consequently, the HG-induced fibronectin expression was blocked by the dominant negative PI 3 K and Akt. Interestingly, plasmid-derived expression of miR-214 attenuated the increment of PTEN by the dominant negative PI 3 K or Akt in the presence of HG, resulting in increase in mTORC1 activity and expression of fibronectin.

Conclusions: These results are the first demonstration for a key role of PI 3 K/Akt signaling in HG-induced miR-214 expression. Furthermore, our data give evidence for a positive feedback loop involving the PI 3 K/Akt/mTORC1/miR-214 and PTEN for driving tubular fibrosis.

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TH-PO885

Inhibition of MicroRNA-451 Increases Metabolic Acidosis in a Mouse Model of Insulin Resistance and Early Diabetic Nephropathy

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Background: Metabolic acidosis (MA) is a common complication of diabetic nephropathy (DN) and is associated with an increased risk of end-stage renal failure. MA has major systemic consequences which include protein wasting, inflammation, insulin resistance, worsened hypertension and bone disease. Several studies suggest a renal protective role of microRNA-451 (miR-451) in ameliorating progression of DN. The current study aimed to elucidate the role of miR-451 in the development of MA in a mouse model of insulin resistance.

Methods: Male TALLYHO/Jng mice (insulin resistant and obese) were placed on a high-fat diet (60% kCal) and divided into two treatment groups. Mice received 8 consecutive weekly intraperitoneal injections of locked nucleic acid (LNA) miR-451-inhibitor or LNA-scramble (2 mg/kg bw; n =8/treatment). 24-hr urine was collected at 2-week intervals. Mice were humanely euthanized after 12 weeks and kidneys harvested.

Results: LNA-miR-451-inhibitor reduced renal expression of miR-451 6-fold in inhibitor treated mice ($p=0.0002$). Masson's Trichrome revealed inhibition of miR-451 increased collagen deposition by 68% ($p=0.007$). Blood chemistry revealed higher blood Na+ concentrations (2.4%; $p=0.007$) and anion gap (165%; $p=0.01$) in the mice treated with inhibitor versus vehicle control. There was also a strong trend for lower blood TCO_2 (12.6%; $p=0.06$) and HCO_3 (13.6%; $p=0.06$) in inhibitor-treated mice. There were no significant differences in serum K+ and Cl-. Western blotting analysis of cortex homogenates revealed significant increases in aquaporin-2 (52.8%, $p=0.03$), the sodium bicarbonate cotransporter (NBCe1) (28.3%, $p=0.02$) and SNAT3 (80.7%, $p=0.0008$) in inhibitor-treated mice. Additionally, there was a strong trend for an increase in the a-subunit of the epithelial sodium channel (ENaC) (35.5%, $p= 0.05$) in inhibitor-treated mice.

Conclusions: These findings suggest miR-451 may protect against the development of acidosis in the setting of insulin resistance and early diabetic nephropathy, further supporting its potential use as a therapuetic target for DN. Upregulation of transporters involved in proximal-tubule ammoniagenesis are likely a response to the acidosis.

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TH-PO886

Diabetes Potentiates the Differentiation of Bone Marrow-Derived Cells into Glomerular Endothelium

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Background: Diabetes causes its complication including neuropathy and nephropathy, and these disorders could share a common mechanism. Recently, it has been shown that bone marrow-derived cells (BMDCs) play a role in the development of diabetic neuropathy. In particular, BMDCs expressing TNF-α reach peripheral neuronal systems to cause functional disorders. However, it remains unclear if BMDCs are involved in the kidney injury of diabetes. We thus hypothesized that BMDCs cause diabetic nephropathy (DN). To test our hypothesis, we examined the role of BMDCs in mice with DN.

Methods: We transplanted the total bone marrow of GFP-Tg mice into wild type mice and then induced diabetes by intraperitoneal injection of 55mg/kg streptozotocin (STZ) for five consecutive days. At 6 and 20 weeks after STZ injection, mice were sacrificed for analyses. Non-diabetic control mice were injected citrate buffer only.

Results: We first confirmed using FACS analysis that over 98% of BMDCs of recipient mice were GFP positive. Immunofluorescence study demonstrated that the number of GFP-positive BMDCs in diabetic glomerulus was significantly higher than that in non-diabetic glomerulus. Most GFP-positive cells were also positive for CD31 and isolectin B4, but negative for podocin, α8 integrin and F4/80, suggesting BMDCs could differentiate into glomerular endothelial cells. Interestingly, the number of residential endothelial cells (GFP-negative endothelial cells) were identical between diabetic and non-diabetic glomerulus. These data suggest that BMDCs could contribute to the development of neovascularization in DN.

Conclusions: BMDCs arrive at glomerulus and they may be involved in neovascularization in diabetic mice. BMDCs could play a potential role in the development of DN.

TH-PO887

Myo-Inositol Oxygenase Modulates the Progression of Renal Fibrosis in Diabetes via Oxidant and ER Stress

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Background: Myo-inositol oxygenase (MIOX) is a renal tubular specific enzyme and its overexpression is associated with increased oxidant stress and renal fibrosis. Excessive ROS generation leads to accumulation of misfolded proteins in endoplasmic reticulum (ER) causing ER stress. How MIOX serves as a nodal molecule for regulating the progression of diabetic tubulopathy via oxidant and ER stress in hyperglycemia remains unexplored.

Methods: A diabetic state was induced with the administration of STZ in wild type (WT), MIOX transgenic (TG) and MIOX$^{-/-}$ (KO) mice. In addition, *MIOX*$^{-/-}$ (KO) mice were cross bred with *Ins2* ^{Akita} mice to generate mice with double mutation (*Ins2* ^{Akita}*/MIOX-KO*) to assess if genetic deletion of MIOX ameliorates the progression of tubulo-interstitial injury in *Ins2* ^{Akita} mice.

Results: The expression of GRP78/Bip, a marker of ER stress, and another ER stress regulator, i.e., transcription factor X-BOX binding protein-1 (XBP-1), were increased in kidneys of WT and MIOX-TG mice with STZ-induced diabetes and *Ins2* ^{Akita} mice. Interestingly, by EMSA and ChiP assays MIOX expression was noted to be regulated by XBP-1. MIOX-KO and *Ins2* ^{Akita}*/MIOX-KO* had reduced expression of XBP1 and GRP78/Bip in diabetic state, and the kidneys of these mice had reduced tubulo-interstitial injury and fibrosis. Concomitantly, the extent of renal cellular redox was reduced in MIOX-KO and *Ins2* ^{Akita}*/MIOX-KO* mice, while markedly accentuated in WT, MIOX-TG and *Ins2* ^{Akita} mice, as indicated by perturbed NADPH:NADP ratios and increased DHE, and DCF staining in renal tissues. The assessment of relevant signaling molecules revealed an increase in the expression of p-PDK1, p-PKC in kidneys of MIOX-TG mice. Likewise, expression of TGF-β and Smad 3, 4 were relatively high in diabetic WT and MIOX-TG, and *Ins2* ^{Akita} mice. The expression of the signaling molecules were marginally affected in KO mice. Similar results were observed in *in vitro* HK-2 cells studies with MIOX over-expression and gene disruption of MIOX as well as the XBP1, a hallmark of ER stress.

Conclusions: These findings identify a link between the biology of MIOX and oxidant and ER stress and delineate the role of MIOX as a nodal molecule in the pathogenesis of tubulo-interstitial fibrosing injury in diabetic state.

Funding: NIDDK Support

TH-PO888

Allogeneic "Neo-Islets," Composed of Mesenchymal Stem and Islet Cells, Are Immune Protected and Control, After i.p. Administration, Auto-Immune Type 1 Diabetes Mellitus in Pet Dogs

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Background: Curative T1DM therapies are needed that do not depend on potentially toxic anti-rejection drugs, encapsulation devices or the requirement for up to 5 pancreas donors per islet transplant. We demonstrated that allogeneic, ip administered "Neo-Islets" (NIs), aggregates of cultured islet cells (ICs) and immune- and cyto-protective Adipose Derived Stem Cells (ASCs), reestablished durable normoglycemia through omental engraftment and splenic and omental upregulation of Tregs, in autoimmune T1DM NOD mice without immunosuppressive agents. Comparable euglycemia was achieved with dog-derived NIs in STZ-diabetic NOD/SCID mice (*SCTM* 2017;6:1631). Here we report on an FDA supervised pilot study (*INAD 012-776*) using this NI therapy in 2 insulin-dependent pet dogs.

Methods: Insulin dependent (≥ 6 months), diabetic pet dogs, ≤12 kg, were included, 6 enrolled; 3 treated, and 2 (Dogs 1 and 2, male) followed for 6 months. Pre-treatment serum from Dog 1 and Dog 2 was tested for the presence of islet autoantibodies, and comorbidities and blood glucose levels were treated. 2x10e5 allogeneic NIs per kg b.wt. were then given i.p. Blood glucose levels, insulin requirements and formation of antibodies to allogeneic NIs were closely monitored.

Results: Prior to treatment Dog 1 had no islet autoantibodies, suggesting insulin resistance, while Dog 2 had islet autoantibodies, indicating autoimmunity. Both dogs have improved glycemic control. Dog 2's insulin requirements have decreased by 50% after 6 months. Neither dog developed antibodies to the administered NIs, and no adverse events related to treatment were observed.

Conclusions: This ongoing pilot study in diabetic dogs demonstrates that NI therapy progressively reduces insulin requirements. This was achieved, without anti-rejection drugs. NIs, as engineered here, provide a novel therapy that, we posit, has significant translational relevance to clinical T1DM. We thank site PIs Drs. Rance Sellon, WSU, Pullman, WA, Natasha Loy Son and Julie Fisher, Veterinary Specialty Hospital, San Diego, CA, for their excellent collaboration.

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TH-PO889

Effect of DsbA-L on Renal Ectopic Fat Deposition and Lipid-Related Kidney Damage in Diabetic Nephropathy

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Background: Emerging evidence suggests that ectopic fat deposition (EFD) in the kidney is related to the progression of diabetic nephropathy (DN), but the mechanism remains elusive. Disulfide-bond A oxidoreductase-like protein (DsbA-L) also known as Glutathione S-transferase kappa 1 (GSTK1), which has been demonstrated to regulate adiponectin multimerization, alleviate endoplasmic reticulum stress and prevent obesity-induced inflammation and insulin resistance. But the role of DsbA-L in renal EFD and lipid-related kidney damage is unknown.

Methods: In this study, patients with DN, DsbA-L deficiency mice (DsbA-L$^{-/-}$ mice), DsbA-L overexpression mice and HK-2 cells, a human proximal tubular cells line were used. Differentially expressed genes were identified by transcriptome in the kidney tissues of mice. Oil red o staining, electron microscope and immunostaining of adipocyte differentiation-related protein (ADRP) were used to observe or detect the lipid depostion in the kidney tissues of DN patients or mice.

Results: Here, we identified decreased expression of disulfide - bond A oxidoreductase-like protein (DsbA-L) and increased expression of adipocyte differentiation-related protein (ADRP) in the kidney of diabetic mice. Further, obvious lipid droplets (LDs) deposition and decreased DsbA-L expression were observed in the kidney of diabetic mice, accompanied by abnormal levels of phosphorylation of 5'AMP-activated kinase (p-AMPK), p-adipose triglyceride lipase (p-ATGL), p-3-hydroxy-3-methylglutaryl- CoA reductase (p-HMGCR), collagen I and fibronectin (FN). The above alterations were further increased in diabetic DsbA-L$^{-/-}$ mice. Overexpression of DsbA-L ameliorated high glucose (HG)-induced intracellular LDs deposition, whereas DsbA-L siRNA treatment aggravated it and was accompanied by reduced levels of p-AMPK, p-ATGL and p-HMGCR in HK-2 cells, a human proximal tubular cells line. Additionally, HG plus palmitic acid (PA) enhanced the expression of interleukin-1β and interleukin-18, which was further increased after DsbA-L siRNA treatment, but was alleviated by cotreatment with an AMPK activator. In the kidneys of DN patients, LDs deposition was negatively associated with DsbA-L expression but positively correlated with kidney damage.

Conclusions: Collectively, DsbA-L protects against renal EFD and lipid-related kidney damage via AMPK pathway.

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TH-PO890

Attenuated Lymphatic Proliferation Ameliorates Diabetic Nephropathy and High-Fat Diet-Induced Renal Lipotoxicity

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Background: Lymphangiogenesis occurs in response to renal injury in renal proximal tubular epithelial cells (PTECs) and infiltrating macrophages and is correlated with the degree of renal interstitial fibrosis. Diabetes and high-fat diet-induced renal lipotoxicity causes glomerular sclerosis and tubulointersitial fibrosis, but its possible involvement with regard to lymphangiogenesis has not been elucidated. Peroxisome proliferative-activated receptor (PPAR)a plays an important role against lipotoxicity under the control of AMP-activated protein kinase (AMPK). We evaluated whether fenofibrate has a renoprotective effect by ameliorating lipotoxicity-induced lymphangiogenesis.

Methods: Eight-week-old male C57BLKS/J *db/db* mice and spontaneously hypertensive rats (SHRs) were fed either a normal chow or a high-fat diet (HFD) and fenofibrate for 12 weeks and were evaluated for biochemical parameters and renal phenotypes.

Results: In *db/db* mice, fenofibrate inhibited the accumulation of intra-renal lipids by increasing the expression of PPARa and phosphorylation of AMPK. It decreased lymphatic growth, as represented by decreases in the expression of lymphatic endothelial hyaluronan receptor-1 (LYVE-1) and podoplanin, along with decreases in vascular endothelial growth factor-C (VEGF-C) and vascular endothelial growth factor receptor-3 (VEGFR-3). Consequently, fenofibrate reversed mesangial expansion, tubulointerstitial fibrosis and chemokine-induced inflammatory cell infiltration by improving apoptosis and oxidative stress. In HFD SHRs, fenofibrate attenuated renal lymphatic proliferation and inflammation by decreasing lipotoxicity-induced oxidative stress and apoptosis through PPARa-AMPK phosphorylation. In cultured HK2 cells and RAW 267 cells, fenofibrate prevented palmitate- and high glucose-induced expression of VEGF-C, VEGFR-3, and LYVE-1 via activation of PPARa-AMPK-pACC signaling and enhanced expression of M1 phenotype macrophage.

Conclusions: A causal relationship between lipotoxicity and lymphatic proliferation with a cellular link to macrophage activation can be speculated; pro-inflammatory M1 type macrophages may be primarily involved in the development of intrarenal lymphangiogenesis through stimulation of VEGF-C and by its transdifferentiation into lymphatic endothelial cells.

TH-PO891

Basigin/CD147 Exacerbates Diabetic Kidney Disease Dependent of Proteinuria

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Background: CD147/Basigin (Bsg), a glycosylated transmembrane protein, contributes to cell survival, migration, cancer invasion and inflammation. We have so far demonstrated its pathophysiological roles in the kidney diseases, ranging from the occurrence of acute kidney injury accompanied by ischemia to progression of renal fibrosis and lupus nephritis. However, the mechanism of diabetic kidney disease (DKD) involving Bsg remains unknown. We therefore focused on Bsg function in the development of DKD with proteinuria.

Methods: Two independent mice models were performed using wild-type (*Bsg*$^{+/+}$) or Bsg-deficient (*Bsg*$^{-/-}$) *mice treated with streptozotocin or overloaded by bovine serum albumin, respectively. Primary proximal tubular epithelial cells (PTECs) derived from Bsg*$^{+/+}$ or *Bsg*$^{-/-}$ *mice and human PTECs were exposed to high glucose (30mM) or albumin. In clinical study, DKD patients (N=52) registered with UMIN Clinical Trials Registry (8016) were treated with spironolactone 25 mg once daily for 8 weeks. The relationships between urinary Bsg values and clinical indicators were examined.*

Results: While *Bsg*$^{-/-}$ *mice induced by protein overload ameliorate the development of tubulointerstitial injury, no obvious difference in the two genotypes representing DKD was found. In clinical study, DKD patients showed higher plasma and urinary Bsg values and marked Bsg inductions in injured tubulointerstitium. Plasma and urinary Bsg levels showed close correlations with eGFR and proteinuria, but not HbA1c, respectively.* DKD patients treated with spironolactone showed a striking reduction of urinary Bsg values as well as albuminuria. A close association between reduction rates of urinary Bsg values and albuminuria was observed. In *in vitro* study, Bsg inductions in primary PTECs after exposure of albumin, but not high glucose, were found in a concentration-dependent fashion. *Bsg silencing and gene deficiency in PTECs limited inflammation-related chemotactic activation such as MMPs and MCP-1.*

Conclusions: *Bsg plays an indispensable role in the development of DKD evoked by proteinuria through the activation of inflammatory signaling.*

TH-PO892

Different Renoprotective Mechanism of TMX-049, a Novel Xanthine Oxidoreductase Inhibitor, from Losartan: The Importance of Renal Tubule for Diabetic Kidney Disease Treatment

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Background: Diabetic kidney disease (DKD) is a major renal complication of diabetes. Although the glomerulus has been considered as the primary site of injury, recent studies have suggested that renal tubule is also the prominent site. Current medications such as losartan (Los) exert the renoprotective effects by reducing intraglomerular pressure. However, there is no drug which targets tubular injury. Xanthine oxidoreductase (XOR) is an enzyme producing uric acid and its inhibitors have been reported to improve albuminuria in DKD patients. To date we found that XOR is mainly expressed in renal tubule in rats, suggesting the target site of XOR inhibitor may be renal tubule. To determine the renoprotective effect of TMX-049, a novel XOR inhibitor, and the importance of renal tubule as a target site for DKD treatment, we examined them using animal models of DKD and albumin-induced tubular injury.

Methods: 1. Male ZDF rats were orally administrated TMX-049 or Los for 13 weeks. 2. Male unilateral nephrectomized rats were intraperitoneally injected with bovine serum albumin and orally administrated with TMX-049 or Los for 3 weeks. Urinary albumin, and KIM-1 as a tubular injury marker, were measured. XOR activity in the renal cortex was measured and histological and immunohistochemical analyses were performed.

Results: XOR, mainly expressed in renal tubule, was increased in ZDF rats, consistent with the increased XOR activity in renal cortex. TMX-049 but not Los inhibited XOR activity. In addition, TMX-049 as well as Los decreased urinary albumin and KIM-1 excretions, and ameliorated histological damage in both glomerular and tubular region in ZDF rats. Albumin induced the damage in tubular region and urinary KIM-1 excretion, indicating tubular injury by albumin, while there were no changes in glomerular region. Consistent with ZDF rats, XOR activity in renal cortex was increased in albumin-treated rats. Importantly, TMX-049 attenuated albumin-induced tubular damages whereas Los failed.

Conclusions: TMX-049 attenuated renal tubular damage by inhibiting tubular XOR, leading to suppress renal injury. These results suggest the therapeutic potential of TMX-049 and the importance of renal tubule as a target site for DKD treatment.

TH-PO893

Metabolic Differences in Diabetic Kidney Disease Patients with and Without Albuminuria

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Background: The classical paradigm describing diabetic kidney disease (DKD) as a linear progression with stages of glomerular hyperfiltration, progressive albuminuria, and subsequent declining GFR is being recently challenged. 25-50% of DKD with eGFR <60ml/min/1.73m^2 do not have albuminuria, and the underlying pathology in this group is not well studied. We studied the metabolic differences in unselected well-matched DKD patients with (DKD A1+) and without (DKD A0) albuminuria.

Methods: 41 patients with DKD, defined as diabetes mellitus with eGFR <60mL/min/1.73m^2, and 60 healthy age- and sex-matched controls were randomly chosen from the general population (HUNT-3 study, 2006-08, Norway). Urine samples were analyzed and 75 organic acids quantified using gas chromatography-mass spectrometry (GC-MS, 4-6 calibration points, CV 10-20%). Kidney function was followed over 10 years.

Results: 15 of 41 DKD patients (37%) had ACR <3.0mg/mmol. Age and sex were similar in the healthy control, DKD A0 and DKD A1+ groups (~ 71 years, p=0.3; and 40% males, p=0.6). Baseline eGFR was identical in DKD A0 and A1+ (51 vs 51 ml/min/1.73m^2). They also had similar BMI, BP, BP medication, physical activity and education (p>0.4 for all), while DKD A0 had more never-smokers (p=0.002). PLS-DA analysis of the organic acid metabolites showed that the three groups separated moderately, with DKD A0 positioned between controls and DKD A1+ patients (Figure 1). When comparing the two DKD groups, we found 22 metabolites with VIP scores ≥1.0, i.e. considered to contribute significantly to separation. Top metabolites were hexanol glycine, lactic acid and keto-glucatic acid. Enrichment analysis based on these metabolites showed that citric acid cycle, Warburg effect, glucose-alanine, keton body metabolism, and fatty acid biosynthesis were the most affected pathways (p<0.05 and ~ 5-fold enriched for all).

Conclusions: DKD patients with and without albuminuria differ substantially in their metabolic disturbances and could represent different clinical phenotypes

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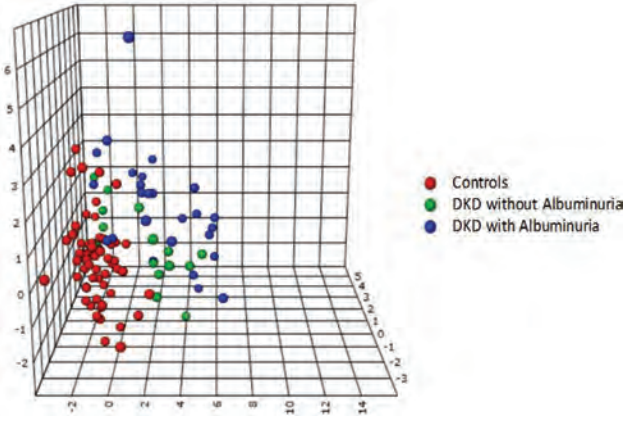

TH-PO894

Haploid Deletion of TRPC1 Gene Produces Hypercalcemia, Anemia, Diabetes, and Renal Failure, as Diploid Deletion Causes Obesity, Metabolic Syndrome, Hyperparathyroidism, Liver Steatosis, and Larger Bone Mass

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Background: The gene encoding the canonical transient recpetor potential 1 channel (TRPC1) is ubiquitously expressed. It is known to be involved in signal transduction by changing intracellular Ca, cytokine & hormone secretion, cell proliferation & differentiation. Gene deletion is now known to produce a myriad of abnromal but nonlethal phenotypes, including hypercalcemia, anemia, diabetes, renal failure, obesity, metabolic syndrome, hyperparathyroidism, hepatic steatosis & increased bone mass. We tested the hypothesis of relative gene dosge in these phenotypes by studying ♂ littermates of all 3 genotypea born to only +/- breeders.

Methods: Standard metabolic studies, glucose tolerance tests, & routine lab chemistry were done from age 1 to 22 m. Mouse ELISA were used to measure insulin, PTH, adipokines & FGF-23. Creatinine (Cr) was measured by HPLC & glomerular filtration rate (GFR) by inulin or Cr clearance.

Results: In +/- mice, like the null, we found fasting hyperglycemia at 3 m, diabetes at 6 m, hypercalcemia at 7-12 m, anemia at 11 m, & reduced GFR of 40% at 16 m. However, only in null mice could we document the following phenotypes: hyperphagia, excessive

weight gain, obesity, hypertriglyceridemia (all at 2-4 m), reduced serum FGF 23 at 3-5 m, metabolic syndrome at 6 m, increased serum leptin & reduced adiponectin at 7 m, hepatic steatosis at 12 mon, hyperparathyroidism despite hypercalcemia & hypocalciuria [like the human familial hypocalciuric hypercalcemia (FHH)] at 12 m, & increased bone mass at 19-22 m. Liver triglyceride content was elevated only in null mice. If haploid deletion replicates the phenotypes of diploid deletion, the degree of abnormalities was uniformly ccomparable.

Conclusions: We conclude: 1. Since haploid deficiency of TRPC1 gene produces anemia, diabetes, hypercalcemia & renal failure, the usual normal phenotypes would require both wild type alleles. 2. Since diplid deficiency is needed to produce hyperphagia, obesity, metabolic syndrome, FHH, hepatic steatosis & increased bone mass, the corresponding normal phenotypes can be maintained by 1 wild type allele. 3. Additional insights on the pathobiology will depend on studies in tissue-specific TRPC1 gene deletion.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-PO895

In Vivo Evidence of Role of Diabetes in Accelerating Kidney Tumorigenesis

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Background: Our published clinical data show a strong risk of diabetes in increasing of renal cell carcinoma in a cohort study of kidney cancer patients whereas 25.4 % of kidney cancer patients have history of diabetes and our recent clinical data showed that RCC patients with history of diabetes increased by 33.3%. The increasing incidence of diabetes in our population will increase the risk of solid tumors including renal cell carcinoma (RCC). The mechanism by which diabetes enhances certain pathways to develop kidney tumor is largely unknown.

Methods: The inherited renal tumor was identified in TSC2+/- animal model, which is naturally heterozygous for mutation in tumor suppressor genes, Tuberous Sclerosis Complex (TSC). The majority of tumors observed in the kidney of TSC2+/- mice originate from renal proximal tubules develop around age of 12 months. We have generated a new mouse model of TSC2+/-/dbdb-/- by cross breed TSC2+/- and dbdb mice to investigate whether diabetes accelerates tumors in new mouse model at early ages.

Results: At the day of sacrificing, WT and TSC2+/- mice showed normal blood glucose levels (80-109 mg/dL), while db/db and TSC2+/-/dbdb mice showed ranges of hyperglycemia between 405-510mg/dL measured by Glucometer in overnight fasting animals. Our novel in vivo data showed for the first time that diabetes accelerates kidney tumor size to 4-fold and number to 2-fold in TSC2+/-/dbdb new mouse model compared to TSC2+/- mice at 10 months old. Data show that no significant difference in tumor size and number between TSC2+/-/dbdb and TSC2+/- mice at age of 8 months. We didn't recognize any tumor in WT and db/db mice at this age. Next, we performed RNA sequencing in RNA isolated from kidney cortex of WT, db/db, TSC2+/- and TSC2+/-/dbdb mice at age of 10 months. The sequencing data show different patterns of downregulation and upregulation of several genes between TSC2+/-/dbdb, TSC2+/- and dbdb compared to WT mice that have significant interest in regulation of tumorigenesis.

Conclusions: Our data provided in vivo evidence of role of diabetes in accelarting kidney tumorigeneis. These data suggest that short term of diabetes is not effective to enhance tumorigenesis in TSC2+/-/dbdb mice and longer exposure to hyperglycemia is required to initiate tumorigenesis. These data confirmed for the first time that diabetes is a major risk factor for increasing kidney cancer.

Funding: Veterans Affairs Support

TH-PO896

Relationship Between Endothelial Damage and Expression of Tropomyosin on Peritubular Capillary During the Progression of Experimental Obstructive Nephropathy

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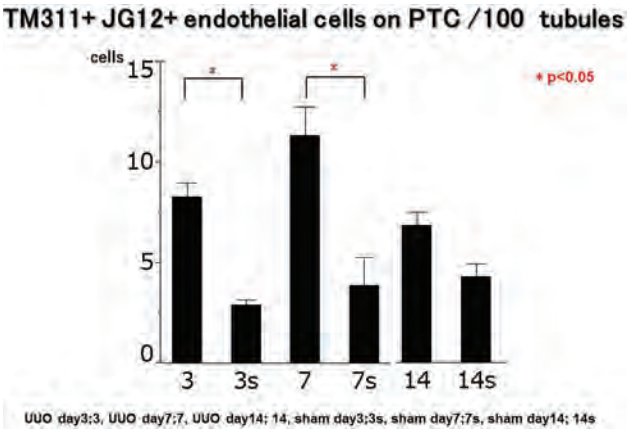
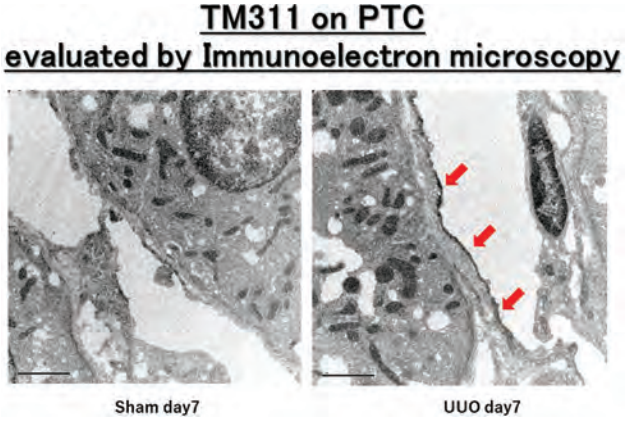
Background: Tubulointerstitial injury(TI) is a major determinant factor in progressive renal diseases. Although the injuries to peritubular capillary (PTC) network is crucial for the progression of TI, it has been few reported about marker for detecting endothelial damage on PTC. We investigated expression of Tropomyosin (TM), one of the actin-associated proteins on PTC during the progression of experimental obstructive nephropathy.

Methods: Male Wister rats (7 week old) were subjected to UUO or sham-operation, and kidneys were harvested on days 3, 7 and 14 post-surgery after pimonidazole infusion for evaluation of low oxygen area. We evaluated the expression of TM on PTC by immunostaining and immunoelectron microscopy. And real-time polymerase chain reaction, and western blot were performed. To clarify the mechanism, we assessed the expression of TM in human umbilical vein endothelial cells (HUVEC) exposed to hypoxia condition.

Results: The expression of TM on PTC significantly increased on day 3, reached a peak at day 7, and decreased on day14 by immunostaining. Also, TM was identified at cytoplasm of PTC by immunoelectron microscopy 7 days after operation, not identified in sham rats. In UUO, TM significantly expressed at low oxygen area, tended to co-express with Ki67. We confirmed the increased expression of TM in the whole kidney. In HUVEC, 12 hours hypoxia condition induced the expression of TM in immunofluorescent staining.

Conclusions: TM is a protein related to angiogenesis and increased the expression on PTC at the early stage of TI. This fact suggested TM might be a marker of endothelial damage on PTC to play a work for the protection against hypoxia damage.





TH-PO897

Oral Administration of Paramylon, a β-1,3-D-Glucan Isolated from Euglena gracilis Z Protects Against Renal Damage in CKD Rats

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Background: Paramylon is a β-1,3-D-Glucan that is stored by *Euglena gracilis Z* and a large porous molecule and plays various roles in chemical storage, ion exchange, and as a molecular sieve. It has been demonstrated to have anti-allergy effects and enhance immunological functions. Now available treatments are limited in the progression of chronic kidney disease (CKD). The aim of this study is to investigate the effect of Paramylon in CKD rats.

Methods: CKD was induced in 8-week-old male Wistar rat by 5/6 nephrectomy (Nx). A normal diet was given for 8 weeks in Sham control or in Nx rats. A diet containing 5% paramylon (PAR) obtained from euglena Co., Ltd was given for 8 weeks in Nx + PAR rats.

Results: There were no significant differences of the body weight, diet intake, and water intake between Nx and Nx + PAR groups. Increases in serum urea nitrogen and urinary protein excretion in Nx were significantly suppressed in Nx + PAR. Nx + PAR also showed histologically milder disease when compared to Nx (glomerular sclerotic score 1.8±0.4 vs. 0.9±0.2, means±SEM, $p<0.05$; tubular injury score 2.8±0.3 vs. 1.0±0.2, $p<0.05$; fibrosis area (%) 4.0±0.7 vs. 2.7±0.5, $p=0.15$; the number of interstitial PCNA-positive cells per high-power field 72±10 vs. 36±6.5, $p<0.05$).

Conclusions: Our data suggest that Paramylon may be a novel compound against the progression of renal damage in CKD rats.

TH-PO898

Altered Expression of the Renal Prostaglandin E2 Signaling System in Kidney Tissue from Patients with Hydronephrosis and Renal Fibrosis

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Background: Renal fibrosis is the final common pathway in chronic kidney diseases (CKD). Increased prostaglandin E_2-EP_4 receptor signaling through increased EP_4 receptor expression has been suggested to attenuate renal fibrosis in mice using the unilateral ureteral obstruction (UUO) model. It is unknown if patients with hydronephrosis and renal fibrosis show similar regulation of the renal prostaglandin E_2 signaling system. We tested the hypothesis that hydronephrosis and renal fibrosis is associated with increased renal COX-2 and EP_4 receptor expression in humans.

Methods: Kidney tissue was collected from patients diagnosed with hydronephrosis undergoing unilateral nephrectomy (n=12) at the Dept. of Urology, Odense University Hospital. Normal appearing kidney tissue from age- and gender matched subjects undergoing nephrectomy due to renal cell carcinoma (n=12) was used as control. The percentage of the cortical region affected by interstitial fibrosis was scored and expression of the prostaglandin E_2 signaling system was determined by qPCR.

Results: Mean age was 54 years [range 26-78 years] in the hydronephrosis group and 55 years [range 28-78 years] in the control group. All patients in the control group showed minimal or no signs of renal fibrosis (0-10%). In the hydronephrosis group, 4 patients showed mild (10-25%), 3 patients moderate (26-50%) and 2 patients severe fibrosis (50-100%). 3 patients showed minimal or no signs of renal fibrosis. No significant changes in COX-2, COX-1 or PTGES mRNA was detected. In kidney cortex, a significant upregulation of EP_2 receptor mRNA was detected in the hydronephrosis group compared to controls and a concomitant downregulation of the EP_3 receptor mRNA level. No significant changes in EP_1 or EP_4 receptor mRNAs were seen. In outer medulla, a significantly reduced expression of the EP_3 receptor was seen in the hydronephrosis group. No changes in EP receptor expression were seen in the inner medulla.

Conclusions: In conclusion, hydronephrosis and renal fibrosis in humans is associated with altered renal EP_2 and EP_3 receptor expression. No changes were detected in COX-2 and EP_4 receptor expression as has been described in mice. Results suggest the EP_2 and not the EP_4 receptor to be dominant in PGE_2 receptor signaling during renal fibrogenesis in humans.

Funding: Private Foundation Support

TH-PO899

Mechanisms of High Salt Intake-Increased (Pro)renin Receptor Expression in the Nephron of Dahl Salt-Sensitive Rats

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Background: We recently reported that high-salt (HS) intake increased the (P)RR expression by 3-5 fold in several nephron segments of Sprague-Dawley rats (Peptides 63: 156-162, 2015). The present study examined the mechanisms of the HS-intake increased (P)RR expression in Dahl-Salt sensitive (DS) rats.

Methods: Male DS rats were fed a normal salt (NS) diet (0.6%NaCl) and a HS diet (8%NaCl) for 4weeks. A part of the rats fed the HS diet were treated orally with xanthine oxidase (XO) inhibitor, febuxostat (Feb, 10mg/kg/day) or mineralocorticoid receptor (MR) antagonist, spironolactone (Spi, 100mg/kg/day). Additionally, deoxycorticosterone acetate (DOCA, 50mg/kg/week) administered to DS rats fed the NS diet for 4weeks. The (P)RR expression in the kidney sections and proximal tubules (PT) was examined by immunoblot and immunohistochemical analyses. XO activity in the CO was measured.

Results: HS intake increased the blood pressure, and Feb and Spi decreased the HS intake-increased blood pressure ($p<0.01$). HS intake increased the XO activity by 1.7 fold ($p<0.01$), and febuxostat blocked completely the activity. HS intake increased the (P)RR expression in the cortex by 22.6 fold ($p<0.001$) and the PT by 4.9 fold ($p<0.01$). Feb and Spi inhibited the HS intake-increased (P)RR expression in the cortex by 55% and 89%, respectively ($p<0.001$). Feb inhibited the HS intake-increased (P)RR expression in the PT by 69% ($p<0.001$), but Spi did not change the expression. Immunohistochemical analysis revealed that HS intake increased the (P)RR expression in the PT and distal tubules (DT) and that Feb inhibited the expression in the PT, and Spi inhibited the expression in the DT. In addition, DOCA increased the (P)RR expression in the cortex by 80% ($p<0.001$) and the DT, but not in the PT.

Conclusions: HS intake-increased (P)RR expression is enhanced in the PT and distal tubules of DS rats. The mechanisms of HS intake-increased (P)RR expression may be MR-dependent manner in the DT and XO-dependent manner in the PT.

TH-PO900

Olmesartan Attenuates Kidney Injury in Experimental Alport Syndrome

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Background: As angiotensin-converting enzyme 2 (ACE2) was identified as a negative regulator of the renin-angiotensin-aldosterone system, there have been many reports concerning its role in several tissues, including kidney. We have reported that ACE2 expression and activity in the kidney are reduced in experimental Alport syndrome (AS) and olmesartan has known as increased ACE2 activity.

Methods: To examine the effects of olmesartan treatment in AS, we used the Col4a3$^{-/-}$ mice. Mice were divided into three groups: saline-treated wild type mice group, saline-treated Col4a3$^{-/-}$ mice, and Ang-(1-7) treated Col4a3$^{-/-}$ mice group. Olmesartan medoxomil (5 mg/kg/day) was administered from 4 to 7 weeks of age via drinking water.

Results: Treatment with olmesartan led to decreased urinary NGAL excretion in 7-week-old *Col4a3*$^{-/-}$ mice. Pathological changes were attenuated by olmesartan treatment. Olmesartan ameliorated kidney fibrosis as shown by decreased expression of profibrotic genes, less accumulation of extracellular matrix proteins, and inhibition of TGF-β signaling. Further, increases in proinflammatory cytokine expression, macrophage infiltration, inflammatory signaling pathway activation, and heme oxygenase-1 (HO-1) levels in *Col4a3*$^{-/-}$ mice were also reduced by olmesartan treatment. Lastly, olmesartan influenced the turnover of renal ACE2, as it suppressed expression of TNFα-converting enzyme (TACE), a negative regulator of ACE2.

Conclusions: In summary, treatment with olmesartan alters angiotensin peptide metabolism in kidneys of *Col4a3*$^{-/-}$ mice and attenuates the progression of AS nephropathy.

TH-PO901

Therapeutic Targeting of GSK3β Rectifies Profibrogenic Plasticity of Renal Tubular Epithelial Cells in Progressive CKD

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Background: Renal tubular cells play a key role in chronic kidney injury. After a prolonged persistent injury beyond self-healing capacity, renal tubular cells will resort to maladaptive plasticity and undergo dedifferentiation, growth arrest and convertion to profibrogenic phenotypes that ultimately lead to renal fibrosis. Evidence suggests that glycogen synthase kinase (GSK) 3β is centrally implicated in kidney injury. However, its role in maladaptive renal tubular cell plasticity is unknown and was explored here.

Methods: In cultured renal tubular cells expressing diverse GSK3β mutants or treated with GSK3β inhibitors, TGFβ1-induced phenotypic changes were evaluated. In mice with tubular specific knockout of GSK3β or in mice treated with microdose lithium folic acid-induced chronic kidney injury was examined.

Results: TGFβ1 treatment triggered renal tubular cell dedifferentiation, marked by conversion from cuboidal to dispersed spindle shape, loss of cell tight junction molecules like E-cadherin and ZO-1, and *de novo* expression of vimentin. In addition, growth inhibition was noted as shown by cell cycle arrest at G2/M phase. Moreover, increased extracellular matrix proteins like collagen I and fibronectin, as well as overproduction of profibrotic cytokines, such as PAI-1 and CTGF, was evident after TGFβ1 exposure. All these profibrogenic phenotypes were reinforced in cells expressing the constitutively active mutant of GSK3β, but largely abolished by ectopic expression of a dominant negative mutant or by GSK3β inhibitors. Mechanistically, GSK3β blockade potentiated CREB activity and subsequently antagonized the TGFβ1/Smad signaling, which drives tubular cell profibrogenic plasticity. Moreover, structural rather than transcriptional β-catenin was up-regulated after GSK3β inhibition, denoting a strengthened cell tight junction. So did cyclin D1, an essential element for cell cycle progression. *In vivo*, in folic acid-injured mice, tubular cell dedifferentiation, G2/M arrestrenal and PAI-1 and CTGF expression were all mitigated by GSK3β gene ablation or by microdose lithium, a standard GSK3b inhibitor, concomitant with attenuated tubular atrophy and renal fibrosis.

Conclusions: GSK3β is likely a pragmatic therapeutic target for correcting profibrogenic plasticity of renal tubular cells in CKD to improve renal fibrosis.

TH-PO902

Proximal Tubule ATR in Humans and Mice Is a Key Regulator of the DNA Repair Response Protecting the Kidney Against Maladaptive Repair and Fibrosis After Tubular Injury

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Background: Renal proximal tubular epithelial cells (RPTECs) comprise the bulk of the renal parenchyma and are the primary target of a variety of insults to the kidney. Maladaptive repair of RPTECs has been implicated in kidney fibrosis through induction of cell cycle arrest at G2/M. The DNA damage response (DDR) is a mechanism of DNA repair that is responsible for maintaining genome integrity. We hypothesize that inhibition of DDR, through deletion of the DNA damage sensor ataxia telangiectasia and Rad3 related (ATR), would worsen the fibrotic response in RPTECs.

Methods: Human kidney biopsy tissue was analyzed from 11 patients with interstitial fibrosis and elevated serum creatinine and 9 cases with minor glomerular abnormalities and good preservation of tubules. Kidney organoids were generated from human pluripotent stem cells. An active form of ATR and the marker of DNA damage (γH2AX) were studied by immunocytochemistry along with KIM-1 to evaluate whether DDR correlates with eGFR or fibrosis. We generated RPTC-specific conditional ATR knockout ($ATR^{RPTC-/-}$) mice by crossing ATR floxed ($ATR^{fl/fl}$) with $ATR^{+/-}$ and tamoxifen-inducible RPTC-CRE driver (SLC34a1-CreERT2) mice and evaluated kidney injury, fibrosis and cell cycle arrest following ischemia/reperfusion, cisplatin and ureteral obstruction-induced injury in these mice.

Results: Humans with chronic fibrotic kidney disease and human kidney organoids treated with cisplatin have activation of ATR and extensive DNA damage in proximal tubules with an inverse correlation between p-ATR and DNA damage marked by γH2AX in human biopsies. $ATR^{RPTC-/-}$mice exhibited greater kidney functional impairment, DNA damage, and fibrosis in response to kidney injury induced by either bilateral ischemia reperfusion, cisplatin or unilateral ureteral obstruction. $ATR^{RPTC-/-}$mice had increased G2/M arrested cells after these kidney injuries.

Conclusions: DDR is activated in human kidney disease and ATR plays a protective role against tubular cell injury, death and fibrotic response. Proximal tubule ATR activation is a key component of the DDR which confers a protective effect by mitigating maladaptive repair and consequent fibrosis that follows kidney injury.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO903

Proximal Tubule Angiotensin II Type 1 Receptor-Associated Protein Regulates Kidney Aging and Lifespan Through Sirtuin1-Mediated Pathway

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Background: The kidney is easily affected by aging-associated changes including tubulointerstitial fibrosis and tubular atrophy. Angiotensin II type 1 receptor (AT1R)-associated protein (ATRAP), which was originally identified as a molecule that binds to AT1R, is highly expressed in the kidney. Previously, we have shown that ATRAP suppresses hyper-activation of AT1R signaling, but does not affect the physiological AT1R signaling pathway. This time, we hypothesized that proximal tubule ATRAP suppresses aging-related kidney fibrosis through Sirtuin1-mediated pathway independent of angiotensin signaling.

Methods: ATRAP-knockout mice (KO mice) and their wild-type control mice (WT mice) were fed the standard diet and maintained until death to estimate their life spans. Their growth, physiological parameters and aging-related organ damages in the hearts, aortas and kidneys were analyzed in both groups. To further investigate the mechanism exacerbating aging-related kidney fibrosis in KO mice, the expression of the pro-survival genes was examined using human tubular epithelial cells.

Results: KO mice exhibit a normal age-associated appearance without any evident alterations in physiological parameters, including blood pressure and cardiovascular and metabolic phenotypes. However, in KO mice compared with wild-type mice, the following takes place: (1) age-associated renal function decline and tubulointerstitial fibrosis are more enhanced; (2) renal tubular mitochondrial abnormalities and subsequent increases in the production of reactive oxygen species are more advanced; and (3) lifespan is 18.4% shorter (median lifespan: 100.4 vs. 123.1 week). As a key mechanism, age-related pathological changes in the kidney of KO mice correlated with decreased expression of the pro-survival gene Sirtuin1. Furthermore, in cultured human proximal tubular epithelial cells, deletion of ATRAP also downregulated mRNA expression levels of Sirtuin1 under serum starvation condition.

Conclusions: These results indicate that proximal tubule ATRAP regulates renal Sirtuin1 expression and plays an important role in inhibiting aging-related kidney changes and protecting the normal lifespan.

TH-PO904

Dicer Deficiency in Proximal Tubules Exacerbates Renal Injury and Tubulointerstitial Fibrosis in Diabetes and UUO Models by Upregulating Smad2/3 Expression

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Background: Renal fibrosis is a common pathological feature in chronic kidney disease, including diabetic kidney disease (DKD) and obstructive nephropathy. Multiple microRNA species have been implicated in the pathogenesis of both DKD and obstructive nephropathy. Dicer is a key RNase III enzyme for microRNA biogenesis, which has been shown to play an important role in kidney development and renal ischemia-reperfusion injury. However, the role of Dicer in diabetic and obstructive kidney diseases remain unclear.

Methods: Dicer was specifically ablated from Kidney proximal tubules in mice by breeding Dicer-floxed mice with PEPCK-Cre mice. Proximal tubule Dicer knockout (PT-Dicer-KO) mice and wild-type (WT) mice were subjected to STZ treatment to induce DKD or unilateral urethral obstruction (UUO) to examine renal hypertrophy, renal injury and fibrosis.

Results: We found that Dicer-KO in proximal tubules deteriorated renal interstitial inflammation, tubular injury, and tubulointerstitial fibrosis without significantly affecing renal hypertrophy following STZ treatment. Dicer-KO exacerbated renal injury and tubulointerstitial fibrosis in the UUO model as well. At the molecular level, Dicer deficiency induced Smad2/3 expression in proximal tubules, which may contribute to the enhanced tubulointerstitial fibrosis in both STZ-diabetes and UUO models.

Conclusions: Our results provide further support for the regulatory role of Dicer and associated microRNA production in the development of chronic renal pathologies in DKD and obstructive nephropathy. Dicer deficiency may up-regulate Smad2/3 and increase renal apoptosis to enhance the progression of chronic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO905

Lactate Induced Interstitial Fibroblasts Activation and Extracellular Matrix Accumulation in Folic Acid Induced AKI

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Background: Recent studies have indicated a substantial proportion of acute kidney injury (AKI) patients may undergo chronic kidney disease (CKD) in long term follow-up. However, the mechanisms are still unclear. Previous evidences affirmed that interstitial myofibroblasts play a key role in AKI-CKD transition. In previous tests, we observed folic acid (FA) injection could induce extracellular matrix (ECM) deposition. Further researches revealed tubular epithelial and interstitial cells proliferate after FA-AKI and the later was significantly delayed than the former. Meanwhile, we confirmed there was active glycolysis in proliferative tubular epithelial cells and secreted abundant lactate after FA-AKI injury. Thus, we speculated the glycolysis metabolic end-product lactate secreted by injured renal tubular epithelial cells induced the activation of interstitial fibroblasts and led to ECM accumulation in folic acid AKI models.

Methods: We checked whether lactate itself could induce fibroblasts activation and express fibrotic proteins. In vivo, rat kidney fibroblast (NRK-49F) were exposed to lactate at different concentration and time interval, harvested and subjected to different detection methods. Secondly, different glycolytic inhibitors 2-deoxyglucose (2-DG) and oxamate were explored in FA treatment mice. Lactate production at acute injured phase was measured. We further verified whether ECM deposition was alleviated after suppressing lactate production. Finally, we preliminary explored the possible molecular mechanisms of lactate in the activation of interstitial fibroblasts.

Results: Lactate could induced NRK-49F cells activation and expressed abundant fibrotic proteins such as alpha-smooth muscle actin (α-SMA), fibronectin (FN). Both 2-DG and oxamate could inhibit the production of lactate by renal tubular epithelial cells and alleviated FA-AKI associated ECM deposition. The protective effects improved with the dose increased and 2-DG seemly more excellent. Lactate may stimulate fibroblasts via altering fibroblasts energy metabolism or affecting proliferative associated cells growth factors expression in fibroblasts.

Conclusions: Lactate secreted by injured renal tubular epithelial cells may play a key role in the activation of fibroblasts and ultimately led to abundant ECM accumulation in folic acid induced acute kidney injury.

Funding: Government Support - Non-U.S.

TH-PO906

Hepatic Alkaline Phosphatase Activity Is Increased in CKD and Is Regulated by the Intestinal Microbiota

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Background: Patients with chronic kidney disease (CKD) exhibit a pro-inflammatory phenotype that may partially result from intestinal dysbiosis and gut barrier dysfunction. A major function of liver alkaline phosphatase (ALP) is the neutralization of microbial toxins that enter the portal circulation from the intestine. The purpose of this study was to characterize expression and activity levels of liver ALP in both mice and humans with CKD, and explore the role of the intestinal microbiota in regulating ALP activity.

Methods: We first assessed liver ALP expression (Western blot) and function (ALP activity assay) in two CKD mouse models (*Col4a3*$^{-/-}$ and adenine diet) and non-CKD controls. Next, we confirmed the generalizability of our findings to humans by assessing ALP expression and function in liver samples from deceased tissue donors with advanced CKD or normal kidney function (n=10/group). Lastly, we performed fecal transplant studies to examine how repopulating the intestine of wild-type mice with microbiota from either CKD or control mice impacted liver ALP expression and function.

Results: CKD mice (*Col4a3*$^{-/-}$ model) exhibited a 50% higher liver ALP protein expression ($P<0.05$), that was accompanied by a 10-fold greater liver ALP activity (CKD 3,140 vs. non-CKD 294 mU/mg protein; $P<0.001$). Similar findings were observed in mice with CKD induced by chronic adenine ingestion. Despite markedly higher liver ALP activity in CKD mice, serum ALP activity was equal between CKD and non-CKD mice. Next, we observed 3-fold higher liver ALP activity in human CKD livers (CKD 6,624,488 vs. non-CKD 2,459,531 mU/mg protein; $P=0.09$), but no obvious difference in total protein expression. Lastly, transplantation of CKD stool into wild-type mice resulted in substantially higher liver ALP protein expression and ALP activity compared to wild-type mice transplanted with non-CKD stool (ALP activity: CKD stool 5,104 vs. non-CKD stool 863.4 mU/mg protein; $P<0.05$).

Conclusions: Both mice and humans with CKD exhibit higher liver ALP activity that may be partially stimulated by factors derived from the CKD microbiome. We speculate that enhanced liver ALP activity is important for neutralizing microbial toxins that enter the portal circulation as a result of gut dysbiosis and barrier dysfunction in CKD.

Funding: NIDDK Support

TH-PO907

PI3K/Akt/NFκB Signaling Pathway Might Be the Potential Injury Pathway in IgG4-Related Urinary Disease

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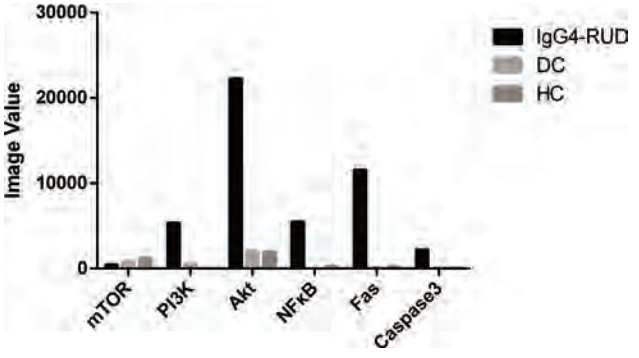
Background: Diffuse lymphocytes infiltration and diverse inflammatory factors activation represent the inflammation status of IgG4-related disease(IgG4-RD), while its specific pathogenesis remains confusing, especially in IgG4-related urinary disease (IgG4-RUD). This study aims to preliminarily investigate the potential inflammatory and injury pathway of IgG4-RUD via urinary exosomes.

Methods: Four untreated biopsy proven IgG4-RUD inpatients, two IgG4-RD patients without urinary system involvement(disease control, DC) and two healthy controls(HC) were enrolled from Feb to May, 2018 in Peking Union Medical College Hospital. Disease activity was assessed using IgG4-RD Responder Index(RI). Urinary exosomes were isolated from fresh morning urine via ultracentrifugation method. Two-color Western blot was conducted to semi-quantify the expression of mTOR, PI3K, Akt, NFκB, Fas and caspase3 in urinary exosomes. Image data were analyzed using Image Studio Ver.5.2.

Results: Among the IgG4-RUD inpatients, two were diagnosed of retroperitoneal fibrosis, one of IgG4-related kidney disease and the other of IgG4-related ureteral lesion. All patients denied diabetes mellitus, other autoimmune disease and cancer history. Mean

disease duration was 67.5 months(6-120). For clinical parameters, mean serum IgG4 was 12307.5mg/L(3030-17900), IgG 27.76g/L(22.02-38.06), SCr 419.1μmol/L(146-690), and 24hUP 0.93g(0.43-1.23). Serological inflammatory markers as ESR 59.75mm/h(8-109), hsCRP 3.18mg/L(2.12-7.16). All patients were disease active with mean RI of 8(6-10). Compared with DC or HC group, the mean expression of PI3K(5300 vs 22.55 vs 437), Akt(22200 vs 1935 vs 2008), NF-κB(5455 vs -22.5 vs 259) and Fas(11517.5 vs 67.35 vs 176) were all obviously higher in urinary exosomes of IgG4-RUD, and caspase3 was expressed only in the ureteral lesion patient. mTOR was not detected.

Conclusions: Urinary exosomes could be a noninvasive injury indicator for IgG4-RUD, and PI3K/Akt/NFκB signaling pathway might play a part in tissue injury.



TH-PO908

Multiparametric MRI for Assessment of CKD: Correlation with Histology and Progression

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Background: Multiparametric Magnetic Resonance Imaging (MRI) allows non-invasive assessment of renal structure and function in CKD. Here, MR results are correlated with biopsy and clinical measures at baseline, with repeat scanning after 1 year to assess progression.

Methods: 26 CKD patients (Stage 3-4, eGFR 20–59ml/min/1.73m^2, 19M, 56±15yrs) were scanned within a median 53 days from renal biopsy, data were also collected on age-matched healthy volunteers (HVs). At baseline, patients were scanned twice, two weeks apart, to assess reproducibility. Histological fibrosis quantification was performed on renal biopsies with sirius red staining to measure % interstitial fibrosis (IF). GFR was determined using Iohexol clearance and urine PCR was measured. Clinical and MRI assessments were repeated at 1 year. Scanning was performed on a 3T Philips Ingenia scanner and included T1 mapping and diffusion weighted imaging as markers of fibrosis and inflammation, arterial spin labelling to assess perfusion, T2* mapping as a marker of oxygenation, and measures of kidney volume and renal artery flow. Analysis was performed using in-house software to create multiparametric maps. Baseline MR data were assessed against clinical measures and biopsy results, year 1 data was analysed to assess progression.

Results: Cortex T1 was significantly increased in CKD patients compared to HVs (CKD:1559±18,HV:1435±19ms, p<0.001). Cortex diffusion was reduced in CKD patients, but not significantly. There was no significant difference in kidney volume or T2* between CKD patients and HVs. Cortex perfusion (CKD:86.8±10,HV:199.5±12ml/100g/min) and renal artery flow (CKD:156.9±10,HV:227.4±10ml/100g/min) were significantly lower in CKD (p<0.001). GFR was correlated with cortex perfusion, diffusion, T1 and renal artery flow. The strongest MRI measure to correlate with IF score was perfusion, whilst glomerular sclerosis correlated with cortex T1. The mean GFR did not vary significantly across 1 year, however patients fell into 2 groups; those with improved (n=8) and declined (n=12) renal function. There was a trend for change in T1 to be associated with progression of disease severity.

Conclusions: This work demonstrates MRI can differentiate pathophysiological changes in CKD and can be used as a method to assess progression of CKD.

TH-PO909

SerpinA3K Is Abnormally Found in Urine of Patients with CKD from Different Etiologies

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Background: We previously identified serpinA3K by high-resolution mass spectrometry as an early biomarker of acute kidney injury to CKD transition in rats. This study was designed to determine whether serpinA3K could be abnormally detected in urine from CKD patients and to evaluate its specificity in kidney diseases, compared with urines from patients with other pathologies without renal dysfunction.

Methods: We included 74 patients with CKD of different etiologies such as: FSGS, class III, IV or V lupus nephritis (LN), ANCA associated vasculitis (AAV), and diabetic nephropathy (DN) that were compared with 10 healthy volunteers. In addition, we included 17 patients with other pathologies and normal renal function: hepatic cirrhosis (HC), pancreatitis (Pan), and rheumatoid arthritis (RA). SerpinA3K was evaluated in urine (Western blot) and in renal biopsies (immunohistochemistry).

Results: In HC, Pan and RA patients without renal dysfunction urine serpinA3K was not detected. In Table 1 are the main results of the CKD patients. In addition, immunohistochemistry analysis showed that serpinA3K was expressed in tubular epithelial cells, and translocated from the cytoplasmic region to the luminal membrane in CKD patients.

Conclusions: Urinary serpinA3K was detected in all patients with CKD. Urine serpinA3K titers closely correlated with the renal fibrosis observed by histopathological analysis (p<0.0001). Moreover, this biomarker was able to differentiate between class III/IV and class V LN, in spite of severe proteinuria in these patients. These results suggest that urine serpinA3K comes from damaged kidney cells and could be used as a specific biomarker of ongoing renal inflammation, fibrosis and therefore CKD. SerpinA3K is found in the urine of CKD patients from different etiologies and correlates with renal fibrosis. SerpinA3K constitutes a specific promising CKD biomarker.

Funding: Government Support - Non-U.S.

	Volunteers (n=10)	FSGS (n=14)	LN III (n=18)	LN IV (n=18)	LN V (n=11)	Vasculitis (n=9)	Diabetic Nephrotic (n=4)
Age (years)	26 ± 0.9	36 ± 0.1	31 ± 2.5	30 ± 2.7	32 ± 4.3	57 ± 5.2	52 ± 6.1
Female Gender (%)	45.5	66.6	75	88.6	81.8	77.7	75
Serum creatinine (mg/dL)	0.8 ± 0.0	1.1 ± 0.1	1.2 ± 0.3	1.6 ± 0.3	0.7 ± 0.0	2.4 ± 0.4♦	2.2 ± 0.5♦
Proteinuria (g/24h)	0 ± 0.0	5.8 ± 1.1*	4.18 ± 0.6*	8.4 ± 0.7*♦	3.0 ± 0.7*	1.9 ± 0.5*♦	3.3 ± 1.3
Prot/UCr (g/g)	0 ± 0.0	4.3 ± 0.9*	3.9 ± 0.7*	8.4 ± 0.8*	2.9 ± 0.4*	2.3 ± 0.6♦	3.2 ± 2.1
Interstitial fibrosis (%)	-	24 ± 4.7	17.5 ± 2.9	26.1 ± 4.5	10 ± 2.8	32.2 ± 5.1*♦	No Biopsy
Tubular atrophy (%)	-	21 ± 5.2	17.5 ± 3.4	24.7 ± 4.5	9.5 ± 2.9	41.1 ± 7.0	No Biopsy
UserpinA3K (O.D)	3.0 ± 0.3	447 ± 48*♦	335 ± 49*	349 ± 53*	82 ± 29	497 ± 116*♦	538 ± 84*♦
UserpinA3K/UCr (O.D/mg)	0.23± 0.04	7.1 ± 1.1*♦	7.1 ± 2.1*	5.9 ± 1.9*	1.3 ± 0.4	10.3 ± 2.5*♦	9.8 ± 2.9*

*p<0.05 vs. Vol, ♦ p<0.05 vs. LN V, ¤ p<0.05 vs. FSGS, ♯ p<0.05 vs. LN IV, • p<0.0
FSGS: Focal Segmentary Glomerulosclerosis, LN: Lupus Nephritis, OD optical der

TH-PO910

Levels of Biomarkers of Extracellular Matrix Turnover in Serum and Urine Reflect the Burden of Fibrosis in Kidney Biopsies from IgA Nephropathy and ANCA-Associated Vasculitis Patients

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Background: Renal fibrosis is a common feature of chronic kidney disease (CKD) and is characterized by an imbalanced turnover of extracellular matrix (ECM) components. It is associated with progression to end-stage renal disease, the need for dialysis or renal transplantation and with mortality. ECM biomarkers describing the morphological changes in the kidney tissue are potentially detectable in serum and urine before markers of loss of kidney function, such as serum creatinine, due to the fact that changes in the tissue precede and are the cause of changes in function.

Methods: The cohort consisted of 49 and 47 patients with IgA nephropathy (IgAN) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), respectively. We measured a fragment of collagen type III degradation generated by MMP-9 (C3M) and a fragment of type VI collagen formation, the C5 domain of the α3 chain (PRO-C6), in paired serum and urine samples using novel ELISAs. Renal biopsies were taken at the time of sample collection. Interstitial fibrosis was quantified according to the Banff classification, and in addition, scored according to the MEST-C classification (IgAN) or classified based on AAV morphology (AAV).

Results: Urinary C3M inversely correlated (r=-0.43, p<0.0001) and PRO-C6 (in urine and serum) correlated (r=0.51, p<0.0001 and r=0.35, p=0.0009, respectively) with the level of histological fibrosis in the kidney. Whereas urinary C3M decreased, PRO-C6 increased with CKD stages and Banff scores in both patients with IgAN and AAV. In IgAN patients, urinary C3M and PRO-C6 (in urine and serum) gradually decreased and increased, respectively, with interstitial fibrosis/tubular atrophy according to MEST-C. In addition, all three ECM markers were able to separate the AAV patients with biopsies classified as sclerotic from patients with biopsies classified as focal.

Conclusions: In this study, we demonstrated that C3M and PRO-C6, novel biomarkers of ECM turnover, not only correlated with decline in kidney function, but actually reflect the burden of fibrosis in the kidneys, as confirmed by the association with the extent of kidney fibrosis in biopsies.

TH-PO911

Sequential Changes of Gut Microbiota According to the Stages of CKD

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Background: Recent evidences suggest that the microbiome profile is altered in patients with end-stage renal disease (ESRD) compared to healthy population. However,

sequential changes of gut microbiota according to the stages of chronic kidney disease (CKD) have been explored rarely.

Methods: We prospectively enrolled 139 patients including CKD patients underwent kidney biopsy, ESRD patients waiting for kidney transplantation, and 35 kidney donors from three tertiary hospitals. The composition of microbiota was analyzed using extracted metagenomic DNA from the feces by Illumina MiSeq system. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation.

Results: Total of 194 subjects were enrolled and divided into 4 groups according to their renal function as follows; 55 healthy control, 47 CKD stage 1-2, 42 stage 3-5 without receiving dialysis, and 50 stage 5 with maintenance dialysis. The mean eGFR of each groups were 103.4±15.2, 93.3±17.4, 29.6±20.4, and 7.1±2.5 mL/min/1.73 m^2, respectively. The bacterial operational taxonomic units, diversity and richness were significantly different among 4 groups. Next, we compared 35 genera, which account for more than 1% of the sample composition in at least 1/10 of the total samples, among groups. Fourteen of the 35 genus groups showed significant differences among groups. Among those genera, *Alistipes, Pseudoflavonifractor, Ruminococcus_g4* and *Hungatella* showed statistically significant increasing trend according to CKD groups and *Lachnospira*, *Dialister* and *Haemophilus* showed statistically significant decreasing trend according to the CKD groups with or without CKD 5D. *Blautia* showed an increasing trend according to the CKD group, but when the CKD 5D was included, the trend disappeared. Compared with CKD3-5ND and CKD 5D, *Prevotella, Bifidobacterium* and *Agathobacter* decreased after dialysis, and *Clostridium* and *Pseudoflavonifractor* increased after dialysis. The genera showing a change by dialysis and the genera showing a trend according to CKD stage showed different patterns except for *Pseudoflavonifractor*.

Conclusions: We found specific fecal microbiotas that changed according to the CKD stage, and they differed from the microbiota which was altered by dialysis. Further studies on the association of these microbiotas with CKD progression are needed.

TH-PO912

Glycolysis Inhibitors Suppress Renal Interstitial Fibrosis via Divergent Effects on Fibroblasts and Tubular Cells in Kidneys

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Background: Renal interstitial fibrosis is a common pathological feature of chronic kidney disease that may involve changes of the metabolism in kidney cells.

Methods: In this study, we first showed that blockade of glycolysis with two inhibitors [Dichloroacetate-DCA and shikonin] reduced renal fibrosis in the mouse model of unilateral ureteral obstruction (UUO).

Results: Both inhibitors evidently suppressed the induction of fibronectin and collagen 1 in obstructed kidneys, while DCA also showed inhibitory effect on collagen IV and a-SMA. Histological examination also confirmed less collagen deposition in DCA treated kidneys. We also examined renal apoptosis by TUNEL assay and identified significant suppression of apoptosis after glycolysis blockage by both DCA and shikonin. We further examined their effects on fibrotic changes in cultured renal proximal tubular BUMPT cells and renal NRK-49F fibroblasts (cells). While glycolysis inhibitors reduced fibronectin and a-SMA production in NRK-49F cells, no obvious effect or even induction of fibronectin or a-SMA was detected in BUMPT cells during TGF-b1 or hypoxia stimulation.

Conclusions: Altogether, these results suggest that inhibition of glycolysis may reduce renal interstitial fibrosis by suppressing renal apoptosis and fibrotic alterations in fibroblasts.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO913

Uremic Toxin Decreases Intestinal Defense Peptides and Barrier Functions in Chronic Renal Failure Mice

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Background: Alterations of intestinal bacterial flora and intestinal barrier function in chronic kidney disease (CKD) have been reported to affect on uremic toxin influx. However, alteration mechanisms of microbiota and intestinal barrier have not been elucidated. Antimicrobial peptide contributes to maintenance of microbiota. We examined whether uremic toxin decreases intestinal antimicrobial peptide and barrier function in chronic renal failure model mice.

Methods: We used male ICR-derived glomerulonephritis (ICGN) mice for renal failure group. Gene expression in ascending colon was analyzed by microarray analysis and quantitative real-time PCR (qPCR). Gene expression patterns of a whole bacterial flora in the intestine were analyzed by terminal restriction fragment length polymorphism analysis method. Fecal and serum bacteria products (phenol, para-cresol, indole/indole sulfateand skatole) were examined by quantitative chemical analysis. In vitro experiment, Caco-2 cells were exposed to indoxyl sulphate at clinically relevant concentrations (0.1-0.5 mM). Expressions of defensins and tight junction molecules were analyzed by qPCR and ELISA.

Results: Microarray analysis showed antimicrobial peptide, defensin, significantly decreased in ICGN mice. Defensin alfa1 and beta1 mRNA expressions in ascending colon were reduced in ICGN mice compared with control mice. The ratio of pathogenic bacteria clostridia was increased, and the ratio of opportunistic pathogen bacteroides was decreased in intestinal bacterial flora of ICGN mice. Fecal bacteria products phenol and para-cresol were increased in feces of ICGN mouse. Barrier function associated molecules, such as C-type lectin and tight junction, were significantly decreased in ICGN. Intestinal permeability in ICGN was increased compared to ICR mice. Indoxyl sulphate significantly decreased the expressions of C-type lectin and tight junction in Caco2 cells. Indoxyl sulphate also significantly decreased defensin mRNA and protein expression in Caco2 cells.

Conclusions: Uremic toxin decreases intestinal antimicrobial peptides which induce gut microbiome alteration in CKD. Uremic toxin also decreases intestinal barrier function molecules which increase Intestinal permeability in CKD. Both are combined and contribute to the loss of intestinal barrier function in CKD.

Funding: Government Support - Non-U.S.

TH-PO914

Hyperoside Diminishes Tubulointerstitial Fibrosis in Obstructive Nephropathy via Targeting Pericyte-Myofibroblast Transition

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Background: Pericyte-myofibroblast transition (PMT) plays an important role during the progression of tubulointerstitial fibrosis (TIF) in chronic kidney disease (CKD). Blocking PMT has been recognized as a potential target for anti-fibrotic therapy. In China, hyperoside (HYP), a bioactive component of *Abelmoschus manihot*, has been frequently used to treat TIF in CKD patients. However, the therapeutic mechanisms *in vivo* of the dose-effects of HYP on TIF by targeting PMT and its signaling activation remained unclear.

Methods: Twenty-five rats were divided into 5 groups, the sham, the vehicle, the high dose of HYP, the low dose of HYP and the imatinib groups. The different doses of HYP, imatinib and distilled water were administrated with intraperitoneal injections or oral for 2 weeks before and after the induction of TIF by unilateral ureteral obstruction (UUO), respectively. Rat's general status, 24 h urinary protein, urinary *N*-acetyl-beta-*D*-glucosaminidase, blood biochemical parameters, tubulointerstitial morphological changes, the markers of PMT such as platelet-derived growth factor receptor (PDGFR)β, α-smooth muscle actin (αSMA) and vimentin, as well as the key signaling molecular expressions in PDGFR pathway and vascular endothelial growth factor receptor (VEGFR) pathway in the kidney were observed, respectively.

Results: TIF was induced in the obstructed kidneys of the UUO model rats. PMT was triggered, marked by the increased expressions of PMT markers in peritubular pericytes. In addition, TIF was aggravated by PMT and could be significantly improved by the high dose of HYP and imatinib *in vivo*, reflected by inhibiting PMT markers' expressions in peritubular pericytes and attenuating ECM accumulation and collagen deposition in renal interstitium. HYP and imatinib could block PMT through inhibiting PDGFR and VEGFR signalings activation. Furthermore, the effects of HYP at the high dose were partially superior to those of imatinib.

Conclusions: In this study, we clarified that the high dose of HYP, superior to imatinib, can attenuate TIF through blocking PMT and inhibiting the key signaling molecular expressions in PDGFR and VEGFR pathways. These findings may partly explain the therapeutic mechanisms of HYP in treating CKD, and further suggest that targeting PMT and its signaling activation may provide new strategies for TIF treatment in CKD.

Funding: Veterans Affairs Support, Government Support - Non-U.S.

TH-PO915

Honokiol decreases TGF-β1 Induced Renal Fibroblast Activation by Regulation of TGF-β1/Smad Signaling Pathway

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Background: In progressive renal disease, tubulointerstitial fibrosis is a final common feature. These fibrotic process is characterized by inflammation, excessive extracellular matrix deposition and organ dysfunction. Modulation of renal fibrogenesis may be one of the promising therapeutic targets for attenuating the progression of chronic kidney diseases. Honokiol is a natural biphenolic compound derived from the bark of magnolia trees and has anti-inflammatory, anti-oxidative, anti-tumor and neuroprotective effects. In this study, we investigate the effect of honokiol on TGF-β1-induced real fibroblast activation and unilateral ureteral obstruction (UUO)-induced renal fibrosis.

Methods: Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 10 days. Honokiol (5 mg/kg) was treated by intraperitoneal injection for 7 days before induction of renal fibrosis and continued for 10 days. Histologic examination and Western blot analysis for α-smooth muscle actin (α-SMA), type I collagen and intercellular adhesion molecule (ICAM)-1 were performed. *In vitro* experiments were performed using rat renal fibroblast cell line (NRK-49F cells). Cell proliferation and migration were evaluated by XTT assay and wound healing assay. TGF-β1-induced renal fibroblast activation was evaluated by Western blot analysis.

Results: Treatment of TGF-β1 increased significantly proliferation and cell migration of NRK-49F cells compared to that of vehicle treated cells. Honokiol treatment decreased TGF-β1-induced renal fibroblast proliferation and activation in a dose dependent manner. TGF-β1 treatment increased the levels of phospho-Smad2 and 3 in NRK-49F cells, and honokiol significantly decreased the levels of phosphorylation of Smad2 and 3. In in vivo experiment, honokiol decreased UUO-induced renal tubular injury and renal fibrosis. Honokiol also decreased UUO-induced renal inflammation by regulation of phosphorylation of NFκB p65.

Conclusions: These results suggest that honokiol has a beneficial effect on UUO-induced tubulointersitial inflammation and fibrosis by regulation of TGF-β1/Smad signaling pathway.

Funding: Government Support - Non-U.S.

TH-PO916

6-BIO Attenuates TGFβ-Induced Fibrosis by Suppression of Transcription Factor AP-1 and SP-1 of Plasminogen Activator Inhibitor Type-1 in the Human Renal Proximal Tubular Epithelial Cells

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Background: PAI-1 is expressed at high levels in several both acute and chronic kidney diseases, and leading to activation of lung, liver, kidney fibrosis. We investigated whether 6-BIO, a glycogen synthase kinase-3β inhibitor, attenuates fibrosis by PAI-1 inhibition in TGFβ-induced proximal tubular (HK2) cells injury.

Methods: The effects of 6-BIO in TGFβ-induced cell fibrosis were determined using human renal proximal tubular epithelial (HK-2) cells. The effects of TGFβ and 6-BIO on cell viability were determined using EZ-CyTox assays. The protein and mRNA expression of PAI-1, Collagen I, Collagen IV, CTGF, SMAD, PI3K/AKT, MAPK, and NF-κB was determined by semiquantitative immunoblotting and RT-PCR. To study the factors that regulation of PAI-1 expression, we analyzed the promoter activities of transcription factors AP-1 and Sp-1 were determined by luciferase assays.

Results: Treatment of TGFβ increase expression of PAI-1, Collagen I, Collagen IV, and CTGF in HK-2 cells. Furthermore, TGFβ-treatment induces the activation of p-SMAD2/3, SMAD4, p-AKT, p-ERK1/2, p-p38, and p-JNK MAPK signal pathway as well as NF-κB nuclear transactivation. AP-1 and SP-1 promoter luciferase activity is increase by TGFβ treatment. 6-BIO pretreatment decreases PAI-1, Collagen I, Collagen IV, CTGF fibrotic protein expression in TGFβ-induced HK-2 cells. 6-BIO decreases the increased NF-κB nuclear transactivation, p-SMAD2/3, SMAD4, p-AKT, p-ERK1/2, p-p38, and p-JNK MAPK pathway in HK-2 cells. Additionally, pretreatment of 6-BIO attenuates AP-1 and SP-1 promoter activity.

Conclusions: Treatment of 6-BIO may exert anti-fibrotic effect by controlling SMAD, PI3K/AKT, MAPK, and NF-κB signal pathways via inhibition of the transcription factor AP-1 and SP-1 of PAI-1 in TGFβ-treated HK-2 cells.

Funding: Government Support - Non-U.S.

TH-PO917

Lymphangiogenesis Within Kidney and Its Draining Lymph Nodes Mediates Renal Inflammation and Fibrosis

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Background: Lymphangiogenesis has been reported in kidney transplant and chronic kidney diseases (CKD). Here, we demonstrate a crucial role for the newborn lymphatic vessels (LVs) within kidney and its draining lymph nodes (RDLNs) in driving intrarenal inflammation and fibrosis.

Methods: In the present study, we examined the lymphangiogenesis within kidney and RDLNs in different renal interstitial fibrosis models. Conditional knockdown of LVs in LYVE-1-Cre/iDTR mice and knockdown of lymphangiogenesis by sVEGFR3-FC or sLYVE-1-FC were adopted to observe the relationship between LVs with renal inflammation and fibrosis. CCR7 neutralizing antibody were used to blocking CCR7/CCL21, to further explore the role of CCR7/CCL21 in immunocytes recruitment.

Results: Lymphangiogenesis occurs in kidney and its DLNs after renal injury, which mainly results from the local proliferation of pre-existing lymphatic endothelium. The newborn LVs like the inherent LVs essentially express C-C chemokine ligand 21 (CCL21). The expansive LVs system play an important role in the recruitment of more CCR7+ dendritic cells(DCs) and lymphocytes into RDLNs and spleen, and finally inducing systemic lymphocyte expansion. Blocking CCR7+ cell recruitment into RDLNs and spleen by genetically or biologically knockdown of LVs, or inhibiting CCR7+ cell expansion using CCR7 neutralizing antibody, attenuated intrarenal inflammation and fibrosis.

Conclusions: We show a previously unidentified role for lymphangiogenesis in regulating intrarenal inflammation and fibrosis, which uncovered novel strategies for preventing CKD progression.

Funding: Government Support - Non-U.S.

TH-PO918

Inhibition of Fibronectin Polymerization Attenuates Ischemia-Induced Kidney Fibrosis

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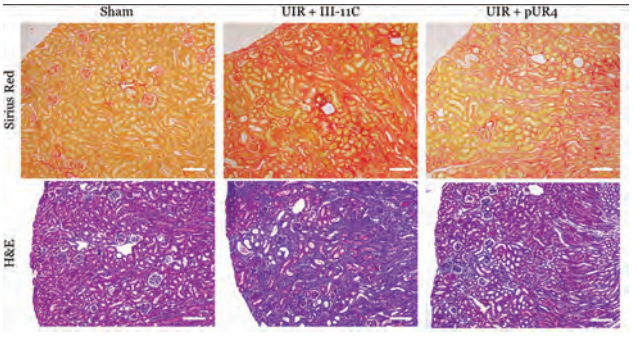
Background: Fibrosis is a hallmark of chronic kidney disease (CKD), regardless of pathophysiologic origin. After injury, activation of tissue fibroblasts leads to increased extracellular matrix (ECM) deposition and adverse tissue remodeling. Fibronectin (FN) is a vital component of the ECM that orchestrates the composition and organization of numerous matrix and cell surface proteins. The current study tested the hypothesis that treatment with the peptide pUR4, which inhibits cell-mediated FN polymerization, would mitigate ischemia-induced tissue remodeling and preserve renal morphology.

Methods: A mouse model of unilateral ischemia/reperfusion (UIR) injury was created by placement of an atraumatic clamp on the left renal artery for 30 minutes, followed by 14 days of reperfusion. Daily IP injections of pUR4 (25mg/kg), control inactive peptide (III-11C; 25mg/kg) or PBS were started on the same day (concomitant), or 7-days post-UIR (delayed). After 14 days, mice were sacrificed and both the left (injured) and right (uninjured) kidneys were collected; animals were assessed for evidence of injury by histology and immunofluorescence.

Results: Inhibition of FN polymerization with delayed (but not with concomitant) pUR4 treatment decreased renal FN expression and deposition following UIR (1.0 (III-11C) vs. 0.56 (pUR4), p=0.01, n=4 each). Delayed pUR4 administration alleviated the characteristic UIR-induced decrease in kidney weight (5.4 vs. 6.5mg/kg body weight, p=0.009; n=12 for III-11C, n=14 for pUR4). Moreover, delayed pUR4 decreased cortical fibrosis (by picrosirius Red staining) compared to III-11C (12.1 vs. 6.0%, p=0.0009, n=12 or 14, respectively) but not medullary fibrosis (20.2 vs. 14.4%, p=0.18). Histologic evaluation also revealed preserved tubule morphology with delayed pUR4 treatment.

Conclusions: Collectively, these experiments provide evidence that decreasing FN polymerization may attenuate the progression of CKD following renal ischemic injury.

Funding: Other NIH Support - NHLBI - T32, Private Foundation Support



TH-PO919

Inhibition of Fibronectin Fibrillogenesis Attenuates Progression of Fibrosis in Animal and Kidney Organoid Models

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Background: Renal fibrosis is the principal pathological process underlying the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD). Fibronectin (FN) assembly is required for collagen matrix deposition and localized activation of TGF-ß. We hypothesize that interfering with FN polymerization would attenuate fibrosis in *in vitro* and *in vivo* kidney fibrosis models.

Methods: Mice were subjected to unilateral ureteral obstruction (UUO) and treated with fibronectin polymerization blocking peptide (pUR4) and control peptide (CIII-11C) to evaluate the therapeutic benefit of blocking FN assembly in attenuating or reversing fibrosis progression. We evaluated the efficacy of pUR4 peptide in attenuating kidney fibrosis in two different treatment modalities. In parallel treatment model, we evaluated the therapeutic efficacy in halting or slowing the progression of fibrosis by injecting pUR4 (i.p, 100 mg/kg) & CIII-11C (i.p, 100 mg/kg) from day 5 - day 10 post-UUO every day. In successive treatment model, we evaluated the efficacy of the pUR4 in halting or reversing the established fibrosis by giving pUR4 from day 10 – day 15 post-UUO. Mice were sacrificed at the end of the study and urine, blood and tissues were collected. Efficacy of pUR4 peptide was also evaluated in cisplatin induced kidney organoid models of fibrosis.

Results: *In vivo*, pUR4-treatment reduced fibrosis in both parallel and successive model of UUO induced fibrosis. pUR4 treated mice display reduced picrosirius red staining as compared to & CIII-11C treated mice in both treatment modalities. There was a corresponding decrease in urinary markers including KIM-1, MCP-1, IL-6, NGAL and microalbumin in pUR4 treated mice in both the models. Levels of collagen 1, α-SMA and CTGF were significantly reduced in pUR4 treated mice in both the models. In kidney organoids, pUR4 treatment diminished fibrilogenesis and accumulation of fibronectin and collagen after repetitive cisplatin injury induced fibrosis.

Conclusions: In the current study, we demonstrated that blocking fibronectin fibrillogenesis halts progression of kidney disease in experimental models of kidney fibrosis. Thus, interfering with the FN polymerization may offer a new therapeutic strategy for treating kidney fibrosis

Funding: NIDDK Support

TH-PO920

SMOC2 Mediates Renal Fibrosis by Activation of Inflammation and Fibroblast to Myofibroblast Differentiation

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Background: Fibrosis is a common end stage of nearly all chronic inflammatory organ diseases including chronic kidney diseases (CKD). Secreted modular calcium-binding protein 2 (SMOC2) belongs to the secreted protein acidic and rich in cysteine (SPARC) family of matricellular proteins whose members are known to modulate cell-matrix interactions. SMOC2 has been shown to contribute to CKD by regulating

initiation and progression of kidney fibrosis. We therefore investigated the mechanisms responsible for signaling activation pathways by SMOC2 resulting in its fibrogenic effect.

Methods: To determine SMOC2 expression in CKD, three mice CKD models were employed: ***Alport nephropathy mice model (caused by a null mutation of the a3*** chain of collagen type IV), RNA-Seq was performed to determine extracellular matrix genes in this model; ***Parabiotic aging model*** generated by parabiosis sugery for 4 weeks and unilateral ureter obstruction (UUO) surgery in 5 and 10 days, separately; ***Sequential ischemia-nephrectomy CKD model*** was generated by bilateral ischemia reperfusion (Bi-IRI) and unilateral nephrectomy surgeries time-dependently. RT-PCR and western-blot were employed to determine fibrotic gene mRNA and protein expression in these three models. To investigate the mechanism of SMOC2 triggered fibrogenesis and activation of fibrogenic signaling pathways, SMOC2 protein was used to stimulate interstitial fibroblasts and human primary proximal tubular epithelial cells.

Results: We found that SMOC2 is in the top 10 DEGs of extracellular matrix genes in Alport mice. SMOC2 gene and protein were highly expressed in Col4a3 knockout (KO) mice tissue compared to wildtype (WT) mice. Furthermore, SMOC2 over expression in fibrosis was also confirmed in parabiotic-UUO kidney disease model and in-house developed CKD model. Mechanistically, SMOC2 activates Smad and MAPK signaling in fibroblast and proximal tubular epithelial cells, which are both inhibited by TGFbRI inhibitor (SB431542) and MAPK p42/44 inhibitor (U0126). SMOC2 also promotes inflammatory gene expression such as IL-6 and TNFa.

Conclusions: SMOC2 is a key signaling molecule mediating fibrogenesis, and modulating of SMOC2 may provide a new potential therapeutic target for chronic kidney diseases.

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TH-PO921

K-Cadherin Expression Regulates Activation State of Transcription Factors in the Presence and Absence of TGF-β1

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Background: K-cadherin (Cadherin 6) is an atypical type I cadherin with high expression in the kidney where it is exclusively expressed in the proximal tubule. Unlike other cadherins in the tubule K-cadherin is expressed basally directly adjacent to the basement membrane. Disruption and loss of renal K-cadherin expression is associated with progressive diabetic nephropathy. Disruption of the precise cellular localisation has been reported in Renal Cell Carcinoma. Recently we have reported a similar disruption in biopsies from renal transplants. The alteration of K-cadherin expression in cancer and fibrosis suggests a potential role in regulating gene expression.

Methods: HKC clone 8 cells, a transformed human PTEC line which do not have detectable K-cadherin protein, were transfected with human K-cadherin pcDNA3.1 expression vector (1µg). Cells were fixed and stained for K-cadherin and visualized by using a 3D deconvolution microscope. Primary human PTECs (K-cadherin positive), control HKC8 (HKC8 K-) and transfected HKC8 cells (HKC8 K+) were grown on non-coated plastic and collagen IV coated dishes and exposed to 2.5 ng/ml TGF-β1 for 5 min before cells were lysed and analysed by western blot.

Results: HKC8 K+ cells showed K-cadherin expression similar to that expected in primary cells, localised in vesicular Golgi-type structures as well as at the cell periphery and was predominantly found in the basal layer. Regulation of important transcription factors Elk1, Erk5a & Erk5b were investigated. TGF-β1 induced an increase of phospho-Elk1 in HKC8 K- cells grown on collagen IV but a reduction in phospho-Elk1 in HKC8 K+ cells. The expression of K-cadherin had no effect on TGFβ-induced phospho-Elk1 in cells grown on plastic. In primary PTECs grown on collagen IV TGFβ1 reduced phospho-Elk1 levels. Although TGFβ1 induces phosphorylation of Erk5a it has no effect on the levels of activated (phosphorylated) Erk5b. However, the expression of K-cadherin alone significantly increased phospho-Erk5b.

Conclusions: The basal expression of K-cadherin appears to be critical in regulating transcription factor activation in human primary proximal tubule cells due, at least in part, to its interaction with collagen IV. Disrupted expression seen in cancer and during renal injury will result in alteration of gene activation and cellular responses.

TH-PO922

Latent Transforming Growth Factor Beta Binding Protein 4 (LTBP4) Deficiency Attenuates the Severity of Renal Fibrosis

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Background: Transforming growth factor beta (TGFβ) has been proved to be related to fibrosis including renal fibrosis that is characterized by the accumulation of extra-cellular matrix (ECM). LTBPs are recognized to direct and facilitate TGFβ action through several mechanisms. Moreover, the complexity of progression of renal injury remains vague. The intensive investigation of the mechanism will lead us understand the potential therapy for patients. We propose that ltbp4 can be an essential regulatory factor in renal injury because of its variety.

Methods: To create renal fibrosis model, we did unilateral ureteral ligation (UUO) in mice and check echocardiography to exam the cardiac contractility every other weeks. *Ltbp4S-/-* mice were used to investigate the potential regulatory role of ltbp4 in renal fibrosis related to TGFβ signaling. Protein and RNA extraction were collected for real-time PCR, RNA-Seq, and down-stream signaling, protein-protein interaction, and proteomics analysis.

Results: Up-regulation of ltbp4 had been noted 14 days after UUO at gene and protein levels. The major area of ltbp4 expression in the renal tissue was around proximal tubules areas and glomerular area was absent of expression. In addition, α-smooth muscle actin (SMA), kidney Injury Molecule-1 (KIM-1) and monocyte chemoattractant protein-1 (MCP-1) expression at mRNA level increased significantly following the UUO surgery but in ltbp4S-/- mice, the expression had been drastically reduced. KIM-1, pSMAD2, pEKR and platelet-derived growth factor receptors beta (Pdgfrb) were increasing at protein levels after renal injury. Immunofluorescence staining studies revealed less expression of Pdgfrb, F4/80 and collagen I in ltbp4S-/- mice. TGFB receptors are speculated to be interacted with ltbp4, leading to abnormal down-stream signaling in ltbp4-deficient environments.

Conclusions: Reduced macrophage infiltration had been noted in renal injury tissue among post-UUO surgery *ltbp4S-/-* mice. Moreover, renal myofibroblasts expressed less Pdgfrb. In ltbp4-deficient environment, the severity of inflammation and renal injury induced by UUO can be reduced.

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TH-PO923

Cleavage of the Matricellular Regulators of Fibrosis, CCN2, and 3 at the Third Intermodular Junction

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Background: CCN proteins are modular matricellular factors with roles in cancer and fibrosis. Members of the family consists of 4 modules encoded by 4 exons. The strucuture contributes to their role regulating interactions between cells and matrix. CCN2/CTGF is a fibrogenic factor with actions in the lung, liver, skin and kidney. CCN3 is reported to counterbalance the actions of CCN2. We have previsouly described the expression and anti-fibrotic effects of CCN3 on proximal tubule cells when we also identified a truncated form consisiting of just the first 3 modules. Here we investigate the enzymatic truncation of both CCN2 & 3 and the resultant effects.

Methods: Human primary proximal tubules were cultured on collagen IV. Protein expression was determined by western blotting and immunofluorescent microscopy. Bioinformatic analysis to identify potential cleavage sites was performed using expasy peptide cutter.. Mass spectrometry was carried out using 2D nano ES-MS/MS analysis after trypsin digestion.

Results: Enzymatic cleavage sites were identified between modules 3 & 4 of CCN2; two for glutamyl peptidase, and one each for HIV-1 retropepsin and MMP9. Accumualtion of secreted full-length CCN2 following TGFβ1 treatment dropped by 72 h following MMP9 induction. We hypotheised MMP9 was cleaving the protein. Co-incubation with the MMP9 specific inhibitor prevented the fall in full length molecule. Full length hrCCN2 potentiated TGFβ-induced fibronectin expression while the 4th module of CCN2 reduced TGF β-induced fibronectin in primary PTEC in culture. Enzymatic cleavage sites were identified between modules 3 & 4 of CCN3 including two for cathepsin K and one for MMP9. Inhibition of MMP9 did not alter the amount of CCN3. Mass Spec analysis of the 39KDa CCN3 isoform also suggrested cathepsin K.Cathepsin K is known to be induced by members of the TGFβ family.

Conclusions: The enxymatic cleavage of CCN2 & 3 acts a postranslational modiification altering the nature of the proteins..Although the potentially opposing factors share a putative MMP9 cleavage site the actually cleavage is performed by different enzymes. The induction of cleavage appears to be part of an endogenous regulatory process by TGFβ. Targeting the enzymatic cleavage of CCN proteins may be an alternative therapeutic approach in fibrosis and cancer.

Funding: Private Foundation Support

TH-PO924

Fibroblast-Specific p90RSK Promotes Epithelial Transdifferentiation and Kidney Fibrosis

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Background: Epithelial integrity and interactions between epithelial cells and other kidney cells play important roles in maintaining normal kidney structure and environment. p90RSK, a serine/threonine kinase, is recently shown to promote diabetic endothelial dysfunction and atherosclerosis, however, the role of p90RSK in chronic kidney disease remains largely unknown.

Methods: We generated a novel fibroblast-specific p90RSK transgenic mouse (RSK-Tg) and established a fibroblast-epitheial coculture system using primary kidney fibroblasts from RSK-Tg and RSK-wt mice and human proximal tubular epithelial cells (HKC-8) to investigate the role of p90RSK in fibroblast-epitheial interactions and kidney fibrosis.

Results: First, we examined the expression of phospho-specific and total p90RSK during the course of chronic kidney injury in the classic unilateral ureter obstruction (UUO) model. It's found that p90RSK is dramatically activated, largely in the interstitial FSP-1-positive fibroblasts. We generated fibroblast-specific p90RSK transgenic mouse, RSK-Tg, and found that this mouse has normal phenotype as the littermate control (RSK-wt). However, after UUO injury, RSK-Tg mice display significantly worse tubular damage, decreased E-cadherin expression, and *de novo* activation of alpha-SMA, as well as increased fibrosis, in comparison with their littermates. We further found, in our *in vitro* fibroblast-epithelial coculture system, that RSK-Tg fibroblasts dramatically induced epithelial activation of β-catenin and its transdifferentiation into myofibroblasts, as indicated by

reduced E-cadherin and *de novo* expression of alpha-SMA. Intriguingly, blocking epithelial β-catenin using siRNA reversed epithelial transdifferentiation.

Conclusions: Thus, it is clear that fibroblast-specific p90RSK activation promotes the epithelial-to-mesenchymal transition (EMT) through activating epithelial β-catenin pathway.

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TH-PO925

The Role of miR-21/Wnt in the Development of Renal Tubulointerstitial Fibrosis Secondary to Aristolochic Acid Induced AKI

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Background: AKI is increasingly recognized as a cumulative risk factor for developing advanced CKD. However, the factors governing the underlying mechanisms remain unclear. Previously we have found that the development of tubulointerstitial fibrosis after AKI was accompanied with an overwhelmed activation of miR-21 and canonical Wnt signaling, while inhibiting miR-21 or silencing Wnt ligands could partially attenuate AKI to CKD transition.

Methods: To explore the interaction between miR-21 and Wnt/β-catenin signaling, we exam the effects of genetic absence or pharmacologic inhibition of miR-21 on the expression of Wnt/β-catenin signaling pathway.

Results: In miR-21$^{-/-}$ mice, or in wild type mice treated with anti-miR-21 oligos, a significant reduction of Wnt1 and Wnt4 canonical signaling was found in the renal tissue, with partially reversal of renal interstitial fibrosis. Although renal abundance of miR-21 remains unchanged either after inhibition or activation of Wnt/β-catenin signaling, down-regulation of β-catenin with early intervention of ICG-001, a typical β-catenin inhibitor was associated with significant attenuation in renal interstitial fibrosis, protein expression of genes coding extracellular matrix as well as the downstream genes of β-catenin. Moreover, inhibiting β-catenin within 24h after aristolochic acid administration, not at a late stage, also attenuated aristolochic acid induced apoptosis and inflammation.

Conclusions: In conclusion, these results suggest that inhibiting miR-21 and β--catenin signaling may be effective approaches to preventing AKI to CKD progression.

TH-PO926

miR-214-3p Is Activated in Fibroblasts in Progressive Renal Fibrosis

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Background: Renal fibrosis is referred to as the final common pathway of progressive kidney disease (Humphreys 2013). miR-214-3p has been demonstrated to be an important promoter of fibrosis in experimental renal fibrosis (Denby 2014) and may function as a therapeutic target. More in-depth study of miR-214's renal cell-type specificity is needed in order to identify its deleterious mechanism in renal fibrosis. Gli1+ myofibroblasts in the kidney have recently been implicated as one of the main contributors to renal fibrosis (Humphreys 2015). The aim of this study was to identify which renal cell types express and upregulate miR-214 in response to renal injury.

Methods: Unilateral ureteral obstruction (UUO) or subtotal nephrectomy (STNx) was performed on mice (C57blk, SV129 or Gli1 reporter mice) and mice culled at 7 days (UUO), 6 or 10 weeks (STNx). During STNx model, metabolic cages were used to obtain urine. At cull, tissue was collected for RNA extraction, histology & FACS, and serum for biochemical analysis. Gene and miRNA expression was determined via qRT-PCR by specific primers and normalised to Ppia (gene) and U6 (miRNA).

Results: miR-214-3p expression significantly increased compared to sham in STNx and UUO models of renal fibrosis. This correlated with increased fibrosis histologically, pro-fibrotic gene expression (via qPCR) and biochemical markers of renal dysfunction (in STNx). Interestingly, miR-214-3p was significantly increased 6-weeks post STNx. LTL+ proximal tubular cells and Pdgfrb+ fibroblasts were found to be the source of miR-214 in UUO animals. STNx was performed on Gli1 reporter mice which revealed a significant increase in renal Gli1 (via FACS & qPCR). Here, miR-214 was upregulated with STNx in Gli1 +ve Pdgfrb -ve, Pdgfrb +ve Gli1 -ve, and dual +ve cells vs sham.

Conclusions: miR-214-3p is upregulated in proximal tubular cells, Pdgfrb+ve cells and Gli1+ve cells following renal injury. STNx kidneys had significantly increased miR-214 expression, correlating with a significant increase in Gli1+ cells within the kidney. This expands on previous work which showed Gli1+ cells to be critical in the development of renal fibrosis in UUO and IRI models, demonstrating the expansion of these cells in a progressive model of renal fibrosis. These data will facilitate the investigation of miR-214-3p's mechanism and as a therapeutic target in renal fibrosis.

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TH-PO927

The Regulation of MicroRNAs on Galactose-Deficient IgA1 and Its Pathogenic Mechanism in IgA Nephropathy

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Background: Abnormal increase of Gd-IgA1 is a recognized pathogenic factor of IgAN. Glycosylation of IgA1 is dependent on 3 key enzymes (C1GALT1, COSMC, ST6GALNAC2). Deposition of Gd-IgA1 in kidney mesangium causes IgAN, whereas the mechanism is not elucidated yet. This study focuses on how microRNA interfere IgA1 glycosylation by targeting C1GALT1, and futher leading to mesangial cell malfunction, thereby shedding light on the mechanism of IgAN.

Methods: Part 1. 1) Screen candidate miRNAs targeting C1GALT1, verification of targeted regulation by Luciferase Reporter System, RT-PCR and Western Blot; 2) Change expression level of miRNA in DAKIKI cell, detect Gd-IgA1/IgA1 in the culture medium by ELISA; 3) Stimulate Human Mesangial Cells with Gd-IgA1 in vitro, analyse cell cycle by Flow cytometry. Part 2. 1) Analyse miRNA expression in PBMC, serum Gd-IgA1 level in IgAN and HC; 2) Conduct RNA-seq of glomerulus, analyse DEGs in different kidney cell types, especially in mesangial cells. Calculate DEGs expression change in HMC stimulated by Gd-IgA1.

Results: In Part 1, We screened out 6 candidate miRNAs possibly targeting C1GALT1. miR-152 most effecienty binds to C1GALT1 3'UTR region, inhibits C1GALT1 at both transcriptional and translational level. Overexpression of miR-152 mimics in DAKIKI obviously increases the Gd-IgA1/IgA1 in the culture medium. Stimulation of HMC by Gd-IgA1 drives the cell cycle towards S phase and G2/M phase, which possibly indicates cell proliferation. In Part 2, expression level of miR-152 was much higher in PBMC of IgAN than of HC. Gd-IgA1 serum concentration was obviously higher in IgAN than in HC. Subgroup analysis revealed that IgA1/IgA ratio is related to S-score in MEST-C Oxford classification system of IgAN. RNA-seq of glomerulus revealed 4 DEGs (SERPINE1, USP2, SOX9, KLF6) closely related to mesangial cells. Stimualting HMC with Gd-IgA1 significantly increased the expression level of those 4 markers, among whom, increasement of SERPINE1 mRNA is the most remarkable, in a dose- and time-dependent manner.

Conclusions: miR-152, which is highly expressed in PBMC of IgAN patients, obstructs the glycosylation process of IgA1 by targeting C1GALT1, resulting in elevation of Gd-IgA1, which will further stimulate kidney mesangial cells, increase the expression level of mesangial cell markers, especially SERPINE1, promote cell proliferation, finally leads to IgAN.

TH-PO928

Regulation of Renal Fibroblast Migration, Contraction, and Myofibroblast Differentiation by LPA-LPA1 Signaling via Specific G Proteins

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Background: Renal fibrosis is a common pathway leading to end-stage renal disease regardless of etiologies. Pathologically, tissue fibrosis is characterized by the accumulation of fibroblasts/myofibroblasts and the excessive deposition and contraction of extracellular matrix. We have previously found the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA_1, contributes to the development of renal fibrosis. However, the precise mechanisms by which LPA-LPA_1 signaling activates renal fibroblasts (RFBs) remain to be determined.

Methods: In this study, we focused on the direct effects of LPA-LPA_1 signaling on RFBs biologies, especially migration, contraction and myofibroblast differentiation. Cultured RFBs were used to examine cell migration, cell contraction and the expression of alpha smooth muscle actin (aSMA), a marker for myofibroblast differentiation, in response to LPA. RFBs were transfected with either LPA_1 siRNA or control siRNA to determine the impact of LPA_1 on RFBs biologies. In addition, we also investigated the involvement of G proteins in the LPA-LPA_1 signaling-associated biologies of RFBs.

Results: RFBs treated with control siRNA were attracted by LPA in a dose-dependent manner, whereas LPA did not stimulate LPA_1 siRNA-treated RFBs migration. In addition to RFBs migration, we also found that LPA directly induced cell contraction and aSMA gene expression by RFBs dependent on LPA_1. To determine the involvement of G proteins in the LPA-LPA_1 signaling, RFBs were transfected with siRNAs targeting G proteins. The chemotactic activity of LPA was significantly inhibited by siRNA treatment against Ga_i class of G proteins. In addition to that, pertussis toxin (an inhibitor of Ga_i) also blocked LPA-induced migration of RFBs. We also found that LPA-LPA_1 signaling enhanced cell contraction and aSMA expression through $Ga_{12/13}$ class of G proteins.

Conclusions: Our results suggest that LPA-LPA_1 signaling directly modulates RFBs biologies dependent on specific G proteins in the pathogenesis of renal fibrosis.

Funding: Other U.S. Government Support

TH-PO929

CCN2 Module-IV Promotes Renal Fibrosis Through Activation of the FAK Pathway in the Tubular Epithelium

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Background: CCN2 is known to mediate the profibrogenic actions of TGF-beta in the kidney. We previously demonstrated that CCN2 promotes renal fibrosis via its module-IV by using mutated-CCN2 knocked-in mice (CCN2m/m) expressing mutated CCN2 lacking module-IV. CCN2 was reported to use FAK, Smad2/3 and LRP6 to promote renal fibrosis. Among these, a significant decrease in p-FAK was found in primary skin fibroblasts derived from CCN2m/m compared with the wild-type cells. In this study, therefore, we examined possible downstream pathways through which CCN2 module-IV promotes fibrosis in the kidney.

Methods: Expression of candidate proteins involved in the early downstream pathways of CCN2 were measured by immunoblotting using kidney samples from CCN2m/m and wild-type mice with or without ureter obstruction (UUO). Additionally, the expression

and localization of other downstream proteins of the FAK pathway in those samples were examined by immunoblotting and immunohistochemistry.

Results: Expression levels of p-FAK, p-Smad2/3 and p-LRP6 were significantly higher in the fibrotic wild-type UUO kidney on day 7 in comparison with the sham-operated control. However, p-FAK, but not p-Smad2/3 or p-LRP6, was significantly lower in the CCN2m/m UUO kidney compared with the wild-type UUO kidney (p-FAK/FAK: 1.1+/-0.1 vs. 2.6+/-0.4, p<0.01). Furthermore, mutant CCN2 showed significantly lower expression levels of p-Akt and total beta-catenin, which are considered downstream pathway proteins of pFAK, in the UUO kidney in comparison with the wild type (p-Akt/Akt: 0.1+/-0.1 vs. 0.6+/-0.2, p<0.03; beta catenin/GAPDH: 1.6+/-0.1 vs. 2.8+/-0.5, p<0.03). Immunohistochemistry revealed that FAK was activated in the tubular epithelium of the fibrotic wild-type UUO kidney, whereas these were significantly suppressed in the CCN2m/m UUO kidney.

Conclusions: CCN2 module-IV activates the FAK pathways in the tubular epithelium and, as a result, fibrosis is promoted in the UUO kidney. To prove this, primary tubular epithelial cells derived from CCN2m/m are being generated to examine the role of CCN2 module-IV *in vitro*.

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TH-PO930

Insulin-Like Growth Factor Binding Protein 3 Specific Binding DNA Aptamer Attenuated Renal Tubular Fibrosis

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Background: Insulin-like growth factor binding protein 3 (IGFBP3) is a predominant IGFBP family member of six IGFBPs. Emerging evidence has indicated that IGFBP3 has cell- and tissue-specific effects, and it is an important mediator of fibrosis in various cell types and the organs. However, to date, the effect of IGFBP3 on renal fibrosis has not been fully evaluated. This study was to investigate whether IGFBP3 is involved in renal tubular fibrosis and IGFBP3 inhibition by aptamer treatment is effective for attenuating renal tubular fibrosis.

Methods: IGFBP3 and fibrosis-related protein expression were evaluated in unilateral ureteral obstruction (UUO) rats. In vitro, the proximal tubular cells (NRK-52E) were treated with TGF-β1 (10 ng/ml). IGFBP3 inhibition was performed by IGFBP3 small interfering RNA (siRNA, 100 pmol/ml) and IGFBP3-binding DNA aptamer (200 pmol/ml) for 48 hours, respectively. Changes of fibrosis related protein expression were examined by real-time PCR and Western blot.

Results: IGFBP-3 and fibrosis-related protein expressions were up-regulated in the kidney of UUO rats. In TGF-β1-stimulated NRK-52E cells, IGFBP3 protein expression was increased in dose- and time-dependent manners. TGF-β1 treatment induced IGFBP3 and fibrosis-related protein expression, including fibronectin and type I collage, in renal proximal tubule cell. IGFBP3 siRNA treatment significantly abrogated the increase in fibrosis-related protein expression induced by TGF-β1. Furthermore, the IGFBP3-binding DNA aptamer also significantly attenuated fibrosis-related protein expression up-regulated by TGF-β1 treatment.

Conclusions: This study suggests that IGFBP3 is significantly associated with pathogenesis of renal tubulointerstitial fibrosis. Furthermore, IGFBP3 aptamer treatment can be a potential therapeutic option for renal tubulointerstitial fibrosis in chronic kidney disease patients.

TH-PO931

Differences in Proximal Tubular Secretion Across Categories of CKD

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Background: Absent a kidney biopsy, the cause of chronic kidney disease (CKD) is determined by clinical assessment, which includes measures of glomerular function (estimated glomerular filtration rate (GFR) and urinary albumin excretion). However, the underlying causes of CKD may also differentially impact non-glomerular tissue, including the proximal tubule. We quantified a set of proximal tubular secretory solutes and compared their clearances among varying causes of CKD.

Methods: We evaluated timed overnight urine specimens from 223 participants in the Seattle Kidney Study, a prospective study of CKD. We used liquid chromatography-mass spectrometry to quantify serum and urine concentrations of ten secretory solutes and calculated clearance of each solute (mL/min). We abstracted CKD causes from review of nephrology clinic notes and categorized these causes as vascular, diabetic, glomerular, and tubulointerstitial kidney diseases. We used one-way analysis of variance to compare differences in solute clearances among the CKD causes and we advanced three solutes for further analyses based on meeting a 5% false discovery threshold. For each significant solute we used linear regression to compare the relative difference in secretory clearance among disease group after adjustment for age, race, gender, body mass index, estimated GFR, and urine albumin to creatinine ratio.

Results: Three secretory solutes met the threshold for significance across the suspected etiologies of CKD: isovalerylglycine, kynurenic acid, and tiglylglycine. Glomerular disease was associated with greater clearances of all three secretory solutes. Diabetic kidney disease was associated with greater isovalerylglycine clearance compared with vascular disease after adjustment (Table).

Conclusions: Secretory solute clearance relative to GFR is higher in CKD patients with glomerular disease compared to vascular disease.

Funding: NIDDK Support

Solute	Adjustment model	Vascular disease [n=75](reference)	Diabetes [n=72] Fold difference (95% CI)	p-value	Tubulointerstitial disease [n=26] Fold difference (95% CI)	p-value	Glomerular disease [n=50] Fold difference (95% CI)	p-value
Isovalerylglycine	Unadjusted	1.0	1.12 (0.88, 1.42)	0.34	1.28 (0.92, 1.77)	0.14	1.55 (1.19, 2.02)	0.001*
	Adjusted	1.0	1.39 (1.13, 1.72)	0.002*	1.05 (0.80, 1.37)	0.72	1.48 (1.18, 1.87)	0.001*
Kynurenic acid	Unadjusted	1.0	1.02 (0.82, 1.27)	0.83	1.12 (0.83, 1.51)	0.45	1.45 (1.14, 1.84)	0.003*
	Adjusted	1.0	1.07 (0.88, 1.30)	0.48	0.97 (0.75, 1.24)	0.79	1.28 (1.03, 1.59)	0.03*
Tiglylglycine	Unadjusted	1.0	1.03 (0.81, 1.30)	0.79	1.14 (0.82, 1.59)	0.39	1.52 (1.17, 1.98)	0.002*
	Adjusted	1.0	1.10 (0.91, 1.35)	0.31	0.96 (0.75, 1.25)	0.79	1.33 (1.07, 1.67)	0.01*

*denotes statistical significance at p-value < 0.05

TH-PO932

Inactivation of KLHL3 Kelch Like Family Member 3 Ameliorates Renal Fibrosis in Unilateral Ureteral Obstructive Mice

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Background: KLHL3 kelch like family member 3 (KLHL3) regulate some electrolyte in kidney tubules. In human, the mutation of KLHL3 induce hypertension, characterized by pseudoaldosteronism (decreasing aldosterone). We evaluated whether the KLHL3 could be fair target of RAAS inhibition, resulting in inhibition of renal fibrosis in unilateral ureteral obstructed (UUO) mice.

Methods: 10-week-old male B6 mice background KLHL3 KO mice and wild type mice were divided into 4 groups; wild, KLHL3 KO, wild with UUO, and KLHL3 KO with UUO. Mice were sacrificed at 7 days after surgery and kidney tissue were collected. Real time RT-PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed.

Results: KLHL3 KO with UUO mice showed improvement of renal cell survival, renal function, and pathologic damage compared to wild type UUO mice. Wild type with UUO kidney showed decrease of renal expression of KLHL3 and WNK4, and increase of renin and angiotensin I receptor, compared to sham mice. However, KLHL3 KO with UUO reduced the renal expression of renin, angiotensin I receptor, alpha-SMA, collagen IV, and TGF-β in UUO kidney, compared to wild type with UUO mice.

Conclusions: KLHL3 KO ameliorate renal fibrosis in UUO kidney via inhibition or renin angiotensin system.

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TH-PO933

Mouse Model of Progression to Chronic Kidney Injury from AKI

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Background: There is no animal model displaying the typical characteristics of CKD following an episode of AKI. Thus, the aim of the present study was to develop an AKI to CKD animal model.

Methods: We first tested whether current AKI models can induce CKD. Bilateral renal ischemia reperfusion (IR) and unilateral renal IR plus uninephrectomy with stepwise lengths of ischemic time were performed in C57BL/6 mice. Then we developed a two-stage AKI to CKD model in C57BL/6 mice. In stage I, IR induced AKI was performed in the left kidney with stepwise lengths of ischemic time, while the right kidney was kept intact. In stage II, after 2 week recovery for the injured left kidney, the intact right kidney was removed. Kidney function and renal injury were evaluated afterwards.

Results: In current IR induced AKI models, the animals either fully recovered if the renal injury was moderate with <18 min bilateral or <15 min unilateral ischemic time, or died if the renal injury was life-threatening with >21 min bilateral or >18 min unilateral ischemic time. No typical CKD feature was observed in these models. In two-stage AKI to CKD models, after removal of the intact right kidneys, the mice with 21 min or 24 min left renal ischemia exhibited the characteristics of CKD, including continuous decline in GFR (from 206.6±9.5 μl/min to 76.3±8.1 μl/min in 21 min group, from 199.2±6.7 μl/min to 49.5±11.3 μl/min in 24 min group), gradual increase in PCr (from 0.13±0.03 mg/dl to 0.43±0.05 mg/dl in 21 min group, from 0.09±0.03 mg/dl to 0.65±0.09 mg/dl in 24 min group), exacerbation in urine albumin-to-creatinine-ratio (from 13±6 μg/mg to 3457±342 μg/mg in 21 min group, from 9±5 μg/mg to 4841±375 μg/mg in 24 min group), histopathological changes including tubular atrophy, interstitial fibrosis, glomerular sclerosis, collapse of glomerular tufts and dilated Bowman's capsule, and transmission electron microscopy ultrastructural alterations including peritubular interstitium expansion, collagen deposition, cellular debris within Bowman's space, GBM thickening, and podocyte foot process effacement. The mice

with 15 min or 18 min left renal ischemia had a full recovery. All mice with 27 min or 30 min left renal ischemia died within 7 days after right kidney removal.

Conclusions: In conclusion, we successfully developed a novel mouse model with a direct transition from renal IRI induced AKI to subsequent progression of CKD.

Funding: NIDDK Support

TH-PO934

The Sulfate Moiety in Indoxyl Sulfate Is Critical for Activation of Aryl Hydrocarbon Receptor–Tissue Factor Axis and 3-Indole Methanol Is a Competitive Antagonist of Indoxyl Sulfate

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Background: Indolic solutes (indoxyl sulfate –IS, Indoxyl acetate -IA) are bonafide uremic solutes with protean systemic manifestations, including prothrombotic effect through activation of the Aryl hydrocarbon receptor (AHR) and tissue factor (TF). Despite its well-established pathogenicity, molecular determinants of IS that regulate its prothrombotic propensities remain unknown.

Methods: A structure activity relationship analysis was performed using a set of commercially available analogs. Activity was compared biochemically using validated AHR and TF activity assays, and visually in a transgenic zebrafish model containing a CYPA1 promoter tethered to a GFP reporter. A newly identified antagonist, indole-3-methanol (3-IM) was confirmed by using an carotid thrombosis model in mice treated with IS, as well as by ability to reduce TF in vascular smooth muscle cells treated with sera obtained from CKD patients with known concentration of IS levels.

Results: Modifying the sulfate moiety of IS altered its ability to increase AHR and TF activities. IA exhibited 100-fold higher AHR activation in cells and zebrafish models than IS. Of a total of thirteen analogs analyzed, five showed an agonistic activity in the presence of IS while one showed no effect. Of seven analogs with antagonistic activity towards IS, 3-IM significantly inhibited IS-induced AHR activation and TF with an IC50 of 50uM. 3-IM showed a potent anti-thrombotic activity in an IS-specific mouse model of thrombosis. Importantly, the downregulation of TF with 3-IM was significantly higher in vascular smooth muscle cells treated with uremic sera compared to cells treated with control sera. The ability of 3IM to suppress TF inversely correlated with the levels of IS in sera of end stagre renal disease patients.

Conclusions: The sulfate moiety is an important determinant of activity of IS in the AHR-TF axis. A non-sulfated analog, 3-IM suppresses TF and thrombosis in an IS-specific manner. These results point to the potential of 3-IM as a new therapeutic in counteracting IS-mediated systemic manifestations.

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TH-PO935

Silence of Central (Pro)renin Receptor Ameliorates Salt-Induced Renal Injury and Oxidative Stress in CKD

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Background: High salt diet promotes renal injury and oxidative stress via the brain and renal RAS axis in CKD rats. (Pro)renin receptor(PRR) can mediate oxidative stress. However, central PRR regulates salt-induced renal oxidative stress in CKD remains undefined. Here we hypothesized that the reduction of central PRR expression could ameliorate oxidative stress and thereby prevent renal injury in high-salt-load CKD rats.

Methods: We used the lentivirus as a vector to screen out the sequences that inhibit the central PRR expression in mature rat hippocampal neural stem cells in vitro. Moreover, we investigated renal oxidative stress, renin-angiotensin system, sympathetic nerve activity and tissue injury in 5/6 nephrectomy CKD model rats fed high dietary salt after silence of central PRR expression by intracerebroventricular (ICV) lentivirus RNAi.

Results: We found that high salt diet contributes to progression of renal injury, fibrosis and oxidative stress in CKD; The expression of PRR in the subfornical organ was decreased after ICV administration of lentivirus RNAi, indicating that shRNA successfully inhibited the expression of PRR in the brain. The expression of tyrosine hydroxylase in neurons of the rostral ventrolateral medulla of the brain, and the serum, renal norepinephrine levels were decreased, indicating that activation of the sympathetic nerve system was prevented by silence of central PRR expression; while kidney H&E staining and Sirius Red staining, as well as Fibronectin, α-SMA, and Collagen I were down-regulated, indicating that inhibition of central PRR can improve renal injury and reduce renal fibrosis. In addition, renal RAS components such as PRR, Angiotensinogen, and Angiotensin II, and kidney NADPH oxidase (Nox2, Nox4) were down-regulated, while renal antioxidant enzymes (CAT, GP1, and SOD1) were up-regulated. These experimental data suggest that silencing PRR expression in the CNS may down-regulate renal RAS expression and reduce renal damage and oxidative stress levels.

Conclusions: Silence of central PRR expression ameliorates renal fibrosis, injury, and oxidative stress in CKD model fed high salt.

TH-PO936

Scavenging Reactive Dicarbonyls Improves Renal Injury: Role of Urinary Isolevuglandin-Modified Lipoproteins and Renal Lymphangiogenesis

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Background: The kidney has a well-developed lymphatic system and lymphangiogenesis occurs in diseased kidney. Our previous studies revealed that proteinuric injury increases urinary lipoproteins which were recently shown to regulate lymphangiogenesis. Isolevuglandins (IsoLG) and related reactive dicarbonyls are lipoxidation products that can modify lipoproteins and degrade their functions. We determined if scavenging dicarbonyls, including IsoLG that block protein modification, can modulate renal lymphangiogenesis and lessen renal injury.

Methods: Nphs1-hCD25 mice (Nep25) expressing podocyte-specific human CD25 become proteinuric after injection of immunotoxin (LMB2). Nep25 mice were treated with the dicarbonyl scavenger, PPM (1g/L) or vehicle from onset of proteinuria until sacrifice (2 weeks). We assessed proteinuria [measured as albumin:creatinine ratio (ACR)], urinary apoAI, IsoLG, KIM-1 (marker of tubular injury), and the renal expression of lymphatic markers (LYVE-1 and podoplanin). *In vitro*, we assessed the effects of apoAI or modified apoAI (IsoLG-apoAI) ± PPM in lymphatic endothelial cells (LEC).

Results: After LMB2 injection, Nep25 mice had significantly higher urinary ACR (32-fold), KIM-1 (35-fold), urinary apoAI (7.3-fold), and IsoLG-protein adduct excretion (1.3-fold). Proteinuric kidneys showed greater immunostaining for apoAI and a denser lymphatic vessel network (podoplanin staining: 2.1-fold). *In vitro*, IsoLG-apoAI increased LEC viability (1.6-fold) and migration (1.1-fold) vs unmodified apoAI. These effects were significantly abrogated by exposure to PPM. *In vivo*, proteinuric Nep25 mice treated with PPM showed reduced lymphangiogenesis (podoplanin: 0.7-fold and LYVE-1: 0.5-fold). PPM treatment also significantly reduced ACR (0.8-fold), urinary KIM-1 (0.7-fold) together with significant reduction in IsoLG excretion (0.4-fold).

Conclusions: We conclude that dicarbonyl scavenger PPM lessens proteinuric renal damage through mechanisms that include preserving lymphatic endothelial cell functionality and diminishing urinary lipoprotein-stimulated renal lymphangiogenesis.

Funding: Other NIH Support - NHLBI

TH-PO937

Identification of C/EBPβ-TMIGD1 as a Novel Renoprotective Pathway

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Background: The management of chronic kidney disease (CKD) patients lacks agents that protects functional renal mass, which predominantly consists of tubules. We recently identified transmembrane and immunoglobulin domain-containing 1 (**TMIGD1**) as a novel receptor expressed predominantly in the proximal tubular epithelial cells. TMIGD1 regulates epithelial cell adhesion and protects kidney epithelial cells from oxidative stress-induced cell injury in cell culture. While, TMIGD1 expression changes in acute kidney injury and chronic CKD mouse models, depending to the stage of disease the in vivo renoprotective function of TMIGD1 remains unknown.

Methods: TMIGD1 transcriptional regulation and promoter were characterized using electrophoretic mobility shift assay (EMSA). Expression of TMIGD1 and C/EBPb were examined in three discrete CKD models – unilateral ureteral obstruction (UUO), Adenine-induced CKD and remnant kidney model (RKM) model through immunofluorescence staining. CRSIPR/Cas9 TMIGD1 $^{+}$/- mice were subjected to adenine-induced CKD model. Targetability of TMIGD1 was demonstrated using TMIGD1 blocking antibody.

Results: C/EBPβ strong interacts with TMIGD1 promoter and stimulates promoter activity of TMIGD1 in HEK-293 cells. C/EBPβ showed nuclear localization in normal renal tubular cells, however, it was lost with the induction of CKD and correlated with the downregulation of TMIGD1 in renal tubules. CRSIPR/Cas9 TMIGD1 $^{+}$/-CKD mice showed a significantly lower kidney weight/body weight ratio suggesting a greater extent of renal atrophy compared to the wild type littermates. Pre-treatment of mice with a TMIGD1 blocking antibody augmented renal tubular damage.

Conclusions: We present C/EBPβ-TMIGD1 axis as a novel renoprotective pathway, which can be explored further to preserve the functional renal mass in CKD.

TH-PO938

Use of Population Management Tools to Identify Patients at High-Risk of ESRD Progression

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Background: The current health care system focuses on treatment rather than prevention of illness. There is inadequate support for patients who are unable to adhere to complex medical therapies. Transition from CKD to ESRD is a perfect example: many patients are not engaged in renal care due to psycho-social issues such as denial, lack of understanding of disease, or lack of financial resources for travel and/or medications. Kaiser

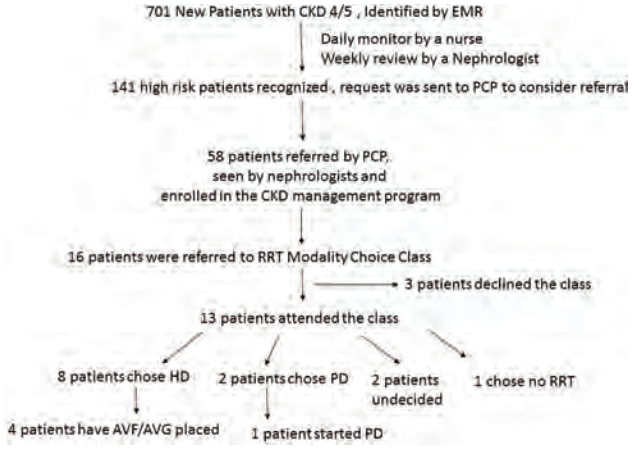
Permanente Northern California (KPNC) is an integrated health care system providing care for 4.3 million members. In 2016, KPNC East Bay Nephrology department started a pilot to identify patients with moderate to advanced CKD who had not received Nephrology care.

Methods: We used our Electronic Medical Record (EMR) system to identify late stage CKD patients (eGFR less than 30 ml/min) who have not been seen by a Nephrologist. The patient list was monitored daily by a nurse and reviewed weekly with a Nephrologist. Nephrologists screened patients to determine if they were appropriate for referral to nephrology specialty care. Primary care providers were contacted with recommendation to review chart and determine if those patients may benefit from referral to nephrology care.

Results: After the implementation of the pilot, many patients who would likely have been "lost to follow up" were captured by this program. The Nephrology team educated patients about the presence of advanced CKD and developed a comprehensive plan of care (Figure).

Conclusions: Establishing a "safety net" by developing an automated process of identifying patients with elevated risk characteristics and enrolling them in a structured CKD care program can potentially lead to a smoother transition to ESRD in our integrated health care system. In addition, this program supports the development of individualized care pathways depending on patient-identified goals of care.

Funding: Private Foundation Support



Population Management of CKD Patients by Building a Safety Net to Identify High Risk Patients

TH-PO939

Treatment of Anemia with Oral and Parenteral Iron Leads to Bone Loss in Juvenile Mice with CKD

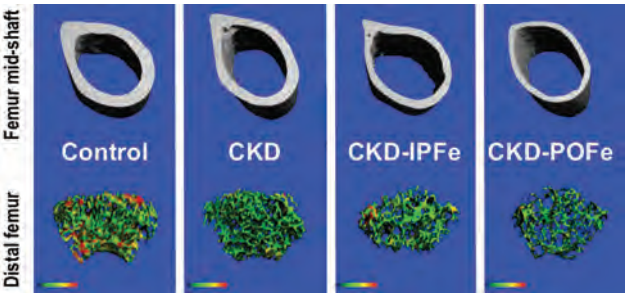
Oleh M. Akchurin,[1] Edwin Patino,[1] Sureshbabu Angara,[1] Divya Bhatia,[1] Vidhi Dalal,[1] Kelly Meza,[1] Stefano Rivella,[2] Mary E. Choi.[1] *[1]Weill Cornell Medicine, New York, NY; [2]Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Anemia is common in children with CKD and is associated with altered iron metabolism. Thus, many children with CKD are receiving iron therapy. Iron sequestration due to elevated hepcidin is a concern in CKD. Iron supplementation induces bone loss in mice without CKD. The effects of iron on bone health in juvenile CKD remain poorly understood.

Methods: CKD in juvenile mice was induced by 8 weeks of a 0.2% adenine diet, post-weaning. Bone histology and micro-CT was compared between four groups of mice: 1. Control (no CKD). 2. CKD without iron supplementation. 3. CKD + weekly 0.5g/kg of iron dextran intraperitoneally (CKD-IPFe). 4. CKD + 0.5% carbonyl iron diet (CKD-POFe). ANOVA was used for statistical analysis. For all reported data, pairwise comparisons between groups 1/2, 2/3, and 2/4 were significant ($p<0.05$).

Results: Renal function was reduced in all CKD groups (serum creatinine 0.22, 0.55, 0.32, and 0.79 mg/dL in groups 1-4 respectively). As expected, mice with untreated CKD were anemic. Treatment with oral and IP iron resulted in improvement of Hgb (13.9, 11.5, 13.1, and 13.3 g/dL in groups 1-4), Hct, MCV, MCH, and RDW. Mice with CKD had thinner and more porous cortical bone, and lower trabecular bone mass compared to controls. Iron treatment resulted in further cortical thinning (Ct.Th 0.18, 0.15, 0.12, 0.10 mm in groups 1-4), and decrease in cortical tissue mineral / apparent density, compared to untreated mice with CKD. Iron treatment also led to further reduction of trabecular bone volume (BV/TV 17.6, 12.2, 8.8, 8.6% in groups 1-4), trabecular number and increase in trabecular separation (Fig), compared to untreated mice with CKD.

Conclusions: Iron therapy improved anemia but was complicated by the loss of cortical and trabecular bone in this model of juvenile CKD. In our ongoing studies we aim to elucidate the underlying mechanisms. Our findings suggest a need to consider potential bone-related effects of iron in optimizing CKD management in children with CKD.



Cortical and trabecular bone micro-CT in four groups of mice

TH-PO940

Translational Medicine in CKD: Therapeutic Targeting of p-Cresyl Sulfate Triggered Nonspecific ROS in Uremic Lung Injury

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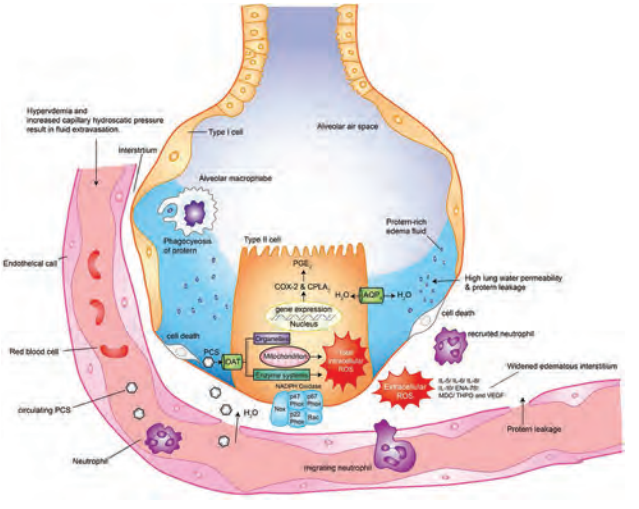
Background: p-Cresyl sulfate (PCS) exerts pro-inflammatory, pro-oxidant, and pro-apoptotic effects on multi-cell systems. Nonetheless, mechanisms and therapies of PCS induced uremic lung injury (ULI) in chronic kidney disease (CKD) remain unclear.

Methods: We analyzed pleural effusions from CKD and non-CKD patients with respiratory distress for uremic toxins, hydroxyl radicals, and chemotactic cytokines. From bedside to bench, cell viability and inflammatory signaling pathways with reactive oxygen species (ROS) were investigated in PCS-treated human alveolar cell model. To mimic human diseases, CKD-ULI mouse model was developed with quantitative comparison of immunostaining and morphometric approach.

Results: Pleural effusions exhibit higher expressions of PCS/ indoxyl sulphate/ hydroxyl radicals/ IL-5/ IL-6/ IL-8/ IL-10/ ENA-78/ MDC/ THPO/ VEGF and leukocyte recruitment with proteinaceous leak in CKD patients. In vitro, PCS promotes alveolar cell death, cPLA2/COX-2 expression, and NADPH oxidase/mitochondria activation-related ROS burst. Intracellular ROS burst is abrogated by non-specific antioxidant (N-acetyl cysteine, NAC), inhibitors of NADPH oxidase and mitochondria-targeted superoxide scavenger. However, only NAC protects against PCS-induced cell death. In vivo, expressions of cPLA2/ COX2/ 8-OHdG, dust cells, recruited leukocytes, alveolar space, plasmatic leakages and interstitial edema increase in lung tissues of CKD-ULI mice, and NAC pretreatment ameliorates ULI and alveolar cell death.

Conclusions: PCS impairs alveolar-capillary integrity through triggering intracellular ROS burst, activating downstream PG pathways, cell death, and recruiting leukocytes to release ROS and multiplex chemoattractants. Our translational research resolves puzzling mechanisms of CKD-ULI, proving that PCS and nonspecific ROS serve as potential therapeutic targets.

Funding: Private Foundation Support



Mechanisms of CKD-ULI

TH-PO941

Sucroferric Oxyhydroxide Ameliorates Glomerular Podocyte and Tubulointerstitial Injury in the Rat Remnant Kidney Model

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Background: Previously, we reported that the elevation of serum phosphate can accelerate CKD progression in the retrospective cohort study (Plos One 2016). In this study, we evaluated the protective effects of sucroferric oxyhydroxide (SF), a phosphate binder, in a rat model of CKD.

Methods: SD rats received 5/6 nephrectomy (RK) and had a normal diet containing 0.3% phosphate. Control rats without 5/6 nephrectomy received the same diet. A subgroup of RK rats received SF (50 mg/g chow; RK+SF). Renal histology was evaluated at 8 weeks.

Results: RK rats showed increased FGF23 levels compared with control rats. Serum phosphate levels were also moderately but significantly increased. SF administration significantly decreased serum FGF23 and phosphate levels in RK rats. Urinary phosphate excretion was also significantly lower in RK+SF rats than RK rats. Of note, albuminuria in RK rats was significantly ameliorated by SF administration at 8 weeks (RK, 8.42 ± 1.49 mg/day versus RK+SF, 2.71 ± 1.15 mg/day; $P < 0.01$). In the PAS-stained kidney sections, SF administration attenuated glomerulosclerosis and tubulointerstitial injury in RK rats. Consistently, gene expression of inflammatory and profibrotic cytokines were significantly lower in the kidney in RK+SF rats than in RK rats. In the glomeruli, we found that the increased expression of desmin, a marker for podocyte injury, was attenuated by SF. Consistently, nephrin protein expression was preserved in RK+SF rats compared with RK rats. The protective effects on podocytes were confirmed by morphological analysis under transmission electron microscope. In von Kossa staining, calcium phosphate was detected neither in RK nor RK+SF rats, indicating that renal injury in this model is independent of ectopic calcification at this stage. Plasma levels of calciprotein particles were significantly lower in RK+SF than RK rats, indicating the reduced mineral stress by SF.

Conclusions: These data indicate that phosphate loading to the kidney causes glomerular and tubulointerstitial injury in the absence of calcium phosphate deposition, and support the pathological role of phosphate loading in CKD progression.

TH-PO942

Adiponectin and Its Receptors in Peripheral Muscle and Fat Tissues of CKD Patients

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Background: Inflammation contributes to protein-energy wasting (PEW) in CKD, but the role of adiponectin (APN), which has anti-inflammatory properties, is not known. APN is secreted preferentially by adipocytes, but also by skeletal muscle. APN binds two receptor isoforms, adiponectin receptor 1 (AR1) and adiponectin receptor 2 (AR2). The aim of this study was to examine the expression of APN and its receptors in skeletal muscle and adipose tissue in CKD patients.

Methods: Muscle biopsies were obtained from 29 CKD (eGFR 8±3 ml/min per 1.73m^2, 15M/14F, age 69 yrs) patients and 14 controls (C) rectus abdominis muscle samples. In this cohort, visceral fat samples were also obtained in 16 CKD and 10 C subjects. The expressions of APN, AR1 and R2 were tested by rtPCR and immunohistochemistry.

Results: *Skeletal Muscle*: APN gene expression and protein were up-regulated, (by 6-3.5 folds with respect to C, $p< 0.001$), AR1 and R2 mRNAs were markedly downregulated (-90 %, $p<0,001$), while protein expression was unchanged in CKD vs. C. *Adipose tissue*: APN, AR1 and R2 mRNAs were upregulate (by 2-7 folds, $p<0.05$) in CKD vs. C. Muscle APN mRNA was directly related to TLR4 protein expression ($r^2=0.33$, $p=0.023$); moreover, APN and IL-6 protein were directly related ($r^2=0.28$, $p<0.01$). Only as a trend, APN protein was related to NF-kB pp65 ($r^2=0.179$, $p=0.056$). Visceral Fat APN was directly related to plasma CRP ($r=0.62$, $p=0.028$).

Conclusions: In conclusion, muscle and visceral fat APN and APN receptors expression pattern is markedly modified in CKD. The APN system appears to respond to chronic inflammation as a compensatory mechanism which helps to maintain body homeostasis.

TH-PO943

NLRP3 Inflammasome Is Activated in Skeletal Muscle of Patients with CKD

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Background: Inflammation in skeletal muscle is implicated in the pathogenesis of insulin resistance and cachexia but why uremia upregulates muscle pro inflammatory cytokines is not completely understood.The NOD-like receptors (NLRs) are a group of pattern recognition receptors which activate the inflammasome platform. Aim of this study was to investigate the NLP3 role in skeletal muscle of CKD patients and the effects of uremic milieu on the NLRP3 pathway and mitochondria homeostasis.

Methods: Rectus abdominis muscle biopsies were collected from CKD5 patients (n= 25, 18M/7F, age 69±10 yrs, eGFR 8±1mL/min 1,73m^2) and from 10 controls (C) (age 68±11 7M/3F, eGFR 100±4mL/min 1,73m^2). NLRP3, IL1β expression was studied by immunohistochemistry, mRNA (NLRP3,IL1β,PGC1α,MFN2, NRF2) by rt-PCR. To assess the effects of uremic milieu, C2C12 myotubes were exposed to 10% normal serum (NS) or Uremic (US) Serum for 5-48 hours (h). NLRP3,IL1β,PGC1α,MFN2,NRF2 were studied by rtPCR, caspase1 by western blot and mitochondria damage by JC1 staining.

Results: In CKD, NLRP3 mRNA and protein were overexpressed (by 16-2 folds, $p<0.05$-0.025). IL1β mRNA was upregulated ($p=0.02$). In vitro, 5 hour US treatment upregulated NLRP3 and IL1β mRNAs (by 71-12 folds $p<0.01$) and caspase1 (+30% $p<0.05$). TAK 242 (1μM) a TLR4 antagonist prevented these effects. In CKD muscle, PGC1α (a mitochondrial biogenesis regulator), MFN2 (involved in mitochondrial fusion and in the mitochondrial network maintenance) and Nrf2 (a player in supporting the mitochondria structural and functional integrity) were significantly elevated (0.05-0.01) respect to C. Moreover, US upregulated PGC1α, MFN2 and Nrf2 (by 2-26 folds $p<0.05$-0.001) and altered mitochondrial membrane potential ($p<0.05$). These effects were partially blocked by TAK 242.

Conclusions: Our data show that NLRP3 inflammasome is activated and mitochondria dysregulated in CKD 5 skeletal muscle. These effects are rescued by TLR4 block, showing a link between TLR4 and inflammasome. TLR4/NLRP3/IL-1β blockade offers a novel method for reducing inflammation in muscle of CKD patients.

TH-PO944

Towards a Standardized Histological Identification of CINAC Patients: Methods and Pitfalls in Microscopic Diagnosis

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Background: Patients with Chronic Interstitial Nephritis in Agricultural Communities (CINAC) demonstrate previously unidentified enlarged granules in the proximal tubular (PT) epithelium, first discovered and easily recognizable on Jones' methenamine silver stained renal biopsies and by autofluorescence. The aim is to 1) identify the nature of the granules, 2) provide a standardized Jones staining protocol for granule identification, 3) evaluate autofluorescence as a rapid diagnostic method and 4) assess EM analysis.

Methods: Formalin fixed deparaffinized renal tissue sections (4μm) of Sri Lanka and El Salvador CINAC patients and patients with proteinuric pathologies were subjected to Jones staining protocols with varying silver solution incubation times. Autofluorescence of 4μm sections was imaged (2-7 secs shutter time), followed by standardized Jones staining of the same tissue section. Immunofluorescence microscopy was performed for the mitochondrial marker COX6c and for lysosomal markers LAMP1 and Cathepsin B. EM of CINAC and proteinuric renal biopsies was performed.

Results: Jones stain invariably revealed the specific PT granules only when the incubation in silver-solution was ≥90 min, surpassing the time (60 min) needed to visualize basement membranes. CINAC biopsies showed PT autofluorescent granules in a pattern similar to the argyrophylic granules, with nearly all autofluorescent granules also being argyrophylic. Most autofluorescent granules were identified as lysosomes with LAMP1 and Cathepsin B. In proteinuric patients, PT argyrophylic and autofluorescent granules may occur. However, on EM, proteinuric lysosomes were round, and did not contain dispersed electron dense aggregates as obseved in CINAC patients.

Conclusions: PT CINAC granules are lysosomes, identifiable by Jones staining with prolonged silver incubation and more rapidly by autofluorescence. EM of PT lysosomes can identify suspected CINAC patients, with or without proteinuria.

TH-PO945

Stanniocalcin-1 Inhibits ER Stress-Induced Apoptosis and Renal Fibrosis via Restoration of ER-Mitochondrial Calcium Communication

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Background: Endoplasmic reticulum (ER) stress is a common feature of several physiological and pathological conditions. ER stress-associated apoptosis plays a role in organ remodeling after insult, and overwhelming ER stress lead to renal cell apoptosis and subsequent fibrosis. Stanniocalcin-1 (STC-1) is a multifunctional glycoprotein which is targeted to the mitochondria to exert putative anti-apoptotic effects. The present study aimed to investigate the effects of STC-1 in ER stress-induced apoptosis and renal fibrosis in human renal proximal tubular (HK-2) cells.

Methods: HK2 cells pretreated with STC-1 (200 ng/ml) for 1 hours followed by treatment with TGF-β (10 ng/ml) for 24 hours. The protein expression of ER stress, apoptosis, and fibrosis markers was determined by semiquantitative immunoblotting.

The level of reactive oxygen species (ROS) was determined by fluorescent microscopy immunofluorescence. Using microscopy and immunocytochemistry, immunolabelling of Ca^{2+}, calcium sensing receptor and inositol 1,4,5-trisphosphate receptor (IP3R) was detected.

Results: TGF-β treatment induced ER stress via upregulation of PERK-eIF2-ATF signaling, and suppressed cytosolic calcium concentration via downregulation of IP3R. Pretreatment of STC-1 attenuated the TGF-β induced up-regulation of PERK-eIF2-ATF4 signaling and restored the cytosolic Ca concentration, thus reducing apoptosis. TGF-β treatment induced mitochondrial ROS generation and cytosolic cytochrome c release. STC-1 pretreatment significantly blocked mitochondrial ROS generation and cytosolic cytochrome C release. TGF-β treatment also induced upregulation of E-cadherin, collagen IV and fibronectin and downregulation of N-cadherin, which was counteracted by STC-1 pretreatment.

Conclusions: Restoration of ER-mitochondrial calcium signal by STC-1 attenuated ER stress induced apoptosis and fibrosis in HK2 cells. The present study suggested that the STC-1 may serve as a potential treatment for renal fibrotic disease.

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TH-PO946

Sex-Specific Renal Pathology Following 5/6 Nephrectomy Is Modulated by miR-146b

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Background: Chronic kidney disease (CKD) presents a complex pathological landscape in both men and women. Many studies have shown miRNAs can be powerful mediators of pathology at the molecular level. Our work focuses on the role of miRNAs in CKD, utilizing the 5/6 nephrectomy (5/6Nx) rat model. We have reported a significant increase in the expression of miR-146b in kidney tissue following 5/6Nx. The present study investigates the contribution miR-146b to CKD, and the relative contribution of sex hormones in modulating the pathology of CKD.

Methods: Male and female Sprague Dawley (SD) rats underwent 5/6Nx or sham surgeries at 10 weeks of age. The 5/6Nx consists of surgical resection of 2/3 of the left kidney and the entire right kidney. Seven weeks later, urine and blood were collected, the rats were euthanized, and the kidneys harvested for downstream application. To study the contribution of miR-146b, wild-type SD rats (WT) were compared to miR-146b null mutants (KO). To study the contribution of sex hormones, intact rats were compared to gonadectomized rats. Histological examination of kidney tissue was performed to assess renal fibrosis. Metabolite and electrolyte levels were measured in blood and urine using a blood gas analyzer. Creatinine clearance (CrCl) and fractional excretion of sodium (FE_{Na}) were derived from plasma and urine concentrations and urine flow rate.

Results: Following 5/6Nx, male WT and KO rats exhibit impaired renal function without significant renal fibrosis; diminished CrCl (WT: 2.09 vs. 0.85 ml/min, KO: 3.28 vs. 0.82 ml/min; sham vs. 5/6Nx) and increased FE_{Na} (WT: 0.12 vs. 0.40%; KO: 0.09 vs. 0.40%). Female WT rats exhibited similar renal dysfunction without fibrosis; reduced CrCl (0.99 vs. 0.28 ml/min) and elevated FE_{Na} (0.17 vs. 0.72%). However, female KO rats exhibited an exacerbation of renal dysfunction and injury compared to WT after 5/6Nx; sharply reduced CrCl (0.28 vs. 0.08 ml/min, WT vs. KO 5/6Nx), elevated FE_{Na} (0.72 vs. 4.43%), and significant fibrosis in the renal cortex (3.30 vs. 13.1% fibrotic area). Ovariectomy ameliorated nearly all structural and functional pathologies.

Conclusions: Our study suggests an important protective role for miR-146b in CKD which may be, in part, via modulation of estrogen signaling in the kidney. Future studies will address specific pathways targeted by miR-146b to elucidate its mechanism of action in CKD.

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TH-PO947

Altering Body Temperatures Response to Heat Modulates Kidney Injury

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Background: Hispanic Americans may be at more risk than African Americans for kidney damage from heat stress due to greater mitochondrial uncoupling because of genetic polymorphisms. Indeed, mitochondrial uncoupling proteins (UCP) dissipate the proton gradient in the mitochondria, resulting in more heat generation instead of ATP synthesis. We therefore hypothesized that the administration of a drug that could induce a mitochondrial uncoupling might result in a greater increase in body temperature following heat exposure, and that this might lead to greater renal damage.

Methods: To test this hypothesis C57BL/6 mice were exposed to 39.5°C for 30 minutes with subcutaneous injection of the chemical uncoupler; 2,4-dinitrophenol (DNP). After heat exposure, mice were returned to room temperature, and received access to water and food freely for one hour to avoid dehydration. The heat exposure was repeated twice per day for 10 days. Body temperature was evaluated with rectal probes.

Results: Body temperature immediately after the heat exposure was increased by heat and DNP (Table1). Albuminuria (uAlb) and BUN were increased in DNP+Heat group (Table1). uAlb correlated with body temperature (R=0.6, p<0.038). CPK was not increased in any groups, indicating an absence of rhabdomyolysis. Renal pathology showed greater tubular cell proliferation (proliferating cell nuclear antigen (PCNA) positive), tubular injury and interstitial macrophage infiltration (F4/80 positive) in the DNP+Heat group (Table1). HSP 70 expression was increased in Heat group and much more in Heat+DNP group.

Conclusions: Increasing body temperature for the same level of heat stress is associated with greater renal injury. Studies should evaluate whether individual temperature responses can predict renal injury in high risk subjects such as sugarcane workers.

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Table1

	Non Treat	DNP	Heat	DNP+Heat
Body tempenature (°C)	37.5±0.36	38.6±0.11*	40.9±0.27*	42.1±0.44*†
Urine albumin/creatinine (mg/gCr)	62±17	41±16	80±33	246±87 †
BUN (mg/dL)	24.7±4.3	25.6±4.0	23.7±2.0	36.8±1.9*‡
PCNA (positive area %)	8.45	6.15	6.00	15.23‡
F4/80 (positive area %)	2.49	1.99	1.38	8.22*‡

*p<0.001 vs NT, **p<0.001 vs NT, DNP, Heat, †p<0.001 vs NT, DNP, p<0.01 vs Heat, ‡p<0.05 vs NT, p<0.001 vs DNP, Heat

TH-PO948

A Novel Conditionally Immortalized Kidney Pericyte Cell Line to Model Myofibroblast Transition

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Background: Gli1-positive resident pericytes and perivascular fibroblasts are the predominant source of kidney myofibroblasts in kidney fibrosis but the study of pericyte to myofibroblast transition is hampered by the absence of appropriate cell culture models.

Methods: We crossed bigenic Gli1-CreER^{t2}; R26tdTomato mice with the 'immorto-mouse,' which expresses a temperature sensitive SV40 gene, and with the 'terminator' mouse, which expresses the diphtheria toxin receptor except after Cre-mediated recombination. After tamoxifen administration, we isolated tdTomato-positive Gli1 cells from kidney, and elimated all non-recombined cells by administration of diphtheria toxin. We characterized these cells ability to differentiate into myofibroblasts using a variety of methods, including scRNA-seq.

Results: Kidney Pericyte-Gli1 (KPG) cells maintain expression of appropriate pericyte cell markers, respond to hedgehog pathway activation and display robust myofibroblast differentiation upon treatment with TGFb. In support of their pericyte identity, co-culture of KPG with endothelium stabilizes capillary formation. Single cell RNA-sequencing analysis (5,000 cells) during the myofibroblast differentiation timecourse identified autocrine ligand-receptor upregulation including the connective tissue growth factor, platelet-derived growth factor and transforming growth factor beta-3 pathways. Strong upregulation of genes in the focal adhesion pathway led us to test the serum response factor inhibitor CCG-203971 which potently inhibited TGFb-induced pericyte to myofibroblast transition. Finally, our single cell analysis identified the unexpected upregulation of nerve growth factor (NGF) in KPG cells treated with TGFb. We confirmed strong NGF upregulation in two mouse kidney fibrosis models, and identified expression of the NGF receptor TrkA in VSMC cells in vivo, suggesting a novel role for perivascular fibroblast-derived NGF signaling to VSMC during kidney fibrosis.

Conclusions: KPG cells accurately model pericyte to myofibroblast transition, and we used them to identify a novel inhibitor of this process and the unexpected upregulation of the NGF pathway during renal fibrosis.

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TH-PO949

Three Dimensional Super-Resolution Microscopy and Automatic Quantification of Podocyte Foot Processes in Humans, Rats, and Mice

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Background: Until today, laborious and time-consuming transmission electron microscopy has been used to assess podocyte effacement in human and rodents. Recently, our group has shown that super-resolution 3D-structured illumination microscopy (3D-SIM) can be applied to visualize individual foot processes in human kidney biopsies. Furthermore, we have developed a software-based approach to quantify the structure of podocyte foot processes named podocyte exact morphology measurement procedure (PEMP). PEMP allows to quantify podocyte injury using filtration slit density (FSD), i.e. filtration slit length per capillary surface area, as the surrogate parameter for podocyte effacement in patients suffering from minimal change disease. As in basic science rodent models are widely distributed, we applied PEMP to mice and rats, the most used rodent models.

Methods: We co-stained 4 µm formalin-fixed and paraffin-embedded sections of healthy human, rat and mouse kidney tissue with antibodies targeted against the slit diaphragm protein nephrin and the actin-associated protein synaptopodin detected by Cy3 and Alexa 488-labeled secondary antibodies, respectively. Subsequently, we imaged these sections by wide-field microscopy, confocal laser scanning microscopy and 3D-SIM. PEMP was performed by FIJI utilizing a custom-built macro that semi-automatically detects the filtration slit and calculates FSD.

Results: In a comparative analysis, we show that only 3D-SIM is able to clearly visualize the nephrin-stained slit diaphragm between synaptopodin-stained foot processes in all three species. Using PEMP, we determined values for FSD in healthy individuals from all three species. The FSD in humans was 3.106 ± 0.024 μm^{-1} (mean ± SEM). The FSD was

significantly higher in rats and mice with a mean value of 3.364 ± 0.049 μm^{-1} and 3.829 ± 0.032 μm^{-1}, respectively. Since foot process width is inversely related to FSD, the width of foot processes continuously increases from mice to rats and humans.

Conclusions: Taken together, we present a method for basic research which allows fast evaluation and quantification of podocyte foot process morphology in rodents by using 3D-SIM on standardized histological material and tissue processing.

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TH-PO950

Lack of P2X7 Receptors Protects Against Pyelonephritis Associated Renal Fibrosis

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Background: Severe urinary tract infections are regularly caused by sub-strains of *E. coli* secreting the pore-forming virulence factor α-haemolysin (HlyA). Repeated cases of pyelonephritis can cause marked renal scarring that subsequently leads to progressive failure. We have previously demonstrated that HlyA releases cellular ATP directly through its membrane pore and that acute HlyA-induced cell damage is completely prevented by blocking ATP-signalling. Moreover, there is substantial evidence that local ATP signalling and $P2X_7$ receptor activation plays a key role in the development of tissue fibrosis. This study investigates the effect of $P2X_7$ receptors in infection-induced renal scarring in a murine model of pyelonephritis.

Methods: Pyelonephritis was induced by injecting 100 mill HlyA-producing, uropathogenic *E. coli* into the urinary bladder of balb/c mice. Pyelonephritis was confirmed by culture of the right kidney at day 5 post infection with concomitant high levels of proinflammatory cytokines (IL-6 and IL-1b) a response similar in both $P2X_7^{+/+}$ and $P2X_7^{-/-}$ mice.

Results: Lack of $P2X_7$ receptor did not influence on the mortality in the mice exposed to bacteria (n_{total} = 131). Fibrosis was first observed 2 weeks post infection. Our data clearly demonstrate that $P2X_7^{-/-}$ mice showed markedly less renal fibrosis following a similar degree of infection compared to $P2X_7^{+/+}$ controls ($p<0.001$), reducing the renal scarring from 1.153 ± 0.0755 mm^{-2} to 0.296 ± 0.036 mm^{-2} (fibrotic areas/mm^2 in the cortex). Similarly, a $P2X_7$ antagonist BBG reduced the formation of fibrosis ($p<0.001$) to 0.3810 ± 0.03532 mm^{-2} in the cortex. Immunohistochemistry revealed comparable degree of neutrophil infiltration in kidneys from $P2X_7^{+/+}$ and $P2X_7^{-/-}$ mice, with diminished macrophage infiltration and reduced neutrophil clearance in $P2X_7^{-/-}$ mice or mice treated with BBG compared to controls.

Conclusions: Hence this study suggests the $P2X_7$ receptor to be an appealing antifibrotic target following renal infections.

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TH-PO951

Genetic Ablation of Spermidine Oxidase Leads to Blunted Production of the Uremic Toxin Acrolein but Does Not Prevent CKD

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Background: The uremic toxin acrolein, a highly reactive aldehyde, is associated with cardiovascular disease and has been linked to chronic kidney disease (CKD). Sources of acrolein include e.g. smoking, lipid peroxidation and spermine metabolism. Spermine oxidase (SMOX) converts spermine to spermidine and generates acrolein.

Methods: Spermine oxidase germline deficient mice (SMOX-/-) were generated by CRISPR mediated gene deletion. Mice were subjected to an LPS challenge to study acute effects on polyamine and acrolein production. To study more chronic effects, renal ischemia reperfusion injury (IRI) or adenine diet induced kidney injury were elicited. 3HPMA, a stable metabolite of glutathione adducted acrolein, was measured in plasma and organs to assess acrolein production.

Results: SMOX deletion resulted in reduced circulating spermidine and acrolein levels. Following an LPS challenge, the acutely elevated acrolein levels, but also plasma creatinine levels particularly in males, were blunted in SMOX-/- animals. Both renal IRI and adenine diet induced chronic kidney injury led to increased circulating levels of acrolein in wild type but not in SMOX-/- animals. However, SMOX-/- did not prevent progression of kidney injury.

Conclusions: SMOX-/- animals responded with a blunted elevation of circulating acrolein levels after acute and chronic reduced kidney function. Reduction of this uremic toxin did not correlate to improved chronic kidney function in the models assessed here. It remains to be established whether reduction of SMOX activity and acrolein levels have a protective role in other cardiovascular diseases.

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TH-PO952

Near-Infrared Autofluorescence Is Useful for Non-Invasive Imaging of Injured Kidneys

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Background: Tubulointerstitial injury (TI) is the final common pathway leading to end-stage renal disease. Because TI is an important therapeutic target in kidney diseases, it is indispensable to establish non-invasive strategies that enable us to evaluate the progression of TI.

Methods: Near-infrared autofluorescence (AF) of injured kidney was non-invasively evaluated by IVIS imaging system. A combination of excitation 710 nm and emission 810-875 nm was used. Two animal models, unilateral ureteral obstruction and folic acid induced nephropathy, in BALB/c mice were analyzed. The origin of the renal AF was analyzed by confocal microscopy. Normal portions of human kidney tissues obtained from surgically resected kidneys owing to malignant tumors were also analyzed (35 patients (male 20, female 15), median age 69 (interquartile range (IQR) 62-74), median estimated glomerular filtration rate (eGFR) 57.25 mL/min/1.73m^2 (IQR 38.9-73.45)).

Results: The AF levels were positively correlated with the progression of TI in both animal models. Microscopic analysis of the kidney sections revealed that the AF was originated from the injured tubular cells. Because porphyrins are intrinsic fluorescent substrates that have near-infrared emission peak, we analyzed renal expression levels of enzymes that participate in the metabolism of porphyrin. Among 10 enzymes, only coproporphyrinogen oxidase (CPOX) was suppressed in the injured kidneys in both animal models, suggesting that coproporphrinogen III, a substrate for CPOX, and its spontaneously oxidized product, coproporphyrin III, were accumulated in the injured kidneys. We found that coproporphyrin III had identical fluorescent properties observed in the injured kidneys. Intraperitoneal injection of δ-aminolevulinic acid, a substrate of porphyrin synthesis, enhanced the AF of injured kidneys. The AF was also enhanced in BALB/c-nct/nct mice, a mice strain that retains only 15% of the wild type CPOX activity. Furthermore, AF levels of human kidney samples were inversely associated with eGFR.

Conclusions: Near-infrared AF derived from coproporphyrin III is useful for non-invasive imaging of TI.

TH-PO953

Tissue-Resident Mucosal-Associated Invariant T (MAIT) Cells in Human Renal Fibrosis and CKD

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Background: MAIT cells are a specialised lymphocyte population associated with chronic inflammatory disorders in peripheral tissues. To date, MAIT cell research has focused primarily on mucosal tissue, with limited studies on non-mucosal organs such as kidneys. In this study, we evaluated MAIT cells in human native kidneys with tubulointerstitial fibrosis, the pathological hallmark of CKD.

Methods: MAIT cells were identified, enumerated and phenotyped from human kidney tissue by multi-colour flow cytometry. Localisation of MAIT cells was performed by immunofluorescence microscopy. MAIT cells and human primary proximal tubular epithelial cells (PTEC) were co-cultured under hypoxic (1% O_2) conditions to examine mechanistic tubulointerstitial interactions.

Results: We detected significantly elevated numbers of MAIT cells (TCR-Vα7.2+ CD161++) in diseased biopsies with interstitial fibrosis compared with diseased biopsies without fibrosis and healthy kidney tissue. The increased numbers of MAIT cells also correlated significantly with loss of kidney function (eGFR). MAIT cells in fibrotic biopsies expressed cytokine receptors (IL-7Rα, IL-18Rα), activation receptor (NKG2D), extravasation marker (CD44) and tissue-resident markers (CD69, CD103). Immunofluorescent staining of fibrotic kidney tissue localised the accumulation of MAIT cells within the tubulointerstitial compartment, adjacent to PTEC. Notably, under *in vitro* pro-fibrotic/hypoxic conditions, PTEC induced the up-regulated expression of tissue-resident markers on MAIT cells.

Conclusions: We provide the first characterisation of MAIT cells in human kidney tissue. Collectively, our data suggest that human MAIT cells are retained as tissue-resident lymphocytes and are positioned to contribute to the fibrotic process via complex interactions with PTEC. Further dissection of kidney MAIT cells is now required for the development of novel CKD therapeutics.

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TH-PO954

RNA Seq Interrogation of a Clinical Kidney Biopsy Biobank Identifies Axl Kinase as an Anti-Fibrotic Target

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Background: Fibrosis is a key manifestation and driver of chronic kidney injury. No safe and effective renal anti-fibrotic agents exist, in part because of the lack of human kidney tissue for study. Well annotated human kidney tissue biobanks are rare given their maintenance costs and the resources required to collect follow-up data. The few biobanks that exist have been primarily interrogated using microarrays, which while enabling multi-gene assessment, is limited to the probes on the array, and usually requires an extra, specially stored biopsy core. Here we describe the interrogation of archived remnants of clinical kidney biopsy tissue using a comprehensive RNA seq-based platform, enabling the study of clinical samples and linking to routinely obtained follow-up data.

Methods: RNA extracted from remnants of 14 frozen clinically indicated kidney transplant biopsies at St. Michael's Hospital (SMH) was subjected to RNA sequencing. Clinical data (age, gender, Banff histologic scores, eGFR values) was collected from the SMH Kidney Transplant Database. Preliminary findings were confirmed in the murine unilateral ureteral obstruction (UUO) model of kidney fibrosis.

Results: The mean slope of eGFR change post-biopsy was -4.8 +/- 8.6 mL/min/yr. 7 biopsies were scored as ci 1 (5 – 25% fibrosis), 6 biopsies as ci 2 (25 – 50% fibrosis), and 1 biopsy as ci 3 (> 50% fibrosis). In addition to known fibrosis-associated transcripts (collagens, TGF-beta, CTGF), we found that mRNA levels of the tyrosine kinase Axl were positively associated with fibrosis score (rho = 0.48, p = 0.03) and negatively with slope of eGFR change post-biopsy (rho = -0.52, p = 0.02). We found a similar increase in Axl mRNA levels in fibrotic UUO kidneys. As Axl mRNA expression was localized primarily to fibroblasts, we next treated NRK49F fibroblasts with an Axl inhibitor (BGB324), finding that Axl inhibition blocked TGF-beta-induced collagen production.

Conclusions: We describe a novel RNA seq-based platform that can interrogate routinely stored remnants of clinically obtained kidney biopsy tissue, enabling the use of archived clinical samples and their associated follow-up data. Our initial studies identified known fibrosis-associated transcripts, and also potential druggable targets that may lead to new anti-fibrotic strategies.

Funding: Private Foundation Support

TH-PO955

The Effect of Complement 3 in Chymase Promoting Renal Interstitial Fibrosis

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Background: To investigate the effect of complement 3 (C3) on chymase promoting renal interstitial fibrosis.

Methods: To establish UUO model with wild type C57BL/6 mice (WT) and C3 gene knockout mice (C3KO). WT mice were intraperitoneally injected with 10mg/Kg chymostatin in the first to fourteenth day after operation. All mice were sacrificed at fourteenth days and ipsilateral renal tissue. Masson staining was used to observe the renal interstitial fibrosis. The expression of C3, tryptase, chymase, rennin, AngII, TGF-β1, MMP9 in renal interstitium were detected by immunohistochemistry or immunofluorescence or real time quantitative PCR or western blot. Chymase activity of renal tissue was detected by kit. ELISA kit was used to detect AngII, C3a, MMP9.

Results: Compared with WTcontrol group, C3, C3a, mast cells, chymase, renin, AngII, TGF-β1, MMP9 significantly increased in WTuuo group (P<0.001). Compared with WTuuo group, renal tubular injury and interstitial fibrosis were attenuated in C3KOuuo group (P<0.001), C3, C3a, mast cells, chymase, renin, AngII, TGF-β1, MMP9 significantly decreased in WTuuo group (P<0.001). Compared with WTuuo group, enal tubular injury and interstitial fibrosis were attenuated in WTuuo+chymostatin group (P<0.001), chymase activity was significantly decreased (P<0.001), the expression of AngII, TGF-β1 and MMP9 reduced significantly in WTuuo+chymostatin group (P<0.01).

Conclusions: Complement 3 may promote renal interstitial fibrosis by participating in recruitment and activation of mast cells.

TH-PO956

Complement 3 Mediated Macrophage Polarization Contributes to Renal Interstitial Fibrosis

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Background: To explore regulation of complement 3 (C3) on polarization of interstitial macrophages and related outcomes in renal fibrosis.

Methods: C57 BL/6 wild type and C3-deficient mice were created for UUO and sacrificed at days 3, 7, 14 after the operation. Obstructed kidneys were collected and assessed. Expression of C3 in kidneys was detected by immunohistochemical staining. Phenotypes of interstitially infiltrated macrophages, interstitial fibrosis, peritubular capillary density, expression of VEGF and inflammatory cytokines were compared between wild type and C3-deficient UUO mice. Propotion of macrophage phenotypes were identified by double immunofluorescence for F4/80 and iNOS or CD206, western blot for iNOS, Arg-1 and CD206. Paraffin sections were stained with HE and Masson's trichrome. Score of tubulointerstitial injury and percent of renal interstitial fiobrotic area were obtained. Peritubular capillary density was detected by CD31 immunohistochemical staining. VEGF164, sVEGFR1, TNF-α, IL-10 were examined by real time quantitative PCR and western blot. Wild type and C3-deficient UUO mice were treated by liposome clodronate in early or late stage respectively then interstitially infiltrated macrophages and interstitial fibrosis were analysed.

Results: C3-deficient UUO mice had milder degree of tubulointerstitial fibrosis and fewer M1 but more M2 interstitial infiltration in early stage compared with wild type mice. This macrophage polarization shift was accompanied with decreased expression of TNF-α and sVEGFR1, increased expression of IL-10 and VEGF164 in kidney, as well as increased peritubular capillary density. Depletion of macrophages ameliorated renal fibrosis in wild type UUO mice but had no effect on C3-deficient UUO mice.

Conclusions: Complement 3 activation has a close relationship with renal interstitium infiltrating macrophages and fibrosis, and contributes to renal interstitial fibrosis by promotion of macrophage polarization, increasement of inflammatory cytokines, reduction of peritubular capillary density in kidney.

TH-PO957

Effect of Long-Term Tubular Overexpression of Hypoxia-Inducible Factor-2a on the Progressive Renal Fibrosis in a CKD Model

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Background: Although hypoxia-inducible factor (HIF) is a key transcriptional factor in the response to hypoxia, and the effect of selective tubular activation of HIF-2α on renal fibrosis was demonstrated recently, there is no study for the effect of long-term tubular activation of HIF-2α on the progressive renal fibrosis.

Methods: We are mainly performed using PAX8-rtTA/tetO-Cre/HIF2dPA-HA transgenic mice(Tg). For the induction of renal fibrosis and CKD, the mice were fed a 0.2% adenine-containing diet for 2, 4, and 6 weeks with doxycycline (DOX, 2mg/ml) administration at day 0. Moreover, isolated primary renal tubular epithelial cells (TECs) from Tg mice were divided into one of four groups: the control, DOX (5ug/ml), TGF-β1(10ng/ml), and DOX+TGF-β1 groups (for 24, 48 and 72 h), *in vitro*. For renal function, Cr and BUN were measured, and real-time PCR, western blotting and immunohistochemical staining were performed.

Results: Serum Cr and BUN levels were significantly higher in WT and Tg CKD mice compared with the control mice at 2, 4 and 6 weeks. However, those levels of only 6-week HIF-2α activated CKD mice were significantly decreased compared to those in 6-week WT CKD model. The WB (fibronectin, E-cad/α-SMA, type I collagen) and IHC also showed the increased renal fibrosis in WT CKD mice at 2, 4 and 6 weeks compared with control mice. However, in only 6-week Tg CKD mice, the increased fibrosis was significantly attenuated compared to that in the same week WT CKD mice. In vitro, the increased fibronectin and type I collagen protein expressions after TGF-β1 stimulation were significantly decreased in the 72 h HIF-2α continuous activation except for 24 and 48 h groups.

Conclusions: These findings showed that long-term HIF-2α activation in CKD might inhibit the progression of renal fibrosis and improve renal function, which suggests that long-term renal HIF-2α activation could represent a new therapeutic way in CKD.

Funding: Other NIH Support - Natioinal Research Foundation of Korea (NRF-2013R1A1A2009837)

TH-PO958

Nrf2 Activator, RTAdh404, Attenuates Tubular Injury via Eliminating Mitochondrial ROS in Proteinuria Induced Renal Failure Mice

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Background: Severe proteinuria, including that associated with diabetic kidney diseases (DKD), leads to renal failure. Abundant proteinuria produces excessive reactive oxidative species (ROS), which trigger inflammation via mitochondrial dysfunction. Regulation of ROS is one of the potential therapeutic strategyies for DKD with proteinuria. We focused on NF-E2-related factor 2 (Nrf2), which is a master regulator for the cellular defense against oxidative stress. Nrf2 activator has a renoprotective effect by eliminating excessive ROS in ischemic-reperfusion injury. However, the mechanisms of the renoprotective effect of Nrf2 activator are not fully understood, especially in DKD. We thus investigated whether RTAdh404 attenuates proteinuria-induced renal tubular damage via mitochondrial protection.

Methods: Male ICR-derived glomerulonephritis mice (ICGN) were used. The mice were divided into three groups: ICR as a control, ICGN+Vehicle (Vehi), and ICGN+RTA dh404 (dh404). dh404 was administered orally for three weeks (dh404;10 mg/kg/day)). Serum creatinine was evaluated as a marker of a renal function. Mitochondrial function was assessed by COX staining and transmission electron microscope. Next, in vitro study, human proximal tubular epithelial cells (hPTECs) were used to determine the mechanism of renal protective effect by dh404. hPTEC were stimulated with bovine serum albumin (BSA) binding bound to free fatty acid (FFA) and treated with or without dh404 for six hours.

Results: In ICGN+Vehi groups, renal dysfunction, based on the serum creatinine was significantly exacerbated. dH404 was able to treatment attenuated renal dysfunction in ICGN mice. Then Tubulointerstitial injury and fibrotic changes were also significantly worsened in ICGN+Vehi mice. Mitochondrial respiratory enzyme and the mitochondrial formation were injured. These damages were improved in ICGN+dh404 groups. These data suggest that RTA dh404 has a renoprotective effect via mitochondrial protection. In vitro study, hPTECs stimulated with FFA+BSA increased mitochondrial ROS and decreased mitochondrial membrane potential. These changes were improved with treatment of dh404.

Conclusions: RTA dh404 attenuates proteinuria induced tubular cell injury through improvement mitochondrial function via eliminating mitochondrial ROS.

Funding: Commercial Support - Reata Pharmaceuticals

TH-PO959

Endothelial Dysfunction Exacerbates Renal Tubular Cell Injury Through Inflammasome Activation in a Hypertensive Mouse Model

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Background: Chronic inflammation is a common pathway of progressive kidney diseases. One of the mechanism in forming chronic inflammation is NLRP3 inflammasome activation. We reported that aldosterone induced hypertension progress tubular interstitium injury via NLRP3 inflammasome activation. However, it is unclear how NLRP3 inflammasome is regulated in the kidney. On the other hand, it is reported that nitric oxide(NO) derived from iNOS suppress inflammasome activation in macrophage. So, we investigated whether or not NO derived from eNOS suppress inflammasome activation in hypertensive kidney disease because it is well known that endothelial dysfunction promotes progressive kidney disease.

Methods: Six weeks male C57BL/6 mice (WT) and eNOS deficient mice (eNOSKO) were used. These mice were divided into four groups (WT, WT-Ald, eNOS, and eNOS-Ald). Aldosterone (Ald) was continuously administered for four weeks by infusion pump. Next, eNOS/ASC double deficient mice (eNOS/ASC DKO) were generated to investigated whether inhibition of inflammasome activation can reduce kidney injury caused by endothelial dysfunction. Finally, we explored the molecular mechanisms underlying the regulation of inflammasome activation by endothelial dysfunction. Bone marrow-derived macrophages (BMDMs) were stimulated with ATP after priming LPS and simultaneously primed with S-nitrosoglutathione (GSNO) as an NO donor or Bay41-2272 as a sGC stimulator.

Results: NLRP3 inflammasome activation was increased in the kidneys of the eNOS-deficient mice, and tubulointerstitial fibrosis was accelerated. Suppression of inflammasome activation by knocking out ASC prevented tubulointerstitial injury in the eNOS knockout mice, indicating that the eNOS-NO pathway is involved in the development of kidney dysfunction through acceleration of NLRP3 inflammasome in macrophages. ATP stimulation with LPS priming caused NLRP3 inflammasome-dependent cell death and IL1beta secretion. While GSNO inhibited this activation, it did not affect the sGC stimulator. This data suggests that NO can suppress NLRP3 inflammasome activation directly in macrophages.

Conclusions: eNOS-NO pathway could be a therapeutic target for the treatment of chronic kidney disease associated with endothelial dysfunction.

Funding: Government Support - Non-U.S.

TH-PO960

Tenascin-C-Rich Extracellular Microenvironment Impairs Renal Tubular Integrity and Promotes Renal Fibrosis

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Background: Tenascin-C (TNC), an extracellular matrix glycoprotein, is the major component of fibrogenic niche that facilitates renal fibrosis through multiple mechanisms. We previously reported that focal expression of TNC after injury sets up a favorable microenvironment for fibroblast activation and proliferation. However, whether such a TNC-rich niche also affects tubular cell integrity and phenotype remains unclear.

Methods: Serum and biopsy specimens from CKD patients as well as various CKD animal models were used. TNC and its downstream signaling was manipulated or therapeutically inhibited *in vivo*. The 2-Dimensional and 3-Dimensional culture of human kidney proximal tubular cells (HKC-8) and mouse primary proximal tubular epithelial cells were applied.

Results: ELISA results demonstrated that TNC level significantly elevated in the serum of CKD patients, and consistently its expression was also induced in kidney biopsy specimens from CKD patients with different etiologies. *In vitro*, TNC significantly promoted HKC-8 cell migration and induced them to undergo epithelial-mesenchymal transition (EMT). Similarly, TNC also impaired the integrity of mouse primary proximal tubular epithelial cells by triggering EMT. Using de-cellularized kidney tissue scaffold (KTS) isolated from fibrotic kidneys, we found that TNC-enriched KTS facilitated tubular epithelial cell EMT, whereas TNC-deprived KTS inhibited it. Mechanistically, TNC induced integrin αvβ6, activated focal adhesion kinase (FAK), leading to the activation of ERK signaling. Blockade of FAK signaling abolished TNC's ability to induce tubular cell EMT in vitro. In mouse models of CKD induced by unilateral ureteral obstruction or ischemia/reperfusion injury, knockdown TNC or specific inhibition of FAK signaling with small molecule inhibitor repressed partial EMT and ameliorated fibrotic lesions.

Conclusions: These studies unveil that TNC-rich extracellular niche plays a critical role in impairing tubular cell integrity by inducing partial EMT. Our data also indicate that blockade of TNC/FAK signaling is a novel strategy for therapeutic intervention of renal fibrosis.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO961

rAAV6-Mediated miR-29b Delivery Suppresses Renal Fibrosis

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Background: Renal fibrosis is a common feature of CKD, which has no available specific treatment. Micro RNAs (miRNAs) are short endogenous non-coding RNAs that regulate various cellular processes. Previous studies showed that miR-29b inhibits renal fibrosis in mice models. Therefore, miR-29b replacement therapy represents a promising approach for treating renal fibrosis. However, an efficient method of kidney-targeted miRNA delivery has yet to be established. Recombinant adeno-associated virus (rAAV) vectors have great potential for clinical application. The distinct AAV serotypes exhibit different tissue tropisms. For kidney-targeted gene delivery, the most suitable AAV serotype has yet to be established. Here, we identified the most suitable AAV serotype for kidney-targeted gene delivery, and determined that AAV-mediated miR-29b delivery can suppress renal fibrosis *in vivo*.

Methods: We used the normal rat kidney fibroblast cell line (NRK-49F), rat TEC line (NRK-52E), and human kidney proximal TECs to determine which AAV serotype is suitable for kidney-targeted gene delivery *in vitro*. To determine transduction efficiency, GFP-positive cells were identified by flow cytometry after the infection of rAAV serotype 1–9 vectors containing the *EGFP* gene. Next, we went on to investigate the transduction efficiency of mouse kidney by using rAAV serotype 1–9 vectors *in vivo*. We injected rAAV vectors into the renal pelvis. To determine transduction efficiency, GFP expression was measured seven days after injecting rAAV vectors carrying the *EGFP* gene Finally, we investigated whether rAAV6-mediated miR-29b delivery can suppress renal fibrosis in a unilateral ureteral obstruction (UUO) mouse model.

Results: We found that rAAV6 vector is the most suitable for targeting kidney cells regardless of animal species *in vitro* and rAAV6 is the most suitable vector for kidney-targeted *in vivo* gene delivery in mice. Intra-renal pelvic injection of rAAV vectors can transduce genes into kidney TECs. Furthermore, rAAV6-mediated miR-29b delivery attenuated renal fibrosis in UUO model by suppressing *Snail1* expression.

Conclusions: In summary, our study has revealed that rAAV6 is the most suitable serotype for kidney-targeted gene delivery and rAAV6-mediated miR-29b delivery into kidney TECs can suppress established renal fibrosis. Our findings may provide novel information for facilitating kidney gene therapy.

Funding: Government Support - Non-U.S.

TH-PO962

DNM3OS Non-Coding RNA as a New Therapeutic Target in the Context of Renal Fibrosis

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Background: The study of miRNAs in fibroproliferative diseases, and in particular in kidney fibrosis, has underscored their involvement in the key mechanisms of fibrogenesis. In the context of pulmonary fibrosis, the polycistronic RNA DNM3OS, producing the three fibromiRs, miR-199a-5p, miR-199a-3p and miR-214-3p, has recently been described as a regulator of the process fibrosis. Indeed, these three miRNAs participate in TGF-β pathway regulation and in the differentiation of fibroblasts into myofibroblasts. The aim of this study was to evaluate in kidney the anti-fibrotic potential of targeting the non-coding DNM3OS RNA by different oligonucleotide approaches directed against DNM3OS or miR- 199a-5p.

Methods: In a first step, the oligonucleotides were selected according to their anti-fibrotic efficacy in the 3T3 fibroblast cell line. The study then relies mainly on the use of a murine model of renal fibrosis induced by unilateral ureteral obstruction. After evaluating their safety (acute or chronic administration), oligonucleotides formulated for in vivo administration and directed against either miR-199a-5p or DNM3OS (Gapmer) were systemically injected before and after the induction of renal fibrosis. Fibrotic lesions was evaluated by studying the renal expression of fibronectin 1 (FN1) and Collagen 1a1 (COL1A1) genes as well as by the histological analysis of kidney sections by immunohistochemistry and Sirius Red staining.

Results: Our results showed that the administration of oligonucleotides directed against miR-199a-5p or DNM3OS allows a significant reduction in renal fibrosis lesions induced by ureteral obstruction. In particular, we observed a decrease in the expression of extracellular matrix compounds such as FN1 and COL1A1. In addition, tolerance studies (single or chronic) of anti-miR-199a-5p did not reveal any renal or hepatic toxicity of the oligonucleotide in mice.

Conclusions: Overall, in the context of fibroproliferative pathologies, our results underline the interest of the therapeutic targeting of polycistronic RNA DNM3OS based on the modulation of the expression of this non-coding RNA or of one of the miRNAs that it produces using synthetic oligonucleotides. The clinical development of such molecules could eventually limit the progression of fibrosis.

TH-PO963

Therapeutic Effect of siRNA-CD40 on AKI Caused by Reversible Obstructive Nephropathy in Mice

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Background: The costimulatory CD40-CD40L pathway plays a role in kidney inflammation. We have previously reported that renal CD40 upregulation precedes cellular interstitial infiltrate and fibrosis in the unilateral ureteral obstruction (UUO) model. Here we sought to evaluate whether the administration of siRNA anti-CD40 has a therapeutic effect in a reversible UUO mice model (rUUO).

Methods: Eight week-old C57BL6J male mice were divided into four groups: **wild type** (n=6); **rUUO-Sham** (n=8); **rUUO+siRNA Scrambled**, a non-specific siRNA (n=6), and **rUUO+siRNA anti-CD40**, specific siRNA anti-CD40 (n=8). Ureteral clamping was performed on 8 week-old C57BL6J male mice. At day 3 after surgery, the ureteral clamp was removed and nephrectomy of the contralateral kidney was performed. Immediately, PBS, siRNA SC (50μg) or anti-CD40 (50μg) was administrated via the tail vein. Mice were killed 48h hours after. Blood samples at days 0, 3, 4 and 5 were collected for creatinine analysis. Histology and kidney mRNA expression were performed.

Results: The administration of siRNA anti-CD40 was associated with a significant reduction of renal CD40 mRNA expression (Table 1). siRNA anti-CD40 reduced significantly the severity of acute renal failure associated with UUO (Figure 1). Pathologic analysis showed reduction of tubular dilation, F4/80 macrophage infiltration and interstitial fibrosis in animals treated with CD40-siRNA (Table 1). Furthermore, kidney mRNA gene expression analysis showed significantly lower levels of pro-inflammatory cytokines such IL-2 and CCL-2 and pro-fibrotic TGFβ-1 in CD40-siRNA mice.

Conclusions: The administration of siRNA-CD40 therapy at the time of ureter clamp removal in the UUO model reduces the severity of the acute kidney injury and promotes kidney repair.

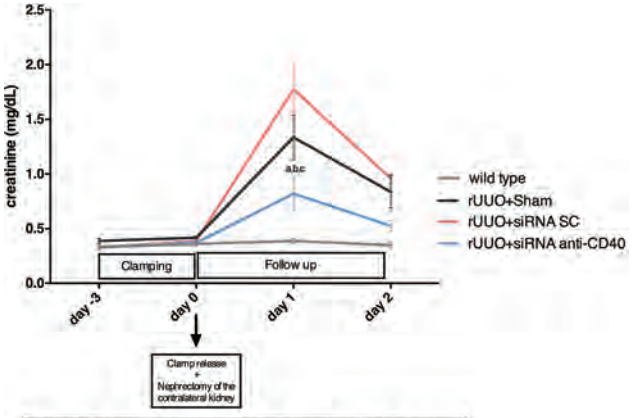

Figure 1. Serum creatinine analysis. Creatinine levels increased showing maximum values at day 1 post clamp release and nephrectomy of the contralateral kidney. siRNA anti-CD40 treated group was the only group displaying significant fewer values compared to rUUO+Sham and rUUO +siRNA SC. a. siRNA anti-CD40 vs wild type; b. siRNA anti-CD40 vs Sham; c. siRNA anti-CD40 vs siRNA SC.

TH-PO964

Pericyte-Myofibroblast Transition Induced Tubulo-Interstitial Injury in a Novel Renal Venous Congestion Rat Model

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Background: Increased central venous pressure in congestive heart failure is responsible for renal dysfunction. However, the knowledge of the underlying mechanisms is limited. We hypothesized that renal interstitial hydrostatic pressure (RIHP) and expansion pressures of the vasa recta are responsible for pericyte detachment resulting renal congestion-mediated fibrosis. We created a novel rat renal congestion model to investigate the effect of renal congestion on hemodynamics and its molecular mechanisms.

Methods: The inferior vena cava (IVC) between the renal veins was ligated by suture in male Sprague-Dawley rats to increase upstream IVC pressure and induce congestion in the left kidney only.

Results: Left kidney congestion reduced renal blood flow in cortex (33.6%, 28.3 to 16.0 mL/min) and in medulla (41.8%, 11.9 to 6.9 mL/min) and glomerular filtration rate (17.2%, 1.16 to 0.20 mL/min/kg BW), and increased RIHP (1.4 fold, 12.6 to 17.6 mm Hg). In the congestive kidneys, hypoxia was observed in the medullary thick ascending limb of Henle. Tubulointerstitial injury, podocyte injury, albuminuria, and reduced creatinine clearance were observed in the congestive kidneys. Molecules related to extracellular matrix expansion, tubular injury, and focal adhesion were upregulated in microarray analysis. Renal decapsulation ameliorated the tubulointerstitial injury (mRNA expression of *Kim1* 15.3 to 4.3 A.U., *αSma* 5.3 to 2.8 A.U.). Electron microscopy captured pericyte detachment in the congestive kidneys. Transgelin and platelet-derived growth factor receptors (PDGFRs), as indicators of pericyte-myofibroblast transition, were upregulated in the pericytes and the adjacent interstitium. Imatinib, a PDGFR inhibitor, ameliorated the interstitial injury.

Conclusions: Our results reveal a novel mechanism of worsening renal function associated with congestive heart failure, and provide a new therapeutic candidate based on a better understanding of the pericyte-myofibroblast transition.

TH-PO965

Varying AKI Types Affect Parietal Epithelial Cell Function with Different Impact on Tubuloglomerular Cross-Talk

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Background: Previously we found that mild tubulointerstitial fibrosis sensitizes the kidney to subsequent glomerular injury. The transition of acute kidney injury (AKI) to chronic kidney disease depends on the severity of AKI. In this study, we explored whether the type of initial proximal tubular (PT) injury impacts the glomerular response to a subsequent injury, and the role of parietal epithelial cells (PECs) in this response.

Methods: We induced AKI by injecting diphtheria toxin (DT) in DTR transgenic mice that express human DT receptor in S2 and S3 PT, or by injecting aristolochic acid (AA) which targets all PT and part of PECs. All mice were mated with NEP25 mice, which express human CD25 on podocytes, and podocyte injury can be induced by immunotoxin (LMB2). Mice underwent LMB2 injection at 6 wks after DT or AA injury, with control mice (PODO) only receiving LMB2 without preceding tubular injury, followed by uninephrectomy 1 wk later and sacrifice 4 wks later. In vitro, PECs were exposed to vehicle or AA for 24h, followed by exposure to supernatant from injured podocytes for 48 hours.

Results: Urinary KIM-1/NGAL recovered to baseline in DT while they remained high in AA mice at wk 6 after injury. AA+LMB2 mice had significantly higher albuminuria than PODO, while DT+LMB2 had no significant increase vs PODO, at 1 wk after LMB2. Columnar PECs may have more stem cell potential vs flat PECs, and columnar/flat PECs ratios were higher in PODO mice and DT+LMB2 than AA+LMB2. Expression of β–catenin and ILK in PECs increased in AA+LMB2, but not in DT+PODO, compared to PODO. WT1+ cell density was decreased in both AA+LMB2 and DT+LMB2 vs PODO. At 4 wks after LMB2, 0/16 PODO and 1/23 DT+LMB2 vs 8/16 AA+LMB2 mice had died. GFR, ACR and glomerulosclerosis were similar among groups in surviving mice. Both DT+LMB2 and AA+LMB2 showed more CD44+/α-SMA+ cells on the glomerular tuft than PODO, suggesting mesenchymal transition of activated PECs. In vitro, AA-treated PECs expressed more ILK and CTGF vs vehicle after cells were exposed to injured podocyte medium.

Conclusions: Tubular injury that involves specific PT segments and PECs, which may serve as stem cells and participate in glomerular rescue after injury, may result in less recovery and increased sensitization of glomeruli to a second hit.

Funding: NIDDK Support

TH-PO966

IL-6 Signaling Triggers Expulsion of Uropathogenic Bacteria from Host Epithelial Cells to Limit UTI Chronicity

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Background: Treatment of urinary tract infections (UTIs) has historically relied on the use of antibiotics which are limited by patient intolerance and rising bacterial resistance. Innate immunity represents an attractive alternative in UTI treatment and prevention; however, its influence on bacterial virulence is not well known. Specifically, IL-6 is induced during UTI, but our understanding of its role in UTI pathogenesis is limited. We sought to determine how IL-6 expression alters urothelial susceptibility to infection and impacts bacterial clearance.

Methods: 6-8 week old female wild type (WT) C57BL/6J and IL-6 knock out (KO) mice were transurethrally infected with uropathogenic Escherichia coli (UPEC). Bacterial burden was assessed by dilution plating; and intracellular bacterial communities (IBC) were enumerated by beta-galactosidase staining. Gentamicin protection assay quantified intracellular bladder bacterial burden. The impact of IL-6 neutralization and IL-6 rescue on IBC formation was studied in WT and IL-6 KO mice, respectively. Neutralization of serum IL-6 was confirmed by ELISA. *In vitro* gentamicin protection assay was used to study the impact of recombinant IL-6 on bacterial attachment, invasion, and expulsion in bladder epithelial cells (BECs). Results were evaluated by Mann-Whitney U test with $p < 0.05$ being significant.

Results: A significant increase in IBCs was observed in IL-6 KO mice vs. WT controls early during infection but resolved 24 hours post infection (hpi). These findings were recapitulated by antibody neutralization of IL-6 in WT mice. The increase in IBCs in IL-6 KO animals was reversed with recombinant IL-6. We confirmed an increase in bladder bacterial burden in IL-6 KO mice by *ex vivo* gentamicin protection assay, which accounts for increased bacteriuria in IL-6 KO compared to WT mice beginning after 24 hpi. *In vitro* experiments in BEC demonstrated that IL-6 treatment significantly increased UPEC expulsion but did not impact invasion or attachment.

Conclusions: IL-6 reduces UTI susceptibility by promoting UPEC expulsion from host epithelial cells, thereby limiting the ability of UPEC to persist intracellularly and form IBCs. Given that IBC formation represents a significant bottleneck event in UPEC survival, these findings suggest a mechanism whereby IL-6 reduces UTI chronicity.

Funding: NIDDK Support, Private Foundation Support

TH-PO967

Mitigation of Radiation Injury by Epoxyeicosatrienoic Acid Mimetic Assessed by Urinary Proteomics

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Background: Radiation exposure due to radionuclide cancer therapy, accident, or radio-nuclear attack could cause radiation induced nephropathy. Non-biased urinary proteomic analysis can identify novel urine biomarkers that precede tissue injury and may be mechanistically relevant.

Methods: 20 male WAG/RijCmcr rats underwent partial body irradiation (PBI) with one leg shielded to allow bone marrow reconstitution. 24 hour urine was collected four weeks after PBI from control (0 Gy) or irradiated (11 Gy) without or with epoxyeicosatrienoic acid (EET) mimetic therapy. Renal injury was assessed by urine protein and urine creatinine. Proteomic analysis was performed on urine (ultrafiltered > 3kDa) using standardized methods. Protein abundance determinations (% Extracted Ion Chromatograph, % XIC) were normalized to total urine protein, urine creatinine, and rat weight. Final protein concentrations are reported as protein/creatinine/weight (mg/g/kg).

Results: Baseline rat weights did not differ according to experimental group. At 4 weeks after PBI the 11 Gy rats weighed significantly less than controls. The radiated rats did not differ in total urine protein, urine creatinine, urine protein/creatinine, or urine volume. Proteinuria occurs starting at six weeks in this model. Mass spectrometry-based proteomics yielded 781 proteins with 99.9% overlap in all experimental groups. The increased abundance of proteins in irradiated rats were largely of extracellular origin and part of biological networks related to nucleic acid, carbohydrate, and collagen metabolism. The EET mimetic significantly changed select proteins related to these networks. Notable changes in mg/creat/body weight were: Malate dehydrogenase 0.06/0.18/0.11, Glyceraldehyde 3 phosphate dehydrogenase 0.05/0.20/0.12, and Lysyl Oxidase 0.01/0.25/0.01.

Conclusions: Radiation exposure results in significant increases in urinary proteins, largely extracellular in origin, related to nucleic acid, carbohydrate, and collagen metabolism. The largest effect was on lysyl oxidase, an enzyme that increases collagen crosslinking which may presage tissue fibrosis in this model. This offers some insight into the known therapeutic benefits of the EET mimetic.

Funding: Veterans Affairs Support

TH-PO968

Urinary Extracellular Vesicles (uEVs) Have Unique Characteristics as Demonstrated by Imaging and Spectral Cytometry

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Background: Urinary extracellular vesicles (uEVs) provide a source of valuable biomarkers for kidney and urogenital diseases. Analysis of uEVs is challenging due to its intrinsic complexity. Imaging flow cytometry (iFC) allows detection of particles that are < 200 nm in size and has a high level of sensitivity for small particle fluorescence. In addition, spectral flow cytometry (sFC), which is based on whole spectrum analysis, can be used to further characterize the findings of the iFC analysis.

Methods: First morning void urine, blood and saliva (internal auto fluorescent control) were centrifuged at relative centrifugation force RCF of 4.600g for 30 minutes. The supernatants was further centrifuged at 20,000g to collect EVs. uEVS were stained with different annexin V conjugates: FITC, PE, PerCPCy5.5, Pacific Blue™, Brilliant Violet 421, Brilliant Violet 510, APC, Alexa Fluor® 647 respectively. Gating strategy was based on the low scatter of the unstained uEVs and the negative control was all fluorescent probes alone in buffer. Stained and unstained EVs from urine, plasma and saliva were evaluated

Results: Acquisition of uEVs alone in iFC showed an interesting auto-fluorescence emission in channel 5 (λ_{ex} 660 nm; λ_{em} 740 nm) for camera 1 and channel 11 (λ_{ex} 660 nm; λ_{em} 740 nm) for camera 2. Auto fluorescence emission in channel 11 was caused by excitation from the violet laser (λ_{ex} 405 nm) and red laser (λ_{ex} 642 nm). Auto-fluorescence in Channel 5 was caused by excitation of both blue (λ_{ex} 488 nm) and yellow laser (λ_{ex} 561 nm). Spectral analysis of unlabelled uEVS, plasma EVs (pEVs), and saliva EVs (sEVs) showed that this auto-fluorescence was unique and specific for uEVs. Spectrum plots showed a distinct signature

Conclusions: While imaging flow cytometry represents a major advancement in the identification of uEVs, our results suggest that unexpected additional complication of the analysis originated from the auto-fluorescence with a peculiar spectral emission that needs to be taken into account when multicolor antibodies panels are planned. Likewise, choice of AV fluorochrome conjugate should be carefully considered.

Funding: Other NIH Support - Internal funding

TH-PO969

Enrichment and Identification of Ubiquitinated Proteins in Urinary Extracellular Vesicles

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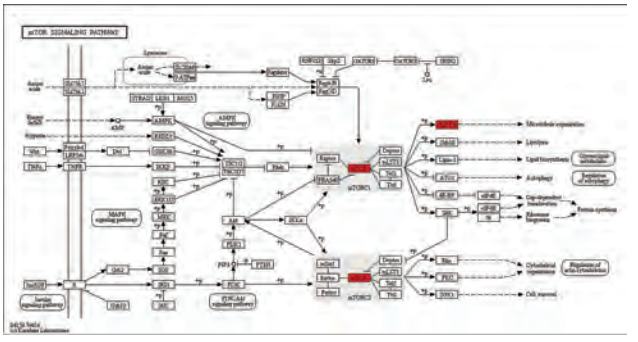
Background: Urinary extracellular vesicles(uEVs) is widely considered to represent pathological events in the kidneys and the urogenital epithelium. Ubiquitin mediates proteolysis through the enzymatic conjugation of UB to proteins that contain primary degradation signals. The aim of our current study was to establish a method to enrich and identify ubiquitinated protein in uEVs.

Methods: After 2000g centrifugation, supernatant 2000g was obtained from 1st morning urine. Then supernatant 2000g was processed by Hydrostatic dialysis filter using dialysis membrane with a molecular weight cutoff (MWCO) of 1,000 kDa. Protein-A Sepharose® IgG was used to concentrate ubiquitinated proteins, which is based on the binding of antibodies to Sepharose beads and subsequent cross-linked by Dimethyl pimelimidate(DMP). Coomassie staining, western blot and mass spectrographic analysis were used to characterize the ubiquitinated protein in uEVs.

Results: Ubiquitinated proteins in uEVs are enriched successfully. We detected 60 specific sites of 37 ubiquitinated proteins. These ubiquitinated proteins were mainly enriched in the biological process categories of cellular process. Most of the ubiquitinated proteins in the cellular component category occurred in the nucleus. The KEGG enrichment pathway analysis of these ubiquitinated proteins suggested that ubiquitination maybe play an indispensable role in the regulation of the mTor signaling pathway.

Conclusions: We provides a simplified method to enrich and identify ubiquitinated proteins in uEVs. 60 specific sites of 37 ubiquitinated proteins were discovered. Till now, all screening ubiquitinated proteins in urinary EVs of this study have not been previously reported. These method and findings allows the possibility to further chronic kidney disease studies in uEVs related to ubiquitinated proteins.

Funding: Government Support - Non-U.S.



The proteins in red were identified in mTOR of this project

TH-PO970

Circulating Exosomes Mediate Inter-Organ Communication in Type 2 Cardiorenal Syndrome

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Background: Inter-organ crosstalk plays an essential role in regulating tissue homeostasis, injury repair and the pathogenesis of multi-organ dysfunction. Cardiorenal syndrome type 2 (CRS2) is characterized by chronic abnormalities in cardiac function causing progressive chronic kidney disease (CKD). However, the mediators connecting heart and kidney are poorly characterized. In this study, we report that exosomes produced by injured heart plays a vital role in mediating cardiorenal connection in mouse model of transverse aortic constriction (TAC).

Methods: Four weeks after TAC, mice were randomized into three groups: 1) sham control; 2) TAC mice; 3) TAC mice injected daily with cyclopamine (CPN), a specific small molecule inhibitor of hedgehog signaling. At 8 weeks after TAC, all animals were sacrificed. Urine, blood, heart and kidney tissues were collected for analysis. Exosomes were isolated from mouse serum, and incubated with normal rat kidney interstitial fibroblast (NRK-49F) cells.

Results: At 8 weeks after TAC, cardiac hypertrophy and fibrosis were prominent, as evidenced by increased expression of β-myosin heavy chain, α-actin and fibronectin. Echocardiography also revealed an impaired cardiac function in TAC mice. These cardiac lesions were accompanied by an upregulation of sonic hedgehog (Shh) and increased production of exosomes in cardiac tissue. Blockade of Shh signaling by CPN ameliorated cardiac injury and restored heart function. Notably, TAC mice also developed kidney lesions secondary to chronic heart failure, manifested by proteinuria, kidney fibrosis and renal upregulation of Shh. CPN mitigated all these lesions in the kidneys. Serum derived from TAC mice was able to induce renal interstitial fibroblast activation in vitro, indicating the circulating factors as mediators of cardiorenal connection. Furthermore, exosomes isolated from TAC serum was sufficient to cause fibroblast activation and matrix production. Western blot demonstrated the presence of Shh and Smo in the isolated exosomes from TAC serum, but not in the exosomes from the control serum.

Conclusions: These studies demonstrate that heart-derived, circulating exosomes are a unique and effective vehicle to deliver Shh to the kidney after TAC. Targeted inhibition of Shh signaling could be a promising therapeutic strategy for protecting both heart and kidney in cardiorenal syndrome.

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TH-PO971

Renal NMDA Receptor Mediates the Amino Acid Induced Vasodilation Through Connecting Tubule-Glomerular Feedback (CTGF)

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Background: The intravenous infusion of amino acids increase the renal blood flow and glomerular filtration rate, and it used to quantify the renal functional reserve. Similarly, high protein diet promotes the progression of chronic kidney diseases in part due to an increase in the renal blood flow, and glomerular pressure. Those glomerular effects are thought to be related to a vasodilation mediated by the amino acids that are released from the diet. However the vasodilator mechanism related to the amino acids in kidney is unknown. Kidney expresses the amino acid receptor N-methyl-D-aspartate (NMDA) that is activated by glutamate and glycine. Our lab described an intrinsic kidney feedback mechanism called CTGF that by sensing sodium in the connecting tubule (CNT) induces the dilation of the afferent arteriole (Af-Art). We hypothesize that in the kidney through the NMDA receptors the amino acids induce Af-Art dilation by activating CTGF.

Methods: By using double-perfusion of Af-Art and CNT technique *in vitro* (rabbit) and Stop-Flow Pressure (SFP) technique *in vivo* (Sprague Dawley Rat), we test the Af-Art dilation induced by CTGF when the CNT perfuse with glycine plus glutamate 10^{-3}M with or without the NMDA blocker MK-801.

Results: *In vitro,* in pre-constricted Af-Arts, addition of glycine plus glutamine to the CNT increases the Af-Art dilation (EC_{50} 10.7) vs. control (EC_{50} 24.5; $p<0.001$), and that dilation is blocked by CTGF blocker benzamil, suggesting that glycine plus glutamine enhanced CTGF. When we add the NMDA receptor blocker MK-801 to the CNT, the increased CTGF response is blunted. *In vivo,* the intratubular infusion of the amino acid induces vasodilation (SFP mmHg 37.9±2.6 vs. 28.6±1.9 control; $P<0.01$) and that vasodilation is blocked by benzamil.

Conclusions: Renal vasodilation induced by amino acid is mediated by the CTGF through the NMDA receptor in the connecting tubule. The activation of the CTGF by amino acids explain the basis of the renal functional reserve test and provide potential mechanism to prevent the renal damage associated with high protein diet.

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TH-PO972

Autophagy Protects Kidney Proximal Tubules from Phosphate-Mediated Mitochondrial Dysfunction

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Background: Autophagy is one of the major degradation pathways in the cell and maintains cellular homeostasis in various settings. Hyperphosphatemia is associated with a faster progression of chronic kidney disease (CKD), as well as an increased risk of cardiovascular mortality. However, molecular mechanisms of phosphate-mediated kidney injury are largely unknown.

Methods: We investigated the pathogenesis of phosphate-mediated kidney injuries in the proximal tubular epithelial cells(PTECs) with a focus on autophagy and mitophagy, and the effects of autophagy deficiency and enhancement on kidney morphology and function during phosphate overload.

Results: In GFP-MAP1LC3 transgenic mice, high phosphate(HP) diet continuously stimulated autophagy in the PTECs. In novel mitophagy-reporter mice (mito-QC), HP diet also increased the number of mitolysosomes (mitochondria-containing autolysosomes) exclusively in the PTECs. High concentration of inorganic phosphate (Pi) in the medium increased PINK1/Parkin expression as well as autophagic activity in cultured PTECs. High Pi not only induced mitochondrial ROS production and mitochondrial permeability transition pore (mPTP) opening, but also reduced mitochondrial membrane potential, ATP production and oxygen consumption rate, all of which were significantly exaggerated by autophagy deficiency. A ROS scavenger, *N*-acetylcysteine (NAC), blocked mPTP opening, reduced PINK1/Parkin-dependent mitophagy, and successfully alleviated phosphate-mediated cellular damages. HP diet-fed mice showed mitochondrial dysfunction, reactive oxygen species (ROS) production, apoptosis, and inflammasome activation in the kidney, which were significantly exaggerated by autophagy deficiency. Finally, HP diet-fed proximal tubule-specific Rubicon knockout mice, in which autophagic flux is genetically enhanced, ameliorated HP-mediated kidney injuries.

Conclusions: Phosphate overload induces mitophagy in PTECs, which is indispensable for maintaining proper mitochondrial functions. Enhancing autophagic activity could be a promising way to suppress CKD progression.

TH-PO973

A Circadian Pattern in Urine Exosome Excretion Is Not Influenced by Sex or Food-Water Deprivation: Implications for Biomarker Normalization

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Background: Urine exosomes are extracellular vesicles released by all cells along the nephron and represent a promising source of non-invasive biomarkers. Many candidate urine exosomal biomarkers have been described, yet none have reached clinical use, in part because how to normalize them is unknown, as urine flow rate or concentration can vary by over an order of magnitude. We previously showed that urine exosome excretion displays a circadian pattern in male rats (peak at 21:00), but little is known about what factors modulate urine exosome release.

Methods: Timed urine samples from healthy rats (n=6M, 6F) were collected over 24 hr in six 4-hr fractions. A subset of these rats (n=4) underwent a second matched 24 hr collection with 13 hr of food and water deprivation spanning the full dark (active) period. Urine exosomes were isolated by ultracentrifugation and counted by Nanoparticle Tracking Analysis.

Results: 24 hr urine exosome excretion varied widely between animals (CV=71%). To study the circadian pattern, variability was reduced by normalizing exosome excretion for each fraction to the peak excretion rate for each animal. Normalized urine exosome excretion displayed a similar circadian pattern in both male and female rats. There was no correlation between urine exosome excretion and urine flow rate (Male: $r^2=0.004$, Female: $r^2=0.04$). Food-water deprivation had no detectable impact on exosome excretion but significantly increased exosome concentration 13-17 hr after removal of food and water ($p=0.03$), likely due to decreased urine output.

Conclusions: Urine exosome excretion displays a distinct circadian pattern that complicates the measurement of urine exosomal biomarkers. The observed pattern in urine exosome excretion was neither sex specific nor affected by food-water deprivation. Spot urine concentration of exosomal biomarkers can be normalized by exosome concentration. This adjusted measure of biomarker content per exosome appears to be independent of time of collection, sex or food-water intake. Proper exosomal biomarker normalization will be essential in advancing promising candidates to clinical use and can uncover patterns otherwise obscured by natural biological variation, increasing their clinical utility and enabling the reliable use of spot urine measurements instead of timed collections.

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TH-PO974

Tertiary Lymphoid Tissue Is a Novel Histological Marker Reflecting Local Injury and Inflammation in Murine and Human Kidneys

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Background: Tertiary lymphoid tissues (TLTs) are ectopic lymphoid tissues that are formed under various pathologic conditions such as autoimmunity and infection, and support priming of immune responses. We previously demonstrated that aged but not young mice exhibited multiple TLTs after AKI, which underlie maladaptive repair. TLTs were also detected in human aged and diseased kidneys, yet the comprehensive understanding is lacking and the clinical relevance remains controversial.

Methods: We analyzed human renal TLTs utilizing surgically resected kidneys from aged patients (N=69) and pyelonephritis patients (N=16) and proposed a novel staging scheme of TLTs. To validate this, we utilized murine TLT model utilizing aged mice subject to IRI. In this model, TLTs develop and expand as ischemic time or the time after IRI increase.

Results: TLTs in both human groups shared a perivascular, periglomerular and subcapsular location as well as similar components such as a homeostatic chemokine CXCL13, but exhibited heterogeneity in phenotype. We classified TLTs into three developmental stages based on the presence of follicular dendritic cells and germinal centers, and demonstrated in mice that the TLT stages advanced with the extent of kidney injury. Dexamethasone treatment after TLT formation decreased the size of TLTs, accompanied with improvement of renal inflammation and fibrosis, indicating the reversibility of TLTs. Consistently, the kidneys of aged patients with CKD exhibited more frequent and more advanced stages of TLTs than those without CKD, and pyelonephritis kidneys exhibited more frequent TLTs with more advanced stages than aged CKD kidneys.

Conclusions: Spatial and developmental similarities of TLTs in both groups indicated that TLT formation might not be disease-specific but rather a common pathological process. On the other hand, the phenotypic heterogeneity of TLTs reflected severity of kidney injuries, which explained the high frequency and advanced stages of TLTs in the kidneys with severe pyelonephritis. The reversibility of TLTs also indicated the potential of TLT-associated molecules as a novel candidate of biomarkers reflecting renal injury. Taken together, our data provide a mechanistic framework for studying TLT formation as a previously unappreciated pathological pathway in kidney disease progression in mouse and human.

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TH-PO975

p90RSK Modulates Fibroblast-Epithelial Communication

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Background: Tubular epithelial damage is one of the prominent hallmarks of both acute and chronic kidney injury. Emerging evidence illuminates the fundamental role of intercellular communication in maintaining the integrity of kidney structure and environment. P90RSK is a serine/threonine kinase induced in the fibrotic kidneys. However, its role in kidney fibrosis remains unknown.

Methods: We examined p90RSK activation in human kidney samples. We generated a novel fibroblast-specific p90RSK transgenic mouse (RSK-Tg) and established a fibroblast-epitheial coculture system using primary kidney fibroblasts from RSK-Tg and RSK-wt mice and human proximal tubular epithelial cells (HKC-8) to investigate the role of p90RSK in fibroblast-epitheial interactions

Results: We discoved that p90RSK phosphorylation was increased in the kidney samples from patients with chronic kidney disease. We also found that RSK-Tg mice displayed enhanced renal fibrosis and increased tubular epithelial cell death after obstructive injury than their littermates (RSK-wt), indicating a role of p90RSK in fibroblast-epithelial communication. We established an *in vitro* fibroblast-epithelial coculture system using primary kidney fibroblasts from RSK-Tg and RSK-wt mice and human proximal tubular epithelial cells (HKC-8), and found that RSK-Tg fibroblasts dramatically aggregated staurosporine or H_2O_2-induced epithelial apoptosis. We further discovered that RSK-Tg fibroblasts constantly produced and released higher level of H_2O_2 into the coculture medium causing epithelial oxidative stress and nuclear translocation of β-catenin. Intriguingly, blockade of reactive oxygen species (ROS) reduced RSK-Tg fibroblasts-induced β-catenin and epithelial apoptosis. Moreover, knockdown of β-catenin by RNA silencing eliminated RSK-Tg fibroblast-induced epithelial cell death.

Conclusions: Thus, it is clear that fibroblast-p90RSK mediates epithelial cell death through ROS-activated β-catenin pathway.

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TH-PO976

CMV Modifies Disease Progression in a Mouse Model of Sepsis

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Background: Sepsis is the leading cause of death in hospitals and accounts for around 250,000 deaths in the U.S. anually. Despite its prominence as a global health concern, relatively little is understood about the mechanisms associated with survival or mortality. This is, in part, due to the failure of promising data from animal models to translate into measurable benefits during clinical trials. Hence, improving trial and animal model design are two main focuses in the field. We are approaching this issue by considering the effect of a history of infection on sepsis progression. A major difference between mice and human patients is their exposure to pathogens. Nearly all patients will have a latent infection of some kind and understanding how this may influence the septic syndrome is an important healthcare priority.

Methods: Cecal contents were collected from B6-background mice and processed into a working-stock slurry. Sepsis was induced in experimental mice via i.p. injection of slurry stock induce to life-threatening sepsis. Prior to sepsis, some experimental mice were injected with MCMV and allowed to progress to latency (60+ days). Septic mice were monitored frequently and survival, body weight, and clinical score were recorded. Upon reaching an endpoint, serum and tissue were collected for further analysis.

Results: When CMV-naive and CMV-latent male mice were given body weight-adjusted doses of cecal slurry, all CMV-naive mice succumbed within 2 days while all CMV-latent mice survived out to 13 days (experimental endpoint). Upon further investigation, CMV-latent mice were found to have greater preservation of MHC class II on splenic dendritic cells which correlated with a greater representation of splenic CD3+ cells while CD19+ cell representation was unchanged. Analysis of mice treated with an LD50 dose of slurry for 48 hours revealed that CMV-latent mice also trended toward lesser clinical scores, controlled body weight loss, and higher serum levels of IFNγ, IL-12p70, and IL-1β. BUN levels were elevated in the serum of all mice at 48 hours, but we did not detect any CMV-specific alterations.

Conclusions: The data suggest that CMV is modifying the early progression of sepsis and favoring less severe disease. These effects appear to stem from experience of the immune system leading to a better regulated inflammatory response and preservation of specific lymphocyte populations.

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TH-PO977

Realization and Future Applications of LCM from Renal Formalin-Fixed Paraffin-Embedded Slices

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Background: Kidney transplantation(KTx) damage surveillance is relevant in clinical practice. Renal biopsy(RBx) is essential to guide a specific treatment. Laser capture microdissection(LCM) combining molecular biology and histology is a novel approach. Using LCM, we aim to test the expression of some pathologic markers in different renal compartments starting from formalin-fixed paraffin-embedded(FFPE) samples.

Methods: The principal difficulties present in LCM realization were the poor quantity and quality of the FFPE samples related to not RNA suitable sample procession. The late housekeeping Ct coupled with the uncertain RNA amount, caused by infiltrating inflammatory cells and by the fibrosis presence, lead us to opt for a cDNA pre-amp. Since RNA quality has a significant impact on reference gene stability, samples quality was evaluated by means of the housekeeping stability. Among the housekeeping examined, RPL4 had the best Ct and stability.

Results: After verifying the reliability of the selected SsoAdvanced PreAmp Supermix Bio-Rad kit, the method was first used in two different RBx (RBx-A: biopsy without histological alteration; RBx-B: biopsy from a KTx patient with initial transplant glomerulopathy). Then, the most promising biomarkers evidenced were validated in two RBx from the same KTx patient in distinct CKD progression phase (RBx-C1: no injuries;RBx-C2: initial chronic allograft nephropathy, associated to severe interstitial fibrosis) Renal fibrosis: our result suggested a DDR1-TGFβ-COLIII-COLI- chronological formation of the fibrotic matrix in all RBx-B compartments. The same gene expression trend was observed in the RBx-C1 with a later collagens protein formation in the RBx-C2. Predictive biomarkers: Among the biomarkers, Klotho resulted the earliest with a downregulation in RBx-B and RBx-C1. Periostin, although later than Klotho, showed a great damaged compartment discrimination capacity resulting higher in both RBx-B and RBx-C2 glomeruli.

Conclusions: The method presented permits to obtain reliable results in LCM from FPPE samples. Furthermore, it is reproducible, easy and fast. In the future, a study in KTx-RBx of the relationship between RNA-expression at different renal sites and clinical and biochemical parameters and of its predictive role of KTx outcome will be possible.

TH-PO978

Pathological Characteristics of USAG-1 and BMP-7 Expression in Rats with CsA nephrotoxicity

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Background: CsA-nephrotoxicity is associated with decreased renal bone morphogenetic protein-7 (BMP-7) expression. Uterine sensitization-associated gene-1 (USAG-1), a kidney-specific BMPs antagonist, plays an important role in processing renal damage. The study aimed to evaluate the renal expression of USAG-1 and BMP-7 induced by CsA in a rat model.

Methods: Eight BrlHan:WIST@Jcl (GALAS) rats were assigned to two groups: control (untreated) and CsA (orally received CsA 10 mg/kg body weight). After 28 days, the renal tissues were examined for CsA toxicity, specifically, tubulointerstitial damage and arteriolopathy, by light microscopy. Furthermore, the area of USAG-1 and BMP-7 expression was scored by immunohistochemical staining.

Results: The CsA group showed mild interstitial fibrosis, but no arteriolohyalization and tubular atrophy. Two of the 4 rats in the CsA group presented findings similar to those observed during the early stage of focal segmental glomerulosclerosis (FSGS) development, such as enlargement of glomeruli and foam cells. In these 2 rats, high focal USAG expression and significantly decreased BMP-7 expression were also noted. In contrast, a broad area with BMP-7 expression was observed in the kidney of the 2 rats from the CsA group that presented fewer FSGS-like findings and in the control rats (no CsA nephrotoxicity).

Conclusions: In this study, the characteristic histologic changes of CsA-nephrotoxicity were not observed, but FSGS-like findings were noted. USAG expression may contribute to BMP-7 suppression, resulting in FSGS-like pathology that leads to CsA-nephrotoxicity. Furthermore, an imbalance in USAG-1 and BMP-7 expression may also be involved in CsA-induced nephrotoxicity.

TH-PO979

Ionizing Radiation Could Cause Cellular Senescence in Kidney and Late-Onset Kidney Dysfunction - Experiment Using Radiation Nephropathy Rat Model

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Background: Cellular senescence is one of the major risk factors for chronic kidney disease. Cellular senescence is caused by a variety of stressors, such as ionizing radiation (IR). The kidney is known as radiosensitive organ, however the association between cellular senescence and kidney dysfunction is still unclear.

Methods: 7-8-week-old male rats received unilateral IR of 18 Gy on the left or right kidney (irradiated kidney) whereas normal rats received sham IR (normal kidney). We compared the presence of cellular senescence, kidney dysfunction, and pathological changes at 9 months after the IR. Cellular senescence was defined by positive staining for SA-β-gal and p21, increased mRNA expression level of p21, and senescence associated secretory phenotype (IL-6). Pathological evaluation was performed focusing on glomerular findings, which were evaluated in 50 glomeruli. Endothelial cell was detected by CD31 staining. We also confirmed the endothelial senescence by vitro fashion with rat cultured endothelial cells received IR of 20 Gy with 25 days culturing.

Results: As shown in Table, markers of cellular senescence were elevated only in irradiated kidney. Regarding kidney dysfunction, irradiated rats showed higher proteinuria, and greater serum level of BUN. Pathological findings suggested strong endothelial cell injury in irradiated kidney with greater TMA and collapsing glomeruli, and reduced endothelial cell numbers. We confirmed endothelial cell senescence in vitro model, showing increased positive staining for SA-β-gal, expression level of p21 and IL-6.

Conclusions: Taken together, these data suggested IR could cause cellular senescence in the kidney and lead to resultant kidney dysfunction. The cellular senescence of glomerular endothelial cells may be associated with TMA and glomerular collapse, that lead to kidney dysfunction.

Marker of Cellular Senescence		Irradiated kidney	Normal kidney	p value
SA- SA-β-gal positive area (%)		31.8	2.4	p<0.001
mRNA				
p21		17.7	1.2	p=0.033
IL6		14.7	4.08	p=0.006
Marker of Kidney Dysfunction		**Irradiated rats**	**Normal rats**	**p value**
BUN (mg/dl)	Pre	16.9 (15.6-18.3)	17.1 (16.3-17.4)	0.897
	9 months	24.3 (22.2-26.4)	18.9 (17.7-21.0)	0.018
Proteinuria (mg/day)	Pre	4.4 (3.6-5.2)	4.4 (3.8-5.0)	0.243
	9 months	11.7 (6.5-11.3)	4.4 (3.8-5.0)	0.032
Pathologic Findings		**Irradiated kidney**	**Normal kidney**	**p value**
TMA (%)		8.4	0	p<0.001
Collapsing (%)		48.8	2.0	p<0.001
CD31 positive cell numbers		3.2	12.2	p<0.001

TH-PO980

Serotonin Receptor Expression in the Normal Adult Human Kidney and in Glomerular Diseases

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Background: Serotonin (5-HT) is the phylogenetically oldest neurotransmitter and acts *via* specific receptors. Serotonin receptors 5-HT_{2A} and 5-HT_{2B} are G-protein-coupled and mediate vasoconstriction and hypertension. The 5-HT_{2A} receptor is also engaged in blood coagulation and wound healing. Little is known about the function of 5-HT and its receptors 5-HT_{2A} and 5-HT_{2B} in the normal kidney or during renal disease.

Methods: Localization of 5-HT_{2A} and 5-HT_{2B} receptors was analysed by immunohistochemistry in the human healthy kidney and during renal disease. Serum 5-HT and urine 5-HT metabolite 5-HIAA concentrations were measured by HPLC. *In vitro* studies were performed to identify the role of 5-HT_{2A} and 5-HT_{2B} receptors in primary murine glomerular parietal epithelial cells (PECs). Mice with 5-HT_{2A} and 5-HT_{2B} deletions are available.

Results: In the normal human kidney (living donor biopsies), 5-HT_{2A} and 5-HT_{2B} receptors localized to PECs, proximal tubuli and the loop of Henle. In all renal diseases investigated, 5-HT_{2A} and 5-HT_{2B}-expression in tubuli was maintained. In glomeruli, the number of 5-HT_{2B}-positive cells increased significantly with disease. Serum 5-HT concentrations were significantly reduced in patients with rapidly progressive glomerulonephritis (RPGN), whereas 5-HT metabolite concentrations in tendency increased in the urine of these patients. By immunofluorescence, glomerular 5-HT_{2B}-positive cells could be identified as PECs. In biopsies of patients with IgA nephropathy or RPGN, the cell diameter of 5-HT_{2B}-positive PECs was significantly increased in comparison to receptor-negative PECs. In primary PECs *in vitro*, removal of serotonin from culture medium reduced the expression of activation markers. *Vice versa,* activation of 5-HT_{2A} and 5-HT_{2B} receptors induced an overexpression of CXCR4 and VCAM.

Conclusions: In summary, we demonstrate for the first time the constitutive expression of 5-HT_{2A} and 5-HT_{2B} receptors in the adult human kidney with glomerular upregulation in different renal diseases. Our studies identify PECs as the primarily cell type involved in serotonin receptor upregulation in glomerular disease. Further *in vivo* studies in murine models of glomerular disease are currently under way in order to elucidate the potential pathophysiological role of these receptors.

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TH-PO981

What Is the Sufficient Minimum Number of Glomeruli in a Kidney Biopsy to Detect Nephrosclerosis?

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Background: The number of glomeruli present is often used to determine the sufficiency of a kidney biopsy sample (e.g., at least 10 glomeruli). The assumption is that with fewer glomeruli, the biopsy findings are too imprecise to draw inferences regarding the underlying pathology in the kidney. The true amount of nephrosclerosis (global glomerulosclerosis, fibrosis, and arteriosclerosis) is expected to not depend on the number of glomeruli of the biopsy.

Methods: We studied 2,915 implantation needle core kidney biopsies from living kidney donors at three transplant centers. The number of glomeruli, the % globally sclerotic glomeruli (%GSG), the amount of interstitial fibrosis (number of fibrosis foci), and the severity of arteriosclerosis (% intimal narrowing) were quantified on digital images of a single PAS-stained section. A beta-binomial model was used to estimate the mean whole-kidney %GSG and the biological (between-kidney) variability in %GSG, number of fibrosis foci, and %intimal narrowing for the number of glomeruli on the biopsy section.

Results: Fewer glomeruli on biopsy correlated with both a higher mean %GSG (16% increase per 10 fewer glomeruli) and more between-patient variability in %GSG in the kidney (See figure). Because of this, the probability of the whole kidney having %GSG >10% with the biopsy %GSG>10% was 45% with 1-9 glomeruli and 31% with 10 or more glomeruli. Similar findings were seen for interstitial fibrosis and arteriosclerosis.

Conclusions: A lower number of total glomeruli correlated with increasing nephrosclerosis and is consistent with the concept of nephron dropout/decreased cortical volume. The presence of fewer glomeruli on a kidney biopsy is itself informative of pathology and is not always indicative of an inadequate sample. It also may represent cortical scarring and volume loss. Thus, requiring a minimum acceptable number of glomeruli should be applied cautiously when interpreting renal biopsies.

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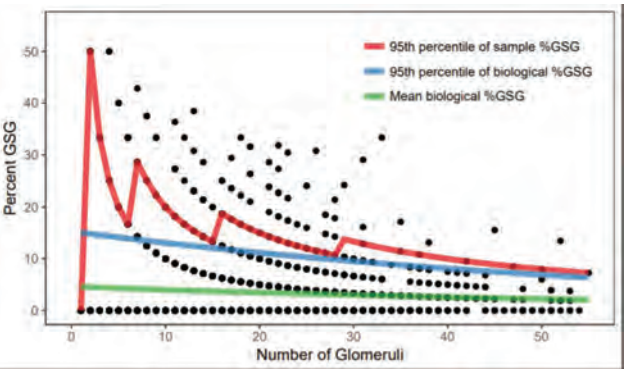

TH-PO982

The Clinical Features and the Expression of suPAR and ApoA-1 in Focal Segmental Glomerulosclerosis

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Background: Our purpose is to explore whether serum and urine suPAR and ApoA-1 can be used as markers in patients with FSGS and to evaluate the value of serum and urine suPAR and ApoA-1 in predicting FSGS.

Methods: Subjects were selected by inclusion and exclusion criterias, divided into four groups: FSGS group, MN group, IgAN group and healthy group. Serum and urine samples were collected. Serum and urine suPAR levels and urine ApoA-1 levels were detected in each group by ELISA and analyzed. Their correlations with gender, age, urea nitrogen, creatinine, 24h urinary protein, eGFR, serum albumin, total cholesterol, and triglyceride were also analyzed.

Results: Serum suPAR levels of FSGS group were higher than the MN group, IgAN group and healthy control group ($P < 0.05$); in FSGS group, serum suPAR was positively correlated with serum creatinine ($P < 0.05$), negatively correlated with eGFR ($P > 0.05$). There was no significant correlation with gender, age, urea nitrogen, 24h urinary protein, serum albumin, total cholesterol and triglyceride ($P > 0.05$). Urine suPAR levels of FSGS group were higher than the MN group, IgAN group and healthy group ($P < 0.05$); in FSGS group, Urine suPAR was positively correlated with 24h urinary protein ($P < 0.05$), but no significant correlation with gender, age, Urea nitrogen, serum creatinine, eGFR,serum albumin, total cholesterol and triglyceride ($P > 0.05$). Urine ApoA-1 levels of FSGS group, MN group and IgAN group were higher than healthy group($P < 0.05$). There was no significant difference among FSGS group, MN group and IgAN group ($P > 0.05$). There was no significant correlation with dender, age, serum albumin, urea niteogen, serum creatinine, eGFR, total cholesterol and triglyceride ($P > 0.05$). The best predictive value of serum suPAR for FSGS was 3280.28 pg/ml; the area under the curve of AUC was 0.831 (95%CI, 0.736-0.926), with sensitivity of 74.2% and specificity of 81%. The area under the curve of AUC for urine suPAR levels in predicting FSGS was 0.781 (95%CI, 0.673-0.890), with sensitivity of 71% and specificity of 77.8%. AUC for urinary APoA-1 in predicting FSGS was 0.483 (95%CI, 0.356-0.610) with sensitivity of 45.2% and specificity of 48.1%.

Conclusions: The value of serum suPAR level in predicting primary FSGS is higher than that of urine suPAR and ApoA-1. Serum suPAR is expected to be a serological marker for auxiliary diagnosis of FSGS.

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TH-PO983

The Effect of Sertraline on Reduction of Albuminuria Due to the Inhibition of Caveolae Pathway Through Glomerular Endothelial and Epithelial Cells

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Background: Previously, we have reported the caveolae mediated endocytosis, transcytosis, and exocytosis of albumin through glomerular endothelial cells as a new etiology of urinary albumin excretion (J Cell Biochem 116; 1065-9: 2015, J Cell Physiol 232; 3565-73: 2017). The selective serotonin reuptake inhibitor, sertraline, inhibited the

dynamin which played a pivotal role for fission of caveolae from cell membrane in caveolae endocytosis. We hypothesized that sertraline might reduce the albuminuria by interfere the caveolae mediated intracellular trafficking pathway.

Methods: In this study, we analyzed whether the dynamin inhibitor sertraline interfered the albumin internalization through caveolae in glomerular epithelial and endothelial cells, and sertraline reduced the amount of albuminuria in puromycin aminonucleoside induced nephrotic syndrome modeled mice (PAN mice) as a novel treatment of glomerulonephritis.

Results: In vitro studies, western blotting analysis and immunofluorescence (IF) study showed that dose dependent (5 and 10 μM) treatment of sertraline significantly reduced the expression of albumin in glomerular endothelial and epithelial cells ($P<0.01$), though the Caveolin-1 (Cav-1) expression was not reduced. In vivo analysis, the electron microscopic findings showed that the foot process fusion and swelling of endothelial cells in dimethyl sulfoxide (DMSO) treated PAN mice as vehicle and also sertraline treated PAN mice, and the IF analysis showed the stronger Cav-1 expression on capillaries in both mice in comparison to normal control mice ($P<0.0001$). However, the amount of proteinuria was not increased in sertraline treated PAN mice in comparison to normal control mice (0.05 vs. 0.02 mg/mgCre, $p=0.17$), though it was significantly increased in DMSO treated PAN mice (0.12 vs. 0.02 mg/mgCre, $P=0.0027$).

Conclusions: Though the foot process fusion, endothelial swelling, and caveolin-1 expressions were occurred, albumin internalization into glomerular endothelial and epithelial cells and albuminuria in PAN mice were reduced by sertraline. These results indicated that sertraline interfered albumin internalization thorough caveolae by inhibition of dynamin and resulted in reduction of albuminuria. Sertraline might become the novel therapeutic option to reduce albuminuria in glomerulonephritis.

TH-PO984

Identification of Cytoplasmic Proteins Associated with Ephrin-B1 at the Slit Diaphragm of Podocyte: PDZ Proteins, Par6, Par3 and NHERF2 Are Associated with Ephrin-B1

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Background: We have recently reported ephrin-B1 interacts with nephrin via their extracellular domains in cis form and plays an essential role at the slit diaphragm. We also reported the phosphorylated ephrin-B1 activates the JNK signaling independently of nephrin phosphorylation (JASN 2018). Because ephrin-B1 has a PDZ binding motif in its C-terminus, it is estimated that PDZ proteins interact with ephrin-B1. However, the cytoplasmic proteins interacted with ephrin-B1 in podocyte and the precise signaling pathways activated by the phosphorylated ephrin-B1 remain unclear.

Methods: To identify the proteins associated with ephrin-B1, we performed the gene expression profiling of glomerular sample of the podocyte-specific ephrin-B1 knockout (KO) mice. We found PDZ proteins, Par6, Par3 and NHERF2 were evidently downregulated, but the expressions of other PDZ proteins, ZO-1, MAGI1, CASK, which are already reported to be expressed at the slit diaphragm, were not changed. In this study the expression of Par6, Par3 and NHERF2 and their interaction with ephrin-B1 were analyzed.

Results: The decrease in mRNA expressions of Par6, Par3 and NHERF2 were confirmed with real-time RT-PCR (Par6, 20 ± 11%, $p<0.01$, Par3, 14 ± 9% to control, $p<0.05$, NHERF2, 17 ± 6%, $p<0.001$). The immuno-staining intensity of these proteins in glomeruli was decreased and their staining pattern evidently changed in the KO mice. Dual labeling analyses showed Par6, Par3 and NHERF2 were colocalized with ephrin-B1 in normal glomeruli. The immunostaining of these molecules as well as ephrin-B1 were clearly decreased in the nephrotic state caused by PAN injection. The remaining Par3 and Par6 in this proteinuric state were dissociated from ephrin-B1. By contrast, the remaining NHERF2 was still colocalized with the remaining ephrin-B1. Immunoprecipitation assay showed Par3 interacted with both ephrin-B1 and nephrin, and Par6 interacted with ephrin-B1 but not with nephrin. It is also observed that the phosphorylation of ephrin-B1 inhibited its interaction with Par6 and Par3.

Conclusions: Par6, Par3 and NHERF2 interact with ephrin-B1 and may contribute to the maintenance of the structure and the function of slit diaphragm cooperated with ephrin-B1.

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TH-PO985

Chronic High-Dose Candesartan Therapy Promotes Podocyte Recruitment from Glomerular Parietal Epithelial Cells Involving Suppression of GSK3β Signaling

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Background: Evidence suggests that non-podocyte cells like glomerular parietal epithelial cells(PEC) contribute to podocyte repopulation and glomerular filtration barrier(GFB) repair in chronic kidney disease(CKD). Angiotensin blockades, as the standard of care for CKD, however, only exhibit a marginal effect on podocyte regeneration. At doses higher than recommended, angiotensin blockades are known to exert an extra anti-proteinuric and renoprotective effect. This study aims to explore if this additional benefit is associated with podocyte regeneration.

Methods: After unilateral nephrectomy, spontaneously hypertensive rats received variable doses (standard, 5 mg/kg/d; high, 25 mg/kg/d; and ultrahigh, 75 mg/kg/d) of candesartan for 14 months. Renal expression of podocyte and PEC markers was evaluated.

Results: Despite a comparable effect attained by all doses on normalizing systemic hypertension, high and ultrahigh dose candesartan exhibited a more potent proteinuria-reducing effect that is independent of blood pressure control. Accordingly, glomerulosclerosis was improved by candesartan in a dose dependent mode. The variable outcomes in proteinuria is suggestive of disparity in GFB integrity. Indeed, increasing doses of candesartan progressively augmented the number of podocytes, marked by WT-1 staining. This effect seems to be attributable to new podocyte recruitment from PEC, because the number of cells in glomerular tufts positive for both synaptopodin and Pax2, a PEC marker, was increased. This coincided with a potentiated transdifferentiation of PEC to podocyte phenotypes in parietal epithelia. In contrast, PEC activation, probed by CD44 expression in glomeruli, was diminished by candesartan in a dose dependent fashion. Glycogen synthase kinase (GSK)3β, a multitasking serine/threonine protein kinase, has been recently implicated in impaired podocyte regeneration. In the diseased kidney, glomerular expression of GSK3β was amplified, predominantly located to PEC and podocytes. Increasing dose of candesartan progressively obliterated glomerular overexpression of GSK3β, concomitant with an improved glomerular histology and podocyte integrity.

Conclusions: Chronic high-dosage candesartan therapy is able to potentiate podocyte derivation from PEC *via* inhibition of GSK3β signaling and attenuate glomerular injury.

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TH-PO986

DGKE Gene Variants in C3 Glomerulopathy

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Background: DGKE is intra-cellular lipid kinases that phosphorylate the diacylglycerol (DAG) to phosphatidic acid (PA). Normal expression of DGKE is found in podocytes, endothelium, and platelets. Evidence of some variants of DGKE is reported in association with glomerular microangiopathies and found to have some overlapping feature with membranoproliferative glomerulonephritis (MPGN). As a pilot study, we screened patients of C3G in addition to alternative complement pathway related gene with focus on DGKE gene which confirmed its involvement in aHUS.

Methods: DNA from blood (EDTA) was isolated. Whole exome sequencing, clinical exome sequencing and targeted sequencing (15 genes; CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CD46, CFI, CFB, DGKE, C3, THBD, CFD, and properdin) were performed in 5 cases of C3GP. Test findings were analyzed and correlated with clinical outcome of these five patients.

Results: In addition to CFH and CFHR5 gene variants, whole exome sequencing in two cases revealed two variants in DGKE gene i.e. c.1583G>A (missense variants) and c.183G>A (synonymous variant) in case 1 whereas in case 2, only one variant c.579A>C (synonymous variant) was documented. Clinical exome sequencing was performed in case 3 which showed a variant in exon 6 of DGKE gene (c.998C>G). This variant is of undetermined significance that results in the amino acid substitution of Glycine for Alanine at codon 333 (p.Ala333Gly; ENTST00000284061). Targeted sequencing in other two patients showed c.579A>C (case 4) and c183G>A (case 5) variants in DGKE gene. Of 5 cases, case 1 and 2 are from the same family with the history of renal disease in the family. Case 1 expired and other receive a renal transplant. Case 3 had a history of UTI in childhood followed by MPGN on renal biopsy, which rapidly progressed to end-stage renal disease (ESRD)/underwent transplant and had graft failure in 16 months followed by graft nephrectomy. Patient 4 and 5 also had rapid progression to ESRD.

Conclusions: In present pilot study, the mutation/variants found in DGKE gene showed that genetic defects in C3G is not only limited to alternative complement pathway-related genes. Hence, we strongly recommend the screening of DGKE in all C3G patients. More data is needed to validate our findings.

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TH-PO987

Transcription Factor Dach1 in Podocytes

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Background: Podocyte injury is crucial for the progression of chronic kidney diseases (CKD). Transcriptional factors, *Wt1*, *Mafb*, and *Foxc2*, are highly expressed in normal podocytes and rapidly decreased upon injury. These play important roles in maintaining normal podocyte function. We aim to find transcriptional factors with similar expression patterns, and study the function in podocytes.

Methods: We combined NEP25 mice, an immunotoxin-inducible podocyte injury model, with RiboTag mice, in which podocyte-specific polysome mRNAs can be yielded by immunoprecipitation in glomerular homogenate. We analyzed gene expression changes of normal and injured podocytes by microarray.

Results: We found the following 8 transcription factor mRNAs were highly expressed in normal podocytes and rapidly decreased after injury; *Wt1*, *Mafb*, *Foxc2*, *Tcf21*, *Foxd2*, *Banp*, *Hoxc6*, and *Dach1*. We focused on *Dach1* because SNPs of *DACH1* gene were associated with the progression of CKD by genome-wide association studies. RT-PCR analysis confirmed that *Dach1* mRNA was concentrated in normal podocytes (7.33±0.68-fold vs glomerulus) and decreased in podocytes injured by immunotoxin (0.371±0.0053-fold vs normal podocytes). Immunostaining showed that Dach1 protein was intensely expressed in the nucleus of normal podocytes and decreased upon injury not only in NEP25 model but also in adriamycin nephropathy and HIV-associated nephropathy models.

DACH1 protein was also expressed in human normal podocytes and the expression was decreased in diabetic nephropathy, lupus nephritis, and IgA nephropathy but not in minimal change disease. Kockdown of *Dach1* by siRNA in murine primary cultured podocytes suppressed the proliferation and DNA synthesis of podocytes, contrasting to the growth inhibitory effect of DACH1 previously reported in cancer cells. The DNA binding sites of DACH1 are reported to co-localize with those of FOX family members. Suppression of *Dach1* gene by siRNA in murine primary cultured podocytes decreased the expression of Foxc2-target genes, *Podxl* and *Dpp4* (0.624±0.12 and 0.626±0.29-fold, respectively), suggesting that Dach1 may modulate or collaborate with Foxc2 in podocytes.

Conclusions: Dach1 is highly expressed in normal podocytes and downregulated upon injury. This transcription factor may play a role in maintaining normal podocyte function.

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TH-PO988

miR-466o-3p Promotes Podocyte Injury Through Targeting WT1

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Background: Podocytes are highly specialized cells that maintain normal function of the glomerular filtration barrier. Dysregulation of Wnt/β-catenin signaling has been linked to podocyte injury; however, the underlying mechanism remains incompletely understood. In this study, we explored the roles of microRNA in mediating Wnt/β-catenin-triggered podocyte dysfunction and proteinuria.

Methods: Mouse podocytes were transiently transfected with expression vector encoding constitutively activated β-catenin (pDel-β-cat) or empty vector (pcDNA3). The differential expression of microRNA between these two groups was analyzed microarray assay and bioinformatics analysis. The role of miR-466o-3p in podocyte biology was investigated in vitro and in vivo. The BALB/c mice were randomly divided into 3 different groups: i) sham control; ii) ADR mice injected with empty vector pcDNA3; iii)ADR mice injected with miR-466o-3p plasmid. Urine, blood and kidneys were collected at 1 week after ADR injection.

Results: We identified multiple miRNAs whose expression was modulated by β-catenin activation in podocytes. Real-time RT-PCR validated that miRNA-466o-3p was upregulated in cultured podocytes after β-catenin activation and in kidney tissues after adriamycin (ADR) injection. *In situ* hybridization demonstrated that miR-466o-3p was up-regulated in glomerular podocytes. Bioinformatics analysis and luciferase reporter assay confirmed that miR-466o-3p directly targeted WT1 mRNA. Furthermore, overexpression of miR-466o-3p downregulated WT1 protein *in vitro* and promoted podocyte injury, although it did not affect WT1 mRNA level. Conversely, inhibition of miR-466o-3p alleviated β-catenin induced podocyte injury. In ADR model, Overexpression of miR-466o-3p inhibited WT1, aggravated podocytes injury and increased proteinuria in mice.

Conclusions: These studies demonstrate that miR-466o-3p plays a critical role in mediating Wnt/β-catenin-triggered podocyte injury. Our findings uncover a new pathogenic mechanism by which Wnt/β-catenin promotes podocyte injury and proteinuria.

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TH-PO989

Podocyte-Specific Knockdown of PAI-1 Protects Against Podocyte Injury

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Background: Plasminogen activator inhibitor-1 (PAI-1) is upregulated in a variety of fibrotic kidney diseases. Our previous study showed systemic knockout of PAI-1 protects against development of glomerulosclerosis (GS) and podocyte injury in both models of primary podocyte injury and secondary FSGS in the 5/6 nephrectomy model. In this study, we investigated whether knockdown (KD) of PAI-1 only in podocytes can protect against podocyte and glomerular injury.

Methods: We generated inducible podocyte PAI-1 knockdown mice (PAI-1 KD, PAI-1^{floxed}/ rtTA/podocin Cre^{+}) and wild type control (WT, PAI-1^{floxed}/ rtTA/podocin Cre^{-}). A model of secondary mild hypertensive podocyte injury was induced by high salt+uninephrectomy (uNX)+AngII. We also mated PAI-1 KD mice with Nphs1-hCD25 mice (Nep25), which express human CD25 just in podocytes, and develop primary podocyte injury when injected with immunotoxin (LMB2). Podocyte injury and GS were compared in these two models. In vitro, we cultured primary podocytes from these WT and PAI-1 KD mice and exposed cells to AngII or LMB2, respectively.

Results: In vitro primary cultured podocytes showed reduced PAI-1 after doxycycline induction. In vivo, double staining confirmed reduced PAI-1 in podocytes in both models, but increased PAI-1 expression in endothelial cells and mesangial cells. In the Nep25 model, PAI-1 KD in podocytes resulted in less albuminuria (ACR) and GS with more differentiated podocytes than WT (WT-1^{+} cell density, PAI-KD 27.4±1.8 vs. WT 21.8±1.9x10^{-4}/μm^2). In the high salt+uNX+AngII model, although podocytes expressed less desmin (PAI-KD 0.027±0.008 vs. WT 0.051±0.008), a marker of podocyte injury, ACR and mesangial expansion were similar in PAI-1 KD and WT. In vitro, knockdown of PAI-1 induced more podocyte proliferation, adhesion and migration in both LMB2 and AngII injury models, with less CTGF and desmin expression vs WT. ILK was reduced in PAI-1 KD vs WT only in the AngII model.

Conclusions: Knockdown of PAI-1 only in podocytes protected against primary podocyte injury and GS, while there was less effect on GS if the injury involved multiple cells, as seen in the AngII model. Our data further suggest that PAI-1 upregulation of ILK may be one mechanism related to podocyte injury.

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TH-PO990

Deletion of Ste20-Like Kinase SLK Induces Cytoskeletal Changes in Podocytes

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Background: Glomerular epithelial cells (GECs; podocytes) are essential in maintaining glomerular permselectivity. Their function is dependent on an intact actin cytoskeleton. Regulation of the actin cytoskeleton, in part, relies on the assembly of a phospho-ezrin-NHERF2-podocalyxin complex at the apical surface of the podocyte. SLK is a serine/threonine kinase ubiquitously expressed in mammalian tissues, including GECs. SLK was reported to be involved in the arrangement of the actin cytoskeleton and in mediating cell cycle progression. Deletion of SLK in podocytes in mice leads to proteinuria and disruption of podocyte architecture as mice age. The aim of this study was to determine if SLK phosphorylates ezrin in podocytes and is critical in maintaining cytoskeletal integrity.

Methods: We generated a SLK knockout (KO) GEC line by transducing immortalized GECs isolated from mice carrying a floxed SLK allele with tamoxifen-inducible Cre recombinase. We also depleted SLK in GECs using siRNAs. We studied the effect of SLK deletion on phosphorylated ezrin, podocalyxin and F-actin using immunoblotting and immunofluorescence microscopy.

Results: In GECs, both KO of SLK using Cre recombinase and depletion of SLK with siRNAs reduced SLK protein expression and pT183 phosphorylation, which reflects catalytic activity (KO being more effective than siRNA). SLK KO did not affect the rate of proliferation of GECs. Both SLK KO and depletion markedly reduced activation-specific phosphorylation of ezrin, while total ezrin protein levels remained unchanged. Expression of podocalyxin, a protein essential to foot process integrity, was significantly reduced in the SLK KO cells. Levels of F-actin were markedly reduced in SLK KO cells and stress fiber arrangements were altered; however, total actin was unaffected. Treatment of GECs with erlotinib, a chemical inhibitor of SLK, showed effects on F-actin similar to KO of SLK.

Conclusions: SLK is not essential for cell cycle progression in GECs. SLK phosphorylates ezrin, and decreased ezrin phosphorylation due to deletion of SLK leads to reduction in podocalyxin and disruption of the actin cytoskeleton. The result suggests that SLK is important in the maintenance of the ezrin-NHERF2-podocalyxin complex and foot process integrity.

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TH-PO991

FK506 Binding Protein 12 (FKBP12) Is Highly Expressed in Glomerular Podocyte in Kidney: FKBP12 in Podocyte Is Co-Localized with Actin Cytoskeleton and Is Re-Distributed in Injured Podocytes

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Background: FKBP12, a 12 kDa cytoplasmic immunophilin, was identified as a binding protein of FK506 (tacrolimus). Tacrolimus and rapamycin bind to FKBP12 and exhibit immunosuppressant effect through inhibition of calcineurin and mTOR, respectively in T cells. FKBP12 is reported to be expressed in various organs, and the distribution is associated with side effects of these drugs. It is also known that FKBP12 functions independently of these immunosuppressants; for example, FKBP12 binds to TGF-b type 1 receptor and inhibits its signaling. However, the localization and the physiological function of FKBP12 in kidney are not well elucidated.

Methods: mRNA expression of FKBP12 in several tissues and cultured podocytes was analyzed with RT-PCR and its precise localization was investigated with the immuno-histochemical analyses with a specific antibody produced in a rabbit immunized with specific peptide. The FKBP12 expression in injured podocytes was also analyzed.

Results: FKBP12 mRNA expression in whole kidney was lower than in other organ materials such as cerebrum, liver, heart and lung, but the high expression was detected in glomeruli. The histochemical analysis with rat kidney section showed FKBP12 was highly expressed in glomeruli. Dual labeling staining with glomerular cell markers showed the FKBP12 expression in glomeruli was restricted in podocyte and the staining in podocyte was mainly detected at the cytoplasm close to cell membrane. FKBP12 staining in cultured pocoytes was colocalized with cytoskeletal actin. mRNA expression of FKBP12 in glomeruli was downregulated at the initiation phase of nephrotic models, anti-nephrin antibody-induced nephropathy (20.0% to normal, P<0.001) and in PAN nephropathy, a mimic of MCNS (26.0% P <0.001). Immuno-staining of FKBP12 was clearly lowered when proteinuria peaked in PAN nephropathy (staining score, 2.7 vs 3.5 of normal, P<0.05), and in ADR nephropathy, a mimic of FSGS (score 2.9, P<0.05). FKBP12 staining was clearly decreased in the human cultured podocytes treated with ADR (67% to normal; P<0.05) and with serum free medium (61% P<0.05).

Conclusions: FKBP12 is mainly expressed along cytoskeletal actin in podocyte and its altered expression might be associated with cytoskeletal remodeling in podocyte injury.

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TH-PO992

Transcription Factor MAFB is a New Key Regulator of Podocyte Autophagy

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Background: Autophagy is an intracellular catabolic system with protective roles against fasting and cellular damage. Podocytes have high autophagy activity in basal condition; however, their autophagy regulating mechanisms are unclear. To reveal the regulating mechanism of podocyte autophagy, we focused on transcriptional regulation of autophagy related genes.

Methods: We searched the candidate transcription factors which regulate autophagy related genes with the potential to bind to transcription regulatory sites from the web database Motifmap. Next, we sorted the transcription factors which are strongly expressed in podocytes from RNA sequence data of primary culture podocytes. MAFB was extracted as a candidate from the results of these two analyses. To investigate the location of MAFB in the cell, we stained MAFB protein in mouse kidney sections and human podocyte cell lines. To exhibit the transcriptional role of MAFB on autophagy activation, we modified MAFB expression levels in human podocyte cell lines using either overexpression vector or siRNA, and evaluated autophagy activity by LC3-II protein expression. In addition, to reveal the role of MAFB for cell damage, we induced cell damage by incubation with palmitate and evaluated apoptosis and autophagy-related proteins using the cell line of tetracycline-induced overexpression/shRNA of MAFB.

Results: MAFB was localized at nuclear areas in podocytes of mouse kidney sections and human podocyte cell lines. LC3-II protein abundance was significantly increased in the MAFB overexpression group and decreased in siRNA of MAFB group. In cell damage experiments with palmitate, we observed suppression of apoptosis accompanied by high LC3-II protein abundance in the MAFB overexpression group. Phosphorylation of ULK1 proteins, which are well known as a key autophagy regulator, was not significantly changed in any experiment.

Conclusions: We identified the transcription factor MAFB as a novel autophagy regulator independent of phosphorylation of ULK1 in podocytes. The activation of MAFB can be a potential therapeutic target against podocyte damages via autophagy activation.

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TH-PO993

Soluble Form of VCAM-1 Ameliorates Podocyte Injury by Plasma Membrane PTEN Recruitment

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Background: Various types of stresses cause epithelial-mesenchymal transitions (EMTs) and detachments of podocyte that result in glomerular sclerosis. Podocyte has self-defense mechanisms to resist against the stresses by expressing aberrant proteins. Vascular cell adhesion molecule-1 (VCAM-1) is a well-known protein induced by stresses that serve functions in membrane-bound and soluble form (sVCAM-1). However, in podocyte, the link between VCAM-1 and stress resistance remains unknown.

Methods: NEP25 transgenic mouse that develop podocyte-specific injury by immunotoxin injection were used. We assessed podocyte VCAM-1 and its ligand expressions by immunostaining, PCR, and western blot (WB). *In vivo* functions of sVCAM-1 were assessed by inhibiting ADAM17, the shedding enzyme of VCAM-1, by BB94. Immortalized podocyte were used for *in vitro* studies. The podocyte treated with H_2O_2, TGF-β1, sVCAM-1, and bpV were analyzed by immunostaining, real-time PCR, WB, and migration assay.

Results: Podocyte-specific injury of NEP25 mouse induced aberrant podocyte VCAM-1 and ADAM17 expression, which suggests the generation of sVCAM-1. Human focal segmental glomerular sclerosis also expressed podocyte VCAM-1. *In vivo*and *in vitro*podocyte expressed α9β1 integrin, which is the ligand of sVCAM-1.*In vitro*, sVCAM-1 ameliorated TGF-β1 induced podocyte EMT; amelioration of enhanced motility, maintenance of podocyte specific proteins, and inhibition of Akt phosphorylation. Mechanistically, sVCAM-1 recruited PTEN against plasma membrane, which was shown by immunostaining and WB analysis of plasma membrane fraction protein. Blockage of PTEN by bpV diminished the efficacy of sVCAM-1 to ameliorate podocyte EMT. Finally, we treated immunotoxin-injected NEP25 mouse by BB94 to inhibit sVCAM-1 generation that resulted in exacerbation of renal disfunction, urinary protein and glomerular sclerosis.

Conclusions: Aberrant sVCAM-1 generation recruited PTEN against plasma membrane to ameliorate podocyte injury by inhibiting Akt phosphorylation. VCAM-1 expression might be one of the intrinsic self-defense mechanisms to resist against stresses in podocyte.

TH-PO994

Advanced Optical Clearing Protocols Enable Fine Analysis of Glomerulus Three-Dimensionally with Confocal Microscopy

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Background: In order to visualize slit diaphragm of podocyte, it is necessary to use an electron microscopy or super-resolution microscopy. However, there are some disadvantages to these approaches in terms of economics and viewable dimensions. We hypothesized that advanced optical clearing methods with confocal microscopy could enable the three-dimensional (3D) analysis of the fine structure of glomerulus and podocyte.

Methods: From among several advanced optical clearing methods, the following protocols were selected based on the simplicity of the technique and the number of citations: CUBIC, PACT, ScaleS, BABB, iDISCO and SeeDB2. Each protocol with immunostaining against Nephrin were applied to a 1-mm-thick slice of adult rat kidney. We investigated which method was most suitable for observing the fine structure of podocyte with confocal microscopy three-dimensionally. Next, the optimal method among them was applied to anti-glomerular basement membrane (anti-GBM) nephritis rats.

Results: All of these protocols could turn the rat kidney sample transparent. Although each protocol made it possible to visualize the 3D image of the whole glomerulus, a few protocols were capable of visualizing their fine structure of podocytes with confocal microscopy. When analyzing anti-GBM nephritis rat with 3D image, the ratio of the glomeruli with crescent formation in 3D analysis was significantly higher than that in the conventional two-dimensional histological analysis (34.1% versus 14.6%, $p<0.01$). High magnification of the 3D images showed that the meandering pattern of the slit diaphragm was sustained in the vehicle group while it was partially effaced in the anti-GBM nephritis group.

Conclusions: Advanced optical clearing methods enables a pathological 3D diagnosis of glomeruli and has a high sensitivity for pathological lesions. Moreover, using even confocal microscopy, it could visualize the fine structure of podocyte three-dimensionally. Optical clearing methods could make an outstanding contribution to our clinical practices in many aspects.

TH-PO995

A Deep Learning Approach for Detection of Normal and Globally Sclerotic Glomeruli on Whole Slide Images from Renal Biopsy Sections Stained with H&E

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Background: Clinically useful quantitative assessment of renal biopsies requires robust methodologies. We demonstrated that accurate estimates of glomerular global sclerosis (GS) adjusted for age can predict outcomes across proteinuric diseases. However, visual assessment is poorly reproducible and time consuming. To increase efficiency, we present a deep learning-based approach for detection and segmentation (object extraction) of normal and globally sclerotic glomeruli (histologic primitives) digital renal biopsies.

Methods: A convolutional neural network (CNN) architecture based on Alexnext was trained using transfer learning to produce 3 classifiers: (i) normal glomerular tuft, (ii) normal glomerulus (tuft + Bowman's capsule), and (iii) GS. We used 74 cropped images from whole slide images of NEPTUNE renal biopsies sections stained with H&E, divided into training and testing sets.

Results: The detection and pixel level segmentation results for all 3 classifiers was graded via the F-score (A measure of classification accuracy that considers both precision and recall; 1 = perfect, 0 = worst).

Conclusions: The development of these 3 CNNs represents the first step in evaluating renal biopsies using novel machine-human interactive protocols. The classifier "normal glomerulus" is a better denominator compared to "normal glomerular tuft" to estimate percentage of GS. Improvement in F-score for the classifier GS, however, is necessary before automatic assessment of GS adjusted for age can be applied in clinical research and practice. Future steps to implement extended machine-human interactive protocols will include generation of other classifiers for the annotation of additional glomerular, tubulointerstitial and vascular normal and abnormal histologic primitives.

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Model	Magnification	# study subject (cropped images) for training	# study subject (cropped images) for training	Segmentation F-score	Detection rate
Model: Normal glomerular tuft	5X	27 (47 images)	14 (27 images)	0.808	0.938
Normal glomerular tuft	5X	27 (47 images)	14 (27 images)	0.844	0.985
Global glomerulosclerosis	8X	25 (53 images)	15 (35 images)	0.700	0.836

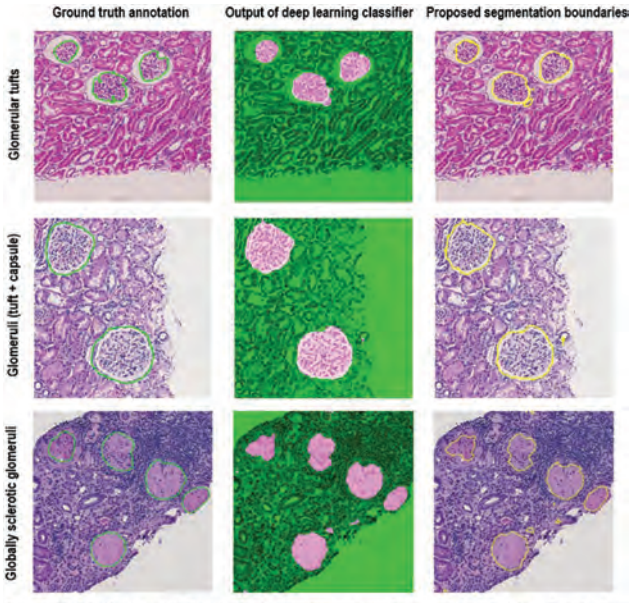

Figure 1: The left column presents the ground truth annotation as a green boundary, the middle column illustrates the output of our deep learning classifiers overlaid in fuchsia on the original images, and the right column shows the proposed segmentation boundary in yellow.

TH-PO996

Activation of Non-MC1R-Mediated Melanocortinergic Signaling Ameliorates Podocytopathy and Proteinuria in Experimental Focal Segmental Glomerulosclerosis (FSGS)

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Background: The clinical effectiveness of melanocortin therapy with adrenocorticotropin in inducing remission of steroid-resistant nephrotic syndrome points to a steroidogenic-independent anti-proteinuric activity of melanocortins. However, which melanocortin receptor(MCR) conveys this beneficial effect is controversial. Moreover, it remains uncertain if a systemic or podocyte specific mechanism is involved. By harnessing the naturally occurring MC1R-null mice and using NDP-MSH, a potent nonsteroidogenic pan-MCR agonist, this study aims to validate if a podocyte-specific MC1R-mediated melanocortinergic signaling mediates the beneficial effect in glomerulopathy, as proposed recently.

Methods: FSGS was induced in wild-type (WT) and MC1R-null mice by Adriamycin, treated with NDP-MSH and was evaluated. Primary podocytes were injured with Adriamycin and cytopathy assessed.

Results: WT mice developed heavy proteinuria after Adriamycin insult, associated with progressive glomerulosclerosis and podocytopathy, marked by loss of podocin and synaptopodin, podocytopenia and extensive foot process effacement on electron microscopy. All these injurious effects were prominently attenuated by NDP-MSH. Surprisingly, MC1R deficiency in MC1R-null mice barely affected the severity of Adriamycin-elicited injury. Moreover, the beneficial effect of NDP-MSH was equally observed in MC1R-null mice to an magnitude comparable to that in WT mice, suggesting that MC1R is likely nonessential for the protective action. A direct podocyte effect seems to contribute, at least in part, to the beneficial effect of NDP-MSH, because Adriamycin-inflicted cytopathic signs in primary podocytes prepared from WT mice were all diminished by NDP-MSH, including loss of podocyte markers, apoptosis, *de novo* expression of podocytopathic B7-1, actin cytoskeleton disruption and podocyte hypermotility. Consistent with *in vivo* findings, NDP-MSH protected the MC1R-null podocytes against Adriamycin injury to a degree equal to that observed in WT podocytes, again suggesting that non-MC1R-transmitted melanocortinergic signaling is responsible for this direct podocyte protection.

Conclusions: Melanocortin therapy protects against podocyte injury and ameliorates proteinuria and glomerulopathy via a non-MC1R-mediated melanocortinergic signaling.

Funding: NIDDK Support

TH-PO997

Phospholipase A2 Receptor 1 Antibody Levels at the Time of Diagnosis Determine Renal Outcome in Patients with Membranous Nephropathy

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Background: Membranous nephropathy (MN) is an autoimmune disease caused by circulating antibodies against the podocyte protein phospholipase A_2 receptor 1 (PLA_2R1-ab) in 80% of cases. PLA_2R1-ab levels correlate with disease activity and treatment response. However, their significance on long-term renal outcome is not clear.

Methods: In this prospective observational multicenter study we investigated the predictive role of PLA_2R1-ab levels for long-term renal outcome in 243 patients with newly diagnosed, biopsy-proven PLA_2R1-associated MN, who had received no immunosuppressive treatment prior to study enrollment. The median follow-up time was 48 months. The primary endpoint was defined as doubling of serum creatinine or development of end-stage renal disease. PLA_2R1-ab levels, proteinuria and serum creatinine were prospectively measured every three months.

Results: 243 patients (171, 70% males; median age 55 years, IQR: 43–66 years) were included in the study. Thirty-six (15%) of the 243 patients reached the study endpoint. Multivariate Cox regression analyses adjusting for all clinical relevant parameters revealed that the following independent predictors significantly increased the risk for reaching the study endpoint: PLA_2R1-ab levels (HR=1.36, 95%CI 1.11–1.66, p=0.003), percentage of tubular atrophy and interstitial fibrosis in the biopsy (HR=1.32, 95%CI 1.03–1.68, p=0.030), relapse of PLA_2R1-ab during follow-up (HR=3.22, 95%CI 1.36–7.60, p=0.008), and relapse of proteinuria (HR=2.60, 95%CI 1.17–5.79, p=0.019). Fifty-four (22%) patients received no immunosuppressive treatment during the study. In 41 (76%) of these patients PLA_2R1-ab spontaneously disappeared during the follow-up, 29 (54%) of them had a complete remission of proteinuria, and 19 (35%) a partial remission. Patients who were not treated with immunosuppressives were more often female and had lower PLA_2R1-ab levels, proteinuria, and serum creatinine at baseline compared to patients receiving immunosuppression.

Conclusions: PLA_2R1-ab levels are, in addition to pre-existing renal damage, a predictive factor for long-term outcome in patients with MN and should be considered when deciding on treatment of these patients.

Funding: Government Support - Non-U.S.

TH-PO998

Anti-PLA2R Antibodies and Outcome in Patients with Membranous Nephropathy

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Background: Personalized treatment for patients with membranous nephropathy (MN) requires accurate prediction of disease course at an early stage. We evaluated the added value of including level of anti-PLA2R antibodies (PLA2Rab) and epitope spreading at baseline in prediction models.

Methods: We included untreated patients with PLA2R-related MN who were referred to our clinic between 1995 and 2016. Patients with nephrotic range proteinuria (UPCR ≥ 3 gram/10 mmol in 24-hours urine) and a creatinine level of ≤ 135 umol/l were included. Outcomes were progression, defined as the need for immunosuppressive therapy because of an increase of serum creatinine level of >30 % from baseline or severe persistent nephrotic syndrome, and spontaneous remission as a competing event. We fitted a Fine and Gray survival model to simultaneously predict the probabilities of progression and spontaneous remission. We included serum creatinine, UPCR and the urinary excretion of $\alpha_1$microglobulin as known prognostic markers, and added sequentially baseline PLA2Rab titers (ELISA) and epitope spreading. We estimated bootstrapped C-statistics and obtained calibration plots at twelve-month intervals during follow-up.

Results: We included 142 patients. Univariate comparison of progressors vs non-progressors is presented in Table 1. Neither PLA2Rab titer nor epitope spreading improved prognostic predictions when combined with known prognostic markers. The C-statistics for respectively progression and remission were between 0.71 and 0.70 at 12 and 60 months follow-up, respectively. The model was well calibrated for both progression and remission.

Conclusions: Whereas baseline PLA2Rab titer and epitope spreading predicted response to treatment in patients with MN, our data from this cohort suggest that their added value over and beyond traditional risk biomarkers for predicting spontaneous remission may be limited.

	Progressors n=92	Non-progressors n=30	P value
Age (years)	53 ± 13	52 ± 13	0.67
Gender (males %)	64 %	72 %	0.56
Screatinine (µmol/l)	95 [81-109]	88 [81-94]	0.07
UPCR (g/10 mmol)	8.2 [6.0-11.17]	5.8 [4.6-7.9]	0.008
Ucl microglobulin (µg/min)	63 [33-96]	30 [20-43]	<.001
aPLA2R titer (RU/ml)	126 [69-248]	54 [33-147]	0.03
Spreading (%)	71 (77 %)	33 (66 %)	0.17
CR CR and 1 epitope CR and 2 epitopes	21 (23 %) 41 (45 %) 30 (33 %)	17 (34 %) 25 (50 %) 8 (16 %)	0.08

TH-PO999

Differences in Outcome in Patients with Membranous Nephropathy with and Without Anti-PLA2R Antibodies

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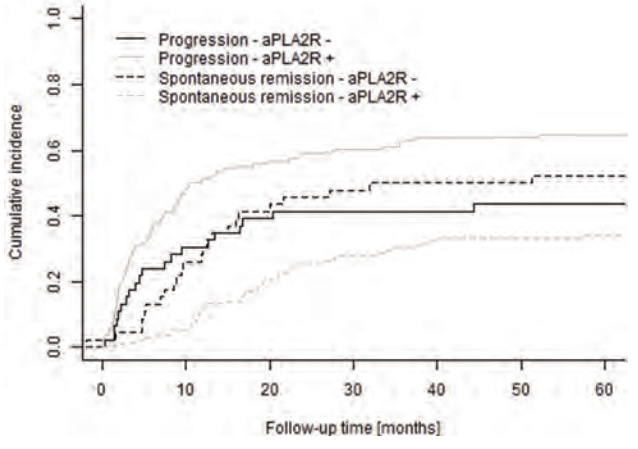
Background: The identification of autoantibodies against PLA2R1 (PLA2Rab) defined membranous nephropathy as an auto-immune disease. There is debate if outcome is different in PLA2Rab-positive and PLA2Rab-negative patients. We evaluated differences in the natural course of primary MN between PLA2Rab-positive and PLA2Rab-negative patients.

Methods: We included untreated patients with MN who were referred to our clinic between 1995 and 2016. Inclusion criteria were nephrotic range proteinuria (Upcr ≥ 3 gram/10 mmol) and a serum creatinine level of ≤ 135 µmol/l. Primary outcome was spontaneous remission, both partial and complete, or progression, defined as the need for immunosuppressive therapy because of an increase of serum creatinine level > 30% or severe persistent nephrotic syndrome. In stored samples PLA2Rab were measured with ELISA (Euroimmun®). A cut-off value of < 14 RU/ml was used to define seronegativity.

Results: In total 182 patients were included. PLA2Rab were detected in 75 % of patients. Clinical characteristics were similar between both groups (table 1). During follow-up, 65% of PLA2Rab-positive patients needed immunosuppressive therapy versus 48% of seronegative patients. At 60 months of follow-up, cumulative incidence of spontaneous remission was 52% vs 34% (p = 0.008) and progression was 43% vs 65% (p=0.02) for PLA2Rab-negative compared to positive patients.

Conclusions: The natural course of MN is more favorable in PLA2Rab-negative patients.

	aPLA2R pos N= 136	aPLA2R neg N=46	P value
Age (yrs)	53 ± 13	55 ± 17	0.449
Gender (% males)	67 %	65 %	0.858
Screatinine (µmol/l)	91 ± 17	88 ± 20	0.303
Upcr (g/10 mmol)	7.2 [5.5-10.9]	7.8 [4.7-9.9]	0.865
PLA2Rab titer (RU/ml)	114 [53-228]	-	-
Interval biopsy and measurement (mo)	2.7 [1.2-9.1]	2.6 [1.5-9.9]	0.865



TH-PO1000

Levels of Anti-PLA2R Antibodies Predictive of Renal Prognosis in Japanese Patients with PLA2R-Associated Primary Membranous Nephropathy

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Background: Measurement of circulating levels of autoantibody against phospholipase A2 receptor (PLA2R) antibody at diagnosis is important for not only differentiation but also for prediction of renal prognosis. Recent studies suggest that a poor renal outcome mainly occurs in patients with PLA2R-associated primary membranous nephropathy (pMN) who have a high level of anti-PLA2R antibody (aPLA2R-Abs) at diagnosis. This study investigated the association between aPLA2R-Abs levels and renal prognosis in Japanese patients with PLA2R-associated pMN.

Methods: We retrospectively enrolled 53 consecutive Japanese patients with biopsy-proven PLA2R-associated pMN (males, 38; median age, 64 [IQR 53-69] years old; observation period, 62 [43-91] months, urinary protein levels, 5 [4-9] g/day) admitted to our hospitals between January 2003 and December 2012. The primary outcome was the cumulative rate of 1.5-fold increase in serum creatinine and all-cause death. Sera were collected at the time of renal biopsy. We identified the levels of aPLA2R-Abs predictive of renal prognosis on the basis of C-index calculated with Cox proportional hazards models.

Results: Median levels of aPLA2R-Abs at diagnosis were 62 [IQR 32-165] RU/ml. Patients with ≥50 RU/ml (35 of 53) showed lower renal survival rates and more reached the outcomes compared to those with <50 RU/ml (17 of 35 vs. 1 of 18, p=0.01). Patients with ≥50 RU/ml also showed significantly lower serum albumin at baseline and received more frequent remission-induction immunosuppressive therapies (p<0.01, p=0.01, respectively). Cox proportional hazards models indicated that a level of ≥50 RU/ml at diagnosis predicted poor renal prognosis (adjusted hazard ratio by age, sex, urinary protein levels and use of immunosuppressive agents within 1 year, 8.3 [95% confidence interval 1.1–62.5, p=0.01]).

Conclusions: APLA2R-Abs levels of ≥50 RU/ml at diagnosis could help predict poor renal prognosis in Japanese patients with PLA2R-associated pMN.

TH-PO1001

Determination of Anti-PLA2R and Anti-THSD7A Antibodies in Brazilian Patients with Idiopathic and Lupus Membranous Nephropathy

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Background: Membranous Nephropathy (MN) is a common cause of nephrotic syndrome in adults. In Brazil, it is the second most frequent cause of glomerulopathies. Incidence variations in between the various studies may reflect patterns of biopsy indication in different countries however, it may also be related to socioeconomical, ethnical or environmental characteristics. In the past years, the role of anti-phospholipase A2 (anti-PLA2R) receptor autoantibodies and the antibody against THSD7A (thrombospondin type 1 domain containing protein 7A) in the pathogenesis of idiopathic MN were described. The determination of these serum and renal tissue antibodies have not yet been performed in the Brazilian population.

Methods: Blood samples were collected from 26 patients diagnosed with MN and 13 patients with Lupus Membranous Nephropathy (LMN), confirmed by renal tissue biopsy (OM and IF). The anti-PLA2R antibody was measured by the ELISA and IIFT techniques and antibodies against THSD7A by IIFT. In addition, routine tests of renal function and proteinuria were also collected. Patients will be followed and evaluated after 6 months and 1 year of the initial consultation.

Results: All 13 patients with LMN were negative for anti - PLA2R and anti - THSD7. A total of 26 patients with MN tested negative for anti - THSD7A. Out of 26 patients, 13 (50%) were anti-PLA2R negative by both ELISA and IIFT. On the other hand, 10 patients (38.4%) were positive by both methods and 3 patients were positive only by IIFT and had intermediate titers by ELISA method, resulting in 13 positive patients (50%). Proteinuria levels in ELISA and IIFT negative patients were 1.98g / vol, 6.7g / vol for ELISA and IIFT positive patients and 2.96g / vol for intermediate ELISA and IIFT positive patients, respectively. In this sample, there was a positive correlation between the anti - PLA2R titers and the levels of proteinuria.

Conclusions: In this Brazilian population of MN patients, there was a 50% positivity for anti - PLA2R. The IIFT technique was more sensitive than the ELISA test. No patient was positive for anti-THSD7A. All patients with LMN were negative for both antibodies. There was a positive correlation between the anti - PLA2R antibodies serum levels and the degree of proteinuria.

Funding: Government Support - Non-U.S.

TH-PO1002

Combined Assessment of Serum Anti-PLA2Rabs and Glomerular PLA2Rags Deposition in Patients with Membranous Nephropathy (MN)

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Background: MN is the most common cause of nephrotic syndrome in adults. The involvement of PLA2R (Ags and Abs) in the pathogenesis of the disease (idiopathic MN) is investigated. The purpose of the study was to correlate the glomerular deposition of PLA2R-antigens (Ags) and circulating serum anti-PA2R-antibodies (Abs) to renal function (eGFR), proteinuria and clinical outcome in patients with idiopathic MN.

Methods: Twenty patients with idiopathic MN met the study criteria. Initial eGFR and proteinuria were recorded at months 0 and 6 as well as the clinical outcome after treatment. Glomerular PLA2R-Ags deposition intensities (mild, moderate, strong) were evaluated with immunohistochemistry. Serum anti-PLA2R-Abs (detectable / undetectable) were also evaluated.

Results: Positive PLA2R-Ags was detected at 81.25%, while detectable anti-PLA2R-Abs in 62.5% of patients. Mean proteinuria values at months 0 and 6 were 9.1 grams and 1.8 grams / 24 hours, respectively. Mean eGFR at months 0 and 6 was 73.1 ml / min / 1.73 m^2 and 75.83 ml / min / 1.73 m^2. Strong glomerular PLA2R-Ags deposition was positively correlated with renal function at time 0 ($p < 0.05$) and reduction in proteinuria at 6 months ($p < 0.01$). Serum anti-PLA2R-Abs levels were not correlated with eGFR and proteinuria at 0 and 6 months. Our results are not in accordance with the literature, probably due to early refferal of the patients.

Conclusions: In conclusion glomerular PLA2R-Ags deposition appears to be more closely correlated with renal function and the rate of proteinuria reduction than serum anti-PLA2R-Abs in patients with idiopathic MN. More studies are needed to prove this predictive role.

TH-PO1003

Optimization of the Cutoff Value for a Commercial Anti-PLA2R ELISA to Diagnose PLA2R-Associated Membranous Nephropathy in Japanese Patients

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Background: Anti-PLA2R antibodies (aPLA2R-Ab) is a potentially useful diagnostic and therapeutic biomarkers for PLA2R-associated primary membranous nephropathy (PLA2R-pMN). aPLA2R-Ab titer is easily quantified by a commercial ELISA kit. However, we observed more false-negative results in our experiments in Japan, when considering the manufacturer's cutoff value (14 RU/ml) for ELISA than with western blot (WB) analysis and a commercial IIFT-CBA, indicating that the manufacture's cutoff value is too high for the diagnosis of aPLA2R-Ab in Japanese PLA2R-pMN patients. Hence, it is important to optimize the cutoff value for ELISA in each region. This study aimed to investigate the optimal index cutoff value of the commercial aPLA2R-Ab ELISA kit for Japanese patients with PLA2R-pMN.

Methods: The aPLA2R-AB in serum samples from 117 patients with biopsy-proven primary membranous nephropathy (MN) were measured by WB and commercial ELISA (EUROIMMUN AG). WB analysis was performed under non-reducing condition and with diluted sera at x1/101. The ELISA was used in accordance with the manufacturer's instructions. Primary MN patients were divided into an aPLA2R-Ab-positive group and a -negative group per the results of WB. Receiver operating characteristic (ROC) curves were plotted to generate the cutoff value for screening aPLA2R-Ab positive patients diagnosed via WB analysis from among all patients with pMN. Furthermore, to confirm the absence of changes in specificity, disease control sera from 30 each patients with secondary MN and other glomerulonephritis were measured by the ELISA.

Results: WB revealed that of 117 patients with pMN, 59 were aPLA2R-Ab-positive; 58, -negative. ROC curve analysis revealed a cutoff value of 5 RU/ml with a sensitivity and specificity of 50% and 93%, respectively. With a cutoff value of 5 RU/ml, none of the aPLA2R-Ab-positive serum samples were screened from disease control groups. The index cutoff value decreased from 14 to 5 RU/ml, thereby improving the sensitivity of the aPLA2R-Ab ELISA from 39% to 48%.

Conclusions: The optimal cutoff value of the aPLA2R-Ab ELISA for Japanese patients with PLA2R-pMN is 5 RU/ml. The cutoff value, thus optimized, of the ELISA enhanced the interpretation and confidence levels in the screening of PLA2R-pMN and eliminated the need for confirmation via WB analysis.

Funding: Government Support - Non-U.S.

TH-PO1004

An Indian Experience with M-Type Phospholipase A2 Receptor (PLA2R) Antibody in Membranous Nephropathy

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Background: Membranous Nephropathy(MN) is one of the common cause of nephrotic syndrome in adults. We present our data, one of the first studies from India, on sensitivity of tissue and serum PLA2R in Membranous nephropathy and its association with disease activity.

Methods: Treatment-naïve biopsy-proven MN patients were included. Anti-PLA2R antibody in serum and PLA2R antigen in tissue was tested at the time of first diagnosis. Disease activity was assessed by measurement of proteinuria, serum albumin and renal function. Detailed history, examination and investigations were performed to rule out a secondary cause of MN.

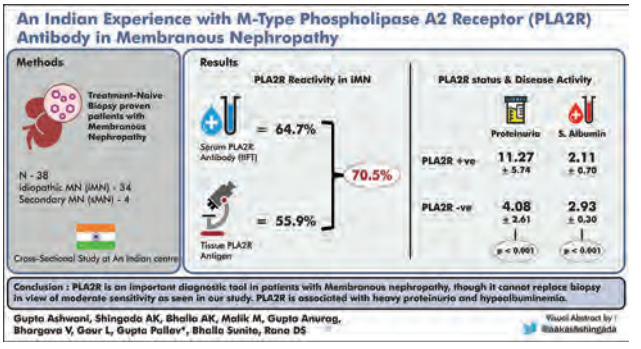
Results: We included 38 patients in the study. Mean age was 45.09 +/- 14.29 yrs (27 males & 11 females). A secondary cause of MN was found in 4/38(10.5%). PLA2R (either serum or tissue) was positive in 25/38(65.8%) patients; 24/34(70.5%) in iMN and 1/4(25%) in secondary MN. Pattern of PLA2R positivity in iMN has been described in the image. PLA2R was associated with heavier proteinuria (11.27 ± 5.74gm/d) vs (4.08 ± 2.61gm) in patients negative for PLA2R($p<0.001$) and significant hypoalbuminemia with serum albumin 2.11g/dl ± 0.7g/dl in PLA2R positive patients vs 2.93 ± 0.3g/dl in patients negative for PLA2R($p<0.001$). No difference was found in serum creatinine between the groups (PLA2R positive - 1.03 ± 0.35 mg/dl vs PLA2R negative – 0.91 ± 0.29mg/dl, p - 0.3).

Conclusions: Though PLA2R is an important diagnostic tool in patients with Membranous nephropathy, yet it cannot replace biopsy, in view of moderate sensitivity as seen in our study. PLA2R is associated with heavy proteinuria and hypoalbuminemia.

Pattern of PLA2R positivity in Idiopathic MN (n=34)

Tissue PLA2R	Serum PLA2R reactivity: Positive	Negative	Total
Positive	17	2	19
Negative	5	10	15
Total	22	12	34

Total PLA2R reactivity – 17+5+2 = 24(out of 34 patients) – 70.5%
Tissue reactivity – 19/34(55.9%)
Serum reactivity – 22/34 (64.7%)



Visual Abstract

TH-PO1005

Transplacental Passage of Phospholipase A2 Receptor Antibodies from Maternal to Fetal Circulation and Secretion into Breastmilk

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Introduction: Phospholipase A_2 receptor (PLA_2R) was described as the major target antigen in idiopathic membranous nephropathy (IMN). During pregnancy, certain maternal antibodies transport across the placenta. Whether PLA2R-Ab crosses over from maternal to fetal circulation is still unknown. We report a case of biopsy proven maternal membranous nephropathy where there was transfer of PLA2R-Ab from maternal to fetal circulation. We further report the first case where PLA2R-Ab is secreted into mother's breast milk.

Case Description: A 33 year old female presented at 30 weeks gestation with nephrotic syndrome. Her initial PLA_2R Ab was 57 RU/mL. At 33 weeks, her pregnancy was complicated by oligohydramnios and worsening of her nephrotic syndrome. Her PLA_2R-Ab titer was noted to progressively increase from 75RU/mL at 34 weeks to 111RU/mL at 36 weeks to 161RU/mL at the time of delivery to 506 RU/mL one month post-partum. At 37 weeks, a 2.29kg male was delivered. Cord blood for PLA_2R-Ab was 59 RU/mL and infant's serum showed PLA_2R-Ab of 57 RU/mL. At 18 days, the infant's urine spot protein:creatinine ratio (P:C) was 0.8 g/g, albumin was 3.5g/dL, with the PLA_2R Ab 3RU/mL (nl). At one month, the infant's P:C normalized with serum albumin of 3.8g/dL, however his PLA_2R-Ab rose to 25RU/mL. Mother's breast milk was assessed by Western blot and IgG4 PLA_2R-Abs against full-length PLA2R were detected.

Discussion: This is the first case of biopsy proven-IMN with rising PLA_2R-Ab confirming transplacental passage of the PLA_2R Ab to the fetus. PLA_2R-Ab was detected in the cord blood and the peripheral circulation at the time of delivery which then decreased to normal by 18 days post-partum. Clinically, the infant had a low albumin level and proteinuria at 2.5 weeks post-delivery which then normalized by his one month follow up visit. Whether this reflects a mild case of neonatal membranous nephropathy is still unknown but possible. Furthermore, we have demonstrated the ability of PLA_2R-Ab to be secreted into breastmilk, likely accounting for the rise in the infant's one month titer. These findings potentially affect the future care of pregnant women with IMN as well as their newborns.

TH-PO1006

108 Cases of Idiopathic Membranous Nephropathy Patients with Clinical and Pathological Analysis

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Background: Idiopathic membranous nephropathy is the most common cause of adult nephrotic syndrome. Its onset is hidden and its progress is slow. The prognosis is different. Analyze the clinical and pathological characteristics of the patients with IMN will help us to get a better understanding of the disease process. The objective was to retrospectively analyze the clinical and pathological features of idiopathic membranous nephropathy in our single center.

Methods: The clinicopathological data of 108 patients with biopsy-proven IMN from January 2013 to December 2017 were analyzed retrospectively. IMN patients were divided into NS and non-NS groups. Analyse the clinical and pathological characteristics of these two groups.

Results: The average age was 57 years and 59.3% were male patients. Compared with patients without NS,IMN patients with NS were older,lower eGFR, higher total cholesterol, low density cholesterol and serum creatinine (P<0.05). The effective rate of conservative treatment in IMN patients without NS was 61.7%.The effective rate of immunosuppressive therapy in IMN patients with NS was 70.8%, and low serum albumin was an independent risk factor for the poor efficacy(p=0.021 OR 1.329). The effective rate of conservative treatment in IMN patients with NS was 47.3%,and low serum albumin was an independent risk factor for the poor efficacy(p=0.042 OR 1.201).

Conclusions: The remission rate of conservative treatment non-NS patients was not low. Hypoproteinemia may be a predictor of poor efficacy with NS patients.

Funding: Government Support - Non-U.S.

TH-PO1007

Associations of HLA Class II Alleles with Clinical Phenotype and Outcome in Patients with Primary Membranous Nephropathy: A Single Amino Acid Makes the Difference

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Background: GWAS and HLA genotyping have revealed associations between HLA alleles and susceptibility to primary membranous nephropathy(pMN), but the associations with clinical phenotypes and kidney outcome are underinvestigated.

Methods: Patients with pMN were included. Associations between HLA alleles and clinical variants were analyzed by Logistic regression. Risk factors for kidney outcome were analyzed by Kaplan-Meier curve and COX regression. Structure of HLA molecules were modelled.

Results: DRB1*0301 was associated with higher level of PLA2R-Ab (OR=1.58, 95%CI 1.13-2.22, *P*=0.008). Although DRB1*1502 differs from DRB1*1501 by a single amino acid and was not risk allele for pMN, it was associated with lower eGFR both at baseline (OR=1.79, 95%CI 1.18-2.72, *P*=0.006) and last follow-up (OR=1.72, 95%CI 1.17-2.53, *P*=0.006), worse renal outcome (*P*=0.013) and higher risk of ESRD (HR=4.52, 95%CI 1.22-16.74, *P*=0.024). DRB1*1502 correlated to higher PLA2R-Ab level [161.4 (28.1, 268.0) vs. 36.3 (2.8, 130.5) U/mL, P=0.013] and showed interaction with DRB1*0301 for the variable(*P*=0.049). Homologous modelling showed the amino acid on position 86 is a valine in DRB1*1501, but a glycine in DRB1*1502, the latter facilitating the formation of a larger pocket 1 in the binding groove.

Conclusions: Our findings show that HLA genes control PLA2R antibody production and pMN severity and outcome. They additionally suggest that DRB1*1502 behaves like a modifier gene with a strong predictor value when associated with HLA risk alleles.

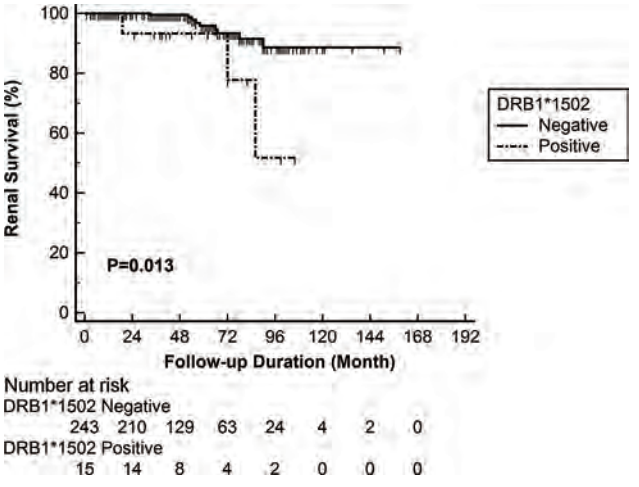

Figure 1. Renal survival curves in pMN patients.

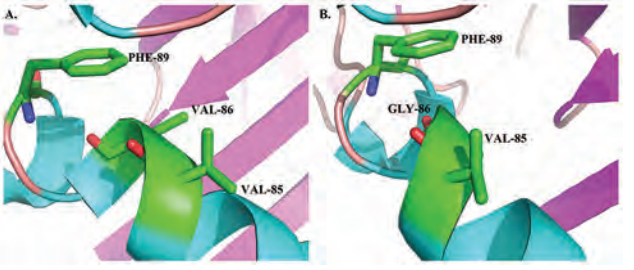

Figure 2. Structure models of pocket 1 of DRB1*1501 and DRB1*1502.

TH-PO1008

The Role of Fumarate on the Outcomes of Membranous Nephropathy: Urine Metabolomics Analysis and Its Experimental Validation

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Background: Anti-PLA_2R antibody (PLA2R Ab) is a useful biomarker in membranous nephropathy (MN), however, the levels of PLA_2R Ab do not always predict the prognosis or treatment response. There are need to seek additional biomarker to predict both of immunosuppressive agent response and renal prognosis. Also, it is not yet known how PLA_2R Ab-antigen reaction causes the changes in podocytes and become a pathogenicity of MN. We aimed to figure out biomarkers predicting the prognosis and treatment response using metabolomics analysis of urine samples.

Methods: The nuclear magnetic resonance-based method was used to examine the urine samples at the time of kidney biopsy from patients with PLA_2R-associated MN and minimal change disease (MCD). The negative control was urine samples from healthy controls.

Results: Metabolites significantly higher in PLA_2R-associated MN than healthy controls were fumarate, choline, mannitol, isoleucine, glucose, valine, leucine, tyrosine, and betaine. Fumarate was the only differential metabolite in PLA_2R-associated MN compared with MCD. PLA_2R-associated MN patients with high urine fumarate levels had a greater risk of composite renal outcome and lower likelihood of having treatment response and achieving remission. The *in-vitro* validation study was performed using primary cultured human podocytes treated with IgG purified from a patient with PLA_2R-associated MN (MN IgG). PLA_2R Ab-antigen interaction in MN IgG stimulated podocytes was confirmed and further identified increased the expression of both fibronectin and Snail, despite decreased fumarate hydratase, WT-1, and ZO-1 expression. Lentivirus-mediated fumarate hydratase activation showed improvement of fumarate hydratase, WT-1 and ZO-1, and attenuation of expression in fibronectin and Snail. Albumin permeability test confirmed that absorbance of albumin was increased in podocytes after activation of MN IgG. The fluorescence intensity of ZO-1 was decreased in podocytes by stimulation of MN IgG. Albumin absorbance and fluorescence intensity of ZO-1 in podocytes were reversed by activation of fumarate hydratase.

Conclusions: These findings suggest that fumarate might play an important role in the progression and disease activity of PLA_2R-associated MN via the regulation of podocyte integrity and renal fibrosis.

TH-PO1009

Serum GDH-15 Predicts the Outcome of Idiopathic Membranous Nephropathy

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Background: Idiopathic membranous nephropathy (IMN) is a major cause of nephrotic syndrome. Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β superfamily and has been associated with chronic inflammatory disease. It has the potential to be a useful prognostic marker in patients with renal diseases, such as diabetic nephropathy and IgA nephropathy. This study examined whether GDF-15 is associated with the clinical parameters in IMN and showed that GDF-15 can predict IMN disease progression.

Methods: A total of 35 patients with biopsy-proven IMN, treated at Chungnam National University Hospital from January 2010 to December 2015, were included. Patients younger than 18 years, those with secondary membranous nephropathy, and those lost to follow-up before 12 months were excluded. Levels of GDF-15 at the time of biopsy were measured using enzymelinked immunosorbent assays. Disease progression was defined as a ≥30% decline in estimated glomerular filtration rate (eGFR) or the development of end-stage renal disease.

Results: The mean follow-up was 44.1 months (range: 16–72 months). Using receiver operating curve analysis, the best serum GDF-15 cut-off value for predicting disease progression was 2.15 ng/ml (sensitivity: 75.0%, specificity: 82.1%, p = 0 007). GDF-15 was significantly related to age and initial renal function. In the Kaplan-Meier analysis, the risk of disease progression increased in patients with GDF-15 ≥ 2.15 ng/ml when compared with those with GDF-15 < 2.15 ng/ml (50.0% versus 9.7%) (p = 0 012). In the multivariate Cox regression analysis adjusted for potential confounders, only GDF-15 was significantly associated with disease progression in IMN (p = 0 032).

Conclusions: The GDF-15 level at the time of diagnosis has a significant negative correlation with initial renal function and is associated with a poor prognosis in IMN. Our results suggest that GDF-15 provides useful prognostic information in patients with IMN.

TH-PO1010

Novel ELISA for THSD7A Autoantibodies in Membranous Nephropathy

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Background: In 2014, THSD7A was identified as a second autoantigen for 2-5% of membranous nephropathy (MN) patients whereas PLA2R1 is the major autoantigen for 70% of patients. Detection and accurate measurement of anti-PLA2R1 and anti-THSD7A titers provide key biomarkers to diagnose MN, monitor disease activity and predict clinical outcome. To date, antibodies in THSD7A-associated MN patients are only evaluated semi-quantitatively by WB and IIFT. We aimed to develop a robust and rapid assay for the quantitative measurement of antibody levels in THSD7A-associated MN patients.

Methods: Screening of 1012 biopsy-proven MN patients led to the identification of 28 THSD7A-positive patients by ELISA. Screening of additional MN patients, mostly PLA2R1-negative, identified 21 more cases, establishing the largest cohort of 49 THSD7A-positive patients to date. We validated the positivity of the 49 patients by ELISA, WB, IIFT and biopsy staining. We analyzed the clinical parameters of this population for age, gender, disease activity and possible links to etiology including malignancy. We described eight patients double positive for THSD7A and PLA2R1 antibodies.

Results: The novel ELISA and commercial IIFT titers correlated significantly (p<0.0001). Among the 49 patients with anti-THSD7A antibodies, 57% were males. Females were younger than males (49 versus 67 years, p=0.003). Levels of anti-THSD7A antibodies were similar between male and female patients and correlated with disease activity and treatment efficacy. The double positive patients had varying antibody titers for both antigens and displayed no clinical difference compared to the rest of the population. Patients with a history of malignancy (16%) were older than others (76 versus 54 years old, p=0.002) and only 3 were diagnosed for malignancy within 2 years of MN diagnosis.

Conclusions: This novel ELISA assay can be used to identify patients with THSD7A-associated MN and monitor antibodies during follow-up. Our data suggest a weak association between MN and malignancy in our population of THSD7A-positive patients.

Funding: Government Support - Non-U.S.

TH-PO1011

Membranous Nephropathy at Diagnosis and Follow-Up: Comparison Between Elderly and Young Patients

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Background: This study aims to evaluate the epidemiological profile between elderly and young patients with Membranous Nephropathy (MN) diagnosed in a single center.

Methods: This was a retrospective cohort study from 1999 to 2017, where clinical, epidemiological, laboratory and histological data of patients with MN accompanied by the Nephrology Department of the Hospital das Clinicas de São Paulo were evaluated. The only exclusion criterion was to have a diagnosis of Systemic Lupus Erythematosus at the time of the renal biopsy.

Results: In these period 219 patients had renal biopsy proving MN, presenting a mean age of 45.3 ± 15.7 years and 53.8% of women. Laboratory data at diagnosis were: serum creatinine median of 1.0 (0.8-1.7) mg/dl; median proteinuria of 6.0 (3.0-8.8) g/day and serum albumin median of 1.8 (1.2-2.5) g/dL. There were 48.4% of patients with hypertension and 35.6% with hematuria at diagnosis. A total of 44 (20%) patients were elderly at diagnosis and comparation with the young patients are in table 1.. Forty patients (18.2%) presented secondary causes, being infectious causes in 18, with hepatitis B in 4 patients; autoimmune causes in 11, with rheumatoid arthritis in 3; and cancer in 11.

Conclusions: MN showed a different epidemiological profile among young and elderly patients, with a predominance of men, hypertension, and increased serum initial creatinine in the latter group. The secondary forms corresponded to less than 20% in these cases, predominating the infectious and autoimmune etiologies.

Comparison between elderly and young patients with MN

	Elderly (≥ 60 years) n=44	Young (<60 years) n=175	p
Male (n/%)	28/63.6	73/41.7	<.05
Hematuria (n/%)	19/43.1	59/33.7	ns
Proteinuria (g/day) -median (quartiles)	5.3 (3.2-8.0)	6.0 (2.9-9.2)	ns
Initial Serum creatinine (mg/dL) - median (quartiles)	1.3 (1.0-2.3)	1.0 (0.7-1.4)	<.05
Arterial hypertension (n/%)	31/70.4	75/42.8	<.05
Infectious etiology (n)	3	15	ns
Autoimmune etiology (n)	2	9	ns
Cancer etiology (n)	4	7	ns
Renal replacement therapy (n/%)	5/11.3	8/4.5	<.05
Death (n)	0	4	

ns- not significant

TH-PO1012

Polymorphisms in the Exon 1 of the MBL2 Gene Are Not Associated with a Poor Prognosis in Membranous Nephropathy

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Background: MBL2 polymorphisms may be associated with the activation of lectin pathway by IgG4 subclass antibodies in membranous nephropathy (MN). Studies involving systemic lupus erythematosus (SLE) have conflicting results, with some data sugesting the association between MBL2 polymorphisms with more severe forms of disease. We investigated whether the prognosis among patients with MN differ according to the presence or absence of these polymorphisms.

Methods: Polymorphisms in the exon 1 of the *MBL2* gene (codons 52, 54 and 57) were evaluated in 59 patients with the two main etiologies of MN in our setting: idiopathic (35 patients) and secondary to SLE (24 patients). We divided the patients into two groups according to the presence or absence of the polymorphisms and analyzed proteinuria as a response parameter after 6 months, 1 and 5 years.

Results: The 59 patients were analysed as their baseline clinical characteristics (Table 1). In both genders, as in both MN etiologies, the presence of polymorphism was predominant. There was no distinction between groups with and without polymorphism with respect to age, initial LDL, serum creatinine (SCr), proteinuria, serum Albumin (SAlb) and blood pressure. After 6 months, 1 year and 5 years, there was no difference in relation to SCr and SAlb among the groups evaluated. No differences in mean and median levels of proteinuria were observed when we compared the patientes with and without *MBL2* polymorphisms after 6 months (4.1 x 3.8, p = 0.838), 1 year (2.1 x 1.7, p = 0.876) and 5 years (0.2 x 1.0, p = 0.110),.

Conclusions: Our data did not support the hypothesis that *MBL2* polymorphisms may be associated with a poor prognosis in patients with MN. Because of the small number of subjects studied, a larger study of MN patients would seem necessary to confirm these findings.

Table 1 Clinical characteristics of patients with MN according to the presence or absence of MBL2 polymorphisms

Characteristics	Polymorphisms in the exon 1 of the MBL2 gene		p-value
	Yes	No	
Number of patients n (%)	50 (83,3)	10 (16,7)	
Baseline Characteristics			
Age (yr) (mean ± SD)	37,3 ± 13,4	38,1 ± 13,4	0,857 #
Males n(%) / Females n(%)	22 (78,6) / 27 (87,1)	6 (21,4) / 4 (12,9)	0,494 *
SBP (mean ± SD)	119,5 ± 26,1	127,2 ± 16,5	0,388 #
DBP(mean ± SD)	78,5 ± 14,9	81,0 ± 13,1	0,596 #
Proteinuria, g/day (median (Q1;Q3))	8,4 (4,7; 11,5)	5,0 (2,5; 7,4)	0,110 **
Serum albumin, g/dl (median (Q1;Q3))	1,9 ± 0,6	2,4 ± 0,9	0,115 #
Serum LDL, mg/dl (median (Q1;Q3))	272,6 ± 172,5	205,7 ± 96,9	0,160 #
SCr, mg/dl (median (Q1;Q3))	0,8 (0,6; 1,0)	0,9 (0,7; 1,2)	0,311 **
Etiology			
Idiopathic n(%)	29 (82,9)	6 (17,1)	1,000 *
Secundary n(%)	20 (83,3)	4 (16,7)	
Immunosuppression			
Yes n(%)	43 (86,0)	7 (14,0)	0,304 *
No n(%)	5 (71,4)	2 (28,6)	
Disease Follow-up (mo) (mean ± SD)	55,3 ± 21,0	57,0 ± 36,1	0,893 *

SCr: Serum Creatinine / SBP: Systolic Blood Pressure / DBP: Diastolic Blood Pressure
(#)Student t test / (*) Fisher's exact test / (**)Mann-Whitney test

TH-PO1013

Elevated Level of Urinary Angiotensinogen Is Correlated with Severity of Idiopathic Membranous Nephropathy (IMN)

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Background: The severity of IMN is a main concern for making a decision whether a patient should be treated with immunosuppressive agents as the treatment will predispose the patient to opportunistic infections. Urinary angiotensinogen (UAGT) has been shown highly correlated with the severity of chronic kidney disease and its relationship with severity of IMN was explored.

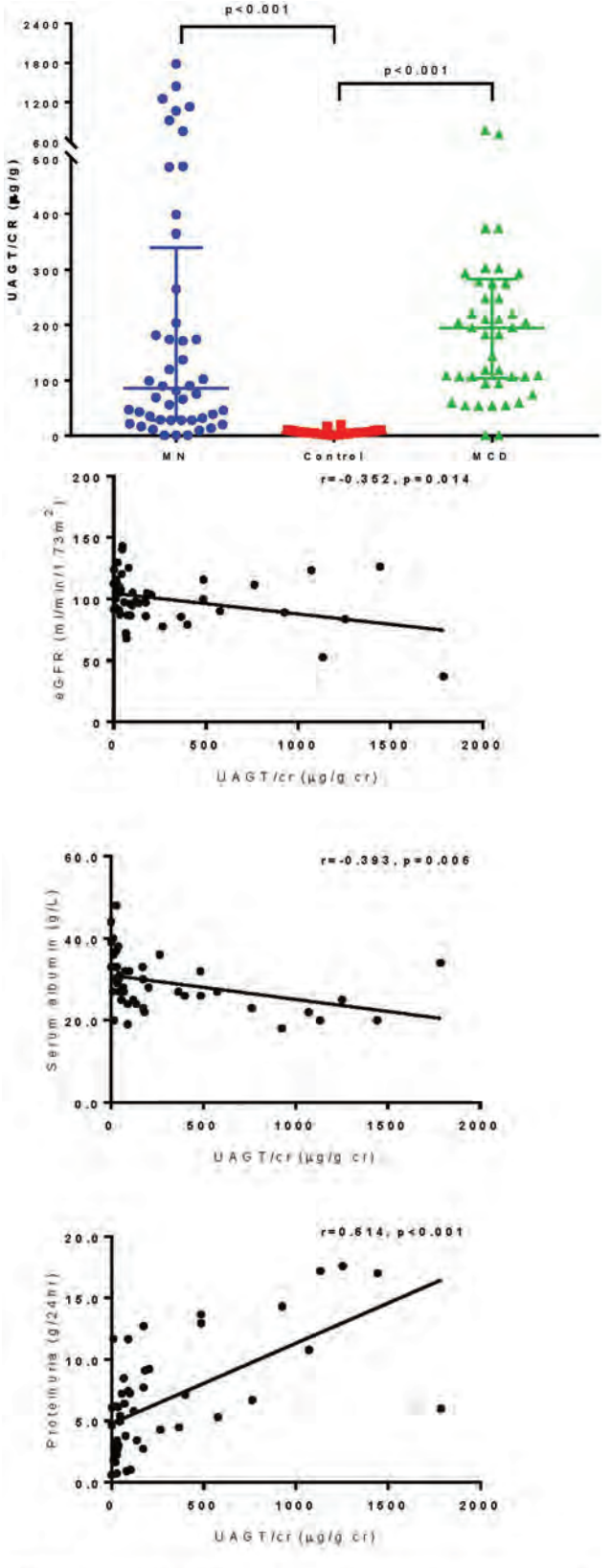
Methods: Data were collected from 48 biopsy-proven IMN, 46 minimal change disease (MCD), and 44 healthy controls. Urine samples were collected before the use of RAS inhibitors. UAGT levels were determined with a method of ELISA.

Results: UAGT levels were not different between IMN and MCD patients, but both of them were higher than those of normal subjects. In IMN patients, UAGT was correlated with serum albumin, estimated glomerular filtration rate and proteinuria. These associations

were not found in MCD patients. Multivariate regression showed that only proteinuria independently determinate the value of UAGT (β=0.649, p<0.001) in IMN patients. ROC curve analysis showed that proteinuria >7.8g/d was associated with higher UAGT level (sensitivity=55.00% specificity=89.29%, p=0.001).

Conclusions: UAGT level is one of severity markers of IMN and may serve as a cofactor in making a treatment decision.

Funding: Government Support - Non-U.S.



UAGT was correlated with eGFR, serum albumin, and proteinuria.

TH-PO1014

Clinical Implications of Pathological Features of Primary Membranous Nephropathy

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Background: The clinical outcome varies considerably in primary membranous nephropathy (pMN). It was controversial whether the histopathological features of pMN could predict treatment response and kidney outcome.

Methods: A retrospective study was conducted in 371 patients with biopsy-proven pMN. Pathological parameters included immunofluorescence staining, membranous Churg's stages, sclerosis, crescent, focal segmental sclerosis lesion, chronic and acute tubulointerstitial injury.

Results: We found that patients with higher intensity of C3 staining, advanced membranous stage, and more severe chronic tubulointerstitial injury presented with higher positivity rate of anti-PLA2R antibodies, higher levels of urinary protein excretion and serum creatinine, and lower level of serum albumin. Univariate Cox regression analysis showed that severe (grade=3) chronic tubulointerstitial injury was a risk factor to the kidney outcome of ESKD and over 50% reduction of eGFR. Multivariate analysis demonstrated it as an independent risk factor to ESKD.

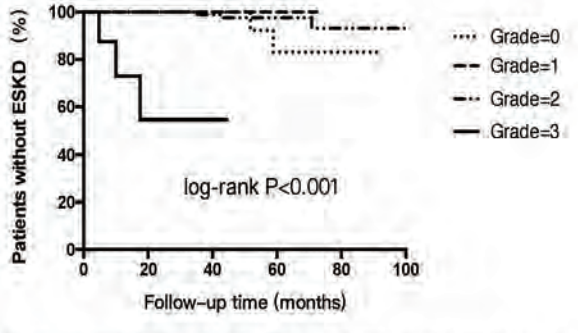
Conclusions: We found the prognostic role of chronic tubulointerstitial injury to the kidney outcome of pMN. This study highlighted the value of kidney biopsy under the widespread usage of anti-PLA2R antibodies for diagnosis and prognosis.

Table. The risk factors of ESKD in patients with pMN

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (increased by 1 year)	1.002 (0.946-1.062)	0.935		
Gender (male)	0.513 (0.230-1.142)	0.102		
Proteinuria (increased by 1g/24h)	1.066 (0.924-1.229)	0.380		
Serum albumin (increased by 1g/L)	0.952 (0.844-1.074)	0.426		
eGFR (increased by 1ml/min per 1.73m²)	0.971 (0.951-0.992)	**0.006**		
Toronto risk score	49.426 (5.758-424.264)	<0.001	5.774 (0.126-264.621)	0.369
Anti-PLA2R antibody positivity	36.361 (0.043-30631.182)	0.296		
Anti-PLA2R antibody level (increased by 20U/mL)	0.911 (0.746-1.112)	0.360		
Anti-THSD7A antibody positivity	0.049 (0.000-785.4)	0.904		
C3 staining				
negative	ref	---		
1+	1.077 (0.404-2.871)	0.882		
2+	0.991 (0.387-2.535)	0.984		
3+	0.689 (0.209-2.275)	0.542		
MN-stage				
I	ref	---		
II	3.020 (0.585-15.599)	0.187		
III	5.741 (0.514-64.088)	0.156		
Global sclerosis (increased by 1%)	0.577 (0.108-3.082)	0.577		
Crescent (increased by 1%)	0.530 (0.057-4.940)	0.578		
Focal segmental glomerular sclerosis (increased by 1%)	0.644 (0.048-8.623)	0.740		
Chronic tubulointerstitial injury				
Grade=0	ref	---	ref	---
Grade=1	0.000 (0.000-0.000)	0.985	0.134 (0.000-511.254)	0.995
Grade=2	0.445 (0.073-2.702)	0.379	1591.985 (0.000-1835.126)	0.959
Grade=3	61.016 (7.747-480.574)	**<0.001**	28485.888(0.000-32700.127)	0.943
Acute tubulointerstitial injury	6.941 (1.649-29.217)	**0.008**	2350.418 (0.000-2947.104)	0.948
Treatments				
ACEI/ARBs	ref	---		
Cyclophosphamide with corticosteroids	3.002 (0.501-18.003)	0.229		
Calcineurin inhibitor w/o corticosteroids	3.479 (0.490-24.722)	0.213		
No remission	14.939 (2.981-68.970)	**0.001**	6.008 (0.526-68.563)	0.149

HR: hazard ratio, CI confidence interval.

Figure. Kaplan–Meier curves analysis for the end stage kidney disease (ESKD) in patients with pMN, with a comparison among the patients with different severity of chronic tubulointerstitial injury.



The patients with severe tubulointerstitial injury (grade 3) had worse kidney outcome during follow-up.

TH-PO1015

Treatment Patterns Among Adults with Membranous Nephropathy in the Cure Glomerulopathy Network (CureGN)

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Background: Patients with membranous nephropathy (MN) and risk factors for progressive disease may benefit from immunosuppressive therapy (IST). Most guidelines and expert opinion recommend a 6-12 mo observation period before initiating IST. Current practice patterns regarding choice and timing of IST in MN remain largely unknown.

Methods: CureGN is an ongoing 70-center prospective cohort study of children and adults with biopsy-proven MCD, FSGS, MN, or IgAN/IgAV. Biopsies were performed between 2010 and 2017. Descriptive statistics were used to assess choice and timing of IST after kidney biopsy. Categorical data are presented as frequencies and % and compared using χ^2 tests; continuous data as median(IQR) and compared using the Kruskal-Wallis test.

Results: As of May 2018, 303 adult MN patients were enrolled in CureGN. Of those, 274 were considered unexposed to IST prior to biopsy, including 267 who received no prior IST and 7 who received steroids alone for a maximum of 6 wks before biopsy. Characteristics at biopsy: age 53 yrs (42-63), 36% Female, 71% White, UP:C 5.7 g/g (3.6-8.5), serum albumin 2.7 g/dl (2.1-3.6), eGFR 81 ml/min/1.73m^2 (57-103). 212/274 (77%) received IST (Table 1) for a median follow-up time of 31 mo (16-50), with 74% of IST treatments started in the first 6 mo after biopsy. 140/274 (51%) received RAAS blockers by 6 mo. Patients treated with IST (vs. untreated) within the first 6 mo after biopsy had higher UP:C (7.1 vs. 4.0 g/g; p<0.01), lower serum albumin (2.4 vs. 3.3 g/dl; p<0.01) and lower eGFR (77 vs. 89; p=0.03) at time of biopsy.

Conclusions: Seventy four percent of treated patients with biopsy proven MN were started on IST within the first 6 mo after kidney biopsy. IST choices were heterogeneous and many patients were treated with steroids alone. Reasons for poor alignment with KDIGO guidelines regarding timing and choice of IST in MN require further exploration.

Funding: NIDDK Support

First therapy	N (%)	Days from biopsy until onset Median (IQR)
Never received therapy	62 (23)	---
Steroids(oral)	59 (22)	15 (6, 100)
CNI	54 (20)	108 (44, 304)
Steroids(oral)+CNI	24 (9)	88 (67, 164)
Ritux	22 (8)	193 (108, 289)
CYC(oral)	17 (6)	88 (57, 189)
Steroids(oral)+ CYC(oral)	15 (5)	44 (15, 143)
MMF	9 (3)	112 (60, 384)
Steroids(oral)+MMF	3 (1)	11 (7, 50)
Steroids(oral)+Ritux	2 (1)	55 (47, 63)
Steroids(oral)+Steroids(IV)	2 (1)	34 (9, 59)
CYC(IV)	1 (0)	55 (55, 55)
Steroids(IV)	1 (0)	356 (356, 356)
Steroids(IV)+Ritux	1 (0)	131 (131, 131)
Steroids(oral)+CNI+ CYC(IV)	1 (0)	14 (14, 14)
Steroids(oral)+Steroids(IV)+Ritux	1 (0)	197 (197, 197)

IQR, interquartile range; CNI, calcineurin inhibitors; Ritux, rituximab; MMF, mycophenolate mofetil; CYC, cyclophosphamide.

Table 1. First IST among MN adult patients with no previous exposure to IST (N=274)

TH-PO1016

Immunosuppressive Therapy for Children with Membranous Nephropathy: A Report from the Cure Glomerulopathy Network (CureGN)

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Background: Membranous nephropathy (MN) is a rare cause of nephrotic syndrome in children. Current practice patterns regarding choice and timing of immunosuppressive therapy (IST) remain largely undescribed.

Methods: CureGN is an ongoing multi-center prospective, observational cohort of children and adults with biopsy-proven MCD, FSGS, MN, or IgAN/IgAV. Biopsies were performed between 2010 and 2017. Descriptive statistics were used to assess choice and timing of IST after incident kidney biopsy. Categorical data are presented as frequencies and percentages and compared using chi-square tests; continuous data as median(IQR) and compared using the Kruskal-Wallis test.

Results: Forty-one children with MN were enrolled. Thirty participants without pre-biopsy IST exposure (N=29) or exposed to steroids only within 6 weeks before biopsy (N=1) were treated as IST naïve and included in the analysis. Median age at time of biopsy was 14 yrs (12-16). 57% were female. Median urine protein to creatinine ratio (UP:C) was 3.8 (1.3-7.4), serum albumin was 2.2 g/dl (1.7-3.1), and estimated GFR was 107 mL/min/1.73m2 (84-137). 21/30 (70%) of patient received IST (Table 1), with 81% of IST treatments started in the first 6 months after biopsy. 15/30 (50%) were treated with RAAS blockers by 6 months. Treated patients with IST (vs. untreated) by 6 months after biopsy had similar UP:C (3.8 vs. 3.4 g/g; p=0.60), serum albumin (2.4 vs. 2.1 g/dl; p=0.81) and eGFR (119 vs. 100; p=0.56) at time of biopsy.

Conclusions: Corticosteroids and calcineurin inhibitors were the main agents used in children with biopsy-proven MN. Therapies were started early within the first 6 months after biopsy in 81% of patients, deviating from current KDIGO practice guidelines.

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First therapy	N (%)	Days from biopsy until onset Median (IQR)
Never received therapy	9 (30)	---
Steroids(oral)	6 (20)	8 (2, 50)
Steroids(oral) + calcineurin inhibitors	6 (20)	46 (8, 312)
Calcineurin inhibitors	4 (13)	37 (20, 159)
Mycophenolate	2 (7)	57 (13, 100)
Rituximab	2 (7)	272 (38, 506)
Steroids(IV) + rituximab	1 (3)	4 (4, 4)

Table 1. First IST used in pediatric-onset MN patients with no IST treatment before biopsy (n=30)

TH-PO1017

Response to Therapy Is Poor in Anti-PLA2R Positive Idiopathic Membranous Nephropathy Patients as Compared to Anti-PLA2R Negative Patients

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Background: Idiopathic membranous nephropathy (IMN) is associated with Anti-PLA2R antibody expression on podocytes. We aimed to decipher the efficacy of tacrolimus (Tac) plus prednisolone, changes in anti-PLA2R level and differences in response to therapy in anti-PLA2R+ve and -ve patients.

Methods: In the study, total 101 (77 IMN and 24 seconday MN) patients were included. All secondary MN (15 diabetic, 7 lupus, 1 HBV and 1 collagen disease) were excluded. All IMN(n=77) patients were treated with combination of prednisolone (1mg/kg alternate day) and Tac 0.1mg/kg/day (target trough 6-10 ng/ml first 6 months(M) and 4-6 ng/ml for next 3M and then tapering by 1/3 each months to stop at 12M. Anti-PLA2R level was estimated at baseline, 3M, 6M,12M and end of follow-up (13 to 55, median 36 months). Total remission, complete(CR) and partial (PR), relapse and side-effects were recorded and compared between Anti-PLA2R +ve and -ve groups.

Results: Of the 77 patients, at 3M 60(77.92%) CR-37, PR-23 ; 6M 61(79.22%) CR-53, PR-8; at12M 53(68.86%) CR-47, PR-6 achieved remission. Eight (10.38%) relapsed during tapering and 16(20.77%) showed no response at 12M. At the end, 68.51% remained in remission and 31.48% relapsed. Out of 77 patients, 51 (66.3%) were anti-PLA2R +ve. Remission rate was lower in anti-PLA2R+ve than -ve (36/51 vs 24/26; p=0.03) at 3M; (36/51 vs 25/26; p=0.009) at 6M; and (31/51 vs 22/26; p=0.03) at 12M. PLA2R level was decreased by 60.38% and 77.56% at 3M and 6M respectively. Relapse rate was higher in anti-PlA2R +ve than–ve patients(P=0.02). There was significant correlations between PLA2R level and 24h proteinuria at baseline (r=0.72), 3M(r=0.81) and 6M(r=0.76). During therapy 4 patients develop new diabetes, 4 cutaneous tinea, 1 osteonecrosis of femur head, 1 carpal tunnel syndrome, 3 tremor and 10 upper GI symptoms. eGFR decreased significantly (p=0.003) by 26.5% at end, which normalized after stopping Tac. Five non-responsive patients had doubled of serum creatinine and progressively deteriorated eGFR. To note, 4 females had succesful pregnancy and delivery, of them one had relapse after delivery.

Conclusions: Anti-PLA2R+ve IMN patients had poor response and more relapses as compared to PLA2R-ve patients. Remission with Tac and pred therapy is comparable to historical Ponticelli regimen with lesser side effects.

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TH-PO1018

Treatment of Moderate and High-Risk Idiopathic Membranous Nephropathy with Intravenous Cyclophosphamide Pulses and Oral Steroid

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Background: Idiopathic membranous nephropathy (IMN) is one of the most frequent causes of nephrotic syndrome in adults with risk of progression to end-stage renal disease. Proteinuria portend worse renal outcomes and is a risk factor for cardiovascular morbidity. The standard treatment includes oral cyclophosphamide and prednisone. Little is known about the efficacy of the treatment with pulse intravenous cyclophosphamide and oral steroid in moderate and high-risk patients and the factors associated with non-response.

Methods: A retrospective cohort study was performed on the data of patients with idiopathic membranous nephropathy. We included patients with biopsy-proven IMN treated with pulses of intravenous cyclophosphamide (750 mg/m2) and oral steroid between June 2012 to December 2017. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as frequencies or proportions. Comparisons of continuous and categorical variables were performed using Student's t-test and the Chi.square test, respectively. A *p value* of <0.05 was considered statistically significant. The odds ratios (OR) with their corresponding 95% confidence intervals (CI) were estimated.

Results: Sixty-one biopsy-proven IMN patients were included. The patients were predominantly male (72.1%), with mean age of the sample of 47.75 ± 12.49 years. The average eGFR was 88.85 ± 29.92 ml/min/1.73 m2 and mean baseline proteinuria was 12.13 ± 5.4 g/day. During the median follow-up duration of 26.52 ± 21.14 months, overall remission was achieved in 82% (50 cases), partial remission in 45.9% (28 cases) and complete remission in 36.1% (22 cases). The treatment failure was observed in 18% (11 cases). Adverse events related to treatment were reported in 18%. Peak proteinuria greater than 8 g/day (OR:1429, 95% CI:1192-1713) and non-reduction of proteinuria greater than 50% at month 3 (OR:3333, 95% CI:2183-5.090) were associated with the treatment failure.

Conclusions: Pulse intravenous cyclophosphamide and oral steroid is a therapeutic alternative in the treatment of idiopathic membranous nephropathy with a low incidence of adverse events. Peak proteinuria high-risk greater than 8 g/day and non-reduction of proteinuria greater than 50% at month 3 of treatment are factors associated with treatment failure.

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TH-PO1019

Rituximab in Primary Membranous Nephropathy Systematic Review and Meta Analysis

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Background: Primary membranous nephropathy is a kidney limited, autoimmune disease caused by circulating antibodies directed against phospholipase A2 receptor (PLA2R), a cell surface trans membrane receptor expressed on the surface of podocytes of the renal glomeruli. As our understanding of PMN has evolved and B cell played a major role in PMN, there has been paradigm shift in the treatment of PMN and Rituximab has emerged as a potential treatment. **Objectives**: to assess the effects of Rituximab in primary membranous nephropathy

Methods: Search methods: we searched the following databases up to January 26, 2018: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Conferences organized by the following organizations: The American Society of Nephrology, Canadian Society of Nephrology, and International Society of Nephrology. We also search trial registries. **Selection criteria**: We included randomized controlled trials and non-randomized studies with a minimum follow-up duration of 12 month that have investigated the effect of Rituximab compared to standard of care in patients diagnosed with PMN. We assessed the following outcomes: proteinuria remission, AntiPLAR2 depletion and adverse events. **Data collection and analysis:** two reviewers independently extracted data from the **included studies**: The treatment effect (dichotomous variable) was assessed using risk ratio with 95% confidence intervals (CIs). We performed meta-analyses for 6 month and 12 month follow-ups.

Results: Main results: two randomized trials (202 participants) were included in the final analysis. At six month, RR 1.01(95% CI0.42 to 2.42) of proteinuria remission with rituximab compared to standard of care in PMN, and at twelve months RR 1.40, (95% CI 0.89 to 2.29). Additional data from three cohort studies showed RR 1.11(95% CI 0.70 to 1.76) of proteinuria remission with rituximab compared to standard of care in PMN at 12 months

Conclusions: conclusions: there is insufficient evidence to draw conclusions that rituximab is more effective with less adverse events than standard of care in primary membranous nephropathy. There is a need for further research in this area with larger sample size and longer term follow up.

TH-PO1020

Five-Year Outcomes of Idiopathic Membranous Nephropathy and Nephrotic Syndrome After a Combination Treatment with Mizoribine and Low-Dose Prednisone

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Background: Patients with idiopathic membranous nephropathy (IMN) showing persistent high-grade proteinuria have the highest risk for developing end-stage renal failure. We previously reported the favorable short-term outcomes of treatment with mizoribine followed by low-dose prednisone. The purpose of the present study was to assess the long-term efficiency of this combined treatment in a larger number of patients.

Methods: Between 2004 and 2014, 22 patients with IMN and nephrotic-range proteinuria were administered the combined treatment. Mizoribine was initiated at a dose of 150 mg/day; after 1–3 months, 20 mg/day prednisone was added. The dosage of prednisone or mizoribine was tapered according to the urinary protein-to-creatinine ratio (P/C). For some of the patients who experienced side effects, relapse, or no response (NR), other immunosuppressive regimens were substituted. We evaluated patient outcomes for up to 5 years after initiating the combination therapy. The statuses of patients who were not followed up after the achievement of complete remission (CR), defined as a decrease in urinary P/C to <0.5, were assessed through a follow-up interview

Results: Before treatment, patient urinary P/C ranged from 3.7 to 15.9 g/g. At 1, 2, and 3 years after combination therapy, 68%, 77%, and 77% of patients attained CR, respectively. The 5-year actual rates for CR, partial remission, NR, two-fold Cr increase, and death were 82%, 14%, 5%, 5%, and 0%, respectively. Sixteen patients (73%) stopped treatment after 9–53 months of combination therapy. In patients who achieved at least one CR, the 3-year actual risk of relapse was 11%. Side effects, including fracture, were observed in four patients.

Conclusions: The addition of prednisone after mizoribine monotherapy resulted in fast and safe remission in a high proportion of patients with IMN and nephrotic syndrome. The risks associated with immunotherapy might be decreased by the initial prescription of mizoribine alone, which may act as a base for establishing therapy, followed by low-dose prednisone treatment.

TH-PO1021

Mycophenolate Mofetil and Tacrolimus versus Tacrolimus Alone for the Treatment of Idiopathic Membranous Glomerulonephritis: A Randomised Controlled Trial

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Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. Tacrolimus (TAC) is effective in inducing remission of proteinuria; however relapses after TAC withdrawal are common. We aimed to investigate if the addition of mycophenolate mofetil (MMF) to TAC reduces the relapse rate of nephrotic syndrome in patients with MN after treatment withdrawal.

Methods: A single centre randomised controlled trial was undertaken from 2008 to 2014; patients with biopsy proven idiopathic MN were recruited and randomly assigned to receive MMF and TAC or TAC alone. Treatment was for 1 year initially; once patients were in remission for 12 months the MMF was stopped and TAC tapered over 6 months in both groups. The primary outcome was the efficacy of MMF in preventing relapse of nephrotic syndrome on withdrawal of TAC.

Results: We randomly assigned 40 patients, 20 of whom received MMF and TAC and 20 received TAC alone. Both groups had similar baseline characteristics. Retrospective anti phospholipase A2 receptor (PLA2R) biopsy staining showed similar PLA2R positivity in both groups. Follow up was until primary endpoint or for a minimum of 3 years. The time to relapse after treatment withdrawal was similar in the two groups. 40% of patients (n=8) in the TAC/MMF group relapsed after treatment withdrawal compared to 35% (n=7) in the TAC group; there was no statistically significant difference in the relapse rate between the two groups (p=0.77). Both treatments were equivalent in achieving remission; 85% of patients in the TAC/MMF group and 75% in the TAC group reached complete remission (p=0.7). There was a trend to earlier remission in the TAC/MMF group; median time to remission 40 weeks compared to 54 weeks with TAC alone, but this was not statistically significant (p=0.46). Both treatments were well tolerated with similar adverse events.

Conclusions: The addition of MMF to TAC did not protect from relapse of nephrotic syndrome due to idiopathic MN compared to treatment with TAC alone; both groups showed similar remission rates and adverse events. The treatment was well tolerated and further studies are needed to investigate if high risk subgroups may benefit from combination therapy.

TH-PO1022

Symptoms and Health-Related Quality of Life (HRQOL) in Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) can affect patients' HRQOL in profound and differing ways. Better understanding patient perspectives on disease experience may identify important outcomes to consider in clinical trials and facilitate more patient-centered care. To our knowledge, symptoms and HRQOL have not been richly characterized among individuals with MN. We sought to address this gap by exploring patient experiences with MN with a focus on symptoms and HRQOL.

Methods: We conducted 45-60 minute semi-structured interviews with 13 adults with primary MN. Inclusion criteria included active disease in the last 5 years and non-dialysis dependence. We used purposive sampling to achieve heterogeneity on relevant demographic and clinical characteristics. Interviews were recorded and professionally transcribed. Transcripts were coded independently by two team members and analyzed for concepts and themes.

Results: Participants ranged 40-68 years old, with 46% male and 85% Caucasian. Each had lived with MN for 1-14 years (5.3 ± 4.4), had peak proteinuria ranging from subnephrotic to 23 g, and serum albumin ranging from normal to 1.5 g/dL. Treatment regimens included steroids (N=6), cyclophosphamide (N=6), calcineurin inhibitors (N=7), rituximab (N=9), and conservative management (N=2). The most common symptoms were 1) lower extremity edema (92%), 2) fatigue (77%), 3) pain or discomfort due to swelling (62%), 4) weight gain (46%), and 5) sleep changes (38%). Other reported symptoms included cramping, itching, and irritability. We identified 5 major themes: 1) experiencing sacrifice and loss, 2) feeling powerless in the face of disease, 3) navigating uncertainty, 4) living with constant worry, and 5) developing strategies and evolving perspective to cope. Overall, participants frequently struggled with the substantial physical, emotional, social, and/or financial effects of MN; yet, with time, many developed adaptive coping skills and often changed their outlook on life for the better.

Conclusions: These data shed light on the substantial burdens born by individuals with primary MN. Development of a MN-specific patient-reported outcomes instrument that captures symptoms and HRQOL is an important next step to facilitate focus on patient-centered outcomes in research and clinical care.

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TH-PO1023

Prevalence of Renal Dysfunction Among Rheumatoid Arthritis Patients in Jordan

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Background: Rheumatoid Arthritis (RA) is an autoimmune disorder characterized by inflammation of multiple synovial joints, it can affect other organs such as kidneys. RA can affect the kidneys by direct effect of the disease itself, or secondary to the drugs used to treat the disease; both biological agents as well as simple analgesics like non-steroidal anti-inflammatory drugs(NSAIDs). Clinico-pathological correlations showed that the most common pathological findings on renal biopsy were secondary amyloidosis, membranous nephropathy, less commonly RA can cause rapidly progressive glomerulonephritis

Methods: Using our electronic records, we retrospectively evaluated RA patients in our tertiary referral hospital between 2010 – 2016 with at least one year follow up, renal dysfunction was defined as the presence of hematuria and/or at least +1 proteinuria on dipstick urine analysis on at least 2 occasions, and/or abnormal serum creatinine values. Glomerular filtration rate was calculated using CKD-EPI equation

Results: We evaluated 233 patients with a diagnosis of RA, mean age was 54.5 years, females were 84.9% vs. 15.1% for males, for baseline characteristics see Table 1. 44 patients (18.8%) presented with microscopic hematuria, 16 (6.9%) with proteinuria, only 5 (2.1%) presented with both microscopic hematuria and proteinuria. At presentation 48.2% were on NSAIDs, 16 (6.9%) patients treated with methotrexate, 52(22.3%) were treated with anti-TNF, 26 (11.1%) continued on NSAID's. At last follow up: 32 (13.7%)patients had microscopic hematuria, 22 (9.4%) with proteinuria, and 7 (3%) with both microscopic hematuria and proteinuria. eGFR at last follow up was 93.2 ml/mi (±22.3) compared to 97.1ml/min at presentation only 2 patients underwent renal biopsy, both had concomitant IgA nephropathy in their biopsies.

Conclusions: Renal dysfunction is not uncommon in RA patients, though more careful evaluation and attention to urine analysis and microscopy for renal dysfunction is required

Baseline characteristics

Age	54.5 (±47.2)
Male	40(15.1%)
Female	225(84.9%)
DM	24(9.1%)
HTN	41(15.5%)
ACEi/ARB	24(9.1%)
eGFR	97.1ml/min(±22.5)

TH-PO1024

Small Kidney Size Relative to Body Mass Is a Risk Factor for Renal Function Deterioration in IgA Nephropathy Patients

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. However, identifying IgAN patients at higher risks for renal function decline is still a challenge. Recent investigations have proposed kidney size to be a risk factor for renal function decline in kidney transplantation recipients. Therefore, this study aimed to investigate whether kidney size has an effect on renal function deterioration rate in patients with IgAN.

Methods: Retrospective analysis was preformed from electronic medical records of 516 biopsy-proven IgAN patients. Kidney length was considered as the longest longitudinal diameter from sonographic measurements obtained at the time of biopsy. The average length of both kidneys was divided by body mass index for each individual to make adjustments for subject size (BMI-adjusted kidney size). Renal outcome was defined as a composite of a ≥ 50% decline in estimated glomerular filtration rate (eGFR) from baseline or the onset of end-stage renal disease.

Results: The mean age of the patients was 40.4 ± 12.1 years and 211 patients (40.9%) were male. The mean eGFR was 79.6 ± 28.3 mL/min/1.73 m^2 and the average kidney length was 102.8 ± 8.8 mm at baseline. The median follow-up duration was 51 months. When the patients were grouped into tertiles based on BMI-adjusted kidney size, renal outcome occurred in 30 (17.0%), 25 (14.0%), and 12 (7.4%) patients in the 1st, 2nd, and 3rd tertile groups, respectively. The amount of proteinuria was lowest and eGFR was highest in the 3rd tertile of BMI-adjusted kidney size group. Multivariate Cox proportional analysis revealed that the risk of renal outcome significantly lower in the 3rd tertile group as compared to the 1st tertile group (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.21-0.93; P = 0.031). Additionally, the risk of renal outcome significantly decreased as the BMI-adjusted kidney size increased (HR, 0.55; 95% CI, 0.36-0.86; P = 0.008). These results remained robust even after adjustments were made for confounding factors including baseline eGFR and proteinuria.

Conclusions: Small kidney size could be a risk factor for renal function decline in IgA nephropathy patients. Simple sonographic kidney size measurements may help stratifying progression risk in patients with IgA nephropathy.

TH-PO1025

External Validation of the Kidney Failure Risk Equation in Biopsy Proven IgA Nephropathy

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Background: The Kidney Failure Risk Equation (KFRE) has been externally validated in over 30 multi-national multiple aetiology chronic kidney disease (CKD) cohorts. It has high discrimination and good calibration for endstage renal disease (ESRD) events. However, KFRE has not been validated in IgA nephropathy (IgAN). Risk factors for IgAN progression to ESRD may be different to those used in KFRE. Therefore, our aim was to perform an independent, external validation of the 2 and 5-year 4-variable KFRE in adults with biopsy proven IgAN.

Methods: Using electronic records for the Leicester Renal Network, UK, we assessed model performance of the 2 and 5-year 4-variable KFRE. The C-statistic was used to assess discrimination. Calibration of the KFRE was assessed using the linear predictor's calibration slope and observed versus predicted event rates plots with risk categories of 0 to <5%, ≥5% to <25% and ≥25%.

Results: The cohort consisted of 353 individuals with biopsy proven IgAN, of whom 166 had CKD stages 3-5 at their biopsy date. In CKD stages 3-5, mean age was 49.2 (SD 14.4) years, 30.1% were female, mean EPI eGFR was 37.6 l/min/1.73m^2 (SD 13.5) and median ACR was 52.2 (IQR 2.2 to 124.6) mg/mmol. 59 (35.5%) ESRD events occurred over median follow-up of 3.6 (IQR 1.5 to 7.7) years. For eGFR and ACR nearest to the date of biopsy, discrimination by KFRE was good (Harrell's C-statistic 0.71, 95% CI 0.62 to 0.81), although possibly inferior to the published model (Harrell's C-statistic 0.90, 95% CI 0.87 to 0.93). The linear predictor for calibration was 0.29 (95% CI 0.14 to 0.44). Calibration plots suggested that risk was over estimated at 2 and 5 years for low (<5%) KFRE predicted risk groups. For higher risk groups, the model was well calibrated. Results were similar when earliest available, instead of biopsy, eGFR and ACR were used in KFRE.

Conclusions: In an independent, external validation of KFRE in biopsy proven IgAN, discrimination was good but calibration was poor in lower predicted risk individuals. For patients with biopsy proven IgAN, the KFRE may need model adjustment, particularly for lower predicted risk individuals. Adjustments may be required to existing variables and/or inclusion of other variables, such as Oxford Classification histology findings, before KFRE can be used for prognostic purposes in IgAN.

TH-PO1026

Combinatory Approach of Oxford Classification Allows a Tailored Prediction of Renal Death in IgA Nephropathy

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Background: The prognostic of IgA nephropathy (IgAN) is highly heterogeneous, ranging from isolated hematuria to End-Stage Renal Disease (ESRD). The Oxford classification has been developed and recently updated to stratify patients according to the risk of progression considering histological elementary lesions. From a clinical standpoint, each patient has a proper combination of Oxford classification lesions, but the knowledge about the distribution and the prognostic impact of such combinations is lacking. Our study describes the distribution of those combinations in our population and evaluate their particular association with renal death.

Methods: This retrospective, monocentric cohort study included all Caucasian patients with biopsy-proven IgAN since 1979. Renal biopsies were scored by one pathologist blinded to the clinical data and according to the Oxford classification. We analyzed the distribution and grouped the patients according to the combination of histological MESTC score components to assess their risk to progress to ESRD (cox model, non adjusted and adjusted on proteinuria, hypertension, eGFR).

Results: A total of 695 patients were retained for analysis (mean age and proteinuria respectively 38.6 years and 1.04 g/day). The distribution of combinations was heterogenous: Most frequent lesions were M0S0E0T0C0, S1 alone, combined S1 and T1 alone, as shown in Figure 1. M0S0E0T0 was set as the reference (Hazard Ratio (HR) for progression =1). The higher and significant unadjusted risk for progression was found for the association S1E1T1 (HR 38.14 [14.9;97.7]), S1T1 (HR 24.87 [12 ; 51.7]), S1E1C1 (HR 8.02[3.38;19.01]), M1S1E1 (HR 7.69[2.36;25.0]), S1E1 (HR 3.88 [1.22;12.39]) as shown in Figure 2. Isolated S1 (HR 1.35 [0.52;3.5]), isolated M1 (HR 1,43 [0,18;11,3]), were not significantly associated with renal death contrary to isolated T1 (HR 14.7 [4.39;43.5]) and isolated E1 (HR 5.34 [1.46;19.5]).

Conclusions: This combinatory approach of Oxford classification lesions allows to identifying the unbalanced histological combinations with better homogeneity in renal outcomes prediction. Isolated M1 and S1 lesions did not seem to associate with ESRD.

TH-PO1027

Genome-Wide Study Investigating Potential Loci Associated with Risk of ESRD in IgA Nephropathy Patients

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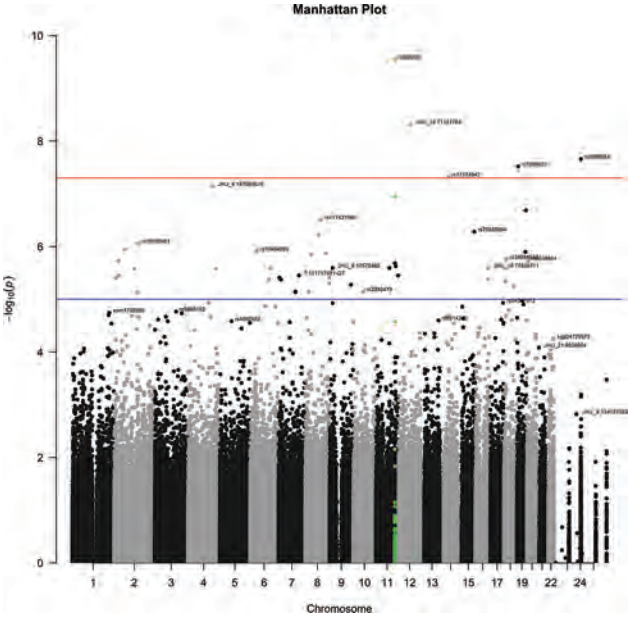
Background: End-stage renal disease (ESRD) is one of the most critical outcomes of IgA nephropathy (IgAN). Although genetic factor might have some effect on this outcome within IgAN patients, a genome-wise study regarding ESRD outcome was scarce, particularly in Korea which is known to have high incidence and worse prognosis of IgAN.

Methods: We performed genome-wide association and survival analyses including native kidney IgAN patients in Korea. Retrospectively collected 695 native IgAN patients were screened for inclusion. Genome-wide associations were calculated with logistic regression and cox regression analyses.

Results: After quality control, 691 patients and 603,128 single nucleotide polymorphisms (SNPs) were included in the analysis. Although an association analysis dealing ESRD as a binomial outcome did not show any significantly associated SNPs after Bonferroni correction, survival analysis including renal survival from birth revealed that following SNPs were significantly associated with risk of ESRD; rs655250, rs17574942, rs7259423, and rs5989654. When we applied less stringent threshold value, there was suspicious association of clusters of SNPs on chromosome 11, including rs655250 which showed the most significant p value, on gene coding NCAM1 (CD56). When time from IgAN diagnosis to ESRD was included as the survival duration, adjusted for age and sex at the time of IgAn diagnosis, following SNPs showed significant association with ESRD outcome; JHU_1.247982701, rs13095453, JHU_7.26585574, exm813062, rs2151745.

Conclusions: Potential gene loci identified in our analysis may be associated with risk of renal failure in IgAN patients. Further validation and expansion of our results may reveal association between genetic factors and IgAN prognosis.



TH-PO1028

Association of the CMIP Gene Single Nucleotide Polymorphism with Serum Lipids Parameter of IgA Nephropathy

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Background: The effect of dyslipidemia on cardiovascular complications and renal progression in IgAN has been confirmed. The CMIP gene was recently found to be closely related to TC, LDL-C and HDL-C levels. The relationship between dyslipidemia of IgAN and CMIP gene polymorphism has not been reported so far.

Methods: Study subjects were selected in the First Affiliated Hospital of Guangxi Medical University from August 2010 to December 2017. TC, TG, HDL-C, LDL-C, ApoA1 and ApoB levels were tested. Blood samples were extracted for DNA, PCR amplification, electrophoresis imaging. PCR products were sent to measure genotypes. The genotypic and allelic frequencies were measured. We explored the relationship between CMIP gene SNPs and serum lipid levels, and analyzed the risk factors of dyslipidemia.

Results: The study included 543 patients, 51.7%were dyslipidemia. The genotype and allele frequency of *CMIP* rs16955379 were statistically different between the two groups ($P < 0.05$). TG, HDL, BP, tubular atrophy and interstitial fibrosis(TA/IF) were significantly different between *CMIP* rs16955379 C allele carriers and non-carriers. TC, BP, Scr, UA, urine protein, renal dysfunction, and TA/IF were significantly different between *CMIP* rs2925979 A allele carriers and non-carriers. TC level was associated with rs16955379

C allele carrier, hypertension, alcohol and UA. TG level was associated with renal dysfunction, rs16955379 C alleles carrier, alcohol, smoking, BMI, UA, and TA/IF. HDL was associated with rs16955379 C allele carrier, UA, renal dysfunction, and mesangial cell proliferation. LDL was associated with rs16955379 C allele carrier, hypertension, and UA($P < 0.05$, respectively). There was a linkage disequilibra(LD) between rs16955379 and rs2925979, and rs2925979G-rs16955379T was the most common haplotype. The haplotype frequencies of *CMIP* SNPs were significantly different between dyslipidemia and normal group ($P < 0.05$).

Conclusions: About half of IgAN patients had dyslipidemia. The genotypic and allelic frequencies of rs16955379 were significant different between dyslipidemia group and normal group. There were significant differences in several lipid levels between *CMIP* SNPs different allele carriers. There was a LD between rs292597 and rs16955379. The most common haplotype was rs2925979G-rs16955379T. The related haplotypes increased the risk of dyslipidemia in IgAN.

Funding: Government Support - Non-U.S.

TH-PO1029

Pathologic Tonsillar Findings Similar to Immunoglobulin A Nephropathy in Patients with Frequently Relapsing Nephrotic Syndrome

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Background: Several studies have reported that regulatory T (Treg) cells are of critical importance for maintenance of tolerance in not only immunoglobulin A nephropathy (IgAN) but also nephrotic syndrome (NS). The pathologic tonsillar findings in IgAN differ significantly from those in chronic tonsillitis. However, the pathologic tonsillar features in patients with NS are unclear.

Methods: Immunohistochemical staining for tonsillar CD4, CD8, HLA-DR and cytokeratin was performed in 8 patients with frequently relapsing nephrotic syndrome (FRNS) who underwent tonsillectomy for chronic tonsillitis,. The patients were in complete remission, and were followed on low-dose prednisolone for FRNS.

Results: In 6 of 8 patients, T-cell nodules were enlarged by infiltration of HLA-DR-positive cells. Infiltration with both CD4-positive and CD8-positive cells was prominent in interfollicular areas. Cytokeratin staining showed that the layer of crypt epithelium was replaced by squamous epithelium.

Conclusions: The efficacy of tonsillectomy for IgAN is thought to be due to regulation of tolerance abnormalities. Replacement from the layer of crypt epithelium implies involution of lymphoepithelial symbiosis. The distribution of CD4 and CD8 is characteristic in the tonsils of those with IgAN. These pathologic findings in FRNS patients suggest the existence of a similar tolerance abnormality in the tonsils of those with NS. Our results may help to clarify intolerance in NS. Further studies are necessary to clarify the clinical efficacy of tonsillectomy for NS patients.

TH-PO1030

The Predictive Value of Crescents in Adult Henoch-Schölein Purpura Nephritis

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Background: To study the predictive value of crescents in adult Henoch-Schölein purpura nephritis(HSPN).

Methods: We retrospectively analyzed 275 adult patients with biopsy proven HSPN in the First Affiliated Hospital of Zhejiang University, and divided the patients into 4 groups: 99 patients in none crescent croup(NC), 34 patients in segmental crescents group(SC), 109 patients with circumferential crescents ≤25% were categorized into group C1, and 33 patients with crescents >25% were categorized into group C2. Data including serum creatinine(Scr), evaluated glomerular filtration rate(eGFR), 24h urine protein and mean arterial pressure were compared, and primary outcome was defined as ≥50% reduction of eGFR from baseline in 2 years, doubling of serum creatinine (Scr), or end stage renal disease (ESRD). ESRD was defined by reaching an eGFR of <15ml/min/1.72m^2 or requiring maintaining renal replacement therapy for more than 3 months. Univariate analysis and multivariate analysis were used to compare the outcome.

Results: There were no significant difference in gender or age($p>0.05$). Differences in Scr($p=0.002$), eGFR($p=0.007$), 24h urine protein ($p<0.001$)were found significant. The median Scr level of NC, C1,C2, SC group were 59.0(51.0, 75.0)μmol/L,66.0(52.5, 77.0)μmol/L, 72.0 (55.0, 94.0) μmol/L, 68.0(56.5,118.0) μmol/L, respectively. Further analysis showed that patients with crescents (including segmental crescents) have a higher Scr level than those without crescents. The urine protein level of each group were 0.75(0.42,1.53),1.17(0.63,2.02)g, 1.60(0.86,3.00)g, 2.48(1.12,4.63) g, respectively. The median follow-up duration was 56(33,85) months, and 18 patients reached renal endpoint. Kaplan Meier analysis suggested that the renal outcomes were significantly different($p=0.002$), the renal survival rates of NC, C1, C2, SC group were 96%, 88.1%, 78.8%, 100%, respectively. And Cox model suggested that a crescent ratio of more than 25% is an independent predictor of poor renal outcome.

Conclusions: A crescent ratio of more than 25% is an independent predictor of poor renal outcome in adult patients with Henoch-Schölein purpura nephritis.

TH-PO1031

Crescentic Lesions in IgA Nephropathy: Impact on Outcome

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Background: Recently, IgAN Classification Working Group has published an update to the Oxford Classification that recommends changing the MEST to a MEST-C score, defending that the fraction of crescents are associated with outcome. Nevertheless, the role of crescentic lesions is still controversial and needs better characterization. The aim was to study the impact of the crescents in the outcome in our population.

Methods: A total of 88patients with biopsy-proven IgAN between January'07 and December'17 were re-assessed using the MEST-C, in this retrospective analysis. The composite outcome was defined as 50%decline in eGFR or ESRD. We compare two groups:with crescents(N=24,27%)and with no crescents.

Results: The baseline characteristics were similar between the groups. The patients with C had more proteinuria and hypoalbuminemia at presentation but had similar eGFR. Endocapillary hypercellularity and segmental glomerulosclerosis lesions were higher in patients with crescents($P<0.02$). During a mean follow-up of 55.4months, 50% of the patients with crescents reached the composite outcome compared with27%of patients without($P<0.05$). Survival curves are presented. ESRD were more likely in the first group($P<0.02$) and50% decline in eGFR was more frequent but was not statistically significant. The independent predictors of composite outcome were eGFR at presentation, proteinuria, presence of crescents and moderate to severe interstitial fibrosis and tubular atrophy. In a multivariable Cox analysis, crescents(HR3.33, CI95%1.24-8.90, $p<0.02$), eGFR(HR0.16,$p<0.001$) and no immunosuppressive therapy(IST) (HR3.23,$p<0.05$)were associated with an increased risk of developing the composite outcome. IST was based on corticosteroid therapy, in 4cases prednisolone and cyclophosphamide were administrated. The survival at 96months in patients without IST was71%if they had no crescents and 42% if had any crescent($P=0.022$). The survival among those that were treated with IST was 80% if had no crescents (vs51%,$P=0.124$).

Conclusions: Crescents, along with higher eGFR at presentation, were an independent prognostic factor in our population. The main histologic alterations associated with the outcome were severe interstitial fibrosis, tubular atrophy and crescents. Our study suggests that crescent have value in predicting renal outcomes in our population with IgAN.

TH-PO1032

Urinary Soluble CD163 Level Predicts Renal Prognosis of IgA Nephropathy

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Background: In IgA nephropathy (IgAN), crescent percentage was added to the make the new Oxford MESTC scores system recently. Macrophage is the most important inflammatory cell type in crescent and CD163 is a specific marker for M2c macrophage. Its soluble form (sCD163) is present in the bio-fluid in inflammation.sCD163 may serve as a biomarker for macrophage activation but its role in renal prognosis is unknown.

Methods: 115 patients of IgAN were studied. Clinical parameters including blood pressure, urinary protein, creatinine and eGFR at renal biopsy and the last follow-up were recorded. The renal end point was defined as ESRD or the eGFR declined >50% or serum creatinine doubled during the follow up. The serum and urinary level of sCD163 were determined by ELISA.

Results: The cohort were divided into three groups according to the crescent percentage. Urinary sCD163 in group C2 (crescents in>25% of glomeruli) were significantly elevated compared to that in group C1 (crescents in <25% of glomeruli) and group C0 (no crescent). Urinary sCD163 level was negatively correlated with eGFR and positively correlated with serum creatinean and proteinuria. Urinary sCD163 level was associated with M,E,S and C scores. There was a significantly positive correlation between urine urinary sCD163 level and the percentage of crescents. Renal end points developed in 12 patients during the 42.6±7.4 months of follow-up. Most importantly, our results showed that increased urinary sCD163 level was significantly associated with poor renal outcome.

Conclusions: The level of urinary sCD163 was closely related to clinical and pathological features in IgAN and it can serve as a non-invasive biomarker to reflect the severity of IgAN. An increased urinary sCD163 level was related with poor renal outcome in patients with IgA nephropathy.

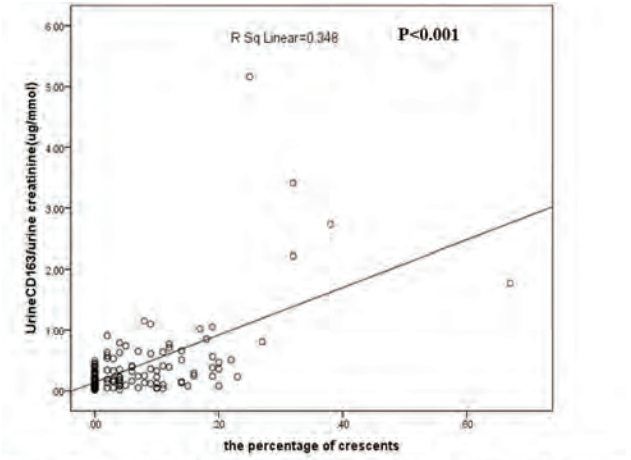

Figure1 The correlation between urinary sCD163 and the percentage of crescents

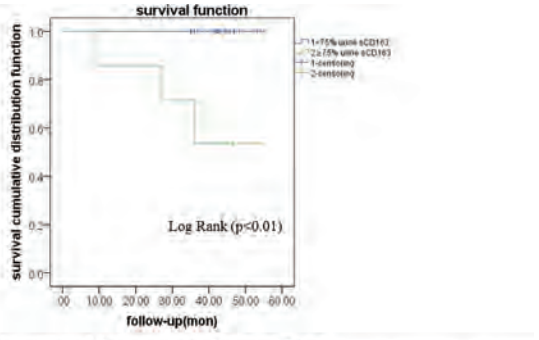

Figure 2 The survival function of urinary sCD163

The 75% urinary sCD163 =0.69(ug/mmol); A low concentration corresponded to those cases were below the 75% of all cases, and a high concentration corresponded to those cases were above the 75% value.

TH-PO1033

Prognostic Value of Mesangial C3 and C4d Deposition in IgA Nephropathy

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Background: Activation of complement system can play an important role in the pathogenesis of IgA nephropathy (IgAN). C3 and C4d can be representative markers of alternative and lectin pathway, respectively. We studied whether mesangial C3 or C4d deposits can predict adverse renal outcome better than conventional risk factors and determined relative contribution of each pathway to disease progression.

Methods: A total of 265 patients with biopsy-proven IgAN between 2000 and 2013 were enrolled. The degree of C3 was evaluated by immunoflurorescence staining and graded as 0, 1+, 2+, and 3+. We also determined C4d deposition by immunohistochemistry. The study endpoint was a composite of a ≥ 30% decline in estimated glomerular filtration rate or the onset of end-stage renal disease.

Results: During a mean follow-up of 6.8 years, 82 (30.9%) patients reached the composite end point. In the fully adjusted multivariable model, risk of reaching renal outcome was significantly higher in patients with mesangial C3 deposition of 2+ to 3+ (HR, 1.89; 95% CI, 1.11-3.20; P = 0.019) than in those with the deposition of 0 to 1+. In addition, patients with positive C4d deposition had a 1.9-fold increased risk of adverse outcome compared with those without deposition (HR, 1.90; 95% CI, 1.07-3.40; P = 0.03). The risk was highest in patients with both C3 and C4d deposition (HR, 2.61; 95% CI, 1.08-6.27; P = 0.03). Adding mesangial C3 deposition to risk prediction model significantly increased the integrated discrimination improvement and the net reclassification improvement, whereas C4d-added model did not. However, adding both mesangial C3 and C4d deposition together significantly improved risk prediction over C3-added model.

Conclusions: This study showed that mesangial C3 and C4d deposition were independent risk factors for renal progression. In addition, predictability of C3 was superior to that of C4d. C4d may play an additive role in increasing predictive power.

TH-PO1034

The Role of Expression of Toll-Like Receptors 4 and 9 in Stratification of Severity of IgA Nephropathy

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Background: The onset of IgA nephropathy (IgAN), characterized by glomerular deposition of IgA immune complexes, is often associated with synpharyngitic hematuria. Innate immune responses mediated by toll-like receptors (TLR) may play a role in IgAN onset and/or progression. Here, we assessed the expression of TLR 4, 7, 8, and 9 in renal-biopsy specimens from patients with IgAN, with different degree of proteinuria and eGFR, compared with normal kidney specimens from cadavers and a disease controls (ANCA vasculitis).

Methods: Expression of TLR 4, 7, 8, and 9 was assessed using immunohistochemical staining of paraffin-embedded renal-biopsy tissue specimens with specific antibodies and evaluated semiquantitatively by light microscopy. Linear discriminant analysis (LDA) was used to test whether intrarenal staining of TLR 4, 7, 8, and 9 distinguished patients with IgAN (n=34) from controls. Moreover, patient with IgAN represented four subgroups based on eGFR and proteinuria. All biopsies of patients with IgAN were scored according to the Oxford Classification.

Results: LDA showed that TLR 4, 7, 8, and 9 staining was more intense in specimens from IgAN patients than in normal kidney tissues. LDA also distinguished four subgroups of patients with IgAN based on MEST scoring. The intensity of intrarenal staining of TLRs discriminated four groups of IgAN divided according severity of renal impairment and proteinuria.

Conclusions: Intrarenal staining of TLRs together with clinical parameters (serum creatinine, eGFR, and proteinuria) analyzed by LDA may be helpful in assessment of disease prognosis. **References:** Supported by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 00023728 (Institute of Rheumatology) and by PROGRES Q25/LF1. JN was supported in part by grants DK078244 and DK082753 from the National Institutes of Health.

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TH-PO1035

Clinical and Pathological Characteristics of Patients with HBV-Associated IgA Nephropathy: A Case Series

Bogdan Obrisca, Roxana A. Jurubita, Bogdan M. Sorohan, Oana C. Ion, Andreea Andronesi, Gener Ismail. *Fundeni Clinical Institute, Bucharest, Romania*.

Background: A higher prevalence of hepatitis B surface antigen (HBsAg) is reported in patients with IgA nephropathy (IgAN) from endemic areas. However, little is known about the clinicopathological characteristics and outcome of these patients. We sought to characterize a cohort of patients with IgAN and HBsAg (HBsAg-IgAN).

Methods: Medical records of 110 patients with biopsy-proven IgAN, between 1999 and 2017, were retrospectively reviewed. Of these, 10 patients had HBsAg. Clinical and pathological characteristics (MEST-C score) at baseline, and outcomes were compared between HbsAg positive and negative IgAN patients.

Results: 10 patients (9.1%) with HBsAg-IgAN (mean age: 47 ± 20 years) were identified in our cohort. Mean eGFR, hematuria, and 24-hour proteinuria were 47 ± 20 ml/min, 50 ± 60 RBC/µl and 2.3 ± 2.8 g/day, respectively. The percentage of patients that showed M1, E1, S1, T1 and C1 were 80%, 10%, 70%, 50% and 20%, respectively. By comparison to patients with HBsAg negative IgAN, there was a tendency towards a worse renal function at baseline with more severe features on kidney biopsy (fewer patients showing E lesions and more with crescents, segmental sclerosis and interstitial fibrosis). 30% of patients had a halving of eGFR (within 27 ± 20 months), versus 14% (within 45 ± 42 months) of patients with HBsAg negative IgAN. All patients received antiviral therapy, 40% having undetectable viral load at biopsy, 40% having a HBV-DNA below 1000 IU/l (mean 264 ± 357 IU/l) and 20% having over 1000 IU/l (mean 11000 ± 8680 IU/l). 40% of patients received additional immunosuppressive treatment (IS). There were no significant differences in terms of renal survival between those with high versus low viral replication and between those receiving antiviral therapy alone and combined antiviral/IS therapy. Additionally, patients receiving combined antiviral/IS therapy didn't show any sign of HBV reactivation.

Conclusions: HBV-associated IgAN patients had a worse renal function at baseline, with more severe activity and chronicity features, both clinically and pathologically, as compared to HBsAg-negative IgAN patients. These characteristics determined a more rapid decline of renal function in our cohort of HBV-associated IgAN.

TH-PO1036

Using the Oxford Classification in Assessing the Therapeutic Effects in IgA Nephropathy: A Secondary Analysis from a Randomized Clinical Trial

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Background: The Oxford Classification established a consensus on pathologic features that could predict the risks of progression of IgA nephropathy(IgAN). Clinically, histopathology is essential for both evaluating the severity of the lesions and guiding therapeutic strategies for IgAN. It remains a challenge whether or not Oxford Classification can guide therapeutic strategies. The aim of the analysis was to evaluate if the oxford classification can predict the therapeutic effects for patients receiving telmisartan and/or clopidogrel with/without leflunomide.

Methods: The multicentre, prospective, double-blind, double-dummy RCT was conducted between July 2010 and June 2012 in Beijing, China. The results were published in Chinese Medical Journal in 2016. There were 162 cases, who were diagnosed in Chinese PLA General hospital, included in this secondary analysis. The complete or partial remission was defined as 24 hour proteinuria <0.3g or ≥30% reduction and stable kidney function. Stable kidney function was defined as increase in serum creatinine less than 26.4umol/L at week 24. The other was defined as ineffectiveness. The logistical regression was used to analyse the relationship between the character of Oxford classification and the effect.

Results: Multiple logistic regression analysis showed that both of 24 hour proteinuria≥1g (Odds Ratio(OR)=2.13, 95%CI 1.04-4.36) and taking leflunomide(OR=5.70, 95%CI 2.66-12.24) were the advantage factors. Only tubular atrophy/interstitial fibrosis >50% were the risk factor(OR=18%, 95%CI 8%-40%). Especially, we found that there were interaction between mesangial hypercellularity >0.5 and leflunomide.

Conclusions: This secondary analysis supports the oxford classification for IgAN has capacity to predict the therapeutic effects for patients receiving telmisartan with leflunomide. Mesangial hypercellularity >0.5 maybe the potential character of taking leflunomide.

Funding: Government Support - Non-U.S.

TH-PO1037

Clinical Impact of Endocapillary Proliferation with Modified Cutoff Point in IgA Nephropathy Patients

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Background: Predictive values of mesangial proliferation (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and crescents (C) among 19-validation studies of Oxford Classification were discrepant, in particular among Asian IgA nephropathy (IgAN) patients. These validation studies indicate that cutoff points of MESC score in the Oxford Classification may not be generalizable. Thus, we aimed to improve clinical value of MESC scores by modifying cutoff points.

Methods: A total of 104 IgAN diagnosed from 2001 to 2012 by renal biopsy, and retrospectively evaluated at Nagoya University Hospital. Cutoff point for modified (M′E′S′C′) was determined by receiver operating characteristic curve in association with renal outcome in the training cohort. Clinical value of the Oxford MESTC vs M′E′S′C′ cutoff points were analyzed by Kaplan-Meier and Cox regression for renal outcome in the validation and all cohort.

Results: Of 104 participants 12.5% of them reached renal outcome over 6.25 [4.16-9.61] years of follow-up. The modified cutoffs were defined ≥40%, ≥10%, ≥20%, and ≥5% in glomeruli for M′E′S′C′ respectively. In univariate analysis, E′, S′, and T were significantly associated with renal outcome. Whereas, the Oxford MESC, M′, and C′ in the training and validation cohort demonstrated no significant association with renal outcome. By multivariate analysis in the presence of eGFR, only E′ was a significant predictive factor for renal outcome.

Conclusions: The E′ with modified cutoff point of 10% significantly improved predictive value for renal outcome in IgAN. Clinical value of modified cutoff points for M′E′S′C′ scores should be validated with various cohort studies in different regions.

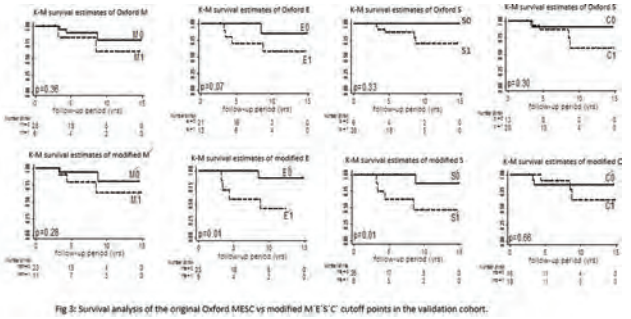

Fig.3: Survival analysis of the original Oxford MESC vs modified M′E′S′C′ cutoff points in the validation cohort.

TH-PO1038

Steroid Responsiveness on Remission of Urinary Abnormalities According to the Pathological Lesions in IgA nephropathy: A Japanese Multicenter Prospective Cohort Study

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Background: The effectiveness of steroids on clinical course and its indication in IgA nephropathy (IgAN) are controversial.

Methods: 797 patients with IgAN were included. Treatment groups were defined by steroid (ST) and tonsillectomy (TX): group 1; ST-TX-, groups 2; TX only, group 3; ST only, group 4; TX+ST+. Acute lesions (AL) such as cellular or fibrocellular crescent, or tuft necrosis, chronic lesions (CL) such as fibrous crescent, segmental or global glomerulosclerosis, Japanese histological grade (HG) and Oxford classification (MEST-C) were evaluated. The endpoint was the remission of urinary abnormality within 24 months. The remission of proteinuria (UPR) was defined less than 0.3/day. The remission of hematuria (OBR) was defined less than 5 RBC/HPF. Clinical remission (CLR) was defined UPR and OBR. The effect of treatment groups, and pathological parameters on UPR, OBR, and CLR was analyzed by logistic model.

Results: The mean age was 38, the median of UP was 0.58, mean eGFR was 76.9. The median AL, CL was 3.8, and 20%. AL and CL were tertile categorized with 0 and 7.7 % for AL and 13.3 and 30.8% for CL as cutting values. HG1 to 4 was 61, 26, 10, and 2.8 %. M1, E1, S1, T1-2 and C1-2 were 24, 36, 81, 27, 62 %. The treatment group 1 to 4 was 35, 5, 25 and 40 %. Group 3 and 4 showed significant positive effect on UPR, OBR and CLR with reference (ref) group 1. The effect of group 4 with ref group 3 was significant on OBR. AL3 showed significant positive effect with ref AL1 on UPR and CLR. CL2 and CL3 showed significant negative effect with ref CL1 on UPR. CL3 showed significant negative effect on CLR. HG2 and HG3-4 showed significant negative effect on UPR with ref HG1. HG3-4 showed significant negative effect on CLR. E1 showed significant positive effect on UPR. M1, S1, T1-2 showed significant negative effect on UPR with ref M0, S0, and T0. On CLR, C1-2 showed significant positive effect with ref C0, and T12 showed significant negative effect with ref T0.

Conclusions: Steroid was significantly effective on proteinuria and hematuria. Higher percentage of acute lesions showed significant effect of steroid on proteinuria. The additional effect of tonsillectomy to steroid was found on hematuria.

Funding: Government Support - Non-U.S.

TH-PO1039

Primary Efficacy Analyses from a Phase 2 Trial of the Safety and Efficacy of Bardoxolone Methyl in Patients with IgA Nephropathy

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Background: Bardoxolone methyl (BARD) has been shown to significantly increase eGFR in patients with CKD and type 2 diabetes and Alport syndrome suggesting that the anti-inflammatory and anti-fibrotic effects of BARD may target the common pathways contributing to GFR loss in multiple forms of CKD. As a result, a Phase 2 trial (PHOENIX, NCT03366337) was initiated to test the hypothesis that BARD will improve kidney function in patients with IgA nephropathy (IgAN) as well as other forms of CKD.

Methods: The Phase 2 open-label, multicenter study enrolled a cohort of 26 patients with biopsy-confirmed IgAN. Eligible patients were 18 to 65 years of age with eGFR values between 30 to 90 mL/min/1.73 m^2 and urine albumin to creatinine ratio (UACR) ≤ 2500 mg/g. Patients received BARD at an initial dose of 5 mg, dose-escalated to 20 mg (for patients with baseline UACR ≤ 300 mg/g) or to 30 mg (for patients with baseline UACR > 300 mg/g) and were treated for 12 weeks. The primary efficacy endpoint was the change from baseline eGFR after 12 weeks of treatment. Interim results for the cohort enrolling patients with IgAN are described herein.

Results: At data cutoff on May 15th, 2018, 5/26 (19%) of the enrolled patients with IgAN had completed the study. From a mean (± SE) baseline eGFR of 46.2 ± 2.5 mL/min/1.73 m^2, BARD treatment resulted in a significant increase from baseline in eGFR of 7.8 ± 1.8 mL/min/1.73 m^2 ($p<0.0001$) at Week 12. The improvements were consistent, and 4 of the 5 (80%) patients had increases from baseline in eGFR > 5 mL/min/1.73 m^2 at Week 12. No patients have discontinued from the study and no serious AEs considered related to BARD have been reported in this ongoing trial.

Conclusions: BARD was generally well tolerated and significantly increased eGFR in patients with IgAN. In patients with other forms of CKD, short term eGFR increases with BARD are predictive of durable eGFR improvements and additional studies are needed to study the longer-term effects of BARD on eGFR in IgAN.

Funding: Commercial Support - Reata Pharmaceuticals

TH-PO1040

Corticosteroid Therapy in IgA Nephropathy

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Background: Corticosteroid therapy is used in patients with IgA nephropathy(IgAN) with persistent proteinuria, but there is a lack of cosensus about its overall benefits. There is a paucity of data about steroid use in Indian patients who have an aggressive clinical course. This study aims to look at the response to steroid therapy in Indian patients with IgAN.

Methods: Patients with biopsy proven primary IgAN treated with oral corticosteroids from 2012 to 2017 with minimum 12 months follow up were included in the study. MEST-C score was assigned as per the Oxford classification to all biopsies. All patients received oral prednisolone 1mg/Kg/day for 8-12weeks followed by gradual tapering over 6-12 months. Complete remission(CR) was defined as 24-hour urine protein of <500 mg/d with stable eGFR and partial remission(PR) was defined as atleast 50% reduction in proteinuria with stable eGFR with a decline of proteinuria to <3.5g/day.

Results: Of the 94 patients included in study, 64.9% were males with mean age of 30.4±11.9 years. Mean proteinuria was 5.2±2.6 g/day and 53.2% had gross or microscopic hematuria. Mean serum creatinine was 1.4±0.6 mg/dl and mean eGFR was 75. 4± 48.1 ml/min/1.73m^2. 77.7% patients had received ACEi/ARB before starting steroid therapy. The distribution of MEST lesions were: M1-70(74.5%), E1-7(7.5%), S1-56(59.6%), T1-26(27.7%) lesions and T2-7(7.5%). 9(9.6%) patients had crescents[C1-7(7.5%), C2-2(2.1%)]. 42(44.7%) patients responded to steroid therapy (CR-22, PR-20), of whom 7 patients had one steroid responsive relapse during the follow up and three were steroid dependent. On univariate analysis,S1 lesions on biopsy (p=0.011) and eGFR<30ml/min/1.73m^2(p=0.056) predicted steroid resistance. Serious adverse effects were seen in 16 (17.0%) patients mainly comprising of infections (13) with 4 patients developing Tuberculosis. One patient died due to pulmonary nocardiosis.

Conclusions: Steroid therapy reduces proteinuria in 44.7% patients with IgAN. However it is associated with serious infectious complications. The presence of S1 lesion and renal dysfunction at baseline predict poor response.

TH-PO1041

The Global, Regional, and National State of CKD Epidemiology from 1990 to 2016: An analysis of the Global Burden of Disease Study

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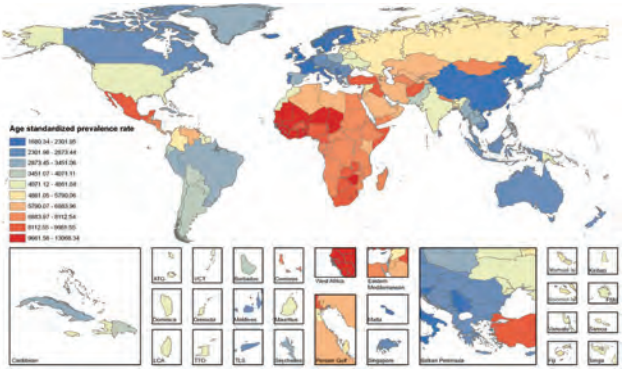
Background: The last quarter century witnessed significant population growth, aging, and major changes in epidemiologic trends which may have shaped the state of chronic kidney disease (CKD) epidemiology. The GBD study provides a detailed epidemiologic assessment of 333 diseases and injuries and 84 risk factors by age and sex on a global scale and for 195 countries and territories.

Methods: Data collected from the GBD study will be used to describe the change in burden of CKD from 1990 to 2016. In this work, we used the Global Burden of Disease (GBD) study methodologies to describe the change in burden of CKD including decomposition analysis to understand factors that drove change and frontier analysis that evaluate the relationship between burden of CKD and socio-demographic development.

Results: Globally, incidence of CKD increased by 88.76%, prevalence increased by 86.95%, death due to CKD increased by 98.02%, and DALYs increased by 62.21%. Measures of burden varied substantially by level of development and by geography. Decomposition analyses showed that the increase in CKD DALYs was driven by population growth and aging; globally and in most GBD regions, age-standardized DALYs rates decreased. More of the CKD burden (62.96%) was in low and lower-middle-income countries; there was an inverse relationship between age-standardized CKD DALYs rate and healthcare access and quality (r=-0.52). Frontier analyses showed significant opportunities for improvement at all levels of the development spectrum.

Conclusions: Our results demonstrate that the global toll of CKD is significant, rising, and unevenly distributed; it is primarily driven by demographic expansion and in some regions significant tide of diabetes epidemic. Opportunities exist to reduce CKD burden at all levels of development.

Funding: Veterans Affairs Support



TH-PO1042

Generalizability of SPRINT-CKD Cohort to CKD Patients Referred to Renal Clinics

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Background: It is unknown whether the SPRINT-CKD sub-cohort is representative of CKD patients under nephrology care. We compared risk profile and outcomes of SPRINT-CKD versus a pooled cohort of four prospective studies enrolling consecutive patients with CKD stage I-V under nephrology care from >6 months in 40 Italian outpatient renal clinics.

Methods: In referred cohorts, we implemented the same inclusion/exclusion criteria adopted in SPRINT and the same endpoints: (1) a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure and CV death (2) all-cause mortality and (3) end-stage renal disease (ESRD) as a composite of chronic dialysis, transplantation or 50% eGFR decline. Referred CKD patients were compared with those in SPRINT-CKD randomized to standard BP arm because management in this group is comparable to that performed in clinical practice where SBP target <140 mmHg is usually pursued. To compare outcomes, we only considered for analysis the events occurring no later than 4.8 years after enrolment, i.e. the maximum follow up available in SPRINT.

Results: From the initial pooled cohorts (n=3225), we deleted 338 duplicate patients, 27 patients without data on SPRINT selection criteria and 13 subjects lost to follow-up. Out of the evaluable 2847 patients, only 20.1% (n=571) of the patients of the referred cohorts could have been potentially eligible for SPRINT trial. These patients had a worse risk profile at baseline (Table). At a median follow-up of 4.0 years (IQR 2.8-4.8), we registered 85 CV events (50 fatal), 78 all-cause death with annual incidence rates higher than those observed in the SPRINT standard group (Table).

Conclusions: In conclusion, we suggest that the SPRINT-CKD cohort is poorly representative of "real-world" CKD population. Ad hoc trials are needed in referred CKD population.

	SPRINT Standard group (n=1316)	Referred CKD cohort (n=571)
Age (years)	71.9±9.5	72.1±9.4
Women (%)	39.6	42.2
Body mass index (kg/m^2)	29.5±5.8	27.4±4.8
Current smoker (%)	8.1	11.2
Clinical CVD (%)	19.5	25.7
Framingham risk score (%)	27.2±24.7	31.9±14.6
Framingham risk score >15% (%)	78.2	87.5
Systolic/Diastolic BP (mmHg)	139±16/75±12	142±10/80±10
eGFR$_{MDRD}$ (mL/min/1.73m^2)	47.9±9.5	38.1±10.6
Proteinuria (mg/day)	NA	190 [70-430]
Urinary ACR (mg/g)	14 [6-44]	NA
Antihypertensive medications (n)	2.11±1.01	2.14±1.00
Statin use (%)	53.4	29.2
Aspirin use (%)	55.5	21.4
Incidence rate of adverse events		
CV outcome (%/year)	3.19	4.13
All cause death (%/year)	2.21	3.64
ESRD (%/year)	0.41	2.80

Demographics and clinical characteristics at baseline, and incidence rates of endpoints in the two groups

TH-PO1043

Explaining Racial Inequality in Albuminuria Through Multiple Mediators

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Background: Previous studies have shown that blacks have a higher prevalence of albuminuria than whites and that certain risk factors may account for that racial inequality. No research, however, has assessed the role of multiple risk factors collectively as mediators of the race effect.

Methods: Using cross-sectional data from the 2007-2010 National Health And Nutrition Examination Surveys for 6700 non-Hispanic black and white adults, ages 20+, we applied flexible mediation analysis (medflex, R package) to decompose the total effect of black race on albuminuria prevalence (albumin/creatinine ratio ≥30 mg/g) into direct and indirect (mediated) effects for combinations of 4 potential mediators: diabetes; hypertension; obesity (body mass index ≥30 kg/m^2), and low vitamin D level (25[OH]D3 <50 nmol/L). For each set of mediators, we estimated odds ratios (OR; 95% CI) for the direct, indirect and total effects and the percentage of the total effect that was mediated; ORs were adjusted for age, sex and non-mediating confounders.

Results: The weighted mean albuminuria level was 32 mg/g in blacks and 23 mg/g in whites; the adjusted OR for the total effect of black race on albuminuria was 1.61 (1.23, 2.11). The % mediated by each risk factor treated separately was 50% for low vitamin D, 44% for diabetes, 27% for hypertension, and 12% for obesity. When all 4 mediators were analyzed jointly, the direct-effect OR was 1.10 (0.65, 1.86), the indirect-effect OR was 1.46 (1.23, 1.74), and 84% of the total effect was mediated by these 4 risk factors. Excluding low vitamin D reduced the percentage mediated to 46%; doing the same with the other 3 mediators reduced the percentage mediated to no less than 70%.

Conclusions: The 4 risk factors treated as mediators in this study—especially low vitamin D and diabetes—appear to explain most of the racial difference in albuminuria prevalence in the United States. Although causal inference is limited by the cross-sectional design and possible residual confounding, the findings suggest that much of the racial inequality may be preventable through improvement of the risk-factor profile in blacks. As we learn more about how to control vitamin D level, the long-term impact on the incidence of chronic and end-stage renal disease could be appreciable.

Funding: Other U.S. Government Support

TH-PO1044

Disparities in CKD Progression Across Racial Groups in Two Large Health Systems

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Background: Disparities exist in progression of chronic kidney disease (CKD) across racially diverse groups. The University of California, Los Angeles Health (UCLA) and Providence St. Joseph Health (PSJH) systems formed a CKD and At-risk CKD Data Registry to inform advances in population health, individual behaviors, social and physical environment, and precision medicine.

Methods: CKD progression was determined across self-reported racial/ethnic groups in the database (>3.1 million patients) that was populated from electronic health records of adults treated at UCLA and PSJH from 2006 to 2016. Eligibility in the Registry was based on identification of CKD, and at-risk for CKD defined by hypertension, diabetes, or pre-diabetes. Linear regression coefficients for individual trajectories were calculated for patients having at least 3 eGFRs (CKD-EPI-creatinine). Individuals were classified by change in eGFR over time. Linear mixed models were used to assess racial differences in eGFR trajectories, controlling for age, gender, and time-varying measurements of systolic blood pressure, hemoglobin A1C, and renin angiotensin system inhibitor use.

Results: Patients with statistically significant eGFR decline (≥2-3 mL/min/1.73m^2/year; n=182,959, 16%) had a baseline of 79±26 mL/min/1.73m^2 (mean±SD) versus 81±23 mL/min/1.73m^2 in non-decliners (n=980,022, 84%). Non-White were more likely than White patients to experience eGFR decline after adjustment for relevant covariates in multi-variable models. Mortality rate for patients with significant eGFR decline was >3 times higher than in patients without eGFR decline.

Conclusions: In this large data registry from electronic health records at UCLA and PSJH, after multi-variable adjustment Non-White patients with CKD or at-risk for CKD are more likely to experience eGFR decline, which was associated with higher risk of mortality. Future directions include assessing eGFR decline by race/ethnicity and mortality risk in our unique cohort.

Funding: Private Foundation Support

TH-PO1045

The Impact of Gender on Inpatient Mortality of Hypertensive Latino Patients Across CKD Stage 3 to ESRD in the United States

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Background: HTN and CKD are two of the most important risk factors for CVD, a major cause of death in the US population. The impact of gender or menopausal age in this equation remains unclear on how it affects the Hispanic population. Studies comparing the difference in inpatient mortality between male and female with hypertension and CKD are sparse. Our aim was to determine if gender in Latino population affect the inpatient survival rate among hypertensive patients across different CKD stages.

Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, female hypertensive with chronic kidney disease (stage 3, 4, 5 or ESRD) patients were matched with hypertensive males at a 1:1 ratio. We compared inpatient mortality, per CKD stage, length of stay and total hospital charges between male and females. Analyses were performed using SAS version 9.3.

Results: Among 227,923 hospitalized hypertensive patients, 118,132 (51.83%) were males and 109,791 (48.17%) females. There was 18.76% females with CKD3, 10.31% with CKD4, 3.85% with CKD 5 not on dialysis and 67.17% with ESRD. Similarly there was 19.47% men with CKD 3, 9.54% with CKD4, 3.63% with CKD5 not on dialysis and 67.43% with ESRD on dialysis. In-hospital mortality was higher for males compared to females before match, (3.89 vs 3.74 p= 0.05), but non significant after matching the groups (3.85 vs 3.79 p= 0.48). Studying the effect of menopausal age, we find Latino women <50y to have less mortality risk compared to matched group of men irrespective of CKD stage while it is not different when comparing Men and women >50y with CKD stages 3 to 5. Post menopausal women with ESRD have a significantly higher mortality compared to men (5.15% vs 4.24%; p<0.0001). Hospitalized hispanic men had higher hospital charges (63,686 vs 61,667 dollars,p=0.001) even though hispanic women had a significantly longer mean length of stay (6.74 vs 6.70 days,p=0.001).

Conclusions: Mortality in Hispanic women with CKD 3 to 5 compared to men, is reduced when < 50y, comparable after >50y and increased when on dialysis. Further studies are needed to elucidate the possible links of menopause and sex hormones with in-hospital mortality of hypertensive hispanic patients.

TH-PO1046

Impact of Kidney Function on Quality of Anticoagulation in Adults with Atrial Fibrillation: The CVRN WAVE Study

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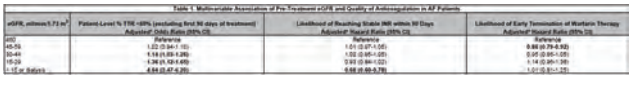
Background: Despite the development of direct oral anticoagulants, warfarin remains an important anticoagulation option for stroke prevention in adults with CKD. However, the impact of kidney function on the quality of anticoagulation for atrial fibrillation (AF) has not been well-defined.

Methods: Across 5 participating healthcare systems in the Cardiovascular Research Network (CVRN), we identified all adults with diagnosed AF who initiated warfarin and had ≥1 follow up international normalized ratio (INR) measurement. We used multivariable logistic regression, Cox regression and Kaplan-Meier curves to assess the relationship between estimated glomerular filtration rate (eGFR) by CKD-EPI with three metrics of quality of anticoagulation: patient-level %TTR, time to achieve a stable INR [between 2.0-3.0], and early warfarin termination. Stroke and bleeding risk factors were ascertained from health system electronic health records.

Results: Among 24,634 eligible patients, mean age was 73 years and 44% were women. Baseline eGFR (ml/min/1.73 m^2) was 64% for eGFR ≥60, 22% for eGFR 45-59, 11% for eGFR 30-44, 2.5% for eGFR 15-29 and 2% for eGFR <15 or receiving dialysis. Patient-level %TTR ranged from 43% for eGFR <15 or dialysis to 66% for eGFR ≥60, with a graded increased adjusted odds of poorer anticoagulation control with lower eGFR. Overall, 77% reached a stable INR within the first 90 days of therapy, with only eGFR <15 or dialysis significantly associated with a longer time to reach stable INR. There was no significant association of kidney function with early warfarin termination.

Conclusions: In adults with AF starting warfarin, we found graded increased odds of suboptimal %TTR with lower eGFR. While only eGFR <15 or dialysis was associated with a lower chance of reaching a stable INR within 90 days, eGFR did not appear to influence the likelihood of stopping warfarin within the first 12 months of treatment.

Funding: Other NIH Support - NHLBI



TH-PO1047

Trends in Statin Use Among Those with CKD in the United States, 1999 to 2014

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Background: Chronic kidney disease (CKD) has been recognized as a risk factor for cardiovascular disease (CVD). Statins have been shown to reduce CVD events in those with CKD not on dialysis, and CKD has been suggested as a candidate for determining statin therapy in cholesterol-focused guidelines. Statins have been shown to be used by a minority of those with CKD. Descriptions of temporal tends and disparities in statin use among those with CKD, identifying those who may benefit most from inclusion of CKD in such guidelines, are needed.

Methods: We studied trends in statin use among adult participants of the National Health and Nutrition Examination Survey, years 1999-2014, with creatinine-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or albumin-creatinine ratio ≥ 30 mg/g. Differences among racial/ethnic, other demographic, and comorbid characteristics were also examined.

Results: 28.9% of those with CKD used a statin. Encouragingly, statin use rose across the four eras studied (P < 0.001), though they may have begun to plateau after 2010: 1999-2002, 17.1%; 2003-2006, 27.0%; 2007-2010, 33.4%, and 2011-2014, 35.6%. While albuminuria increased the likelihood of statin use (23.6% vs 12.2%, P < 0.001), a greater effect was seen among those with reduced eGFR < 60 ml/min/1.73m^2 compared to those with preserved eGFR (41.4% vs 11.4%, P < 0.001). Those of Hispanic race/ethnicity with CKD received fewer statins: 15.4% compared to 32.0% for white, 26.2% for black, and 24.6% for other race/ethnicity (P < 0.001). Statin use was more prevalent among males with CKD than females (32.4% vs. 26.3%, P < 0.001). In age, sex, and race/ethnicity adjusted models, statins were associated with: era (adjusted odds ratio (AOR) 1.77 [95% CI: 1.44-2.17] for 2003-2006, 2.51 [95% CI: 2.04-3.08] for 2007-2010, and 2.94 [95% CI: 2.34-3.70] for 2011-2014, vs. 1999-2002) and Hispanic race/ethnicity (AOR 0.62 [95% CI: 0.50-0.78] vs. white). Other multivariate associations (P < 0.05) were older age, male sex, BMI ≥ 30 kg/m^2, diabetes mellitus, hypertension, myocardial infarction, heart failure, and stroke.

Conclusions: Statin use has increased over time but remains the case for the minority in community-based CKD. Those of Hispanic race/ethnicity with CKD receive the fewest statins while males with CKD receive statins more often than females. Further research into such disparities is needed.

TH-PO1048

Statin Use Remains Suboptimal Among US Veterans with Stage 3-5 Non-Dialysis Dependent CKD

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Background: Statin use is one of the few interventions demonstrated in clinical trials to reduce cardiovascular disease (CVD) in adults with non-dialysis dependent chronic kidney disease (CKD-ND). KDIGO guidelines published in 2013 recommend statin use for adults age ≧50 years with CKD-ND. We previously reported suboptimal statin use during calendar year 2012 in U.S. Veterans with stage 3-5 CKD-ND with only 62.1% using statins overall and only 21.8% of Veterans with CKD-ND in absence of diabetes, clinical CVD or hyperlipidemia using statins. In this study, we reexamined statin use during calendar year 2015 among U.S. Veterans age ≧50 years with stage 3-5 CKD-ND.

Methods: We used data from the VA Corporate Data Warehouse which includes demographics, inpatient and outpatient encounter diagnosis and procedure codes [International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD9/10-CM) and Current Procedural Terminology codes], outpatient pharmacy prescriptions reported by Veterans, and patient labs. Information on medications dispensed within the VA system was obtained from the Managerial Cost Accounting National Data Extracts which contains medications names and supply durations. Data were linked with the Medicare files to capture health care use and medications dispensed from non-VA pharmacies. CKD status was based on presence of at least two estimated glomerular filtration rate (eGFR) values < 60 ml/min/1.73 m^2 in outpatient laboratory data spaced 90+ days apart. Co-morbidities were defined by ICD9/10 codes.

Results: There were 242,865 Veterans age ≧50 years with at least two eGFR values <60 ml/min/1.73 m^2 spaced 90+ days apart during calendar year 2014 with no history of dialysis or transplantation. Mean age was 76.4 years (standard deviation 9.6) and 96.7% were male and most were white with 14.9% reporting black race. During calendar year 2015, 68.7% of these Veterans with stage 3-5 CKD-ND were using statins. Among Veterans with CKD-ND accompanied by diabetes or CVD, statin use was 75.1%. In contrast, only 36.6% of Veterans with CKD-ND in absence of diabetes, CVD or hyperlipidemia were using statins.

Conclusions: Statin use appears to have increased among Veterans with stage 3-5 CKD-ND but use still remains suboptimal, especially among those CKD-ND in the absence of diabetes or clinical CVD.

Funding: Veterans Affairs Support

TH-PO1049

US Veterans with Stage 3-5 Non-Dialysis Dependent CKD Are More Likely to See a Cardiologist Than a Nephrologist

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Background: Nephrology care has been shown to improve outcomes and delay or even prevent end-stage renal disease (ESRD) in adults with established chronic kidney disease (CKD) but many never see a nephrologist. We examined the percentage of U.S. Veterans with -5 non-dialysis dependent CKD (CKD-ND) with at least one nephrology clinic encounter during calendar year 2015. We also examined the percentage of adults with CKD-ND with at least one cardiology clinic encounter during calendar year 2015 and examined whether referal patterns for nephrology or cardiology differed by race.

Methods: We used data from the VA Corporate Data Warehouse which includes demographics, inpatient and outpatient encounter diagnosis and procedure codes [International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD9/10-CM) and Current Procedural Terminology (CPT) codes], and patient labs. Since a percentage of Veterans receive their care from non-VA sources, we linked data from the Center for Medicare & Medicaid Services administrative databases to capture non-VA health care use. CKD status was based on presence of at least two estimated glomerular filtration rate (eGFR) values < 60 ml/min/1.73 m^2 in outpatient laboratory data spaced 90+ days apart.

Results: There were 242,865 Veterans age ≧50 with at least two eGFR<60 ml/min/1.73 m^2 spaced 90+ days apart during calendar year 2014 with no history of dialysis or transplantation. Mean age was 76.4 years (standard deviation 9.6) and 96.7% were male and most were white with 14.9% reporting black race. In this group with stage 3-5 CKD-ND, 16.6% saw a VA nephrologist and 6.1% saw a Medicare reimbursed nephrologist while 21.4% saw a VA cardiologist and 19.5% saw a Medicare reimbursed cardiologist. Compared to whites with stage 3-5 CKD-ND, black Veterans with stage 3-5 CKD-ND were more likely to see a VA or Medicare reimbursed nephrologist (31.8% vs. 20.1%, p<0.001) but less likely to see a VA or Medicare reimbursed cardiologist (32.3% vs. 38.7%; P < 0.001).

Conclusions: Veterans with stage 3-5 CKD-ND are almost twice as likely to receive cardiology care than nephrology care although this differs somewhat by race. Increasing nephrology referral rates for patients with CKD-ND should be a priority for health systems in order to delay or prevent ESRD.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO1050

Environmental Chemical Exposures in African Children with CKD: H3 Africa Cohort Experience

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Background: Environmental chemical exposures are linked to oxidative stress and kidney injury in children and adults. This applies to short-lived organic compounds such as bisphenol A and phthalates and persistent synthetic chemicals such as perfluoroalkyl acids (PFAAs). Most investigations to date have been conducted in developed countries with few data about environmental chemical exposures in children living in Africa.

Methods: Clinical and laboratory data about pediatric patients enrolled in the H3 Africa observational cohort study including age, gender, BMI, serum creatinine, eGFR, proteinuria were collected. Serum samples that had been collected at enrollment were retrieved from the Biorepository and analyzed for PFAAs and polybrominated diphenyl ethers (PBDEs) and DDE presticides using established methods. Proteinuria was assessed in a first morning urine sample. Results are presented as mean±SD.

Results: 86 patients with CKD (41 M:45 F), age 12.6±2.6 yr old, were included in this nested case control study. The eGFR was 75±4 and the albumin:creatinine ratio was 65±186. The chemical exposures are summarized in the Table. There was no association between exposure (log of serum concentration) to PFAAs and proteinuria. However, controlling for age, gender, and BMI, there was an inverse relationship between eGFR and exposure to PFNA, -21.2 [95% CI:-41.6 - 0.8] and PFDA -18.3 [95% CI:-35.3 - -1.3] ml/min/log unit increase in exposure and a trend towards a similar effect for PFOS. PBDE/DDEs were detected in a small fraction of children and because of small sample size associations with effect markers were not made

Conclusions: PFAA exposure is substantially lower in H3 Africa participants than in healthy US children, age 12-19 enrolled in NHANES 2003-2010. However, even at these lower levels of exposure there was an adverse association between select PFAAs and GFR. These studies indicate the feasibility of measuring environmental chemical exposure in developing countries. The impact of these chemical exposures on kidney function will require larger cohorts of children followed for more extended periods of time.

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Serum PFAA levels: H3 Africa Pediatric Patients

Chemical	PFOS	PFOA	PFHxS	PFHxA	PFDA	PFNA
Concentration (ng/ml)	2.4±1.8	0.53±0.34	0.3±0.2	0.7±1.0	0.2±0.1	0.34±0.14

TH-PO1051

Risk Factors for Albuminuria and Reduced eGFR in Sub-Saharan Africans: Findings from the H3Africa Kidney Disease Research Network Project

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Background: Chronic kidney disease (CKD) in sub-Saharan Africa (SSA) is among the most common non–communicable diseases ravaging the sub-continent. Data on comprehensive epidemiology of CKD phenotypes and genotypes are lacking from the region. The H3Africa Kidney Disease Research Network (H3Africa KDRN) was established to develop the first Pan-African study in CKD and to rapidly build capacity for genomic studies of kidney disease in Africa. The objective of this analysis was to characterize risk factors associated with albuminuria and low eGFR among the participants in the study.

Methods: Participants were enrolled from 8 clinical sites from 4 participating countries. We determined prevalent risk factors by collecting biometric that includes albuminuria and eGFR, the later was calculated using CKD - EPI equation. Crude and adjusted odds were determined for the risk factors for albuminuria of > 30mg/g and eGFR < 60 ml/min/1.73m^2.

Results: Among the 3,323 participants with a median age of 45.73±15.5yrs, 57.3% were female. We observed that hypertension, Diabetes mellitus (DM), smoking and occurrence of CVD were significantly associated with albuminuria and reduced eGFR while gender was significantly associated with albuminuria (Table 1 and 2).

Conclusions: Hypertension, diabetes mellitus and cigarette smoking are the most prevalent risk factors for CKD in this study and are independently associated with albuminuria and low eGFR in SSA.

Funding: NIDDK Support

Risk Factors independently associated with albuminuria and Reduced eGFR

Risk factor for Albuminuria	Crude OR (95% CI)*	Adjusted OR (95% CI)**	Risk factors for reduced eGFR	Crude OR (95% CI)*	Adjusted OR (95% CI)**
Age	1.00, (0.99, 1)	1.00, (0.99, 1)	Age	1.01, (1.00, 1.01)	1.01, (1.00, 1.01)
Gender	0.62, (0.54, 0.72)	0.63, (0.55, 0.74)	Gender	0.42, (0.36, 0.48)	0.42, (0.36, 0.49)
BMI	0.99, (0.97, 1)	0.99, (0.97, 1)	BMI	0.96, (0.95, 0.98)	0.97, (0.95, 0.98)
DM	1.60, (1.35, 1.89)	1.54, (1.28, 1.86)	DM	1.71, (1.44, 2.02)	1.48, (1.23, 1.77)
Hypertension	2.80, (2.42, 3.24)	3.18, (2.69, 3.77)	Hypertension	4.74, (4.04, 5.57)	5.14, (4.32, 6.13)
Smoking status Yes vs No	1.85, (1.33, 2.54)	1.48, (1.05, 2.07)	Smoking status Yes vs No	2.39 (1.74, 3.25)	2.21, (1.60, 3.03)
Alcohol	0.98, (0.80, 1.20)	0.91, (0.73, 1.13)	Alcohol	0.73 (0.58, 0.90)	0.87, (0.69, 1.08)
CVD	3.03, (2.12, 4.34)	2.89, (1.99, 4.21)	CVD	4.19 (3.18, 6.14)	4.75, (3.39, 6.68)
Country	1.10, (0.95, 1.26)	1.05, (0.91, 1.22)			
eGFR	4.19 (3.18, 6.14)	4.75, (3.39, 6.68)			

BMI-Body mass index, CI-Confidence interval eGFR-estimated glomerular filtration rate, CVD-Cardiovascular disease, OR-Odds ratio. * Unadjusted, ** Adjusted for age, gender, recruitment status and country of origin.

TH-PO1052

CKD Epidemiology in Rural East Africa: The SEARCH-CKD Study

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Background: Little is known about CKD epidemiology among individuals living in Sub Saharan Africa (SSA) who may have heightened burden of kidney disease similar to African Americans due to shared genetic susceptibility. Non-infectious diseases and ongoing HIV epidemic can lead to significant CKD burden in SSA. Assessment of CKD burden in this region thus far has been limited by small studies or focus in urban areas. We sought to comprehensively ascertain the burden of CKD and its risk factors in rural areas, where most of the population resides.

Methods: We conducted a home-based assessment of CKD and its risk factors among a stratified random sub-sample of a large ongoing, population-based HIV test-and-treat trial in rural Uganda and Kenya (SEARCH study, NCT01864603). Prevalent CKD was defined as an eGFR <60 mL/min/1.73m2 or dipstick proteinuria ≥1+. Exposures of interest including traditional risk factors for CKD (hypertension, diabetes and HIV), were measured at mobile community health campaigns according to the SEARCH study protocol. We used household census population and sampling weights to estimate the community-based prevalence of CKD. To assess the association of potential risk factors with CKD, we used multivariable log-link Poisson models.

Results: We enrolled 5,035 participants from 30 communities (median age 41 [IQR 31-53], 64% female). The overall CKD prevalence was 8.0% (95% CI 7.2-9.0%), and varied by region: Eastern Uganda, 13.0% (11.1-15.2%), Kenya, 7.1% (5.8-8.6%) and Western Uganda, 3.7% (2.7-5.1%). Over half (52%) of persons with CKD did not have hypertension, diabetes, or HIV. Independent risk factors associated with higher CKD prevalence included being from Eastern Uganda (prevalence ratio [PR] 1.97; 95% CI 1.50-2.60), increasing age (PR 1.03; 95% CI 1.02-1.04) and HIV infection (PR 1.58; 95% CI 1.28-1.97).

Conclusions: In rural East African communities, the prevalence of CKD is high and varies by region considerably. While HIV was associated with greater CKD prevalence, over half of the CKD cases could not be attributed to HIV, hypertension or diabetes. Further research and interventions are needed to address the burden of CKD in this vulnerable population where chronic dialysis and transplant are often unavailable.

TH-PO1053

Prevalence of Proteinuria, Glycosuria, and Hypertension in a Walk-In Clinic in Rural Tanzania

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Background: Non-communicable diseases (NCD) including chronic kidney disease (CKD) and the typically comorbid conditions of diabetes mellitus (DM), hypertension (HTN), and cardiovascular disease represent increasing public health challenges in low- and middle-income countries. The present studies were conducted to explore the hypothesis that there are previously underappreciated and interrelated epidemics of CKD, DM, and HTN in rural Tanzania.

Methods: We recently reported prevalence estimates for CKD(Stages III-V) of 12.4%; Stage I or II HTN of 19.9% and DM(HbA_{1c}>6.5%) of 14.8% for a random sample of 712 residents in rural Tanzania. To assess HTN, DM, and CKD further, we obtained a single BP measurement and obtained random urine samples for dipstick measurement of glycosuria and proteinuria for individuals that voluntarily appeared at a walk-in clinic that was part of the overall study

Results: Table: Normal BP was reported for 33% (296/897) and prehypertension was reported for 35 % (317/897). Glycosuria and proteinuria were highly correlated (p≤0.001, Chi-Square). Glycosuria but no proteinuria was observed in 1.5%(13/833) of the samples; proteinuria but no glycosuria was present in 4.6%(38/833); and both proteinuria and glycosuria were present in 1.6%(14/833). Increasing age but was associated with HTN or DM but gender not. HTN was associated with overweight/obese but DM was not. DM and HTN were associated with each other(p≤ 0.002, Chi-square).

Conclusions: In summary, although the data are undoubtedly biased by the methodology available to us, we observed high prevalence of HTN, glycosuria and proteinuria in a community walk-in clinic that are consistent with the high rates of CKD, HTN, and DM observed in our earlier study. It is imperative that additional studies be performed to carefully asses the prevalence of these non-communicative diseases and their causes so that effective prevention and treatment strategies can be directed at reducing of the risk of kidney disease, DM, HTN and the expected cardiovascular complications that will follow in rural Tanzania

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	HTN STAGE 1	HTN STAGE 2	GLYCOSURIA	PROTEINURIA	OVERWEIGHT	OBESE
PERCENT	20.4	11.3	3.3	6.4	14.9	18.3
N/N	183/897	101/897	27/845	53/834	122/821	150/821

TH-PO1054

Trends in CKD Prevalence in the KEEP Mexico from 2008 to 2017

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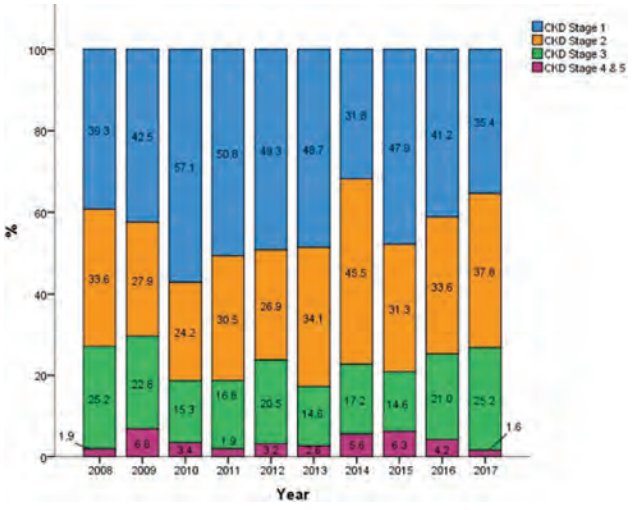
Background: The Kidney Early Evaluation Program (KEEP) is a screening and educational program aimed at detecting CKD among adults with risk factors, such as DM, HTN, family history of these conditions or CKD. In 2008 the Mexican Kidney Foundation adapted KEEP; since then, 67 screening campaigns have been performed

Methods: Adults with DM, HTN, family history of DM, HTN, or CKD participated from 2008 to 2017. All completed a questionnaire and BP, weight, and height were measured. Albuminuria and serum creatinine were obtained, and GFR was estimated

(CKD-EPI). Age-adjusted analyses were done to describe trends in CKD prevalence for almost a decade

Results: 6,885 patients with risk factors for CKD participated in a single KEEP Mexico program from 2008 to 2017. Mean age of participants was 49.7 ± 14.5 years, 69% were women. Prevalence of DM and HTN were 36.9%, and 39.5% respectively. Mean duration of DM and HTN were 10.1 and 8.5 years respectively. CKD prevalence was 30.2%, with CKD 1-2 being the most frequent stages. CKD prevalence increased over the study period, particularly at the expense of stage 2. Prevalence of stage 1 decreased and of stages 3, 4 & 5 remained virtually unchanged. CKD prevalence among patients with DM, HTN, or both was 25.3%, 21%, and 33.2% respectively, and increased over time

Conclusions: CKD prevalence in the KEEP Mexico has increased over a decade, with the most significant increase in stage 2. CKD prevalence is higher in patients with both DM and HTN compared with those with either risk factor. Further analyses are being conducted to determine the factors associated with these trends. A longitudinal analysis of KEEP participants previously reported showed that a high proportion of patients who initially tested positive for CKD were eventually confirmed to have the disease



TH-PO1055

Risk Factors for CKD Progression in the Mexican Chronic Renal Insufficiency Cohort (MCRIC) Study

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Background: Chronic kidney disease (CKD) is a major public health problem in Mexico. However, little is known about the risk factors for progression of kidney disease among individuals with CKD living in Mexico.

Methods: MCRIC is an ongoing, prospective observational cohort study of adults with CKD recruited from a referral center in Mexico City, with entry estimated glomerular filtration rate (eGFR) 20-60 ml/min/1.73 m^2. Using data from 257 participants who completed at least two study visits, we conducted Cox proportional hazards regression analysis to evaluate risk factors for CKD progression defined as 30% decline in eGFR from baseline.

Results: At study entry, mean age was 56.6 ± 0.8 years, 72.2% were male, 23% reported current cigarette smoking, and 53% had a diagnosis of diabetes. Mean body mass index (BMI) and systolic blood pressure (SBP) were 28.2 ± 4.5 Kg/m^2 and 123.4 ± 19.6 mmHg, respectively. The mean baseline eGFR was 41.1 ± 15.4 ml/min/1.73m^2, and the median (IQR) urine protein excretion 633 (124-2460) mg/24 hours. During a median follow-up of 1.9 years, there were 57 CKD progression events (event rate 11.3 per 100 person-years). In unadjusted analysis, significant predictors of CKD progression included diabetes (HR, 95% CI, 2.00, 1.15-3.50) and higher log-transformed urine protein (1.62, 1.34-1.95). After adjusting for age, sex, SBP, baseline eGFR and diabetes, only proteinuria remained a significant predictor (1.64, 1.33-2.04).

Conclusions: This cohort of adults with CKD in Mexico experienced a high rate of CKD progression which was significantly associated with baseline proteinuria. Long-term follow-up is needed to better understand risk factors for CKD progression in this population.

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TH-PO1056

Survey of Migrant Dialysis Patients Discloses a Majority with Paraquat or Other Agrochemical Exposure: A Potential Etiology for CKDu

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Background: Chronic kidney disease of unknown etiology (CKDu) is a global epidemic of renal disease. Prior studies have reported associations of CKDu with Leptospira, heat and heavy metal exposures, and agricultural chemical use. From a screen of migrant workers with ESRD at a Houston safety net hospital, we identified Gramoxone (paraquat herbicide) exposure as a possible etiologic factor. Further, we found that repetitive administration of low dose paraquat to mice resulted in renal pathology similar to that of CKDu. We expanded our survey to an outpatient safety net dialysis unit that primarily serves migrants with ESRD.

Methods: 155 patients were screened at our outpatient dialysis unit. Of these, 38 met inclusion criteria and were surveyed. Exclusion criteria included known causes of primary or secondary renal disease (e.g. diabetes, hypertension, SLE, IgA, etc.). Included patients were also negative for viral hepatitis, HIV, ANA, ANCA, or monoclonal gammopathies.

Results: Average patient age at presentation was 40 (range 24-60) and 36 of 38 surveyed patients were male. 58% (22) were from Mexico, 37% (14) from El Salvador, and one each from Guatemala and Honduras. Before immigration, 27 (71%) lived in a farm/village and 11 (29%) lived in urban area. 76% (29) reported living in hot climate and 74% (28 patients) had worked in agriculture for an average of 10+/-6 years prior to immigration. 16% (6) of patients had rare use of NSAID. 29% (11 patients) reported use of Gramoxone (paraquat-based herbicide) by name, while 22 (58%) patients reported prior herbicide and/or pesticide exposure but could not identify agents; the average duration of exposure was 10+/-5 years. 58% (22) consumed well water, and of patients with herbicide/pesticide exposure, 18 (82%) consumed well water.

Conclusions: Patients with CKDu encountered at a Houston safety net hospital consist of migrant workers, predominantly male and young. Before immigrating to the US, most of the patients lived in hot mountainous climate, in a farm/village. They did not consume sweetened drinks and their main hydration solution consisted of well water. We found no clear identifiable risk factors for uCKD, except for chronic exposure to paraquat/Gramaxone in farm workers and consumption of well water.

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TH-PO1057

Chronic Interstitial Nephritis in Agricultural Communities (CINAC) Is Strongly Associated with Pesticides

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Background: Pesticides are hypothesized as a main etiological factor behind CINAC. Our aim was to see whether pesticides are associated with CINAC.

Methods: A case control study was carried out in a CINAC endemic region in Sri Lanka. Confirmed cases with CINAC (N=125) and controls (N=180) were recruited to the study. Socio-demographic and data related to usage of applying pesticides were studied. Participant's urine samples were analyzed using ELISA to determine the levels glyphosate and paraquat.

Results: In the epidemiological study, we found CINAC is strongly associated with overall pesticide application (OR 2.34, 95% CI; 0.97-5.57), use of glyphosate (OR 5.12, 95% CI; 2.33-11.26) and use of paraquat (OR 4.53, 95% CI; 1.23-10.03) adjusted for age, sex, education, family history of CINAC and exposure modifiers. In the analytical study it has been shown that creatinine adjusted values of urinary glyphosate in CINAC cases (12.7 µg/g creatinine) was significantly higher when compared to non-endemic controls (2.4µg/g creatinine). Further, we found paraquat residues are still present in urine samples (Mean 1.08, Min-0, Max-11.42 µg/g creatinine) obtained from people living in CINAC endemic regions despite parquet had been banned in 2010 in Sri Lanka. Similar association between CKD and pesticide usage is previously reported. In 2015 Lebov and colleagues have shown herbicides alachlor, atrazine, metolachlor, paraquat, and pendimethalin, and the insecticide permethrin are associated with end stage renal disease (ESRD) in USA among licensed pesticide applicators.

Conclusions: Epidemiological and toxicological findings suggest CINAC is a toxic nephropathy associated with paraquat and glyphosate.

TH-PO1058

Far from the "Hot Coast": Prevalence of Mesoamerican Nephropathy (MeN) in a Cooler Mountain Community of Nicaragua

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Background: MeN is an "epidemic" of chronic kidney disease (CKD) of unknown etiology, affecting populations of Nicaragua (N) and other pacifical coast regions wich are all caracterized by high temperature. Dehydration, volume depletion and heat stress are all risk factors for MeN commonly linked to strenuous work conditions during seasonal harvest. In a previous study, we have found an high prevalence of MeN (26,4%) in a general population (GP) sample of a costal city (Leon, N). The pecularity of our results has been a census based general population analysis, and not a selected group of subjects as reported in the majority of the previous studies published on this issue, mainly involving sugar cane agricoltural workers. The aim of the present study was to investigate MeN prevalence in the

general population of a city (Condega, N), which is located at 560 feet above sea level, very far from the pacific coast, with different mean temperatures (daily mean 22C° vs 30 C°of Leon) and farmer activities (mainly coffee).

Methods: Out of a GP population of 28.481 inhabitants, we ramdomly selected 1024 subjects aged ≥ 18 years. The final sample of population we have studied counted 976 subjects, mean age 41.84 ± 16.73; 457 males and 519 females. Blood and urine samples were collected to estimate glomerular filtration rate (eGFR-CDK-EPI, mL/min/1.73 m2) and urine albumin excretion (UAE, albumin mg/creatinine g).

Results: Among 976 participants to the study, 725 (74.28%; mean age 39.7; 358 males and 385 females) had normal eGFR; 251 (25.7 %; mean age 46.53; 106 males and 145 females) manifested CKD (14.3 % stage 1, 16.7 % stage 2, 35.1% stage 3a, 12.4% stage 3b, 10.8% stage 4, 10.4% stage 5). Out of 173 participants in stage 3-5 of CKD, 143 (82,7%) had UAE<30 mg/g, 23 (13,3%) had UAE>30 mg/g <300 mg/g and only 7 (4%) had UAE> 300 mg/g

Conclusions: In Nicaragua, even far from the high temperatures of the pacific cost, the prevalence of MeN seems to be very high. The cause(s) of MeN remains still unknown. However, there is more than dehydration, volume depletion and heat stress.

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TH-PO1059

eGFR, CKD Epidemiology in a Nicaraguan High Risk Area for Mesoamerican Nephropathy (MeN)

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Background: MeN is linked with field working at sea level (mainly sugarcane) CKD and death in young age. Chinandega department has the two biggest sugarcane country plantations in El Viejo and Chichigalpa, CKD prevalence figures and etiology are unknown. On 2017 we enrolled age 12-22 people for a three years study to detect CKD precociously, assess CKD prevalence and risk factors, facilitate nephrological medical consult.

Methods: Population is 51746, by double randomization sampling 1202 record were completed. Plasma creatinine, blood pressure (BP), weight, height were measured; a questionnaire on occupation, water source, medical history, use of nSAID was administered. eGFR<60ml/min' was diagnostic for CKD with Schwartz bedside for children and CKD-EPI for adults (Schw_CKD_EPI). eGFR via combined full age spectrum formula (FAS) for children and CKD-EPI for adults (FAS_CKD_EPI) was calculated to choose the best suited formula for longitudinal eGFR follow-up and to compare different communities (Pearson bivariate). Schw_CKD_EPI eGFR was used for continuous and quartiles variable analyses by Anova and χ squared testing respectively. CI by Jeffreys method.

Results: Schw_CKD_EPI was 101±21, CKD-EPI 121±14, FAS_CKD_EPI 118±18. Schwartz vs FAS r=-790, p<.001. CKD prevalence was 0.75% (CI 0.31-1.36). Three municipalities had cases: Corinto 0,67% (CI 0.12-3.6),Chichigalpa 0.78%(CI 0.22-2.8), El Viejo 0.73% (CI 0.28-1.5). There was no relationship between eGFR and previous and actual occupation, medical antecedent i.e.dengue n=133, leptospirosis n=6, recurrent urinary tract infections n=209, previous episodes of dehydration n=119, frequent tonsillitis n=542, chikungunya n=293, malaria n=36, water source, fluid intake, frequent use of nSAID n=408, BP. Three communities (LM, KI, MA) were at extremes for eGFR. Differences in eGFR were better discriminated (p<.05) with FAS_CKD_EPI than Schw_CKD_EPI (pNS): LM 127±20 vs 88±18, KI 110±19vs 105±18, MA 129±12 vs. 93±17 respectively.

Conclusions: CKD prevalence is very high, well above NHANES 2011-14 age 20-39 (0.3%). No clues about causality come from our baseline data. In the subsequent years of study FAS_CKD_EPI use is advisable to focus geographical areas of investigation and health interventions, moreover its closeness with CKD-EPI values would help eGFR follow up from pediatric to adult age.

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TH-PO1060

Identifying CKD of Unknown Etiology in Sri Lanka

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Background: A kidney disease of unknown cause is common in Sri Lanka's lowland region. No evidence exists to inform an approach to a non-invasive clinical diagnosis.

Methods: In a prospective study to determine whether non-invasive measures can identify CKDu, we surveyed 600 new patients coming to nephrology clinic in a hospital servicing endemic regions over one year. 87 underwent kidney biopsy; 43 (49%) had a pathology diagnosis of tubulointerstitial disease. Using logistic regression, we tested the association of nine pre-selected factors with likelihood of tubulointerstitial nephritis on biopsy. We used bootstrap validation to calculate the model validated AUC. We tested a Full model and five parsimonious models.

Results: AUC for the Full model to predict CKDu was 0.82. A parsimonious model with age, serum albumin, and urine dipstick for protein had an AUC of 0.84 and bootstrap calibration slope of 0.84 (Table 1); with PPV 82.9% and NPV 80.4%. Patients with diabetes or hypertension recommended for kidney biopsy did not experience lower odds of a CKDu diagnosis.

Conclusions: We developed a standardized approach relying on non-invasive measures to identify probable cases of CKDu in Sri Lanka. Such an approach can strengthen CKDu surveillance, geographic mapping and rigorous investigations into cause via case-control studies.

Funding: Clinical Revenue Support

Predictors	Full model	Parsimonious model
Urine dipstick negative for protein	+	+
Age (cubic spline)	+	+
HTN	+	
Diabetes	+	
Serum albumin	+	+
Hematuria	+	
No pyuria	+	
Potassium	+	
Woman	+	
Urine dipstick negative * Serum albumin	+	+
C statistic	0.89	0.87
Sensitivity	83.7	79.1
Specificity	79.6	84.1
Positive predictive value	80.0	82.9
Negative Value	83.3	80.4
Bootstrap Validated C statistic	0.82	0.84
Calibration slope	0.59	0.84

TH-PO1061

KIM-1 as an Early Biomarker of Kidney Injury in Agricultural Communities in Sri Lanka

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Background: Chronic kidney disease of unknown etiology (CKDu) is common among agricultural communities in Sri Lanka (SL), with prevalence between 10–15%. No definitive causes for CKDu has been identified. Early detection through community screening is essential for estimating true prevalence and guiding preventive management.

Methods: Inhabitants of selected villages in SL who worked in rice, sugarcane or vegetables farming, and a village of fishermen were recruited (647, male 61%, mean age 44.7 y). Estimated GFR, urine albumin, and KIM-1, were measured. Logistic regression analysis was used to determine the odds ratios for underlying kidney proximal tubule (PT) injury (urinary KIM>250 pg/mg creat).

Results: Kidney disease, defined by GFR<60 ml/min and/or albuminuria >300 mg/mg, was present in 9% of the population. KIM-1 negatively correlated with eGFR, positively correlated with urine albumin (r~0.2; p<0.01, for both). KIM-1 levels were elevated in 27% of the population who had no defined kidney disease, indicating that these subjects have underlying PT injury and may be more prone to developing CKD. KIM-1 levels were higher in farmers than in fishermen (151±75 vs 36±21 pg/mg; p=0.01). Among farmers, vegetable farmers had the highest levels (310±54 pg/mg; p<0.01). Wasgamuwa, an endemic CKDu rice farmer community, had the highest percentage of kidney disease (24%) and higher levels of KIM-1 when compared to Agunukolapallassa, a non-endemic CKDu rice farmer community (454±93 vs 50±20 pg/mg; p<0.01). Importantly, 62% of Wasgamuwa farmers had KIM-1 levels >250 pg/mg, indicating that a significant fraction of this population may have subclinical kidney injury. Farmers have ~5 times higher risk of having underlying PT injury than fishermen, independent of age, sex, diabetes and hypertension (OR 4.8, 95%CI: 2.6 to 8.9; p<0.01). Among farmers, vegetable farmers were twice at risk of having underlying PT injury than sugarcane farmers, after adjusting for age, sex, diabetes, hypertension and farming duration (OR 2, 95%CI, 1.2 to 3.9; p=0.04).

Conclusions: KIM-1 is a potential biomarker for screening populations at risk for underlying kidney injury in endemic and non-endemic areas of CKDu in SL.

TH-PO1062

Prevalence and Prognosis of CKD in Italy: The Role of Demographic Shift Towards Older Age Groups

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Background: Prevalence of chronic kidney disease(CKD) stages 3-5 in Europe is variable(1.0-5.9%), but lower than in United States(US)(13%). In Italy, real-world data is uncertain as previous studies were limited by methodological sampling and lack of prognostic data. To address this issue, we designed a population study based on administrative data, including the elderly typically under-represented. Objectives:to estimate CKD 3-5 stages prevalence in the resident population of a Tuscan city health unit(Empoli ASL), with sub-analysis in diabetic and hypertensive patients;to calculate the relative risk(RR) of myocardial infarction, stroke, heart failure, peripheral artery disease and death;to standardize data on the whole regional population.

Methods: All individuals referring to Empoli ASL were reviewed through the Tuscany Regional Agency for Health database. Patients>45yrs with a serum creatinine determination(SCr) in 2011-2013 by isotopic dilution mass spectrometry to estimate GFR by CKD-EPI equation were included and stratified in CKD 3a, 3b, 4-5(Renal Replacement Therapy patients excluded). Crude and standardised prevalence by sex, age and comorbidity were recorded. RR of death and cardiovascular events was assessed by Multivariate Cox analysis(controls=GFR>60ml/min).

Results: Of the 238,873 Empoli residents, 79,277(78%) were>45yrs and performed at least one SCr. 9082(11.4%) had GFR<60ml/min and 686(0.87%) had GFR<30ml/min. Age and sex distribution of CKD 3-5 showed higher prevalence in females and older age(p <0.0001)(Tab1). eGFR<60ml/min prevalence in the standardized general population>45yrs was 10.5%: stage 3a=7.1%, 3b=2.6%, 4-5=0.8%. Prevalence increased with age, in 45-74yrs group was 4.4%, in the group>85yrs: stage 3=36.5%, 4-5=4.1%(Fig1). RR of death and cardiovascular events in Tab2.

Conclusions: This is the first Italian study to evaluate CKD prevalence with a large sample (238,000 inhabitants, 6.2% Tuscany population). CKD prevalence in 45-74yrs in Tuscany resulted 4.4% (lower than US and among the lowest in Europe), however including age>45yrs it reached 10.5%, highlighting the higher prevalence in the elderly, associated with more age-related comorbidities. The comparison of CKD prevalence between Europe and US, usually based on age group 45-74yrs, underestimates the real prevalence in European countries.

TH-PO1063

Determinants of Intraregional Differences in Renal Function in the Northern Netherlands: The Lifelines Cohort Study

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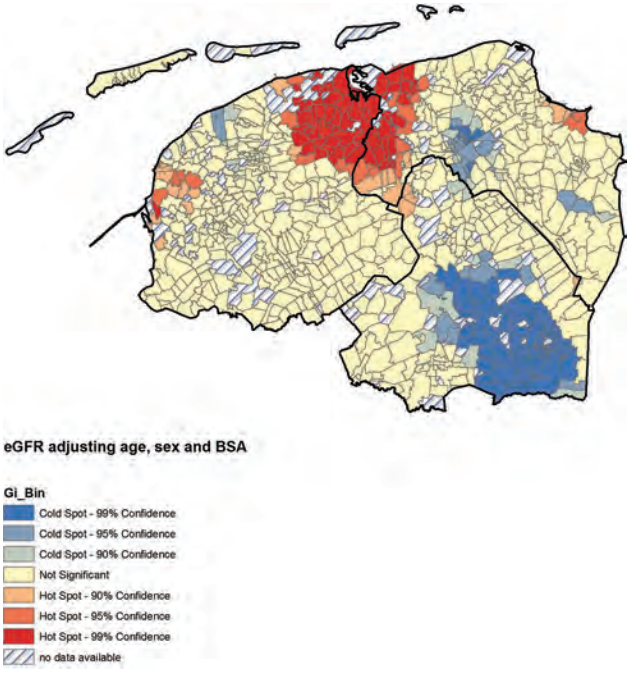
Background: Although interregional disparity in CKD prevalence has been reported globally, it is unclear which factors drive renal function clustering within regions. We studied the intraregional distribution of renal function in the Northern Netherlands and identified factors associated with its geographic variability.

Methods: We included 130,545 participants in LifeLines, a prospective population-based cohort in the Northern Netherlands. Spatial analysis was performed to identify spatial clusters of eGFR (CKD-EPI), and multivariable logistic regression was used to identify demographic, clinical and environmental factors associated with 99% confidence hot *vs* cold spot clusters.

Results: Significant spatial clustering of high (hot spot) and low (cold spot) eGFR was found independent of age, sex and BSA (Figure). Participants in cold spot area had lower eGFR (95.47±15.50 *vs.* 98.47±14.61 ml/min/1.73 m^2) and lower 24h creatinine clearance (126.75±35.48 *vs.* 130.94±33.72 ml/min) compared to those in hot spot area (p<0.05). In multivariable logistic regression, blood pressure (OR for being in cold spot: 1.01 [95% CI 1.00-1.01]), BMI (1.03[1.03-1.04]), serum potassium (0.38[0.34-0.43]), diuretics use (0.73[0.60-0.90]), education level (1.10[1.05-1.15]) and urbanity (2.77[2.66-2.88]) were all independently associated with spatial distribution of renal function (model R^2=0.301). Subanalysis in 6,535 individuals showed that PM10 (3.67[3.07-4.39]), PM2.5 (5.02[3.90-6.47]), NO_2 (1.11[1.07-1.15]) were independently associated with renal function distribution, respectively.

Conclusions: Intraregional clustering of renal function was observed in the Northern Netherlands; determinants included blood pressure, BMI, serum potassium, diuretics use, education level, urbanity, and air pollution.

Funding: Government Support - Non-U.S.



TH-PO1064

Incidence of CKD Stages 1-5 in Iceland

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Background: Chronic kidney disease (CKD) is a major public health problem with a prevalence in the range of 5-10%, but its incidence is less clear due to lack of longitudinal data. The aim of this study was to estimate the incidence of CKD stages 1-5 based on serum creatinine (SCr) measurements, albuminuria and other markers of kidney damage.

Methods: In this retrospective study from 2008 to 2016, we obtained all standardized SCr and urine protein measurements from every clinical laboratory in Iceland. Information on age, sex, kidney-specific diagnoses and co-morbid conditions were also retrieved from nationwide electronic medical records. eGFR was calculated from SCr using the CKD-EPI equation. Incidence of CKD was defined as presence of kidney damage or eGFR <60 mL/min/1.73m^2 for more than 3 months, in individuals without CKD at study entry. Kidney damage was defined as albuminuria or presence of kidney-specific diagnoses including glomerular diseases and structural kidney abnormalities. CKD was staged according to the KDOQI guidelines. Incidence rates were standardized to the EU27 population.

Results: We obtained 2,049,482 SCr values for 213,011 individuals. The median (range) age was 63 (18–109) years; 47% were men. A total of 205,484 did not have evidence of CKD upon study entry, of whom 21,160 developed CKD during the study period. The annual age-standardized incidence of CKD 1–5 per 100,000 was 1,023 in men and 1,323 in women. The annual age-standardized incidence of CKD per 100,000 in men was 117 for stage 1, 153 for stage 2, 514 for stage 3A, 184 for stage 3B, 58 for stage 4 and 16 for stage 5 CKD. In women, the age-standardized incidence of CKD per 100,000 was 198 for stage 1, 141 for stage 2, 678 for stage 3A, 247 for stage 3B, 63 for stage 4 and 12 for stage 5 CKD.

Conclusions: This nationwide Icelandic study comprising SCr values and other markers of kidney damage from the majority of the Icelandic population indicates a CKD incidence of approximately 1% per year, although slightly higher in women than men.

Funding: Government Support - Non-U.S.

TH-PO1065

Association Between CKD and Socioeconomic Status: The Korea National Health and Nutrition Examination Survey 2010-2015

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Background: The prevalence of chronic kidney disease (CKD) has been increasing. CKD affects in the patients' aspects regarding economic, social and emotional status. However, few recent studies dissecting the socioeconomic characteristics focused on CKD patients. We examined associations of CKD with annual income levels, education, smoking and alcohol consumption status, and emotional status independent of age and sex.

Methods: We performed a cross-sectional study of 23,701 participants with CKD, using data from the Korea National Health and Nutrition Examination Survey (KNHANES), obtained from 2010 to 2015. CKD was defined as dipstick positive proteinuria or estimated glomerular filtration rate<60mL/min/1.73m^2. The same number of participants was propensity score matched by age and sex (each group n=1,952). Clinical and socioeconomic characteristics of two groups were analyzed.

Results: For participants with CKD versus without CKD, the estimated prevalence of hypertension and diabetes was 41.8% versus 32.4% and 24.3% versus 13.6%, respectively (each P<0.001); from the lowest to the highest, the income quartiles were 26.1%, 24.7%, 25.2%, 24.0% versus 22.6% 24.4% 26.0%, 27.0%, respectively (P=0.038). The Education level was lower in patients with CKD than in normal subjects. There were more irregular workers in the CKD group. In CKD group, current smoker was higher than non CKD group (26.8% versus 21.8%, P<0.001) but case with no history of alcohol drinking in the past year was also higher (28.3% versus 20.6%, P<0.001). Depressive symptoms for two consecutive weeks and suicidal ideation were higher in CKD group (12.2% versus 8.8%, P<0.001; 9.8% versus 7.2%, P<0.001, respectively). In logistic regression, the risk of CKD was 1.21 (95% CI 1.00-1.46, P=0.393) in lowest quartile of income group, 1.25 (95% CI 1.00-1.56, P=0.049) and 1.11 (95% CI 0.84-1.46, P=0.453), respectively, in the order of the quartiles based on the highest group. After adjusting, the risk of CKD was 1.17 (95% CI 0.97-1.42, P=0.085), 1.24 (95% CI 0.99-1.57, P=0.059) and 1.19 (95% CI 0.89-1.57, P=0.226), respectively.

Conclusions: Patients with CKD are associated with other chronic disease, low annual income, low education level, irregular workers, high smoking rate, and depressive mood contributing substantially to the burden for CKD.

TH-PO1066

Recent Prevalence and Characteristic of CKD Including Diabetic Kidney Disease Among Participants of Nationwide Health Check Program in Japan

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Background: Diabetic kidney disease (DKD) is most important target of intervention for improvement of outcome of chronic kidney disease (CKD). Recent prevalence and characteristic of CKD including DKD among a Japanese general population are not fully elucidated.

Methods: Subjects were residents from 27 of the 47 prefectures in Japan who enrolled in national health insurance and participated in annual health check program including a CKD screening in 2015 (n=1,059,888; age, 40-74 years; male, 42.8%; diabetics [HbA1c≥6.5% or undergoing pharmacotherapy for diabetes], 12.3%). CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+. CKD comorbid with diabetics was regarded as DKD. Cross-sectional analysis of the distribution of GFR (G) and albuminuria (A) categories by sex/age group among participants were performed. (A1: <1+, A2: 1+, A3: ≥2+ by dipstick)

Results: The distribution of each G and A categories are summarized in **Table**. Thus, in this screened population, the crude prevalence of CKD was 19.7%, and those with reduced renal function classified between G3-5 accounted for 16.6%. Among diabetics, the crude prevalence of CKD was 27.7% and was higher than in non-diabetics across all age groups with tendency that became noteworthy in younger population. (**Figure 1**) As for the distribution of G and A category among DKD, G3a and A1 were most prevalent in the age groups ≥65 years. (**Figure 2**)

Conclusions: Recent prevalence of G3-5 might slightly increase compared with similar cross-sectional analysis in 2008 (Iseki K, et al. Clin Exp Nephrol 16: 244-249, 2012). The overwhelming majority of aged DKD remain mild to moderate renal dysfunction without albuminuria. Therefore, it is important for screened DKD that strategic allocation of health resources according to age and individual risk would be established.

Funding: Government Support - Non-U.S.

Table Distribution (%) of each GFR-albuminuria (G-A) categories among screened population

	A1	A2	A3
G1	12.1	0.4	0.1
G2	68.2	2.0	0.6
G3a	13.7	0.7	0.4
G3b	1.2	0.2	0.2
G4+5	0.1	0.1	0.1

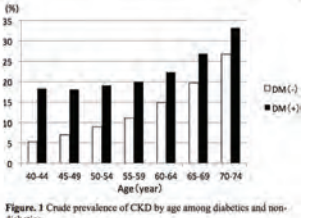

Figure. 1 Crude prevalence of CKD by age among diabetics and non-diabetics

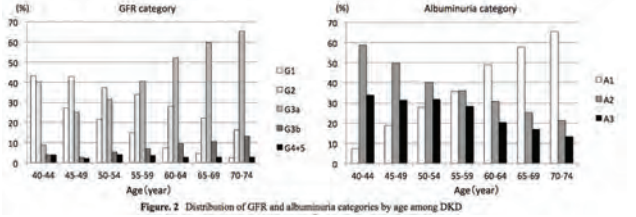

Figure. 2 Distribution of GFR and albuminuria categories by age among DKD

TH-PO1067

Prevalence of CKD in the Punjab, Northern India: A Comparison with the United States

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Background: India is witnessing a disturbing growth in non-communicable diseases (NCDs), including CKD. Recently, a WHO STEPS survey was conducted in the state of Punjab in northern India to collect data from the adult population on NCD risk factors (2014-2015). We sought to compare the prevalence of CKD and its risk factors between this large state in northern India and the US.

Methods: Data from 1,928 participants in the Punjab survey and 5,588 in the US (National Health and Nutrition Examination Survey- NHANES, 2013-2014) with complete information on estimated glomerular filtration rate and albuminuria were examined. Both regions used multi-stage stratified sampling designs to collect data representative of the general population. All analyses used sampling weights.

Results: The average age in the Punjab sample of adults (age 20 years+) was significantly lower than the US (39.2 vs. 47.5 years, p<0.0001) and had a higher proportion of males (57.8% vs. 48.1%, p<0.0001). The US had a much higher percentage of high school or higher education and private health insurance coverage (p<0.0001). In the US body size was much larger in terms of height, weight, BMI, and waist circumference. While smoking and obesity were higher in the US, diabetes and hypertension were much more common in Punjab (39.6% vs. 10.7% and 49.5% vs. 39.8%, respectively, p<0.0001). No differences were seen in the prevalence of cardiovascular disease or triglyceride levels, although the US had higher total cholesterol. Significant differences were seen in the prevalence of CKD markers, with lower prevalence of eGFR < 60 ml/min/1.73m^2, but markedly higher albuminuria (see Table).

Conclusions: We report a strikingly high prevalence of albuminuria in the Punjab (with well over a third of the adult population being affected!), and much higher prevalence of both DM and HT compared with the US. In contrast, the prevalence of eGFR <60 was relatively low. These findings need to be further confirmed, and if true have enormous public health and resource implications for a low-middle income country such as India, specifically in the realm of CKD, cardiovascular disease and other NCDs.

Measure	Punjab (2014-2015) Mean (SE) or %	US (2013-2014) Mean (SE) or %	P value
Creatinine (μmol/L)	0.70 (0.01)	0.91 (0.01)	<0.0001
eGFR (mL/min/1.73m^2)	113.9 (1.1)	93.0 (0.6)	<0.0001
eGFR < 60 mL/min/1.73m^2	2.0 %	7.5 %	<0.0001
Albumin: Creatinine ratio [ACR (mg/g; median)]	25.5 (2.5)	7.0 (2.9)	<0.0001
Albuminuria (ACR > 30 mg/g)	47.3 %	10.1 %	<0.0001

TH-PO1068

Targeted Screening for Albuminuria in Diabetes Mellitus: A Strategy Worth Revisiting?

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Background: Albuminuria is a risk factor for cardiovascular disease (CVD), kidney disease and their progression. Current guidelines recommend screening all people with diabetes (DM) for albuminuria to identify those at greatest risk. However, only 40% of DM patients currently receive albuminuria screening. We assessed patient characteristics associated with albuminuria in people with DM.

Methods: Associations between individual characteristics (self-reported and biometric) and albuminuria (albumin-to-creatinine ratio of ≥30 mg/g) were assessed among 4,222 individuals with DM (self-reported, or HbA1c > 7%), aged 20+ years, from the National Health and Nutrition Examination Survey (1999-2014), using multivariable survey-weighted logistic regression. We assessed model predictive ability using Harrell's c-statistic.

Results: Mean age was 59 (range 20-85+) years and the prevalence of albuminuria was 30.3% (95% CI: 28.7-31.8%). Significant predictors of albuminuria are shown in the Table below (c-statistic = 0.67, indicating moderate prediction of albuminuria).

Conclusions: In this study several self-reported and biometric characteristics were independently associated with albuminuria and collectively, moderately predictive of albuminuria. Targeted screening of people with DM at high risk for albuminuria may improve albuminuria detection and in turn, may help with prevention or management of CVD and kidney disease.

Funding: Other U.S. Government Support

Risk Factor	Mean (SEM) or %[1]	Adjusted Odds Ratio[2]	95% Confidence Interval (CI)	p-value
Age:				
20-24 years	0.6%	1.01	0.30 – 3.38	0.99
25-64 years	62.1%	1.00	-	Ref
65-74 years	22.7%	1.40	1.14 – 1.73	0.002
75 + years	14.6%	2.17	1.71 – 2.76	<0.001
Male (vs. female)	50.8%	1.45	1.18 – 1.77	<0.001
Race/ethnicity:				
White	55.4%	1.00	-	Ref
Black	15.1%	1.40	1.15 – 1.71	<0.001
Mexican American	9.2%	1.94	1.53 – 2.44	<0.001
Other Hispanic	6.2%	1.03	0.62 – 1.70	0.92
Other non-Hispanic	14.1%	1.92	1.30 – 2.82	0.001
Current smoking (yes v. no)	17.8%	1.42	1.12 – 1.81	0.005
Uncontrolled high BP* (yes v. no)	75.9%	2.14	1.65 – 2.77	<0.001
CVD (yes v. no)	25.1%	1.48	1.24 – 1.78	<0.001
Total cholesterol (per 50 mg increase)	192 (1.0)	1.21	1.10 – 1.32	<0.001
High Uric Acid** (yes v. no)	23.4%	1.52	1.21 – 1.90	<0.001
Physical activity^ (yes v. no)	53.6%	0.81	0.68 – 0.98	0.026
High HbA1c^^ (yes v. no)	53.0%	1.81	1.49 – 2.19	<0.001

[1]Mean or proportion of risk factor in population; [2]Adjusted odds ratio for association between risk factor and albuminuria; *Uncontrolled high BP (blood pressure) = SBP (systolic BP) ≥ 140mmHg or DBP (diastolic BP) ≥90; **For men: Uric Acid > 7.2 mg/dl and women: Uric Acid > 6.1 mg/dl; ^Answered yes to the question "in a typical week do you do any moderate to vigorous intensity exercise for at least 10 minutes continuously?"; ^^HbA1c (hemoglobin A1C) > 7%; Abbreviations: CVD= cardiovascular disease; SEM=standard error of the mean. Multivariable model includes all measures in table, plus non-significant predictors body mass index, low HDL, dietary Na+ and K+ intake, and ACE/ARB use.

Adjusted odds ratios and 95% confidence intervals for the association between characteristics and albuminuria in people with diabetes

TH-PO1069

Population Estimates of Predicted Risk of Kidney Failure Among Individuals with Hypertension in Rural Bangladesh, Pakistan, and Sri Lanka - Health Systems Perspective

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Background: South Asia is suffering an increasing burden of hypertension, chronic kidney disease (CKD) and end-stage kidney disease (ESKD). We estimated the proportion and number of individuals aged≥40 years with hypertension and CKD carrying a high risk for ESKD in rural Bangladesh, Pakistan, and Sri Lanka.

Methods: We analyzed baseline data from ongoing Control of Blood Pressure and Risk Attenuation (COBRA) study on 2643 hypertensives aged≥40 years recruited via door-to-door sampling in 30 rural communities in Bangladesh, Pakistan, and Sri Lanka. Serum creatinine was measured, and CKD-EPI eGFR was computed. Predicted risk of kidney failure at five years was computed using 4-variable (age, sex, albuminuria, eGFR) Kidney Failure Risk Equation (KFRE) in hypertensives with CKD Stage 3 or worse (eGFR <60 ml/min/1.73 m^2). Country-level population statistics from 2016 World Bank Data were used to project population estimates of these conditions.

Results: See attached table

Conclusions: There is a high burden of CKD progressive to ESKD in hypertensive individuals in rural South Asia. There is noticeable cross-country heterogeneity in the proportion and number of hypertensive individuals with CKD Stage 3 or worse (highest in Sri Lanka), proportion at high risk of ESKD (highest in Pakistan), and the absolute number at high risk of ESKD (highest in Bangladesh). Countries in South Asia, need immediate public health measures to prevent onset and progression of CKD including establishing timely referrals to nephrologists, and accessible renal replacement therapy programs. **Limitations:** KFRE has not been validated for use in South Asian rural health systems. Our population estimates of CKD are limited to individuals with hypertension.

Funding: Government Support - Non-U.S.

	Bangladesh	Pakistan	Sri Lanka
Total population in 2016, n	162,951,560	193,203,480	21,203,000
Rural population in 2016, n	105,861,481	117,421,345	17,300,164
Rural population aged≥40 years, n	25,904,885	22,055,055	6,302,214
Proportion of hypertension among rural adults aged≥40 years,%	26.8	21.7	39.8
Rural hypertensives aged≥40 years, n	6,942,509	4,785,947	2,508,281
Proportion of CKD Stage 3 or worse among rural hypertensives aged≥40 years,%	11.8	2.9	48.0
Rural hypertensives aged≥40 years with CKD Stage 3 or worse, n	819,216	138,792	1,203,975
Proportion of high risk (≥10%) for renal failure among rural hypertensives aged≥40 years with CKD Stage 3 or worse,%	11.8	30.0	4.7
High risk (≥10%) for renal failure among rural hypertensives aged≥ 40 years with CKD Stage 3 or worse, n	118,511	66,504	46,601

Hypertensive individuals with chronic kidney disease(CKD) at high risk for end-stage kidney failure (ESKD) in rural communities in Bangladesh, Pakistan and Sri Lanka

TH-PO1070

CKD and At-Risk of CKD Registry: CURE-CKD

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Background: Most healthcare systems have not been proactively prepared to identify patients with or at-risk of chronic kidney disease (CKD) to improve care and clinical outcomes. The aim of this study was to classify and describe these patients in two large healthcare systems.

Methods: PSJH and UCLA healthcare systems collaboratively formed a registry (CURE-CKD) from their respective electronic health records (EHR). Participants were identified by a diagnosis of CKD or at-risk of CKD (diabetes, hypertension, pre-diabetes) by ICD-9/10 codes, guideline-based clinical criteria, and medication specific to a particular condition from the years 2006-2016.

Results: CURE-CKD includes 2,401,403 individuals. The table shows baseline characteristics by CKD (N=554,051) and at-risk of CKD (N=1,847,352) groups.

Conclusions: Real world, practice-based evidence can be used to classify patients as a platform for strategies to prevent CKD progression and complications as well as incident CKD.

Funding: Private Foundation Support

Demographics	CKD (N=554,051)		At-Risk (N=1,847,352)	
Gender	n	%	n	%
Men	241,938	44	898,991	49
Women	312,081	56	947,810	51
Race				
White	404,713	73	1,252,779	68
Black	26,685	5	86,421	5
Asian	28,581	5	103,186	6
Not Classified	85,811	16	376,127	20
Dwelling location				
Rural	66,410	12	210,411	11
Urban	482,829	87	1,621,077	88
Conditions	n	%	n	%
Diabetes*	249,259	45	597,030	32
Hypertension*	388,121	70	1,370,551	74
Pre-diabetes*	87,174	16	315,095	17
Clinical Characteristics	mean	SD	mean	SD
Age (years)	71	18	57	17
eGFR (mL/min/1.73m2)	61	26	90	21
Systolic blood pressure (mm Hg)	130	18	130	16
HbA1c (%; diabetes subset)	7	2	7	2
CKD stage	n	%	n	%
CKD 1-2	247,385	45	-	-
CKD 3	233,903	42	-	-
CKD 4	32,845	6	-	-
CKD 5	19,611	4	-	-
CKD unstaged**	20,307	4	-	-

*diabetes, hypertension and/or pre-diabetes are not mutually exclusive conditions, **identified by ICD code without CKD stage

TH-PO1071

Baclofen Usage in Patients with Diminished Kidney Function

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Background: Baclofen, a muscle relaxant, is primarily excreted via the kidneys. As per pharmacy dosing guidelines, it is contraindicated in paients with eGFR <30cc/min and on dialysis.

Methods: We examined all orders in 2017 for baclofen across 15 hospitals in two large health systems. For each order, we determined the dose and frequency ordered and whether a dose was actually administered. Renal function was determined using the CKD-EPI equation based upon the most proximate serum creatinine at the time of the baclofen order. Presence of dialysis was based upon any order for HD or PD placed during the same visit within 7 days prior to baclofen order. The physician notes were then reviewed from the start date of baclofen administration- 2 days after it was discontinued to see if any new neurological symptoms arose (headache, dizziness, weakness, nausea, vomiting, seizures, lethargy, hallucinations, agitation)

Results: Over 2652 unique orders were placed for baclofen in one health system informatics records. 131 orders were in patients with eGFR <30cc/min (4.9%), 93 (71%) resulted in at least one dose administered to the patient. Similar baclofen usage was seen at second institution with 1182 inpatient unique orders with 95 occurring in patients with eGFR <30cc/min (8%). 86% of the orders were NOT PRN orders, while remaining were PRN orders. Muscle spasms and hiccups were the indications for PRN orders. 46% of the patients- females; 58% -white vs 18% AA; 20% patients were ESKD on dialysis; 8% were incident dialysis patients (required initiation of HD this admission). Most baclofen orders were written by internal medicine (84%) services followed by surgical (7%) and others (4%). 80% of the orders were written by either attendings (50%) or residents (50%), and the remaining 20% by NP/PAs. 42% of the orders led to neurological symptoms findings.

Conclusions: Baclofen was ordered in 5-8% of patients with significantly impaired kidney function. Most baclofen orders were standing medications rather than PRN, and were ordered at high doses, increasing the toxicity risk. A significant percentage of the orders were written by internal medicine physicians. This study highlights the need for an urgent education of renal clearance of several medications such as baclofen to prescribing staff & pharmacists.

TH-PO1072

The Burden of Polypharmacy in Patients with CKD: The GCKD Study

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Background: Patients with chronic kidney disease (CKD) bear a substantial burden of comorbidities leading to the prescription of multiple medications. However, data on medication use patterns in this population is scarce. This study uses data of a longitudinal, multicentre study in CKD patients to evaluate drug use trajectories as well as the prevalence of polypharmacy and its associated risk factors over 4 years of observation.

Methods: We analyzed data of 5217 patients aged 18– 74 years with an estimated glomerular filtration rate (eGFR) between 30–60 ml/min/1.73m^2 or an eGFR ≥60 and overt proteinuria (>500 mg/d) who participated in the German Chronic Kidney Disease (GCKD) study. Self-reported data on current medication use assessed at baseline (2010-2012) and after 4 years of follow-up were used for this analysis. Prevalence and risk factors associated with polypharmacy (defined as the use of ≥5 drugs/d) as well as initiation or termination of polypharmacy were evaluated using multivariable logistic regression.

Results: The prevalence of polypharmacy at baseline and follow-up was almost 80 % and ranged from 62 % in patients with eGFR >90 ml/min/1.73m^2 to 86 % in those with eGFR 30–45 ml/min/1.73m^2. Patients took on average 7 medications per day (range 0-20), most frequently beta blockers, ACE-inhibitors and statins. In multivariate analysis, female sex and a lower educational level were independently associated with polypharmacy. Increasing CKD stage, age and BMI as well as diabetes mellitus, cardiovascular disease and a history of smoking were significantly associated with both, the prevalence of polypharmacy and the maintenance of polypharmacy over time. Comorbid diabetes mellitus was a significant risk factor for the initiation of polypharmacy in CKD patients (OR 2.46, p=0.003).

Conclusions: This study highlights the medication burden in CKD patients and strongly suggests that further research is needed to address the risks of polypharmacy in this vulnerable population.

Funding: Government Support - Non-U.S.

TH-PO1073

Opiate and Non-Opiate Analgesic Use and Mortality Among CKD Patients Transitioning to Dialysis

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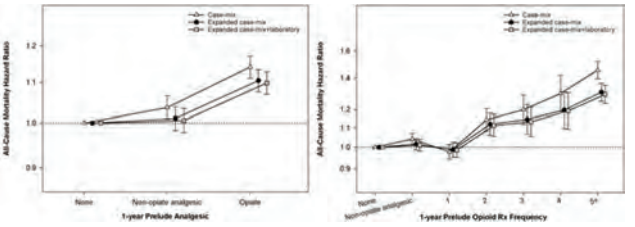
Background: Population based studies show there is a high prevalence of chronic kidney disease (CKD) patients suffering from chronic pain. While opiates are frequently prescribed as analgesics, there may be toxic accumulation of metabolites, particularly among those with non-dialysis dependent CKD (NDD-CKD) progressing to end-stage renal disease (ESRD). We thus sought to examine the association of opiate vs. non-opiate analgesic use during the pre-ESRD (prelude) period with post-ESRD mortality risk among NDD-CKD patients transitioning to dialysis.

Methods: We examined a national cohort of US veterans with NDD-CKD who transitioned to dialysis over 2007-14. Among patients who had receipt of prescriptions in the Veterans Affairs (VA) Healthcare System within one year of transitioning to dialysis, we examined the association of pre-ESRD analgesic use (opiate analgesic, non-opiate analgesic, vs. no analgesic use) with post-ESRD all-cause mortality risk using adjusted Cox models.

Results: Among 57,764 patients who met eligibility criteria, pre-ESRD opiate use was associated with higher post-ESRD mortality risk (ref: no analgesic use), whereas non-opiate analgesic use was not associated with higher death risk in expanded case-mix adjusted analyses: HRs (95%CIs) 1.11 (1.08-1.13) and 1.01 (0.98-1.04), respectively. In sensitivity analyses, increasing frequency of opiate prescription in the one-year prelude period was associated with higher post-ESRD mortality risk: (ref: no analgesic use): HRs (95%CIs) 0.99 (0.95-1.02), 1.12 (1.06-1.18), 1.15 (1.07-1.23), 1.20 (1.10-1.31), and 1.31 (1.25-1.37) for 1, 2, 3, 4, and ≥5 prescriptions, respectively.

Conclusions: In NDD-CKD patients transitioning to dialysis, more frequent pre-ESRD opiate use was associated with higher post-ESRD death risk, whereas non-opiate analgesic use was not associated with higher mortality. Further studies are needed to identify non-opiate based interventions for pain management in this population.

Funding: NIDDK Support



TH-PO1074

Polypharmacy in Older Patients Developing Advanced CKD in 6 European Countries: Results from the EQUAL Study

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Background: Polypharmacy is increasing in the general population. We aimed to describe associations with the number of prescribed medications to identify patients who are most likely to experience polypharmacy.

Methods: The EQUAL Study follows patients aged 65+ years from 6 European countries whose eGFR dropped to ≤20 ml/min/1.73m^2 for the first time. Demographic, clinical and medication data were collected at baseline. Univariable and multivariable linear regression were used to determine the association between baseline factors (age, sex, education, eGFR, comorbidity and country) and number of medications.

Results: Recruited patients (n=1647) had a mean age of 76.4 years (SD 6.7) and 65.2% were male. Multimorbidity was common; the mean Charlson Comorbidity Index (CCI) was 7 (SD 1.9). The mean number of medications was 8 (SD 3.6, range 0-21) and 75% of patients were on >5 medications. In the univariable analysis, all age groups except >85 years were on more medications than the reference group (65-70 years). Each additional CCI point was associated with 0.48 additional medication (p<0.001). As education attainment increased, people were on fewer medications. German patients were on 1.72 additional medications and Swedish patients were on 3.68 fewer medications when compared to the UK (both p<0.001). Sex and eGFR had no association with number of medications. After adjusting for country, education and CCI, the number of medications was only associated with age in the most elderly group. Those >85 years were on 1.41 fewer medications compared to those aged 65-70, table 1.

Conclusions: Polypharmacy was common amongst EQUAL recruits, but the relationship with age is complex. Unlike the general population where polypharmacy increases even to the oldest age groups, the oldest EQUAL recruits were on fewer medications. This contrast may reflect de-prescribing.

Table 1. Linear regression of number of medications by age group

Age group (years)	Univariable			Multivariable (country, education)			Multivariable (country, education, CCI)		
	Regression coefficient	P value	95% CI	Regression coefficient	P value	95% CI	Regression coefficient	P value	95% CI
65-70	Reference	-	-	-	-	-	-	-	-
71-75	0.92	<.001	0.41-1.43	0.42	0.109	-0.09-0.94	0.06	0.817	-0.57-0.45
76-80	0.67	0.009	0.17-1.17	0.42	0.106	-0.09-0.92	-0.20	0.443	-0.70-0.30
81-85	0.64	0.021	0.10-1.20	0.32	0.276	-0.25-0.89	-0.65	0.028	-1.24--0.07
>85	0.14	0.685	-0.56-0.85	-0.69	0.056	-1.4-0.02	-1.41	<.001	-2.11--0.71

TH-PO1075

Assessing Baseline Medication Use in CKD: An Analysis of the SHARP-ER Study

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Background: Medication use of patients with CKD in Australia is accepted as high, but systematic, national data has not been available. The Pharmaceutical Benefits Scheme (PBS), a national program providing medication subsidies in Australia, offers a novel means of medication use pattern assessment in CKD based on routinely collected data. We assessed baseline medication use in CKD patients of the SHARP-ER study using PBS data.

Methods: Australian participants from the SHARP-ER study, a 5-year post-trial (2010-2015) extended follow-up of SHARP participants known to be alive at the end of the trial (study of cholesterol-lowering in CKD) in Australia, New Zealand and Malaysia, were linked to the PBS. Prescription medication dispensation in the year prior to SHARP-ER baseline, defined as the first study visit which occurred 1.5-2 years following the final SHARP visit, were obtained. We examined medication use (receipt of ≥1 prescription) from any of the following medication groups: cardioprotective (blood pressure-lowering, lipid-lowering, glucose-lowering, anticoagulant, antiplatelet, anaemia treatment), anti-infective, immunosuppressant, proton pump inhibitor (PPI) treatment and others.

Results: Of 304 participants, 86 (28.3%) were on maintenance dialysis at baseline. Overall, there were 11,272 unique prescriptions dispensed in the year prior to baseline which included those for cardioprotective (58.4%), anti-infective (9.6%), immunosuppressive (7.6%), PPI (12.6%) treatment and others (11.6%). On average, patients were prescribed 6 different medications (IQR:4-8). The distributions of medication use across the medication groups in the 304 participants were: 92.8%, 68.4%. 25.3%, 53.3% and 54.3%, respectively. The proportion of patients receiving ≥3 medication groups was significantly higher among those on dialysis (76.7% vs. 64.7%;p=0.04) compared with non-dialysis CKD patients.

Conclusions: PBS data in patients with moderate-to-severe CKD suggests a high medication burden primarily directed at cardiovascular risk mitigation. Further longitudinal assessments of cardioprotective and anti-infective medication use according to patient characteristics are needed.

Funding: Government Support - Non-U.S.

TH-PO1076

Sleeping Pills and Risk of CKD? A Nationwide Population-Based Retrospective Cohort Study

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Background: Sleeping disorder has long been connected with chronic kidney disease (CKD). But the correlation between sleeping pills and CKD has not been in-depth exploration. This study aimed to evaluate the potential harm of sleeping pills on the risk for CKD and CKD progression to dialysis-requiring end-stage renal disease (ESRD).

Methods: In a population-based cohort study of 204,176 sleeping pill users within 989,753 individuals, after exclusion criteria (those with sleeping pills use less than 3 months, with acute kidney injury, CKD and ESRD diagnosis before sleeping pills use, with obstructive sleep apnea and non-apnea sleep disorder, with age less than 18 years and gender unkown), a total of 183,321 sleeping pills users were compared to 366,642 individuals without sleeping pills use followed up for 13 years after been diagnosed as CKD (ICD-9-CM). Using propensity score matching, we analyzed the type of sleeping pills related to risk of CKD and CKD progression to ESRD by Cox proportional hazards regression with adjustment for sex, age, and comorbidities.

Results: Sleeping pills use was associated with increased risk for CKD after adjusting underlying comorbidities (aHR 2.002, 95% CI 1.790-2.333, p <0.001). Despite high social economic status (insured premium more than 35,000 Taiwanese dollars) and those with hyperlipidemia, those with sleeping pills use among most comorbidities are correlated with risk of CKD. Persistent use of sleeping pills after CKD also increased the risk of concurrent ESRD (aHR 7.981, 95% CI 5.117-10.986, p <0.001). After subgroup analyzing for sleeping pill use, flurazepam (p=0.198), lorazepam (p=0.051) and triazolam (p=0.125) are the drugs with no significance in correlation to CKD risk increasing.

Conclusions: Sleeping pills use was associated with increased risk of CKD and ESRD. Further studies are warranted to confirm these findings.

TH-PO1077

The Economic Burden of CKD Progression Among Patients with and Without Major Adverse Cardiac Events (MACE) in the US

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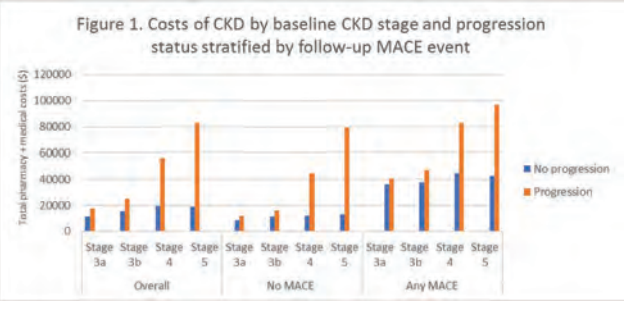
Background: Little is known about the costs of CKD progression among patients with cardiovascular disease. The objective of this study was to assess the economic burden of CKD progression among CKD patients with and without MACE.

Methods: Optum claims data were used to identify patients with baseline non-dialysis dependent CKD (stages 3a, 3b, 4 and 5) in 2013 using estimated glomerular filtration rate (eGFR) based on the Kidney Disease Outcomes Quality Initiative (KDOQI) diagnosis criteria. Patients were followed through 6/30/2017 to assess CKD progression defined as worsening CKD stage from baseline. Annualized all-cause costs were assessed between patients with and without defined CKD stage progression and then stratified by the presence or absence of follow-up MACE.

Results: 57,597 CKD patients were identified in 2013, among which 35,975, 16,982, 4,340 and 299 had CKD stages 3a, 3b, 4 and 5, respectively. Among those without MACE (n=47,004), mean annualized all-cause costs increased from stage 3a ($8,398) to 5 ($12,711) in those without stage progression and from stage3a ($12,062) to 5 ($79,093) in those with stage progression. Mean annualized all-cause costs among patients with ≥1 MACE (n=10,593) were from $35,924 for stage3a to $42,479 for stage5 without stage progression and from $40,687 (stage 3a) to $97,013 (stage 5) with stage progression. Overall, CKD progression costs for the entire cohort increased from stage3a ($6,010) to stage5 ($66,737) (P for trend < 0.001). The trends were consistent among those with and without MACE.

Conclusions: Progression of CKD increases the economic burden in patients regardless of MACE status but healthcare costs are higher in those with MACE compared to those without MACE. Preventing renal function decline could reduce economic burden seen in patients with advanced CKD stages and MACE.

Funding: Commercial Support - GlaxoSmithKline



TH-PO1078

Prior Military Service Associated with CKD: Analysis of the Behavioral Risk Factor Surveillance System

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Background: While military service is associated with health promoting and compromising factors, prior work shows that veterans report poorer overall health and higher prevalence of many health compromising behaviors compared to the civilian population. Although some evidence suggests that veterans may be at higher risk for cardiovascular disease, there is a paucity of evidence regarding other medical conditions, such as chronic kidney disease (CKD). We sought to determine if CKD is more common among veterans by analyzing data from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System (BRFSS).

Methods: We performed a cross-sectional study of BRFSS from 2011 to 2016. The presence of CKD and prior military service were determined by self-report. Standard statistics were used to compare demographic data and health behaviors between groups with and without prior military service. Weighted univariate and multivariable logistic regression analyses were performed to compare the odds of CKD development based on military status. *A priori* subgroup analyses stratified by race were also examined.

Results: Our search yielded a total of 2,861,628 subjects for analysis, 14.8% (n=369,844) of whom had prior military service. Individuals with prior service were more likely to have CKD (3.9% vs 2.6%; p<0.001). On univariate analysis, military service was associated with CKD development [odds ratio (OR) 1.55, 95% confidence interval (CI) 1.50-1.61; p<0.001). While attenuated, this difference remained significant in the multivariable model (OR 1.12, 95% CI 1.07-1.17; p<0.001). On analysis of racial subgroups, white subjects with prior military service were more likely to report CKD compared to those without prior military service (OR 1.15, 95% CI 1.09-1.21; p<0.001) in the multivariable model. No significant difference was observed in black (OR 1.07, 95% CI 0.92-1.25; p=0.40) or Hispanic (OR 1.15, 95% CI 0.93-1.41; p=0.20) subjects.

Conclusions: While differences seem to exist across racial strata, these results from a nationally representative sample support an association between prior military service and CKD. Further research is needed to determine why veterans are at a higher risk for CKD to guide treatment and prevention efforts.

Funding: Other U.S. Government Support

TH-PO1079

Housing Insecurity and Risk of Kidney Disease in an Urban Population

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Background: Housing insecurity is characterized by high housing costs or unsafe living conditions that prevent general self-care and threaten independence. It is associated with decreased healthcare access, and increased risk for chronic diseases and medical complications. The objective of this study was to examine the association between housing insecurity, incident chronic kidney disease (CKD) and rapid kidney function decline.

Methods: Data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (Baltimore, MD) was used for this longitudinal analysis. Housing insecurity was defined as answering yes to the question, "Can you afford a suitable home?" at the HANDLS wave 3 visit. We used multivariable logistic regression to compare risk of rapid kidney function decline (loss of > 5ml/min/1.73m^2 eGFR per year over a median of 3.5 years), incident reduced eGFR (< 60 ml/min/1.73m^2) and incident albuminuria (albumin-creatinine ratio [ACR] > 30mg/g), between participants with and without housing insecurity.

Results: Of the 1354 HANDLS participants included, mean age was 48 years, 40% were male and 57% were African American. A total of 443 (32.7%) were housing insecure. After a median of 3.5 years follow up, rapid kidney function decline, incident reduced eGFR and incident albuminuria occurred in 213 (15.7%), 68 (5.2%) and 80 (6.6%) participants respectively. After multivariable adjustment, housing insecurity was associated with increased odds of incident albuminuria but there were no statistically significant associations between housing insecurity and rapid kidney function decline or incident reduced kidney function (**Table**).

Conclusions: Housing insecurity was associated with increased risk for incident albuminuria in an urban population. The prevalence of housing insecurity among persons with CKD and its impact on kidney outcomes is worthy of further study.

Funding: Other NIH Support - National Institute on Aging

Table. Logistic regression results. Odds ratios (OR) for rapid eGFR decline, incident eGFR < 60 ml/min/1.73m^2, and incident ACR >30mg/g for those with versus without housing insecurity.

	Rapid eGFR Decline			Incident Reduced eGFR			Incident Albuminuria		
Model	N	OR	95% CI	N*	OR	95% CI	N**	OR	95% CI
Model 1	1354	1.23	0.91, 1.67	1308	0.67	0.38, 1.18	1206	1.99	1.26, 3.14
Model 2	1324	1.25	0.90, 1.72	1280	0.86	0.44, 1.67	1178	1.83	1.08, 3.09

Model 1: unadjusted.

Model 2: adjusted for age at enrollment, sex, race, poverty level, baseline eGFR, albumin-creatinine-ratio, systolic blood pressure and diabetes.

*Excluded individuals with eGFR < 60ml/min/1.73m^2 at baseline..

**Excluded individuals with ACR >30mg/g at baseline.

TH-PO1080

Association Between Religiosity and Risk of End-Stage Kidney Disease (ESKD) Among Blacks and Whites in the Southeastern United States

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Background: Religiosity is associated with improved outcomes in chronic illnesses via healthy behaviors and is prevalent among blacks as a means to cope with health-related stress. No study of religiosity in kidney disease has examined its association with objective measures of physical health such as progression to ESKD.

Methods: The Southern Community Cohort Study is a large prospective cohort of low socioeconomic status blacks and whites in the southeastern U.S. Using a case-cohort design, we examined the association between religiosity and ESKD among 737 incident ESKD cases ascertained by USRDS linkage and a probability sampled subcohort (n=4,238). Religiosity was recorded at enrollment via three self-reported items: frequency of church service attendance; degree of spirituality; and degree of comfort from religion. We constructed Cox regression models, accounting for sampling weights, of time to ESKD in relation to each religiosity item, and adjusted for demographic, psychosocial (social support, depressive symptoms), and clinical variables (including diabetes, hypertension, estimated glomerular filtration rate). Interaction between each religiosity item and race was statistically significant (p<0.01).

Results: Overall, 24% of blacks, compared to 18% of whites, reported the highest frequency of service attendance (>once/week); 57% and 72% of blacks reported very high spirituality and high degree of comfort from religion, respectively, compared to 51% and 56% of whites. Among blacks, hazard ratios (HR) and 95% confidence intervals (CI) for ESKD associated with the highest vs. lowest categories of service attendance, spirituality, and comfort from religion were 0.74 (0.57-0.97), 0.66 (0.54 to 0.80), and 0.23 (0.15-0.36), respectively. Among whites, the corresponding estimates were 0.28 (0.16-0.50), 1.08 (0.66-1.77), and 1.11 (0.44-2.78).

Conclusions: Frequent attendance at religious services is associated with a decreased risk for ESKD among socioeconomically-disadvantaged black and white adults. Among blacks, spirituality and comfort from religion are also associated with decreased ESKD risk. Engaging blacks in faith-based community settings may be a culturally-relevant way to facilitate healthy behaviors to decrease kidney disease progression.

Funding: NIDDK Support

TH-PO1081

CKD Self-Management in Older Adults

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Background: Chronic kidney disease (CKD) patients are asked to engage in self-management behaviors in order to manage the disease and mitigate its sequelae. However, an examination of self-management behaviors and their association with clinical outcomes in older adults has not been well characterized.

Methods: Data from the Chronic Renal Insufficiency Cohort were analyzed using latent class analysis (LCA) to identify behavior patterns among those <65 and ≥65 years of age. LCA was based on body mass index, diet, physical activity, blood pressure, smoking, and hemoglobin A1c. Logistic regression assessed association of select factors to behavior patterns. Cox proportional hazards models were used to examine association of behavior patterns with cardiovascular events, CKD progression, and death. Results stratified by diabetes.

Results: Three behavior patterns (healthy, obese/sedentary, non-obese/smoking) were identified separately among age groups. Less healthy patterns included those with more depression, lower education, and self-efficacy. In older adults, less healthy patterns were associated with inadequate health literacy, less social support, and physical functioning. Among <65 years, the obese/sedentary pattern had increased hazard of death, CKD progression (diabetics), and cardiovascular events (non-diabetics), and the non-obese/sedentary pattern had an increased hazard of death (diabetics), and cardiovascular events (non-diabetics). Among 65+ years, the obese/sedentary and non-obese/smoking patterns were associated with increased death and CKD progression (non-diabetics), see Table.

Conclusions: Self-management behavior engagement patterns are associated with risk of important outcomes among CKD patients. These patterns may be able to identify high-risk groups and be targeted for aggressive management.

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	<65 yrs Non-Diabetes (n=1, 484)	<65 yrs Diabetes (n=1,315)	65+ yrs Non-Diabetes (n=547)	65+ yrs Diabetes (n=593)
Death				
Obese/Sedentary vs. Healthy Pattern	2.17 (1.09-4.29)	1.37 (1.01-1.86)	2.97 (1.43-6.19)	0.89 (0.67-1.17)
Non-Obese/Smoking vs. Healthy Pattern	2.13 (0.75-6.02)	2.50 (1.39-4.50)	3.47 (1.48-8.11)	1.18 (0.72-1.93)
CKD Progression				
Obese/Sedentary vs. Healthy Pattern	1.22 (0.95-1.55)	1.34 (1.13-1.59)	1.06 (0.70-1.61)	0.97 (0.69-1.34)
Non-Obese/Smoking vs. Healthy Pattern	1.12 (0.70-1.79)	1.46 (0.96-2.21)	1.85 (1.07-3.22)	0.62 (0.32-1.24)
Atherosclerotic Cardiovascular Event				
Obese/Sedentary vs. Healthy Pattern	1.59 (1.04-2.43)	1.26 (0.98-1.63)	0.61 (0.38-1.00)	1.12 (0.76-1.64)
Non-Obese/Smoking vs. Healthy Pattern	2.97 (1.49-5.90)	1.40 (0.75-2.61)	1.36 (0.74-2.50)	1.32 (0.67-2.59)

TH-PO1082

Markers of Modifiable Health Behaviors, Cardiovascular Events, Death, and CKD

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Background: Chronic kidney disease (CKD) guidelines focus on modifiable health behaviors in the effort to decrease the risk of death and atherosclerotic events, both of which are increased in CKD. However, the effectiveness of these recommendations is relatively unknown since they were based largely on general population research. We examined the relationship of markers of modifiable health behaviors and clinical outcomes among those with and without CKD.

Methods: Data pooled from Atherosclerotic Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Cardiovascular Health Study. CKD defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73^2. Markers of modifiable behaviors: physical activity, blood pressure, smoking, diet, body mass index, and fasting blood glucose. Multivariable adjusted Cox proportional hazards models estimated risk of death and a composite of atherosclerotic events. Effect modification was explored for age.

Results: Those with CKD (n = 8,542): mean 59.7 yrs, eGFR 54.7; without CKD (n=19,188): mean 60.2 yrs, eGFR 77.3. There was evidence of an interaction by age with behaviors for both outcomes. Results reported by <65 and 65+ yrs (see Table). Overall,

recommended markers of health behaviors were associated with decreased death and atherosclerotic events. Particularly, controlled BP had a stronger association in CKD.

Conclusions: Markers of modifiable behaviors were associated with reduced risk of death and atherosclerotic events in CKD and without CKD. Blood pressure control had a stronger association among those with CKD.

Funding: NIDDK Support

Targets for Health Behaviors

Reported HR (95% CI)	Non-CKD	CKD	Non-CKD	CKD
Death	<65 years (n=11,732)	<65 years (n=6,000)	≥65 years (n=5,936)	≥65 years (n=2,051)
Non-Smoking	0.48 (0.45-0.52)	0.44 (0.40-049)	0.66 (0.59-0.73)	0.75 (0.62-0.90)
BP <130/80 mmHg	0.72 (0.66-0.80)	0.71 (0.63-0.81)	0.91 (0.84-0.99)	0.80 (0.70-.92)
BMI ≥18.5 to <25 kg/m2	1.13 (1.04-1.22)	1.00 (0.89-1.12)	1.22 (1.13-1.32)	1.16 (1.02-1.31)
Phys Activity >150 min/wk	0.92 (0.85-1.00)	0.98 (0.88-1.09)	0.73 (0.67-0.79)	0.73 (0.64-0.83)
Diet Score ≥3	0.91 (0.84-0.98)	1.04 ((0.95-1.15)	0.95 (0.88-1.02)	0.91 (0.80-1.03)
Fasting blood glucose <126	0.74 (0.63-0.87)	0.61 (0.50-0.73)	0.67 (0.59-0.77)	0.87 (0.70-1.06)
Atherosclerotic Events				
Non-Smoking	0.60 (0.54-0.67)	0.62 (0.54-0.71)	0.81 (0.68-0.96)	1.00 (0.74-1.36)
BP <130/80 mmHg	0.84 (0.74-0.94)	0.76 (0.65-0.88)	0.82 (0.72-0.93)	0.75 (0.62-0.92)
BMI ≥18.5 to <25 kg/m2	0.85 (0.76-0.95)	0.88 (0.76-1.02)	1.04 (0.92-1.16)	1.00 (0.83-1.21)
Phys Activity >150 min/wk	0.99 (0.90-1.10)	1.12 (0.97-1.29)	0.80 (0.71-0.90)	0.81 (0.68-0.98)
Diet Score ≥3	0.92 (0.84-1.01)	1.12 (0.99-1.26)	1.05 (0.94-1.17)	1.10 (0.92-1.31)
Fasting blood glucose <126	0.63 (0.52-0.76)	0.81 (0.64-1.04)	0.66 (0.55-0.80)	1.00 (0.75-1.32)

TH-PO1083

Health Literacy and Rapid Kidney Function Decline

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Background: Health literacy is the ability to understand basic health information. Cross-sectional studies have revealed an association between limited health literacy and lower eGFR in those with CKD. The association of health literacy and kidney function over time has not been described, therefore, we conducted a prospective analysis of this question.

Methods: We studied 1,603 Healthy Aging in Neighborhoods of Diversity across the Life Span study participants with preserved kidney function (eGFR ≥ 60 mL/min/1.73 m^2). A Rapid Estimate of Adult Literacy in Medicine test score of ≤ 60 indicated limited health literacy. We used multivariable logistic regression to assess the association of health literacy with rapid kidney function decline (eGFR loss ≥ 3 mL/min/1.73 m^2 per year over median of 5 years).

Results: Participants' mean age was 48 years. The prevalence of limited health literacy was 29.7% (n=476). Participants with limited health literacy were more likely to be male (50.4% vs 37.1%), African American (74.8% vs 52.4%), living in poverty (51.9% vs 31.2%), have less educational attainment (mean 11.3 vs 13.3 years of schooling), and be current smokers (53.1% vs 41.5%) than persons with adequate health literacy (p<0.05 for all). Both literacy groups had similar baseline levels of eGFR, systolic BP, self-reported hypertension, and diabetes. A total of 218 (13.6%) participants had rapid kidney function decline at follow-up. The unadjusted odds of rapid kidney function decline among those with limited health literacy compared to adequate health literacy was 1.20 (95% CI: 0.81-1.77). After adjusting for age, sex, race, poverty status, education, smoking status, BP, and diabetes, there was still no association (OR 0.99, 95% CI: 0.67-1.47). A series of alternate outcomes (rapid eGFR decline of ≥3% decrease per year, eGFR decrease of ≥25% over a median of 5 years, incident eGFR<60, and incident albuminuria) revealed results consistent with the primary outcome.

Conclusions: There was no association between health literacy and various measures of kidney function decline in this cohort. Although previous cross-sectional analyses have shown an association between health literacy and kidney function, this finding was not present in this prospective analysis. Factors other than health literacy may have more influence over early loss of kidney function.

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TH-PO1084

Family Relationships and Self-Reported Outcomes in Patients with Moderate or Advanced CKD: Findings from the French CKD-Renal Epidemiology and Information Network (CKD-REIN) Study

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Background: Social support is associated with higher well-being in chronic kidney disease (CKD), but has only been explored in ESRD patients. We describe family profiles and their associations with self-reported quality of life and depression in patients with moderate or advanced CKD.

Methods: Four questionnaires were administrated to 3,033 adult patients with CKD stage 3-5 under nephrology care: the 12-item Family Relationships Index (FRI) to assess family relationships through 3 subscales [***family cohesion*** (degree of support within the family), ***family expressiveness*** (extent to which family members express feelings) and ***family conflict*** (amount of conflict among family members), the KDQoL scale to measure CKD effects, burden, and symptoms, the SF-12 to assess mental and physical composite scores (MCS, PCS), and the CES-D scale for depression symptoms. Comparisons between profiles were adjusted for age, sex, and living status.

Results: Based on 2,004 patients (median age 68, 68% men, 20% living alone, 56% stage 3 CKD) with complete data for the FRI, cluster analysis yielded 3 family profiles (Upper Figure). Patients with profile 3 (the highest family cohesion and expressiveness, and the lowest conflict) had the best patient-reported outcomes. In comparison, patients with profile 1 (the lowest family cohesion and expressiveness, and intermediate conflict) had significantly lower KDQoL and SF-12 scores (p<.001) (Lower Figure), and a higher prevalence of self-reported depression symptoms, 9% vs 6% (p<.001). Patients with profile 2 (high family cohesion, intermediate expressiveness, and highest conflict) did not differ significantly from those with profile 3.

Conclusions: Family environment plays a crucial role in patients' adaptation to CKD. Accounting for it could allow health professionals to better assist their patients.

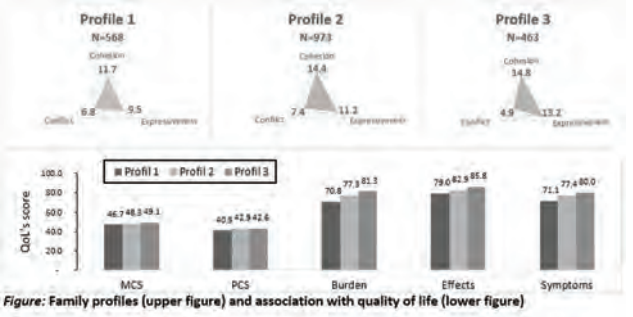

***Figure:* Family profiles (upper figure) and association with quality of life (lower figure)**

Score range: 4-16 (FRI: Cohesion; Conflict; Expressiveness); 0-100 (KDQoL: Burden, Effects, and Symptoms; SF12: MCS and PCS). Quality of life scores were adjusted for age, sex, and living status.

TH-PO1085

Association of Social Support with CKD Among African-Americans

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Background: Low social support (LSS) negatively affects health behaviors. Because disease self-management and lifestyle modifications improve outcomes in chronic kidney disease (CKD), we sought to examine the independent association of LSS with CKD prevalence or rapid renal functional decline (RRFD) in African Americans at risk of CKD incidence or progression in the Jackson Heart Study (JHS).

Methods: The JHS is a prospective cohort of African Americans within the Jackson, MS metropolitan area. At baseline (2000-2004), social support was assessed using the Interpersonal Support Evaluation List (ISL); a 16-item survey with four subscales: appraisal, belonging, self-esteem, and tangible support. ISL scores < 32 indicate LSS. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m2 or a urine albumin/creatinine ratio (ACR) ≥30mg/g in those with an eGFR ≥ 60ml/min/1.73m2. We conducted multivariable logistic regression to evaluate the association between LSS and CKD prevalence in the general JHS cohort, as well as the association of LSS and RRFD (defined as a > 30% decrease in eGFR over a 10 year period) among JHS participants with diabetes, hypertension, or CKD at baseline. Models were adjusted for baseline sociodemographics, comorbidities and ACR.

Results: Of 5301 JHS participants, 4015 (76%) completed the ISL. 843 (21%) had LSS. Participants with LSS (vs. high) were more likely to have lower income (47% vs. 28%), be current or former tobacco users (39% vs. 30%), have diabetes (25% vs. 21%), and CKD (14% vs. 12%) (all p<0.05). After multivariable adjustment, LSS was not independently associated with prevalent CKD or with RRFD. However, a low self-esteem subscale score was associated with increased odds of prevalent CKD [OR 1.06 (95% CI 1.01-1.12)].

Conclusions: Overall, LSS was not independently associated with CKD outcomes among African Americans in the JHS, but low-self-esteem was associated with CKD. Self-esteem may have a role in CKD management and warrants further study.

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TH-PO1086

Tele-Nephrology to Provide Efficient and Patient-Centered Ambulatory Care

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Background: Subspecialty referrals in ambulatory care in the U.S. have doubled in the last decade. According to an AAMC-commissioned study in 2017, there will be a projected a shortage of up 61,800 nonprimary care specialists by 2030. We evaluated whether the incorporation of tele-nephrology within ambulatory care could improve efficiency and patient-centeredness.

Methods: In a large Veteran's Affairs health system, we assessed outpatient utilization of tele-nephrology via e-Consults (e-C), defined as either electronic, telephonic or video communication with the referring provider and/or the patient. We implemented a pilot to pro-actively triage eligible renal consults in patients 75 or older (Grp I) to be initially addressed via e-Consults compared to those < 75 (Grp II). e-C assessments and ability to completely address the consult without need for in-person (IP) visit were compared by Chi-square or Fishers tests.

Results: In FY 2016-17, of the 1,803 consults, inital e-C assessments were peroformed on 172 (9.5%), leaving 1,631 IP visits. Since the pilot, between 1/1/18 and 5/29/18, 249 renal consults were received of which, 9% (22/249) patients were Grp I. 86% (19/22) in Grp I underwent initial e-C assessments compared to 14% (33/227) in Grp II ($p < 0.001$). Of the initial e-C assessments 26% (5/19) in the Grp I were completed by avoiding IP visit; whereas 42% (14/33) in Grp II were completed without IP visit ($p = 0.37$). Pilot Grp I was 100% male (mean age of 81.3; mean serum creatinine 1.84 mg/dl); 78% were diabetic and 78% hypertensive. They resided between 2 and 42 miles from the clinic, and 20% were receiving home-based primary/hospital care. The mean time to complete an e-C assessment was 1.43 days from date of referral, as compared to > 30 day wait for IP visit. Along with comprehensive medical review, 93% received renal-specific diagnostic assessments (lab tests, radiology tests, medication review management). Overall, initial e-C (52/249) created 21% efficiency; and created 8% capacity (19/249) by avoiding the need for IP visits, with same resources.

Conclusions: e-Consults reduced time to initial renal assessment, allowed prompt diagnostic testing, medication management, and avoided travel burden for patients and relatives. Tele-nephrology models of ambulatory care delivery can improve efficiency, enhance patient-safety, and reduce real and opportunity costs.

Funding: Clinical Revenue Support

TH-PO1087

CKDApps: A Systematic Evaluation of Patient-Facing Smartphone Apps for CKD by Patients and Nephrologists

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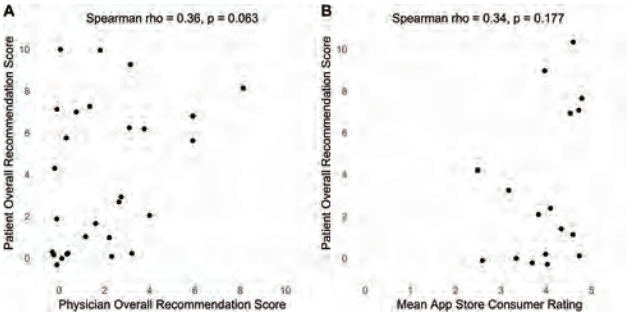
Background: Many aspects of chronic kidney disease (CKD) management rely heavily on patient self-care, including medication and dietary adherence, self-monitoring of blood pressure, and daily physical activity. There is growing evidence that incorporating technology, specifically smartphone-based applications (apps), can help support self-care in CKD and chronic disease more generally.

Methods: We identified apps targeting CKD patients by conducting a search of the Apple App Store (iOS) and Google Play Store (Android) using the following 4 phrases: "kidney disease," "renal," "dialysis," and "kidney transplant." We considered the first 50 apps for each search term on each app store. We modified a previously described framework for assessment of mobile health apps to account for kidney disease-specific content areas and evaluated apps on their clinical focus, types of patient engagement, quality, usability, safety, and cost. Engagement and quality were assessed by both a patient and a nephrologist, usability was assessed by patients, and safety was assessed by nephrologists.

Results: Our search strategy identified 174 unique apps on Android and 165 unique apps on iOS. After excluding apps that were not related to kidney disease, not patient-facing, or were last updated prior to 2014, 12 Android-only apps, 11 iOS-only apps, and 5 dual-platform apps remained. Patient and nephrologist ratings showed a positive correlation that was not statistically significant ($p = 0.063$, see Figure). Consumer ratings on the app stores did not correlate with patient ratings ($p = 0.177$).

Conclusions: Only a small subset of CKD apps are highly rated by both patients and nephrologists. Patients' impressions of app quality are not directly linked to consumer app ratings or nephrologist impressions. Efforts to develop and disseminate apps for CKD self-care should involve direct patient input.

Funding: NIDDK Support



Relationship between (A) nephrologist and patient ratings and (B) consumer and patient ratings.

TH-PO1088

Attitude, Motivation, and Barriers to Exercise in Patients with CKD: A Focus Group Study

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Background: Physical activity is remarkably low in patients with chronic kidney disease (CKD). Data suggests that exercise is beneficial for patients with CKD. The adjusted risk of death and end stage renal disease is lower in CKD patients who are physically active compared to those who are inactive. Despite the benefits of exercise in patients with CKD, the majority of patients remain sedentary. The purpose of this formative evaluation was to identify CKD patient attitudes, beliefs and barriers to exercise.

Methods: Adult individuals from the Denver Metro area with CKD stage 3 and 4 who were not currently physically active were recruited for 10 focus groups (3 in English speaking males, 3 in English speaking females, 2 in Spanish speaking males and 2 in Spanish speaking females) from May 2016 to December 2016. Focus groups were transcribed verbatim and transcripts were coded and thematically analyzed.

Results: A total of 41 individuals participated in the study. 51.2% were female and 44% were Hispanic. The majority of the participants held a CKD diagnosis for 1-7 years. Participants recognized the benefits of physical activity on both physical and mental health but physical activity was not viewed to have a significant impact on CKD. Social support was a strong motivational factor to physical activity. Social support was preferred from friends, family, or peers with similar health conditions. Spanish speaking participants saw family as a barrier if the family member was not directly participating in physical activity. Additional barriers to physical activity included poor health, fatigue, a fear of worsening their disease and lack of guidance from their nephrologist. Spanish speaking participants in particular expressed frustration with their nephrologist's lack of advice regarding exercise.

Conclusions: Barriers and motivators to physical activity were similar amongst male and female participants with CKD. Lack of advice from nephrologists regarding exercise was a significant barrier. Physical activity interventions in patients with CKD should include not only increased patient self-efficacy and social support but also counseling and prescribing of exercise by nephrologists.

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TH-PO1089

Quality of Life of Patients with CKD: A Cross Sectional Analysis from the ICKD Cohort

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Background: Improving symptoms and function in daily life are important patient centered outcomes in chronic diseases. Health-related quality of life (QOL) is an important key indicator of how a condition affects the patient's life, and QOL has been expressed as the subjective assessment of the impact of disease and its treatment across the physical, psychological and social domains of functioning. We report QOL in patients with early stages of CKD who have been enrolled in the ICKD study.

Methods: All subjects, who had been enrolled in the on-going, multi-centric ICKD cohort study and had KDQOL-36™ survey data recorded at baseline, were eligible for the present study. We assessed QoL by KDQOL-36™. Raw scores are converted to subscale scores using the Microsoft Excel tool (KDQOL-36™ Scoring Program, v 2.0). These subscales are Mental Component Summary (MCS), Physical Component Summary (PCS), Symptoms, Effect and Burden. Each subscale category is scored between 0-100, with higher scores indicating better quality of life. demographic and socioeconomica as well as clinical parameter were studied for association with QOL. Low QOL was defined as subscale score that was 1 SD less than the mean for the respective subscale.

Results: The mean scores for KDQOL-36™ subscales were 48.81±9.93, 44.17±9.49, 65.29±31.40, 81.31±24.70 and 86.68±21.43 for PCS, MCS, burden, effects and symptoms,

respectively. Urban residence, non-vegetarian dietary pattern, education below high school, occupational exposure and lower income were associated with lower scores across all KDQOL-36 subscales (p<0.05). Professional workers had high score across all KDQOL-36 subscales compared to farmers, housewife and unemployed subjects (p<0.01). Increasing quartile of annual income ws associated with higher scores in all subscales (p<0.01). Urban residence, occupational exposure and housewife status were associated with low QOL across all KDQOL-36™ subscales (p<0.05). Education below high school, lower eGFR, low annual income and BMI <18 kg/m^2 were associated with low QOL in all subscale scores (p<0.01) except in symptoms subscale.

Conclusions: We identified the association between a number of clinical and socio-economic variables related and one or more KDQOL-36™ subscales.

Funding: Government Support - Non-U.S.

TH-PO1090

A Worrisome Explosion: Time Series Analysis of Kidney Cancer Incidence in the United States

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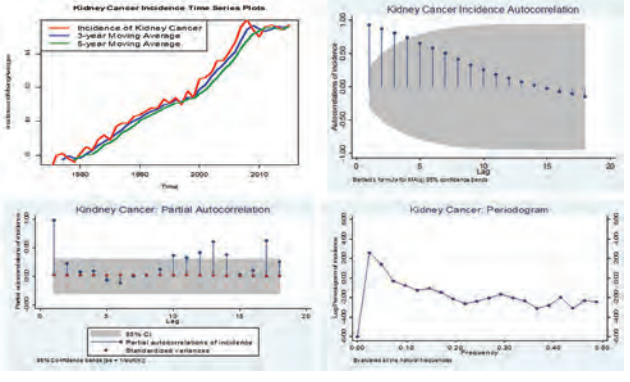
Background: With over 500,000 adults in the US suffering from kidney & renal pelvis cancer and 65,000 new cases are estimated to be diagnosed in 2018 (representing 3.8% of all new cancer cases), kidney cancer poses a major public health challenge and remains a significant source of healthcare cost and mortality. Between 1975-2015, national incidence of kidney cancer more than doubled from 7.1 to 15.7 per 100,000 population.

Methods: Annual time series data covering 1975-2015 is collected from NCI's SEER. Level and smoothed (moving average, 3-year and 5-year) time series plots are obtained (details in Figure 1). Autocorrelation and partial autocorrelation functions obtained from the time series data point to a long memory in the data generating process and help us in understanding the magnitude of rising in renal cancer incidence during the last half-century. Augmented Dickey-Fuller (ADF) tests are performed to check the stationarity in the time series data.

Results: ADF tests using the standard estimation equation rejected stationarity of the incidence data for lag lengths 1, 3, and 5 points to the presence of strong non-stationarity in longitudinal incidence in kidney cancer. The results pointing to non-stationarity hold even after controlling for trend, and random walk with or without drift.

Conclusions: Analysis of 41 years of kidney cancer incidence data strongly establishes that kidney cancer incidences have been increasing statistically significantly over time. The incidence has more than doubled in the last half-century. Current evidence does not support any immediate possibility of a reversal in that increasing trend. Results point to a strong need for urgent interventions and robust public health awareness campaigns aimed at slowing or perhaps reversing the explosive trend in kidney cancer incidence.

Figure 1: Time Series Properties of the Kidney Cancer Incidence Data (SEER 1975 – 2015)



TH-PO1091

Referral to Nephrology Care and Mortality Risk in People with Stage 4 CKD: A Population-Based Study

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Background: Guidelines recommend referral for specialist kidney care when estimated glomerular filtration rate (eGFR) is <30 ml/min/1.73m^2 (stages 4-5 CKD). These recommendations are largely based on studies in people treated with dialysis showing 40% lower mortality with predialysis care of at least 4 months vs. shorter or no predialysis care. The effects of nephrology referral for the broader population of CKD patients are unknown. We examined the association between referral to nephrology care and mortality risk in people with stage 4 CKD.

Methods: Using population-based administrative and laboratory data, we identified all adults, residing in Alberta, with at least two consecutive outpatient measurements of eGFR ≥15 to <30 ml/min/1.73m^2 spanning more than 90 days between 2002 and 2014. Patients were followed from date of the first eGFR after the 90-day qualifying period (study entry) until the earliest of death, out-migration from the province, or March 31, 2015. We used outpatient nephrology visit for at least once as a proxy for referral to nephrology care. We estimated hazard ratios (HRs) and confidence intervals (CIs) for all-cause mortality with nephrology referral (vs. no referral) and whether this effect varied by age, adjusting for baseline demographics and key laboratory and clinical characteristics, and using methods that address immortal time bias and time-varying confounding potentially affected by previous exposure status.

Results: Of the 15,315 study participants, 78% were ≥75 years old; 35% were referred to a nephrologist (median time-to-referral 8 months); and 67% died (median time-to-death 2.6 years). People who were referred were younger and had less comorbidity. Compared to non-referral, referral at any time during follow-up was independently associated with 12% lower mortality (HR 0.88; 95% CI, 0.83-0.93). The association was stronger in people aged <70 years (HR 0.80; 95% CI, 0.68-0.95) and absent in people aged ≥90 years (HR 1.05; 95% CI, 0.88-1.24).

Conclusions: Among people with stage 4 CKD meeting the criterion for nephrology referral, most of them are very old and the survival benefit of nephrology referral may be smaller than expected and become smaller with older age.

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TH-PO1092

Decline in Glomerular Filtration Rate Before and After Multidisciplinary Care Referral in Moderate to Advanced CKD

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Background: The multidisciplinary care (MDC) model has been used in our hospital for years. We investigated whether the outpatient chronic kidney disease (CKD) treatment by the MDC contributed to the inhibition of the progression of renal failure.

Methods: This study provides a retrospective review of the individual rates of estimated glomerular filtration rate (eGFR) decline (ml/min/1.73m^2/year) for the 6 months before and after referral in 40 referrals with stages 3–5 CKD to one renal unit between March 2010 and June 2012. The MDC team consisted of a nephrologist, nurses, dieticians, and other professionals.

Results: The Age and eGFR at the time of referral was 66 ± 12 and 14.7 ± 6.6 ml/min/1.73m^2 (mean ± SD), and the mean observation period was 395 days (172 to 862 days). The decrease in the eGFR before and after the referral was significantly improved from -8.0 ± 8.0 ml/min/1.73m^2/year to -1.3 ± 5.9 ml/min/1.73m^2/year (P<0.01). Blood pressure also reduced significantly (139/80 to 133/73mmHg, P<0.05).

Conclusions: The outpatient renal failure treatment by using multidisciplinary care might contribute to the suppression of renal failure.

TH-PO1093

Comparing Glomerular Filtration Rate Measured by Radionuclide Imaging with Creatinine Based Equations

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Background: Glomerular filtration rate (GFR) is the best index of kidney function. Creatinine based equations (CBE) are recomended by guidelines. In Colombia sometimes we use radionuclide imaging(RI) with ^{99m}Tc-DTPA to measure GFR thinking that it could be better. The aim of this study is to estimate correlation and concordance between this method and eGFR with CBE.

Methods: We included patients who had standarized creatinine and GFR meassured with ^{99m}Tc-DTPA RI in the same week from 4 institutions in Bogota, Colombia between November 2008 and October 2017. We excluded patients with expected source of error in CBE and RI. CBE used were CKD-EPI, MDRD4 and Cockcroft Gault adjusted to body surface (CGa). We estimated the correlation with Spearman coefficient and concordance with kappa coefficient for CKD diagnosis (<60ml/min/1.73m^2) and CKD grades. We considered p<0.05 as statistically significant.

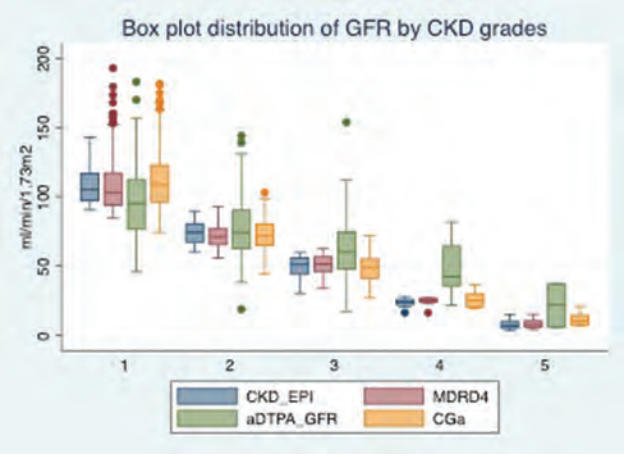
Results: We included 421 patients. Mean age 54 years (± 17.1), 46.8% female, mean eGFR 75.9 (± 26.6), 76.3 (± 28.8), 77.1 (± 31.6) and 77.9 (±28.4) ml/min/1.73m^2 with CKD-EPI, MDRD4, CGa and RI respectively; 29.4% had eGFR less than 60. There were no differences of mean. In the graph, we show the distribution by grades of CKD. The correlation was good between equations, but acceptable when comparing CBE with 99mTc-DTPA RI. Weighted kappa concordance between CBEs was good but for ^{99m}Tc-DTPA RI compared to all CBE was fair.(Table)

Conclusions: GFR with ^{99m}Tc-DTPA RI had a low correlation and fair concordance compared with CBE. There are no reasons to consider RI as a better tool. And also, is an expensive test with limited availability.

Spearman coeficiente and weighted Kappa coefficient by CKD grades 1 to 5.

	CKD-EPI	MDRD4	99mTc-DTPA
MDRD4	ρ=0.98 κ=0.92		
CGa	ρ=0.94 κ=0.82	ρ=0.91 κ=0.75	ρ=0.50 κ=0.36
99mTc-DTPA	ρ=0.57 κ=0.40	ρ=0.55 κ=0.39	

All p<0.00001



TH-PO1094

Improved Time to eGFR Decline Outcomes in Glomerular Disease

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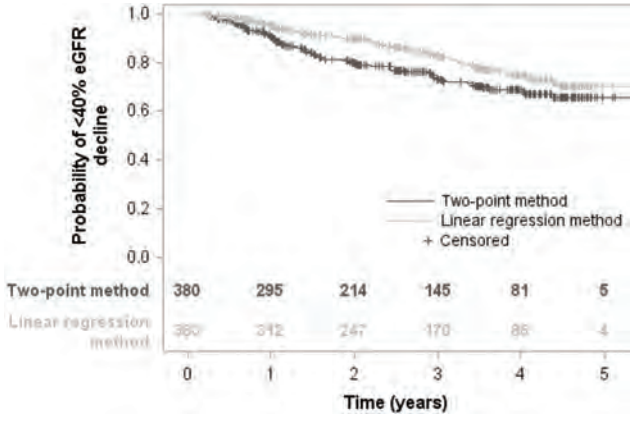
Background: The standard method of using two estimated glomerular filtration rate (eGFR) measures to calculate time to a percentage decline in eGFR may result in inaccurate event times due to eGFR variability and restriction of events to study visit times. We propose fitting a regression line to all observed eGFR measures to improve accuracy and power of time to percentage decline in eGFR outcomes.

Methods: Using data from the Nephrotic Syndrome Study Network (NEPTUNE) of patients with minimal change disease, focal segmental glomerulosclerosis, or membranous nephropathy, we compared time to 40% decline in eGFR using both event time calculation methods. We also used computer simulations to assess power and accuracy of event times under both methods. Parameters for the simulations, such as eGFR variability, percent missing eGFR observations, and correlation between successive eGFR measurements, imitated NEPTUNE data.

Results: 380 NEPTUNE patients with a mean of 6.5 eGFR measurements over a mean of 33 months of follow-up were included in the analysis. Among these patients, 91 had a 40% decline in eGFR using the two-point method, while 68 had a 40% decline in eGFR using our proposed linear regression method. For patients who had an event under both methods (n=64), the two-point method estimated earlier event times compared to the linear regression method (Figure 1). Under simulated data conditions, the standard two-point method was less accurate in estimating event times than our proposed regression method, particularly with high eGFR variability or more missingness. The two-point method was also less powerful in detecting time-to-event differences between groups.

Conclusions: Using our proposed regression method to estimate time to a percentage decline in eGFR increases accuracy and power. Reducing noise in outcome estimation with our proposed method increases the ability to discover treatment or biomarker effects.

Funding: NIDDK Support



Kaplan-Meier estimates of the probability of a 40% decline in eGFR using NEPTUNE data.

TH-PO1095

Validation of the Kidney Risk Failure Equations (KFRE) in Patients with CKD in Singapore

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Background: Accurate identification of patients with CKD at risk of progressing to require renal replacement therapy (RRT) would allow optimal care. Tangri et al developed models to predict progression in patients with CKD stages 3-5 (eGFR 10-59ml/min/1.73m^2) to kidney failure using data from Canadian cohorts. The aim of our study is to validate the 4-variable and 8-variable KFREs in the multiethnic population in Singapore.

Methods: Demographics, clinical and laboratory data of patients with CKD stages 3-5 referred from primary care physicians to TTSH Renal Department between 1 January 2009 to 31 December 2012 were collected. Kidney failure was defined as the initiation of chronic dialysis or kidney transplant. The 2 year and 5 year kidney failure risks were predicted using the 4-variable(age, sex, albuminuria and eGFR) and 8-variable(4-variable and calcium, phosphate, bicarbonate and albumin) models. This was compared with actual kidney failure rate at 2 and 5 years of follow up. Patients who died before kidney failure were excluded. Model performance was evaluated using the area under the receiver operating characteristic curve (ROC-AUC) and by comparing the observed and predicted risks of kidney failure.

Results: The KFRE models were validated using 2,238 and 1,845 patients for the 2 and 5 year kidney failure risks respectively. 158 (7.1%) and 355 (15.9%) patients developed kidney failure at 2 years and 5 years respectively. ROC-AUC for the 4-variable KFRE at 2 and 5 years are 0.921 (95% confidence interval [CI] 0.899-0.943) and 0.866 (CI 0.844-0.887) while those for the 8-variable KFRE are 0.925 (CI 0.905-0.945) and 0.862 (CI 0.840-0.883) respectively. The mean differences between the observed and predicted kidney failure risk was lower for the 4 variable equation compared to the 8 variable equation at 2 and 5 years.

Conclusions: Discrimination of the 4-variable and 8-variable KFRE were similar and were able to predict the progression to kidney failure in our patients. To further improve the accuracy of the KFRE, we would need to recalibrate the 8-variable equation for our local multiethnic population

Mean difference between observed and predicted risks

	2 years risk	5 years risk
4-variables KFRE	-1.5%	-2.9%
8-variables KFRE	-4.1%	-8.6%

TH-PO1096

Lower Diastolic Blood Pressure Increases the Risk of Mortality and Progression to ESRD – Multicenter Large Cohort Study

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Background: Higher systolic blood pressure (BP) is known to be associated with an increased risk of cardiovascular events and mortality in chronic kidney disease (CKD) patients. However, the clinical impacts of diastolic BP and the ideal diastolic BP target in Asian elderly CKD patients have not been well studied.

Methods: A multicenter CKD cohort from 2001 to 2016 was used. We examined the associations of systolic and diastolic BP with all-cause mortality and progression to end-stage renal disease (ESRD) using multivariate Cox proportional hazards regression models.

Results: A total of 13,700 patients with complete data for multivariable analysis were enrolled. Systolic BP showed a U-shaped association with mortality and a linear association with progression to ESRD. Systolic BP greater than 140 mmHg or diastolic BP less than 50 mmHg was significantly associated with higher mortality, regardless of the presence of diabetes or hypertension. In subgroup analysis of age, the patients with diastolic BP < 60 mmHg and aged < 50 years, or diastolic BP < 50 mmHg and aged < 70 years had a higher risk of mortality compared to those with diastolic BP 70-79 mmHg after adjusted systolic BP (age < 50, hazard ratios [HRs], 4.46; 95% confidence interval [95% CI], 2.38 to 8.35; age 50-59, HRs, 2.92; 95% CI, 1.33 to 6.38; age 60-69, HRs 2.84; 95% CI, 1.49 to 5.43). However, there was no association in those aged ≥ 70 years. The risk for progression to ESRD was also increased with diastolic BP < 60 mmHg (HRs 1.20; 95% CI, 1.01 to 1.43). The risk for mortality and progression to ESRD was also increased with diastolic BP < 60 mmHg in patients with diabetes (HRs 2.65; 95% CI, 1.67 to 4.22; HRs 1.43 95% CI 1.01-1.89).

Conclusions: In the CKD patients, lower diastolic BP was significantly associated with mortality and progression to ESRD; however, the effects were reduced in elderly patients (≥ 70 years).

TH-PO1097

Prevalence and Clinical Outcome of Apparent Treatment Resistant Hypertension in CKD in Korea: Korean Cohort Study for Outcome in Patients with CKD (KNOW-CKD)

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Background: It is not well defined the prevalence and clinical outcome of apparent treatment resistant hypertension(ATRH) in Korean CKD patients. The present study was aimed to investigate the prevalence of ATRH, and its effects on the renal and cardiovascular outcomes and all-cause mortality.

Methods: We collected data of 1878 patients with hypertension in the Korean Cohort Study For Outcome in Patients with Chronic Kidney Disease(KNOW-CKD) to understand ATRH. The definition of ATRH is; 1) systolic blood pressure(BP)≥140mmHg or diastolic BP≥90mmHg with 3 classes of antihypertensive agents, 2) any BP with 4 antihypertensives, at baseline.

Results: 374(19.9%) patients revealed ATRH. Presence of ATRH was associated with baseline renal function, sex, diabetes, severity of proteinuria, BMI, and prior history of myocardial infarction. Patients with ATRH showed higher risk of adverse renal outcome than non-ATRH patients. The adjusted renal event hazard ratio(HR) was 1.362[95% CI 1.079-1.719], p=0.0093. Cardiovascular outcome and all-cause mortality were not statistically different (0.884[0.528-1.481], 1.731[0.898-3.338]). The risk of renal events increases with lower baseline renal function. Patients with eGFR<30 ml/min/1.73m2 and eGFR 30~60 showed higher HR than patients with eGFR≥ 60(24.547[12.082-49.875], 4.278[2.072-8.833]). In subgroup analysis, patients used loop diuretics at baseline had higher HR (1.361[1.076-1.720]). Patients who didn't achieved BP goal(140/90mmHg) with 4 antihypertensives showed higher risk of renal event risk(2.189[1.469-3.269]).

Conclusions: Our study shows that ATRH is associated with high risk of adverse renal outcome in patient with chronic kidney disease. Especially patients with ATRH and CKD stage III~V need more careful approach and management to prevent worsening of renal function.

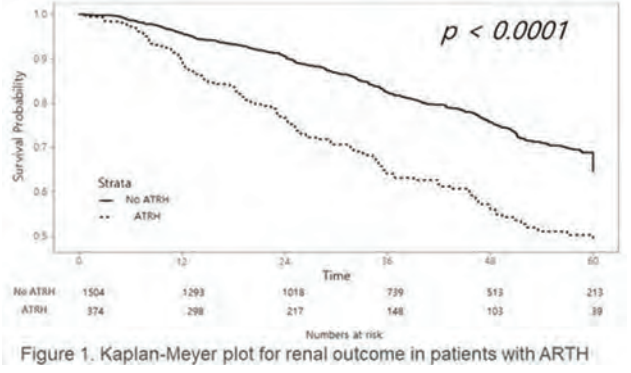

Figure 1. Kaplan-Meyer plot for renal outcome in patients with ARTH

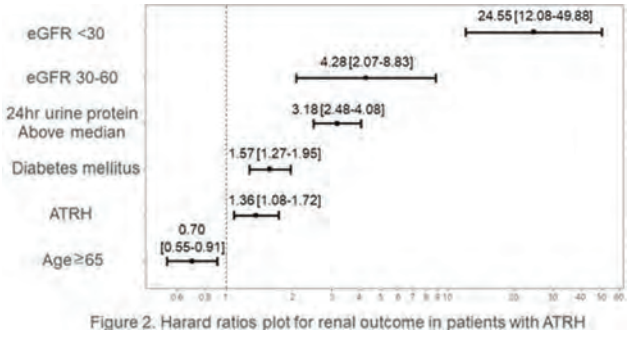

Figure 2. Harard ratios plot for renal outcome in patients with ATRH

TH-PO1098

The Interactions Between Proteinuria, Activity of Fibroblast Growth Factor 23, and Serum Phosphate on Renal Progression in Patients with CKD: A Result from the KNOW-CKD Study

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Background: Both of proteinuria and hyperphosphatemia are well known risk factors of CKD progression. Recent experimental study reported that proteinuria increases serum phosphate by decreasing biologic activity of fibroblast growth factor 23 (FGF-23). We examined this relationship in a large chronic kidney disease (CKD) cohort and evaluated combined effect of proteinuria, FGF-23 activity, and serum phosphate on CKD progression.

Methods: This prospective longitudinal study was conducted with 1909 patients from CKD stage 1 to 5. The activity of FGF-23, measured by fractional excretion of phosphate (FEP)/FGF-23 ratio, was compared according to the degree of proteinuria. Primary outcome was CKD progression defined as ≥50% decline of estimated glomerular filtration rate (eGFR), doubling of serum creatinine, start of dialysis, or kidney transplantation.

Results: The patients with more proteinuria had significantly higher serum phosphate levels from CKD stage 2 to 5 than those with less proteinuria. In addition, there was a negative relationship between 24 hour urine protein (24h UP) and FEP/FGF-23 ratio (γ, -0.07; P = 0.005). In addition, after matching variables associated with serum phosphate, patients with more proteinuria had higher serum phosphate (P < 0.001) and FGF-23 (P = 0.012), and lower FEP/FGF-23 ratio (P = 0.007) compared to those with less proteinuria. In the matched cohort, low FEP/FGF-23 ratio was a risk factor of CKD progression (hazard ratio, 0.86 per 1 log increase; 95% confidence interval, 0.79-0.94; P = 0.001), and there was significant interaction between 24h UP and FEP/FGF-23 ratio (P = 0.027). Furthermore, 24h UP and serum phosphate also had a significant interaction on CKD progression (P < 0.001).

Conclusions: Proteinuria is associated with decreased biologic activity of FGF-23 and serum phosphate. Furthermore, diminished activity of FGF23 is an independent risk factor for renal progression in proteinuric CKD patients.

TH-PO1099

Association Between Serum Lipid Profiles and Progression of CKD: KNOW-CKD Study

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Background: Dyslipidemia has been linked to an increased risk of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). However, the role of individual lipid parameter in the development of in the progression of CKD is not well established.

Methods: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 1,939 patients who measured total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were included in the analysis. Study endpoint was a composite of a ≥ 50% decline in estimated glomerular filtration rate or the onset of end-stage renal disease.

Results: The mean age was 53.8 ± 12.2 years and 1,192 (61.5%) patients were males. The mean serum concentrations of TC, LDL-C, HDL-C, and TG were and 174.1 ± 38.9, 96.9 ± 31.3, 49.3 ± 15.5, and 156.6 ± 96.9 mg/dl, respectively. During a median follow-up of 3.0 years, 421 patients (21.7%) reached the composite end point. In the fully adjusted multivariable Cox models, HDL-C was significantly associated with increased risk of CKD progression (HR, 1.11 per 10 mg/dl increase; 95% CI, 1.01-1.22; P = 0.03), while TC (HR, 0.99 per 10 mg/dl increase; 95% CI, 0.95-1.03; P = 0.53), LDL-C (HR, 1.01 per 10 mg/dl increase; 95% CI, 0.97-1.06; P = 0.68), and TG (HR, 0.99 per 10 mg/dl increase; 95% CI, 0.98-1.01; P = 0.35) were not. However, areas under the curve of these 4 lipids were similar and none of the parameters did not improve the net reclassification improvement and the integrated discrimination improvement for the progression of CKD.

Conclusions: HDL-C only was significantly associated with CKD progression. However, all lipid parameters had limited roles in improving risk stratification for adverse renal outcome.

TH-PO1100

Serum Bilirubin Is a Significant Prognostic Marker for Renal Progression and Mortality in Patients with CKD

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Background: Mildly elevated bilirubin could protect kidney damage by reducing oxidative stress. However, it is still unclear that serum bilirubin level can predict clinical outcomes in the patients with CKD. The aim of our study is to investigate the association of serum bilirubin and clinical outcomes in CKD patients.

Methods: A total of 5479 patients who visited nephrology clinic at Seoul National University Boramae Medical Center between 2006 and 2016 were enrolled. Patients were divided 4 groups according to different baseline serum total bilirubin levels. Primary outcome was ESRD and secondary outcome was all-cause mortality. We conducted Cox analysis to evaluate the association between all-cause mortality and ESRD progression. Age, sex, eGFR, hypertension, and diabetes were included as covariates.

Results: Mean serum bilirubin level was 0.7±0.5 mg/dL. A total of 1029patients were a group with the lowest serum bilirubin level (0.5 mg/dL<Bb) and 1723patients had bilirubin level between 0.5mg/dL and 0.7mg/dL.1658patients had bilirubin level between 0.7 g/dL and 1.0mg/dL, 1069 patients with more than 1.0 mg/dL bilirubin. Low bilirubin groups were older and had more hypertension and diabetes. Also, eGFR of low bilirubin groups was lower than that of high bilirubin group. During the follow-up period of 79.4±10.3 months, 412 patients developed ESRD and 691 patients were dead. In the multivariate cox analysis, the higher serum bilirubin level groups had significantly lower risk of ESRD progression, while the group with the lowest mortality rate was not the group

with highest bilirubin level but the group with mildly elevated bilirubin(0.7≤Bb<1.0mg/dL) representing reverse J shaped curve.

Conclusions: The lower serum total bilirubin level was significantly related with ESRD progression and mortality. Total serum bilirubin can be used as early biomarker for predicting ESRD development and survival in CKD patients.

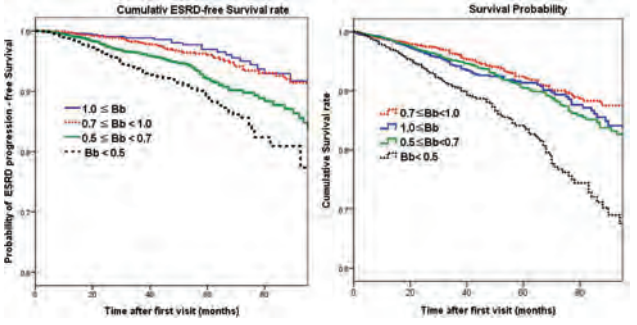

Figure 1. Survival curves showing ESRD risk and mortality according to bilirubin levels.

TH-PO1101

The Relationship Between Body Mass Index (BMI) and Outcomes in Health and CKD

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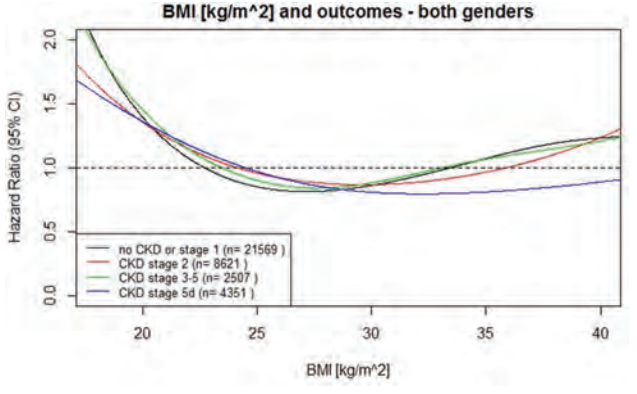
Background: In the general population the relationship between BMI and mortality is U-shaped, while in the hemodialysis (CKD 5D) population lower risk at higher BMI was observed. Pathophysiologic explanations exist, but disease may also act as a statistical collider creating a "selection bias by death". We studied the relationship across CKD stages and in various subpopulations.

Methods: We studied healthy subjects, CKD patients at various stages (NHANES 1999 to 2010), and CKD5D patients dialyzing in Renal Research Institute (RRI) clinics. We constructed Cox proportional hazard models and depicted hazard ratios over a wide BMI range using spline functions and evaluated differences between subsets stratified by age (</>= 55 years), gender, race, and ethnicity. We also constructed polynomial models to test for an interaction between CKD stage and BMI in the Cox models. Akaike Information Criterion (AIC) was computed to determine the most accurate model.

Results: We studied 21569 healthy subjects, 8621 CKD stage 2 patients, 2507 CKD stage 3-5 patients, and 4351 CKD5D patients. We found consistently an inverse association between BMI and mortality in CKD5D patients and variations in the other subsets. While the interaction between CKD stage and BMI were significant in all constructed models, the final model with the lowest AIC value include only an interaction between CKD5D and BMI.

Conclusions: Our data show a consistent U-shaped relationship between BMI and all-cause mortality in the general population, but an "obesity paradox" in CKD5D. While the biological reasons are elusive, the consistency of the observation across all analyses suggests a pathophysiological relationship in concert with CKD acting as a statistical collider.



Spline function of hazard ratio of all-cause mortality over a 3-year follow-up period as a function of body mass index (BMI).

TH-PO1102

Race, Gender, and the Participation Gap: Evaluation of Clinical Trials in Kidney Disease

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Background: Disparities in kidney disease by race, ethnicity, and sex are well documented. However, the representation of these groups in randomized controlled trials (RCTs) is largely unknown. Here, we aim to determine differences in gender and race participation in kidney disease RCTs.

Methods: The ClinicalTrials.gov electronic database was searched from January 1, 1970 to January 1, 2018, with the following keywords: "kidney disease," "chronic kidney disease" (CKD), "acute kidney injury" (AKI), "hemodialysis" (HD), "peritoneal dialysis", "glomerulonephritis" (GN), "kidney stones", "kidney transplant", or "polycystic kidney disease" (ADPKD). RCTs that were registered as completed and which reported results were eligible for inclusion. We limited our search to studies which were conducted in United States and published in the English language. Two reviewers independently extracted race and gender data onto standardized extraction forms.

Results: The initial search provided 2436 citations with 339 studies (CKD 109; HD 75; AKI 44; GN 40; Transplant 33; ADPKD 19; Misc. 19) potentially eligible for inclusion. Of the 339 trials (n=102,361, mean age 56±12 years), sex was reported for 98% (n=100,452) of trial participants. Women accounted for 43% of participants overall, with similar percentages in non-dialysis CKD RCTs and dialysis RCTs. Race was reported for 60% (n= 61, 697), of which 78.5% were Caucasians, 15.6 % African American (AA), 3.7% Hispanics, 1.5% Asians, 0.6% American Indians and 0.1% were Native Hawaiian. In HD RCTs, Caucasian (44.9%) and AA (42.0%) were equally represented, and Hispanics accounted for 9.6% of trial participants. Low recruitment of AA (3.2% and 11.6%, respectively) and Hispanics (5.8% and 0.7%, respectively) was observed in both transplant and AKI RCTs.

Conclusions: Our findings suggest that racial minorities, especially AA and Hispanics, and women are less likely to be enrolled in clinical trials. Future studies should focus on addressing the barriers to recruitment of women and minorities in RCTs, in order to achieve representative RCT populations.

TH-PO1103

Sex and Racial Differences in Pre-Dialysis Hospitalization in Incident ESRD Patients

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Background: Pre-dialysis hospitalization is an independent predictor of mortality, and significant contributor to health care costs in patients with end stage renal disease. Sex and racial differences in the pre-dialysis hospitalizations has not been studied for incident dialysis patients.

Methods: We evaluated 165,452 adult patients who initiated dialysis between 1/1/2010 and 12/31/2014 from the United States Renal Data System with linked claims for Medicare Part A and Part B or Medicare Primary Other as the primary payer for the entire two years prior to dialysis initiation. Using case-mix adjusted logistic regression models, we examined the impact of race and sex on the two year pre-dialysis hospitalization as the primary outcome identified using ICD-9 codes.

Results: Mean age was 73 ± 11 years. In the study sample, 54.3% were men. 65% were Whites, 21.6% were Blacks, 8.9% were Hispanics, 3.5% were Asians, and 0.9% were Native Americans. Overall, 77% of patients had at least one pre-dialysis hospitalization. Among the causes of pre-dialysis hospitalization, 28.6% of patients experienced cardiovascular hospitalization, 12.4% had infection hospitalization, 11.5% had both cardiovascular and infection hospitalization and 24.5% had neither cardiovascular nor infection hospitalization. Overall, one-year all-cause mortality was 30.7%. Women had higher odds of pre-dialysis hospitalization as compared to men (odds ratio [OR], 1.17; 95% confidence interval [CI], 1.14-1.20]). In adjusted analyses, as compared to Whites patients, odds of pre-dialysis hospitalization was lower among Asians (OR, 0.55; 95% CI, 0.52-0.59]), and Hispanics (OR, 0.80; CI, 0.77-0.84); and was not statistically significant for Black patients or Native Americans.

Conclusions: Among dialysis patients, women have 17% higher odds of pre-dialysis hospitalization as compared to men. As compared to White patients, Asians have 45% lower odds and Hispanics have 20% lower odds of pre-dialysis hospitalizations. Process of care and biological factors need to be explored further to understand the reasons behind these disparities associated with pre-dialysis hospitalization.

TH-PO1104

Pregnancy Outcome Predictors Among Japanese Patients with CKD

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Background: Studies on pregnant patients with chronic kidney disease (CKD) have been performed worldwide; however, data on the size of the study population, race, as

well as information on CKD are limited. On account of limited data rendering the studies non-generalizable, some of the guidelines remain controversial, thereby restricting their application in clinical practice. We conducted a retrospective cohort study to address this problem by clarifying the association between CKD status and pregnancy outcomes.

Methods: Patients with CKD who gave birth or miscarried at our institution between January 1, 2010, and December 31, 2017 were selected as the study population. Clinical data were collected from medical records. We analyzed the correlations between CKD status (age, body mass index, estimated glomerular filtration rate [eGFR], urinary protein-creatinine ratio [UP], mean blood pressure [MBP], and antihypertensive drug use [HTND]) at the time of referral and severe adverse events (SAE). We also focused on the incidence of small-for-gestational-age (SGA) infants and birth weight (BW).

Results: The study included 113 pregnancies among 88 patients. Median age was 32 years (interquartile range [IQR]: 29-36). Median eGFR was 101.8 ml/min/1.73 m^2 (IQR: 80.9-120.3). Median UP was 0.17 g/gCr (IQR: 0.04-1.1). Of the 88 patients, most were Japanese, 28 had IgA nephropathy, 15 had nephrotic syndrome. SAE in 34 cases included severe pregnancy-induced hypertension, preterm delivery, emergency cesarean section, neonatal intensive care unit admission, low BW, and fetal death. Multivariate logistic regression analysis showed that SAE was correlated with age (odds ratio [OR]=1.14, p=0.025), eGFR (OR=0.98, p=0.013), MBP (OR=1.05, p=0.033), and HTND (OR=4.00, p=0.025). BW was correlated with age (t=-2.20, p=0.03), UP (t=-2.05, p=0.043), and HTND (t=-2.36, p=0.021) according to multivariate linear regression analysis (R-squared =0.20). However, UP alone was a predictor for SGA (OR=1.42, p=0.021) according to multivariate logistic regression analysis.

Conclusions: As in previous reports, eGFR was found to be a predictor of SAE. However, we found that it was UP rather than kidney function that might affect child growth. Therefore, the mechanism of SAE development and the effect on child growth might be different among CKD pregnancies.

TH-PO1105

Anti-Mullerian Hormone in Women with CKD

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Background: Although CKD is recognised to impact female fertility, underlying pathophysiological mechanisms are poorly understood. Serum concentrations of anti-Mullerian hormone (AMH) are used in women without CKD as a marker of ovarian reserve, which is a key component of female fertility. There are limited data on the utility of serum AMH quantification in women with CKD.

Methods: Serum AMH was quantified by Roche Elecsys AMH assay in 163 women with CKD (30 CKD stage 1, 37 Stage 2, 26 Stage 3a, 31 Stage 3b, 21 Stage 4, 18 Stage 5) seeking pregnancy advice. Values were compared to assay-specific percentiles.

Results: In women with CKD there was no correlation between eGFR and age-corrected AMH centile (r=-0.001, p=0.98). There was a strong correlation between AMH and age (r=-0.5, p<0.0001). Women with CKD had a lower age-corrected AMH concentration compared to women without CKD across all CKD stages (p=<0.0001 to 0.007). The effect of CKD on AMH was greatest for women <35 years (p=0.002-0.03).

Conclusions: Women with CKD have lower levels of serum AMH compared to women without CKD, across all stages of CKD. This suggests that women with CKD have reduced ovarian reserve. The clinical significance of a lower serum AMH, especially in women with CKD <35 years, warrants further investigation. There is no evidence that renal clearance modifies serum AMH concentration.

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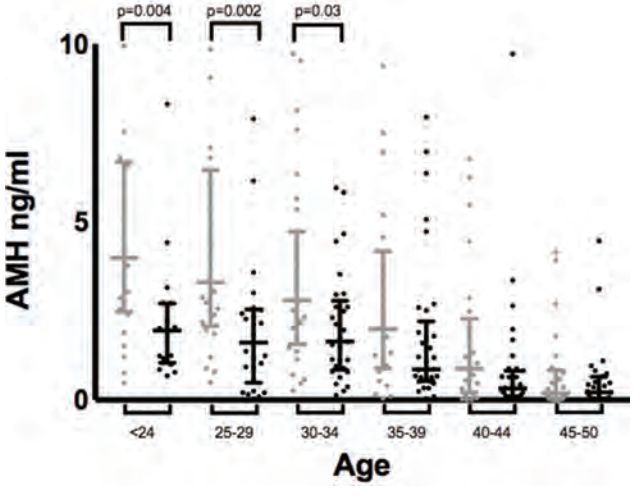

Age-specific serum AMH concentrations (median ± IQR) in women with CKD (black) compared to controls (grey)

TH-PO1106

The Impact of Gender on Inpatient Mortality of Hypertensive Patients with CKD3 to ESRD in the US

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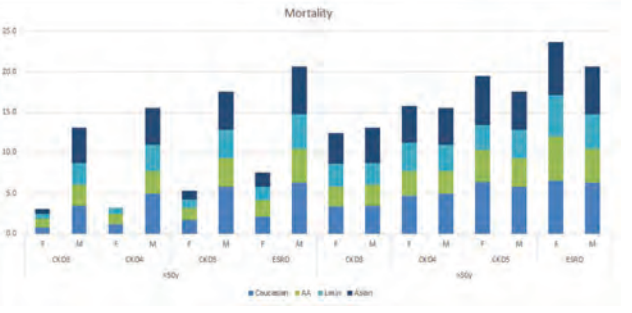
Background: HTN and CKD are 2 of the most important risk factors for CVD in the US population.The impact of gender or race in this equation remains unclear. Studies comparing the inpatient mortality between males and females with HTN and CKD are sparse. Our aim was to determine if gender in the US population and menopausal age, affect the inpatient survival rate of hypertensive patients across CKD stages.

Methods: Data was extracted from the 2005-2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, hypertensive female with CKD (stage3-5 + ESRD) patients were matched with hypertensive males at a 1:1 ratio. We compared inpatient mortality per CKD stage, menopausal age and race. Analyses were performed using SAS9.3.

Results: Among 2,121,750 hospitalized hypertensive patients, 51.5% were males and 48.5% females. There was 32.1% females with CKD3, 14.7% with CKD4, 3.4% CKD5 and 54% with ESRD. Similarly, 32.7% of males have CKD3, 13.2% CKD4, 3.2% CKD5 and 50.9% with ESRD. In-hospital crude mortality was significantly higher for males compared to females at CKD stages 3 (3.1 vs 3.3% p<0.0001), CKD4 (4.1 vs 4.4%p=0.0004) and ESRD (5.1 vs 5.2%p=0.0039) but was non-significant in CKD5 not on dialysis (4.7 vs 4.8%p=0.45). Factoring menopausal age for each race group, we find women<50y old to have significantly less mortality than men, across all CKD stages and races. Women> 50y have similar mortality rate to men with CKD 3,4 or 5; while women>50y with ESRD have a significantly higher mortality than ESRD men of similar race group (fig1).

Conclusions: Inpatient mortality risk of women compared to men through stages of CKD 3 to ESRD, appears to be reduced in pre-menopausal women, comparable after menopause and increased when on dialysis, irrespective of the race group. Further studies are needed to elucidate the possible links of menopause and the effect of gender with mortality in patients with hypertension and CKD and to assess if this holds true in outpatient settings.



TH-PO1107

Impact of Thyroid Hormones on Kidney Function in Patients with a Renal Transplant – A Retrospective Data Analysis

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Background: High levels of thyroid-stimulating-hormone (TSH) correlate with reduced estimated glomerular filtration rate (eGFR) and an increased risk of developing chronic kidney disease (CKD), even in euthyroid patients. Thyroid-hormone-replacement-therapy has been shown to delay progression of end-stage renal disease in sub-clinically hypothyroid patients with CKD. However, the presence of such a link after kidney transplantation (NTX) has not been previously investigated. This study tested whether TSH levels are associated with eGFR in patients with a renal transplant.

Methods: 398 patients who received an NTX between 2003 and 2016 in Vienna, Austria, were included in this retrospective study. Thyroid and kidney function parameters were collected at 12 and 24 months post NTX. Linear regression models estimated the association between thyroid- and renal function. Functional variables at both time-points or their differences over time were used to avoid within-individual correlations in a longitudinal setting. Multivariable linear regression models were employed to adjust main effect estimates due to potential confounding factors: BUN/creatinine ratio, tacrolimus plasma levels, CRP, BMI, gender, age.

Results: A linear regression analysis comparing the changes in eGFR and TSH between months 12 and 24 post NTX showed a significant inverse correlation (p=0,0183). For every 1-unit increase in the change of TSH over 12 months eGFR decreased by 1,39 ml/min in the same time frame. The strongest confounder in this comparison was BUN/creatinine ratio. TSH had no impact on eGFR when values 12 and 24 months post NTX were compared: p=0,6296 or p=0,8578, respectively.

Conclusions: Normothyroid renal graft recipients with increasing TSH values between the months 12 and 24 post NTX had less stable, even decreasing eGFR levels. The single thyroid and kidney function values at selected time-points did not show a correlation. Prospective randomized placebo-controlled studies are underway to clarify whether treatment with thyroid hormones reaching low-normal TSH levels could enhance eGFR of patients with a kidney graft.

TH-PO1108

Creating Axes of Kidney Tubule Health: A Factor Analysis of Biomarkers in SPRINT

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Background: Several biomarkers of kidney tubule function and injury associate with cardiovascular disease (CVD) and mortality risks, but associations are weakened by their physiological overlap and inter-correlation. Factor analysis is an agnostic method to condense information by analyzing covariance of measurements. We hypothesized that factor scores would represent underlying physiology and be associated with outcomes independently of eGFR and albuminuria.

Methods: Among 2,376 SPRINT participants with eGFR <60, we measured urine levels of kidney tubule injury (IL-18, NGAL, KIM-1, MCP-1, YKL-40) and function (α-1 microglobulin, β-2 microglobulin, uromodulin), and serum levels of PTH and FGF23. Factor analysis utilized principal-component factor estimation and promax rotation. We used Cox models to evaluate associations of factor scores with composite CVD, heart failure (HF), and all-cause death.

Results: Mean age was 73±9, 40% female, and mean eGFR 46±11. Factor scores reflected biology: there were two injury factors, Factor 1 comprised by IL-18, NGAL, and YKL-40; Factor 2 by MCP-1 and KIM-1; one factor of proximal tubule reabsorption, Factor 3, α-1 and β-2; and one factor of renal reserve: Factor 4, uromodulin, PTH, and FGF23. After adjusting for eGFR, albuminuria, and CVD risk factors, Factors 1, 3, and 4 were associated with CVD risk (**Table**), and Factor 1 was associated with HF. Factors 1 and 4 were associated with higher mortality risk. In participants without prior CVD or HF, Factor 3 was more strongly associated with CVD (HR 1.28, 95%CI 1.08-1.52) and HF (1.36, 1.02-1.81) (p-for-interaction=0.03, 0.04).

Conclusions: Combining biomarkers into factors may be an efficient method to create biologically plausible axes of kidney tubule health that have important associations with CVD risk, independently of glomerular markers.

Funding: NIDDK Support

Adjusted Associations of Factor Scores (per SD) with CVD, HF, and Death in SPRINT-CKD Participants

	CVD Composite (events = 306) Adjusted HR (95%CI)	Heart Failure (events=123) Adjusted HR (95%CI)	All-Cause Death (events=233) Adjusted HR (95%CI)
Factor 1: IL-18, YKL-40, NGAL	1.14 (1.01 - 1.28)	1.17 (1.02 - 1.33)	1.21 (1.02 - 1.44)
Factor 2: MCP-1, KIM-1	1.07 (0.94 - 1.22)	1.14 (0.97 - 1.33)	1.17 (0.94 - 1.46)
Factor 3: α-1, β-2	1.18 (1.04 - 1.34)	1.01 (0.88 - 1.16)	1.13 (0.93 - 1.37)
Factor 4: uromodulin, PTH, FGF23	1.21 (1.07 - 1.38)	1.40 (0.95 - 1.28)	1.36 (1.13 - 1.63)

Adjusted for age, sex, race, randomization arm, eGFR, ACR, history of CVD/HF, number of hypertensive agents, SBP, DBP, HDL, total cholesterol, triglycerides, statin use, smoking.

TH-PO1109

Plasma TNF Receptor Concentrations After Hospitalization with AKI and Long-Term CKD and Mortality

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Background: Plasma tumor necrosis factor receptor (TNFR)1 and TNFR2 provide prognostic information in ambulatory patients with diabetic kidney disease, but their utility in patients after an episode of AKI is unknown.

Methods: Hospitalized adults with and without AKI were enrolled in a parallel, matched cohort from 4 centers between 2009-2015 and had plasma TNFR1 and TNFR2 measured at the outpatient baseline visit within 3 months post-discharge. We tested for associations between biomarkers, expressed continuously and by quartiles, with time until the composite kidney outcome (CKD incidence, CKD progression, or ESRD) and death via a multivariable Weibull regression model that accounted for (1) the 1:1 matching of adults and (2) competing risk. We adjusted for demographics, comorbidities, AKI status during hospitalization, and concurrent eGFR, UACR, and CRP at the baseline visit.

Results: Among 1377 participants, median concentrations of TNFR1 and TNFR2 decreased from 3976 [IQR 2791-5936] and 8485 [IQR 5865-12774] pg/mL during hospitalization, to 2829 [IQR 2064-4162] and 6661 [IQR 4758-9692] pg/mL at the post-discharge baseline visit, respectively. The composite CKD outcome occurred in 257 (19%) and death before CKD occurred in 212 (15%) over a median follow-up of 4.2 years, and these events occurred more frequently in those with higher concentrations of each biomarker. After adjustment for a comprehensive panel of covariates, plasma TNFR1 and TNFR2 were independently associated with both the CKD outcome and death (**Figure**).

Conclusions: In hospitalized patients that survived at least 3 months, plasma TNFR1 and TNFR2 provide additional risk-stratification for kidney outcomes and death, even after accounting for concurrent measures of kidney function, albuminuria, and systemic inflammation.

Funding: NIDDK Support

Exposure	Composite CKD Outcome		Death	
	Incidence (%)	Adjusted HR (95% CI)*	Incidence (%)	Adjusted HR (95% CI)*
TNFR1				
Continuous (per log2)	-	2.0 (1.4-2.8)	212 (15%)	3.6 (2.4-5.4)
1st Quartile	25 (7%)	Ref	21 (6%)	Ref
2nd quartile vs. 1st	60 (17%)	1.8 (1.1-3.0)	36 (11%)	0.9 (0.5-1.5)
3rd quartile vs. 1st	71 (21%)	1.9 (1.2-3.2)	59 (17%)	1.3 (0.8-2.3)
4th quartile vs. 1st	101 (29%)	1.9 (1.1-3.2)	96 (28%)	2.2 (1.1-3.9)
TNFR2				
Continuous (per log2)	-	1.7 (1.3-2.3)	-	2.3 (1.6-3.2)
1st Quartile	28 (8%)	Ref	25 (7%)	Ref
2nd Quartile vs. 1st	57 (17%)	1.9 (1.2-3.0)	39 (11%)	0.8 (0.5-1.4)
3rd Quartile vs. 1st	74 (22%)	2.6 (1.6-4.1)	49 (14%)	1.0 (0.6-1.7)
4th Quartile vs. 1st	98 (28%)	2.0 (1.2-3.4)	99 (29%)	1.7 (1.0-2.9)

*Adjusted for race, sex, age, BMI, smoking status, history COPD, CVD, AKI status (vs. no AKI), CKD status (vs. no CKD), sepsis during hospitalization, 3-month eGFR, 3-month UACR, 3-month CRP, and clinical site.

Association of Plasma TNFR1 and TNFR2 with Outcomes in the ASSESS-AKI Study

TH-PO1110

Elevated Soluble ST2 Levels but Not Galectin-3 Is Associated with Renal Progression and Adverse Clinical Outcomes in Non-Dialysis Patients with CKD

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Background: Soluble ST2 (sST2) and Galectin-3, novel biomarkers of heart failure and cardiovascular stress, predict cardiovascular event and mortality. However, the relationships with renal function and adverse outcomes are less certain. The purpose of this study was to determine whether sST2 and Galectin-3 associated with chronic kidney disease (CKD) progression and adverse clinical outcomes.

Methods: We measured baseline sST2 and Galectin-3 concentrations in CKD patient cohort at our institution included between October 2013 and December 2014. The primary outcome was CKD progression (≥50% reduction in estimated GFR [eGFR] from the baseline or reach to the end-stage renal disease [ESRD]). The secondary outcome was the composite of CKD progression, cardiovascular event, or death. We used Cox proportional hazards model to evaluate associations between sST2 and Galectin-3 level with renal and composite outcomes.

Results: A total of 312 patients were enrolled in this study. At baseline, sST2 was directly associated with serum creatinine (r = 0.492, P < 0.001) and urine protein-to-creatinine ratio (UPCR) (r = 0.309, P < 0.001). Galectin-3 was also directly associated with serum creatinine (r = 0.164, P = 0.004) and UPCR (r = 0.136, P = 0.027). Cox regression analysis showed that baseline sST2 level was independently predicted the CKD progression (hazard ratio [HR] per SD increase in log-transformed sST2 concentration, 16.383; 95% confidence interval [CI], 3.362 – 79.836; P = 0.001) and composite outcome (HR, 5.430; 95% CI, 1.459 – 20.213; P = 0.012) after adjustment for confounding factors. However, baseline Galectin-3 level was associated with CKD progression and composite outcome only in crude analysis, lost its statistical significance after adjustment for confounding variables.

Conclusions: In conclusion, elevated levels of sST2 are significantly associated with renal progression and adverse clinical outcomes in non-dialysis patients with CKD.

TH-PO1111

Serum Metabolomic Biomarkers Associated with Neurocognitive Dysfunction in Youth with CKD

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Background: CKD is linked to worse neurocognitive (NC) outcomes, possibly related to effects of uremic toxins on the brain. Aims of this study are (1) to compare serum metabolomic profiles of children and young adults with CKD to healthy controls and (2) to evaluate the association between serum metabolite levels and NC outcomes in individuals with CKD.

Methods: Serum untargeted metabolomic profiling (Metabolon, Inc.) was performed in individuals aged 8-25 years with CKD Stage 2-4 (n=65) and matched healthy controls (n=69). Metabolite levels in CKD vs. control groups were compared by multivariable linear regression, with metabolite level as the outcome variable and CKD vs. control as the explanatory variable, adjusted for age, gender, obesity and race. Using the subset of metabolites that differed in CKD vs. controls after Bonferroni correction (threshold p=5.7x10e-7), the relationship of metabolite level and NC outcome within the CKD group was analyzed by multivariable linear regression, with NC composite score as the outcome variable and metabolite level as the explanatory variable, adjusted for estimated glomerular filtration rate (eGFR), glomerular vs. non-glomerular disease, maternal education, income, age, gender, obesity and race. The NC composite score was calculated using the mean

of z-scores within 4 domains: intelligence, attention regulation, working memory and executive function.

Results: 233 of the 876 metabolites identified differed significantly between CKD and control groups after Bonferroni correction, including metabolites previously found to be associated with CKD and NC dysfunction such as those within the kynurenine/tryptophan and glutamate pathways. Within the CKD group, 6 of the 233 metabolites examined were associated with NC composite score (raw p values <0.05), but the association was not significant after Bonferroni correction.

Conclusions: Youth with CKD have significantly different metabolomic profiles than healthy controls. We did not find an association between metabolite levels and composite NC outcome in the CKD group. However, use of a composite NC score may mask differences in individual NC domains, and adjusting for eGFR may mask associations with renally-cleared metabolites. Future analyses will include examining the relationships of metabolite levels with individual NC domains.

Funding: NIDDK Support

TH-PO1112

Robotic Technology Quantifies Cognitive Deficits in Multiple Domains for ESRD Patients

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Background: Cognitive impairment is highly reported among chronic kidney disease (CKD) patients, particularly in stage 5 CKD. Lack of validated assessments for quantifying cognition in CKD patients can lead to difficulty in determining the prevalence and degree of this impairment. Robotic technology, such as the KINARM, may be able to detect cognitive deficits associated with CKD, particularly because the KINARM has been shown to identify subtle neurocognitive deficits in ischemic stroke patients. Importantly, these subtle deficits may correlate better with quality of life assessments than routine clinical testing. Objective: To quantify the neurocognitive deficits of patients with stage 5 CKD.

Methods: Recruitment was performed at a CKD clinic in a tertiary medical centre. Eligible patients were stage 5 CKD patients with no history of neurodegenerative disease or stroke. Consented patients performed a neuropsychological battery that included: the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and a robotic assessment (KINARM, BKIN Technologies, Kingston ON). The RBANS measures 5 cognitive domains along with giving an overall composite score, whereas the KINARM Standard Tests quantifies sensorimotor and neurocognitive control of the upper limb.

Results: From July 2015-April 2018, 30 patients were recruited. On the RBANS, only 3/30 patients scored outside the normative range (defined as >1.96 SD, representing the 95% performance of healthy controls) on the composite total score which measures global impairment. There was variability of impairment across domains, ranging from 0/30 on language to 8/30 on the visuospatial domain. In contrast, compared to age and gender matched controls, approximately one-third of patients were impaired on six of the nine tasks performed. These tasks correspond to deficits in: attention (10/30), sensorimotor (9/30), visuospatial (13/30), visuomotor (11/30), overriding of automatic response (10/13), and executive function (11/30).

Conclusions: Robotic technology can detect cognitive impairments in a higher proportion of patients with stage 5 CKD compared to a traditional neuropsychological assessment tool. The clinical relevance of these cognitive impairments needs further investigation.

Funding: Government Support - Non-U.S.

TH-PO1113

Inflammatory Biomarkers Improve Prediction of Sertraline Treatment Response in CKD

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Background: Inflammation may mediate depression, and CKD is associated with elevated inflammatory markers and depression prevalence. We studied whether baseline inflammation predicts treatment response to sertraline in individuals with CKD and depression.

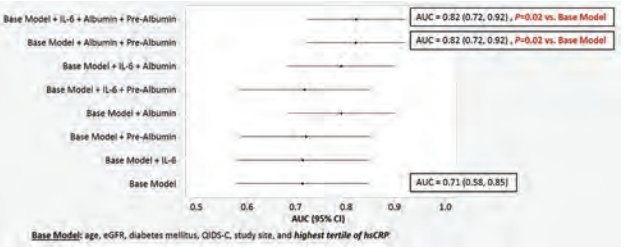
Methods: In 193 participants with stage 3-5 CKD and depression randomized to sertraline or placebo in the double-blind Chronic Kidney Disease Antidepressant Sertraline Trial (CAST), we measured baseline albumin, pre-albumin, interleukin-6 (IL-6), and high sensitivity C-reactive protein (hsCRP). Outcomes were a ≥3-point decrease (*improvement*) and ≥50% decrease (*response*) in depressive symptoms, assessed by the Clinician-Rated 16-Item Quick Inventory of Depression Symptomatology (QIDS). Logistic regression measured associations of inflammatory markers with outcomes after covariate adjustment. Inflammatory marker x treatment interaction $P<.1$ was considered significant. The areas under the curve (AUC) for nested models predicting response were compared using non-parametric tests.

Results: Mean age was 58±13 years, 58% were Black, 42% White, and 18% Hispanic. HsCRP correlated with baseline QIDS score (r=.19, $P<.05$). In the sertraline group, hsCRP was higher in those who did vs. did not achieve improvement, median (IQR): 5.0 (1.7-8.6) mg/L vs. 1.4 (0.6-3.7), $P=.005$, and response, 5.0 (2.0-14.6) vs. 2.7 (0.8-6.0), $P=.03$. A 1 log-unit increase of hsCRP independently predicted a differential degree of improvement and response to sertraline vs. placebo (**Table**). Baseline QIDS, eGFR, age, diabetes, site, and hsCRP (highest tertile) predicted sertraline response, AUC (95% CI) .71 (.58, .85). Addition of albumin and pre-albumin (lowest tertile) and IL-6 (highest tertile) improved the AUC to .82 (.72, .92), $P=.02$ (**Figure**).

Conclusions: Higher baseline hsCRP was independently associated with depressive symptom improvement and response to sertraline. Inflammatory biomarkers may identify CKD patients more likely to benefit from sertraline.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences, Veterans Affairs Support, Private Foundation Support

Outcome	All participants aOR (95% CI) N=193	Sertraline aOR (95% CI) N=97	Placebo aOR (95% CI) N=96	hsCRP x treatment group interaction P value
Improvement	1.32 (1.00, 1.74)	1.67 (1.11, 2.52)	0.92 (0.63, 1.34)	0.03
Response	1.29 (0.97, 1.71)	1.56 (1.08, 2.26)	0.90 (0.58, 1.39)	0.06



TH-PO1114

Expression of MMPS and TIMPS Is Differentially Regulated in Cataract Tissue of Patients with CKD and Diabetes Mellitus (DM) or Both

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Background: Cataract is a common preventable cause of blindness particularly amongst diabetics and recent reports suggest an increased incidence in patients with CKD. Matrix metalloproteinases MMPS and their regulators, including tissue inhibitors of MMPS (TIMPS) are variably expressed in lens tissue and may play a role in the genesis of cataract formation. This may result from direct modulation of extracellular matrix or be secondary to cell cycle events or other pathways

Methods: We prospectively evaluated 270 patients (age range, 46-93 years; mean, 71 years) who had phacoemulsification cataract surgery with intraocular lens implantation. Cataracts were graded at time of surgery, noting the presence of renal impairment (eGFR<60ml/min), type 2 diabetes mellitus and use of hypolipidemic drugs. For analysis, subjects were categorized according to presence of absence of diabetes mellitus and the presence or absence of CKD. mRNA was extracted from 123 patients, and real time PCR performed for MMPs 1,2,3,9,14 and 15 and TIMPS 1,2,3 and 4. All samples were corrected for the housekeeper gene 18S

Results: Age and CKD but not DM were associated with higher grade cataracts. MMPs 1,3,14 and TIMPS 1,2, and 3 were readily quantifiable by RT PCR. Only low levels of MMP 2 and 9 were observed and could only be quantified as present or absent. MMP15 and TIMP 4 were not detected. Non-diabetic patients with CKD EGFR < 60 ml/ml had relatively increased expression of MMP1,3,14 and TIMPs 1,2, and 3. There were no detectable differences in MMP 2 and 9. The presence of DM eliminated many differences, with higher levels of MMP 14 and TIMPs 2 and 3 in patients without CKD compared to those with CKD and DM. Hypolipidemic agents modified MMP and TIMP expression in patients with eGFR> 60 ml/min but not CKD. In non-diabetic patients, the product of TIMP 1 or 2 and MMP-3 alone were highly predictive of renal impairment with ROCs of 0.88 and 0.89 respectively. In patients with DM and CKD only TIMP-2 x MMP3 was predictive of CKD with an AUC of 0.74

Conclusions: CKD, diabetes and hypolipidemic agents differentially regulate the expression of MMPS and TIMPs in cataracts. These regulators may be important in the pathogenesis and relevant to potential therapeutic interventions for slowing cataract formation

Funding: Clinical Revenue Support

TH-PO1115

Type III Collagen Turnover Is Associated with Disease Progression and Mortality in CKD Patients from the Renal Impairment in Secondary Care Cohort

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Background: Renal fibrosis is a major underlying pathological feature in patients with chronic kidney disease (CKD) and strongly predicts progression to end-stage renal disease. We hypothesized that non-invasive assessment of the development and remodeling of fibrosis may have utility for linking dynamic in situ pathology with clinical outcomes. We

focused on type III collagen (COL III), one of the most abundant collagens in renal fibrosis, utilizing PRO-C3 to assess COL III formation and C3M for COL III degradation.

Methods: We measured serum (S)-PRO-C3 and S-C3M and urine (U)-PRO-C3 and U-C3M in 499 patients from the Renal Impairment In Secondary Care (RIISC) study. RIISC is a prospective, observational cohort of patients with moderate to advanced CKD. One-year disease progression was defined as a decline in eGFR >30% or commencing renal replacement therapy within 12 months. Results were adjusted for potential confounders including age, gender, pulse pressure, eGFR, and urinary albumin:creatinine ratio. Median follow-up was 46 months (range 0–72).

Results: U-PRO-C3 and S-PRO-C3 levels increased significantly with increasing CKD stage ($p<0.0001$), but were very weakly correlated (rho=0.1, p=0.03). Conversely, U-C3M levels decreased with increasing CKD stage ($p<0.0001$); there was no change in S-C3M levels with increasing CKD stage. The odds ratio (OR) for one-year disease progression for a doubling in U-C3M was 0.29 (95% CI 0.17-0.51, $p<0.0001$) and 0.47 (95% CI 0.23-0.96, p=0.04) in the adjusted model. Interestingly, the levels of U-C3M divided by S-C3M gave rise to a hazard ratio for development of end-stage renal disease of 0.79 (95% CI 0.63-0.99, p=0.04) in the adjusted model. S-PRO-C3 levels at baseline was able to predict mortality with hazard ratios per-doubling of S-PRO-C3 of 2.03 (95% CI 1.31-3.16, p=0.002) in the adjusted model.

Conclusions: In conclusion, we have found a dysregulated balance between COL III formation and degradation in patients with CKD, and show that this is associated with an increased risk of adverse outcomes. These findings need urgent replication in an independent cohort; if confirmed they have implications for pathotyping and therapeutic targeting in patients with CKD.

Funding: Commercial Support - Nordic Bioscience

TH-PO1116

Neutrophil/Lymphocyte Ratio in Prediction of Disease Progression in Patients with Stage 1-4 CKD in China: Results from the Chinese Cohort Study of CKD (C-STRIDE)

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Background: Chronic kidney disease (CKD) leads to end-stage renal failure and cardiovascular events. An attribute to these progressions is abnormalities in inflammation, which can be evaluated using the neutrophil/lymphocyte (N/L) ratio. We aimed to investigate the association of N/L ratio with the progression of ESKD, CVD and all-cause mortality in Chinese patients with stages 1-4 CKD.

Methods: A total of 1341 stages 1-4 CKD (18–74 years of age) patients with complete N/L and other relevant clinical variables were included in the current analysis.. Patients were divided according to the median of baseline N/L ratio (≥2.26 or <2.26). ESKD was defined at time to start hemodialysis, peritonal dialysis or renal transplantation. CVD risk was determined with onset of new CVD events. All-cause mortality was recorded at time of decease. The follow-up was censored at June 30, 2017. Cox regression analysis was used in estimating the association between N/L and the outcomes.

Results: Baseline N/L ratio was related to anemia rate, total serum cholesterol, eGFR, blood pressure, uric acid, CKD-MBD rate, cardiovascular disease, ACR and metabolic acidosis. The study duration was 4.35 year(IQR 2.86-5.26). Patients with N/L ratio ≥2.26 were at risk of developing ESKD (HR 1.687(95% CI:1.288,2.209))and all-cause mortality (HR 3.220(95% CI:1.174,8.834))compared to patients with N/L ratio <2.26 ($P<0.05$); We did not observe a significant association between abnormal N/L and CVD risk in the multivariable adjusted model.

Conclusions: Our results suggest that N/L ratio other than hs-CRP is associated with the risk of ESKD and all-cause mortality in Chinese patients with stage1-4 CKD. N/L ratio is an easily accessible and useful marker for monitoring CKD patients in clinical practice.

Funding: Government Support - Non-U.S.

TH-PO1117

Endothelial Cell Injury Marker CD146 Evaluates Disease Severity and Predicts Renal Outcomes of Early Diabetic Nephropathy

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Background: Glomerular endothelial cell injury plays a crucial role in the development of diabetic nephropathy (DN). CD146, an endothelial marker, was shown to increase in chronic kidney disease (CKD), but its role in DN remains unknown.In the current study, we examined the circulating levels of sCD146 in plasma and renal expression of CD146 in kidney biopsies of DN patients at different CKD stages. We evaluated whether CD146 could be used to assess the severity of disease and predict renal outcomes in DN at early stages.

Methods: 159 non-dialysis type 2-DN patients from 2008 to 2015 were enrolled to measure the plasma concentration of soluble CD146 (sCD146). 94 diabetes mellitus (DM) patients without DN and 100 healthy subjects were used as controls. The patients with CKD stage 1-3 were referred as early stages. Another independent cohort of 48 patients with biopsy-proved DN was used for the immunohistochemistry study of CD146. Renal outcomes were defined as doubling of serum creatinine, progression to end-stage renal disease or death.

Results: The plasma levels of sCD146 was upregulated in patients with DN compared to those without DN. Elevated plasma sCD146 was inversely associated with renal function and proved to be a more optimal marker than urine albumin creatinine ratio (UACR) to evaluate disease severity in these DN patients. Staining of kidney sections showed that CD146 was co-localized with endothelial marker CD31 and its expression increased in DN when compared with minimal change disease (MCD) and normal controls. The positive area of CD146 staining in kidney was correlated with the severity of pathological changes in these DN patients. Survival analysis suggested that both plasma levels of sCD146 and the biopsy expression of CD146 were correlated with the renal outcomes.

Conclusions: Plasma CD146 levels and its renal expression are associated with kidney injury and renal function and could be potentially developed as a marker to predict renal outcomes in patients with early stages of DN.

Funding: Government Support - Non-U.S.

TH-PO1118

Expression of CPT1α in Human Kidney Biopsy Samples Predicts the Deterioration of Renal Function and Progression of Tubulointerstitial Fibrosis

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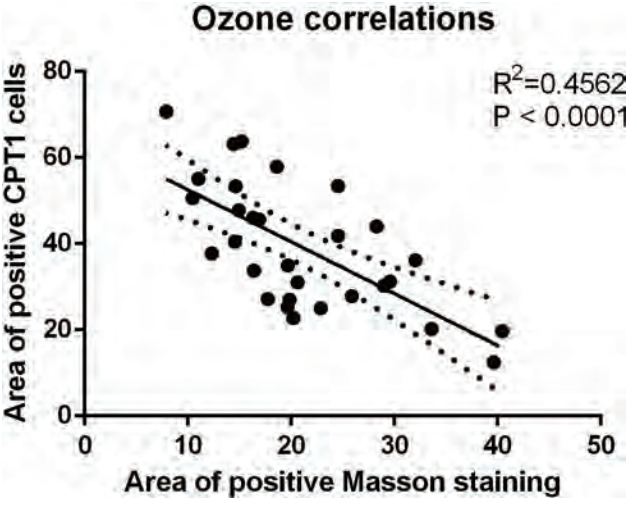
Background: Fatty acids are the preferred energy source for proximal tubule cells, defective fatty acid oxidation (FAO) leads to intracellular lipid accumulation, which plays an important role in the pathogenesis of kidney fibrosis. CPT1α is the rate limiting enzyme for FAO. In this study, we investigated whether expression of CPT1α in human biopsy samples predicts the progression of renal disease.

Methods: This was a retrospective cohort study enrolled 30 patients in our hospital from May 2015 to December 2015. The clinical data were collected and renal biopsy samples were immunhistochemically stained with CPT1α. Lipid droplets accumulation was detected by Oil Red O staining. Interstitial fibrosis was evaluated by Masson's trichrome staining. The association of CPT1α with lipid droplets accumulation, degree of renal fibrosis and decline rate of eGFR was investigated.

Results: In kidney biopsy samples, lipid droplets accumulation suggested damage in fatty acid metabolism. Expression of CPT1α was decreased in fibrosis area. Moreover, CPT1α level was negatively correlated to area of lipid droplet deposition and the area of fibrosis (fig. 1). Furthermore, expression of CPT1α is negatively correlated with the decline of eGFR per year.

Conclusions: These results suggest that expression of CPT1α in human kidney biopsy samples may predict the decline of renal function and progression of renal interstitial fibrosis. CPT1α may service as a novel biomarker for prognosis of renal disease.

Funding: Government Support - Non-U.S.



TH-PO1119

Urinary Mitochondrial DNA Level as a Biomarker of Tissue Injury in Non-Diabetic CKD

Zhongping Wei, Cheuk-Chun Szeto. *The Chinese University of Hong Kong, Sha Tin, China.*

Background: Chronic kidney disease (CKD) is a global public health issue and an important economic burden to the health care system. However, the underlying mechanism of progressive renal function loss in CKD, it still remains incompletely understood. Emerging evidence shows that mitochondrial dysfunction plays an important role in the pathogenesis and progression of chronic kidney disease (CKD). We study the relation between urinary mitochondrial DNA (mtDNA) levels and renal dysfunction in non-diabetic CKD.

Methods: We recruited 102 non-diabetic CKD patients, 43 of them had kidney biopsy that showed non-specific nephrosclerosis. Urinary mtDNA level was measured by digital

polymerase chain reaction, and compared to baseline clinical, biochemical, histological parameters as well as renal function decline in the subsequent 48.3 ± 31.8 months.

Results: Urinary mtDNA was easily detectable. The median urinary mtDNA level was 1519.4 (501.61 – 3131.23) million copy/mmol creatinine. There were modest but statistically significant positive correlations between urinary mtDNA level and baseline estimated glomerular filtration rate (GFR) ($r = 0.427$, $p < 0.001$) and proteinuria ($r = 0.376$, $p < 0.001$). For patients with kidney biopsy, urinary mtDNA level also inversely correlated with the severity of glomerulosclerosis ($r = -0.537$, $p < 0.001$), tubulointerstitial fibrosis ($r = -0.309$, $p = 0.029$). Urinary mtDNA level predicts renal event-free survival by univariate analysis (unadjusted hazard ratio [HR] 0.685, $p = 0.033$), but the predictive value of urinary mtDNA level fell short of statistical significance ((adjusted hazard ratio [HR] 0.808, 95%CI 0.331 – 1.968, $p = 0.638$) after adjusting for confounding factors.

Conclusions: Urinary mtDNA levels correlate with baseline renal function, proteinuria, and the severity of histological damage in non-diabetic CKD. Our result suggests that urinary mtDNA level may be a surrogate marker of the degree of permanent renal parenchymal damage in non-diabetic CKD.

Funding: Government Support - Non-U.S.

TH-PO1120

Reassessment of Native and Transplant Renal Biopsy Complications and Risk Factors as Performed by Nephrologists from a Large Australian Renal Unit

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Background: Renal biopsies are the gold standard for diagnosis for many renal conditions. Approximately 250 renal biopsies per million population are performed in Australia per annum, 75 per million in the USA. In Australia biopsies are performed percutaneously under ultrasound guidance with spring loaded needles predominantly by nephrologists. Worldwide minor complications (5-30%) and major complications (1-7%) have been reported. Risk factors include hypertension, acute kidney injury, aspirin use, gender, BMI. There remains limited high quality data on biopsy complications and risk factors. We conducted a single centre audit of percutaneous renal biopsies with the aim to clarify complication rates and identify risk factors.

Methods: We retrospectively reviewed 997 native and transplant renal biopsies performed by nephrologists or trainees at our large tertiary renal and transplant centre between October 2015 to April 2018. Risk factors were recorded on a regulated form and review of the medical records. Major bleeding was defined as transfusion, embolisation or surgical management. Minor complications included macroscopic haematuria, urinary retention, non-diagnostic sample and pain.

Results: We report a total of 58 (5.8%) complications with 12 (1.1%) major complications and 46 (4.7%) minor complications. No nephrectomies or deaths were recorded. Macroscopic haematuria and pain were the most common. We found a significant increase in complications with systolic blood pressure >160 mmHg but no difference with diastolic blood pressure >90 mmHg. Of the 197 patients on aspirin, 17 (29.3%) had complications compared to those not on aspirin (5.1%, p=0.06). Urea ≥ 20 mmol/L had increased complications compared to Urea < 20 mmol/L(7.9% vs 5.3%, p=0.232). Males were more likely to have complications than females (10.2% v 3.2%, p<0.001). There were no increase in complications from BMI or gauge. 38(3.4%) patients recorded an incidental decrease in haemoglobin of > 10g/L but only 2 of these had documented complications.

Conclusions: Complication rates following percutaneous renal biopsies have markedly improved. Ongoing collection of prospective data and increase size of study is required. Detailed data will help provide further insight into the risks of renal biopsies and potential modifiable risk factors.

TH-PO1121

Pre-Renal Biopsy (PRB) Ultrasound (US) Assessment: Does It Count?

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Background: PRB is an important technique providing relevant information to guide diagnosis and treatment in renal disease. As an invasive procedure it has complications, mainly bleeding related. At present, routine US assessment post PRB is recommended to diagnose haemorrhagic and/or vascular complications. In our centre a PRB drill (SimPRB) is done routinely by the same nephrologists who will perform the procedure to evaluate its feasibility and rule out any anomalies that could prevent the patient from being biopsied.

Methods: We retrospectively analyzed all SimPRB done by Interventional Nephrology in our centre from January 2014 until December 2017. Our aim was to assess SimPRB findings and their influence on PRB technique. During SimPRB we evaluate each patient's position and apnea tolerance, kidney US anatomy, previous renal abnormalities (like hydronephrosis and congenital deffects) and renal depth. This enables our team to avoid renal lesions and select needle size, puncture area and trajectory. Also, it allows interventional nephrologists to assess risks and benefits of PRB technique.

Results: Of 277 SimPRB done in the study period, 163 were male, 88 kidney transplants (KT) and 151 native kidneys (NK, 91% left sided). In 37 cases (13,3%) SimPRB found abnormalities and modified the technique: 7 patients were considered unsuitable for PRB and 30 had a relevant anomaly that modified the PRB procedure. SimPRB findings that contraindicated PRB were: hydronephrosis (n=2), bladder cancer (n=1), patient refusal (n=1), patient unable to tolerate apnea (n=1) and thinned parenchymal thickness (n=2 NK). In 30 cases SimPRB modified PRB technique changing the selected puncture area: cysts in usual puncture area (n=11), severe scoliosis (n=2), prone position intolerance (n=3), inaccesible KT pole (n=1) and right NK biopsy (n=13).

Conclusions: The SimPRB offers a first PRB approach for both patient and interventional nephrologist, reducing the number of failed procedures, anxiety and uncertainty about the technique. Also, SimPRB minimises complications and unnecessary hospital stays, thus improving patient safety and care. We suggest SimPRB should be included as a routine part of pre PRB protocols.

TH-PO1122

Transient Hypotension After Renal Biopsy Did Not Predict Major Bleeding Complication

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Background: The vasovagal reflex during the renal biopsy is likely to be considered less serious. We revealed that the reflex was one of the uncomfortable complications that impair QOL of the patients (Yoichi T et al. Clin Exp Nephrol., 2018). Here, we aimed to examine the association between the transient hypotensive events and the amount of retroperitoneal bleeding, accurately quantified by computed-tomographic (CT) images of all patients after the renal biopsy. And, we conducted a risk assessment of the major complication.

Methods: This is a single-center retrospective observational study. A total of 454 Japanese patients underwent ultrasound-guided renal biopsy at our hospital from 2013 through 2017. Demographic factors, eGFR, hemoglobin concentration, platelet counts, and renal volume were included as covariates. Renal and bleeding volumes were 3D-reconstructed from CT images. Major complications (blood transfusion, angiographic intervention and bladder obstruction) were defined as primary outcome and peritoneal bleeding volume as secondary outcome. Logistic regression analysis was used to control the possible confounders related to bleeding complications.

Results: Accurately measured by using the CT images, the retroperitoneal bleeding of total 454 patients had median amount of 40.3 mL (IQR: 19.6 - 88.2). Transient hypotensive events occurred in 26 patients (5.7%), with major bleeding complications occurring in 18 patients (3.9%). Significant difference was found in the retroperitoneal bleeding between the groups with and without transient hypotensive event (median 237.6 mL [IQR: 2.34 - 638.4] vs. median 38.9 mL [IQR: 1.00 - 974.0], $P = 0.0011$). A transient hypotensive event was associated with retroperitoneal bleeding of 100 mL or more by using logistic regression model (adjusted odds ratio 4.9 [95%CI: 2.12 - 11.30], $P < 0.001$). The hypotensive events, however, did not associated with major bleeding complications, and the risk factors for the complications were observed in lower eGFR and lower hemoglobin concentration before the biopsy, consistent with previous reports.

Conclusions: The vasovagal reflex after renal biopsy predicted substantial amount of retroperitoneal bleeding, but it had no association with the major bleeding complications. Major complication would develop owing to the other potential etiologies besides the absolute amount of bleeding.

TH-PO1123

Optimising Renal Perfusion Measurement with Arterial Spin Labelling

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Background: Arterial spin labelling is a magnetic resonance imaging technique, allowing measurement of renal perfusion without a contrast agent. The optimal manner of image analysis is not known, and we sought to determine which ASL measurement correlates with measured glomerular filtration rate (GFR).

Methods: Healthy volunteers underwent measurement of glomerular filtration rate (GFR) by technetium-99m dimercaptosuccinic acid (DMSA) renography; CKD-EPI eGFR was calculated from serum creatinine. Renal anatomy was evaluated on HASTE imaging whilst ASL was performed using flow sensitive alternating inversion recovery (FAIR) labelling and true fast imaging with steady state precession (True-FISP) acquisition. Perfusion was measured in regions of interest in cortex and whole kidney. The perfusion of each kidney was calculated as a factor of renal volume and whole kidney perfusion, whilst total kidney perfusion was the sum of right and left kidney perfusion.

Results: 12 healthy volunteers were recruited with an age of 50.8±13.7 years, and eGFR of 100.9±13.3 ml/min/1.73m^2, DMSA GFR was 97.3±23.4 ml/min/1.73m^2, mean cortical perfusion was 259.3±56 ml/min/100g, mean whole kidney perfusion was 215.6±35.4 ml/min/100g, and total kidney perfusion was 766.5±186.5 ml/min. In an analysis of 24 kidneys, there was significant correlation between single kidney GFR and kidney perfusion ($r=0.6$, $p=0.0018$) but not cortical ($r=-0.041$, $p=0.85$) or whole kidney perfusion ($r=0.091$, $p=0.67$). In an analysis of each individual, there was significant correlation of total GFR with total kidney perfusion ($r=0.71$, $p=0.01$).

Conclusions: Assessment of renal physiology using ASL MRI may be best expressed by measurement of total renal perfusion.

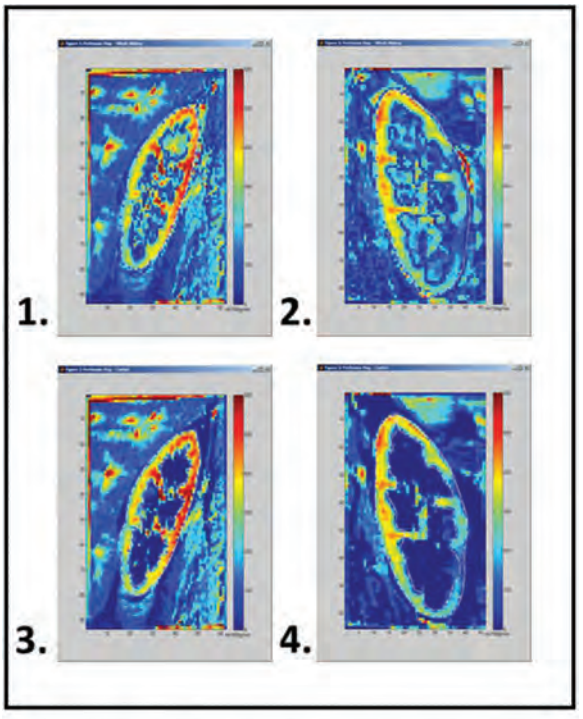

Figure 1. ASL MRI perfusion maps from a potential live donor demonstrating whole kidney (1 & 2) and cortical (3 & 4) perfusion

TH-PO1124

Functional MRI Defined-Renal Cortex Hypoxia Is a Proteinuria-Independent Predictor for Progression of CKD

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Background: Progression of chronic kidney disease (CKD) is characterized by tubulointerstitial fibrosis and glomerulosclerosis. Chronic hypoxia followed by inflammation may be key to this process. Until now, however, there has been no means of evaluating this noninvasively. Here, we employed blood oxygen level-dependent (BOLD) and diffusion-weighted (DW) magnetic resonance imaging (MRI) to assess renal tissue oxygenation and fibrosis, respectively, and evaluated their correlation with clinical parameters in a single-center, longitudinal, retrospective observational study over five years.

Methods: We examined the prognostic significance of the T2* values of BOLD MRI and apparent diffusion coefficient (ADC) values on DW MRI at the cortex and medulla as well as diabetes mellitus, mean blood pressure, estimated glomerular filtration rate, serum urate levels, and proteinuria. Rate of decline in eGFR was calculated by linear regression analysis using changes in estimated glomerular filtration rate (eGFR) during the observation period. MRI was performed with a 1.5 T Imager (Sonata®; Siemens, Erlangen, Germany) and a six-channel body coil. Both T2* and ADC maps were generated using software in the MRI scanner.

Results: A total of 91 patients were enrolled. Participants, male = 51 (56.0%), were aged 55.8 ± 15.6 years. Thirty-eight (41.8%) had diabetes mellitus, and the eGFR was 49.2 ± 28.9 mL/min/1.73 m^2 at the time of enrollment. ADC values, but not T2* values, of renal cortex were well correlated with eGFR at the start point. Neither the ADC nor T2* values of the renal medulla showed significant correlation with clinical parameters due to large variations. The rate decline in eGFR per year (ΔGFR) during the observation period was -1.92 ± 3.00 mL/min/1.73 m^2. Multiple linear regression analysis revealed that ΔGFR was significantly correlated with eGFR at the start point, the amount of proteinuria, and the T2* values (t=2.980, p=0.004), but not with the ADC values.

Conclusions: Hypoxia as determined by low T2* values using functional MRI is a clinically valuable parameter that affords a proteinuria-independent predictor of CKD progression.

Funding: Private Foundation Support

TH-PO1125

Magnetic Resonance Measurements of Intra-Renal Oxygenation and Fibrosis and Change in Kidney Function: COMBINE Trial

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Background: Prior studies report differences between health and CKD in intrarenal oxygenation and fibrosis, as measured by MRI. Data on longitudinal relationships of MRI biomarkers with change in eGFR are limited.

Methods: We obtained baseline and follow up renal MRI in 87 of 205 participants of the COMBINE trial, which was a randomized, double-blinded, 12-month, 4-group parallel study of nicotinamide and lanthanum carbonate vs. placebo in individuals with CKD stages 3-4. Relaxation rate R2* was the BOLD MRI index; higher values of R2* may represent decreased oxygenation. Apparent diffusion coefficient (ADC) was the diffusion MRI index; lower values of ADC may be due to greater fibrosis. We evaluated longitudinal data from all 87 participants to test the hypotheses that higher R2* values and lower ADC values are associated with decline in eGFR.

Results: The mean baseline eGFR was 32.6±7.58 and the mean subject-specific eGFR slope was -2.1±4.15 ml/min/1.73 m^2/year. We observed minimal changes in R2* and ADC values over 12 months. Baseline R2* and ADC did not correlate with eGFR slope (R2* cortex: r=0.03; p=0.76; ADC cortex: r=0.17, p=0.12). However, change in ADC from baseline to end of study correlated with eGFR slope (r=0.22; p=0.04). Participants with diabetes and rapid eGFR decline (>3 ml/min/1.73 m^2/year) had the lowest baseline and follow up ADC values and individuals without diabetes and without rapid eGFR decline had the highest values (Table).

Conclusions: R2* and ADC remained stable during 12 months. While R2* did not correlate with change in eGFR, change in ADC correlated with faster decline in eGFR, and individuals with diabetes and rapid loss of eGFR had the lowest baseline and follow up ADC. Larger studies with longer duration are needed to further test BOLD and diffusion MRI measurements as possible imaging biomarkers of kidney function.

Funding: NIDDK Support

	All Patients (N=87)		Diabetic, Rapid Progressors (N=18)		Diabetic, Non-rapid Progressors (N=27)		Non-Diabetic Rapid Progressors (N=14)		Non-Diabetic, Non-rapid Progressors (N=28)		
Variable	n		n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	p
Baseline Average ADC (cortex) (10-3mm2/s)	87	1.46 ± 0.16	18	1.36 ± 0.17	27	1.45 ± 0.12	14	1.47 ± 0.13	28	1.54 ± 0.19	< .01
F12 Average ADC (cortex) (10-3mm2/s)	87	1.49 ± 0.17	18	1.37 ± 0.21	27	1.50 ± 0.10	14	1.47 ± 0.16	28	1.58 ± 0.16	< .01

TH-PO1126

Use of Multi-Parametric Functional MRI to Identify Progressive CKD

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Background: Only a quarter of those with stage 3 CKD will progress to end stage kidney disease over 10 years [PMID: 22545920]. Hence, there is a need for novel markers to identify individuals at risk of progressive CKD. The chronic hypoxia hypothesis suggests that progressive CKD involves loss of peritubular capillaries leading to hypoxia which results in development of fibrosis [PMID: 25401039]. MRI can evaluate perfusion, oxygenation and fibrosis using arterial spin labeling, blood oxygenation level dependent (BOLD) and diffusion MRI respectively. We evaluated a cohort of diabetic patients with CKD stage 3 using these three techniques to determine whether we can identify patients at risk of progressive CKD.

Methods: 41 patients (median eGFR = 49 (40 to 62) mL/min/1.73m2) participated in this IRB approved study. MRI data were acquired using 3T scanner. Following baseline MRI, each individual received 20 mg furosemide *iv*, and BOLD MRI scans repeated. R2* was used as BOLD MRI parameter, higher values of which indicate lower tissue oxygenation. Lower values of apparent diffusion coefficient (ADC) suggest higher levels of fibrosis. Annual loss of renal function (eGFR_slope) was estimated using eGFR measurements obtained from electronic medical records over a period of 2-7 years. MRI data and their associations with baseline eGFR, eGFR_slope were analyzed using Spearman correlation and linear regression analyses using SPSS.

Results: R2* was not associated with eGFR or eGFR_slope. Medullary response to furosemide (ΔR2*_Medulla) (ρ = 0.401, p= 0.014) and cortical perfusion (ρ= 0.441, p = 0.009) showed positive association with annual loss of eGFR. Cortical ADC was associated with cortical perfusion; but not with eGFR or eGFR_slope. The association for ΔR2*_Medulla (but not the cortical perfusion) *vs.* eGFR_slope remained significant even after adjusting for baseline eGFR, age, BMI, gender, systolic blood pressure and blood

glucose. In those individuals (n=9) with > 3 ml/min annual loss of eGFR, ΔR2*_Medulla (1.90 ± 2.53 *vs.* 5.39 ± 3.65 s^{-1}; p = 0.007) and cortical perfusion (88.99 ± 30.31 *vs.* 117.11 ± 34.76 ml/min/100gm; p = 0.045) were lower compared to the rest.

Conclusions: Quantitative functional MRI measurements may be useful in identifying individuals with moderate but progressive CKD. Larger prospective studies should be performed to confirm these associations.

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TH-PO1127

Diffusion Weighted Imaging for Quantification of Cyst Volume in ADPKD

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Background: In autosomal dominant polycystic kidney disease (ADPKD), kidney enlargement is mainly due to cyst growth and associates with renal function decline. Whilst total kidney volume is quite easy to be quantified, total cyst volume (TCV) is difficult and time consuming. In the last decades a number of different magnetic resonance imaging (MRI) modalities have been proposed to investigate renal structure, microstructure, and function. This study proposes a novel method to automatically quantify TCV in ADPKD patients using diffusion weighted MRI (DWI).

Methods: T2-weighted MRI and DWI (Figure 1A) were performed in 15 patients with ADPKD enrolled in the EuroCYST Initiative in Bergamo Hospital (Italy). TCV was quantified on each T2-weighted MRI using an accurate semi-automated method assumed as reference [Caroli et al. Lancet 2013]. Each DWI was processed using a bi-exponential model. The histogram of the pure diffusion component (D) was thresholded using the Otsu method, to separate cyst from non-cystic renal parenchyma, and TCV was automatically computed based on this threshold. DWI-computed TCVs were finally compared with the reference values.

Results: Fluid-filled kidney cysts were denoted by higher D values than non-cystic volume (Figure 1B). DWI-computed TCV highly and significantly correlated with TCV quantified on T2-weighted MRI (rho = 0.99, p <0.001)(Figure 1C), despite the former consistently underestimating TCV (DWI-computed TCV = 1144±1068 mL; reference T2-weighted TCV = 1356±1256 mL).

Conclusions: Current findings suggest that our method can be used to automatically quantify TCV on DWI to accurately estimate the extension of renal structural changes in ADPKD. The proposed method may be useful to monitor disease progression as well as to evaluate the effect of pharmacological intervention. **Acknowledgements.** This study was funded in part by ERA – EDTA (EuroCYST Initiative).

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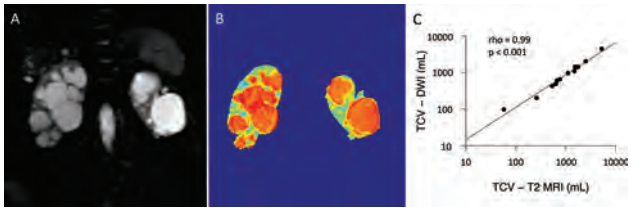

TH-PO1128

Implications of ADPKD Diagnosis at Young Age: A Post Hoc Analysis of the TEMPO 3:4 Trial

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Background: In ADPKD, there is currently limited information whether early diagnosis and management improve outcomes. We studied the implications of early diagnosis on outcome.

Methods: A post hoc analysis of TEMPO 3:4, a prospective, double-blind RCT in adults with ADPKD, with eCr ≥60 mL/min and TKV ≥750 mL. Comparison between patients diagnosed at age ≤18 years (childhood diagnosis [CD]) and >18 years (adult diagnosis [AD]).

Results: Patients were classified as CD in 20%, AD in 76% (Table 1), and unknown age at diagnosis in 4% (not shown) of the cases. At time of TEMPO 3:4 inclusion, CD were younger and had better eGFR than AD (Table 1). There were no significant differences in TKV, hypertension or RAASi use. Rates of TKV growth and eGFR changes by age at diagnosis are shown in Table 2.

Conclusions: The characterization of CD patients in TEMPO 3:4 shows that these participants were more severely affected based on a larger age-adapted TKV. Despite this fact, yearly TKV increase and loss of eGFR in the placebo arm of the study showed a tendency (NS) to be milder in the CD cohort. These data suggest the need for further evaluation of early intervention in the treatment of ADPKD.

Funding: Commercial Support - Otsuka Pharmaceutical Development and Commercialization Inc.

Table 1. Characteristics at inclusion

Parameter	CD (n=294)	AD (n=1148)	P-value
Male sex, n (%)	147 (50)	598 (52)	NS
RAASi use, n (%)	199 (68)	839 (73)	
Hypertension, n (%)	238 (81)	952 (83)	
CKD I, n (%)	128 (44)	374 (33)	
CKD II, n (%)	125 (43)	563 (49)	
CKD III, n (%)	40 (14)	208 (18)	
Mean age at inclusion (SD)	34.2 (8.1)	39.8 (6.4)	<.0001
Mean eGFR (SD)	87.4 (23.9)	80.1 (20.7)	<.0001
Median TKV (IQR)	1508 (1075,2153)	1453 (1068,1990)	0.2545

Age in years; eGFR in mL/min/1.73m², TKV in mL.

Table 2. Outcome parameters

Subgroup	Treatment	Mean % TKV Growth/Year (SD)	P Treatment Effect	Median Change eGFR/Year (SD)	P Treatment Effect
CD	Placebo	5.0 (5.4)	0.0133	-2.9 (5.3)	0.0242
	Tolvaptan	3.3 (4.7)		-2.0 (38)	
AD	Placebo	5.8 (5.3)	<.0001	-3.7 (5.9)	<.0001
	Tolvaptan	2.6 (5.9)		-2.7 (22)	

TH-PO1129

Integrase Strand Transfer Inhibitor and Progression to CKD in an Outpatient Cohort of HIV-Infected Patients

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Background: Recently introduced integrase strand transfer inhibitor (INSTI)-based regimens are highly effective in suppressing HIV viral load and have increased long-term survival of people living with HIV. The kidney outcomes among patients on INSTI regimens have not been compared.

Methods: The study included Center of AIDS Research (CFAR) HIV Clinical Cohort participants initiating an INSTI-based regimen (raltegravir [RAL], dolutegravir [DTG] and cobicistat-boosted elvitegravir [EVG/c]). Changes in eGFR over time were modelled using linear regression with restricted cubic splines. Multivariable Cox proportional hazards models were used to assess time to the first occurrence of low eGFR (<60 mL/min/1.73m²) in the full sample and in a sample restricted to tenofovir (TDF) users. Multivariable models were controlled for baseline age, sex, race, injection drug use as a mode of transmission, CD4 cell count, history of AIDS-defining illness, cardiovascular disease, hypertension and its pharmacological treatment, and diagnosis of diabetes and its pharmacological treatment. Patients were censored at death, lost to follow-up or October 1st, 2016.

Results: The anchor-agents for the 920 patient-regimens consisted of RAL (n= 156, 17%), DTG (n= 360, 39%) and EVG/c (n=404, 44%). eGFR remained relatively stable over time on all three INSTI-based agent treatment, following some minimal variation over the first few months on the regimen. Compared to EVG/c, RAL was not associated with a faster progression to low eGFR (overall sample, hazard ratio [HR]: 1.08; 95% Confidence Interval [C.I.]: 0.65, 1.77 and TDF-restricted sample, HR: 0.98; 95% C.I. 0.55, 1.72). Compared to EVG/c, DTG was associated with a faster progression to low eGFR in the TDF-restricted sample (HR 1.75; 95% C.I. 1.00, 3.06), but not in the full sample (HR 1.33; 95% C.I. 0.79, 2.25).

Conclusions: The changes in eGFR over time observed for DAG regimen may be due to tubular creatinine secretion inhibition rather than kidney injury, although progression to low eGFR might be accelerated with DTG use among TDF users.

Funding: NIDDK Support, Other NIH Support - NIHMD, NHLBI

TH-PO1130

Effect of Treatment of Chronic Hepatitis C Virus (HCV) Infection with Glecaprevir/Pibrentasvir (G/P) on Renal Biomarkers in Patients with CKD Stage 3b, 4, or 5

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Background: Chronic HCV infection is associated with CKD development and progression to end-stage renal disease (ESRD). HCV elimination may reduce risk of CKD progression. G/P, an all-oral pangenotypic HCV direct-acting antiviral (DAA) regimen, has minimal renal excretion. G/P is approved for patients (pts) with compensated liver disease and any degree of renal impairment, including ESRD, with high cure rates. Here we explore the impact of G/P on renal biomarkers in pts with CKD stage 3b, 4, or 5.

Methods: EXPEDITION-5 was a Phase 3b trial evaluating efficacy and safety of G/P for 8, 12, or 16 weeks (wks) in pts with CKD stage 3b, 4, or 5. Pre- and posttreatment

C-reactive protein, tumor necrosis factor-α, urine protein/creatinine ratio (PCR), urine albumin/creatinine ratio, and urine neutrophil gelatinase-associated lipocalin concentrations will be evaluated.

Results: 101 pts enrolled. Baseline characteristics are shown (**table**). 83% of pts received 8 wks of G/P. Sustained virologic response at posttreatment wk 12 (SVR12) was 97% with no virologic failures. There were no DAA-related serious adverse events (AEs) or clinically relevant lab abnormalities. 2 predialysis pts discontinued due to AEs. In predialysis pts (N=24), eGFR (mean±SD, mL/min/1.73 m^2) did not change from screening (27.1±9.2) to posttreatment wk (PTW) 4 (27.4±11.6); mean PCR was 2.7 g/g at baseline and 2.6 g/g at PTW4/12; 41% of pts had ≥30% improvement in PCR after G/P.

Conclusions: G/P for 8–16 wks was not associated with eGFR deterioration in predialysis pts. Preliminary data suggest G/P may improve PCR in a substantial number of pts. Other renal biomarker analyses will be presented.

Funding: Commercial Support - AbbVie

Baseline Characteristics in EXPEDITION-5

Characteristic		Predialysis N=24	Dialysis* N=77	Overall N=101
Age, years, mean±SD		64.6±10.7	57.3±10.6	59.0±11.0
Compensated cirrhosis, n (%)		5 (21)	8 (10)	13 (13)
CKD stage, n (%)	Stage 3b	7 (29)	0	7 (7)
	Stage 4	17 (71)	0	17 (17)
	Stage 5	0	77 (100)	77 (76)
Medical history, n (%)	Diabetes	15 (63)	27 (35)	42 (42)
	Hypertension	23 (96)	65 (84)	88 (87)
	Cardiovascular disease	23 (96)	67 (87)	90 (89)

*4 pts were receiving peritoneal dialysis; all other pts were receiving hemodialysis.

TH-PO1131

Effect of Ledipasvir and Sofosbuvir (LDV/SOF) on Kidney Function and Urinary Biomarkers in Patients (Pts) with Proteinuric CKD

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Background: HCV infection is associated with CKD incidence and progression. HCV may lead to immune-complex mediated glomerulonephritis, however HCV also promotes atherosclerosis, insulin resistance and chronic inflammation. We sought to determine whether HCV treatment improves kidney function, as assessed by biomarkers of kidney disease.

Methods: NCT02503735 was an investigator-initiated pilot trial that used SOF/LDV to treat pts with HCV genotype 1 or 4 and proteinuria (>300mg proteinuria/g Cr). Baseline proteinuria, cystatin-c, and creatinine were compared to on treatment values and post-therapy values. Insulin resistance (IR) was calculated by HOMA-IR. Urine biomarkers were measured by Luminex. The primary outcome was change in natural log proteinuria-to-creatinine (UPC) ratio from baseline to 12-weeks post SOF/LDV compared by paired t-test.

Results: 10 pts began 12-weeks of LDV/SOF mean age 64 (SD 10), 70% male, 60% White, 30% Black, 10% Native American. 4/10 had cirrhosis. 8/10 were cured of HCV, 2 relapsed. Baseline eGFR was 63.2 mL/min/1.73m2 (SD 26.2), baseline proteinuria was 1.05g/g (SD 0.95). Baseline to post-treatment values are in **Table 1**. Non-diabetic pts cured of HCV (pts 1-4) all had improvement in proteinuria: 1.8g/g, (SD 1.6) to 0.69g/g (SD 0.7g/g) (p=0.01). Diabetic pts and pts with HCV relapse had worsening proteinuria 0.77g/g, (SD 0.3) to 2.2g/g (SD 1.4) (p=0.05). Complement and cryoglobulins normalized in the majority, IR decreased slightly.

Conclusions: Non-diabetic pts with HCV-associated CKD had substantial improvement in proteinuria when HCV was eradicated with SOF/LDV.

Funding: Commercial Support - Gilead Sciences

Pt	Viral Outcome	Diabetes	Baseline: Creatinine	Cystatin C	Proteinuria UPC Ratio	Cryocrit	Low C4	CRP	Homa-IR	Follow-Up 12 Weeks After SOF/LDV: Creatinine	Cystatin C	Proteinuria UPC Ratio	Cryocrit	Low C4	CRP	Homa-IR
1	Cured	No	1.00	1.43	3.56	4%	Yes	1.7	4.3	0.93	1.37	1.78	None	No	11.8	3.7
2	Cured	No	1.35	2.14	0.50	1%	Yes	16	4.7	1.45	2.11	0.12	2%	Yes	9.2	2.5
3	Cured	No	0.78	0.80	1.44	3%	Yes	0.9	1.7	0.79	0.76	0.76	1%	No	5.0	1.9
4	Cured	No	1.30	1.02	0.39	None	No	0.1	3.6	1.66	1.03	0.11	None	No	0.6	5.4
5	Cured	Yes	1.22	1.09	0.84	None	No	0.3	6.7	1.25	0.87	2.18	None	No	0.5	9.3
6	Cured	Yes	1.03	0.64	1.13	3%	Yes	1.5	19.8	0.79	0.56	1.00	None	No	1.9	17.2
7	Cured	Yes	1.53	2.42	1.15	1%	No	0.5	5.5	1.91	2.75	2.01	None	No	4.1	3.7
8	Cured	Yes	1.68	2.00	0.68	2%	No	0.2	2.2	2.02	2.14	4.36	None	No	0.1	1.2
9	Relapsed	No	1.42	1.84	0.31	2%	No	3	3.8	1.48	1.63	0.35	ND	No	9.1	2.4
10	Relapsed	No	0.77	0.67	0.53	None	No	0.3	4.8	0.69	0.71	2.18	None	No	0.4	6.7

Abbreviations: Pt = patient, UPC = urine protein to creatinine, CRP = c-reactive protein, HOMA-IR = homeostatic model assessment of insulin resistance

TH-PO1132

Ankle Brachial Index Is Associated with Cardiovascular and Renal Events in Patients with CKD: Result from the KNOW-CKD Study

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Background: Vascular calcification of the media is an independent and strong predictor of cardiovascular risk in patients with chronic kidney disease (CKD). Ankle brachial index (ABI) is a useful tool for diagnosis of medial calcification as well as peripheral artery disease. However, few studies are reported its relation to the renal progression and risk of cardiovascular events in patients with CKD. We examined this relationship in a large CKD cohort.

Methods: In this prospective longitudinal study, we enrolled 2115 patients from the KoreaN cohort study for Outcome in patients with CKD (KNOW-CKD). The patients were categorized into low ABI (≤ 0.9), borderline ABI (0.9–1.1), normal ABI (1.1–1.3), or high ABI (≥ 1.3). The relationship between ABI and cardiovascular events (myocardial infarction, stroke, cerebral hemorrhage, or congestive heart failure), renal progression (as ≥ 50% decline of estimated glomerular filtration rate (eGFR), doubling of serum creatinine, or start of dialysis) was analyzed using Cox regression.

Results: Renal progression and cardiovascular events were occurred 330 (15.6%) and 86 (4.3%) in patients, respectively, during the median follow-up of 26.9 months. Compared to patients with high ABI, patients with low ABI had a lower prevalence of renal progression (low ABI: 17.5% vs. high ABI: 24.7%), whereas had a higher risk of cardiovascular events (low ABI: 17.3% vs. high ABI: 7.2%). In Cox regression model, patients with low ABI were at higher risk of cardiovascular events even after adjustments (hazard ratio [HR], 4.41; 95% confidence interval [CI], 1.63–11.9; P = 0.003), but high ABI had no significant risk of cardiovascular events (HR, 1.18; 95% CI, 0.46–3.07; P = 0.731) than those with normal ABI. However, there was no significant association between patients with low or high ABI and a risk of renal progression after adjustment.

Conclusions: Low ABI (≤ 0.9) is related to higher risk of cardiovascular events in patients with CKD. Measuring ABI might serve as a useful tool for predicting cardiovascular events in Korean CKD patients.

TH-PO1133

Association Between Serum Lipid Profiles and Cardiovascular Outcomes in CKD Patients: KNOW-CKD Study

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Background: Dyslipidemia has been linked to an increased risk of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). However, the role of individual lipid parameters in the development of cardiovascular events in the CKD population is not well established. Here, we analyzed the relative contribution of 4 lipid profiles such as total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) to the risk of cardiovascular morbidity and mortality in patients with non-dialysis CKD.

Methods: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 1,728 patients who measured TC, LDL-C, HDL-C, and TG and were not previously diagnosed with cardiovascular disorders were included in the analysis. Study endpoint was a composite of major cardiovascular events or death.

Results: The mean age was 52.9 ± 12.1 years and 1,023 (59.2%) patients were males. The mean serum concentrations of TC, LDL-C, HDL-C, and TG were and 175.5 ± 38.5, 98.0 ± 31.2, 49.8 ± 15.6, and 156.9 ± 96.6 mg/dl, respectively. Among 1,728 patients, 860 (49.7%) patients were treated with lipid-lowering drugs. During the median follow-up duration of 3.0 years, 105 patients (6.1%) reached the composite end point. In the fully adjusted multivariable Cox models, HDL-C (HR, 1.05 per 10 mg/dl increase; 95% CI, 0.92-1.12; P = 0.50), TC (HR, 1.03 per 10 mg/dl increase; 95% CI, 0.98-1.09; P = 0.23), LDL-C (HR, 1.03 per 10 mg/dl increase; 95% CI, 0.97-1.10; P = 0.36), and TG (HR, 1.00 per 10 mg/dl increase; 95% CI, 0.98-1.02; P = 0.75) were not associated with increased risk of cardiovascular events or death. Furthermore, areas under the curve of these 4 lipids were similar and none of these parameters improved net reclassification improvement and integrated discrimination improvement for the prediction of cardiovascular morbidity and mortality.

Conclusions: This study showed that four lipid profile parameters did not predict the future adverse outcomes nor improved cardiovascular risk stratification in patients with CKD.

TH-PO1134

Kidney Function Decline Affects Endothelial Dependent Flow Mediated Dilation Independently of HDL, LDL, and HsCRP

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Background: Patients with CKD have a significant cardiovascular morbidity & mortality. Endothelial function is the earliest manifestation in the continuum of atherosclerosis. We investigated the relationship between glomerular filtration rate (GFR) and endothelium-dependent vascular function in a nondiabetic population.

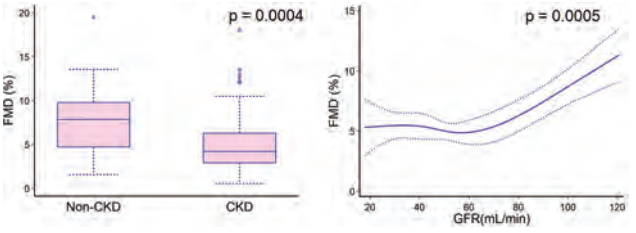
Methods: Participants were 89 CKD patients and 22 with normal GFR who underwent brachial artery flow-mediated dilation (FMD_{BA}) by high resolution ultrasound. Clinical evaluation, renal function tests, lipid profile and high sensitivity C-reactive protein (hsCRP) assays were performed on all study participants. Multivariable linear regression models with robust standard errors were used to investigate the dose-response relationship between FMD% and estimated GFR (eGFR) – modeled as a restricted cubic spline with 4 knots. Covariates were age, sex, race, body mass index (BMI), systolic blood pressure (SBP), hsCRP, HDL and LDL cholesterol. Skewed variables were log transformed.

Results: Over 71% of participants were male, 21% were African-American. The mean (SD) age was 63.2 (13.7) years. Median (25^{th}, 75^{th}) FMD% was lower among CKD patients

compared to controls [4.2 (2.9, 6.3) vs. 8.5 (4.8, 10.4); p = 0.0004] (**figure 1**). After full adjustment for baseline covariates, CKD patients had a significant 3.2% (95% CI: 0.7, 5.7, p = 0.01) lower FMD%. Percent FMD had a significant inverse correlation with age (r = -0.36, p = 0.001). In a minimal model adjusted for age, sex, race and BMI, eGFR had a significant (p = 0.0006) positive nonlinear relationship with FMD% with a trough on the dose-response curve occurring at an eGFR ~ 60mL/min/1.73m^2 (**figure 1**). The association remained significant (p = 0.0005) after further adjustment for SBP, log hsCRP, log HDL and log LDL.

Conclusions: Endothelium-dependent vascular function diminishes across the kidney function continuum, independently of traditional CVD risk factors. Further investigation into the underlying mechanisms involved maybe warranted.

Funding: Veterans Affairs Support



TH-PO1135

Insulin Sensitivity, Systemic Inflammation and GFR as Key Determinants of Arterial Stiffness

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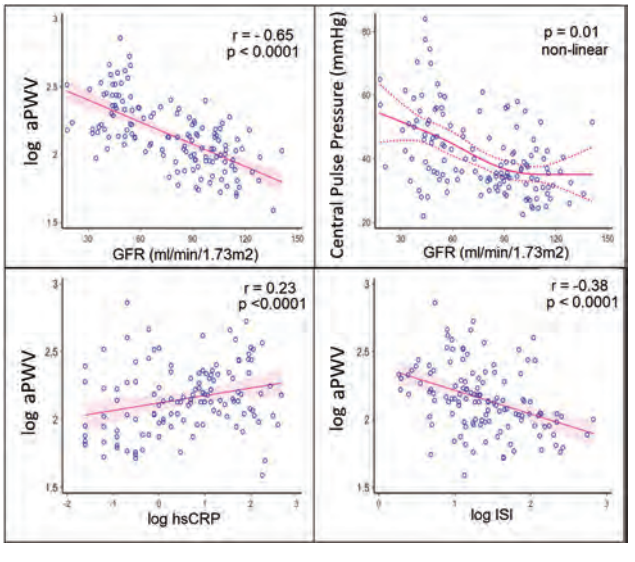
Background: Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD). The underlying mechanisms of the burden of CVD in CKD remains poorly understood. We investigated the relationship of GFR, aortic arterial stiffness and the mediating effects of systemic inflammation and insulin sensitivity.

Methods: We studied 136 patients: 50 CKD and 86 normal GFR. Aortic pulse wave velocity (aPWV) was measured via transcutaneous tonometry. Insulin sensitivity index (ISI) was measured by hyperinsulinemic euglycemic clamp; high sensitivity C-reactive protein (hsCRP) and eGFR were measured at baseline. Sequential multivariable linear regression with robust standard errors was used to study determinants of aPWV and perform mediation analyses.

Results: Median age was 54 years; 51% were female and 38% African-American. Patients with CKD had significantly higher aPWV [10.7±2.2 vs. 7.7±1.4, p < 0.0001] compared to controls. Log aPWV was inversely correlated with eGFR (r = - 0.65, p < 0.0001) and log ISI (r = -0.38, p < 0.0001); and was positively correlated with age (r = 0.73, p < 0.0001), BMI (r = 0.17, p = 0.02) and log hsCRP (r = 0.23, p <0.0001). In the model adjusted for: age, sex, race, BMI and smoking, a 10 ml/min decrease in eGFR was associated with a 2.1% increase (95% CI: 0.8, 3.3, p = 0.001) in aPWV. Further adjustment for log ISI and log hsCRP attenuated the eGFR effect (percent increase in PWV = 1.4%, 95% CI: - 0.2, 3.0, p = 0.1). GFR had a significant (p = 0.01) inverse nonlinear association with CPP that became insignificant when adjusting for hsCRP and/or ISI [Figure 1].

Conclusions: Declining GFR is associated with increased aPWV and CPP. These adverse vascular outcomes in CKD are partly mediated by systemic inflammation and insulin resistance. Targetting both IS an/or inflammation could reduce CVD risk in CKD patients.

Funding: Veterans Affairs Support, Private Foundation Support



TH-PO1136

Association of Serum Uromodulin with Mortality and Cardiovascular Disease in the Elderly – The Cardiovascular Health Study

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Background: Uromodulin is released by renal tubular cells into the serum (sUMOD) and urine. Lower urine UMOD has been linked to mortality and cardiovascular disease but much less is known about sUMOD. We evaluated the association of sUMOD with those outcomes in community-dwelling older adults.

Methods: We measured sUMOD in a random subcohort of 933 participants enrolled in the Cardiovascular Health Study. The association of sUMOD with all-cause mortality, incident heart failure (HF) and incident CVD (myocardial infarction, stroke and mortality due to coronary disease or stroke) were evaluated using multivariable Cox regression, adjusting for study participants' demographics, estimated glomerular filtration rate (eGFR), albuminuria and CVD risk factors. Generalized additive models with splines were used to address the functional form of sUMOD with outcomes. Due to non-linear associations of sUMOD with all outcomes, 2.5% of the values on either end of the sUMOD distribution were excluded from the analyses, limiting the range of sUMOD to 34.3 - 267.1 ng/ml.

Results: The mean age was 78±5 years, 40% were male, and 15% were non-white. Mean sUMOD level was 127±64 ng/ml, eGFR was 63 ml/min/1.73 m^2 and 42% had CKD defined as eGFR<60 ml/min/1.73 m^2. Patients in the lower sUMOD ranges had lower eGFR and higher albuminuria. During a median follow-up of 9.9 years, 805 patients died, 283 developed HF and 274 CVD. In multivariable analysis higher sUMOD was independently associated with lower mortality and CVD, and a trend for HF (Table).

Conclusions: Low sUMOD is independently associated with mortality and CVD in the elderly.

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Table: Associations of serum uromodulin with mortality and cardiovascular outcomes

Outcome	Univariate HR (95%-CI)	Multivariate HR (95%-CI)[a]
Mortality	0.73 (0.67-0.80)	0.89 (0.80-0.99)
Heart failure	0.68 (0.59-0.80)	0.84 (0.70-1.01)
Cardiovascular disease	0.68 (0.58-0.79)	0.80 (0.67-0.96)

Cox regression analysis for a serum uromodulin (sUMOD) range of 34.3-267.1 ng/ml (SD=63.6). Hazard ratio (HR) for each 1-SD higher sUMOD.
[a] adjusted for age, sex, race, clinic site, body-mass index, level of education, estimated glomerular filtration rate, albumin-creatinine ratio, diabetes, smoking status, systolic blood pressure, serum cholesterol, (log) serum C-reactive protein, lipid-lowering medication, antihypertensive medication, prevalent heart failure and cardiovascular disease (CVD, for the mortality outcome), prevalent CVD (for the heart failure outcome) and prevalent heart failure (for the CVD outcome)

TH-PO1137

Kidney and Cardiac Parameters – Which Are More Important in Predicting Circulatory Congestion and Mortality Risk in CKD? Insights from a 5-Year Prospective Analysis

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Background: Chronic kidney disease (CKD) patients are frequently complicated with circulatory congestion (CC). However, factors predicting the risk of CC are poorly understood.

Methods: 300 CKD stage 3-5 subjects (Mean age, 60±10yrs, 56.3% men) were randomly recruited from a University Teaching Hospital. All underwent 2D-echocardiography & tissue Doppler imaging (TDI) to assess cardiac structure & function, bloods & first void urine collection for eGFR & urine protein to creatinine ratio (UPCR), & blood pressure measurement.

Results: eGFR (mean±SD): 33 ± 17ml/min per 1.73m^2. Urine UPCR: 139 ± 202mg/mmol creatinine. All subjects were followed prospectively for a median of 68 (IQR, 30, 70) mths, 25% were complicated with CC or died from other causes. In the multivariable Cox regression analysis considering clinical, hemodynamic, biochemical, echo & TDI

parameters, eGFR (P=0.002) & UPCR (P=0.006) exhibited independent significance in predicting the risk of CC & mortality. Additional adjustment for cardiovascular medications including renin-angiotensin system blockers, beta-blockers, & diuretics did not change the significance of eGFR & UPCR in predicting CC & mortality. In a receiver-operator-characteristics curve analysis, UPCR showed the largest area under the curve (AUC) (0.78, 95% confidence intervals [CI], 0.72 - 0.84) in predicting the composite endpoint of CC & mortality, followed by eGFR (0.75, 95% CI, 0.69 - 0.81) & the ratio of early mitral inflow velocity to peak mitral annulus velocity (E/Em ratio, a marker of left ventricular [LV] filling pressure) (0.74, 95% CI, 0.67 – 0.80). The AUC of LV mass index & ejection fraction was 0.72 (95% CI, 0.65 - 0.79) & 0.50 (95% CI, 0.42 – 0.58), respectively.

Conclusions: Both proteinuria & eGFR exhibited independent significance & were more powerful than cardiac structural & functional parameters in predicting CC & mortality risk in CKD. Among the cardiac parameters, diastolic dysfunction outweighed systolic dysfunction in predicting CC & mortality risk. Further intervention study is needed to evaluate whether retarding proteinuria & CKD progression may effectively lower the incidence of CC and improve clinical outcomes of CKD patients.

TH-PO1138

Effect of Fructooligosaccharide on Endothelium Function in CKD Patients: A Randomized Controlled Trial

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Background: Microbiota-derived uremic toxins have been associated with increased cardiovascular risk in chronic kidney disease (CKD). This has encouraged the investigation of alternative paths to modulate gut environment with ensuing reduction of toxin production, inflammation and endothelial dysfunction. This trial aimed to evaluate the effect of the prebiotic fructooligosaccharide (FOS) on endothelial dysfunction in CKD non-dialysis patients.

Methods: The 3-month double-blind randomized controlled trial included 46 non-diabetic CKD patients [52% men; 57.6±14.4 years; eGFR: 21.3±7.3 mL/min/1.73m]. Intervention and placebo consisted in 12g/day of FOS or maltodextrin, respectively. P-cresyl sulfate (PCS), indoxyl sulfate (IS), Interleukin 6 (IL6) were evaluated. Endothelial dysfunction was assessed through stroma derived factor 1 alfa (SDF1α), serum nitric oxide (NO) and flow-mediated dilatation (FMD).

Results: Aside for the intervention group being older (53.4±16.0 vs 61.9±11.4,p=0.04) the groups were homogeneous. During the study, renal function, electrolytes, remained stable in both groups. A downward trend in PCS serum levels (52.86±30.68 vs 43.06±32.43mg/L,p=0.07) was observed in the treated group. Regarding inflammation, IL6 decreased in this group (3.14±2.22 vs 2.65±1.37 pg/mL, p=0.04). There was no difference in NO, SDF1α levels and FMD (Figure 1). In an exploratory analysis, including only patients with less damaged endothelium at baseline (FMD≥2.2% median), we observed that treated group had significant greater values of FMD after 3 months (p=0.04).

Conclusions: There was no effect of FOS on endothelial function in the studied population. Nonetheless, in patients with less damaged endothelium at baseline, we could observe an improvement of endothelial dilatation in the treated group, which could suggest a potential impact of FOS in the recovery of endothelial function.

Funding: Government Support - Non-U.S.

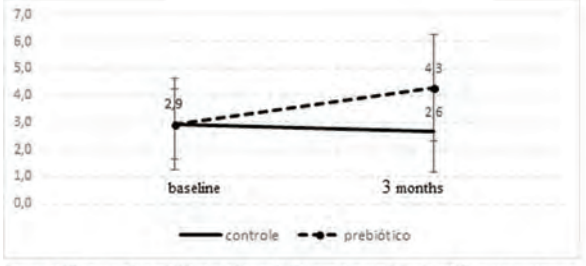

Figure 1. GEE (group effect p=0,356; time effect p=0,460; interaction p=0,253) adjusted for creatinine clearance and PCS

TH-PO1139

Representation of Kidney Disease in Peripheral Artery Disease Therapy: A Systematic Review of Randomized Controlled Trials

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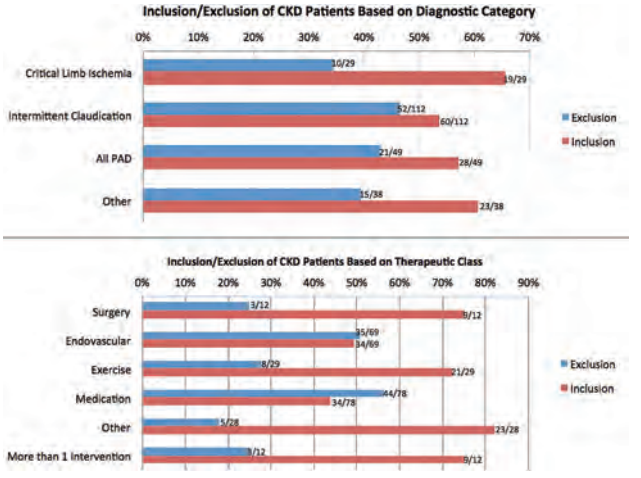
Background: Kidney disease (KD) patients have a higher risk of peripheral artery disease (PAD) with worse outcomes than the general population. We assessed the inclusion of KD patients in randomized controlled trials (RCT) of PAD therapy.

Methods: We searched PubMed for RCTs of PAD therapy that reported clinical outcomes, randomized ≥ 50 subjects and were published in English from 01/2000 to 04/2018. Two independent reviewers selected studies and extracted data, including trial characteristics, criteria for KD patients' exclusion, proportion of KD patients and number of subgroup analyses by non-renal or renal parameters.

Results: We included 228 trials randomizing 122924 subjects. KD patients were excluded in 98 (42.6%) trials with 29 (29.6%) of these not reporting kidney specific exclusion criteria. The remainder excluded KD patients based on varied cutoffs for creatinine, glomerular filtration rate and need for dialysis. Trials assessing ACC/AHA class I or II recommendations were less likely to exclude KD patients (38.4 % vs 51.2%, p=0.04). Characteristics associated with a higher likelihood of KD patient exclusion were multicenter studies (47.4% vs. 33.8% in single center studies, p=0.04), industry funding (53.5% vs. 35.0% in academic grant or government-funding, p=0.02) and smaller patient samples (43.2% of studies with <100 subjects, vs 10.0% of studies with ≥1000 subjects, p=0.04). Only 9.6% (22/228) of the trials reported kidney function and 1.3% (3/228) reported subgroup analyses based on it. Exclusion of KD patients by diagnostic category and therapeutic class is depicted in the Figure.

Conclusions: Numerous PAD trials exclude KD patients, a majority uses non-specific renal criteria. Including KD patients in PAD trials is needed to improve the quality of evidence for interventions in this vulnerable population.



TH-PO1140

CKD and Incident Hearing Loss

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Background: There is a strikingly high prevalence of sensorineural hearing loss among patients with chronic kidney disease (CKD), with estimates ranging from 36 to 77%. However, the etiology of hearing loss in CKD is not well-understood. In the only prior longitudinal study, estimated glomerular filtration rate ($eGFR_{CysC}$) <60 mL/min/1.73 m^2 was significantly associated with a 50% higher 20-year cumulative incidence of hearing impairment. We assessed whether lower baseline eGFR calculated using serum creatinine (SCr) was associated with incident hearing loss, and whether rapid decline in eGFR over time was associated with an evenhigher risk.

Methods: SCr was measured in 1843 individuals without hearing loss at the start of the Epidemiology of Hearing Loss Study in 1993. Follow-up SCr assessments were conducted at 5 (n=1500) and 10 (n=1086) years. The $eGFR_{Cr}$ was estimated using the CKD-EPI equation. Hearing tests were conducted at baseline, and at 5, 10, and 15 year follow-up visits. The risk of hearing loss was assessed as a function of baseline $eGFR_{Cr}$, as well as a function of a 20% decline in $eGFR_{Cr}$ between baseline and 5 years, and between 5 and 10 years. Incident hearing loss was defined as pure-tone average >25 dB for thresholds at 0.5, 1, 2, and 4 kHz. Cox proportional hazards regression was used to adjust for sex, cholesterol, smoking, waist circumference, schooling, NSAIDs, loop diuretics, hypertension, and diabetes.

Results: During 15,676 person-years of follow up, there were 802 cases of incident hearing loss (Table 1). There was no significant association between lower baseline $eGFR_{Cr}$ and incident hearing loss. There was also no association after stratifying by sex or age. Decline in $eGFR_{Cr}$ was not associated with incident hearing loss.

Conclusions: There were no significant associations between baseline $eGFR_{Cr}$ or decline in $eGFR_{Cr}$ and risk of incident hearing loss.

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Table 1: Multivariate-Adjusted Hazard Ratios for Risk of Hearing Loss by Baseline eGFR and eGFR Decline, EHLS 1993-2010

	Baseline eGFRCr (ml/min/1.73 m2)		
	0 to <60	60 to <90	90+
Cases(n)	86	495	221
Person-years	1060	8674	5942
HR(95%CI)	1.06 (0.83-1.35)	1.00 (ref)	1.09 (0.91-1.29)
	eGFRCr Decline ≥20%		
	No	Yes	
Cases(n)	328	52	
Person-years	6853	854	
HR(95%CI)	1.00 (ref)	1.42 (0.82-1.54)	

TH-PO1141

Factors Influencing Approval Rates of Peripherally Inserted Central Catheters (PICCs) in Patients with Kidney Disease

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Background: Current guidelines recommend against placement of peripherally inserted central catheters (PICCs) in stage 3-5 CKD without nephrology consultation in an attempt to preserve veins for future arteriovenous fistula access creation for hemodialysis. In many instances, nephrology input is also required for PICC placement for patients with acute kidney injury (AKI). With no official guidelines delimiting patients appropriate for PICCs, the consult burden on renal fellows can be significant. Here we attempted to determine medical and demographic factors influencing our practice patterns for approving PICC placement to develop objective guidelines identifying patients who unanimously are or are not appropriate for PICCs to potentially reduce the burden of consults.

Methods: We identified over 100 patients in whom a PICC consult was placed to nephrology over 10 months at 3 separate hospitals. We evaluated the PICC approval rate accounting for age, gender, serum creatinine at time of consult and baseline, CKD stage, AKI stage, diabetes, hypertension and end-stage comorbidities (cirrhosis, heart failure, malignancy, dementia, hospice). PICC placement decision for the initial 51 patients was adjudicated by the first year class of clinical fellows and 1 attending nephrologist in a blinded manner.

Results: Of the 51 adjudicated patients, 24/51 (47%) had universal agreement between both the original consulting fellow and the adjudicating fellows and attending. Presence of end-stage diagnosis, hospice status and advanced age were the major factors predictive of universal agreement for PICC placement while stage 4-5 CKD in younger patients correlated highly with nephrology recommending against PICC placement.

Conclusions: These preliminary data suggest that certain patient characteristics (such as an end-stage diagnosis) correlate highly with PICC approval including in patients with CKD stage 3-5 who may otherwise be excluded from PICC placement based on strict guidelines. Further analysis is currently underway to facilitate the development of an objective criteria list which can be used to standardize decision-making regarding PICC placement amongst nephrology practitioners and provide guidance to practitioners as to when a nephrology consult is indicated.

Funding: Clinical Revenue Support

TH-PO1142

Optimal Treatment for Prevention of Recurrent Thrombosis After Idiopathic Renal Infarction

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Background: Idiopathic renal infarction (iRI) is rare but associated with significant morbidity. Recurrent episodes of systemic thrombosis have been reported after diagnosis. Anticoagulation and antiplatelet therapy have been previously described, but no prior studies have established an optimal treatment regimen following iRI.

Methods: We performed a retrospective cohort study of 104 iRI cases (2003-2018) confirmed by review of the military electronic medical record (EMR). iRI was defined by the absence of cardioembolic, hypercoagulable or vasculopathy risk factors. The cases were divided into groups receiving (n=48) and not receiving (n = 56) anticoagulation therapy. The non-anticoagulation group was further divided into antiplatelet (n=37) and no therapy (n=19) subgroups. All cases were reviewed for evidence of the primary outcomes of recurrent arterial thrombosis, de novo venous thrombosis, and bleeding events over the maximum duration of follow up available in the EMR.

Results: Median follow up was 53 months (IQR 27-99) following iRI. There was no significant difference in the incidence of recurrent arterial thrombosis between the anticoagulation group and the non-anticoagulation group [4% (2/48) vs. 0% (0/56), p =0.21] or between the anticoagulation group and the antiplatelet subgroup [4% (2/48) vs. 0% (0/37), p =0.50]. There was also no significant difference in the incidence of de novo venous thrombosis (different cases than arterial thrombosis) between the anticoagulation group and the non-anticoagulation group [4% (2/48) vs. 0% (0/56), p =0.21] or between the anticoagulation group and the antiplatelet subgroup [4% (2/48) vs. 0% (0/37), p =0.50]. More iRI patients in the anticoagulation group had a bleeding event than both the non-anticoagulation [13% (6/48) vs. 0% (0/56), p=0.008] and antiplatelet [13% (6/48) vs. 0% (0/37), p=0.03] subgroups.

Conclusions: Anticoagulation after iRI is not associated with a reduction in either recurrent arterial thrombosis or de novo venous thrombosis, but is associated with an increased risk of bleeding. This study suggests that antiplatelet agents may be the best treatment option following iRI, but further evaluation is warranted in a randomized study.

Funding: Other U.S. Government Support

TH-PO1143

Acute Pancreatitis (AP) in CKD5 and Kidney Transplant (Tx) Recipients: Results of a US Nationwide Analysis

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Background: The prevalence of AP in CKD5 has not been clearly defined. **The aim of this study** was to compare the prevalence, etiology and outcomes of AP in CKD5 and kidney tx recipients with those without CKD using a large national database

Methods: Using the Nationwide Inpatient Sample (NIS) database, 433,805 patients hospitalized in 2014 with ICD-9 admission code for AP were identified. All patients were >18 yrs old and had no history of pancreas tx. Patients with AP and CKD5 not on dialysis (n=690), CKD5 on dialysis (n=11,415) and kidney tx recipients (n=1,320) were identified and were propensity-matched in a 1:1 fashion and regressed against gender, age, ethnicity and Charlson Comorbidity Index to patients with AP and no CKD (n=13,425). A multivariate logistic regression was constructed to adjust for other variables such as patients' median income, hospital region, hospital size and teaching status

Results: Results are presented in **Table 1**. Adjusted prevalence of AP was comparable between the non-CKD, CKD5, and kidney tx populations. Crude and adjusted mortality was higher in CKD5 and kidney tx patients. CKD5 patients were more likely to develop shock and require ICU than the non-CKD group. Alcoholic and gall stone AP were more common in non-CKD group while hypercalcemia AP was more common in the CKD5 group

Conclusions: 1)The adjusted prevalence of AP is comparable between non-CKD patients, CKD5 and kidney tx recipients. 2)Adjusted mortality is more than double in CKD5 and kidney tx recipients comapred to non-CKD patients. 3)Dialysis-dependent CKD5 patients hospitalized with AP had highest rate of shock and ICU stay compared to non-CKD patients. 4)Hypercalcemia is the main cause of AP in the CKD5 population irrespective of dialysis need

Prevalence, mortality and etiology of AP in patients without CKD, with CKD5 and in kidney tx recipients

	No CKD (n=13,425)	CKD5 no dialysis (n=690)	CKD5 with dialysis (n=11,415)	Kidney Tx (n=1,320)
Unadjusted AP prevalence (per 1,000 persons)	11.4	11.3	12.7	14.8 (P<0.01 between groups)
Adjusted OR of AP (95% CI)	Ref.	1.15 (0.8-1.6) P=0.4	1.01 (0.9-1.1) P=0.4	0.9 (0.7-1.1) P=0.3
Unadjusted inpatient mortality	1.8%	4.5%	5.6%	3.3% (P<0.01 between groups)
Adjusted inpatient mortality	Ref.	2.13 (0.9-4.9) P=0.08	2.72 (2.2-3.3) P<0.01	2.29 (1.1-4.5) P=0.02
Shock	Ref.	0.78 (0.3-1.7) P=0.5	1.53 (1.4-1.7) P<0.01	1.1 (0.6-1.9) P=0.7
ICU admission	Ref.	0.63 (0.3-1.3) P=0.2	1.32 (1.1-1.5) P<0.01	0.82 (0.5-1.4) P=0.5
Hypercalcemia	Ref.	4.26 (1.9-9.7) P<0.01	1.52 (1.1-2.8) P=0.02	1.68 (0.7-4.1) P=0.2
Gall stone	Ref.	1.09 (0.7-1.6) P=0.7	0.8 (0.7-1.0) P=0.01	0.57 (0.4-0.8) P<0.01
Alcohol	Ref.	0.48 (0.3-0.8) P=0.01	0.22 (0.2-0.3) P<0.01	0.10 (0.05-0.2) P<0.01

TH-PO1144

Surprise Question and Time-to-Hospitalization in Advanced CKD

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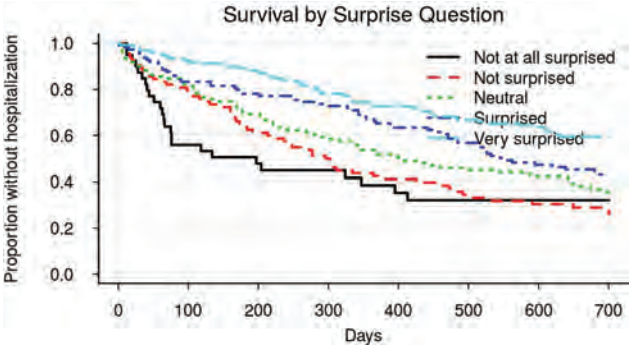
Background: Hospitalization is a common and high-risk event for patients with CKD. The surprise question (SQ) is a provider-based subjective health measure (i.e., "Would you be surprised if this patient died in the next 12 months?") that associates with mortality in advanced CKD; however, the association with hospitalization has not been examined.

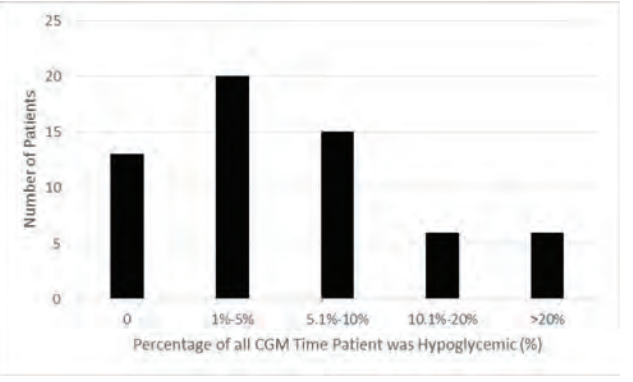
Methods: We enrolled 488 ambulatory patients with stage 4 or 5 CKD who were ≥ 60 years of age and followed in nephrology clinic. Providers were asked the SQ using a binary and 5-point Likert scale following each office visit. Hospitalizations were determined by linkage to a statewide health database. Death was determined through linkage with national or local public health records as well as obituary searches. Other covariates were abstracted by chart review using structured forms. We determined hazard ratios for time to first hospitalization using cox proportional hazards regression. In addition to the SQ Likert scale, our multivariable model included age, gender, race, marital status, insurance status, diabetes, hypertension, cardiovascular disease, heart failure, malignancy, liver disease, chronic lung disease, number of hospitalizations in the prior year, number of medications, BMI, eGFR, serum albumin, and hemoglobin.

Results: 293 (60%) patients were hospitalized. Median time to first hospitalization was 591 days in patients with SQ binary 'surprised' answer versus 277 days in 'not surprised' counterparts. 16 (3.3%) patients died before a hospitalization. The Likert SQ response was significantly associated (p = 0.01) with time to hospitalization with hazard ratios (95 % CI) of 1.67 (0.88 – 3.17), 2.25 (1.46 – 3.5), 1.60 (1.08 – 2.37), and 1.51 (1.01 – 2.26) for 1 (not at all surprised), 2, 3, and 4, respectively (versus reference: 5 very surprised).

Conclusions: Provider response to the SQ is associated with time-to-hospitalization in older adults with Stage 4 and 5 CKD. Future studies should examine whether the SQ is useful in identifying patients with high healthcare utilization.

Funding: Private Foundation Support





TH-PO1145

Determinants of Renal Function After Nephrectomy for Renal Cell Cancer in Ethnic Minorities

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Background: Renal cell cancer, unless metastasized at the time of diagnosis, is treated by partial or radical nephrectomy. Nephrologists are often consulted to predict renal function outcome especially for those with CKD. There is paucity of data on this subject for ethnic minorities.

Methods: Electronic medical records of all patients who underwent partial or radical nephrectomies from 2007 to 2017 in a large inner-city public teaching hospital were reviewed. Inclusion criteria included pathologic confirmation of renal cell cancer. Patients who had repeat nephrectomy of the contralateral kidney were excluded. Demographics, co-morbidity, preoperative and up to two years of postoperative laboratory data were reviewed. CKD was defined as eGFR < 60ml/min/1.73m^{2}and acute kidney injury was staged by AKIN criteria (KDIGO, Kidney Int. (suppl) 2012)

Results: 422 patients met the criteria for the analysis. Percentage of African Americans, Hispanics and Caucasians was 36, 31, 29 respectively. Males: Females-62% vs 38% with no ethnic differences. African Americans were older-mean age of Hispanics, Caucasians and African Americans was 51, 53, 56 respectively (P<0.001). Diabetes was present in 24% with no ethnic difference. Hypertension was present in 49% with disproportionate 51% of these being African Americans. 11% had baseline CKD with majority (63%) being African Americans. Partial nephrectomy was performed in 40% compared to radical nephrectomy in 60% with no group differences. Postoperative AKI developed in 54% of patients and was significantly higher with radical nephrectomy than partial nephrectomy (68% vs 39% P< 0.001). At 3 months, postoperative CKD increased to 34%, remained about this level at 2 years and African Americans, Caucasians, Hispanics constituted 52, 24, 16 percent (P=0.001) respectively. Associations with postoperative CKD were African American ethnicity, preexisting CKD, radical nephrectomy, diabetes mellitus, and postoperative AKI (P<0.001 for all)

Conclusions: African Americans compared to other ethnic groups have disproportionately increased risk of chronic kidney disease following nephrectomy and this is partly explained by the higher baseline CKD.

TH-PO1146

Hypoglycemia Is Common in Patients with Type 2 Diabetes and CKD

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Background: It is unclear what the incidence of hypoglycemia is among patients with type 2 diabetes mellitus (T2DM) and non-dialysis chronic kidney disease (n-CKD). The magnitude of the problem remains largely unknown, as previous studies have generally relied on random laboratory blood testing to define hypoglycemia in this population. The purpose of our study was to use continuous glucose monitoring (CGM) to determine the frequency and severity of hypoglycemia in stable outpatients with T2DM and n-CKD.

Methods: We studied 60 patients with T2DM and n-CKD defined as eGFR 0-45 ml/min. Patients wore the CGM (Abbott FreeStyle Libre Pro) for 14 days, with glucose recorded every 15 minutes, with a maximum of 1,344 glucose measurements. Blood tests were performed in the fasting state at the end of the 14 day CGM. Hypoglycemia was defined as plasma glucose below 70 mg/dL.

Results: All 60 patients had analyzable data, having worn the CGM for a mean of 12.7±2.9 days. Mean age was 72.4±10.4 years, 75% of patients were men, 15% were black, and mean eGFR 25.6±10.5. The mean glucose concentration was 152.2±56.6 mg/dL. 47/60 (78.3%) patients had at least one hypoglycemic episode. The mean number of episodes was 7.8±9.6, with a range of 0-53 episodes. The mean number of minutes of hypoglycemia was 1574±2350. This represents a mean of 7.8±11.0% of total measurement time being hypoglycemic (figure), compared to studies in T2DM without CKD where the number is closer to 1.5%.

Conclusions: Hypoglycemia is very common among patients with T2DM and CKD. Extra glucose monitoring is advisable to avoid adverse events.

Funding: Clinical Revenue Support

FR-PO001

T Cell-Derived Cytokines in Urine as Biomarkers for Clinical Diagnosis of Acute Interstitial Nephritis

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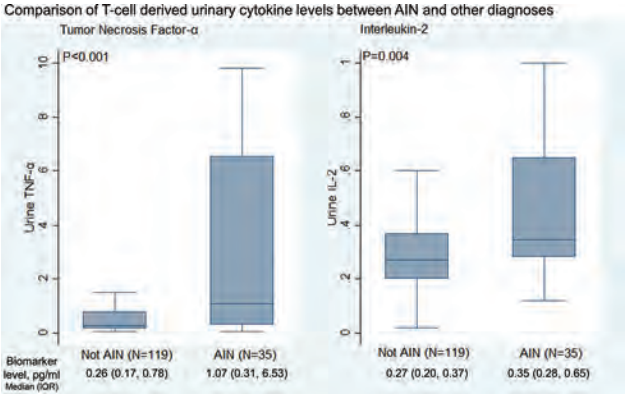
Background: The current clinical diagnosis of acute interstitial nephritis (AIN) is challenging as it relies on combining a high-index of clinical suspicion with subsequent biopsy confirmation. We hypothesized that AIN is a T cell-mediated process and tested urine for cytokines associated with T cell immunity as biomarkers for clinical diagnosis of AIN

Methods: We enrolled consecutive participants who underwent a kidney biopsy for evaluation of acute kidney disease at 2 academic hospitals from 2015 to 2017. We measured 6 cytokines associated with T cell-mediated inflammation (TNFα, IFNγ, IL2, IL4, IL5, and IL13) in urine samples collected before the biopsy. We established AIN diagnosis through adjudication of histological images by 3 independent renal pathologists. We considered univariable and multivariable associations of clinical variables and biomarkers with AIN to develop a clinical diagnostic model

Results: Of the 154 participants, 35 (23%) had AIN and 119 had other diagnoses including acute tubular injury (n=37), diabetic kidney disease (n=15), arterionephrosclerosis (n=18), glomerular disease (n=40), and others (n=9). Patients with AIN had higher levels of TNFα and IL2 (Figure). The AUC for AIN diagnosis based on clinicians' pre-biopsy diagnosis was 0.59 (0.50-0.69). The AUC of a model containing urinary markers of inflammation (pyuria) and glomerular injury (hematuria and proteinuria) was 0.72 (0.62-0.81), which increased on addition of TNFα and IL2 to 0.82 (0.73-0.90; P<0.001) and 0.76 (0.67-0.85; P=0.009), respectively

Conclusions: Urine cytokines associated with T cell immunity were higher in patients with AIN as compared with those who had other diagnoses. These biomarkers significantly improved discrimination for AIN compared to clinicians' prebiopsy suspicion of AIN

Funding: NIDDK Support, Private Foundation Support



FR-PO002

The Association of Plasma Inflammatory Mediators with CKD and Mortality After AKI: The ASSESS-AKI Study

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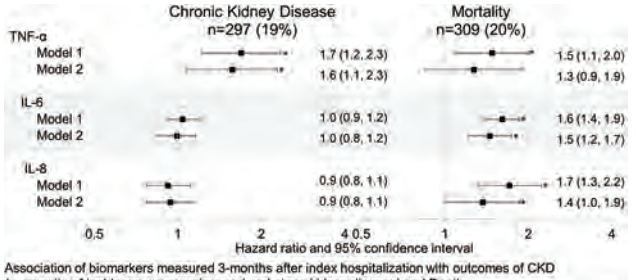
Background: Inflammation contributes to development and progression of chronic kidney disease (CKD) after acute kidney injury (AKI) in preclinical studies. We evaluated the association of plasma inflammatory mediators with clinical outcomes in the longitudinal cohort of the ASSESS-AKI study

Methods: The ASSESS-AKI study is a multicenter, prospective cohort of participants hospitalized with AKI and matched non-AKI controls (n=769 pairs). We collected plasma samples collected during the index hospitalization and 3-months after discharge. We measured 10 inflammatory mediators [interferon (IFN)γ, tumor necrosis factor(TNF)α, interleukin (IL)1β, IL2, IL4, IL6, IL8, IL10, IL12p70, and IL13] using a MesoScale multiplex assay. We tested the independent association of these mediators with (a) chronic kidney disease (CKD) composite outcome, which included CKD incidence, progression, and end-stage kidney disease, and (b) death using a multivariable trivariate Weibull regression model

Results: The CKD composite outcome occurred in 297 (19%) participants and 309 (20%) died after 4.8 (3.4, 5.9) years of follow-up. Participants with AKI were more likely to experience CKD outcome than non-AKI participants [207 (27%) vs. 90 (12%)]. In a multivariable analysis controlling for eGFR, albuminuria, smoking, body mass index, and AKI status, TNF-α levels at both hospitalization and 3-months after discharge were associated with higher risk of CKD (**Figure**), whereas none of the other biomarkers were associated with CKD. At 3 months after hospital discharge, IL6 and IL8 levels were associated with an increased risk of death, which remained significant after controlling for C-reactive protein.

Conclusions: Among the plasma inflammatory biomarkers, TNFα levels measured during hospitalization and 3-months after discharge were independently associated with CKD, whereas IL6 and IL8 at 3-months after discharge were associated with increased mortality.

Funding: NIDDK Support



Association of biomarkers measured 3-months after index hospitalization with outcomes of CKD (composite of incidence, progression, and end-stage kidney disease) and Death.
Hazard ratio per doubling in biomarker level. Model 1 controls for AKI during index hospitalization, CKD diagnosis prior to enrollment, eGFR, site, BMI, smoking status, COPD, age, sex, race, albuminuria. **Model 2** additionally controls for C-reactive protein. Asterisks indicate P<0.05

FR-PO003

Kidney Biopsy-Related Complications in Hospitalized Patients with Acute Kidney Disease

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Background: We used data from the Yale biopsy cohort and Nationwide Inpatient Sample (NIS) to evaluate rates and risk factors of biopsy-related complications including adjudicated procedure-related bleeding requiring blood transfusions or angiographic interventions and death

Methods: We used data from the Yale biopsy cohort and Nationwide Inpatient Sample (NIS) to evaluate rates and risk factors of biopsy-related complications. We looked at complications including adjudicated procedure-related bleeding requiring blood transfusions or angiographic interventions and death

Results: Between 2015-2017, 159 hospitalized patients underwent a kidney biopsy at Yale for AKD evaluation. Median age of participants was 59 (47-68) years, 68 (43%) were women, 80 (51%) had stage 1 AKI, and 42 (27%) had stage 2 or higher AKI. Of these, 12 [9 (5-15)%] required a blood transfusion for biopsy-related bleeding and 3 [2 (1-5)%] required an intervention. Of the 4 [3 (1-6)%] deaths during hospitalization, none were related to the biopsy. We identified lower hemoglobin and platelet levels, female sex, trainee as proceduralist, and larger needle gauge as risk factors of post-biopsy transfusion (Table). Higher blood urea nitrogen was associated with higher rates of transfusion in patients who did not receive desmopressin [n=32 (20%)], but not in those who received desmopressin (interaction P=0.008). Among the 53,315 hospitalizations with kidney biopsies between 2012-2014 in the NIS, 925 (2%) required an intervention, similarly to the Yale cohort (P=0.88).

Conclusions: Hospitalized patients experience higher risk of post-biopsy complications and several risk factors such as lower hemoglobin and platelet count, female sex, and larger needle gauge are associated with this risk.

Funding: NIDDK Support, Private Foundation Support

Risk factors for post-biopsy bleeding requiring blood transfusion

Risk factor	Biopsy-related Transfusion (N=12)	No Biopsy-related Transfusion (N=147)	P-value*
Platelet count	112 (86, 189)	209 (150, 285)	0.003
Hemoglobin level	8.5 (7.4, 8.7)	9.4 (8.1, 10.4)	0.007
Female	9 (75%)	59 (40%)	0.02
BUN (No desmopressin)^	61 (59, 91)	38 (30, 52)	0.02
BUN (Desmopressin given)	70 (54, 120)	56 (37, 78)	0.16
Trainee	11 (92%)	88 (62%)	0.04
Needle gauge 16 (vs. 18)	10 (83%)	78 (53%)	0.04

*All risk factors with P<0.05 shown. ^Interaction P=0.008

FR-PO004

Assessment of Utility of Urine Sediment Microscopy in Hepatorenal AKI

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Background: Microscopic examination of the urinary sediment (MicrExUrSed) is a useful diagnostic tool in acute kidney injury (AKI). However, its performance has not been examined in AKI in patients with end-stage liver disease (ESLD). Hepatorenal syndrome type 1 (HRS-1), a type of AKI in ESLD, is difficult to diagnose despite the existence of the International Club of Ascites (ICA) criteria. We hypothesized that MicrExUrSed improves accuracy of diagnosis of acute tubular injury (ATI) in ESLD patients with AKI.

Methods: MicrExUrSed was performed in patients with AKI stage ≥ 2 with or without ESLD over a 6-month period. HRS-1 was defined by the ICA criteria. Urine Na <20 mEq/L, urine volume <500 ml, mean arterial pressure <75 mmHg and serum Na <135 mEq/L were supportive criteria. Definite HRS-1 was defined as: ICA + supportive criteria were met. Possible HRS was defined as: only ICA criteria were met. No HRS was defined as: ≥1 ICA criteria was not met. Urinary cast scores (based on Chawla *et al* and Perazella *et al*) were assigned to each specimen. Chawla scores (CS) 3-4 and Perazella scores (PS) 2-3 were deemed consistent with ATI and not HRS-1.

Results: Distribution of casts (>25% lpf with ≥1 cast) differed between the ESLD (n=35) and non-ESLD (n=44) groups. Hyaline casts (HC), renal tubular epithelial cell casts (RTECC) and waxy casts (WC) were identified more often in ESLD compared to non-ESLD [57 vs 29% (p<0.05); 26 vs 5% (p<0.01) and 20 vs 5% (p<0.05) for HC, RTECC and WC], but not granular casts [43 vs 61%]. In the ESLD group, total bilirubin was significantly higher for those with RTECC [35.9 vs. 6.4 mg/dL (p<0.0001)] suggesting pathogenesis of bile cast tubulopathy. A diagnosis of Definite HRS-1 was assigned to 6 (17%), Possible HRS-1 to 14 (40%) and No HRS-1 to 15 (43%) patients. Addition of MicrExUrSed changed the diagnosis in 11 (31%) patients: Definite HRS-1 was changed to No HRS-1 in 2 and Possible HRS-1 was changed to No HRS-1 in 9, changing the final No HRS-1 count to 26 (74%) and HRS-1 to 9 (26%). Nonetheless, vasoconstrictor therapy to treat HRS-1 was given to 23 (66%) patients.

Conclusions: MicrExUrSed can aid in the diagnosis of AKI in ESLD by identifying those with evidence of ATI, i.e., not consistent with HRS-1, with potential implications on the use of vasoconstrictor therapy and/or dialysis decisions.

FR-PO005

Impact of Porto-Pulmonary Hypertension in the Course of Hepatorenal AKI

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Background: Porto-pulmonary hypertension is prevalent in cirrhotic patients. However, its impact on the clinical course of hepatorenal acute kidney injury (AKI) has not been previously investigated. We hypothesized that echocardiographic evidence of pulmonary hypertension affects the interplay between change in mean arterial pressure (MAP) and course of hepatorenal AKI during vasoconstrictor therapy as well as the overall renal outcome.

Methods: We conducted a prospective observational study of hospitalized patients with AKI stage ≥ 2 (AKIN) and cirrhosis over a 4-month period. Daily MAP and serum creatinine (sCr) values were collected, as well as pulmonary arterial pressure (PAP) estimated by echocardiography at the time of AKI. Patients were divided into PAP tertiles: 1st ≤30, 2nd 31-40, 3rd >40 mmHg. Daily change in MAP (ΔMAP) and daily change in sCr (ΔsCr) from baseline were computed. Renal outcome chosen was need for renal replacement therapy (RRT).

Results: Among 52 patients, 19 (37%) were female, mean age was 56 (range 25-75). Baseline values were median MAP 76 (IQR 71–84) mmHg, median sCr 2.3 (IQR 1.7–3.7) mg/dL, median serum albumin 2.3 (IQR 1.8–3) g/dL and median total bilirubin 4.1 (IQR 1.8–27.2) mg/dL. A significant inverse correlation was found between ΔMAP and ΔsCr on the following day (r = -0.20, p=0.0003) throughout the course of AKI. PAP was obtained in 36 patients. The correlation between ΔMAP and ΔsCr within each PAP tertile were:

≤30: r = 0.08 (p=0.37), 31-40: r = -0.36 (p=0.002) and >40: r = -0.40 (p=0.0006). Thus, as PAP increases, a negative correlation between ΔMAP and ΔsCr on the following day strengthens. Furthermore, there was a trend for an increased need for RRT within those in the highest tertile of PAP (need for RRT: 28.6%, 33%, and 70%, for the 1st, 2nd, and 3rd tertiles, respectively (p=0.0511, chi-square for trend).

Conclusions: Cirrhotic patients with more severe pulmonary hypertension exhibit a significantly stronger negative correlation between ΔMAP and ΔsCr, suggesting that those with higher PAP may display increased sensitivity to improved kidney function upon optimization of MAP with vasoconstrictors. Moreover, higher PAP is associated with greater need for RRT, adding complexity to the pathogenesis of hepatorenal AKI.

FR-PO006

Angiopoietin-2 Predicts Mortality and Kidney Outcomes in Decompensated Cirrhosis

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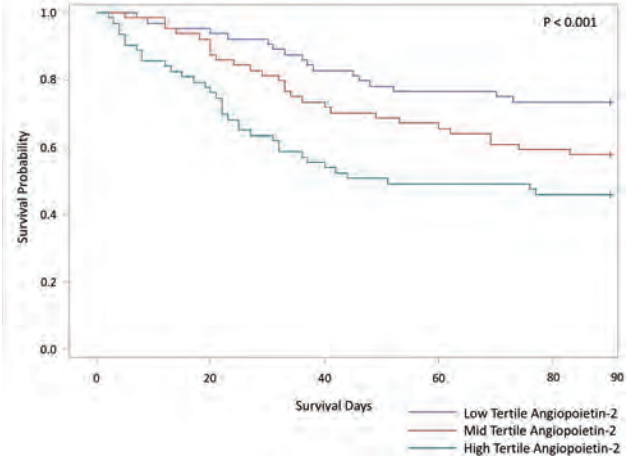
Background: AKI in decompensated cirrhosis has limited therapeutic options and novel mechanistic targets are urgently needed. Angiopoietin-2 is a context-specific antagonist of Tie2, a receptor that signals vascular quiescence. Considering the prominence of vascular destabilization in decompensated cirrhosis, we evaluated Angiopoietin-2 to predict clinical outcomes.

Methods: Serum Angiopoietin-2 was measured in a prospective cohort of hospitalized patients with decompensated cirrhosis and AKI. Clinical outcomes were examined over a 90-day period and analyzed according to Angiopoietin-2 levels. Primary outcome was 90-day mortality.

Results: We analyzed 191 patients (median Angiopoietin-2 level 18.2 [IQR 11.8, 26.5] ng/mL). Median MELD score was 23 [17, 30] and 90-day mortality was 41%. Increased Angiopoietin-2 was associated with increased mortality (died 21.9 [13.9, 30.3] ng/mL vs. alive 15.2 [9.8, 23.0] ng/mL; p <0.001), higher AKIN stage (stage I 13.4 [9.8, 20.1] ng/mL vs. stage II 20.0 [14.1, 26.2] ng/mL vs. stage III 21.9 [13.0, 29.5] ng/ml; p = 0.002) and need for renal replacement therapy (16.5 [11.3, 23.6] ng/mL vs. 25.1 [13.3, 30.3] ng/mL; p = 0.005). The association between Angiopoietin-2 and mortality was significant in unadjusted and adjusted Cox regression models (p ≤ 0.001 for all), and improved discrimination for mortality when added to MELD score (integrated discrimination increment 0.067; p = 0.001).

Conclusions: Angiopoietin-2 was associated with mortality and other clinically relevant outcomes in a cohort of decompensated cirrhotic patients with AKI. Further experimental study of Angiopoietin/Tie2 signaling is warranted to explore its potential mechanistic and therapeutic role in this population.

Funding: NIDDK Support, Private Foundation Support



90-day survival by Angiopoietin-2 tertile. Low (<13.5 ng/mL), Mid (13.5-23 ng/mL), High (> 23 ng/mL)

FR-PO007

Post-Discharge Long-Term Outcomes of the Dialysis-Requiring AKI During the Perioperative Period of Liver Transplantation

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Background: Patients undergoing liver transplantation (LT) are prone to acute kidney injury (AKI), which is known to decrease patient survival, and considerable portion of AKI patients require renal replacement therapy (RRT) during the perioperative period of LT. Nevertheless, long-term outcomes among the patients requiring RRT are not thoroughly evaluated yet.

Methods: The nationwide, population-based cohort study was conducted. Adult patients received LT in tertiary hospitals of Korea between 2006 and 2015 were considered. Patients who underwent RRT or received LT prior to the index admission were excluded. The RRT group consisted of the patients received RRT during the perioperative period of LT and the control group included the patients who did not underwent RRT.

Results: Of 8,421 patients underwent LT, 5,911 received RRT. Among the patients received RRT, 802 underwent continuous renal replacement therapy (CRRT). All-cause mortality [adjusted hazard ratio (HR) 1.52 (1.26-1.83), P<0.001] and progression to end-stage renal disease (ESRD) [adjusted HR 2.93 (2.34-3.66), P<0.001] were increased in RRT patients (Table 1). However, the risk of MACE [adjusted HR 1.17 (0.80-1.70), P=0.430] were similar between the two groups. Among the patients who received RRT, all-cause mortality [adjusted HR 2.92 (1.48-5.76), P=0.002] was worse in CRRT group, compared to intermittent renal replacement therapy (IRRT) group. ESRD progression [adjusted HR 0.36 (0.24-0.52), P<0.001] was improved with CRRT application and the risk of MACE [adjusted HR 1.11 (0.42-2.94), P=0.832] was comparable between the two groups.

Conclusions: Requirement of RRT during the perioperative period of LT had worse long-term mortality and ESRD progression compared to the patients who did not receive RRT. The risk of MACE in patients underwent RRT was comparable to the control groups.

Funding: Commercial Support - Baxter (LSO-18-70260)

Table 1. Prognosis of patients underwent RRT

	Model 1		Model 2	
	HR (95% CI)	p-value	adjusted HR (95% CI)	p-value
Mortality	1.14 (0.95-1.36)	0.162	1.52 (1.26-1.83)	<.001
MACE	1.03 (0.71-1.49)	0.876	1.17 (0.80-1.70)	0.430
Progression to ESRD	3.22 (2.60-3.99)	<.001	2.93 (2.34-3.66)	<.001

HR = hazard ratio, CI = confidential interval.

Model 1 was an unadjusted simple model.

Model 2 was adjusted for age, sex, comorbidities, and the etiology of liver disease.

FR-PO008

Cisplatin-Induced Kidney Injury Is Transient and Associated with Short-Term Elevation of Urine Interleukin-18 in Patients with Testicular Cancer

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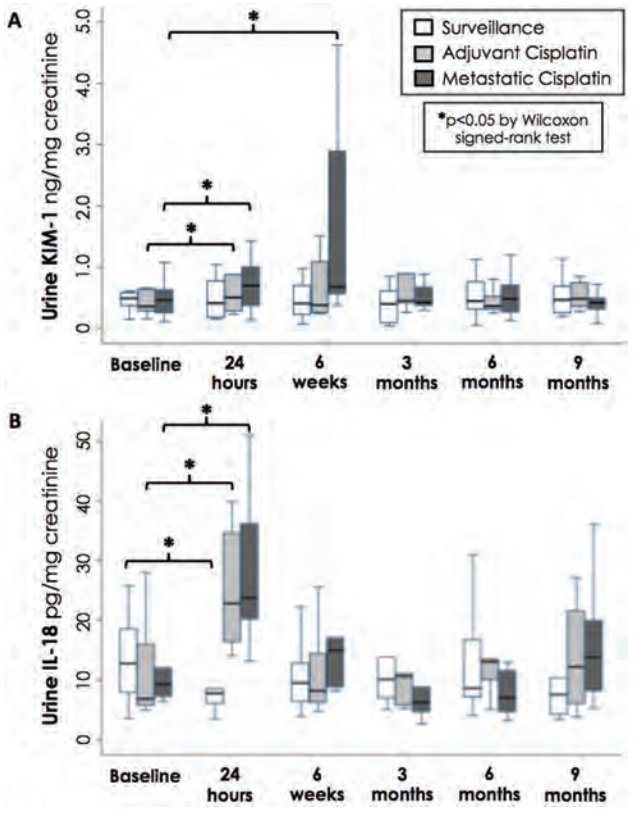
Background: Cisplatin causes acute kidney injury (AKI) but changes in urinary AKI biomarkers are not well defined in clinical practice. We investigated short- and medium-term AKI using novel biomarkers over 9 months in patients with testicular cancer treated with cisplatin.

Methods: Prospective observational study of men with testicular cancer in 3 groups following orchiectomy: 1) surveillance; 2) adjuvant cisplatin (1-2 cycles); 3) metastatic disease with high dose cisplatin (3-4 cycles). Blood/urine was collected at 6 visits: baseline, 24h, 6 weeks, 3, 6 and 9 months for renal injury markers.

Results: 27 men (median age 34y [IQR 31-40y]) were recruited: surveillance (N=10); adjuvant cisplatin (N=7); metastatic cisplatin (N=10). Urine tubular injury markers (interleukin-18 [IL-18], neutrophil gelatinase-associated lipocalin [NGAL], vascular endothelial growth factor [VEGF], kidney injury molecule-1 [KIM-1]), urine albumin/creatinine ratio (ACR) and serum cystatin C (CysC) were elevated at 24h and 6 weeks (KIM-1) post cisplatin in adjuvant and metastatic groups (all: P<0.05 *vs.* baseline). These normalized by 6 weeks (IL-18, NGAL, VEGF, ACR, CysC) and 3 months (KIM-1). eGFR was within normal range throughout. Urine IL-18 rose in both cisplatin groups at 24h (median [IQR]: adjuvant 24h 22.8 [16.4-34.7] *vs.* baseline 6.8 [5.7-15.9]; metastatic 24h 23.7 [20.1-36.1] *vs.* baseline 9.2 [7.2-11.9] pg/mg, P<0.05) and returned to baseline by 6 weeks.

Conclusions: Cisplatin nephrotoxicity is reversible over 3 months and is evident with use of novel biomarkers. Elevation of IL-18 supports a major inflammatory renal insult. This provides evidence to support investigation of anti-inflammatory drugs to prevent cisplatin toxicity.

Funding: Government Support - Non-U.S.



FR-PO009

Role of Plasma Cystatin C and Urine NGAL in Prediction of AKI and Mortality in Patients with Acutely Decompensated Cirrhosis: A Prospective Cohort Study

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Background: Acute kidney injury (AKI) is the most frequent and devastating complication in cirrhotic patients. Emerging evidence suggests that novel biomarkers could predict AKI earlier than conventional markers and better predict prognosis in these patients.

Methods: To determine the incidence and prognosis of AKI in acutely decompensated cirrhotic patients and also test whether plasma cystatin C, urine neutrophil gelatinase-associated lipocalin (NGAL) or tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor 7 (IGFBP7) could predict the development of AKI and prognosis.

Results: Of 111 patients, 45 (40.5%) developed AKI during hospitalization. Although 53.3% of AKI episodes were transient, stage 1 AKI, overall mortality was significantly higher compared to those without AKI (25% vs. 46.5%, p=0.02). Although initial BUN and serum creatinine were not different, plasma cystatin C and urine NGAL at the time of admission were significantly increased in patients who developed AKI and also death. Plasma cystatin C and urine NGAL were independently associated with the development of AKI after adjusting for clinical variables including age, co-morbidity, and Child-Pugh score. [plasma cystatin C, odds ratio (OR) 2.09; 95% confidence interval (CI), 1.01-4.35), urine NGAL, OR 1.04, CI 1.01-1.05]. Although these biomarkers failed to predict mortality independent of clinical variables, urine NGAL significantly improved the accuracy of MELD in predicting mortality.

Conclusions: The incidence of AKI is high and even minor increase in serum creatinine is associated with high mortality in decompensated cirrhosis. Novel biomarkers including plasma cystatin C or urine NGAL might be useful in the earlier diagnosis of AKI and also in predicting mortality in acutely decompensated cirrhotic patients.

FR-PO010

Utility of Serum Cystatin C (SCysC) to Assess AKI and Day 90 (D90) Major Kidney Adverse Events (MAKE90) Following Cardiac Surgery (CS) in Subjects Treated with QPI-1002

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Background: QPI-1002 (QPI), a siRNA targeting p53, is being developed for acute kidney injury (AKI) following CS. KIDGO guidelines recommend assessment of renal function based on SCysC in settings where serum creatinine (SCr) may be unreliable (e.g. decreasing muscle mass).

Methods: Initial results from a global Phase 2 double-blind study with QPI for AKI (N=341: QPI=165, Placebo (PL)=176) (NCT#02610283) (presented at ASN 2017: SA-OR124). SCr and SCysC levels were both measured.

Results: QPI significantly reduced (↓) AKI (35.4 % QPI vs 50.6% PL; p=0.0047), ↓AKI severity across all grades (p=0.002), and ↓ AKI duration (p=0.0016) assessed by SCysC similarly to SCr (ASN 2017). In a higher risk subpopulation [proteinuria, low baseline eGFR, and/or insulin dependent diabetes, (N=241)], QPI ↓MAKE (Death, RRT or a ↓in eGFR by 25%) at D90 using eGFRCys (37% QPI vs 51% PL; RRR=29%; p=0.024), but not using eGFRCr. To determine the cause of the divergence of SCr and SCys eGFRs at D90, subjects were grouped by the discordance of SCr and SCys after the method of Grubb using the differences of eGFRs between baseline and D90. Groups were as per Figure 1. The Concordant population (N=114) also had a treatment effect in favor of QPI using eGFRCr for MAKE90 (RRR23%). The largest discordant group, Discordant 1 (N=55), compared to Concordant population, had longer ICU stays (6 vs 4.4 days), more MACE events (10.9 vs. 6.2 %) and had muscle mass loss expressed as ↓sarcopenia index (Kashani et al 2018) with a 28% decrease.

Conclusions: SCr and SCys post CS (D1-D5) were concordant and QPI-1002 significantly reduced the incidence, severity and duration of AKI by either analyte. QPI significantly ↓MAKE 90 in a subpopulation of higher risk subjects when evaluated by SCys. Consistent with other reports, SCr appeared to overestimate eGFR at D90 as compared to SCys in a subset of subjects at risk for decreased SCr production.

Funding: Commercial Support - Quarkpharma Fremont, CA

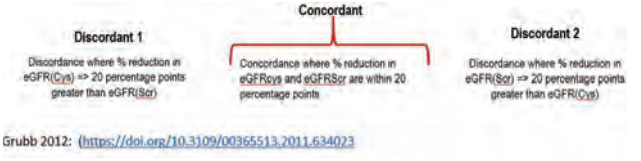

Figure 1

FR-PO011

Improving the Kinetic GFR by Taking Volume Changes into Account

Sheldon Chen. *MD Anderson, Houston, TX.*

Background: The kinetic glomerular filtration rate (GFR) equation was developed to estimate the kidney function even as the serum creatinine is changing. One shortcoming of the equation is that it assumes a constant volume of distribution for the creatinine. The volume in hospitalized patients can fluctuate quickly and drastically. For example, in hypotension and multiorgan failure, aggressive volume resuscitation would dilute the creatinine concentration, slowing down a rise in creatinine and making the acute kidney injury (AKI) appear milder.

Methods: To undo the confounding effects of volume change, we improved the kinetic GFR model by introducing variables to describe the ongoing influence of volume change. In the upgraded model, we solved its differential equation to yield a formula that predicts how the serum creatinine would evolve, as determined by the creatinine generation rate, creatinine clearance rate (~GFR), and now a volume change rate. Clinically, the starting and ending creatinines are measured by the lab, so the equation is rearranged to solve for the kinetic GFR.

Results: The new kinetic GFR equation was tested in multiple patients, some of whom had extreme changes in volume. In all cases, incorporating volume information resulted in the calculated GFR being correctly adjusted, concordant with: 1) Volume Gain → A) AKI looks less severe; GFR is actually lower, or B) renal recovery looks very robust; GFR is actually not as high, and 2) Volume Loss → A) AKI looks quite severe; GFR is actually not as impaired, or B) renal recovery looks unimpressive; GFR is actually higher than believed. Case: a 66-year-old woman has ischemic lactic acidosis and hypotension (87/53 mm Hg). She was given normal saline at 300 mL/h. NS plus the many intravenous drips (pressors and antimicrobials) added up to a net volume gain of 5 liters in 12 hours. With oliguria, her serum creatinine rose from 0.84 to 1.25 mg/dL over a 16-hour period, encompassing the above 12 hours. The old equation would calculate a kinetic GFR of 48.3 mL/min. The new

equation would calculate a kinetic GFR of 38.6 mL/min. The difference of 9.7 mL/min was due to massive volume gain, which masked the true severity of her AKI.

Conclusions: Body volume changes can significantly affect creatinine kinetics. The new volume-adjusted equation improves the precision of kinetic GFR estimation, which could aid in diagnosis and medication dosing.

FR-PO012

Evaluation of Finger-Stick Point of Care Creatinine Assay for Early Diagnosis of AKI in the Community

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Background: Acute kidney injury (AKI) is a major health problem which occurs in the context of infection in more than 50% of cases. Recent guidance for sepsis mandates the delivery of a sepsis bundle within one hour of presentation in patients with suspected infection and AKI. However, the majority of these cases arise in the community. Primary care physicians need to make a decision for hospital referral at the first assessment. The aim of this study was to evaluate finger-stick capillary point of care (POC) creatinine (Cr) testing for real time diagnosis of AKI and evaluate its role in the clinical decision making process during the assessment of sepsis in nursing home residents.

Methods: The precision of the POC Cr assay was measured as coefficient of variation (CV) ie the ratio of the standard deviation to the mean over 5 repeated measurements. Correlation, reliability and agreement were estimated by using Pearson's correlation, Intraclass Correlation Coefficient calculation and the Bland-Altman method respectively. POC Cr from finger-stick capillary samples, along with concurrent serum Cr samples measured by Siemens Advia 2400 Jaffe in our laboratory, were collected from nursing home residents and A&E patients.

Results: Mean CV from 9 samples with 5 repeated measurements was 0.044±0.018 (min=0.018, max=0.081). There were 70 paired samples from 66 patients aged 78±17. POC Cr was 116±64umol/L and Serum Cr 84±41umol/L. Pearson correlation was 0.804 (p=0.000), Figure 1A. Average Intraclass Correlation Coefficient was 0.843 (confidence interval 0.748-0.903, p=0.000). Bland-Altman plot is presented in Figure 1B. Mean difference between POC Cr and Serum Cr was 32±39, 4 values were outside the limits of agreement defined as mean difference ±1.96 SD (95% confidence interval) and 3 of 4 were above 200.

Conclusions: Finger-stick POC Cr has good agreement with laboratory method and may be used to assist clinical decision making. It can reliably detect severe AKI stages 2 and 3. POC Cr tends to overestimate serum Cr and has decreased agreement in Cr values above 200 umol/L.

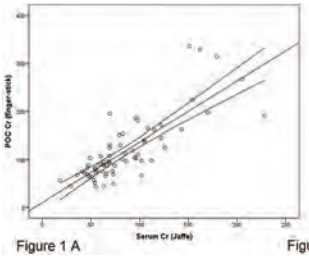

Figure 1 A

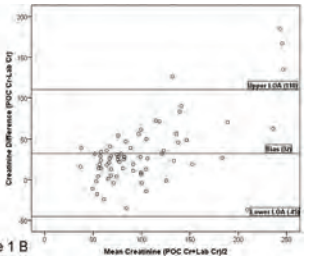

Figure 1 B

FR-PO013

Leucine Rich α-2 Glycoprotein Is a Novel Urinary and Serum Biomarker for AKI

Tomohiro Eguchi, Yoshio Terada, Yoshinori Taniguchi, Hirofumi Nishikawa. *Kochi University, Nankoku city, Japan.*

Background: Leucine-rich α-2 glycoprotein (LRG) is one of serum glycosylated proteins with 347 amino acids, and reported that serum LRG is a novel disease activity biomarker for rheumatoid arthritis and inflammatory bowel disease. However, little is known about the role of LRG in acute kidney injury (AKI) pathogenesis. We examined renal LRG expression and urinary LRG level using mice AKI model and clinical samples.

Methods: We evaluated LRG mRNA and protein expression in kidney in the bilateral renal ischemia-reperfusion injury (IRI) mice AKI model. We also examined immunohistological examination of LRG localization by confocal microscopy, and measured serum and urinary LRG levels. We evaluate the mechanism of LRG regulation using cultured renal tubular cells (NRK-52E cells). In clinical study, we measured urinary LRG in contrast media-induced AKI patients using ELISA, and immunohistological examination of LRG in AKI and minimal change renal biopsy samples.

Results: In mice with IRI-induced AKI, renal mRNA and protein expression of LRG were induced from 6 h and 12 h and peaked at 24 h and 48 h after IRI, respectively. In control mice kidney, only a very few expression of LRG was observed. Immunohistological examination showed that LRG expression was observed mainly on renal tubular cells in AKI mice. The LRG positive tubular cells are mainly co-stained with AQP1 using confocal microscopy. We also find that serum and urinary LRG levels were up-regulated in IRI-induced AKI from 12h. In NRK-52E cells, TNF-alpha and LPS stimulated LRG expression. Notably, in contrast media-induced AKI patients, urinary LRG levels were increased from 6 h. LRG staining were enhanced in AKI renal-biopsy samples mainly at proximal tubules. In contrast, only a few LRG staining was observed in minimal change renal biopsy samples.

Conclusions: Our results demonstrate that LRG is up-regulated in renal tissues in both mice and human AKI, and that urine and serum LRG are increased in early phase of AKI. Inflammatory cytokines such as TNF-alpha stimulates expression of LRG in renal tubular cells. Thus, urine and serum LRG could serve as a potential early biomarker in AKI.

FR-PO014

Performance of Urinary Osteopontin for the Prediction of AKI Prognosis and Clinical Outcomes in Critically Ill Adults

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Background: Osteopontin (OPN) is a secreted phosphoprotein whose expression is upregulated in several experimental models of acute kidney injury (AKI). Due to the localisation of its expression, it has been suggested to be a marker of injury to the ascending limb of the loop of Henle. OPN expression is increased in regenerating proximal tubular cells following injury and it may play a role in renal repair and regeneration. The full extent of the role of OPN in human AKI is incompletely understood. We hypothesised that OPN levels may predict adverse outcomes, such as AKI progression and mortality, in critically ill patients.

Methods: The Dublin Acute Biomarker Group Evaluation (DAMAGE) Study is a prospective multicenter observational study investigating the utility of several urinary biomarkers for the diagnostic and prognostic assessment of AKI in critically ill adults. We conducted a subgroup analysis of this cohort to evaluate whether urinary OPN levels could predict which patients would develop progressive AKI and other adverse clinical outcomes.

Results: The final analysis included a total of 33 patients with a mean age of 59.3 years (S.D. 17.5). Urinary OPN levels normalised to urinary creatinine on Day 1 and on the day of AKI diagnosis did not differ significantly between survivors to day 30 and non-survivors. There was no statistically significant difference in urinary OPN levels between those who met the criteria for progression (a composite of progression to a higher KDIGO AKI stage, renal replacement therapy or death) and those who did not. There was a significant difference in the distributions of urinary OPN levels in patients who survived to the time of ICU discharge and those who did not (p=0.043).

Conclusions: In conclusion, although the sample size for this subset analysis is small, the lack of major difference in estimated risks between groups (odds ratios: ~0.99-1.01 per 100 mg/g OPN/creatinine), even when adjusted for study centre, appears to show that OPN levels measured on Day 1 or on the day of AKI diagnosis is unlikely to be a predictor of AKI progression or survival.

FR-PO015

Biomarkers of Kidney Injury and Repair and Risk for Future Kidney Events: The ASSESS-AKI Study

Jeremy Puthumana,[3] Kathleen D. Liu,[2] Edward D. Siew,[4] William B. Reeves,[5] Jonathan Himmelfarb,[6] Steven G. Coca,[7] Alan S. Go,[8] Chi-yuan Hsu,[9] Talat Alp Ikizler,[13] Mark M. Wurfel,[15] Amit X. Garg,[10] James S. Kaufman,[14] Paul L. Kimmel,[11] Vernon M. Chinchilli,[12] Chirag R. Parikh.[1] ASSESS-AKI Study Investigators *[1]Yale University and VAMC, New Haven, CT; [2]University of California at San Francisco School of Medicine, San Francisco, CA; [3]Yale School of Medicine, New Haven, CT; [4]Vanderbilt University School of Medicine, Nashville, TN; [5]University of Texas Health Science Center San Antonio, San Antonio, TX; [6]Kidney Research Institute, Seattle, WA; [7]Icahn School of Medicine at Mount Sinai, New York, NY; [8]Kaiser Permanente Northern California, Oakland, CA; [9]University of California San Francisco, San Francisco, CA; [10]London Health Sciences Centre, London, ON, Canada; [11]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [12]Penn State College of Medicine, Hershey, PA; [13]Vanderbilt University Medical Center, Nashville, TN; [14]VA New York Harbor Healthcare System, New York, NY; [15]University of Washington, Seattle, WA.*

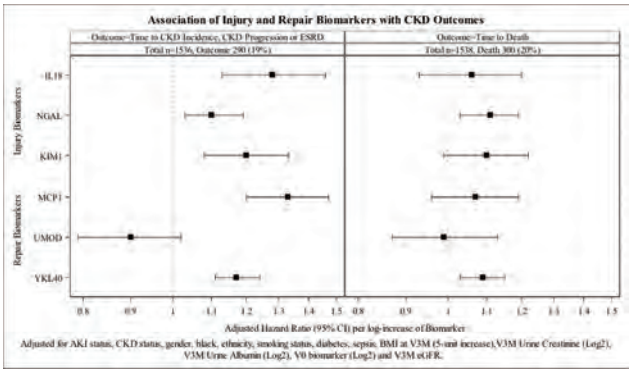
Background: Acute kidney injury (AKI) is a complex disorder associated with increased risk of CKD and mortality. While kidney function may improve after an episode of AKI, subclinical kidney damage may remain that connotes propensity for GFR decline over time. We sought to examine the utility of biomarkers associated with renal injury and repair during and after AKI.

Methods: In a prospective longitudinal parallel cohort study, we enrolled 769 adults hospitalized with AKI and 769 hospitalized adults without AKI from 4 centers in North America. Interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemoattractant protein-1 (MCP-1), uromodulin (UMOD), and YKL-40 were measured in urine samples collected during index hospitalization and outpatient follow-up at 3 months. We followed patients for a median of 4.2 years and assessed the association of the biomarkers with a composite renal outcome (CKD incidence, CKD progression, or ESRD) and death.

Results: Urinary biomarkers at the time of index hospitalization were not significantly associated with the composite renal outcome or death. As shown in **Figure,** urinary IL-18, NGAL, KIM-1, MCP-1, and YKL-40 at 3 months were independently associated with risk of renal events in adjusted analyses. In addition, higher urinary NGAL and YKL-40 levels at 3 months were independently associated with increased risk of mortality.

Conclusions: Urine biomarkers were detectable at 3 months, suggesting ongoing inflammation, repair, and fibrosis even after clinical AKI has resolved. Biomarker levels at 3 months identify patients at risk for renal events and death.

Funding: NIDDK Support



FR-PO016

Early increase in Renal Injury Urinary Biomarkers Associated with AKI Development in Major Elective Non-Vascular Abdominal Surgeries

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Background: There are few data on the incidence of acute kidney injury (AKI) diagnosed by KDIGO criteria and the role of renal injury urinary biomarkers (uBMs) for predicting AKI in patients (pts) submitted to major elective non-vascular abdominal surgeries (MENVAS).

Methods: A total of 225 pts were evaluated, peri-operatively and from the ICU admission up to 7 days. Serum Creatinine (SCr) was assessed before surgery and once a day up to 7d or until ICU discharge. Hourly Urinary Ouput (ml/kg/h) was measured daily. AKI was diagnosed using either SCr or/and urinary output (UO) according to KDIGO definitions. Urine sample was collected 1 day before surgery (baseline), 30 min, 12 and 24h after ICU admission. Five uBMs were assessed: monocyte chemotactic protein 1 (MCP-1), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), microalbuminuria (μalb) and neutrophil gelatinase-associated lipocalin (NGAL) by Luminex x-MAP method. Data are presented as median (first and third quartiles) or frequency. Statistical significance was p<0.05.

Results: Overall, age was 55±15y, 58,2% were female, hospital LoS was 17,7±16.9d, ICU LoS was 3.2±3.2d and mortality was 6,7%. A total of 126 pts (56%) developed AKI - majority KDIGO I (77,8%). Those developing AKI KDIGO II and III had significantly higher BMs values compared to pts AKI KDIGO I or non-AKI in all studied times, but the SCr didn't rise at the same period (IMAGE 1). UO has the best performance: 77,6% pts (KDIGO I) and 89,3% (KDIGO II and III) in 6h; NGAL showed a good performance 24h after ICU admission.

Conclusions: We found a strikingly high incidence of MENVAS-associated AKI diagnosed by KDIGO criteria in patients admitted ICU. Those who developed more severe AKI showed significantly higher uBMs in all times studied, including the preoperative period. uBM increase earlier and before SCr.

Funding: Government Support - Non-U.S.

uBM X KDIGO	BASELINE			30 minutes - ICU			12H - ICU			24H - ICU		
	Non-AKI	KDIGO I	KDIGO II e III	Non-AKI	KDIGO I	KDIGO II e III	Non-AKI	KDIGO I	KDIGO II e III	Non-AKI	KDIGO I	KDIGO II e III
MCP-1 (ng/mg)	0.1 (0.05 - 0.24) ***	0.12 (0.05 - 0.24) **	0.34 (0.13 - 0.88)	0.46 (0.21 - 1.56) **	0.51 (0.31 - 1.03) ##	2.42 (0.53 - 5.73)	0.6 (0.45 -1.49) *	0.63 (0.25 - 1.17) ***	2.03 (0.69 - 6.17)	0.64 (0.26 - 1.66) *	0.67 (0.3 - 1.38) ##	2.09 (0.62 - 8.94)
IL-18 (pg/mg)	17.0 (7.4 - 37.0)	14.7 (7.5 - 32.6)	16.8 (11.2 - 101.0)	20.4 (10.8 - 78.1)	22.0 (10.3 - 57.6)	54.7 (14.1 - 233.5)	22.5 (11.8 - 84.7)	17.0 (7.8 -66.5)##	63.4 (17.3 - 211.9)	23.5 (9.7 - 74.5)	18.5 (9.6 - 56.0)	37.9 (15.3 - 254.5)
KIM-1 (μg/mg)	0.15 (0.07 - 0.38) **	0.16 (0.06 - 0.48) ##	0.45 (0.22 - 1.17)	0.4 (0.15 - 0.83) ***	0.44 (0.21 - 0.90) ##	0.96 (0.42 - 1.88)	0.76 (0.31 - 1.63) *	0.66 (0.23 1.63)#	2.03 (0.56 - 3.64)	1.02 (0.36 - 1.96) **	1.09 (0.38 - 2.02) ##	1.99 (1.23 - 5.83)
μAlb (μg/mg)	6.2 (2.2 - 19.6) ***	6.9 (2.4 - 14.2) ###	20.0 (8.5 - 59.7)	27.5 (12.2 - 52.9) *	28.0 (17.2 - 49.4) *	57.2 (24.8 - 89.5)	22.4 (8.3 - 47.6)	16.4 (9.6 -31.4) *	32.0 (13.6 - 57.3)	22.9 (10.3 - 43.5)	22.7 (10.1 - 39.8)	32.8 (17.1 - 75.5)
NGAL (pg/mg)	25.7 (13.8 - 56.9) *	28.3 (12.5 - 69.5) *	55.4 (24.1 - 119.2)	37.9 (17.3 - 74.1) **	44.7 (21.0 - 131.3)	100.6 (28.5 - 449.3)	33.1 (13.1 - 69.8) ***	10.7 (30.8 - 84.4) ###	125.8 (54.1 - 633.4)	44.6 (20.5 - 133.4) **	67.5 (29.3 - 181.7)	243.3 (32.0 - 1857.0)
Cr (mg/dL)	0.81 (0.66 - 0.97)	0.79 (0.65 - 1.01)	0.83 (0.68 - 0.94)	0.81 (0.66 - 0.98)	0.83 (0.65 - 1.06)	0.84 (0.69 - 0.97)				0.85 (0.65 - 1.28)	0.78 (0.60 - 1.18)	0.89 (0.73 - 1.12)

KDIGO II/III vs AKI-: * p<0.05; ** p<0.01; *** p<0.001; KDIGO II/III vs KDIGO I: * p<0.05; ** p<0.01; *** p<0.001

FR-PO017

Diagnostic Utility of Serial Microscopic Examination of the Urinary Sediment in AKI

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Background: Urine microscopy is a clinical tool of diagnostic and prognostic value in acute kidney injury (AKI). However, the natural history and timing of cast formation remains underexplored. A single inspection of a urine specimen during the course of AKI is a mere snapshot that depends on the day of inspection. We hypothesized that longitudinal inspection of the urinary sediment provides additional diagnostic information otherwise not identified in a single inspection.

Methods: Microscopic examination of the urinary sediment (MicrExUrSed) +/- Sternheimer-Malbin stain was undertaken in all patients with AKI stage ≥ 2 who were seen on consultation in an inpatient nephrology service during a 6-month period. MicrExUrSed were done on the day of consult (day 1), 48 hours later (day 3) and 96 hours later (day 5). Urinary cast scores (based on Chawla *et al* and Perazella *et al*) were assigned to each specimen. Chawla scores (CS) 3-4 and Perazella scores (PS) 2-3 were categorized as consistent with acute tubular injury (ATI), whereas CS 1-2 and PS 0-1 were categorized as non-diagnostic for ATI (non-ATI). Worsening AKI was defined as a rise in serum creatinine (sCr) ≥ 0.3 mg/dL at either day 3 or 5.

Results: At least 2 serial specimens were collected in 60 patients (mean age 58, 32% women, mean sCr at day 1 3.8 mg/dL). Overall, CS and PS category changed over time in 16 (27%) patients, and the change was observed at day 3 in almost all cases (15 of 16). On day 1, a CS and PS consistent with non-ATI was assigned to 31 (52%) patients. Among those 31 patients, CS and PS changed from non-ATI category to ATI in 9 (24%) at day 3. Those 9 patients accounted for 32% of the total 38 with ATI score. Patients with worsening AKI were more likely to change their score from non-ATI to ATI compared to those with stable or improved AKI [relative risk 3.3 (CI: 1.0 – 10.9) for CS (p = 0.047); 8.3 (CI: 1.1 – 63.1) for PS (p = 0.041)].

Conclusions: Serial MicrExUrSed reveals diagnostic findings of ATI otherwise not identified in a single examination, particularly in specimens of patients with worsening AKI. A repeat MicrExUrSed within 48 hours may be warranted in cases of worsening AKI with unclear etiology.

FR-PO018

Serum Procalcitonin as a Predictor for the Development of AKI in Critically Ill Patients

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Background: Procalcitonin (PCT) has been recognized as one of useful markers for the diagnosis of systemic inflammatory response syndrome. In addition, it has been reported that PCT is affected by renal function. However, there are few studies regarding the relationships between PCT and the development of acute kidney injury (AKI). Hence, we investigated whether serum PCT levels at the time of admission can predict the development of AKI and clinical outcomes.

Methods: We retrospectively analyzed data of 790 patients in whom PCT were measured on admission to the intensive care unit. We attempted to investigate that the serum PCT level at the time of admission could be as a predictor for development of AKI according to the groups classified in to the septic and the non-septic patients and risk factor for all-cause mortality.

Results: The serum PCT levels were significantly higher in patients with AKI than in those without AKI (P < 0.001). After adjustment of confounding factors, PCT still remained an independent risk factor for AKI (odds ratio [OR], 2.096; 95% confidence intervals [CI], 1.378–3.190; P = 0.001). The OR (95% CI) for AKI development among those with and without sepsis were 2.620 (1.230–5.582, P = 0.013) and 1.928 (1.119–3.321, P = 0.018), respectively.

Conclusions: Serum PCT level could be used as a marker to predict the possibility of AKI in critically ill patients admitted to the ICU.

FR-PO019

Endogenous Ouabain (EO) as Predictor of AKI and Post-Operative Outcomes

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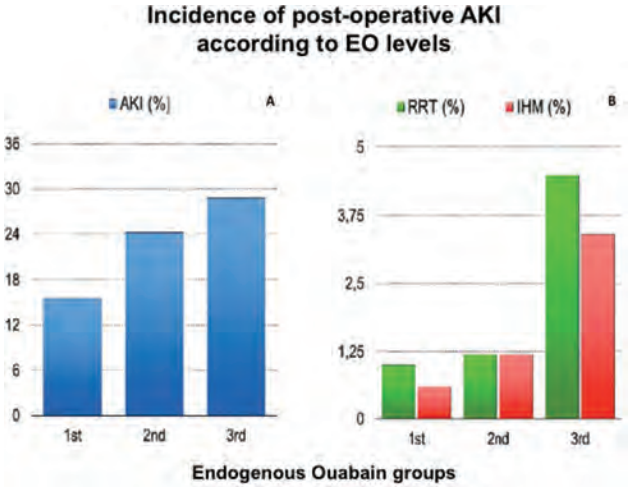
Background: AKI is a frequent complication of cardiac surgery. A large number of novel postoperative biomarkers have been proposed to assess the risk of AKI. However, there are neither preoperative biomarkers nor robust validated risk models that predict AKI. EO is an adrenal stress hormone with hemodynamic and renal effects. Our group have already reported that higher pre-operative EO levels are associated with a worse renal outcome after cardiac surgery. Our aim is to confirm levels of EO as predictive biomarker of AKI in a larger population.

Methods: EO preoperative level was measured in 1097 patients admitted for elective cardiac surgery. For the analysis, patients were grouped according to EO preoperative levels: 1st group EO<133 pmol/L; 2nd EO 133-210 pmol/L; 3rd EO>210 pmol/L. According to the 3 groups, it was evaluated 1) incidence of AKI, 2) requirement of RRT and 3) total in-hospital mortality (IHM).

Results: In this extended population, we confirmed our previous observations for the great impact of preoperative EO level in the development of post-operative AKI. Patients with the highest EO values (>210 pmol/L) had highest postoperative AKI incidence (28.9% vs. 24.3% vs. 15.6%, p<0.0001, fig 1) and required more RRT (p=0.006) postoperatively. Moreover, we observed a relationship between EO and total In Hospital Morality (IHM occurred in 3.2% of patients presenting the highest levels of EO; p=0.028). All results were corrected for main clinical variable associated to post-operative AKI (as age, sex, EF, basal eGFR, surgery type, history of hypertension/diabetes; re-intervention).

Conclusions: These results confirmed preoperative EO level as predictive for the outcomes in patients undergoing cardiovascular surgery: subjects with the highest level of

preoperative plasma EO experienced the worst outcomes (increased incidence of AKI, use of RRT and IHM).



FR-PO020

Optimization of a Novel 5-Plex Panel for AKI

Candace M. Adamo,[1] Eibhlin M. McCole,[2] Ciaran Richardson,[2] Timothy H. Carlson,[1] Grainne Donnellan,[2] Amar Sethi.[1] *[1]Pacific Biomarkers, Seattle, WA; [2]Randox Teoranta, Dungloe, Ireland.*

Background: Since creatinine is a lagging index of AKI progression, studies are now underway to qualify a new set of biomarkers for detecting drug-induced kidney injury (DIKI). Here, following optimization, we present performance data for a novel multiplex composed of urine AKI biomarkers.

Methods: The AKI multiplex panel quantifies KIM-1, cystatin C, clusterin, OPN and NGAL levels in urine. Multiplex results were compared to those from ELISA using urine from one cohort (n=60) treated with a preservative prior to freezing, and urine from a second cohort (n=122) left untreated. Cross reactivity for each analyte with non-panel related proteins was tested. Interfering substances were tittered to determine non-interfering concentrations (within ± 10%). Potential interferents assessed included human albumin (HA), hemoglobin, bilirubin, pH, glucose, sodium chloride and creatinine.

Results: Comparison of preserved urine biomarkers obtained using the two analytical methods provided correlations (r^2) of 0.816, 0.970, 0.842, 0.718, and 0.741 for KIM-1, NGAL, cystatin C, clusterin and OPN, respectively. Slopes were 0.32, 0.87, 1.33, 0.53, and 1.06, respectively. The methods were poorly correlated for unpreserved urine with r^2 ranging from 0.203 to 0.705. Cross reactivity was <1% for all tested non-panel, related proteins. Interfering concentration for HA was <0.5 mg/mL for clusterin and was insignificant for remaining biomarkers. Hemoglobin interference was <62.5 µg/mL for clusterin and insignificant for all other biomarkers. Bilirubin, glucose, sodium chloride and creatinine interferences were insignificant for all biomarkers.

Conclusions: All five biomarkers tested with the novel panel and predicate ELISA methods correlated well when preserved urine was used. Recovery of some urinary AKI biomarkers is susceptible to variability, which can be controlled with preservative. No clinical significant interference was observed for several substances known to be present in urine and cross-reactivity for non-panel proteins was not significant. Previously reported performance of this multiplex combined with the present data demonstrate good multiplex selectivity, and document an *in vitro* diagnostic that fills the need for a robust and cost-effective approach to diagnosis and monitoring of DIKI.

FR-PO021

Histopathological Features of Acute Tubular Necrosis in Native Kidney Correlate with Clinical Outcomes

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Background: Acute kidney injury (AKI) is a life-threatening complication of critical illnesses and is associated with increased morbidity and mortality. Acute tubular necrosis (ATN) is a frequent cause of AKI; however, few studies have examined the histopathological features of ATN as prognostic factors of kidney function recovery in native kidneys. Our aim is to describe histopathological features of ATN systematically and correlate with clinical outcomes.

Methods: Analyses included adult patients who underwent kidney biopsy for AKI unrelated to kidney transplantation at Mayo Clinic Rochester from January 1st, 2000 through December 31st, 2015 and ATN was the primary histological diagnosis (n = 46). Biopsies were reviewed by a kidney pathology consultant (SS) semi-quantitatively. Features of ATN included vacuolization, the presence of tubular debris, tubular distension, tubular cell flattening, and the extent of interstitial fibrosis and tubular atrophy (IFTA). To evaluate the factors associated with kidney recovery, patients were divided into two groups: recovery (n = 28, serum creatinine (SCr) level at 30 days decreased by 0.3 mg/dL and renal replacement therapy (RRT) liberated) vs. no recovery (n = 18).

Results: The median age at time of biopsy was 67 [IQR 58, 75] years old; of which 50% were males, 91% Caucasian, with Charlson comorbidity index of 5 [IQR 4, 7], and SCr 3.9 mg/dL [IQR 2.2, 5.2] at the time of biopsy. 35 (76%) patients were inpatient, 9 (20%) required intensive care unit (ICU) admission, and 10 (22%) required RRT at time of biopsy. Twenty eight (61%) patients recovered kidney function within 30 days of biopsy. The presence of 3+ debris on biopsy was associated with a higher chance of recovery (Figure 1).

Conclusions: Among patients with AKI with biopsy-confirmed ATN, 61% recovered kidney function within 30 days of biopsy and recovery was associated with increased presence of tubular debris.

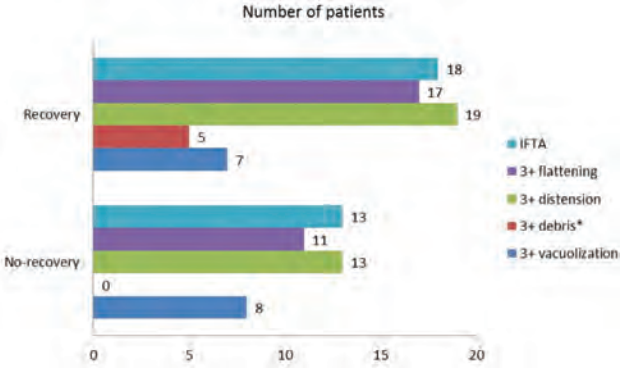

Figure 1 Histopathologic features of ATN in patients with and without recovery. *P-value <0.05.

FR-PO022

A Furosemide Excretion Stress Test (FEST) Predicts AKI Progression and Mortality After Sepsis

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Background: The furosemide stress test (FST) has been shown to be a sensitive and specific predictor of progression to AKIN stage III in the ICU. FST measures the volume of urine produced after a furosemide bolus. Furosemide is actively excreted by the proximal tubules into the lumen where it inhibits NKCC2 in the thick ascending limb. We hypothesize that furosemide excretion (FEST) will be a more direct measure of tubule health than diuresis (FST). We developed a protocol for FST and FEST in mice and tested this hypothesis in a murine model of septic-AKI and in a human cohort.

Methods: Sepsis was induced in male and female CD-1 mice by cecal ligation and puncture (CLP). The FST/FEST started at 42 hours post-CLP. 1 mg/kg furosemide s.c. was given and urine collected for 12 hours. The mice were monitored until 7 days post-CLP. Furosemide concentration was determined by a new reverse phase HPLC assay in the mouse urine samples and urine samples from 49 patients in the PASSKI cohort.

Results: In the mouse model a moderate severity of sepsis was used and similar mortality was seen in the males and females. In the male group, from 79 mice 32 survived to 42 hours and underwent FST/FEST with 19 mice surviving to 7 days compared to 60/23/14 in the females. Urine production during the 12 hour collection varied from 0.08 to 2.62 ml. Urine production post-challenge and the fraction of furosemide recovered predicted mortality [AUC ROC values of 0.92 for FST in males, 0.95 for FST in females, 0.87 for FEST for males, and 1.00 for FEST in females]. Both FST and FEST predicted time of death in males (R^2 = 0.30 and 0.75), males and females combined (R^2 = 0.26 and 0.74) but not females alone. FST and FEST correlated with kidney NKCC2 mRNA levels (R^2 = 0.35 and 0.46), and weakly with BUN, ALT and CK. In the human cohort, FST and FEST were comparable in predicting progression to KDIGO stage III (AUC ROC values of 0.864 for FST and 0.848 for FEST).

Conclusions: In both the mouse model and human cohort the furosemide stress test and furosemide excretion stress test perform similarly with FST slightly superior in predicting mortality or progression. The furosemide excretion stress test predicted time to death in the mouse model.

Funding: NIDDK Support

FR-PO023

Loop Diuretic Challenge to Predict the Need for Renal Replacement Therapy Among Patients with Stage III AKI

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Background: A poor response to a high dose loop diuretic challenge (LDC) predicts the progression of stage I and II acute kidney injury (AKI). Performance of this diagnostic test in stage III AKI is unknown. The objective of this study was to determine if poor response to LDC among patients with stage III AKI predicted the need for renal replacement therapy within 24-hours ($dialysis_{24h}$).

Methods: We included adults (≥18 years) admitted or transferred to medical or general surgical ICUs at Mayo Clinic, Rochester, MN between Jan 1, 2004, to Dec 31, 2016. Patients with stage III AKI were identified by an electronic surveillance tool using AKIN criteria. We then identified patients who received LDC, defined as at least 1mg/kg intravenous bolus dose of furosemide or equivalent intravenous bolus dose of bumetanide after the diagnosis of stage III AKI. We excluded patients with the end-stage renal disease, organ transplantation or who died within 24 hours of LDC. We modeled post-LDC urine output as a restricted cubic spline and compared the area under the curve (AUC) for urine output (mL) at 2h (UOP_{2h}) and 6h (UOP_{6h}) after LDC to predict $dialysis_{24h}$.

Results: We included 687 patients with stage III AKI who received LDC. The patients who received $dialysis_{24h}$ were younger (63.9 ± 14.5 years vs. 67.6 ± 15.6 years, p= 0.008), had lower Charlson comorbidity indices (4.9±2.4 vs. 5.8±2.7, p< 0.001) and higher SOFA scores on the day of LDC (10.4±3.9 vs. 8.2±3.4, p< 0.001). Both median total 2 hours (UOP_{2h}) and 6 hours (UOP_{6h}) urine output after LDC were lower in patients who needed $dialysis_{24h}$ (UOP_{2h} 48ml vs. 138ml, p<.001; UOP_{6h} 210ml vs. 616ml, p< 0.001) but UOP_{6h} was better in predicting $dialysis_{24h}$ (Area under the curve 0.71 vs. 0.67, p= 0.02). The sensitivity and specificity of a UOP_{6h} cutoff of ≤600ml to predict $dialysis_{24h}$ was 80.9% & 50.5% and for a cutoff of ≤300cc was 64.2% & 68.2%.

Conclusions: Among patients with AKI stage III the UOP_{6h} after loop diuretic challenge had a modest discriminant capacity to identify dialysis initiation within the next 24 hours. Though its predictive power seems better in earlier stages of AKI, LDC may be a useful adjunct to assess dialysis needs in patients with advanced AKI.

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FR-PO024

The Effect of Serum Neutrophil Gelatinase-Associated Lipocalin on Discontinuation of Continuous Renal Replacement Therapy in Critically Ill Patients with AKI

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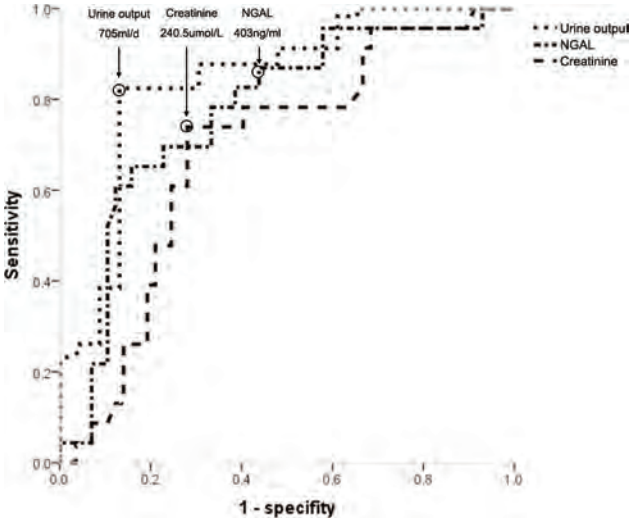
Background: To determine the optimal time for discontinuing continuous renal replacement therapy (CRRT) for critically ill patients with acute kidney injury (AKI) by evaluating serum Neutrophil gelatinase-associated lipocalin (NGAL).

Methods: Patients treated with CRRT at least 24 hours for AKI in ICUs were divided into "success" and "failure" groups according to their renal replacement therapy requirement within 7 days after the initial discontinuation of CRRT.

Results: 80 AKI patients were divided into the success (n = 57) and failure groups (n = 23). The patients in failure group was associated with higher mortality compared with successful group (39% vs.14%, p = 0.017). There were significant differences in serum NGAL, creatinine level and urine output at discontinuation between two groups. In patients without sepsis (n = 55), serum NGAL and urine output were found as significant predictors of successful cessation. The area under receiver operating characteristic (AUROC) to predict successful discontinuation of CRRT was 0.85 for NGAL and 0.82 for urine output. NGAL of 403 ng/ml had highest sensitivity (71%) and specificity (85%), as well as urine output of 695 ml/d with highest sensitivity (86%) and specificity (72%). However, in septic patients (n = 25), urine output, but not serum NGAL (OR, 0.990, p =0.43), was a significant variable (OR, 1.005, p =0.044), and the AUROC was 0.861 (p = 0.003), with a cutoff of 793.5 ml (sensitivity 75%, specificity 100%).

Conclusions: Serum NGAL was a significant factor to predict successful CRRT discontinuation in non-septic patients. However, urine output, rather than serum NGAL, was a significant predictor in septic AKI patients.

Funding: Clinical Revenue Support



AUROC and cutoff of NGAL, creatinine and urine output for successful CRRT discontinuation in all included patients

FR-PO025

Different Roles of Functional and Structural Markers Measured at Discontinuation of Renal Replacement Therapy for AKI

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Background: Severe acute kidney injury (AKI) which requires renal replacement therapy (RRT) has been reported to show unacceptably high mortality of 50% or more. Successful discontinuation of RRT is supposed to be associated with better outcomes. Although functional and structural markers have been evaluated in AKI, little is known about their roles in predicting outcomes when measured at the time of RRT discontinuation.

Methods: We performed a prospective single-center cohort study. Patients received continuous RRT (CRRT) for AKI between August 2016 and March 2018 in the intensive care unit of The University of Tokyo Hospital (Tokyo, JAPAN) were analyzed. Clinical parameters and urine samples were obtained at CRRT discontinuation. Successful CRRT discontinuation was defined as neither resuming CRRT for 48 hours nor receiving intermittent hemodialysis during 7 days from the CRRT termination. Major adverse kidney events (MAKEs) was defined as death or dialysis requirement or more than 25% reduction of eGFR from the baseline at day 90.

Results: 73 patients who received CRRT for AKI were analyzed. 59 discontinued patients and 14 un-discontinued patients were identified. Among kinetic eGFR, urine volume, urinary NGAL and urinary L-FABP, urine volume had the highest AUC [95%CI] 0.91 [0.80-0.96] with the cut-off value of 740 ml/day. For predicting MAKEs at day 90, urinary NGAL had the highest AUC 0.76 [0.62-0.86], whereas kinetic GFR and urine volume failed to show statistical significance (kinetic eGFR AUC 0.49 [0.35-0.63], urine volume AUC 0.59 [0.44-0.73]).

Conclusions: Our prospective study revealed functional marker of urine volume could predict successful weaning of RRT, on the other hand, structural maker of urinary NGAL could predict long-term renal outcomes. This indicates different roles of functional and structural makers in predicting the outcomes of severe AKI requiring RRT.

Funding: Government Support - Non-U.S.

FR-PO026

Urinary Biomarkers and Renal Recovery at 4 Months After Community Acquired AKI: A Prospective Study in a Tertiary Care Hospital

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Background: Acute kidney injury (AKI) in developing countries is most commonly community acquired. Despite advances in the epidemiology of AKI, prognostication remains a significant challenge. We studied the ability of urinary biomarkers to predict renal recovery at four months after community-acquired AKI

Methods: We studied 78 patients with community-acquired AKI (AKIN stage 1 to 3) at the Department of Nephrology, PGIMER, Chandigarh. Serum and urine samples were collected at admission, discharge and, at 1 and four months after discharge. Renal recovery was defined as eGFR (CKD EPI)>60 ml/min/1.73m2 and urine protein to creatinine ratio <500 mg/g at four months after discharge. We investigated whether urinary biomarker (uL-FABP, uNGAL, uKIM-1) at hospital discharge could predict failure to recover renal function at four months after discharge

Results: 75(96%) patients had AKIN stage 3 AKI and other 3 patients had AKIN stage 2 AKI. 21(27%) patients had failed to recover renal function at four months of discharge. Median urinary NGAL and urinary KIM-1 were significantly lower in patients with renal recovery (n=57) compared to those with persistent renal dysfunction (n=21). However, the differences in the median urinary L-FABP was not statistically different between the two groups (p-value = 0.55). Urinary NGAL and uKIM-1, individually predicted failure to recover renal function at four months after community-acquired AKI with AUCs of 0.71 (95% CI, 0.26 to 0.55) and 0.68 (95% CI, 0.52 to 0.84), respectively.

Conclusions: This is the first prospective study to evaluate urinary biomarkers as an outcome-specific biomarker in patients with community-acquired AKI cohort. The results of this study indicate that urine NGAL and uKIM-1 are an independent predictor of failure to recover renal function after community-acquired AKI

FR-PO027

Kinetic eGFR Can Predict AKI Recovery Earlier, Especially in Patients with CKD

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Background: The kinetic estimated glomerular filtration rate eGFR (KeGFR) obtained via consecutive serum creatinine (sCr) values is reportedly useful for predicting renal recovery after acute kidney injury (AKI). However, no studies have determined which patients can benefit using the KeGFR model. We predicted recovery from AKI with consecutive KeGFR and sCr values, comparing the usefulness of KeGFR.

Methods: This retrospective cohort study included patients admitted to our intensive care unit (ICU) from April 2014 to March 2016 and diagnosed with AKI after ICU admission. We defined renal recovery day as the first day when increasing consecutive sCr values turn to decrease or decreasing consecutive KeGFR values turn to increase,

comparing each recovery length from AKI. We examined patient characteristics when the KeGFR model was superior in predicting recovery from AKI.

Results: During the study period, 972 patients were admitted to our ICU and 74 were finally studied. On admission, median age was 75.5 (IQR: 64.0-83.0) years, median baseline sCr was 0.81 (IQR: 0.63-1.04) mg/dL, and median baseline eGFR was 65.0 (IQR: 51.1-77.6) mL/min/1.73 m^2. AKI recovery length was statistically shorter in KeGFR model than sCr model (median [IQR], 1.0 [1.0-2.0] vs 1.0 [1.0-2.0], p<0.01). In 17 (23.0%) patients, using the KeGFR model predicted AKI recovery earlier than when using the sCr model. Among those whose AKI recovery was predicted better than when using the sCr model, the baseline sCr was likely higher (median [IQR], 0.80 [0.61-0.93] vs 0.97 [0.79-1.42], p<0.01), baseline eGFR was likely to be lower (median [IQR], 68.0 [54.2-80.9] vs 51.6 [35.8-64.1], p=0.01), and the proportion of patients with CKD was higher (n [%], 18 [31.6] vs 13 [76.5], p<0.01). Other factors such as age, sex, mean blood pressure, sequential organ failure assessment score, infusion volume, and body weight were not associated with predicting early AKI recovery using the KeGFR model.

Conclusions: KeGFR can predict recovery from AKI earlier, especially in patients with a higher baseline sCr, lower baseline eGFR, and CKD. Using the KeGFR model, we can confirm the efficacy of our AKI therapy early, which would enable prompt and accurate management of patients with CKD.

FR-PO028

Post-AKI eGFR and ACR and Future Risk of Kidney Disease Progression

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Background: Some have advocated routine post-dischage nephrology follow-up for hospitalized patients who experienced AKI. We hypothesize that post-hospitalization eGFR and proteinuria levels risk stratify patients bettter than presence or severity of AKI.

Methods: We studied 1603 adult ASSESS-AKI study participants (PMID: 20799966). ASSESS-AKI prospectively enrolled hospitalized patients with and without AKI in a parallel, matched cohort. All participants had an outpatient baseline research study visit 3 months post-discharge when eGFR, ACR and comorbitidies were ascertained. Cox models were used to examine predictors of kidney disease progression, defined as time to halving of eGFR or ESRD.

Results: Median age of the study population was 66 (IQR 56-74) yrs; eGFR 69 (51-90) ml/min/1.73m2, ACR 14 (7-56) mg/g. 38% were female, 13% black, 3% Hispanic, and 41% had diabetes mellitus (DM). 772 participants had AKI and 831 did not. Most cases of AKI were mild to moderate in severity (72% stage 1, 15% stage 2). 139 participants had kidney disease progression after a median follow-up of 4.8 yrs. Severity of AKI was associated with kidney disease progression in simple and multivariable Cox models (Table). However, taking into account AKI severity did not materially improve risk stratification beyond a Cox model which contained basic demographics, DM status, SBP, BMI, eGFR and ACR (C-statistic 0.83 vs. 0.82). A Cox model with post-AKI ACR alone had a C-statistic of 0.81. (Similar results were seen when AKI was captured as presence or absence rather than staged by severity.)

Conclusions: Post-hospitalization levels of eGFR and ACR should guide triaging for implementation or intensification of reno-protective measures more so than presence or severity of AKI during hospitaliation. Patients who have preserved eGFR and low ACR after hospitalization have good renal prognosis and may not need referral to nephrology, regardless of whether AKI occured or not.

Funding: NIDDK Support

	Unadjusted	Unadjusted	Unadjusted	Adjusted*	Adjusted*
AKI stage 1	3.08 (2.08-4.55)				1.70 (1.12-2.58)
AKI stage 2	2.89 (1.51-5.22)				1.66 (0.85- 3.26)
AKI stage 3	5.02 (2.84-8.90)				3.02 (1.66- 5.47)
eGFR (per 10 ml/min/1.73m2)		1.53 (1.41-1.66)		1.31 (1.21- 1.42)	1.28 (1.18- 1.39)
ACR (mg/gm)(per doubling)			1.54 (1.45-1.62)	1.32 (1.23- 1.42)	1.33 (1.24- 1.42)
	C statistic 0.49	C statistic 0.76	C statistic 0.81	C statistic 0.82	C statistic 0.83

*adjusted for center, demographics, SBP, BMI

FR-PO029

Recovery and Survival at Three Months Following Dialysis-Dependent AKI

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Background: Recovery from dialysis-dependent AKI is desirable because long-term dialysis is associated with significant morbidity and mortality. We examined how previous CKD stage, aetiology of AKI and co-morbidities influenced survival and dialysis dependence at three months after initial presentation.

Methods: 245 consecutive cases of AKI requiring RRT were identified from a tertiary referral centre in the UK, treated between 2008 and 2018. Baseline demographic and comorbidity data were extracted and logistic regression was used to assess the association of these characteristics with the primary outcome of renal recovery and survival at three months, in uni- and multi-variate models.

Results: Median age was 66 years (IQR 56.5-75). The most common diagnosis was ATN (60%) followed by vasculitis (9%) and myeloma (8%). At three months after presentation, 187 (76%) individuals were dialysis independent and 30 (12%) had died. Unadjusted and adjusted odds ratios (OR) are shown in table one. (Odds >1 means factor was associated with worse outcome).

Conclusions: This single centre study demonstrated that prior CKD stage and a history of cancer and higher were of the strongest predictors of renal recovery and survival at three months. This could assist clinical decision making and information given to patients.

Table 1: Unadjusted and adjusted odds ratios (OR) for association of patient characteristics with dialysis dependence and/or mortality at three months post presentation

Variable	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age (decades)	1.25	1.03-1.53	0.024	1.11	0.80-1.55	0.447
Male sex (ref female)	1.10	0.61-1.98	0.757	1.03	0.41-2.63	0.944
Diagnosis (ref ATN)						
Myeloma	2.62	0.98-6.99	0.054	3.80	0.68-21.4	0.130
Vasculitis	3.28	1.29-8.31	0.012	3.56	0.77-16.5	0.104
Obstruction	2.62	0.87-7.94	0.088	1.23	0.26-5.85	0.799
Other	1.31	0.54-3.21	0.553	2.17	0.62-7.48	0.220
Previous CKD						
Stage 2	1.13	0.22-5.86	0.887	1.13	0.19-6.91	0.887
Stage 3	3.10	1.18-8.12	0.021	2.68	0.83-8.67	0.100
Stage 4	4.13	1.35-12.6	0.013	4.56	1.22-17.1	0.024
Stage 5	2.76	0.71-10.7	0.142	4.25	0.95-19.1	0.059
Co-morbidities						
History of cancer	2.14	1.11-4.14	0.023	3.11	1.19-8.08	0.020
Prior vascular disease *	1.76	1.00-3.09	0.049	1.76	0.66-4.69	0.261
Prior diabetes mellitus	0.80	0.44-1.45	0.459	1.02	0.38-2.74	0.971
Dementia	2.58	0.36-18.7	0.348	1.65	0.12-23.5	0.710

*not included in final model

FR-PO030

AKI Followed by Complete Recovery Is Associated with Higher Risk of Upper Gastrointestinal Bleed

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Background: Recovery from dialysis dependent AKI is associated with future risk of upper gastrointestinal bleed (UGIB). To date, no studies have explored the association between complete recovery from non-dialysis dependent AKI and future risk of UGIB. We aim to determine the long-term risk of UGIB after a hospital admission complicated by non-dialysis dependent AKI followed by complete recovery of kidney function in a propensity score-matched cohort of cases and controls.

Methods: We identified 1140 AKI cases (AKI Network definition) with complete kidney function recovery at the time of discharge (serum creatinine <1.10 times the pre-admit baseline value) during hospital admission between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 1140 controls (no AKI during index admit) based on a propensity score including: age, sex, race, prior inpatient visits, all components of the Charlson Comorbidity index, baseline creatinine, and admission season. The primary outcome was time to UGIB, defined by ICD-9 codes. Cox proportional hazards models were adjusted for prior UGIB, liver disease, and peptic ulcer disease (PUD) and censored for death.

Results: Baseline characteristics among the cases and controls were similar: age 62±17 years, 46% female, 92% white, baseline creatinine 0.9 ± 0.2 mg/dL. During a median post-discharge follow-up of 13 months, 646 (57%) cases and 470 (41%) controls had an UGIB. The risk of UGIB was 1.6 times higher among patients with AKI followed by complete recovery compared to controls (Hazard Ratio 1.65 [95% CI, 1.46 – 1.86]; p <0.0001). After adjusting the model for prior UGIB, liver disease, and PUD, the risk of UGIB was still higher among the patients with AKI followed by complete recovery compared to control group (Hazard Ratio 1.50 [95% CI, 1.32 – 1.69]; p <0.0001).

Conclusions: In this cohort, non-dialysis dependent AKI during a hospital admission, despite complete recovery of kidney function, was associated with future UGIB compared to patients without AKI. Future studies are needed to further investigate this relationship.

Funding: Veterans Affairs Support

FR-PO031

AKI Followed by Complete Recovery Is Associated with Greater Risk of Subsequent Venous Thromboembolism

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Background: Acute kidney injury (AKI) is associated with long-term morbidity including chronic kidney disease and heart disease. Recent data suggest that AKI is associated with increased long-term event rates such as sepsis, cancer, and venous thromboembolism (VTE). A prior study included patients with dialysis-requiring AKI with recovery but the degree of kidney function recovery was unclear. We aim to determine the

risk of VTE following a hospital admission complicated by AKI with complete recovery in a propensity score-matched cohort of cases and controls.

Methods: We identified 1139 AKI cases (AKI Network definition) with complete kidney function recovery by the time of discharge, defined as serum creatinine <1.10 times the pre-admit baseline value, during a hospitalization between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 1139 controls (no AKI during index admit) based on a propensity score including age, sex, race, number of prior inpatient visits, baseline creatinine, season of admission, and all co-morbidities in the Charlson Comorbidity index. The primary outcome was time to VTE. Cox proportional hazards models were adjusted for history of prior VTE and cancer and censored for death.

Results: Baseline characteristics among the cases and controls were similar: age 62 ± 17 years, 46% female, 92% white, serum creatinine 0.9 ± 0.2 mg/dL. During a median [IQR] post-discharge follow-up of 65 [9-89] months, 246 cases (22%) and 73 controls (6%) developed new VTE. In the unadjusted Cox model AKI with complete recovery was with a nearly four-fold increase in hazard ratio for subsequent VTE (HR 3.99 [95% CI, 3.06 – 5.18]; p <0.0001). This association did not change after adjusting for prior VTE and cancer diagnosis (HR 3.82 [95% CI, 2.94 – 4.97]; p <0.0001).

Conclusions: AKI with complete recovery is associated with increased risk of VTE. These data further support the idea that AKI is associated with long-term events dysfunction independent of decreased kidney function. Future research is needed to determine the mechanism of long-term changes following AKI.

Funding: Veterans Affairs Support

FR-PO032

The Risk of Major Adverse Kidney Events After AKI: A Systematic Review and Meta-Analysis

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Background: Acute kidney injury (AKI) is a common consequence of acute illness and is associated with high morbidity and mortality. Robust estimates of the long-term outcomes of AKI, using consensus definitions of exposure, are needed to inform clinical practice and guide optimal allocation of healthcare resources.

Methods: A systematic search was performed through EMBASE, MEDLINE, and grey literature sources to identify cohort studies reporting an association between AKI and chronic kidney disease (CKD), end-stage kidney disease (ESKD) or death. All studies published between 2004 and 2018 involving hospitalised adults were eligible if they defined AKI according to consensus definitions (RIFLE, AKIN, or KDIGO), included a non-AKI control group, and followed patients for at least 1 year. Risk of bias was assessed using the Newcastle-Ottawa Scale. Random effects meta-analysis was used to combine adjusted hazard ratios between studies. Subgroup, sensitivity and meta-regression analyses were performed to investigate potential sources of heterogeneity.

Results: The systematic search retrieved 6369 citations, of which 81 studies comprising more than 2 million participants were eligible for inclusion. One-third of studies were in cardiovascular surgery patients and one-third were performed in Europe. Reporting of methods was incomplete in many studies. The most common sources of bias were poor representativeness of patient cohorts, and insufficient duration and completeness of follow up. Funnel plot asymmetry reflected a lack of small studies with negative effects. AKI was associated with a significantly increased risk of death across all subgroups: angiography (HR 3.07, 95%CI 2.12-4.46), cardiovascular surgery (HR 1.75, 95%CI 1.55-1.98), intensive care (HR 1.47, 95%CI 1.32-1.65), and hospital (HR 1.41, 95%CI 1.26-1.56). The risk of death increased from stage 1 (HR 1.35, 95%CI 1.27-1.44) to stage 3 (HR 2.76, 95%CI 2.28-3.35). AKI was associated with increased risks of CKD (HR 2.86, 95%CI 2.09-3.91) and ESKD (HR 4.81, 95%CI 3.04-7.62). Heterogeneity between studies was high.

Conclusions: AKI was associated with inferior long-term survival and an increased risk of adverse renal outcomes. The risk of a poort outcome increased with greater AKI severity. Patients undergoing angiography and cardiovascular surgery were at greatest risk.

FR-PO033

Contrast-Induced AKI and Adverse Clinical Outcomes Risk in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis

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Background: Recent studies have shown associations between contrast-induced acute kidney injury (CI-AKI), in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS), and increased risk of adverse clinical outcomes in ACS patients undergoing PCI; however, the estimates are inconsistent and vary widely.

Methods: EMBASE, PubMed, Web of Science™ and Cochrane Library databases were systematically searched from inception to December 16, 2016 for cohort studies assessing the association between CI-AKI and any adverse clinical outcomes in ACS patients treated with PCI. We calculated the pooled risk ratios (RRs) with 95% confidence intervals (CI) of these outcomes. Heterogeneity was explored by subgroup analyses.

Results: We identified 1857 articles in electronic search, of which 23 (n=33080) were included. Our meta-analysis revealed that CI-AKI significantly increased the risk of all-cause mortality (18 studies; n= 28367; RR=3.16, 95% CI 2.52–3.97; I^2 =56.9%), short-term all-cause mortality (9 studies; n=13895; RR=5.55, 95% CI 3.53–8.73; I^2 =60.1%), major adverse cardiac event(7 studies; n=19841; RR=1.49, 95% CI: 1.34–1.65; I^2=0), major adverse cardiovascular and cerebrovascular event (3 studies; n=2768; RR=1.86, 95% CI: 1.42–2.43; I^2=0) and stent restenosis (3 studies; n=130678; RR=1.50, 95% CI: 1.24–2.81; I^2=0), respectively, in ACS patients undergoing PCI. Subgroup analyses showed the study design, sample size and prevalence of CI-AKI might have effect on pooled RR.

Conclusions: CI-AKI may be a prognostic marker of adverse outcomes in ACS patients undergoing PCI. More attention should be paid to diagnosis and management of CI-AKI.

FR-PO034

Post-Trans-Catheter Aortic Valve Implantation AKI Stage 3 Requiring Renal Replacement Therapy and Mortality in Patients with Severe Aortic Stenosis and High Surgical Risk

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Background: Trans-catheter aortic valve implantation (TAVI) is an established treatment for severe symptomatic aortic stenosis (AS) in high surgical risk patients. However, post TAVI complications affect outcomes. Acute kidney injury (AKI) stage 3 requiring renal replacement therapy (RRT) after TAVI has been associated with high hospital mortality. Efforts to understand the factors that contribute to increase morbidity and mortality in patient undergoing TAVI are needed in order to decrease their morbidity and mortality.

Methods: The data of patients who underwent TAVI between 2012 and 2014 from the nationwide inpatient sample database was analyzed in this investigation. ICD-9-CM codes were used to identify hospital admissions for TAVI (procedure codes: 35.05 and 35.06) and new AKI stage 3 requiring RRT post-TAVI (diagnostic codes 584.5 to 584.9 plus procedure code 39.95). The primary outcome was AKI stage 3 requiring RRT post-TAVI. Stata/IC 14.2 was used to identify predictors of the primary outcome using multivariable regression analysis.

Results: An estimated total of 41,050 patients underwent TAVI during the pre-specified study period. Patient mean age was 81.1 years, 47.7 were women and 81% were white. 685 (1.7%) patients developed AKI stage 3 requiring RRT after TAVI. Hospital mortality was 30.7% in this subgroup. Multivariable regression analysis identified trans-apical approach (OR [95%CI], 1.67 [1.13-2.46]), preexisting chronic kidney disease (CKD) (OR [95%CI], 1.84[1.30-2.61]), non-elective TAVI (OR [95%CI], 2.24[1.58-3.18]), heart failure (OR [95% CI], 2.48 [1.58-3.90]], and procedural or post-procedural mechanical circulatory support (MCS) use (OR [95%CI], 3.39[1.77-6.50]) as predictors for AKI stage 3 requiring RRT.

Conclusions: Patients complicating with AKI stage 3 requiring RRT after TAVI have a high hospital mortality. Preexisting CKD, trans-apical approach, non-elective TAVI, development of heart failure and the need for MCS were significantly associated with AKI stage 3 after TAVI.

FR-PO035

AKI After Non-Cardiac Surgery as an Independent Predictor of Infection and Malignancy During Long-Term Follow-Up

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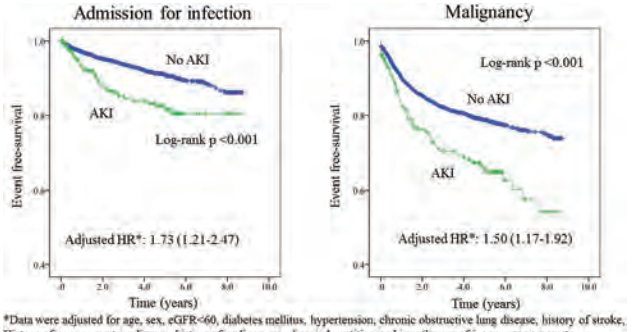
Background: Previous studies showed that acute kidney injury (AKI) was an independent predictor of all-cause mortality and cardiovascular events. However the associations between AKI and non-cardiac outcomes have not been studied.

Methods: This is a retrospective observational study. Inclusion criteria were adults who underwent non-cardiac surgery under general anesthesia from 2007 to 2011. Exclusion criteria were urologic and obstetric surgeries, subjects missing creatinine values perioperatively, or subjects on dialysis preoperatively. Exposure of interest was AKI within 7 days of surgery by KDIGO criteria. Outcome variables were admission for infection and diagnosis with malignancy (including recurrence). When the outcome was malignancy, subjects who underwent palliative resection of malignancy were excluded. Statistical analyses were performed using Kaplan-Meier curve and Cox regression analyses.

Results: Among 3,939 subjects, there were 289 events of AKI (7.3%). During median follow-up of 4.0 years, there were 291 admissions for infection and 668 were diagnosed with malignancy. Event-free survival among subjects with AKI was significantly lower. After adjustments for potential confounders, AKI was significantly associated with admission for infection and the diagnosis of malignancy (HR 1.73 [1.21-2.47] and 1.50 [1.17-1.92], respectively). Subgroup analyses stratified by age, sex, or history of malignancy yielded similar results. Among subjects with AKI, 11.4 % did not recover renal function during index admission for the surgery. Analyses excluding subjects without recovery of renal function did not change the results.

Conclusions: AKI was an independent predictor of infection and malignancy during long-term follow up after non-cardiac surgery, irrespective of recovery of renal function. There is a possibility that AKI predisposes patients to long-term immunosuppressed state.



*Data were adjusted for age, sex, eGFR<60, diabetes mellitus, hypertension, chronic obstructive lung disease, history of stroke, History of coronary artery disease, history of malignancy, chronic hepatitis, smoking, the use of immunosuppressants, corticosteroid, or chemotherapeutic agents

FR-PO036

Renal Dysfunction and In-Hospital Mortality Among Critically Ill Patients with Stroke

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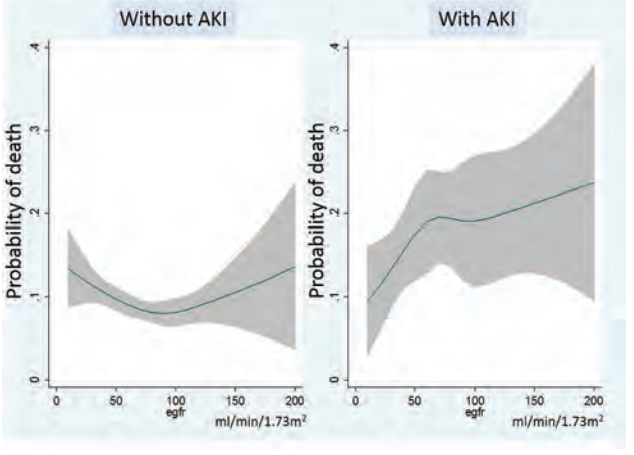
Background: The interplay between baseline renal function and acute kidney injury (AKI) on in-hospital mortality among critically ill patients hospitalized for stroke is largely unknown.

Methods: We used the multicenter eICU Collaborative Research Database to identify 4,736 adult non-dialysis patients admitted to ICU with acute stroke between 2013 and 2015. Baseline renal function was defined as estimated glomerular filtration rate (eGFR) calculated by the MDRD equation based on the first serum creatinine within 24 hours of ICU admission. AKI was defined based on the Kidney Disease: Improving Global Outcomes guidelines. We used a multivariable logistic regression with a restricted cubic spline of eGFR and an interaction with AKI to estimate the probability of in-hospital mortality according to baseline eGFR among patients who did and did not develop AKI.

Results: The mean age of the patients was 68.6 ± 14.8 years, 48.6% were male, and 80.8% were Caucasian. The mean eGFR on admission was 72.5 ± 30.7 ml/min/1.73m^2 with 18.0% (n = 852) presenting with an eGFR between 90 and 120 ml/min/1.73m^2 and 40.6% (n = 1,922) between 60 and 90 ml/min/1.73m^2. Patients with lower eGFR were older, more likely to have diabetes, require intubation, and have lower Glasgow coma scales. There were 460 deaths (9.8%) during hospitalization. After adjusting for confounding, both reduced (eGFR <45, odds ratio (OR), 1.83; 95% confidence interval (CI), 1.20-2.79) and highly elevated eGFR (≥120, OR, 1.37; 95% CI, 0.69-2.74) were associated with increased mortality when comparing to eGFR between 75 and 90 ml/min/1.73m^2. The figure shows that AKI was associated with higher in-hospital mortality and the relationship between eGFR at baseline and mortality was significantly different among those with and without AKI.

Conclusions: Both eGFR on admission and AKI are strong predictors of in-hospital mortality and the impact of eGFR is stronger among patients who develop AKI.



FR-PO037

AKI in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease Necessitating Hospitalization

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Background: Acute kidney injury (AKI) on patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remained unknown, and little is known about the differences between community-acquired AKI (CA-AKI) and hospital-acquired AKI (HA-AKI) in patients with AECOPD. Thus, we compared prevalence, risk factors, and outcomes for these patients with CA-AKI and HA-AKI.

Methods: Between January 2014 and January 2017, data from adult inpatients with AECOPD were analyzed retrospectively. In all, 1768 patients were included.

Results: Prevalence of CA-AKI was 15.8% and that of HA-AKI was 5.5%, giving an overall AKI prevalence of 21.3%. Comparing with patients without AKI, patients with AKI were more likely to require mechanical ventilation (38.7% *versus* 19.1%; $P < 0.001$), non-invasive mechanical ventilation (20.4% *versus* 16.0%; $P = 0.044$), invasive mechanical ventilation (18.3% *versus* 3.1%; $P < 0.001$), and intensive care unit (ICU) admission (33.7% *versus* 12.9%; $P < 0.001$). Patients with AKI had a longer duration of ICU stay (9 days *versus* 8 days; $P = 0.033$), a longer hospitalization (13 days *versus* 10 days; $P < 0.001$), and a higher inpatient mortality (18.0% *versus* 2.7%; $P < 0.001$). Patients with CA-AKI had a higher prevalence of chronic kidney disease (CKD) and lower prevalence of chronic cor pulmonale than patients with HA-AKI. Risk factors for developing HA-AKI and CA-AKI were similar: being elderly, requirement for mechanical ventilation and a history of coronary artery disease and CKD. Patients with HA-AKI were more likely to have stage-3 AKI and worse short-outcomes. In comparison with CA-AKI, patients with HA-AKI were more likely to require non-invasive mechanical ventilation (31.3% *versus* 16.8%; $P = 0.003$), and had a longer duration of mechanical ventilation (11 days *versus* 8 days; $P = 0.020$), longer hospitalization (14 days *versus* 12 days; $P = 0.038$), and higher inpatient mortality (32.0% *versus* 13.2%; $P < 0.001$). Those with HA-AKI had worse (multivariate-adjusted) inpatient survival than patients with CA-AKI (hazard ratio, 1.7 [95% CI, 1.03–2.81; $P = 0.038$] for the HA-AKI).

Conclusions: AKI was common in patients with AECOPD requiring hospitalization, and had a worse prognosis. CA-AKI was more common than HA-AKI but otherwise demonstrated similar demographics and risk factors. Nevertheless, patients with HA-AKI had worse short-term outcomes.

FR-PO038

In-Hospital Mortality of AKI in Those with and Without HIV at a Tertiary Hospital in South Africa: A 2-Year Retrospective Cohort Study

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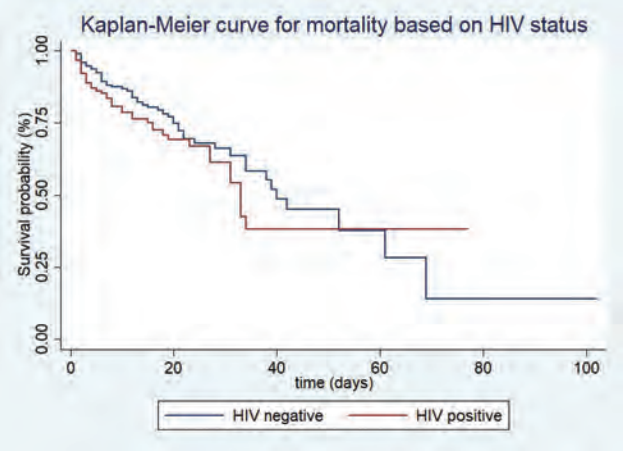
Background: Acute kidney injury (AKI) in HIV patients in Sub-Saharan Africa is a common cause for hospitalisation and is associated with high morbidity and mortality. There is a paucity of comparative epidemiological data regarding the outcome of AKI in those with and without HIV from the African continent. The primary outcome was to determine the overall in-hospital mortality of AKI.

Methods: This was a single centre study of all consecutive adult patients with AKI referred to the renal unit at Tygerberg Hospital for the period from 1 January 2015 to 31 December 2016. AKI was defined as a recent normal serum creatinine (< 3 months) and/or normal kidney sizes on ultrasound examination (> 100 mm length). Those with proteinuria > 3.0 g/day were excluded. Kaplan Meier curves and logistic regression were used to assess survival and identify factors predicting mortality.

Results: We identified a total of 291 patients with AKI of which 116 (39.9%) were HIV positive. Overall, 91 (31%) patients died of which 40 (34.5%) were HIV positive and 51 (29.1%) were HIV negative (P = 0.34). At hospital admission, more HIV positive patients had tuberculosis (81.5% vs. 18.5%, P < 0.01) and had higher admission serum creatinine (551.1 umol/L vs. 190 umol/L, P < 0.01). Of those that died, the HIV positive patients were younger (41 years vs. 52 years, P < 0.01), were predominantly Black (87.5% vs. 23.5%, P < 0.01) and were predominantly admitted to medical wards (92.5% vs. 41.2%, P < 0.01). There was no difference in mortality regardless of renal replacement therapy (P = 0.50). Logistic regression identified Mixed race (OR 2.47, P = 0.02), HIV (OR 2.69, P < 0.01) and surgical ward admission (OR 2.05, P = 0.03) as strong predictors for death.

Conclusions: Overall in-hospital mortality of AKI was high. HIV was associated with a greater risk of death that may be the result of late presentation of both the AKI as well as the HIV.



FR-PO039

Incidence and Outcomes of Acute-on-CKD - The French CKD-REIN Cohort Study

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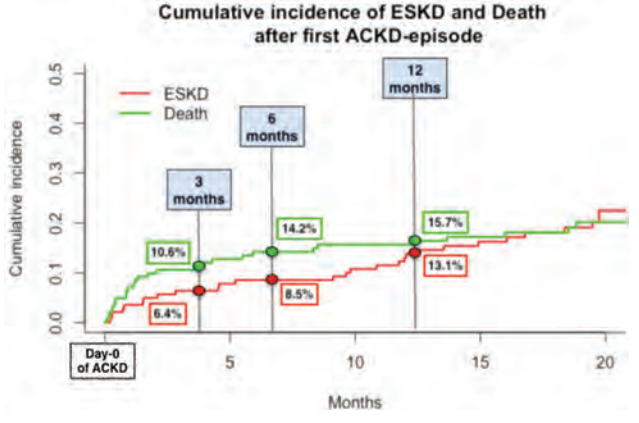
Background: Incidence and outcomes of *de novo* acute kidney injury (AKI) are well documented, but less is known about acute-on-chronic kidney disease (ACKD).

Methods: We estimated ACKD incidence rate over 1-year follow-up in 2375 patients with any type of CKD stages 3-4, but without past AKI at baseline. AKI events were defined and classified according to KDIGO 2012, and validated by an expert committee. Cause-specific Cox regression models identified factors associated with full renal recovery, defined by <10% increase in post AKI serum creatinine as compared with baseline creatinine, during the year post-AKI. We estimated cumulative incidences for the competing risks of end-stage kidney disease (ESKD) and death after ACKD. The hazard ratios [HR, 95% confidence intervals] of these outcomes associated with ACKD during the first year of follow-up were estimated by cause-specific Cox regression models, adjusted for sex, age, eGFR, and albuminuria.

Results: Overall, 142 patients (mean age 70 years, 69% men, mean eGFR 29mL/min/1.73m^2, 50% with severely increased albuminuria -A3 range-) experienced a first AKI-event (25% outpatient) at a rate of 6 per 100 person-years: 73% were staged 1, 12% staged 2, and 13% staged 3. One hundred patients (70%) achieved full renal recovery, within a mean time of 4 months after AKI. Pre-renal AKI (HR=2.54 [1.42;4.54]), dehydration (HR=1.76 [1.00;3.17]) and drug-related AKI (HR= 2.04 [1.11;3,75]) were significantly associated with full renal recovery. The cumulative incidences of ESKD and death after ACKD reached 13.1% and 15.7% at 12 months, respectively (Figure). ACKD was significantly associated with increased ESKD risk (adjusted HR=2.13 [1.32; 3.46]) and mortality (adjusted HR=2.07 [1.11; 3.83]).

Conclusions: ACKD is common and, despite a high rate of full renal recovery, it is associated with very high risks of both ESKD and death.



Post-ACKD outcomes.

FR-PO040

Renal Outcomes of Laparoscopic versus Open Surgery in Patients with Rectal Cancer: A Propensity Score Analysis

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Background: The laparoscopic approach in abdominal surgery is widely used and has many advantages over open surgery (OS). However, the renal outcomes of laparoscopic surgery (LS) are still not proven in rectal cancer. Thus, we compared the renal outcomes between LS and OS in patients with rectal cancer.

Methods: We conducted a retrospective cohort study of 1633 patients who underwent rectal cancer surgery between 2003 and 2017. Postoperative acute kidney injury (AKI) was determined according to the serum creatinine criteria of the Kidney Disease: Improving Global Outcomes classification. AKI stage 2 or 3 were classified as severe AKI and AKI recovery was defined as return of serum creatinine to < 1.2 times the baseline level.

Results: Among 1633 patients, 1072 patients (65.6%) underwent LS. The incidence of postoperative AKI in LS was significantly lower than in OS (9.3 vs. 17.3%, $p < 0.001$, respectively). After matching propensity scores (1:1), 395 patients were included in each group. LS group still demonstrated a significantly lower incidence of postoperative AKI than OS group (9.9 vs. 15.9%, $p = 0.011$, respectively). The operation time ($p < 0.001$), estimated blood loss ($p < 0.001$), incidence of transfusion ($p < 0.001$) in LS group were significantly lower than in OS group. However, there were no differences in incidence of severe AKI ($p = 1.000$), AKI recovery ($p = 0.962$) and in-hospital mortality ($p = 0.249$) between two groups. Cox proportional hazard models revealed that LS group had lower incidence of postoperative AKI than OS group (HR, 0.599; 95% CI, 0.402-0.893; $p = 0.012$). In subgroup analysis, LS had much lower incidence of postoperative AKI than OS in patients with American Society of Anesthesiologists (ASA) score ≤ 2 (HR, 0.516; 95% CI, 0.314-0.850; $p = 0.009$) and in patients who did not receive neoadjuvant chemotherapy (HR, 0.519; 95% CI, 0.295-0.912; $p = 0.023$).

Conclusions: This study showed that LS may reduce postoperative AKI in patients with rectal cancer and that its beneficial effect may be associated with operation time or intraoperative bleeding events and be dominant in patients with low ASA score and no neoadjuvant chemotherapy.

FR-PO041

Postoperative Blood Transfusion Predicts AKI in Patients with Rectal Cancer

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Background: Preoperative anemia and perioperative transfusion are associated with postoperative acute kidney injury in cardiovascular surgery, but little is known about their relationship in patients with rectal cancer surgery. Thus, we investigated whether postoperative blood transfusion may predict postoperative acute kidney injury in patients with rectal cancer.

Methods: We collected 1328 patients who underwent rectal cancer surgery from a single-center prospective cohort between 2003 and 2017. Postoperative acute kidney injury (AKI) was determined according to the serum creatinine criteria of the Kidney Disease: Improving Global Outcomes classification.

Results: Among 1328 patients, 134 patients (10.1%) received blood transfusions and 1194 patients (89.9%) did not receive. American Society of Anesthesiologists (ASA) score ($p < 0.001$), preoperative hemoglobin ($p < 0.001$), albumin, operation time ($p < 0.001$), amount of intraoperative bleeding ($p < 0.001$) showed differences in the two groups. Overall AKI incidence was 12.6% and severe AKI incidence was 1.2%. The incidence of postoperative AKI in the transfused group was significantly higher than in no blood transfusions group (10.2% vs 2.3%, $p < 0.001$, respectively) and similar result was observed in severe AKI (1.1% vs 0.4%, p=0.007, respectively). Cox proportional hazard models revealed that the AKI incidence was different according to preoperative hemoglobin concentration (HR, 0.894; 95% 0.827-0.968; p=0.05) and transfusions (HR, 2.692; 95% 1.822-3.976; $p < 0.001$). But, there was no difference in perioperative changes in hemoglobin. Two of category of preoperative hemoglobin concentrations (>12 and 10.1-12.0) were associated with a risk of postoperative AKI, whether patients was received transfusions or not (OR, 3.676; 95% 1.703-7.933; p=0.01 and OR, 2.589; 95% 1.209-5.545; p=0.014, respectively).

Conclusions: This study showed that postoperative blood transfusions may increase postoperative AKI in patients with rectal cancer. It is also possible that close monitoring of blood transfusions after surgery may improve AKI outcomes in patients with rectal cancer.

FR-PO042

Association of Dietary Intakes with the Incidence of AKI During Chemoirradiation Using High-Dose Cisplatin in Patients with Head and Neck Cancer

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Background: Cisplatin (CDDP)-based chemotherapy and radiotherapy can impact on nutrition intake because of reduction of eating ability. However, it remains to be fully clarified whether changes of nutritional status is associated with the development of CDDP-induced acute kidney injury (AKI). So, we aimed this study to clarify the nutritional impact on incident AKI in head and neck cancer patients with chemoradiotherapy.

Methods: We assessed nutritional parameters and dietary intakes just before and during the chemoradiotherapy including 66-70 Gy with CDDP 80 mg/m^2 on Days 1, 22 and 43 in 84 head and neck cancer patients (age: 61±10 years old, male/female=72/12). Nutritional intervention was conducted to reach the recommended intake of energy (30 kcal/kg/day) and protein (1.0-1.2 g/kg/day), considering with enteral, parenteral nutrition and oral intake. Adjustments were made during treatment, aiming to maintain stable or improving nutritional indicators.

Results: Thirty-three episodes of AKI developed in 30 patients (35.7%) during the 3 courses of CDDP administration (stage 1, N=28; stage 2; N=2, stage 3; n=3). Serum creatinine increased at the end of chemo-radiotherapy to a greater extent in AKI (0.79±0.19 to 1.16±0.38 mg/dL) than in non-AKI patients (0.73±0.18 to 0.87±0.51 mg/dL). No difference was found in basal energy (1,345±538 vs. 1,356±537 kcal/day) and protein intakes (53±21 vs. 53±22 g/day) between AKI and non-AKI patients. CDDP-based chemoradiotherapy decreased body weight (BW) by -5.6±6.4% during the therapy. A significantly greater decrease of BW was observed in AKI than in non-AKI patients (-7.5±5.9 vs. -4.6±6.4%, p<0.05). There was also a significantly lower intake of energy (909±392 vs. 1,166±421 kcal/day, p<0.05) and protein (37±0.7 vs. 46±17 g/day, p<0.05). A stepwise regression analysis revealed that energy and protein intakes and % decrease of BW at the end of treatment were significantly associated with the incident AKI (p<0.05).

Conclusions: The findings suggest that poor dietary intake during the platinum-based chemoradiation was associated with acute kidney toxicity. A more aggressive dietary support may be required to mitigate the onset of CDDP-induced AKI in patients with head and neck cancer.

FR-PO043

Effects of Obesity on Mortality in Critically Ill Patients with AKI

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Background: The prevalence of obesity is rising in the critically ill population, but little data exists on outcomes in critically ill obese patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT). In this study, we assessed the impact of obesity on rates of mortality in patients with AKI initiated on RRT.

Methods: We conducted a secondary analysis of the Acute Renal Failure Trial Network (ATN) database, which compared less-intensive to more-intensive RRT dosing strategies in critically ill patients. Weights >128.5 kg, exceeding the max dose capabilities of the Prisma machine at the time, were excluded. Modalities used were CVVHDF and HD, often with cross-over during the admission. In the overweight patients who received CVVHDF, 88% received a dose reduction. The overweight group was defined as 'actual weight 30% greater than ideal body weight'. We categorized patients into an overweight group and a standard weight group (all other patients). A subgroup analysis looked separately at those who received CVVHDF at some point during the admission (CVVHDF group) and those who received no CVVHDF (HD only group). Our primary outcome was 60-day mortality. We used logistic regression to adjust for demographics, SOFA score and Charlson score.

Results: In the combined CVVHDF and HD cohort, the 60-day mortality rate was 45% (n=235, mean BMI 35.1) in the overweight group and 55% (n=633, mean BMI 25.7) in the standard weight group. Compared to the standard weight group, the overweight group had a 45% improved odds of survival, which persisted after illness severity adjustments (OR 0.55 [95% CI, 0.32-0.90]; p=0.016). Among patients receiving HD only, the overweight group had improved odds of survival (OR 0.42 [95% CI 0.21-0.84]; p=0.015). In contrast, there was no survival benefit in the overweight patients receiving CVVHDF (OR 0.83 [95% CI 0.52-1.21]; p=0.3).

Conclusions: Overweight patients with AKI had improved survival compared to the standard weight group. However, the survival benefit was only observed in overweight patients who received HD only, not CVVHDF. This benefit seems to parallel the protective effect of obesity seen in outpatient HD populations. Loss of benefit in the CVVHDF group is likely multifactorial. More outcomes studies in overweight and obese patients with AKI in the ICU are needed.

FR-PO044

Cannabis Use and Its Association with Incidence of AKI in Advanced CKD Patients Transitioning to ESRD

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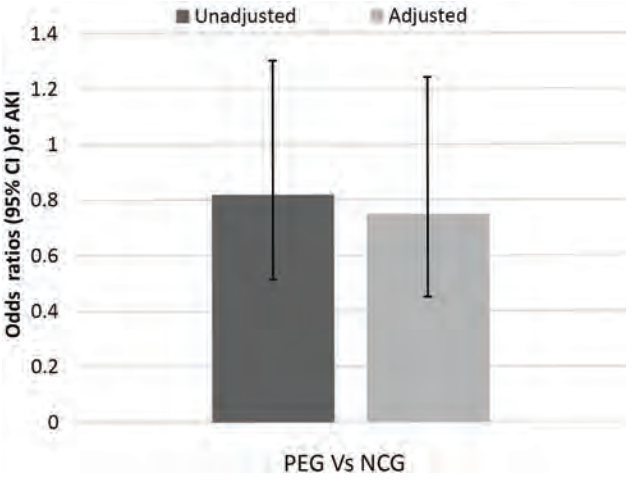
Background: Cannabinoid receptors are expressed in the kidneys and their stimulation may have both harmful and beneficial effects. Synthetic cannabinoid use is associated with acute kidney injury (AKI) in case reports, but the effects of cannabis use on the incidence of AKI in patients with advanced CKD is unknown.

Methods: We examined 2,416 US veterans who transitioned to dialysis during 2007-2014 and had undergone urine toxicology tests up to one year prior to dialysis, and had serial serum creatinine levels measured within 7 days after the test. We compared patients whose toxicology tests were positive for cannabis alone (primary exposure group, PEG, N=76) with those whose tests were negative (negative control group, NCG, N=1,138). AKI was defined according to KDIGO creatinine–based criteria. We examined the association of cannabis use with AKI using logistic regression adjusted for sociodemographics, comorbidities, medications, and vital signs.

Results: The mean (SD) age of the cohort was 60.6 (9.3) years; 97% were male, 46.7 % were African American and 76.4% were diabetic. AKI occurred in 58.6% of the cohort. Cannabis use was not associated with the odds of AKI in crude or in multivariable adjusted models (multivariable adjusted odds ratios (and 95%CI) in PEG vs. NCG: 0.75 (0.45-1.24); Figure 1).

Conclusions: Cannabis use in advanced CKD patients is not associated with the incidence of AKI.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO045

Role of Sweat and Core Body Temperature in AKI During Marathon

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Background: The strenuous physical activity of marathons is associated with AKI in runners. Given the increasing participation in marathons, it is important to understand the etiology behind runners' AKI to allow for future preventative measures. We hypothesized that sodium loss from sweat along with a rise in core body temperature during the race will be associated with AKI *via* thermoregulatory vasodilation and shunting of blood away from kidneys to muscles and skin. To test this hypothesis we conducted a prospective study of 22 runners participating in the 2017 Hartford Marathon.

Methods: Vital signs, blood and urine samples were collected 24 hours pre-marathon, and immediately post-marathon. We measured conventional and novel biomarkers. We also measured continuous core body temperature using Zephyr® technology and sweat volume and sodium using PharmChek® patches during the race. We performed linear regression analyses to determine the association between sweat sodium and core body temperature with kidney injury.

Results: Runners ranged from 22 to 63 years of age, had 2 to 25 years of running experience and 52% were males. Runners lost an estimated median range of 2.34 (0.50 to 7.21) grams of sodium, 2.47 (0.36 to 6.81) liters of volume *via* sweat and had temperatures of 101.12 (96.44 to 105.8)°F during race. The change in weight ranged from 1.81 (0.18 to 5.08) kg. 56% developed AKI based on creatinine definition and 83% had a positive urine microscopy for acute tubular injury. Runners with AKI and higher sweat sodium had higher increases in several injury, inflammatory and repair biomarkers (Figure). Sweat sodium and temperature were not associated with change in creatinine or urine microscopy during the race.

Conclusions: Runners have substantial rise in core body temperature and extensive weight loss mainly via sweat sodium and volume losses. The mechanisms associated with thermoregulatory vasodilation and associated reduced blood flow to the kidney may provide insights into the pathophysiology of runners' AKI.

Funding: NIDDK Support

Fold change in biomarkers form pre-race to immediately post-race stratified by AKI status and sweat sodium levels

Biomarkers	No AKI (n=10)	AKI (n=12)	P	Sweat Sodium <2.34 g (n=11)	Sweat Sodium ≥2.34g (n=11)	P
Fold change in plasma biomarkers from pre to post race Median (IQR)						
IL-10	.32 (7.7, 71.3)	53.8 (20.8, 88.2)	0.28	56.0 (8.8, 119.9)	34.5 (14.2, 84.6)	0.65
IL-13	1.2 (1.0, 1.4)	1.4 (1.0, 3.7)	0.36	1.0 (0.8, 1.4)	1.7 (1.3, 3.7)	0.02
IL-1β	1.1 (1.1, 1.2)	1.3 (1.3, 2.0)	0.01	1.2 (1.1, 1.4)	1.3 (1.1, 1.5)	0.39
IL-8	3.7 (2.5, 4.9)	5.9 (4.1, 6.9)	0.08	4.4 (2.4, 5.7)	4.8 (4.0, 6.8)	0.24
KIM-1	0.8 (0.8, 1.4)	1.3 (0.9, 1.4)	0.09	0.9 (0.8, 1.4)	1.3 (0.9, 1.4)	0.24
NGAL	1.8 (1.4, 2.0)	2.5 (2.0, 2.9)	0.01	1.9 (1.2, 2.5)	2.1 (1.9, 4.0)	0.08
IFN	0.9 (0.8, 1.2)	0.7 (0.7, 1.0)	0.34	0.8 (0.7, 1.2)	0.7 (0.84, 1.1)	0.43
TNF	1.3 (1.1, 1.5)	1.8 (1.4, 2.4)	0.06	1.5 (1.1, 1.9)	1.6 (1.24, 2.2)	0.43
YKL-40	1.4 (1.1, 1.5)	1.6 (1.3, 2.0)	0.11	1.4 (1.1, 1.5)	1.7 (1.3, 2.4)	0.02
Fold change in urine biomarkers from pre to post race Median (IQR)						
NGAL	3.1 (1.6, 11.1)	13.0 (5.5, 48.4)	0.03	5.6 (1.6, 11.8)	13.0 (1.9, 53.5)	0.26
MCP-1	10.6 (3.2, 17.4)	60.8 (6.2, 188.7)	0.08	10.5 (3.1, 75.3)	60.8 (10.7, 250.5)	0.05
YKL-40	8.8 (3.5, 9.8)	8.2 (4.0, 32.7)	0.45	6.8 (3.4, 11.0)	8.2 (4.0, 48.5)	0.43

FR-PO046

Phenotypes of Volume Status in AKI Patients and Their Association with Intradialytic Hypotension

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Background: Intradialytic hypotension (IDH) is a common complication during intermittent dialysis (IHD) in hospitalized patients. It is associated delay in organ failure and renal recovery, and a common reason for modality change and continuous renal replacement therapy (CRRT) initiation.. Knowledge of patient volume status could help tailor the ultrafiltration rate and prevent episodes of IDH This study aim to evaluate the association of volume status based on sonographic profiles before IHD and occurrence and severity of IDH. Intradialytic hypotension (IDH) is a common complication during intermittent dialysis (IHD) in hospitalized patients. It is associated delay in organ failure and renal recovery, and a common reason for modality change and continuous renal replacement therapy (CRRT) initiation.. Knowledge of patient volume status could help tailor the ultrafiltration rate and prevent episodes of IDH This study aim to evaluate the association of volume status based on sonographic profiles before IHD and occurrence and severity of IDH.

Methods: We conducted a prospective observational study including all consecutive AKI patients requiring IHD in the intensive care unit. Bedside sonography to evaluate inferior Vena Cava Colapsability (cIVC) measurement and B lines were assessed by two different trained attending physicians. Volume status profile was classified into 4 groups: (1) B Lines (+) cIVC (-); (2) B lines (+), cIVC (+); (3) B lines (-) cIVC (-); (4) B lines (-) / iICV (+)

Results: Of 248 patients 42% were classified as G1; 22% G2, 20% of group (3) and 16% of group (4). (55%) had at least one episode of hypotension during therapy, with different frequency among the groups ($p < 0.001$). Hypotension was more frequent in group (4) (85%), $p < 0.001$ versus others, and less frequent in group (1) (22%, $p < 0.001$ versus others). In the multivariate adjusted analysis, the risk of IDH remained different among the groups ($p< 0.001$) and group (4) exhibited the highest hazard ratio (HR = 6.58. 95% CI 3.22- 8.24).

Conclusions: Bedside sonography assessing B lines determination and cIVC can be used to define volume status profile in critically ill patients and risk of hypotension during IHD. Further studies are needed to design adequate targeted treatments

FR-PO047

Hyperchloremia Is Associated with AKI in Pediatric Patients with Septic Shock

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Background: Hyperchloremia is associated with increased mortality in pediatric septic shock patients, and associated with increased rate of acute kidney injury (AKI) in adults. It is unknown whether hyperchloremia is associated with AKI in pediatric patients.

Methods: We tested the hypothesis that hyperchloremia is associated with increased rates of severe AKI in pediatric patients with septic shock. We performed a retrospective analysis of a pediatric septic shock database that included 619 children with septic shock from 29 PICUs in the U.S. We considered the minimum, maximum, and mean chloride values as separate hyperchloremia variables within the first 7 days of PICU admission. We considered hyperchloremia as a dichotomized variable defined *a priori* as a serum concentration ≥110mmol/L. We used multivariable logistic regression to determine the association between these hyperchloremia variables and outcomes, after adjusting for illness severity and age. Our primary outcome variable was day 3 AKI, defined as KDIGO stage 2 or 3.

Results: There were 125 subjects with AKI and 494 subjects with no AKI. Subjects with AKI were younger (1.7 years; IQR 0.7-5.4 v. 3.5 years; IQR 1.3-7.1; $p <0.001$) and had higher PRISM-III scores (15; IQR 9-24 v. 11; IQR 7-16; $p <0.001$). There were 42 subjects with a minimum chloride ≥110mmol/L, 117 subjects with a mean chloride ≥110mmol/L, and 359 subjects with a maximum chloride ≥110mmol/L. A minimum chloride ≥110mmol/L was associated with increased odds of AKI (odds ratio, 2.4; 95% CI, 1.2-4.9; $p = 0.014$). A mean chloride ≥110mmol/L was associated with increased odds of AKI (odds ratio, 1.8; 95% CI, 1.1-2.9; $p = 0.014$).

Conclusions: Hyperchloremia is independently associated with severe AKI in pediatric patients with septic shock. Further evaluation of the optimal fluid to be used in resuscitation of these patients is warranted.

Funding: Other NIH Support - National Institutes of Health Grants R35GM126943 and R01GM108025

Variable	Odds Ratio	95% CI	p value
Minimum Cl ≥110	2.4	1.2-4.9	0.014
PRISM	1.1	1.0-1.1	<.001
Age	0.9	0.9-1.0	0.009
Mean Cl ≥110	1.8	1.1-2.9	0.014
PRISM	1.1	1.0-1.1	<.001
Age	0.9	0.9-1.0	0.012

FR-PO048

Chloride Abnormalities Are Independently Associated with Mortality in Critically Ill Children

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Background: Chloride disturbances in critically ill adults are associated with mortality. The impact of chloride disturbances on outcomes in critically ill children is unknown. The purpose of this study was to determine if there is an association between mortality and 1) admission chloride levels and 2) changes in the chloride level following initial resuscitation in critically ill children.

Methods: We retrospectively studied all PICU patients (01/2014 – 12/2015) at Children's Hospital Colorado, excluding those 1) aged < 90 days or > 25 years, 2) without admission laboratory tests, 3) end stage renal disease, 4) a disorder of chloride transport and 5) admitted for diabetic ketoacidosis. Patients were stratified based on admission chloride levels (hypochloremia, <100 mEq/L; normochloremia, 100-109 mEq/L and hyperchloremia ≥110 mEq/L). Additionally, they were dichotomized based on the change in chloride (ΔCl) in the first 24 hours (< 5 mEq/L, ≥ 5 mEq/L). Multivariate logistic regression and analysis of covariance were performed to determine the impact of chloride derangements on mortality and length of stay respectively.

Results: 2022 patients were included; overall mortality was 4% (n = 77) and day 2 AKI occurred in 18% (n = 318). Hypochloremia, hyperchloremia, and ΔCl ≥ 5 mEq/L occurred in 7%, 21%, and 12% respectively. Hypochloremia and ΔCl ≥ 5 mEq/L were independently associated with a 4.57 (95% CI: 1.65 - 12.66) and a 3.17 (95% CI: 1.61 - 6.26) greater odds of mortality respectively, after adjusting for confounders. In ANACOVA models, hypochloremia and hyperchloremia were associated with an estimated increase in the expected length of hospital stay of 1.2 days (95% CI: 1.0 - 1.5; p=0.03), and 1.2 days (95% CI: 1.0 - 1.4 p=0.02) respectively. ΔCl ≥ 5 mEq/L was associated with an estimated increase in the expected time on mechanical ventilation of 1.3 days (95% CI: 1.0 - 1.4; $p = 0.02$).

Conclusions: Hypochloremia and ΔCl ≥ 5 mEq/L in the first 24 hours of admission are common and independent risk factors for mortality in critically ill children after adjusting for confounders. Further studies are needed to address the mechanism by which chloride disturbances increase mortality in critically ill children.

FR-PO049

Subclinical AKI Is Associated with Adverse Outcomes in Critically Ill Neonates and Children

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Background: Acute kidney injury (AKI) is associated with adverse outcomes. Research in AKI has focused on identifying early biomarkers capable of detecting kidney injury before the rise in serum creatinine. However, whether AKI could be diagnosed in the absence of the classic signs of clinical AKI, and whether the condition of subclinical AKI, identified by using structural or functional biomarkers in the absence of oliguria or increased serum creatinine levels, is clinical significant, remained to be elucidated in critically ill children. The aims of the study were to investigate the association of urinary cystatin C (uCysC) level and mortality, and determine whether uCysC-positive subclinical AKI was associated with adverse outcomes in critically ill neonates and children.

Methods: In this prospective cohort study, uCysC levels were serially measured during the first week after intensive care unit (ICU) admission in a heterogeneous group of patients (n=510) presenting to a tertiary neonatal (n=239) and pediatric (n=271) ICU. The term of "uCysC(–)" or "uCysC(+)", indicating the absence or presence of tubular injury, was defined by the optimal cut-off value of the peak uCysC to predict ICU mortality.

Results: The initial and peak uCysC levels had odds ratios of 1.19 and 1.26 (per 10,000 ng/mg uCr increase), and achieved the area under-the-receiver-operating-characteristic curve of 0.76 and 0.81, respectively, for predicting ICU mortality. At the optimal cut-off value of 1,260 ng/mg uCr, the peak uCysC displayed sensitivity of 79.2% and specificity of 72.3% for predicting mortality. Among all patients, 130 (25.5%) developed uCysC(+)/AKI(–) status during the first week after admission. The adjusted odds ratio for patients with uCysC(+)/AKI(–) status being associated with an increased risk of mortality was 9.34 ($P<0.001$), compared to those with uCysC(–)/AKI(–). Patients with uCysC(+)/AKI(–) spent 2.8 times as long in ICU compared to those with uCysC(–)/AKI(–).

Conclusions: Both initial and peak uCysC levels are independently predictive of mortality in critically ill neonates and children. Subclinical AKI may occur without

detectable loss of kidney function, and uCysC-positive subclinical AKI was associated with worse clinical outcomes in this population.

FR-PO050

The Relationship Between Statin Use and 1-Year Mortality After Severe AKI

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Background: The potential survival benefits of statin use in patients with dialysis-requiring acute kidney injury (AKI) are still not known. We examined the association between statin use and 1-year mortality in patients with dialysis-requiring AKI.

Methods: This nationwide population-based retrospective cohort study included 6091 hospitalized patients with dialysis-requiring AKI (1271 statin users and 4820 statin non-users) retrieved from the National Health Insurance Research Database of Taiwan between January 1, 2000, and December 31, 2012. All patients were followed up until December 31, 2013. Primary outcome was 1-year mortality after dialysis-requiring AKI. All primary analyses were performed using the intention-to-treat approach.

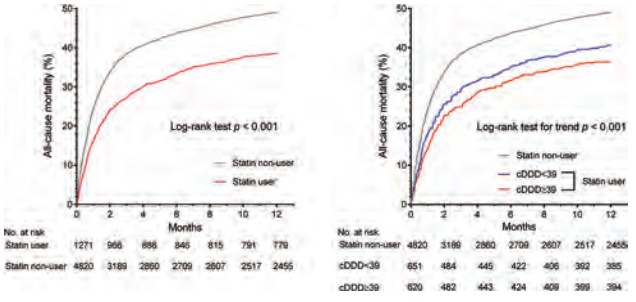
Results: During the 1-year follow-up period, 492 of 1271 (38.7%) statin users and 2365 of 4820 (49.1%) statin non-users died after dialysis-requiring AKI. Statin use was independently associated with lower risks of 1-year all-cause mortality (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.73-0.91; p<0.001) and in-hospital all-cause mortality (HR, 0.82; 95% CI, 0.72-0.94; p=0.004). The survival benefit of statin treatment was dose-dependent and consistent across subgroups based on sensitivity analyses.

Conclusions: Statin use was independently associated with reduced risks of 1-year and in-hospital mortality in patients with dialysis-requiring AKI. However, further clinical trials are warranted to confirm our results.

Incidence and risk of 1-year mortality in patients with dialysis-requiring AKI

Cohorts	Events (n/N)	Incident rate	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Statin non-users	2365/4820	68.7 (65.9–71.5)	1 (Reference)		1 (Reference)	
Statin users	492/1271	46.6 (42.4–50.7)	0.71 (0.65–0.79)	<.001	0.81 (0.73–0.91)	<.001
Stratified by cDDD						
cDDD <39	266/651	50.3 (44.3–56.4)	0.77 (0.67–0.87)	<.001	0.87 (0.76–0.99)	0.04
cDDD >=39	226/620	42.8 (37.2–48.3)	0.66 (0.58–0.76)	<.001	0.75 (0.65–0.87)	<.001
P for trend				<.001		<.001

Incident rate: 1000 person-years



Kaplan-Meier curves for the cumulative incidences of all-cause mortality in statin users and non-users. cDDD = cumulative defined daily dose.

FR-PO051

The Association of Fenofibrate with Kidney Tubular Injury in a Subgroup of Participants in the ACCORD Trial

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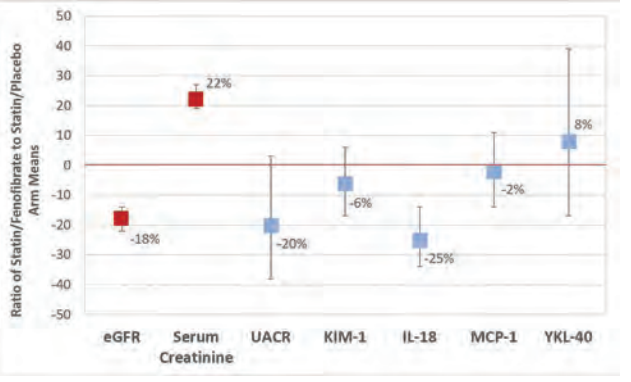
Background: In ACCORD, 48% of those randomized to fenofibrate demonstrated a ≥20% increase in the concentration of serum creatinine within 4 months, a finding consistent with other trials. The effect of fibrates on markers of kidney tubular injury is unknown.

Methods: We obtained stored urine samples from a subgroup of 571 ACCORD participants randomized to either placebo (n= 329) or fenofibrate (n=242) where all patients also received statins. Our outcome was 2-year changes in the concentration of two urine biomarkers of injury: kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and 2 urine biomarkers of repair: YKL-40 and monocyte chemoattractant protein (MCP-1), along with the changes in eGFR and urine albumin to creatinine ratios (UACR) measured from random samples. We adjusted for clinical variables and randomization arm and compared the changes in the markers via analysis of covariance (ANCOVA).

Results: Baseline clinical characteristics and measures of eGFR (88 ml/min/1.73m^2), UACR (12 mcg/mg), and all 4 biomarkers were similar in the 2 groups. At 24 months, eGFR was 14.2 ml/min/1.73m^2 lower with fenofibrate vs. placebo and serum creatinine was 0.18 mg/dl higher. In contrast, UACR and all 4 urine biomarkers of kidney injury or repair were similar or decreased from baseline in fenofibrate vs. placebo (**Figure**). In a stratified analysis, even participants with the highest quintile 24-month decrements in eGFR with fenofibrate (-30.4 to -73.5 ml/min/1.73 m^2) still had lower or unchanged UACR and urine biomarkers.

Conclusions: These findings indicate the increase in the concentration serum creatinine with fibrates is not due to intrinsic damage to kidney tubule cells.

Funding: NIDDK Support



24-month change in eGFR, Serum Creatinine, UACR and Urinary Kidney Injury and Repair Biomarkers in ACCORD Participants Randomized to Fibrates vs. Placebo

FR-PO052

The LncRNA Profile in Control and Ischemically Injured Kidneys of Old Mice

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Background: The expression profile of lncRNA is hardly known in the control and injured kidneys of old mice. We investigated the influence of aging on the lncRNA profile after renal ischemia-reperfusion (IR) injury in mice.

Methods: The left renal pedicle of adult (9.4±0.3 months, n=7) and old (28.5±1.2 months, n=8) C57BL/6N mice was clamped for 20 min. The right kidney was left intact. Plasma urea and urine NGAL (uNGAL) were measured prior to and 7 days after reperfusion. On day 7 tubular injury was evaluated by histology (PAS, HE) and KIM1 mRNA (qPCR) expression. The extent of fibrosis (FN1) and senescence (p21) was analyzed with qPCR. Long non-coding RNA profile (90 lnc) was examined with qPCR array.

Results: Older mice had higher baseline uNGAL (old: 285.7±93.8 ng/mg Crea vs. adult: 78.0±9.1 ng/mg Crea, p<0.05) and milder kidney injury (p<0.05). KIM1 (8.3x; p<0.001), FN1 (2x; p=0.05) and p21 (3.8x; p<0.05) mRNA levels were higher in their non-ischemic kidneys relative to the adult group. There was no significant difference in baseline plasma urea levels between the two groups (old: 75.9±10.2 mg/dl vs. adult: 57.6±5.3 mg/dl). Following IR tubular injury increased in both groups (p<0.05) with KIM1 (adult: 202x, old: 19.5x, p<0.0001) and FN1 (adult: 8.5x, old: 3x, p< 0.001) mRNA compared to the contralateral control kidneys. uNGAL level was higher after IR compared to the baseline (old: 3817±1975 ng/mg Crea, p<0.0001; adult: 2833±1201 ng/mg Crea, p<0.001). p21 mRNA increased only in the ischemic kidneys (4.5x, p<0.01), compared to the contralateral control. The plasma urea concentration increased only in the old group following 7 days of reperfusion (140.7±25.6 mg/dl, p<0.01). From the 81 measureable lncRNAs 8 increased and 1 decreased only by IR. Old age only influenced 1 lncRNA expression. Further 12 lncRNA expression was influenced by both IR and old age.

Conclusions: Our results demonstrated significant tubular damage and decreased renal function in the kidneys of old mice, in accordance with the literature. We have also found that several lncRNAs were differentially expressed in old and adult mice in both the control and ischemic kidneys. New National Excellence Program (Human Resources Department)

Funding: Government Support - Non-U.S.

FR-PO053

miR-146a Targeted to Splenic Macrophages Prevents Sepsis-Induced Multiple Organ Injury Including AKI

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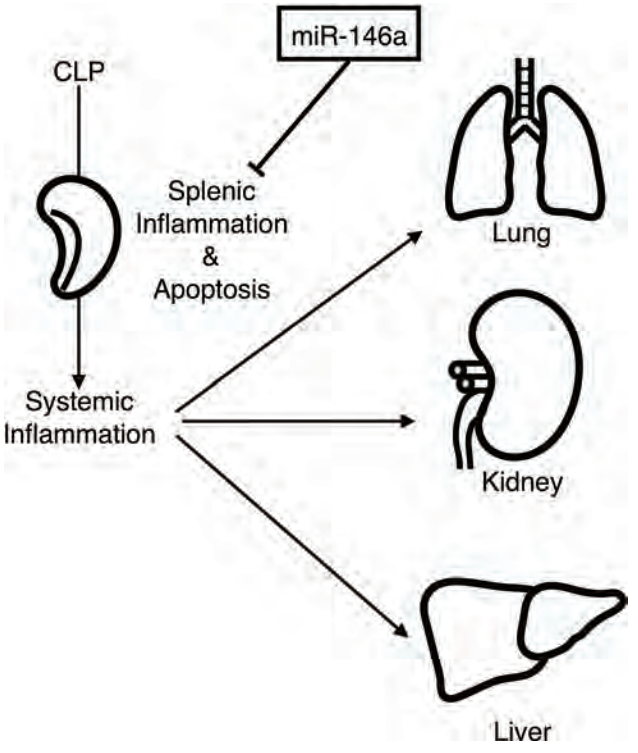
Background: To date, additional pathophysiology and new drug concept need to be provided in patients with multiple organ injury due to sepsis. microRNAs (miRNAs) have garnered attention as potent oligonucleotide therapeutics. The aim of the present study is to investigate the pathophysiological role of exogenous miR-146a in sepsis-induced acute kidney injury (AKI).

Methods: *In vitro* study, RAW264.7 cells were transfected with miR-16, miR-126, miR-146a, miR-200b, or a negative control, then treated with 1 mg/ml lipopolysaccharide (LPS) for 6 hours. *In vivo* study, young C57BL/6 mice were intravenously injected a mixture of miR-146a-expressing plasmid and polyethyleneimine (PEI). 7 days after transfection, sepsis was induced via cecal ligation and puncture (CLP).

Results: Among tested miRNA, miR-146a showed the best suppressive efficacy, whereby transcriptional activity of NF-κB was decreased by targeting IRAK-1 and TRAF6 in RAW264.7 cells. Treatment with the miR-146a-expressing plasmid/PEI complex significantly decreased the level of serum inflammatory cytokines, attenuated organ injury including kidney injury, and led to increased survival in CLP-induced polymicrobial sepsis. miR-146a-expressing plasmid was abundantly distributed in splenic macrophages, but not in kidney cells. The miR-146a-treated CLP mice also showed a significant decrease in NF-κB activation and apoptosis in splenocytes. Splenectomy diminished the anti-inflammatory effects of miR-146a.

Conclusions: The induction of miR-146a in splenic macrophages prevents excessive inflammation and sepsis-induced multiple organ injury, including AKI. This study provides a pathophysiological breakthrough in the relationship between splenic macrophages and sepsis-induced AKI.



FR-PO054

MicroRNA-219c Dependent Mincle Is Critical for Maintaining Proinflammatory Phenotype of Macrophage in Renal Inflammation

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Background: Macrophages are a key inflammatory cell that plays a critical role in renal inflammation and fibrosis. Our previous study demonstrated that the pattern recognition receptor, Mincle is essential for maintaining inflammatory phenotypes of M1 macrophages in acute renal inflammation. However, the mechanism through which Mincle expression was regulated and its relation with different macrophage phenotypes remains largely unknown.

Methods: Unilateral urethral obstruction model of renal injury was established at day 1, 3, 7 to observe the dynamic change of Mincle expression and its relation with macrophage phenotype. For *in vitro* study, LPS and IL4 was used to induce M1, M2 polarization to explore Mincle expression in the process of phenotype switching. The regulatory effects of microRNA-219c in Mincle expression and kidney inflammation were also determined.

Results: During progression of renal inflammation in UUO model, Mincle^{+} macrophage significantly increased at day 1 while it decreased rapidly with theincreasing M2 macrophage infiltration. During macrophage phenotype switch, Mincle mRNA and protein was enhanced in LPS-primed M1 macrophage, while its expression decreased in M2 macrophage. Interestingly, Mincle overexpression induced proinflammatory phenotype polarization and also reversed the phenotype switching to M2 macrophage from either M0 or M1 macrophages. Bioinformatic analysis showed that Mincle was a potential target of microRNA-219c. Interestingly, microRNA-219c was reduced in injured kidney of UUO model when Minlce was upregulated at day1. Mincle protein was reduced in RAW264.7 with microRNA-219c mimic treatment. And the luciferase reporter gene assay confirmed that microRNA-219c was a novel regulator of Mincle expression. To explore the effect of microRNA-219c in renal inflammation, microRNA-219c was overexpressed in mice via lentivirus injection. Impressively, Mincle and inflammatory cytokines CCL2, IL6 mRNA was remarkably reduced in UUO kidney compared to empty vector group.

Conclusions: MicroRNA-219c was a novel regulator of Mincle which is critical for maintaining proinflammatory macrophage phenotype and contribute to renal inflammation. Targeting microRNA-219c-Mincle may represent as a novel therapy for macrophage-dependent kidney injury.

Funding: Government Support - Non-U.S.

FR-PO055

MicroRNA-132 Mediates Tubular Cell Sensitivity and Increases Kidney Injury in Mice

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Background: MicroRNAs regulate multiple signaling pathways that can affect disease progression. We previously reported that miR-132 was upregulated in kidney tubular epithelial cells following injury with nephrotoxic chemicals and was positively correlated with kidney injury in mice and humans.

Methods: MiR-132 knockout (KO) mice and wild-type (WT) littermate controls were subjected to folic acid (FA) nephropathy (250 mg/kg, ip). Kidney structure and function was assessed by widely established methods. Cyclic immunofluorescence was conducted to evaluate 21 proteins representing inflammation, proliferation and DNA damage on the same fixed kidney tissue. For mechanistic investigations, tandem mass tag proteomics was conducted and targeted pathways were probed using Human Proximal Tubular Epithelial Cells (HPTECs) transfected with miR-132 mimics or inhibitors.

Results: In miR-132 KO mice, FA injections resulted in 37% less tubular injury and 64% lower levels of blood urea nitrogen after 2 days compared to WT mice ($p<0.05$). At day 2, tubular cell proliferation, DNA damage and inflammation were also decreased in miR-132 KO mice relative to WT. Interestingly, miR-132 KO and WT mice had similar kidney damage at day 1, demonstrating that miR-132 KO mice recovered more quickly despite less tubular cell proliferation. On the other hand, proteomics revealed that miR-132 overexpression in HPTECs upregulated proteins involved in promoting cell cycle progression. Out of the 9 proteins predicted to be miR-132 targets, RASA1 (inhibitor of Ras) and SOD2 (detoxifier of mitochondrial reactive oxygen species) were confirmed. In HPTECs, overexpression of miR-132 increased cell count by 69% while miR-132 inhibition decreased cell count by 33% ($p<0.05$). Testing the functional importance of these data in an injury setting, when HPTECs overexpressing miR-132 were treated with cisplatin there was ~2.5-fold increase in cell death ($p<0.05$).

Conclusions: Upregulation of miR-132 following kidney injury increases the sensitivity of the kidney to further damage. Therefore, inhibition of miR-132 may offer a therapeutic benefit for acute kidney injury and limit the extent of kidney damage.

Funding: Other NIH Support - Outstanding New Environmental Sciences 524 (ONES) award from NIH/NIEHS (ES017543)

FR-PO056

Effect of NLRP3 on Rhabdomyolysis-Induced AKI Model

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Background: Recent studies suggested NOD-like receptor, pyrin domain containing-3 (NLRP3) inflammasome contribute renal injury in rhabdomyolysis. However, a role of the inflammasome-independent tubular epithelial NLRP3 in rhabdomyolysis-induced acute kidney injury (RAKI) has not clarified yet. We investigated the role of both inflammasome-independent tubular NLRP3 and inflammasome-dependent NLRP3 in RAKI and evaluated the possibility of NLRP3 as the treatment target of RAKI.

Methods: HK-2 cells and THP-1 cells were treated with myoglobin to mimic the rhabdomyolysis environment in vitro. A glycerol-induced rhabdomyolysis animal model was used to generate RAKI model in NLRP3 knock-out (KO) and wild-type (WT) mice.

Results: Apoptosis increased by myoglobin-induced injury in HK-2 cells; however, the number of apoptotic cells significantly decreased in siNLRP3 treated HK-2 cells. The increase of inflammatory cytokines, IL-1β and IL-18, by myoglobin-induced injury in THP-1 cells attenuated by siNLRP3 treatment. The RAKI NLRP3 KO mice showed a marked decrease in serum creatine levels, renal KIM-1, and histologic renal injury scores than in RAKI WT mice. Apoptotic markers such as PARP and cleaved caspase-3 in the kidney decreased in NLRP3 KO mice compared with WT. Also, inflammatory cytokines such as IL-6, TNF-α, and IL-1β decreased in RAKI NLRP3 KO.

Conclusions: In conclusion, the deficiency of NLRP3 protected kidneys from RAKI by both inflammasome-independent and -dependent ways. The depletion of NLRP3 directly reduced the renal tubular cell apoptosis and blocked the NLRP3 inflammasome activation of the macrophage after RAKI. Our results suggest that NLRP3 could play the essential role in RAKI and be a candidate as a treatment target.

Funding: Government Support - Non-U.S.

FR-PO057

A New Mouse Model for Septic AKI with Vasopressor Support

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Background: Sepsis, a common cause of acute kidney injury (AKI), is a dysregulated host response to infection that leads to multiple organ dysfunction. Currently, there is no specific therapy for sepsis/AKI. Patients with sepsis-induced AKI are treated with supportive care including fluids and vasopressors to manage hypotension. While blood pressure maintenance in sepsis patients is routine, blood pressure measurement and management is notoriously absent in small animal models. We established a mouse model of septic-AKI with conscious hemodynamic monitoring and vasopressor treatment. We hypothesize that stabilizing blood pressure with norepinephrine (NE) will partially mitigate the severity of sepsis-AKI, perhaps changing the responsiveness to specific treatments.

Methods: In CD-1 mice (n=22), we inserted a telemetry device into the left carotid artery to monitor blood pressure, and catheterized the right jugular vein for IV drug delivery. After recovery, sepsis-AKI was induced by cecal ligation and puncture (CLP). NE was administered IV via an osmotic minipump. Hemodynamics were recorded by telemetry from 24 hr before to 24 hr post-CLP. Glomerular filtration rate (GFR) was measured by loss of transcutaneous fluorescence of IV injected FITC-sinistrin.

Results: Surgical anesthesia caused transient 1 hr hypotension and bradycardia. Despite variability, septic NE-treated mice fell into 2 groups. In the first group (n=8), the effect of NE was short. The blood pressure increased for ~4 hr then dropped to septic-shock levels (<65mmHg). In the second group (n=12), NE effect lasted longer. The blood pressure rose to normal (90-110 mmHg) and remained constant for ~20 hr. In 2 outliers, the blood pressure fluctuated over 24 hr. The heart rate was consistent in all groups; returning to normal (650-750 bpm), then decreasing 3-5 hr later. We measured GFR in mice that survived to 24 hr; 2 mice from the second group had a normal GFR of 742 and 871 uL/min/100gBW.

Conclusions: We successfully delivered intravenous NE and monitored hemodynamics in septic mice. We found substantial mouse to mouse variability in blood pressure, making it crucial to monitor individual NE responses. NE had the expected hemodynamic response in blood pressure stability in over half of the mice.

Funding: NIDDK Support

FR-PO058

A Novel Contrast-Induced AKI Mouse Model Based on Low-Osmolar Contrast Medium

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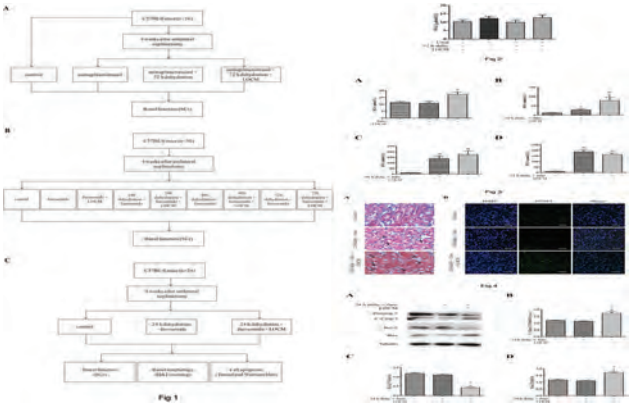
Background: The contrast-induced acute kidney injury (CI-AKI) has been becoming the third common cause of hospital-acquired acute kidney injury. An ideal animal model is essential for understanding the pathophysiology of CI-AKI. This study provides a novel, efficient and reproducible CI-AKI model which was developed in mouse by administrating a low-osmolar contrast medium (LOCM).

Methods: First, we applied the frequently-used pretreatments (uninephrectomy and water deprivation), which combined with HOCM on rats could induce CI-AKI, on mice with LOCM. Secondly,we attempted to find a novel preatment suitable for mouse and LOCM by combining two classic pretreatments(uninephrectomy, water deprivation and furosemide administration). Finally, we evaluate the kidney damage of the novel model.

Results: This mouse model possessed a significant reduction in renal function, severe renal tissue damage, and increased renal tubular cells apoptosis, indicating that LOCM is a feasible inducer for CI-AKI mice model.

Conclusions: We found that uninephrectomy(UPHT) combined with 24h water deprivation and furosemide administration 20 min before LOCM (iohexol, 10 ml/kg) application is a feasible pretreatment to establish a novel CI-AKI mouse model.

Funding: Other NIH Support - National Natural Science Foundation of China



FR-PO059

Neonatal AKI in a Juvenile Rabbit Model Results in Reduced Nephron Number Assessed by MRI

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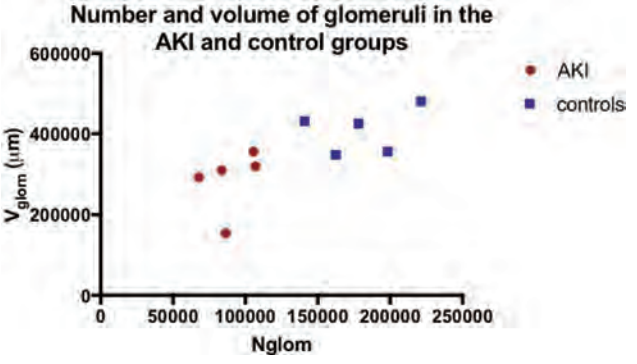
Background: Acute kidney injury (AKI) affects 30% of preterm neonates. Preterm neonates develop AKI during nephrogenesis conferring a risk for chronic kidney disease. Current monitoring practices cannot detect microstructural changes in the kidney. Our objective was to assess if the renal microstructure, number (N_{glom}) and volume (V_{glom}) of the glomeruli, is affected by AKI during nephrogenesis using cationic ferritin enhanced MRI (CFE-MRI).

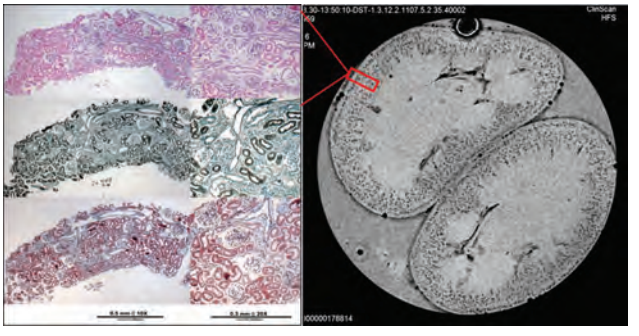
Methods: New Zealand rabbits were used as nephrogenesis occurs for 3 postnatal weeks. The AKI group received indomethacin and gentamicin at week #1 for four days. At six weeks, the AKI and control groups (5/grp) were injected with cationic ferritin, euthanized and kidneys were imaged (7T ClinScan GRE pulse sequence:TR:80/TE:20, thickness 0.17, FOV 29, 448*448 matrix, FA 25°). N_{glom} and V_{glom} were determined by threshold guiding with a watershed transformation.

Results: Body and kidney weights were significantly lower in the AKI group. The kidney/body weight and renal function measured by serum creatinine was not different between the groups. N_{glom} and V_{glom} were lower in the AKI group (N_{glom}: 86387 vs 178093, p=0.01; V_{glom}: 319044 vs. 425029 μm^3, p=0.01), Fig 1. AKI kidneys had a layer of glomeruli which were not labeled and undetectable by MRI. On histological assessment, the glomeruli in the undetectable region were shrunken, immature and lacked tubules (Fig 2).

Conclusions: Neonatal AKI from gentamicin and indomethacin causes permanent glomerular reduction without glomerular hypertrophy. Tools such as CFE-MRI that allow us to visualize and quantify renal microstructure to detect early CKD and evaluate the nephrotoxic potential of medications during nephrogenesis.

Funding: Private Foundation Support





FR-PO060

Experimental Aristolochic Acid Nephropathy: A Model to Study AKI-to-CKD Transition

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Background: Even though impaired kidney function is classified into two distinct categories, the acute (AKI) and the chronic (CKD) kidney disease, recent epidemiologic and mechanistic studies demonstrated that AKI and CKD are interconnected. Indeed, AKI is a risk factor for the development of CKD. In this regard, molecular and cellular mechanisms underlying the AKI-to-CKD transition are unclear, mainly due to a lack of appropriate experimental models. In the present study, we aim to highlight the benefit of using the experimental aristolochic acid (AA) nephropathy (AAN) model to further delineate the progression of CKD from an AKI episode.

Methods: C57BL/6J male mice were randomly subjected to daily ip injection of vehicle or AAI solution (3,5mg/kg) for 4 days. Mice were then euthanized at different time-

points to determine key biological markers of the AKI-to-CKD transition using urine and plasma assays, histological and molecular analyses.

Results: AA-treated mice developed a biphasic evolution of renal dysfunction and morphological alterations. First, an AKI phase (day 5) was demonstrated as attested by a significant increase in plasma creatinine along with PTEC necrosis as well as proteinuria. Later, during the progression of AKI to CKD, increased in oxidative stress and inflammatory cell infiltration (macrophages and lymphocytes) were characterized. Finally, chronic phase (day 20) was characterized by an extensive tubular atrophy and a massive tubulo-interstitial fibrosis as attested by Red Sirius staining and increased in pro-fibrotic gene expression.

Conclusions: AKI-to-CKD transition has clinical importance since patients surviving an episode of AKI present a significant risk of progression to CKD. However, the mechanisms by which AKI might initiate the CKD onset have not been fully defined. A better understanding of these mechanisms could lead to identify key biomarkers as well as new therapeutic strategies to prevent and treat AKI or impede progression to CKD. In this regard, animal models of AAN could represent a useful tool to provide important insights into the underlying mechanisms of AKI-to-CKD transition.

Funding: Government Support - Non-U.S.

FR-PO061

Low Nephron Endowment-Induced Compensatory Nephron Hypertrophy Causes ER Stress Making the Nephrons More Susceptible to Injury

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Background: Functioning nephrons respond to nephron deficits by increases in size and mass but not in number. Such a growth response is called compensatory nephron hypertrophy (CNH), which can occur in many situations. However, the pathogenic role of CNH in determining the susceptibility and severity of AKI and the underlying molecular mechanisms remain poorly understood.

Methods: We generated an *mVPS34* gene-floxed mouse and crossed it with a HoxB7. Cre mouse. Utilizing a long-term selective breeding strategy for a low HoxB7.Cre activity, we established a stable sub-strain of renal collecting system-specific mVPS34 knockout (*KO*) mice with a genotype of $mVPS34^{flox/flox}$;$HoxB7.Cre^{(+)}$. These *KO* mice were challenged with bilateral renal ischemia/reperfusion (I/R) insults at 8 weeks of age. Gender-matched littermates with a genotype of $mVPS34^{flox/flox}$;$HoxB7.Cre^{(-)}$ were used as controls (*Ctrl*).

Results: The *KO* mice appear healthy, with normal levels of BUN, serum creatinine, and blood pressure (measured by telemetry). Using the newly developed accurate glomerular counting method, we found that *KO* mice have a 60% congenital nephron deficit, compared to *Ctrl* littermates: 11066 ± 776.5 (*N*=8 mice) vs. 27915 ± 1293 (*N*=11 mice) nephrons/mouse, with both left and right kidneys containing similarly lower nephron numbers. The mean renal glomerular and tubular areas of *KO* mice were significantly larger, with a 38% increase in single nephron GFR, confirming congenital nephron deficit-induced CNH. A 15-minute ischemia followed by 24 hours of reperfusion caused markedly more severe ischemia-reperfusion injury (IRI) and significant increases in both serum creatinine (Scr) and BUN in *KO* mice while *Ctrl* mice exhibited minimal structural damage but had no increase in either Scr or BUN. A 30-minute I/R also caused IRI in both *KO* mice and *Ctrl* mice, with significantly more severe morphological and functional damage in KO mice than in Ctrl mice. Mechanistic studies revealed markedly higher levels of Bip and C/EBP homologous protein (CHOP) in the *KO* mice, indicating the elevation of ER stress.

Conclusions: The congenital CNH caused by mVPS34 deletion in collecting duct is more susceptible and severe to ischemic nephron injury, which is likely mediated by elevated ER stress.

Funding: NIDDK Support, Government Support - Non-U.S.

FR-PO062

Repetitive Ischemic Injuries to the Kidneys Result in Lymph Node Fibrosis and Impaired Healing

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Background: The contribution of the kidney-draining lymph node (KLN) to the pathogenesis of ischemia-reperfusion injury (IRI) of the kidney and its subsequent recovery has not been explored in depth. In addition, the mechanism by which repetitive IRI contributes to renal fibrosis remains poorly understood.

Methods: Transgenic mice were used. Ischemia Reperfusion Injury (IRI) surgeries on mice were performed using clamps. Aseptic techniques were used to culture cells. Protein and mRNA were extracted according to generally accepted techniques. Light and electron microscopy were used in addition to immunofluorescence staining.

Results: Herein, we have found that IRI of the kidney is associated with expansion of high endothelial venules (HEVs) and activation of fibroblastic reticular cells (FRC) in the KLN, as demonstrated by significant expansion in the extracellular matrix. The lymphotoxin α signaling pathway mediates activation of FRCs. Chronic blockade of the LTα –LTβr axis with lymphotoxin β receptor immunoglobulin (LTβr-Ig) resulted in marked alteration of the KLN as well as augmentation of renal fibrosis. In the acute setting, depletion of FRCs reduced T cell activation in the KLN and ameliorated renal injury 2 days post-IRI. Repetitive renal IRI was associated with senescence of FRCs, fibrosis of the KLN, and renal scarring. FRC administration promoted repair of the kidney and KLN

Conclusions: Our study is novel in emphasizing the critical role of FRCs in KLN in both the initiation and repair phases of injury following IRI of the kidney. We also highlight the potential of FRCs as a cellular therapy to control inflammation and promote renal repair following IRI important in the progression of renal fibrosis.

Funding: Other NIH Support - National Institute of Allergy and Infectious Disease, Commercial Support - Mallinckrodt Pharmaceuticals, Private Foundation Support

FR-PO063

Interferon Regulatory Factor 4 in Macrophages Promotes Renal Fibrosis Following Severe AKI

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Background: Acute kidney injury (AKI) is characterized by abrupt and reversible kidney dysfunction, and incomplete recovery from AKI leads to chronic kidney injury. Macrophage proliferation and polarization to an M2 phenotype plays a key role in recovery from AKI. However, M2 macrophages can produce profibrotic factors such as TGF-β and FIZZ1/RELMα, and their persistence may contribute to interstitial fibrosis when recovery from AKI is incomplete. Interferon regulatory factor 4 (IRF4) plays an important role in macrophage M2 polarization. The present study examined the potential role of macrophage IRF4 in recovery from AKI.

Methods: Wild type (WT, $IRF4^{f/f}$) or macrophage $IRF4^{-/-}$ (LysM-Cre; $IRF4^{f/f}$) mice (male, 3 months old, C57BL/6) were uninephrectomized, immediately followed by unilateral I/R with renal pedicle clamping for 32 min. Mice were sacrificed after 4 weeks.

Results: The effectiveness of macrophage IRF4 deletion was confirmed by qPCR in isolated renal macrophages. In cultured bone marrow monocytes, IRF4 deletion led to significant increases in LPS/IFN-γ-induced proinflammatory cytokines/chemokines. Macrophage $IRF4^{-/-}$ mice had delayed functional recovery during the first five days of recovery and more histologic injury at 5 days post I/R. At four weeks post-severe AKI, kidneys of $IRF4^{-/-}$ mice had marked decreases in M2 markers, IL-4Rα, CD206, FIZZ1/RELMα, CD209, and B7-H4 as well as decreases in proinflammatory cytokines/chemokines, IL-1α, IL-1β, IL-6, IL-23, CCL3, iNOS, TNF-α, and IFN-γ. Surprisingly, macrophage $IRF4^{-/-}$ mice had less severe kidney injury, as indicated by fewer protein casts and dilated tubules and less tubular atrophy. Sirius red and Masson's Trichrome staining showed less renal interstitial fibrosis and decreased mRNA and protein levels of profibrotic and fibrotic components, TGF-β1, TGF-β2, CTGF, α-SMA, fibronectin, collagens I, III, IV as well as decreased immune cell infiltration in macrophage $IRF4^{-/-}$ mice.

Conclusions: Macrophage IRF4 facilitates functional and structural recovery of kidneys from AKI, possibly due to inhibiting proinflammatory cytokines/chemokines. When recovery from AKI is incomplete, IRF4-mediated pro-fibrotic, M2 polarization of macrophages/dendritic cells may contribute to development of fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO064

Hydrodynamic Isotonic Fluid Delivery Following Renal I/R Reduces Inflammation Associated with the AKI-to-CKD Transition

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Background: AKI represents a significant risk factor for CKD. T cells, most notably, Th17 cells, play an important role in the transition from AKI to CKD. We've previously shown that retrograde hydrodynamic delivery of isotonic fluid (HIFD) improved renal function in established AKI between 24-48 hours following ischemia and reperfusion injury. This improvement was associated with decreased inflammation and vascular congestion. However, it is unknown whether HIFD manifests sustained effects on renal function, inflammation and secondary development of CKD.

Methods: S.D. rats underwent left unilateral I/R: 35 min with right Unx to induce AKI. 24 hours later, renal function was evaluated (serum creatinine; SCre) and rats received either HIFD into the renal vein or 0.5ml of saline into the vena cava (VC) as control. The animals were then allowed to recover for 20 weeks while regularly monitoring renal function. Inflammatory cells were evaluated in kidney 20 weeks post-surgery.

Results: Rats were stratified into either moderate (SCre <3.0 mg/dl) and severe (SCre >3.0 mg/dl) injury groups based upon serum creatinine at 24 hours post I/R. In the severe injury group, sCre tended to be reduced between 24 to 48hrs by HIFD treatment relative to VC-treated rats (HIFD: -0.34 vs. VC: +0.03 mg/dl); HIFD had no effect on SCre between 24-48 hours in the mild injury group. At 20 weeks post I/R, the number of renal mononuclear cells were significantly reduced by HIFD treatment in both moderate (41%) and severe (54%) injury as compared to VC-treated rats. In addition, there was a significant reduction in Th17 cells (CD4+IL17+) following HIFD in both the moderate (HIFD: 889.7 vs. VC: 2480 cells/gram kidney; $p<0.05$) and severe groups (HIFD: 1351 vs. VC: 3838 cells/gram kidney; $p<0.05$). HIFD-treated rats also demonstrated significant reductions in CD4+IFNγ+ T cells (HIFD: 477.4 vs. VC: 1529 cell/gram kidney; $p<0.05$) compared with VC-treated rats in the severe group.

Conclusions: Renal vein HIFD treatment following established AKI reduces inflammation associated CKD progression. HIFD treatment improved chronic renal

inflammation despite the lack of improvement in renal function in moderately injured animals. Therefore, HIFD represent a novel therapeutic strategy for prevention of CKD following AKI.

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FR-PO065

Significance of Pax2 Reactivation After Kidney Injury

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Background: *Pax2* is a transcription factor necessary for kidney development. It has been reported that homozygous mutation of *Pax2* is embryonic lethal. On the other hand, *Pax2* expression in the mature kidney is almost diminished. However, it has been reported that *Pax2* is reactivated in the proximal epithelial tubular cells at the recovery phase of the injury. It has also been reported that *Pax2* is involved in stimulation of cell proliferation. In this study, we examined the effect of reactivating *Pax2* on kidney injury.

Methods: To determine the function of *Pax2* reactivation in mouse proximal tubules of kidneys, we generated kidneyproximal tubule-specific *Pax2* conditional knockout (K/O) mice. We generated a transgenic mouse that expresses Cre recombinase under the control of the promoter of the kidney androgen-regulated protein (KAP) gene (*Pax2* flox/flox; KAP-Cre^{+}male mouse). Kidney ischemia was induced in male mice of 6-week-old C57BL/6J (B6) male mice and conditional K/O mice. The left renal artery and vein of these mice were clamped for 60 min to induce ischemia -reperfusion (I/R) injury. Kidney tissues were removed for examination 2, 4, 7 or 14 days after I/R. We evaluated cell proliferation (immunohistochemical staining of Ki-67 and BrdU), inflammation (immunohistochemical staining of F4/80 and CD3) and fibrosis (sirius red staining and hydroxyproline assay). We also conducted similar experiments on *Pax2* hetero K/O mice and *Pax2* siRNA induction mice.

Results: In B6 male mice, the number of *Pax2* positive cells and mRNA expressions increased after I/R. Immunohistochemical analysis of CD3 and F4/80 showed at increasing number of the in inflammatory cell infiltration in conditional K/O mice ($p<0.05$). In analysis of interstitial fibrosis, the area ratio of sirius red staining and the hydroxyproline assay were higher in conditional K/O mice at day 14 after I/R ($p<0.05$). The number of Ki-67 positive cells was decreased in conditional knockout mice at day 2 after I/R ($p<0.01$). Almost of all the Ki 67-positive cells were co-positive with BrdU. In addition, the area ratio of sirius red staining was also higher in *Pax2* hetero K/O mice and *Pax2* siRNA induction mice at 14 days after I/R ($p<0.05$).

Conclusions: Reactivation of Pax2 after ischemia reperfusion injury may be involved in cell proliferation and interstitial fibrosis suppression in the injured kidney.

FR-PO066

Loss of Proximal Tubular Krüppel-Like Factor 15 Exacerbates Renal Injury

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Background: Although several causes contribute to the development of kidney fibrosis and eventual CKD, repeated bouts of acute tubular injury secondary to DNA damaging tubular toxins remains a major cause. Krüppel-Like Factor 15 (KLF15), a zinc-finger transcription factor that is expressed in renal stromal and proximal tubule (PT) cells was recently shown as a potential mediator of kidney fibrosis. KLF15 expression is reduced in early and late stages of human kidney fibrosis as compared to healthy control subjects. We sought to determine the mechanism by which tubular KLF15 serves a key mediator of DNA-damage induced PT injury leading to AKI and CKD.

Methods: PT-specific *Klf15* knockout mice (*Klf15*$^{\Delta Pepck}$) were generated by crossing *Klf15*$^{fl/fl}$ mice with *Pepck-Cre* mice. We utilized low-dose Aristolochic Acid I (AAI) to model DNA-damage induced PT injury, 3 mg/kg every three days for 2 weeks (active phase), followed by 2 weeks for remodeling (chronic phase), with DMSO as control. RNA-Seq was performed in active and remodeling phase samples.

Results: *Klf15*$^{\Delta Pepck}$ mice demonstrated worse renal function (elevated serum urea nitrogen and creatinine), increased PT injury (AQP1 & lotus lectin redistribution and reduced expression) and changes in fibrotic markers compared to AAI-treated *Klf15*$^{fl/fl}$ mice in the acute and chronic phase. RNA-seq analysis showed that integrin signaling and focal adhesion pathways were upregulated in AAI-treated *Klf15*$^{fl/fl}$ mice. In the active phase a subset of 36 genes in metabolic & oxidative stress pathways were downregulated in *Klf15*$^{\Delta Pepck}$ but not in *Klf15*$^{fl/fl}$ and have KLF15 predicted binding sites (BS). In the chronic phase versus DMSO a subset of 13 genes including additional members of Focal adhesion, Regulation of actin cytoskeleton, integrin signaling and Inflammation pathways were upregulated in *Klf15*$^{\Delta Pepck}$ but not in *Klf15*$^{fl/fl}$ and have KLF15 BS. In the active to chronic transition a subset of 55 genes including additional members of Cell adhesion, Cell differentiation and Integrin signaling pathways were upregulated in *Klf15*$^{\Delta Pepck}$ but not in the *Klf15*$^{fl/fl}$ and have KLF15 BS.

Conclusions: These data suggest that the loss of tubular KLF15 exacerbates AAI-induced AKI and CKD, which is mediated by metabolic, focal adhesion and integrin signaling pathways.

Funding: NIDDK Support

FR-PO067

Identifying the Target of Pro-Regenerative Compound, PTBA, to Improve Post-AKI Repair

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Background: Despite the high prevalence of AKI, no approved therapeutic directly repairs renal tubular epithelial cells (RTEC). We discovered a small molecule, phenylthio butanoic acid (PTBA), which improves post-AKI survival, RTEC dedifferentiation & proliferation, & attenuates fibrosis in various models of AKI. *In vitro* studies suggest histone deacetylase 8 (HDAC8) as a PTBA target. We utilize *hdac8* mutant zebrafish to investigate loss-of-function in a nephrotoxin model of AKI. HDAC8 deacetylates structural maintenance of chromosomes 3 (SMC3), a subunit of cohesin involved in sister chromatid cohesion & subsequent segregation. Without HDAC8, there is a perturbance of SMC3 acetylation resulting in G1/S delay. G1/S arrest has been reported as a protective mechanism to allow RTEC proliferation, while G2/M arrest produces pro-fibrotic factors. We hypothesize HDAC8 inhibition dysregulates the SMC3 acetylation cycle, thereby promoting G1/S delay rather than G2/M arrest in RTECs, acting as a protective mechanism.

Methods: We utilized *hdac8* null mutant fish to investigate changes in the repair response. To analyze injury response at a cellular level, we utilized immunohistochemistry to characterize cell cycle phases: EdU (S), PCNA (S), & Phospho-Histone H3 (pH3) (G2/M). We compared Smc3^{Ac} changes, a potential downstream target of Hdac8, in wild types & *hdac8*$^{-/-}$ by western blot & profiled the acetylome in wildtype, mutant, & compound treated zebrafish larvae.

Results: Upon gentamicin induced AKI, *hdac8*$^{-/-}$ fish exhibited increased survival as compared to genetically wildtype larvae. In assessing cell cycle changes, we identified an increased number of PCNA+ & EdU+ RTECs in *hdac8*$^{-/-}$. However, *hdac8*$^{-/-}$ showed a lower number of pH3+ RTECs, a marker of G2/M. Upon investigating SMC3^{Ac} levels, we observed increased SMC3^{Ac} in *hdac8*$^{-/-}$ larvae.

Conclusions: HDAC8 inhibition & SMC3 acetylation is a potential mechanism for increasing post-AKI repair. Genetic ablation of *hdac8* shows enhanced post-AKI survival. Cell cycle analysis suggests absence of Hdac8 activity increases PCNA & EdU, S-phase markers, while lowering G2/M arrest. This increase in S phase & decrease in G2/M may be attributed to the lack of interaction between Hdac8 & Smc3. Overall, we identified a target for HDAC8 & SMC3 as a potential molecular pathway for RTECs to prefer G1/S delay, rather than G2/M as a protective mechanism during AKI.

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FR-PO068

Senescence Associated Secretory Phenotype: Role of Plasminogen Activator Inhibitor-2 (PAI-2) in Acute and Chronic Kidney Disease

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Background: One of the important mechanisms that play a role in age-related kidney disease is cellular senescence and the senescence associated secretory phenotype (SASP), which activates fibroblasts and causes immune cell infiltration. We identified plasminogen activator inhibitor-2 (PAI-2) as an upregulated secreted protein in senescent primary tubular epithelial cells (PTEC). PAI-2 is best known for its expression by macrophages, which are integral in post-injury kidney repair. Therefore, we intended to study the role of PAI-2 in the renal tubular SASP and immune surveillance in AKI and CKD.

Methods: Microarray was used for SASP analysis in PTEC. PAI-2 mRNA expression was tested in PTECs after treatment with Phorbol and γ-irradiation. HEK cells transduced with PAI-2 were co-cultured with fibroblasts. PTEC and bone marrow derived macrophages (BMDM) were extracted from wild type (WT) and PAI-2 knock out (KO) mice. To assess differences in post-injury repair, PAI-2 WT and KO mice were subjected to ischemia/reperfusion (I/R) and unilateral ureteral obstruction (UUO).

Results: PTEC derived from PAI-2 KO mice showed higher proliferation and lower expression of senescence marker p16INK4a after Phorbol treatment. In co-culture assays secreted PAI-2 activated fibroblasts. BMDMs extracted from WT mice had a stronger inflammatory phenotype after activation with LPS and IFNγ. While in acute phase post I/R PAI-2 KO kidneys had a reduced damage load, PAI-2 KO was associated with enhanced chronic damage during the later phase of I/R. In UUO, the KO kidney had more damage in acute as well as chronic phase. WT kidneys compared to KO showed steady decline in classically as well as alternatively activated macrophages in the later time points in both forms of injury.

Conclusions: PAI-2 is produced and secreted by tubular cells upon stress and during senescence. In the peritubular milieu, PAI-2 plays a heterogeneous role by promoting senescence and activating fibroblasts. It also strongly affects macrophage polarization and infiltration. While PAI-2 might have damaging effects during early renal injury our results indicate that PAI-2 is needed for long-term adaptation. In summary, PAI-2 is a novel renal SASP component which has an important impact on kidney adaptive repair.

FR-PO069

Tubular Epithelial Proliferation Accelerates Tubular Atrophy After Kidney Injury Through Its Contractile Capacity

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Background: Tubular atrophy is a common pathological finding in kidney fibrosis and is characterized by flattened tubular epithelia surrounded by thickened tubular basement membrane (TBM). After injury, neighboring epithelia exert strong mechanical forces on the area surrounding the damaged site in order to close the wound. We hypothesize that the regeneration of tubular epithelia during repair itself drives the TBM to shrink, resulting in tubular atrophy.

Methods: In order to mimic the mechanical effects of tubular epithelia during repair on the TBM *in vitro*, tubular epithelial cells (NRK52E) were cultured on a thin floating collagen gel, and its changes by various stimuli were assessed. In *in vivo* experiments, we performed a clonal analysis of solely labeled tubular epithelia using bigenic mice with the proximal tubule-specific tamoxifen-inducible Cre gene (SLC34a1GCE) and tdTomato reporter gene. We then investigated the role of focal adhesion kinase (FAK), a key molecule in the mechanosensing of focal adhesion and the modulation of actin polymerization, during kidney injury and repair.

Results: An *in vitro* analysis showed that the active proliferation of NRK52E caused the floating gel to shrink and become thick, similar to the TBM of atrophic tubules. The TGFβ treatment accelerated gel contraction, whereas the inhibition of actin polymerization by a FAK or ROCK inhibitor suppressed it. An *in vivo* clonal analysis after severe ischemia reperfusion injury (IRI), together with upregulation of TGFβ, showed that tubules containing a larger clone number were more likely to be atrophic and lose terminally differentiated tubular markers. In contrast, tubules containing a large clone number were not atrophic in mild IRI kidneys, and differentiated tubule markers were preserved. Based on the active phosphorylation of FAK in the tubular epithelia and interstitial fibroblasts in IRI kidneys, an *in vivo* clonal analysis showed that the administration of a low dose of the FAK inhibitor ameliorated the atrophy of tubules with a larger clone size and interstitial fibrosis.

Conclusions: The present *in vitro* and*in vivo* results indicate that tubular atrophy after severe kidney injury is associated with the active proliferation of tubular epithelia through its contractile capacity induced by upregulation of TGFβ and subsequent actin polymerization.

FR-PO070

Nephrectomy Induced Renal Repair After AKI Prevents Progression to CKD by an Early Immunosuppressive Action

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Background: Enhanced renal repair is defined as the remarkable repair of an acutely injured kidney upon removal of the healthy contralateral kidney. If the latter kidney is left in place, repair is only marginal and the injured kidney turns fibrotic. It is yet unclear to which extent and by which molecular mechanism a nephrectomy is able to alter the fate of injured kidney cells.

Methods: Acute kidney injury was induced by left ischemia/reperfusion (I/R) after which either right nephrectomy (Nx) or mock-Nx was performed 3 days later. Wild type C57BL/6J mice underwent 21 min of ischemia at 36°C. Control mice underwent mock-I/R and mock-Nx surgery. Mice were euthanized at either 7 days or 6 weeks after I/R. Kidneys were weighed and qPCR analysis of the profibrotic genes Col1, Col4, TGFbeta and CCN2 was performed. Masson/H&E stain was used to microscopically evaluate histopathology and the extent of collagen deposition. RNA-sequencing was used to compare differential gene expression.

Results: In the I/R without Nx group the median left kidney-to-body weight ratio (mg/g) at week 6 was 2.8 (range 2.1-3.1), whereas that of its right healthy kidney was 6.7 (range 6.4-7.0), indicating severe atrophy in the injured left kidney. In the Nx group, left kidney-to-body ratio was 6.9 (range 6.0-7.3) and that of its right kidney at the time of Nx 6.5 (range 5.9-7.5). When no Nx was performed, Col1, Col4, TGFbeta and CCN2 were upregulated 18-, 5-, 7- and 3-fold compared to controls at week 6, respectively. In case of Nx, this decreased to 5-, 2-, 2-, and 0-fold upregulation. On a histological level, Nx strongly attenuated cortical atrophy and tubulo-interstitial fibrosis. Preliminary whole transcriptome RNA-seq analysis at day 7 showed differential expression of 534 genes (257 up, 277 down) of which immune response and MAPK pathways were most significantly downregulated upon Nx.

Conclusions: In conclusion, Nx performed 3 days after I/R has an early immunosuppressive action and attenuates renal atrophy and fibrosis in C57BL/6J mice. This murine model is a useful alternate tool to further study the mechanism of physiology-driven enhanced renal recovery.

FR-PO071

Pannexin1 Regulates Intracellular ATP in a Cisplatin Model of AKI

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Background: Pannexin1 (Panx1) is a membrane channel that can release ATP upon injury, thereby exacerbating inflammation. We reported that *Panx1* deficiency protects kidneys from ischemia-reperfusion injury (IRI). We found significant differences in kidney ATP between *Panx1* KO and control kidneys after injury and hypothesized that retention of ATP is a universal protective mechanism in AKI, including the cisplatin model.

Methods: Global *Panx1* KO and WT mice (n=4) were subjected to 26min bilateral kidney ischemia and 24h of reperfusion. Global (n=8) and proximal tubule (PT, n=4) *Panx1* KO mice and appropriate controls (n=6 and 4, respectively) were given cisplatin (20 mg/kg, ip). Injury was assessed 72 h later by plasma creatinine (PCr), blood urea nitrogen (BUN) and weight loss. Whole kidney ATP was obtained by chloroform extraction of kidney homogenates. CRISPR/Cas9 was used to generate stable *Panx1* KO in murine proximal tubule cells (TKPTS). Cells were treated with 20 μM cisplatin overnight or 20 μM antimycin A for 1 hour to induce injury. Intracellular ATP concentration was measured using luminescent assay.

Results: At baseline, global *Panx1* KO had less ATP (normalized to tissue weight) in whole kidney homogenates than WT mice (n=8 and 9; 0.59 vs. 1.00; $p<0.05$). Following IRI kidney ATP was higher (2.9 vs. 1.0; $p<0.05$) and PCr was lower (0.48 vs. 1.45 mg/dL; $p<0.01$) in *Panx1* KO than in WT mice. After cisplatin, BUN was higher in *Panx1* KO than WT mice (81.74 vs. 58.46 mg/dL; $p=0.07$) but there was no difference in kidney ATP (0.89 vs. 0.92; $p=0.879$). Similarly, after cisplatin, BUN (113.8 vs. 61.49 mg/dL; $p<0.05$) and body weight loss (21.76 vs. 17.37%; $p<0.05$) was higher in PT-specific *Panx1* KO than WT mice. Kidney ATP was not greater in PT-*Panx1* KO than WT mice (1.31 vs. 1.00; $p=0.34$) after cisplatin treatment. Cultured *Panx1* KO cells retained more ATP than controls after cisplatin (54 vs. 36%, $p<0.0001$) or antimycin A (66 vs. 49%, $p<0.001$) treatment.

Conclusions: These results show that Panx1 influences ATP balance in cisplatin injury setting. PT-specific *Panx1* deletion is sufficient to exacerbate injury, contrary to *in vitro* observations that *Panx1* knockout tubules retain more ATP after antimycin A or cisplatin stimulation. The complex role of intracellular ATP homeostasis in AKI will require additional investigation.

Funding: NIDDK Support

FR-PO072

Paricalcitol Ameliorates Cisplatin-Induced AKI by Inhibiting Cell Pyroptosis

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Background: Cisplatin is a classic and effective chemotherapeutic agent, but its kidney toxicity has restricted its application. Vitamin D receptor (VDR), as an important nuclear receptor, is involved in the pathogenesis of acute and chronic kidney diseases. The VDR agonist paricalcitol exerts a protective effect on a variety of acute kidney injury. In this study, we investigated the protective effect and mechanism of paricalcitol in cisplatin-induced acute injury.

Methods: Eight week old male VDR KO mice and WT mice were randomly divided into 6 groups (n=6): (A) WT+Control, (B) WT+Cisplatin, (C) WT+Cisplatin+Paricalcitol, (D) KO, (E) KO+Cisplatin, (F) KO+Cisplatin+Paricalcitol. Pretreatment of paricalcitol (0.2mg/kg, intraperitoneally injected) was performed for five consecutive days. On the sixth day, cisplatin (20 mg/kg) was intraperitoneally injected to induce acute kidney injury (AKI). Samples were collected 72 hours after cisplatin injection. Real-time PCR and Western blot were used to detect the expressions of renal apoplexy-associated proteins such as NLRP-3, caspase-1 and IL-1β. Renal pathological specimens were subject to HE staining to assess the degree of renal tubular injury.

Results: 1. 72 hours after cisplatin injection, mice in groups B, C, E and F became depressed and ate less. The levels of Cr, BUN and CysC were significantly higher in groups B, C, E and F ($p<0.05$), as compared with those in groups A and D, while mice in group E showed the most serious renal damage ($p<0.05$). 2. The mRNA and protein levels of NLRP-3, caspase-1 and IL-1β in groups B, C, E and F were significantly higher than those in group A and D ($p<0.05$). The increase of the three mRNAs/proteins in group E was most significant ($p<0.05$), and the expression of the three proteins in group C was lower than that in group B. 3. HE staining indicated that the renal tubular injury index in group C was significantly lower than that in group B ($p<0.05$). The renal tubular injury index was highest in group E ($p<0.05$).

Conclusions: VDR plays an important role in cisplatin-induced AKI. The VDR agonist paricalcitol possibly reduce cisplatin-induced AKI by inhibiting cell pyroptosis.

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FR-PO073

Retinoic Acid Alleviates Cisplatin Induced Kidney Injury Through Activation of Autophagy

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Background: Retinoic acid (RA) reduces injury, inflammation, and fibrosis in models of acute renal injury, including toxin and ischemia reperfusion AKI, but little is known about its effect on cisplatin induced kidney injury.

Methods: We examine the effects of RA on cisplatin induced kidney injury in vivo and introduce a murine model of cisplatin induced kidney injury by retro-orbital injection of cisplatin both in WT and autophagy-related gene 5–knockout mice. Renal function test, LDH test, HE staining, PCR, immunoblots and immunofluorescence were used in the study. And in vitro, NRK cells were treated with and without cisplatin and were transfected with GFP-LC3 plasmid. Data are representatives of at least three experiments and expressed as means ± SD. Statistical analysis was conducted using the GraphPad Prism software. Statistical differences in multiple groups were determined by multiple comparisons with ANOVA followed by homogeneity test for variance. $P<0.05$ was considered as significantly different.

Results: Cisplatin group mice exhibited typical features of clinical cisplatin induced kidney injury including renal histology changes, higher level of NGAL and plasm creatinine. In WT mice, RA alleviated cisplatin induced dilation and necrosis of renal tubular epithelial cells and improved renal function and upregulated autophagy. Knockout mice showed more severe kidney injury as was indicated by worsening renal function, more tissue damage. And the protective effect of retinoic acid was not significant in knock out mice as autophagy was blocked. In vitro, RA protected proximal tubular epithelial cells from cisplatin induced injury, inhibited apoptosis and promote the proliferation of epithelial cells after cisplatin induced injury and upregulated autophagy which were confirmed by higher level of LC3 -II / LC3 -I ratio, lower level of P62 by immunoblots and more autophagy punctae after transfection of GFP-LC3 plasmid.

Conclusions: RA alleviates cisplatin-induced kidney injury via upregulating autophagy.

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FR-PO074

Cisplatin-Induced AKI: Preconditioning Protects by mRNA-Independent Proteome Alterations

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Background: Acute kidney injury is one of the most common kidney diseases, resulting in significantly increased morbidity and mortality. Unfortunately, strategies for prevention or causal treatment are lacking in routine clinical practice. During the last years it has been shown in animal models, that a number of preconditioning protocols have a protective effect.

Methods: We characterized two of these strategies - calorie restriction and hypoxic preconditioning - in a mouse model of cisplatin-induced acute kidney injury. To investigate the underlying mechanisms, we used multi-layered omic data (transcriptome, proteome, and N-degradome for measuring proteolytic activity) and functional parameters of preconditioned and non-preconditioned cisplatin-treated animals. These parameters were generated from identical animals and integrated bioinformatically.

Results: Both protocols significantly reduced cisplatin-induced acute kidney injury. Bioinformatic analysis revealed mRNA-independent proteomic changes affecting the extracellular compartment, mitochondrial function and tubular transporters. Interestingly, our analyzes showed a strong dissociation of protein and mRNA expression after cisplatin treatment. In the animal cohort, the degree of mRNA-protein dissociation showed a strong correlation ($R> 0.95$) with the degree of damage. N-degradome analysis revealed that most post-transcriptional changes were determined by Arg-specific proteolytic processing. This involved a characteristic cisplatin-induced complement activation, which was prevented by preconditioning. In addition, amyloid and acute phase proteins accumulated within the cortical parenchyma. Extensive analyzes of damage-associated molecular patterns (DAMPs) suggest that the transcription-independent deposition of serum amyloid P could play a key role in the contribution of the microenvironment to renal damage.

Conclusions: This study provides new insights into the pathogenesis of cisplatin-induced acute kidney injury and the molecular mechanisms that underly organ protection through preconditioning through multi-omic phenotype correlations.

FR-PO075

Celastrol Ameliorates Cisplatin Nephrotoxicity by Inhibiting NF-κB and Improving Mitochondrial Function

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Background: Celastrol (CE) is an active ingredient of Chinese medicine Tripterygium wilfordii which is clinically used to treat immune diseases. Currently, celastrol is documented as a potent agent for treating cancer and inflammatory disorders. The present study was to investigate the effects of celastrol on cisplatin (Cis) nephrotoxicity and the underlying mechanisms.

Methods: In vivo, C57BL/6 mice were treated with cisplatin (20 mg/kg) with or without celastrol administration (1 mg/kg/day). After 3 days treatment, mice were sacrificed and the kidney and blood samples were collected for analysis. In vitro, renal tubular epithelial cells (RTECs) were treated with cisplatin (5 μg/ml) with or without celastrol treatment (50 nM).

Results: Pretreatment with celastrol markedly ameliorated cisplatin-induced kidney injury as shown by the improved renal function (BUN: Cis group 75.2±10.7 vs. Cis+CE group 31.1±10.9mmol/L, $p<0.001$; serum creatinine: Cis group 1.2±0.3 vs. Cis+CE group 0.37±0.18 mg/dl, $p<0.001$; and cystatin C: Cis group 16.0±1.68 vs. Cis+CE group 11.3±1.89 ng/ml, $p<0.001$), kidney morphology (PAS), and oxidative stress (MDA) in line with a robust blockade of renal tubular injury markers of KIM-1 (-86.97%) and NGAL (-82.09%). Meanwhile, renal apoptosis and inflammation were also strikingly attenuated in celastrol-treated mice. In vitro, celastrol inhibited cisplatin-induced cell apoptosis (-34.31%), suppressed NF-κB activation (-54.53%), and improved mitochondrial function shown by the restored mtDNA copy number (+29%), mitochondrial membrane potential (+61.09%), and OXPHOS activity (+1.67 folds) in cisplatin-treated renal tubular cells.

Conclusions: Our study suggested that celastrol could suppress NF-κB and improve mitochondrial function to protect against cisplatin nephrotoxicity. Celastrol serves as a promising drug for the treatment of AKI.

FR-PO076

Lactate Improves Survival in Mice with Sepsis Through HCA2 Activation

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Background: Sepsis is characterized by systemic inflammation due to infection and is the most common cause of acute kidney injury (AKI) in critically ill patients. During sepsis, activation of pro-inflammatory pathways results in dysfunction of mitochondria and cells, leading to multi-organ failure.

Methods: Wild-type and *Hca2*$^{-/-}$ mice were undergone cecal ligation and puncture (CLP) to induce sepsis. For survival study, we monitored the mice for 2 weeks after CLP. For treatment study, we administered either normal saline or lactated Ringer's solution once a day for total of 3 injections. The isolated peritoneal fluid or cells were subjected to ELISA assay and real time RT-PCR analyses.

Results: Here we show that: 1) in peritoneal immune cells from mice undergone cecal ligation and puncture (CLP), hydroxycarboxylic acid receptor 2 (HCA2) expression increased in parallel with pro-inflammatory cytokines; 2) survival rates for *Hca2*$^{-/-}$mice after CLP were lower than for wild-type mice (~40% vs. ~80%) 2 weeks after CLP-induced sepsis, suggestive of a protective role for HCA2 in sepsis; 3) early mortality of *Hca2*$^{-/-}$mice were associated with higher pro-inflammatory cytokine production in *Hca2*$^{-/-}$peritoneal fluid compared to wild-type; 4) administration of lactated Ringer's (LR) has beneficial effects on mortality in wild-type mice (but not *Hca2*$^{-/-}$mice) during sepsis; 5) unlike normal kidneys, kidneys in the setting of sepsis expressed *Hca2*; 6) LR administration attenuated sepsis-associated AKI, partly restored expression of the key regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma coactivator-1-a(PGC1a), and reduced pro-inflammatory cytokine production. Our data suggest that lactate-induced activation of HCA2 regulates a negative feedback loop during sepsis to decrease the inflammatory response.

Conclusions: The data further suggest that fluid resuscitation with LR solution may benefit patients with sepsis, particularly those with sepsis-associated AKI treated with potentially lactate-depleting renal replacement therapies (RRT).

Funding: Clinical Revenue Support

FR-PO077

Preconditioning Mice with a Pharmacologic Activator of AMPK Ameliorates Ischemic AKI by Activating Akt

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Background: We have reported that preconditioning renal tubular cells (RTCs) with A-769662 (a novel small molecule activator of AMPK), reduces the death of renal tubular cells (RTCs) induced by metabolic stress *in vitro* and ameliorates the severity of ischemic AKI in mice. (Liebertal, W. et al: American J Phyiol Renal Physiol 311:F731-739, 2016). Our objective in this study was to determine whether Akt plays a role in mediating these effects of A-769662.

Methods: We knocked down expression of the beta-domain of AMPK by > 85% using shRNA ("KD" RTCs). In control RTCs a "scrambled" shRNA was used. Ischemic AKI was induced by subjecting the kidneys to ischemia-reperfusion injury (IRI).

Results: Preconditioning control cells with A-769662 increased the phosphorylation (activity) of AMPK, and reduced the death of these cells induced by exposing them to metabolic stress. However, in KD cells A-769662 had no measurable effects on the activation of AMPK or on their survival after stress. These data show that the activation of AMPK by A-769662 is profoundly impaired in KD RTCs. A-769662 activated Akt in control but not in KD RTCs. These findings demonstrate that the activation of Akt by A-7609662 is AMPK-dependent, and not the result a nonspecific "off target" kinase. It also shows that AMPK acts upstream of Akt. We show, that inhibiting Akt with a specific Akt inhibitor in control cells during the preconditioning period, reduced the pro-survival effect of A-769662 by ~50%. These findings suggest that Akt contributes to the pro-survival effects of A-7698662 *in vitro*. We next evaluated the role of AMPK and Akt in modulating the severity of ischemic AKI *in vivo*. We show that preconditioning mice with A-769662 activated AMPK and Akt in the renal cortex, and that inhibiting Akt, while having no effect on the activation of AMPK, reduced the activation of Akt. Finally, we provide novel evidence, that A-769662 ameliorates the severity of ischemic AKI, and that Akt contributes to this effect.

Conclusions:) A-769662 activates AMPK and Akt in control RTCs and in the kidneys of mice; ii) the activation of Akt by A-760662 is mediated by AMPK; iii) The activation of Akt contributes to the pro-survival effects of A-769662 *in vitro*, and to the beneficial of A-769662 in ischemic AKI *in vivo*; iv) the mechanisms responsible for the activation of Akt by AMPK remain to be elucidated

Funding: Commercial Support - Dialysis Centers Incorporated, Private Foundation Support

FR-PO078

Metabolic Alterations Following Renal Ischemia Reperfusion in Rats

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Background: Acute kidney injury (AKI) is a major health issue, associated with high morbidity, mortality, fibrosis and CKD. Ischemia reperfusion injury (IRI) during surgical procedures such as coronary artery bypass grafting or transplantation can cause AKI. In this study, we sought to characterize the timecourse of molecular and cellular pathophysiological consequences of IRI in the rat.

Methods: Sprague-Dawley rats underwent 45-minute bilateral ischemia followed by reperfusion for 1, 4, 8, 12, 24, 48, 72 hours (hr) or 14 days. We characterized renal injury by measuring plasma and urine biomarkers at all timepoints. We also evaluated tubular injury/repair and subsequent development of renal fibrosis. To delineate IR-induced metabolic changes, we examined gene expression of metabolic pathways including pyruvate handling, fatty acid oxidation, oxidative stress, and mitochondrial homeostasis. We also evaluated NAD^+ utilization and biosynthesis using mass spectrometry and ELISA based methods.

Results: IR-AKI resulted in varying kinetics of plasma and urinary biomarkers. Plasma creatinine and NGAL were elevated 4hr post AKI, and peaked at 24hr, whereas BUN increase was slightly delayed. Urinary NGAL and KIM-1 had similar time-dependent profiles peaking at 24-48hr, whereas urinary FABP-1 excretion peaked at 4hr, then rapidly declined. Tubular and vascular injury were evident 4hr post AKI with proliferation occurring from 24 - 72hr. Gene expression analysis revealed downregulation of proximal tubular cell-specific genes, which suggests loss or de-differentiation. By day 14 post injury, there was clear biochemical and histological evidence for fibrosis despite normal GFR. Renal IRI negatively affected the expression of genes regulating oxidative stress, mitochondrial function, pyruvate handling and fatty acid metabolism through the reperfusion phase. Furthermore, data revealed reduced gene expression of NAD^+ biosynthetic enzymes concomitant with a drop of NAD^+, increased NAD^+ utilization and breakdown products.

Conclusions: Together, our data reveal dysregulation of metabolic processes that contribute to the pathophysiology of IR-induced AKI and may allow for investigation of previously unexplored therapeutic avenues.

Funding: Commercial Support - Astellas

FR-PO079

GSK3β-Mediated Keap1-Independent Regulation of Nrf2 Antioxidant Response: A Molecular Rheostat of AKI-to-CKD Transition

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Background: How acute kidney injury(AKI) is transformed to chronic kidney disease(CKD) remains elusive. Evidence suggests that glycogen synthase kinase(GSK)3β, a pivotal mediator of Keap1-independent regulation of Nrf2 defense, contributes to kidney injury. Whether GSK3β-mediated Nrf2 regulation is involved in AKI to CKD transition is unknown and was explored here.

Methods: Mice with renal tubule-specific GSK3β knockout and control mice were injured with folic acid. Nrf2 response and CKD transition were evaluated. In cultured renal tubular cells expressing GSK3β mutants, hydrogen peroxide-elicited chronic injuries and Nrf2 response were examined.

Results: Following folic acid injury, mice developed AKI with ensuing CKD transition, characterized by variable degrees of tubular cell atrophy, growth arrest and interstitial fibrosis. This lingering injury of renal tubules was parallelized by sustained oxidative stress that coincided with an impaired Nrf2 antioxidant defense, marked by mitigated Nrf2 nuclear accumulation and blunted induction of its target antioxidant enzymes. The initiation of Nrf2 signaling, however, seems unaffected since cytoplasmic Nrf2 in injured tubules was persistently elevated. Moreover, renal expression of Keap1, a key repressor of Nrf2, was barely associated with the magnitude of CKD transition. In contrast, GSK3β was persistently overexpressed and hyperactive in renal tubules during CKD transition. Likewise, in patients who developed CKD following AKI related to diverse etiologies, GSK3β overexpression was evident in renal tubules and concomitant with impaired Nrf2 response and oxidative damages. Mechanistically, Nrf2 defense agaisnt oxidative stress was sabotaged in renal tubular cells expressing a constitutively active mutant of GSK3β in a Keap1-independent mode, in parallel with an exacerbated cell cycle arrest, dedifferentiation, apoptosis and extracellular matrix overproduction. Conversely, ectopic expression of dominant negative GSK3β reinforced Nrf2 response and diminished cytopathic changes. *In vivo* in folic acid-injured mice, targeting GSK3β in renal tubules *via* gene knockout or by microdose lithium reinstated Nrf2 response and hindered CKD transition.

Conclusions: GSK3β-regulated of Nrf2 may serve as a pragmatic therapeutic target for modifying the long-term sequelae of AKI.

Funding: NIDDK Support

FR-PO080

Efficacy of Low Intensity Pulsed Ultrasound on an AKI Mouse Model via the Prevention of Endoplasmic Reticulum Stress and Apoptosis

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Background: Acute kidney injury (AKI) is associated with high mortality rates and often predisposes patient to development of chronic kidney disease. Renal ischemia/reperfusion injury (IRI) is a major cause of AKI. The mechanisms of IRI have been found to be included endoplasmic reticulum (ER) stress, inflammatory responses, hypoxia, and generation of reactive oxygen species. Low intensity pulsed ultrasound (LIPUS), which is a kind of therapeutic ultrasound, has been shown to exert therapeutic effects on bone healing and accelerate the healing process. The effect and mechanism of LIPUS on AKI still remain unclear. Here, we investigated the therapeutic effect and possible mechanism of LIPUS on IRI.

Methods: We use a mouse model of unilateral IRI with nephrectomy of the contralateral kidney in the presence or absence of LIPUS treatment (3 MHz, intensity 0.1 W/cm^2, 20 mins, 50% duty factor) 5 day before and 1 day after surgery.

Results: The results showed that renal function markers (e.g. BUN, creatinine), ER stress-related molecules (e.g. GRP78, eIF2-α, CHOP) and apoptotic markers (e.g. Bax, caspase-3) were significantly increased in the kidneys of mice with IRI for 24 h, which could be significantly reversed by LIPUS treatment. The histopathological examination showed that the lesser renal tubular injury and inflammation were observed in IRI+LIPUS mice than in IRI alone mice.

Conclusions: Taken together, LIPUS treatment showed the benefits for renal protection in IRI mice. These findings suggest that LIPUS therapy may be used to serve as an auxiliary tool for management of AKI.

FR-PO081

UCP2-Dependent Improvement of Mitochondrial Dynamics Preserves AKI

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Background: Acute kidney injury (AKI) is a public health concern with high morbidity and mortality rate in hospitalized patients and the survivors have increased risk of progression to chronic kidney disease. Mitochondrial damage is the critical driver of AKI-associated dysfunction and loss of tubular epithelial cells; however, the pathways that mediate these events are poorly defined.

Methods: AKI was induced by ischemia/reperfusion injury. We generated proximal tubular cells specific uncoupling protein 2 (UCP2) knockout mice to investigate the role of UCP2 on AKI. Primary tubular epithelial cells were cultured under normoxia or hypoxia conditions. Mitochondrial dynamics were evaluated by electron microscopy, western blot analysis and immunofluorescent staining.

Results: Here, in murine ischemia/reperfusion-induced (I/R-induced) AKI model, we determined that mitochondrial damage is associated with the level of renal UCP2. In hypoxia-damaged proximal tubular cells, a disruption of mitochondrial dynamics demonstrated by mitochondrial fragmentation and disturbance between fusion and fission was clearly indicated. *Ucp2*-deficient mice suffered I/R injury experienced more severe AKI and mitochondrial fragmentation than wild-type (WT) mice. Moreover, Genetic or pharmacologic treatment increased UCP2 expression, improved renal function, reduced tubular injury and limited mitochondrial fission. In cultured proximal tubular epithelial cells, hypoxia-induced mitochondrial fission was exacerbated in Ucp2$^{-/-}$ cells, while increase of UCP2 improved hypoxia-induced disturbance between mitochondrial fusion and fission. Furthermore, modulation of UCP2 suggested its role in preserving mitochondrial integrity by preventing loss of membrane potential and reducing subsequent mitophagy.

Conclusions: Together, our results indicate that UCP2 is protective against AKI and suggest that enhancing UCP2 to improve mitochondrial dynamics has potential as a strategy for improving outcomes of renal injury.

Funding: Government Support - Non-U.S.

FR-PO082

AATF/Che-1 Controls Ribosomal Biogenesis Through Direct Binding of Ribosomal RNA and R-Protein Encoding mRNAs

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Background: AATF/Che-1 (Apoptosis Antagonizing Transcription Factor) is an RNA Pol II binding transcription factor that has been shown to play crucial roles in multiple essential cellular pathways - e.g. DNA damage response and mTOR signaling. It further has been linked to acute kidney injury. However, the exact molecular function of this protein is not known.

Methods: We have identified AATF as a putative RNA binding protein (RBP) in murine kidney cells. Here, we use Enhanced Crosslinking and Immunoprecipitation (eCLIP) as well as RNA editing followed by sequencing (TRIBE) techniques to identify both coding and non-coding RNAs bound by AATF. Binding of RNA as well as validation of specific targets was done by PNK assays and RIP-qPCR. Using TALEN-mediated genome engineering, we have created a set of transgenic cell lines that express GFP-tagged WT AATF or AATF mutant proteins. In addition, we perform MS/MS studies to uncover proteins interacting with AATF.

Results: Here we validate AATF as an RNA binding protein and identify hundreds of RNA targets bound by AATF. Analysis of transcripts bound by AATF were enriched for ribosomal and other non-coding RNA biotypes. More specifically, the 45S rRNA precursor was one of the most enriched transcripts bound to AATF. Moreover, both structural constituents of the RNP and components of the ribosome biogenesis machinery were strongly overrepresented among the mRNA transcripts. Both the 45S pre-ribosomal precursor and its product, 18S rRNA, were depleted upon knockdown of AATF. However, AATF did not only interact with RNA molecules associated with ribosomal function and integrity, but also with a large number of protein components of the rRNP and other RNA binding proteins.

Conclusions: Our study validates AATF as an RNA binding protein and reveals yet another link between rRNA metabolism, nucleolar integrity and other essential pathways such as the DNA damage response. An impact on ribosome abundance and functionality mediated by RNA binding could be an important feature of the role of AATF in carcinogenesis and may open new ways to address its role as a potential therapeutic target. To this end, a better understanding of its molecular function is of great importance.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO083

The mRNA Interactome of Ciliated Renal Cells and Its Modulation by Hypoxia

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Background: RNA-binding proteins (RBPs) are fundamental regulators of cellular biology and affect every step in processing RNA-biology. The scale of their impact has been shown by recent studies that have linked RBPs to a number of human pathologies, ranging from neurological disorders and ischemia reperfusion injury to tumor growth. Despite this central role in cell biology, the global effect of RBPs in the kidney has not been assessed until now. Here, we identify the first set of RBPs in ciliated renal epithelial cells under both hypoxic and normoxic growth conditions.

Methods: Using Oligo(dT) beads to precipitate mRNA-protein complexes on ciliated mIMCD-3 cells, we aimed to identify the kidney-specific mRNA interactome using mass spectrometry. Cells were either exposed to hypoxia or grown under normoxic conditions. In parallel, the proteome of whole cell lysates was identified to assess the abundance of total protein in comparison to RBPs detected using the same conditions. Using TALEN-generated transgenic human cell lines, specific candidates were validated as RNA binding protein with the Polynukleotide (PNK) assay, showing RNA bound directly to the proteins of interest. Localization of the RBPs was analyzed using immunofluorescence.

Results: Our data revealed over 350 significant mRNA interactors and more than 300 candidate RBPs, 84 of which have not been described as RBPs in common data bases. We define these proteins as the renal epithelial cell mRNA interactome. The PNK assay validated all chosen candidates as RBPs and indeed showed direct binding to RNA. Since the whole cell proteome did not show these RBPs to be differentially expressed upon exposure to hypoxia, we hypothesize that the increased detection of RBP candidates in the hypoxic samples is indeed due to differential binding to their target transcripts.

Conclusions: Our data identify the first set of RBPs specific to ciliated renal epithelial cells and show that hypoxia can modulate RNA-binding, adding another regulatory layer to the diverse biology of the kidney. Using established human transgenic cell lines, we are now aiming for functional studies of individual candidates in order to address their impact on hypoxia signaling and their impact of preconditioning-mediated increase of viability both in vitro and in vivo.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO084

AICAR, an AMPK Activator, Protects Against Cisplatin-Induced AKI Through JAK/STAT/SOCS Pathway

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Background: Cisplatin causes acute kidney injury (AKI) through proximal tubular injury. We investigated protective effect of the adenosine monophosphate protein kinase (AMPK) activator 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) against cisplatin induced AKI. We investigated whether AMP-kinase activator AICAR ameliorates cisplatin induced AKI and through JAK/STAT/SOCS pathway.

Methods: Male Sprague-Dawley rats were randomly divided into four groups: control, AICAR, cisplatin and cisplatin + AICAR groups. On day 1, SD rats were injected with single dose of cisplatin (7 mg/kg, i.p.). From day 1 to 5, AICAR was administered to rats at 100mg/kg i.p. daily. Blood urea nitrogen (BUN) and the serum creatinine were measured. The kidneys were harvested on the day 5. Renal damage was analyzed in sections stained with Hemotoxylin and Eosin (H&E). Renal tissues were also examined for immunohistochemistry and western blot for p-AMPK, KIM1, cleaved caspase 3 and JAK/STAT/SOCS. For *in vitro* studies, NRK-52E normal rat kidney cells were treated with cisplatin and/or AICAR. By western blot, we also confirmed the expressions of p-AMPK and JAK/STAT/SOCS pathway in NRK-52E cells.

Results: A single injection of cisplatin caused marked increase of the serum creatinine and BUN levels on day 5. Peak BUN and serum creatinine levels were decreased by treatment with AICAR. As compared to the cisplatin group, acute tubular necrosis (ATN) score was improved in rats treated with cisplatin + AICAR. AICAR was protective against cisplatin induced acute tubular injury by up-regulating p-AMPK expression and down-regulating KIM-1 and cleaved caspase 3. JAK2/STAT1/SOCS1 pathway was down-regulated by AICAR treatment in our *in vivo* and *in vitro* study. AICAR was protective against cisplatin induced acute tubular injury by up-regulating p-AMPK expression in NRK-52E cells. Protein expression levels of JAK2/STAT1 were markedly ameliorated in NRK-52E cells by AICAR.

Conclusions: Thus, the present study demonstrates the protective effect of AICAR in cisplatin-induced ATN and shows a new renoprotective mechanism through JAK2/STAT1/SOCS1 pathway and apoptosis inhibition. This study suggests that activation of AMPK activator, AICAR might ameliorate the cisplatin induced AKI.

FR-PO085

NAD+ Augmentation Improves Cell Survival Against Cisplatin via Enhanced Mitophagy

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Background: Cisplatin nephrotoxicity is a common cause of acute kidney injury. Activation of autophagy in the renal tubule may be protective against cisplatin. We previously reported that nicotinamide adenine dinucleotide (NAD+) precursor treatment ameliorated cisplatin nephrotoxicity in mice. Given the role of NAD+ in mitochondrial function and homeostasis, we investigated if the protection afforded by NAD+ augmentation against cisplatin involved the induction of mitochondrial autophagy, i.e., mitophagy. Mitophagy has been traditionally difficult to quantify, requiring co-staining of cells with mitochondrial and lysosomal dyes which can be cytotoxic, non-specific, or both. Recently, a pH-sensitive non-toxic biosensor protein, mtKeima, has been developed to track the fraction of mitochondria that undergo autophagy and breakdown in the acidic lysosome.

Methods: We developed a stable renal tubular cell line expressing mtKeima, which we treated with cisplatin (10 mM) or vehicle. Another set of cells were pre-treated with the NAD+ precursor nicotinamide mononucleotide (NMN, 1 mM) 30m prior to cisplatin or vehicle. General autophagy was assessed by Western Blot for LC3 and p62. Cells were imaged 24h after treatment on a confocal microscope with two sequential excitations 440 nm and 559 nm and a 570 to 695 nm emission range. A mitophagy index was calculated by determining the ratio between the area of the red (acidic) and green (basic) emission.

Results: LC3 and p62 revealed no differences in response to cisplatin or NMN. However, cisplatin markedly inhibited mitophagy ($p<0.05$, 2-fold change). Conversely, NMN enhanced basal mitophagy ($p<0.001$, 4-fold change). Pre-treatment of cisplatin-exposed cells with NMN abrogated the decline in mitophagy induced by cisplatin ($p<0.001$, 6-fold change). Finally, application of the lysosome inhibitor, chloroquine, enhanced cisplatin toxicity.

Conclusions: Whereas traditional measurements of autophagy were uninformative, use of mtKeima illuminated a specific reduction in mitophagy triggered by cisplatin. This effect was abrogated with the addition of NMN. Our results indicate that preservation of mitophagy with its safe mitochondrial disposal, rather than generalized autophagy, may be critical for renal tubular cells to resist cisplatin. Further, NAD+ supplementation may represent a therapeutic option for the treatment of cisplatin nephrotoxicity.

Funding: NIDDK Support

FR-PO086

Nrf2 Attenuates Tubular Epithelia Cell Transdifferentiation in Response to Hypoxia Through Regulating CTGF Secretion

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Background: Nuclear factor erythroid 2-related factor 2 (Nrf2) is a well-known regulator of oxidant and xenobiotic metabolism. We previously reported that Nrf2 ameliorates renal tubular transdifferentiation in mice on day 5 after unilateral ureteral obstruction (UUO); however, the mechanism of attentuation remains unclear. We aimed to clarify whether Nrf2 regulates the connective tissue growth factor (CTGF)/WNT pathway, which is a key pathway in tubular epithelia cell transdifferentiation.

Methods: Normal rat kidney-52E (NRK52E) tubular cells were divided into four groups: scramble control, Nrf2-knockdown (Nrf2-KD) control, scramble hypoxia (5%), and Nrf2-KD hypoxia groups. Expression levels of CTGF and WNT signaling pathway (p-Lrp6 and β-catenine) were detected by western blotting. Then, we used siRNAs to silence CTGF and Nrf2 simultaneously and to measure WNT signaling and vimentin, a transdifferentiation marker. We also investigated the expression of c-fos, a known transcription regulator of CTGF, and the expression of a group microRNAs as post transcription factors of CTGF. In addition, we evaluated the expression of CTGF in the kidneys of *Nrf2*$^{+/+}$ and *Nrf2*$^{-/-}$ mice 5 days after UUO by immunostaining and western blotting.

Results: We found that Nrf2 deletion significantly increased CTGF expression in response to 5% of hypoxia in NRK52E cell line. In hypoxia treated NRK52E cells, deletion of Nrf2 promoted expression of p-Lrp6 and β-catenine as well as vimentin. The overexpression of p-Lrp6, β-catenine and vimentin due to only silencing Nrf2 was decreased by double silencing Nrf2 and CTGF. Nrf2 knockdown increased expression of c-fos and p-c-fos in NRK52E cells. However, Nrf2 knockdown showed no regulation of post-transcription factors such as miR-26a, miR-26b, miR-30a and miR-133. Similarly, expression of CTGF and activity of WNT signaling were increased in *Nrf2*$^{-/-}$ mice compared to those in *Nrf2*$^{+/+}$ mice on the 5th day after UUO operation.

Conclusions: Nrf2 attenuated tubular epithelial cellular transdifferntiation may be mediated by downregulating WNT signaling pathway through inhibiting CTGF secretion in tubular epithelial cells. This suggests that Nrf2 activator might be a potential agent to slow down the progression from acute renal tubular damage to chronic tubulointerstitial fibrosis.

Funding: Government Support - Non-U.S.

FR-PO087

Nrf2 Interactions with the HIF System May Determine Long Term Outcomes After AKI

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Background: Acute kidney injury (AKI) affects up to 1 in 5 hospitalized patients and is associated with an increased risk of developing chronic kidney disease. AKI is commonly caused by ischemia and proximal tubular epithelia are particularly vulnerable to injury. HIF-1α (Hypoxia-inducible factor-1α) and Nrf2 (Nuclear factor erythroid 2-related factor 2) are transcription factors with protective effects against AKI. Studies suggest an association between HIF system activation and Nrf2 activity but this has not been extensively studied in the kidney.

Methods: C57BL/6 mice were subjected to kidney ischemia-reperfusion to induce AKI. Ischemia times were titrated to induce mild to severe injury and kidneys were harvested at various acute and chronic timepoints post-reperfusion. To simulate mild and severe injury conditions *in vitro*, proximal tubular HK-2 cells were exposed to either nutrient replete or nutrient deficient conditions, respectively, in the presence of HIF activation with cobalt chloride ($CoCl_2$). Immunoblotting, qPCR, RNA interference, serum creatinine, and histologic methods were used.

Results: Kidneys obtained 24 h after mild injury had elevated protective Nrf2 activity, as evidenced by expression of the Nrf2 target gene *Nqo1*, and this was associated with minimal histologic injury at late timepoints. Kidneys exposed to severe injury failed to upregulate *Nqo1*, and this was associated with the development of chronic injury and fibrosis. Similarly, HK-2 cells exposed to mild stress conditions using nutrient replete media with $CoCl_2$ led to *Nqo1* upregulation, but cells exposed to nutrient deficient conditions with $CoCl_2$ did not show *Nqo1* induction. HIF-1α appeared to exert a negative effect on Nrf2 since HIF-1α knockdown enhanced *Nqo1* expression. HIF-1α activation also suppressed Nrf2 nuclear localization in nutrient deficient conditions.

Conclusions: Our data suggest there is a threshold of severity at which AKI leads to the development of progressive CKD, and disparate outcomes may be partly determined by Nrf2 activity. Also, we demonstrate differential regulation of Nrf2 by HIF activation in mild and severe injury conditions. Overall, our results show that there is an association between Nrf2 and the HIF system that may determine the long-term outcome of the kidney.

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FR-PO088

Nrf2 Deficiency Aggravates Folic Acid-Induced AKI Through Upregulation of Renal Ferroptosis in Mice

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Background: The role of nuclear factor erythroid 2-related factor 2 (Nrf2) in folic acid (FA)-induced acute kidney injury (AKI) remains unstudied so far. Ferroptosis is demonstrated to be involved in FA-induced AKI. We aim to verify whether Nrf2 deletion aggravated FA-induced AKI in mice and to investigate the corresponding mechanism.

Methods: Male Nrf2$^{+/+}$ and Nrf2$^{-/-}$mice were injected FA (100 mg/kg) intravenously to induce AKI. NaHCO3 was used as the vehicle. AKI was evaluated by serum creatinine (Scr), blood urea nitrogen (BUN), and tubular damage on PAS staining 48h after FA injection. Meanwhile, we examined four types of tubular cell death including tubular necrosis, apoptosis (TUNEL staining), pyroptosis (*Caspase1*, *Pycard*, and *Txnip-1/2*), and ferroptosis (*Gpx4* and *Acsl4*). We also examined the renal expression of Nrf2-associated genes such as pro-inflammatory cytokines (*Il6* and *Tnfα*) and antioxidative factors (*Nqo1*, *Gclc*, and *Gclm*) in Nrf2$^{-/-}$mice compared to that in Nrf2$^{+/+}$ mice. In addition, we explored the influence of Nrf2 deletion on the activity of methylenetetrahydrofolate dehydrogenase (MTHFD), which is an enzyme involved in FA systemic metabolism.

Results: AKI occurred in both Nrf2$^{+/+}$ and Nrf2$^{-/-}$ mice. AKI features such as Scr, BUN, tubular damage degree on PAS staining, and tubular necrosis scores were more severe in Nrf2$^{-/-}$ mice than in Nrf2$^{+/+}$ mice. The number of TUNEL positive nuclei in kidneys of Nrf2$^{-/-}$ mice was higher than that in Nrf2$^{+/+}$ mice. However, the above four pyroptosis biomarkers showed no difference in the kidneys of both Nrf2$^{+/+}$ and Nrf2$^{-/-}$ mice. Interestingly, renal anti-ferroptosis gene *Gpx4* expression was downregulated while pro-ferroptosis gene *Acsl4* was upregulated. In addition, renal pro-inflammatory *Il6* and *Tnfα* genes were increased and antioxidative *Nqo1*, *Gclc*, and *Gclm* genes were decreased in Nrf2$^{-/-}$ mice compared to in Nrf2$^{+/+}$ mice. Further, we found FA increased the activity of MTHFA; however, no difference of this enzyme was seen in Nrf2$^{-/-}$ mice compared to Nrf2$^{+/+}$ mice.

Conclusions: Nrf2 deficiency aggravates FA-induced AKI in mice. Acute tubular protective roles of Nrf2 may be mediated by a combination of mechanisms such as anti-inflammation, antioxidative response, anti-apoptosis, and anti-ferroptosis.

Funding: Government Support - Non-U.S.

FR-PO089

The Protective Role of Nrf2 Against Aristolochic Acid (AA)-Induced Renal Tubular Epithelial Cell Injury

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Background: Aristolochic acid nephropathy(AAN) is a rapidly progressive tubulointerstitial disease induced by aristolochic acid(AA) and there are currently no effective treatments for it. Nrf2, as a major regulator of antioxidant response, has been proven by numerous studies to be protective in acute kidney injury and chronic kidney disease progression. However, its role in AA-induced kidney injury has not been elucidated yet. We previously demonstrated that Bardoxolone methyl(BARD) ameliorates AA-induced acute kidney injury through Nrf2 pathway. In this study, we further assessed the role of Nrf2 in AA-induced renal tubular epithelial cell injury.

Methods: NRK-52E cells were incubated with different concentrations of AA for 0-24 hours to evaluate cell viability, Nrf2 signaling pathway protein levels, ROS production, and cell apoptosis/necrosis. The role of Nrf2 in AA-induced ROS production and cell apoptosis/necrosis was determined through Nrf2 knockdown by its specific siRNA or Nrf2 overexpression by Nrf2 plasmid, respectively. Cell viability was evaluated by MTT. Cells were labeled with DCFH-DA for detection of ROS by flow cytometry. The cells also doubly labeled with Annexin V and propidium iodide(PI) for measurement of cell apoptosis/necrosis by flow cytometry. Expression of Nrf2 and its downstream protein HO-1 and NQO1 was analyzed by western blotting.

Results: AA increased intracellular ROS production and cell apoptosis/necrosis in a time-dependent manner. Meanwhile, the cell viability and the expression of Nrf2 signaling pathway proteins (Nrf2, HO-1, NQO1) were significantly decreased. Downregulation of Nrf2 by its specific siRNA further increased ROS levels(25.2±12.5 vs 8.5±2.5, P<0.05) and cell apoptosis/necrosis(50.21±5.65% vs 35.81±0.97%, P<0.05), and reduced the expression of Nrf2 signaling pathway proteins(P<0.05). Conversely, overexpression of Nrf2 significantly decreased AA-induced ROS production and cell apoptosis/necrosis(24.12±1.61% vs 32.61±0.81%, P<0.01). The expression of Nrf2 and its downstream protein HO-1 were significantly upregulated compared with non-Nrf2 transfected group(P<0.05).

Conclusions: Impaired Nrf2 signaling pathway is one of the mechanisms of AA-induced renal tubular epithelial cell injury, and activation of Nrf2 can ameliorate the cell injury by its antioxidant effect.

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FR-PO090

The Effect and Mechanism of Leptin in Ischemia Reperfusion Induced AKI

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Background: Ischemia-reperfusion (IR)-induced acute kidney injury (AKI) is one of the most common causes of AKI, but the underlying pathogenesis is poorly understood. And there are little reports about the role of leptin in IR-induced AKI.

Methods: Bilateral renal ischemia (30 min)/reperfusion (48hrs) injury (IRI) model was performed using ob/+ mice (wild type) and ob/ob mice (Leptin deficient). Blood samples were collected for renal function evaluation and the kidneys were removed for histological examination and protein detection.

Results: Compared with the sham groups, both of the I/R groups showed significantly higher levels of serum urea nitrogen and creatinine, which were even much higher in the ob/ob/I/R group than those in the ob/+/I/R group. No obvious tubular damage and TUNEL positive cells were observed in the sham groups, but severe tubular lysis, loss of brush border, sloughed debris in tubular lumen space and TUNEL-positive cells were observed in the I/R groups and were much more obvious in the ob/ob/I/R group than those in the ob/+/I/R group. Significantly increased Caspase3, Caspase9 and LC3 II protein expression and decreased p-mTOR protein expression were detected in both of the I/R groups comparing with the sham groups, these changes were more significantly in the ob/ob/I/R group than in the ob/+/I/R group. P-AMPK,P-PTEN,P-AKT,P-ERK protein were significantly down-regulated and PTEN protein was significantly up-regulated in both of the I/R groups compared with the sham groups, these changes were were much more remarkable in the ob/ob/I/R group than in the ob/+/I/R group.

Conclusions: After IRI, Mice showed impaired renal function, damaged kidney tubules and increased apoptosis and autophagy, which were significantly more obvious in the ob/ob/I/R group than in the ob/+/I/R group. The ob/ob/I/R group showed remarkably increased PTEN protein and decreased P-AMPK,P-PTEN,P-AKT,P-ERK protein than the ob/+/I/R group. All the above results suggests that leptin may participates in the pathogenesis of I/R-induced AKI by regulating autophagy via a complicated network composed of mTOR dependent pathways, as well as by regulating apoptosis.

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FR-PO091

A Single Dose of Lithium Attenuates Rhabdomyolysis-Associated AKI

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Background: Acute kidney injury (AKI) is the most severe complication of rhabdomyolysis. Evidence suggests that glycogen synthase kinase 3β (GSK3β) inhibition protects against AKI. Treatment with a single dose of lithium, a selective inhibitor of GSK3β, accelerated recovery of renal function in models of cisplatin and ischemia/reperfusion- induced AKI. The aim of this study was to evaluate the efficacy of a single dose of lithium in the treatment of rhabdomyolysis-induced AKI in rats.

Methods: Male Wistar rats aged 3 months were allocated to four groups: 1- Control: received saline 0.9% intraperitoneal (IP); 2- Lithium: rats treated with a single IP injection of lithium chloride 80 mg/Kg body weight (BW) ; 3- Glycerol (50%, 5 ml/kg intramuscular,IM); 4- Glycerol plus Lithium: glycerol 50%, 5 ml/kg IM + lithium chloride 80 mg/kg IP injected 2 hours after glycerol administration. After 24 h the animals were anesthetized to measure inulin clearance (GFR, ml/min/100g BW). At the end of the clearance experiments the rats were euthanized, blood and kidney were collected to evaluate plasma levels of creatine phosphokinase (CPK), expression of GSK3β in renal tissue and kidney histological damage score.

Results: As described in the table below, glycerol-injected rats showed markedly reduction of GFR, increase of CPK levels, exaggerated increase of GSK3β renal expression and higher kidney injury score. A single dose of lithium administration ameliorated all these alterations.

Conclusions: Lithium treatment attenuated renal dysfunction in a model of rhabdomyolysis-associated AKI by improving inulin clearance and reducing kidney injury score. These therapeutic effects were due to an inhibition of renal GSK3β and were associated with a decrease in muscle injury. This may represent a new therapeutic approach for rhabdomyolysis-induced AKI. (FAPESP 2015/11933-3; 2015/05513-1)

Parameters	Control n=6	Lithium n=6	Glycerol n=6	Glycerol+ Lithium n=7
GFR ml/min/ 100gBW	1.01±0.07	0.86±0.07	0.36±0.06[a]	0.86±0.06[f]
CPK U/L	247±26	146±24	721±87[ad]	268±19[f]
GSK 3β %	99±9	120±11	646±71[ad]	328±53[cef]
Renal Injury score	0.08±0.02	0.08±0.02	1.62±0.25[ad]	0.87±0.30[cefg]

Data are expressed as mean±SEM. a p<0.001, c p<0.05 vs Control; d p<0.001, e p<0.01 vs Lithium ;f p<0.001, g p<0.05 vs Glycerol.

FR-PO092

Stress Granule Plays a Protective Role in Renal Proximal Tubular Cells

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Background: Stress granule (SG) is one type of cytoplasmic structures formed in eukaryotic cells upon certain types of stress. Further study disclosed that SG mainly contains RNA-binding proteins (RBPs) and mRNAs. SGs are widely regarded as one mechanism for cells to survive a harsh insult. However, little is known about SG biogenesis in renal tubular cells.

Methods: To explore how tubular cells form SGs to a series of interventions, we applied different kinds of stressors to cultured mouse (BUMPT) and rat (RPTC) proximal tubular cells as well as a short period of ischemia/reperfusion to mouse kidneys.

Results: It was found that glycolytic inhibitors such as 2DG (2-deoxy-D-glucose) and 3PO (3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one) can induce SG formation within 30 minutes in cultured BUMPT and RPTC cells. Similarly, SGs are induced by inhibitors for the respiratory chain of mitochondria such as sodium azide and CCCP (carbonyl cyanide m-chlorophenyl hydrazone). Interestingly, cisplatin, a common chemotherapy drug for many types of cancers, hardly induces SG formation. Ischemia/reperfusion to mouse kidneys can induce SG formation in renal proximal tubular cells. To further test the role of SGs in renal tubular cells, we stably knocked down G3BP1, a SG core protein, in BUMPT and RPTC cells by shRNA viral transduction. As expected, knockdown of G3BP1 partially disrupts the assembly of SGs. After azide or cisplatin treatment, more dead cells were found morphologically in knockdown cells in comparison to controls, accompanied by increment in cleaved caspase-3 expression. Re-introduction of exogenous G3BP1 into knockdown cells can rescue the cell death phenotype.

Conclusions: All taken together, SGs can form in cultured renal proximal tubular cells at certain conditions and kidneys after ischemia/reperfusion. Intervention on SG biogenesis may provide an approach to lessen the severity of a series of renal diseases.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO093

Upregulation of Hypothalamic Arginine Vasopressin by Bilateral Nephrectomy in Transgenic Rats Expressing Arginine Vasopressin-Enhanced Green Fluorescent Protein

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Background: Acute loss of kidney function is a critical internal stressor. The paraventricular nucleus (PVN) of the hypothalamus is an integrative site of the neuroendocrine and autonomic nervous systems that deals with a variety of aversive stressors. Hypothalamic arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH) in the parvocellular division of the paraventricular nucleus (pPVN) play important roles in the regulation of stress responses. However, hypothalamic AVP dynamics after acute kidney injury remain unclear.

Methods: We generated transgenic rats that express the AVP-enhanced green fluorescent protein (eGFP) fusion gene. Since eGFP fluorescent intensity is a quantitative indicator of AVP synthesis in the transgenic rats, we evaluated AVP-eGFP fluorescence in the hypothalamus after the rats had undergone bilateral nephrectomy. We then examined AVP gene expression by in situ hybridization histochemistry. Finally, we quantified Fos-Like immunoreactivity (IR) cells, which are used as a marker of neural activity, in several brain regions which modulate biological responses to severe stressors by controlling AVP synthesis.

Results: After bilateral nephrectomy, eGFP fluorescent intensities were significantly increased in the pPVN, but not in the magnocellular PVN. The mRNA levels of *eGFP*, *AVP*, and *CRH* in the pPVN were significantly increased after bilateral nephrectomy. Bilateral nephrectomy also caused a marked increase in Fos-IR in the locus coeruleus, nucleus of the solitary tract, area postrema, and rostral ventrolateral medulla, which are responsible for modulating sympathetic nervous system activity.

Conclusions: Bilateral nephrectomy caused upregulation of AVP synthesis and neuronal activity. Further studies are needed to identify the neural and/or humoral factors that activate the central AVP system after bilateral nephrectomy.

FR-PO094

Recognition of Apoptotic Cells by Viable Proximal Tubular Epithelial Cells (PTEC) Induces Death Receptor (DR)-Dependent Death of PTEC, but in a Ligand-Independent Manner

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Background: We have shown that mouse kidney PTEC have distinct non-competing receptors for apoptotic and necrotic targets. Receptor-mediated recognition of apoptotic, but not necrotic, targets induces apoptotic death of PTEC responders.

Methods: Responder cells were BU.MPT cells, a conditionally immortalized PTEC line. Target cells, induced to undergo apoptosis or necrosis, were homologous (BU.MPT) or heterologous (DO11.10 lymphocytes) cells.

Results: Apoptotic target-induced death of PTEC responders is profound (~100% by 48-72 h). Target-induced apoptotic death appears to involve death receptors (DRs), as

supported by the following data. First, death is associated with signaling events typical of DR-mediated apoptosis in type II epithelial cells, including cleavage of caspase-8, cleavage of the pro-apoptotic Bcl-2 family member BID to tBID, and activation of caspase-3. Second, PTEC constitutively express the DRs DR5, Fas, and TNFRI, as assessed by flow cytometry, and DR expression is significantly decreased following exposure to apoptotic targets, consistent with receptor activation and internalization. A fourth DR, DR3, is not expressed constitutively by PTEC, but is induced following exposure to apoptotic targets. Third, decreased DR expression correlates with activation of caspase-3 and induction of apoptosis. Surprisingly, DR activation appears to occur in a ligand-independent manner. No DR ligand (DR-L) expression (TRAIL, FasL, or TNF) is seen in responder PTEC by flow cytometry (surface or intracellular) or by ELISA (secreted into media). Moreover, target-induced apoptosis of PTEC responders was not prevented by inhibitors of DR-L, nor was it induced by addition of soluble DR-L.

Conclusions: Exposure of viable PTEC to apoptotic (but not necrotic) targets induces PTEC apoptosis via DR-dependent mechanisms. Surprisingly, target-induced apoptosis occurs in a ligand-independent manner, with recognition of apoptotic (but not necrotic) targets leading to DR-L-independent egagement of DRs. We hypothesize that PTEC injury *in vivo* is characterized by two distinct waves of cell death. In the 1st, PTEC death is the direct result of ischemic or other injury. In the 2nd, PTEC death is independent of injury, and the result of DR activation by recognition of adjacent dead or dying cells.

Funding: Clinical Revenue Support

FR-PO095

Dynamin Regulates Membrane Tension in Renal Epithelial Cells by Establishing Architecture of Actin Cortex

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Background: The GTPase dynamin is essential for podocyte structure and function as it plays a role in regulating endocytosis and the actin cytoskeleton. Previously, we showed that dynamin can directly bind to actin and regulate actin polymerization. Importantly, our studies demonstrated that pharmacological targeting of dynamin with a small molecule, Bis-T-23 that promotes formation of dynamin oligomerization (Dyn^{OLIGO}), ameliorated kidney injury in animal models of human kidney disease by recovering functional actin structures in injured podocytes. Recently, dynamin is also reported to orchestrate the global actomyosin cytoskeleton that underlies renal epithelial cell polarity independent from its role in endocytosis. Here, we expand the role of Dyn^{OLIGO} to include regulation of membrane tension, and thus endocytosis in renal epithelial cells by establishing architecture of actin cortex.

Methods: Polarized renal epithelial cells (Inner Medular Collecting Duct) were used for this study. Atomic force microscopy was utilized to determine membrane tension. Actin polymerization assays were performed with cell lysates from IMCD cells. The structure of actin filaments was evaluated by electron microscopy of negatively stained specimens. Endocytosis was examined in IMCD cells stably expressing eGFP-clathrin light chain by Total Internal Reflection Fluorescence Microscopy, followed by computer-based image analysis.

Results: Using a combination of distinct dynamin mutants and Bis-T-23 we show that Dyn^{OLIGO} defines the length of actin filaments in conjunction with gelsolin. In addition, we show that dynamin crosslinks actin filaments into distinct structures in conjunction with its oligomerization state and the length of the actin filaments. Importantly, our data demonstrate that Dyn^{OLIGO} regulates membrane tension most likely by defining and crosslinking cortical actin. Furthermore, dynamin's effect on cell surface tension indirectly influences the speed of clathrin coated pit maturation in polarized renal epithelial cells.

Conclusions: Our study defines a novel role for Dyn^{OLIGO} cycle as a direct regulator of membrane tension and indirect regulator of endocytosis by orchestrating actin cortex architecture in polarized renal epithelial cells.

Funding: NIDDK Support

FR-PO096

Mucin 1 Prevents Accelerated Shedding of Kidney Injury Molecule-1 Following Ischemic Renal Injury

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Background: Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein that is rapidly induced after kidney injury in the proximal tubule (PT). The ectodomain of KIM-1 is cleaved and thereby constitutively shed into the urine providing a sensitive biomarker for kidney injury. It was reported recently that a transcription factor STAT3 is phosphorylated by extracellular signal-regulated kinases 1 and 2 (ERK1/2) and/or checkpoint kinase 1 (ChK1) following kidney injury and thereby upregulates KIM-1. KIM-1 also has anti-inflammatory role as it mediates phagocytosis of apoptotic and necrotic cells (efferocytosis) following kidney injury. However, the accelerated shedding of KIM-1 regulated by p38 MAPK blocks efferocytosis as the excess soluble KIM-1 acts as a decoy to cell-associated KIM-1. Mucin 1 (Muc1) is a transmembrane glycoprotein found primarily in the distal nephron that is also induced in the PT following kidney injury. We previously published data showing that Muc1 plays a protective role during ischemia-reperfusion injury (IRI) by stabilizing both HIF-1a and b-catenin.

Methods: More recently, using our hanging-weight protocol of 20 min ischemia and 48 h recovery, we observed a significant two-fold higher level of urinary KIM-1 as well as more severe kidney injury in Muc1 KO mice when compared to wild-type (WT) littermates. There was no significant difference in the levels of neutrophil gelatinase-associated lipocalin (the distal tubule injury biomarker NGAL) between Muc1 KO and WT littermates. Based on these findings, we tested the hypothesis that Muc1 plays a protective role during IRI by modulating the pathways known to regulate PT KIM-1 activity.

Results: Immunoblots of kidney tissue revealed that levels of both ERK1/2 and ChK1 were significantly higher in Muc1 KO mice when compared to WT littermates. Furthermore, the cytoplasmic and nuclear levels of active STAT3 were significantly higher and thus KIM-1 levels in Muc1 KO mice when compared to WT littermates. Moreover, levels of phosphorylated p38 MAPK are significantly higher in Muc1 KO mice when compared to WT littermates which enhances KIM-1 shedding, and consequently more severe kidney injury.

Conclusions: These results support the likelihood that Muc1 regulates KIM-1 function by regulating both its expression and shedding following kidney injury.

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FR-PO097

Gene Deletion of the Na-Glucose Cotransporter SGLT2 Does Not Affect Kidney Injury or Recovery in a Murine Model of Severe AKI

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Background: In normoglycemia, the renal Na-glucose cotransporter SGLT2 reabsorbs ~97% of filtered glucose in the early proximal tubule, while SGLT1 reabsorbs the remaining glucose in the downstream S3 segment. Pretreatment with an SGLT2 inhibitor appeared protective at 24 hrs after ischemia-reperfusion (IR)-induced acute kidney injury (AKI) in mice (PLoS ONE 11(7):e0160478, 2016). Here we determined whether gene knockout of SGLT2 (KO) affects kidney injury or recovery following IR.

Methods: Male KO and wild-type (WT) mice (C57BL/6J) underwent sham surgery (Sham) or IR (25 min of bilateral renal artery clamping) under ketamine/xylazine anesthesia, while body temperature was maintained at 36-37°C (n=7-15/group). Urine and blood were collected at several time points. GFR was measured 14 days after IR by plasma elimination kinetics of FITC-sinistrin in conscious mice. Kidneys were harvested 23 days after IR for renal gene expression analysis by RT-qPCR.

Results: On day 1 after IR, plasma creatinine (by LC-MS-MS) increased to similar levels in KO-IR and WT-IR (1.96±0.19 vs 1.87±0.25 mg/dL, NS) vs Sham groups (0.14±0.01 vs 0.11±0.01 mg/dL, NS); fractional urinary glucose excretion (based on creatinine) increased from 27 to 62% in KO-IR and from 0.1 to 20% in WT-IR. IR reduced urine osmolality and increased plasma osmolality to a similar extent in KO-IR and WT-IR; this was associated with a similar increase in urinary KIM-1 to creatinine ratio, a marker of proximal tubule injury. On day 14, GFR was similarly reduced in KO-IR and WT-IR (2.4±0.2 vs 2.8±0.3 µL/min/g BW, NS) vs Sham groups (12.0±0.8 vs 11.9±0.9 µL/min/g BW, NS). On day 23, plasma creatinine (0.28±0.03 vs 0.32±0.03 mg/dL, NS) and plasma osmolality were partially restored in KO-IR and WT-IR, and urine osmolality and renal mRNA expression of Na-2Cl-K cotransporter NKCC2 were reduced at similar levels vs. Sham groups. Moreover, renal mRNA expression of markers of injury, fibrosis, inflammation and oxidative stress (KIM-1, type 1 collagen, TGFB1, MCP-1, NOX2) was significantly and similarly increased in KO-IR and WT-IR versus Sham groups.

Conclusions: Absence of SGLT2 did not affect the initial injury and impairment of kidney function or the subsequent partial kidney function recovery in a mouse model of IR-induced severe AKI.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO098

Urinary Symmetric Dimethylarginine Reflects Mild Renal Damage After Cisplatin Treatment in Rats

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Background: Serum symmetric dimethylarginine (SDMA) correlates with renal function, but the usefulness of measuring urinary SDMA levels is unclear. Here, we studied if urinary SDMA levels reflected mild nephropathy after cisplatin (CDDP) treatment that failed to increase serum creatinine (SCr) in rats.

Methods: [*Single CDDP treatment*] Eight-week-old male Wistar-ST rats were divided into control and CDDP groups, treated with saline and CDDP 1 mg/kg intraperitoneally, respectively. SCr, blood urea nitrogen (BUN), and urinary and serum SDMA levels were measured before and 5 days after treatment. SDMA was measured by ultra performance liquid chromatography-tandem mass spectrometry. Damage to proximal tubules (PTs) was evaluated by H&E staining. mRNA expression levels of organic anion transporter1 (Oat1) which transports SDMA were measured by real-time PCR. [*Multiple CDDP treatment*] We formed groups that were treated with saline and CDDP 1 mg/kg every 7 days (day 0, 7, 14, and 21) to study the effects of multiple CDDP treatment cycles. SCr, BUN and serum

and urinary SDMA levels were measured at day 0 and day 5 in each cycle. Damage of PTs were studied 28 days after treatment. Statistical analysis was performed by Welch's *t*-test.

Results: [*Single CDDP treatment*] SCr and BUN unchanged 5 days after treatment between control and CDDP groups. However, necrosis of PTs was partly observed in the CDDP group. Urinary SDMA levels in the CDDP group significantly increased on day 5 ($P<0.01$); serum SDMA levels did not change. mRNA expression levels of Oat1 unchanged between control and CDDP group. [*Multiple CDDP treatment*] SCr and BUN did not change even after 3 CDDP treatment cycles compared with control group. In CDDP group, heteromorphic regenerating endothelium was observed. Urinary SDMA in CDDP group was significantly increased compared with control group from day 5 until the endpoint ($P<0.01$).

Conclusions: Urinary SDMA levels reflect the mild damage of PTs after CDDP treatment, which SCr and BUN could not reflect. Thus, urinary SDMA may be a better biomarker than SCr and BUN.

FR-PO099

Involvement of Acid-Sensing Ion Channels in Ischemia/Reperfusion Induced Kidney Injury

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Background: Acidic microenvironment is commonly observed in ischemic tissue. In the kidney, extracellular pH dropped from 7.4 to 6.5 within 10 min initiation of ischemia. Acid-sensing ion channels (ASICs) represent a family of H^+-activated Na^+ channels. Among six ASICs subunits, ASIC1a and ASIC3 are high proton sensitive, which can be activated by pH drops from 7.4 to 7.0 or lower. However, ASIC1a is the only one that is permeable to Ca^{2+} besides Na^+. Thus, activation of ASIC1a can mediate the intracellular Ca^{2+} accumulation and play crucial roles in apoptosis of neuron. The aim of the present study was to test the hypothesis that extracellular acidosis caused by ischemia increases renal epithelia cell apoptosis through ASIC1a-mediated calcium entry.

Methods: Immunofluorescence double staining and confocal analysis were applied to observe the co-localization of ASICs with AQP1 (proximal tubule marker), THP (thick ascending limbs and distal tubule marker) and Synaptopodin (podocyte marker). ASIC1a inhibitor PcTx-1 and ASIC3 inhibitor APETx-2 was injected previously to IR operation. After that, the pathological and functional injury of the kidney was assessed by PAS staining and serum creatinine, and the apoptosis of kidney epithelia cells was measured by TUNEL staining and immunohistochemical reaction of caspase3. To demonstrate the underlying mechanism of ASICs induced renal IRI, HK-2 cells was pretreated with PcTx-1 before hypoxia, the intracellular concentration of Ca^{2+}, mitochondrial transmembrane and apoptosis was measured by Fluo-4/AM, JC-1 and AnnexinV/PI and analyzed by flow cytometry.

Results: ASIC1a was found to be co-localized with AQP1 and Synaptopodin. ASIC3 was detected majorly in podocyte and mesenchyma. IRI up-regulated the expression of ASIC1a, however, had little effect on ASIC3, both in vivo and in vitro. Additionally, blocking ASIC1a by administration of PcTx-1 protects kidney from ischemia/reperfusion injury. Inhibition of ASIC3 by APETx2 had no significant effect on renal ischemia/reperfusion injury. Moreover, Blocking ASIC1a attenuated ischemia/reperfusion induced Ca^{2+} overflow, loss of mitochondrial transmembrane potential and apoptosis in HK-2 cells.

Conclusions: The results revealed that ASIC1a localized in the kidney proximal tubular and contributed to ischemia/reperfusion induced kidney injury. Consequently, targeting the ASIC1a may prove to be a novel strategy for AKI patients.

Funding: Clinical Revenue Support

FR-PO100

Mechanisms of Sex-Dependent Development of Acute Renal Failure - Insights from Preconditioning Experiments

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Background: Experimental work on acute kidney failure in mice shows a clear sex distribution - the severity of renal failure in females is significantly lower than in males, however, the mechanisms are not clear. Interestingly, preconditioning (caloric restriction, hypoxia) prevents acute kidney injury (AKI) reliably. The aim of the work is to evaluate sex-specific mechanisms of the protective effect of caloric preconditioning.

Methods: 14 week old male and female C57Bl6 wild-type mice underwent no preconditioning serving as a control group or four weeks of a calorie-restricted diet as a method of preconditioning prior to ischemia-reperfusion-injury (IRI). Afterwards, we compared control animals with animals after CR and males and females by phenotyping (histology, urea).

Results: IRI led to a pronounced kidney damage in males compared to a significantly lower damage in females. CR can completely prevent kidney failure in males. There is no significant improvement in the female mice compared to the untreated females. For further investigations, we performed a transcriptome analysis after preconditioning and were able to demonstrate the downregulation of a cytochrome P450 enzyme, Cyp4a12a, which is predominantly expressed in male mice. Cyp4a12a is necessary for the enzymatic production of 20-HETE, a derivative of arachidonic acid, which has an influence on renal regulation of blood pressure and volume retention. After the treatment of preconditioned animals with 20-HETE, the protective effect of caloric restriction can be abrogated. This suggests a possible relationship between the effect of preconditioning, sex, and a reduction of the concentration of 20-HETE.

Conclusions: The fact that female animals show a significant reduction of damage compared to males emphasizes the importance of the sex-specific analysis of the development of acute renal failure. In addition, we can report on the effect of caloric restriction and sex depending on the concentration of 20-HETE for the first time.

FR-PO101

Selective Vasopressin V1a Receptor Antagonism Improves Renal Oxygenation and Perfusion in AKI

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Background: Vasopressin (AVP) is a neurohormone with a well understood role in urinary volume control via activation of V2 receptors expressed in the collecting duct. The function of renal V1a receptors, which are broadly expressed on vascular smooth muscle cells throughout the medullary vasa recta, in mesangial as well as in macula densa cells, is less well understood. Since reduced blood supply and tissue hypoxia are frequent findings in kidney diseases, we aimed to investigate the potential benefit of selective V1a antagonism (using relcovaptan, SR 49059) in rat models of acute kidney injury (AKI).

Methods: The effects of relcovaptan on renal blood flow (RBF) and tissue oxygenation were investigated in isolated perfused rat kidneys as well as in anesthetized rats (n=7 per group) via Laser Doppler Flowmetry in settings of increased AVP levels induced by either infusion of AVP or renal ischemia/reperfusion injury (I/RI).

Results: Relcovaptan (0.3–300 nM; $p<0.001$) significantly improved the AVP-mediated (50 nM) reduction of perfusate flow in concentration-dependent manner while having no effect on urine excretion. *In vivo*, infusion of AVP (50 ng/kg/min i.v.) significantly increased mean arterial pressure (137±3; mean±SEM) which was normalized by relcovaptan in a dose-dependent manner (108±3; $p<0.01$). Infusion of AVP reduced both renal perfusion and tissue oxygenation (pO_2; 7.5±4). Relcovaptan dose-dependently restored renal perfusion and significantly increased pO_2 (30.7±6.4; $p<0.01$). Systemic hemodynamic parameters remained stable under I/RI conditions and concomitant infusion of relcovaptan. Fifteen minutes of ischemia resulted in decreased levels of both RBF and pO_2 after reperfusion in comparison with basal levels. In contrast, selective V1 a receptor antagonism significantly improved pO_2.

Conclusions: Selective V1a inhibition exerts beneficial effects on renal oxygenation under different pathological settings and might be a promising therapeutic approach to improve kidney hypoxia and subsequently kidney function in conditions of increased AVP levels, such as AKI and CKD.

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FR-PO102

Partitioning Defective Par1a Deletion Attenuates Renal Fibrosis in Mice

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Background: Chronic kidney disease (CKD) affects 1 in 7 U.S. adults; CKD leads to both increased morbidity and mortality. CKD progression correlates with tubulointerstitial fibrosis. As shown in mouse models, fibrosis is driven by Notch and Wnt activation. Notch and Wnt are important renal developmental pathways. In prior work from our laboratory focused on the developing kidney, Notch signaling pathway expression was decreased in Par1a/b mutant mice (*Par1a+/-:Par1b-/-*). Par1a and 1b are serine threonine kinases: they regulate protein trafficking, cell-cell adhesion, cell-matrix adhesion and the actin cytoskeleton. Par1a and 1b are paralogues and compensate for one another: while *Par1a+/-:Par1b-/-* mice die after birth, individual Par1a or 1b knockout mice have no renal developmental phenotype. We hypothesized: Loss of Par1a or 1b would attenuate Notch signaling and renal fibrosis.

Methods: To examine the expression of Par1a/b and Notch signaling components in renal injury, immunoflorescence (IF) staining was performed; Par1a and 1b paralogue specific antibodies were used. For acute kidney injury, mice were injected with 20 mg/kg cisplatin injection i.p. For chronic kidney injury, folic acid nephropathy and unilateral ureteral obstruction were used. To test the role of Par1a in renal fibrosis, folic acid injection (250 mg/kg dissolved in 300 mM NaHCO3) was performed in *Par1a-/-* and *Par1a+/+* mice. Vehicle injected mice served as controls. To detect renal fibrosis, Picrosirius red staining of collagen was performed. Quantification of 20x images was performed using Image J.

Results: Par1b expression increased in acute kidney injury, while Par1a expression increased predominantly in chronic kidney injury models. Consistent with other studies, Notch signaling component expression also increased following kidney injury. Folic acid injected *Par1a-/-* mice had decreased renal fibrosis: as quantified by sirius red staining, percent area of fibrosis was 12 +/- 6.8 % in folic acid treated *Par1a+/+* vs 3 +/- 2.2% in *Par1a-/-* kidneys. (p-value <0.01)

Conclusions: Par1a and Notch signaling pathway member expression are increased in renal fibrosis mouse models. In mice, Par1a deletion was protective against fibrosis. Par1a is a potential modifier of Notch activation during renal fibrosis.

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FR-PO103

A Downstream Molecule of 1,25-Dihydroxyvitamin D3, Alpha-1-Acid Glycoprotein, Protects Against Mouse Model of Renal Fibrosis

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Background: Renal fibrosis, the central feature of the progression of chronic kidney disease, is associated with unremitting renal inflammation. 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), the active form of vitamin D, has been reported for its anti-renal fibrotic effect in model of unilateral ureteral obstruction (UUO), but its molecular mechanism is still unknown.

Methods: ICR mice (male, 4-week-old) were randomized and anaesthetized before the abdomen was opened, then the left ureter was ligated with 4-0 silk and the abdomen was closed with sutures. 1,25(OH)2D3 was administered *i.p.* daily from day 0 to day 6 of the UUO treatment. Alpha-1-acid glycoprotein (AGP) was administered *i.v.* daily from day 1 to day 6 of the UUO treatment. Mice were sacrificed on day 7 after surgery. Phorbol 12-myristate 13-acetate (PMA)-treated THP-1 cells or HepG2 cells were treated with 1,25(OH)2D3 or AGP and incubated for 48 hr. LPS were incubated for 48 hr. Real-time PCR, immunofluorescence and Picrosirius Red staining were performed.

Results: Renal fibrosis and inflammation observed in the kidney of the UUO mice were attenuated by the treatment of 1,25(OH)2D3. Interestingly, the plasma protein level of AGP, a downstream molecule of 1,25(OH)2D3, was increased following the administration of 1,25(OH)2D3 to healthy mice. Additionally, the increase of *ORM1*, an AGP gene, was observed in 1,25(OH)2D3-treated HepG2 cells and THP-1-derived macrophages. To investigate the involvement of AGP, exogenous AGP was administered to the UUO mice, resulting in attenuated renal fibrosis and inflammation. Regarding the mechanism, we found the mRNA expression of CD163, a monocyte/macrophage marker with anti-inflammatory potential, was increased in THP-1-derived macrophages under 1,25(OH)2D3 or AGP stimulus, respectively. Moreover, AGP prevented lipopolysaccharide-induced macrophage activation.

Conclusions: We found for the first time that AGP could be a key molecule in the protective effect of vitamin D against renal fibrosis. AGP may function as an important immune regulator, replacing vitamin D to offer therapeutic strategy for renal inflammation and fibrosis.

FR-PO104

Reduction of Excess Renal Iron Acquisition Diminishes Tubular Injury in Experimental Focal Segmental Glomerulosclerosis

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Background: Renal iron accumulation as a result of proteinuria is suggested to play a role in progression of chronic kidney disease (CKD). Here, we studied the molecular mechanisms of renal iron loading in experimental focal segmental glomerulosclerosis (FSGS; Thy-1.1 mouse model) and investigated if reduction in renal iron loading decreased tubular injury.

Methods: Thy-1.1 mice were injected with a monoclonal anti-Thy-1.1 antibody (mAb) or saline as control and sacrificed immediately after injection (D1), day 8 (D8) or day 22 (D22).

Results: Injection of mAb resulted in immediate and persistent albuminuria ($p<0.01$). Renal injury in mAb-injected mice was confirmed by standard histology, increased urinary kidney injury markers KIM1 ($p<0.05$) and NGAL ($p<0.01$) and elevated renal mRNA expression of *IL-6* ($p<0.001$) and *HO-1* ($p<0.01$). Increased distal tubular iron accumulation was observed with increasing renal injury in mAb-treated mice. QPCR analysis indicated distal iron accumulation via the NGALR and not transferrin receptor-1 (TfR1). *In vivo* silencing of renal NGALR resulted in significantly reduced *HO-1* and *L-ferritin* mRNA levels at D8 (both $p<0.05$), indicating reduced iron accumulation and injury. Systemic iron depletion by iron-deficient diet reduced renal iron accumulation and urinary KIM1 and NGAL on D8 (both $p<0.05$), but not D22. Interestingly, the iron-deficient diet did not reduce renal *IL-6* mRNA, whereas an iron-rich diet diminished *IL-6* (D22, $p<0.001$) and urinary KIM1 ($p<0.05$) and NGAL ($p<0.001$) on D8 and D22, despite concurrent increased iron deposition and oxidative stress as indicated by HO-1 immunostaining and mRNA expression ($p<0.001$). Alternatively, we aimed to prevent excess renal iron deposition by reducing glomerular protein filtration (captopril; CA) or iron chelation (deferoxamine; DFO) for 7 days after mAb injection. Both CA and DFO reduced renal iron accumulation, and urinary KIM1 and NGAL ($p<0.05$) on D8, which did not last until D22, suggesting requirement for continuous treatment.

Conclusions: In conclusion, our results indicate that prevention of excess renal iron accumulation could be useful to halt progression of tubular injury in CKD. However, disturbances in systemic iron balance are not feasible, warranting a targeted renal approach.

Funding: Private Foundation Support

FR-PO105

TRPM7 Is a Potential Therapeutic Target in Progressive Renal Disease

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Background: Unilateral Ureteral Obstruction (UUO) is a representative model of nephritis with progressive tubulointerstitial injury and renal fibrosis occurring by inflammation that is suitable for investigating the cellular and molecular events that occur during progressive renal fibrosis associated with cell proliferation and apoptosis. Blocking tubular epithelial cell proliferation is crucial to preventing the renal tubule dilation and the progression of kidney damage. TRPM7 belongs to the Transient Receptor Potential Melastatin family of ion channels. Our work shows that TRPM7 is a Ca^{2+}- and Mg^{2+}-conducting ion channel fused with a functional kinase. TRPM7 plays a key role in a variety of diseases, including malaria invasion, neuronal death in ischemia, cancer and cardiac fibrillation. TRPM7 is aberrantly over-expressed in lung, liver and heart fibrosis. It is also overexpressed after renal ischemia-reperfusion, an event that induces kidney injury and fibrosis. However, the role of TRPM7 is unclear in kidney fibrosis.

Methods: We created UUO mouse model, compared the expression level of TRPM7 in UUO kidneys and control kidneys at Day7 using qRT-PCR, western blotting assay and immunohistochemistry. Our lab's drug screening efforts have identified waixenicin A that is the currently only specific and potent TRPM7 inhibitor. Using NRK49F and NRK52E cells, we investigated the inhibitory efficacy of waixenicin A on MTT cell growth assay.

Results: The expression levels of TRPM7 mRNA and protein in UUO kidneys were higher than control kidneys, TRPM7 particularly increased on tubular epithelial cells. The TRPM7 positive cell number increased twice on both of renal tubular epithelial cells and tubulointerstitial cells in UUO kidneys compared to control kidneys. Waixenicin A inhibited the cell growth of renal epithelial cells and fibroblasts *in vitro*.

Conclusions: TRPM7 up-regulated in progressing inflammatory renal damage, waixenicin A could be capable of inhibiting kidney cell proliferation and fibrosis in renal disease.

Funding: Private Foundation Support

FR-PO106

Apolipoprotein L1 Is Associated with Larger HDL Particles in CKD

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Background: Apolipoprotein L1 (**ApoL1**) is a potential mediator of inflammatory kidney injury and disease progression. Two polymorphisms in the APOL1 gene (G1 and G2) increase the risk of chronic kidney disease (**CKD**) in Blacks. The mechanism of injury may involve ApoL1 expressed within the kidney (e.g., in podocytes) and/or ApoL1 secreted by the liver (i.e., in plasma). We have previously demonstrated that ApoL1 is depleted from the HDL2/3 fraction of plasma in patients with lower eGFR. In this study, we aimed to quantify the distribution of ApoL1 within plasma to help clarify the biochemistry of ApoL1.

Methods: We determined ApoL1 phenotype and plasma concentrations using targeted mass spectrometry (**MS**) among 424 participants from the Seattle Kidney Study, a racially diverse, well-characterized cohort of patients with CKD. For 20 participants, we used asymmetric flow field-flow fractionation (**AF4**) to fractionate plasma into 40 fractions, which were each analyzed using MS to determine relative concentrations of ApoL1.

Results: Plasma concentration of ApoL1 was associated with age, race, and ApoL1 phenotype (**Table 1**). In addition, both plasma concentration of ApoL1 and the ratio of the amount of ApoL1 in HDL to total plasma ApoL1 were directly correlated with eGFR. However, only the ratio of ApoL1 in HDL to total ApoL1 was significantly associated with eGFR, after controlling for age, race, and phenotype, which suggested that ApoL1 is located in a different fraction of plasma in CKD. We then used AF4 and MS to determine that ApoL1 is associated with larger particles (similar to HDL1 particles containing ApoE) in participants with lower eGFR, after controlling for race and genotype ($p<0.01$).

Conclusions: These results demonstrate that plasma ApoL1 is biochemically different in patients with reduced eGFR, which may be related to the role ApoL1 plays in the progression of CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

	Total ApoL1 in plasma		Ratio of ApoL1 in HDL to total plasma ApoL1	
Independent variable	**% Change**	**p-value**	**% Change**	**p-value**
Age (per year)	0.57% lower	<.001	0.12% higher	0.73
Race (Black) [1]	40% higher	<.001	63% lower	<.001
1 ApoL1 risk allele [1]	34% higher	<.001	66% lower	<.001
2 ApoL1 risk alleles [1]	15% higher	0.045	66% lower	<.001
eGFR (per loss of 10 ml/min/1.73m2)	1.7% lower	0.024	11% lower	<.001
eGFR (per loss of 10 ml/min/1.73m2) [2]	<.01% lower	0.89	12% lower	<.001

[1]White or G0/G0 individuals as comparator. [2]Model with age, race, number of risk alleles, and eGFR included.

FR-PO107

Inhibiting ApoL1 Translocation to Mitochondrial Matrix Can Protect Against Risk Variant Mediated Cytotoxicity

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Background: African Americans with two copies of ApoL1 risk variants (G1 and G2) are at high risk of developing chronic kidney disease. The subcellular localization of ApoL1 based on imaging studies has been a subject of conflicting reports.

Methods: HEK293 stable cells that express G0, G1, G2 in the presence of tetracycline were made using the T-Rex system. Cells were transfected with siRNA for specific outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM) translocase machinery components and then ApoL1 expression was induced with tetracycline. After ApoL1 induction, mitochondrial and cytosolic fractions were prepared by differential centrifugation and presence of ApoL1 in each fraction was determined by immunoblotting. We also measured oxygen consumption rate using a Seahorse assay and measured cytotoxicity after knocking down specific OMM and IMM components.

Results: Using a biochemical approach to study ApoL1 localization, we found a large fraction of G0 as well as G1 and G2 in the mitochondria. Protease digestions of isolated mitochondria demonstrated that ApoL1 protein had been translocated into the mitochondrial matrix. siRNA knock-down of OMM protein TOMM20, which is involved in recognizing matrix-targeting presequences on nuclear-encoded proteins, reduces ApoL1 levels in mitochondria. TOMM20 knockout also rescues G1 and G2 mediated mitochondrial dysfunction as measured by oxygen consumption rate and reduces cell death. Knock-down of TIMM23/TIMM17 complex components, which are essential for translocating matrix-targeted proteins, rescues G1- and G2-mediated cytotoxicity whereas knock-down of TIMM22, which is essential for protein insertion into the IMM, has no effect.

Conclusions: G1 and G2 need to translocate to mitochondrial matrix to induce toxicity. Since both G0 and risk variants are translocated to the mitochondrial matrix, elucidating different behavior of these variants after mitochondrial translocation will be important for understanding why only the risk variants cause kidney injury.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities, Other U.S. Government Support, Commercial Support - Vertex Pharmaceuticals

FR-PO108

Combined Effects of GSTM1 Deficiency and Podocyte-Specific APOL1 G0 and G2 Transgene on Blood Pressure and Albuminuria in a Mouse Model of CKD

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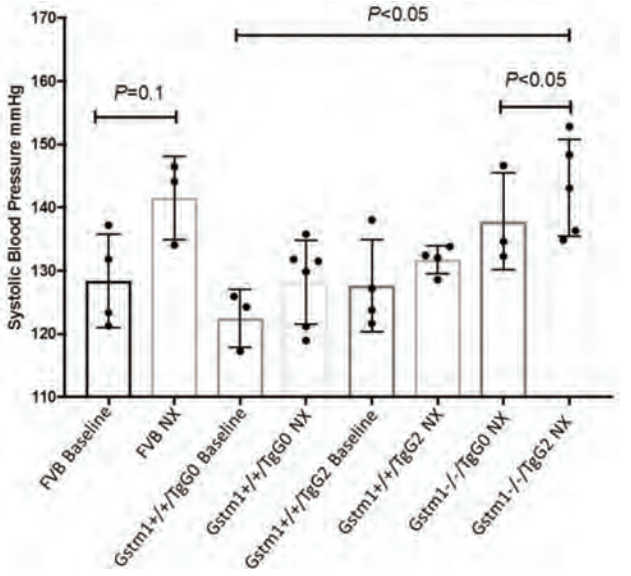
Background: We reported that *GSTM1* null allele (*GSTM1(0)*) is associated with accelerated kidney disease progression in the African Americans Study of Kidney Disease (AASK) participants, and those carrying both *GSTM1(0)* and *APOL1* risk variants had the worst composite outcomes. This suggests a potential interaction between these 2 genes in CKD. Transgenic mice expressing the human *APOL1* high risk variants in podocytes did not show kidney disease at baseline; however, females developed preeclampsia during pregnancy. The objective of this study was to investigate whether GSTM1 interacts with APOL1 to influence hypertension (HT) and kidney disease development in a mouse model of CKD.

Methods: We generated *Gstm1* deficient mice on the FVB background. We crossed the FVB *Gstm1-/-* mice with FVB podocyte specific *APOL1* G0 or G2 Transgenic mice (TgG0 and TgG2), respectively. The offspring were subjected to subtotal nephrectomy (Nx). Wild-type FVB were used as controls. After a 10-day training period, baseline systolic blood pressure (SBP) and SBP 6-8 weeks after Nx were measured using tail-cuff method. Urinary albumin and creatinine were measured using commercially available ELISA kits. Data are reported as means ± SD.

Results: There were no significant differences in albumin/creatinine ratios among groups. However, *Gstm1-/-/APOL1TgG2* mice had significantly higher SBP compared to other groups and also higher than *Gstm1-/-/APOL1TgG0* ($P < 0.05$) (see graph).

Conclusions: In experimental CKD, mice carrying podocyte specific *APOL1* G2 Tg and deficient of GSTM1 enzyme have worst HT, independent of albuminuria. These results suggest a potential interaction between these two genes in the development of HT in CKD.



Gstm1-/-/APOL1TgG2 mice had significantly higher SBP compared to other groups.

FR-PO109

Glomerular Endothelial Cell Senescence Drives Aged-Related Glomerulosclerosis via PAI1

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Background: Chronic kidney disease (CKD) is a major public health problem with a prevalence that dramatically increases with age. One of the most frequent histological lesions observed in elderly is glomerulosclerosis. However, its pathophysiology is still unclear. A recent study indicated that cellular senescence may be implicated since targeted apoptosis of senescent cells in aging murine models delays glomerulosclerosis. However, how cellular senescence triggers the development of glomerulosclerosis is unknown. Elucidating this issue was the aim of our study.

Methods: In this aim, we used several murine models including wild type and transgenic mice experiencing physiological and accelerated aging.

Results: As expected, 24 months-old mice developed sclerotic glomeruli as compared to 4 months-old mice. Beta-galactosidase and 53BP1 staining revealed increased glomerular cell senescence with age. Interestingly, colocalization experiments demonstrated that senescence interested almost exclusively endothelial cells. Consistently, we observed that endothelial glomerular cells were blocked in G1. This phenotype was associated with an increased expression of several components of the senescence associated secretory phenotype (SASP). Among these, plasminogen activator inhibitor 1 (PAI1), a senescence inducer and mediator, was particularly interesting, since its expression increased in endothelial cells. These results were confirmed in an experimental mouse model of accelerated aging (sublethal irradiation at 8 weeks and sacrifice 12 months later) as well as in patients treated with genotoxic. Interestingly, specific deletion of PAI1 in endothelial cells prevented cell senescence and the development of glomerulosclerosis during physiological aging in transgenic *VECad-CreXPAI1$^{flox/flox}$* mutant mice. Podocytes loss was also decreased in transgenic mice, suggesting a cross-talk between endothelial cells and podocytes.

Conclusions: In conclusion, our study uncovers the critical role played by endothelial senescence in the development of glomerulosclerosis and podocyte rarefaction in aging and identified PAI1 as a novel promising therapeutic target for preventing age-related CKD progression.

Funding: Government Support - Non-U.S.

FR-PO110

The Roles of Uremic Toxin Early Elimination on AKI to CKD Transition

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Background: The post-AKI fibrosis is emerging as a major driver of progressive CKD. However, the cause of abnormal renal recovery after AKI is multifactorial and still poorly understood. Indoxyl sulfate (IS) is a protein-bound uremic toxin produced by bacterial metabolism of the amino acid tryptophan, which excreted through organic anion transporter on renal tubular epithelial cells into urinary and generally accumulates in patients with CKD. Although the adverse effects of IS on CKD progression have been well documented, its impacts on post-AKI fibrosis are still unknown. Accordingly, we investigated whether

AKI induces an increased level of serum IS and its role in AKI to CKD transition. Also, the therapeutic potency of early elimination of uremic toxins by absorbent Kremezin (AST-120) was tested.

Methods: In animal study, the two-step unilateral ischemia reperfusion injury with contralateral nephrectomy (hereafter abbreviated as UIRI) was used as a post-AKI fibrosis model. Briefly, C57BL/6 mice were subjected to 30 minutes unilateral ischemia reperfusion injury and contralateral nephrectomy were conducted at day10, and then sacrificed at day 15. All mice are randomly divided into: (1) Sham, (2) UIRI, (3) UIRI + indole, (4) UIRI + indole+ AST-120, and (5) UIRI + AST-120. For in vitro investigation, HK-2 cells were treated with 1mM IS for 48 h, followed by 12 hours of hypoxia and 24 hours of reperfusion (H/R) to explore the underlying mechanism.

Results: In our animal studies, we observed an increased serum IS levels without simutaneous accumulation of small uremic toxin molecules following 10 days of UIRI. Furthermore, AST-120 administration actually reduced deterioration of renal function caused by UIRI combined with high protein intake. We also revealed the possible mechanisms underlying the IS-enhanced proximal tubule damage after AKI. IS exposure potentiated H/R-induced G2/M cell cycle arrest, which also aggravated ER stress-mediated epithelial mesenchymal transition (EMT) as demonstrated by 4-PBA-treated rescue experiments.

Conclusions: Our results support the pathological role of uremic toxins in post-ischemic AKI fibrosis, and low protein diets would be recommended to prevent advanced kidney disease progression. Furthermore, elimination of IS by AST-120 is likely to prove useful for the prevention/treatment of post-AKI renal impairment.

Funding: Government Support - Non-U.S.

FR-PO111

Kidney Genome Atlas: A Whole-Genome Landscape of More Than 2,000 Kidney Disease Patients

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Background: Chronic kidney disease (CKD) is a heterogeneous disease affecting more than 30 million people in the US, which is about 10% of the US population. Despite the urgent need for targeted therapeutics, the understanding of the mechanistic basis of CKD including the genetic variants that potentially drive it has lagged other diseases (e.g. cancer) for decades.

Methods: Here we report the generation and initial analysis of the Kidney Genome Atlas (KGA), the world's largest whole-genome landscape of individuals with molecularly defined kidney diseases. Focusing initially on focal segmental glomerulosclerosis (FSGS), related disorders, and diabetic kidney disease (DKD), KGA contains whole genome sequences (>30X coverage) from more than 2,000 patients and 2,500 matched healthy controls. Each genome is linked to longitudinal clinical records and for a subset of 500 patients, the atlas also includes matched transcriptomic data from microdissected glomerular and tubulointerstitial samples.

Results: The KGA has enabled the discovery of genetic variants associated with kidney disease and the integration of genomic and transcriptomic data to identify kidney disease-specific expression quantitative trait loci (eQTLs). The atlas also provides the foundation for establishing the relationships between genetic variants, histologic diagnoses, and quantitative clinical phenotypes of kidney function and disease progression. Computational integration of these datasets will enable the prioritization of candidate variants with putative disease modulating effect. Investigating and validating biological pathways derived from these analyses can also be used to stratify patients into subtypes most likely to respond to specific targeted therapies.

Conclusions: The KGA is a valuable resource fueling our understanding of the molecular mechanisms of kidney diseases at the whole genome scale.

Funding: Commercial Support - Goldfinch Bio.

FR-PO112

Sodium and Phosphate Dietary Additives Exacerbate Progression of CKD and Lead to Early Mortality

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Background: Fibroblast growth factor 23 (FGF23) increases in response to high phosphate diets and states of impaired phosphate excretion, such as chronic kidney disease (CKD). Excess FGF23 hasemerged as a novel and powerful risk factor for cardiovascular disease (CVD) and death in patients with CKD and in the general population. Multiple studies have shown that excess FGF23 is often due to high consumption of processed foods, enriched in phosphate and sodium additives, that stimulate FGF23 production and increase risks of death. We hypothesized that consumption of excess phosphate stimulates FGF23 production, and that presence of CKD and simultaneous consumption of excess sodium exacerbates FGF23 negative outcomes.

Methods: To investigate the effects of dietary intake of phosphate and sodium on cardiovascular and CKD disease progression, 5 week old wild-type (WT) and Col4a3^{KO} (CKD) mice were fed a control (Ctr), high sodium (HN), high phosphate (HP), or a high sodium-high phosphate (HPN) diet for 18 weeks. We assessed survival, renal function and serum FGF23 in 23 week old mice.

Results: Phosphate and/or sodium did not impact renal function or overall survival in WT mice. In contrast, HP, HN and HPN diets further impaired renal function in CKD animals compared to CKD-CTR mice. HP and HN diets decreased survival in CKD mice, CKD-HN and CKD-HP mice showing an average survival of 26 and 22 weeks, repectively, compared to CKD-CTR mice that live in average 34 weeks ($p<0.05$). Interestingly, phosphate and sodium in HPN diet did not show additive effects on the overall survival of CKD mice (27 weeks). Consumption of phosphate in HP and HPN diets increased ($p<0.05$) FGF23 in WT mice, by 20 fold in WT-HP and by 3 fold in WT-HPN compared to WT-CTR mice, whereas HN did not affect FGF23 levels in WT mice. CKD-CTR mice showed increased FGF23 (3 fold) compared to WT-CTR mice. HP, HN and HPN diets all increased FGF23 in CKD groups, with the highest increase found in CKD-HP mice (20-fold) while CKD-HN and CKD-HPN animals showed only 3 and 5 fold increase respectively, in FGF23 ($p<0.05$ vs CKD-CTR).

Conclusions: Overall, our data suggest that consumption of high phosphate rather than high sodium raises FGF23 in CKD, exacerbates decline in kidney function, and leads to early mortality.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

FR-PO113

Translational Profiling and RNA-Seq of Proximal Tubule Reveals Gender-Specific Transcriptional Patterns, Tubulointerstitial Signaling, and lncRNA Regulation During Kidney Fibrosis

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Background: Proximal tubule epithelial cells (PTEC) are central mediators of interstitial fibrosis in CKD. We applied Translating Ribosome Affinity Purification (TRAP) followed by RNA-seq to precisely measure the gene expression landscape of PTEC during renal fibrosis.

Methods: Bigenic Slc34a1^{GFPCreERT2}; R26$^{eGFP-L10a}$ mice received tamoxifen to activate expression of eGFP-L10a in PTEC with subsequent unilateral ureteral obstruction (UUO) surgery. Kidneys were harvested at day 5 or 10. Each group included three female and four male mice. PTEC-specific polysomal mRNA was isolated by affinity purification, and each sample sequenced to a depth of 30 million reads. Extensive informatic analysis identified critical genes and pathways, which were validated by *in situ* hybridization.

Results: Unexpectedly, we identified a group of genes with sexually dimorphic expression patterns including neuronal regeneration related protein (Nrep), interleukin 34 and nuclear factor interleukin-3-regulated protein (Nfil3). For both sexes, serpin family A member 10 (Serpina10), vascular cell adhesion molecule 1 (Vcam1), SRY-box 9 (Sox9), and nerve growth factor (Ngf) top the list of PTEC-specific highly upregulated genes after UUO. Functional annotations transcriptional changes in PTEC implicate the interleukin-1β and tumor necrosis factor signaling pathways in mediating tubule-interstitial crosstalk. Contrary to published reports, PTEC strongly upregulated Indian hedgehog (Ihh), not Sonic hedgehog (Shh), during renal fibrosis. All results were validated by quantitative PCR and *in situ* hybridization. Finally, two long intergenic noncoding RNAs (Snhg18 and predicted gene 20513) and microRNA 6358 were strongly upregulated in injured PTEC, suggesting novel regulatory roles in fibrosis. None of these genes have been described in kidney previously.

Conclusions: This is the first comprehensive RNA-seq-based transcriptional profile of PT cells during fibrosis. We reveal unexpected gene expression differences in male vs. female PT, validate novel pathways mediating tubule-interstitial crosstalk and identify novel lncRNA upregulation not previously associated with kidney.

Funding: NIDDK Support

FR-PO114

BION-1301: A Novel Fully Blocking APRIL Antibody for the Treatment of IgA Nephropathy

John Dulos, Paul Vink, Hans Van eenennaam, Andrea Van elsas. *Aduro Biotech Europe, Oss, Netherlands.*

Background: A PRoliferation Inducing Ligand (APRIL, TNFSF13) is a ligand for the receptors B cell maturation antigen (BCMA) and Transmembrane activator and CAML interactor (TACI). APRIL serum levels were found to be enhanced in patients diagnosed with IgA Nephropathy (IgAN) and treatment with an anti-mouse APRIL antibody reduced serum IgA and proteinuria increase in an IgAN mouse model (Kim Y.G. et al. PLOS one Sep 8, 2015). Altogether suggesting that the APRIL-axis is important in IgAN pathology and strongly supporting the development of our anti-APRIL antibody, BION-1301 to treat IgA nephropathy (IgAN).

Methods: BION-1301 affinity, binding to APRIL and blocking capacity to BCMA and TACI was characterized using Biolayer Interferometry and ELISA. A sinlge-dose non-human primate (NHP) PK and tolerability study was performed administering intravenous (i.v.) BION-1301 at 0.3, 3 and 30 mg/kg. Preclinical safety was assessed in a 4-week repeat-dose NHP study using weekly i.v. doses of 10, 30 and 100 mg/kg. In human primary B-cell cultures the effect of (anti-)APRIL on IgA production, BCMA and TACI expression was assessed.

Results: We developed a novel humanized high-affinity anti-APRIL antibody BION-1301 (KD 0.4 ± 0.15 nM, EC50 0.29 ± 0.05 nM). Its epitope was mapped to the BCMA and TACI binding site conferring fully blocking capacity to BION-1301. Blocking potency

(IC50) was 1.61± 0.78 nM (BCMA) and 1.29 ± 0.89 nM (TACI) respectively. The mouse anti-human parental antibody hAPRIL.01A inhibited APRIL-dependent B-cell proliferation and IgA production in vitro and in vivo (Guadagnoli et al. Blood Jun 23;117, 2011). In B-cell cultures, hAPRIL.01A reduced IgM, IgA and IgG-secreting cells after CpG pulse and APRIL stimulation. Following administration of a single-dose of BION-1301 to NHP, PK parameters typical for human IgG4 antibodies were observed, and confirmed a lack of tolerability issues. In a 4-week repeat dose NHP study BION-1301 demonstrated a favorable safety profile (No Observed Adverse Event Level was 100 mg/kg). Chronic exposure to BION-1301 led to a significantly reduced IgA level vs baseline of -50±14, -52±14, -59±7 % at 10, 30 and 100 mg/kg respectively.

Conclusions: Here, we report the in vivo and in vitro mechanism of action of a novel humanized APRIL neutralizing antibody modulating IgA, support the development of BION-1301 for the treatment of IgAN.

Funding: Commercial Support - Aduro Biotech

FR-PO115

Follistatin as a Novel Therapeutic Agent in CKD

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Background: Chronic kidney disease (CKD), characterized by progressively worsening glomerular and interstitial fibrosis accompanied by declining kidney function, is a major cause of morbidity and mortality. Follistatin (FST) is a glycoprotein which neutralizes members of the TGFβ superfamily, most prominently the activins. It does not directly inhibit TGFβ1. Recent studies have shown an increase in activin A in serum of mice with CKD. Here we assess the therapeutic efficacy of FST in a mouse model of CKD with reduced renal mass and proteinuria.

Methods: Male CD1 mice underwent either a 5/6 nephrectomy or sham surgery, after which 5μg human recombinant FST (PB01, Paranta Biosciences Ltd) or vehicle was given intraperitoneally every other day for 9 weeks. At endpoint, blood pressure, renal function, albuminuria and renal pathology were assessed.

Results: Activin A was significantly upregulated in the serum and kidneys of mice with CKD. Activation of Smad3, a downstream mediator of activin A signaling, was increased in CKD kidneys. This was inhibited by FST. Mice with CKD had elevated blood pressure, a significantly diminished glomerular filtration rate (GFR) and severe albuminuria. Pathologically, mice with CKD had prominent glomerulosclerosis and tubulointerstitial fibrosis, assessed using trichrome and picrosirius red staining. Immunoblotting showed increases in the profibrotic cytokine CTGF and the matrix proteins fibronectin, collagen Iα1 and collagen 4α1. Clinically, FST improved blood pressure, GFR and albuminuria, and pathologically both glomerulosclerosis and tubulointerstitial fibrosis were significantly attenuated.

Conclusions: Our data support a prominent pathologic role for the TGFβ family member activin A in CKD. We show that administration of the activin neutralizing protein FST is effective in preserving kidney structure and function and in attenuating the progression of CKD. These data highlight the promising role of FST as a novel renoprotective agent in CKD.

Funding: Government Support - Non-U.S.

FR-PO116

miR299a-5p Is a Pathogenic Driver of Renal Fibrosis in CKD

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Background: Chronic kidney disease (CKD) is a major cause of morbidity and mortality. It is characterized by glomerular and interstitial fibrosis. Glomerular mesangial cells (MCs) are a major contributor to glomerular fibrosis. Previously, we identified that caveolin-1 (cav-1) is required for basal and TGFβ1-induced MC synthesis of matrix proteins. The protective phenotype of cav-1 knockout (KO) MCs against fibrosis is associated with increased expression of a TGFβ family member neutralizing protein, follistatin (FST). To better understand the mechanism of FST upregulation and identify novel therapeutic targets, we performed a quantitative screen in cav-1 wild-type (WT) and KO MCs to identify differentially regulated miRNAs that bind to and regulate the 3'UTR of FST.

Methods: *In vitro* studies were carried out in primary MCs isolated from cav-1 WT and KO mice using standard molecular biology techniques. For *in vivo* studies, a 9-week 5/6 nephrectomy (5/6 Nx) mouse model of CKD was used.

Results: Expression and activity of miR299a-5p was significantly decreased in KO MCs which express high levels of FST. We confirmed that miR299a-5p regulates the 3'UTR of FST. In KO cells, FST downregulation increased TGFβ1-induced matrix synthesis. We thus examined whether miR299a-5p regulated this process. In WT MCs, TGFβ1 increased miR299-5p expression and downregulated FST, while exogenous FST reduced TGFβ1-induced matrix synthesis. Importantly, downregulation of miR299a-5p increased FST expression and decreased TGFβ1-induced matrix synthesis. Conversely, in KO cells, overexpression of miR299a-5p decreased FST expression and enhanced TGFβ1-induced matrix synthesis. These data demonstrate that miR299a-5p suppression of FST expression augments ECM production in response to TGFβ1, a key contributor to the pathogenesis of CKD. In the 5/6 Nx mouse model of CKD, we further identified significantly elevated expression of both TGFβ1 and miR299a-5p.

Conclusions: miR299a-5p expression is increased in the kidneys of mice with CKD. miR299a-5p augments TGFβ1-induced ECM production in glomerular MCs through downregulation of the antifibrotic protein FST. These data suggest that miR299a-5p plays a pathogenic role in the development and progression of renal fibrosis. Its inhibition thus represents a potential novel therapeutic target for the treatment of CKD.

Funding: Government Support - Non-U.S.

FR-PO117

Cyclophilin D Deficiency Is Not Protective in Aristolochic Acid Nephropathy

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Background: Cyclophilins are a family of enzymes which regulate protein folding. Of these enzymes, cyclophilin D (CypD) facilitates mitochondrial-dependant cell death during pathological conditions. CypD-/- mice are protected from acute kidney injury (AKI) following renal ischaemia/reperfusion injury, and exhibit less renal fibrosis in the unilateral ureteric obstruction model. However, the contribution of CypD in the transition of AKI to chronic kidney disease (CKD) is not known. The aim of this study was to determine the role of CypD in promoting the transition of AKI to CKD using the aristolochic acid-induced nephropathy (AAN) model.

Methods: Groups (n=10) of wild type (WT) and CypD-/- mice on the C57BL/6J background were given intraperitoneal injections of 2mg/kg aristolochic acid every 2nd day for 28 days. Mice were killed on day 28. Controls were untreated.

Results: AAN caused >2.5-fold rise in serum creatinine (sCr) in WT mice (34.3±9.9mmol/L vs 13.5±2.3mmol/L in controls; P<0.0001), with evidence of tubular damage (KIM-1 & α-Klotho mRNA levels; P<0.0001), increase in tubular cell death (cleaved caspase-3+ cells; P<0.0001), and significant renal fibrosis (collagen IV immunostaining, and collagen I & α-SMA mRNA levels; all P<0.0001 vs controls). CypD-/- mice were not protected from AA-induced renal dysfunction (sCr 37.0±14.3 mmol/L; P=N.S.), and showed no reduction in tubular damage, cell death or renal fibrosis. Further analysis showed that AAN in WT mice caused loss of peritubular CD31+ capillaries (P<0.0001), and infiltration of macrophages (CD68 & CD206 mRNA levels; P<0.0001) and T-cells (CD3 & IL-2 mRNA levels; P<0.0001). CypD-/- mice were not protected from peritubular capillary loss or macrophage infiltration in AAN. However, CypD-/- mice showed reduced T-cell infiltration and activation (CD3 & IL-2 mRNA levels; P<0.0001), including Th1 cells (T-bet mRNA levels; P<0.05).

Conclusions: CypD does not contribute to the transition of AKI to CKD in experimental AAN.

FR-PO118

Polymyxin and Neomycin (P+N) Attenuates Inflammation and Fibrosis in Unilateral Ureteral Obstructed (UUO) Kidney by Altering Macrophage Phenotype

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Background: Gut bacteria have been shown to modulate inflammation in both acute and chronic kidney injury. P+N are non-absorbable antibiotics that are used to sterilize the gut. UUO mice develop acute inflammation in one kidney after surgery which progresses to fibrosis within 7 days. We wanted to investigate if gut sterilization by P+N can affect inflammation and fibrosis in UUO mice.

Methods: UUO surgery was done by the method adapted from Vanderbilt O'Brien Center. One group of mice was treated with P+N 7 days before UUO. One group was untreated (UT). Control mice did not receive surgery or treatment (C). Mice were sacrificed 3 days (n=5/group) and 10 days (n=5/group) after UUO. Macrophage (Mo) and macrophage phenotype M1 and M2 were determined by flow cytometry. Inflammation markers MCP1, IL1β, and fibrosis marker α-smooth muscle actin (SMA) were assessed by immunoblot. Lipopolysaccharide (LPS) was measured by LAL assay.

Results: 3 Days post UUO: P+N treatment did decrease Mo influx in kidney but not Mo phenotype (Table). Only MCP1 increased in UT kidney compared to C, and P+N significantly lowered it (p<0.05). 10 Days post UUO: Although Mo in the kidneys of both groups was significantly higher, UT had more M1 and less M2 compared to P+N (Table). High levels of MCP1, IL-1β and SMA were lowered by P+N. Average plasma LPS in 5 normal mice (C) was 0.8 EU/ml. LPS of UT mice was 3.7±0.32 EU/ml, 3 days after UUO and remained high (3.1±0.3 EU/ml) even after 10 days of UUO. In contrast, LPS levels of P+N group (1.1±.3 EU/ml) after 10 days was not different from group C.

Conclusions: LPS is known to modulate inflammation and Mo phenotype. M1 and M2 phenotypes are known to modulate fibrosis and inflammation respectively. Increased inflammation and fibrosis in UT (10 days) can be attributed to increased M1 and decreased M2. A decrease in inflammatory markers and fibrosis in P+N corresponds to the increased M2 and decreased M1 in this group. P+N can only act at the intestinal level and reduction of systemic LPS by this treatment implies that the gut might be a source of kidney inflammation.

Table

	CD45+CD11b (Mo)		CD45+ CD11b Ly6Chi (M1)		CD45+ CD11b Ly6Clo (M2)	
	UT	P+N	UT	P+N	UT	P+N
3 day UUO	30.8± 22.3	5.7±0.4*	73.4±17.9	59.7±12.2	25.2±17.6	39.5±7.5
10 day UUO	95.5±3.7	83.1±11.3	82.5±6.7	61.3±17.4*	15.5±5.5	36.9±10.5*

*p<0.05 compared to UT

FR-PO119

Breast Regression Protein-39 (BRP-39) Promotes Fibrosis Following AKI by Inducing Matrix Expression by PDGFRβ+ Myofibroblasts

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Background: Maladaptive repair after unilateral ischemia-reperfusion injury (U-IRI) leads to sustained low-level mRNA expression of chitinase-3-like1(*Chi3l1*, protein name BRP-39). We have recently shown that persistent expression of BRP-39 promotes interstitial fibrosis following maladaptive kidney repair. At the whole kidney level, PDGFRβ+ myofibroblast accumulation was not significantly different in the injured wild-type (WT) and Brp-39 knockout. However, there was a significant decrease in the expression of collagen 1α1(*Col1a1*), collagen 3α1(*Col3a1*) and fibronectin(*Fn1*) by myofibroblasts in the injured kidney of BRP-39 knockout compared to the WT kidney. Here,we investigated the role of BRP-39 in PDGFRβ+ myofibroblast matrix gene expression during the acute kidney injury(AKI) to chronic kidney disease transition.

Methods: Male WT mice (9–11 weeks) subjected to U-IRI for 30 minutes. The injured kidney was removed on day 14 after U-IRI, and primary renal myofibroblasts were isolated via magnetic activated cell sorting using PE-tagged PDGFRβ antibody. Purity of the PDGFRβ+ myofibroblasts assessed by qPCR for PDGFRβ mRNA. Primary myofibroblasts were grown for 4 days in culture (~70% confluence), then stimulated with recombinant BRP-39 (0.5 μg/ml) or vehicle control for 24-hour followed by qPCR for *Col1a1*, *Col3a1* and *Fn1*.

Results: Primary PDGFRβ+ myofibroblasts were enriched 5.7fold compared to the initial population(n=7,p=0.04) and were also enriched for expression of the postulated BRP-39 profibrotic receptor, *Crth2* (n=7, p=0.004). The expression level of *Pdgfrb* and *Crth2* in these cells were 9.1 and 3.7fold higher than in immortalized fibroblast cell lines (NRK49 and NIH3T3). Stimulation of PDGFRβ+ myofibroblasts with BRP39 resulted in 3.4fold in *Fn*1 expression(p=0.038,n=6) with no significant effect on *Col1a1* or *Col3a1*. Preliminary findings (n=2, pooled from 8 kidneys) show with the addition of TGFβ1 (20 ng/ml) and PDGFβ (10 ng/ml) with BRP39 resulted in a further increase in fibronectin expression (dct = 8.489±5.22 vs 3.34±4.62)

Conclusions: We show that freshly isolated myofibroblasts express high levels of the profibrotic receptor,*crth2* and directly respond to BRP39 by increasing fibronectin expression. These *in-vitro* findings suggest that BRP39 and/or the *crth2* receptor may serve as therapeutic targets to limit fibrosis after AKI

Funding: NIDDK Support

FR-PO120

AMPK Activation Improves Tissue Oxygenation in CKD

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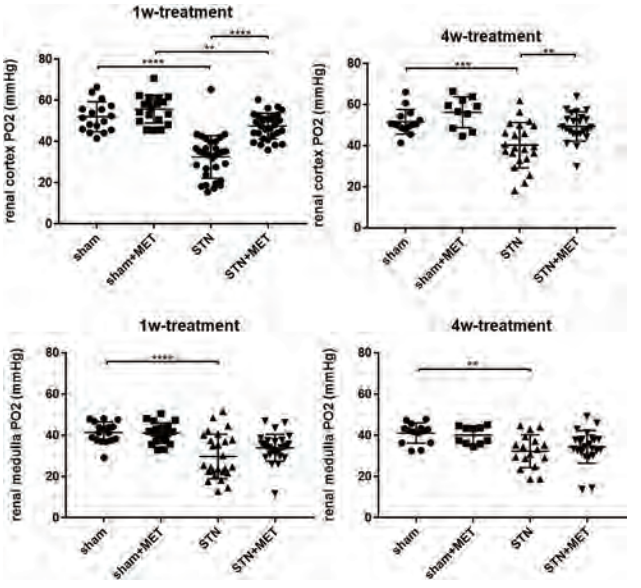
Background: Progressive intra-renal hypoxia is implicated in the pathogenesis of CKD. However, effective therapies to target intra-renal hypoxia are very limited. We have previously reported early alterations in renal oxygenation and oxygen demand-supply mismatch leading to hypoxia in subtotal nephrectomy (STN), a well-established experimental model of CKD. AMP-activated protein kinase (AMPK) is an important cellular metabolic sensor and regulator, which is dimished in CKD. In this study, we evaluated the quantitative changes in renal tissue oxygenation and the impact of AMPK activation by metformin (MET) on hypoxic and metabolic stress adaptation in STN.

Methods: Male Wistar rats were randomly divided into four groups/two time points: sham, sham+MET (250 mg/kg/day oral gavage), STN, STN+MET, and 1-week or 4-week treatment. Rats were anesthetized and placed on a temperature-controlled table. Left jugular vein, left femoral artery, and urinary bladder were cannulated. Intrarenal oxygen tension (pO2) was measured in the renal cortex and medulla by a Clark-type microelectrode (Unisense) after 60-min equilibration period.

Results: At 1-week post-STN, renal cortical pO2 declined in STN (33±10 vs. 52±7 mmHg in shams, $p<0.0001$). MET treatment improved the STN-induced decreased cortical pO2 (47±6 mmHg) ($p<0.0001$). At 4-week time point, renal cortical pO2 continued to be lower in STN (40±11 vs. 52±6 mmHg in shams, $p=0.0008$). MET prevented the STN-induced decrease in cortical pO2 (49±7 mmHg) ($p=0.0031$). However, in the renal medulla, the STN-induced decreased pO2 was not rescued by MET at both time points.

Conclusions: Our findings demonstrate that tissue oxygen tension is reduced in the STN kidneys in early and late stages. This was prevented by AMPK activation with metformin treatment in the renal cortex. Impact of AMPK activation on tubular transport and metabolism in STN is being investigated.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO121

PGE2 EP1 Receptor Deletion Worsens Hypertensive Kidney Disease in TTRhRen Mice, Promoting Glomerular Podocyte and Endothelial Cell Injury

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Background: Prostaglandin E2 (PGE2) regulates glomerular hemodynamics, renin secretion, and tubular transport. PGE2 EP1 receptors promote renal injury in diabetes, and EP1 deletion improves hyperfiltration, albuminuria, and fibrosis in several diabetic models. The role of PGE2/EP1 in hypertension remains controversial. The purpose of this study was to examine the contribution of PGE2/EP1 to long-standing hypertensive kidney disease.

Methods: Male FVB EP1-/- mice were bred with hypertensive TTRhRen mice (Htn) to evaluate kidney function and injury at 24 wks of age in 4 groups: wild-type (WT), EP1-/-, Htn, HtnEP1-/-. Blood pressure was measured by tail vein, and glomerular filtration rate (GFR) was estimated by FITC-inulin clearance. Urine was collected over 24 hrs in metabolic cages, and urine albumin was measured by ELISA. Total RNA was isolated from renal cortex for quantitative PCR analysis. Ultrastructural injury was assessed by electron microscopy. Urine microparticles were characterized by flow cytometry.

Results: Systolic blood pressure was elevated in Htn mice (150 mmHg) compared to WT mice (110 mmHg), but unchanged by EP1 deletion. However, EP1 deletion resulted in significantly increased albuminuria (>10-fold WT and >3-fold Htn) and reduced FITC-inulin clearance (50% of WT) in HtnEP1-/- mice, independent of blood pressure changes. Cyclooxygenase (COX)-2 mRNA was increased in all mice lacking EP1. Ultrastructural injury to podocytes and glomerular endothelium was prominent in HtnEP1-/- mice compared to Htn and WT mice: including widened subendothelial space, subendothelial lucent zones and focal lifting of endothelium from the glomerular basement membrane with focal subendothelial cell debris. This injury was associated with increased podoplanin-positive urine microparticles indicative of podocyte damage.

Conclusions: EP1 deletion increases albuminuria and reduces GFR in Htn mice, due to significant injury to podocytes and glomerular endothelium. Taken together, the data suggests that EP1 receptors play a protective role in hypertensive kidney disease. Highlighting the importance of carefully examining disease context (eg. diabetes vs hypertension) when characterizing underlying disease processes.

Funding: Government Support - Non-U.S.

FR-PO122

Superiority of ACF-TEI, a Novel Uremic Toxin Adsorbent, to Classical Oral Adsorbent in In Vitro and In Vivo Adsorption Profiles

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Background: Uremic toxins (UTs) such as indoxyl sulfate (IS) accumulate in the blood of patients with impaired renal function. Since several observation studies have demonstrated a link between serum UT levels and clinical outcomes, UTs have much attention as key factors in the progression of chronic kidney diseases (CKDs) and cardiovascular diseases. Spherical activated carbon (AST-120) adsorbs UTs and those precursors such as indole in the intestinal tract and excretes them out of the body with feces, leading to reduce serum UT levels. Therefore AST-120 is effective in improving symptoms of uremia and delaying the introduction to dialysis in CKD patients. However, the oral adsorbents comprising AST-

120 have insufficient adsorption performance and need to be taken at high daily doses. To improve their compliance and efficacy, we focused on activated carbon fiber (ACF) and have identified a novel and potent oral UT adsorbent, ACF-TEI. In this study, we analyzed *in vitro* adsorption profiles of ACF-TEI and compared *in vivo* efficacy of ACF-TEI and AST-120 on serum IS levels. We also evaluated the effects of ACF-TEI on renal fibrosis in rat model of kidney injury.

Methods: As for the *in vitro* adsorption profiles, we examined the adsorption of precursors including indole and p-cresol, and digestive enzymes. In *in vivo* studies, we compared the effects of ACF-TEI and AST-120 on serum IS concentrations in rat model of CKD and dog model treated with tryptophan, a precursor of indole. To evaluate the effects on renal fibrosis, cisplatin-induced nephrotoxicity (CDDP) model were used.

Results: Compared with AST-120, ACF-TEI showed more potent capacity and speed in adsorbing the UT precursors. ACF-TEI had a low capacity to adsorb digestive enzymes and the capacity was comparable to that of AST-120. In rats and dogs, ACF-TEI reduced serum IS levels more potent than AST-120. ACF-TEI decreased serum and renal IS levels, urinary excretion of KIM-1, and a-SMA expression in CDDP model.

Conclusions: The adsorption capacity and efficiency of ACF-TEI were superior to AST-120. In addition, ACF-TEI reduced the serum IS levels more potent than AST-120 in *in vivo* models. Thus, ACF-TEI is expected to show more beneficial effects than AST-120 in clinical.

FR-PO123

Megalin Deletion Prevents Long-Term Loss of Glomerular Filtration Rate After Rhabdomyolysis

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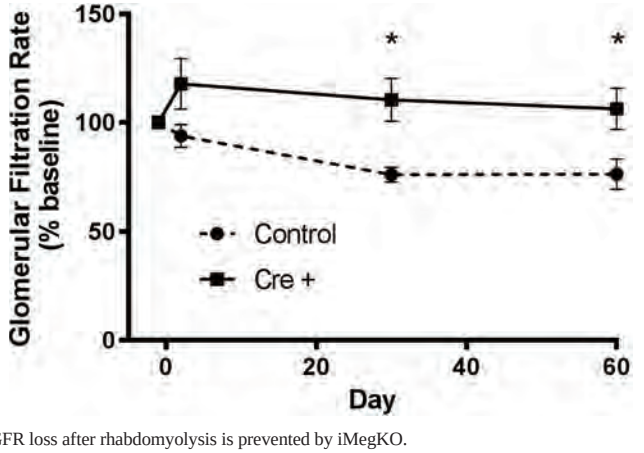
Background: Rhabdomyolysis, caused by injury, physical training, or medication, causes acute kidney injury and can lead to chronic kidney disease. Treatment is limited to supportive care and urinary alkalization, which is controversial. No specific therapy exists, but myoglobin-induced tubular epithelial apoptosis is a mechanism. Myoglobin undergoes tubular endocytosis via megalin, therefore we hypothesized that proximal tubule-specific megalin deletion would ameliorate chronic loss of glomerular filtration rate (GFR) caused by rhabdomyolysis.

Methods: Proximal tubule-specific inducible megalin deletion mice (iMegKO, LRP2 fl/fl NDRG1-CreERT2) were generated by breeding megalin floxed mice (a gift of Professor T. Willnow, Max Delbruck Institut) with NDRG1-CreERT2 (a gift of M. Yanagita, Kyoto University). Tamoxifen (150 mg/kg body weight) was injected intraperitoneally to 7 iMegKO and 7 cre- littermate control mice (all 8-12 week-old males) for 5 days, 2 weeks before rhabdomyolysis was induced by 50% glycerol injection (6.5 ml/kg). Before glycerol and 2, 30, and 60 days after injection, glomerular filtration rate (GFR) was measured by FITC-sinistrin transcutaneous clearance. After injection, all GFR measurements were expressed as %baseline. Statistical analysis was by repeated measures 2-way ANOVA.

Results: Tamoxifen only induced deletion of megalin in cre+ mice. Megalin deletion reduced GFR (745±42mL/min/100g body weight in iMegKO vs 872±35 μL/min/100g body weight in control, P<0.05). iMegKO mice did not demonstrate reduced GFR on day 2, maintaining baseline GFR to 60 days (102% baseline, ns), whereas in controls, glycerol injection induced significant, sustained decline in GFR at 30 and 60 days (76±7% baseline, p=0.005 compared with baseline, p=0.02 compared with KO).

Conclusions: Proximal tubule-specific deletion of megalin ameliorates chronic renal functional loss caused by experimental rhabdomyolysis.

Funding: Veterans Affairs Support



GFR loss after rhabdomyolysis is prevented by iMegKO.

FR-PO124

Estimating the Health Economic Outcomes of Serum 25-Hydroxyvitamin D and Intact Parathyroid Hormone Levels in Stage 3-4 CKD: The Impact of Treatment Timing

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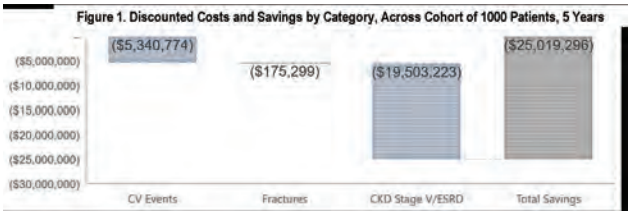
Background: Serum 25-hydroxyvitamin D (25D) and intact parathyroid hormone (iPTH) levels in patients with Chronic Kidney Disease (CKD)are associated with meaningful clinical outcomes, including cardiovascular (CV) events, fractures, CKD progression, and death. This study estimated differences in outcomes (CV events, fractures, and CKD progression) and costs due to changes in 25D and iPTH levels associated with vitamin D (vit D) therapy among patients with CKD not on dialysis.

Methods: A cost-consequence model taking a Medicare payer perspective was developed to estimate the economic and clinical consequences of increasing 25D and lowering iPTH in stage 3-4 CKD patients. The base case Markov model assumed a 1000-patient cohort with 1-year cycles and a 5-year time horizon. Correction of 25D and iPTH level and associated clinical events were based on published meta-analyses. Costs of clinical events were based on data from national public databases.

Results: Across a 1,000-person cohort, increasing 25D and lowering iPTH may avert about 202 CV events, 6 fractures and 230 patient-years in the CKD stage 5/dialysis state. The estimated offsets total about $25 million (Figure 1). The analysis is sensitive to the cost inputs and the effectiveness of correcting 25D and iPTH. Under scenario analysis, when excluding the stage 5/dialysis, the total savings over a 1,000-person cohort is about $4.7 million, mainly attributable to averted CV events.

Conclusions: Vit D therapy in stage 3-4 CKD appears to be cost-saving by offsetting CV events, fractures, and CKD progression, although it may also be associated with such adverse events (AE) as hypercalcemia, hyperphosphatemia, and increased FGF23; further research is warranted to assess whether vit D treatment with extended-release calcifediol results in improved outcomes without these AEs.

Funding: Commercial Support - OPKO



FR-PO125

Multiple, Systemic Effects of PHD Inhibitors Signify an Anti-Fibrotic and Anti-Inflammatory Impact on Cardiovascular Complications in the Remnant Kidney

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Background: Hypoxia plays a crucial role in the progression of chronic kidney disease(CKD) which is associated with fibrosis, inflammation and oxidative injury. Previous studies suggest that prolyl hydroxylase inhibitors(PHD inhibitors), stabilizers of hypoxia-inducible factors (HIFs), could be applied in acute organ injuries like renal ischemia-reperfusion and myocardial infarction. However, the effect of PHD inhibitor on CKD and its cardiovascular consequences remains unknown.

Methods: Male Sprague-Dawley rats underwent 5/6 nephrectomy (remnant kidney: RK). Rats were divided into three groups: (1)sham operation rats (2)RK rats with normal diet (3) RK rats with 0.005% enarodustat(PHD inhibitor) diet since 1 week before 5/6 nephrectomy. L-NNA(20 mg/L), NO synthase inhibitor, was supplemented in drinking water to accelerate the CKD model. At 6 weeks after 5/6 nephrectomy, kidney and heart were harvested after the echocardiography.

Results: Systolic blood pressure was lower in RK-Enarodustat group than in the RK group, but the difference did not reach statistical significance. Blood urea nitrogen and serum creatine levels at 2, 4, 6 weeks were reduced in the RK-Enarodustat group, whereas there was no difference in urinary protein excretion between the two groups. The number of ED-1-positive cells was significantly less in the RK-Enarodustat group (43.7±7.7 per ×200 field) than in the RK group (100.8±14.2, P<0.01). And, the number of infiltrated CD206 macrophages, the M2 macrophages, was also less in the RK-Enarodustat group. Immunohistochemical analysis revealed a significant decrease in nitrotyrosine accumulation in tubules in the RK-Enarodustat group(7.6±1.3 vs 11.5±0.9, p=0.036). In heart, the number of ED-1, CD206-positive infiltrating macrophages and picrosirius red staining showed significant reductions in the RK-Enarodustat group. Anterior and posterior wall thicknesses, markers for cardiac hypertrophy, were markedly less in the RK-Enarodustat group than in the RK group, whereas there was no difference in fractional shortening, ejection fraction and E/A.

Conclusions: These data show that PHD inhibitors significantly improve inflammation, oxidative stress and fibrosis in remnant kidney and may also mediate beneficial effects in cardiovascular complications.

FR-PO126

Targeted Ablation of Distal Cerebrospinal Fluid-Contacting Nucleus Alleviated Renal Fibrosis in CKD

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Background: The distal cerebrospinal fluid-contacting nucleus (dCSF-CNs) is thought to be a linkage between the cerebrospinal fluid and brain. The potential function of dCSF-CNs in development of CKD is poorly understood. We hypothesized that dCSF-CNs might exert a signaling transmission effect on the cascade reaction of renin-angiotensin system (RAS) in the progression of kidney injury, and that ablation of the dCSF-CNs might alleviate the local RAS and renal fibrosis in five-sixths nephrectomied (5/6Nx) rat model.

Methods: Rats were subjected to intracerebroventricular (icv) administration of artificial cerebrospinal fluid (aCSF) followed by five-sixths nephrectomied or sham operation, or icv administration of Cholera toxin subunit B conjugated with saporin (CB-SAP) for dCSF-CNs lesion before five-sixths nephrectomied. The effect of CB-SAP treatment on ablation of dCSF-CNs was confirmed via double immunofluorescence staining. The expression levels of RAS components, NOX_2 and c-fos in SFO, PVN and hippocampus, as well as the numbers of Tyrosine Hydroxilase and c-fos positive cells in RVLM were detected. The expression levels of RAS components (AGT, ACE, AT1R, ACE2, Mas receptor), NADPH oxidase (NOX_2, catalase), inflammatory cytokines (MCP-1, IL-6), fibrotic readouts (fibronectin, collagen I) in kidney were compared.

Results: Compared with 5/6Nx rats, the number of CB-labelled neurons in dCSF-CNs decreased in CB-SAP treated rats. Treatment with CB-SAP down-regulated the expression levels of RAS components (AGT, Ang II, AT1R), NADPH oxidase (NOX_2, catalase), inflammatory cytokines (MCP-1, IL-6), fibrotic readouts (fibronectin, collagen I) in rats, and up-regulated the protein levels of ACE2 and Mas receptor, compared with CKD rats. Increased numbers of Tyrosine Hydroxilase and c-fos positive cells were observed in the RVLM of 5/6Nx rats, but that were decrease under the influence of ablation of dCSF-CNs.

Conclusions: Targeted ablation of the dCSF-CNs might alleviate renal inflammation and fibrosis in the development of chronic kidney injury through inhibiting activation of inhibit the cerebral and renal RAS/ NADPH oxidase.

Funding: Government Support - Non-U.S.

FR-PO127

A Novel, Selective TRPC6 Antagonist Reduces Renal Interstitial Fibrosis in the Mouse Unilateral Ureteral Obstruction Model

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Background: A role for dysregulation of the non-selective cation channel TRPC6 in the development of FSGS is well-established based on the identification of multiple gain-of-function mutations in humans which cause disease by cytoskeletal alterations in podocytes, leading to impairment of the glomerular filtration barrier. Despite the strong evidence linking elevated TRPC6 activity to CKD, no inhibitors have advanced to clinical testing due to challenges associated with achieving selectivity against related ion channels and identifying compounds with a suitable pharmacokinetic profile for oral dosing.

Methods: A novel TRPC6 antagonist, BI 749327, was characterized with in vitro electrophysiology measurements using HEK293 cell transfectants and in vivo in the mouse unilateral ureteral obstruction (UUO) model of renal fibrosis.

Results: BI 749327 has a manual patch-clamp IC_{50} value of 13 nM against TRPC6 and 85- and 42-fold selectivity against TRPC3 and TRPC7, respectively. Oral gavage dosing with BI 749327 produced plasma exposures predicted to provide potent 24 hour inhibition. Treatment of mice undergoing UUO surgery with BI 749327 inhibited the development of fibrosis as measured by hydroxyproline incorporation. TRPC6 dependent inhibition was confirmed as mice lacking TRPC6 had a similar reduction in fibrosis in the UUO model when compared with BI 749327 treated wild-type mice and by the demonstration that the compound had no further effect on fibrosis development in this model when administered to TRPC6 deficient mice.

Conclusions: The opportunity for treatment with a TRPC6 antagonist to inhibit renal fibrosis in addition to restoring podocyte calcium homeostasis further highlights the therapeutic potential of this mechanism for the treatment of CKD. These results are the first demonstration of in vivo benefit in a disease model with TRPC6 pharmacological inhibition, and BI 749327 provides a tool for further evaluating TRPC6 inhibition for the treatment of CKD.

Funding: Commercial Support - Boehringer Ingelheim Pharmaceuticals, Hydra Biosciences

FR-PO128

Cerebral Microvasculature Impairments Induced Dementia in CKD

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Background: Structural and functional impairments of brain microvasculature result in white matter hypo-perfusion and ischemia are major causes of Cerebral small vessel disease (CSVD). Recently, chronic kidney disease (CKD) has been identified as a significant risk factor for stroke and dementia as well as CSVD. Interestingly, both kidney and cerebral microvasculature share similar anatomical and physiologic characteristics particular in their endothelium. The goal of this study was to elucidate the molecular mechanisms of CKD induced cerebral microvasculature dysfunction and consequences neurological diseases.

Methods: CKD mice model was generated by 5/6 nephrectomy on C57BL/6 mice. Transcriptomic profiling of calcification medium (CM) and hyperglycemia medium (GM) treated primary human brain microvascular endothelial cells (HBMECs), *in vitro*, and human arteries collected from CKD (n=20), CAD (n=15) and healthy donors (n=20) were subjected to RNA sequencing, *ex vivo*. In addition, incidence and risk of dementia in CKD from a population-based study using the Taiwan National Health Insurance database with 1,000,000 subjects from 2000 to 2009.

Results: Our results showed that CKD mice had decreased myelinated nerve fibers in the corpus callosum and cerebral cortex and loosening myelinated fibers in the corpus callosum. Collagen IV accumulation in brain microvasculature and serum phosphate levels were significant increased in CKD mice compared to control mice. Tight junction (TJ) proteins occludin, claudin-5, and ZO-1 were down-regulated in both CM/GM-treated primary HBMECs. In human arteries, both claudin-5 and ZO-1 genes were down-regulated in CKD group together with anti-apoptotic gene Bcl2. Furthermore, cell viability decreased and caspase-3 mediated apoptosis increased as well as Collagen IV expression in CM treated HBMECs. The subsequent risks of dementia were 2.208-fold (Diabetes + CKD); 1.638-fold (CKD); 1.527 fold (Diabetes) higher in comparison with healthy cohort.

Conclusions: Our data show for the first time that TJ dysfunction in cerebral microvascular dysfunction occurs in CKD may play a role in dementia. It provides a potential mechanism for the development of CSVD in CKD patients. Our results may benefit CKD patients to reduce the following CSVD and dementia through controlling blood phosphate levels and maintain TJ's function.

Funding: Private Foundation Support

FR-PO129

Evaluation of Allostatic Load as a Mediator of Sleep and Kidney Outcomes in Blacks

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Background: Poor sleep associates with adverse chronic kidney disease (CKD) outcomes yet the biological mechanisms underlying this relation remain unclear. One proposed mechanism is *via* allostatic load (AL) – a cumulative biologic measure of stress. Using data from the Jackson Heart Study (JHS), we examined the potential mediating effect of AL on the relation between sleep patterns and kidney outcomes

Methods: We examined the association of self-reported sleep duration: very short, short, recommended, and long (≤5, 6, 7-8, or ≥9 hours per 24 hours, respectively) and self-reported sleep quality: high (excellent/very good) vs. good vs. low (poor/fair) with prevalent baseline CKD (Exam 1), estimated glomerular filtration rate (eGFR) decline, and incident CKD at follow-up (Exam 3). CKD was defined as eGFR <60ml/min/1.73m^2 or urine albumin-to-creatinine ratio ≥30mg/g. Models were adjusted for demographics, comorbidities and kidney function. We further evaluated AL (quantified at baseline using 11 biomarkers from neuroendocrine, metabolic, autonomic, and immune domains) as a mediator of these relations.

Results: Among 5177 JHS participants, 40% slept the recommended 7-8 hours; 25%, 29% and 6% reported very short, short and long sleep duration, respectively. Participants with very short sleep duration (vs. 7-8 hours) had greater odds of prevalent CKD (odds ratio [OR] 1.31, 95% confidence interval [CI] 1.03-1.66) after adjustment. Very short, short or long sleep duration (vs. 7-8 hours) were not associated with any other kidney outcomes over a median follow-up of 8 years. Low sleep quality (vs. high) associated with greater odds of prevalent CKD (OR 1.26, 95% CI 1.00-1.60) and 0.18 mL/min/1.73m^2 (95% CI 0.00 to 0.36) faster eGFR decline per year over follow-up. AL did not mediate the associations of sleep duration or sleep quality with kidney outcomes.

Conclusions: Very short sleep duration and low sleep quality were associated with adverse kidney outcomes in this all black cohort, but AL did not appear to mediate these associations. Future work should investigate the role of other biologic mediators in the relation between sleep and CKD outcomes in blacks.

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FR-PO130

Chemokine Ligand 14 Could Be a Possible Biomarker of CKD Progression

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Background: Chemokine ligand 14 (CCL14), a ligand for CCR1, has been known as a M2 polarizing marker and chemotactic cytokine, which is expressed by fibroblast, monocyte, etc. Although it was first isolated from the hemofiltrate of chronic renal failure patients, its expression pattern in chronic kidney disease have never been investigated.

Methods: To elucidate concentration change of CCL14 in chronic kidney disease, we performed urine proteomic analysis using three patients' random urine per each CKD1 and 5. For validating tissue expression of CCL14, kidney biopsy tissues of three normal, nine CKD 3, and eight CKD 5 patients were evaluated by immunohistochemistry. Among CKD 3 group, patients with GFR decrease more than 5 ml/min/1.73 m^2 within a year were considered to have rapid progression. We also evaluated kidney tissue expression of CCL14 in acute tubular necrosis that is a well-known etiology of chronic kidney disease if it recurs frequently. For in vitro study, primary cultured human tubular epithelial cells (hTECs) and glomerular endothelial cells (GECs) were treated with rTGFβ for inducing fibrosis, and CCL14 expression level was measured using western blotting.

Results: In urine proteomics analysis, we discovered CCL14 showed a 122-fold increase in CKD 5 patients' urine comparing to CKD 1 ($p<0.001$). In other hands, in human kidney biopsy tissue, CKD 3 patients with rapid progression showed higher expression level of CCL14 (17.33±4.13) compared to non-progressive CKD 3 (10.12±3.60) ($p=0.032$), control (12.48±2.49) ($p=0.019$), and CKD 5 (9.63±5.52) ($p=0.049$). CRP was adversely lower in progressive CKD 3 patients compared to others ($p=0.017$), and interstitial inflammation or fibrosis pattern was not different ($p=0.861$). In kidney tissue of patients with acute tubular necrosis, CCL14 expression level was 1.6-fold higher than those of normal cases ($p=0.015$). In in vitro assay, CCL14 expression was increased 2 folded by treating rTGFβ in GEC cells.

Conclusions: CCL14 expression tends to increase in patients with progressive CKD or acute tubular necrosis. Moreover, its expression is increased by a rTGFβ-enriched fibrotic environment. Our results suggest CCL14 could be a possible biomarker of CKD progression that pre-existing inflammatory marker or pathologic variables could not predict.

FR-PO131

Pathogenesis of Chronic Renal Injury Following Acute Nephrotoxicity by Gentamicin

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Background: Subjects recovering from acute kidney injury (AKI) may develop renal fibrosis and chronic kidney disease (CKD) by unclear mechanisms that may involve innate immunity (InIm). In rats exposed to nephrotoxic agents, AKI is followed by mild fibrosis. Whether this process proceeds to CKD later on has not been examined. Here we investigated 1) whether renal injury resulting from treatment with Gentamicin (G) progresses to CKD in the long run by; 2) the role of InIm in this process.

Methods: Male Munich-Wistar rats received daily sc injections of G, 80 mg/kg, during 9 days. Control rats (C) received vehicle only. Rats were studied at 1, 30 and 180 days after G, to assess:Creatinine Clearance (Cl_{Cr}, mL/min), Albuminuria (ALB, mg/24h), Glomerular ischemia (%GI), Cortical Collagen 1 (%Coll) and Fibronectin (%FN), Macrophages (Mø) and AngII+ cells (/mm^2), as well as renal KIM1 and IL1β (pg/mg), αSMA, TLR4, NFkB (nuclear p65) and IL6 (xC)

Results: At Day 10, GI, tubular injury, ALB and low Cl_{Cr} were associated with marked inflammation and InIm activation. Partial reversal of these changes was seen at Day 30, along with incipient fibrosis. At Day180, worsened ALB was seen along with prominent GI and renal fibrosis, although inflammation was attenuated.

Conclusions: G leads to AKI, strong inflammation and InIm activation. In the long run, glomerular injury develops along with renal fibrosis. Since InIm activation and inflammation abate with time, the mechanisms of these late effects might involve other mechanisms, such as direct participation of tubular cells. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	10 days		30 days		180 days	
	C	G	C	G	C	G
ClCr	0.9±0.1	0.2±0.1*	1.2±0.1	1.0±0.1*	1.5±0.2	1.6±0.1
KIM1	13±5	8658±1241*	57±24	392±62	28±18	62±11
ALB	3±1	19±3*	3±1	3±1	11±3	27±5*
GI	0	4±1*	0	3±1*	0	13±2*
αSMA	1.0±0.1	3.6±0.5*	1.0±0.1	1.5±0.1*	1.0±0.1	1.2±0.2
Coll	1.4±0.2	2.1±0.3	1.3±0.2	4.8±0.4*	1.4±0.3	5.4±0.4*
Fibro	2.4±0.4	2.6±0.2	2.8±0.6	5.2±0.3*	2.4±0.3	6.2±0.4*
AngII+	2±1	10±2*	2±1	14±2*	3±1	7±1*
Mø	20±4	297±39*	22±5	125±18*	39±23	75±8
TLR4	1.0±0.1	3.7±0.3*	1.0±0.1	2.5±0.6*	0.9±0.2	2.2±0.4*
NFkB	1.0±0.1	4.8±0.8*	1.0±0.1	0.7±0.2	0.8±0.2	1.7±0.1
IL6	1.0±0.1	4.0±0.5*	1.0±0.1	1.5±0.1*	1.0±0.1	1.3±0.2
IL1β	1.1±0.2	8.4±1.5*	2.0±0.6	8.6±1.3*	3.0±1.7	3.1±0.8

*p<0.05 vs resp. C

FR-PO132

Apabetalone Downregulates Factors and Pathways Associated with Vascular Calcification

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Background: Apabetalone, an oral small molecule BET inhibitor, reduced the incidence of major adverse cardiac events (MACE) in patients with CVD and improved eGFR in a subgroup with CKD in phase 2 trials. Because vascular calcification (VC) is associated with MACE, effects of apabetalone on processes associated with VC were examined.

Methods: Plasma proteomics was conducted in CVD patients receiving apabetalone in the 3 month (ASSERT) and 6 month (SUSTAIN & ASSURE) phase 2 trials, as well as patients with stage 4/5 CKD that received a single 100mg dose. Coronary artery VSMCs were used to examine effects of apabetalone on transdifferentiation & calcium deposition.

Results: Apabetalone significantly reduced circulating levels of VC markers in CVD patients in phase 2 trials, including alkaline phosphatase, osteopontin and osteoprotegerin. Plasma proteomics of CKD patients (n=8) indicated activation of molecular pathways driving VC including IL-6 signaling, BMP-2 signaling & RANK signaling in osteoclasts. Downregulation of these pathways by apabetalone was predicted in the CKD cohort 12hrs post-dose. In VSMCs cultured in osteogenic conditions, apabetalone opposed induction of transdifferentiation markers & inhibited calcium deposition. BRD4 is a transcriptional regulator & target of apabetalone. ChIP-seq showed transdifferentiation of VSMCs to a calcifying phenotype promoted re-distribution of BRD4 on chromatin, resulting in fewer BRD4-rich enhancers (118 in osteogenic, 288 in basal). 38 genes were uniquely associated with BRD4-rich enhancers in osteogenic vs basal conditions; several of the genes have been linked to calcification. Apabetalone reduced BRD4 on many of these enhancers, which correlated with decreased gene expression. Bioinformatics indicated BRD4 may cooperate with specific transcription factors to promote calcification.

Conclusions: Involvement of BRD4 in VSMC transdifferentiation & calcification is a novel discovery. Further assessment of apabetalone as a therapeutic for VC is warranted. The impact of apabetalone on biomarkers, renal function & CVD outcomes in patients with impaired kidney function is being evaluated in a subgroup of the phase 3 BETonMACE trial.

Funding: Commercial Support - Resverlogix Corp.

FR-PO133

The Role of Periostin in Aging Process

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Background: Periostin, a matricellular protein, has been reported in diverse processes and pathologies in tissue remodeling through the promotion of adhesion, cell survival, cellular dedifferentiation, and fibrogenesis. However, its role in aging process is unknown.

Methods: We analyzed tissues from 2-months and 24-months old wild-type and Postn null (Postn-/-) mice and performed high throughput RNA-Sequencing of kidney tissue in aged mice. The genes showing altered expression were confirmed by qRT-PCR analysis.

Results: At 24-months old Postn null mice had preserved kidney tissue and less markers of senescence than wild-type mice. The gross appearance and the kidneys of aged WT mice were bigger and heavier than young WT mice. Serum creatinine levels were also higher in the aged WT mice compared to those in the young WT mice. However,

all these changes were diminished in the aged Postn null mice; serum creatinine levels were considerably lower in aged Postn null mice than in aged WT mice. Apparent tubular atrophic changes, interstitial fibrosis, and collagen fiber deposition which were prominent in the aged WT mice than in the young WT mice, were remarkably alleviated in aged Postn null mice. Furthermore, the expressions of periostin were also attenuated in aged Postn null mice compared to in aged WT mice. Also, we found that many of the changes in gene expression that occur during the aging process by periostin.

Conclusions: The data obtained in this study should expand our knowledge on the periostin mediated aging and provide molecular mechanism. Periostin inhibition could have protective effects in aging process.

FR-PO134

Diverse Associations Between Oxidative Stress and Thromboxane A2 in Hypertensive Glomerular Injury

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Background: In addition to lowering blood pressure, therapeutic strategies to ameliorate hypertensive renal injury need to be established. In this study, we studied the possible contribution of thromboxane A_2 (TXA_2) which contributes to impaired renal hemodynamics under pathological conditions and potently stimulates reactive oxygen species generation, to the development of regional heterogeneity in hypertensive glomerular injury. We examined the impact of the inhibition of TXA_2 synthesis in relation to its antioxidant effects on regional glomerular injury.

Methods: Experiments were performed using male stroke-prone spontaneously hypertensive rats (SHRSP) and Wistar–Kyoto rats (WKY) at 5, 10 and 15-week age, respectively. We investigated systolic blood pressure (SBP), the degree of glomerular injury (glomerular sclerosis index: GSI), urinary albumin excretion (UAE), serum creatinine concentration (Cr), urinary 8-OHdG excretion, thromboxane synthase (TXAS) and heme oxygenase-1 (HO-1) gene expression. We also evaluated difference in GSI and each gene expression between superficial and juxtamedullary glomeruli. Then we investigated the effect of tempol (an intracellular antioxidant) and ozagrel (TXAS inhibitor).

Results: Juxtamedullary glomeruli showed higher GSI after 10 weeks of age in both rats. TXAS and HO-1 mRNA expression was enhanced in both superficial and juxtamedullary glomeruli in SHRSP compared with that in age-matched WKY. Notably in juxtamedullary glomeruli, TXAS expression was progressively enhanced as rats grow. Neither tempol nor ozagrel had any effect on SBP or Cr in SHRSP. Ozagrel but not tempol improved GSI in both superficial and juxtamedullary glomeruli. Tempol significantly increased TXAS expression in superficial but not juxtamedullary glomeruli, whereas ozagrel suppressed it.

Conclusions: Under the established severe hypertension, the glomerular injury as well as TXAS expression was augmented. Since these changes were attenuated by ozagrel but not tempol, the TXA_2–TPR pathway and oxidative stress participate and interact together to promote hypertensive glomerular injury. Moreover, our results indicated that TXA_2 inhibition may be a better therapeutic target than ROS inhibition to inhibit the aggravation of hypertensive glomerular injury at an advanced stage.

FR-PO135

Upregulation of a Urea Transporter in Uremic Heart Promotes Cardiac Fibrosis and Increases Vimentin

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Background: Cardiac abnormalities are linked to increased morbidity and mortality in chronic kidney disease (CKD) patients. CKD induces hypertension and retention of water, urea, and salt within the body. These are strongly related with the cardiovascular disease known as uremic cardiomyopathy. Uremic cardiomyopathy consists of left ventricular hypertrophy and interstitial fibrosis. Urea transporters (UT) are mainly involved with the urine concentrating mechanism in the kidney medulla. There is an isoform of UT-A in heart, but its role is not well known. We investigated the role of UT in mouse heart with a focus on the uremic heart.

Methods: To create a CKD model, C57BL6 mice underwent a 5/6 nephrectomy (5/6Nx), and were given 0.45-1% NaCl water to drink. Mice were sacrificed at 8 weeks after surgery. Heart tissue and blood were harvested. Mouse blood pressure measurements were determined by the tail cuff method. Cell culture studies were performed using mIMCD3 cells that were stably transfected with UT-A1. Immunohistochemistry was performed on paraffin sections. Protein expression levels were detected by western blot.

Results: BUN was 28.9 mg/dL (sham) and 56.6 mg/dL (5/6Nx) ($P < 0.05$) proving success of the CKD model. In mouse heart, cardiac fibrosis of CKD mice was confirmed by Masson's Trichrome staining of paraffin-sections. The protein abundance of UT-A was increased 1.4-fold and the pro-fibrosis marker vimentin was increased 1.7-fold in CKD mice vs. sham mice. Using immunohistology, we found that vimentin was also increased in CKD heart. In vitro, the amount of vimentin protein was increased 3.7-fold in UT-A1 overexpressing cells compared with empty vector control mIMCD3 cells. Both systolic blood pressure (129 mmHg (5/6Nx) vs 116 mmHg (sham)) and heart to body weight ratio; (7.18 mg/g (5/6Nx) vs 4.73 mg/g (sham)) were increased ($P < 0.05$) in CKD mice 8 weeks after surgery.

Conclusions: The upregulation of UT-A in uremic heart was associated with an increased vimentin protein level, which could be related with increased cardiac fibrosis in chronic kidney disease.

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FR-PO136

CKD Mediates Cardiac Dysfunction by Recruiting Monocyte Derived Inflammatory Macrophages

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Background: The relationship between chronic kidney disease (CKD) and accelerated cardiac disease is complex and not fully explained by traditional cardiovascular risk factors. Macrophages have critical roles in both kidney and cardiovascular disease, however a mechanistic link is not well described.

Methods: Using the folate induced nephropathy and 5/6 nephrectomy mouse models of CKD, we show that monocyte derived macrophages infiltrate heart tissue in large numbers but not other organs.

Results: We show using monocyte/macrophage transgenic reporters, with flow cytometry, imaging and qPCR, that the cardiac macrophage pool switches phenotype to a pro-inflammatory state during CKD. This cellular infiltrate was associated with an increase in cardiac remodeling through changes in extracellular matrix gene expression, cardiomyocyte enlargement and decrease in cardiac function, as shown by reduced ejection fraction. This phenotype was rescued by global knockout of C-C chemokine receptor type 2 ($CCR2^{-/-}$), associated with monocytopenia, during folate nephropathy. Measurement of specific chemokine expression in heart and plasma identified a unique chemokine axis, involving overexpression of CXCL10 that was also present in the plasma of CKD patients.

Conclusions: This work uncovers a novel pathway via CXCL10 that mediates cardiac inflammatory monocyte derived macrophage infiltration in the context of CKD, thus identifying new biological targets for improved diagnosis, prognosis and treatment of cardiomyopathy risk in CKD patients.

FR-PO137

Role of Primary Cilia in Kidney Fibrosis

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Background: The primary cilium is an organelle, present at the cell surface and plays a role as an antenna. The primary cilium mediates cell proliferation, differentiation, death, and planar cell polarity. Recently, it has reported that transforming growth factor (TGF)-β receptors are localized and concentrated within the primary cilium in human mesenchymal stem cells. Also, the primary cilium regulates the transdifferentiation into myofibroblast of human adipose progenitor cells. We investigated a role of the primary cilium in renal fibroblast-myofibroblast transdifferentiation through regulating TGF-β1 receptors and the modulating cilia would attenuate interstitial fibrosis in unilateral ureteral obstruction (UUO) model.

Methods: NRK-49F cells were differentiated into myofibroblasts with TGF-β1. Using immunocytochemistry staining and western blot, the primary cilium and the fibroblast-myofibroblast transdifferentiation in NRK-49F cells were studied. UUO was performed to evaluate the interstitial fibrosis.

Results: The primary cilium is crucial for the maintenance of the myofibroblasts phenotype and for TGF-β1-induced Smad phosphorylation. Knock-down of cilia proteins such as SMO, Arl13b, and IFT88 decreased the expression of α-SMA and Smad signaling. TGF-β receptors localized to the primary cilium in NRK-49F cells, especially when the cells are cytokinesis cycle. Colchicine, an inhibitor of microtubule polymerization, and HPI-4, ciliogenesis inhibitor, attenuates cilia growth and TGFβ1-induced fibrosis. In addition, colchicine treatment attenuates interstitial fibrosis in UUO mice kidney.

Conclusions: We provide the evidence that the primary cilium is indispensable for the transdifferentiation from fibroblast into myofibroblast by modulating TGF-β1 receptors. The cilia targeted therapy could be a promising option for attenuating renal fibrosis.

FR-PO138

The Dual Blockade Losartan/Erlotinib Attenuates Inflammation and Fibrosis Formation in Vitamin D Deficiency Rats Submitted to 5/6 Nephrectomy

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Background: 5/6 nephrectomy (N) is a classical experimental model of chronic kidney disease (CKD). Some studies have been linking vitamin D deficiency (VDD) to inflammatory process and renal fibrosis formation (RFF). Besides the beneficial effects of AII type I receptor antagonists, many efforts have been made to investigate alternative pathways related to RFF and inflammation. We evaluated the effects of the dual blockade including losartan (L) and erlotinib (E), an inhibitor of the epidermal growth factor receptor (EGFr) activity on CKD in rats under VDD.

Methods: Male Wistar rats received a vitamin D free (D) diet for 90 days. On day 30, rats were submitted to N surgery. Four groups were studied: D+N; D+N+L (50 mg/Kg/day in drinking water for 53 days); D+N+E (6 mg/Kg/day intraperitoneally for 53 days); D+N+L+E (dual treatment). We measured serum levels of 25(OH)D and aldosterone by ELISA; inulin clearance (Cin); mean arterial pressure (MAP); proteinuria; immunoblotted for TGF-β1, TGF-α and p-EGFr; performed IHC for CD206 and CD68; and evaluated interstitium enlargement by fraction interstitial area (FIA).

Results: All animals had untedectable levels of 25(OH)D. L+E treatment improved renal function and decreased MAP and proteinuria. L+E treatment reduced the expression of TGF-β1, TGF-α and p-EGFr, attenuating the expansion of FIA. Also, L+E mitigated the inflammatory profile of macrophages.

Conclusions: The dual blockade L+E ameliorated the course of CKD by retarding RFF and modulating the inflammatory phenotype of macrophages. (FAPESP 2015/05513-1; 2015/11933-3)

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	N+D	N+D+L	N+D+E	N+D+L+E
Cin (mL/min/100g BW)	0.39±0.02	0.63±0.04[a]	0.50±0.03	0.60±0.04[b]
MAP (mmHg)	163±4	108±2[a]	147±4[cd]	107±1[ag]
Aldosterone (pg/mL)	3692±390	1496±319[a]	3266±644[f]	1650±252[bi]
Proteinuria (mL/24 h)	24.5±2.7	13.8±1.3[a]	15.8±1.5[a]	11.5±0.7[a]
TGF-β1 (%)	100±3	32±3[a]	33±9[a]	36±6[a]
TGF-α (%)	100±6	33±4[a]	33±9[a]	36±6[a]
p-EGFr (%)	100±2	71±3[a]	88±4[cd]	59±3[afg]
FIA (%)	22.5±0.5	13.1±0.8[a]	14.7±0.9[a]	10.4±0.4[acg]
M2 macrophages - CD206+ (%)	0.11±0.01	0.32±0.02[c]	0.30±0.04[b]	0.41±0.05[a]
M1+M2 macrophages - CD68+ (%)	0.94±0.05	0.75±0.03[c]	0.69±0.04[c]	0.60±0.06[a]

Data are expressed as mean±SEM. BW, Body weight. a p<0.001, b p<0.01, c p<0.05 vs N+D; d p <0.001, e p<0.01, f p<0.05 vs. N+D+L; g p<0.001, i p<0.05 vs N+D+E.

FR-PO139

Proteinuric Renal Injury Modulates Intestinal Lymphangiogenesis and Functionality of Plasma and Lymphatic HDL

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Background: Evidence suggests that in addition to plasma, critical changes in lipoprotein metabolism occur in the lymphatic circulation. Proteinuric renal injury changes lipoprotein levels and homoeostasis. Liver is a major regulator of lipoprotein metabolism, however, intestines also play a role, including synthesis of apolipoprotein AI (apoAI), the major protein in HDL. We examined how proteinuric renal injury affects intestinal handling of apoAI and functionality of HDL.

Methods: We studied Sprague-Dawley rats injected with puromycin aminonucleoside (PAN) or saline (C). Lymph was collected in conscious animals by indwelling mesenteric lymph duct cannulation. Lymphatic vessels were identified by immunohistochemistry (IHC) and RT-qPCR of podoplanin (PD). Functionality of HDL was assessed by cytokine response (TNFa, IL-6, Il-12 and iNOS/Arg1 ratio) in macrophages exposed to apoB-depleted HDL fractions isolated from plasma and lymph by RT-qPCR. HDL-cholesterol (HDL-C)/apoA1 ratio served as a HDL-particle size marker.

Results: PAN significantly increased urinary albumin creatinine ratio vs C. Intestines of PAN had significant increase in PD$^+$lymphangiogenesis and enlargement of lacteals accompanied by higher mesenteric lymph flow (6.3±1.7 vs 0.8±0.4ml/h). VEGFA was significantly elevated in PAN lymph and plasma (2.8-fold and 2.2-fold, respectively). Plasma HDL of PAN caused significantly greater macrophage inflammatory response [TNFa, IL-6, Il-12 (3.5-fold, 5.1-fold, 6.4-fold, respectively)] vs C. By contrast, HDL from mesenteric lymph of PAN was not pro-inflammatory and rather significantly decreased iNOS/Arg1 vs controls (0.5-fold). Although PAN did not change intestinal expression of apoA1 mRNA and IHC showed lower ileal apoAI than C, hepatic apoAI mRNA expression was significantly higher (3.9-fold). However, total output of apoAI in mesenteric lymph (apoAI quantity over time) was significantly higher in PAN (59.4±24.7 vs 11.2±6.5μg/h). Although HDLC/apoA1 ratio in lymph was similar, this ratio doubled in plasma of PAN (129.2±45.2 vs 60.0±21.1).

Conclusions: PAN renal injury increases intestinal lymphangiogenesis, mesenteric flow, composition and functionality of lymphatic HDL which is distinct from functionality of plasma HDL.

FR-PO140

Measurement Characteristics of Proximal Tubular Secretory Solutes

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Background: Reliable measurements of proximal tubular solute clearance, a vital kidney function, have been elusive. We developed targeted liquid chromatographic-tandem mass spectrometric methods to quantify 16 endogenously produced secretory solutes in serum and urine. We tested diurnal variation of each solute, determined their kidney clearances, and assessed associations with the estimated glomerular filtration rate (GFR) in studies of healthy subjects and those with chronic kidney disease (CKD).

Methods: Among healthy controls, we measured plasma concentrations of each solute at 7 time points throughout the day. We calculated 24-hour urinary clearances from timed urine collections using the weighted 24-hour mean plasma value of each solute. We determined the diurnal within-subject coefficient of variation (CV) of plasma concentration for each solute. We investigated associations of derived clearances with estimated GFR in 239 participants from the Seattle Kidney Study, a cohort study of CKD.

Results: Three of the 16 solutes had implausible kidney clearance values and 4 exhibited high diurnal variation (Table). Nine solutes demonstrated reasonable diurnal stability and plausible clearance values. The clearances of these solutes correlated with GFR among CKD patients.

Conclusions: We identified 9 solutes that show promise for estimating proximal tubular secretory clearance - cinnamoylglycine, indoxyl sulfate, p-cresol sulfate, isovalerylglycine, kynurenic acid, pantothenic acid, pyridoxic acid, tiglylglycine, and xanthosine.

Funding: NIDDK Support

	Healthy controls			CKD patients		
	24h mean plasma concentration (ng/ml)	Within-subject CV of 24h concentration	Clearance (ml/min)	Plasma concentration (ng/ml)	Clearance (ml/min)	Correlation with eGFR
Hippurate	113.7	64.0%	485	239.5	521	0.361
Cinnamoylglycine	13.2	33.6%	156	31.2	76	0.267
Indoxyl sulfate	1475.6	27.0%	34	7653.7	18	0.553
p-cresol sulfate	15822.0	32.2%	8	101683.6	4	0.508
3-hydroxyhippurate	18.6	64.5%	2911	40.3	2284	0.177
Adipic acid	204.9	29.3%	11	260.1	14	0.049
Dimethyluric acid	19.2	123.5%	448	59.0	296	0.434
Isovalerylglycine	5.7	32.7%	351	8.0	217	0.424
Kynurenic acid	12.6	15.6%	121	32.2	81	0.479
Pantothenic acid	42.8	13.0%	41	93.2	24	0.350
Pyridoxic acid	44.7	10.6%	51	185.9	34	0.515
Suberic acid	305.0	26.0%	0.97	889.3	0.52	0.010
Succinic acid	1577.8	29.8%	0.62	1879.0	0.62	-0.014
Tiglylglycine	9.1	30.8%	229	21.6	133	0.464
Trimethyluric acid	2.3	73.4%	380	6.2	221	0.163
Xanthosine	1.5	13.4%	963	15.8	305	0.276

FR-PO141

Deubiquitinase Inhibitor PR-619 Reduces Smad4 Expression and Suppresses Renal Fibrosis in Mice with Unilateral Ureteral Obstruction

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Background: Deubiquitinating enzymes (DUBs) remove ubiquitin from their substrates and, together with ubiquitin ligases, play an important role in the regulation of protein expression. Although transforming growth factor (TGF)-β1-Smad signaling is a central pathway of renal fibrosis, the role of DUBs in the expression of TGF-β receptors and Smads during the development of renal fibrosis remains unknown.

Methods: In this study, we investigated whether PR-619, a pan-DUB inhibitor, suppresses fibrosis in mice with unilateral ureteral obstruction (UUO) and TGF-β1-stimulated normal rat kidney (NRK)-49F cells, a rat renal fibroblast cell line. Either the vehicle (dimethyl sulfoxide) or PR-619 (100 μg) was intraperitoneally administered to mice after UUO induction once a day for 7 days.

Results: Administration of PR-619 attenuated renal fibrosis with downregulation of mesenchymal markers, extracellular matrix proteins, matrix metalloproteinases, apoptosis, macrophage infiltration, and the TGF-β1 mRNA level in UUO mice. Although type I TGF-β receptor (TGF-βRI), Smad2, Smad3, and Smad4 protein expression levels were markedly increased in mice with UUO, administration of PR-619 suppressed only Smad4 expression but not TGF-βRI, Smad2, or Smad3 expression. PR-619 also had an inhibitory effect on TGF-β1-induced α-smooth muscle actin expression and reduced Smad4 levels in NRK-49F cells.

Conclusions: Our results indicate that PR-619 ameliorates renal fibrosis, which is accompanied by the reduction of Smad4 expression.

Funding: Private Foundation Support

FR-PO142

Regulating Hyaluronan Deposition Attenuates Tubulointerstitial Fibrosis in Ureteral Obstruction

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Background: Renal fibrosis is an end-stage outcome of chronic kidney disease(CKD) without foreseeable cure. However, we recently found that interleukin-10 (IL-10) can abrogate dermal fibrosis by regulating hyaluronan(HA), an abundant glycosaminoglycan in the extracellular matrix (ECM). Here, we hypothesize that promoting the expression of the high molecular weight(MW) HA form attenuates renal fibrosis by regulating ECM remodeling and reducing inflammation.

Methods: *in vivo*: we used the UUO model in the presence or absence of IL-10 to assess the HA role. UUO/sham kidneys were collected at d3,7,14&21 for RNA, ELISA, and/or IHC analyses. HA synthases(HAS1-3) and hyaluronidases(HYAL1-2) enzyme levels were determined by qPCR and immunoblotting (IB), while HA MW was confirmed by gel electrophoresis. To test loss of function effects, we fed mice with 4-methylumbelliferone(4-MU,5%), a HA synthesis inhibitor, and evaluated the outcomes.*in vitro*: renal fibroblasts(FB) were isolated from C57BL/6J mice to measure total HA by pericellular matrix assays. α-

SMA, HAS1, 2 and p-STAT3 expression were also assessed by IB at 48h. Mean ±SD; p-values by ANOVA.

Results: *in vivo*: HAS1 & HAS2 expression was upregulated in normal and 4MU-fed UUO mice compared to control mice from d3 onwards. ELISA showed that total HA levels steadily increased from d3-14 for UUO mice, and up to d21 for IL-10-treated UUO mice. In normal diet mice, lenti-IL-10 resulted in decreased kidney fibrosis and preserved tubular integrity in comparison to controls. IL-10-treated 4-MU diet mice did not attenuated fibrosis. HA gel electrophoresis showed that unlike control/sham kidneys, d3&7 UUO kidneys had a previously unreported $1.5x10^6$D HA form. *in vitro*: A 1.88-fold increase in HA-rich matrix formation was shown with 24h of IL-10 stimulation, and the effect was abrogated by HYAL. Significant increased HAS2, α-SMA, & p-STAT3 in the IL-10-treated FBs after 48h. $p<0.05$

Conclusions: Our study provides the first evidence that injured mouse kidney expresses increased levels of an ultra-high MW HA variant not found in normal kidneys. This suggests that HA is critical for kidney function, homeostasis, and architectural integrity. Understanding the mechanisms behind HA-mediated in renal fibrosis could lead the design and application of innovative therapeutics.

Funding: Other NIH Support - NIGMS, Clinical Revenue Support

FR-PO143

A Critical Role of Histone Methyltransferase EZH2 in Mediating Renal Epithelial-Mesenchymal Transition and Renal Fibrogenesis

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Background: EZH2 (Enhancer of Zeste Homolog 2) is a methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3) and functions as an oncogenic factor in many cancer types. Its role in renal epithelial-mesenchymal transition (EMT) remains unknown.

Methods: In this study, we examined the effect of EZH2 inhibition on EMT and renal fibrosis in the kidney following unilateral ureteral obstruction (UUO).

Results: We found that EZH2 and H3K27me3 were highly expressed in the kidney of mice with and cultured mouse kidney proximal tubular cells (TKPT) undergoing EMT. Inhibition of EZH2 with 3-deazaneplanocin A (3-DZNeP) attenuated renal fibrosis, which was associated with preserving E-cadherin expression and inhibiting vimentin upregulation in the obstructed kidney. Treatment with 3-DZNeP or transfection of EZH2 siRNA also inhibited TGF-β1-induced EMT of TKPT. Injury to the kidney or cultured TKPT resulted in upregulation of Snail1 and Twist, two transcription factors, and downregulation of PTEN, a protein tyrosine phosphatase associated with inhibition of PI3K-AKT signaling; EZH2 inhibition or silencing reversed all those responses. 3-DZNeP was also effective in suppressing epithelial arrest at G2/M phase and dephosphorylating AKT and β-catenin in in vivo and in vitro.

Conclusions: These data indicate that EZH2 activation contributes to renal EMT and fibrosis through activation of multiple signaling pathways and suggest that EZH2 would be a novel therapy for treatment of renal fibrosis.

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FR-PO144

Single Nephron Dynamics in Patients with Obesity-Related Glomerulopathy

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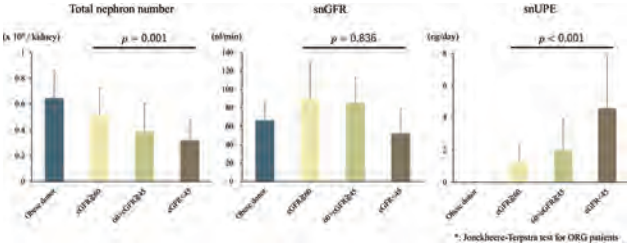
Background: The etiologies and mechanisms underlying the progression of obesity-related glomerulopathy (ORG) remain largely unknown, and the urinary protein excretion (UPE) level is the only predictive factor for renal outcome. ORG is characterized by renal histopathological findings of low glomerular density with glomerulomegaly, related to glomerular hyperfiltration. In this study, we estimated total nephron number and related factors in patients with ORG at different stages of the disease.

Methods: The total nephron number was calculated using a simplified method based on combined use of unenhanced computed tomography and non-sclerotic glomerular density in renal biopsy. Single-nephron glomerular filtration rate (snGFR) and single-nephron UPE (snUPE) were calculated by dividing eGFR or UPE by total nephron number, respectively. The glomerular volume (GV) was estimated from the measured mean glomerular area. Obese kidney transplantation donors were included in the study as a control group.

Results: Among the 30 Japanese ORG patients included in the study, total nephron number ranged from 153000 to 1061000 per kidney and was inversely correlated with GV (r = –0.366, p = 0.047). The snGFR was correlated with GV (r = 0.631, p < 0.001), and snUPE was correlated with the degree of glomerulosclerosis (r = 0.633, p < 0.001). None of these parameters associated with total nephron number showed a correlation with body mass index (BMI). Patients with advanced renal impairment were characterized by diminished snGFR and markedly elevated snUPE level (**Figure**). Among the ORG patients with preserved renal function (eGFR ≧ 45 mL/min/1.73 m^2, n = 22), total nephron number was identified as a factor associated with UPE at diagnosis, independent of eGFR and BMI.

Conclusions: There is a close relationship between difference in total nephron number and severity of ORG, in relation to changes in the single nephron dynamics. Compensatory failure of glomerular hyperfiltration may be a characteristic of advanced ORG.



FR-PO145

Analysis of the Peritubular Capillaries and Lymphatics in a Model of Renal Injury and Repair

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Background: Chronic kidney disease has a diverse range of aetiologies, but all are associated with alterations in the renal interstitial microvasculature. We hypothesised that renal injury promotes loss of peritubular capillaries leading to tubular cell hypoxia, but conversely lymphatic vessel density may increase as a compensatory response to reduce inflammation and facilitate repair.

Methods: C57Bl/6 mice underwent unilateral ureteric obstruction (UUO) or sham surgery. After 7 days of UUO, 8 mice were culled while in the remaining mice the ureter was re-implanted into the bladder to relieve obstruction (R-UUO) for 1, 2 and 4 weeks (n=6-8). Kidneys were harvested and analysed by flow cytometry, immunostaining, RNAseq, qPCR and electron microscopy.

Results: Flow cytometry demonstrated a 16-fold increase in the proportion of dead $DAPI^+/CD31^+$ endothelial cells (ECs) in UUO kidney v sham (p=<0.001). CD31 quantification by IHC revealed a doubling in areas of capillary rarefaction in UUO v sham (p=<0.001), with the degree of rarefaction falling by 31% following R-UUO (p=<0.001). Electron microscopy analysis demonstrated a reduction in peritubular capillary fenestrations and an increase in EC vacuolation, which partially reversed following R-UUO. While the density of $Lyve\text{-}1^+$ lymphatic vessels remained similar in UUO kidney v sham, there was a doubling of lymphatic vessels after 4 weeks of relief of obstruction ($p<0.05$). RNAseq and qPCR analysis of renal cortex revealed a reduction in Vegfa in UUO v sham, which partially reversed following R-UUO. Conversely there was a significant up-regulation of Vegfc and Vegfd, most notably following R-UUO. Gene expression of Vegfr3 increased in UUO compared with sham ($p<0.01$), and this persisted through to week 4 after R-UUO. Dual immunofluorescence for VEGFR3 and LYVE-1 determined that the increase in VEGFR3 staining occurred largely in $CD31^+/Lyve1^-$ vessels, most likely peritubular capillaries. This was confirmed by flow cytometry with the proportion of $CD31^+/podoplanin^-$ cells that co-expressed VEGFR3 increasing from 7% in sham to 36% in UUO kidney.

Conclusions: Our data suggest that peritubular capillary rarefaction occurs following renal injury and only partially improves following cessation of injury. Therapies that prevent capillary rarefaction may reduce secondary renal injury and augment repair.

Funding: Private Foundation Support

FR-PO146

The Role of Complement C1r and C1s Serine Proteases in Kidney Fibrosis

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Background: We previously reported increased expression of C1q in kidney cells as a pathophysiologic mechanism leading to kidney fibrosis. The classical pathway of complement activation is initiated by the assembly of the C1 complex which consists of C1q and serine proteases C1r and C1s. We hypothesize that activation of classical pathway in kidney cells contributes to tubulointerstitial fibrosis, and tested this idea in mice with global deletion of C1r.

Methods: We performed real time-PCR, immunohistochemistry, in situ hybridization, western blotting and microarray based gene expression analysis in wild type (WT) and in C1r-/- mice subjected to unilateral ureteral obstruction (UUO) or folic acid injury (FA). We overexpressed human C1r in human tubular epithelial cells

Results: Administration of FA or UUO injury in WT mice led to upregulation of C1r and C1s mRNA and protein in whole kidney tissue. In situ hybridization and immunohistochemistry localized increased expression of these proteases to distal tubular epithelial cells. C1r deletion reduced fibrosis in both animal models. While kidney inflammation and complement activation measured by increased expression of C3 fragments were significantly reduced in the FA model, C3 formation and inflammation were not affected in the UUO mice, despite the reduction in fibrosis. While C1r-/- mice had reduced C1s expression, stable transfection of human C1r in renal epithelial cells led to increased expression of both C1r and C1s. Gene expression arrays corroborated downregulation of probe sets representing C1r and C1s in kidney tissue of C1r-/- mice, as well as downregulation of genes associated with connective tissue and collagen. C1r-/- mice treated with FA had reduced expression of genes associated with increased inflammation.

Conclusions: In conclusion our studies support the role of classical complement pathway activation during fibrosis via increased expression of C1r in distal tubular epithelial cells and identify C1r as a novel potential therapeutic target for the treatment of progressive kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO147

Loss of C5aR1 in Foxd1+ Stromal Cells Reduces Kidney Fibrosis

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Background: Recent studies have identified a population of perivascular mesenchymal cells in the kidney that express the transcription factor Foxd1. These cells are called resident fibroblasts or pericytes. Fate-mapping studies have identified these pericytes and resident fibroblasts as the major precursor population of interstitial myofibroblasts in animal models of kidney disease. We previously reported increased synthesis of complement components including anaphylatoxin receptor C5aR1 in PDGFβR-positive pericytes isolated from murine models of fibrosis. Reduced expression of C5aR1 using global deletion of C5aR1 ameliorates renal fibrosis. We hypothesize that deletion of C5aR1 in Foxd1-expressing cells can lead to reduced myofibroblast production, reduced inflammation, and reduced kidney fibrosis.

Methods: C5aR1GFP$^{fl/fl}$ mice were generated by inserting LoxP sites flanking exon 2 as previously reported. C5aR1GFP$^{fl/fl}$ mice were crossed with mice expressing Cre-recombinase under control of the Foxd1 promoter to generate Foxd1-Cre-C5aR1GFP$^{fl/fl}$ mice. Eight week old Foxd1-Cre-C5aR1GFP$^{fl/fl}$ mice and C5aR1GFP$^{fl/fl}$ (control mice) received intraperitoneal injections of either vehicle (sodium bicarbonate) or folic acid+sodium bicarbonate (FA). Two weeks later kidney tissue was harvested for analysis. Primary mouse pericytes were isolated from the kidneys of Foxd1CreC5aR1GFP$^{fl/fl}$ and C5aR1GFP$^{fl/fl}$ following FA-injury as previously reported

Results: Immunohistochemical analysis, flow cytometry, quantitative RT-PCR and western blots demonstrated reduced inflammation and reduced fibrosis in whole kidney tissue from Foxd1CreC5aR1GFP$^{fl/fl}$ mice treated with FA when compared to control mice. Cytokine production measured by Luminex assays in cell supernatants from cultured PDGFβR^{+} cells isolated from kidneys of FA-treated mice demonstrated that the absence of C5aR1 receptor in cultured pericytes reduces inflammatory cytokine production including IL6, TNFalpha, and MIP2.

Conclusions: The loss of C5aR1 in Foxd1 stromal cells reduces kidney fibrosis and reduces inflammatory response of kidney pericytes. These results support the role of increased expression of pericyte C5aR1 in the pathogenesis of kidney fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO148

Study of the Expression of Renal PCSK9 in the Rrm2b Mouse Model of Nephrotic Syndrome

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Background: 85% of American chronic disease patient presenting nephrotic syndrome (NS) have high levels of low density lipoprotein cholesterol (LDL-c), compared to only 31.5% in the American general population. A factor from the kidney might be responsible for the increased susceptibility for high levels of LDL-c in NS patients. Proprotein convertase subtilisin/kexin type 9 (PCSK9) was shown to play an important role in the regulation of LDL-c levels in the liver. PCSK9 is expressed in the kidney at a lower level of expression compared to the liver, but its role in this organ is not clear. We decided to study the expression and the role of PCSK9 in NS in the Rrm2b mouse, a model collapsing glomerulopathy.

Methods: Male Rrm2b Control (+/+) and knock-out (-/-) mice (6 mice/group) were studied every week between the age 5 and 12 weeks. Albuminuria, PCSK9 and cholesterol serum levels were assessed. PCSK9 gene and protein expression in liver, kidney, intestine and serum were studied by RealTime PCR, Western blot, and confocal microscopy.

Results: Rrm2b$^{+/+}$ mice do not develop albuminuria, hypercholesterolemia, or high levels of serum PCSK9. Compared to controls, Rrm2b$^{-/-}$ develop albuminuria from the age of 7 weeks (from 425±239 μg/18h at 7 weeks to 3895±381 at 10 weeks (P<0.001)). Serum PCSK9 levels significantly increase from the age of 8 weeks (from 19.75±5.21 ng/ml at 8 weeks (P<0.05) to 55.54±13.07 at 10 weeks (P<0.01)). Serum total cholesterol levels significantly increase from the age of 8 weeks (from 124.16±10.27 mg/dl at 8 weeks (P<0.05) to 567.58±72.96 at 10 weeks (P<0.001)). PCSK9 gene expression is relatively unchanged as animal age. PCSK9 protein expression was shown by Western blot to increase in the renal cortex from the age of 9 weeks, and decrease in the liver from the age of 7 weeks. By confocal microscopy, PCSK9 was shown to co-localize with Aquaporin-2, indicating expression in the collecting duct where its expression is increased from the age of 7 weeks.

Conclusions: As Rrm2b$^{-/-}$ mice age and develop NS, PCSK9 protein levels increase in the kidney and serum, and decrease in the liver. Collecting duct expressed PCSK9 may play an important role in the initiation of hypercholesterolemia in NS in the Rrm2b mouse model, as a link between the kidney and the liver.

FR-PO149

Nephron Loss Reduces Excretion of Urinary Extracellular Vesicles

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Background: Urinary extracellular vesicles (uEVs) are emerging as non-invasive biomarkers for various kidney diseases. We previously showed that the uEV-marker CD9 decreases with disease progression in autosomal dominant polycystic kidney disease (ADPKD; Salih *et al.*, J Am Soc Nephrol 2016). Therefore, here, we hypothesize that nephron loss decreases uEV excretion.

Methods: We quantified uEVs in two different settings of nephron loss, including donor nephrectomy and ADPKD with progressive decline of estimated glomerular filtration rate (eGFR). We obtained spot and 24-hour urine samples from 20 kidney donors the day prior and 3 months after nephrectomy, and from 27 ADPKD patients at baseline and after a median follow-up time of 3 years. uEVs were quantified using 3 techniques, including EVQuant (a novel technique which counts individual fluorescently labeled EVs after immobilization in a matrix), nanoparticle tracking analysis (NTA), and a time-resolved fluorescence immunoassay (TRFIA) capturing CD9+ uEVs.

Results: Baseline kidney function correlated with uEV excretion in both healthy donors (EVQuant vs. eGFR: R^2 0.41, P = 0.01) and ADPKD patients (CD9-TRFIA vs. mGFR: R^2 0.23, P = 0.02). Donor nephrectomy reduced eGFR by 32 ml/min/1.73m^2 or 38% after 3 months. uEV excretion decreased by 18% as analyzed by EVQuant (95%CI: 6-31%), 21% by NTA (95%CI: 7-34%) and 22% by TRFIA (95%CI: 3-42%). In the ADPKD cohort the average loss in eGFR was 4.1 ml/min/1.73m^2/year (95%CI 2.9-5.2), or 18% after 3 years (95%CI 13-23%). In this period, the number of uEVs reduced by 22% (95%CI: 9-36%, as analyzed by TRFIA).

Conclusions: Nephron loss reduces uEV excretion both after donor nephrectomy and in progressive ADPKD. Therefore, it is important to adjust for uEV excretion when performing cross-sectional or longitudinal analyses of uEVs in patients with reduced kidney function.

FR-PO150

Deconvolving Bulk Disease Expression Datasets Using Markers Identified from Single-Cell Sequencing Data Defines CKD Associated Cell Types

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Background: Elucidating changes in cell type composition across diseases can provide insight into pathology-related alterations in kidney tissue. Single-cell data from tumor nephrectomy tissue allows the identification of cell type markers in the adult human kidney. By integrating this information with bulk expression data from 223 biopsies from the European Renal cDNA Bank cohort (ERCB), we identify cell type proportion alterations across 9 diverse glomerular diseases.

Methods: We first identify cell type specific genes in an unbiased, data-driven manner from eight adult kidney single cell 10X Genomics expression datasets from tumor nephrectomy tissue. We extract markers from the single-cell expression data using the Seurat R package (Butler et al., 2018). We then expand these cell type specific marker sets by identifying additional cell type specific marker genes using computational nanodissection (Ju et al., 2013) and perform pathway enrichment analysis. Using our expanded set of marker genes, we deconvolve microdissected glomerular bulk expression data from the ERCB cohort using CellCODE (Chikina et al., 2015) to identify differences in cell type composition across patients with diverse kidney diseases.

Results: Both the cell type specific marker genes identified from single-cell data and the additional cell type marker genes identified by nanodissection show relevant functional enrichments. Consistent with prior knowledge, we find that podocyte markers are lost in diseased patients compared to living donors, monocyte markers are elevated in immune-mediated diseases such as lupus nephritis relative to other kidney diseases, and mesangial/ vascular smooth muscle cell markers are elevated in diabetic nephropathy. Multiple cell type markers are correlated with GFR, with podocyte markers positively correlated and parietal epithelial cell markers negatively correlated

Conclusions: Integrating single-cell and bulk expression data provides insight into cell composition changes across diverse kidney diseases. Our approach illustrates the power of leveraging and integrating multimodal data types to understand the molecular underpinnings of disease processes.

Funding: NIDDK Support

FR-PO151

MicroRNA-34a Induces Renal Aging by Regulating SIRT1/p53/p21 Pathway and Promoting the Expression of Senescence-Associated Secretory Phenotype (SASP)

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Background: An increasing number of investigations suggest that small non-coding microRNAs play an important role in the regulation of genes involved in various kidney disease. MicroRNA-34a (miR-34a) has been recently implicated in cardiac, endothelial, endothelial progenitor cell, vascular smooth muscle cell senescence, however, its contribution to the aging process of kidney has not been explored so far. The aim of the present study was to analyze miRNA expression profiles and the rule of miR-34a in mice kidney during the aging process.

Methods: The kidneys of male C57BL/6 mice at different ages (3 months, 12 months and 24 months, n=5 per group) were used. Total RNA was extracted using Trizol reagent following the manufacturer's procedure. The total RNA quantity and purity were analysis of Bioanalyzer 2100 with RIN number >7.0. Approximately 1 ug of total RNA were used to prepare small RNA library according to protocol of TruSeq Small RNA Sample Prep Kits. And then we performed the single-end sequencing (36bp or 50bp) on an Illumina Hiseq 2500 at the LC-BIO following the vendor's recommended protocol. In addition, the results were assessed by real-time PCR and western blotting in kidneys of mice.

Results: Several up- and downregulated miRNAs were identified in the mice kidneys at 3 different ages. We observed the upregulation of miR-26a, miR-214, miR-34a, miR-34c, miR-29c, miR-199a, miR-21a, miR-27a, miR-195a and miR-23a, whereas miR-335, miR-200b, miR-378a, miR-151, miR-486a, miR-615, miR-378 were downregulated in the aging mice kidneys. We found that miR-34a was highly expressed in kidneys isolated from old mice. Moreover, its well-known target, the longevity-associated protein SIRT1, was significantly downregulated during aging in both kidney tissue and HK-2 cells. miR-34a overexpression in HK-2 cells caused cell cycle arrest along with enhanced p21 and p53 protein levels and reduced SIRT1 protein expression. Furthermore, miR-34a ectopic expression induced the expression of SASP, including TNF-α, IL-1α, IL-6, plasminogen activator inhibitor-1 and monocyte chemoattractant protein-1.

Conclusions: In conclusion, our findings suggest that aging-associated increase of miR-34a expression plays an important role in renal aging by inhibition of SIRT1 and activation of p53/p21 pathway as well as the induction of SASP.

Funding: Government Support - Non-U.S.

FR-PO152

Weekly Subcutaneous Mutated Human Angiopoietin – Like 4 (8520) Improves CKD in Diabetic Rats via an Anti-Endothelial Apoptosis Mechanism

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Background: We previously showed that single intravenous dosing of recombinant mutated human Angptl4 (8520) reduces proteinuria for over 2 weeks in diabetic rats (Clement L, Mace C, et al Nature Medicine Jan 2014). We now tested whether subcutaneous doses in diabetic rats would reduce CKD.

Methods: We treated male ZSF1 rats (n = 5 rats / group) with 8520 or rat albumin once a week subcutaneously in declining doses, starting with 500 μg per dose on Week 0 (W0) to 125 μg on Week 9, to 100 μg on Week 15 and 50 μg on Week 16, after which the treatment was stopped and rats sacrificed on W20. Food and water intake, proteinuria, blood glucose, plasma human Angptl4 levels and serum parameters were measured periodically.

Results: Pharmacokinetic assessment of plasma human Angptl4 (8520) levels showed elevated levels between W1 and W15 at dose ranges between 500 μg and 100 μg subcutaneously per week. Plasma levels were statistically similar at doses between 500 μg and 125 μg. Plasma creatinine was significantly lower in the treatment group ($P < 0.01$ to $P < 0.001$) between doses 500 and 125 μg, and BUN between 500 and 100 μg ($P < 0.05$). 18-hour proteinuria was mostly similar between treatment and control groups, and as were the plasma glucose and triglyceride levels. Histological improvement revealed very significant improvement morphometric parameters in the treatment compared to control group. TUNEL staining for apoptosis revealed very significant reduction in interstitial capillary endothelial apoptosis in the treatment Vs. the control group ($P < 0.001$).

Conclusions: Weekly subcutaneous doses of mutated human Angptl4 in ZSF1 rats improves GFR at doses between 500 and 125 μg. Despite sub-therapeutic doses and stopping treatment towards the end, morphology was significantly improved, suggesting a memory effect. The absence of effects on proteinuria and the highly significant difference in interstitial capillary endothelial apoptosis suggests that the beneficial effects of subcutaneous dosing are mediated by preserving interstitial capillaries and presumably promoting repair in the treatment group.

Funding: NIDDK Support

FR-PO153

miRNA Profiling of Kidney Disease Indicates a Conserved Role for miRNA99 Family

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Background: MicroRNAs (miRNAs) are short non-coding RNA molecules that play a crucial role in cellular homeostasis by regulating gene expression. Lately, miRNAs have become important therapeutic targets. To determine consistently altered miRNAs that could causally affect chronic kidney disease (CKD) development, we sought to define miRNA profiles in kidneys of five different CKD models and validated these results in patient samples.

Methods: miRNA fraction was isolated from the kidneys of wildtype mice or mice with CKD induced by 1) unilateral ureteral obstruction (UUO), 2) folic acid (FA) administration, 3) transgenic expression of Notch intracellular domain in tubule cells, 4) transgenic expression of PGC1α in podocytes and 5) transgenic expression of APOL1 risk allele in podocytes. Small RNA sequencing was followed by miRNA alignment and abundance quantification. qPCR analysis and *in situ* hybridization were used to validate candidate miRNAs differentially expressed in CKD. We used microRNA mimics and inhibitors to understand the role of miRNA in cultured renal tubule cells.

Results: We detected differences in levels of 457 miRNAs among all analyzed models of kidney disease. miR-99 family consisting of 99a, 99b and 100, were significantly downregulated in all five models. *In situ* hybridization for miR-99 family on wildtype, UUO, and FA kidney sections showed that these miRNAs were expressed widely in normal tubules but absent or significantly downregulated in injured/dedifferentiated tubules. Importantly, human renal biopsy sections also showed significant downregulation in the expression of the miR-99 family in CKD patients, compared to healthy volunteers. Furthermore, transfection of HKC8, a human proximal tubule cell line, with miR-99a and 100 mimics improved epithelial characteristics and reduced proliferation. We identified IGF1 and mTOR as likely targets of miR-99 family in kidney tubule samples.

Conclusions: We found that miR-99a, 99b and 100 are significantly downregulated across all examined CKD models and human subjects, implying a causal role in disease. Upregulation of miR-99 family *in vitro* significantly decreased expression of mTOR, IGF-1, cell proliferation and improved epithelial characteristics, suggesting a crucial regulatory function. In summary, miR-99 family could be potential therapeutic targets for CKD.

Funding: NIDDK Support

FR-PO154

The Effect of Autophagic Flow in the Phenotype Transformation of Macrophage M1/M2

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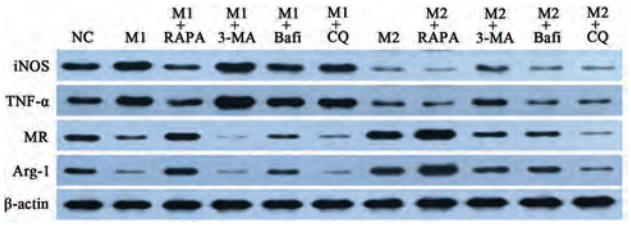
Background: Macrophage infiltration is an important histopathological feature of kidney disease, and its activation state in the microenvironment is the main factor determines disease prognosis. Autophagy is a process in which lysosomes degrade their own damaged and excess proteins. It's highly dynamic, also known as autophagic flow. In this study, macrophages were cultured in vitro to fully observe the levels of autophagic flow and the effects on the M1/M2 phenotype transformation.

Methods: The macrophages RAW264.7 were stimulated with IFN-γ+LPS and IL-4 for 24h to induce M1 and M2 activation. Use of autophagosome-generating activator (RAPA), autophagosome production inhibitor (3-MA), autolysosome fusion inhibitor (BAFA) and autolysosome degradation inhibitor (CQ) to intervene M1/M2 for 24h. The expression levels of M1 markers, M2 markers and autophagy markers were detected by western blot and immunofluorescence. Then using an electron microscope to observe autophagic flow.

Results: 1. The expression of M1 markers (iNOS, TNF-α) increased with IFN-γ+LPS. Instead, IL-4 stimulated activation of M2 that the levels of MR and Arg-1 increased. 2. Autophagy-related proteins LC3 and Beclin-1 had higher level in M2 cells with the level of autophagy specific degradation protein p62 decreased, suggesting the autophagy level of M2 cells was higher than that of M1 cells. 3. The autophagosome formation, fusion of autophagosomes with lysosomes, autolysosome formation, and substrate degradation were observed by EM. 4. For M1 cells, RAPA increased the expression of LC3, Beclin-1 and p62, while those decreased with 3-MA. After BAFA intervention, the expression of LC3 and Beclin-1 decreased, when p62 was significantly increased. But the expression of LC3-II, Beclin-1 and p62 showed a tendency to increase after CQ intervention. 5. Activation of autophagy induced the transformation of M2 cells, while inhibition of autophagy induced M1 activation.

Conclusions: Autophagic flow can regulate the mutual transformation of macrophage M1/M2 phenotype. But changes in a single marker can't confirm the level of autophagy in the cell, the dynamic changes in autophagy flow need to be evaluated.



FR-PO155

Molecular Magnetic Resonance Imaging of Allysine to Quantify Renal Fibrogenesis

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Background: Chronic kidney disease (CKD), most commonly caused as result of type-2 diabetes or ischemic/hypertensive nephropathy, currently affects 12% of all adults in the US. The fibrotic deposition and remodeling of extracellular matrix proteins to form cross-linked collagen fibers is a characteristic feature of CKD and eventually results in end stage renal disease. Critical to fiber formation is the enzymatic production of allysine on collagen, which facilitates fibril cross-linking through condensation reactions with neighboring allysine and lysine residues. We have developed a novel Gd-based MRI probe, GdOA, designed to target allysine for noninvasive imaging of active fibrogenesis in kidney disease.

Methods: The ability of GdOA to detect fibrogenesis was evaluated in two animal models of CKD - nephrotoxic serum nephritis (NTN) and Col4a3-/- Alport mice. For the NTN model, 129/SvEv mice were dosed at day 0 with 250 μg Sheep IgG and then with 125 μL sheep anti-rat GBM serum on day 5. Control animals received PBS injections. Animals were imaged 7 days post GBM serum injection. For the Alport model, wild type and Col4a3-/- mice were imaged at 6-10 weeks of age to assess mild and advanced stages of disease. Following MRI, kidneys were collected and assessed for hydroxyproline (HYP) content and tissue histology.

Results: The NTN model resulted in diffuse tubular injury, glomerulosclerosis, and mild fibrosis. GdOA resulted in a 6.9 fold increase in ΔR1 (probe relaxivity) in the cortex of the NTN group compared to control mice ($p = 0.048$). Hydroxyproline content in tissue was 1.88 fold higher for NTN animals compared to control animals ($p = 0.0004$) and ΔR1 showed positive correlation with increasing HYP concentrations ($r = 0.625$). In the Col4a3-/- mice, Gd-OA was able to detect early stages of disease and also correlated with increasing HYP concentrations.

Conclusions: The requirement of allysine for the crosslinking of ECM proteins makes it a valuable biomarker of fibrogenesis. GdOA is an oxyamine derivative of GdDOTA designed for targeted binding to allysine, with minimal off-target accumulation and rapid renal excretion. GdOA MRI demonstrated a strong correlation with the extent of disease in two animal models of CKD and therefore might provide a novel means to quantify early stages of renal fibrosis in patients.

Funding: NIDDK Support

FR-PO156

Nicorandil Plays a Protective Role Against Renal Fibrosis in Unilateral Ureteral Ligation Models via Reducing TGF-β1/Collagen Expression and Improving Energy Metabolism

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Background: As one of most important metabolic sensors, ATP-sensitive potassium channels (KATP) could regulate cellular activity to meet energetic demands. It has also been demonstrated that KATP plays a protective role on several ischemia-associated diseases. However, there are few studies to clarify whether KATP opener could directly improve renal function or renal fibrosis in unilateral ureteral ligation (UUO) models. This experimental study was designed to clarify the effect and mechanism of nicorandil (a KATP opener) on renal dysfunction, extracellular matrix expression and ATP generation in mice renal fibrosis model caused by unilateral ureteral ligation.

Methods: Mice UUO models were developed and observed at 7th and 14th day after operation. There were three groups in our study: sham-operation (n=12), UUO (n=12), UUO+nicorandil (n=12). In nicorandil treatment group, nicorandil was injected intraperitoneally daily (20mg/kg/d) for 12 days from the third day of UUO operation. Renal function and ATP synthesis (using an ATP assay kit, FLAA, Sigma, USA) were detected at 7th and 14th day after operation. Masson trichrome staining was performed to analyze collagen generation. TGF-β1 and Smad3 were detected by Western blot.

Results: Compared with sham-operation group, UUO groups had a significantly higher serum level of creatinine (7th day: 55.9±4.8 vs. 35.7±3.2μmol/L, $P<0.01$; 14th day: 82.0±7.8 vs. 35.2±6.2μmol/L, $P<0.01$). Nicorandil treatment not only reduced serum creatinine level (7th day: 45.7±3.6 vs. 55.9±4.8μmol/L, $P<0.05$; 14th day 64.3±5.5 vs. 82.0±7.8μmol/L, $P<0.01$), but also reduced collagen volume fraction (7th day: 10.5±2.8% vs. 17.6±3.8%, $P<0.01$; 14th day: 16.4±3.8% vs. 34.2±5.2%, $P<0.01$). We also found that TGF-β1 and Smad3 expression were significantly reduced in nicorandil treatment group. Furthermore, renal ATP synthase was also improved significantly (sham operation group: 8.55±2.74 nmol/L; UUO group: 2.92±1.96 nmol/L; UUO+nicorandil group: 4.88±1.48 nmol/L, $P<0.05$).

Conclusions: KATP opener nicorandil protected against UUO-induced renal fibrosis, which were associated with TGF-β1/collagen expression and energy metabolism recovery.

Funding: Government Support - Non-U.S.

FR-PO157

Vitamin D Receptor (VDR) Expression Determines Initiation and Progression of Renal Lesions in HIV-Transgenic Mice with Variable Angiotensinogen (Agt) Copies

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Background: Agt transgenic mice have been shown to carry higher serum and cellular levels of Angiotensin II levels and associated downstream effects. Since Ang II has been shown to play a role in the progression of HIVAN, we hypothesized that mice with enhanced expression of Agt would display a rapid progression of renal lesions in a mouse model of HIVAN. We evaluated the effect of different copies of Agt in the initiation and progression of HIVAN in genetically engineered HIVAN mice (Tg26) expressing variable copies of Agt.

Methods: Control and Tg26 mice with 2 (Tg26/Agt-2) and 4 (Tg26/Agt-4) copies of Agt were evaluated for severity of renal lesions, arteriosclerosis and hypertension at 8 weeks and 16 weeks. Renal cortical sections were stained with Sirus red and PAS. RNA was extracted from renal tissues and probed for AT1, AT2, VDR, and molecules involved in profibtotic and epithelial-mesenchymal transition (EMT) pathways. Renal lesions were graded for their severity.

Results: Tg26/Agt-4/8wks showed lower blood pressure ($P<0.01$) vs. Tg26/Agt-2/8 wks, while Tg26/Agt-4/16wks displayed higher blood pressure vs. Tg26/Agt-2/16wks. Tg26/Agt-4/8wks displayed attenuated expression of PAI-1 vs. Tg26/Agt-2/8wks; however, Tg26/Agt-4/16wks showed 3-fold greater PAI-1 expression than to Tg26/Agt-2/16wks. Tg26/Agt-2/8wks displayed attenuated expression of VDR and enhanced production of Ang II vs. Tg26/Agt-4/8wks; however, this pattern reversed at 16 wks. Tg26/Agt-4/8wks displayed attenuated expression of AT1 and AT2 and down-regulation of Tert, TGF-β, Snail, and vimentin when compared to Tg26/Agt-2/8wks. Nonetheless, all these markers were comparable between these groups at 16 wk of age. Tg26/Agt-2/8wks developed renal lesions which were more advanced than Tg26/Agt-4/8wks. Conversely, Tg26/Agt-4/16wks displayed more advanced renal lesions vs. Tg26/Agt-2/16wks

Conclusions: Tg26/Agt-4 displayed slower progression of HIVAN initially at 8 weeks associated with enhanced renal tissue VDR expression and attenuated expression of AT1, TGB-β, PAI-1, Tert and EMT markers. However, Tg26/Agt-4 at 16 wks displayed accelerated growth due to attenuated VDR expression leading to high blood pressure, upregulation of EMT and profibrotic molecules.

Funding: NIDDK Support

FR-PO158

Sodium-Glucose Cotransporter 2 Inhibition Does Not Ameliorate Renal Progression in Adriamycin-Induced Nephropathy

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Background: Sodium-glucose cotransporter 2(SGLT2) inhibitors target SGLT2 in renal proximal tubules and promotes glycosuria in type 2 diabetic mellitus, resulting in lowering blood glucose. Clinical studies have shown that SGLT2 inhibitors attenuate the progression of diabetic nephropathy, which results were not merely associated with improved glucose control. To understand the related mechanisms, we investigated the effects of SGLT2 inhibitior dapagliflozin (DAPA) in a mouse model of adriamycin (ADX)-induced nephropathy.

Methods: ADX induced nephropathy model resulted in severe proteinuria and progressive glomerulosclerosis. Seven week old Balb/c mice were divided in five groups;1) control with vehicle, 2) control with DAPA 3mg, 3) ADX(11.5mg/kg) with vehicle, 4) ADX(11.5mg/kg) with DAPA 1mg, 5) ADX(11.5mg/kg) with DAPA 3mg. With ADX injection, DAPA was administered via gavage for 2 weeks. Molecular analyses using RT-PCR, western blot and immunohistochemistry were performed.

Results: DAPA administration was associated with decreased systolic blood pressure (SBP) in control group, but not among ADX injected groups. DAPA administration did not alleviate proteinuria, glomerular sclerosis and interstitial fibrosis in the ADX-induced nephropathy. Also, there were no differences in the expressions of TGF-β, Smad2 and collagen IV in the renal cortex of ADX with DAPA groups compared to ADX control group. Expression of macrophage marker ED1 was significantly increased in the kidney of ADX control group. DAPA administration in ADX groups decreased macrophage infiltration in the renal medulla, whereas no significant difference was observed in the renal cortex. SGLT2 expressions in the kidney were decreased in DAPA groups as expected. Strangely, the expressions of SGLT2 increased in the medulla of ADX with DAPA groups.

Conclusions: SGLT2 inhibition with dapagliflozin had no effect on reduction in proteinuria and inflammatory changes in renal cortex of ADX-induced nephropathy. Our study suggest that SGLT2 inhibition may modulate inflammation in the renal medulla, which effect may have been masked by massive insult of cortex. More experimental studies on renal injury model is needed to clarify the underlying mechanisms.

FR-PO159

Comprehensive Transcriptomic Mapping of Baseline and Pathological Human Kidneys at Single-Cell Resolution

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Background: The heterogeneity of cell types and states in human tissues pose challenges for precision medicine and targeted therapeutics as not all patients present the same disease phenotype or treatment response. Most of our current understanding of cell-types comes from comprehensive histological observations of surface proteins and other molecules, gathered over the decades. However, recent advances in single cell and spatial genomics, such as single-cell RNA-Seq, now allow us to classify large numbers of individual cells by their profiles. In this study, as part of the Human Cell Atlas initiative, we aim to catalog cell-types in human kidney specimens obtained from healthy donors and patients with kidney diseases.

Methods: Discarded tissue from tumor nephrectomies was subjected to single-cell dissociation or single-nucleus isolation, the latter applicable to frozen tissue as well. Droplet-based single-cell or single nucleus RNA-Seq libraries were prepared, PCR amplified and sequenced. Single-cell profiles were clustered, and clusters were annotated post hoc based on known marker genes.

Results: We identified over 10 known cell-types, from around 2,000 cells from discarded healthy tissue. Recovered cell-types included both renal parenchymal and immune cells. Heterogeneity was observed in collecting duct and proximal tubular cells. Data-driven markers were inferred for the cell-types.

Conclusions: We have established working single-cell dissociation protocols optimized specifically for human kidney specimens with paired reproducible analyses and insights. Proportions of cell-types will be reported with more confidence as we gather more samples, and in comparison with specific disease phenotypes.

Funding: Private Foundation Support

FR-PO160

The Impact of Carbon Monoxide Poisoning on Long-Term Risk of CKD: A Nationwide, Population-Based Study in Taiwan

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Background: Risk of chronic kidney disease (CKD) in patients with carbon monoxide poisoning (COP) and the hyperbaric oxygen (HBO) therapeutic effect had not been investigated.

Methods: Patients that survived after COP during index hospitalizations from 2000 to 2013 were identified in nationwide administrative registries. In a cohort study of 989,753 patients, we enrolled 8,616 COP patients and matched 34,464 comparison cohort as the non-COP group by propensity scores. Using this adjusted data, a possible association between COP and the risk of developing CKD was estimated using a Cox proportional hazard regression model. We further compared cumulative risk of CKD among COP patients stratified by HBOT with Kaplan-Meier analysis and the log-rank test.

Results: After a mean follow-up period of 4.28 years, the incident CKD rate was 261 per 10000 person-years. The COP group had higher risk (adjusted hazard ratio: 6.150; P < 0.001) than the non- COP group when measured over 4 years after CKD diagnosis. After stratification, the risk of CKD remarkably increased independent of status regarding sex, age, season and comorbidities (hypertension, diabetes mellitus, congestive heart failure, stroke, chronic obstructive pulmonary disease, liver cirrhosis, coronary artery disease, arrhythmia or hyperlipidemia) in the COP cohort. Age-specific COP to non-COP hazard was the greatest in the youngest group (18-29 years) (adjusted HR=34.18, 95% CI = 29.47–39.653). Additionally, HBOT did not result in statistically significant reduction in the risk of CKD in the COP cohorts (P=0.188, long-rank test).

Conclusions: The patients that survived after COP had a higher incidence of developing CKD. The results suggest that clinicians should enhance postdischarge follow-up of kidney function among COP patients

FR-PO161

The Presence of Simple Renal Cyst Is Associated with Increased Risk of Albuminuria in Young Adults

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Background: It is well-known that the prevalence of simple renal cyst increases with age. However, simple cysts are occasionally found in adults younger than 40 years of age. This cross-sectional study evaluated the clinical significance of simple renal cysts in young adults, focusing on the associations with hypertension and albuminuria.

Methods: Adults younger than 40 years who received comprehensive medical checkup from January 2005 to December 2013 were included. Simple renal cysts were identified by ultrasonography.

Results: Among 5832 young adults, renal cysts were found in 276 subjects (4.7%). Subjects diagnosed with polycystic kidney disease (n=5) or medullary sponge kidney (n=1) were excluded from the analyses. A single cyst and multiple cysts were found in 234 (4.0%) and 42 (0.7%) subjects, respectively. The locations of single cyst were cortex in 187, medulla in 26, and parapelvic region in 21. In univariate logistic regression analyses, age, male sex, body mass index, waist circumference, systolic blood pressure (SBP), hypertension, current smoking, high-density lipoprotein cholesterol, and uric acid levels were associated with a higher prevalence of simple cysts. Multivariate analyses of cysts showed that age (OR, 1.07; CI, 1.02-1.12), SBP (OR, 1.01; CI, 1.00-1.02), and hypertension (OR, 1.85; CI, 1.24-2.76) had independent associations with the presence of simple cysts. The subjects with cysts had a higher prevalence of albuminuria (defined as a urine albumin to creatinine ratio > 30μg/mg) than those without cysts (11.2% vs. 4.5%, P <0.001). Multivariate analyses of albuminuria revealed that the presence of simple renal cysts was associated with a 2.32-fold increase in the risk of albuminuria (95% CI, P <0.001). The location of the cysts was not related to the prevalence of albuminuria.

Conclusions: Age, SBP, and hypertension history were independently associated with simple renal cyst in adults younger than 40. The presence of the renal cyst was an independent risk factor of albuminuria.

FR-PO162

Renal Prognosis Evaluation with Contrast-Enhanced Ultrasound

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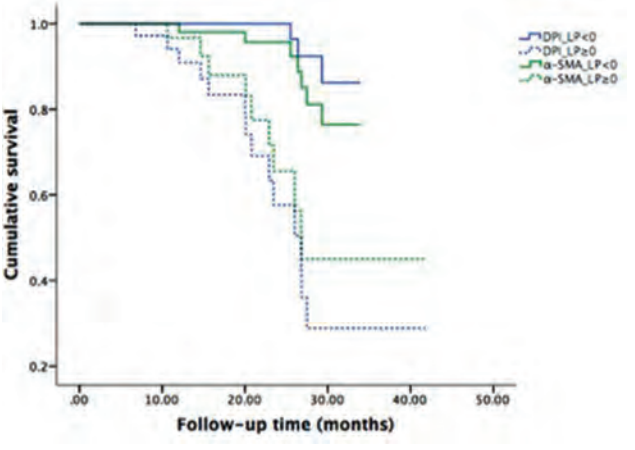
Background: The purpose of this initial study was to confirm the ability of contrast-enhanced ultrasound (CEUS) to detect and predict renal function changes in chronic kidney disease (CKD) patients. The prognostic efficacy of CEUS parameters was compared with that of the renal pathology.

Methods: Patients with biopsy-proved CKD and received CEUS were enrolled in this study. CEUS was performed after an intravenous bolus injection of 1.5 ml SonoVue (BR1; Bracco Milan, Italy). Time-intensity curves (TICs) and quantitative indexes were created using QLAB quantification software. All biopsies were analyzed with α-SMA immunohistochemistry. The Cox proportional hazards model retrospectively investigated risk factors on kidney survival.

Results: A total of 140 patients were followed for a median period of 22.0 months. In total, 18 (13%) patients exhibited CKD progression. Lower derived peak intensity (DPI) and higher resistance index (RI) was noted in CKD progression group. Multivariate Cox regression analysis revealed that the DPI associated with progression of kidney disease. Based on which, linear predictor score (LP) was made. Kaplan-Meier curve showed that DPI had the similar ability as fibrosis to estimate the risk of kidney progression for each CKD patient. Patients with a LP-DPI≥0 were less likely to recover from CKD progression. The area under the receiver operating characteristic (ROC) curves for the model of DPI was 0.82 (95%CI, 0.60-0.96, P<0.001) with a sensitivity of 82% and a specificity of 78%.

Conclusions: This study demonstrated that the DPI might be the most valuable CEUS parameter for the evaluation of renal function deterioration risk. The DPI could serve as an independent predictor of the long-term prognosis of CKD patients.



Kaplan-Meier plots showing renal survival stratified by linear predictor score (LP) from the multivariate Cox proportional hazards model included DPI and α-SMA.

FR-PO163

Doppler Indexes of the Renal Cortex Are Independently Related to Renal Perfusion in Hypertensive CKD Patients

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Background: In many studies, Resistive Index measured in segmental or interlobular intrarenal arteries has been used interchangeably as an equivalent of renal perfusion. Due to the diverging region of measurement, achieved indexes are significantly different. However, they were not compared to the renal perfusion estimated in the independent

method. The study aimed to investigate relations between different renal Doppler indexes (segmental renal Resistive Index (sRI), cortical renal Resistive Index (cRI), cortical renal Pulsatility Index (cPI)) and Renal Perfusion (RP) measured in contrast-enhanced computed tomography.

Methods: In fifteen patients (6F, 9M; age 61.5 ±19.3) with unilateral renal artery stenosis, ultrasound examination (GE Logic P6) with the estimation of sRI (a mean of 3 measurements using a Pulsed Wave Doppler); cRRI and cRPI (3-5 seconds movie of Color Doppler with PixelFlux software [Chameleon Software, Germany]) was performed. Then contrast-enhanced multidetector computed tomography (GE Discovery 750 HD) of renal and intrarenal arteries was completed, and a Renal Blood Flow in a whole cortex (cRBF, [mL/s/100g]) was measured. The data from 15 kidneys without a stenotic artery were considered for statistics. Based on creatinine, estimated glomerular filtration rate (eGFR) was calculated using MDRD formula.

Results: Values of intranenal indexes were estimated: sRI = 0.710 ±0.107; cRI = 0.751 ±0.185; cPI = 1.515 ±0.614, whereas mean RP = 206.8 ±64.9 ml/s/100g and eGFR = 54.8 ±29.6 ml/min/1.73m^2. All intrarenal Doppler indexes correlated significantly with age, eGFR, and with each other. In addition, cRI and cPI correlated with RP ($r = -0.547$, $p < 0.05$ and $r = -0.655$, $p < 0.05$, respectively). The multivariable regression analysis adjusted to age and eGFR showed independent connection between cRI and RP ($b = -0.55$; $R^2 = 0.30$, $p < 0.035$). In the same regression model, cPI independently related to RP ($b = -0.65$; $R^2 = 0.43$, $p < 0.008$). However, relation to RP was not significant for sRI ($p < 0.112$).

Conclusions: Doppler indexes measured in renal cortex area are independently related to the renal perfusion. Renal Resistive Index in segmental arteries should not be considered as a marker of renal cortical blood flow

Funding: Government Support - Non-U.S.

FR-PO164

Oral Bisphosphonate Use and Renal Function Decline in Patients with CKD

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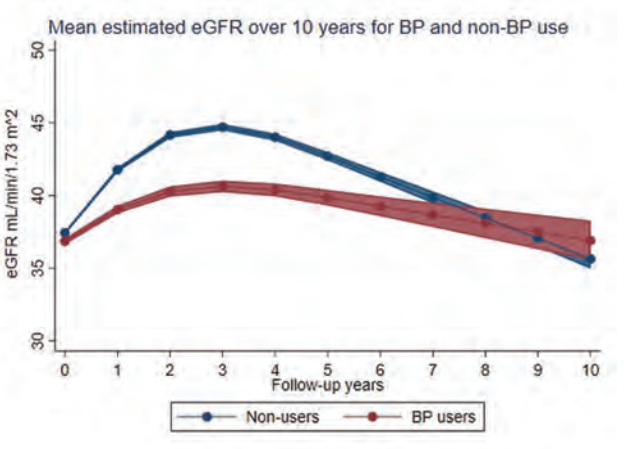
Background: Oral bisphosphonates (BP) are contraindicated in patients with moderate-severe chronic kidney disease (CKD) due to concerns regarding their effects on renal function. The aim of this study was to assess the effect of BP use on CKD stage worsening and annual changes in estimated glomerular filtration rate (eGFR) over time.

Methods: Patients aged 40+ with an eGFR<45 in UK primary care (CPRD) linked to hospital records. Followed for up to 10 years. BP users censored 210 days after the last BP prescription. Unexposed patients could become exposed; 10-year follow up re-started. Users were matched to up to 5 non-users using propensity scores (PS), stratified by the number of years of follow-up. Cox regression was used to estimate the hazard ratio (HR) of stage worsening. The rates of annual eGFR changes were estimated by the slopes of a mixed effect model with cubic splines and an interaction between BP use and time.

Results: 31275 patients (6309 BP users) were included in the PS matched analyses. 3,978 (13%) patients moved to a later stage. The HR for BP users was 1.69 (95% confidence interval (CI): 1.58, 1.80). Annual eGFR changes were different for BP users and non-users (Figure). In the first three years, the mean eGFR increased at the rate of 2.58 (2.50, 2.66) and 0.91 (0.65, 1.17) mL/min/1.73 m^2 per year for non-users and users, respectively. They were followed by slow decline slopes of -0.80 (-0.89, -0.70) and -0.24 (-0.55, 0.08) per year. No significant difference in mean eGFR after 8 years.

Conclusions: BP use has a 70% higher likelihood of worsening in CKD stages. Further research is needed to understand the longitudinal changes in eGFR trajectories.

Funding: Government Support - Non-U.S.



FR-PO165

Proton Pump Inhibitor Use and Progression to Major Adverse Renal Events: A Competing Risk Analysis

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Background: Proton pump inhibitors (PPIs) are commonly prescribed in primary and secondary care. PPIs are associated with acute tubulointerstitial nephritis, but their association with chronic kidney disease (CKD) is uncertain. We aimed to determine if PPI use is associated with adverse renal outcomes or survival in patients with CKD.

Methods: We conducted a retrospective observational cohort study comprising patients with CKD attending a secondary referral renal clinic between 01/01/2006 and 31/12/2016. Baseline exposure variables at start of PPI (PPI group) or study inception (control group) were derived for relevant clinical, socio-demographic and biochemical data. The primary outcome was a composite measure of doubling baseline creatinine or end stage renal disease (ESRD) denoted *Major Adverse Renal Events* (MARE). We defined tubular dysfunction as potassium or magnesium below laboratory normal range. A competing risks survival analysis evaluated the association between PPI exposure and MARE, with the competing risk of death.

Results: There were 7765 patients referred to a secondary care renal clinic during the study period: 6734 were included in the analysis of which 2928 were prescribed a PPI. The PPI group had more men (51.3 vs 48.7%, p=0.04) with higher GFR (35.6 vs 32.0, p<0.001), but similar burden of cardiovascular disease (69.2 vs. 67.4, p=0.13) and diabetes (61.8 vs 63.9%, p=0.09), and the same age (68.5 vs 68.0 years, p= 0.02). There was more tubular dysfunction in the PPI group (59.2 vs. 54.2%, p<0.001). In a competing risks survival analysis, there was no difference between progression to death (p=n/s), but greater progression to MARE in the PPI group (log rank p<0.001). After adjustment for the competing risk of death, the factors associated with progression to MARE were tubular dysfunction (SHR 2.33, 95% CI 20.80-2.60, P<0.001), diabetes (SHR 1.39, 95% CI 1.26-1.54, P<0.001) and hypereosinophilia (SHR 1.71, 95% CI 1.53-1.92, P<0.001). PPI use was not associated with increased risk of progression to MARE on multivariable adjustment.

Conclusions: PPI use may not be associated with progression to MARE in patients with renal impairment. Tubular dysfunction, hypereosinophilia and diabetes were associated with MARE regardless of PPI use. Further prospective analysis is required to validate these findings

FR-PO166

Discontinuation of Proton Pump Inhibitors in Patients with CKD

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Background: Proton pump inhibitors (PPIs) are commonly used medications in the US and are historically well tolerated. Recent studies have linked PPI use to development of chronic kidney disease (CKD) and end-stage renal disease (ESRD). We investigated whether discontinuation of PPIs in patients with CKD results in slower kidney disease progression compared to patients who continued PPIs.

Methods: This is a retrospective chart review of patients with established CKD taking a PPI from January 1, 2014 to December 31, 2014. Patient's eligible for inclusion were those with established CKD, defined as 2 eGFR measurements of < 60 ml/min/1.73m^2 at least 90 days apart, who were on a PPI from January 1, 2014 to December 31, 2014, with a medication possession ratio (MPR) of ≥70%. Patients were excluded if they were on dialysis at baseline and did not have baseline and final eGFR measurements. We compared baseline eGFR to a final eGFR after at least 6 months of discontinuation or continuation of a PPI.

Results: 100 patients in the PPI discontinuation group and 97 patients in the PPI continuation group met study inclusion criteria. Baseline renal function in the PPI

continuation group was eGFR of 47.9 ml/min/1.73 m^2 and 50.7 ml/min/1.73 m^2 in the PPI discontinuation group. Final eGFR in the PPI continuation group was significantly higher at 51.1 ml/min/1.73m^2 (p=0.01). Final eGFR in the PPI discontinuation group was 51.8 ml/min/1.73m^2 (p=0.3). The average time between baseline and final eGFRs was 270 days in the PPI continuation group and 301 days in the PPI discontinuation group. There was no statistically significant difference in the change in eGFRs between groups (95% CI -5.48-2.03; p=0.37).

Conclusions: Discontinuing a PPI after one year of continuous use in patients with CKD did not impact change in renal function after one year.

FR-PO167

Determining the Association of Allopurinol Prescription on Progression of Renal Dysfunction and Progression to Renal Replacement Therapy in Patients with CKD

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Background: Reports in the literature link hyperuricaemia with incident chronic kidney disease CKD. However, the relationship between allopurinol prescription and progression of renal dysfunction is not well understood. We aimed to determine the association of allopurinol prescription and changes in kidney function amongst patients with CKD.

Methods: A retrospective cohort study of 1,123 patients of a tertiary teaching hospital registered in the CKD.QLD registry between January 2011 and August 2017 (minimum of 2 years follow-up). Subject demographics (age), health data (BMI, comorbidities, laboratory test results) and allopurinol prescription were extracted from integrated medical records. Delta eGFR (CKD-EPI)was calculated as the difference between latest eGFR and initial eGFR. Subjects were stratified into two groups based on prescription of allopurinol.

Results: Subjects prescribed allopurinol were older (70.7 vs 65.8; p<0.01), had higher BMI (32.3kg/m^2 vs 30.5kg/m^2; p<0.01), worse renal function (35.2mL/min/1.73m^2 vs 43.6mL/min/1.73m^2; p<0.01), higher urate level (0.47mmol/L vs 0.42mmol/L; p<0.01) as well as higher proportion of diabetes (54% vs 46%; p=0.04), dyslipidaemia (54% vs 41%; p<0.01), hypertension (84% vs 72%, p<0.01) and gout (54% vs 11%; p<0.01). The proportion of subjects treated with allopurinol increased with CKD stage; stage 1:1.5%, stage 2:7.1%, stage 3: 21.7%, stage 4: 21.4% stage 5:17.3%. Prescription of allopurinol did not have a significant association with delta eGFR in patients with hyperuricaemia (1.8mL/min/1.73m^2/yearvs 1.6mL/min/1.73 m^2/year; p=0.2) or gout (2.2mL/min/1.73m^2/year vs 1.8mL/min/1.73m^2/year; p=0.5). Nor was allopurinol prescription in the subgroup with serum urate level < 0.36mmol/L associated with a significant change in delta eGFR (3.5mL/min/1.73m^2/year vs 1.6mL/min/1.73m^2/year;p=0.17). Multivariate analysis adjusting for age and comorbidities found no significant association of allopurinol prescription with either delta eGFR or progression to kidney replacement therapy (p>0.05).

Conclusions: Allopurinol prescription was more prevalent in advanced CKD. However, it did not appear to be independently associated with deterioration of kidney function.

FR-PO168

Association Between Plasma Myostatin Levels and Loop Diuretic Use in Non-Dialysis-Dependent CKD Patients

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Background: Myostatin (MSTN) is mainly synthesized in skeletal muscles and acts as a negative regulator of skeletal muscle mass. It is up-regulated in patients with chronic kidney disease (CKD) and considered to be associated with the development of sarcopenia. Recently, we have reported that loop diuretics, commonly used in patients with advanced CKD, suppress skeletal muscle differentiation (Mandai S. Sci Rep. 2017). So far, the association between serum MSTN (sMSTN) levels and loop diuretic use is unknown.

Methods: We conducted a cross-sectional study comprised of 362 non-dialysis-dependent CKD patients over 20 years of age. The primary outcome was sMSTN levels. Multiple linear regression analyses were conducted to assess the associations between sMSTN levels (logarithmically transformed) and baseline characteristics including skeletal mass index (SMI). Interaction between loop diuretic use and SMI to sMSTN levels was estimated after stratifying patients by loop diuretic use. We calculated SMI as follows: Total body skeletal muscle mass measured by DEXA was divided by height squared.

Results: Median age was 71 years, 64.4% were male, mean SMI was 6.49 kg/m^2, mean eGFRcysC was 39.0 ml/min/1.73m^2, median sMSTN level was 1130 pg/ml, and 14.6% were treated with loop diuretics. Multivariate analysis showed that sMSTN levels were positively correlated with SMI (β=0.128, *P*<0.001), and negatively with eGFRcysC and loop diuretic use (β=-0.004, *P*=0.005 and β=-0.231, *P*<0.001, respectively). When stratified by loop diuretic use, adjusted coefficient β of SMI for sMSTN was higher in patients treated with loop diuretics than in patients not treated with loop diuretics (β=0.237, *P*=0.001 and β=0.118 *P*<0.001), respectively).

Conclusions: Loop diuretic use was independently associated with lower sMSTN levels. This result indicates that loop diuretics serve as negative regulator of skeletal muscle mass and therefore sMSTN levels may be attenuated by negative feedback. However, the increase of sMSTN level associated with SMI among the patients treated with loop diuretics was larger than those without loop diuretics. Other potential factors which elevate sMSTN levels in patients treated with loop diuretics are suggested to affect the relationship between sMSTN levels and SMI.

FR-PO169

Circulating ADAM17 Activity as a Marker of CKD Progression

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Background: Several substrates for ADAM17 have been identified, including TNF-α, EGFR ligands, L-selectin, VCAM-1 and angiotensin converting enzyme(ACE)2. We have studied circulating ADAM17 in chronic kidney disease(CKD) patients from the NEFRONA cohort study.

Methods: 2032 patients without history of CV disease from an observational and multicenter study (NEFRONA project) divided into two groups: non-dialysis CKD stage 3-5 patients and control patients were studied. Baseline circulating ADAM17 activity was analyzed using a fluorimetric assay in plasma samples. Increased serum creatinine and dialysis requirement after 24months of follow-up depending on basal circulating ADAM17 activity were studied. Logistic regression analyses were used to identify predictors of increasing serum creatinine and risk of dialysis requirement.

Results: Circulating ADAM17 activity was significantly increased in CKD3-5 patients as compared to CONT(p<0.05). Baseline circulating ADAM17 activity was higher in patients with a 30% increase in serum creatinine levels after 2 years(p<0.05). Circulating ADAM17 activity was also higher in patients that needed dialysis in comparison with patients that maintained kidney function(p<0.05). After multivariate logistic regression analysis we found an interaction between sex and sADAM17 activity for increasing 30% serum creatinine, dialysis requirement and composite renal outcome(p<0.05). Therefore, we decided to perform the analysis stratifying by sex. Increased ADAM17 activity was independently associated with CKD progression regarding 30% increase in serum creatinine, dialysis requirement and composite renal end point but only in males. In females, ADAM17 activity was not associated with CKD progression.

Conclusions: Circulating ADAM17 activity was increased in CKD patients. Circulating ADAM17 activity was increased in patients that doubled serum creatinine and/or patients that need dialysis therapy being an independent predictor of worsening renal function in males.

Funding: Government Support - Non-U.S.

	30% increase in serum creatinine				Dialysis requirement				Composite renal end point			
	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
MALES												
sADAM17 media (214.9)	2.72(1.59-4.66)	**0.000**	2.11(1.20-3.72)	**0.009**	3.20(1.77-5.77)	**0.000**	1.27(0.64-2.50)	**0.000**	0.32(2.11-4.87)	**0.000**	1.67(1.08-2.58)	**0.022**
Diabetes	0.93(0.52-1.66)	0.793	0.91(0.52-1.61)	0.851	1.10(0.62-1.94)	0.742	0.68(0.31-1.51)	0.243	0.93(0.60-1.43)	0.728	1.23(0.78-1.92)	0.369
Age (265 years)	0.89(0.55-1.44)	0.633	1.04(0.62-1.84)	0.871	0.46(0.24-0.79)	**0.006**	0.75(0.40-1.41)	**0.373**	0.87(0.60-1.00)	**0.005**	0.83(0.54-1.27)	0.383
Smoking	1.29(0.70-2.34)	0.414	1.25(0.67-2.34)	0.490	2.06(1.14-3.70)	**0.015**	1.84(0.94-3.52)	0.066	1.49(1.06-2.83)	**0.019**	1.42(0.90-2.22)	0.131
eGFR	0.96(0.94-0.96)	**0.000**	0.96(0.94-0.99)	**0.001**	0.83(0.79-0.87)	**0.000**	0.83(0.79-0.87)	**0.000**	0.93(0.92-0.93)	**0.000**	0.94(0.91-0.93)	**0.000**
FEMALES												
sADAM17 media (214.9)	1.71(0.63-2.20)	0.033	0.71(0.34-1.41)	0.329	1.28(0.78-2.18)	0.304	0.92(0.51-1.27)	0.191	1.22(0.81-1.89)	0.302	0.62(0.37-1.04)	0.069
Diabetes	0.83(0.44-1.80)	0.665	0.93 (0.43-2.09)	0.894	0.93(0.49-1.74)	0.833	1.08(0.48-2.43)	0.859	1.34(0.68-3.93)	0.418	1.01(0.57-1.79)	0.980
Age (265 years)	0.83(0.56-0.66)	**0.002**	0.53(0.34-0.78)	**0.008**	0.62(0.38-1.08)	0.091	0.81(0.43-1.78)	0.603	0.48(0.30-0.18)	**0.002**	0.48(0.29-0.81)	**0.005**
Smoking	1.71(0.73-3.89)	0.211	1.42(0.58-3.33)	0.445	0.65(0.24-1.83)	0.336	0.91(0.28-2.91)	0.198	0.94(0.43-1.78)	0.782	1.13(0.54-2.33)	0.764
eGFR	0.94(0.91-0.97)	**0.000**	0.94(0.91-0.97)	**0.001**	0.76(0.71-0.82)	**0.000**	0.76(0.71-0.82)	**0.000**	0.89(0.87-0.92)	**0.000**	0.89(0.86-0.92)	**0.000**

FR-PO170

Association of Serum Uromodulin with ESRD and Kidney Function Decline in the Elderly – The Cardiovascular Health Study

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Background: Uromodulin is released by tubular epithelial cells into the serum (sUMOD) and low levels are associated with tubular atrophy and interstitial fibrosis (IF/TA). However, little is known about the association of sUMOD with long-term kidney outcomes in the elderly, a population with a high prevalence of IF/TA.

Methods: We assessed the association of sUMOD with end-stage-renal-disease (ESRD) in a random subcohort (n=933) plus all additional cases of ESRD in the Cardiovascular Health Study using a modified Cox regression analysis. We also evaluated the association of sUMOD with kidney function decline (≥30% decline of estimated glomerular filtration rate (eGFR) at 10 years of follow up) using logistic regression. Sampling for the latter was from the random subcohort as well as all additional cases. Models were adjusted for demographics, eGFR, albuminuria and other risk factors.

Results: Mean age of the random subcohort was 78 years, 40% were male, and 15% were non-white. Mean±SD sUMOD level was 127±64 ng/ml and eGFR was 63±19 ml/min/1.73 m^2. 53 participants experienced ESRD during a median follow-up 9.9 years. Higher sUMOD was associated with lower hazard for ESRD in univariate analysis (Figure). In multivariable analysis each 1 SD higher sUMOD was associated with a 63% lower risk of ESRD (HR 0.37 (95%-CI 0.14-0.95)). 179 participants experienced kidney function decline. In demographic adjusted analyses, higher sUMOD was associated with lower

odds of kidney function decline (OR 0.75 (0.60-0.95)); after multivariable adjustment, the association was attenuated and no longer significant (OR 0.88 (0.68-1.14)).

Conclusions: Low levels of sUMOD may identify persons at increased risk for ESRD.

Funding: NIDDK Support, Other NIH Support - This work was supported by grants from the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK) R01 DK098234 (to JHI and MGS) and from the National Institutes of Aging (NIA) R01AG 027002 (to MJS and MGS). The Cardiovascular Health Study was supported by contracts HHSN268201200036C, HHSN268200800007C, and N01HC-85079 through N01HC-85086, N01HC-35129, N01HC-15103, N01HC-55222, N01HC-75150, N01HC-54133, and N01-HC85239 and grant U01 HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contributions from the National Institute of Neurological Disorders and Stroke. Additional support was provided by R01AG023629 from the NIA. PD was supported by National Institutes of Health grant P50 DK096418. PSG is supported by National Institutes of Health training grant 5 T32 DK007777-13.

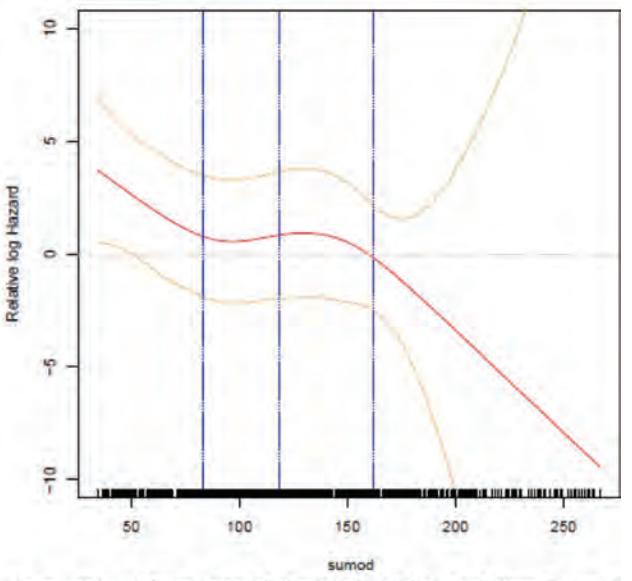

Figure: Association of serum uromodulin (sumod) with End-Stage Renal Disease. The model was fitted using restricted cubic splines with sumod as the exposure variable. The red solid line indicates the individual logarithmic hazard ratio, the yellow dotted lines the individual 95%-confidence interval. The vertical dotted purple lines separate the quartiles according to sumod levels. The lowest and highest 2.5% of the observations were excluded to minimize the influence of extreme values and outliers.

FR-PO171

Monocyte as a Marker of Renal Damage in Patients with Glomerular Hyperfiltration and Early CKD

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Background: Experimental studies have shown that monocyte/macrophages play an important role in progression of chronic kidney disease (CKD). Recent epidemiologic study also suggests a significant association between higher monocyte count and risk of incident CKD in humans. Glomerular hyperfiltration (GH) is known as an early marker of progressive CKD in diverse clinical conditions. However, not all patients with GH progressed to CKD and monocyte may be associated with renal injuries caused by GH. The purpose of this study is to examine whether higher monocyte count is associated with GH and progressive kidney disease.

Methods: A longitudinal observational cohort study was performed using data from regular health checkup examinations in tertiary hospital during 2004-2017. We analyzed 56,258 adults at initial examination and selected 16,695 adults who had initial estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73m^2 with at least two tests of eGFR in follow-up analysis. Monocyte count was categorized into sex-specific quartiles. GH was defined as the upper 2.5 percentile of eGFR in the total population.

Results: The monocyte count showed a U-shaped association with eGFR. The monocyte count was significantly higher in participants with eGFR ≥ 120, 60-74, 45-59, 30-44, and <30 ml/min/1.73m^2 compared with those with eGFR 90-104 ml/min/1.73m^2 at initial examination (N=56,258, P≤0.025). The highest quartile of monocyte count was independently associated with GH in multivariate analysis compared with the lowest quartile (OR, 1.278; 95% CI, 1.070-1.525). In participants without GH, the highest quartile of monocyte count was associated with the higher risk of ≥ 25% eGFR decline (RR, 1.859; 95% CI, 1.254-2.755) and the development of proteinuria (RR, 1.377; 95% CI, 1.135-1.671) compared with lowest quartile. In participants with GH, the highest quartile was also associated with increased risk for the development of proteinuria (RR, 5.833; 95% CI, 1.196-28.453), but was not associated with ≥ 25% eGFR decline.

Conclusions: Higher monocyte count is associated with progressive CKD. In addition, monocyte count could be a marker to identify patients at risk for progression of kidney disease in GH.

FR-PO172

The Plasma Growth Differentiation Factor-15 Levels as Useful Biomarker for Renal Impairment in the Elderly: Korean Frailty and Aging Cohort Study

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Background: Growth differentiation factor-15 (GDF-15) expression has been reported to increase in response to tissue damage, and has recently emerged as a useful biomarker for various diseases. Although accumulating evidence supports the prognostic value of GDF-15 in renal impairment, few studies have analyzed it in the elderly. Thus, we conducted a cross-sectional study to investigate the association between plasma GDF-15 level and renal function in the elderly.

Methods: The present study was based on the baseline data of the Korean Frailty and Aging Cohort Study (KFACS), a nationwide cohort study that began in 2016. Of the 1,559 participants assessed in the first year, 443 with available plasma GDF-15 data were enrolled in this study. We investigated the association of plasma GDF-15 level with clinical and biochemical parameters. The study population was divided into two groups according to renal function (chronic kidney disease [CKD] and non-CKD groups) to analyze diagnostic predictive value for CKD.

Results: In a simple regression analysis, the level of plasma GDF-15 was negatively correlated with the estimated glomerular filtration rate (eGFR; $r = -0.383$, $p < 0.001$). In multiple linear regression analysis, GDF-15 level was still significantly correlated with eGFR, even after adjusting for other parameters ($r = -0.259$, $p < 0.001$). Plasma GDF-15 level was significantly higher in the elderly with CKD than in those with non-CKD (2364.025 ± 1052.23 ng/L and 1451.23 ± 835.79 ng/L, respectively, $p < 0.001$). The optimal cut-off value for CKD-predicting GDF-15 level was 1699.4 pg/mL (76.5% sensitivity and 76.0% specificity), as determined by receiver operating characteristic curve. The area under the curve was 0.793 ± 0.033 (95% CI 0.729-0.857, $p < 0.001$).

Conclusions: Our results suggest that plasma GDF-15 level can be a useful biomarker for renal impairment in the elderly. Further large and prospective studies of extended duration are needed.

FR-PO173

Wide Pulse Pressure as a Risk Factor for Kidney Dysfunction

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Background: The risk of kidney dysfunction due to hypertension has been drawing attention especially for people who have the characteristics of advanced arteriosclerosis. However, the relationships from the aspect of systemic arteriosclerosis were not well known. Pulse pressure (PP) is a routinely measured vital sign and is thought to reflect the arteriosclerosis of elastic arteries. The aim of this study is to clarify the relationships between pulse pressure for development of kidney dysfunction. Risks related to systolic blood pressure (SBP) according to wide pulse pressure was also studied.

Methods: People aged 40 years or older who had a medical checkup in Kanazawa city were included in the analysis. Kidney dysfunction was defined as a decline of eGFR by 30% from baseline. PP was classified as normal (40–60 mmHg) and wide (>60 mmHg). Cox proportional hazard model was used to estimate the risks for kidney dysfunction associated with wide PP and SBP.

Results: A total of 36,134 people was included in the analysis. The mean age was 69 years. Incidence rates of kidney dysfunction for people with normal and wide PP were 8.1 and 15.2 (per 1000 person-years), respectively. After multivariable adjustments, hazard ratio for the kidney dysfunction associated with wide pulse pressure compared with normal pulse pressure was 1.40 (95% CI 1.25 – 1.57). In the stratified analysis by baseline PP, hazard ratios related to higher SBP (+10 mmHg) in normal and wide PP group were 1.14 (95%CI 1.07 – 1.22) and 1.12 (95%CI 1.06–1.19), respectively. Among the people with wide PP, people with baseline SBP ≥160 mmHg showed significant risk (HR 1.52 [95%CI 1.03–2.24]) compared with the people with SBP 120 – <130 mmHg (reference), whereas SBP 130 – 160 mmHg was not related to significant risks.

Conclusions: Wide PP was associated with higher risks for kidney dysfunction. More studies are needed regarding the risks related to mild hypertension accompanied by wide PP.

FR-PO174

Trends in Angiotensin Converting Enzyme Inhibitor and Angiotensin II Receptor Blocker Use Among Those with CKD in the United States

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Background: Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (ACE/ARB) are first-line anti-hypertensives in chronic kidney disease (CKD). Even though evidence-based treatment of hypertension has changed considerably, and hypertension is common in CKD, nationally-representative, contemporary information regarding ACE/ARB use in CKD is lacking.

Methods: We examined ACE/ARB trends and racial/ethnic and other demographic disparities among adult National Health and Nutrition Examination Survey participants from years 1999 to 2014 with creatinine-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or albumin-creatinine ratio (ACR) ≥ 30 mg/g.

Results: 33.9% of participants with CKD used ACE/ARB. Although ACE/ARB use in CKD rose across the four eras studied ($P < 0.001$), estimates changed little in the last 3 eras:

1999-2002, 24.1%; 2003-2006, 33.0%; 2007-2010, 38.0%; and 2011-2014, 38.7%. ACE/ARB use was greater in those of non-Hispanic white (35.3%) and black (37.0%) and lower in those of Hispanic (25.4%) and other (28.7%) race/ethnicity. In models that adjusted for age, sex and race/ethnicity, ACE-ARBs were associated ($P < 0.05$) with: era (adjusted odds ratios (AOR) 1.52 [95% CI: 1.21-1.92] for 2003-2006, 1.94 [95% CI: 1.56-2.41] for 2007-2010, and 2.07 [95% CI: 1.64-2.62] for 2011-2014, vs. 1999-2002) and non-Hispanic black race/ethnicity (AOR 1.41 [95% CI: 1.18-1.68], vs. non-Hispanic white). Other multivariate associations included older age, male sex, BMI ≥ 30 kg/m^2, diabetes mellitus, hypertension, cardiac failure, and myocardial infarction.

Conclusions: ACE/ARB use is the exception in community-based CKD. Although use increased early in the current millennium, subsequent estimates remained static. When age and sex are considered, disparities against participants from racial/ethnic minority subgroups were not apparent.

FR-PO175

Kidney Function Outcomes Following RAAS Inhibition in Patients with Heart Failure

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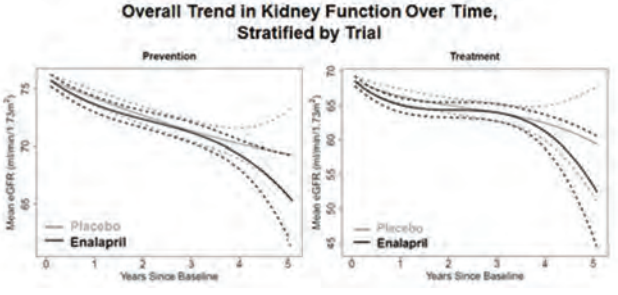
Background: Blockade of the renin-angiotensin-aldosterone system (RAAS) is beneficial for cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF), but is also associated with decline in estimated glomerular filtration rate (eGFR). Long-term kidney outcomes after RAAS inhibition remain unclear in HFrEF.

Methods: We performed a retrospective analysis of the Studies Of Left Ventricular Dysfunction (SOLVD) trials, in which participants with HFrEF were randomized to enalapril vs placebo in the Treatment Trial (n=2423) if symptomatic, and in the Prevention Trial (n=4094) if asymptomatic. Joint models were used to estimate rate of decline in eGFR. Multivariable Cox models were used to evaluate the association of enalapril vs placebo for the following 3 outcomes at any timepoint: 1) ≥0.3 mg/dl increase in serum creatinine, 2) ≥30% decline in eGFR, and 2) incident CKD Stage 4 or 5 as defined by new eGFR ≤30 ml/min/1.73m^2.

Results: A total of 6,517 participants randomized to enalapril (n=3254) or placebo (n=3263) were included in this analysis. Mean baseline eGFR was higher in Prevention vs Treatment (76.2±18.6 vs 69.5±19.8 ml/min/1.73m^2, p<0.01). Over a median follow-up of 24 months, mean eGFR declined at similar rates, -1.6 (95% CI -1.8,-1.4) for Prevention vs -1.7 ml/min/1.73m^2/year (95% CI -2.0, -1.5) for Treatment (p=0.51) (Figure). Only 1.4% in Prevention Trial and 4.5% in Treatment Trial reached CKD stage 4 or 5. In adjusted analyses, randomization to enalapril was associated with a higher hazard of increase in creatinine by ≥0.3 mg/dl (HR of 1.32, 95% CI 1.18, 1.47), decline in eGFR by ≥30% (HR 1.33, 95% CI 1.18, 1.50) and CKD Stage 4 or 5 (HR 1.43, 95% CI 1.05, 1.95).

Conclusions: GFR decline on average was slow in both trials and only a small percentage of patients with HFrEF reached incident CKD Stage 4 or 5 over a median of 2 years. Randomization to enalapril carried a higher risk of reaching all kidney function endpoints but it remains to be determined whether these differences are of clinical importance.

Funding: Other NIH Support - T32 grant: 1T32DK07777



FR-PO176

Long-Term Incense Use and the Risk of ESRD

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Background: Animal study suggests exposure to incense burning has deleterious effects on kidney function and architecture. However, the association between domestic incense burning and risk of end-stage renal disease (ESRD) has not been reported previously.

Methods: We investigated this association in the Singapore Chinese Health Study, a prospective population-based cohort of 63,257 Chinese men and women of 45-74 years of age in Singapore at recruitment during 1993-1998. Information on the practice of incense burning at home, diet, lifestyle and medical history was collected at baseline interviews. ESRD cases were identified through linkage analysis with the nationwide Singapore Renal Registry through 2015. We used Cox proportional hazards regression analysis to estimate hazard ratio (HR) and 95% confidence interval (CI) of ESRD associated with domestic incense burning.

Results: Among cohort participants, 76.9% were current incense users. After an average 17.5 years of follow-up, 1,217 (1.92%) ESRD cases were documented. Compared to never users, the multivariable-adjusted HR for ESRD was 1.05 (95% CI, 0.80 to 1.38) for former users and 1.26 (95% CI, 1.02 to1.57) for current users of incense. The ESRD risk was restricted only to current daily users with a history of more than 20 years; HR was 1.25 (95% CI, 1.07 to 1.46), compared with non-current users. Conversely, those who did not use incense daily or those who had used daily for ≤ 20 years had no increased risk.

Conclusions: Our findings demonstrate that long-term daily exposure to domestic incense burning could be associated with a higher risk of ESRD in Singapore Chinese.

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FR-PO177

The Association Between Lead and Cadmium Co-Exposure and the Renal Dysfunction

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Background: Cadmium (Cd) and lead (Pb) exposure both can induce kidney damage. However, the effects of combined exposure to Cd and Pb on renal function at environmental levels have not been fully clarified. In this study we investigate the renal function in a Chinese population co-exposed to Cd and Pb.

Methods: A total of 331 subjects (215 women and 116 men), living in either a control or a polluted area, were included in this study. Cd and Pb in blood and urine (BCd, BPb, UCd, and UPb), and kidney effect markers including urinary N-acetyl-β-D-glucosaminidase (UNAG) and estimated glomerular filtration rate (eGFR), were determined, and the association between exposure markers and renal effects biomarkers were analyzed.

Results: The exposure levels in the polluted area were significantly higher than in the control area (all $p < 0.01$). The eGFR of subjects in the polluted area was decreased compared with that in the control area ($p < 0.01$). The subjects with high BCd/BPb (BCd ≥ 2 μg/L, BPb ≥ 100 μg/L) or high UCd/UPb (UCd ≥ 3 μg/g creatinine, UPb ≥ 10 μg/g creatinine) showed higher UNAG and UALB levels compared with other subgroups ($p < 0.01$). The probability of having elevated UNAG in subjects with high BCd/BPb was greater than those for with low BCd/BPb [odds ratio (OR) = 2.6, 95% CI: 1.4-4.7], low BCd/high BPb (OR =3.1, 95% CI: 1.4-6.6), and high BCd/low BPb (OR = 1.7, 95% CI: 0.9-3.2). The OR of subjects with low UCd and high UPb, high UCd and low UPb, and high UCd/UPb were 2.9 (95% CI: 1.4-5.7), 3.3 (95% CI: 1.5-7.2), and 7.7 (95% CI: 4.0-14.7), respectively, compared with those with low UCd/UPb. The risk of decrease in eGFR was also higher in subjects with high UCd/UPb than for those with low UCd/UPb (OR =7.2, 95% CI: 0.8-62.2).

Conclusions: Our data demonstrate that Cd and Pb exposure, alone or in combination, are associated with renal impairment. In addition, co-exposure to Pb and Cd propagates the renal tubular dysfunction compared with Cd or Pb exposure alone.

FR-PO178

Association of Hyperuricemia to Mesoamerican Nephropathy

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Background: Mesoamerican nephropathy (MeN) is considered a new entity among chronic kidney diseases (CKD), but still of uncertain etiology (CKDu). Some risk factors and characteristics identified through previous cross-sectional studies are: agriculture work -mainly sugar cane work-, hot environment, hyperuricemia and dysuria. The aim of our study was to reassess the role of hyperuricemia in adult subjects with altered kidney function (AKF) and without diabetes mellitus (DM) and hypertension (HTN), traditional risk factors of CKD.

Methods: The studied sample came from 10 communities in a known hotspot of MeN in El Salvador (Bajo Lempa region). We used a cross sectional design where incoming participants were grouped depending on different exposures: Group 1: previous diagnose of DM and/or HTN, and agriculture work; group 2: DM/HTN without agriculture; group 3: agriculture without DM/HTN, and group 4: non-DM/HTN without agriculture. They were included independent of previous diagnosis of CKD or hyperuricemia. Our primary outcomes were: AKF, defined by elevated serum creatinine (SCr) or eGFR <60 mL/min/1.72m2 (MDRD equation), and hyperuricemia, defined by elevated serum uric acid (male: >7 mg/dL, female: >6 mg/dL) or daily intake of allopurinol prescribed by a physician.

Results: 681 subjects were included: 58.4% female, mean age 42 years (SD ± 17.291) with the following distribution: group 1: 14 subjects, group 2: 20 subjects, group 3: 282 subjects, and group 4: 365 subjects. Frequency of AKF for each corresponding group: 78.5%, 45%, 23.40%, and 18.63%, p=0.000. The frequency of hyperuricemia in subjects without AKF was 15.68%, and with AKF 43.27%, p=0.000. Comparing all subjects with AKF and hyperuricemia we found that working in agriculture presented higher frequency (62.2%, p=0.006). Comparing those in groups 2 and 3 with AKF for hyperuricemia we found a frequency of 44.44% and 54.44%, respectively. With a multivariate analysis, DM, HTA, dysuria, and hyperuricemia were statistically associated to AKF (p<0.0001) but not agriculture work (p=0.094) or ever working in sugar cane culture (p=0.252).

Conclusions: More research with stronger design is needed to study this factor as it might seem that uric acid has a role in AKF in this region, mostly in those without traditional risk factors (CKDu).

FR-PO179

The Impact of Hyperuricemia on Kidney Failure and Mortality in a Multi-center CKD Cohort: An Instrumental Variable Analysis

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Background: Hyperuricemia is an independent risk factor for mortality, cardiovascular disease, and renal disease in general population. However, the relationship between hyperuricemia with kidney failure and death in chronic kidney disease (CKD) remains controversial.

Methods: The study investigated the association between uric acid with all-cause mortality, end stage renal disease (ESRD) in 42,253 CKD patients in a multi-center cohort from 2001 to 2016. We used the regional prevalence of hyperuricemia (uric acid ≥ 6.8 mg/dL) as an instrument to test our hypothesis that hyperuricemia is associated with ESRD and mortality.

Results: In all subjects, the mean uric acid level was 5.4 ± 1.8 mg/dL. During a median year follow-up, there were 3,556 (8.42%) of renal failure and 5,094 (12.06%) of death in this cohort. Using an instrumental variable analysis after adjusting confounders such as age, diabetes, hypertension and estimated GFR (eGFR), we found evidence suggesting a causal relationship between hyperuricemia and increased risk of all-cause mortality (HR 3.131, 95% CI 2.043-4.797, P < 0.001). This tendency was consistent regardless of gender (male: HR 2.270, 95% CI 1.338-3.851, P = 0.002, female: HR 2.656, 95% CI 1.459-4.834, P = 0.001). On the contrary, higher uric acid concentrations were independently associated with reduced risk for kidney failure in the entire participants (HR 0.539, 95% CI 0.318-0.915, P = 0.022), especially in patients with reduced renal functions (eGFR below 30, HR 0.189, 95% CI 0.098-0.366, P < 0.001).

Conclusions: Instrumental variable analysis supports that uric acid concentration is an independent risk factor for all-cause mortality, while hyperuricemia might have protective effect for ESRD, especially in reduced renal function.

FR-PO180

Physical Activity Is Associated with the Incident CKD in Subjects with Normal Renal Function: Community Based Prospective Cohort Study

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Background: Physical exercise has a beneficial effect on the prevention of cardiovascular disease and diabetes via improvement in the cardio-metabolic disturbances and is associated with better survival in patients with various chronic diseases as well as general population. However, the effects of physical activity on renal outcomes remains unclear. We aimed to investigate the association between daily physical activity and the development of chronic kidney disease (CKD) in relatively healthy population with normal renal function.

Methods: Data were retrieved from the Korean Genome and Epidemiology Study, a prospective community-based cohort study. Daily physical activity was estimated by semi quantitative daily activity questionnaire. The eGFR calculated by the CKD-EPI equation from a total of 8,261 subjects were followed up biennially from 2001 to 2014. The primary endpoint was incident CKD, defined as a composite of eGFR <60 mL×min^{-1}×1.73 m^{-2} and/or the development of proteinuria during the follow up period.

Results: The mean age of study subjects was 52.0 years and 3,953 (47.9%) participants were male. At baseline, the mean eGFR was 94.16 ± 14.16 mL×min^{-1}×1.73 m^{-2}. And the average daily physical activity was 1443.3 ± 896.5 MET*h. During a mean follow-up duration of 119.2 (79.1 – 159.3) months, CKD newly developed in 1,518 (18.4%) subjects. The incidence of proteinuria and eGFR decline lower than 60 mL×min^{-1}×1.73 m^{-2} were 288 (3.5%) and 1,319 (15.9%) subjects, respectively. When divided into quartiles according to daily physical activity, Kaplan-Meier analysis revealed that the risk of CKD development in the highest quartile (Q4) was significantly lower than that of the lowest quartile (Q1) (P <0.001). This association was remained significant even after adjustments were made for confounding factors by multivariable Cox proportional hazards model. (HR [95% CI] = 0.75 [0.65–0.87], P < 0.01).

Conclusions: High physical activity is independently associated with decreased risk of incident CKD in healthy population with normal renal function.

FR-PO181

Effect of Exercise Intensity on Autoregulation of GFR in Patients with CKD Stage 2

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Background: Several studies have showed that aerobic exercise improves cardiovascular function in patients with CKD. On the other hand, glomerular filtration rate (GFR) significantly decreased during severe exercise in healthy young men (Kawakami S, et al. 2018). The purpose of this study was to determine the association of GFR with intensity of exercise in patients with CKD stage 2.

Methods: Renal blood flow (RBF) was assessed by Duplex ultrasound. GFR was estimated by serum cystatin-C (eGFRcys). FF was calculated with eGFRcys/RBF (1-hemtocrit). Eight males with CKD stage 2 (eGFRcys: 60-89/min/1.73m^2) participated in the study, consisting of three separate trials using a cycle ergometer. The first is a maximal graded exercise test. The second is a multi-stage exercise test to determine their lactate threshold (LT). The third is a multi-stage exercise test (4 minutes/stage) at intensities of 60%, 80%, 100%, 120%, and 140% of LT.

Results: eGFRcys significantly decreased and FF significantly increased (eGFRcys: 73±14min/1.73m^2, FF: 0.44±0.17) after strenuous exercise (p< 0.01). eGFRcys did not decrease until 100% of LT was attained, and showed slight reduction at 120% of LT and 140% of LT (eGFRcys: 76±10min/1.73m^2 and 72±9min/1.73m^2) relative to its resting value. FF was significantly higher at 100% of LT (FF: 0.46±0.16), compared to its resting value (p< 0.01). Heart rate (HR) and the norepinephrine level (NE) also increased with the intensities of LT (HR: p< 0.01, NE: p< 0.05). (Fig. 1)

Conclusions: Our results demonstrate that GFR does not change during exercise until the LT is attained, although FF increases. These findings suggest that patients with CKD stage 2 might be able to maintain their GFR during exercise up to 100% of LT.

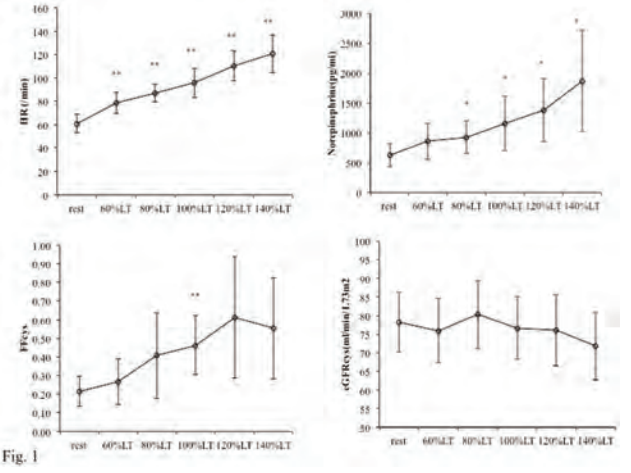

Fig. 1

FR-PO182

Concomitant Acute Pyelonephritis and Obstruction Duration Affects Renal Outcome in Obstructive Uropathy by Urolithiasis

Seongyup Yeo, Jin Ho Hwang. *Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea*.

Background: Urolithiasis related obstructive uropathy is one of increasing causes of CKD, which commonly encountered in clinical field. Obstruction release from urolithiasis can be easily delayed with a lack of suggested golden time to prevent renal function deterioration. Here, we investigated the clinical significance and renal outcomes of urolithiasis related obstructive uropathy.

Methods: This is a study of 1646 from 2315 patients in urolithiasis related obstructive uropathy cohort which is recruited between Jan. 2005 and Dec. 2015. Clinical outcomes were evaluated with respect to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: Median duration of obstruction (elapsed time to release obstruction) was 6 days and APN was accompanied in 14.3% of patients. Patients with HT, DM, and CKD had significantly higher rates of APN accompanied by obstructive uropathy. In the patients whose obstruction was relieved within 2 days from the symptom onset, 8.7% showed spontaneous release of obstruction. There was a significant increase in the number of APN (P=0.008) and AKI (P=0.002) patients who underwent early treatment of obstruction within 6 days from the symptom onset. People with Grade 1 or 2 hydronephrosis tended to release obstruction earlier, and those with Grade 3 or 4 had a higher rate of obstruction release after 7 days. In the patients with concomitant APN, mean age was older (59.4 vs 51.9 years-old, P<0.001), AKI occurred more frequently (73.7% vs 32.9%, P<0.001), estimated GFR (eGFR) at the last follow-up visit was lower (80.9 vs. 86.9 ml/min/1.73m2, P=0.024), and the use of NSAIDs were lower (49.3% vs. 74.9%, P<0.001). The AKI grades by KDIGO showed worse renal outcome in advanced stage (P=0.001). When we adjusted gender, age, HT, DM, use of NSAIDs, APN, AKI grades, and obstruction release over 2 days for a multivariate analysis, APN (HR 2.2, CI 1.01-4.65; P=0.047) and the obstruction release after 2 days (HR 3.55, CI 1.34-9.38; P=0.011) were independently associated with eGFR decrease of >30%.

Conclusions: In urolithiasis related obstructive uropathy patients, concomitant APN was strongly associated with renal function deterioration after obstruction release. The elapsed time to release obstruction also affected to renal function.

FR-PO183

IgG4-Related Kidney Disease (IgG4-RKD) a Large Single-Institution Study

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Background: IgG4-related disease (IgG4-RD) is an immune-mediated condition that can involve any organ, often by mass-forming inflammatory lesions. The kidney is usually affected in a pattern of tubulointerstitial nephritis (TIN); membranous glomerulonephritis (MGN) is another recognized pattern.

Methods: A retrospective biopsy (bx) - and nephrectomy-based study from a single institution with clinicopathological correlation was performed in cases of IgG4-RKD diagnosed between 1/2001 and 5/2018.

Results: 101 patients (80 M, 21 F) were identified with IgG4-RKD on bx (n= 96) or nephrectomy (n= 5), with a histologic pattern of TIN (94%) and/or MGN (15%). Race/ethnicity included white non-Hispanic (65%), African-American (11%), Asian (11%), Hispanic (11%), and American Indian (3%). The mean age was 62 years (range 20-84). Mean creatinine (SCr) at bx was 3.4 mg/dl (median 2.6 mg/dl, range 0.9-11.0 mg/dl). The primary indication for bx or nephrectomy was acute or chronic renal failure (68%), proteinuria (9%), or abnormal imaging (23%). Overall, 39% had renal masses. Extra-renal involvement was present in 85%. Serum IgG and/or IgG4 was increased in 88%. 29% had positive antinuclear antibody. Serum complement (C3 and/or C4) was decreased in 63%. Plasma cell-rich TIN was present in all cases of TIN and 93% showed an increase in IgG4+ plasma cells (focal >10 cells/40x field). Interstitial fibrosis was severe in 65% of cases, moderate in 15%, mild in 20%. 15% had MGN; of those with MGN, 71% also had a component of TIN. None showed granulomatous inflammation. 70% showed tubular basement membrane immune complex deposits by IF or EM. Follow-up was available in 49 patients (49%), with a mean length of 17 months. 98% were treated with immunosuppression (prednisone in 64%, rituximab in 6%, both 10% and other in 19%). 80% of patients with elevated SCr responded to therapy.

Conclusions: In our study, the most common manifestation of IgG4-RKD is TIN with functional impairment rather than mass lesions. MGN is not uncommon. Clinical features of IgG4-KRD included a higher prevalence of hypocomplementemia. Notably, 15% of patients have renal-limited disease. Immunosuppressive therapy improves renal function in the majority of patients.

FR-PO184

The Impact of Kidney Disease Etiology on the Association Between eGFR and Albuminuria with ESRD and All-Cause Mortality in the GCKD Cohort

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Background: Chronic kidney disease (CKD) is classified according to cause of kidney disease, estimated glomerular filtration rate (eGFR) and albuminuria, but risk prediction mainly relies on eGFR and albuminuria. We investigated the impact of kidney disease etiology on the association of kidney disease measures with adverse outcomes.

Methods: We studied 5,214 patients with CKD in the German Chronic Kidney Disease (GCKD) study, where the treating nephrologists assessed the cause of kidney disease. We grouped causes according to the KDIGO guideline with sensitivity analyses for alternative classifications. We analyzed the relative hazard of end-stage renal disease (ESRD) and all-cause mortality as a function of eGFR and urinary albumin-creatinine-ratio (UACR) using age, sex, German origin, systolic blood pressure, smoking, diabetes, BMI and history of cardiovascular disease as covariates. We tested for interaction between eGFR and UACR with cause of kidney disease in a Cox proportional hazards model.

Results: We observed 237 ESRD events and 418 deaths over 4.5 years of follow-up. Risk of ESRD and mortality increased with lower eGFR and higher UACR in each of the CKD causes where sample size was adequate. In the ESRD model, interaction of CKD cause was only present for eGFR with cystic or congenital diseases (p=0.004, see Table), although power to detect modest interactions is limited. For all-cause mortality, no significant interaction was observed between CKD cause and eGFR or UACR.

Conclusions: KDIGO staging of ESRD and mortality risk by eGFR and albuminuria is valid across different causes of CKD, although the eGFR relationship to ESRD risk is stronger in cystic or congenital kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

Cause of kidney disease	Prevalence in cohort, N=5,214	Incidence proportion of ESRD (events/N)	HR (95% CI) per 15 ml/min decrease in eGFR	p-value of interaction	HR (95% CI) per log10 increase in UACR	p-value of interaction
Glomerular diseases	36.5%	6.5% (124/1,902)	2.38 (1.89–2.94)	0.18	2.30 (1.78–3.09)	0.70
Tubulointerstitial diseases	7.4%	1.8% (7/386)	11.36 (2.33–55.55)	0.17	1.93 (0.68–5.47)	0.61
Vascular diseases	26.7%	2.8% (39/1,393)	6.41 (3.57–11.62)	0.15	1.84 (1.20–2.82)	0.26
Cystic and congenital diseases	4.3%	8.9% (20/224)	16.13 (6.67–38.46)	0.004	2.07 (0.97–4.43)	0.62
Other diseases	5.5%	2.8% (8/287)	8.40 (2.70–26.32)	0.18	2.74 (1.09–6.87)	0.91
Unknown disease	19.6%	3.8% (39/1,022)	3.56 (2.04–6.17)	reference	2.58 (1.76–3.92)	reference

Prevalence of CKD causes, incidence and HRs for ESRD associated with lower eGFR or higher UACR and p-values of the interaction between cause and eGFR/UACR, adjusted for age, sex, German origin, systolic blood pressure, smoking, diabetes, BMI, CVD history

FR-PO185

A Whole Blood Adsorber Particle for Future Applications in the Treatment of CKD Patients

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Background: Hydrophobic uremic toxins accumulate in patients with chronic kidney disease, contributing to a highly increased cardiovascular risk. The clearance of these uremic toxins by current hemodialysis techniques is limited due to their high binding affinity to plasma proteins, which prevents their removal through the pores of dialysis membranes. Adsorber techniques may be an appropriate alternative and/or additional technique to increase hydrophobic uremic toxin removal.

Methods: We developed an extracorporeal adsorber particle for efficient adsorption of these uremic toxins. The whole blood adsorber particle consists of a porous, activated charcoal core with a hydrophilic surface coating of cross-linked polyvinylpyrrolidone. The adsorption capacity of the particles was quantified by analytical chromatography after incubation or perfusion of the particles with an aqueous serum albumin solution or blood, each containing mixtures of hydrophobic uremic toxins.

Results: The particle hemocompatibility was assessed by quantifying the production of thrombin-antithrombin III complex (TAT) and complement component 5a (C5a) as well as leukocyte and thrombocyte counts in blood. A time-dependent increase in hydrophobic uremic toxin adsorption was depicted and all tested toxins showed a high binding affinity to the adsorber particles. Further, the particle showed a good hemocompatibility without significant effects on C5a, TAT or thrombocyte concentration, although leukocyte counts were slightly reduced

Conclusions: In conclusion, the whole blood adsorber particle is hemocompatible and shows a high adsorption capacity towards hydrophobic uremic toxins. Thus, it is an interesting candidate for further *in vivo* studies with the aim to increase the efficiency of conventional dialysis techniques and reduce mortality in CKD patients.

FR-PO186

Effect of Periodontal Therapy on CKD: Findings of the Kidney and Periodontal Disease (KAPD) Pilot Randomized Controlled Trial

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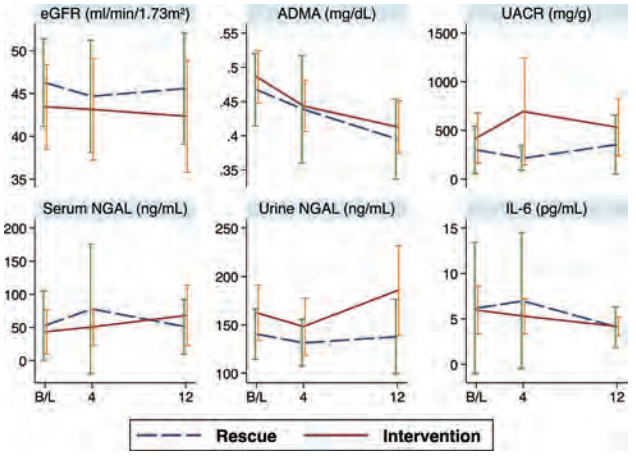
Background: CKD and periodontal disease (PD) disproportionately affect poor and minority populations. Observational studies suggest PD may be a modifiable CKD risk factor. The KAPD study (NCT01802216) was a pilot RCT to assess the feasibility of recruiting and retaining patients from a diverse, public hospital setting and to determine the variability of kidney and inflammatory biomarkers in response to PD treatment.

Methods: We randomly enrolled 51 adult patients with moderate/severe PD and CKD to immediate PD treatment (whole mouth deep cleaning + local minocycline to deep pockets, n=34) or delayed treatment with rescue (deep cleaning for worsening tooth sites, n=17) every 4 months for a 12-month protocol, with biomarkers assessed at baseline, 4-month, and 12-month study visits.

Results: Of enrolled patients, 82% were non-white; 47% had seen a dentist within the last 2 years; and 80% completed all 4 visits of the 12-month protocol (28 intervention, 13 rescue). 6 delayed treatment patients (35%) required rescue treatment. For intervention group, biomarkers of vascular injury (ADMA), and inflammation (IL-6) improved; tubular injury (urine NGAL) worsened; and UACR improved while serum NGAL worsened (markers of glomerular injury). Changes among UACR and serum NGAL in the rescue group were opposite, but similar otherwise.

Conclusions: KAPD demonstrated enrolling and retaining patients from a diverse, public hospital setting in a 12-month trial is feasible. There was variability in kidney and inflammatory biomarkers in response to PD treatment. Rescue treatment may have obscured decisive treatment effect. A larger trial is needed to determine the extent to which PD treatment may slow CKD progression.

Funding: NIDDK Support, Commercial Support - Valeant Pharmaceuticals, Private Foundation Support



eGFR, estimated glomerular filtration rate; ADMA, asymmetrical dimethylarginine; UACR, urine albumin/creatinine ratio; NGAL, neutrophil gelatinase-associated lipocalin; IL-6, Interleukin-6

FR-PO187

Quantitative Analysis: Patient Experiences and Preferences About Being Informed of a CKD Diagnosis

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Background: Patients with chronic kidney disease (CKD) are often unaware of their diagnosis. Doctors may be hesitant to inform patients of a CKD diagnosis and may use heterogeneous terms when doing so. We examined patients' experiences and preferences about being informed of a CKD diagnosis.

Methods: 202 adults with CKD Stages 1-5 completed a cross-sectional survey between April 2015-May 2016. Survey questions focused on: patient experiences being informed about a CKD diagnosis, preferences about verbiage patients use to describe their CKD diagnosis ("Which of the following words or phrases do you use to talk about your kidney problem?"), and when patients thought they should have been told about their diagnosis ("If you had the choice, when would you have wanted to know that you had kidney disease?").

Results: Mean (SD) age was 59 (16) years. 48% were male, 78% Caucasian, 17% African American, 73% had CKD Stage 3-5, 51% had an annual income > $50K, and 95% had ≥ H.S. education. Most patients were first told they had CKD by a kidney doctor (n=87, 47%) in an outpatient setting (n=138, 72%). Others learned of their diagnosis from primary care doctors (33%), ER doctors (7%), and "others," e.g. inpatient providers (9%). Other settings included the hospital (15%), ER (7%), and at home via phone call (6%). Thirty percent of patients reported DM and/or hypertension as the cause of their CKD, and 49% did not recall being told or did not know the cause. Most patients preferred multiple terms to refer to their diagnosis; the majority used "kidney disease" (82%) and "chronic kidney disease" (65%), followed by "decreased kidney function" and "elevated creatinine" (both 61%). Least used terms were "kidney injury" (12%) and "renal insufficiency" (18%). Ninety-six percent felt patients should be informed of their CKD diagnosis upon identification by their doctor. Only 4% felt it was acceptable for the doctor to determine if informing the patient mattered or to not inform patients at all.

Conclusions: Most patients were not told about their CKD diagnosis until they saw a kidney doctor in an outpatient setting. Nearly half did not know the cause of their CKD. Preferred verbiage is largely congruent with current guidelines. In contrast to doctors' perspectives, patients feel they should be informed of their CKD diagnosis as soon as it is identified by a doctor.

Funding: NIDDK Support

FR-PO188

Development and Validation of an Electronic (e) Phenotype for CKD

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Background: Identifying CKD patients is an essential step for surveillance, research recruitment and quality improvement (QI). Using diagnostic codes to identify CKD patients is challenged by widespread under-diagnosis of CKD. An electronic CKD phenotype based on data widely available in the electronic health record could facilitate identification of patients likely to have CKD.

Methods: A working group of patients, nephrologists, primary care providers and informaticists developed the ePhenotype. Five clinical sites implemented the ePhenotype. Each site collected study population demographics (age, race, sex), labs (eGFR, UACR, UPCR, UA) and dialysis/transplant status. The ePhenotype determined CKD status (eGFR <60 ml/min/1.73m^2, UACR ≥30 mg/g), CKD stage and chronicity (prior lab value indicative of CKD 90+ days prior). Four sites conducted a blinded, manual validation on a random subsample of the population across CKD status. Diagnostic accuracy (proportion of patients with correctly identified CKD stage) and sensitivity/specificity of the ePhenotype for identifying CKD, dialysis and transplant were calculated for each site and overall.

Results: The validation population included 1,680,334 patients across 4 sites with average age 49.8±18.5. Of these, 58.7% were female, 10.4% were black, 59.3% had at least 1 eGFR and 40.6% had any proteinuria measurement. The proportion of patients with any proteinuria measurement varied across sites (20.2% to 52.1%) and increased as eGFR decreased. The ePhenotype was successfully implemented at all sites. Diagnostic accuracy for identifying CKD stage was 98%. Sensitivity and specificity, respectively, across the validation sites were 99.3% and 98.5% for CKD, 94.5% and 90.7% for dialysis and 97.3% and 91.1% for transplant (Table 1).

Conclusions: The ePhenotype was successfully implemented at multiple sites with a high degree of accuracy and has the potential to facilitate identification of patients with CKD for surveillance, research and QI.

Funding: NIDDK Support

ePhenotype Performance

Site	CKD			Dialysis			Transplant		
	Population size	Sensitivity (95% CI)	Specificity (95% CI)	Population size	Sensitivity (95% CI)	Specificity (95% CI)	Population size	Sensitivity (95% CI)	Specificity (95% CI)
Total	206	99.3% (96%, 100%)	98.5% (92.1%, 100%)	231	94.5% (87.6%, 98.2%)	90.7% (84.6%, 95.0%)	160	97.3% (85.8%, 99.9%)	91.1% (84.6%, 95.5%)
Minnesota	58	100% (89.7%, 100%)	95.8% (78.9%, 99.9%)	58	97.8% (88.2%, 99.9%)	92.3% (64%, 99.8%)	58	100% (69.2%, 100%)	97.9% (88.9%, 99.9%)
Christiana Care	70	100% (92.9%, 100%)	100% (83.2%, 100%)	72	92.3% (64%0, 99.8%)	98.3% (90.9%, 100%)	72	100% (54.1%, 100%)	98.5% (91.8%, 100%)
Columbia	60	100% (91.2%, 100%)	100% (83.2%, 100%)	80	86.4% (65.1%, 97.1%)	91.4% (81.0%, 97.1%)	80	94.1% (71.3%, 99.9%)	90.5% (80.4%, 96.4%)
UCSF	18	92.9% (66.1%, 99.8%)	100% (39.8%, 100%)	21	100% (71.5%, 100%)	40% (12.2%, 73.8%)	10	100% (39.8%, 100%)	50% (11.8%, 88.2%)

FR-PO189

A Machine Learning Approach to Identifying Patients at Risk of Developing Incident CKD

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Background: Chronic Kidney Disease (CKD) is an under-identified condition and current methodology for identifying patients at risk of developing incident CKD is limited. Identifying patients who are high risk for CKD can improve awareness while delaying onset and progression of CKD. Machine learning algorithms can be used to stratify risk of those likely to develop incident CKD. Previous work has defined CKD using ICD codes or a limited number of eGFR readings.

Methods: Data from 1,780,262 patients with no baseline CKD in the Veterans Affairs healthcare system was analyzed. We used a random forest classifier to 1) predict incident CKD (eGFR >90 progressing to eGFR <60) and 2) predict the development of advanced CKD (eGFR >60 progressing to eGFR <45) utilizing information on patient demographics, comorbidities, laboratory values, and medication use. We excluded eGFR values during an AKI episode using an algorithm and selected sustained eGFR periods using slope-based analyses. One, two, and five-year prediction models were generated.

Results: The performance of the prediction models are summarized in Table 1. As models predict on outcomes across longer time ranges the lab values become less important while the comorbidities rise in importance. At the top risk quartile, our one year incident CKD model has an AUC of 0.839, a sensitivity of 0.754, and a specificity of 0.751, and our one year development of advanced CKD model has an AUC of 0.871, a sensitivity of 0.825, and a specificity of 0.751.

Conclusions: We demonstrate the ability to leverage advanced machine learning models to predict CKD incidence using longitudinal data commonly available in EHR systems. Future studies should validate our model in a clinical setting.

Funding: Veterans Affairs Support, Commercial Support - pulseData

Table 1

	Metric	One Year	Two Year	Five Year
eGFR of > 90 predicting decline to eGFR of < 60 (incident CKD stage 3a and above)	AUC	0.839	0.808	0.791
	Outcome	0.282%	0.572%	2.034%
	Sensitivity (top quartile)	0.754	0.723	0.651
	Specificity (top quartile)	0.751	0.753	0.758
eGFR of > 60 predicting decline to eGFR of < 45 (incident CKD stage 3b and above)	AUC	0.871	0.853	0.830
	Outcome	0.191%	0.474%	2.018%
	Sensitivity (top quartile)	0.825	0.784	0.739
	Specificity (top quartile)	0.751	0.753	0.760

FR-PO190

Rural Disparities in Estimated Glomerular Filtration Rate Changes in Patients with and at-Risk of CKD

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Background: Little is known about chronic kidney disease CKD progression among rural versus urban dwelling patients. The study aim was to determine associations of residential location with estimated glomerular filtration rate (eGFR) over time in patients with and at-risk for CKD.

Methods: Providence and UCLA healthcare systems collaboratively formed a CKD and at-risk CKD registry from electronic health records (n=3,118,853). Participants were identified by diagnosis of CKD, at-risk for CKD (diabetes, pre-diabetes, or hypertension) by ICD-9/10 codes and condition-specific criteria from 2006-2016. The primary outcome was eGFR (CKD-EPI-creatinine) including ≥3 values over ≥90 days, and the main covariate of interest was rural versus urban dwelling defined by Rural-Urban Commuting Area codes. Other pre-specified covariates in the random effects regression model included: age, gender, race; and time-varying covariates: HbA1c, systolic blood pressure, and angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE/ARB) usage.

Results: Baseline characteristics: 59±17 years of age, 56% female, 10% rural dwelling, 86% White, 6% Black or African American, and 7% Asian. Baseline eGFR was 60.6±22.5 mL/min/1.73m^2 in the CKD cohort and 90.0±18.3 mL/min/1.73m^{2}in the at-risk cohort. For both the CKD and at-risk cohort, patients dwelling in a rural versus an urban location experienced a nearly 4 mL/min/1.73m^{2}greater annual decline in eGFR (B = -3.81, 95% CI: -4.21 - -3.42, p<0.001) over a median of 5 years, controlling for other covariates. eGFR decline significantly varied across race and was inversely associated with age, time, and ACE/ARB usage. eGFR decline was positively associated with female sex and systolic blood pressure. HbA1c was not associated with eGFR change.

Conclusions: In patients with CKD and at-risk for CKD, rurality independently associated with faster loss of kidney function compared to urban dwelling. Facilitators and overcoming barriers to better care are needed for these patients in rural locations.

Funding: Private Foundation Support

FR-PO191

Monitoring Quality of Care for CKD in the United States

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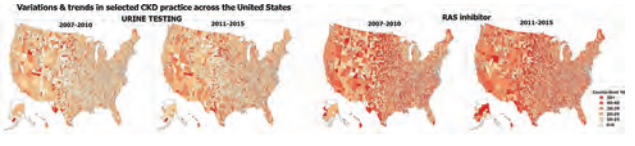
Background: Monitoring quality of CKD care and understanding geographic variation in care quality are important for improving patient outcomes; however this topic has received limited attention. We examined quality of care measures for CKD and geographic variation in elderly Medicare beneficiaries in the United States.

Methods: We analyzed the 5% sample of the Medicare fee-for-service population linked with Part D medication claims data from 2007 to 2015. We selected elderly (≧65 years) patients with diagnosed CKD (by ICD-9 codes) and examined their care in repeated annual crossections. We assessed 4 key CKD quality indicators including urine albumin testing, renin-angiotensin (RAS) inhibitors use, not receiving (i.e., <14 days per month prescription) of non steroidal anti-inflammatory drugs (NSAIDs), and receiving nutritional consultation. Variation in these practices by age, sex, race, comorbidities (diabetes, hypertension and history of cardiovascular disease) and county of residence, were examined. A multivariate logistic model identified factors associated with urine albumin testing and RAS inhibitor use.

Results: Of the total 2,162,085 elderly CKD patients, 43.1% were 80 years or older, 44.8% had diabetes, and 86.4% had hypertension. We observed steady increase in urine testing (from 21.5% in 2007 to 29.5% in 2015) and RAS inhibitor use (31.8% in 2007 to 40.6% in 2015) (each p for trend <0.01). During the same follow-up years, nutritional guidance was received in under 2%, but NSAIDs avoidance was observed in over 95%. County-level variation (Figure) in urine testing and RAS inhibitor use ranged widely from 0 to >50%, and increased over time. Age <80 years, diabetes, and hypertension, were associated with higher odds of urine testing and RAS inhibitor use.

Conclusions: Significant practice gaps and variations exist across the US for selected quality indicators of CKD care in older adults. More research into this area is vital as quality of care monitoring has potential to inform policy and practice improvements for this patient population..

Funding: NIDDK Support



FR-PO192

Urinary Biomarkers of Tubular Dysfunction and Risk of CKD Progression Among SPRINT Participants

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Background: Tubular atrophy on biopsy is a strong predictor of kidney disease progression, but tubular health is poorly quantified by traditional measures including estimated glomerular filtration rate (eGFR) and albuminuria. We hypothesized that urinary biomarkers of tubule dysfunction would be associated with faster kidney function decline in persons with chronic kidney disease (CKD).

Methods: We measured baseline urine concentrations of α1-microglobulin (α1m), β2-microglobulin (β2m), and uromodulin among 2,428 participants of the Systolic Blood Pressure Intervention Trial who had an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. We used linear mixed models to evaluate biomarker associations with annualized relative change in eGFR.

Results: At baseline, the mean age was 72±9 years and eGFR was 48±11 ml/min/1.73m^2. Over a median follow-up of 3.8 years, higher concentrations of urine α1m and β2m and lower concentrations of urine uromodulin were independently associated with faster annualized eGFR decline (**Table**). There were no statistically significant interactions by intervention arm (p>0.3 for all biomarkers).

Conclusions: Among hypertensive, nondiabetic patients with CKD, urinary biomarkers of tubular dysfunction were independently associated with subsequent declines in kidney function.

Funding: NIDDK Support, Veterans Affairs Support

Associations of urinary biomarkers with annualized relative change in eGFR among SPRINT participants with CKD at baseline (N = 2,428)

Biomarker	Demographic-adjusted β (95% CI)	Multivariable- adjusted β (95% CI)
α1-microglobulin	-0.57 (-0.69, -0.44)	-0.57 (-0.70, -0.45)
β2-microglobulin	-0.21 (-0.27, -0.15)	-0.20 (-0.26, -0.15)
Uromodulin	0.48 (0.33, 0.62)	0.48 (0.33, 0.62)

β coefficient represents % eGFR change in ml/min/1.73m2/year per doubling of the biomarker. Demographic-adjusted model includes age, sex, race, intervention arm and urine creatinine. Multivariable-adjusted model additionally includes baseline eGFR, urine albumin, smoking status, history of cardiovascular disease, number of antihypertensive medications, systolic blood pressure, diastolic blood pressure, body mass index, high-density lipoprotein, and total cholesterol.

FR-PO193

Kidney Tubular Damage and Risk of Cardiovascular Disease and Mortality Among SPRINT Participants with CKD

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Background: Novel urine biomarkers have enabled earlier detection of kidney tubular damage, but their prognostic value for adverse cardiovascular outcomes is uncertain. We hypothesized that urinary biomarkers of tubular injury would be associated with higher risks for cardiovascular events and mortality in persons with chronic kidney disease (CKD).

Methods: We measured urine concentrations of interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein-1 (MCP-1), and chitinase-3-like protein-1 (YKL-40) among 2,377 participants of the Systolic Blood Pressure Intervention Trial who had an eGFR<60 ml/min/1.73 m^2. We used Cox proportional hazards models to evaluate biomarker associations with CVD events and all-cause mortality.

Results: At baseline, the mean age was 72±9 years and eGFR was 48±11 ml/min/1.73m^2. Over a median of 3.8 years, 305 CVD events (3.6% per year) and 233 all-cause deaths (2.6% per year) occurred. After multivariable adjustment, including baseline eGFR and albuminuria, higher urine IL-18 and YKL-40 concentrations were independently associated with higher mortality risk (**Table**). The biomarkers did not have statistically significant associations with CVD events. Associations were similar when stratified by randomization arm.

Conclusions: Among hypertensive, nondiabetic patients with CKD, urine IL-18 and YKL-40 were independently associated with higher mortality risk but not with CVD events. The remaining markers were not associated with CVD or mortality risk.

Funding: NIDDK Support

Associations of urine biomarkers with CVD events and mortality among SPRINT participants with CKD at baseline (N = 2,377)

Biomarker	CVD events Hazard Ratio (95% CI)	All-cause mortality Hazard Ratio (95% CI)
IL-18	1.06 (0.96, 1.18)	1.14 (1.01, 1.29)
KIM-1	0.93 (0.86, 1.02)	0.96 (0.86, 1.06)
NGAL	1.03 (0.96, 1.11)	1.03 (0.95, 1.12)
MCP-1	1.04 (0.94, 1.15)	1.03 (0.91, 1.17)
YKL-40	1.04 (0.99, 1.10)	1.08 (1.02, 1.14)

Hazard ratios per doubling in biomarker. Models adjust for age, sex, race, intervention arm, baseline eGFR, urine albumin, urine creatinine, smoking status, history of CVD or heart failure, number of antihypertensive medications, statin use, systolic and diastolic blood pressures, body mass index, and lipid profiles.

FR-PO194

Serum Metabolites Associated with Kidney Function Decline

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Background: Small molecules that associate with subsequent GFR decline in patients with CKD may help uncover novel pathophysiological mechanisms of disease or treatment targets.

Methods: Among 960 participants in the African American Study of Kidney Disease and Hypertension (baseline mGFR 47 +/- 15 ml/min/1.73 m^2), we evaluated the associations of 961 named and unnamed serum metabolites identified through untargeted metabolomic profiling with decline in measured GFR over time using linear mixed models and a median of 11 measures of mGFR over 4.1 years. We selected metabolites associated with mGFR decline ($p<0.05$) and subsequently assessed their associations with ESRD over a median of 8.9 years using Cox models (Bonferroni-corrected $p<0.05$). Analyses were adjusted for study arm, age, sex, smoking, heart disease, body-mass index, systolic blood pressure, log-transformed proteinuria, and, in the Cox model, baseline measured GFR.

Results: There were 112 metabolites associated with change in mGFR over time in AASK ($p<0.05$). Fourteen were also associated with ESRD after correcting for multiple comparisons ($p<0.0004$). All 14 metabolites were negatively associated with baseline mGFR. The top three metabolites associated with ESRD were 1-methylhistidine, erythronate, and O-sulfo-L-tyrosine. Six of the 14 were in the phosphatidylethanolamine pathway.

Conclusions: Several metabolites, including six in the phosphatidylethanolamine pathway, may relate to ESRD risk. Further studies are needed to determine if these associations are causal.

Funding: NIDDK Support

Compound	Sub Pathway	Rho with Baseline mGFR	Beta mGFR decline	P-value mGFR decline	Hazard Ratio for ESRD	P-Value ESRD
1-methylhistidine	Histidine Metabolism	-0.59	-0.31	7.35E-03	1.72	2.88E-10
erythronate	Aminosugar Metabolism	-0.69	-0.28	1.93E-02	1.72	3.51E-08
O-sulfo-L-tyrosine	Chemical	-0.66	-0.28	2.62E-02	1.52	3.00E-06
X - 24513	Unknown	-0.74	-0.27	2.31E-02	1.57	5.25E-06
1-stearoyl-2-linoleoyl-GPE (18:0/18:2)	Phosphatidylethanolamine (PE)	-0.17	-0.27	1.69E-02	1.35	6.48E-06
X - 24422	Unknown	-0.56	-0.33	5.42E-03	1.36	9.39E-06
1-methylimidazoleacetate	Histidine Metabolism	-0.66	-0.34	4.73E-03	1.43	1.01E-05
1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)	Phosphatidylethanolamine (PE)	-0.22	-0.34	2.43E-03	1.34	1.98E-05
gulonate	Ascorbate and Aldarate Metabolism	-0.64	-0.28	1.66E-02	1.49	3.56E-05
1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)	Phosphatidylethanolamine (PE)	-0.24	-0.29	9.15E-03	1.31	5.76E-05
1-stearoyl-2-oleoyl-GPE (18:0/18:1)	Phosphatidylethanolamine (PE)	-0.13	-0.25	2.35E-02	1.29	6.28E-05
X - 12686	Unknown	-0.58	-0.53	8.46E-06	1.40	6.66E-05
1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	Phosphatidylethanolamine (PE)	-0.19	-0.30	6.72E-03	1.29	7.15E-05
1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)	Phosphatidylethanolamine (PE)	-0.18	-0.26	1.96E-02	1.30	7.50E-05

Top Metabolites Associated with mGFR decline and ESRD in AASK

FR-PO195

The Burden of Adverse Drug Events in Patients with Moderate or Advanced CKD: The CKD-REIN Study

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Background: Little is known about the burden of adverse drug events (ADEs) in chronic kidney disease (CKD). We assess the incidence rate of ADEs and describe the suspected prescribed drugs associated with the main reported ADEs in the CKD-REIN cohort.

Methods: The CKD-REIN study includes 3033 outpatients (65% men) with CKD (estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2). ADEs were identified from medical records, hospital discharge reports, or patient interviews. All reported ADEs were reviewed by pharmacist experts who coded the type of events and the associated suspected drugs. Incidence rates were estimated by Poisson regression, overall and by patient characteristics.

Results: At baseline, patients' median age was 69(IQR, 60-76), median eGFR was 32(IQR, 23-41)mL/min/1.73m^2 and the median number of medications was 8 per day. During a median follow-up of 2.3 years, 777 ADEs were reported in 545 patients, 27% of whom had at least two. The overall incidence rate of ADEs was 10.7[95%CI, 9.9-11.4] per 100 person years, with significantly higher rates in women than men, and in patients with diabetes, lower eGFR, cardiovascular history and with a higher number of medications at baseline; it did not differ significantly according to age. Renin-angiotensin system inhibitors (RASi) (15%), antithrombotic agents (13%) and diuretics (9%) were the drug classes most frequently associated with ADEs. As expected, main ADEs were increased serum creatinine and hypotension with RASi and diuretics, hemorrhage with antithrombotic agents, and cough with RASi. Of note, 71% of ADEs led to discontinuing treatment and 16% to modifying treatment dose. Among the 777 evaluated ADEs, 161 (21%) were reported among inpatients, either as a cause of hospitalization or an incident event, 2.2[95%CI, 1.9-2.6] per 100 person years, four of which were linked with death. The drugs most frequently involved in ADEs associated with hospitalization or death, were vitamin K antagonists (n=39) and heparin (n=7).

Conclusions: The burden of ADEs is high in patients with CKD and led to discontinuing drugs prescribed to slow CKD progression and reduce cardiovascular complications. The impact of ADEs and resulting prescription changes on CKD outcomes need to be evaluated.

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FR-PO196

Urine Markers of Kidney Tubule Cell Injury and Kidney Function Decline: Results from SPRINT Trial

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Background: Tubulo-interstitial fibrosis and atrophy are important risk markers for chronic kidney disease (CKD) progression on kidney biopsy, but are not evaluated in clinical testing. We examined the association between urinary kidney tubule injury biomarkers with subsequent loss of kidney function in persons with non-diabetic CKD who participated in The Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: Among 2428 SPRINT participants with CKD (eGFR <60 ml/min/1.73m^2) at baseline, we measured urine concentrations of markers of *injury* (interleukin-18 [uIL-18], kidney injury molecule-1[uKIM-1], and neutrophil gelatinase-associated lipocalin [uNGAL]), *inflammation* (monocyte chemoattractant protein-1 [uMCP-1]) and *repair* (human cartilage glycoprotein-40 [uYKL-40]). We used linear mixed models to evaluate the associations of each biomarker with annualized change in eGFR; and used proportional hazards regression to evaluate the renal composite outcome of 50% eGFR decline, transplant or end-stage renal disease.

Results: At baseline, the mean age was 73±9 years and mean eGFR was 46±11 ml/min/1.73m^2; 60% were men and 66% were white. During 3.8 years mean follow-up, there were 87 composite renal events. In adjusted continuous models, higher uIL-18, uNGAL and uYKL-40 concentrations were associated with faster eGFR decline (Table). Associations with the renal composite endpoint appeared non-linear, with heightened risk in the highest quartile. The high quartiles of uKIM-1 (hazard ratio 2.84 [95% CI 1.31 to 6.17), uYKL-40 (1.95 [1.08 to 3.51]) and uMCP-1 (2.43 [1.13 to 5.23]) were each associated with risk of the renal composite outcome relative to the lowest quartiles. Associations were similar in the two randomization arms.

Conclusions: Urine markers of tubule cell injury provide information about risk of subsequent loss of kidney function independent of eGFR and albuminuria. Future studies are required to determine if dynamic changes in urine tubule injury markers provide information on subsequent risk of CKD progression.

Funding: NIDDK Support

Table: Association of Urine Markers of Tubule Injury with Annualized Relative Change in eGFR and 50% Kidney Function Decline, ESRD, or Transplant

Biomarkers (per doubling)	Annualized relative change in eGFR	50% kidney function decline, ESRD or transplant
	β (95% CI)	Hazard Ratio (95% CI)
Urine IL-18, pg/mL	**-0.14 (-0.25, -0.04)***	1.06 (0.89, 1.26)
Urine KIM-1, pg/mL	-0.08 (-0.16, 0.01)	1.07 (0.85, 1.35)
Urine NGAL, ng/mL	**-0.11 (-0.20, -0.02)#**	1.01 (0.89, 1.15)
Urine MCP-1, pg/mL	-0.06 (-0.15, 0.03)	1.16 (0.93, 1.46)
Urine YKL-40, pg/mL	**-0.09 (-0.15, -0.02)##**	**1.10 (1.02, 1.19)**

*P <0.01, #P <0.05, ##P< 0.001; abbreviation: ESRD, end stage renal disease, CI, confidence interval, eGFR, estimated glomerular filtration rate
Model adjusted for age, sex, race, randomization arm, urine creatinine, eGFR, urine albumin, systolic blood pressure, diastolic blood pressure, number of blood pressure medications, history of cardiovascular disease, smoking, body mass index, high-density lipoprotein and total cholesterol

FR-PO197

Markers of Kidney Tubule Function and Risk of Cardiovascular Disease Events and Mortality in the SPRINT Trial

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Background: Biomarkers of tubule injury, inflammation and fibrosis have emerged as prognosticators of kidney and cardiovascular disease (CVD) outcomes. However, markers of tubular *function* have not been adequately evaluated as risk factors for CVD.

Methods: Using a sample of 2,377 persons with CKD at the baseline SPRINT visit, we evaluated the association of three urinary markers of tubular function; alpha-1 microglobulin (α1m), beta-2 microglobulin (β2m) and uromodulin with CVD events, heart failure and all-cause mortality using Cox regression over 3.7 years of follow up. Markers were log-transformed given skewed distributions.

Results: Mean age was 73 years, 40% were woman, 26% black, and mean glomerular filtration rate (GFR) was 46±11 ml/min/1.73m². In multivariable analyses, each two-fold higher α1m was associated with a 33%, 31%, 61% and 85% greater risk of composite CVD, mortality, CVD death and acute coronary syndromes (ACS), respectively [table]. There was no association of β2m with any of the outcomes. Each two-fold higher uromodulin was associated with a 22%, 30% and 31% lower adjusted risk of composite CVD, HF and CVD death, respectively. These associations were not modified by baseline CVD or intervention arm.

Conclusions: Among non-diabetic persons with CKD, biomarkers of tubular function are associated with incident CVD and mortality independent of GFR and albuminuria.

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Association of tubular function biomarkers with clinical outcomes among SPRINT participants with CKD

	Composite CVD	All-cause Mortality	Heart Failure	CVD Death	ACS
Events	305	233	123	67	27
Alpha-1 microglobulin*	**1.33 (1.12 - 1.58)**	**1.31 (1.08 - 1.59)**	0.97 (0.77 - 1.22)	**1.61 (1.18 - 2.21)**	**1.85 (1.15 - 2.99)**
Beta-2 microglobulin*	1.00 (0.88 - 1.13)	0.91 (0.79 - 1.05)	1.05 (0.97 - 1.13)	0.99 (0.90 - 1.10)	0.90 (0.78 - 1.05)
Uromodulin*	**0.78 (0.68 - 0.90)**	0.86 (0.73 - 1.01)	**0.70 (0.56 - 0.87)**	**0.69 (0.50 - 0.93)**	0.84 (0.95 - 1.06)

*per doubling of biomarker
Adjusted for: Age, sex, race, intervention arm, urine creatinine, GFR, urine albumin, smoking, BMI, systolic & diastolic blood pressure, number of anti-hypertensive medications, prevalent CVD, heart failure, HDL, total cholesterol, triglycerides, statin use and other tubular function biomarkers

Association of tubular function biomarkers with clinical outcomes among SPRINT participants with CKD

FR-PO198

Urinary PTH1R: Novel Predictor of Mineral Metabolism Disorder and Renal Outcome of CKD

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Background: There is short of early predictor of mineral metabolism disorder and renal outcome in patients with chronic kidney disease (CKD). This study aimed to explore the association of urinary parathyroid hormone 1 receptor (PTH1R) with mineral metabolism markers, and the predictive value for renal outcome in CKD.

Methods: 29 healthy controls and 140 diabetic nephropathy (DN) patientswere enrolled as discovery cohort and 200 general CKD patients were enrolled as an independent validation cohort. All patients were followed up for at least 1 year and measured the intact PTH (iPTH), fibroblast growth factor 23 (FGF23) in baseline serum and PTH1R in baseline urine. Urinary PTH1R was normalized to urine creatinine and log transformed [uPTH1R/Cr($\log_{10}$)].The composite renal endpoint was defined as end-stage renal disease (ESRD) or 30% reduction of baseline eGFR during follow-up.

Results: In discovery cohort, DN patients had a significantly higher mean uPTH1R/Cr($\log_{10}$) level compared with healthy control (2.53±0.61 pg/mg versus 1.89±1.14 pg/mg, P<0.01). uPTH1R/Cr($\log_{10}$) was significantly increased in DN patients with eGFR of 60~75 ml/min/1.73m², which was earlier than serum FGF23 and iPTH. Baseline uPTH1R/Cr($\log_{10}$) was associated with serum calcium (r=-0.224, P<0.01), serum FGF23 (r=0.232, P<0.05), and eGFR slope (r=0.318, P<0.001). 59 patients in discovery cohort entered into composite renal endpoint during follow-up. Cox regression analysis showed that higher uPTH1R/Cr($\log_{10}$) had a significantly higher risk for renal outcome [HR=2.190; 95%CI(1.048,4.575), P<0.05]. Validation cohort confirmed that uPTH1R/Cr($\log_{10}$) was an independent risk factor for renal outcome [HR=1.573; 95%CI(1.094,2.263), P<0.05] in general CKD patients. Addition of uPTH1R/Cr($\log_{10}$) to eGFR and proteinuria could significantly improve the prediction value for renal outcome (likelihood ratio test, P<0.001).

Conclusions: Urinary PTH1R was an independent risk factor for renal outcome in CKD patients, and was a novel biomarker of disordered mineral metabolism.

FR-PO199

The Association of Blood Urea Nitrogen to Creatinine Ratio with Renal and Cardiovascular Outcomes in CKD: The CRIC Study

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Background: Above a traditional cutoff point of 20, a blood urea nitrogen to creatinine ratio (BUN/Cr) has been suggested to be a marker of neurohormonal activation (NHA) which could contribute to progressive chronic kidney disease (CKD), cardiovascular disease (CVD) and higher mortality. We therefore examined the association of baseline BUN/Cr with these outcomes among persons with CKD.

Methods: [2] We examined 3908 adult participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Cox regression was used to examine BUN/Cr as a categorical predictor (< 20, 20-<25, 35-<30, and >=30) and a continuous predictor using splines. Outcomes included time to end-stage renal disease (ESRD), congestive heart failure (CHF), atherosclerotic events (stroke, myocardial infarction, and peripheral artery disease), atrial fibrillation, and all-cause mortality. Cox models were adjusted demographics, clinical and laboratory characteristics.

Results: Among the 3908 participants included in the analysis, mean age and eGFR was 57.7 (11.0) years and 44.9 (16.9) ml/min/1.73m2 respectively. Participants were 41.6% white and 45.2% female. Higher BUN/Cr was associated with increased risk of CHF, atherosclerotic events, atrial fibrillation, and overall mortality, but not with ESRD when examined as a continuous (Figure 1) or categorical predictor (Table 1)

Conclusions: Higher BUN/Cr is associated with an increased CVD risk and mortality but not ESRD among persons with CKD.

Funding: NIDDK Support

Table 1 Hazard Ratios (95% CI) for ESRD and CVD Outcomes

BUN/Cr	ESRD	CHF	Non-CHF CVD	Afib	Mortality
< 20	ref	ref	ref	ref	ref
20-<25	.85 (.69-1.03)	1.32 (1.05-1.69)	1.36 (1.06-1.75)	1.12 (.84-1.48)	1.12 (.89-1.40)
25-<30	.98 (.75-1.29)	1.50 (1.10-2.05)	1.45 (1.00-2.09)	1.18 (.79-1.76)	1.39 (1.02-1.90)
>30	.98 (.66-1.47)	2.25 (1.52-3.33)	1.35 (.77-2.37)	2.71 (1.75-4.21)	1.93 (1.31-2.84)
P value	.40	< .001	< 0.05	< 0.001	.004

Model was adjusted for age, race, gender, diabetes, hypertension, prior CVD, smoking status, history of hepatitis B/C, history of any cancer, systolic blood pressure, BMI, fat free mass, diuretic use, ACEARB use, corticosteroid use, eGFR, hemoglobin, 24 hour urine creatinine, 24 hour urine urea nitrogen, 24 hour urine protein, FGF-23, albumin

Table 1

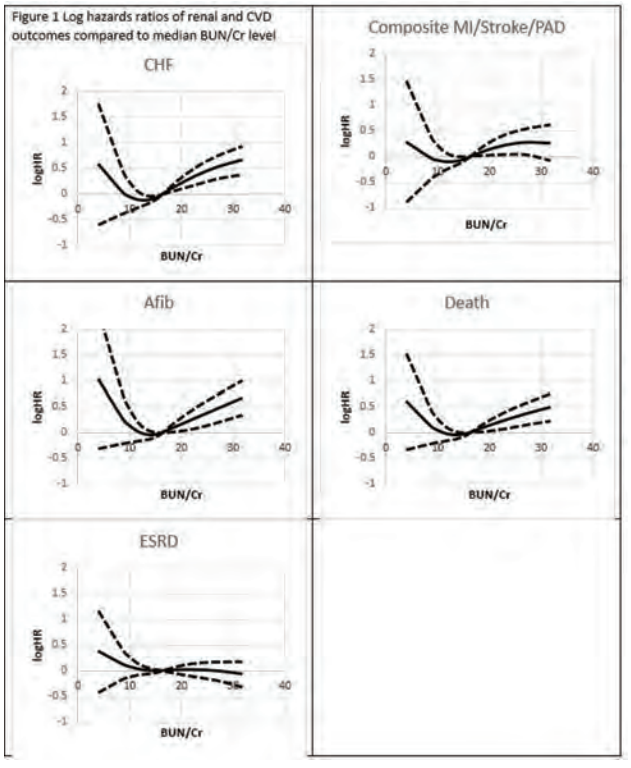

Figure 1

FR-PO200

Urine Citrate Excretion Non-Invasively Verifies Reduced Acid Retention in Response to Dietary Acid Reduction in CKD 2 Patients Without Metabolic Acidosis

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Background: Some CKD stage 2 (eGFR=60-89 ml/min/1.73 m2, CKD 2) patients without metabolic acidosis (defined as plasma total CO_2 <22 mM) nevertheless have acid (H^+) retention and decreasing H^+ retention with dietary H^+ reduction slows eGFR decline. Current methods to verify a decrease in H^+ retention and thereby establish clinical effectiveness of dietary H^+ reduction require cumbersome and invasive methods with limited clinical utility. We explored the utility of urine citrate excretion to non-invasively verify decreased H^+ retention in response to dietary H^+ reduction in CKD 2 patients without metabolic acidosis.

Methods: We measured H^+ retention and 8-hour urine citrate excretion ($U_{citrate}V$) in macroalbuminuric, non-diabetic CKD 2 (n=40) and CKD stage 1 (eGFR >90 ml/min/1.73 m2, CKD 1, n=26) patients with hypertension-associated nephropathy but without metabolic acidosis (mean plasma total CO_2 25.9±0.8 and 26.4±0.6 mM, respectively). H^+ retention was measured before and after dietary H^+ reduction with 30 days of base-producing fruits and vegetables (F+V) by comparing observed to expected increase in plasma [HCO_3] in response to retained HCO_3 (dose minus $U_{HCO3}V$) 6 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body weight HCO_3 apparent space of distribution.

Results: H^+ retention was higher in CKD 2 than CKD 1 (28.1±9.4 vs. 5.2±12.0 mmol, respectively, p<0.01) but $U_{citrate}V$ was lower in CKD 2 than CKD 1 (187±40 vs. 335±125 mg, respectively, p<0.01). F+V did not decrease H^+ retention in CKD 1 (p=0.88) but did so in CKD 2 (to 18.4±17.4 mmol, p<0.01 vs. baseline) and increased $U_{citrate}V$ (to 245±70 mg, p<0.01 vs. baseline) in CKD 2. Overall Pearson Correlation for $U_{citrate}V$ with H^+ retention after F+V was -0.71 (p<0.001). A mixed effects regression model showed $U_{citrate}V$ to be strongly predictive of H^+ retention (p<0.001) so that for every 1 mg increase in $U_{citrate}V$, H^+ retention decreased 0.096 mmol.

Conclusions: $U_{citrate}V$ non-invasively verifies decreased H^+ retention in response to 30 days of F+V in CKD 2 patients without metabolic acidosis. It should be further explored as a method to establish clinical effectiveness of dietary H^+ reduction in CKD patients with comparatively well-preserved eGFR and no metabolic acidosis, but who are at risk for nephropathy progression.

FR-PO201

Urine Citrate Excretion Non-Invasively Identifies Changes in Acid Retention over Time in CKD 2 Patients Without Metabolic Acidosis

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Background: Some CKD stage 2 (eGFR=60-89 ml/min/1.73 m^2, CKD 2) patients without metabolic acidosis (conventionally defined as plasma total CO_2 <22 mM) nevertheless have acid (H^+) retention that appears to exacerbate nephropathy progression, increases as eGFR decreases over time (Goraya et al, AJP, 2018), and this increase in H^+ retention might be ameliorated with chronic oral $NaHCO_3$. Current methods to measure H^+ retention are cumbersome and invasive so we explored the utility of urine citrate excretion to non-invasively identify changes in H^+ retention over time.

Methods: We measured H^+ retention and 8-hour urine citrate excretion ($U_{citrate}V$) in macroalbuminuric, non-diabetic CKD 2 patients with hypertension-associated nephropathy without metabolic acidosis (plasma total CO_2 >24 mM) given 0.5 meq/kg bw/day $NaHCO_3$ (HCO_3, n=40), 0.5 meq/kg bw/day NaCl (NaCl, n=40), or usual care (UC, n=40) and assessed them yearly for 10 years. H^+ retention was measured at baseline and 10 years by comparing observed to expected increase in plasma total CO_2 in response to retained HCO_3 (dose minus $U_{HCO3}V$) 2 hours after oral $NaHCO_3$ bolus (0.5 mmol/kg bw), assuming 50% body weight HCO_3 apparent space of distribution.

Results: Baseline H^+ retention and $U_{citrate}V$ were not different among groups. The 10-year vs. respective baseline value in HCO_3 was not different for H^+ retention (15.7±12.6 vs. 18.1±14.9 mmol, p=0.90) or $U_{citrate}V$ (204±43 vs. 195±49 mg, respectively, p=0.30). By contrast, the 10-year vs. respective baseline value in NaCl was higher for H^+ retention (27.5±15.2 vs. 19.2±16.7 mmol, respectively, p<0.01) and lower for $U_{citrate}V$ (158±47 vs. 193±52 mg, respectively, p<0.01). Similar to NaCl, 10-year vs. respective baseline value in UC was higher for H^+ retention (22.1±11.2 vs. 17.4±9.9 mmol, respectively, p<0.01) and lower for $U_{citrate}V$ (164±42 vs. 187±40 mg, respectively, p<0.01). A generalized linear model for repeated measures, adjusted for time, showed that $U_{citrate}V$ was a predictor of H^+ retention overall (p<0.01) and within each of the 3 groups (p<0.05).

Conclusions: $U_{citrate}V$ non-invasively identifies changes in H^+ retention over time in CKD 2 patients without metabolic acidosis. It should be further explored to follow clinical effectiveness of dietary H^+ reduction in CKD patients without metabolic acidosis.

FR-PO202

Urine Chloride levels Are Associated with CKD Progression in CKD Patients

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Background: Tubuloglomerular feedback is the physiologic mechanism responsible for autoregulation of GFR and renal blood flow. This response is mainly driven by chloride level in the distal tubules, thus prevents glomerular hypertension. Here, we studied the relationship between urinary chloride level and CKD progression.

Methods: Data were retrieved from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease cohort. Among 2,238 participants, a total of 2,019 patients were eligible for the analysis after excluding patients with missing data. Patients were categorized into 3 groups according to baseline tertiles of random urinary chloride excretion : < 76, 76-115, and ≥ 116 mEq/L. The study endpoint was a composite of >50% decrease in eGFR, or ESRD.

Results: The mean age was 53.7 ± 12.1 years, and 1234 (61.2%) patients were male. During a median follow-up of 2.8 years, 436 (21.6%) participants reached the renal endpoint. CKD progression occurred in 236 (34.8%), 159(24.1%), and 41(6.0%) patients in the lowest, middle, and highest tertile groups (P < 0.001), respectively. Compared to the lowest tertile, the middle (HR, 0.811; 95% CI, 0.660-0.997; P=0.047) and highest (HR, 0.619; 95% CI, 0.434-0.882; P=0.008) tertiles were significantly associated with decreased risk of adverse renal outcome in multivariable models after adjustment of confounding factors. This association was consistently observed in adjusted multivariable model where

urinary chloride was entered as a continuous variable (HR per 10 mEq/L increase, 0.961; 95% CI, 0.931-0.993; P=0.016) There was a significant interaction between urinary chloride level and eGFR (P=0.009) and the significant association between urinary chloride level and CKD progression was evident particularly in patients with eGFR < 60ml/min/1.73m^2; HR in the highest tertile was 0.444 compared to the lowest tertile (95% CI, 0.287-0.686; P < 0.001).

Conclusions: This hypothesis generating study showed that higher urinary chloride level is associated with the progression of CKD.

FR-PO203

Serum Chloride Associates with CKD Progression

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Background: Chloride is the predominant extracellular anion in the body, serving important functions including maintenance of electroneutrality, modulation of renin secretion, and regulation of renal sodium transport. Limited data suggest it may predict mortality in heart failure, chronic kidney disease (CKD), and pulmonary arterial hypertension. Recent randomized trials in hospitalized patients have also shown that administration of crystalloid intravenous fluids with lower chloride concentration may have better renal outcomes than fluids with higher chloride concentration. However, chloride has not been studied longitudinally for CKD progression.

Methods: 536 subjects with predominantly stage 3 and 4 CKD were recruited into a prospective cohort study from a nephrology clinic at a single academic medical center. Renal function was re-assessed longitudinally. Logistic and Cox regression models were created for outcomes of upper quartile of annualized estimated glomerular filtration rate (eGFR) decline and > 30% decline in eGFR, respectively. Baseline chloride was modeled continuously as an independent variable, and models were adjusted for potential confounders including co-morbidities, proteinuria, and relevant serum labs and medications.

Results: Median follow-up time was 1.7 years. At baseline, median age was 73, 62% were male, 52% diabetic, 91% hypertensive, and median eGFR was 36 mL/min. Median serum chloride at baseline was 105 mEq/L (interquartile range 102-107 mEq/L). In fully adjusted models, higher serum chloride significantly associated with greater likelihood of upper quartile of annualized eGFR decline (OR 1.09 per 1 mEq/L increase in serum chloride, p = 0.031), and greater hazard of > 30% eGFR decline (HR 1.06 per 1 mEq/L increase in serum chloride, p = 0.036).

Conclusions: In this cohort of CKD patients, higher serum chloride levels associated with increased risk of eGFR decline. Chloride may be a useful, readily available biomarker to aid in predicting CKD progression. Further studies are needed to determine if there is causality, and if so to elucidate pathophysiology and delineate possible treatment strategies.

Funding: Clinical Revenue Support

FR-PO204

Association of Serum Bicarbonate Levels with Kidney Function Decline in Patients with Polycystic Kidney Disease

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Background: Lower serum bicarbonate levels are associated with kidney disease progression in patients with chronic kidney disease. Whether serum bicarbonate levels are associated with kidney disease progression in patients with polycystic kidney disease (PKD) is unknown. We tested the hypothesis that lower bicarbonate levels are associated with kidney function decline in patients with PKD.

Methods: We included 774 patients from the HALT-PKD Study A (N=395) and B (N=379) with baseline serum bicarbonate levels and at least three measurements of estimated glomerular filtration rate (eGFR). Bicarbonate was examined as a continuous variable and in categories (≤ 24, 25-28 and >28 mEq/L, with 25-28 mEq/L as the reference group). The outcome was yearly change in slope of eGFR. Linear regression models were used to examine the association between serum bicarbonate and change in eGFR.

Results: The mean (SD) age was 43 ± 10 years. The mean (SD) serum bicarbonate and eGFR at baseline was 26.7 ± 2.4 mEq/L and 70 ± 26 ml/min/1.73m2, respectively. Participants with serum bicarbonate ≤ 24 mEq/L had lower eGFR, higher body mass index (BMI) and systolic blood pressure (SBP) than those with bicarbonate levels >24 mEq/L. In the fully adjusted model, each 1 mEq/L increase in serum bicarbonate level was associated with a 0.1 ml/min/1.73m^2 increase in annual slope of eGFR (β 0.1 ml/min/1.73m^2, 95% CI 0.002 to 0.15, p=0.04). A serum bicarbonate level ≤ 24 mEq/L was associated with a yearly decline in eGFR slope in unadjusted analysis and in partially adjusted analysis, but only trended towards significance in the fully adjusted model (p=0.09).

Conclusions: Lower serum bicarbonate levels are associated with an increased risk of decline in eGFR in patients with PKD.

Funding: Other NIH Support - NHLBI

β Estimate (95% CI)

Serum Bicarbonate mEq/L	Unadjusted	Model 1	Model 2
Per 1 mEq/L increase	0.1 (0.05 to 0.2)	0.1 (0.02 to 0.18)	0.1 (0.002 to 0.15)
≤ 24	-0.7 (-1.22 to -0.16)	-0.5 (-1.06 to -0.04)	-0.4 (-0.93 to 0.07)
25-28	REF	REF	REF
> 28	0.3 (-0.15 to 0.78)	0.2 (-0.20 to 0.69)	0.2 (-0.26 to 0.64)

Model 1: adjusted for age, gender, race, treatment randomization

Model 2: adjusted for model 1 plus smoking, cardiac history, BMI, SBP, baseline eGFR and urine albumin to creatinine ratio

FR-PO205

Association Between Changes in Pre-Transition Sodium with Post-Transition Mortality and Hospitalization Among Patients Transitioning to Dialysis

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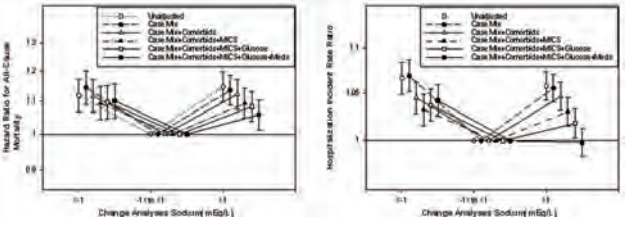
Background: Disturbances in the serum sodium metabolism are common in advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). Additionally, CKD patients transitioning to dialysis-dependent ESRD have a particularly high mortality risk within the first month of transition. Thus, we examined the relationship between pre-ESRD change in sodium and post-ESRD outcomes.

Methods: We retrospectively examined a cohort of 22,644 veterans transitioning to ESRD between 2007-2015. Patients were grouped into three categories according to their change in sodium. Changes in sodium from 6 to 3 months prior to ESRD transition were calculated by using a mixed-effects model. We explored the association between change in sodium levels, with post-ESRD transition overall all-cause mortality using Cox proportional hazard models, and hospitalization incident rate ratio (HIRR) with Poisson regression. Associations were examined across multiple levels of adjustments including case-mix variables, markers of malnutrition and inflammation, glucose and medications.

Results: Mean age of the total cohort was 67±11 years and median change in sodium level was 0.4 (-1.1,2.0) mEq/L. Both, increasing and decreasing sodium levels were associated with a higher all-cause mortality risk in the fully adjusted model (HR 1.10, 95%CI 1.05-1.15) [figure 1A]. A similar pattern was observed for HIRR across hierarchical adjustments; however the association was attenuated for increasing sodium levels in the fully adjusted model (HR 1.06 95%CI 1.01-1.10) [figure 1B].

Conclusions: Changes in pre-ESRD serum sodium are associated with post-transition death risk and HIRR. Monitoring pre-transition sodium levels may help identify patients at risk for adverse outcomes after ESRD transition.

Funding: NIDDK Support



FR-PO206

Effect of Dietary Salt Intake on Renal Outcomes in Advanced CKD Patients

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Background: The present study analyzed the effect of dietary salt intake on renal outcome for Asian CKD patients. The study is conducted on large number of CKD patients at stages G3a, G3b and G4, with long term follow-up. This study suggests the optimal amount of salt intake for advanced CKD patients.

Methods: Our data were extracted from The KoreaN cohort study for Outcome in patients With CKD (KNOW-CKD). A total of 1,409 CKD patients at stages G3a, G3b and G4, who were enrolled in the KNOW-CKD from 2011 to 2016 were included in the analysis. After excluding 413 patients with incomplete data to define 24-hour urine sodium excretion, 996 non-dialysis CKD patients were finally analyzed. Dietary salt intake, assessed by 24-hour urine sodium excretion, was divided into quartile groups. Second quartile (Q2, 6.72 ~9.14 g salt/day) was regarded as the reference group. Estimated glomerular filtration rate (eGFR) was assessed by CKD-EPI (Cr) equation based on isotope dilution mass spectrometry (IDMS)-traceable creatinine measured at a central laboratory. eGFR slope was analyzed by mixed model from the subjects who repeatedly measured the serum creatinine level more than 4 times at 6- to 12-month interval. Composite renal event is defined either as eGFR halving or as initiation of renal replacement therapy (RRT). Each component of composite renal event was also analyzed.

Results: During the mean 45.6 months of follow-up, 225 subjects developed the composite renal event. After adjustment for confounders including baseline eGFR, multiple Cox regression showed that the risk of composite renal outcomes is significantly higher in the highest quartile group (Q4, salt intake > 11.89 g/day, HR 1.86, p<0.024). Multiple linear regression showed that eGFR slope was not independently associated with daily salt intake (b=-0.02, P=0.23).

Conclusions: High salt intake, assessed by 24 hour urine sodium excretion, is associated with increased risk of CKD progression in advanced CKD.

FR-PO207

Effect of Aldosterone-Renin Level on Glomerular Filtration Rate Slope in Patients with Primary Aldosteronism: A Retrospective, Multi-Center Cohort Study

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Background: Primary aldosteronism (PA) is recognized as renin-independent aldosterone overproduction, leading to glomerular hyperfiltration. Recent studies demonstrated higher morbidity of renal damage in PA patients compared with essential hypertension. In this study, we aimed to investigate the association of renin-aldosterone levels with adrenalectomy-induced estimated glomerular filtration rate (eGFR) decrease. Furthermore, we also sought to investigate whether renin-aldosterone level affect eGFR slope in PA patients who did or didn't undergo adrenalectomy.

Methods: This is a multicenter retrospective cohort from the Japan Primary Aldosteronism Study. In a total of 2,814 patients with PA, we identified three groups, A) 487 patients who underwent adrenalectomy, B) 284 patients who did not undergo adrenalectomy with follow-up data, and C) 106 patients who underwent adrenalectomy with follow-up data. In group A, we evaluated the predictors of adrenalectomy-induced eGFR decrease for aldosterone producing adenoma by linear regression model. In groups B and C, we analyzed associations between renin-aldosterone levels and annual eGFR decline (mL/min/1.73 m^2/year) by partial spearman correlation analysis, and the association was also assessed using ordinal logistic regression models adjusted for clinical cofounders.

Results: In group A, suppressed plasma renin activity (PRA) was an independent predictor for adrenalectomy-induced eGFR decrease. In group B, suppressed PRA was significantly correlated with higher annual eGFR decline ($r = -0.13$, $P = 0.036$). Furthermore, quartiled PRA was also associated with annual eGFR decline in ordinal logiostic regression model (adjusted cumulative odds ratio = -0.087, P = 0.019), although these associations could not be identified in group C.

Conclusions: Our study demonstrated that excess aldosterone levels with renin suppression affects eGFR slope, and glomerular hyperfiltration is one of the explanation of this association. Furthermore, suppressed PRA which indicate the inadequate mineralocorticoid receptor blockade might be a marker for steeper eGFR slope in patients with PA.

Funding: Government Support - Non-U.S.

FR-PO208

High Renin-Aldosterone Ratio and Lateralization Index Are Associated with Adverse Renal Outcomes in Primary Aldosteronism Patients Who Underwent Adrenalectomy

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Background: Previous studies reported that renal impairment develop in PA patients after adrenalectomy. However, aldosterone-induced glomerular hyperfiltration can lead to masked preoperative renal dysfunction in PA patients. We aimed to elucidate risk factors for renal impairment after adrenalectomy in these subjects.

Methods: In this retrospective study, total 109 PA patients and 193 pheochromocytoma patients as control, who underwent adrenalectomy between January 2006 and November 2017 at Yonsei University Severance Hospital, were enrolled. Acute kidney injury (AKI) after adrenalectomy was defined as increase in serum creatinine >0.3 mg/dL or decrease in eGFR >30% from preoperative baseline values. Postoperative chronic kidney disease (CKD) was defined as eGFR <60mL/min/1.73m^2 for more than 3 months post-adrenalectomy. In all PA patients, adrenal vein sampling was performed to evaluate aldosterone and cortisol levels in each adrenal glands.

Results: Study patients, mean age was 49.6 years and 140(46.4%) were male. Among 109 PA patients, the incidence of AKI and CKD were 28 (25.7 %) and 34 (31.2 %). Meanwhile, among 193 pheochromocytoma patients, the incidence of AKI and CKD were 21(10.9%) and 6(3.1%). Multivariable regression analysis showed high relation of PA patients resulting in CKD compared to pheochromocytoma (Odds ratio 64.8). Univariable regression analysis identified coexisting diabetes mellitus (DM), duration of hypertension, high adrenal venous sampling (AVS) aldosterone-cortisol ratio and lateralization index as risk factors for development of postoperative CKD in PA patients. The AVS aldosterone-cortisol ratio in non-CKD and CKD patients were 84.93 and 113.86. Also lateralization index in non-CKD and CKD patients were 10.33 and 19.80.

Conclusions: Present study demonstrated incidence of CKD was more frequent in PA patients compared to pheochromocytoma patients post-adrenalectomy. Also, high AVS aldosterone-cortisol ratio and lateralization index are independent risk factors for adverse renal outcomes in PA patients post-adrenalectomy.

FR-PO209

Urinary Angiotensinogen Predicts Progressive CKD After an Episode of AKI

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Background: One of the major obstacles to prevent AKI-CKD transition is the lack of effective methods to follow and predict the ongoing kidney injury in AKI survivors.

Methods: In this study, we test the utility of urinary angiotensinogen (UAGT) for dynamically evaluating renal structural changes and predicting AKI-CKD progression by using both mild and severe bilateral renal ischemia/reperfusion injury mice. Furthermore, we evaluated the value of UAGT in predicting AKI-CKD progression in patients with acute tubular necrosis.

Results: UAGT returns to pre-ischemic levels 14 days after mild AKI followed by kidney architecture restoration, whereas sustained increase in UAGT accompanies by ongoing renal fibrosis after severe AKI. UAGT at day 14-42 correlates with renal fibrosis 84 days after AKI. For predicting fibrosis at day 84, the area under receiver operating characteristics curve of UAGT at day 14 is 0.81. Persistent elevation in UAGT correlates with sustained activation of intrarenal renin-angiotensin system (RAS). Abrogating RAS activation markedly reduced fibrosis, consistent with a role of kidney RAS activation in AKI-CKD progression. Moreover, RAS intervention early in the course of AKI-CKD transition is more beneficial than late intervention in reducing renal fibrosis. Similar changes in the UAGT were observed in patients with AKI-CKD transition.

Conclusions: Our study suggests the potential use of UAGT in motoring renal structural recovery over time and the beneficial effect of early RAS intervention in reducing fibrosis after renal function recovery from AKI.

FR-PO210

Estradiol and Renal and Cardiovascular Outcomes in Women with CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: The incidence of end-stage renal disease (ESRD) and cardiovascular disease is lower in women than men. This observation may be explained by the protective effect that endogenous estrogens may have on vascular function. We evaluated the association of estradiol levels with renal and cardiovascular outcomes in women with chronic kidney disease (CKD).

Methods: Prospective, longitudinal study of 1125 women with measured plasma 17b-estradiol by electrochemiluminescent immunoassay at the second annual CRIC visit. We used multivariable mixed-effects and Cox models to examine the association of estradiol with estimated glomerular filtration rate (eGFR) slope, incident ESRD (dialysis or transplantation), atherosclerotic events (myocardial infarction/revascularization, stroke or peripheral arterial disease) and all-cause mortality.

Results: Overall mean (SD) age was 59.6 (10.9) years, and median (IQR) estradiol level 15.8 (8.5-30.2) pg/mL. Compared with women in the highest estradiol quartile (Q4), women in the lowest quartile (Q1) were more likely to be older (63.0 vs. 50.0 years), non-Hispanic white (56.8 vs. 37.4%), and post-menopausal (96.5 vs. 44.2%); and less likely to have diabetes (36.8 vs. 45.9%) and obesity (39.6 vs. 54.1%). Mean eGFR in ml/min/1.73m^2 was higher in Q1 (46.9) compared with Q4 (45.9). Median urine protein-creatinine ratio was similar in the two quartiles (0.09 vs. 0.10). Over a median follow-up of 6.9 years, 189 women developed ESRD, 121 had an atherosclerotic event, and 165 died. In mixed effects models adjusted for relevant demographic and clinical characteristics, the difference in eGFR slope between Q1 and Q4 was 0.34 ml/min/1.73m^2/year (p=0.5). We found no significant association between estradiol (Q1 vs. Q4) and ESRD (HR 0.61, 95% CI 0.35-1.09), atherosclerotic events (HR 0.59, 95% CI 0.29-1.19) or death (HR 0.75, 95% CI 0.4-1.41). The results were unchanged in analyses stratified by menopausal status.

Conclusions: In this cohort of women with CKD, estradiol levels were not associated with renal outcomes, cardiovascular events or death.

Funding: NIDDK Support

FR-PO211

Association of Thyroid Function with Prevalence and Development of CKD

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Background: Previous cross-sectional studies indicated an association between hypothyroidism and kidney dysfunction, but few studies have investigated aboutthyroid dysfunction and chronic kidney disease (CKD), especially whether thyroid dysfunction is a risk factor for CKD development.

Methods: Using the data of annual health check-ups, we evaluated a relationship of thyroid dysfunction with CKD prevalence and development by a multivariate logistic regression analysis. In cross-sectional and longitudinal studies, 16,390 subjects and 7,609 subjects were analyzed, respectively. We categorized the subjects into four groups based on their serum thyroid-stimulating hormone (TSH) concentrations;below-normal (TSH

<0.54 mU/L), lower-normal (0.54–2.40 mU/L), higher-normal (2.40–4.26 mU/L) and above-normal (>4.26 mU/L). As covariate factors, age, gender, obesity, hypertension, dyslipidemia, hyperuricemia, diabetes mellitus, proteinuria, and hematuria were adjusted in cross-sectional study. In longitudinal study, the baseline eGFR was added to the covariate factors of the cross-sectional study.

Results: The cross-sectional study revealed a positive correlation between the TSH concentration and CKD prevalence. Compared with the lower-normal TSH group, the odds ratios (ORs) and 95% confidence intervals (CI) of CKD prevalence were 0.609 (0.452–0.821, p= 0.001) for the below-normal group, 1.492 (1.332–1.672, p<0.001) for the higher-normal group, and 1.900 (1.568–2.302, p<0.001) for the above-normal group. The longitudinal study revealed that the risk of CKD development within three years was significantly higher in the above-normal TSH group compared with the lower-normal TSH group: OR 1.578, 95% CI 1.016–2.451, p= 0.042. However, no significances of CKD development risk in the below-normal TSH group and the higher-normal TSH group were observed.

Conclusions: Our data indicated that a higher TSH concentration has a positive correlation with CKD prevalence, and that a high TSH concentration is a risk factors for CKD development. These results suggest thatthyroid function screening might be informative in patients whose eGFR declines without a clear cause, and thyroid hormone replacement therapy for hypothyroidism patients could have an effect on preventing CKD development.

FR-PO212

Thyroid Hormones and CKD in the German CKD (GCKD) Study

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Background: Clinical and translational research support a connection between kidney and thyroid function, e.g. hypothyroidism and low triiodothyronine (FT3) levels in combination with normal thyroid stimulating hormone (TSH) levels (= Euthyroid Sick Syndrome: ESS) and CKD. The relationship between these conditions and CKD progression is understudied. We evaluated the longitudinal association of TSH, free thyroxine (FT4), FT3, and thyroid diseases with a composite endpoint of renal events.

Methods: Thyroid markers were measured at baseline using standard laboratory methods. GFR was estimated using the CKD-EPI formula. Over four years of follow-up, 449 renal events occurred among 4,391 GCKD participants. Renal events included ESRD (dialysis, transplantation), acute kidney injury, or renal death abstracted from hospital records by trained personnel. Cox proportional hazard models of time to the composite outcome adjusted for age, sex, study site, smoking, BMI, history of cardiovascular disease, diabetes mellitus, and proteinuria were evaluated for continuous thyroid markers as well as for thyroid diseases (hypothyroidism: TSH>3.29, FT4≥9.8-18.8 or TSH>3.29, FT4<9.8; ESS: TSH≥0.49-3.29, FT3<3.3).

Results: Mean age was 60 years, with 59.4% males. Medians were TSH: 1.2 mIU/L, FT4: 14.3 pmol/L and FT3: 4.2 pmol/L; hypothyroidism and ESS were present in 5.0% and 5.4%. Thyroid hormone substitution was 21.0%. No association was observed for TSH and FT4, FT3 was significantly associated (HR 0.8, 95%CI 0.7-0.9). Compared to euthyroid patients, hypothyroid patients had a 1.6-fold higher risk and patients suffering from ESS had a 2.0-fold higher risk of reaching the composite endpoint (Table 1). Excluding patients on thyroid medication: the associations with FT3 and ESS remained (FT3: HR 0.7, 95%CI 0.7-0.9; ESS: HR 1.9, 95%CI 1.3-2.7), the association with hypothyroidism disappeared.

Conclusions: Lower FT3 levels, hypothyroidism and ESS were associated with a higher risk of a composite renal endpoint in a population with CKD stage 3 and at risk for thyroid dysfunction.

Funding: Government Support - Non-U.S.

Association results between the composite renal endpoints and thyroid function

	Hazard Ratio	95% Confidence Interval	p-value
FT3	0.8	0.7-0.9	<.001
Hypothyroidism	1.6	1.1-2.2	0.008
ESS	2.0	1.5-2.6	<.001

FR-PO213

A Dose Dependent Relationship Between Hypothyroidism and CKD within a Real-World Clinical Environment

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Background: Whether hypothyroidism (HT) engenders chronic kidney disease (CKD) is unknown. We sought to determine whether HT and different thyroid states are associated with CKD among a large diverse population.

Methods: A cross sectional study was performed among individuals with concurrent thyroid stimulating hormone (TSH) and creatinine measurements within Kaiser Permanente Southern California health system (1/1990-12/2017). Rates of CKD across different thyroid states were compared. Multivariable logistic regression analysis adjusted for age, sex, race, and comorbidities was performed to estimate odds ratios (ORs) for CKD by thyroid state. HT was defined as TSH>4mcIU/mL and/or receipt of thyroid hormone replacement. HT was further categorized into 1) hypothyroid state (HS): TSH>4mcIU/mL regardless of thyroid hormone replacement, and 2) attenuated-hypothyroid state (AS): TSH<4mcIU/mL and on thyroid hormone replacement. Euthyroid (ET) was defined as TSH<4mcIU/mL and on no thyroid hormone replacement. The primary outcome was CKD defined as eGFR<45mL/min/1.73m^2.

Results: A total of 378,101 individuals were identified. Among 114,872 (30.4%) meeting criteria for HT, 31,242 (27.2%) were HS and 83,630 (72.8%) were AS. Compared to ET individuals, multivariable OR (95% confidence interval) for CKD (eGFR<45mL/min/1.73m^2) were 1.59 (1.52-1.66) and 1.12 (1.08-1.16) for HS and AS respectively when compared to ET (Table 1).

Conclusions: Within a real-world clinical environment, there is a greater likelihood of CKD associated with HT. A stronger association was seen among those with HS compared to those with AS. Our findings suggest that there may be a dose dependent relationship between thyroid function and CKD. Whether treatment of hypothyroidism among CKD patients may improve and alter the course of CKD is an area warranting future investigation.

Table 1. Odds ratios of CKD (eGFR<45mL/min/1.73m^2) across each thyroid state

Thyroid State	Crude OR (95% CI)	Adjusted OR (95% CI) [1]	Adjusted OR (95% CI) [2]
Hypothyroidism	1.51 (1.47-1.55)	1.25 (1.22-1.29)	1.25 (1.21-1.29)
Hypothyroid state	2.02 (1.94-2.11)	1.56 (1.49-1.63)	1.59 (1.52-1.66)
Attenuated hypothyroid state	1.33 (1.28-1.37)	1.13 (1.10-1.17)	1.12 (1.08-1.16)
Euthyroid	Reference	Reference	Reference

[1]Adjusted for demographics including age, sex, and race

[2]Additionally adjusted for hypertension and diabetes

FR-PO214

Prevalence of CKD, Xanthine Oxidase Inhibitor Treatment, and Serum Uric Acid Control in US Adults with Gout: NHANES 2007–2014

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Background: Gout is the most common form of inflammatory arthritis, mainly caused by elevated serum uric acid (sUA). The American College of Rheumatology recommends lowering sUA to <6 mg/dL for gout patients, most commonly achieved by lifestyle changes and xanthine oxidase inhibitor (XOI) treatment. Elevated sUA is also associated with the prevalence of chronic kidney disease (CKD). This study aims to estimate the prevalence of CKD among US adults (age ≥20 years) with gout, stratified by XOI treatment status and sUA control (<6 mg/dL).

Methods: This cross-sectional study was conducted using the National Health and Nutrition Examination Survey (NHANES) 2007–2014 including patients who had ever been told by a doctor that they had gout. CKD was categorized based on 2012 Kidney Disease: Improving Global Outcomes using estimated glomerular filtration rate (eGFR; CKD-EPI equation) and urine albumin-creatinine ratio. Descriptive analyses were performed accounting for the survey's complex sampling design.

Results: Of 20,880 participants (representing an estimated 207 M US non-institutionalized adults), 899 (representing 7.8 M) had gout. Among the gout population, 4.9 M (63%) had uncontrolled sUA, 2.8 M (36%) had moderate or higher risk of CKD, and 2.2 M (28%) were taking an XOI. Of the gout population who were not taking an XOI, the majority were uncontrolled regardless of CKD risk (Table).

Conclusions: Among gout patients, more than one third have moderate or higher risk of CKD, and less than one third are currently treated with XOI and of those, 43% have uncontrolled sUA. Therefore, gout patients may benefit from sUA-lowering treatment options that are consistent with their renal function.

Funding: Commercial Support - Ironwood Pharmaceuticals, Inc.

Table. Prevalence of CKD by eGFR, albuminuria, and sUA control among US adults with gout, XOI-treated and untreated

eGFR	Subtotal n (%)	Gout patients currently taking XOI						Subtotal n (%)	Gout patients not currently taking XOI					
		A1 (%)		A2 (%)		A3 (%)			A1 (%)		A2 (%)		A3 (%)	
		sUA <6mg/dl	sUA ≥6mg/dl	sUA <6mg/dl	sUA ≥6mg/dl	sUA <6mg/dl	sUA ≥6mg/dl		sUA <6mg/dl	sUA ≥6mg/dl	sUA <6mg/dl	sUA ≥6mg/dl	sUA <6mg/dl	sUA ≥6mg/dl
G1	453 (20.5%)	10.7%	6.3%	1.4%	1.5%	0.5%	N/A	1,823 (32.8%)	10.0%	16.8%	1.9%	2.8%	0.2%	1.1%
G2	1,034 (46.7%)	23.2%	17.5%	3.8%	1.0%	0.2%	1.0%	2,607 (46.9%)	11.8%	29.2%	1.6%	3.7%	0.2%	1.4%
G3a	397 (17.9%)	5.7%	4.1%	3.6%	2.1%	2.0%	0.6%	677 (12.2%)	1.6%	8.0%	0.5%	1.5%	0.2%	0.8%
G3b	194 (8.8%)	1.9%	1.4%	3.8%	1.2%	1.3%	2.6%	317 (5.7%)	0.4%	2.3%	0.4%	2.3%	N/A	0.8%
G4	136 (6.2%)	0.9%	1.4%	0.8%	0.8%	N/A	1.5%	109 (2.0%)	N/A	0.7%	N/A	0.5%	N/A	0.8%
G5	29 (0.9%)	N/A	N/A	N/A	0.6%	N/A	0.2%	22 (0.4%)	N/A	N/A	0.1%	N/A	0.1%	0.1%
Total	2,212 (100%)	42.3%	30.7%	11.0%	7.3%	4.0%	4.8%	5,555 (100%)	23.8%	56.0%	4.5%	10.9%	0.9%	4.0%

Note: n=population estimate in 1000s; eGFR=Estimated glomerular filtration rate;
G1= eGFR ≥90 ml/min/1.73 sqm (Normal or high GFR);
G2= eGFR 60-89 ml/min/1.73 sqm (Mildly decreased GFR);
G3a= eGFR 45-59 ml/min/1.73 sqm (Mildly to moderately decreased GFR);
G3b= eGFR 30-44 ml/min/1.73 sqm (Moderately to severely decreased GFR);
G4= eGFR 15-29 ml/min/1.73 sqm (Severely decreased GFR);
G5= eGFR <15 ml/min/1.73 sqm (Kidney failure GFR);
A1= Albumin-creatinine ratio <30 mg/g (Normal to mildly increased albuminuria);
A2= Albumin-creatinine ratio 30-300 mg/g (Moderately increased albuminuria);
A3= Albumin-creatinine ratio >300 mg/g (Severely increased albuminuria);
= low risk of CKD; = moderately increased risk of CKD; = high risk of CKD; = very high risk of CKD

FR-PO215

Urate-Lowering Therapy for Asymptomatic Hyperuricemia in Patients with CKD: Controversial Role of Renal Outcome

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Background: Because serum uric acid increases as the glomerular filtration rate (GFR) falls, hyperuricemia has also been associated with chronic kidney disease (CKD). Although there are plausible evidences that hyperuricemia represents a risk factor for the progression of CKD, causal role of uric acid is still controversy in CKD patients with asymptomatic hyperuricemia.

Methods: We performed a retrospective single center study, enrolling 935 asymptomatic hyperuricemia patients with stage 3 - 4 CKD, between 2006 and 2018. By using propensity score matching, we matched 290 patients with and without urate-lowering therapy pairs from 935 patients. CKD progression was defined as a >30% reduction in GFR over 2 years. The changes in GFR over time compared between patients with and without urate-lowering therapy using a linear mixed model.

Results: In matched patients, the mean age was 63.2 ± 12.7 years, and 561 patients 60% was diabetic nephropathy. Mean estimated glomerular filtration rate (eGFR) was 44 ± 11 ml/min/1.73 m^2. Serum uric acid level was significantly higher in treatment group 8 ± 2 vs 12 ± 3 mg/dL). During the mean follow-up of 120 ± 48 months, the proportion of CKD progression was not different between treatment group and no treatment group (41.5% vs. 39.5%, p = 0.34). In addition, the overall rate of decline in GFR was also comparable between two group (p = 0.45).

Conclusions: Uric acid-lowering therapy may be controversy in delaying the progression of CKD. Therefore, further randomized controlled trials should be performed to confirm the effect of urate-lowering therapy on the progression of CKD.

FR-PO216

Stage of CKD Does Not Affect the Velocity of Tophus Reduction in Patients with Chronic Refractory Gout Treated with Pegloticase

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Background: Impaired renal function is a recognized comorbidity of gout and gouty tophi may be more frequent in those with renal dysfunction. It is not known however, whether the velocity of resolution of tophi in response to urate lowering therapy is affected by renal insufficiency.

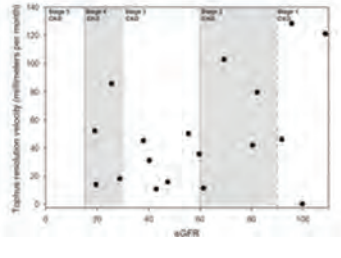
Methods: This analysis used results from two 6-month randomized controlled trials of pegloticase in patients with chronic refractory gout to address this issue. The velocity of tophus resolution was determined in 18 patients with chronic gout refractory to oral urate lowering therapy who responded to pegloticase administered at a dose of 8 mg every 2 weeks (q2w) with sustained serum urate reductions (<6 mg/dL) over 6 months. eGFR was determined at baseline and after 3 and 6 months of treatment. Tophi were photographed at baseline, 3, 4.5, and 6 months and measured using Computer-Assisted Photographic Evaluation technology. At baseline, the mean area of photographed tophi was 585.8 mm^2.

Results: Complete resolution of all tophi photographed was achieved by 34.8% of the patients. Using linear regression analysis, the velocity of tophus resolution for all the patients was calculated to be 60.1 mm^2 per month. There was no significant relationship between baseline eGFR and velocity of tophus resolution (p=0.5). In addition, there were no significant differences in the velocity of tophus resolution for patients with Stage 1 chronic kidney disease (CKD) vs Stage 2 CKD (P=0.7), Stage 3 CKD (P=0.9), or Stage 4 CKD (P=0.7).

Conclusions: The results from this analysis thus indicate that renal impairment does not compromise the ability of pegloticase to resolve tophi rapidly in patients who respond with sustained reductions in serum urate.

Funding: Commercial Support - Horizon Pharma

Relationship between baseline eGFR and velocity of tophus reduction in patients with chronic refractory gout who were biochemical responders to pegloticase (8 mg, q2w)



FR-PO217

Association of Renal Dysfunction and Development of Tophi in Subjects with Chronic Refractory Gout

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Background: Many, but not all patients with chronic gout develop tophi, and the factors that govern tophus formation are not fully understood. Several studies have suggested impairment of renal function increases the risk for development of tophi, but others have not.

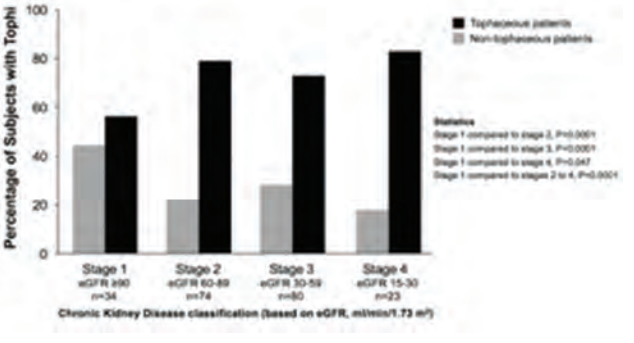
Methods: This analysis addressed the relationship between estimated glomerular filtration rate (eGFR) and the presence of tophi in patients with chronic refractory gout, as well as effects of tophus resolution on eGFR using results from two randomized controlled trials of pegloticase in chronic gout patients.

Results: Overall, 73% of the 212 subjects in these trials had clinically apparent tophi at baseline and 27% did not. Subjects with tophi were significantly older than those without tophi (56.7 vs 51.9 years, P=0.034) and had a significantly longer disease duration (16.3 vs 11.7 years, P=0.0072). Subjects with tophi also had a significantly lower eGFR than those without tophi (59.8 vs 67.9 mL/min/1.73 m^2, P=0.0495). Subjects with advanced renal disease were also more likely to have tophi. Persistent serum urate lowering and resolution of tophi in subjects treated with pegloticase had no significant effect on eGFR despite a significant decrease in the urinary uric acid:creatinine ratio.

Conclusions: These results indicate that chronic refractory gout patients may present with or without clinically apparent tophi and that there is a significant association between the presence of renal dysfunction measured by eGFR and the frequency with which chronic refractory gout patients manifested tophi. However, persistent serum urate lowering and tophus resolution had no significant effect on eGFR over the period of observation in this group of subjects.

Funding: Commercial Support - Horizon Pharma

Frequency of tophi in subjects with different CKD categories of renal function



FR-PO218

Evaluation of the Effects of Allopurinol on Metabolic Acidosis in Patients with CKD

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Background: Chronic kidney disease(CKD) is a disabling disease with multiple complications. Increased serum level of uric acid due to glomerular filtration rate (GFR) impairment is an importance and the lack of a similar study In Iran, this study was designed to evaluate the effect of allopurinol on metabolic acidosis in patients with renal failure.

Methods: In this randomised controlled trial (RCT) study, 50 patientswithCKDstage II-IV, who referred to Ghayem Hospital, were selected and randomly divided into two equal groups of 25 subjects. In addition to standard treatments, the intervention group received 100 mg allopurinol tablet for 3 months and the control group received placebo. Demographic data were obtained from each subject. Serum uric acid level, creatinine, pH blood and bicarbonate levels were obtained at the initiation of treatment and at the end of the third month.

Results: The mean age of subjects was 54.04±12.62 years. The most common cause of CKD was Diabetes Mellitus (36.0%). Allopurinol administration resulted in a significant increase bicarbonate and PH(p<0.001 each) compared to control group. A significant reduction in uric acid (p<0.05) and increase in GFR (p<0.05) was observed in both groups.

Conclusions: Allopurinol may ameliorate metabolic acidosis, glomerular filtration and uric acid in patients with CKD

FR-PO219

Post-Discharge Readmission Outcomes Following Hyperkalemia-Related Hospitalization

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Background: The objective of this study was to compare post-discharge outcomes, including hospital readmission rates, lengths of stay (LOS) per readmission, and total inpatient days, between hospitalizations in patients with and without hyperkalemia (HK).

Methods: Adults with available potassium lab results and at least one hospitalization were identified from a large US claims database (1/1/2010-12/31/2014). Hospitalizations with an HK diagnosis (ICD-9 276.7) were defined as case hospitalizations (cases), and hospitalizations from patients without HK (no HK diagnosis, no potassium lab tests above 5.0 mEq/L, and no sodium polystyrene sulfonate use) were defined as control hospitalizations (controls). Cases and controls were required to have continuous enrollment from 6 months prior to admission to 12 months after discharge from the hospitalization. Controls were matched 1:1 to cases on age, chronic kidney disease (CKD) stage, dialysis treatment, heart failure (HF), renin-angiotensin-aldosterone system inhibitor (RAASi) use, major diagnostic categories, and selected diagnosis-related groups. Readmission rates, LOS per readmission, and total inpatient days during the 1-year post-discharge period were assessed using Wilcoxon signed-rank and McNemar tests. Analysis was repeated in patients with CKD and/or HF.

Results: A total of 5,377 hospitalizations with HK (cases) were matched to hospitalizations without HK (controls). Compared with controls, cases had higher rates of readmission (30-day: 12.5% vs. 8.4%; 60-day: 18.3% vs. 12.7%; 90-day: 24.3% vs. 16.8%). Cases also had longer LOS per readmission (8.1 vs. 7.1 days) and more total inpatient days (10.5 vs. 5.8 days) during the 1-year post-discharge period (all p<0.001). In patients with CKD and/or HF, cases had higher rates of readmission (30-day: 13.8% vs. 9.4%, 60-day: 19.8% vs. 14.3%, 90-day: 26.5% vs. 19.2%), longer LOS per readmission (8.4 vs. 7.4 days), and more total inpatient days (12.4 vs. 7.2 days) during the 1-year post-discharge period compared with controls (all p<0.001).

Conclusions: Post-discharge, hyperkalemia-related hospitalizations were associated with higher readmission rates, longer lengths of stay per readmission, and higher total inpatient days.

Funding: Commercial Support - AstraZeneca

FR-PO220

What Characterizes the Patients Who Develop Repeated or Persistent Hyperkalemia? A Population-Based Laboratory Study of Potassium Trajectories in Patients with CKD

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Background: Hyperkalemia (HK) (defined as blood potassium (K^+) >5.0 mmol/L) is common among patients with chronic kidney disease (CKD) and associated with adverse outcomes. Little is known about the characteristics of patients with repeated and persistent HK.

Methods: Observational laboratory study of all patients with CKD in Northern Denmark, 2000-2012. For all CKD patients with an incident HK event, we examined K^+ trajectories over 6 months. We described patient characteristics associated with persistent HK (2 or more elevated K^+ tests >5.0 mmol/L with ≤1 normal K^+ test in between) and repeated HK (2 or more elevated K^+ tests separated by ≥2 normal K^+ tests).

Results: In 157,283 patients with CKD (median age 73 years, 59% females, median number of annual K+ tests =4), 28% (n=43,845) had a subsequent HK event detected. Within 6 months after the first HK, 29% had died, 45% had no additional high K+ value, while 26% (n=11,390) fell into persistent or repeated HK pattern. FIGURE shows K+ trajectories for patients with persistent (A:2 high K+ tests, n=3,936; B:3 high tests, n= 1,236; C:≥4 high tests, n=974) or repeated HK (D, n=5,244). Important baseline predictors for persistent or repeated HK include low eGFR (prevalence ratio (PR)=2.40 (95% CI 1.91-3.01) for eGFR <15), severity of first HK event (PR=3.98 (95% CI 3.05-5.18) for K+ 6.0-6.5 mmol/L), and use of ACE-inhibitors (PR=1.32 (95% CI 1.23-1.41)) or spironolactone (PR=1.59 (95% CI 1.43-1.78)).

Conclusions: Repeated HK and persistently elevated K+ levels are common in CKD patients. The use of readily identifiable clinical predictors can help identify patients at highest risk, who can benefit most from effective K+ management.

Funding: Commercial Support - AstraZeneca

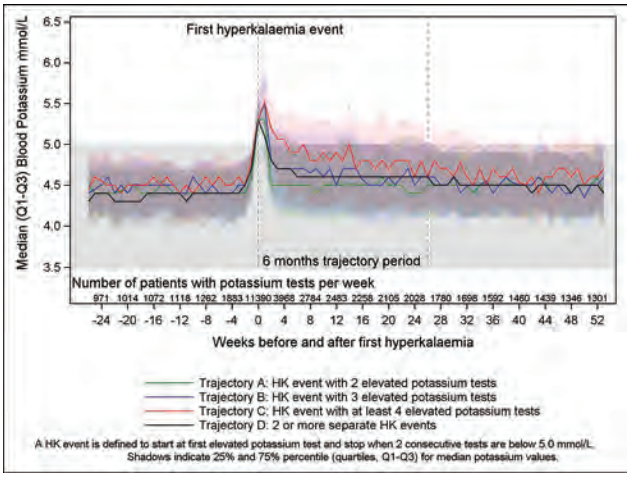

FIGURE. Median K+ before and after a first HK event in 11,390 CKD patients with persistent or repeated HK trajectories over 6 months

FR-PO221

Assessing the Impact of Hyperkalemia on Patient-Reported Quality of Life: A Global Analysis of the KDQOL-36 in a Real-World CKD Patient Population

Susan Grandy,[1] James Jackson,[2] Lei Qin,[1] Rebecca Moon,[2] Megan Scott,[2] Eirini Palaka.[3] *[1]Astrazeneca, Gaithersburg, MD; [2]Adelphi Real World, Macclesfield, United Kingdom; [3]AstraZeneca, Cambridge, United Kingdom.*

Background: Hyperkalemia (HK), defined as abnormally high serum potassium (K^+>5mmol/L), is common in patients with chronic kidney disease (CKD) because of the effects of kidney disease on K^+ homeostasis. Management of HK includes strict adherence to a low K^+ diet which can be unhealthy and an added burden to patients. Evidence describing the impact of HK on patient reported outcomes is limited. The objective of this analysis was to assess the impact of HK on the Quality of Life (QoL) of non-dialysis (ND) CKD patients using the Kidney Disease Quality of Life Instrument (KDQOL), a validated CKD-specific questionnaire.

Methods: Data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes were pooled to create a cross-sectional dataset of unique patients, including global data from physicians and their ND CKD patients across EU-5, China and USA. Patients completed the KDQOL, a disease specific self-report measure targeted at the particular concerns of individuals with kidney disease. CKD ND patients with HK (K^+ >5.0 mmol/L) and without HK (i.e. those with normal K^+ levels 3.5-5.0 mmol/L) were stratified to study the association between HK and QoL. Multivariate analysis was used to identify the association between HK and QoL, adjusting for age, sex, eGFR levels, and presence of heart failure and diabetes.

Results: Results of the KDQOL analysis showed that ND patients with HK (n=216) had significantly lower mean QoL scores compared to those without HK (n=933) for 3 of the 5 KDQOL domains: burden of kidney disease (54.9 vs. 60.8; p=0.011), effects of kidney disease (69.6 vs. 76.1; p=<0.001) and physical health (39.1 vs. 41.6; p=0.001). Additionally, patients with HK had numerically lower scores for the remaining 2 KDQOL domains compared to patients without HK, namely symptoms/problems (80.1 vs. 82.1; p=0.134) and mental health (45.3 vs. 46.8; p=0.073).

Conclusions: This study highlights the negative impact of HK on the quality of life of CKD ND patients globally. HK contributes to the overall CKD disease burden, leading to further decrements in quality of life compared to patients without HK. Effective management of hyperkalemia may improve quality of life in this patient population.

Funding: Commercial Support - AstraZeneca

FR-PO222

Quality of Life in CKD Patients with Hyperkalemia in the US: Results from the KDQOL-36

Susan Grandy,[1] James Jackson,[2] Lei Qin,[1] Rebecca Moon,[2] Megan Scott,[2] Eirini Palaka.[3] *[1]Astrazeneca, Gaithersburg, MD; [2]Adelphi Real World, Macclesfield, United Kingdom; [3]AstraZeneca, Cambridge, United Kingdom.*

Background: Hyperkalemia (HK), defined as abnormally high serum potassium (K^+ >5mmol/L), is common among patients with Chronic Kidney Disease (CKD) and is associated with increased risk of mortality and hospitalization. Over 6% of CKD patients in the US have HK, four times the corresponding rates in the general US population. The Kidney Disease Quality of Life Instrument (KDQOL) is a 36-item survey specifically targeting concerns of individuals with CKD, to identify the disease burden on quality of life (QoL). Limited real-world data exist on the impact of HK on the QoL of CKD patients in the US. While low K^+ diet is key for HK management, the established poor dietary habits of the US population together with the lack of universal health coverage and limited social support increase the importance of better understanding the impact of HK on the QoL of US CKD patients.

Methods: Real-world data of unique CKD non-dialysis (ND) patients from the 2015 and 2018 US Adelphi CKD Disease Specific Programmes were pooled and analyzed. Patients completed the KDQOL questionnaire, while physicians reported information on patient demographics, disease characteristics and comorbidities. Patients with and without HK (normal K^+ 3.5-5.0 mmol/L) were compared. The association between HK and QoL was measured using multivariate analysis adjusting for age, sex, eGFR level, and presence of heart failure and diabetes.

Results: Based on the results from US CKD ND patients with HK (n=64) and without HK (n=312), HK patients had significantly lower QoL scores across four of the five KDQOL domains, compared to those without HK: burden of kidney disease (54.4 vs. 66.0; p=0.023), effects of kidney disease (69.7 vs. 80.2; p=0.010), physical health (38.7 vs. 42.2; p=0.020) and mental health (44.8 vs. 48.9; p=0.018). US patients with HK also had a lower score on the fifth symptoms/problems domain compared to those without HK, without this difference being statistically significant (83.2 vs. 85.2; p=0.455).

Conclusions: CKD ND patients with HK in the US experienced a greater negative impact on their QoL compared to patients without HK, as they experienced higher disease burden, and a greater physical and mental impact. Effective management of K^+ levels has the potential to maintain or improve QoL in this patient population.

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FR-PO223

Secondary Hyperparathyroidism Is Associated with Erythropoietin Deficiency and Endogenous Erythropoietin Resistance in Patients with CKD

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Background: Erythropoietin (EPO) deficiency and resistance to endogenous EPO is an important pathophysiological feature in anemia of chronic kidney disease (CKD). Secondary hyperparathyroidism is known to contribute to anemia of CKD. We aimed to investigate the associations between parathyroid hormone (PTH) and anemia, EPO deficiency, and endogenous EPO resistance in patients with CKD.

Methods: This study included 409 patients with CKD [glomerular filtration rate (GFR) < 60 ml/min/1.73m^2] who were not on dialysis therapy. Patients on exogenous EPO therapy and patients with iron deficiencies were excluded. Endogenous EPO resistance was assessed by calculating the ratio of endogenous EPO to hemoglobin (Hb) (endogenous EPO/Hb ratio). The associations of Hb level, endogenous EPO level, and the endogenous EPO/Hb ratio with clinical and laboratory variables were investigated by univariate and multivariate analyses.

Results: In univariate analysis, intact PTH level was correlated negatively with the Hb level (r = -0.403, P < 0.001) and endogenous EPO level (r = -0.108, P = 0.029). The intact PTH level was correlated positively with the endogenous EPO/Hb ratio (r = 0.139, P = 0.005). Multiple regression analysis revealed that the intact PTH level remained significantly associated with the Hb level (β = -0.136, P = 0.006), endogenous EPO level (β = -0.148, P = 0.016), and the endogenous EPO/Hb ratio (β = 0.131, P = 0.021), even after adjusting for other confounding factors, including the levels of the inflammatory marker C-reactive protein.

Conclusions: Secondary hyperparathyroidism exhibited significant associations with anemia, EPO deficiency, and endogenous EPO resistance in CKD patients. These associations were independent of inflammation status.

FR-PO224

Fibroblast Growth Factor 23 and Adiposity in Patients with CKD Stages 3 and 4

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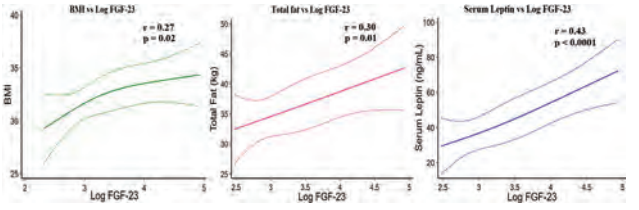
Background: Adiposity has been associated with higher Fibroblast Growth Factor 23 (FGF23) levels in patients with normal kidney function. If this relationship is observed in patients with moderate chronic kidney disease (CKD) is unknown. We investigated the relationship between adiposity and FGF23 in a cohort of patients with stages 3-4 CKD.

Methods: This was a cross-sectional investigation of 71 CKD patients who underwent body composition and anthropometric assessments. Dual energy x-ray absorptiometry (DEXA) scans were used to measure total fat mass and body mass index (BMI) was computed using baseline weight and height measurements. Biomarkers included estimated glomerular filtration rate (eGFR), serum leptin, FGF23, high sensitivity C-reactive protein (hsCRP) and serum lipids. Ordinary least squares regression with the sandwich estimator of variance was used to investigate the relationship between FGF23 and measures of adiposity (BMI, total fat mass) and the pro-atherogenic adipocytokine leptin. Log-transformation was performed for variables with considerable skewness.

Results: Mean (SD) age was 66 (12) years, 26% of participants were female, 23% were African-American. Median eGFR was 46.9 ml/min/1.73m2 (IQR 41.9, 52.8), median BMI was 31(IQR: 27, 35). Log FGF23 had a significant positive correlation with BMI (r = 0.27, p = 0.02), total fat mass (r = 0.30, p = 0.01) and serum leptin (r = 0.43, p < 0.0001). After full adjustment for age, sex, race, eGFR, log hsCRP, log HDL and log triglycerides, a 50% increase in FGF-23 was associated with 1 unit [95% I: 0.1, 1.9; p = 0.03] increase in BMI, 2.5 kgs [95% CI: 0.2, 4.8; p = 0.03] increase in total fat mass and a 6.7 ng/mL [95% CI: 1.0, 12.4; p = 0.02] increase in serum leptin.

Conclusions: We report in patients with stage 3 & 4 CKD a cross-sectional association between higher FGF23 and higher adiposity (BMI, total fat mass and the pro-atherogenic adipocytokine, leptin). The causes and the implications of these associations need to be further investigated. Particularly in bone and vascular health.

Funding: Veterans Affairs Support



FR-PO225

Elevated Serum Osteoprotegerin Associates with Microbiota-Derived Phenylacetylglutamine and Vascular Calcification in CKD

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Background: Increasing evidence indicate that a complex interplay between reduced renal function, altered bone metabolism and increased levels of metabolites produced by the gut microbiota drives vascular calcification (VC) which causes considerable morbidity and mortality in patients with chronic kidney disease (CKD). Here we investigated if osteoprotegerin (OPG), an osteocyte-derived inhibitor of bone formation, is associated with phenylacetylglutamine (PAG), a gut microbial metabolite, and VC in CKD stage 5 patients.

Methods: In 112 living donor kidney transplant (LD-Rtx) recipients (63% males; median age 47 years), associations between severity of VC (score 0 to 3; evaluated by histological examination of epigastric artery specimens collected at LD-Rtx), and serum OPG and PAG were investigated. Patients with VC grade 0 (n=17) and 1 (n=51) were combined into Group 1, representing no or minimal VC (n=68), and those having moderate (score 2; n= 29) or extensive (score 3; n= 15) VC were combined into Group 2 (n=44).

Results: Group 2 patients had significantly higher OPG levels than Group 1 patients with no or minimal VC. In Spearman's rank correlations, OPG was positively associated with age, bone specific alkaline phosphatase, PAG, high-sensitive C-reactive protein and percentage calcification. Multivariate regression analyses showed that after adjustments for age, sex, diabetes and smoking habits, 1-SD higher level of PAG (β=0.35 P<0.001) was independently associated with 1-SD higher OPG level (adjusted r^2=0.44). OPG was significantly associated with VC score after adjustments for age, sex, diabetes, smoking habits and PAG (OR [95% CI]: 2.05 [1.08, 3.89]; p=0.03).

Conclusions: While gut microbiome assessed by PAG is closely related with bone metabolism as assessed by OPG in CKD patients, serum OPG is a strong predictor of biopsy-verified VC, independent of gut microbiota status as assessed by PAG.

FR-PO226

Serum Procalcitonin Level May Predict Secondary Hyperparathyroidism Resistance Among CKD Patients

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Background: Secondary hyperparathyroidism (SHPT) is common among CKD patients stage 3-5D. Frequently, patients reveal resistance to the conventional medications including vitamin D and oral cinacalcet. Inflammation was postulated as a potential cause of such resistance. The aim of this study is to assess if serum procalcitonin (PCT) level may be useful to predict SHPT resistance among CKD patients.

Methods: In this prospective study, 516 CKD patients attending nephrology clinic at a tertiary hospital were recruited. Inclusion criteria included: (1) eGFR < 60 ml/min for more than 3 months or patients were on regular hemodialysis. (2) serum intact parathormone (iPTH) level ≥ 300 pg/ml. Exclusion criteria included: (1) patients who had a kidney transplant, (2) patients had an evident infection at the time of the initial visit, and (3) patient was already receiving either vitamin D supplementation or oral cinacalcet. PCT and C reactive protein (CRP) levels were measured for each patient during the initial visit. iPTH was measured monthly. Resistance was defined as less than 30% reduction in initial iPTH level despite three months of maximally tolerated cinacalcet and vitamin D therapy. Multiple regression analysis and ROC curve tests were performed to assess the causality between PCT level and SHPT resistance.

Results: 482 patients completed the study. The mean age of patients was 61.4 ± 11.2 years. Female patients were 49%. Mean eGFR was 38 ± 17 ml/min/1.73 m^2. Mean baseline iPTH was 845 ± 314 pg/mL. Serum PCT level was significantly higher among patients with resistance to SHPT therapy (mean PCT was 0.90 ± 0.28 vs 0.42±0.16 ng/mL; 95% CI: -0.5316, -0.4284; p .001). The area under the ROC curve for PCT, CRP, and age were 0.89, 0.71 and 0.65 respectively.

Conclusions: Serum procalcitonin level may be useful to predict resistance to therapy for secondary hyperparathyroidism among chronic kidney disease patients.

FR-PO227

The Oxidized Form of Serum Albumin, Non-Mercaptalbumin Is Significantly Associated with Renal Function and Anemia in CKD Patients

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Background: Human mercaptalbumin (HMA; reduced form of serum albumin) and non-mercaptalbumin (HNA; oxdized form of serum albumin) have been known to be an indicator for evaluating oxidative stress in the systemic circulation, including patients with end stage renal disease.

Methods: We investigated factors associated with fraction of HNA (f(HNA)) in 112 pre-dialysis CKD patients (age 63.6±14.0 years; 59 males and 53 females), using a newly established, anion-exchange column packed with a hydrophilic polyvinyl alcohol gel, along with high performance liquid chromatography.

Results: The means f(HNA) in CKD patients was 30.0 ±6.13%, whose value was higher than that reported in healthy subjects f(HNA) 25.1±3.0%. Age, estimated glomerular filtration rate (eGFR), blood urea nitrogen, hemoglobin, sodium-chloride, phosphate, intact parathyroid hormone (PTH), and fibroblast growth factor (FGF)-23 levels correlated significantly with plasma f(HNA) (ρ=0.302, $p<0.001$;ρ=-0.436, $p<0.001$; ρ=0.457, $p<0.001$;ρ=-0.382, $p<0.001$;ρ=-0.324, $p<0.001$;ρ=0.265, p=0.001; ρ= 0.367, p=0.001;ρ= 0.419, $p<0.001$;respectively). In multiple regression analyses, age (β=0.200, p=0.014), eGFR (β=-0.238, p=0.009), hemoglobin (β=- 0.346, p<0.001), and ferritin (β=0.200, p=0.019), were associated significantly and independently with f(HNA) (R^2=0.356, p<0.001). In addition, concerning factors related to CKD-mineral and bone disorder(CKD-MBD), intact-PTH (β=0.218, p=0.049) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels (β=-0.178,p<0.001) were significantly and independently associated with serum f(HNA) (R^2=0.339, p<0.001), although fibroblast growth factor-23 were not.

Conclusions: We demonstrated that impaired renal function and renal anemia were strongly associated with oxidization of serum albumin. We also demonstrated that, intact PTH and $1,25(OH)_2D$ are significant factors associated with the redox states of serum albumin. Our findings suggest the importance of management of hemoglobin and ferritin levels, and appropriate control of CKD-MBD factors in regard to better redox state of albumin in CKD patients.

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FR-PO228

Bortezomib in the Treatment of Kidney Light Chain Amyloidosis

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Background: Light-chain amyloidosis is a clonal plasma cell disorder. It can cause kidney injury including proteinuria and abnormal renal function. This study is in order to evaluate the efficacy of Bortezomib in the treatment of Kidney Light Chain Amyloidosis

Methods: This is a retrospective study. All participants were recruited from Department of Nephropathy, Shanghai Ruijin Hospital between February 2013 to February 2018. The diagnosis of Kidney light chain amyloidosis(KAL) was based on kidney biopsy. All the patients were given BD therapy per month (Bortezomib 1.3mg/m2 BSA on day 1,4,8,11, Dex on day 1-4 and 8-11). The primary outcome was kidney complete response(CR) defined as at least 50% reduction in 24-hour urinary protein(24hUP) compared to baseline, plus the decrease of estimated GFR(calculated by EPI-Creatinine equation) was less than 25% compared to baseline. Partial response(PR) was defined as 24hUP reduction within 20%~50%. Non response was defined as 24hUP reduction less than 20% or the decrease of eGFR more than or equal to 25%.

Results: Thirty patients were diagnosed as KAL in this study. Of all the patients, 18 (60%) were male and mean age was 56 (35-69) years old. Totally, 24 (80%) patients were λ type KAL, 6 (20%) patients were κ type KAL. Nineteen patients (63.3%) were CKD stage 1, 8 patients (26.7%) were CKD stage 2 and 3 patients (10%) were CKD stage 3~5. The mean frequency of BD therapy was 3.8 (1-12) times and the mean follow-up period was 8.21 (3-28) months after advanced remission or treatment. Finally, 12 of 30 patients (40%) reached CR,4 reached PR (13%). After BD therapy, the 24hUP was significantly decreased compared to baseline (3.6 vs 5.2 g/24h, P<0.05), serum albumin was increased (23.9 vs 28.13g/L, P<0.005)and there was no decrease of eGFR(83.9 vs 87.9, p=0.228).(Figure 1)

Conclusions: Bortezomib was effective in the treatment of patients with KAL and the renal remission rate of our study was 53%.

	Before treatment	After treatment	P value
mean 24hUP	5214.0	3585.9	0.012
(mg/24h)	(12156-517)	(9018-253)	
mean serum albumin	23.9	28.1	0.005
(g/L)	(36-10)	(49-12)	
mean serum creatinine	90.5	93.2	0.252
(μmol/L)	(412-45)	(598-44)	
EPI-GFR	83.9	87.9	0.228
(ml/min·1.73m²)	(124.0-13.0)	(134.9-8.4)	

Bortezomib in the Treatment of Kidney Light Chain Amyloidosis

FR-PO229

Treatment of Multiple Myeloma Related Kidney Disease by Bortezomib

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Background: Only few evaluate the efficacy and safety of bortezomib in the treatment of multiple myeloma(MM) related kidney disease.

Methods: It is a retrospective cohort study. All the eligible patients were enrolled from Department of Nephropathy, Shanghai Ruijin Hospital between Sep 2009 and Aug 2017. Patients diagnosed MM with renal insufficiency were enrolled while patients with relapsed MM were excluded. All the subjects were given a bortezomib based treatment, including PD(bortezomib, dexamethasone)/PAD(bortezomib, adriamycin, dexamethasone)/ PCD(bortezomib, cyclophosphamide, dexamethasone). The primary outcome was clinical remission. Definition of hematological remission and renal response were according to the criterion made by IMWG(International Myeloma Working Group).

Results: Totally, 53 patients with MM related kidney diseases were recruited in this study. Of the 53 cases, 34M & 19F, mean age 59(35-86)y/o, median urinary protein 4.2g/24h, serum albumin 30g/L, EPI-eGFR 19ml/min, 10 cases received dialysis therapy. The MM type included 11 IgA,5 IgD,16 IgG,21 Light chain. Of 28 cases with renal biopsy, 6(21%)amyloidosis, 14(50%) cast nephropathy, 6(21%) tubulointerstitial lesions, 2(8%) light chain deposition disease(LCDD). The medium follow-up time was 7(3-47)months. Of 32 cases that taken at least 4 cycles of bortezomib treatment, hematological remission showed that 14(44%) achieved CR,9(28%)achieved PR,7(22%)were stable, 2(6%) were relapsed;23/32 baseline eGFR<60ml/min, renal response showed that 5(22%) achieved CR,1(4%)achieved PR,12(52%)achieved MR,5(22%)were stable. Of 10 cases that dialysis dependent, 5 got rid of dialysis. After treatment, patients showed improvement in clinical features.(Fig 1&2)

Conclusions: Bortezomib can significantly reduce urinary protein, increase EPI-eGFR and improve prognosis of MM related kidney disease, which means making patients benefit.

Table1 Efficiency after 4 cycles of treatment(n=32)

Clinical features	Baseline	Posttreatment	P value
Serum Albumin(g/L)	32(19-42)	38(24-45)	0.004
Urinary protein(mg/24h)	3184(107-15035)	265(85-5005)	0.000
EPI-eGFR(ml/min·1.73m²)	25.3(4-127)	47.5(8-110)	0.000
Hemoglobin(g/L)	88(55-130)	117(90-151)	0.000

Table2 Efficiency after 1-3 cycles of treatment(n=21)

Clinical features	Baseline	Posttreatment	P value
Serum Albumin(g/L)	29(14-41)	36(18-43)	0.013
Urinary protein(mg/24h)	5197(1360-14346)	1533(125-10712)	0.203
EPI-eGFR(ml/min·1.73m²)	15(5-100)	15(7-93)	0.826
Hemoglobin(g/L)	84（51-140）	94（54-141）	0.433

FR-PO230

Direct Oral Anticoagulants vs Warfarin Across CKD Stages: Mortality Outcomes in US Veterans

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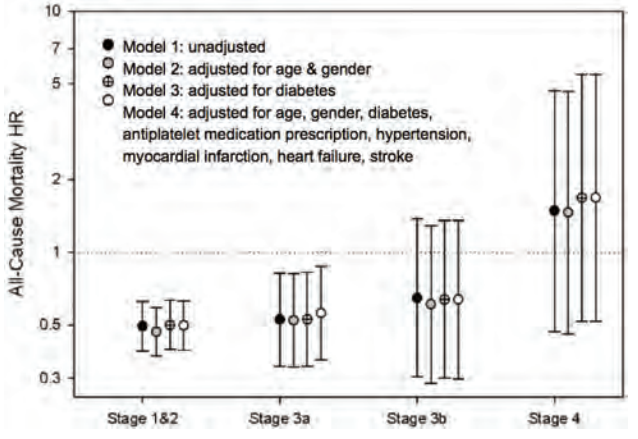
Background: For over 50 years warfarin was the only oral anticoagulant available and was shown to prevent stroke and improve survival in the general population. However, evidence to support use of anticoagulation in patients with advanced CKD has been controversial. Direct Oral Anticoagulants (DOACs) became available in the past decade but outcomes data in CKD is limited. In this project we examined mortality outcomes associated with DOACs vs. warfarin therapy in the Veterans Affairs (VA) database.

Methods: In a national cohort of US veterans, we identified patients who were initiated on warfarin or DOAC treatment between 1/1/2012-12/31/2013. Cox models were used to calculate mortality hazard ratios across stages of kidney disease (or no kidney disease) with multivariable adjustment for age, gender, race and baseline comorbidities (diabetes, hypertension, heart failure, myocardial infarction, prior stroke, antiplatelet medications).

Results: The cohort included 27,787 patients of which 73% were non-CKD, 15% were CKD stage 3a, 5% were CKD stage 3b, and 1% were CKD stage 4. There were no CKD stage 5 patients on DOACs. Patients had a mean±SD age of 69±10 years and included 19% diabetics, 15% African-Americans and 2% Hispanics. Patients on warfarin were more likely to be older, African-American, and have pre-existing comorbidities. Compared to warfarin, patients initiated on DOAC medication had a lower risk of death in non-CKD and CKD stage 3a groups; however associations were attenuated and trended toward a reverse association in later stage CKD [Figure].

Conclusions: In a national cohort of US veterans DOACs were associated with a lower mortality risk in non-CKD and early stage CKD. Further studies with larger patient numbers are warranted to evaluate outcomes of DOACs vs. warfarin therapy in later stage CKD.

Funding: Veterans Affairs Support



FR-PO231

The Bleeding Risk of Adding Pentoxifylline to Aspirin in Patients with CKD

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Background: Pentoxifylline (PTX) is found renoprotective in chronic kidney disease (CKD) by the effects of antiinflammation, antifibrosis and improvement on hemorheology. CKD is a risk factor of cardiovascular disease, therefore many patients with CKD are under antiplatelet treatment to prevent it. CKD is also known associated with a greater risk of bleeding. Herein, we want to know if adding on PTX in CKD patients who already under aspirin therapy will increase the risk of bleeding.

Methods: The National Health Insurance Research Database in Taiwan was used to identify patients who had diagnosis of CKD and under aspirin treatment longer than 3 months after CKD diagnosed. The exclusion criteria were having major bleeding events within one year prior the CKD diagnosed, liver cirrhosis, thrombocytopenia and history of hospitalization within three months before study index date. Patients who received PTX after aspirin were selected as study group (PTX group), the remaining patients who without PTX treatment and matched on age, gender and years of CKD diagnosis were selected as control group. The study outcome was any event of intracranial hemorrage (ICH) or gastrointestinal(GI) bleeding after using PTX. A conditional logistic regression model was used to estimate the risk of bleeding in PTX treated patients.

Results: A total 607 patients in PTX group and 1214 in control group were analyzed. The mean age of both groups was 65.7+/-12.4 yeas old. PTX group had higher percentage of diabetes mellitus (DM)(44.48% vs 35.91%, p<0.001) and stroke history (18.29% vs 14.33%, p=0.029). The percentage of ICH and GI bleeding events was 1.48% and 14.83% in the PTX group; 1.89% and 11.86% in the control group, without significant difference. The risk of having a bleeding event was not significant different between PTX group and control group after adjusting the comorbidities of DM, hypertension, hyperlipidemia, stroke history and end stage renal disease. (Adjusted Odds Ratio(AOR) of ICH: 0.78, 95% Confidence Interval(CI): 0.38-1.62; AOR of GI bleeding: 1.4, 95%CI :0.98-1.72).

Conclusions: Add-on PTX in CKD patients who under aspirin treatment would not increase the risk of ICH and GI bleeding.

FR-PO232

Is the Use of Opioids and Benzodiazepines Among Patients with CKD Stages 3-5 Associated with Postoperative Outcome?

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Background: Preoperative use of opioids and benzodiazepines (BZDs) has been associated with adverse outcomes following surgery. The aim of this study was to examine the use of opioids and BZDs among individuals with chronic kidney disease (CKD) in association with postoperative outcomes.

Methods: This was a retrospective study of adult patients who underwent non-cardiac surgery at the University Hospital in Reykjavik in 2006-2015. Clinical data was obtained from electronic medical records. CKD stages 3-5 was defined according the the KDIGO classification system. Patients were considered to be using opioids or BZDs if they had filled a prescription within six months prior to surgery and a daily defined dose (DDD) was determined for all patients. Survival of CKD patients using opioids and BZD was compared to propensity score-matched (PSM, 1:1) control group of CKD patients not using these medications.

Results: A total of 42,600 patients underwent non-cardiac surgery during the 10-year study period, of whom 6973 (16.4%) had preoperative CKD 3-5, with 3877 (9.1%), 1845 (4.3%), 578 (1.4%) and 673 (1.6%) having stages 3A, 3B, 4 and 5, respectively. Preoperatively there were 8008 (19%), 3327 (8%), 2888 (7%) individuals taking opioids, BZDs and both opioids and BZDs, respectively. CKD patients were more often treated with BZDs (10.5% vs. 7.3%) and both opioids and BZDs (8.6% vs. 6.4%) than patients without CKD (p<0.001). CKD patients received a median (interquartile range, IQR) of 47 (20-112) DDD of opioids and BZDs over the 6 month period, compared with 33 (13-93) DDD in those without CKD (p<0.001). Preoperative use of opioids or BDZs among CKD patients was not associated with worse 30-day (97% vs. 96%, p=0.1) or one-year survival (86% vs. 86%, p=0.66) compared to the PSM control group. In an analysis limited to individuals with CKD stage 3B or higher, who were prescribed >90 DDD in the six months preoperatively, 30-day (96% vs. 97%) and one-year survival (84% vs. 84%) was similar to controls.

Conclusions: In this surgical cohort we found that patients with CKD were more commonly prescribed opioids, BZDs or both, but quantity of prescribed medications was modest. With this prescription pattern, adverse effect on postoperative survival was not observed.

Funding: Government Support - Non-U.S.

FR-PO233

Marijuana Use and Kidney Outcomes in the ASSESS-AKI Cohort

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Background: Legal recreational and medicinal use of marijuana (MJ) is increasing worldwide. Animal kidney injury models show that activation of the cannabinoid receptor CB1 can exacerbate kidney disease while activation of CB2 may be protective. Whether these effects apply to whole plant MJ remains to be determined.

Methods: We conducted a post-hoc analysis of MJ usage as a risk factor for kidney function decline and albuminuria in the ASSESS-AKI parallel matched cohort study that enrolled hospitalized adults with and without AKI from 4 US centers between 2009-2015, with a median of 4.1 years of follow-up. MJ usage was defined as responding yes to "have you used MJ since your last study visit?" at least once on any study visit questionnaire. Nonusers were defined as always responding no to this question. Kidney function decline was defined according to the parent study protocol. Association between MJ usage and the categorical and continuous outcomes were determined using multivariable Cox regression and linear mixed models, respectively.

Results: MJ users represented 113 of 1599 (7%) participants, were younger (mean age 54 vs. 65 years), mostly white (78%), men (78%), and were more likely to be heavy tobacco users (≥20 cigarettes/day; 26% vs. 8%). Baseline eGFR was higher in users vs. non-users (87 +/- 30 mL/min/1.73 m^2vs. 69 +/- 26 mL/min/1.73 m^2), while baseline UACR was similar (120 +/- 80 in users vs. 99 +/- 72 in nonusers). In those with baseline eGFR ≥60 mL/min/1.73 m^2, MJ use was not associated with incident CKD (adjusted HR 0.93; 95% CI, 0.5-1.8) or differences in eGFR slope over time (mean difference -0.12 mL/min/1.73 m^2/year, *P*=0.7). In contrast, in those with baseline eGFR <60 mL/min/1.73 m^2, MJ users had more rapid eGFR decline vs. nonusers (-3.2 vs -1.4 mL/min/1.73 m^2/year,*P*=0.002) and had a strong trend towards higher risk for CKD progression (adjusted HR 2.7; 95% CI, 0.83 to 8.5). MJ usage was not associated with the rate of change in UACR over time in those with (*P*=0.4) and without CKD (*P*=0.2).

Conclusions: MJ usage was associated with more rapid eGFR decline in those with baseline CKD, but not in those without CKD, nor was it associated with changes in albuminuria over time in those with or without CKD. Reasons for the effect modification by CKD status regarding MJ and kidney function should be explored.

Funding: NIDDK Support

FR-PO234

Cannabis Use and Its Association with eGFR Decline in Advanced CKD Patients Transitioning to ESRD

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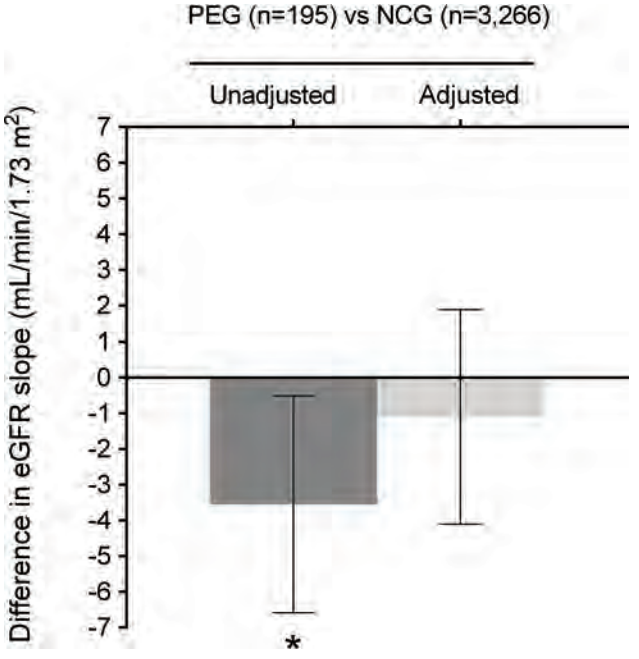
Background: The renal safety of cannabis use in patients with advanced CKD is unknown.

Methods: We examined 6,788 US veterans who transitioned to dialysis during 2007-2014 and had undergone urine toxicology tests within a year before the dialysis initiation. We compared patients whose toxicology tests were positive for cannabis alone (primary exposure group, PEG, N=195) with those whose tests were negative (negative control group, NCG, N=3,266). We estimated slopes of eGFR and the effect of inter-individual cannabis use on intraindividual slopes in multilevel mixed-effects models with random intercepts and slopes adjusted for sociodemographics, comorbidities, medications, and vital signs.

Results: The mean (SD) age of the cohort was 60.5 (9.6) years; 97% were male, 46 % were African American and 72% were diabetic. The median (IQR) eGFR slope was -10.9 (-17.2, -6.1) ml/min/1.73m^2/year. Cannabis use was associated with significantly steeper eGFR slopes in the unadjusted model (Figure 1, estimated slope in the PEG compared to NCG group (95% CI) -3.55 (-6.58, -0.51) ml/min/1.73m^2/year, P=0.02) However, after multivariable adjustments cannabis use was not associated with steeper slopes.

Conclusions: Cannabis use is not associated with more rapid loss of kidney function in patients with advanced CKD.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO235

Efficacy and Safety of Endothelin Receptor Antagonist on Renal Outcomes

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Background: Preclinical studies suggest that blockade of the endothelin receptor reduces proteinuria and may confer renal protection. The aim of this systematic review and meta-analysis was to summarize evidence from randomized controlled trials (RCT) concerning the benefits and risks of ERA on renal outcomes.

Methods: MEDLINE, Embase and Cochrane Central Register of Controlled Trials were searched for RCTs evaluating ERAs in adults that reported renal outcomes. The primary outcome was kidney failure (end-stage kidney disease, renal failure, or doubling of creatinine, or as reported by the authors). The secondary outcomes were change in kidney function (estimated glomerular filtration rate or creatinine clearance), albuminuria and systolic blood pressure from baseline to last measurement, all-cause mortality, cardiovascular mortality and adverse events. Treatment effects were summarized using random-effects meta-analysis.

Results: Six RCTs (3963 participants, median sample size 333, median follow-up 15 weeks) met eligibility criteria. There was substantial heterogeneity in baseline kidney function and study population. Compared to placebo, ERA significantly reduced the risk of kidney failure (2 trials, risk ratio [RR] 0.75, 95%CI 0.56, 0.93). Compared to placebo, ERA significantly reduced albuminuria (3 trials, SMD -1.19, 95%CI -1.86, -0.53), and systolic blood pressure (weighted mean difference [WMD] -5.86, 95%CI -10.62, -1.09 mm Hg). ERA treatment was associated with a short term decrease in kidney function (5 trials, standardized mean difference [SMD] -0.11, 95%CI -0.22, 0.00). ERA had uncertain effect on all-cause mortality (4 trials, RR 1.62, 95%CI 0.62, 4.29), and pulmonary edema (2 trials, RR 2.07, 95%CI 0.65, 6.59); but increased the risk of systemic edema (6 trials, RR 1.90, 95%CI 1.29, 2.79).

Conclusions: Short-term trials suggest that ERA treatment may reduce the risk of kidney failure and reduce albuminuria. Adequately powered RCTs with long-term follow-up are required to evaluate whether ERA treatment improves renal outcomes.

FR-PO236

Effect of a Carbonaceous Adsorbent on the Progression of CKD

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Background: AST-120 (Kureha Chemical, Tokyo, Japan) is an oral spherical carbonaceous adsorbent, which was approved for use in delaying the initiation of dialysis and ameliorating the symptoms of uremia in patients with progressive chronic kidney disease (CKD). It adsorbs the precursor of indoxyl sulfate in the intestines and prevents indoxyl sulfate production. Indoxyl sulfate, initially identified as a major uremic toxin that causes uremic symptoms, contributes to CKD progression. Although international multicenter prospective trials of AST-120 did not slow progression of CKD in patients with moderate to severe CKD, present study evaluated the efficacy of AST-120 in preventing the progression of CKD and its indication in our Japanese cohort.

Methods: Antihypertensive therapy using renin-angiotensin-aldosterone inhibitor (RAS-i) and a low-protein diet is conventionally used to treat patients with CKD. We retrospectively recruited 218 patients with CKD treated with AST-120 from 2014 to 2015. Changes of serum levels of blood urea nitrogen (BUN) and eGFR were analyzed for 4 years, from 1 year before medication. Moreover, we elucidated the recommended timing of initiation of AST-120 administration.

Results: The mean eGFR and BUN at the baseline were 24.1 ml/min/1.73m^2 and 35.9 mg/dL, respectively. Decline of eGFR before AST-120 treatment was -4.9 ml/min/1.73m^2/year. After 1-year and 3-year medication with AST-120, the decline of eGFR was significantly improved to -0.7 and -0.9 ml/min/1.73m^2/year, respectively. Increase slope of BUN also improved +4.7 to +1.9 mg/dl/year after 3-year administration with AST-120. We next divided patients into 3 groups depending on baseline eGFR, *i.e.*, >50 eGFR ≥*40, >40 eGFR* ≥30 and eGFR<30 ml/min/1.73m^2 groups. The effect of AST-120 to prevent progression of CKD was the highest in >50 eGFR ≥40 group in which decline of eGFR was -9.9 to -1.2 ml/min/1.73m^2/year during intervention period.

Conclusions: Present study suggests that treatment with AST-120 may delay progression of CKD. Especially, AST-120 administration is recommended to initiate relatively maintained renal function (>50 eGFR ≥40). Those findings provided insight into management of CKD patients.

FR-PO237

Improvement in Kidney Function upon Discontinuation of Fenofibrate in Outpatient Nephrology Consultations for CKD

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Background: It has been noted in observational and interventional trials that individuals exposed to fenofibrate can exhibit a rise in serum creatinine (sCr) concentration. However, it is not known to what extent this phenomenon impacts kidney function in patients who are referred to a nephrology clinic for consultation for chronic kidney disease (CKD).

Methods: We prospectively collected data in patients referred to a nephrology clinic for new evaluation of a recent rise in sCr or CKD who underwent discontinuation of fenofibrate to assess the effect of that intervention on kidney function, i.e., sCr and estimated glomerular filtration rate (eGFR). Fenofibrate was discontinued when no other cause for a recent rise in sCr or CKD was identified at the time of consultation.

Results: A total of 16 patients (69% women, 75% white, 56% type 2 diabetes, 31% peripheral arterial disease, 19% NASH) were captured over 1.5 years, median baseline sCr 1.9 (1.1 – 2.4) mg/dL and eGFR 34 (22 – 57) ml/min; proteinuria was absent in 13 (81%) patients. At 3 months (n = 16), median sCr decreased to 1.4 (0.9 – 2.2) mg/dL ($p < 0.01$) and median eGFR increased to 45 (27 – 71) ml/min ($p < 0.05$). At 6 months (n = 14), median sCr decreased to 1.5 (0.9 – 2.2) mg/dL ($p < 0.05$) and median eGFR increased to 42 (26 – 71) ml/min ($p = 0.08$). A ≥ 30% rise in eGFR was observed in 50% of patients at 3 months and it persisted in 46% and 50% of patients at 6 and 12 months, respectively. Median relative change in eGFR was +29% (+7 to +83), +24% (-13 to +68) and +29% (0 to +78) at months 3, 6 and 12, respectively. Triglyceride level increased by > 2-fold in 4 patients during follow up, whereas it remained within the same range in the remaining 12 patients (only 3 required gemfibrozil).

Conclusions: Discontinuation of fenofibrate in patients referred for CKD evaluation can result in sustained improvement in kidney function. There is a need to raise awareness among primary practitioners about this phenomenon that prompts consultations to nephrology. Furthermore, these proof-of-concept pilot data may serve as rationale for a prospective controlled study

FR-PO238

Ketosteril Effects on Advanced CKD: Implications from Taiwan Population-Based Study

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Background: Chronic kidney disease (CKD) is a risk factor for mortality and morbidity. Many clinical studies to investigate whether lowering protein intake with ketoacid analogue (LPD-KA) supplement can attenuate the progression of CKD which were unable to have a definite conclusion. This study aims to evaluate the benefit of LPD-KA in patients with advanced CKD.

Methods: The study analyzed encrypted datasets from Taiwan's National Health Insurance Research Database. The exposure group was the LPD-KA which fulfilled the medication possession rate > 90% during the first 90 days of follow up and the comparison group was non-users. Outcomes included mortality, dialysis, cardiovascular event, sepsis and blood transfusion at 2-year follow up. Diabetes mellitus (DM) was a stratum variable of interest.

Results: The data of 2654 patients in the LPD-KA group and 5308 propensity score matched patients in the LPD-KA naive group between January 1, 2001 and December 31, 2013 were analyzed. Patients on LPD-KA had lower mortality (8.1% vs. 11.5%; hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.59-0.81) and lower composite cardiovascular events (10.1% vs. 12.5%; HR 0.78, 95% CI 0.68-0.90). When stratifying analyses by DM, LPA-KA had beneficial effects on composite cardiovascular events and dialysis in patients without DM, but not in patients with DM (P for interaction < 0.05). The LPD-KA prolonged the dialysis for a median of 1.8 months (P < 0.001) in the non-DM group, but not in the DM group (0.2 month, P = 0.515).

Conclusions: LPD-KA might be a effective therapy for patient of CKD especially in patients without DM. Cardiovascular and infective event is less in LPD-KA group. Further investigation with earlier treatment to improve the outcome is warranted.

FR-PO239

Effects of Brazilian Green Propolis Extract on Proteinuria in CKD Patients: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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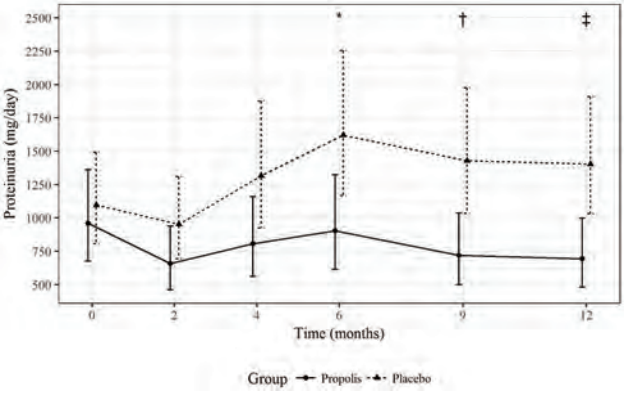
Background: Chronic kidney disease (CKD) is a public health problem of global proportions, and proteinuria is associated with disease progression. Brazilian green propolis (GP) is a natural resin that bees collect from plant sap, presenting anti-inflammatory, immunomodulatory and anti-oxidant properties. We tried to determine whether GP extract can reduce proteinuria and alter the estimated glomerular filtration rate (eGFR).

Methods: This was a randomized, double-blind, placebo-controlled study including 32 patients with diabetic or non-diabetic CKD; between 18 and 90 years of age; with an eGFR of 25-70 ml/min/1.73m^2; and with proteinuria (>300mg/day) or micro- or macro-albuminuria (urine albumin-to-creatinine ratio >30mg/g uCr or >300mg/g uCr, respectively). The patients were randomly assigned to receive GP (n=18) or placebo (n=14) at a dose of 500 mg/day and were followed for 12 months.

Results: Proteinuria (mg/24h) was significantly lower in the GP group than in the placebo group—695 (95% CI: 483-999) vs. 1403 (95% CI: 1031-1909)—(p=0.004). This finding was independent of variations in eGFR and systemic hemodynamics, which did not show differences between the groups during the follow-up. There was also a significant reduction of the urinary monocyte chemoattractant protein-1 (pg/mg uCr) was also significantly lower in the GP group than in the placebo group—58 (95% CI: 36-95) vs. 98 (95% CI: 62-155)—(p=0.038). At the dose used, GP was found to be safe and well tolerated.

Conclusions: Our findings broaden the perspectives for the use of GP as a natural adjuvant in reducing proteinuria in CKD. (ClinicalTrials.gov identifier: NCT02766036; Supported by FAPESP)

Funding: Government Support - Non-U.S.



* P = 0.023; † P = 0.006; ‡ P = 0.004; Propolis vs. Placebo.

FR-PO240

Molidustat, a Daily Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, and Vascular Endothelial Growth Factor in Patients with CKD

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Background: Hypoxia-inducible factor (HIF) transcriptionally upregulates a large number of genes including erythropoietin (EPO) and vascular endothelial growth factor (VEGF). EPO gene upregulation is helpful in treating anemia, whereas VEGF upregulation could potentially exacerbate conditions such as diabetic retinopathy or malignancy. We studied whether molidustat is linked to changes in VEGF concentrations and related adverse events (AEs) in patients with chronic kidney disease (CKD).

Methods: Three Phase 2b studies (A: 16 weeks, placebo-controlled, fixed-dose; B: 16 weeks, darbepoetin-controlled, variable-dose; and C: up to 36 months, darbepoetin-controlled, extension) were conducted in anemic subjects with CKD who were not on dialysis. Plasma VEGF concentrations were compared between baseline and last visit. We also assessed adverse events (AEs) of diabetic retinopathy (DR), macular degeneration (MD) and malignancy as these may potentially be influenced by VEGF. Subjects with proliferative diabetic retinopathy and previous or concurrent cancer at baseline were excluded from the studies.

Results: The results of VEGF concentrations are shown in Table 1. DR and MD as AEs were reported in none of 101 subjects in (A), in 1 of 92 subjects (1.0%) in (B), and in 2 of 103 subjects (1.9%) in (C) in molidustat group. None were reported in comparator groups in the three studies. Malignancy as AEs were reported in 1 of 101 subjects (1.0%) in (A), in 1 of 92 subjects (1.0%) in (B), and in 3 of 103 subjects (2.9%) in (C) in molidustat group. In 2 of 41 subject (4.9%) AE was reported in darbepoetin group (C).

Conclusions: No notable differences in changes of VEGF from baseline to last visit between molidustat and comparator groups were observed. Comparable numbers of subjects with an AE of DR, MD and malignancy in molidustat and comparator groups were identified. Due to the small number of treated patients the findings will need to be confirmed in larger Phase3 studies.

Funding: Commercial Support - Bayer AG

Table1. VEGF concentrations at baseline and last visit

VEGF (pg/mL) mean± SD	A		B		C	
	Molidustat (n=101)	Placebo (n=20)	Molidustat (n=92)	Darbepoetin (n=32)	Molidustat (n=103)	Darbepoetin (n=41)
concentration at baseline	133.2±147.3	137.8±163.5	138.3±164.7	109.4±71.9	135.3±127.8	114.6±83.3
concentration at last visit	157.7±167.3	104.6±102.2	141.1±120.0	111.2±85.6	118.4±114.4	116.3±108.9

FR-PO241

Primary Efficacy Analyses from a Phase 2 Trial of the Safety and Efficacy of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Bardoxolone methyl (BARD) has been shown to significantly increase eGFR in patients with CKD and type 2 diabetes or Alport syndrome suggesting that the anti-inflammatory and anti-fibrotic effects of BARD may target common pathways contributing to GFR loss in multiple forms of CKD. Inflammation seems to correlate with disease initiation and progression in polycystic kidney disease (PKD). As a result, a Phase 2 trial (PHOENIX, NCT03366337) was initiated to determine if BARD will improve kidney function in patients with autosomal dominant PKD (ADPKD).

Methods: The open-label, multicenter study enrolled 31 patients with ADPKD with genetic confirmation of PKD1 mutation. Eligible patients (18 to 65 years of age) had eGFR values between 30 to 90 mL/min/1.73 m^2 and urine albumin to creatinine ratio (UACR) ≤ 2500 mg/g. Patients received BARD at an initial dose of 5 mg, dose-escalated up to 20 mg (for patients with baseline UACR ≤ 300 mg/g) or up to 30 mg (for patients with baseline UACR > 300 mg/g) and were treated for 12 weeks. The primary efficacy endpoint was the change from baseline eGFR after 12 weeks of treatment. Interim results are described herein.

Results: At data cutoff on May 15th, 2018, all 31 of the patients had completed Week 4 and 8/31 (26%) had completed the study. From a mean (±SE) baseline eGFR of 47.7 ± 2.4 mL/min/1.73 m^2, BARD treatment resulted in a significant increase in eGFR of 6.6 ± 0.9 mL/min/1.73 m^2 (n=31; p<0.0001) at Week 4 and 12.0 ± 1.4 mL/min/1.73 m^2 (n=8; p<0.0001) at Week 12. The improvements were consistent, all 8 (100%) of the patients had increases in eGFR at Week 12. UACR was not significantly different from baseline. No patients have discontinued from the study and no serious AEs considered related to BARD have been reported in this ongoing trial.

Conclusions: BARD was generally well tolerated and significantly increased eGFR in patients with ADPKD. In patients with other forms of CKD, short term eGFR increases with BARD are predictive of durable eGFR improvements and additional studies are needed to study the longer-term effects of BARD on eGFR in ADPKD.

Funding: Commercial Support - Reata Pharmaceuticals

FR-PO242

One-Year Data Report from "CARDINAL": A Phase 2/3 Study of Bardoxolone Methyl in Patients with Alport Syndrome

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Background: A Phase 2/3 trial (CARDINAL, NCT03019185) was initiated to determine if bardoxolone methyl (BARD) will improve eGFR in patients with Alport syndrome (AS). Primary efficacy analyses from the Phase 2 portion of the trial previously showed that BARD increased eGFR by 13.4 mL/min/1.73 m^2 (n=30, p<0.0001) after 12 weeks of treatment. Interim results for patients who have completed 48 weeks of treatment are described herein.

Methods: The Phase 2 open-label portion of the trial enrolled patients on stable RAAS blockade, ages 12 to 60 years, with confirmed diagnosis of AS, eGFR values from 30 to 90 mL/min/1.73 m^2, and urinary albumin to creatinine ratio (UACR) ≤ 3500 mg/g. Patients received once-daily doses of BARD at 5 mg and dose-escalated to 20 mg or 30 mg (for patients with baseline UACR > 300 mg/g), as tolerated. Following the Week 48 visit, patients stopped receiving BARD during a 4-week withdrawal period before completing the Week 52 visit.

Results: As of May 15, 2018, 13/30 (43%) of the enrolled patients had received 48 weeks of treatment, and 8 patients had Week 52 data. Treatment with BARD produced mean increases in eGFR of 14.0 mL/min/1.73 m^2 at Week 48 (n=13; 95% CI: 9.5 to 18.5; p<0.0001). Moreover, after one year of treatment with BARD and withdrawal of drug, eGFR remained above baseline with mean increases in eGFR of 5.6 mL/min/1.73 m^2 at Week 52 (n=8; 95% CI: 0.3 to 10.9, p=0.04). Geometric mean UACR also increased, but log UACR/eGFR ratios were unchanged from baseline. The most commonly reported AE was muscle spasms, which were generally mild to moderate in severity, with no evidence of muscle toxicity. No drug-related serious AEs or discontinuations had been reported in the ongoing Phase 2 portion of the trial at the time of data cutoff.

Conclusions: In patients with AS, BARD was generally well tolerated and produced improvements in kidney function that were sustained for up to one year and remained significantly above baseline following treatment withdrawal. The Phase 3 double-blind, randomized, placebo-controlled portion of the trial that will enroll up to 150 patients is underway.

Funding: Commercial Support - Reata Pharmaceuticals

FR-PO243

A Randomized Trial of Ferric Citrate in Advanced CKD: Safety

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Background: We hypothesized that provision of fixed dose ferric citrate (FC), independent of serum phosphate (P) or degree of anemia, would improve multiple biochemical manifestations of advanced chronic kidney disease and reduce associated complications.

Methods: Patients with eGFR ≤ 20 ml/min (50% eGFR ≤ 15 ml/min), P ≥3.0 mg/dL, hemoglobin (Hb) >8.0 g and who were not anticipated to start dialysis within 8 weeks were randomized 2:1 to received fixed dose FC, (two per meal) or standard of care treatment (SOC). 199 patients (133 FC, 66 SOC) attended at least 1 follow-up visit. Patients were seen monthly for 9 months, or, for individuals who started hemo- or peritoneal dialysis, for 3 months thereafter.

Results: Baseline characteristics were similar with the exception of diabetes, which was more common in the SOC arm. Mean baseline eGFR was 14 ml/min. Table 1 shows the proportion of patients with any AE and serious AEs by treatment arm. "Gastrointestinal" (GI) was the only SOC in which related AE's occurred in ≥ 5% of FC patients: discolored feces (28%), constipation (12%) and diarrhea (9%). No related serious adverse events occurred. Annualized admission rates were lower with FC than with SOC (median (10%, 90% range), 0 (0,1.9) versus 0 (0,5.2), Wilcoxon Rank Sum p=0.001). After adjusting for age, race, sex, baseline eGFR and diabetes, treatment with FC significantly reduced hospital admissions (p=0.002) and hospital days (p=0.0006).

Conclusions: In this randomized, unblinded trial in patients with advanced CKD, treatment with fixed-dose FC resulted in an increase in GI AEs and a reduction in annualized hospital admission rates and hospital days. Larger, placebo-controlled trials of FC in this patient population are warranted to determine the reproducibility of these findings.

Funding: Commercial Support - Keryx

	All Adverse Events		Serious Adverse Events	
Organ System Class	Ferric Citrate (%)	Standard of Care (%)	Ferric Citrate (%)	Standard of Care (%)
Blood and Lymphatic System	5.2	2.9	1.5	
Cardiac Disorders	9.6	11.8	4.4	4.4
Endocrine Disorders	< 1.0			
Eye Disorders	3.0			
Gastrointestinal Disorders	46.7	13.2	2.2	5.9
General	9.6	10.3	< 1.0	1.5
Hepatobiliary		4.4		1.5
Immune System	< 1.0			
Infections and Infestations	29.6	38.2	3.7	16.2
Injury, poisoning	6.7	10.3	< 1.0	
Investigations	1.5	2.9		
Metabolism	9.6	8.8	< 1.0	2.9
Musculoskeletal	5.9	11.8	1.5	1.5
Neoplasms	5.2	1.5		
Nervous System	5.2	5.9	< 1.0	4.4
Psychiatric	< 1.0	4.4		
Renal and Urinary	7.4	10.3	3	8.8
Reproductive	1.5			
Respiratory	12.6	10.3	2.2	2.9
Skin	3.0	2.9		
Vascular	6.7	8.8	1.5	4.4

FR-PO244

Effects of Renal Denervation in Patients with Versus Without CKD: Results from the Global SYMPLICITY Registry with Follow-Up Data of 3 Years

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Background: Activity of the sympathetic nervous system (SNS) is increased in hypertensive patients with chronic kidney disease (CKD). We tested the hypothesis that hypertensive patients with CKD enrolled in the Global Symplicity Registry (GSR) show different patterns in blood pressure (BP) outcomes in the short- and long-term follow-up.

Methods: The GSR (NCT 01534299) is a prospective, open-label, international, multicentre observational study for assessment of safety and effectiveness of renal denervation (RDN) among real-world patients treated with the Symplicity™ RDN system (Medtronic, Santa Rosa, CA, USA). Inclusion criteria are age ≥18 years and eligibility for RDN. 24-h ambulatory BP was assessed at pre-specified time-points (6, 12, 24 and 36 months). For the current analyses, enrolled patients (N=1600) were stratified based on baseline estimated glomerular filtration rate in <60 vs. ≥60ml/min/1.73m^2 into with (N=383) and without (N=1217) CKD groups.

Results: Patients with CKD were significantly older (p<0.0001) and were treated with more antihypertensive medications (p<0.0001) compared to patients without CKD. 24-h ambulatory diastolic (but not systolic) BP was lower in patients with compared to without CKD (152.9±19/81.3±13 vs. 153.2±18/87.2±14 mmHg, p=0.6380/<0.0001), resulting in an increased pulse pressure. In patients with and without CKD, 24-h ambulatory BP was reduced after RDN compared to baseline values at all time-points (all p<0.01). There was no difference in 24-h ambulatory systolic BP reduction after RDN in favor of patients with compared to without CKD, even after adjustment (Table).

Conclusions: Hypertensive patients with CKD did not show a greater short-term or long-term decrease in 24-hour ambulatory BP.

Changes in ambulatory BP (mmHg)

	CKD	6 mo	12 mo	24 mo	36 mo
number	with/without	(n=163/545)	(n=146/499)	(n=100/337)	(n=77/248)
delta systolic	with	-4.7±19	-4.8±19	-5.5±21	-9.5±19
delta systolic	without	-7.4±17	-7.6±19	-8.3±19	-8.1±20
p-value*		0.060	0.254	0.154	0.488

*adjusted for baseline 24-h ambulatory BP, age and gender

FR-PO245

Meta-Analysis on the Effects of Intensive (INT) Blood Pressure (BP) Control on Incident CKD and ESRD

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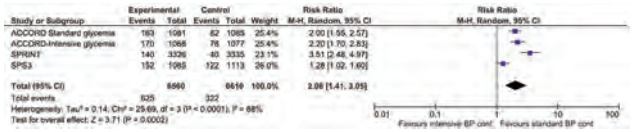
Background: We examined the hypothesis that the effects of INT BP control on kidney outcomes could differ by the level of baseline kidney function.

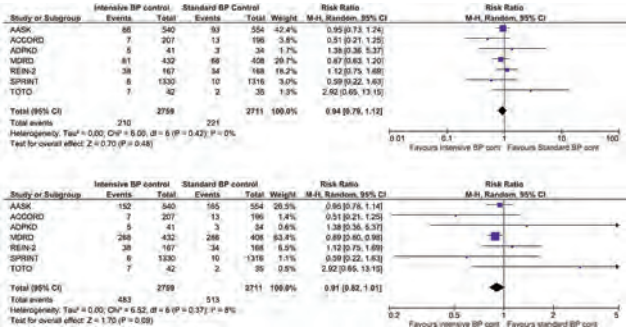
Methods: We performed a literature search and included studies that met one of the following criteria: 1. included participants without CKD at baseline and data for incident CKD were available and 2. included participants with stage 3/ 4CKD and data for ESRD available. We excluded BP studies that randomized by medications but not a BP goal, lifestyle intervention studies, with follow-up < 1 year or did not report the above outcomes. The estimates were pooled using a random effects model.

Results: Of the 3470 potentially relevant studies, 30 studies were extracted and 8 studies were included for analysis. There were 625 incident CKD events in 6560 non-CKD participants in 3 studies (Fig 1). Compared to the standard BP goal, intensive BP lowering had higher risk of incident CKD (RR 2.08, 95% CI 1.41 to 3.05). There were 210 ESRD events in 2759 CKD participants during the trial phase in 7 studies (Fig 2, panel A) with a RR of 0.94 (95% CI 0.79-1.12) for intensive vs. standard BP control. Two (MDRD and AASK) studies reported legacy folllow-up ; including these there were 483 ESRD events with a RR of 0.91, 95% CI 0.82-1.01 (Fig 2, panel B).

Conclusions: While INT BP lowering has higher risk of incident CKD in non-CKD, it might potentially reduce the risk of ESRD in CKD. Further RCTs of INT BP lowering in CKD participants are warranted to establish the risk-benefit ratio.



Effects of intensive BP control on incident CKD in non-CKD participants



Effects of intensive BP control on ESRD in participants with CKD in main trial phase (panel A) and entire legacy follow-up (panel B)

FR-PO246

Effects of Alkali Therapy on Renal Outcomes: A Systematic Review and Meta-Analysis

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Background: Preclinical studies suggest that treatment of metabolic acidosis may slow the progression of chronic kidney disease (CKD). The aim of this systematic review is to summarize evidence from randomized controlled trials (RCTs) concerning the benefits and risks of alkali therapy on renal outcomes.

Methods: Medline, Embase and Cochrane Central Register of Controlled Trials were searched for RCTs with at least 3 months of follow-up in patients with CKD defined as eGFR <60mL/min/1.73m2 or the presence of albuminuria that reported renal outcomes. Treatment effects were summarized using random-effects meta-analysis.

Results: Eight trials involving 679 participants (median sample size 80, median follow-up 12 months) evaluating sodium bicarbonate treatment were eligible for inclusion. Of these, 3 trials were a placebo-controlled studies. Overall, risk of bias was unclear or high risk. Compared to no study medication or placebo, treatment with sodium bicarbonate resulted in slower decline in kidney function (7 trials, standardized mean difference [SMD] for change from baseline in glomerular filtration rate or creatinine clearance 0.29 [95%CI 0.11, 0.48]. Sodium bicarbonate abrogated increases in serum creatinine from baseline (4 trials, weighted mean difference [WMD] -0.07 [95%CI -0.12, -0.03] mg/dL) and reduced the risk of end-stage kidney disease (4 trials, risk ratio [RR] 0.44 [95%CI 0.22, 0.88]). Sodium bicarbonate had uncertain effects on proteinuria (3 trials, SMD -0.27 [95%CI -0.59, 0.05]) and systolic blood pressure (6 trials, WMD 0.27 [95%CI -3.01, 3.56] mm Hg). Data for effects of sodium bicarbonate on death and adverse events were scant.

Conclusions: Alkali therapy with sodium bicarbonate may slow the progression of CKD. Adequately powered RCTs are required to evaluate the benefits and risks of alkali therapy in CKD.

FR-PO247

Are Treatment Effects on eGFR Decline Greater in Patients with Faster Underling Disease Progression? A Report from an NKF FDA Workshop

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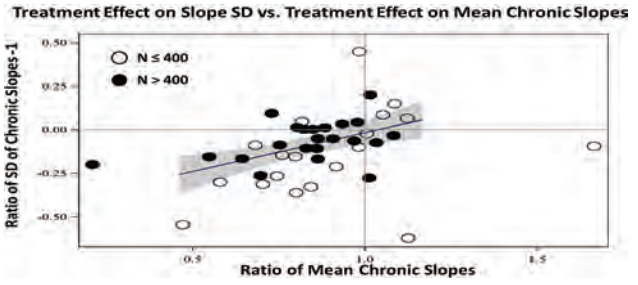
Background: Analyses at the individual and trial level support the validity of eGFR slope as a surrogate endpoint in chronic kidney disease (CKD) RCTs. The gain in statistical power for eGFR slope vs. the clinical endpoint of doubling serum creatinine or kidney failure is limited if treatments reduce the rate of eGFR decline proportionally to the rate of CKD progression (attenuating slopes of fast more than slow progressors), rather than uniformly (attenuating slopes independent of progression rate) [Greene et al, this meeting]. By definition, proportional effects, but not uniform effects, attenuate the standard deviation (SD) as well as mean of eGFR slopes. We describe the effects of treatments on the slope SD in past RCTs to inform selection of endpoints in future RCTs.

Methods: We used mixed effects analyses to estimate treatment effects on the mean and SD of eGFR slopes after 3 months follow-up (chronic slopes) for 47 CKD RCTS (59074 patients), and used meta-regression to relate the ratio of the chronic slope SDs to the ratio of mean chronic slopes between treatment and control groups while accounting for random error in each RCT.

Results: The figure shows that treatments that reduce the mean chronic slope also often reduce the SD, indicating that effective treatments tend to slow progression more in faster than in slower progressors. The slope of the meta-regression line is 0.45 ± 0.13, about half way between 0 (corresponding to uniform effects) and 1 (corresponding to proportional effects), suggesting treatment effects are usually intermediate between uniform and proportional.

Conclusions: Effective treatments usually reduce CKD progression by effects that are intermediate between uniform and proportional. For intermediate effects, our simulation studies demonstrate that slope-based endpoints can substantially reduce required sample sizes and follow-up times when there is no acute effect and baseline eGFR is high [Greene et al, this session].

Funding: Private Foundation Support



FR-PO248

Optimizing Patient Enrollment in Clinical Trials Based on Albuminuria Inclusion Criteria

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Background: Clinical trials in CKD enroll patients with elevated urinary albumin:creatinine ratio (UACR) levels to enrich the population for high renal risk patients. Screen failure rates are often high due to high intra-individual variability in UACR. We tested whether a screening approach with more flexible UACR thresholds would decrease screen failure rate without adversely impacting on overall study duration.

Methods: We performed a post-hoc analysis on data from the ALTITUDE trial. We selected patients randomized to placebo treatment with a baseline UACR >300 mg/g and eGFR between 30 and 60 ml/min/1.73m^2 at the first visit (pre-screening). We then used stepwise lower UACR cut-offs at the next qualifying visit (e.g. 300 (base scenario), 210, 150, 30 mg/g) as inclusion criteria. For each scenario we calculated the number of eligible patients and number of renal endpoints (ESRD/ doubling serum creatinine/ renal death). Based on these data we performed simulations for a future trial. We calculated the duration of enrollment and total duration of the clinical trial to accrue 961 endpoints, which provided 90% power to detect a 20% risk reduction assuming a renal event rate of 5.6% (base scenario).

Results: 848 patients (median UACR 1239 mg/g; median eGFR 44 ml/min/1.73m^2) were eligible for the base scenario. Lowering the UACR qualification threshold increased the number of eligible patients (thus decreasing screen failures) and resulted in only a modest decrease in average renal event rate. In simulations, lowering the UACR cut-off accelerated enrollment and did not increase overall trial duration to reach 961 events.

Conclusions: Relaxing UACR based inclusion criteria in a population with documented UACR levels in the protocol required range decreases screen failure rates without prolonging trial duration. This approach may increase recruitment feasibility and site investigators' motivation.

Table 1

	Observed data in ALTITUDE			Simulations for future trial	
UACR criteria qualifying visit (mg/g)	Eligible patients (N)	Renal events (N)	Renal event rate (% per year)	Duration enrollment (months)	Clinical trial duration (years)
300	848	117	5.6 (4.6-6.7)	24.0	4.2
210	923	122	5.3 (4.4-6.4)	21.9	4.3
150	958	126	5.3 (4.4-6.3)	20.9	4.2
30	988	129	5.3 (4.4-6.3)	20.0	4.2
0	995	129	5.2 (4.4-6.2)	19.8	4.2

FR-PO249

Using E-Consults in Nephrology to Improve Renal Care: A 5-Year Experience in the Miami VAMC

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Background: Electronic consultations (E-consults) are defined as asynchronous, consultative, provider-to-provider communications within a shared electronic health record or web-based platform. The primary objective of an E-consult is to expedite and improve patient care by increasing access to specialty knowledge and expertise without the need for a face-to-face visit. E-consults provide a virtual clinical discussion by the specialist after the information is reviewed and returned with suggestions and recommendations. Our review study evaluates our 5-year experience using this consultative method.

Methods: This is a retrospective study that evaluated 745 E-Consults for the Nephrology section at the Miami VAMC during a 5-year period (2013-2018). Data was obtained and included the following: gender, age, reason for the consult, time to answer the consult and improvement of the patient's condition after the consult. A simple survey was given to the referring health care provider to evaluate the quality of the E-consult and their satisfaction.

Results: The nephrology section answered the consult in an average of 40 hours. 95% were male patients (N=708), median age was 62.3 years old. The reasons for consulting: Chronic Kidney Disease 54% (N=401), proteinuria workup and co-management 16% (N=118), uncontrolled hypertension 12% (N=90), recommendations and clearance to use medications in patients with CKD grades III, IV and V 7% (N=52), electrolyte and metabolic disorder management 6% (N=43), contrast-induced nephropathy prevention 5% (N=41). 82% (N=611) of the E-consults resolved the referral, 18% (N=134) of the E-consults needed the patient to have a face-to-face encounter. In a scale from 1-5, where 5 is the highest and 1 lowest, health care providers satisfaction was 4.5, quality of the E-consult was 4.7, consult answer their concerns was 4.4. All health care providers (N=22) stated that they will continue to use E-consults.

Conclusions: E-consults improve the care of patients with renal conditions. They decrease waiting times and facilitate the access and evaluation of patients that need evaluation of a nephrologist. Referring health care providers were satisfied with the outcome of the E-consult and will continue to use in the renal care of their patients.

FR-PO250

The Effect of Integrated Care on the Rate of GFR Decline: A Community Hospital Approach

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Background: Due to limited amount of nephrologists in Thailand, most of CKD patients are taking care by primary care physicians especially in the rural area. To improve the quality of CKD care in the community hospital level, we had designed the integrated care model which composed of 2 main components including hospital-based multidisciplinary team (MDT) and community care network (CCN) at village level. In our previous study, integrated care model was effective in slowing progression of CKD. It is challenging if this model could be implemented in routine practice.

Methods: We are conducting a quasi experimental study. Patients aged 18-70 years old with stage 3 or 4 CKD were enrolled from 5 district hospitals. All patients were managed by integrated care teams. Hospital-based MDT provided group education, individual counselling in addition to standard CKD care. CCN team performed individual counseling and monitoring on proper lifestyle modification, protein and salt intake assessment. All patients will have hospital visit every 3 months and will receive home visit by CCN twice a year.

Results: 914 stage 3 and 4 CKD patients were enrolled. Mean age was 62±6.13 years. 37.2%,43.7%,19.1% of the cohort were in CKD stage 3A, 3B and 4, respectively. Diabetic kidney disease was the leading cause of CKD. Mean eGFR at baseline were 40.38±10.26 ml/ min/1.73 m^2. Baseline SBP and DBP were 128±17.07 and 73±10.56 mmHg, respectively. 79.9% of the study cohort had negative proteinuria by urine dipstick. The rate of eGFR change at 1 year of follow-up was – 0.838±10.06 ml/min/year. Patients with baseline BP less than 140/90 mmHg had a slower rate of eGFR decline when compared with patients with baseline BP 140/90 mmHg or more [-0.554±10.53vs-1.62±8.50 ml/min/year;*P*=0.04]. Patients with baseline proteinuria 1+ or more had greater rate of eGFR decline than those with negative proteinuria [-2.35±11.26vs-0.401±9.77 ml/min/year;*P*=0.001].

Conclusions: Our study revealed that this integrated care model has a beneficial effect on slowing the rate of eGFR decline in CKD stage 3-4 patients. Baseline BP and degree of proteinuria are 2 main factors that were significantly associated with greater rate of eGFR decline. Our study shows that the integrated care model could be successfully implemented at the community hospital level. It seems promising this integrated care could be implemented in another developing countries.

Funding: Private Foundation Support

FR-PO251

Cost Analysis of a Virtual Monitoring System to Reduce Suboptimal Initiation of Dialysis

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Background: Patients with kidney failure require renal replacement therapy in the form of dialysis or kidney transplant to survive. Optimal initiation of dialysis includes outpatient, elective implementation of a patient's chosen modality once clinical indications for dialysis are met. Despite interdisciplinary nephrology care teams, suboptimal initiation requiring hospitalization occurs in approximately 30% of patients and is estimated to cost Canadians $33 million per year. Virtual monitoring in high-risk chronic kidney disease (CKD) patients may decrease the rate of suboptimal initiations and therefore decrease hospitalization expenses. The objective of this study is to evaluate the cost savings of a virtual monitoring program in high-risk CKD patients.

Methods: We constructed a decision analytic Markov model from the perspective of the Canadian health payer. A virtual monitoring strategy was compared with the status quo. Costs of a suboptimal initiation, CKD multidisciplinary clinic care, and for receiving dialysis were taken from a review of the literature. Probability of kidney failure was calculated based on the Kidney Failure Risk Equation (Tangri et al, JAMA, 2011), and risks of mortality on dialysis and with late stage CKD were taken from national dialysis registries. Effectiveness of the intervention was assumed to be similar to other virtual monitoring interventions in chronic disease patients and evaluated in sensitivity analyses (baseline relative risk reduction (RRR) of a suboptimal dialysis start 0.39).

Results: Compared with the status quo the virtual monitoring system was associated with a cost savings of $762.29 per patient enrolled in the intervention. With threshold analysis we found that the RRR of a suboptimal dialysis start afforded by the intervention would have to be reduced to 0.255 to reach cost neutrality. In univariate sensitivity analyses

the most influential variables included the probability of kidney failure per month, the relative risk reduction afforded by the intervention, the hospitalization cost of a suboptimal dialysis initiation, and the proportion of kidney failure starts that are assumed to be suboptimal.

Conclusions: Allocation of funds toward implementation of a virtual monitoring system with the potential to decrease rates of suboptimal dialysis initiation can produce significant cost savings.

FR-PO252

The End of the CKD Journey - Who Starts Renal Replacement Therapy and Who Dies Without It Among CKD Patients in Public Renal Speciality Practices in Queensland, Australia

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Background: Persons with CKD who start renal replacement therapy (RRT) in Australia are well characterised, but the characteristics and outcomes of those who do not start RRT are less well understood. We examined the fate of patients with CKD in selected public renal specialty clinics in Queensland (in the CKD.QLD registry) and compare those who started renal replacement therapy (RRT) with those who died without RRT.

Methods: 6,371 patients in CKD.QLD (54% males, mostly CKD stages 3b, 4 and 5), were followed from date of informed consent until the start of RRT, death, or a censor date of June 30, 2016. Outcomes and causes of death were ascertained from Queensland Health records. Median follow-up (IQR) was 2.8 (3) years, with a total of 15,714 person years.

Results: By the censor date, 605 (9.5%) patients had started RRT, at a median (IQR) age of 63 (20) years and 837 (13.1%) had died without RRT, at median (IQR) age 78 years (14). RRT incidence rates per 100 person years for males and females respectively were 3.8 vs 2.7, p=0.001, and death rates were 5.8 vs 4.8, p=0.001. Among deaths without RRT, 377 (45.5%) mentioned terminal ESKF or chronic renal failure, an additional 193 (23.3%) mentioned CKD, and 57 (6.9%) mentioned AKI, with no gender differences.

Conclusions: Most of these patients with relatively advanced CKD experienced a "renal death" (started RRT or died with ESKF). Rates were higher for males. More died without RRT than started RRT. They were relatively distinct populations: average ESKF-free survival was 15 years longer for patients who did not start RRT (78 vs 63 years). About half the deaths without RRT were ESKF deaths, while another 30% mentioned a renal diagnosis. Ascertainment renal failure and CKD in death certificates was very good.

Funding: Government Support - Non-U.S.

FR-PO253

Developing a System to Track and Reinstate Kidney Patients Lost to Follow-Up

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Background: In the care of chronic diseases, reducing the patients lost to follow-up (LTFU) is an important way to improve outcomes. At our tertiary academic center, we identified that approximately **24%** of patients seen over six months had been instructed to follow-up in the clinic but did not within the recommended time frame. We designed a method to trigger an alert for these patients and contact them to schedule appointments.

Methods: Leveraging alerts from our electronic medical record (EMR), we generated an LTFU report that identifies patients who did not return to the clinic as requested by the providers. The alerts were dependent on physician participation in an EMR follow-up trigger. Clinical staff called these patients and classified them into three groups: scheduled (appointment made successfully), no need to return (patients transitioned to dialysis, transferred to another nephrologist, or died), or call back (unable to reach or refused appointment). We also recorded individual conditions that could contribute to LTFU.

Results: Physician participation in the EMR trigger system was 76.5%. Over nine months, using our EMR alert and calling system, we reduced the percentage of LTFU patients from 24% to 3.8%. Of the 418 LTFU patients, we successfully scheduled 225 (54%) patients, identified 34 (8.1%) no need to return patients, and continued to reach out monthly to 157 (38%) patients. Among patients LTFU, a majority did not provide a reliable method to be contacted.

Conclusions: Retention in care is associated with improved outcomes. Our study identified a method by which patients LTFU were identified. Majority of the patients were able to have appointments successfully scheduled. Vulnerable patients may benefit from early identification of risk of LTFU. A limitation of our study is that we lack outcome data on patients who were LTFU and the development and implementation of the system is time-intensive.

FR-PO254

Longitudinal Kidney Care Program and Its Impact on Decreasing Hospitalizations and Increasing Home Dialysis as the First Choice for Dialysis

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Background: The economic and morbidity burden of kidney disease has substantially increased in the past decade. With innovations on the pipeline for novel dialysis modalities, there is a lack of system-based practice applications in patients with kidney disease to decrease hospitalizations. We have initiated a systematic approach in educating patients with renal failure based on risk of progression to end stage kidney disease and assessed its efficacy in decreasing hospitalizations.

Methods: Retrospective analysis of patients in our nephrology practice who were hospitalized between January 2017 to January 2018. Also the rates of early home dialysis initiation were analyzed. ESRD patients were not included in the analysis for hospitalizations. The reason for hospitalizations were based on the admission diagnosis.

Results: The database included 4367 patients at low risk of progression and 1954 patients at a higher risk of progression based on the NKF heat map. The aggregate episode rate for hospitalization per 100 patients was calculated. The rate of hospitalizations was computed for three years. The first year serves as a control as the LKCP was not initiated at that time. The 2 years after that is when the program was actively implemented. The results are shown in Figures 1 and 2.

Conclusions: There is a significant reduction in hospitalizations and early initiation of home dialysis with a well-structured kidney care program that includes a multidisciplinary approach. These methods need to be validated in a much larger cohort for mortality risk and cost savings calculated with real time data from payors.

Figure 1:

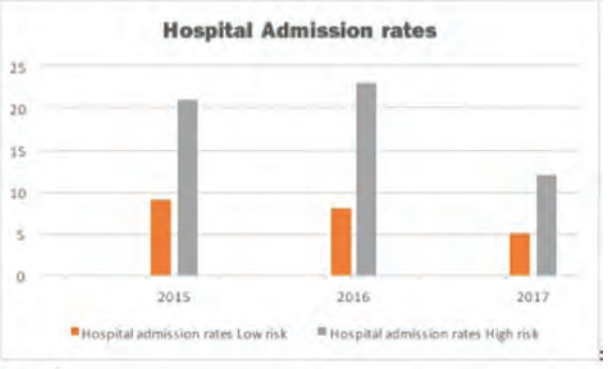
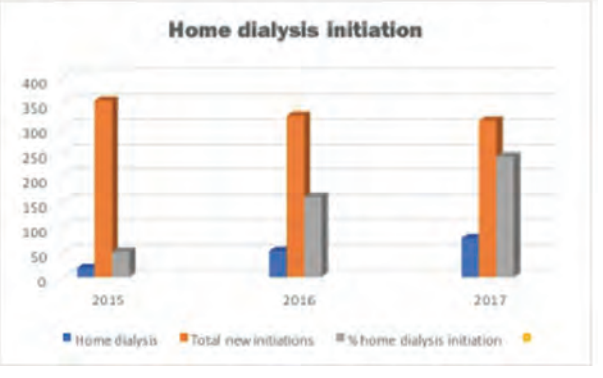


Figure 2:



FR-PO255

Improving Patient and System Outcomes Through Integrated Care for CKD

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Background: In British Columbia Canada, patients with Chronic Kidney Disease not on dialysis (CKD-ND) are cared for by interprofessional kidney care clinics (KCC's) using an integrated chronic disease model of care within a system which includes decision support

and clinical pathways, a single information system, feedback and audit systems, process and outcomes measures, provincial education of health care providers, policy makers, and patients, and dedicated patient focused funding. The BC-KCC's are integrated into a larger province wide renal network, with accountability for patient and system outcomes.

Methods: We describe the impact of a series of initiatives in KCC's to standardize education and support decision making and access for home- based therapies (HBT), conservative care (CC) and pre-emptive transplantation (Tx) over time. Initiatives were introduced sequentially, using change management and adult education principles, with materials developed by a diverse group of health care professionals and supported administratively with provincial dissemination.

Results: In March 2018, the cohort has 10,979 pts; mean age 71, median GFR 33 ml/min/1.73m2 at registration; 54% are male, 50% DM and 43% have CVD. 1285 new pts and 1017 pts exited KCC. Table 1 describes the 6 monthly prevalence of key outcomes over time. Documented treatment decisions for those with GFR <20 have increased slightly, as has formal symptom assessments, and numbers of pts choosing and starting on HBT and following conservative care pathways.

Conclusions: An integrated approach based on fundamentals of chronic care models has led to improved patient outcomes systemwide in BC.

Table 1. Kidney Care Clinic Key Outcomes Over Time

Indicator	BC					
	Apr 2015-Sep 2015	Oct 2015-Mar 2016	Apr 2016-Sep 2016	Oct 2016-Mar 2017	Apr 2017-Sep 2017	Oct 2017-Mar 2018
eGFR <20 mL/min & modality decision documented: (%)	76	72	73	76	75	78
Conservative Care chosen (%)	23	24	25	24	25	31
eGFR<15 ml/min & assessed for symptoms (mESAS) within the 6-month period (%)	n/a	n/a	18	24	28	42
Chose PD & started on PD (%)	66	72	73	73	73	76
Pre-emptive tx (# of patients)	23	20	20	19	13	29

FR-PO256

Emerging Treatment Options for Anemia Associated with CKD: Success of Online Medical Education at Improving Knowledge and Confidence of Nephrologists

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Background: As emerging therapies hold promise to improve treatment of anemia in patients with CKD, clinicians are in need of updates on development of new drugs that may ultimately influence their practices. We sought to assess baseline knowledge related to emerging treatments for CKD-related anemia and determine if online continuing medical education (CME) activities could improve the clinical knowledge and confidence of nephrologist in the area of Hypoxia-Inducible Factor Prolyl Hyproxylase Inhibitors (HIF-PHIs).

Methods: The effect of two online, CME-certified, roundtable video discussion activities were analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and McNemar's chi-squared test (5% significance level, $P < .05$) assessed educational effect for each activity. The activities launched November 18, 2016 and December 21, 2016, and data were collected through December 20, 2016 and February 1, 2017, respectively.

Results: In total, 264 nephrologists answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation in both CME activities: 10% more nephrologists ($P = .035$) correctly identified safety and efficacy data for an emerging HIF-PHIs 38% more nephrologists ($P < .001$) accurately characterized recently released data from a Medicare population of CKD patients On the 2 activities, 43% (n=126) and 38% (n=138) reported increased confidence in understanding of new therapies in development for the treatment of iron deficiency anemia in patients with CKD Continued educational gaps: About a third of nephrologists did not recognize new data presented at a major medical conference related to emerging HIF-PHIs

Conclusions: This study demonstrates the success of online, video-based roundtable discussion on improving knowledge and confidence of nephrologists related to emerging treatments for anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Developed through an independent educational grant from AstraZeneca

FR-PO257

A Streamlined Electronic Decision Support for the Management of Patients with CKD

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Background: Caring for patients with CKD requires the management of multiple medical conditions and is highly complex, data-driven and difficult to consolidate. Increased time spent on electronic health records (EHRs) is frequently perceived as an impediment to patient-centered care and has been shown to increase physician burnout. We have created a streamlined, electronic dashboard and decision support tool to consolidate CKD management, enhance efficiency and improve the clinician's work experience.

Methods: A total of 6 core content areas, 14 decision support notifications and over 90 data elements were systematically arranged into a single dashboard within our institution's EHR. This was further enriched by links to professional literature and patient handouts. To assess the impact of this decision support tool, we conducted a survey amongst providers at our single tertiary care center.

Results: We received over 300 responses. 12% were Nephrology attendings/fellows, 24% were primary care physicians and 64% were medical residents. Amongst responders, 60% used the tool in their clinical practice. It is used primarily in the outpatient setting (69%), and most frequently for the assessment of CKD etiology/stage (48%), management of mineral and bone disorders (29%) and anemia management (22%). The streamlined CKD dashboard and decision support tool was considered by 56% of respondents as helpful in preventing physician burnout.

Conclusions: While EHRs are frequently cited as a major source of physician burnout, an enhanced user interface can lead to an improved work experience. The widespread voluntary adoption of our CKD dashboard and electronic decision support suggests opportunities for EHRs to impact CKD management, enhance efficiency, and improve the clinician's work experience. Our data further suggests benefits of augmenting decision support and automated guidance while caring for patients with CKD.

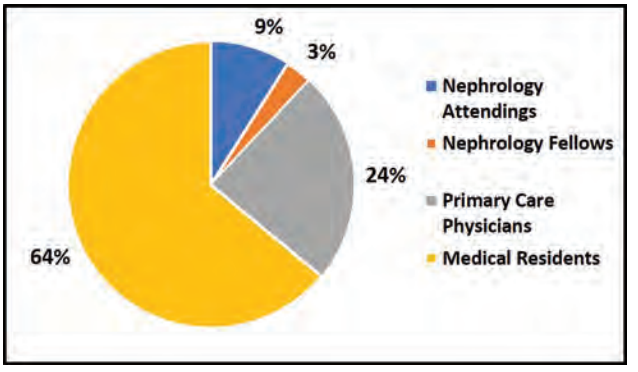

Figure 1. User deomgraphics of the decision support tool.

FR-PO258

Implementation of a CKD Panel Management Tool for Resident Physicians

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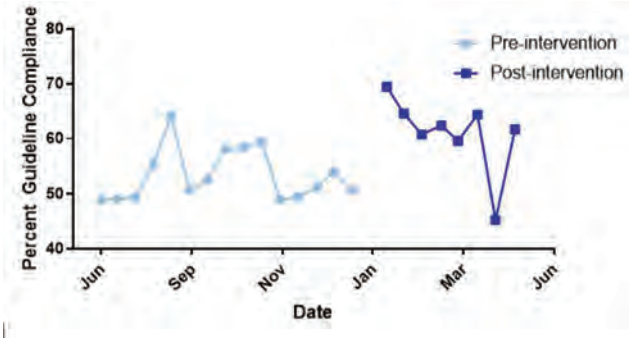
Background: Chronic kidney disease (CKD) affects approximately 1 in 7 adults and over one million Veterans served by the Veterans Health Administration (VHA). These patients are at increased risk for numerous adverse sequelae, including anemia, metabolic acidosis (MA), proteinuria, mineral bone disease (MBD), and hypertension. Clinical practice guidelines have been published by the Kidney Disease: Improving Global Outcomes work group to assist clinicians in managing the sequelae of CKD, but guideline compliance was low in a test cohort of patients cared for by residents working at a VHA Medical Center.

Methods: We designed a panel management tool to provide an automated summary of guideline-based interventions relevant to each patient seen in clinic. Residents received up to 16 recommendations per patient – eight focusing on work-up of anemia, five on MBD, and one each on uncontrolled hypertension, evaluation for albuminuria, and correction of MA. Guideline compliance, both overall and for specific domains of care, was compared pre- and post-intervention using a two-sided t-test.

Results: We identified 365 encounters with patients with at least stage III CKD (eGFR < 60 ml/min/1.73 m^2) during the six months prior to intervention, and 272 encounters in the first four months of our intervention. Guideline compliance increased from $53.5 \pm 1.3\%$ pre-intervention to $61.0 \pm 2.5\%$ post-intervention ($p < 0.01$). In a subgroup analysis, there were significant improvements in MBD testing ($40.0 \pm 2.4\%$ vs $53.0 \pm 2.9\%$) and albuminuria screening ($25.6 \pm 2.0\%$ vs $42.1 \pm 3.3\%$).

Conclusions: Implementation of a panel management tool achieved significant improvement in overall guideline compliance, with particular efficacy in the domains of MBD and albuminuria screening. The short time course of the intervention may have limited our ability to assess for improvement in blood pressure control and MA. This effective tool could be universally applied to improve the management of CKD by VHA providers.

Funding: Veterans Affairs Support



FR-PO259

eGFR in the Emergency Department as a Predictor of In-Hospital Mortality in Pneumonia

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Background: Pneumonia is a global leading cause of mortality. Severity-assessment scores in pneumonia are crucial for guiding the treatment. Community-based studies have demonstrated the association between pre-existing low estimated glomerular filtration rate (eGFR) and outcomes in pneumonia. However, whether a single eGFR measurement in the emergency department can predict in-hospital mortality in pneumonia remains to be investigated.

Methods: This hospital-based, retrospective cohort study was conducted at Wan Fang Hospital and included 1554 patients hospitalized with pneumonia between January 2013 and December 2015. Patients under 20 years of age were excluded. The main predictor was eGFR in the emergency department calculated according to the equation suggested by Chronic Kidney Disease Epidemiology Collaboration. The outcomes included in-hospital mortality, intensive care unit (ICU) admission, need for ventilator, durations of hospital and ICU stay, and ventilator use. Receiver operating characteristic (ROC) curve and Youden criteria for determining the optimal cut-off value of eGFR to predict in-hospital mortality were used and confirmed using a multivariate logistic regression model.

Results: Of 1554 patients, 263 (16.9%) had chronic kidney disease (CKD) and demonstrated higher C-reactive protein (CRP) levels and SMART-COP score and more events of multilobar pneumonia, acute kidney injury, ICU admission, and in-hospital mortality. Patients with higher pneumonia severity scores tended to have lower eGFR. eGFR of 55.89 mL/min/1.73m^2 was the optimal cut-off value for predicting in-hospital mortality. Multivariate logistic regression analysis adjusted for sex, co-morbidities, CRP, liver function tests, and SMART-COP score demonstrated that eGFR <55.89 mL/min/1.73m^2 had odds ratio of 3.2 (95% confidence interval: 2.3–4.4) for in-hospital mortality.

Conclusions: Low eGFR in the emergency department is associated with higher pneumonia severity. eGFR <55.89 mL/min/1.73m^2 is an independent predictor of in-hospital mortality in patients hospitalized with pneumonia.

FR-PO260

The Effect of Peer Mentoring on Active Engagement Among Patients with Advanced CKD

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Background: Peer mentoring is an effective strategy in patient education and has been proposed as an effective model for active patient engagement. This study compares the effect of peer mentoring (face-to-face and online) with usual care on active engagement among patients with chronic kidney disease (CKD).

Methods: Patients with stage 4 or stage 5 CKD were randomly assigned either to face-to-face (FTF) peer mentoring, online peer mentoring, or usual care (control). For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly FTF visit. For the online mentorship, the frequency of contact by mentor was weekly by the online platform, and more frequently as initiated by the mentee. The mentorships were maintained for at least 6 months. Usual care participants received a printed copy of an information handbook and were encouraged to discuss questions with their care team. We used the 13-item validated Patient Activation Measure® (PAM) at baseline and at 12 months to assess change in level of engagement. Univariate and multivariate analyses were used to compare the change in PAM scores from baseline to 12 months.

Results: A total of 130 patients completed the 12 month assessment. Baseline PAM score and demographic characteristics (mean age, educational attainment, gender and race distribution) were similar among the 3 groups. There was a significant improvement in the mean PAM score for the online peer mentoring group (69.7±15.6 vs. 76.44 ± 13.96; p=0.02). There was a slight (non-significant) improvement in PAM among the FTF group and no change in PAM among the control group. Improvements in PAM stage (by at least one level) were seen among 33% of the FTF, 48.7% of the online and 22.7% of the control group. PAM was decreased by at least one stage among 36% of the FTF, 12.8% of online and 31.8% of control group.

Conclusions: Compared with face-to-face mentoring and information only education, online peer mentoring is associated with improved scores in Patient Activation Measure and PAM stage among patients with advanced CKD. **Funding: PCORI**

Funding: Other U.S. Government Support

FR-PO261

The Effect of Peer Mentoring on Caregiver Burden Among Caregivers of Patients with CKD

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Background: Caregivers play a fundamental role in the treatment and management of patients with chronic kidney disease (CKD). Caregiver burden may result from providing care to patients with CKD and is often overlooked by clinicians. Peer mentoring is an effective educational strategy which may result in improvement in caregiver burden. This study compares the effect of peer mentoring (face-to-face and online) with usual care on caregiver burden among caregivers of patients with CKD.

Methods: A 16-hour structured program trained CKD patients and their caregivers to become peer mentors to newly diagnosed patients with CKD and their caregivers. Caregivers of patients with stage 4 or stage 5 CKD were randomly assigned either to face-to-face (FTF) peer mentoring, online peer mentoring, or usual care (control). For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly FTF visit. For the online mentorship, the frequency of contact by mentor was weekly by the online platform, and more frequently as initiated by the mentee. The mentorships were maintained for at least 6 months. Usual care participants received a printed copy of an information handbook about care of the patient with CKD. We used the Zarit Burden Interview (ZBI) to measure caregiver burden at baseline and at 12 months. The ZBI is a self-administered questionnaire of 22 items, which measures the impact of caregiving in psychological, physical and social domains. The items are ranked on a five-point Likert scale and the total score is calculated; higher scores indicating heavier burden. Univariate and multivariate analyses were used to compare the change in ZBI scores from baseline to 12 months.

Results: A total of 61 caregivers completed the 12 month assessment. Baseline ZBI score and demographic characteristics (mean age, highest grade of education, gender and race distribution) were similar among the 3 groups. There was a significant decrease in the mean ZBI score for the online mentoring group (23.9±10.7 vs. 12.8 ± 12.3; p=0.03). There was a slight (non-significant) improvement in ZBI among the FTF group and among the control group.

Conclusions: Compared with face-to-face mentoring and information only education, online peer mentoring is associated with improved scores in caregiver burden among caregivers of patients with advanced CKD. **Funding: PCORI**

Funding: Other U.S. Government Support

FR-PO262

Optimizing the Utility of Patient Experience Surveys to Advance the Quality of Renal Care

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Background: Patient experience is an essential indicator for advancing person-centred care. Although many patient experience measures are validated in chronic disease populations, how they can be utilized in guiding improvement in renal care is understudied. Thus, we verified how results of a validated patient experience survey can be used to guide improvement in the continuum of renal care.

Methods: A validated 20-item instrument, Patient Assessment of Chronic Illness Care (PACIC), was mailed out to >13,000 eligible patients receiving non-dialysis and dialysis care in British Columbia, Canada. The responses were descriptively analyzed by subscale (five dimensions in PACIC) and modality of care. Priority matrix analysis was also performed to identify specific areas of improvement.

Results: Nearly 4,000 patients responded (30% response rate). More than 75% of respondents rated the overall quality of kidney services as "excellent" or "very good." Based on the survey responses, the area of highest satisfaction was the overall organization and delivery of care, and areas of improvement included "goal setting" and "follow-up." Priority matrices by modality identify unique improvement opportunities (Fig 1) not otherwise apparent from conventional analysis by highlighting aspects of care highly associated with overall perception of the renal services quality.

Conclusions: Measuring patient experience across a diverse renal population yields important insights. When analyzed with respect to the overall perception of quality of kidney services, the utility of PACIC results is enhanced in that it can guide strategic action planning specific to each modality of renal care, with a greater potential for positively impacting those living with kidney disease.

Funding: Government Support - Non-U.S.

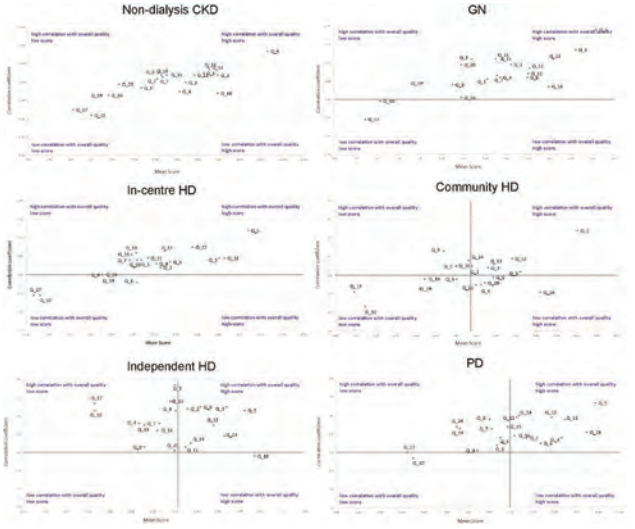

Fig 1. Priority matrices by modality

FR-PO263

Impact of a Phone App on the Referral to Nephrology

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Background: Several factors might influence nephrology referral decisions by clinicians, including lack of training about guidelines regarding timing or indications. In the 21st century tools as phone apps can make knowledge more accessible.

Methods: Prospective quasi-experimental study. We studied referral to nephrology in the Hospital Costa del Sol of 2015. In 2016 we perform formative lectures to the principal departments that refer patients to nephrology of phone "Nefroconsultor" that recommends referrals attending to KDIGO criteria. We studied referral of 2017 after intervention.

Results: 628 patients with a mean age of 68 years-old, 63% were male, a mean creatinine at time of referral of 1,5mg/dL and a glomerular filtration rate of 46 ml/min/1,73m^2 (CKD-EPI). Comparing before and after intervention, previous implantation of phone app 333 patients were referred while after 295 patients were referred, a 10,1% less (p=0,001). There were no differences in age (p=0,13); gender (p=0,197); serum creatinine (p=0,59) and glomerular filtration rate CKD-EPI (p=0,41). In 2015, 132 patients of 333 met stablished KDIGO criteria of referral (39,8%) while in 2017 200 patients of 295 (60,2%) and considered well referred (p=0,001). The increase of intervention success was of a 28,8% (binomial effect size display with Cohen'd effect size of 0,751). Previous the app 208 patients of 333 (63,2%) were referred with data of albuminuria while after 258 of 295 patients (89% p=0,001). The increase of intervention success was of a 25,7% (Cohen'd effect size of 0,744). Referral including urine sediment improved from a 69,3% to 87,2% (p=0,001) with an increase of intervention success of 12,2% (Cohen'd 0,28). Multivariate regression analysis using referral meeting KDIGO criteria as dependent variable and adjusting by age, sex and department of provenance, 2017 was associated with a correct referral with a odds ratio of 3,57 (IC 95%: 2,52-5,05) compared to 2015 (p=0,001). Proteinuria as the reason of referral to nephrology also increased from a 24% to a 34,8% (p=0,004).

Conclusions: The use of a tool as phone app (Nefroconsultor) improves the referral to nephrologist a 28,8% attending to referral stablished criteria. The app also increases the study of albuminuria and urine sediment at the moment of referral, increasing proteinuria as reason of referral. UNDER REVIEW CJASN.

FR-PO264

Evaluation of the Efficacy of CKD Support Decision-Making Application: How It Changes Home Blood Pressure and Kidney Functions

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Background: Disease management in patients with chronic kidney disease (CKD) is complicated. Appropriate information provision and daily self-monitoring of parameters such as blood pressure are required. Therefore, this study aimed to evaluate how a chronic kidney disease support decision-making application (CKD-SDM) app in patients with CKD affects the blood pressure, kidney functions, and disease-management knowledge at home.

Methods: This study was a randomized, controlled trial involving 54 patients with stage 3, 4, or 5 non-dialysis CKD. The intervention group was provided with a tablet equipped with the CKD-SDM app. An automated sphygmomanometer for home blood pressure monitoring (HBPM) was used in both groups for 8 weeks. The primary outcome measure is change in HBPM data from baseline to 8 weeks. Secondary outcomes are changes in renal functions and self-management knowledge level on CKD.

Results: The mean (SD) age, eGFR, and HBPM (morning and evening) of participants were 70.7±11.0 years, 37.0±14.4 ml/min per 1.73 m^2, and 133.7±11.5/78.3±8.9 and 130.5±13.4/76.0±8.9 mmHg, respectively. No significant differences between groups were observed at baseline. After 8 weeks, HBPM reduction in both groups were -5.8/-1.5 vs. -3.1/-0.7 mmHg in the morning and -6.1/-3.3 vs. -4.0/-1.5 mmHg in the evening, with no significant differences between the two groups. In the female intervention group, the morning systolic blood pressure (SBP) difference significantly decreased, -7.7 vs. -2.6 mmHg ($p<0.05$). All kidney functions were not significantly different. Similarly, the self-management knowledge level on CKD was not significantly improved in the intervention group.

Conclusions: Eight weeks of intervention with CKD-SDM app did not reduce the overall HBPM, despite the improved SBP observed in the female intervention group. In the future, we have to plan larger and long-term studies to evaluate HBPM reduction and kidney functions in patients with CKD. Trial Registration: This study is registered in the UMIN Clinical Trial Registry (000025792).

Funding: Government Support - Non-U.S.

FR-PO265

Patient Language and Guideline-Concordant Care Among Individuals with CKD in Primary Care

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Background: Patients with a language barrier are at risk for poor communication and inadequate management of chronic conditions. We assessed the quality of Chronic Kidney Disease (CKD) management in primary care for non-English speakers compared to English speakers.

Methods: Using EHR data (2014-2015), we evaluated the association of non-English language preference with guideline-concordant care among adults with CKD in a primary care clinic in San Francisco where interpreters are available. Outcomes included: testing for albuminuria (all) and A1c (patients with diabetes); prescription of ACEi/ARB and statins; BP at goal < 140/90 and A1c<7 (patients with diabetes). We used multivariate modified Poisson regression to estimate relative risks of each outcome.

Results: Among 1,726 patients, mean age was 66 ±10, 26% were Asian, 14% Black and 7% Hispanic. 88% had Medicare and 10% Medicaid. Compared to English speakers, non-English speakers had higher prevalence of comorbidities (cerebrovascular disease, 16% vs. 12%; diabetes, 57% vs. 41%; and hypertension, 89% vs. 81%) and more frequent primary care visits, but similar eGFR (49 vs. 48 ml/min/1.73m^2). In unadjusted comparisons, non-English speakers were more likely to be tested for albuminuria and have a prescription for statins, but there were no differences in ACEi/ARB prescription, BP or A1c control. After adjustment, differences were mostly attenuated.

Conclusions: Overall, most guideline measures were sub-optimally met. However, there was consistent care across language preference: in a single clinic with access to professional interpreters, non-English language preference was not associated with differences in guideline-concordant processes of care for CKD.

Funding: NIDDK Support

Rates of Guideline-Concordant Care by Language Preference

Process of Care	English Speaker (%)	Non-English Preference (%)	Adjusted* RR (95% CI)
Testing for albuminuria	41	53	1.03 (0.90,1.17)
A1c testing in diabetics	98	98	0.99 (0.96,1.02)
Statin prescription	66	77	1.01 (0.94,1.09)
ACE/ARB prescription	72	73	0.90 (0.82,0.99)
BP control	75	74	1.05 (0.96,1.14)
A1c <7 in diabetics	77	59	0.97 (0.75,1.25)

*Fully adjusted (age, sex, race, insurance type, number of PC visits in the study period, CKD stage, count of comorbid conditions if applicable)

FR-PO266

Evaluation of CKD Symptom Management Algorithms and Patient Information Sheets in Two Kidney Care Clinics

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Background: As renal function declines, symptoms related to chronic kidney disease (CKD) become more prevalent and impact quality of life. To address symptom management systematically in patients with eGFR ≤ 15 mL/min not on dialysis, the British Columbia Provincial Renal Agency (BCPRA) developed 8 symptom management algorithms and patient information sheets. The objectives of this project are to assess patients' symptom burden before and after implementation of these tools and to assess patient and staff satisfaction.

Methods: We conducted a prospective quantitative and qualitative study at 2 Kidney Care Clinics (KCCs). Five patients who were followed with the symptom management algorithms for nausea, low appetite, pruritis, and fatigue/insomnia were interviewed to assess satisfaction with care received via the algorithms and patient information sheets. Symptom burden was assessed pre and post algorithm use using a validated symptom assessment tool (Edmonton Symptoms Assessment Score (ESAS)). Next, focus groups with renal nurses (RNs) and renal dieticians (RDs) were conducted to assess provider satisfaction with the tools.

Results: Following assessment of 5 patients, ESAS score improved for 4 patients after a mean (SD) follow up of 80 (13) days. Patients reported that recommendations provided were somewhat helpful for symptom and quality of life improvement and that the patient information sheets were helpful and easy to use. Of the 13 RNs and RDs in the focus groups, 12/13 were satisfied or very satisfied with the algorithms and 13/13 were satisfied or very satisfied with the patient information sheets. Major themes identified by patients and providers included their satisfaction with the ability to improve standardized care, patient education, patient-centered care, accountability, and follow-up.

Conclusions: Following implementation of BCPRA symptom management algorithms, we were able to show a reduction in symptoms for patients with a GFR ≤ 15 mL/min not on dialysis using validated symptom management tools. Patients and providers found the information sheets/algorithms helpful and easy to use.

FR-PO267

The Prevalence of Uremic Symptoms and Their Association with Adverse Outcomes in CKD

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Background: Fatigue, anorexia, and pruritus are important patient-reported symptoms of CKD. Their prevalence and association with adverse outcomes in patients with non-dialysis dependent CKD have not been well established or characterized.

Methods: Among 3,639 participants of the ongoing Chronic Renal Insufficiency Cohort Study (CRIC), we assessed fatigue, anorexia, and pruritus using the KDQOL-36, administered at baseline and then annually. We calculated a uremic symptom score (U-Score) by averaging the 3 symptom scores for each person. We determined the time-varying association of each symptom and the U-Score with the risk of CKD progression (50% reduction in eGFR or ESRD), death and first cardiovascular disease (CVD) events, using Cox models adjusted for demographic, clinical, and laboratory variables, including eGFR and albuminuria.

Results: At baseline, mean age was 58 yrs and eGFR was 45 ml/min/1.73m^2. The prevalence of fatigue was 52%, anorexia, 21%, and pruritus, 42%; each were associated with lower eGFR (p<0.001). During a median follow-up of 6.1 yrs, a higher U-Score (more symptoms) was significantly and positively associated with all outcomes (Table). Each individual symptom was associated with the risk of CKD progression; anorexia and fatigue were associated with death; none of the individual symptoms was associated with first CVD event.

Conclusions: A uremic symptom score, derived from three commonly reported symptoms, is associated with adverse outcomes in patients with non-dialysis dependent CKD. Our findings highlight the importance of patient-reported symptoms and underscore the need for unraveling their pathogenesis.

Funding: NIDDK Support

Association of Uremic Symptoms with Outcomes

	CKD Progression		Death		First CVD Event	
Events	1192		922		957	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
U-Score[1]	**1.05 (1.02-1.08)**	**0.003**	**1.07 (1.03-1.10)**	**<.001**	**1.04 (1.01-1.08)**	**0.02**
Individual Symptoms[2]						
Fatigue	**1.20 (1.06-1.36)**	**0.01**	**1.15 (1.00-1.32)**	**0.05**	1.09 (0.95-1.25)	0.2
Anorexia	**1.17 (1.03-1.34)**	**0.02**	**1.31 (1.13-1.51)**	**<.001**	1.09 (0.94-1.26)	0.2
Pruritus	**1.15 (1.02-1.29)**	**0.02**	1.06 (0.92-1.21)	0.4	1.07 (0.94-1.22)	0.3

[1]HR per 10-point higher score (more symptoms).

[2]HR for presence vs. absence of symptoms.

Adjusted: age, sex, race, income, education, marital status, smoking, alcohol use, DM, HTN, CVD, BMI, eGFR, BUN, albumin, cholesterol, urine albumin

FR-PO268

Perceived Significance of Engagement in CKD Research Priority Setting Among Stakeholders: A Qualitative Study

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Background: Patients and other stakeholders are increasingly engaging as partners in research, although how they perceive such experiences, particularly over the long term, is not well understood. We sought to characterize how participants from a chronic kidney disease (CKD) research priority-setting project conducted two years previously perceived the significance of their involvement.

Methods: This was a qualitative study involving participants across Canada from a prior CKD research priority-setting project. We purposively sampled across stakeholder roles (i.e. patients with non-dialysis CKD, caregivers, healthcare professionals, and policymakers) and engagement types (i.e. involvement on the project's steering committee and/or final prioritization stage). We conducted individual, in-depth Interviews, which we analyzed using an inductive, thematic analysis approach.

Results: We conducted 23 interviews across all stakeholder roles and engagement types, and characterized three themes. Participants identified research engagement as an opportunity to facilitate integration of distinct CKD stakeholder communities (i.e. patients/caregivers and healthcare professionals/researchers). All participants appreciated the experiences that stakeholders, and particularly patients, brought to research, which furthered their understanding of the CKD lived experience and the value of patient-oriented research. Stakeholders suggested that their involvement in the project helped re-focus their commitment CKD research and care, which encompassed a subsequent interest in research engagement and patient-centered care approaches.

Conclusions: When reflecting on their of experience engaging in CKD research prioritization, stakeholders viewed the significance of their involvement in relation to the integration of different CKD communities, an appreciation of the CKD experience, and a re-focusing of their commitment to research and CKD care. Findings highlight considerations for future health research that engages stakeholders, and in particular those living with CKD or other chronic illnesses, as research partners.

FR-PO269

Accurate Estimation of Arterial pH from Venous pCO2 and Venous CO2: An Easy Solution to an Old Problem

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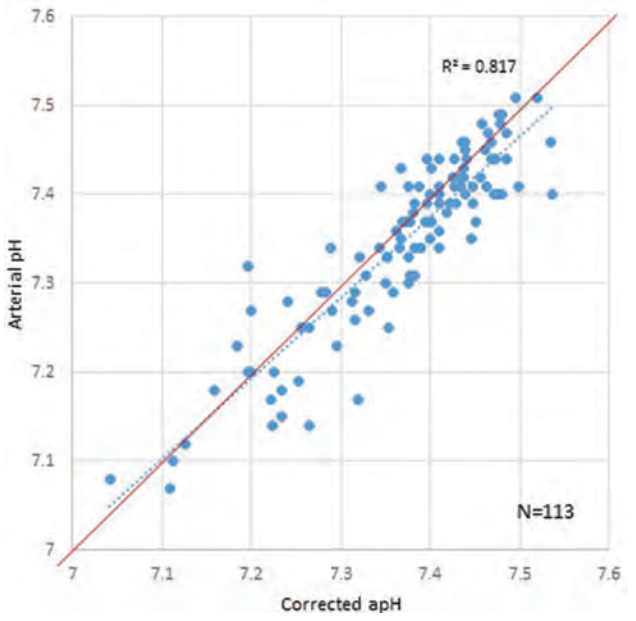
Background: Plasma CO2 from venous blood (vTCO2 or vCO2) is often used as a surrogate for arterial bicarbonate (aHCO3). Arterial PCO2 (aPCO2) can be estimated from the venous PCO2 (vPCO2) using regression equations derived from correlative studies. If the pH is recalculated using vPCO2, the HCO3 (numerator in the Henderson Hasselbalch equation) is also impacted thereby limiting the accuracy of the corrected pH. We reasoned that with proper validations of vCO2 as a surrogate for aHCO3 and vPCO2 corrected to reflect aPCO2, the arterial pH (apH) can be readily estimated from venous blood and the venous pH will not be needed. Here we tested this concept.

Methods: We analyzed a de-identified database of venous and arterial blood gases performed in the clinical lab of Northwestern Medicine, Chicago, USA. ABG, VBG and electrolyte panel were examined in 113 samples obtained simultaneously. Additionally, concurrent data for arterial and venous PCO2 obtained from 3911 samples and collected from various hospital departments was used for a regression equation to calculate aPCO2 from vPCO2. Pearson correlations and Bland-Altman analysis were done to examine the limits of agreement.

Results: vCO2 was in close agreement with the aHCO3 (R^2=0.93 P<0.001; 95% limits of agreement were 2.89 to -2.89 mmol/L, mean bias= -0.2 ±1.59). aPCO2 was estimated from vPCO2 to yield corrected PCO2 (cPCO2) using a regression equation, cPCO2=2.3+0.82*vPCO2. The apH was then calculated using this cPCO2 and vCO2 as follows: apH = 6.1 + log vCO2 / 0.03 x cPCO2. The corrected apH showed a close correlation and agreement with measured apH (R^2=0.81 P<0.001 (fig1) and 95% limits of agreement 0.46 to -0.39, mean bias 0.04±4.4)

Conclusions: 1)CO2 values in venous blood are in close agreement with aHCO3 calculated from the ABG. Accordingly, vCO2 can substitute for aHCO3 to recalculate the pH 2)The corrected vPCO2 and the measured vCO2 allow for an accurate calculation of apH which is close to measured apH. Moreover, this avoids altogether the measurement of venous pH which is not a good reflection of apH.



FR-PO270

Anion Gap (AG) Improves the Prediction of Ionized Hypocalcemia (HC) in Critical Care

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Background: The physiologically active form of total serum calcium (sCa) is ionized (iCa). It is reported in arterial (ABG) and venous (VBG) gas panels. The rest of sCa is bound, mainly to albumin (ALB), or chelated by small anions. Low ALB and high chelating anion levels are common in critical care patients (pts). A popular adjustment of sCa for ALB alone (BMJ 1977) yields a corrected value (cCa) that doesn't detect abnormal iCa well in such pts, perhaps because it ignores the chelating anions. AG reflects the levels of both such anions and ALB, and has been shown to correlate with iCa (Nordin 1989). We tested whether the diagnosis of HC in critical care could be improved by accounting for both AG and ALB.

Methods: In 769 critical care pts, simultaneous values of sCa (units: mg/dL), ALB (g/dL), and AG (mEq/L) were paired retrospectively with closely-timed (<20 min. apart) values of iCa (mM) derived from 309 ABGs (mean pH=7.390) or 460 VBGs (mean pH=7.363). We defined HC as iCa <1.10 in ABGs and, to adjust for the mean pH difference, as <1.11 in VBGs. The prevalence of HC was 28% (86/309) in ABGs and 21% (95/460) in VBGs. A model to predict HC in the ABG cohort was generated by multiple logistic regression with sCa, ALB, and AG as candidate predictors. Next, this model was validated in the VBG cohort. Areas under the ROC curve (AUC) of the model and of cCa were compared. Data are summarized as means [95%CI].

Results: sCa ($p<10^{-10}$), ALB (p<.004), and AG ($p<10^{-5}$) were each significant independent predictors of HC in the ABG cohort, with odds ratios of 0.064 [.029-.142], 2.87 [1.40-5.87], and 1.19 [1.11-1.28], respectively. The overall odds were $6{,}853{,}807\times0.064^{sCa}\times 2.87^{ALB}\times1.19^{AG}$. This model had a better AUC than cCa in both the ABG cohort (0.89 [.84-.93] vs 0.82 [.77-.88]; p<.005) and the VBG cohort (0.89 [.86-.93] vs 0.82 [.77-.87]; p=.0002). The predicted HC rate and the observed rate showed good agreement in the VBG cohort, divided into 4 prediction subgroups, each 25% wide (Table).

Conclusions: Adjusting sCa for both AG and ALB improves the diagnosis of HC. The absolute probability estimates of the logistic model are intuitive and may help clinicians decide when to obtain an ABG.

Funding: Veterans Affairs Support

Predicted and Observed HC Rates in the VBG Cohort

Prediction group (N)	<25% (370)	25 to <50% (44)	50 to <75% (21)	≥75% (35)
Mean predicted rate	7%	35%	64%	90%
Observed rate	9%	48%	71%	96%

FR-PO271

Etiology of the Elevated ΔAG/ΔHCO3 Ratio in Lactic Acidosis: Time for Another Delta?

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Background: The ratio of delta anion gap and delta bicarbonate ($\Delta AG/\Delta HCO_3$) is used to detect co-exisiting acid-base disorders in patients with high AG metabolic acidosis. The $\Delta AG/\Delta HCO_3$ ratio in lactic acidosis (LA) is 1.6-1.8, most commonly postulated to result from lactate anions remaining in the extracellular space while protons are buffered intracellularly. Others have proposed that hypochloremia, resulting from extrusion of cellular cations and resultant expansion of the extracellular compartment during the buffering process in LA, accounts for the increment in AG. This study examined the etiology of the elevated $\Delta AG/\Delta HCO_3$ seen in LA.

Methods: Data were obtained prospectively from adult trauma patients at a level 1 trauma center. Venous samples were drawn prior to administration of intravenous fluids. The associations between ΔLactate and ΔAG, arterial pH and $\Delta AG/\Delta HCO_3$, and serum chloride and $\Delta AG/\Delta HCO_3$ were examined using Pearson's correlations and linear regression models.

Results: 108 patients were included. 63 patients had normal serum lactate levels (≤ 2.1 mM) with a mean AG of 7.1 and a mean lactate level of 1.5 mM, the values used to calculate subsequent ΔAG and ΔLactate values. $\Delta AG/\Delta HCO_3$ was calculated for 45 patients who had elevated serum lactate levels (>2.1 mM). The mean $\Delta AG/\Delta HCO_3$ was 1.86. The mean $\Delta Lactate/\Delta HCO_3$ ranged between 0.95-1.21 and the ΔLactate only explained 24.6% of the observed variance in the ΔAG (Figure). There was no statistically significant association between arterial pH or serum chloride and the $\Delta AG/\Delta HCO_3$ ratio (p = 0.52 and 0.33, respectively).

Conclusions: The high ΔAG that results in an increased $\Delta AG/\Delta HCO_3$ ratio does not appear to be primarily a result of increased extracellular lactate, pH-dependent contribution of anions or cations to the AG, or hypochloremia. Therefore, the high $\Delta AG/\Delta HCO_3$ seen in lactic acidosis is likely a result of unmeasured organic anions, possibly including Krebs cycle intermediates. Further work to identify them needs to be carried out.

Funding: Veterans Affairs Support

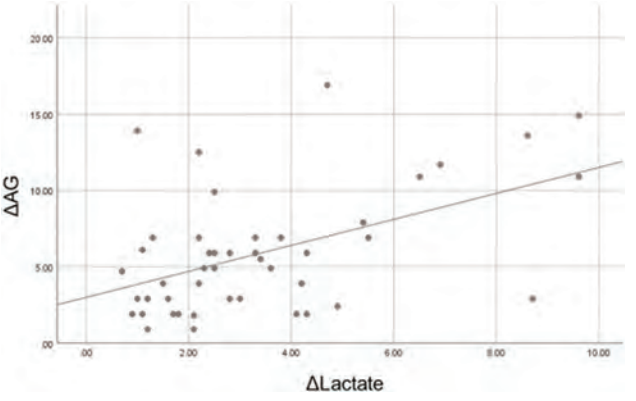

Figure. Correlation between ΔLactate and ΔAG. r = 0.496, p = 0.001.

FR-PO272

Genotype, Not Lactic Acidosis, Predicts Disease Progression in a Cohort of MELAS Patients

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Background: The clinical features of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) are heterogeneous. The role of lactic acidosis and MELAS genotypes in disease severity and progression has not been clarified. This study investigated MELAS phenotype in relation to the presence/severity of lactic acidosis and to the MELAS genotypes (classic [m.3243A>G] and other non-classic mutations).

Methods: MELAS patients in the North American Mitochondrial Disease Consortium (NAMDC) database, hospitalized in the Mayo Clinic for MELAS-related symptoms (up to Jan. 2018), were enrolled. Demographics, disease course, laboratory results, neuroimaging and muscle biopsies were obtained.

Results: Twenty-four (24) participants (15 female) were studied. Total follow-up was 170 person-years (median follow-up, 7.2 [IQR 1.3-11.6] years). The median age of disease onset was 6.5 (IQR 1.0-35.2) years. Headache, confusion, and ↓cognition were the most common initial presentations. 16.7% of the subjects died during the follow-up. Lactic acidosis, defined by serum lactate >2.2 mmol/L, was present in 83.3% of the patients with an average serum level 3.3±1.0 mmol/L. No significant association was found between the presence and severity of lactate levels and MELAS disease presentation and progression. 33.3% and 66.7% of the subjects harbored m.3243A>G and non-classic mutations, respectively. Patients with m.3243A>G mutation had a higher % occurrence of diabetes, hearing loss, cognitive dysfunction, migraine, seizures and stroke-like episodes and a lower % occurrence of skeletal myopathy than the patients with non-classic mutations, 50 *vs* 6.3; 100 *vs* 25; 87.5 *vs* 31.3; 75 *vs* 31.3; 100 *vs* 56.3; 75 *vs* 12.5; 12.5 *vs* 68.8, respectively (all P<0.05). Despite more aggressive treatment with antiepileptic, L-arginine and CoQ/Q10, cardiac functional and cognitive deterioration were more rapid and severe in patients with m.3243A>G mutation (all P<0.05). More diagnostic tests (CSF lactate, muscle biopsy and MRS) were performed for patients with non-classic mutations (P<0.05).

Conclusions: In this cohort of MELAS patients, the m.3243A>G mutation, not the presence or severity of lactic acidosis, was associated with a more severe MELAS phenotype.

FR-PO273

Effects of Treatment of Metabolic Acidosis in CKD: A Systematic Review and Meta-Analysis

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Background: Metabolic acidosis is an important risk factor for disease progression in chronic kidney disease (CKD) that also has significant adverse effects on muscle and bone. We conducted a systematic review and meta-analysis to evaluate the benefits and risks of treatment of metabolic acidosis with oral alkali supplements or reduction of acid load with dietary intervention.

Methods: We searched MEDLINE, Embase, and Cochrane Central Register of Controlled Trials for clinical trials (with a control group) of oral alkali supplementation or low acid-producing dietary intervention in stage 3-5 CKD patients for a minimum of 4 weeks. Data were pooled in a meta-analysis with results expressed as weighted mean difference (intervention versus control; WMD) for continuous outcomes and relative risk (RR) for categorical outcomes with 95% confidence intervals (CI) using a random effects model.

Results: Fourteen clinical trials were included (n=1810 participants). Both oral alkali supplementation and dietary intervention increased serum bicarbonate levels (Table). Treatment resulted in a slower decline in eGFR and a reduction in urinary albumin excretion, along with a reduction in the risk of progression to ESRD (4 trials; n=434; RR 0.32, 95% CI 0.18, 0.56). Important exclusions noted in the oral alkali studies were CKD patients with sodium-sensitive comorbidities (edema, heart failure, uncontrolled hypertension). Oral alkali supplementation was associated with significantly increased urinary sodium excretion, and trends of elevated diastolic blood pressure and increased antihypertensive therapy, although these trends were not statistically significant. Dietary intervention was associated with a significant reduction in systolic blood pressure. Included studies were of moderate quality.

Conclusions: In patients with CKD and metabolic acidosis, an increase in serum bicarbonate concentration induced either by oral alkali supplementation or reduction in dietary acid intake slows the rate of kidney function decline and reduces urinary albumin excretion.

Funding: Commercial Support - Tricida

Outcomes	No. of studies	No. of patients	Mean Difference [95% CI]	P value	I^2 (%)
Serum electrolytes					
Serum bicarbonate (mEq/L)	13	1,765	2.94 [2.09, 3.78]	<0.00001	92
Serum potassium (mEq/L)	4	558	-0.15 [-0.38, 0.07]	0.17	88
Serum calcium (mg/dL)	7	598	0.12 [-0.22. 0.46]	0.49	81
Serum albumin (g/L)	6	553	0.73 [-0.83, 2.30]	0.36	70
Kidney function parameters					
eGFR / CrCl decline (mL/min)	11	1,663	-2.71 [-4.05, -1.38]	<0.0001	51
eGFR / CrCl decline per year (mL/min/year)	9	1,568	-1.86 [-2.58, -1.15]	<0.00001	13
Urinary albumin-to-creatinine ratio (mg/g)	2	203	-51.55 [-75.73, -27.38]	<0.0001	0

FR-PO274

Serum Chloride and All-Cause Mortality in CKD

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Background: We studied the associations of serum chloride with all-cause mortality in non-dialysis dependent CKD.

Methods: We included 62,643 patients with eGFR 15-59 ml/min/1.73 m^2 (twice 90 days apart) and had serum chloride measured using the same assay in a single health care system in this analysis. Cox proportional hazards model (including time-dependent) were used to study the associations between hypochloremia (<98 mmol/l, n=5246) and hyperchloremia (>110 mmol/l, n=702) with all-cause mortality while adjusting for demographics, comorbid conditions including heart failure, use of diuretics and kidney function.

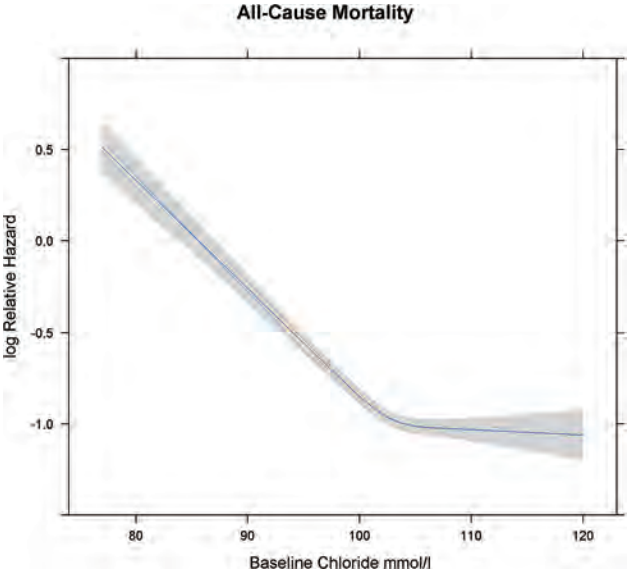
Results: During a median follow-up of 3.8 years, 18,181 patients died. In the Cox proportional hazards model using baseline serum chloride levels, hypochloremia (but not hyperchloremia) was associated with higher risk of death. Analysis of chloride as continuous measure yielded similar results. Restricting the analysis to those with normal serum sodium (n=59,964) yielded similar results. In the model with time dependent repeated measures of serum chloride, both hypochloremia (HR 2.54, 95% CI 1.44, 2.65) and hyperchloremia (HR 1.39, 95% 1.24, 1.55) were associated with higher risk of death. Presence or absence of CHF didn't modify the observed associations.

Conclusions: Among non-dialysis dependent CKD population, hypochloremia is associated with higher risk of death. Further studies examining the potential mechanisms for the observed associations are warranted.

Table 1. Associations of serum chloride with all-cause mortality in CKD

	HR (95% CI)*	HR (95% CI)**	HR (95% CI)* Among those with normal baseline sodium only
Low chloride vs. normal	1.64 (1.56, 1.72)	1.51 (1.42, 1.60)	1.65 (1.56, 1.75)
High chloride vs. normal	1.01 (0.89, 1.13)	0.99 (0.87, 1.12)	0.94 (0.83, 1.08)

*Adjusted for age, sex, race, ckd stage, BMI group, albumin, bicarbonate, diabetes, hypertension, malignancy, heart failure and diuretics
**Adjusted for above plus sodium level



FR-PO275

Chloride Increase Following Continuous Renal Replacement Therapy (CRRT) Initiation Is Associated with Mortality

Benjamin Griffin,[1] Nigel Arruda,[1] Isaac Teitelbaum,[2] Anna J. Jovanovich,[3] Muhammad Aftab,[4] Matthew Barhight,[5] Katja M. Gist,[6] Sarah Faubel.[7] *[1]University of Colorado, Aurora, CO; [2]University of Colorado Health Science Center, Aurora, CO; [3]Denver VA / University of Colorado, Denver, CO; [4]University of Colorado, Anschutz Medical Center, Aurora, CO; [5]Childrens Hospital Colorado, Aurora, CO; [6]University of Colorado, Children's Hospital Colorado, Aurora, CO; [7]University of Colorado Denver, Denver, CO.*

Background: Hyperchloremia is common in critically ill patients, and recent studies are increasingly linking elevated serum chloride with mortality. CRRT can rapidly shift chloride levels, and it is unclear what impact these changes have on patient outcomes. In this study we examined the association between changes in chloride following CRRT initiation and mortality.

Methods: We conducted a retrospective analysis of adult patients initiated on CRRT at the University of Colorado Hospital between July 2015 and September 2016. The main exclusion criterion was death within 24 hours of CRRT initiation. Chloride levels were measured upon admission to the ICU, prior to CRRT initiation, and every 8 hours thereafter until CRRT was discontinued. Changes in chloride were calculated from admission value to CRRT initiation. Changes after CRRT initiation were calculated from the first value following CRRT initiation to the highest value while on treatment. The primary outcome was in-hospital mortality. Logistic regression was used to adjust for SOFA score, body mass index, and gender.

Results: A total of 127 cases were included in the analysis. Average chloride on admission was 102 ± 6.7 mEq/L and 106 ± 8.3 mEq/L at CRRT initiation. After adjusting for all covariables, chloride on admission, though not at CRRT initiation, predicted mortality: for every 1 mEq/L increase in admission chloride there was an 8% increased risk of mortality. Mean changes in chloride from admission to CRRT initiation and from CRRT initiation to end of therapy were 3.6 ± 7.4 mEq/L and 2.8 ± 3.5 mEq/L respectively. Change in chloride from admission to CRRT initiation was not significantly associated with in-hospital mortality. Notably, change in chloride of 1 mEq/L following CRRT initiation was associated with a 15% increased risk of mortality.

Conclusions: Hyperchloremia upon ICU admission is associated with increased mortality. Increases in chloride levels following CRRT initiation are also associated with mortality, even after adjusting for illness severity. The role of chloride in critical illness, particularly in those requiring CRRT, warrants further investigation.

Funding: Other NIH Support - T32 DK 007135

FR-PO276

Phosphorous and Magnesium Nadirs Following Continuous Renal Replacement Therapy (CRRT) Initiation Are Associated with Mortality

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Background: Severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is common in the intensive care unit, complicating 5% of all admissions. As CRRT therapy fluids typically contain no phosphorus and low magnesium concentrations, CRRT is known to rapidly deplete these electrolytes, and their repletion during CRRT is often required. Studies examining the impact of these electrolyte losses on patient mortality have been inconclusive. The purpose of this study was to examine the impact of phosphorous and magnesium levels on mortality in the setting of CRRT.

Methods: We conducted a retrospective analysis of adult patients initiated on CRRT at the University of Colorado Hospital between July 2015 and September 2016. Patients were excluded if they died within 24 hours of CRRT initiation. Phosphorous and magnesium levels were collected at CRRT initiation and every 8 hours thereafter. The primary outcome was in-hospital mortality. Logistic regression was used to adjust for SOFA score, body mass index, and gender.

Results: A total of 155 cases were included in the analysis. Mean phosphorous and magnesium levels at the time of CRRT initiation were 5.4 ± 2.7 mg/dL and 2.28 ± 0.58 mg/dL, respectively. Neither baseline levels nor changes from baseline were associated with mortality. However, higher nadir levels of both phosphorous and magnesium were independently associated with mortality, even after adjusting for confounders.

Conclusions: While baseline phosphorous and magnesium values were not associated with mortality, nadir levels were. We expected lower nadir levels to be associated with mortality, but observed the opposite. Lower nadir levels may have been indicative of higher dose or higher quality of CRRT. The frequency and quantity of electrolyte repletion were not evaluated in this study. Further investigation into the role of phosphorous and magnesium in AKI requiring CRRT is warranted.

Funding: Other NIH Support - T32 DK 007135

Table 1. Final multivariate models for in-hospital mortality

Variable	OR (95% CI)	p-value
Final Phosphorous Model*		
Initial Phosphorous	1.06 (0.88 – 1.26)	0.6
Nadir Phosphorous	1.60 (1.13 – 2.24)	0.007
Final Magnesium Model*		
Initial Magnesium	0.94 (0.44 – 2.00)	0.9
Nadir Magnesium	6.78 (1.64 – 28.02)	0.008

* Final model was adjusted for SOFA score, body mass index, and gender

FR-PO277

Comparison of Indicators of Fluid Overload in Hemodialysis Patients

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Background: Fluid overload (FO) contibutes to mortality in hemodialysis (HD) patients and is often undiagnosed. FO is determined by physical exam including systolic and diastolic blood pressure (SBP, DBP), lung crackles (rales), lower extremity edema (LEE), and jugular venous distention (JVD). Other signs of FO include serum n-terminal pro-BNP (BNP) and findings on chest x-ray (CXR) or thoracic computed tomography (CT). Point-of-care ultrasound is a as powerful tool for determination of FO via measurements of the inferior vena cava (IVC) and quantitative 28-point lung ultrasonography for B-line score (BLS). We present a cohort study of HD patients comparing indicators of FO.

Methods: Patients with ESRD on HD were enrolled from a large urban emergency department at a referral center. Patients were excluded if they were unable to consent. Indicators of FO were obtained prior to first HD including BLS (0-280). IVC size and collapse was graded by 2 independent observers on a 4-point scale. 10 indicators of FO (BLS, IVC, CXR, CT, BNP, rales, LEE, JVD, SBP, DBP) were compared against presence or absence of FO as determined by the treating nephrologist or on chart review.

Results: Of 101 patients enrolled, median age was 60, 51% were male, 84% identified as Black or African American. Comorbidities included 65% diabetic, 27% coronary artery disease, 33% airways disease, 40% had systolic heart failure, 75% diastolic heart failure. Median dialysis vintage was 33 months. Access type was 54% arteriovenous fistula, 29% graft, and 17% catheter. ESRD vintage was 33 months. Residual renal function was minimal. 62% of patients had FO on arrival and 27% of visits were for FO. BLS was available for 101 patients with median score of 34. Area under the receiver-operator characteristic curve (AUC) was 0.95 for BLS [95% CI 0.92-0.99] with optimal cutoff of 30. AUC was 0.60 for edema [0.53-0.68], 0.60 for rales [0.54-0.66], 0.53 for JVD [0.50-0.56], 0.53 for SBP [0.41-0.65], 0.49 for DBP [0.38-0.61]. IVC was obtained on 37 patients AUC 0.78 [0.61-0.95]. BNP was obtained on 39 patients AUC 0.80 [0.63-0.98]. CXR was obtained on 76 patients AUC 0.71 [0.61-0.80]. CT was available on 20 patients AUC 0.91 [0.81-1.00].

Conclusions: Quantitative BLS outperforms conventional physical exam, serologic, and other imaging indicators in determination of FO in HD patients.

FR-PO278

Fluid Overload Is Associated with Major Adverse Kidney Events in Critically Ill Patients with AKI Requiring CRRT

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Background: Fluid overload (FO) has been associated with adverse outcome. The purpose of this study was to examine the association between FO and major adverse kidney events (MAKE) in critically ill patients with AKI requiring CRRT.

Methods: This was a single-center, retrospective, cohort study of ICU patients that suffered from AKI requiring CRRT. Patients with ESRD, kidney transplant or baseline eGFR <15 were excluded. FO was defined as cumulative fluid balance (from hospital admission to CRRT initiation) expressed as a percent of admission body weight. MAKE was determined up to 90 days following hospital discharge and consisted of the composite of mortality, RRT dependence and failure to recover at least 50% of baseline eGFR if not on RRT. A secondary outcome of ventilator-free days was also examined. Multivariable logistic regression and linear regression models were conducted.

Results: A total of 481 patients were included in the study. The median (IQR) FO was 9.9% (2.8 – 20.2%). FO ≥10% (clinical cut-off reportedly associated with adverse outcome) was found in 238 (49.5%) of patients on the day of CRRT initiation. MAKE was more frequent in patients with FO ≥10% vs <10% (79.4% vs 71.6%, p=0.047). After adjustment for demographics, comorbidity, acuity of illness, time from ICU admission to CRRT initiation, and baseline eGFR, FO ≥10% was independently associated with MAKE (OR, 1.60, 95% CI, 1.02 – 2.52). Furthermore, for each one-day increment from ICU admission to CRRT initiation, there was a 3% increase in the adjusted odds of MAKE (p=0.02). FO ≥10% was also associated with less ventilator-free days in adjusted models (p<0.01).

Conclusions: FO ≥10% on the day of CRRT initiation was independently associated with major adverse kidney events and less ventilator-free days in critically ill patients that suffered from AKI requiring CRRT. FO should be a clinical parameter routinely included in the evaluation of CRRT need in critically ill patients.

Funding: Other NIH Support - Early Career Pilot Grant from NCATS/NIH

FR-PO279

Fluid Overload Predicts Mortality in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

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Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is common in the intensive care unit (ICU) and has a mortality rate of >50%. Fluid overload (FO) >10% of body weight has been shown to be deleterious in ICU patients, but studies specifically evaluating patients with severe AKI requiring continuous renal replacement therapy (CRRT) remain limited. Furthermore, the effects of volume removal following CRRT initiation are not well described. The purpose of this study was to examine the impact of (1) FO at CRRT initiation and (2) fluid removal on in-hospital mortality.

Methods: We conducted a retrospective analysis of adult ICU patients who underwent CRRT for a minimum of 24 hours at University of Colorado Hospital from September 2015 to July 2016. Patients were characterized by fluid balance at initiation of CRRT and total volume removed by CRRT during their hospitalization. The primary outcome was in-hospital mortality. Logistic regression was used to adjust for Sequential Organ Failure Assessment (SOFA) score, gender, and body mass index.

Results: A total of 87 patients were included in the final analysis, of which 41 (47.1%) patients had FO >10% of body weight at the time of CRRT initiation. Negative fluid balance on CRRT was achieved in 64 (73.5%) patients. The adjusted odds ratio for mortality in those with >10% FO was 2.69 (Table 1). There was no association between mortality and negative fluid balance on CRRT.

Conclusions: Our study adds to prior studies showing that fluid overload is independently associated with increased mortality in ICU patients requiring CRRT. However, we found no significant association between fluid balance during CRRT and mortality. The effect of fluid balance on mortality in ICU patients requiring RRT, both before and after RRT initiation, merits further investigation.

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Table 1. Final multivariate model for in-hospital mortality

Variable	OR (95% CI)	p-value
Fluid Overload > 10%*	2.69 (1.02 – 7.14)	0.046
Negative Fluid Balance on RRT^	1.16 (0.39 – 3.02)	0.9
SOFA Score	1.14 (0.97 – 1.34)	0.1
Female Gender	0.79 (0.32 – 1.99)	0.8
Body Mass Index	1.02 (0.96 – 1.34)	0.5

* Comparison group is Fluid Overload < 0%

^ Comparison group is Positive Fluid Balance on RRT

FR-PO280

Liver Stiffness Reflecting Renal Congestion Predicts Renal Outcome in Patients with Congestive Heart Failure

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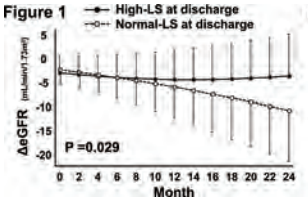
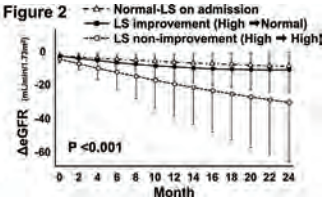
Background: Renal congestion is one of the underlying mechanisms for acute kidney injury in congestive heart failure (CHF). Reportedly, ultrasonographic liver stiffness (LS), originally developed for assessment of liver cirrhosis, reflects right atrial pressure (RAP) with great accuracy in CHF without liver cirrhosis. However, its association with renal congestion and its clinical relevance remain uncertain.

Methods: In this prospective cohort study (*JACC Cardiovasc Imaging* 2018), we enrolled inhospital patients with acute heart failure in an educational hospital. LS was evaluated in all participants. Using longitudinal inhospital data, we investigated the association between time-dependent LS and kidney length. High-LS was defined as ≥9 kPa (75 percentile, corresponding to RAP of ≥8.9 mmHg). Exposures were LS levels at discharge and changes in its levels during hospitalization. An outcome was eGFR change over time after discharge. We employed a multivariable mixed effects model with time-dependent eGFR as a dependent variable. In sensitivity analyses, we used coarsened exact matching to balance the baseline clinical characteristics.

Results: Among the 251 patients, median eGFR, BNP, LS at discharge, and follow-up were 54.7 mL/min/1.73m^2, 188.7 pg/mL, 6.3 kPa, and 12.0 months, respectively. During hospitalization, in patients with eGFR>30 mL/min/1.73m^2, LS decrease was observed in parallel with decrease in kidney length (P=0.01), suggesting a rationale to use LS as a proxy of renal congestion. After adjustment for 16 factors including BNP, ejection fraction, and blood pressure, patients with high-LS at discharge had lower eGFR over time than the rest of the patients (P=0.03) (Figure 1). In patients with LS improvement from high- to normal-LS during hospitalization, eGFR trajectory was higher than that in patients without improvement (P<0.01) and comparable to that in patients with normal-LS on admission (P=0.81) (Figure 2).

Conclusions: LS reflecting renal congestion predicts worse renal outcome in CHF. Renal function should be followed up carefully in patients with a high LS value at discharge.





FR-PO281

Simplified, Simulated Sodium Kinetic Modeling for Correction of Hyponatremia by Continuous Venovenous Hemofiltration

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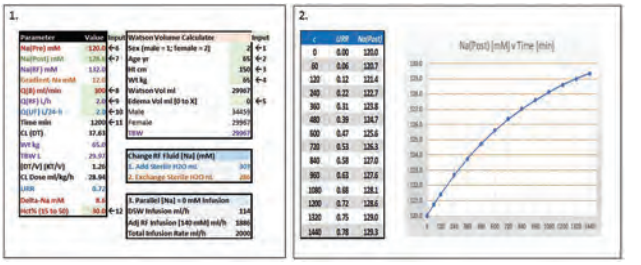
Background: Management of hyponatremic, oliguric patients is challenging using conventional dialytic therapy. Osmotherapy, targeted plasma sodium concentration [Na] elevation, delivered by continuous renal replacement therapy (CRRT), must be safely achieved without overcorrection of [Na], i.e., >6 to 8 mmol/L in 24 hours. Predictive modeling of controlled osmotherapy requires an appreciation of CRRT and ongoing Na kinetics. Utilizing an approach based on near-equivalence of Na dialysance and urea reduction ratio (URR), we developed a model that calculates [Na] elevations precisely using predilution continuous venovenous hemofiltration (CVVH), and contrasts the conventional strategy of using replacement fluid [Na] as the post-treatment goal [Na].

Methods: The model defines the post-treatment [Na] (Na_{Post}) at time (t), thereby defining ΔNa, the difference between pre-therapy [Na] (Na_{Pre}) and Na_{Post}. A [Na] gradient (,Na = Na_{RF} – Na_{Pre}) is defined by URR, derived from Na dialysance (D). Because D approximates K_{Urea}, URR is derived from Watson volume, treatment time, and D, determined by Q_B (hematocrit-adjusted blood flow rate), Q_{RF} (RF rate), and Q_{UF} (ultrafiltration rate). URR represents the time-varying decrease of ,Na, i.e., Na_{post} = [(1 – URR) × Na_{Pre} + (URR × Na_{RF})] and Na_{RF} = Na_{Pre} + (ΔNa/URR).

Results: The model calculates, tabulates, and plots time-varying Na_{Post}. Panel 1 of figure displays model input and output parameters for a hypothetical scenario of an anuric hyponatremic patient with tabulated data and graph in panel 2. Model extensions permit simultaneous initial targeting of Na_{Post}, URR, or effluent dose. Integrated calculations determine RF dilutions or infusion rates of parallel hypotonic solutions when RF solutions cannot be adjusted.

Conclusions: We conclude that safely controlled osmotherapy of oligoanuric, hyponatremic patients by predilution CVVH is feasible, and can determine time-varying Na_{Post}. Validation of the model in various clinical scenarios of hyponatremia is required to support utility.



FR-PO282

Continues Renal Replacement Therapy: A Simple Approach for Treating Hyponatremia

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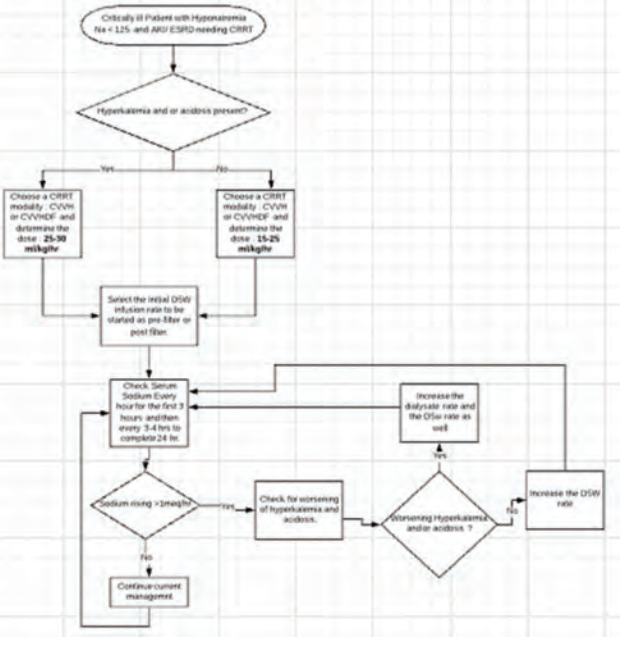
Background: Severe hyponatremia (serum sodium(Na) <125) is frequently seen in critically ill patients. Often, this is unresponsive to fluid restriction, diuretics or 3% saline. The combination of hyponatremia and acute kidney injury (AKI) needing continuous renal replacement therapy (CRRT) makes management of hyponatremia challenging. Indication for CRRT include acidosis, volume overload & electrolyte abnormalities. Dialysate/replacement fluid solutions used during CRRT have a standard Na concentration of 140 meq/L. When dosed at 25-30 ml/kg/hr there is a risk of rapid correction of Na level & osmotic demyelination syndrome. There is limited data for CRRT in correcting hyponatremia. Few complex formulas help to calculate the appropriate CRRT dose for Na correction, providing adequate clearance. We report our experience of managing 33 cases with severe hyponatremia using CRRT.

Methods: Out of 33 patients with severe hyponatremia, 28 had AKI stage III needing CRRT & 5 had ESRD. 30 patients required vasopressor support. CRRT was initiated in all for correction of Na at 15-25 ml/kg/hr. Pre-pump infusion of D5W was added to dilute the replacement fluid. All the patients had the serum Na level checked every hour for the first 3 hours and then every 3-4 hours once a Na 125 mmol/l was reached.

Results: A steady 6-8 mmol/day rise in serum Na level was obtained along with the correction of other abnormalities & no complications.

Conclusions: This case series highlights the applicability of a simplified practical approach without using complex formulas to safely manage severe hyponatremia using CRRT despite a standard Na concentration in the dialysate/replacement solution. Close serum Na monitoring is imperative to adjust the delivered CRRT and D5W infusion doses.



FR-PO283

Sodium Fluctuations and Mortality in a General Hospitalized Population

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Background: Aim of our study was to describe the association between natremia (Na) fluctuation and hospital mortality in a general population admitted to a tertiary medical center.

Methods: We performed a retrospective observational study on the patient population admitted to the Policlinico A. Gemelli Hospital between January 2010 and December 2014 with inclusion of adult patients with at least two Na values available on the biochemistry database and with a normonatremic condition at hospital admission. Patients were categorized according to all Na values recorded during hospital stay in the following groups: hyponatremia, normonatremia, hypernatremia, mixed dysnatremia. The difference between the highest or lowest Na value reached during hospital stay and the Na value read at hospital admission was used to identify the maximum Na fluctuation. Cox proportional hazards models was used to estimate adjusted HRs for hospital mortality with the group of dysnatremia and with quartiles of Na fluctuation. Covariates assessed were age, sex, highest and lowest Na level, Charlson-Deyo index score, cardiovascular diseases, cerebrovascular diseases, dementia, congestive heart failure, kidney disease, eGFR.

Results: 57,156 admissions matched inclusion criteria. Incident dysnatremia was independently associated with in-hospital mortality (incident hyponatremia HR 2.55, 95% CI 2.14, 3.04, p<0.001; incident hypernatremia: HR 5.71, 95% CI 4.69, 6.95, p<0.001; mix-dysnatremia: HR 4.44, 95% CI 3.23, 6.10, p<0.001). We found a higher risk of in-hospital death by linear increase of quartile of Na fluctuation (p trend <0.001) irrespective of severity of dysnatremia (HR of 1.60, CI 95% 1.17, 2.20, p=0.004, in the 4th percentile Na fluctuation compared with the first one; Figure).

Conclusions: Fluctuation of natremia during hospital stay is a prognostic marker for hospital death independently by dysnatremia severity.

Association between quartile of sodium fluctuation (expressed as percentage) and in-hospital mortality

	1st quartile (<1.40%)	2nd quartile (1.40% - 2.13%)	3rd quartile (2.14% - 3.52%)	4th quartile (>3.52%)	p-value trend
N	14,598	14,272	14,505	13,781	
In-hospital death (N, %)	61 (0.4)	63 (0.4)	132 (0.9)	478 (3.5)	
HR crude (CI 95%)	1.00 (Reference)	0.83 (0.59, 1.18)	1.34 (0.99, 1.81)	3.22 (2.47, 4.19) P<0.001	P<0.001
HR adjusted for Na*	1.00 (Reference)	0.75 (0.51, 1.04)	1.10 (0.80, 1.50)	1.86 (1.36, 2.53) P<0.001	P<0.001
HR adjusted (CI 95%)^	1.00 (Reference)	0.67 (0.47, 0.96)	1.01 (0.74, 1.38)	1.60 (1.17, 2.20) P=0.004	P<0.001

*Adjusted for the lowest and the highest serum Na level reached during hospital stay.
^Adjusted for baseline covariates (age, sex, Charlson-Deyo Score, diabetes, cardiovascular diseases, congestive heart failure, neoplasms, eGFR, kidney disease, cerebrovascular disease, dementia, the lowest serum Na level reached in-hospital and the highest serum Na level reached during hospital stay).

FR-PO284

Maintaining Sodium Homeostasis During Liver Transplant - A Novel Approach

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Introduction: Following two cases of osmotic demyelination syndrome (ODS) in patients with near-normal serum sodium (Na) levels (134 mEq/L) at the start of orthotopic liver transplantation (OLT) at our institution, we sought a systems approach for minimizing ODS. Many patients presenting for OLT with hyponatremia have concomitant renal dysfunction necessitating intraoperative continuous renal replacement therapy (CRRT). Intraoperative CRRT using standard dialysate with a Na concentration of 140mEq/L could pose a risk due to rapid Na rise. A multi-disciplinary approach was taken with anesthesiology, nephrology, transplant surgery, and pharmacy to create a pathway for low Na dialysate with a Na concentration of 130mEq/L for OLT patients with hyponatremia that also need intraoperative RRT. Commercially available low Na dialysate does not contain calcium (Ca), which requires frequent replacement at baseline during an OLT. Pharmacy presented the data along with a failure modes and effects analysis (FMEA) to the hospital's drug policy committee and gained approval for compounding calcium into our commercially available low Na dialysate.

Case Description: Following implementation of our system change, a patient presented for OLT with a MELD-Na of 30, hepatorenal syndrome, acidosis, hyperkalemia, and hyponatremia (Na 124). This patient was admitted to the ICU preoperatively and initiated on CRRT with low Na dialysate compounded with Ca while waiting for the liver to arrive. Intraoperative fluid administration, transfusion, electrolytes, and acid-base status were managed in standard fashion plus the addition of low Na dialysate. At the end of the OLT, the Na had only risen to 126 over 14 hours. The low Na dialysate continued three additional days postoperatively in the ICU to allow the Na to gradually normalize. Four days after presentation, the Na was 135 and the patient was transitioned to standard dialysate and never developed ODS. He is currently off dialysis with an eGFR of 33.

Discussion: ODS occurs in approximately one percent of OLT patients with associated high morbidity and mortality. The rate of Na rise is strongly correlated with the development of neurologic changes and standard dialysate can contribute to that. A multi-disciplinary system based approach achieved patient safety and allowed a platform for broader implementation to hyponatremic patients without renal dysfunction.

FR-PO285

Hyponatremia Associated with Development of Sepsis

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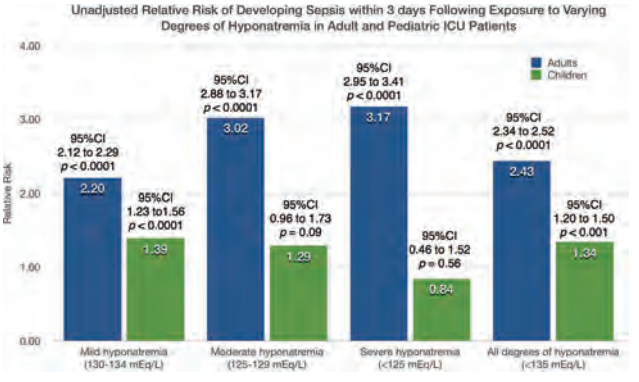
Background: Hyponatremia is a common electrolyte imbalance in critically ill patients and is associated with increased mortality and morbidity. Experimental evidence suggest that hyponatremia may compromise immune cell function. Thus, we sought to determine whether an association between hyponatremia and sepsis was present in critically ill adults and children.

Methods: Data was obtained from databases of 46,329 adult and 12,806 pediatric patients from the ICUs of UPMC hospitals. We included patients with a Na value measured within 6 hours of ICU admission and excluded patients with sepsis on admission. We analyzed the association between hyponatremia by severity (serum Na <135 mEq/L, mild; 130-134 mEq/L, moderate; 125-129 mEq/L, severe <125 mEq/L) and the development of sepsis over 7 days following the occurrence of hyponatremia.

Results: A total number of 39,403 adults and 3,977 children were included in the analysis. 40% of adult patients and 14% of pediatric patients had hyponatremia with rates of sepsis of 24% and 33% respectively. Critically ill patients with hyponatremia were at increased risk of developing sepsis (RR 2.43 for adult, RR 1.34 for pediatric patients). Risk for developing sepsis increased with the severity of hyponatremia in adults.

Conclusions: Critically ill patients with hyponatremia are at increased risk for developing sepsis. Further analysis is required to understand the nature of this relationship and to better control for confounding.



Unadjusted Relative Risk of Developing Sepsis within 3 days Following Exposure to Varying Degrees of Hyponatremia in Adult and Pediatric ICU Patients

FR-PO286

Communication of Hyponatremia and Outcomes

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Background: Prior literature documents the prognostic importance of hyponatremia but it is commonly treated as a peripheral issue during hospital admissions. We seek to quantify the degree to which hyponatremia is reported to outpatient providers and to evaluate factors associated with communication and associations between communication and important clinical outcomes.

Methods: With IRB approval, we conducted a retrospective cohort study of patients admitted to the Weill Cornell Campus of the New York-Presbyterian Hospital in January 2014 with corrected serum sodium <130 mEq/L who survived the index hospitalization. Discharge summaries were reviewed for mention of hyponatremia; charts were reviewed for pertinent clinical data. Patients who did and did not have hyponatremia mentioned in the discharge summary were compared using chi-square (or Fisher's Exact) and Kruskal-Wallis tests for categorical and continuous variables, respectively. Statistical significance was determined be at the 0.05 alpha level.

Results: Hyponatremia was mentioned in 34% of 127 discharge summaries; patients with communicated hyponatremia were older (mean 72 vs 63 years; p=0.003) and had lower nadir (125 vs 128 mEq/L; p<0.001) and discharge sodium (132 vs 135 mEq/L, p=0.002). Communication was associated with diagnosis of hyponatremia within 24 hours of admission (p=0.006) and admission to general medicine (47% communicated) versus other hospital service (27%) (p=0.02). The cause of hyponatremia was more often SIADH (p<0.001) or hypovolemia (p=0.005) in the communication group. Communication of hyponatremia was not associated with improved one-year mortality, readmission or

readmission with hyponatremia. Patients with communicated hyponatremia were less likely to follow up with outpatient providers in our system (60% vs. 81%, p=0.03); of those who followed up in our system, hyponatremia was mentioned in an outpatient provider's note only twice.

Conclusions: Our results suggest that hyponatremia is infrequently communicated to outpatient providers. Higher rates of communication were associated with severity and timing of hyponatremia and hospital service. The lower rate of follow up in patients with communicated hyponatremia and outpatient providers' response may explain the lack of difference in clinically important outcomes. Alternatively, communication may be less for patients planning to follow up internally.

FR-PO287

Hyponatremia and Mortality Among Very Elderly Residents in a Geriatric Health Service Facility

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Background: Hyponatremia is common among elderly patients. This study aimed to examine the prognostic value of hyponatremia among elderly residents in a geriatric facility.

Methods: We retrospectively examined the association between serum sodium levels and mortality among 118 residents (82% female, mean age 85.5 years) in a single geriatric health service facility. We defined hyponatremia as Na <135 mEq/L. On the basis of single measurements of serum sodium at periodic examinations, the patients were divided into hyponatremia and non-hyponatremia groups. Multivariable Cox proportional hazards models were used to evaluate the effect of hyponatremia on mortality from May 2005 to April 2007.

Results: Thirty-three patients (28%) had hyponatremia. Over a 1-year follow-up period, the cumulative survival rate was significantly lower in patients with hyponatremia than in those without hyponatremia. In a multivariate analysis, including traditional risk factors for death, hyponatremia was associated with an increased mortality risk (adjusted hazard ratio, 2.73; 95% confidence interval, 1.01–5.16; $p = 0.047$).

Conclusions: Hyponatremia is common and is a predictor of mortality in the near future among very elderly residents of a geriatric facility.

FR-PO288

Clinical Significance of Serum Sodium in Insomnia Patients

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Background: Hyponatremia is thought to be associated with attention deficits, cognitive decline, gait disturbances, and fracture even if it is asymptomatic. However, there is no study of hyponatremia and its clinical effects in patients with insomnia. We investigated the prevalence of hyponatremia and the clinical relevance of serum sodium concentration in patients with insomnia.

Methods: We retrospectively enrolled patients with a diagnosis of insomnia from January, 2011 to December 2012. Among these, we excluded patients who were being treated with cancer or not cured, or had renal replacement treatment. Hyponatremia was defined as a serum sodium concentration of less than 135 mmol/L. We divided into 3 groups according to serum sodium: tertile 1 (<138 mmol/L), tertile 2 (138.0-140.9 mmol/L), and tertile 3 (≥141.0 mmol/L). Multivariable logistic regression was used to evaluate the association between serum sodium level and all-cause mortality, acute kidney injury (AKI).

Results: A total of 443 patients with insomnia were included, of which 14.9% (n=67) had hyponatremia. Patients with lower serum sodium concentration tended to have lower hemoglobin, calcium, phosphorus and albumin level and older age. During median follow up 48.5 months, 19.8% (n=33), 8.4% (n=12), 2.3% (n=3) patients died in tertile 1, 2, and 3. Twenty one percent (n=35), 11.9% (n=17), 11.3% (n=15) patients experience AKI in tertile 1, 2, and 3. Tertile 1 was significantly associated with all-cause mortality (reference tertile 2 group, Hazard ratio 1.96; 95% confidence interval 0.66 – 5.80; P=0.006) even after adjusted co-variates. However, there was no significant relationship between tertile 1 and AKI.

Conclusions: In patients with insomnia, lower serum sodium is significantly associated with all-cause mortality and thus we should have continuous interest in hyponatremia, and we need to identify the cause of hyponatremia and correct the correctable factors.

FR-PO289

No Added Salt…The Epidemiology of Severe Hyponatraemia in a Tertiary Referral Hospital

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Background: Severe hyponatremia is defined as a serum sodium concentration less than or equal to 120mmol/L and can be associated with mild symptoms (e.g. decreased concentration) to more severe life-threatening symptoms (e.g. seizures and coma). Patients with severe symptomatic hyponatraemia should be managed with hypertonic saline to correct their serum sodium and reduce the morbidity and mortality associated with this condition. In this retrospective study, the aetiology, management and outcomes of severe hyponatraemia were examined over a 5-year period

Methods: All patients admitted to a tertiary referral hospital with serum sodium ≤120mmol/L were identified through the biochemistry laboratory database from January 2013 – December 2017 inclusive. Patient data was extracted from hospital records and included age, gender, presenting complaint, co-morbidities, medications, clinical exam findings, treatment received, laboratory results, length of stay, nephrology consult and in-hospital mortality.

Results: A total of 592 patients met the inclusion criteria, 46.7% (n=277) were male, 24.8% (n=147) were aged >80years. The commonest causes were hypovolaemia (30%, n=178), hypervolaemia (15%, n=89), Syndrome of Inappropriate ADH secretion (13.7%, n=81) and medication induced (15%, n=89), of which thiazides were the most common. The most common symptoms were falls (17.2%, n = 102), confusion (11.6%, n=69) and GI upset (9.7%, n=58). 7.2% (n=43) presented with seizures. Hypertonic saline was indicated in 26.2% (n=155) of cases, but of these only 19.4%(n=30) have it documented as part of their treatment, 5% of total cases. Of the patients who presented with seizure, only 16.3% (n=7) received hypertonic saline. Average length of stay for these patients was 25days. Mortality for an admission complicated by severe hyponatremia was 14% (n=84), with a one year mortality of 27.4% (n=162).

Conclusions: Severe hyponatraemia is associated with significant symptoms, length of stay and 1-year mortality. Hypertonic saline is indicated in the treatment of severe symptomatic hyponatraemia and is proven to be a safe therapy, but only a minority of patients received this important treatment. Further education is required in order to improve the management and outcomes in this patient group.

FR-PO290

Optimal Cut-Off Level of Urine Sodium in Differentiating Hypovolemic Hyponatremia and SIADH

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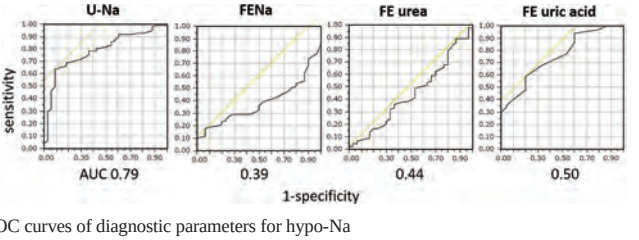
Background: The European clinical guideline recommends using 30 mEq/L as the cut-off level of urine sodium (U-Na) to differentiate hypovolemic hyponatremia (hypo-Na) from others. However, due to the complexity of hyponatremia, we frequently encounter the patients whose U-Na are not completely suppressed and wonder the accuracy of this cut-off level. This study is to examine the diagnostic performance of U-Na and other parameters, and clarify optimal cut-off level of U-Na in patients with hyponatremia.

Methods: In this single-center, retrospective cohort study, we collected data of hospitalized patients with profound hypotonic hyponatremia evaluated by nephrology consultants, defined by serum Na (S-Na) ≦ 120 mEq/L and serum osmolality (Osm) ≦ 280 mOsm/kg H_2O from April 2011 to September 2017. The final diagnosis of hyponatremia was categorized into either hypo-Na or SIADH based on nephrologist evaluation through the hospital course. Patients with urine Osm ≦ 100 mOsm/kg H_2O or diagnosis of polydipsia, adrenal insufficiency and hypervolemia were excluded. The diagnostic accuracy of U-Na, fractional excretion of sodium (FENa), FE urea, and FE uric acid for hypo-Na were evaluated by receiver-operating characteristic (ROC) curves and the areas under the ROC curves (AUC).

Results: Of 130 patients (age 75.7 ± 13.1, 51% of males, minimal S-Na 115 ± 4.1 mEq/L), 97 patients (75%) were diagnosed as hypo-Na. In the ROC curves, U-Na showed the best diagnostic utility in differentiating hypo-Na and SIADH with AUC of 0.79 compared to FENa, FE urea and FE uric acid (AUC of 0.39, 0.44 and 0.50, respectively) (Figure). The optimal cut-off level of U-Na was 56 mEq/L with sensitivity of 64% and specificity of 90%, which was not significantly changed when assessed in patients with diuretics use (n=40) or not (n=90) with cut-off levels of 64 mEq/L and 56 mEq/L, respectively.

Conclusions: U-Na performed the best in differentiating hypo-Na and SIADH in hyponatremic patients with a cut-off level of 56 mEq/L, higher than that recommended in the current guidelines. The diagnostic accuracy was not influenced by diuretics use.



ROC curves of diagnostic parameters for hypo-Na

FR-PO291

Safety and Efficacy of Tolvaptan in Lung Cancer with Hyponatremia Due to the Syndrome of Inappropriate Antidiuretics Hormone

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Background: Hyponatremia is the most common electrolyte disorder in lung cancer patients and has been associated with poor prognosis. We investigated the safety and

efficacy of tolvaptan in lung cancer with the syndrome of inappropriate antidiuretics hormone(SIADH).

Methods: We reviewed medical record database for all lung cancer patients with SIADH treated with tolvaptan. All patients received 7.5mg/day as an initial dose. Overcorrection of serum sodium was defined as an increased of serum sodium exceeding 12 mmol/L over 24 hours or 8 mmol/L over 8 hours.

Results: 41 patients (32 male patients, aged 67.61 ± 10.1 years) with lung cancer treated with tolvaptan were enrolled. Serum sodium increased significantly from baseline during the first 24 hours (122.68 ± 4.54 vs 132.05 ± 4.27 mmol/L, p=0.03), and then plateaued until day 14(134.27 ± 6.11 mmol/L). There was no difference in baseline sodium level according to a type of lung cancer(121.97 ± 3.47 vs 123.68 ± 5.26 mmol/L, p=0.223). In small cell lung cancer, the change was significantly higher (11.09 ± 2.83 mmol/L) than in non-small cell lung cancer (7.36 ± 6.07 mmol/L, P= 0.029). But, there was no difference in the rate of correction between severe hyponatremia(<125 mmol/L) and moderate hyponatremia (p=0.48). Also, there was no difference in the rate of correction according to BMI (p=0.057). No serious adverse events were reported, but in 36.6 % of patient hyponatremia was overcorrected and in 14.6% of patients a slight increase in liver function test was observed.

Conclusions: In patients with lung cancer patient with SIADH, initial dose 7.5 mg tolvaptan was well-tolerated, relatively safe and effective.

FR-PO292

Non-Osmotic Sodium Storage Capacity in Patients with Glycosaminoglycan Alterations

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Background: In the 2-compartment model the kidneys are believed to be solely responsible for matching Na^+ intake and excretion. Recent observations that Na^+ can accumulate in the body without concurrent water retention, via binding to negatively charged glycosaminoglycans (GAG), challenge this model. Type 1 diabetic (DM1) patients are characterized by acquired GAG loss while hereditary multiple exostosis (HME) patients have defective heparan sulfate GAG polymerization due to mutations in either EXT1 or EXT2 genes. We questioned whether non-osmotic sodium storage is impaired in DM1 and HME patients as compared to healthy controls (HC).

Methods: Eight DM1, 7 HME patients and 11 HC were included, all non-smoking males with normal kidney function, BMI and blood pressure. Non-osmotic storage capacity was estimated after acute infusion of 0.54±0.1L hypertonic saline (2.4±0.2%) by measuring plasma $[Na^+]$ and urinary Na^+ and K^+ excretion at various time points during 4-hr follow-up. We compared the observed changes in plasma $[Na^+]$ with the expected changes that were estimated by Adrogue-Madias (AM) and Nguyen-Kurtz formulas, which are based on the 2-compartment model.

Results: Maximum increase (mean (SE)) of plasma $[Na^+]$ was reached 5 minutes after infusion in all 3 groups (DM1, 5.4±0.6; HME, 4.1±0.5, HC 3.5±0.4 mmol/L). The plasma $[Na^+]$ rise 5 minutes after infusion in DM1 was significantly higher than in HC (p=.01), without differences between HC and HME patient (p=.42). The formulas poorly predicted plasma $[Na^+]$ 5 minutes after infusion, with observed changes in plasma $[Na^+]$ exceeding expected changes. When using AM, DM1 showed the biggest discrepancy between observed and expected change in plasma $[Na^+]$ (DM1, -1.98±0.6, p=.01; HME, -0.87±0.5, p=.12; HC -0.31±0.4 mmol/L, p=.46). In all groups, the observed Na^+ and K^+ excretion were significantly lower compared to the expected excretion, but no differences between groups were observed. Blood pressure was not affected by infusion.

Conclusions: DM1 patients have reduced ability for non-osmotic sodium storage, possibly due to a reduced amount of GAGs. HME patients do not show a reduced ability for non-osmotic sodium storage, perhaps by compensatory synthesis GAGs other than heparan sulfate.

FR-PO293

Expression of Sodium Renal Transporters in Urinary Exosomes from Patients with Edema Associated with Cirrhosis, Heart Failure, or Nephrotic Syndrome

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Background: The formation of edema requires sodium retention along the nephron. The molecular pathways in humans leading to salt retention in edematous states remain elusive. The use of urinary exosomes (UE) is a non-invasive powerful tool to study the pathophysiology of renal diseases. Here we analyzed the expression of a variety of renal sodium transporters in UE from patients with and without edema diagnosed with chronic failure of the liver or heart, as well as from patients with nephrotic syndrome.

Methods: We conducted a prospective and observational study. We obtained clinical and biochemical data, as well as urinary samples from adult patients with liver cirrhosis (LC), heart failure (HF) or nephrotic syndrome (NS) (N=9 with, N=9 no-edema for each group) and 5 healthy volunteers as controls. UE from 8 ml of urine were obtained by ultracentrifugation for western blot analysis of SGLT2, NHE3, NKCC2, NCC and ENaC. The amount of UE used per patient was adjusted to urinary creatinine.

Results: Clinical and biochemical data from edema and non-edema patients were similar, except for mild hyponatremia and lower MAP in LC and HF patients with edema, respectively. Analysis of UE of patients with LC showed a significant increase in NHE3 and SGLT2 only in the edema group, while there was decreased NCC expression in the non-edema group. Conversely, NS and HF patients showed increased proximal tubule transporters even in the non-edema group. These patients were also characterized by increased ENaC expression. NKCC2 was only increased in HF patients with or without edema. Interestingly, NCC did not increase in any of the groups.

Conclusions: Our observations suggest that in edematous patients, regardless of the underlying syndrome, the proximal tubule transporters are upregulated and may be the most important cause of sodium retention. Interestingly, NKCC2 was increased in HF patients, but not in LC or NS patients. Down regulation of NCC in some groups suggests that the distal nephron is trying to compensate proximal reabsorption. These results suggest that diuretic therapy in patients with edema could be revisited to explore the use of proximal tubule inhibitors.

Funding: Government Support - Non-U.S.

FR-PO294

Kidney Functional MRI: A Potential Noninvasive Assessment of Early Change and NCC Function in Chinese Gitelman Syndrome Patients

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Background: Gitelman syndrome (GS) is an inherited salt-losing tubulopathy with Na^+-Cl^-cotransporter (NCC) dysfunction. Diffusion kurtosis imaging (DKI) and inteavoxel incoherent motion imaging(IVIM) MRI are functional MRI(fMRI) which could disclose more precise tissue structure and water diffusion. Recently, we observed fMRI associated well with the pathologic changes in IgA nephropathy. In this study we first applied the novel technique in the kidney of GS patients.

Methods: Twenty patients with genetically confirmed GS and 24 age and gener matched healthy volunteers were enrolled. DKI and IVIM were performed at a clinical 3T MR scanner. The DKI parameters (K=mean kurtosis, D=mean diffusivity, ADC=apparent diffusion coefficient) and IVIM parameter(f_p=microvascular perfusion fraction, D_p=pseudodiffusion, D=diffusion coefficients) were generated by a post-processing software. The association between parameters and clinical data were investigated. The in vivo NCC function of patients were evaluated by thiazide test using $_{\Delta}$FECl(the increment of fractional excretion of Cl^-).

Results: The mean age of GS patients was 28.4±10.2y and 45.8% were male with a mean onset age of 22.2±11.7y. At admission, the mean serum $K^+$and Mg^{2+} was 3.22±0.55 mmol/L and 0.68±0.16 mmol/L. GS patients showed decreased reaction to thiazide test. Compared to controls, lower DKI-ADC (1.45±0.19 vs 1.55±0.12,*P*=0.048), which indicating greater diffusion restriction, was observed in the renal medulla of GS. Lower IVIM-DP (117.8±46.0 vs. 151.3±56.3,*P*=0.039) indicating less microvascular perfusion, was observed in the renal cortex of GS. Among GS patients, in DKI the cortex ADC was associated well with plasma upright renin activity and blood pressure. The D value and K value correlated well with serum Cl^-(D: r=-0.670, *P*=0.001; K: r=-0.470, *P*=0.037) and HCO_3^-(D: r=0.709, *P*<0.001; K: r=0.469,*P*=0.037). In the kidney medulla, only K value associated well with serum Cl^- (r=-0.514,*P*=0.020). In IVIM, both the cortex D (r=0.702,*P*=0.035) and medulla D_p(r=-0.683, P=0.048) correlated well with $_{\Delta}$FECl.

Conclusions: DKI and IVIM MRI potentially provides a novel method for examining microvascular perfusion and diffusion in the kidney of GS patients and can serve as a noninvasive assessment of early change and NCC function in Chinese Gitelman syndrome patients.

FR-PO295

Hyponatremia and Renal Dysfunction in Acute Heart Failure

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Background: Acute heart failure (HF) is a common cause of hospitalization and risk factor for hyponatremia (hypoNa) as well as renal dysfunction. Although renal function influences both HF and sodium (Na) regulation, this interrelationship is not studied in acute care settings. Moreover, effect of Na correction in HF during acute care is not known.

Methods: We examined all adults, >18 years of age, requiring 24 or more hours of hospitalization for HF from a national multicenter sample derived from Cerner Health Facts between 1/2010 and 6/2016. Admission Na levels in mEq/L were classified as severe hypoNa (<130), moderate hypoNa (130-134), mild hypoNa (135-139), normal (140-144), or hypernatremia (≥145). By logistic regression adjusted for major confounders, with normal as a reference group, risk of all cause hospital mortality/hospice (primary outcome) or 30-day readmission was modeled for other Na groups. We further assessed effect of correction of Na at discharge relative to admission on the primary outcome as well.

Results: Sample included 109,906 HF patients with median age of 74 years (Q1, Q3, 63, 84); 49% female; 19% Black; median serum Cr 1.2 mg/dL (Q1, Q3, 0.9, 1.7). Na classes were 5% (<130), 13% (130-134), 41% (135-139), 36% (140-144), and 5% (≥145). Overall hospital mortality was 5%; crude mortality rate showed a "U"-shaped relationship by Na classes (p <0.001). Compared to the normal class, adjusted odds ratio (aOR); 95% confidence interval (CI) were 2.3 (2.1-2.6) in Na <130; 1.7 (1.6-1.9) in Na 130-134; 1.2 (1.1-1.3) in Na 135-139; and 1.8 (1.6-2.0) in Na ≥145. Renal dysfunction defined as Cr ≥1.3 mg/dL on admission was associated with increased mortality independent of Na (aOR 1.6; 95% CI, 1.5-1.7) compared to others. Among the 5,130 severe hypoNa patients,

compared to those who corrected from <130 to 130-139, the risk of mortality in patients who remained <130; corrected to normal (140-144); or over corrected (≥145) was aOR 2.1 (95% CI, 1.7-2.6), 2.5 (95% CI, 1.7-3.5), and 10.5 (95% CI, 6.0-18.5) respectively. Overall, 30-day readmission rate was 15%; compared to normal group (14%) it was higher in severe hypoNa (18%, p <0.001) and aOR 1.4 (95% CI, 1.3-1.5).

Conclusions: Management of hypoNa, in concert with level of renal function, is necessary to improve key HF outcomes. However, correcting severe hypoNa to normal or above normal may be harmful in acute HF.

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FR-PO296

Acetazolamide Therapy in Patients with Heart Failure: A Meta-Analysis

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Background: Fluid overload and central sleep apnea are highly prevalent in patients with heart failure (HF). Acetazolamide, although used as one of the first diuretics for heart failure, has not been readily added on as a therapy for diuretic resistance. In addition, its use in sleep apnea disorder has shown promising results, at least in the setting of high altitude conditions. We performed this meta-analysis to assess effects of acetazolamide therapy on 1) fluid and/or electrolytes, and 2)apnea indexes in heart failure patients.

Methods: A literature search was conducted using MEDLINE, EMBASE and Cochrane Database from inception through June 2017 to identify studies evaluating the use of acetazolamide in HF patients. Study results were pooled and analyzed using a random effects model. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017065401).

Results: 9 studies (3 randomized controlled trials and 6 cohort studies) with a total of 229 HF patients were enrolled. After acetazolamide treatment, there were significant decreases in pH (mean difference [MD] of -0.04 [95% CI, -0.06 to -0.02]), pCO2 (MD of -2.06 mmHg [95% CI, -3.60 to -0.53 mmHg]) and serum bicarbonate levels (MD of -6.42 mmol/L [95% CI, -10.05 to -2.79 mmol/L]). Compared with placebo, acetazolamide significantly increased natriuresis (standardized mean difference [SMD] of 0.67 [95% CI, 0.08 to 1.27]), and decreased the apnea-hypopnea index (AHI) (SMD of -1.06, [95% CI, -1.75 to -0.36]) and central apnea index (CAI) (SMD of -1.10, [95% CI, -1.80 to -0.40]), respectively. We found no publication bias as assessed by the funnel plots and Egger's regression asymmetry test with p= 0.20, 0.75 and 0.59 for analysis of the changes of pH, pCO2, and serum bicarbonate levels with the use of acetazolamide in HF patients, respectively.

Conclusions: Our study demonstrates significant reduction in pH, increase in natriuresis, and improvements in apnea indexesamong HF patients with acetazolamide.

FR-PO297

Carbonic anhydrase Inhibitors (CAI) Use in Patients with Respiratory Failure and Metabolic Alkalosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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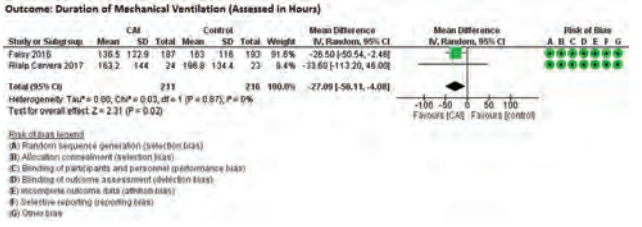
Background: Metabolic alkalosis is common in patients with respiratory failure and may delay weaning in mechanically ventilated patients. The objective of this systematic review is to assess the benefits and harms of CAI therapy in patients with respiratory failure and metabolic alkalosis

Methods: We conducted a comprehensive literature search for relevant randomized clinical trials(RCTs) assessing at least one of the following outcomes:mortality, duration of hospital stay, duration of mechanical ventilation(MV), blood gas parameters, and adverse events. Teams of two review authors independently and in duplicate selected eligible trials then abstracted data, and assessed risk of bias of the included trials. The primary meta-analysis used a random-effects model

Results: We identified 6 eligible RCTs with a total of 564 participants. The synthesized data did not exclude neither a reduction or an increase in mortality or in duration of hospital stay with the use of CAI(Table). There was a decrease in the duration of MV of 27(95% CI -50; -4) hours with CAI use(Figure). CAI therapy resulted in an increase in PaO2, and a decrease in PaCO2, serum bicarbonate and pH. There was an increased risk of adverse events in the CAI group(Table). Quality of evidence was judged to be low for most outcomes

Conclusions: In patients with respiratory failure and metabolic alkalosis, results of our systematic review suggest that CAI therapy has a favorable effect on blood gas parameters. In mechanically ventilated patients, the evidence suggests that CAI therapy may decrease duration of MV. Therefore, this clinically important outcome should be confirmed by future larger RCTs

Outcome	Number of studies	Number of Participants	Statistical Method	Effect Estimate
Mortality	2	427	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.56]
Duration of Hospital Stay (Days)	2	117	Mean Difference (IV, Random, 95% CI)	0.42 [-4.82, 5.66]
PaCO2 (mmHg)	5	185	Mean Difference (IV, Random, 95% CI)	-4.98 [-9.66, -0.30]
PaO2 (mmHg)	3	118	Mean Difference (IV, Random, 95% CI)	11.37 [4.18, 18.56]
Serum Bicarbonate (meq/L)	2	67	Mean Difference (IV, Random, 95% CI)	-5.03 [-6.52, -3.54]
pH	4	165	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.07, -0.01]
Adverse Events	5	508	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.98, 2.99]



FR-PO298

24-Hour Urine Magnesium Excretion in a Multi-Ethnic Asian Population of CKD and Healthy Participants

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Background: Magnesium (Mg) is implicated in bone metabolism, vascular tone, cardiovascular risk, and immunity. Its homeostasis is affected by diet, gut absorption, and kidney filtration, reabsorption, and excretion. Previous studies demonstrated an increase in serum Mg and urine fractional excretion of Mg (FEMg) in chronic kidney disease (CKD). The 24-hour urinary Mg (24UMg; mmol) excretion in a multi-ethnic Asian population of CKD and healthy participants without kidney disease is unknown. We aim to characterize serum Mg, 24UMg, and FEMg in a multi-ethnic Asian population.

Methods: Out of 335 (51% male) consenting participants, 232 (69%) were patients with CKD, and 103 (31%) were healthy individuals without kidney disease, diabetes, or hypertension. Following a 24-hr urine collection, participants underwent glomerular filtration rate (GFR; mL/min/1.73m^2) measurement using Tc^{99m}DTPA, and provided a spot urine and blood. No patients were on Mg supplementation. Data were analyzed on SPSS V23 using standard statistical tests, where appropriate.

Results: Of the 232 patients with CKD, 72 (31.0%) had GFR >60, 99 (42.7%) had GFR 30-60, and 61 (26.3%) had GFR <30; 51.3% were diabetic, and 82.8% were hypertensive. Mean 24UMg values were lower in patients with CKD (2.50±1.25) than healthy participants (2.93±1.45) [p=0.006]. Patients with GFR <30 had lower mean 24UMg values (2.00±1.10) compared to groups 30-60, and >60 (2.64±1.20, 2.75±1.34, respectively) [p=0.001]. Group with GFR <30 had a higher mean serum Mg (p=0.005) and an increased FEMg (p<0.001). 24UMg is associated with GFR (24UMg=2.032+0.009×GFR, p=0.002], which persists after excluding patients on diuretics. 24UMg and GFR is positively correlated in CKD patients with hypertension but not in non-hypertensives and diabetic patients.

Conclusions: Healthy participants have higher 24UMG excretion than CKD patients. With reduced GFR, serum Mg is higher, and 24UMg is lower, and is associated with an increased FEMg in Asian CKD patients.

FR-PO299

Tacrolimus Trough Levels and Risk of Hypomagnesemia in Renal Transplant Recipients

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Background: Magnesium (Mg) is the 2nd most abundant intracellular cation essential to neurochemical transmissions and many enzyme activities. Hypomagnesemia (hypoMg) is a risk factor for cardiovascular and mineral bone disease and in renal transplant recipients (RTR), Tacrolimus (Tac) use is associated with higher risk of hypoMg. However, it is unknown whether Tac trough levels further contributes to the risk of hypoMg. We aimed to investigate the association between Tac use and hypoMg in a large cohort of RTR.

Methods: For this study, we used data from the Transplantlines Biobank and Cohort Study comprising RTR with a functioning graft ≥1 year post-transplantation. Plasma Mg and Tac trough levels were measured using routine laboratory procedures. HypoMg was defined as a Mg level <1.7 mg/dL. Linear and logistic regression were used to assess the association of Tac use with plasma Mg and hypoMg, respectively. In additional analyses, we analyzed whether Tac trough levels were associated with plasma Mg and hypoMg in Tac users.

Results: We included 614 RTR (mean age 56±13 years; 59.2% male) at a median of 4.7 [1.0 - 11.7] years posttransplantation. Mean eGFR was 50±17 ml/min/1.73m^2 and mean

plasma Mg was 1.8±0.2 mg/dL. Of the total population, 170 (28%) RTR had a hypoMg and 378 RTR used Tac with a mean trough level of 5.8±1.8 ug/L. In linear regression analysis, Tac use was associated with lower plasma Mg (β -0.17 [95%CI -0.21;-0.12], $p < 0.001$), independent of age, sex, time after transplantation and eGFR. Similarly, in logistic regression analysis Tac use was independently associated with higher risk of hypomagnesemia (OR 4.5 [95%CI 2.6;7.8], $p < 0.001$). Within Tac users, Tac trough levels were strongly associated with lower plasma Mg (β -0.04 [95%CI -0.05 ; -0.03], $p < 0.001$) and higher risk of hypoMg (OR 1.4 [95%CI 1.2 ; 1.6], $p < 0.001$), independent of potential confounders.

Conclusions: HypoMg occurs in approximately 28% of RTR. Tac use is associated with a > 4 times greater risk of hypoMg. Importantly, we identified a dose-response effect between higher Tac trough levels and lower plasma Mg in Tac users. These results suggest that reducing Tac trough levels may be an effective treatment strategy for hypoMg in RTR treated with Tac.

FR-PO300

Association Between Use of Proton Pump Inhibitors and Hypomagnesemia: A Meta-Analysis

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Background: Hypomagnesemia is associated with an increased risk of cardiac arrhythmia and mortality. The use of proton pump inhibitors (PPIs) has been inconsistently associated with development of hypomagnesemia. To shed more light on this controversy, we performed a meta-analysis to examine the association between use of PPIs and hypomagnesemia.

Methods: The literature search was conducted in MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials (through December 2017) to identify observational studies that examined the association between use of PPIs and development of hypomagnesemia. Random-effects model meta-analysis was used to compute the pooled odds ratio (OR) with 95% confidence interval (CI).

Results: Thirteen cohort studies were identified, totaling 125,280 patients. 38.7% (95% CI 29.5-48.7%) of patients were PPI users. The baseline prevalence of diabetes mellitus and diuretic use was not significantly different between PPI users and non-users. By meta-analysis, use of PPIs was associated with a higher odds for development of hypomagnesemia (pooled odds ratio 1.83; 95% CI 1.26, 2.67; P = 0.002; I^2 = 97%).

Conclusions: The use of PPIs is significantly associated with development of hypomagnesemia. As a result, serum magnesium levels should be monitored in patients receiving long-term PPIs.

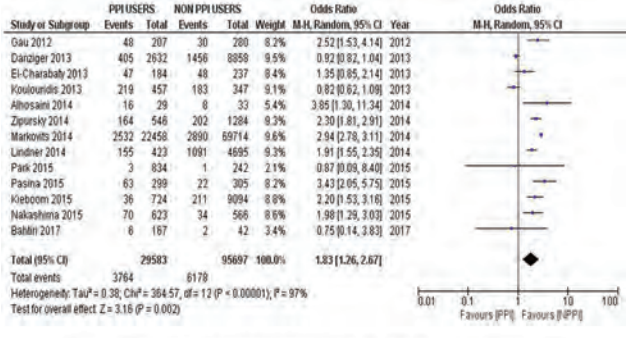

Figure 1. Forest plot of pooled unadjusted odd ratio. PPI, Proton pump inhibitor

FR-PO301

Efficacy and Safety of Patiromer in Participants with Diabetes: A Pooled Analysis

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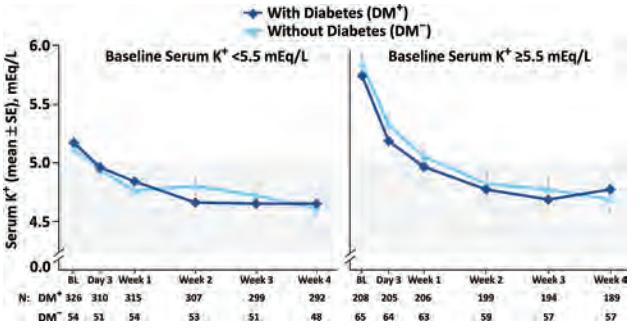
Background: The purpose of this post-hoc pooled analysis was to assess the efficacy and safety of patiromer (PAT) for treatment of hyperkalemia in participants with and without diabetes mellitus (DM^+ and DM^-).

Methods: We analyzed pooled data through Week 4 (Wk4) from 3 trials of PAT. Study participants who took ≥1 PAT dose and had ≥1 post-baseline (BL) serum potassium (sK) measurement were included. Participants were stratified according to DM^+ and DM^-, and assessed for: sK change from BL at Wk4, sK over time, and % with any sK measurement in target range (3.8–5.0 mEq/L).

Results: 653 participants were included; 82% DM^+ (mean BL HbA1c and DM duration: 7.4% and 14 years, respectively). Mean BL sK and eGFR were 5.4 mEq/L and 40.3 mL/min/1.73m² in DM^+, and 5.5 mEq/L and 34.8 mL/min/1.73m² in DM^-. At Wk4, overall mean (SE) sK change from BL was -0.72 (0.02) in DM^+ and -0.88 (0.06) in DM^- (**Figure**). In participants with BL sK ≥5.5 mEq/L, mean (SE) sK changes at Wk4 were -1.01 (0.05) in DM^+ and -1.21 (0.10) in DM^-, and -0.52 (0.03) and -0.51 (0.08), respectively, in DM^+ and DM^- participants who had BL sK <5.5 mEq/L. Regardless of BL sK status, >95% of all DM^+ and DM^- participants achieved any sK measurement in the target range through Wk4. The presence or absence of heart failure or eGFR <45 mL/min/1.73m² did not impact these results. At least 1 adverse event (AE) was reported in 31% of DM^+ and 38% of DM^- participants, most commonly (≥2%) constipation, diarrhea, hypomagnesemia (hypoMg), and nausea. AEs of hypoMg were reported in 2% of both DM^+ and DM^- participants. Lab values of Mg <1.4 mg/dL occurred in 5% and 1% of DM^+ and DM^- participants, respectively. Use of proton pump inhibitors and/or loop diuretics was common (43%) in those who experienced low serum Mg.

Conclusions: In this post-hoc analysis of pooled data, PAT was equally effective and well-tolerated in DM^+ and DM^- participants.

Funding: Commercial Support - Relypsa Inc., a Vifor Pharma Group Company



Figure

FR-PO302

The Association of Sodium Polystyrene Sulfate (Kayexelate™) Use and Adverse Gastrointestinal Events

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Background: Sodium Polystyrene Sulfate (SPS, Kayexelate™) is a commonly prescribed medication for the treatment of hyperkalemia. Case reports implicate the possibility of intestinal injury with SPS with or without sorbitol. In this regard, we set out to assess the risk of GI adverse events (intestinal ischemia, ulceration and perforation, abdominal surgery) with SPS use.

Methods: Population-based, retrospective cohort study of 1,853,866 eligible adults of advanced age (> 66 years) between 1995 and 2015 in Ontario, Canada. A high dimensional propensity score was used to match adults with a SPS prescription to no SPS prescription. The primary outcome was a composite of adverse gastrointestinal outcomes (intestinal ischemia, ulceration/perforation, abdominal survey) within 1-year of initial SPS prescription. Secondary outcomes included each component of the composite primary outcome. Cox proportional hazards were used to examine the association of SPS and a composite of GI adverse events. Additional sensitivity analyses limited to patients with laboratory values (eGFR, serum potassium) and a unrelated dummy outcome (cataracts) were performed. Pre-specificed subgroups of interest were examined using interaction terms.

Results: From 1, 853, 866 eligible adults, 20,020 were prescribed SPS (mean age 78.5 SD 7.7 years, 46% female) and matched. The risk of any adverse GI event was higher with SPS use compared to non-use (n=370 events, HR 1.26 95%CI 1.03-1.55). Among the individual types of GI adverse injury, gastrointestinal ulceration and perforation (HR 1.56 95%CI 1.08-2.25) events were higher with SPS whereas intestinal ischemia and abdominal surgery were similar. Among SPS-users with laboratory values (n= 7557, mean eGFR 44.8 SD 20.3 ml/min/1.73m², mean serum potassium 5.6 SD 0.7 mEq/L), the risk of any adverse GI event was similarly elevated (HR 1.44 95%CI 1.09-1.90). The findings were consistent after additional adjustment for living in a rural residence or a long-term care home and there was no association with SPS use and the dummy outcome (cataracts). The results were consistent across all prespecified subgroups.

Conclusions: The use of SPS is associated with a higher risk of adverse gastrointestinal events. Our findings suggest caution with the use of SPS and alternative treatments for potassium lowering be considered.

Funding: NIDDK Support

FR-PO303

Acid-Base and Electrolyte Disturbances in Severe Hyperemesis Gravidarum

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Background: Hyperemesis gravidarum (HG) is a complication of pregnancy characterized by incessant vomiting and reduced oral intake. However, the effect of severe HG on acid-base and electrolyte balance has not been previously examined.

Methods: A cross-sectional study was conducted to assess for acid-base and electrolyte abnormalities in pregnant women with symptoms of HG that were severe enough to lead to a visit to an emergency room.

Results: A total of 22 women [9 (41%) primigravida] were included over a 6-month enrollment period in a large city hospital. Median age was 25 (17 – 38) and median gestational age was 10 (5 -16) weeks. Median duration of HG prior to arrival was 24 (3 – 63) days. Vomiting episodes per day were 6 (3 – 12) and ketonuria was found in 16 of 22 women (73%). Dehydration was clinically evident in 18 of 22 (82%) and the mean change in body weight was –12%. The mean arterial pH was 7.41 (7.30 - 7.50), mean bicarbonate was 19 mEq/L (14 – 28) and mean pCO_2 was 29 mmHg (19 - 39). Physiological respiratory alkalosis was found in 17 of 22 (77%), metabolic alkalosis from vomiting was present in 10 of 22 (45%) and high anion-gap metabolic acidosis from starvation ketosis in 12 of 22 (55%) patients. Among them, 8 of 22 (36%) presented with a triple acid-base disorder, i.e. simultaneous respiratory alkalosis, metabolic alkalosis and metabolic acidosis. Only 2 (9%) patients exhibited no acid-base disorder. The presence of high anion gap metabolic acidosis was associated with a greater degree of weight loss ($p < 0.05$) and a lower age ($p < 0.05$). In addition, 9 of 22 (41%) patients were hypokalemic [mean K 3.5 mEq/L (2.4 – 4.2)], 7 of 22 (32%) were hyponatremic, and only 1 patient was hypernatremic [mean Na 139 mEq/L (128 – 148)].

Conclusions: Triple acid-base disorder of respiratory alkalosis, metabolic acidosis and metabolic alkalosis is the most common diagnosis in severe HG. Lower age and a greater degree of reduction in body weight are associated with high anion gap metabolic acidosis. Hypokalemia and dysnatremia can also occur. Acid-base/electrolyte assessment in HG is warranted.

FR-PO304

Electrolyte-Related Events Among US Veterans with Hyperkalemia

Csaba P. Kovesdy,[1] Elvira Gosmanova,[2] Steven D. Woods,[3] Jeanene Fogli,[3] Christopher G. Rowan,[4] Jared Hansen,[5] Brian C. Sauer.[5] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]Stratton VA Medical Center and Albany Medical College, Albany, NY; [3]Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA; [4]COHRDATA, LLC, Santa Monica, CA; [5]Salt Lake City VA Medical Center (IDEAS), Salt Lake City, UT.*

Background: Patiromer is a novel sodium-free potassium-binding polymer for treating hyperkalemia. The real-world impact of patiromer and sodium polystyrene sulfonate (SPS) on clinical outcomes is unclear.

Methods: Using the VA Informatics and Computing Environment (VINCI) database, we assessed the percentage of patients with electrolyte-related hospitalizations and emergency department (ED) visits 1, 3, and 6 months before and after the first patiromer and SPS dispensing (index date). Follow-up exposure was classified as of the index date and followed for 6 months (ITT) or censored at discontinuing/switching (continuous exposure, CE).

Results: 193 and 8492 patients initiated patiromer and SPS, respectively. All patients had a pre-index serum potassium ≥5.1 mEq/L and heart failure, diabetes, or renal disease. The percentage of patients with electrolyte-related ED visits and hospitalizations in the ITT population are shown in **Figure**. Although patient numbers were small in the CE population, decreases in electrolyte-related outcomes at months 1, 3, and 6 post-index were observed for ED visits (-2.9%, -9.6%, and -23.1%, respectively, for patiromer, and -4.1%, -4.1%, and -5.7%, respectively, for SPS) and hospitalizations (-1.2%, -3.8%, and -7.7%, respectively, for patiromer, and -0.5%, -0.9%, and -0.4%, respectively, for SPS).

Conclusions: The greatest reduction in electrolyte-related events was observed post-patiromer initiation. Given the limited number of patiromer users in this database, these findings merit additional study.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Group Company

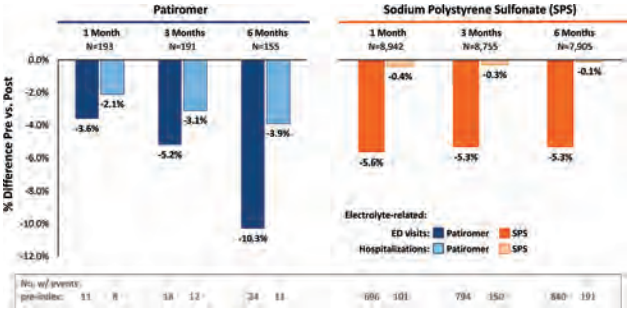

Figure. Difference in % of Patients with Electrolyte-Related ED Visits & Hospitalizations Pre-Index vs. Post-Index in the Patiromer and SPS Cohorts (ITT Analysis)

FR-PO305

Mortality Associated with Hyperkalemia in Medicare Patients

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Background: The objective of this study was to compare all-cause mortality between patients with and without hyperkalemia in the U.S. Medicare population.

Methods: Adult patients with and without hyperkalemia (cases vs. controls), were selected from a 5% random sample from the Medicare population (1/1/2010-12/31/2014). Hyperkalemia was defined as having at least one diagnosis of hyperkalemia (ICD-9-CM 276.7). The index date was a randomly selected claim date with a hyperkalemia diagnosis for cases and a randomly selected claim date for controls. Continuous enrollment for at least 6 months before the index date (baseline period) was required and patients were followed from the index date to death or the end of data availability (study period). Controls were exactly matched one-to-one to cases on age group, chronic kidney disease (CKD) stage, dialysis, and heart failure (HF). Mortality outcomes were analyzed at 36 months. Time to death was estimated with Kaplan-Meier analysis and compared using the log-rank test. Hazard ratios (HRs) were estimated using univariate and multivariate Cox proportional hazards (PH) models.

Results: A total of 157,441 cases were matched to 157,441 controls. Compared with controls in the overall population, cases had higher 3-year mortality rates (47.5% vs. 33.7%) and lower median time to death (40.3 months vs. median not reached). Among the 79,327 matched pairs of patients with CKD and/or HF, the 3-year mortality was higher (59.6% vs. 48.7%) and the median time to death was lower (22.7 vs. 38.4 months) (p for log-rank test<0.001) in cases compared with controls. In univariate Cox PH models, the risk of mortality was significantly higher for cases compared with controls overall (HR: 1.67, 95% CI: 1.65, 1.69) and among patients with CKD and/or HF (HR: 1.44; 95% CI: 1.42, 1.46) (all p<0.001). After adjusting for age, gender, region, diabetes, hypertension, and Charlson Comorbidity Index, the risk remained higher for cases compared with controls in the overall population (HR: 1.49, 95% CI: 1.48, 1.51) and among patients with CKD and/or HF (HR: 1.37, 95% CI: 1.35, 1.39) (all p<0.001).

Conclusions: In this study of Medicare patients, hyperkalemia was associated with increased mortality.

Funding: Commercial Support - AstraZeneca

FR-PO306

Association of Potassium Level and Mortality in Massive Health Record Databases

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Background: Dyskalemias have been associated with mortality in studies of small to moderate samples. However the association of potassium (K) with mortality across the spectrum of renal function (est. glom. filtration rate, eGFR) remains poorly defined. Our aim was to characterize this relation in the **Cerner** Healthfacts database which abstracts data from 1/3 of US healthcare facilities over a period of 10 years.

Methods: Serum K levels, demographics, eGFR (CKD-Epi) and comorbidity (Charlson) collected within 24 hours of all adult patient encounters in Healthfacts were analyzed after excluding patients on dialysis. The most recent K level was associated with each death recorded in Healthfacts. Relative mortality risks (RR) were calculated by Poisson Generalized Estimating Equations, that accounted for the repeated measures of K levels in the same individual. Cubic splines were used to model the relation of K with death in fully adjusted models.

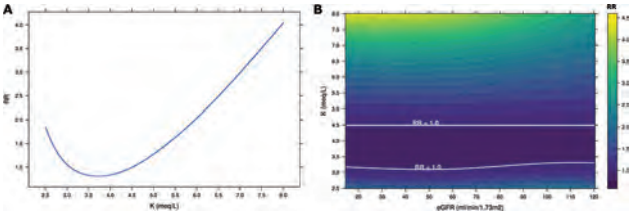
Results: We analyzed 20,697,035 K measurements in 15,376,693 individuals. Patients with CKD were more likely to be older, non-white and have higher K levels (Table). The RR of death with K level was U-shaped; the lowest RR was observed for K: 3.5-4.5 meq/l (Fig A). Hyperkalemia (K>5.5 meq/l) was associated with higher RR in those with low eGFRs (Fig B, p<0.001 for the interaction between eGFR and K).

Conclusions: The RR for hyperkalemia was higher relative to hypokalemia.The interaction between eGFR and K level reflects the variable causes of high K in patients with CKD & the inability of the kidneys to rapidly excrete the K load. Further studies are needed to understand this complex relationship.

Funding: Commercial Support - Dialysis Clinic, Inc

	eGFR (ml/min/1.73m2)				
	15-30	30-45	45-60	60-90	>90
N (measurements)	825,283	1,579,185	2,371,562	7,341,935	8,579,070
N (individuals)	567,685	1,123,320	1,795,917	5,469,704	6,420,067
Age (y)	73 ± 14	75 ± 13	72 ± 13	63 ± 15	45 ± 15
Whites (%)	77%	82%	82%	81%	68%
Males (%)	43%	42%	43%	45%	42%
Inpatient (%)	46%	36%	30%	24%	20%
Charlson Score	2.5 ± 2.8	1.8 ± 2.4	1.2 ± 1.9	0.8 ± 1.5	0.5 ± 1.3
Serum K (meq/l)	4.5 ± 0.8	4.3 ± 0.6	4.2 ± 0.6	4.1 ± 0.5	4.0 ± 0.5

All % refer to encounters



FR-PO307

Course and Outcomes of Hyperkalemia in Hospitalized Patients

Etienne Macedo,[2] Linda Awdishu,[1] Euyhyun Lee,[2] Ravindra L. Mehta.[2] *[1]UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA; [2]University of California San Diego Medical Center, La Jolla, CA.*

Background: Hyperkalemia (High K) is a common complication among hospitalized patients contributing to increased hospital stay and costs. In this study, we determined the incidence and severity of hyperkalemia and characterize its recognition, treatment, and complications in different hospital settings and patient populations.

Methods: Data regarding patient location, comorbidities, medications in use before/after High K detection and outcomes were extracted from the EMR of all adult patients with at least 2 consecutive K>5mEq/L during a hospital stay at an academic medical center. Need for ICU admission, dialysis, number of drugs to treat HighK, land ength of ICU/hospital stay were assessed during hospitalization. Mortality was recorded for the duration of the observation period.

Results: From January 1, 2013, to November 30, 2015, 133,807 hospitalized patients had at least one potassium assessment. Of these patients, 13,748 (10.3%) had at least one K≥ 5mEq/L, and 2,150 (1.6%) had two consecutive values, within 7 days, ≥ 5 mEq/L. Almost half of the highK episodes were present at hospital admission, and the majority of these cases were from the emergency room (ER) 497 (23%), ward 1318 (62.9%), and ICU 280 (13.4%). Of 1,815 patients with hyperkalemia diagnosis in the ward or ER, 225 (12%) were transferred to the ICU within 24 hours of hyperkalemia diagnosis. 126 (6%) patients that were dialyzed during hospital admission: 78 (61%) were ESRD, 22 (3.4%) AKI, and 104 (6.9%) AKI on CKD. The median length of hospital stay was 9 days and was higher in AKI patients 11 (4-22) vs. 9 (4-17) days in no AKI. Overall, the in-hospital mortality rate in patients with hyperkalemia diagnosis was 12%. Patients with AKI had a higher mortality rate (AKI; 122 (17%) vs. 159 (10%) no AKI). Within the study period interval, 29% of patients with a hyperkalemia episode died. Patients with no previous renal dysfunction showed a greater in-hospital mortality rate 179 (15%) than those with CKD stage 3-5 and ESRD, 67(11.3%) and 25 (6.8%), respectively.

Conclusions: HighK in hospitalized patients is associated with a high mortality rate and increases significantly over the period of observation. Presence of CKD and ESRD is not associated with worse outcomes, whereas development of AKI is associated with increased length of stay and mortality.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Group Company

FR-PO308

Predicting Complicated Hyperkalemia in Hospitalized Patients

Etienne Macedo,[2] Linda Awdishu,[1] Euyhyun Lee,[2] Ravindra L. Mehta.[2] *[1]UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA; [2]University of California San Diego Medical Center, La Jolla, CA.*

Background: Hyperkalemia (HighK) is common in hospitalized patients and can be life-threatening. Patient-related factors and process of care, including drugs, are known to be associated with the development of hyperkalemia. In order to prevent hyperkalemia complications, it is fundamental to identify the cause and provide early treatment. In this study, we evaluated risk factors for complicated hyperkalemia (CK) during hospitalization.

Methods: Data regarding patient location, comorbidities, medications in use before and after HighK detection and outcomes were extracted from the EMR of all adult patients at an academic medical center with at least 2 consecutive K > 5mEq/L during a hospital stay. CK was defined as: (1) maximum K level ≥ 6.5 mEq/L, (2) need for ICU admission within 24h of HighK diagnosis, (3) need for dialysis, if not ESRD, (4) death with K ≥ 5 mEq/L, (5) more than 3 drugs for hyperkalemia treatment initiated after hyperkalemia diagnosis, and (6) more than 8 days for potassium normalization. We divided the cohort into derivation (n= 1,165), and validation (n=985) cohorts, to build and evaluate the performance of the model. The Least absolute shrinkage and selection operator (LASSO) with 10-fold cross-validation was used to build the model.

Results: From January 1, 2013, to November 30, 2015, 133,807 hospitalized patients had at least one K assessment. Of these patients, 13,748 (10.3%) had one K value higher than 5 mEq/L, and 2,150 (1.6%) had two consecutive values, within 7 days, more than 5 mEq/L. CK occurred in 822(38%) of patients; 488(42%) derivation and 334(34%) in the validation cohort. The majority of the patients, 1,193 (55%) had eGFR > 60ml/min, and 1310 (61%) fulfilled criteria for AKI during the admission, 192 (9%) were ESRD. Mortality in CK was significantly higher, 200(24.3%) vs. 71(5.3%) HighK group (p<0.001). Presence of hypotension, cardiopulmonary diagnosis, fluid overload, infection and ICU location were independently associated with CK. ESRD, myopathy and HIV diagnosis were protective factors. The model AUC was 0.70 in the derivation and 0.64 in the validation dataset.

Conclusions: HighK is common in hospitalized patients and associated with high mortality. A model based on clinical information and process of care may help identify patients with HighK who are at highest risk for complications and require surveillance.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Group Company

FR-PO309

Timing Is Everything: Decreasing Mortality in Severe Hyperkalemia

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Background: Hyperkalemia is a modifiable risk factor for sudden cardiac death; a leading cause of mortality in hemodialysis patients. There is lack of data in literature guiding the treatment of hyperkalemia in hospitalized end stage renal disease (ESRD) patients. The goal of this study was to determine if time to dialysis after severe hyperkalemia will influence mortality in hospitalized ESRD patients.

Methods: We conducted a retrospective study of all adult ESRD patients admitted to the hospital who had hemodialysis for severe hyperkalemia between January 2011- June 2017. Chart review was conducted to determine patient and treatment characteristics. Logistic regression analysis was performed to determine the factors that influenced mortality.

Results: 346 ESRD patients on hemodialysis admitted at our center had severe hyperkalemia during the study period. Mean serum potassium was 7mEq/L. In-hospital mortality in ESRD patients with severe hyperkalemia was 6.9%. Median time to dialysis after serum potassium result was 2.13 hours (25, 75 IQR 0.98, 4.9 hours). Time to dialysis after serum potassium result was associated with a significantly increased risk of mortality in this population (HR 1.007, 95% CI 1.002-1.012, p <0.0045) (Table 1). Logistic regression analyses also determined age, length of stay, serum creatinine and serum albumin level as significant predictors of in-hospital mortality (Table 1). Sex, race, history of diabetes and hypertension, serum potassium level and serum CO2 level did not influence in-hospital mortality in this cohort.

Conclusions: We conclude that early dialysis after serum potassium result in hospitalized ESRD patients with severe hyperkalemia is associated with decreased in hospital mortality.

Table 1: Risk factors for mortality in hospitalized ESRD patients with severe hyperkalemia

Risk Factor	Odds Ratio (95%CI)	p- value
Age, per 1 year	1.07 (1.04-1.11)	0.0001
Length of stay, per 1 day	1.04 (1.02-1.06)	0.0002
Serum Albumin, per 1 g/dL	0.24 (0.07-0.76)	0.02
Serum Creatinine, per 1 mg/dL	0.72 (0.58-0.88)	0.0018
Time from potassium result to dialysis, per 1 hour	1.007 (1.002-1.012)	0.0045

FR-PO310

Changes in Nephrologists' Understanding and Management of Hyperkalemia from 2015 to 2018

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Background: Identifying clinical gaps related to hyperkalemia and its management can inform the development of tools to advance best practices for nephrologists

Methods: Medscape conducted surveys in 2015, 2016, and 2018. The first two were CME-accredited activities consisting of 25 multiple choice, knowledge- and case-based questions aboout hyperkalemia assessment and management. These online surveys were available without compensation or fee. The third online, 14-question, survey was incentivized for nephrologists with monetary compensation for completion. In all surveys, respondents' confidentiality was maintained and responses were de-identified and aggregated prior to analyses. Data collection occurred in 9/22 - 11/22/2015, 11/21 – 12/21/2016, and 4/20 – 4/26/2018.

Results: Participation by nephrologists: 394 in 2015, 131 in 2016, and 50 in 2018 **Significant Changes:** Competence related to management of hyperkalemia rose significantly (P =.018) from 44% in 2016 to 66% in 2018* Competence regarding clinical use of potassium binders grew significantly (P <.001), from 63% to 92% (2016 to 2018, respectively) Nephrologists who reported being very confident increased significantly (P =.04), from 35% to 45% to 60% (2015, 2016, and 2018, respectively)* **Modest Changes:** Hyperkalemia risk assessment understanding grew (58% to 72%, P =.083) as well as recognition of strategies to minimize hyperkalemia risk with RAAS inhibitors (25% to 30%, P =.381) from 2016 – 2018* Knowledge of the mechanism of action of patiromer trended upward each year, 46% to 50% to 56% (2015, 2016, and 2018 respectively, P=.377) * **Ongoing Gap:** Confusion remains around the mechanism of action of ZS9, 49%

(2015), 39% (2016), and 44% 2018, *P* =.046)* Understanding related to the physiology of hyperkalemia and potassium excretion remains low (55% vs 54%, P - .885) from 2015 to 2018* * *results indicate a need for further education*

Conclusions: These surveys demonstrate some improvement in clinical knowledge, competence, and confidence by nephrologists related to hyperkalemia from 2015 to 2018, as well as continued gaps that need to be addressed to improve patient care. Future education in the area of hyperkalemia should focus on improving risk assessment for hyperkalemia, understanding available treatment options, management of hyperkalemia, and also reinforce important points to further increase confidence.

FR-PO311

Calcium-Phosphate Product and Its Impact on Mortality in Hospitalized Patients

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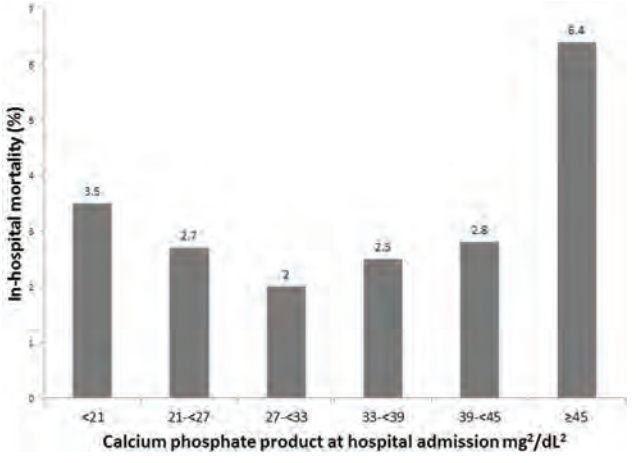
Background: Calcium-phosphate product (CaP) of >55 mg^2/dL^2 is associated with acute or subacute calcification of vascular, cardiac, and other soft tissues. However, the relationship between admission CaP and in-hospital mortality in all hospitalized patients is unclear.

Methods: All adult hospitalized patients who had both admission serum calcium and phosphate levels available between years 2009 and 2013 were enrolled. Admission CaP was categorized based on its distribution into six groups (<21, 21-<27, 27-<33, 33-<39, 39-<45 and ≥45 mg^2/dL^2). The odds ratio (OR) of in-hospital mortality by admission CaP, using the CaP category of 27-<33 mg^2/dL^2 as the reference group, was obtained by logistic regression analysis.

Results: 14,772 patients were studied. The lowest incidence of in-hospital mortality was associated with an admission CaP within 27-<33 mg^2/dL^2. A U-shaped curve emerged demonstrating higher in-hospital mortality associated with both CaP <27 and ≥33 mg^2/dL^2. After adjusting for potential confounders, both CaP <21 and ≥39 mg^2/dL^2 were associated with an increased risk of in-hospital mortality with ORs of 1.60 (95% CI 1.07-2.37), 1.53 (95% CI 1.07-2.18) and 3.46 (95% CI 2.51-4.79) when CaP were within <21, 39-<45 and ≥45 mg^2/dL^2, respectively. Among a subgroup of patients with available serum albumin, the lowest incidence of in-hospital mortality was associated with corrected CaP within 33-<39 mg^2/dL^2. After adjusting for potential confounders, corrected CaP 39-<45 and ≥45 mg^2/dL^2 were associated with an increased risk of in-hospital mortality with ORs of 2.15 (95% CI 1.39-3.33) and 3.90 (95% CI 2.60-5.94) when CaP were within 39-<45and ≥45 mg^2/dL^2, respectively.

Conclusions: CaP levels on admission are associated with in-hospital mortality. Highest mortality risk is observed in hospitalized patients with admission CaP ≥45 mg^2/dL^2.



Admission calcium phosphate product levels and hospital mortality

Outcome	Calcium phosphate product at hospital admission (mg^2/dL^2)					
	<21	21-<27	27-<33	33-<39	39-<45	≥45
Hospital Mortality	41 (8.5)	59 (2.7)	78 (2.0)	91 (2.5)	58 (2.8)	118 (6.4)
Mortality, OR (95%CI)						
Model 1: unadjusted	1.78 (1.20-2.60)	1.32 (0.94-1.87)	1 (ref)	1.25 (0.92-1.70)	1.42 (1.003-2.00)	3.34 (2.50-4.48)
Model 2#	1.60 (1.07-2.37)	1.34 (0.94-1.89)	1 (ref)	1.35 (0.99-1.84)	1.53 (1.07-2.18)	3.46 (2.51-4.79)

#model 2: Adjusted for age, sex, race, GFR, principal diagnosis, Charlson comorbidity score, CAD, CHF, PVD, stroke, DM, COPD, cirrhosis, calcium supplementation

FR-PO312

A Structural Equation Model on Regulatory Network of Phosphate Metabolism in Healthy Individuals

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Background: Basic and clinical studies reveal that the homeostasis of phosphate is maintained by a regulatory network. The factors in the network may change along with the dietary intake of phosphate. The aim of our study was to explore the variation of phosphatoninin with the change of diet.

Methods: A cross-over trial of 6 healthy volunteers was conducted. Each of them was given diet strictly: regular Pi diet (1500 mg/d), low Pi diet (LPD, 500 mg/d) and high Pi diet (HPD, 2300 mg/d), with a wash out period after diet intervention. The data were traditionally detected by ANOVA. In order to overcome limitations of the traditional correlation analysis, we used structural equation model (SEM) as a general framework for a new paradigm of analysis of multiple correlations.

Results: Pi was significantly higher in HPD. In contrast, Ca was lower in HPD. Meanwhile, LDP increased 1,25(OH)D and 25(OH)D. HPD leaded to increasing level of iPTH. With the gradual escalation of Pi intake, the FGF23 were upward trend. However, klotho didn't appear to be affected by dietary intervention by ANOVA. With the traditional comparison, it was difficult to reveal the overall phosphate network regulation. By SEM, we developed 3 networks for phosphate regulation. When healthy individual with regular Pi diet, Ca, Pi, iPTH, FGF23 and klotho formed a precise regulatory network. When HPD or LPD, vitamin D was closely associated with other phosphatonin, suggesting vitamin D played a prominent role in HPD or LPD. FGF23 and klotho had a close relationship in the network, especially in high Pi loads.

Conclusions: By SEM, the importance of klotho in phosphate regulation is revealed with the network diagrams. Meanwhile, the network demonstrates the importance of vitamin D in abnormal phosphate metabolism which need further investigation.

Funding: Government Support - Non-U.S.

	Regular-phosphate diet		Low-phosphate diet		High-phosphate diet	
	Pre-diet	Post-diet	Pre-diet	Post-diet	Pre-diet	Post-diet
Intact PTH (pg/ml)	31.98±2.10	32.38±1.58	32.42±1.98	29.58±1.91	32.23±2.41	37.38±2.21[#*]
FGF23 (pg/ml)	498.54±20.23	501.79±17.27	502.18±20.76	487.68±19.91	495.32±19.27	520.30±25.18
s-klotho (pg/ml)	560.23±15.32	604.93±12.24	590.89±12.10	575.61±12.56	572.45±15.58	575.46±14.51
25(OH)D (ng/ml)	67.54±2.30	69.02±1.71	69.31±1.29	67.00±2.10[#]	67.56±2.56	66.99±1.75[#]
1,25D (pmol/l)	93.51±3.02	91.46±2.92	94.39±2.87	120.25±3.45[#*]	95.19±3.26	94.42±2.30[#]
BAP (ng/l)	0.78±0.03	0.80±0.04	0.79±0.02	0.77±0.03	0.77±0.02	0.69±0.03[#*]
Electrolyte indicators						
Pi (mmol/l)	1.20±0.03	1.34±0.02*	1.21±0.04	1.18±0.02[#*]	1.19±0.02	1.48±0.03[#*]
corrected Ca (mmol/l)	2.17±0.02	2.20±0.02	2.17±0.01	2.26±0.01[#*]	2.18±0.01	2.19±0.01[#]

Figure 1: Pre-diet (at 7am on the 1st day) and Post- diet (24h-average on the 5th day) blood electrolyte measurements and phosphatonin of each diet intervention. *P<0.05 vs pre-diet in the same intervention; #P<0.05 vs regular phosphate diet; $P<0.05 vs low phosphate diet.

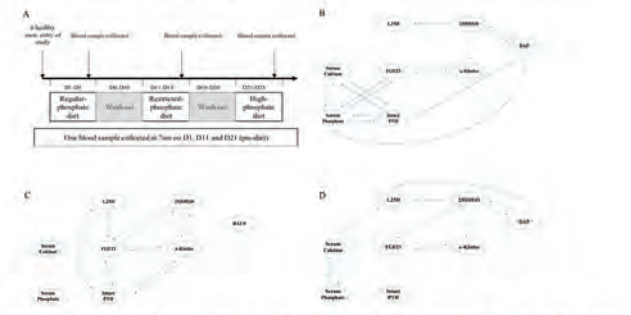

Figure 2: Overall study design (A). Regulatory networks of phosphate metabolism with regular-phosphate diet (B), high-phosphate diet (C), low-phosphate diet (D). Solid line: positive correlation, dashed line: negative correlation.

FR-PO313

Recurrent GATM Mutations Causing Autosomal Dominant Renal Fanconi Syndrome with Progressive Renal Failure

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Background: Inherited renal Fanconi syndrome without extrarenal manifestations, described as Fanconi renotubular syndrome (FRTS), have been reported to be caused by genetic defects in uncertain loci of chromosome 15 (type I), *SLC34A1* (type II) and *EHHADH* (type III). In Type I characterized by autosomal dominant inheritance with late onset FRTS and progressive renal failure, its causative gene mutation is just reported to be caused by *GATM* encoding arginine-glycine aminotransferase (AGAT), an enzyme catalyzing rate-limiting step of creatine biosynthesis.

Methods: A Chinese family with typical autosomal dominant FRTS and progressive renal failure was enrolled. The affected father (age 60 and serum creatinine 6.1 mg/dl with eGFR 12 ml/min) and daughter (age 31, and serum creatinine 1.3 mg/dl, eGFR 50 ml/min) exhibited severe hypophosphatemia and hyperchloremic metabolic acidosis with distinctively osteomalacia as well as hypokalemia despite potassium, alkali, and vitamin D therapy. Sanger's sequencing demonstrated no pathogenic mutations in *SLC34A1* and *EHHADH*. Whole exome sequencing was performed in this family.

Results: Whole exome sequencing discovered a possible culprit missense mutation (p.Thr336Ile) in *GATM*, which mutation was identical to recent report, supporting the pathogenic role of *GATM* mutation in this unique type of FRTS. Localization of T336I mutation on 4th β-sheet was suggested to transform 4th β-sheet into a novel additional interaction surface, resulting in formation of linear AGAT multimer rather than physiological

homodimer by interaction between 2nd β-sheet. Because biallelic mutations in *GATM* causes cerebral creatine deficiency syndrome (CCDS) with neurological symptoms but not FRTS, the role of diminished total AGAT activity in pathogenesis of FRTS is unlikely.

Conclusions: *Uniallelic GATM* mutation clustering to a specific region may play a role in pathogenesis of autosomal dominant FRTS. Generation of GATM T336I knock-in mice is warranted to elucidate the mechanism of FRTS and assess the therapeutic role of creatine administration.

FR-PO314

Intrapartum PDE-5 Inhibition Lowers Blood Pressure and Renal Injury in Young Adult Offspring of Preeclamptic Dahl S Rats

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Background: Up to 10% of pregnancies are complicated by preeclampsia, and up to 15 million Americans are offspring of preeclamptic pregnancies. The Developmental Origins of Health and Disease hypothesis proposes that an adverse intrauterine environment programs the fetus to develop high blood pressure (BP) from early childhood, and evidence shows that offspring of preeclamptic pregnancies have increased risk of hypertension and CKD. Animal models of hypertension in pregnancy have shown that sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor that prolongs NO-cGMP signaling, improves the maternal syndrome of preeclampsia; however, the effects of perinatal use on long term fetal outcomes have not been reported. Here, we test the hypothesis that PDE-5 inhibition during preeclamptic pregnancy improves long-term BP and renal injury in the offspring.

Methods: Female Dahl S rats (n=16) on a 0.3% salt diet, a previously characterized model of preeclampsia, were mated and treated orally with sildenafil (50 mg/kg/day) or vehicle from gestational day 10 to delivery. Lactating dams and offspring were on normal chow for the duration of the study, and measurements were made at 11 weeks of age.

Results: Systolic BP (n=5-9/group, tail cuff) was greater in Dahl S rats of untreated mothers compared to offspring of sildenafil treated dams (VEH: 177±4 mmHg; SLD: 158±2 mmHg; p=0.0001). BP data were pooled due to lack of significant sex differences between treated groups. Tubulointerstitial fibrosis (n=3/group) was measured in kidney sections stained with Masson's trichrome. Tubulointerstitial fibrosis is increased in male Dahl S offspring of untreated mothers as compared with offspring of sildenafil treated dams (Area: VEH: 9.0 ±0.6%; SLD: 5.0 ±0.6%, p=0.006), but no differences were observed in female rats (VEH: 5.3 ±0.7%; SLD: 6.0 ±0.6%). Urine was collected for measurement of urinary protein (Bradford assay), but no significant differences in proteinuria were observed (VEH male: 87 ±23 mg/day; SLD male: 138 ±18 mg/day; VEH female: 64 ±9 mg/day; SLD female: 53 ±7mg/day).

Conclusions: These data support the hypothesis that use of a PDE-5 inhibitor during preeclamptic pregnancy improves the long-term BP and renal injury in the offspring.

Funding: NIDDK Support, Other NIH Support - NHLBI R01, Private Foundation Support

FR-PO315

The Role of Renal Claudin-4 Protein in Salt-Induced Hypertension of Spontaneous Hypertensive and Dahl Salt Rats

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Background: Claudin proteins in the kidney act as Na^+ barrier or Cl^- channel, and hypotension was reported from renal claudin-4 knockout mice due to urinary Cl^- loss. Our previous study showed that salt-sensitive hypertension was associated with upregulation ofclaudin-4 in Dahl salt rats (DSR). Here we extended our work to see if any changes in renal claudin proteins precede the development of salt-sensitive hypertension in spontaneous hypertensive rats (SHR) and DSR.

Methods: Time course studies were undertaken over two weeks for SHR and one week for DSR. SHR were randomly divided into normal salt-loaded (SN, n=4) and high salt-loaded (SH, n=4) rats at each time point. High salt was offered with 8% NaCl diet. Wistar Kyoto rats (WKR) served as controls and were given normal salt diet. DSR were classified into salt-resistant (SR, n=6) and salt-sensitive (SS, n=6) rats, and both groups were given 8% NaCl diet. Systolic blood pressure (SBP), urine sodium excretion, and renal protein expression of claudin-2, claudin-4, claudin-7, claudin-8, and claudin-10 were serially followed.

Results: At baseline, SBP was higher in SHR than in WKR (137 ± 1 vs. 118 ± 1 mmHg, P<0.05). SBP was not different between SN and SH at Day 7, but was higher in SH than in SN (162 ± 1 vs. 156 ± 1 mmHg, P<0.05) at Day 14. WKR had lower SBPs throughout the period (114 ± 1 mmHg at Day 14). At baseline, claudin-4 (123 ± 1 vs. 100 ± 2%, P<0.05) expression increased in SHR compared with WKR. The expression of claudin-4 was not different between SN and SH at baseline, but increased in SH compared with SN from Day 7 (185 ± 4 vs. 130 ± 2%, P<0.05) to Day 14. In DSR, SBP was not significantly different between SR and SS through Day 3, but increased in SScompared with SR (141 ± 2 vs. 119 ± 1 mmHg, P<0.05) at Day 7. From baseline (174 ± 3 vs. 100 ± 3%, P<0.05) to Day 3 (240 ± 4 vs. 100 ± 3%, P<0.05), claudin-4 expression increased in SS compared with SR. Immunofluorescence localization of claudins in the kidney was compatible with the results of immunoblot analysis.

Conclusions: In response to high salt intake, the increase in renal claudin-4 protein preceded the elevation of SBP in both SHR and DSR. Claudin-4 expression also increased in SHR compared with WKR. These findings suggest the contributory role of renal claudin-4 in salt-sensitive hypertension.

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FR-PO316

Role of Na/K-ATPase Signaling in Susceptibility to Hypertension in Salt-Sensitive Animal Models

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Background: Previous studies from our and our collaborative laboratories have indicated that Na/K-ATPase acts as a receptor for reactive oxygen species (ROS), regulating renal Na^+ handling and blood pressure (JBC, 2011; JAHA, 2016). In the present work, the Na/K-ATPase signaling was investigated in the animal models of salt-sensitive hypertension.

Methods: Studies were conducted with tissues from rats and mice made hypertensive by the salt administration. Na/K-ATPase signaling including phosphorylation of c-Src and ERK1/2 and protein carbonylation (DNP, commonly used as a marker for ROS) was assessed by Western blot(WB). Renal function curve was constructed with high salt diets (HS, 2, 4, and 8% NaCl). Urinary and plasma Na^+ levels were measured by flame photometry.

Results: In the Dahl salt-sensitive hypertensive rat (S), the renal proximal tubules (RPTs) contained significantly more protein carbonylation than did the control (Dahl salt-resistant rat, R) RPTs (Fig. A. NC, Normal chow). Qualitatively similar effects were observed on the Na/K-ATPase signaling from the kidney cortex of three obese rat and mouse models (Fig. B-D). As did Dahl S rat, (Fig. A and in JBC, 2011), Na/K-ATPase signaling was not able to be stimulated by HS (Fig. D), leading to blunted urinary Na^+ excretion and salt-sensitive hypertension in obese TALLYHO/JngJ (TH) mice. More importantly, pNaKtide as an antagonist of Na/K-ATPase signaling attenuated protein carbonylation and c-Src phosphorylation stimulated by a high-fat diet (HF, Fig. C).

Conclusions: All four forms of salt-sensitive hypertension showed significant elevation of baseline Na/K-ATPase signaling when compared to their respective controls, indicating that this aberration in Na/K-ATPase signaling may represent a common signaling defect fundamental to the salt-sensitive hypertensive syndrome irrespective of etiology.

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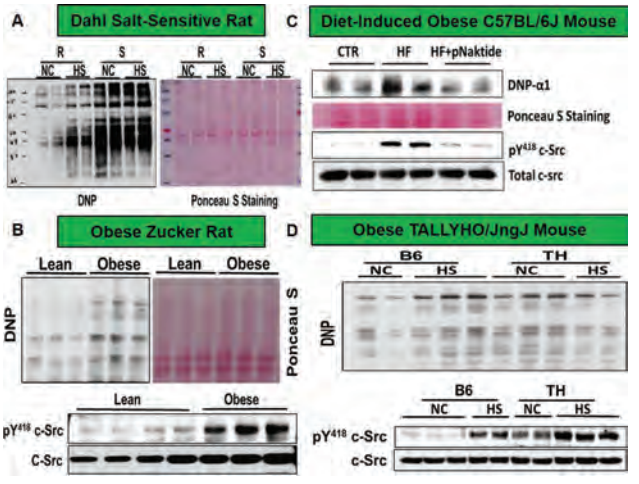

FR-PO317

Tubulo-Glomerular Feedback Independent Hypertension and Kidney Interstitial Fibrosis in DOCA-Salt Mice

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Background: Sodium transporters and tubulo-glomerular feedback (TGF) play important roles in sodium balance and blood pressure maintanence. Renal adenosine-A1 adenosine receptor (A1AR) pathway, which is mediated by Na-K-Cl cotransporter 2 (NKCC2), is involved in the classic TGF mechanism. This study was to observe the role of sodium transporters and A1AR in salt-sensitive hypertension and associated kidney injury.

Methods: Deoxycorticosterone acetate (DOCA)-salt hypertensive mouse model was established by removal of left kidney, implantation of a DOCA pellet (200mg, 60-day release), and feeding with high salt diet (8%NaCl). Arterial blood pressure and urine electrolyte excretion were determined. Pathological changes, protein and mRNA expression of sodium transporters and adenosine-A1AR pathway were measured in mice kidney.

Results: DOCA-salt and uni-nephrectomy treatment in wildtype C57BL/6J mice led to continuous higher blood pressure, accompanied by obvious tubulo-interstitial injury and interstitial fibrosis at different ages (4w, 8w). In DOCA-salt wildtype mice, the Na^+-Cl^- cotransporter (NCC) and NKCC2 upregulation (1.6-1.75 times) were observed in kidney, with activation of adenosine-A1AR pathway (mRNA expression of adenosine synthetase CD73 and A1AR about 2-3 times increased). DOCA-salt mice also showed signs of glomerular hyperperfusion and hyperfiltration, which included polyuria, increased urine sodium excretion and kidney enlargement. Compared with DOCA-salt wildtype mice, the DOCA-salt $A1AR^{-/-}$ mice presented more severe glomerular hyperperfusion and hyperfiltration (including polyuria and increased urine sodium excretion). However, DOCA-salt $A1AR^{-/-}$ mice showed the same degree of hypertension (4w: 125.7±7.4 vs. 127.4±18.8 mmHg; 8w: 135.3±5.2 vs. 141.7±9.5 mmHg; $P>0.05$ both) and renal interstitial fibrosis (4w: 2.05±1.73% vs. 1.52±1.44%; 8w: 10.35±4.86 vs. 9.42±5.95%; $P>0.05$ both), which were compliant with the change of NCC protein expression (4w 1.65 ± 0.19 vs. 1.70 ± 0.18; 8w 1.47 ± 0.21 vs 1.00 ± 0.34, $P>0.05$ both).

Conclusions: DOCA-salt treatment in mice induced hypertension and kidney interstitial fibrosis. The mechanism may lie in NCC activation, instead of NKCC2 associated TGF.

Funding: Government Support - Non-U.S.

FR-PO318

In Obese ZSF1 Rats Salt-Sensitivity of Blood Pressure Is Positively Related to Free Sodium in Skin and Negatively to Bound Sodium in Skin

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Background: Last year we reported that blood pressure in Zucker fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1) rats exposed to deoxycorticosterone acetate (DOCA) and fed a high salt diet is more salt-sensitive in obese than in lean ZSF1 rats ($p<0.0001$). Moreover, obese females were even more salt-sensitive than obese males ($p<0.01$). Only male obese ZSF1 were hyperglycemic and manifested glycosuria (Nguyen et al. ASN 2017). This follow-up study dissects the role of free and bound sodium in the skin on the differences in salt-sensitivity between female and male obese ZSF1 rats.

Methods: Male and female ZSF1 rats, lean (N=4-6/subgroup) and obese (N=6-8/subgroup), were either implanted with a DOCA pellet and fed a high salt diet (6% NaCl) or with a placebo pellet and fed a normal salt diet from 19 weeks of age. Every two weeks, from 18 (i.e prior to pellet implantation) to 26 weeks of age, systolic blood pressure (SBP) and 24-hours urine was collected. To further elucidate the diverging natriuresis-pressure relations in the obese ZSF1, skin sodium content was determined at 26 weeks (N=2-4/group).

Results: On placebo, obese male ZSF1 showed more free sodium in skin than obese females (p=0.03). However, on DOCA+salt, obese females showed higher free sodium compared to obese males (p=0.053). The interaction between sex and DOCA+salt on free sodium in skin was very significant (p=0.002). For bound sodium in skin changes were in the reverse direction (interaction: p=0.036). Overall (N=6), the increase in blood pressure/natriuresis on DOCA+salt from week 18 to week 26 correlated positively with free sodium in skin (r=0.91, P=0.01; Figure 1A) and tended to correlate negatively with bound sodium in skin (r=0.69, P=0.13; Figure 1B).

Conclusions: Our results indicate that in obese ZSF1 rats inverse relations exist between salt sensitivity of blood pressure and free versus bound sodium in the skin. Compartmentalization of sodium in the skin is influenced by sex, which in this model may be associated with differences in glycemia.

Funding: Private Foundation Support

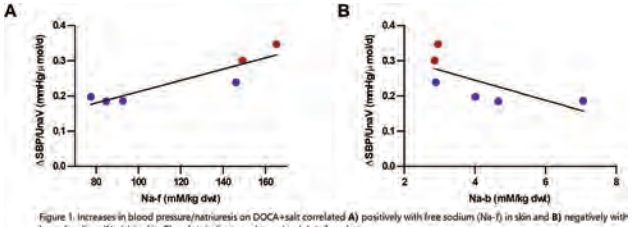

Figure 1. Increases in blood pressure/natriuresis on DOCA+salt correlated **A)** positively with free sodium (Na-f) in skin and **B)** negatively with bound sodium (Na-b) in skin. Blue dots indicate males and red dots females.

FR-PO319

Deletion of SPAK (Stk39) Reduces Hypertension, NKCC2 Phosphorylation and NKCC2 Activity in Dahl Salt-Sensitive Rats

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Background: The Na/K/2Cl cotransporter NKCC2 mediates the NaCl reabsorption in the thick ascending limb (TAL), playing a crucial role in blood pressure regulation. NKCC2 can be phosphorylated by the SPAK kinase (*Stk39*) at $Thr^{96,101}$ and this is thought to activate NKCC2. We found that NKCC2 phosphorylation was 5-fold higher in TALs from Dahl salt-sensitive (DSS) rats. However, the role of SPAK in NKCC2 function and salt-sensitive hypertension remain unclear. We hypothesized that SPAK is involved in salt-sensitive hypertension in part by increasing NKCC2 phosphorylation and activity.

Methods: To test this, we generated SPAK knockout (KO) rats in a DSS genetic background *via* Crispr/Cas9 targeting. We used telemetry to measure systolic blood pressure (SBP) on normal (0.22% Na) or high salt diet (4% Na).

Results: At baseline, SPAK-KO had lower SBP than wild-type DSS (WT) rats (SPAK-KO: 139±1, WT: 153±2 mmHg; p<0.05). After 4 weeks on high salt, SBP rose reaching 162±3 in SPAK-KO and 183±3 mmHg in WT rats (p<0.05). The increase in SBP after feeding a high salt diet was lower in SPAK-KO than WT rats at 7 days (10±1 *vs* 15±1 mmHg, p<0.05), 14 days (14±2 *vs* 19±2 mmHg, p<0.05), and 28 days (22±3 *vs* 30±2 mmHg, p<0.05). We measured total and phospho-NKCC2 in isolated TALs. On normal salt diet, phospho-NKCC2 ($Thr^{96,101}$) over total NKCC2 was 61±25% lower in SPAK-KO (p<0.05), whereas total NKCC2 was not different. After 4 weeks on high salt, phospho-NKCC2 was 62±13% lower in SPAK-KO (p<0.05) whereas total NKCC2 was not different. SPAK-KO rats had a decreased bumetanide-induced natriuresis while on a normal salt diet (UNa WT: 1271±55; UNa SPAK-KO: 843±80 μmol/12h; p<0.05). Lymphocyte infiltration (CD3+) into the kidney after 4 weeks on high salt diet was not different between strains, whereas CD68+ macrophages were lower in SPAK-KO (WT: 266±35, SPAK-KO: 150±6 CD68+/mm^2, p<0.05).

Conclusions: We conclude that SPAK-KO DSS rats exhibit lower SBP at baseline and reduced salt-sensitivity in part caused by lower NKCC2 phosphorylation and activity. In addition, decreased macrophage infiltration in SPAK KO rats supports a potential role for SPAK in renal inflammation during salt-sensitive hypertension.

Funding: NIDDK Support

FR-PO320

Exogenous Mineralocorticoid Administration and Acute Salt Loading Effects on NCC Expression and Activity in Hypertensives with Raised Aldosterone/Renin Ratio (ARR)

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Background: Primary aldosteronism (PA) is a common form of hypertension (HTN) caused by autonomous aldosterone (Aldo) production. Aldo is the major endogenous mineralocorticoid regulating sodium (Na) reabsorption by stimulating the Na-Cl cotransporter (NCC) and the epithelial Na channel (ENaC) in the renal distal tubule. Potassium (K) may also regulate NCC. Exogenous mineralocorticoid and salt loading suppress plasma Aldo, and affect differently NCC and ENaC in human and murine studies.

Methods: Urine samples were collected before and after fludrocortisone suppression testing (FST; fludrocortisone administration and orally salt loading for 4 days) from 13 subjects (10 with HTN and raised ARR and 3 cured of PA by unilateral adrenalectomy); and saline suppression testing (SST; 2L saline infusion over 4h) from 9 subjects (5 with HTN and raised ARR and 4 cured of PA). Urinary exosomes were analysed by immunoblotting.

Results: Significant increases in abundances of NCC (mean 2.97 fold, p=0.04) and pNCC (mean 2.06 fold, p=0.03) by day 4 of FST were observed in 10 with HTN and raised ARR, yet no clear trends of NCC and pNCC were observed in the 3 cured of PA. There were no significant changes in abundance of prostasin, cleaved γ-ENaC and NKCC2 post FST in all 13 subjects, but cleaved γ-ENaC rose post FST (mean 1.17 fold, p=0.05) among the 10 with HTN and raised ARR. There were trends observed towards decreases in abundance of NCC (p=0.09) and pNCC (p=0.07) in 5 with HTN and raised ARR undergoing SST, but not in 4 cure of PA where NCC and pNCC were already low at baseline. The abundances of cleaved γ-ENaC and NKCC2 were unchanged. Plasma Aldo droped in both subjects with HTN and raised ARR (from 328.6 to 180.8 pM, p=0.07) and subjects cured of PA (from 153.75 to 57.25 pM, p=0.05) after SST, but plasma K was unchanged.

Conclusions: Variation of NCC abundance and phosphorylation during FST and SST is detectable in human urinary exosomes. Exogenous mineralocorticoid administration is associated with increases in exosomal NCC and pNCC. The decreases in NCC and pNCC abundance during SST in HTN with raised ARR suggest acute salt loading may induce salt excretion by reducing NCC expression and activity, which may relate to a reduction in plasma Aldo but is independent of plasma K.

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FR-PO321

Stimulatory Effects of NaCl on Tonic Highly Sensitive Cultured Neurons with Renal Afferents

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Background: An important regulatory role of afferent nerve fibers from the kidney has been postulated for a while especially in developing hypertension and counterregulation of salt loading. However, it is not known how salt will act on renal afferent nerves. Hence we wanted to test the hypothesis that even short exposure to low NaCl concentrations will already induce significant action potential generation in cultured neurons with renal axons.

Methods: Over 180 cultured dorsal root ganglion neurons (Th11-L2) of rats with renal afferents *in vitro* were investigated in current clamp mode to asses action potential (AP) generation and classify neurons as tonic (high AP generation upon stimulation) and phasic (AP ≤ 5 upon stimulation). Furthermore, experiments in voltage clamp mode to assess inward currents have been performed. Cultured neurons were exposed to short periods of superfused boli with increasing NaCl concentrations (0.3%, 3%, 4.5%, 10%).

Results: Renal neurons exhibited significant production of action potentials to NaCl superperfusion that was impaired with increasing concentrations of NaCl (0.3%: 36+/-

9.6 APs/10s; 3%: 14.5+/-3.6 APs/10s; 4.5%: 7.8+/-0.7 APs/10s; p<0.05; mean+/-SEM). Superfusion with 10 % NaCl increased AP generation in tonic neurons (15.9+/-3.1 APs/10s, p<0.05; mean+/-SEM) likely due to unspecific e.g. osmotic effects. Phasic neurons were not affected by NaCl. Classification of renal neurons according to their firing pattern (tonic or phasic) revealed the majority of renal neurons to be tonic as previously described.

Conclusions: Superfusion with NaCl in a low concentration led to marked increases of action potential production in tonic, highly active neurons (a characteristic feature of renal innervation) that was impaired with higher superpefused NaCl concentrations in a dose-dependent manner. Hence, NaCl likely influences renal sympathetic nerve activity via the stimulation of renal afferents. However, this effect might be not uniform for all forms and stages of salt loading and hypertension.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO322

Neurogenic SP Facilitates Action Potential Production in Tonic Highly Sensitive Cultured Neurons with Renal Afferents

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Background: Release of the proinflammatory peptide SP from afferent nerves has been shown to influence local inflammation. But SP is also involved in a powerful sympathoinhibitory afferent renal nerve pathway with a long time-constant. Hence we wanted to test the hypothesis that SP also influences action potential production related to TRPV1 receptor stimulation in cultured neurons with afferent axons from the kidney in vivo.

Methods: Cultured dorsal root ganglion neurons (Th11-L2) of rats with renal afferents *in vivo* were investigated in current clamp mode to asses action potential (AP) generation and classify neurons as tonic (high AP generation upon stimulation) and phasic (AP ≤ 5 upon stimulation). Furthermore experiments in voltage clamp mode to assess inward currents. For stimulation of TRPV1 receptors acid of pH 6 was used with and without the addition of SP (0.5 µmol) or CGRP (0.5 µmol).

Results: More than 92 DRG neurons with renal afferents were tested. Addition of SP did not change action potential generation nor inward currents. Proton stimulation (pH 6) of TRPV1 significantly increased action potential production in tonic neurons (0 APs/10s vs. 9.57+/-1.89 APs/10s, p<0.05, mean+/- SEM) and augmented long-term inward currents (baseline -361.7 +/- 89.6 pA vs. -1393.3+/-337.3 pA, p<0.05, mean +/- SEM). The co-stimulation of renal neurons with protons (pH 6) and SP increased the number of action potentials per 10 seconds in tonic neurons (9.57 +/-1.89 APs/10s vs. 16.86+/2.3 APs/10s, p<0.05, mean+/- SEM) as compared to a co-stimulation with CGRP, that was not effective in this respect (13.19+/-1,62 APs/10s vs. 9.57 +/-1.89 APs/10s).

Conclusions: SP in contrast to CGRP facilitated action potential production in tonic, highly active neurons with axons from the kidney (a characteristic feature of renal innervation). Hence, SP might increase the sensitivity of afferent renal nerve pathways thus influencing renal sympathetic nerve control.

Funding: Government Support - Non-U.S.

FR-PO323

Increased Renal Protein Expressions of SLC4A4 and SLC4A5 in Salt-Sensitive C57Bl/6J Mice

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Background: C57Bl/6J mice are salt-sensitive caused, in part, by the dysfunction of the renal dopamine D_1 receptor. However, the role of renal ion transporters in salt-sensitive mice is not well understood.

Methods: Therefore, we studied the effect of varying amounts of sodium intake on the blood pressure (BP) and renal expression of exchanger/transporters/channels for sodium and other ions in salt-sensitive C57Bl/6J mice and salt-resistant BALB/c mice.

Results: We found that 4% NaCl diet given for 1 wk increased the BP (ΔBP=+20 mm Hg) of C57Bl/6J (male, 3 months old, n=5) but not of sex-and age-matched BALB/c mice (n=5). C57Bl/6J mice on high NaCl intake (1.6%, 4%, 6%) had higher BP (ΔBP=+20 mm Hg) relative to when they were on low or normal NaCl intake (<0.09%, 0.6%, 0.8%). The dietary salt-induced increase in BP was observed in anesthetized and conscious, unanesthetized mice, measured by telemetry. There were no differences in water/food intake, urinary excretion, and serum concentrations of Na^+, K^+, and Cl^- between the two mouse strains. However, high salt intake (4%NaCl) increased the renal protein expressions of SLC4A5 (NBCe2) (162±8% *vs.* 100±5%) and SLC4A4 (NBC1) (163±12%) compared with normal salt diet in C57Bl/6J mice, which was not observed in BALB/c mice. By contrast, the 4% NaCl diet increased renal SLC26A6 (Pendrin L1) in both C57Bl/6J (190±1%) and BALB/c (161±8%) mice. Increased NaCl intake did not affect the renal protein expression of NHE3 in either mouse strain. Renal protein expressions of NCC and αENaC, but not of NKCC2 and γENaC, were decreased by high salt diet in BALB/c, but not in C57Bl/6J mice.

Conclusions: We conclude that the salt sensitivity of BP in C57Bl/6J mice is associated with increased renal protein expressions of SLC4A4 and SLC4A5 and impaired salt-mediated down-regulation of NCC and αENaC.

Funding: NIDDK Support, Other NIH Support - HL68686, HL23081, HL074940, HL092196, Private Foundation Support

FR-PO324

Up-regulation of SGLT-5 as a Cause of Fructose-Induced Volume-Dependent Hypertension

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Background: Excessive intake of fructose causes a variety of adverse conditions including obesity, hepatic steatosis, insulin resistance, uric acid overproduction and hypertension which is the most common and significant pathological setting. Cause of the hypertension is not known at present. This study aimed to elucidate the underlying mechanism of fructose-induced hypertension by rat model.

Methods: Male SD rats (7 weeks old) were fed by food containing 60% glucose (GLU) and 60% fructose (FRU) for 3, 6 and 12 weeks. Histological, immunohistological and molecular biological analysis, and gene chip study were applied. No difference of calorie and salt intake of individual animal was daily checked by the measured weight of remaining food.

Results: Mean blood pressure and fractional sodium excretion (FENa) of FRU were both significantly higher (BP 12w-GLU: 94.8±3.4 vs 12w-FRU: 103.7±1.2 mmHg; FENa 12w-GLU: 0.084±0.011 vs 12w-FRU: 0.059±0.08%), suggesting that fructose caused ECF volume-dependent hypertension. Glomerular expansion in FRU (glomerular surface area in 12w-GLU: 7495±181 vs 12w-FRU: 9831±164 µm2) was agreed with the increase in the ECF volume. The expression of GLUT-5, fructose entry pathway, and ketohexokinase, phosphatase of fructose, in the proximal tubule were both up-regulated by fructose. As a candidate of fructose-induced salt reabsorption pathway, NHE3 was focused first because it is principal salt reabsorption pathway of proximal tubule. However, gene expression analysis, immunohistochemistry and immunoblotting of whole and phosphorylated NHE3 indicated negative results. To explore salt transporting molecules responding to fructose, gene chip analysis was conducted, and *Slc5a10*, corresponding to SGLT-5, showed significant up-regulation. The result was confirmed by RT-PCR (12w-GLU: 75.0±5.8% vs 12w-FLU: 230.1±16.0%), and SGLT-1 mRNA was also confirmed to be up-regulated (12w-GLU: 127.9±15.1% vs 12w-FLU: 214.8 ±37.4%).

Conclusions: Excess intake of fructose caused volume-dependent hypertension due to increased salt reabsorption through fructose-induced up-regulation of SGLT-1 and 5.

FR-PO325

Sympathetic Nervous System Regulation of the NCC Is Mediated by α1-Adrenoceptors and OxSR1 to Drive Hypertension

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Background: Recent studies suggest that Sympathetic nervous system (SNS) release of norepinephrine (NE) mediates acute sodium chloride cotransporter (NCC) upregulation via synergistic α1 and β adrenoceptor pathways and oxidative stress responsive 1 (OXSR1) signaling in NCC regulation. **Hypothesis:** NE increases NCC activity via an α1-adrenoceptor and OxSR1 pathway to drive neurogenic or salt sensitive hypertension (HTN, SSH).

Methods: Male Sprague-Dawley (SD) rats receiving a continuous s.c. saline, NE (600ng/min), or NE + terazosin (α1 antagonist, 10mg/kg/day) infusion were fed a 0.6% (NS) or 4% NaCl (HS) diet for 14 days. Naïve or 14 day s.c. terazosin infused spontaneous hypertensive rats (SHR) and Wister Kyoto (WKY) rats were also assessed (N=4/gp). On day 14 basal MAP and NCC activity (peak natriuresis to hydrochlorothiazide [HCTZ]; 2mg/kg) were assessed. NCC, phosphoNCC, and OXSR1 protein levels were assayed via immunoblotting. Expression of adrenoceptor mRNA (α1A-D, β1, β2) was assessed via qPCR using kidney samples from separate groups of rats (N=6/gp).

Results: SD rats remain normotensive on a HS diet and NCC expression and activity is downregulated. NE infusion prevents HS-evoked NCC downregulation, leads to increased OXSR1 expression, and drives SSH. The SHR model of neurogenic HTN shows increased NCC activity and high BP. SHR and NE-infused SD rats show increased expression of α1-adrenoceptor-1D mRNA (SHR: 1.4±0.1 fold increase vs. WKY rats, NE-infused SD rats on NS: 2.2 ±0.5 fold increase, on HS: 2.2±0.4 fold increase vs. respective SD rat diet group). Antagonism of α1-adrenoceptors 1) abolishes SSH and restores HS evoked downregulation of NCC activity in NE-infused SD rats, 2) reduces NCC activity and BP in SHR.

Conclusions: SNS release of NE can modulate NCC activity via an α1-adrenoceptor pathway to evoke SSH and neurogenic HTN. Taken together, we propose a model whereby SNS release of NE activates a linear α1-adrenoceptor pathway that stimulates OxSR1-mediated NCC regulation. Thus, sympathetically driven increases in renal expression of α1-adrenoceptors may contribute to SSH and HTN by driving increases in NCC mediated sodium reabsorption and BP.

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Species	Diet	MAP (mmHg)	Peak ΔUNaV to HCTZ (µeq/min)	Total NCC Expression (ODU/mm²)	Total pNCCT58 Expression (ODU/mm²)	Total OxSR1 Expression (ODU/mm²)
SD sc Saline	NS	124±2	9.7±0.6	1.7±0.4	1.8±0.6	5.2±0.7
	HS	124±1	6.2±0.4*	0.7±0.3*	0.6±0.2*	2.2±0.3*
SD sc NE (600ng/min)	NS	149±4#	10.1±1.3	1.8±0.4	1.9±0.4	9.6±0.8
	HS	189±5*#	10.8±0.4#	2.4±0.9#	2.1±0.4#	10.4±0.6#
SD sc NE + terazosin	NS	152±4#	10.7±1.2	1.9±0.3	1.7±0.4	4.8±0.6
	HS	150±5#Φ	6.1±1.2*Φ	0.6±0.1*Φ	0.6±0.2*Φ	5.1±0.5#Φ
SHR		162±3Ω	18.2±0.7Ω	ND	ND	ND
WKY	NS	118±5	9±0.8	ND	ND	ND
SHR sc terazosin		140±2ΩΦ	11.9±2ΩΦ	ND	ND	ND

Table 1: NS: Normal Salt; HS: High Salt, *p<0.05 vs. respective NS group; #p<0.05 vs. respective SD sc saline HS group; Φp<0.05 vs. respective NE HS group; Ωp<0.05 vs. WKY; $^{\$}$p<0.05 vs. naïve SHR; ND: not determined.

FR-PO326

Increased Proximal Tubule Sodium Avidity Among African Americans vs Whites with CKD Correlates with Blood Pressure

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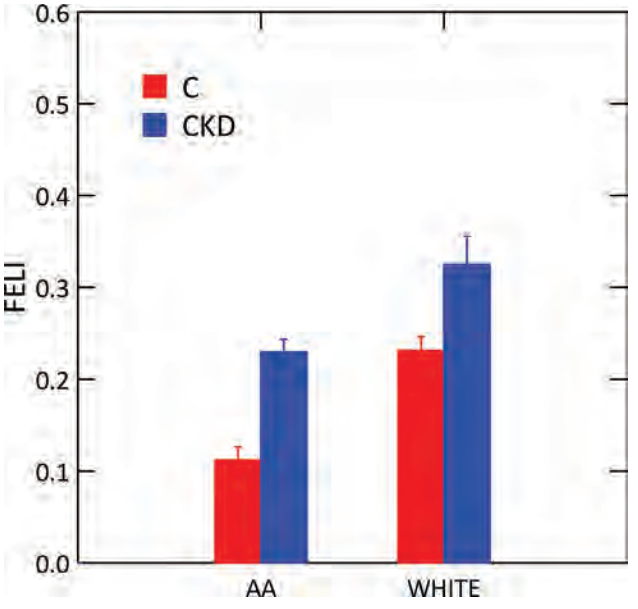
Background: Since African Americans (AA) adapt to higher sodium (Na) intake mainly with a fall in Na reabsorption in the distal nephron and whites (W) via a fall in the higher capacity proximal tubule (PT), AA might be less efficient in adaptation to Na loads. This could lead to greater fluid and Na retention and hypertension both with high Na diet and chronic kidney disease (CKD), which has not been previously studied. We sought to compare patterns of nephron segment Na reabsorption using endogenous lithium and iohexol clearances in individuals across race and levels of kidney function.

Methods: 17 subjects (7 male; 10 AA, 9 of the total with CKD with mean GFR 55 ml/min) were recruited. Subjects with CKD, if treated for hypertension, were weaned off all medication for at least one week prior to study date using a low sodium diet. Subjects could participate in the study day only if their blood pressures (BP) remained <150/90 during the washout. All subjects were placed on an 80 meq/day sodium diet for 1 week prior to study date. Subjects were admitted to the CRC and continuous iohexol infusion (with bolus) was initiated. Urine and serum laboratory measurements including basic chemistries and lithium were collected at baseline and during six 40-minute clearance periods, with a standardized meal served after the 3rd clearance period. BPs were measured with each blood draw.

Results: Fractional excretion of lithium (FELi) was markedly higher in CKD (0.28 vs. 0.15, p<0.0001) and in W (0.27 vs. 0.17, p<0.0001) (Figure). This correlated to mean systolic BP (CKD AA 135 mmHg vs control AA 116 mmHg, p<0.05, and vs W CKD 115 mmMg p<0.001).

Conclusions: PT sodium avidity is significantly higher in AA subjects in health and in CKD and directly correlates with BP.

Funding: NIDDK Support



FR-PO327

Mineralocorticoid Receptor Antagonism by Finerenone Improves Diastolic Dysfunction Induced by CKD in Mice

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Background: Managing the cardiovascular complications of renal failure is a major therapeutic challenge in clinical practice. Mineralocorticoid Receptor (MR) blockade is a highly effective strategy for the management of heart failure, but the use of MR antagonists (MRA) is limited by their side effects rendering them contraindicated in patients with renal failure. Finerenone is a new non-steroidal MRA that has demonstrated in more than 2000 patients with heart failure and additional chronic kidney disease (CKD) as well as in patients with diabetic kidney disease that neither hyperkalemia nor reductions in kidney function were limiting factors to its use. The aim of this study is to characterize the effects of finerenone on the cardiac complications of renal failure in a mouse model of CKD.

Methods: CKD was induced by subtotal nephrectomy (Nx), and finerenone was administered at a low dose (2.5 mg/kg/d) from week 4 to week 10 post-Nx. Cardiac function was assessed by echocardiography and invasive hemodynamic while cardiac fibrosis was measured by Sirius Red staining.

Results: Renal failure induced cardiac systolic and diastolic dysfunctions as well as minor changes on cardiac structure in untreated CKD mice. We also observed alterations in the phosphorylation of proteins playing key roles in the calcium handling (phospholamban, calmodulin kinase II) in these mice. Finerenone prevented most of these lesions without interfering with renal dysfunction.

Conclusions: The benefits of finerenone suggest that MR plays a key role in the development of diastolic dysfunction induced by CKD, thus providing a rationale for further clinical studies with MRAs in patients with CKD.

Funding: Commercial Support - BAYER

FR-PO328

Systemic Succinate Homeostasis and Local Succinate Signaling Control Blood Pressure and Modify Risks for Calcium Oxalate Lithogenesis

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Background: Succinate and citrate are important metabolic signaling molecules. In the kidney, low urinary citrate increases the risk for developing kidney stones, while an elevation of luminal succinate in the juxtaglomerular apparatus increases renin secretion and can cause hypertension. Although the association between kidney stone formation and hypertension is well established in humans, the molecular mechanisms that link these pathophysiologies remain elusive.

Methods: We have utilized electrophysiological measurements, fluorescent imaging and radiolabeled molecules to monitor transport rptoein activity in live cells. In addition we utilized biochemical assays to monitor protein expression and interaction. Finally, slc26a6-/- mice were utilized to test the physiological effects of impaired succinate and citrate homeostasis.

Results: Here, we reveal an intimate relationship between succinate and citrate/oxalate *in vivo* and study the molecular mechanism of this association. Deletion of the succinate/citrate transport inhibitor, the slc26a6 transporter, in male mice resulted in 40% decrease in urinary excretion of succinate, elevated plasma renin and activity-dependent hypertension. Structural modeling confirmed by mutational analysis identified the NaDC-1/slc26a6 interacting surfaces that mediate inhibition of the succinate/citrate transporter, NaDC-1, by slc26a6. This interaction is regulated by the scaffolding protein IRBIT, which interacts with the NaDC-1/slc26a6 complex and is released upon stimulation of the succinate receptor, SUCNR1 to inhibit succinate transport by NaDC-1.

Conclusions: These findings reveal a succinate/citrate homeostatic pathway regulated by IRBIT that controls blood pressure and biochemical risk of calcium-oxalate stone formation and provides a novel potential molecular link between these syndromes. This may have significant clinical implications for stone formation and the associated hypertension.

FR-PO329

Succinate Transport Is Mediated and Regulated by the slc26a6/NaDC-1 Transporters

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Background: The slc26a6/NaDC-1 system controls citrate absorption from the urinary lumen. Urinary citrate chelates free Ca^{2+} thus protecting against Ca^{2+}-oxalate crystallization. Since the slc26a6/NaDC-1 complex mediates and regulates both citrate and succinate transport, a major question that we asked here is whether the same mechanism controls succinate homeostasis and which molecular determinants mediate slc26a6-NaDC-1 interaction and regulation.

Methods: We monitored protein-protein interaction by coimmunoprecipiatation. Succinate transport was monitored using electrophysiological measurements.

Results: Our structural modeling confirmed by mutational analysis identified the slc26a6/NaDC-1 interacting surfaces that mediate regulation of NaDC-1 by slc26a6. To test our model, we monitored the effects of slc26a6 (E613A) and NaDC-1(K107A, R108A) on NaDC-1–slc26a6 interaction by co-immunoprecipitation (coIP). The slc26a6(E613A) mutant showed reduced interaction with NaDC-1 and reduced inhibition of NaDC-1 activity, assayed as Na+-dependent succinate currents. Although expression of slc26a6 was not affected by the (E613A) mutation, slc26a6(E613A) had ~30% lower Cl^-/oxalate exchange activity. The role of NaDC-1(K107) and NaDC-1(R108) in the NaDC-1–slc26a6 interaction is shown. While NaDC-1(R108A) was inactive (not shown), NaDC-1(K107A) retained its activity. Importantly, however, the interaction between NaDC-1(K107A) and slc26a6 was reduced and NaDC-1(K107A) was not inhibited by slc26a6, which strongly inhibits WT NaDC-1.

Conclusions: These results suggest that NaDC-1-mediated succinate transport is controlled by the interaction between the two transporters, and that their interaction is mediated by E613 at the slc26a6-STAS domain and K107 at the NaDC-1 H4c region.

FR-PO330

Succinate Signaling Regulates Succinate Transport

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Background: The SUCNR1 acts as an extracellular succinate sensor and is widely expressed in a variety of epithelial tissues namely the kidney, liver and the intestine. SUCNR1 is a G_q coupled receptor which regulates renin secretion when stimulated in the macula densa. In general, G_q coupled receptors elevate intracellular IP3, that subsequently binds the IP3 receptor (IP3R) and releases IRBIT. IRBIT is the master transport regulator, interacting and modulating the NBC, Slc26a6 and succinate transporters. Here we asked whether succinate receptor stimulation regulates succinate transport via the IP3- IRBIT pathway.

Methods: We monitored SUCNR1 and NaDC-1 mediated succinate transport using fluorescent ion imaging and electrophysiological measurements, respectively. Protein expression was monitored using biochemical techniques.

Results: We found that SUCNR1 activity in transfected human embryonic kidney cells (HEK293) results in intracellular Ca^{2+} release, which is abolished by PLC inhibitor. Moreover, SUCNR1 activity is desensitized by succinate overstimulation. SUCNR1 is expected to result in IRBIT release. We found that IRBIT interacts with the succinate transporter NaDC-1 and regulates succinate transport.

Conclusions: Together, our results suggest that succinate signaling may regulate succinate transport across cellular membranes.

FR-PO331

Low Doses of Intrarenal Bradykinin Induce a Monophasic Sympathoinhibitory Response

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Background: As recently reported intrarenally administered bradykinin induced a biphasic renal sympathetic nerve response (RSNA) with increases and decreases of RSNA but not uniform sympathoexcitation as previously assumed. The high doses necessary to evoke this biphasic response to bradykinin did not suggest a major physiological role of this observation in renal salt and water handling. Hence, we wanted to test the hypothesis that significantly lower doses of intrarenal bradykinin as previously used will induce a merely monophasic renal sympathoinhibition.

Methods: Groups of anesthetized SD rats (n=6-12) were equipped with femoral catheters (blood pressure (BP) & heart rate (HR) recording, drug application), a renal arterial catheter for one time intrarenal administration (IRA) of Bradykinin (BK 5 nM, 5 µl) or Capsaicin (CAP 1 nM, 10 µl) and a bipolar electrode for RSNA recordings; eventually an intravenous (iv) bolus of the NK1-receptor blocker RP67580 (10*10-3M, 15 µl) was given

Results: IRA Bradykinin and IRA CAP decreased RSNA from baseline 3.8±1.2 µV*sec to 1.3±0.7 µV*sec (5 µl, 5 nM BK, $p<0.05$) and 4.0±0.6 µV*sec to 1.6±0.4 µV*sec (10 µl, 1 nM CAP, $p<0.01$). After reaching the lowest point of RSNA activity at 95 min, both groups showed a slight re-increase of RSNA within the following 55 min (from 1.3±0.7 µV*sec up to 2.4±1.3 µV*sec (BK) and from 1.6±0.4 µV*sec up to 1.9±0.4 µV*sec (CAP)). Suppressed RSNA in both groups could be unmasked by systemic (i.v.) administration of the NK1-blocker (1.4±0.4 µV*sec to 5.0±1.9 µV*sec; $p<0.05$ (BK); 3.5±0.6 µV*sec to 9.7±1.7 µV*sec; $p<0.01$ (CAP)).

Conclusions: Bradykinin is able to reduce renal sympathetic nerve activity in doses that are significantly lower than doses inducing a biphasic sympathoexcitatory/-inhibitory response suggesting a physiological role of bradykinin in renal sympathetic nerve control and hence in neurogenic salt and water handling.

Funding: Government Support - Non-U.S.

FR-PO332

NAD(P)H Oxidase 4 Modulates Generation of Hydrogen Peroxide in Rat Aorta and Kidney Glomerulus During High Salt Intake

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Background: NAD(P)H Oxidase 4 (Nox4) is a unique member of a family of oxidoreductases, because it is a constitutively active enzyme that produces specifically hydrogen peroxide (H_2O_2). The purpose of present study is to test the hypothesis that high-salt intake increases H_2O_2 generation in the aorta and kidney glomerulus through Nox4.

Methods: Sprague-Dawley rats were randomly assigned to receive a low-salt (LS, 0.3% sodium chloride) or high-salt (HS, 8% sodium chloride) diet for 7 days. Additional groups of rats on the LS and HS diets received a Nox4 inhibitor (GKT136901, 60mg/g BW) by gavage in the final two days. Fresh aortic rings and kidney glomeruli were prepared for H_2O_2 measurement using Amplex Red ELISA or C_2DCF fluorescence staining for confocal microscopy. Expression of kidney Nox4 protein was accessed by immunohistochemistry in fixed kidney tissue.

Results: Compared with animals maintained on the LS diet, HS enhanced H_2O_2 generation in the aorta ($P=0.019$); animals that received the HS diet had a 47.4% higher H_2O_2 production than animals on the LS diet. Serial scanning using confocal microscopy of aortic specimens stained with C_2DCF demonstrated that intracellular levels of H_2O_2 in both endothelial and smooth muscle layers of the HS-treated animals were higher than the LS group. Treatment of rats with the Nox4 inhibitor reduced intracellular H_2O_2 levels remarkably in both low- and high-salt treated animals. Production of H_2O_2 by kidney glomeruli in rats that received HS was also higher than LS animals ($P<0.001$), and co-incubation with the Nox4 inhibitor (50µM) inhibited H_2O_2 generation in glomeruli of animals receiving both the LS and HS diets ($P<0.001$). Immunohistochemistry of kidney sections showed that Nox4 protein expression was increased in animals that received HS diet, particularly in outer cortex and medulla. CONCLUSION: In summary, rat aortae and kidney glomeruli from rats on a HS diet showed enhanced H_2O_2 generation, which was attenuated by introducing the Nox4 inhibitor. We conclude that Nox4 participated in the modulation of the salt-dependent increase in H_2O_2.

Conclusions: In summary, rat aortae and kidney glomeruli from rats on a high-salt diet showed enhanced H_2O_2 generation, which was attenuated by introducing the Nox4 inhibitor. We conclude that Nox4 participated in the modulation of the salt-dependent increase in H_2O_2.

Funding: Veterans Affairs Support, Other U.S. Government Support

FR-PO333

PeroxisomeProliferator-ActivatedReceptorαAttenuatesHypercholesterolemia-Induced Serum Sulfatide Abnormalities

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Background: As chronic kidney disease (CKD) patients often develop accompanying cardiovascular disease (CVD), an understanding of the developmental mechanisms of CVD is important for nephrologists. Our past studies have demonstrated that serum levels of sulfatides, which belong to glycosphingolipids regulated by peroxisome proliferator-acitvated receptor α (PPARα) and exert anti-platelet and anticoagulation activities, were decreased in end-stage CKD patients and that serum levels of sulfatides in CKD patients with CVD were lower than in those without. Thus, reduced serum sulfatides in CKD patients is potentially related to CVD development. It is also unknown whether hypercholesterolemia, an important CKD risk factor, affects serum levels of sulfatides with or without PPARα involvement.

Methods: We fed a high-cholesterol (HC) diet to wild-type (WT) and *Ppara*-null (KO) mice and examined the serum level changes of cholesterol and sulfatides, sulfatide metabolism, and oxidative stress, another important factor influencing serum sulfatide levels.

Results: The HC diet caused identical levels of hypercholesterolemia in WT and KO mice. Serum levels of sulfatides and the expression level of CST, a major sulfatide synthase, were significantly decreased in both groups due to cholesterol overload, with significantly lower levels in the KO group. On the other hand, oxidative stress was significantly increased in both groups by cholesterol overload, with significantly higher levels in KO mice.

Conclusions: Hypercholesterolemia via cholesterol overload induced a reduction of serum sulfatide levels, suppression of sulfatide synthase expression, and an increase in oxidative stress. PPARα attenuated serum sulfatide abnormalities by maintaining sulfatide synthesis and reducing oxidative stress. PPARα activation therapy may therefore be useful for preventing CVD in CKD patients with hypercholesterolemia.

FR-PO334

Macrophage Myeloperoxidase Deficiency Attenuates CKD Accelerated Atherosclerosis

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Background: Increased myeloperoxidase (MPO) expression and activity are associated with cardiovascular disease in chronic kidney disease (CKD). We recently demonstrated the presence and catalytic activity of myeloperoxidase in vascular lesions of CKD mice. However, it is not known if modulation of MPO alters development and progression of exaggerated atherosclerosis in CKD.

Methods: Male and female LDL receptor-deficient mice were subjected to sham or 5/6 nephrectomy surgery (CKD). These mice were then irradiated and transplanted with bone marrow from MPO knock-out (MPOKO) mice to induce macrophage MPO deficiency. The mice were then maintained on a high-fat diet for 16 weeks. The extent of atherosclerosis was then assessed with oil red O staining of *en face* aortic sections.

Results: As anticipated, the CKD mice had significantly higher plasma creatinine, lower hematocrit, and decreased body weight when compared to the sham animals within the same group. After radiation, the MPOKO mice have decreased hematocrit and body weight but did not have any change in renal function compared to non-irradiated mice. Quantification of aortic oil red O stained lesional area revealed that CKD MPOKO mice had significantly decreased aortic plaque area compared to CKD mice with normal MPO expression. Both sham mice and CKD mice with MPOKO marrow showed decreased atherosclerosis compared to their wildtype counterparts and had no significant change in atherosclerosis when compared with each other.

Conclusions: Our studies demonstrate attenuation of atherosclerosis with macrophage MPO deficiency in CKD mouse model of atherosclerosis. These results strongly implicate macrophage-derived MPO in the pathogenesis of CKD accelerated atherosclerosis.

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FR-PO335

Interleukin-11 Expression Correlates with Hypertensive Kidney Injury in Rat Renovascular Hypertension

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Background: Interleukin-11 (IL-11) was recently identified as a crucial determinant of cardiovascular fibrosis (Schafer et al. 2017, Nature 552:110). We examined IL-11 expression in the heart and the kidney exposed to high blood pressure in renovascular hypertensive rats.

Methods: Two-kidney, one-clip renovascular hypertension (2K1C) was induced in rats; controls (CON) were sham operated. IL-11 expression was measured by RT-PCR in the left ventricle and the right kidney (exposed to high blood pressure). The correlation of renal IL-11 expression with several biomarkers of kidney injury was assessed. We further investigated IL-11 expression in 2K1C rats grouped into rats with malignant versus non-malignant hypertension (based on weight loss, and the number of typical fibrinoid necrosis and onion skin lesions per kidney section of the nonclipped kidney).

Results: At 35 days after clipping, mean arterial pressure was 207±4 mmHg in 2K1C versus 113±3 mmHg in CON (p=0.004). IL-11 expression in the right kidney was elevated 19.6±3.3-fold in 2K1C (N=17) compared to CON (N=8, p<0.001). In left ventricular tissue there was only a non-significant trend towards higher IL-11 expression in 2K1C compared to CON (2-fold, p=0.121). IL-11 in the right kidney in 2K1C correlated with the expression of TGFβ (r=0.72, p=0.001), TIMP-1 (r=0.71, p=0.001), collagen 1 (r=0.68, p=0.001), PDGF (r=0.81, p<0.001) as well as with serum creatinine (r=0.52, p=0.036). There were also correlations with parameters of inflammation including MCP-1 expression (r=0.78, p<0.001) and macrophage infiltration (ED-1 staining, r=0.73, p=0.001) but no correlation with mean arterial pressure (p=0.299). Rats with malignant 2K1C (N=8) had the highest levels of IL-11 expression in the kidney (28.3±3.7-fold versus 11.9±4.1-fold in non-malignant 2K1C, N=9; p<0.01 by ANOVA and Bonferroni; CON N=6).

Conclusions: Expression of IL-11 in the kidney of renovascular hypertensive rats is markedly increased and correlates with parameters of fibrosis, inflammation and loss of function.

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FR-PO336

Dysregulation of a Pro-Inflammatory Signaling Pathway Exacerbates Vascular Calcification Induced by Saturated Fatty Acids

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Background: Vascular calcification is closely associated with cardiovascular mortality in patients with chronic kidney disease (CKD). We previously reported that saturated fatty acids (SFAs) such as stearic acid promote osteoblastic differentiation and mineralization of vascular smooth muscle cells (VSMCs). We recently found that profound activation of aortic IKKb and NFkB-mediated inflammation occurs in mouse models of vascular calcification such as SMC-specific SCD1/2 knockout mice. However, the pathological relevance of a pro-inflammatory signaling pathway to SFA-mediated vascular calcification in CKD is unknown. In this study, we investigated the role of the IKKb-NFkB pathway in the development of vascular calcification induced by SFAs.

Methods: We generated several in vitro models of IKKb-NFkB pathway activation or suppression using a mouse VSMC line, including VSMCs overexpressing constitutively active IKKb (IKKbCA) and IkBa (IKKb deficient) VSMCs (IkBaKO). For in vivo study, we generated SMC-specific IKKb knockout mice by crossing IKKb floxed mice with an SMC-specific Cre transgenic mouse line, SMMHC-Cre$^{(ER)T2}$, to generate SMC-IKKbKO mice.

Results: IKKbCA significantly increased levels of phosphorylated (active) p65, and reduced levels of IkBa protein, a negative regulator of NFkB, resulting in increased expression of NFkB target genes, including IL-6, MCP-1 and iNOS. Importantly, IKKb activation increased the matrix calcium of VSMCs. In addition to IKKbCA, IkBaKO significantly increased expression of NFkB target genes and matrix calcium induced by stearate treatment compared with wild type VSMCs. We next examined whether IKKb inhibition inhibits calcification of VSMCs. shIKKb inhibited stearate-induced up-regulation of NFkB target genes. Unexpectedly, however, IKKb knockdown significantly accelerated stearate-induced vascular calcification. Consistent with the in vitro study, SMC-IKKbKO mice had significantly larger calcified medial lesions under 5/6 nephrectomy.

Conclusions: This study suggests that the IKKb-NFkB pathway positively and negatively regulates mineralization of VSMCs.

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FR-PO337

New Myeloid-Derived Cells Attributing to Cardio-Renal Syndrome

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Background: Cardiovascular disease is connected to chronic kidney disease (CKD), which is well-known as cardio-renal syndrome (CRS). Dysregulation of tissue repair is a pathological process leading to the end stage of organ failure characterized by tissue fibrosis. However, it remains unknown how fibrosis occurs in CRS under CKD.

Methods: To identify bone marrow (BM)-derived cells responsible for the development of CRS, continuous angiotensin II (AII) infusion plus unilateral ureteral obstruction (UUO) (AII+UUO) CRS model was employed using CAG-GFP mice and Col1a2 (Col)-GFP mice, with procedures of parabiosis and bone-marrow transplantation. Flow cytometry was used to identify recruited and migrated cells into the hearts or kidneys and gene expression analyses were followed by cell sorting. We also used immunohistochemistry and co-culture system of sorted cells with mouse embryonic fibroblasts (MEFs) from Col-Luciferase mice.

Results: We newly identified a cluster of myeloid cells, CD45$^+$Sca1$^+$ cells, in the hearts as well as kidneys of the CRS model. The cell type was a globular and mononuclear and this population was significantly increased in number along with the exacerbation of fibrosis. The CD45$^+$Sca1$^+$ cells had an activating potential for collagen production of the cultured MEFs and an ability of producing type 1 collagen by themselves. GeneChip analyses and flow cytometry showed the subpopulation of the CD45$^+$Sca1$^+$ cells, which expressed CCR8.

Conclusions: We could find a new population of myeloid-derived fibrosis-inducing cells, which were associated with cardiac and kidney fibrosis using our CRS model. Further studies are needed to elucidate the full role of this cell population in CRS under CKD.

Funding: Government Support - Non-U.S.

FR-PO338

Renin-Angiotensin System Mediates Renal Vasoconstriction Induced by Acute Renal Venous Pressure Elevation in Rats

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Background: Combined cardiac/renal dysfunction is characterized by elevated renal venous pressure (RVP). Renin-angiotensin system (RAS) is presumably an important mediator of worsening kidney function at a high RVP. In the present study, our hypothesis is that acute RVP elevation increases vascular tone leading to decreased renal vascular conductance (RVC) can be abolished when endogenous angiotensin II (ANG II) is inhibited. Our objective is to evaluate RVP induced renal hemodynamic response during ANG II inhibition.

Methods: Male Lewis rats (350-450g) received a regular sodium diet were randomized as time control or subjected to RVP increase to 20 mmHg. EndogenousANG II was blocked using Enalapril infusion and mean arterial pressure (MAP) was restored by continuous, constant ANG II (ANG II "clamped", n=18) or vasopressin (AVP)(n=11) infusion. To increase RVP, the left renal vein was partially occluded for 120 min following 60 min baseline. MAP, renal blood flow (RBF) and GFR were continuously monitored.

Results: When ANG II was clamped, elevating RVP (0.4±0.3 to 19.6±0.3 mmHg) induced a reduction of MAP by experiment end (Δ -22±4 mmHg, P<0.05). The RVP-induced RVC reduction previously observed in intact rats was completely inhibited (Δ 0.011±0.005 ml/min. mmHg). ANG II clamp did not prevent the decrease of both RBF (Δ -1.9±0.4ml/min, P<0.05), and ipsilateral GFR (Δ -0.77±0.18 ml/min, P<0.05). In AVP-infused animals, RVP increase (0.1±0.4 to 19.6±0.6 mmHg) did not impact MAP (Δ -5.6±4.0 mmHg). Although RBF decreased (Δ -1.3±0.7ml/min, P<0.05), RVC did not decrease (Δ 0.022±0.011 ml/min. mmHg) and the reduction of GFR was attenuated (Δ -0.45±0.15 ml/min).

Conclusions: RVP induced renal vasoconstriction was abolished and reduction in RBF and GFR was attenuated when ANG II was fixed or inhibited. This suggests a primary role for the RAS in the vasoconstriction induced by increased RVP.

FR-PO339

Hypertension and Proteinuria After Antiangiogenic Drugs: Role of the Renin-Angiotensin-Aldosterone System

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Background: Antiangiogenic drugs (AAD) are an effective treatment for many cancers. Hypertension (HTN) and proteinuria (PTN) are frequent side effects of AAD and are common reasons for therapy discontinuation. These effects are thought to be due at least in part to blockade of VEGF in the vasculature and podocytes, but the mechanisms involved are not well understood. Renin-angiotensin-aldosterone system (RAAS) blockade is commonly used for treatment despite the lack of evidence of RAAS activation in this setting. Here, we examine the link bewteen the development of HTN and PTN and intrarenal (IR) RAAS activation.

Methods: Urine albumin/creatinine ratio (ACR) and blood pressure (BP) were measured in 28 prospectively enrolled patients before AAD and on subsequent follow-up visit. Urine angiotensinogen (uAGT) was used as marker of IR RAAS activation and quantified by ELISA, corrected for urine creatinine and assessed for association with HTN and PTN. HTN was defined as BP ≥ 140/90. PTN was defined as > "trace" on urinalysis.

Results: HTN was present in 8 patients at the study start with 50% developing worsening HTN. New HTN developed in 12 patients (60%) and PTN in 10 patients (36%). Mean fold uAGT increase was significantly correlated with fold increase in urine ACR (r=0.39, p=0.04). A 6-fold increase in uAGT was associated with development of HTN and/or PTN, RR= 1.5 (95% confidence interval, 1.1-2.02). Mean fold uAGT increase was greater in patients with incident HTN vs non-HTN and with incident PTN vs non-PTN; however, this trend did not reach statistical significance. Mean baseline uAGT was not predictive of subsequent HTN or PTN.

Conclusions: This study suggests that IR RAAS activation after AAD drugs is responsible at least in part for the development of HTN and PTN in these patients. Larger studies will be needed to better determine whether IR RAAS activation mediates the development of isolated HTN without PTN after AAD.

Association of Hypertension and Proteinuria with Urine Angiotensinogen

Outcome	Neither HTN nor PTN	HTN and/or PTN	Non-HTN	HTN	Non-PTN	PTN
n (%)	7 (25)	21 (75)	12 (43)	16 (57)	18 (64)	10 (36)
Mean baseline uAGT/Cr, SD	14.07 ± 3.75 ng/mg	7.23 ± 2.69 ng/mg	10.27 ± 8.87 ng/mg	7.94 ± 10.98 ng/mg	8.76 ± 8.90 ng/mg	9.26 ± 12.30 ng/mg
p value	0.14		0.54		0.91	
Fold increase uAGT/Cr, SD	1.64 ± 1.14	5.26 ± 6.01	3.40 ± 4.86	5.06 ± 5.89	3.27 ± 4.25	6.30 ± 6.93
p value	0.02		0.42		0.23	

Cr, creatinine; HTN, hypertension; PTN, proteinuria; uAGT, urine angiotensinogen

FR-PO340

ReninNull Cells Synthesize Osteopontin, a Likely Cause of Concentric Renal Arteriolar Hypertrophy

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Background: *Ren1^c* gene knockout (Ren1KO) mice develop renal failure and a characteristic renal vascular lesion consisting of concentric arteriolar hypertrophy. Recently, we discovered that in Ren1KO mice, the cells programmed for the renin phenotype (*Renin^{null}* cells) survive and increase in numbers along the renal arterial tree, maintain the molecular program of the renin phenotype, and integrate in a chaotic, disorderly manner inside the vessel wall, thus contributing to the vascular abnormality. However, how *Renin^{null}* cells are involved in vascular hypertrophy remains to be elucidated.

Methods: We performed transcriptome analysis of renin cells. To isolate renin cells, we generated mice that express yellow fluorescent protein (YFP) under the control of 5 Kb of the 5' regulatory region of the *Ren1^c* gene. YFP-positive cells sorted from the kidneys of Ren1KO mice were processed for single-cell RNA sequencing (scRNA-seq) and compared to cells similarly processed from wild type mice kidneys. RNAs differentially expressed were verified by *in situ* hybridization using digoxigenin-labeled RNA probes. Plasma osteopontin (OPN) level was examined by ELISA.

Results: Differential expression analysis of scRNA-seq showed 364 genes significantly upregulated in *Ren1^c* wild type cells and 1395 genes significantly upregulated in Ren1KO cells. We identified transcripts of 107 genes corresponding to putative secreted proteins whose expression were found to be enhanced in the cells from Ren1KO mice. Using *in situ* hybridization, the expression of the several identified genes was detected in the hypertrophic arterioles at higher level in Ren1KO mice than control mice. *Spp1* gene that encodes OPN is one of the most significantly upregulated genes in *Renin^{null}* cells. With ELISA, we found that plasma OPN level was elevated in Ren1KO mice than control mice.

Conclusions: *Renin^{null}* cells in the hypertrophic arterioles in Ren1KO mice express secreted protein genes including *Spp1* gene. Further study for the function of these genes may elucidate the mechanisms of vascular hypertrophy.

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FR-PO341

Mitochondrial NADP+ Dependent Isocitrate Dehydrogenase (IDH2) Deficiency Aggravates High Fat Diet-Induced Hypertension

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Background: Obesity is a major risk factor for essential hypertension. Oxidative stress is an important pathogenic mechanism of obesity-induced hypertension. Mitochondrial $NADP^+$-dependent isocitrate dehydrogenase (IDH2) plays as a major antioxidant system by production of NADPH, which is an essential player in the glutathione (GSH) and thioredoxin systems for peroxide detoxification antioxidant system. Here, we investigated the role of IDH2 in high fat diet (HFD)-induced hypertension using *Idh2* gene-deleted (*Idh2$^{-/-}$*) mice and wild-type (*Idh2$^{+/+}$*) littermates.

Methods: Eight-week-old *Idh2$^{-/-}$*and *Idh2$^{+/+}$* mice were fed a normal diet (ND) or a HFD for 12 weeks.

Results: HFD accelerated the increase in body weight and mean blood pressure (MBP) compared to those in the ND group in both mice. MBP was higher in *Idh2$^{-/-}$* mice than in *Idh2$^{+/+}$*. Also, the level of cholesterol was greater in *Idh2$^{-/-}$* mice than in *Idh2$^{+/+}$* mice. Whereas, the lipid accumulation in the kidney was greater in *Idh2$^{+/+}$* HFD mice than in *Idh2$^{-/-}$* HFD mice. mRNA levels of renin, angiotensinogen, angiotensin converting enzyme, and angiotensin II receptor type I increased in the HFD mouse kidneys and these increases were higher in *Idh2$^{-/-}$* mouse kidneys than in *Idh2$^{+/+}$* mouse kidneys. However, there were no differences in this renin angiotensin system between ND groups. Mitochondrial damage was observed after HFD feeding in both mice and this damage was more severe in the *Idh2$^{-/-}$* mice than *Idh2$^{+/+}$* mice.

Conclusions: These results indicate that HFD-induced hypertension is worsened by IDH2 gene deletion with greater oxidative stress in the kidneys, suggesting that mitochondrial redox balance is associated with obesity-induced hypertension.

FR-PO342

A New Role of Sox6 in Blood Pressure Regulation

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Background: Hypertension afflicts about 50% of the U.S. adult population, of which half are unresponsive to treatment. As such, new therapies to treat this disease and its complications are necessary. Renin catalyzes the rate limiting step in the renin angiotensin aldosterone system (RAAS) and is produced and stored by Juxtaglomerular (JG) cells in the kidney. The transcriptional mechanisms that govern renin expression are of great importance to develop new treatments for hypertension. Gene expression profiling indicated that the transcription factor Sox6 is highly expressed in JG cells compared to renal Mesenchymal Stromal Cells (MSCs) in the adult kidney. Moreover, *in vitro* Sox6 knockdown decreased the differentiation of renal MSCs into renin producing cells. These results support a previously undefined role for Sox6 in blood pressure control. Several human genetic studies associate Sox6 with hypertension. We hypothesized that Sox6 is a new transcription factor involved in renin expression control.

Methods: Ren1dCre/Sox6$^{fl/fl}$ (Sox6KO mouse), in which Sox6 is deleted specifically in renin expressing cells was used. *In vivo:* JG cell expansion was induced by 10 days of low sodium diet (0.01% Na) and furosemide (0.1 mg/g body weight). Plasma renin concentration measured by elisa. Expression of genes involved in vasoconstriction, calcium (Ca^{2+}) and sodium (Na) metabolism was measured by qRT-PCR.

Results: *In vivo*, at base line specific Sox6 knock-out animals did not alter plasma renin concentration (575±492 ng/mL Sox6-wt vs 984±400 ng/mL Sox6-KO, N=7-11). However, the expression of several genes involved in vasoconstriction, Ca^{2+} and Na metabolism were solely expressed in the Sox6-KO mice. In contrast to the basal state, Sox6 knockout had a dramatic effect during JG cell expansion. As expected, in wild-type mice plasma renin concentration increased during JG cell expansion. Interestingly, there was a concomitant increase in Sox6 expression. In contrast, specific knock out of Sox6 in renin expressing cells halted the increase in the amount of plasma renin concentration during JG cell expansion (186±123 ug/mL Sox6-wt vs 135±68 ug/mL Sox6-KO, N=17-18, $P<0.05$).

Conclusions: These results support a novel role of Sox6 in renin cell fate and thereby in renal development and blood pressure regulation. This opens new possibilities of renin regulation and the development of new therapeutic targets for hypertension.

Funding: Other NIH Support - NHLBI

FR-PO343

The Effect of Microgravity on Central Aortic Blood Pressure

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Background: Blood pressure has been traditionally measured at peripheral arteries. In the past decade evidence has grown, that central aortic blood pressure may be a more powerful predictor for cardiovascular events, but data on its regulation are rare. The present work examines the impact of microgravity on central blood pressure for the first time.

Methods: We performed seven parabolic flights with 22 seconds of weightlessness in each parabola. Hemodynamic parameters including central systolic blood pressure were measured non-invasively in a free-floating position in 20 healthy subjects (19-43 years of age).

Results: Arterial elasticity at rest was normal in all participants (augmentation index 14% [interquartile range IQR 10-22], pulse wave velocity 5.2 m/s [IQR 5.0-5.4]). Transition of 1g to 0g led to a significant increase of central systolic blood pressure from 124 (IQR 118-133) to 127 (IQR 119-133) mmHg ($p=0.017$). Cardiac index augmented significantly from 2.5 (IQR 2.2-2.8) to 2.7 (IQR 2.3-3.0) l/min/m2 ($p<0.001$), whilst peripheral vascular resistance showed a decrease from 1.30 (IQR 1.14-1.48) to 1.25 (IQR 1.15-1.40) s*mmHg/ml ($p=0.037$). Peripheral systolic blood pressure did not change significantly ($p>0.05$).

Conclusions: Whereas there is a multitude of studies on the effects of microgravity on peripheral blood pressure, this study provides first data on central aortic blood pressure. An acute loss of gravity leads to a central blood volume shift with an augmentation of cardiac output. In healthy subjects with normal arterial stiffness the compensatory decrease of peripheral resistance does not outweigh this effect resulting in an increase of central blood pressure.

FR-PO344

MicroRNAs May Predict End-Organ Damage in Severe Hypertension: An Experimental Animal Model

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Background: Severe hypertension is a potentially life-threatening condition if complicated by vital organ failure. The clinical challenge is to differentiate patients in risk of these serious complications from those with solely severely elevated blood pressure. Therefore, we aimed to investigate how hypertension-induced end-organ damage altered the level of circulating microRNAs (miRs) in an experimental model of severe hypertension.

Methods: Dahl salt-sensitive rats were randomized in low-salt (LS, N=20: 0.3% NaCl) or high-salt (HS, N=60: 8% NaCl) diet. Mean systolic blood pressure was 152 mmHg (SD 18,2) in the LS group and 205 mmHg (SD 19,9) in the HS group (p<0,001). Hypertensive encephalopathy (HE) and thrombotic microangiopathy (TMA) were accessed by histology, heart failure with preserved ejection fraction (HFpEF) by echocardiography and endothelial dysfunction (ED) by acetylcholine-induced relaxation.

Results: Partial least squares discriminant analysis (PLS-DA) analysis (VIP-score cut-off at 1.2) predicted 28 miRs for ED, 29 miRs for HE, 30 miRs for HFpEF, and 24 miRs for TMA. ROC curve further identified the miRs that better separate disease from non-disease animals: miR-28-5p for ED (AUC=0.778), miR-151-5p for HE (AUC=0.779), let7c-5p for HFpEF (AUC=0.897), and miR-21-5p for TMA (AUC=0.971). Additionally, we have identified a common signature of circulating miRs using (PLS-DA VIP-score above 1,0) for all 4 outcomes (let-7b-5p, miR-21-5p, miR-484, let-7a-5p, miR-130b-3p, let-7e-5p, and miR-342-3p). Interestingly, KEGG analysis revealed an enrichment of pathways related to TGF-beta signaling (p=3.58E-08), adherens junction (p=6.62E-08), HIF-1 signaling (p=4.43E-04), p53 signaling (p=3,280E-03), and ECM-receptor interaction (p=8.11E-03).

Conclusions: This shows that miRs may serve as biomarkers to identify serious end-organ failure in severe hypertension. Analysis also show that different hypertension induced end-organ failures may be caused by common pathways.

Funding: Government Support - Non-U.S.

FR-PO345

Circulating Extracellular miRNAs in Early Pregnancy and Preeclampsia in Women with Chronic Hypertension

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Background: Women with chronic hypertension (cHTN) are at an increased risk for developing preeclampsia (PE). Development of biomarkers that foretell PE is an unmet objective. We aim to investigate the hypothesis that circulating extracellular miRNA profiles are predictive of PE in women with cHTN.

Methods: Circulating miRNAs in 57 cell-free EDTA plasma samples collected during 9 to 19 weeks of pregnancy from women with cHTN (RO1 HL 48846. PI: P. August), were characterized by small RNA-derived barcoded cDNA sequencing. 39 samples had >1 million reads (30 samples from women who did not develop PE [No PE group] and 9 samples from women who subsequently developed PE [PE group]). We performed differential expression analysis to identify miRNAs discerning the two groups. Criteria for the selection of predictive miRNA included a base mean >5, an absolute fold change (FC) between groups >2, and an unadjusted P <0.05.

Results: Age, gestational age, race, parity, body mass index and baseline blood pressure were not different between the two groups. The PE group was more likely to have a previous history of PE (6/10 vs. 3/24, *P*<0.001). Differential gene expression analysis identified 19 miRNAs in agreement with the above criteria (Table 1).

Conclusions: Validation that circulating levels of 19 miRNAs in plasma may predict the development of PE in women with cHTN may inform pathogenesis and help design prophylactic strategies.

Funding: Other NIH Support - RO1 HL 48846. PI: P. August

Table 1: Circulating Extracellular miRNAs: PE vs. No PE

miRNA	Base Mean	FC	Direction in PE	P-Value
miR-31-3p(1)	7.4	41.9	↓	<0.01
miR-380-5p(1)	6.7	34.8	↓	0.02
miR-450a-1STAR(1)	5.7	30.5	↓	0.00
miR-101-2STAR(1)	12.7	19.7	↓	0.01
miR-874STAR(1)	6.9	17.2	↓	0.04
miR-4772-5p(1)	19.9	10.1	↓	<0.01
miR-4676-3p(1)	10.6	8.7	↓	0.02
miR-579-3p(1)	10.1	7.5	↓	0.01
miR-3942-5p(1)	8.3	7.5	↓	0.02
miR-652STAR(1)	18.0	7.0	↓	0.02
miR-133b(1)	6.6	5.5	↓	0.05
miR-500bSTAR(1)	13.5	4.5	↓	0.04
miR-33aSTAR(1)	41.6	4.1	↓	0.04
miR-3173(1)	32.8	3.7	↓	0.01
miR-518c-3p(1)	14.8	3.5	↑	0.03
miR-758(1)	90.7	3.3	↓	0.04
miR-1296(1)	94.2	2.7	↓	0.01
miR-203(1)	1572.6	2.6	↑	0.01
miR-200c(1)	169.8	2.3	↑	0.03

FR-PO346

Long-Lasting RNAi Therapeutics Targeting Angiotensinogen Induces a Robust and Durable Antihypertensive Effect

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Background: All angiotensin stems from angiotensinogen (AGT). A single dose of small interfering ribonucleic acids (siRNA) targeting AGT may provide long-lasting blood pressure reductions, as it would abolish angiotensin generation. Here we assessed efficacy of AGT siRNA in spontaneously hypertensive rats (SHRs).

Methods: SHRs were treated for 4 weeks with vehicle, siRNA (10 mg/kg; s.c. every 2 weeks), valsartan (31 mg/kg/day; oral), captopril (100 mg/kg/day; oral), valsartan+siRNA, or captopril+valsartan (all groups n=8). Mean arterial pressure (MAP) was measured via radiotelemetry.

Results: Baseline MAP was 137±2 mmHg. ΔMAP was largest after valsartan+siRNA (-67±3 mmHg; P<0.01 vs. captopril+valsartan), followed by captopril+valsartan, captopril, siRNA and valsartan (-55±4, -24±2, -14±1, and -9±2 mmHg, respectively). Valsartan+siRNA reduced cardiac hypertrophy the most (P<0.05 vs. captopril+valsartan). No treatment affected glomerular filtration rate or albuminuria. After 4 weeks, siRNA lowered AGT by 98.6%, which increased to 99.9% in combination with valsartan. All treatments increased renin, the highest rise occurring after valsartan+siRNA. Yet, only valsartan+siRNA lowered angiotensin II. No treatment altered aldosterone. Plasma K^+ tended to increase in all groups, significance being reached only in the valsartan+siRNA group. Both types of dual blockade attenuated normal growth from the second week of treatment onwards.

Conclusions: In conclusion, due to renin upregulation, circulating angiotensin II remained intact even with only 1.4% of AGT left, relative to pretreatment. Consequently, AGT siRNA caused a similar antihypertensive effect as valsartan and captopril. Importantly, when combining siRNA+valsartan, angiotensin II collapsed, and blood pressure decreased synergistically. Given the potential for a low dosing frequency, this novel treatment may address medication adherence problems in patients with resistant hypertension and further development is warranted.

FR-PO347

Impact of Dialysis Access on Right Heart Function

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Background: Arteriovenous shunts (AVS) are the preferred hemodialysis (HD) access over central venous catheters (CVC) due to lower rates of infection and venous complications. However, AVS may be associated with a higher prevalence of pulmonary hypertension (PH), which is linked to poor kidney transplant outcomes. We assessed the relationship between dialysis access and right heart (RH) function (RHF) in a cohort of patients referred to our center for kidney transplantation.

Methods: We conducted a retrospective analysis of patients who underwent transthoracic echocardiogram (TTE) evaluation. We assessed the frequency of PH with estimated pulmonary artery systolic pressure (PASP) ≥ 50 mmHg, right ventricular (RV) dysfunction, and moderate or greater tricuspid regurgitation (TR). Analyses were performed with SAS, using either chi square, ANOVA, or Fisher's exact test.

Results: We identified 448 patients with TTE and known dialysis access: 69.2% AVS, 19.4% CVC, and 11.4% peritoneal dialysis (PD). Demographics and comorbid conditions were similar across access groups, with the exception of gender and dialysis duration (See Table). The prevalence of RH dysfunction (PH, TR, and RV dysfunction) was lowest in PD patients. Among HD patients, TR was significantly more common in CVC than AVS patients, whereas PH and RV dysfunction were not different. Linear regression modeling of estimated PASP found access, age, and diabetes as significant predictors, and again favored PD over CVC and AVS.

Conclusions: PD patients were less likely to have RH dysfunction than HD patients. The effect of CVC vs AVS was less clear; TR was more common in CVC patients while there was no difference in PH and RV dysfunction. Dialysis access decisions are not randomized, possibly leading to differences unaccounted for in our analysis.

	CVC (n=87)	AVS (n=310)	PD (n=51)	P value
Age (mean ± SD)	55.8 ± 17.5	56.3 ± 13.4	55.9 ± 12.8	0.9424
Male (%)	49.4	59.5	70.6	0.047
Months on Dialysis (mean ± SD)	31.3 ± 28.7	40.2 ± 30.2	28.5 ± 15.5	0.0028
Hypertension (%)	87.4	92.3	86.3	0.2016
Diabetes Mellitus (%)	51.7	57.7	52.9	0.5431
Coronary Artery Disease (%)	26.4	21	17.7	0.4227
Obesity (%)	19.5	23.9	17.7	0.4819
PH (%)	11.5	8.7	0	0.0244
RV dysfunction (%)	23.5	15.3	4.2	0.0106
TR (%)	12.9	6.4	0	0.0122

FR-PO348

Carotid Intima-Media Thickness Is a Risk Factor to Cognitive Impairment in Dialysis Patients

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Background: Carotid atherosclerosis is closely related to cardiovascular and cerebrovascular disease. Carotid intima-media thickness (cIMT) measurement by ultrasound is the most widely used noninvasive imaging method to assess carotid atherosclerosis, and was considered as a risk factor and predictor of CV disease. With growing concern about the cognitive impairment (CI) and cerebral small vascular disease (CSVD) problem in ESRD 5D patients, some studies were designed to explore the risk factors of them, without convincing conclusion. In this study, we evaluated the relationship between CIMT and CSVD, CI.

Methods: In this retrospective studies, we analyzed the carotid artery ultrasound results of our dialysis cohort of 2013~2014 CSVD/CI study in which the CSVD were assessed by magnetic resonance imaging and cognitive function were assessed by a cognitive test battery (including: global cognitive function, verbal memory, language ability and executive function). According to cIMT measurement, patients were divided into normal cIMT group (cIMT<1mm) and increased cIMT group (cIMT≥1mm). Multivariable analysis was used to explore the relevance between cIMT and CSVD, CI.

Results: 73 dialysis patients (HD and PD) of our CSVD/CI study cohort of 4 received carotid artery ultrasonography. 54.8% (40/73) was diagnosed as increased cIMT. Compared with normal cIMT group, increased cIMT group, was older (62.4yr vs 52.5yr, p<0.001), with lower serum albumin level (37.4g/Lvs39.4g/L,p=0.046) and lower SCr level (860.7umol/L vs 1007.8umol/L, P=0.010). There were no difference of the prevalence of 3 typical features of CSVD (lacunes, CMBs, and WMHs) between two groups. After multivariable analysis, patients with increased cIMT had a 1.27 fold risk of MMSE score reduce, 2.30 fold risk of MoCA score reduce, 23.53 fold risk of Trails A time delay and 61.56 fold risk of Trails B time delay, but cIMT was not relative to CSVD.

Conclusions: Increased cIMT was an independent risk factor of impairment of global cognitive function, executive function,and the impact of cIMT was not induced by CSVD. Carotid artery ultrasonography may be a useful tool of screening high risk of impaired cognitive function patients.

Funding: Government Support - Non-U.S.

FR-PO349

Impact of Hybrid Therapy with Peritoneal Dialysis and Hemodialysis on Cardiac Events

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Background: The impact of hybrid therapy with peritoneal dialysis (PD) and hemodialysis on cardiac events in PD patients remains unclear.

Methods: PD patients, who underwent the hybrid therapy for at least 3 years, were divided into low cardiac function (LCF, left ventricular ejection fraction [LVEF] < 60%) and normal cardiac function (NCF, LVEF ≥ 60%) groups by cardiac function at the initiation of the hybrid therapy. In these patients, emergency hospitalization rate for cardiovascular diseases (CVDs) (hospitalizations/patient-dialysis years) and echocardiographic parameters (mean ± standard deviation) were evaluated.

Results: The mean age and PD vintage at the initiation of the hybrid therapy in both groups were the followings: LCF group (n = 29), 57.0 ± 11.8 and 3.6 ± 3.3 years; NCF group (n = 64), 58.0 ± 10.8 (P = 0.7) and 4.5 ± 3.2 (P = 0.2) years. The 1-year emergency hospitalization rate for CVDs significantly decreased after the initiation of the hybrid therapy in both groups: LCF group, 0.36 to 0.11 (P = 0.02); NCF group, 0.45 to 0.09 (P < 0.001). In longitudinal analyses for 3 years after the initiation of the hybrid therapy using generalized linear mixed models, in LCF group, LVEF (44.1 ± 15.0%) significantly improved 1 (53.2 ± 18.2%), 2 (55.5 ± 16.7%), and 3 (57.7 ± 17.0%) years after the initiation (every P < 0.05), whereas, in NCF group, LVEF (68.4 ± 5.5%) was maintained at the same level 1 (67.1 ± 7.9%), 2 (66.9 ± 8.7%), and 3 (68.1 ± 9.0%) years after the initiation (every P > 0.05). Moreover, in LCF group, LV mass index (LVMI) (189.1 ± 41.2 g/m^2) decreased 1 (177.7 ± 35.3 g/m^2, P = 0.8), 2 (159.5 ± 44.8 g/m^2, P = 0.008), and 3 (166.4 ± 46.8 g/m^2, P = 0.05) years after the initiation, whereas, in NCF group, LVMI (156.8 ± 44.7 g/m^2) was maintained at the same level 1 (152.8 ± 40.4 g/m^2), 2 (154.6 ± 54.4 g/m^2), and 3 (158.5 ± 52.2 g/m^2) years after the initiation (every P > 0.05).

Conclusions: The hybrid therapy may decrease CVDs and improve cardiac function in PD patients with LCF.

FR-PO350

No Association Was Observed Between Aortic Arch Calcification and Mortality in Hemodialysis Patients

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Background: Vascular Calcification (VC) is common in end-stage renal disease. Previous reports have shown that Aortic Arch Calcification (AoAC) score is associated with poor outcomes in general population. We assessed the utility of AoAC score at initiation of hemodialysis.

Methods: In this study, 115 patients who initiated Hemodialysis in our facility from January 2010 to December 2013 were retrospectively analyzed. The follow-up period was 3 years, and we excluded patients who underwent renal transplantation, transfered to other hospital, and lost to follow up. Two nephrologists retrospectively reviewed chest X-rays to count AoAC score. Using specific scale, we counted the calcification parts from 0 to 16. Patients were classified into 2 groups based on AoAC score : High AoAC score (HC) group (AoAC score ≧ 7) and Low AoAc score (LC) group (AoAC score < 7), and we compared clinical characteristics and outcomes among both groups. Analyses were performed using JMP.

Results: Overall 155 patients were included in the study, 66 % of them were male, mean age was 70.0 ± 10.6 years, mean AoAC score was 6.5 ± 3.6. There was highly significant correlationship between the two nephrologist's AoAC score (r = 0.95, p < 0.05). AoAC score was correlated with age (r = 0.42, p < 0.05) and alkaline phosphatase (ALP) (r = 0.21, p < 0.05), was not correlated with serum phosphate (p = 0.75) and calcium (p =0.50). Kaplan-Meier analysis showed that all-cause mortality rates were significantly higher in HC group compared with LC group (p < 0.05). Logistic regression analysis revealed that HC group patients were significantly high to die within 3 years after initiation of hemodialysis (unadjusted odds ratio 2.90; 95 % CI 1.16 – 7.78; p < 0.05). But, after adjustment for age, sex, presence of diabetes, serum phosphate, calcium, ALP, HC group did not have higher mortality compared with LC group (adjusted odds ratio 1.71; 95 % CI 0.61 – 4.99; p = 0.30).

Conclusions: These results suggested that the severity of Aortic Arch Calcification at initiation of hemodialysis was not an independent risk factor for mortality. But it is well-known, the progression of calcification is associated with poor outcomes, further studies are needed to solve the mechanism of this mysterious discrepancy.

FR-PO351

A Systematic Review of Interventions Targeting Arterial Stiffness in ESRD

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Background: Increased carotid-femoral pulse wave velocity (cf-PWV) in end-stage renal disease (ESRD) patients is indicative of both increased arterial stiffness and high risk for cardiovascular and overall mortality. Several strategies have been studied to decrease arterial stiffness in ESRD, using cf-PWV as a monitoring tool. We conducted a systematic review to explore the effect of these interventions on cf-PWV in ESRD patients.

Methods: MEDLINE, EMBASE and EBM databases were searched for all randomised and observational studies that evaluated interventions to improve arterial stiffness in adults with ESRD. The primary outcome was a reduction of cf-PWV and secondarily, the effects on blood pressure (BP). Study screening, selection, data collection and assessment of methodological quality were performed by two independent reviewers. Study-level effect estimates and pooled estimates were provided by computing the mean differences (MD) and 95% confidence intervals (CI) using the DerSimonian and Laird method and the random effects model.

Results: From 6,607 citations identified, 68 studies met eligibility criteria (randomised: 29; observational studies: 39), and 33 studies were suitable for meta-analysis of 7 interventions (Table). Bio-electrical impedance-guided ultrafiltration (UF), low calcium dialysate, intra-dialytic exercise and calcium channel blockers (CCB) effectively reduced cf-PWV, but only UF and CCB decreased BP compared to standard care. Cholecalciferol or cinacalcet did not affect cf-PWV or BP. Kidney transplantation decreased BP but not cf-PWV compared to dialysis.

Conclusions: Bio-impedance guided UF, low calcium dialysate, exercise and CCB reduce arterial stiffness in ESRD patients. The effectiveness of combining these strategies in decreasing adverse cardiovascular events in ESRD patients requires further study in randomised clinical trials.

Funding: Government Support - Non-U.S.

Intervention	Comparator	# of studies	cf-PWV MD (m/s) [95% CI]	Systolic BP MD (mm Hg) [95% CI]
Bio-impedance guided UF	Clinically guided UF	3	-1.93 [-3.54; -0.31]; **p=0.02**	-4.21 [-7.44, -0.97]; **p=0.01**
Low calcium dialysate	Standard calcium dialysate	7	-1.75 [-2.38, -1.13]; **p<0.0001**	-1.0 [-9.59, 7.59]; p=0.82
Intra-dialytic exercise	No exercise	4	-1.11 [-1.98, -0.24]; **p=0.01**	0.36 [-8.76, 9.49]; p=0.94
Calcium channel blockers	Placebo/standard care	3	-1.27 [-1.99, -0.56]; **p=0.0005**	-27.05 [-40.36, -13.73]; **p=0.0001**
Kidney transplantation	Any dialysis modality	10	-0.41 [-0.95, 0.14]; p=0.14	-8.84 [-12.59, -5.09]; **p<0.0001**
Cholecalciferol	Placebo/standard care	3	-0.23 [-1.16, 1.62]; p=0.74	4.49 [-7.06, 16.03]; p=0.45
Cinacalcet	Placebo/standard care	3	-0.39 [-1.27, 0.49]; p=0.39	-3.72 [-14.72, 7.29]; p=0.51

FR-PO352

Leucine-Rich a-2-Glycoprotein 1 Predicts Cardiovascular Diseases in ESRD Patients

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Background: Plasma Leucine-Rich a-2-Glycoprotein 1 leucine rich α-2 glycoprotein (LRG-1) as a novel serum biomarker for various inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Patients with end-stage renal disease (ESRD) are associated with several health-related adverse outcomes including inflammation, atherosclerosis and premature mortality in individuals. Whether level of Plasma Leucine-Rich a-2-Glycoprotein 1may associate with the clinical status of hemodialysis patients is unknown.

Methods: The immunity in ESRD study (iESRD) recruited 169 hemodialysis patients from southern Taiwan. By history taking and detailed chart reviews, baseline co-morbidities were recorded. Peripheral blood was sampled before hemodialysis session and processed immediately. Plasma levels of LRG1 and high-sensitivity C reactive protein were determined by ELISA. Peripheral blood monocyte and T cell differentiation subsets were determined by multicolor flow cytometry.

Results: Among these patients, 100% were LRG-1-seropositive. In the univariate analysis, log level of LRGwas independently associated with the existence of cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=111.9 95% CI=2.3-5283.3, p=0.016). In a multivariate-adjusted logistic regression model, log level of LRG was independently associated with the existence of cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=150.9 95% CI=2.3-9684.8, p=0.018) afteradjusting for gender, hemoglobin, DM, hypertension and hs-CRP. Level of LRG-1 positively correlated with both IL-6, CRP and WBC, indicating the accumulation of these cytokines participate in the progression of atherosclerosis.

Conclusions: LRG-1positively correlates with the existence of cardiovascular diseases in ESRD patients. Role of LRG-1 and the associated inflammation response should be further investigated in the pathogenesis of atherosclerosis in this patient population.

FR-PO353

Prognostic Value of Left Atrial Volume Index (LAVi) in ESRD Patients

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Background: Cardiovascular Disease is the leading cause of death in End Stage Renal Disease (ESRD) patients. Echocardiographic estimation reveals that left atrial volume Index (LAVi) is increased in diastolic dysfunction of left ventricle, hypertensive heart disease and chronic kidney disease patients. LAVi is an established independent risk predictor for mortality in atherosclerotic heart disease. However, LAVi has not been extensively studied in ESRD population. The aim of this study is to assess the impact of LAVi on cardiovascular mortality in hemodialysis patients.

Methods: From January 1, 2013, through April 30, 2018, we evaluated echocardiographic findings of 91 ESRD patients on maintenance hemodialysis. LAVi was categorized as 1 and 2 (1 < 40 mL/m2 and 2 ≥40 mL/m2). All patients had an ejection fraction of greater than 40%. Patient information was collected and data analysed using SPSS version 22 for windows software package.

Results: Out of 91 patients, 34 patients(37.4%) had LAVi greater than 40 ml/m2. Among 34 patients with LAVi greater than 40ml/m2, 64.7% encountered death. The proportion of death was significantly more in LAVi group 2 than in LAVi group 1 (P=0.007). Unadjusted logistic regression analysis revealed that cardiovascular mortality in LAVi group 2 was 3.4 times higher as compared to LAVi 1 (OR=3.39; 95%CI: 1.39-8.25). In survival analysis the patients with increased LAVi (group 2) were at a greater risk of mortality. Although this group also showed an observable difference in survival and a hazard ratio of 1.5 it was not significant(p=0.197).

Conclusions: Increased LAVI is an independent predictor of cardiovascular mortality in End Stage Renal Disease patients.

	Alive			Number of deaths		Crude OR (95%CI)	P Value	Adjusted OR (95%CI)	P Value
	Group	Number	Percentage	Number	Percentage				
Lavi Group	1	37	64.9%	20	35.1%	3.39 (1.39-8.25)	0.007	3.72 (1.44-9.58)	0.006
	2	12	35.3%	22	64.7%				

FR-PO354

Higher Hemodialysis Product Is Associated with Lower Systolic Blood Pressure in Home Hemodialysis Patients

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Background: Emerging data has clarified that 24-hour ambulatory blood pressure is linearly associated with risk of cardiovascular events. Randomized clinical trials consistently show that increasing hemodialysis (HD) frequency reduces systolic blood pressure (SBP). Thus, the HD prescription may be calibrated to target blood pressure and corresponding cardiovascular risk. We assessed whether Scribner and Oreopoulous' hemodialysis product (HDP) is associated with pre-dialysis SBP in a cohort of home hemodialysis (HHD) patients.

Methods: We analyzed data from US patients who have undergone HHD with the NxStage System One and used Nx2me Connected Health. Data regarding HD frequency, session duration, and pre-dialysis SBP were organized into calendar weeks. We retained all calendar weeks with ≥3 HD sessions. For each calendar week, we calculated the HDP as equal to (mean session duration, in hours) × (number of HD sessions)^2. We fit generalized estimating equations to model separately the associations of pre-dialysis SBP with HDP, HD frequency, and HD hours per week, with adjustment for age and sex.

Results: We analyzed data from 769 patients, 34,340 calendar weeks, and 142,210 HD sessions. Mean age was 54.3 years; 66.4% of calendar weeks were accumulated in male patients. Mean treatment frequency was 4.1 sessions per week, mean (standard deviation) HDP was 56 (28) points, and mean HDP with 3, 4, 5, 6, and 7 sessions was 32, 52, 75, 97, and 122 points, respectively. Mean (standard deviation) pre-dialysis SBP was 135.1 (22.6) mmHg. In a multivariate model, each 10-point increment in the HDP was associated with a 1.5-mmHg decrement (95% confidence interval, 1.1-2.0) in pre-dialysis SBP. Each 5-year increment in age was associated with a 0.4-mmHg increment in pre-dialysis SBP (P = 0.25), and male versus female sex was associated with a 4.8-mmHg increment (P = 0.004). Goodness of fit was best with HDP, moderate with HD frequency, and worst with HD hours per week.

Conclusions: The HDP is a simple-to-use formula that be used to calibrate both treatment frequency and session duration to target a specific change in pre-dialysis SBP. Increased HDP is associated with decreased pre-dialysis SBP, implying that schedules of 3 sessions/week × 3.5 hours/session and 6 sessions/week × 8 hours/sessions are associated with highest and lowest SBP, respectively.

Funding: Commercial Support - NxStage Medical, Inc.

FR-PO355

Effect of Coronary Revascularization on the Association of Elevated Troponin with Post-Dialysis Mortality in Patients with Advanced CKD

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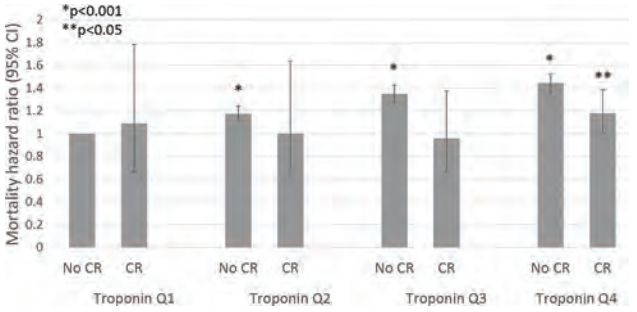
Background: Coronary revascularization (CR), supported by its long-term mortality benefit, is indicated for high risk acute coronary syndrome as evidenced by elevated troponin. Patients with CKD often present with higher and sustained levels of troponin due to reduced clearance, causing diagnostic uncertainty and potentially resulting in fewer patients receiving CR. The incidence of CR and its benefits on long-term mortality in patients with advanced CKD and elevated troponin levels is unclear.

Methods: We examined 16,759 US veterans who had troponin measured during the 3 years prior to start of dialysis. We examined the association between troponin level and future CR, and whether or not future CR modifies the association between troponin levels and subsequent mortality. We modelled the risk of mortality associated with the highest recorded troponin level in time-dependent Cox models including the interaction between troponin and future CR, while adjusting for demographics, comorbidities, smoking status, blood pressure, BMI and baseline eGFR.

Results: Patients were 66±10 years old, 97% male, 37% African-American and 77% diabetic. CR was performed in only 326 patients (2%) following a troponin measurement, and higher troponin was associated with future CR (multivariable adjusted hazard ratio and 95%CI in fourth [>0.25 ng/ml] vs. first quartile [<0.03 ng/ml] of troponin: 6.35 [4.26-9.46]). Death occurred in 11,315 patients (67%). Higher troponin was associated with linearly higher mortality in patients who did not undergo CR (Figure). Patients who underwent CR experienced numerically lower risk of death associated with troponin levels compared to those without CR (Figure), but the interaction was not statistically significant.

Conclusions: CR may be associated with lower post-dialysis mortality in patients with advanced CKD and elevated troponin. The potential benefit of CR in this population needs to be explored further in large prospective studies.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO356

Effects of a Comprehensive Volume Reduction Protocol on Hydration Status and Blood Pressure Control in Hemodialysis Patients

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Background: Chronic volume overload remains one of the most vexing problems in hemodialysis (HD) therapy. The purpose of this study was to investigate the impacts of comprehensive volume reduction protocol focused on reducing dietary sodium intake, blood pressure medications, and post-dialysis weight, on HD patient's hydration status and blood pressure.

Methods: Twenty-three maintenance HD patients (age = 56 ± 13.3y, 48% female) completed a 6-month comprehensive volume control protocol consisting of: 1) weekly intradialytic counseling to reduce dietary sodium intake and interdialytic weight gain (IDWG); 2) persistent reductions in post-dialysis weight; and 3) reductions in prescribed blood pressure (BP) medications. The primary outcome was volume overload (VO) measured by bioelectrical impedance spectroscopy. Secondary outcomes included: IDWG, estimated dry weight (EDW), BP, BP medication prescriptions, and dietary sodium intake.

Results: From baseline (BL) to 6 months (6m), significant improvements were noted in VO (BL 3.9 ± 3.9L (BL) vs 6m 2.6 ± 3.4L, p=0.003), post-dialysis weight (BL 89.4 ± 23.1 kg vs 6m 87.6± 22.2 kg; p = 0.012), and EDW (BL 89.0 ± 23.2 vs 6m 86.7 ± 22.5 kg., p=0.009). There was also a trend for a reduction in monthly averaged IDWG (p = 0.053), and dietary sodium intake (BL 2.9 ± 1.6 vs 6m 2.3 ± 1.1 g/day, p=0.13). Neither systolic BP (BL 160 ± 25 vs. 6m 156 ± 23 mmHg, p=0.56) nor diastolic BP (BL 81 ± 20 vs 6m 79 ± 15 mmHg, p= 0.73) changed, though there was a significant reduction in the total number of BP medications prescribed (BL 3.0 ± 1.0 vs 6m 1.5 ± 1.0 BP meds; p<0.01).

Conclusions: Our comprehensive volume reduction protocol significantly improved HD patient's hydration status. While BP did not change, the reduction in prescribed BP medication number suggests improved BP control. Despite these overall positive findings, the magnitude of change in most variables was modest, and cultural changes in hemodialysis clinics may be necessary to realize more robust results.

Funding: Commercial Support - Renal Research Institute

FR-PO357

Trajectories of Adherence to Thienopyridines After Coronary Stenting in Patients on Dialysis

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Background: Adherence to medications often fluctuates over time. We identified distinct trajectories of adherence to thienopyridines after percutaneous intervention (PCI) with stenting in patients on dialysis and hypothesized that better adherence would be associated with lower risk of cardiovascular events.

Methods: Using the U.S. Renal Data System, we identified all adult patients on dialysis who underwent PCI with stenting from July 2007 to December 2012, filled a discharge prescription for a thieneopyridine, and survived the following 6 months. We applied group-based trajectory modeling to categorize patients into patterns of thienopyridine adherence in the 6 months after discharge. We used Cox regression to estimate the hazard ratios for the composite outcome of myocardial infarction, revascularization, and death associated with each trajectory.

Results: Among 8,296 patients, we identified 4 distinct trajectories of adherence: 1) consistently high adherence, 2) high adherence with gradual decline, 3) moderate adherence with gradual improvement, and 4) moderate adherence with rapid decline (**Figure**). The unadjusted risk of the composite outcome was significantly lower for those with consistently high adherence (**Table**).

Conclusions: Consistently high adherence to thienopyridines was associated with a lower unadjusted risk of cardiovascular events than other trajectories of adherence. Further work to identify correlates of these trajectories may help inform interventions to improve adherence and potentially reduce adverse outcomes.

Funding: NIDDK Support

Hazard Ratios for CV Outcomes

Trajectory (vs. Group 1)	HR (95% Confidence Interval)
Group 1 (consistently high adherence)	reference group
2 (high adherence with gradual decline)	1.15 (1.05-1.25)
3 (moderate adherence with gradual improvement)	1.32 (1.04-1.21)
4 (moderate adherence with rapid decline)	1.19 (1.11-1.28)

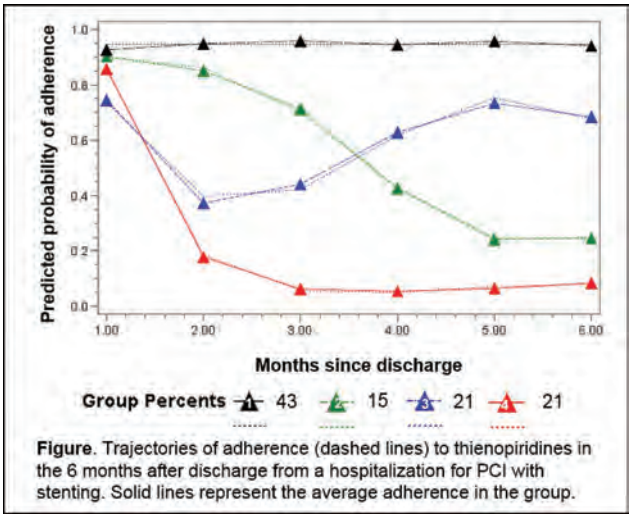

Figure. Trajectories of adherence (dashed lines) to thienopiridines in the 6 months after discharge from a hospitalization for PCI with stenting. Solid lines represent the average adherence in the group.

FR-PO358

The Safety and Efficacy of Clonidine in Hemodialysis Patients: A Systematic Review and Meta-Analysis

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Background: The United States Renal Data System data shows that 20% of hemodialysis (HD) patients are prescribed clonidine to treat hypertension. Clonidine is a centrally acting alpha 2 adrenergic agonist, and the balance between potential efficacy and its known adverse effects is unknown in HD patients. This study systematically reviewed existing evidence and performed a meta-analysis on the safety and efficacy of clonidine in HD patients.

Methods: Keyword and reference search was conducted through February 2018 in PubMed Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov databases. Inclusion criteria were - study design: randomized controlled trials, cohort studies, prospective studies, retrospective studies or case series; subjects: adult HD patients; main outcome: blood pressure and safety; language: English; and article type: peer-reviewed publications.

Results: Eight studies met the inclusion criteria, including two prospective pre-post studies, one double-blind controlled trial, one single blinded placebo-controlled trial, one crossover open-label clinical trial, one retrospective analysis, and two case report series. Study durations ranged from 2 to 8 weeks, with a total sample size of 23. Risk of bias was high for all included studies. Significant side effects and adverse events include hypotension, lightheadedness, drowsiness, dry mouth, and rebound hypertension for oral clonidine, as well as contact dermatitis for patch application. Meta-analysis (random effect model) found short-term clonidine use to be associated with significant improvement in systolic blood pressure (pooled effect: -12.985, 95% CI[7.878, 18.092], p<0.001) while changes in diastolic blood pressure were not statistically significant (-11.119, 95% CI[-22.725, 0.487], p=0.060). There is currently no data on the long-term efficacy of clonidine in dialysis patients.

Conclusions: Despite its widespread use, there is no evidence supporting the long-term use of clonidine in the HD population and significant safety concerns. There is low-quality evidence demonstrating the efficacy of clonidine in lowering blood pressure in HD patients in the short term. Clonidine is poorly tolerated and has a potentially dangerous adverse effect profile. Future studies on anti-hypertensives with known cardiovascular benefits should be studied more rigorously in the HD population.

FR-PO359

Arterial Stiffness as a Risk Factor for Subclinical Coronary Artery Calcification in Predialysis CKD: From the KNOW-CKD Study

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Background: Both arterial stiffness and coronary artery calcification (CAC) are important predictors of cardiovascular disease (CVD) in the general population and in chronic kidney disease (CKD) patients. Recent studies on arterial stiffness and CAC in subjects with preserved renal function have verified the association between the two. However, the relationship is not well evaluated in CKD patients.

Methods: This cross-sectional study analyzed 1,385 predialysis CKD patients from the KNOW-CKD cohort. Participants were divided into four groups according to brachial-ankle pulse wave velocity (baPWV) quartile. Coronary artery calcium score (CACS) were assessed using cardiac computed tomography and CAC was defined as a CACS >100.

Results: CAC prevalence was higher in the higher baPWV groups (6.4%, 9.8%, 23.7%, and 43.8% for the 1st to 4th quartiles of baPWV, respectively, P<0.001). In Tobit regression analyses (Table) that were fully adjusted for traditional and renal cardiovascular risk factors, the CACS ratio comparing the highest and lowest baPWV quartiles was 3.03 (95% CI, 1.59–6.87). Similarly, the OR for CAC in the highest baPWV quartile compared to the lowest quartile was 1.98 (95% CI, 1.09–3.60) in a fully adjusted multivariate logistic model. Results were consistent across analyses with different cutoffs for CAC or with different clinically relevant subgroups.

Conclusions: Increased arterial stiffness measured by high baPWV was associated with CAC in a predialysis CKD cohort. Further studies are required to explore the role of arterial stiffness in the development of CAC and cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.

Multivariate-adjusted CACS ratios according to baPWV

baPWV quartile	Model 1		Model 2		Model 3	
	Ratios (95% CI)	P	Ratios (95% CI)	P	Ratios (95% CI)	P
1	Reference		Reference		Reference	
2	1.29 (0.67–2.50)	0.448	1.11 (0.59–2.09)	0.740	1.11 (0.59–2.08)	0.745
3	3.91 (1.99–7.68)	<.001	2.08 (1.08–4.01)	0.029	2.03 (1.05–3.92)	0.034
4	11.76 (5.8–23.84)	<.001	3.44 (1.66–7.14)	0.001	3.03 (1.59–6.87)	0.001

Model 1: Adjusted for age and sex;

Model 2: Adjusted for model 1 + WHR, systolic blood pressure, diabetes, eGFR, LDL cholesterol, hsCRP, urine protein to creatinine ratio, and current smoking;

Model 3: Adjusted for model 2 + calcium, phosphorus, 25-OH-vit D, and intact PTH

FR-PO360

Vascular Abnormalities in CKD Patients

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Background: CKD patients suffer from excess vascular events. The exact nature of vascular abnormalities and their progression is unknown. The aim of our study was to compare vascular abnormalities and its progression in 3-6 months in different CKD groups and healthy controls.

Methods: A detailed vascular assessment was performed in clinically stable patients (21 CKD stage 2-4, 14 haemodialysis (HD), 22 transplant (TX)) and 21 healthy controls in a quiet, temperature controlled vascular laboratory; at baseline and 3-6 months. Data were analysed with SPSS version 25, P value <0.05 was considered significant.

Results: The carotid intima media thickness (CIMT) differed significantly between all groups at baseline and after 3-6 months. As expected, the lowest values were present in healthy controls and the highest in CKD2-4 and HD patients. Ankle brachial index (ABI) significantly differed between groups at baseline, but not after 3-6 months. Brachial flow mediated dilatation (FMD) didn't differ between groups at baseline or on follow up. Pulse wave velocities (PWV) were significantly different between different groups, with the highest values in HD and CKD2-4 patients and the lowest values in healthy controls. During 3-6 months CIMT increased significantly only in TX patients. ABI significantly decreased in 3-6 months in the CKD2-4 patients. FMD decreased in 3-6 months in TX patients. PWV didn't change significantly in 3-6 months in all groups.

Conclusions: CKD2-4, HD, TX patients and healthy controls differ significantly in CIMT, ABI and PWV, with the most abnormal values present in HD patients. Progression of cardiovascular disease in this short term follow up was variable, with worsening of FMD and CIMT in TX patients.

	CKD2-4	HD	TX	Controls	ANOVA P value
CIMT1 (mm)	7.05±1.44	6.86±1.33	5.89±0.92	5.55 ±1.03	0.000*
CIMT2 (mm)	7.42±1.54	7.08±0.76	6.13±0.98	5.723±1.34	0.001*
CIMT1-CIMT2 P value (pair t-test)	0.522	0.173	0.010*	0.224	
ABI1	1.18±0.17	1.39±0.34	1.28±0.19	1.20±0.08	0.013*
ABI2	1.12±0.18	1.16±0.12	1.24±0.13	1.21±0.11	0.069
ABI1-ABI2 P value (pair t-test)	0.046*	0.736	0.273	0.427	
FMD1 (%)	3.60±2.48	3.03±2.07	4.07±4.06	4.41±2.82	0.577
FMD2 (%)	2.21±1.74	2.11±1.71	2.69±2.19	3.51±2.73	0.292
FMD1-FMD2 P value (pair t-test)	0.059	0.055	0.024*	0.327	
PWV1 (m/s)	10.46±2.54	11.88±2.54	7.88±1.80	6.98±1.27	0.000*
PWV2 (m/s)	10.26±2.44	11.35±2.85	8.41±2.22	7.17±1.50	0.000*
PWV1-PWV2 P value (pair t-test)	0.259	0.422	0.067	0.513	

FR-PO361

The Make-Up of Cardiovascular Disease as Kidney Function Declines: Results from a Population-Based Australian Cohort Study (EXTEND45)

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Background: The pathophysiological process behind cardiovascular morbidity differs between people with Chronic Kidney Disease and the general population. We aimed to examine the relative contributions of myocardial and endoluminal disease to cardiovascular morbidity as kidney function declined.

Methods: Based on data from the EXTEND45 study (the 45 and Up Study linked to hospital and community pathology datasets by the Centre for Health Record and Linkage[CHeReL]), we identified a population-based cohort (2006-2014) of 41,099 people aged ≥45 years who had a measure of kidney function(estimated glomerular filtration rate[eGFR]). Cardiac hospitalisations were identified using ICD-10 codes and classified into endoluminal (all coronary artery diseaxse including complications), myocardial (all cardiac failure and arrhythmias) or other (all valvular disease and infective cardiac processes). We compared the proportion of endoluminal, myocardial and other causes of hospitalisation by KDIGO stage using the Chi-squared test and the trend in proportions between endoluminal and myocardial causes using the Cochran-Armitage trend test.

Results: Of 41,099 participants 3,177 experienced ≥1 hospitalised cardiac event(1901, 837, 439 endoluminal, myocardial and other respectively) over a median follow-up of 1.9 years. Endoluminal causes as a total proportion of cardiac hospitalisation decreased as kidney function declined(64.5%, 61.8%, 57.2%, 53.1%, 50% for Stages 1, 2, 3a, 3b, and 4-5, respectively) while myocardial(26.7%, 25.5%, 27.0%, 28.1%, 29.6% respectively) causes increased(P-value 0.0005) and this trend was significant(P= 0.02). Other causes were also found to increase(8.8%, 12.7%, 15.9%, 18.8%, 20.5% respectively, P-value 0.0005).

Conclusions: The trend towards a decrease in the proportion of endoluminal and an increase in myocardial causes of hospitalisation with kidney function decline was significant. Understanding risk factors that lead to this divergence in cardiovascular morbidity may help reduce the burden.

Funding: Commercial Support - The EXTEND45 Study is funded through peer-reviewed (NSW Cardiovascular Research Network Collaborative Project Grant) and unrestricted industry (from MSD, Amgen and Eli Lilly) research grants.

FR-PO362

Vascular Endothelial Growth Factor C Is Associated with Atherosclerotic Change in Kidney Arteries

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Background: Vascular endothelial growth factor (VEGF) contains five members in humans. Among them, VEGF-C is known to has a crucial role in lymphangiogenesis, however, some studies have shown that the VEGF-C is associated with atherosclerosis as well. In this study, we observed the VEGF-C expression in kidney arteries using kidney biopsy samples.

Methods: VEGF-A, B and C expressions on arteries greater than intralobular artery were assessed by immunofluorescence histochemistry using 185 kidney biopsy specimens obtained at Japan Community Health Care Organization Sendai Hospital. Atherosclerotic change was scored semi quantitatively. Results were compared with patients' baseline characteristics.

Results: One hundred sixty three specimens which contained more than one interlobular artery were eligible for the study. The age of participants ranged from 14 to 85 and biopsy result included various diseases such as glomerulonephritis, diabetes and hereditary disorders. VEGF-A was positive, and VEGF-B was negative in all arterial samples, whereas VEGF-C was positive in 87 and negative 76 samples. VEGF-C positive

group was older (61.0±14.1 vs 46.6±19.9, p<0.001), showed higher cardio-ankle vascular index (8.39±1.36 vs 7.45±1.43, p<0.001) and higher prevalence of hypertension (72.4 vs 40.8%, p<0.001) compared to that of negative group. Body mass index, serum HbA1c level and serum cholesterol level did not show a statistical significance between the two groups.

Conclusions: VEGF-C expression on the artery could be associated with atherosclerosis in the kidney. This new finding is enabled by kidney biopsy which can obtain arterial samples from a wide age range.

FR-PO363

Fibroblast Growth Factor 23 Is Associated with Biomarkers of Cardiomyocyte Stress/Injury in Patients with CKD

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Background: High levels of fibroblast growth factor 23 (FGF23) has been related with left ventricular hypertrophy (LVH) in adults with CKD. In this cross-sectional study, we aimed to determinate the associations between c-terminal FGF23 (ctFGF23), intact FGF23 (iFGF23), serum αKlotho, cystatin C, high sensitive troponin T (hsTnT), prothormone brain natriuretic peptide (NT-proBNP) levels and structural and functional cardiac changes in patients with chronic kidney disease (CKD).

Methods: We enrolled patients with CKD and left ventricular ejection fraction (LVEF) >50%. Patients with atrial fibrillation, history of heart failure, myocardial infarction, pulmonary hypertension, cardiomyopathies, LVEF <50% or parathyroidectomy were excluded. Laboratory parameters including serum creatinine, 24h-proteinuria, mineral bone disorder (calcium, parathormone (PTH), phosphate, tubular reabsorption of phosphate (TRP), phosphate clearance), iFGF23, ctFGF23, serum αklotho, hs-TnT, NT-proBNP were measured. Echocardiographic parameters including LV mass index, relative wall thickness (RWT), volume end-diastolic (VTD), early diastolic mitral annulus velocity (e' velocity), E/e', left atrial volume index (LAVI) and global longitudinal strain (GLS) were measured by the same cardiologist at the same day of blood extraction. The cardiologist was blind for the stage of CKD in each patient.

Results: 120 patients were included. FGF23 was related with 2 biomarkers of cardiomyocyte stress/injury: hsTnT (p<0.05) and NT-proBNP (p<0.05), without finding an association with structural and functional cardiac parameters. However, cystatin C, hsTnT and NT-proBNP were associated with LV mass (p<0.05), RWT (p<0.001), VTD (p<0.001), e'velocity (p<0.001), E/e' (p<0.001), LAVI (p<0.001). We also found that FGF23 was associated with αKlotho (p<0.05), creatinine based-estimated glomerular filtration rate (p<0.001), 24h proteinuria (p<0.001), cystatin C (p<0.001), PTH (p<0.001), TRP (p<0.05).

Conclusions: FGF23 was not associated with structural and functional cardiac changes, but it was associated with two biomarkers of cardiomyocyte stress/injury: hsTnT and NT-proBNP. This finding suggests a relation between FGF23 and remodeling of cardiac tissue in patients with chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO364

Longitudinal Changes of Cardiac Structure and Function in Mild to Moderate CKD: Results from the Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD)

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Background: Abnormal left ventricular (LV) structure and function are associated with increased risk of adverse outcomes among patients with chronic kidney disease (CKD). However, little is unknown regarding the natural longitudinal changes in cardiac structure and function especially in early CKD patients.

Methods: This was a longitudinal study of a subset of participants of the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) who were enrolled from 2011 to 2012. Patients with CKD at stages from G1 to G3b were included if they had serial echocardiograms performed at baseline and again after 4 years. Age, sex, diabetes, CKD stages, hemoglobin, albumin, lipid profile, systolic blood pressure, and baseline LV mass index were included as covariates in the multivariable analysis for risk factors of *de novo* LV hypertrophy (LVH).

Results: A total of 378 patients (57.7% male) were enrolled. The numbers of patients with diabetes and hypertension were 65 (17.2%) and 360 (95.2%), respectively. During the follow-up period for 4 years, mean (SD) estimated glomerular filtration rate was declined from 64.1±27.1mL/min/1.73m^2 to 54.8±30.8 mL/min/1.73m^2. Over 4 years, there was no significant change of LV structure and function among overall subjects. Our subjects were divided into two subgroups based on the baseline eGFR; subgroup I (eGFR ≥60 ml/min/1.73m^2) and subgroup II (30 < eGFR <60 ml/min/1.73m^2). Mean age (SD) was 46.5±11.2 years in subgroup I, and 55.4±10.8 years in subgroup II (*P*<0.001). In subgroup analysis, the prevalence of LVH for subgroup I was similar between baseline and follow-up (18.5% vs. 19.9%). However, for subgroup II, LVH increased from 26.2% at baseline to 52.3% at 4 years. There was no significant change over time in the prevalence of systolic and diastolic dysfunction according to CKD stage. In multivariable logistic regression analysis, only age was associated with development of *de novo* LVH (odds ratio 1.602; 95% confidence interval 1.021-1.105, *P*=0.003).

Conclusions: In conclusion, LV structure and function of mild to moderate CKD patients (eGFR >30ml/min/1.73m^2) did not change significantly over 4 years.

Funding: Other U.S. Government Support

FR-PO365

Lanosterol Synthase and Endogenous Ouabain Cooperate in Blood Pressure Control

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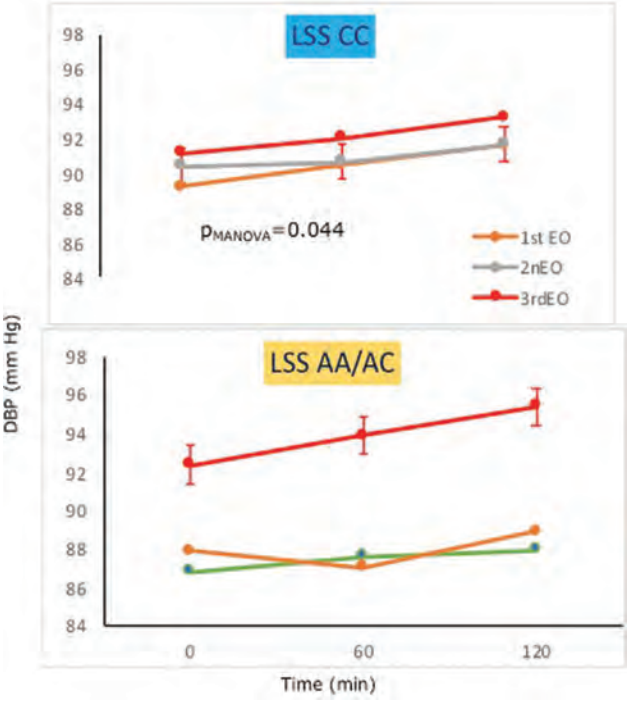
Background: Endogenous Ouabain (EO) is stress hormone secreted from the adrenal glands in response to hemodynamic stimuli. Long term body sodium has been shown to modulate plasma EO levels according to Lanosterol synthase gene polymorphisms. The present study explores the effect of acute saline load according to LSS Gene variants and circulating EO levels in a large cohort of naïve hypertensive patients (NHPs).

Methods: Basal EO was measured in 713 NHPs for acute saline test phenotypes. For the analysis, patients were divided in groups according to tertile distributions of basal EO : 1st group EO <167 pmol/L; 2nd group EO >167 pmol/L and < 268 pmol/L; 3rd group EO >268 pmol/L. In the three groups, we evaluated 1) changes in EO, 2) interaction with LSS variants and 2) blood pressure effects.

Results: Circulating EO was higher among Salt Sensitive NHPs, (geometric mean 224.04 vs 199.81 pM/L,p =0.005) no significant modification was observed during acute maneuvers. However, a significant modulation (p=0.044) was observed between elevated circulating EO and the LSS A variant, and the DBP rise after saline infusion.

Conclusions: These results confirm the role of EO in salt sensitive hypertension. Patients carrying at least one LSS A variant in the presence of elevated EO show an modulatory effect on diastolic BP. The higher affinity of the LSS A variant at tissue levels may account for the enhanced vascular response in these patients. The present findings support a role for LSS and EO in salt adaptation.



FR-PO366

Pharmacologic Control of Arterial Hypertension and Risk of All-Cause Mortality in Older Adults

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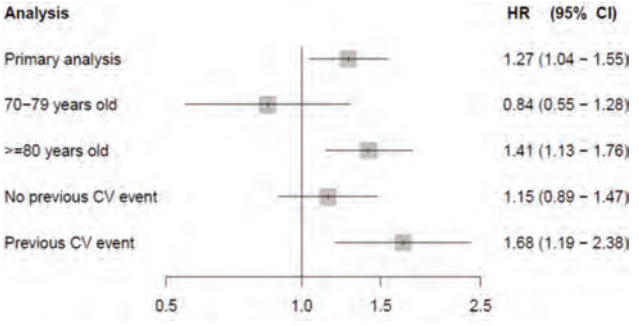
Background: Hypertension is highly prevalent in older adults and can increase the risk of mortality. Real world data on the effects of disease control in this age group are scarce. Thus, the objective of this population-based analysis was to assess whether pharmacologic control of hypertension has an impact on the risk of all-cause mortality in patients ≥70 yrs.

Methods: All patients were participants in the Berlin Initiative Study (BIS). Demographics, lifestyle factors, medication use, and comorbidities were ascertained in face-to-face interviews. Mortality was assessed using health insurance data including the exact date of death. Cox prop. hazards models yielded adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of all-cause mortality associated with systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg ('good' disease control) compared to SBP ≥140 mmHg and/or DBP ≥90 mmHg ('poor' disease control). In secondary analyses we assessed the risk of all-cause mortality after stratifying by age (70-79 vs ≥80 yrs) and previous cardiovascular (CV) events.

Results: Among the 2069 participants of the BIS, 1628 (79%) were treated with antihypertensive drugs at baseline. Of those, 636 (39%) showed good disease control (mean age 81 yrs, 51% female) and 992 (61%) poor disease control (mean age 81 yrs, 53% female). Baseline characteristics were comparable between patients with good and poor disease control except for previous myocardial infarction (23% vs 15%) and albuminuria (23% vs 33%). During a follow-up of 8853 person-yrs, 469 patients died. Compared with poor disease control, good disease control was associated with an increased risk of all-cause mortality (HR, 1.27; 95% CI, 1.04-1.55). This effect was augmented in patients ≥80 yrs (HR, 1.41; 95% CI, 1.13-1.76) and patients with previous CV events (HR, 1.68; 95% CI, 1.19-2.38) (Figure).

Conclusions: Reducing BP below 140/90 mmHg could increase the risk of mortality in older adults, in particular among octogenarians and patients with previous CV event.

Funding: Private Foundation Support



FR-PO367

Influence of Pre-Diabetes Status on the Effects of Intensive Systolic Blood Pressure (SBP) Lowering in the Systolic Blood Pressure Intervention Trial (SPRINT)

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Background: Intensive lowering of SBP increased the risk of incident CKD in people with type 2 diabetes mellitus. Hence, we examined the hypothesis that pre-diabetes increases the risk of incident CKD with intensive SBP lowering in persons without diabetes.

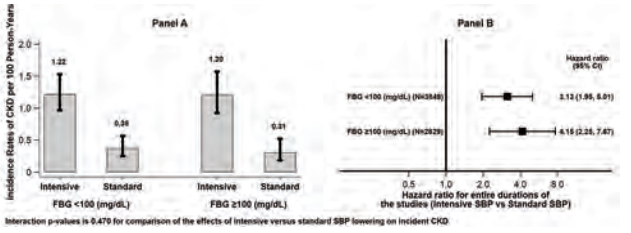
Methods: SPRINT tested the effects of intensive (<120 mm Hg) versus standard (<140 mm Hg) SBP goals on CVD outcomes. Diabetes was an exclusion criteria. Based on fasting blood glucose (FBG), we defined normoglycemic group as FBG < 100 mg/dl and pre-diabetes group as FBG ≥ 100 mg/dl in SPRINT participants without CKD at baseline. We defined incident CKD as ≥ 30% decline in eGFR to < 60 ml/min/1.73 m^2 with a second confirmatory value. We examined in Cox regression models whether the risk for incident CKD with intensive SBP lowering differed by pre-diabetes status.

Results: Of the 6678 non-CKD SPRINT participants, 2829 (42.3%) had prediabetes. The baseline characteristics are summarized in the Table. Over 21155 total years of follow-up, there were 164 incident CKD events. The incidence of CKD was higher in the intensive arm compared to standard SBP arm within normoglycemia and pre-diabetes group (Fig 1), with similar hazard ratios (interaction p = 0.47).

Conclusions: Intensive SBP lowering increased the risk of incident CKD in persons with normoglycemia and prediabetes. There was no evidence that the presence of pre-diabetes modified the risk of incident CKD with intensive SBP lowering.

Funding: NIDDK Support

	FBG<100 N=3849	FBG≥100 N=2829
FBG(mg/dl)	91±6	111±13
Age(yr) #	67±9	66±9
Female(%) #	38	28
Intensive SBP arm (%)	50	50
CVD(%)	18	19
SBP(mm Hg) #	140±16	139±15
DBP(mm Hg)	80±12	79±12
BMI(kg/m^2) #	29±6	33±6
eGFR(ml/min/1.73m^2)	81±16	81±15
Urine albumin creatinine ratio (mg/g)	9(5,17)	9(5,17)



Relative risk differences of incident CKD by intervention arms and prediabetes status

FR-PO368

Associations of Early Decline in eGFR with Cardiovascular Disease (CVD) Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

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Background: SPRINT examined the cardiovascular effects of intensive (INT) vs. standard (STD) SBP goals (<120 vs. <140 mm Hg). INT SBP lowering resulted in early ↓ in eGFR but the clinical implications are unclear.

Methods: In a post-hoc analysis, based on % change in eGFR from baseline to 6 months, we defined four ΔeGFR groups (Table). Using -5 to +5% group as the reference, we related ΔeGFR groups to CVD events that occurred after 6 months in Cox regression models.

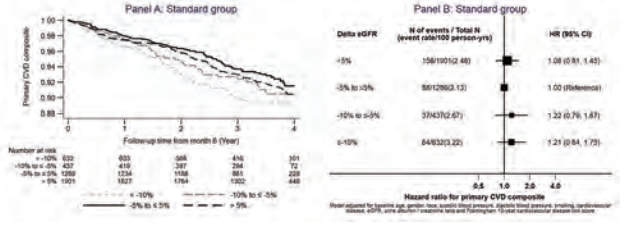
Results: 15% in the STD vs. 26% in the INT SBP arms (p<0.001) had >10% ↓ in eGFR. Key baseline characteristics are summarized in the Table. Unadjusted Kaplan-Meier plots suggested higher incidence of CVD events in the group with >10% ↓ in eGFR within the STD SBP arm, which attenuated in an adjusted Cox regression model (Fig 1). There was no evidence that ΔeGFR groups associated with CVD events in the INT arm (Fig 2).

Conclusions: INT SBP lowering resulted in a higher proportion of persons with >10% ↓ in eGFR but there is no clear evidence that greater ↓ in eGFR was associated with worse CVD outcome in either arm during the trial. Further investigation of the implications of early eGFR ↓ on CVD is warranted.

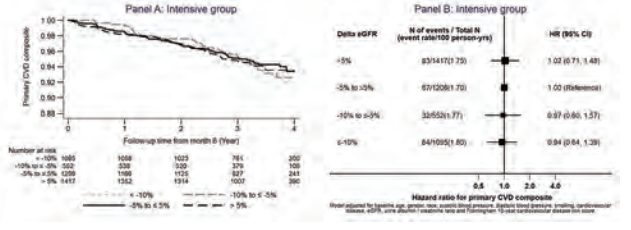
Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS

Baseline characteristics by ΔeGFR groups in STD and INT arms

	STD arm				INT arm			
	≤ -10% N=642	-10% to ≤-5% N=439	-5% to ≤5% N=1,300	> 5% N=1,909	≤ -10% N=1,107	-10% to ≤-5% N=560	-5% to ≤5% N=1,222	> 5% N=1,432
Δ eGFR (%)	-18 (8)	-7 (1)	0.1 (3)	17 (12)	-20 (9)	-7 (1)	-0.1 (3)	16 (11)
Age (yr)	68 (10)	67 (10)	68 (9)	68 (9)	68 (10)	68 (9)	68 (10)	68 (9)
Female	33	34	33	36	34	35	32	40
AA (%)	34	33	31	30	33	33	30	28
SBP (mmHg)	145 (16)	142(15)	140 (15)	137 (15)	143 (16)	140 (15)	139 (16)	137 (15)
DBP (mmHg)	80 (13)	79 (12)	78 (12)	77 (12)	79 (13)	79 (12)	78 (12)	77 (11)
CKD(%)	24	22	24	33	29	25	25	32
CVD (%)	19	19	21	19	21	22	21	19
eGFR (ml/min/1.73m^2)	77 (24)	76 (21)	73 (19)	68 (19)	73 (23)	74 (21)	73 (20)	68 (19)
Urine ACR (mg/g)	11 (6-33)	10 (6-23)	9 (6-21)	9 (5-19)	12 (7-32)	10 (6-20)	9 (6-19)	8 (5-17)



ΔeGFR groups and CVD events in STD arm



ΔeGFR groups and CVD events in INT arm

FR-PO369

Ambulatory Blood Pressure (ABP) Is More Important Risk Factor to Renal Outcome in CKD Patients Than Office Blood Pressures

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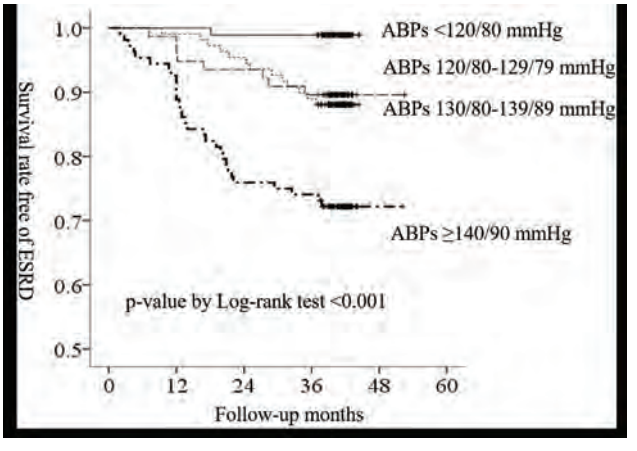
Background: The prognosis of CKD is strongly associated with blood pressure. However, there are few clinical data suggesting which methods is better for measuring blood pressure and what is the target level of blood pressure to prevent CKD progression.

Methods: We enrolled 387 hypertensive CKD patients from three tertiary referral hospitals in Korea who underwent ABP monitoring and followed for 38.0 months. The primary renal outcome was an incident end stage renal disease (ESRD) which data was collected from the ESRD registry of the Korean Society of nephrology.

Results: The mean office blood pressure was 131.9/79.4 mmHg and the mean ABPs was 131.9/79.4 mmHg. The estimated glomerular filtration rate (GFR) and urine protein to creatinine ratio (UPCR) was 45.0 ± 21.6 ml/min/1.73 m^2 and 1.545 ± 2.278 mg/mg creatinine, respectively. There were 13.4 % (52/387) incident ESRD. The risk factors for an incident ESRD were age, GFR, UPCR, product of calcium by phosphorous at renal biopsy and parameters of blood pressures, such as ambulatory systolic blood pressure (ASBP), ambulatory diastolic pressure (ADBP), ABP grouped by the criteria of 120/80, 130/80, and 140/90 mmHg. The rate of incident ESRD in patients with ABP < 120/80 mmHg was 1.2 %, with ABP 120/80-129/79 mmHg, 12.0 %, with 130/80-139/89 mmHg, 10.2 %, and, with ABP ≧ 140/90 mmHg, 25.4 % (p<0.001). The risk ratios of an incident ESRD in patients with ABP 120/79-129/79, 130/80-139/89, and ABP ≧ 140/90 mmHg were 10.643 (95% CI: 1.032-86.980, p=0.027), 7.489 (95% CI: 0.928-60.408, p=0.059), and 13.518 (95% CI: 1.792-101.952, p=0.012) compared to the risk of ESRD in patients with ABP < 120/80 mmHg, respectively (p for trend=0.002), adjusted by risk factors using the Cox's hazard proportional model.

Conclusions: Office blood pressure was not appropriate measurement to guide BP control in CKD patients. Lower criteria of ambulatory blood pressure would be recommended for prevention of ESRD in CKD patients.



FR-PO370

Effect of Chronotherapy on BP Pattern and Renal Function in CKD III-IV: A RCT

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Background: There is higher prevalence of non dipping pattern in antihypertensive CKD patients. we studied the effect of shifting antihypertensives to night time on blood pressure profile of CKD III-IV patients

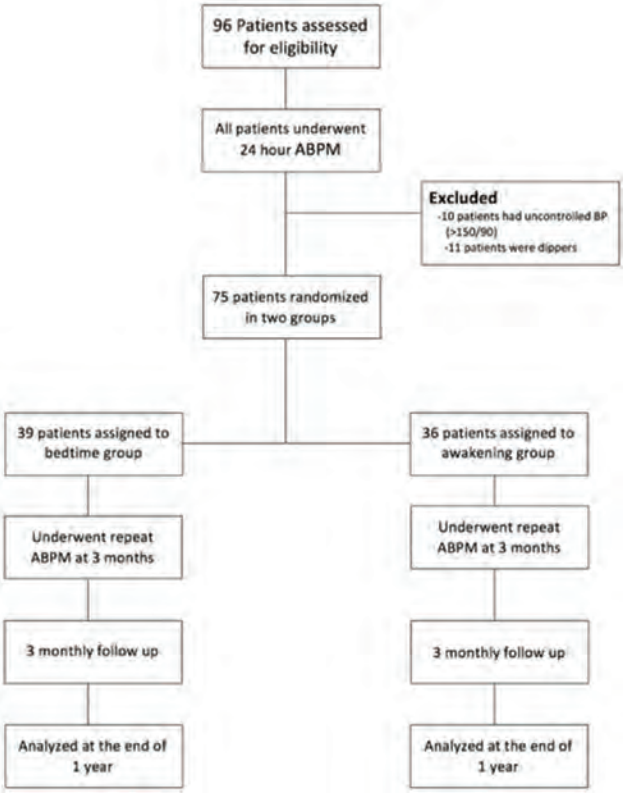
Methods: Study Design: single centre, prospective, RCT **Setting and participants:** CKD III-IV with non dipping pattern on ABPM **Intervention:** the intervention group received all the antihypertensives in the night time, control group continued to take medication in the morning. Both groups were followed for 1 year **Outcomes:** primary outcome was the reversion to dipper status. Secondary outcomes were changes in eGFR and cardiac structure.

Results: 39 patients in bedtime group and 36 patients in awakening group were analysed. 10 patients (24%) reverted to dipping pattern in bedtime group as compared to none in the awakening group. Mean eGFR decrease from 34.59±12.43 to 34.41±11.82 ml/min/1.73m^2 in Bedtime group (p=0.5), in awakening group eGFR decrease from 32.46±13.42 to 29.91±9.97 ml/min/1.73m^2 (p=0.03). Between group difference in eGFRs was significant at 1 year (5.22 [95% CI,4.3-6.1]ml/min/1.73m^2; p= 0.02). Cardiac structure changes showed no significant changes in either group.

Conclusions: Bedtime administration of antihypertensives reverted non dippers to dippers and slowed the decline in eGFR in CKD III-IV compared to morning administration of antihypertensives.

Baseline Characteristics

Variables	Awakening group	Bedtime group
Creatinine, mg/dL	2.32±0.68	2.18±0.58
No. of hypertension medications	2.58±1.1	2.67±0.96
Awake systolic mean, mmHg	131.64±13.13	133.31±13.47
Sleep systolic mean, mmHg	124.94±13.14	126.49±13.83
24 hour systolic mean, mmHg	128.72±13.29	130.92±13.21
Awake diastolic mean, mmHg	84.36±11.67	83.21±11.67
Asleep diastolic mean, mmHg	76.31±12.55	78.36±13.67
24 hour diastolic mean, mmHg	79.28±11.43	80.59±11.24



Flow diagram

FR-PO371

Non-Dipping Blood Pressure Profile Does Not Predict a Risk for Developing CKD in Normotensives

Tomoharu Ida, Tetsuro Kusaba, Keiichi Tamagaki. *Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: Lack of nocturnal blood pressure (BP) fall (non-dipper), a potent risk of future kidney dysfunction, is frequently observed in chronic kidney disease (CKD) patients. However, whether non-dipping pattern of BP profile in normotensive CKD patients is still a risk for progression of kidney disease is unknown. The aim of our retrospective cohort study is to elucidate the impact of non-dipping BP profile with normotensives on the incidence of ESRD and the CKD progression.

Methods: 1198 CKD patients (age:68.6 ± 12.0, eGFR:33.1 ± 18.2 ml/min/1.73m^2, avg ± SD) who underwent ambulatory BP monitoring (ABPM) were enrolled into our analysis. According to their nocturnal BP dipping pattern (>10%: dipper or <10%: non-dipper) and the average 24hr BP (>130/80 mmHg: hypertensive or <130/80 mmHg: normotensive), the patients were divided into 4 groups. Primary composite outcomes including 40% reduction of eGFR from baseline or reaching ESRD were assessed. We also performed the multivariate regression analysis of the factors considered to have significant relationship for the incidence of primary outcomes.

Results: 86.3% of patients were non-dipper and half of them were normotensive. The average observation period was 4.76 ± 2.75 (avg ± SD) years. Overall, the composite outcomes occurred in 45.6% of patients and it was highest in hypertensive non-dipper group (60.0%). In normotensive patients, there was no difference in the incidence of primary outcome between non-dipper (32.0%) and dipper (29.6%). Multivariate regression analysis showed that amount of urinary protein (95% CI 0.74-0.91) and 24hr BP (95% CI 0.67-0.81), not BP dipping rate (95% CI 0.98-1.01), were relevant for the incidence of primary outcomes.

Conclusions: ABPM based analysis demonstrated that non-dipping pattern of BP does not predict the risk for the kidney disease progression in normotensive CKD patients.

FR-PO372

Association of Major Adverse Cardiac Events in Patients Taking Direct Oral Anticoagulants (DOACs) in Patients with CKD

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Background: Clinical trials provide conflicting evidence for the use of DOACs in the prevention of major adverse cardiac events (MACE). Patients with chronic kidney disease (CKD) are at an exceptionally high risk for MACE. We set out to assess the association of DOAC use compared to no oral anticoagulant or warfarin, and MACE, hemorrhage and all-cause mortality in patients with CKD.

Methods: Population-based retrospective cohort study of 241, 045 eligible adults of advanced age (≥ 66 years) in Ontario, Canada from 2009-2016. A high dimensional propensity score was used to match new DOAC use to either no anticoagulant or warfarin. The study outcomes were major cardiac events (MACE), hemorrhage requiring hospitalization and all-cause mortality. DOAC exposure was modeled using Cox and Fine & Gray sub-distribution hazards models to examine the association with outcomes. Outcomes by level of kidney function, albuminuria and DOAC type were also examined.

Results: We matched 6,039 DOAC (mean [SD] age, 77.2 [7.0] years; 44.9% women), users with a high dimensional propensity score to non-anticoagulant users. There were a total of 560 (46% DOAC users) MACE, 178 hemorrhages (47% DOAC users) and 768 (31.3% DOAC users) deaths during the follow-up time. DOAC use, compared to no anticoagulant use, was associated with a higher risk of MACE (sHR 1.20 95%CI 1.04-1.39) and hemorrhage requiring hospitalization (sHR 1.36 95%CI 1.03-1.80) whereas all-cause mortality was lower (sHR 0.74 95%CI 0.61-0.91). Among DOAC and non-anticoagulant use, the risk of hemorrhage and all-cause mortality differed by DOAC type whereas all-cause mortality differed by eGFR. We further matched 5,581 DOAC to warfarin users. There were a total of 460 (56% DOAC users) MACE, 177 hemorrhages (49% DOAC users) and 581 (61% DOAC users) deaths during the follow-up time. DOAC use, compared to warfarin use, was associated with a comparable risk of MACE, hemorrhage and all-cause mortality. Among DOAC and warfarin users, the risk of all-cause mortality but not MACE or hemorrhage differed by eGFR.

Conclusions: DOACs did not lower the risk of major cardiac events compared to no DOAC use or warfarin in patients with or without CKD. Further studies to determine if specific DOAC dosages reduce MACE in CKD are required.

FR-PO373

Duration of Dual Antiplatelet Therapy in Patients with CKD and Drug-Eluting Stents: A Meta-Analysis

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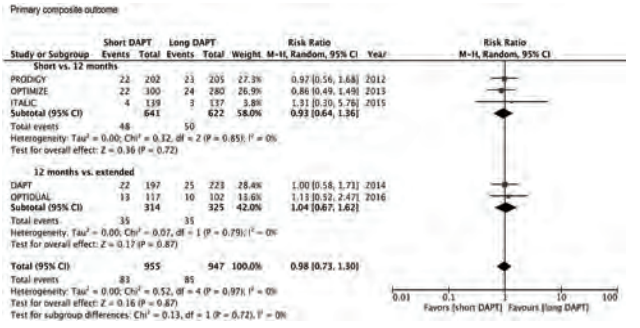
Background: Whether prolonged dual antiplatelet therapy (DAPT) is more protective in chronic kidney disease (CKD) patients with drug-eluting stents (DES) compared with shorter DAPT is uncertain. This meta-analysis examined whether shorter DAPT in patients with DES and CKD is associated with lower mortality or major adverse cardiovascular event rates compared with longer DAPT.

Methods: A Medline literature research was conducted to identify randomized trials in patients with DES comparing different DAPT duration strategies. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke, or stent thrombosis (definite- probable). The secondary outcome was major bleeding. A random-effects model was used.

Results: Five randomized controlled trials were included (1,902 CKD patients). Short DAPT (≤6 months) was associated with a similar incidence of the primary outcome, compared with 12-months DAPT among patients with CKD (Figure). Twelve-months DAPT was also associated with a similar incidence of the primary outcome compared with extended DAPT (≥30 months) in the CKD subgroup (Figure). Numerically lower major bleeding event rates were detected with shorter vs. 12-month DAPT (RR 0.68, 95% CI 0.29-1.60, p=0.38) and 12-month vs. extended DAPT (RR 0.82, 95% CI 0.34-1.94, p=0.65) in CKD patients.

Conclusions: Short DAPT may be preferred to longer DAPT in CKD patients with DES.



Forest plot showing the impact of short (≤6 months), 12-month, and extended (>=30 months) dual antiplatelet therapy on the composite primary outcome, a composite of all-cause mortality, myocardial infarction, stroke, and stent thrombosis (definite or probable) in patients with chronic kidney disease.

FR-PO374

Direct Oral Anticoagulants vs Warfarin: Stroke Outcomes in CKD Patients

Drake A. Edgett,[1,2] Alissa Dratch,[1,2] Elani Streja,[1,2] Ekamol Tantisattamo,[2] Kamyar Kalantar-Zadeh,[1,2] Wei Ling Lau.[2,3] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]University of California, Irvine School of Medicine, Orange, CA; [3]Visiting Fellow at OptumLabs, San Francisco, CA.*

Background: CKD patients are at higher risk of ischemic and hemorrhagic stroke. For over 50 years warfarin was the only oral anticoagulant available for stroke prevention. Direct Oral Anticoagulants (DOACs) became available in the past decade but outcomes data in CKD is limited. In this project we examined ischemic stroke outcomes associated with warfarin vs. DOAC therapy in the OptumLabs® Data Warehouse (OLDW).

Methods: This was a retrospective analysis of de-identified claims and electronic health record data for privately insured and Medicare Advantage enrollees in a large, private, U.S. health plan. Adults aged ≥18 years with claims data between 10/1/2010-11/30/2017 were included. Stroke events were captured between index prescription date and censor date (earliest date of index medication stopped, death, or end of follow up). Cox models were used to calculate hazard ratios of time to first stroke. Poisson models were used for stroke incident rate ratios. Associations were evaluated with multivariable adjustment for age, gender, race and baseline comorbidities (diabetes, hypertension, heart failure, myocardial infarction, prior stroke, antiplatelet medications).

Results: The cohort included 340,732 patients of which 90% were non-CKD, 9% were CKD stage 3-4, and 1% were CKD stage 5/ESRD. Patients had a mean±SD age of 67±13 years, and included 30% diabetics, 10% African-Americans and 6% Hispanic. Patients on warfarin were more likely to be older, African-American, ESRD, and have pre-existing comorbidities. Across all strata, patients on warfarin had a faster time to first stroke and a higher incidence of stroke events [Table].

Conclusions: In a large nationwide database, DOACs were associated with a lower risk of ischemic stroke as compared to warfarin therapy. Randomized controlled trials are warranted to further investigate this observed superiority of the newer anticoagulant therapies.

Subgroup	n	Ischemic Stroke outcomes Median (interquartile range) of follow up: 65 (31, 196) days	
		Incident Rate Ratio warfarin vs. DOACs (95% CI)	Hazard Ratio warfarin vs. DOACs (95% CI)
Non-CKD	304,956	1.64 (1.63, 1.66)	1.23 (1.20, 1.27)
CKD 3-4	31,189	1.29 (1.25, 1.32)	1.17 (1.11, 1.26)
CKD 5/ESRD	4,587	2.21 (1.99, 2.44)	1.45 (1.15, 1.83)

FR-PO375

Kidney Failure and Mortality in Older Live Kidney Donors with Hypertension

Fawaz Al Ammary,[1] Xun Luo,[1] Allan Massie,[1] Macey L. Henderson,[1] Deidra C. Crews,[1] Jacqueline Garonzik wang,[1] Daniel C. Brennan,[1] Alexander C. Wiseman,[2] Dorry L. Segev.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]University of Colorado at Denver and Health Sciences Center, Denver, CO.*

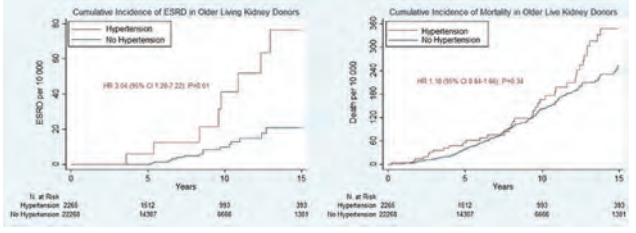
Background: Hypertension in otherwise healthy, screened older live kidney donor candidates has been viewed as safe. However, hypertension guidelines have evolved and long-term outcomes for these donors have not been explored, which may bring this practice into question.

Methods: We used a US cohort of 24,533 older donors (≥50-year-old), including 2265 with predonation hypertension, to quantify the 15-year end-stage renal disease (ESRD) and mortality risk in donors with hypertension vs. those without hypertension. From 2004-2016, hypertension was defined as documented predonation use of antihypertensive therapy, regardless of systolic/diastolic blood pressure (SBP/DBP); from 1999-2003, when there was no documentation of antihypertensive therapy, hypertension was defined as predonation SBP≥140 or DBP≥90 mmHg.

Results: Older donors were 88.1% white, 5.6% Hispanic, and 6.3% black. Estimated 15-year ESRD risk was 77 per 10,000 (95%CI:38-155) for donors with hypertension (mean SBP=137.7 mmHg) vs. 21 per 10,000 (95%CI:12-37) for donors without hypertension (mean SBP=123.4 mmHg); (adjusted hazard ratio [HR] 3.04; 95%CI:1.28-7.22; *P*=.01). In the years when predonation use of antihypertensive therapy was available, risk of ESRD was 6.21-fold higher (95%CI:1.20-32.17; *P*=.03) for donors using antihypertensive therapy (mean SBP=131.9 mmHg) vs. those not using antihypertensive therapy (mean SBP=123.9 mmHg); this inference remained similar after further adjustment for SBP<125. There was no evidence of association between donor hypertension and 15-year mortality risk (HR 1.18; 95%CI:0.84-1.66; *P*=0.34).

Conclusions: Older kidney donor candidates with hypertension may be viewed as potentially high-risk for ESRD. These findings may help inform discussion with older candidates considering kidney donation; long-term monitoring is warranted. .

Funding: NIDDK Support



FR-PO376

High Variability of Initial 24-Hour Systolic Blood Pressure After ICU Admission Is Associated with Mortality

Soon hyo Kwon,[1] Moo Yong Park,[2] Hyoungnae Kim,[2] Hyunjin Noh.[2] *[1]Soonchunhyang University, Seoul, Republic of Korea; [2]Soonchunhyang University Hospital, Seoul, Republic of Korea*.

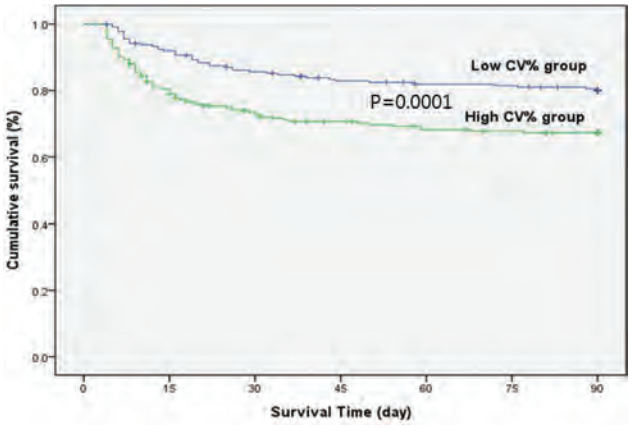
Background: Increased blood pressure variability predicts long-term outcomes in cardiovascular and kidney disease. This study aimed to determine whether variability of initial 24-hour systolic blood pressure (SBP) affects mortality in critically ill patients.

Methods: In a retrospective study, we enrolled patients who had been admitted to 2 adult intensive care units (ICU) in a single center between Nov. 2015 and Oct. 2017. All patients were under active treatment. Variability of patients' blood pressure was assessed by initial 24-hour SBP coefficient of variation (CV) after ICU admission. CV was measured as standard deviation of SBP divided by mean of SBP. Patients were categorized into two groups based on SBP CV. The effect of SBP variability on 90 day mortality was analyzed.

Results: Of the 451 patients (male 56 %) were analyzed, 25.7% of patients died within 90 days. The mean SBP CV was 7.6 ± 1.4 % in low CV group (n=225) and 13.6 ± 3.2 % in high CV group (n=226). In Kaplan-Meier survival analysis, 90 day mortality of high CV group was higher than that of low CV group (p = 0.001) (Figure 1). A Cox analysis showed that high CV in SBP was an independent risk factor for death compared to low CV in SBP (HR 1.87; 95% CI, 1.26-2.77; p = 0.002) after adjust of age, sex, comorbidities, inotropic agents and SBP.

Conclusions: Higher SBP variability in critically ill patients was associated with high mortality. This suggests that variability of blood pressure would be helpful for prediction of prognosis and treatment in ICU patients.

Funding: Government Support - Non-U.S.



FR-PO377

AKI Followed by Complete Recovery Is Associated with Higher Stroke Risk

Joao P. Teixeira,[2] Zhiying You,[3] Benjamin Griffin,[2] John R. Holmen,[4] Titte Srinivas,[5] Michel Chonchol,[2] Sarah Faubel,[6] Anna J. Jovanovich.[1,2] *[1]Denver VA, Denver, CO; [2]University of Colorado, Aurora, CO; [3]UC Denver, Aurora, CO; [4]Intermountain Healthcare, Murray, UT; [5]Intermountain Medical Center, Murray, UT; [6]University of Colorado Denver, Denver, CO*.

Background: Acute kidney injury (AKI) has been shown to be associated with a future increased risk of adverse cardiovascular events. However, there are fewer data specifically analyzing the risk of stroke after AKI and they have been somewhat mixed. While severe (stage III) AKI has been shown to be independently associated with an increased risk of future stroke, the effects of less severe AKI or AKI with recovery are unclear. We aim to determine the risk of stroke following an admission complicated by AKI with complete recovery in a propensity score-matched cohort of cases and controls.

Methods: We identified 1139 AKI cases (AKI Network definition) with complete kidney function recovery at the time of discharge, defined as serum creatinine <1.10 times the pre-admit baseline value, during a hospitalization between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 1139 controls (no AKI during index admit) based on a propensity score including age, sex, race, prior inpatient visits, season of admission, baseline creatinine, and all components of the Charlson Comorbidity index. The primary outcome was time to post-discharge stroke, as defined by ICD-9 codes. Cox proportional hazards models were adjusted for history of prior stroke and atrial fibrillation and censored for death.

Results: Baseline characteristics among the cases and controls were similar: age 62 ± 17 years, 46% female, 92% white, serum creatinine 0.9 ± 0.2 mg/dL. During a median [IQR] post-discharge follow-up of 68 [17-92] months, 99 cases and 36 controls had a stroke. In the unadjusted model, AKI with recovery was associated with a greater than 3-fold increased risk of stroke (HR 3.08 [95% CI, 2.10 – 4.52]; p <0.0001). This association did not change after adjusting for prior stroke and atrial fibrillation (HR 3.27 [95% CI, 2.21 – 4.2]; p <0.0001).

Conclusions: Among patients from an integrated health care delivery system, AKI followed by complete recovery was independently associated with an increased risk of incident stroke. These data add to prior studies linking AKI with an increased long-term risk of cardiovascular events.

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FR-PO378

Health Plan Coverage Duration and Annualized Healthcare Costs in Patients with ADPKD in a Managed Care Population

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Background: ADPKD is a rare inherited systemic disease characterized by progressive kidney enlargement and worsening of kidney function leading to end stage renal disease, and transplant. Hypertension occurs in 70% of patients and contributes to disease progression, and cardiovascular morbidity and mortality. Even for long-term progressive diseases, US health plans often focus on short-term outcomes rather than prevention due to patients' short retention in health plans. This study assesses health plan retention rates and direct healthcare costs of ADPKD patients with hypertension.

Methods: Patients diagnosed with ADPKD were selected from the Optum Clinformatics 2007-2017 US research database. ADPKD was identified using ICD9/10 codes: 753.12, 753.13, Q61.2, and Q61.3. Patients were required to have continuous medical and pharmacy benefits for 6 months pre- index date (baseline period) and ≥6 months post-index date. The index date was the date of ADPKD diagnosis. Duration of plan coverage was reported for the overall population and annual healthcare costs reported in patients with and without hypertension.

Results: A total of 9,361 patients met inclusion criteria, of whom 85% had hypertension. Mean enrollment duration was 36.5 months with a median of 28.1 months. Forty-three percent of patients had 1-2 years coverage, 18% 2-3 years coverage, 12% 3-4 years coverage, 8% 4-5 years coverage, and 18% greater than 5 years coverage. Mean annual direct healthcare costs were higher for patients with ADPKD and hypertension ($50,850) compared with ADPKD only ($16,135), p<0.001. In patients with ADPKD and hypertension, outpatient costs were the primary source of costs with a mean of $18,025, followed by inpatient costs ($15,957), pharmacy costs ($8,022), emergency room visits ($1,476), office visits ($993), and home health costs ($504).

Conclusions: The study findings indicate that most patients with ADPKD retain their health plan coverage for a relatively long period, including those with the most prevalent comorbid condition in this population. Direct healthcare costs were higher among patients with comorbid hypertension. Since these patients incur higher healthcare cost, health plans and decision makers may benefit from earlier disease management strategies for ADPKD.

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FR-PO379

Clinical Feature and Diagnosis of Primary Hyperaldosteronism

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Background: Primary aldosteronism(PA) is the most common form of secondary hypertension, with an estimated prevalence of 10% of hypertensive patients. Patients with PA have higher cardiovascular morbidity and mortality than age- and sex-matched patients with essential hypertension and the same degree of blood pressure elevation. Early checkup is extremely important to prevent cardiovascular event, stroke and renal dysfunction.

Methods: We retrospectively analyzed the clinical features of the patient with PA who were diagnosed from 2014 to 2018.

Results: We analyzed 36 cases with PA who were not treated with RAS inhibitor or diuretic drug at the time of screening test for PA. The average age was 49 years old. The cases of serum K < 3.5 were only 20%, and adrenal adenoma detected by CT scan was 42.9%. The median of aldosterone-to-renin ratio (ARR) was 841.9 (206-4370), however, in cases with adrenal adenoma, the median ARR was significantly high level with 1299.4 (300-4370). The correct diagnostic rate of diagnoses of saline test, furosemide test and captopril test was 77.1, 71.4 and 65.7%, respectively. There was a trend that the accuracy of captopril test was low in patients with low eGFR. The correct diagnostic rate of combination of saline and furosemide tests would be the best. The 90 percentile of the serum potassium in patients with PA was 4.4 mEq/L, however, those in patients with over 40 years old were 4.5 mEq/L.

Conclusions: Present study suggested that screening test for PA should be performed in cases with serum potassium was less than 4.3 mEq/L in hypertensive patients. Especially, in cases with over 40 years old, the screening of the PA with ARR should be performed. In addition, the correct diagnostic rate of diagnoses of captopril test was low compared with other screening test. Combination of salin and furosemide tests suggested to be proposed in present study.

FR-PO380

A Cross-Talk Between TGFbeta Receptor (TGFbR) and PDGF Receptor-Beta (PDGFRb) Controls mTORC1-Mediated Mesangial Cell (MC) Hypertrophy and Fibrotic Protein Expression

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Background: TGFb induces MC hypertrophy and matrix protein expression via noncanonical mTORC1 during the progression of diabetic nephropathy. The mechanism of mTORC1 activation is not clear. Since its activation requires tyrosine kinase activity, we considered a cross-talk between TGFb serine-threonine kinase and PDGFRb tyrosine kinase in this process.

Methods: Human glomerular MCs in culture and OVE 26 diabetic mice were used. PDGFRb inhibitor, activation/inactivation-specific phospho-antibodies, siRNA and plasmid-derived expression vector transfection, ^{35}S-Methionine incorporation and immunoblotting were used.

Results: In MCs, TGFb increased the activating phosphorylation of PDGFRb in a time-dependent manner. This phosphorylation was inhibited by the TGFbRI and PDGFRb inhibitors SB431542 and JNJ, respectively. Importantly, JNJ did not have any effect on TGFb-stimulated phosphorylation of receptor-specific Smad 3 while SB inhibited its phosphorylation. JNJ also inhibited the phosphorylation of PDGFRb at Tyr-751, the PI 3 kinase binding site, in response to TGFb, resulting in inhibition of Akt phosphorylation at both Thr-308 and Ser-473. Transfection of siRNA against PDGFRb confirmed these results. Importantly, JNJ and siRNA targeting PDGFRb blocked the phosphorylation of the Akt substrate PRAS40, a negative regulator of mTORC1 activation. To determine the mTORC1 activity, we measured the phosphorylation of S6 kinase and rps6. Inhibition of PDGFRb as well as its siRNA mitigated TGFb-induced mTORC1 activity that resulted in attenuation of MC hypertrophy. Similarly, JNJ and siPDGFRb inhibited TGFb-stimulated fibronectin expression in MCs. Finally, in the renal cortex of OVE 26 diabetic mice, expression of TGFb was significantly increased concomitant with phosphorylation of PDGFRb, which were associated with increased Akt phosphorylation and mTORC1 activation that lead to increased fibronectin expression.

Conclusions: Our results provide the first evidence for a functional role of PDGFRb downstream of TGFbR to activate Akt/mTORC1 axis for MC hypertrophy and matrix protein expression. We propose to test PDGFRb-specific inhibitor in preclinical models of diabetic nephropathy.

Funding: Veterans Affairs Support

FR-PO381

Quercetin Ameliorates Podocytes Injury via Inhibition of Oxidative Stress and TGF-β1/Smad Pathway in DN Rats

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Background: An increasing number of investigations revealed that podocytes play a crucial role in the development and progression of diabetic nephropathy (DN). The bioflavonoid quercetin, an antioxidant, may be a potential alternative to ameliorate podocytes injury in DN rats. The aim of this study was to investigate the protective effect and underlying mechanism of quercetin on podocyte injury in rats with diabetic nephropathy.

Methods: SD rats (180-220g) were randomly divided into four groups: normal control (NC), diabetic nephropathy (DN), DN treated with low-dose quercetin (DN+LQ) and DN treated with high-dose quercetin (DN+HQ). All diabetic rats were induced by a single intraperitoneal injection of streptozotocin at concentration 60 mg/kg, and quercetin was administered daily with an oral dose of 50 mg/kg (DN+LQ) or 100 mg/kg (DN+HQ) 1 week after STZ injection, NC and DN rats were administered vehicle only. Blood glucose and body weight were measured every 2 weeks, and albuminuria was measured every 4 weeks. All animals were sacrificed after 12 weeks of treatments. Then HE, PAS staining and electron microscope were performed to observe kidney tissue and podocytes. Immunohistochemical stainig and western blotting were performed to explore the expression of podocin, nephrin, desmin, TGF-β1, p-Smad2, and p-Smad3 and Smad7. The contents of SOD, GSH and MDA were examined by ELISA.

Results: In the present study, quercetin markedly decreased blood glucose levels, kidney-to-body weight ratio, albuminuria, creatinine clearance rate, blood urea nitrogen, triglycerides and significantly attenuated oxidative stress compared with the DN group. Moreover, quercetin was observed to inhibit podocyte effacement and decrease the thickness of glomerular basement membranes. Mechanistically, quercetin significantly increased the expression of podocyte-specific markers nephrin and podocin and decreased expression of the podocyte injury marker desmin in DN rats. Quercetin also inhibited activation of the TGF-β1/Smad signaling pathway in DN rats by decreasing expression of TGF-β1, p-Smad2, and p-Smad3, and increasing Smad7 expression.

Conclusions: Quercetin administration ameliorated podocytes injury in DN rats, possibly by inhibiting oxidative stress and the TGF-β1/Smad signaling pathway. Thus, quercetin may be manipulated to act as a potential drug for prevention of early diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO382

TGF-β1 Increases LTBP-2 via RelA, and Elevated LTBP-2 Stimulates TGF-β1 Secretion via ERK, Forming a Positive Feedback Vicious Loop and Resulting in the De-Differentiation of Proximal Tubules

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Background: Latent transforming growth factor-β-1 binding protein-2 (LTBP-2) does not bind to transforming growth factor-β1 (TGF-β1) unlike other LTBPs. Reportedly, serum LTBP-2 levels were elevated statistically; thus, it is considered as a potential prognostic marker in the progressive stages of diabetic kidney disease. Although LTBP-2 seems to regulate the TGF-β1 bioactivity, except direct bindings, the effect of LTBP-2 in the kidneys is unclear.

Methods: We evaluated the regulatory mechanism of the LTBP-2 expression and primary function of LTBP-2.

Results: In wild-type mice, **LTBP-2** is expressed only in **proximal tubules (PTs)**. Diabetic nephropathy, such as STZ and *db/db* mice, demonstrated remarkably upregulated LTBP-2 in PTs. UUO models also marginally increased LTBP-2 immunostaining in collecting tubules but not in PTs. By treating humoral factors that are considered crucial mediators in the pathogenesis of diabetic renal injury or renal fibrosis, such as high glucose, AGE, angiotensin II, TGF-β1, TNF-α, and interleukin 6, only the **TGF-β1** administration markedly elevated the LTBP-2 mRNA and protein expression in time- and dose-dependent way in cultured PTs. TRANSFAC analysis, luciferase assays, and EMSA revealed that the promoter region spanning –1666 to –1436, especially the **RelA** binding site, was essential for the basal LTBP-2 gene promoter activity and TGF-β1–induced LTBP-2 gene upregulation. **Erk** phosphorylation was markedly elevated by the transfection of LTBP-2 cDNA vector into HK-2 cells, resulting in the de-differentiation of PTs such as reducing E-cadherin expression, increasing fibronectin expression, and TGF-β1 secretion. Conversely, LTBP-2 siRNA administration under TGF-β1 treatment silenced Erk phosphorylation, resulting in blocking the de-differentiation of PTs. When cells were treated with Erk inhibitor, these phenotypic changes were prevented.

Conclusions: Renal fibrogenetic changes in diabetic nephropathy were attributed to the upregulation of LTBP-2 via the RelA activation by TGF-β1. Elevated LTBP-2 triggers the stimulation of TGF-β1 secretion via Erk signaling, forming a **positive feedback vicious loop** and resulting in the **de-differentiation** of PTs. Overall, silencing LTBP-2 is a novel therapeutic target for blocking diabetic tubulopathy or fibrotic changes.

FR-PO383

Smad3 Regulates Cell Fate Through Silencing of Enhancer and Superenhancer Elements During the Specification of iPSC Derived Kidney Organoids

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Background: Critical pathological features of diabetic nephropathy are now accepted to include dysregulation of epigenetic processes as evidenced by the observed differential methylation in patients with or without progressive disease. We recently demonstrated a novel direct interaction between Smad3 and EZH2, the enzymatic component of the PRC2 complex, during cell fate specification and TGFβ mediated epithelial dedifferentiation. Targeting this interaction in iPSC derived renal organoids protected against TGFβ mediated tubular epithelial dedifferentiation. Here we further delineate the molecular mechanism underlying this interaction.

Methods: Co-localisation of Smad3 and EZH2 was analysed and visualised using ChIP-Atlas (www.chip-atlas.org). Putative superenhancers (SE) were identified using the Illumina BaseSpace platform. Differential expression of SE target genes in healthy and CKD kidney samples were analysed using Nephroseq (www.nephroseq.org). Target genes were further analysed during the specification of iPSC derived kidney organoids and during TGFβ mediated epithelial dedifferentiation using quantitative real-time PCR.

Results: ChIP-seq identified Smad3 and EZH2 co-localisation at specific loci in human ESCs, and newly occupied enhancers in ESCs and iPSCs treated with activin A. Bioinformatic analysis of these sites identified 243 putative SEs potentially regulated by Smad3/EZH2. Further analysis identified a number of these putative SE target genes that are silenced in normal adult kidney but whose expression is significantly increased during disease. These included critical determinants of cell fate including ZIC3, ZIC5, and DPPA4. Further analysis by RT-PCR indicated a TGFβ dependent downregulation of genes within this cohort suggesting a novel mechanism of gene repression during both development and disease. Functional analysis of enhancer reporter activity verified a Smad3/EZH2 dependent mechanism.

Conclusions: We propose that this complex forms a molecular switch that regulates enhancer and/or promoter access through epigenetic mechanisms and controls gene silencing, informing the fundamental mechanisms through which subsets of genes are switched on and off during fate specification and during the pathogenesis of diabetic nephropathy.

FR-PO384

LRG1 Promotes DN Progression by Enhancing TGF-β-Induced Angiogenesis

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Background: Glomerular endothelial dysfunction and neoangiogenesis have long been implicated in pathogenesis of diabetic nephropathy (DN). However, specific molecular pathways contributing to these processes in the early stages of DN injury is not well understood. Our recent transcriptomic profiling of isolated glomerular endothelial cells identified number of pro-angiogenic genes that were upregulated in the diabetic mice, including leucine-rich alpha-2 glycoprotein-1 (LRG1). LRG1, a secreted glycoprotein belonging to a leucine-rich repeat family, was previously shown to promote neovascularization in models of ocular disease by potentiating the TGF-β/ALK1 signaling in endothelial cells. However its role in kidney cells, particularly in the setting of DN, was not known.

Methods: We analyzed the expression pattern of LRG1 in murine and human diabetic kidneys in comparison to normal kidneys by utilizing the RNA-sequencing data of isolated glomeruli and by RNA in situ hybridization. We examined the effects of high glucose conditions on LRG1 cultured murine glomerular endothelial cells (mGECs) in vitro. We then examined the effects of genetic ablation of *Lrg1* in DN progression in diabetic mice at 12 weeks and at later time point of 20 weeks post diabetes induction.

Results: We found that *LRG1* mRNA expression is significantly increased in glomeruli of mouse and human diabetic kidneys and that its expression localizes predominantly with the glomerular endothelial cells (GECs). High glucose conditions led to the upregulation of LRG1 expression in cultured mGECs, and shRNA-mediated knockdown of *Lrg1* led to reduction in endothelial tube formation in vitro. Genetic ablation of *Lrg1* in mice markedly attenuated diabetes-induced angiogenesis, albuminuria and glomerulopathy at 12 and 20 weeks of diabetes. These improvements were associated with reduced ALK1-Smad1/5/8 activation and with reduced number of GECs in glomeruli of diabetic mice. Moreover, we found that plasma LRG1 levels were associated with worsened renal outcome in type 2 diabetic patient cohort from Bio*Me* Biobank.

Conclusions: Together, our results identify LRG1 as a potential novel pathogenic mediator of glomerular angiogenesis in diabetic kidneys and a risk factor of DN progression, and suggest that LRG1 may be a promising therapeutic target against the disease progression.

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FR-PO385

Mesangial Matrix Expansion Attenuated by All-Trans Retinoic Acid Through Direct Suppression of Bone Morphogenetic Protein 4 in Mouse Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) leads to mesangial matrix expansion, resulting in glomerulosclerosis and renal failure. Collagen IV (COL4), a major component of the mesangial matrix, is positively regulated by bone morphogenetic protein 4 (BMP4)/suppressor of mothers against decapentaplegic (Smad1) signaling. All-trans retinoic acid (atRA) treatment has a beneficial effect on several kidney disease models, although the effect on mesangial matrix expansion in DN remains unclear. AtRA is a representative ligand for retinoic acid receptor (RAR), which heterodimerizes with retinoid X receptor (RXR). Because RAR/RXR heterodimer binds to RA response element (RARE) and regulates various gene transcriptions, the therapeutic effect of atRA on DN through BMP4 regulation by RAR/RXR–RARE was investigated in the present study.

Methods: Streptozotocin was given to male ICR mice at 12 weeks old for diabetes induction. Both control mice and diabetic mice were given all-*trans* retinoic acid (atRA, 15 μg/gBW) intraperitoneally thrice weekly from 16 weeks old to 24 weeks old. Animal kidneys were harvested at 24 weeks. AtRA or specific agonists for each subtype of RAR were added to cultured mouse mesangial cells for 24 h (from 1 nM to 1 μM). The RAR binding capacity to RARE, suggested by genome analysis, was confirmed by ChIP analysis. The functional role of the putative RARE was confirmed by a reporter assay.

Results: Mesangial matrix expansion worsened in diabetic mice and was associated with increased BMP4, phosphorylated Smad1, and COL4. These levels were attenuated after atRA administration. In cultured mesangial cells, BMP4 and COL4 expression levels were significantly decreased by atRA or low concentrations (1 nM) of RARα agonist but not by 1 nM of RARβ or γ agonists. Two putative regions with significant homology to RARE were identified around the mouse *Bmp4* gene. ChIP analysis and subsequent reporter assays indicated the binding of one putative RARE of the *Bmp4* gene to RARα and RXR, resulting in suppression of BMP4 expression.

Conclusions: AtRA directly suppressed BMP4 via RARα/RXR heterodimer binding to a unique RARE, resulting in amelioration of mesangial matrix expansion in diabetic mice. These findings provide a novel regulatory mechanism for treatment of DN.

Funding: Government Support - Non-U.S.

FR-PO386

The Hippo Pathway in the Regulation of the Epithelial-to-Mesenchymal Transition of Renal Proximal Tubular Epithelial Cell in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease in the world. Epithelial-to-mesenchymal transition (EMT) of renal proximal tubular epithelial cells (PTECs) is an important mechanism in the progression of interstitial fibrosis in DN. Recently, Hippo pathway was recognized as a regulator of cell proliferation, differentiation and apoptosis and may be potential therapeutic targets in many kidney diseases.

Methods: In order to study whether the Hippo pathway regulate EMT of PTECs in DN, we cultivated the db/db type 2 diabetic model mice and normal or high glucose stimulated HK-2 cells (human PTECs). We detected the levels of Hippo pathway and EMT of HK-2 cells and PTECs in db/db mice. We administrated verteporfin, a YAP inhibitor, and detected the change of EMT.

Results: Compared with the littermates, db/db mice developed microalbuminuria at the age of 20 weeks and showed obvious kidney hypertrophy from the 4th week. Then, we found that the expression of phosphorylated YAP at serine 127 (p-YAP-S127) in PTECs was obviously increased. While, the total YAP level did not change significantly. We also found that the protein levels of epithelial markers (Ecadherin, ZO-1, and CK-18) were significantly decreased in db/db mice, while the mesenchymal markers (Vimentin, α-SMA) was elevated and these changes were consistent with EMT. Similar changes have been found in HK-2 cells. In high glucose stimulated HK-2 cells, p-YAP-S127/total YAP ratio was increased, epithelial markers were decreased and the mesenchymal markers was elevated (i.e., the onset of EMT). At the same time, we extracted the nuclear and cytoplasmic fraction in normal or high glucose stimulated HK-2 cells. The total YAP level in the cytoplasm was increased, while that in the nucleus was decreased. In addition, administration of verteporfin, which could reduce the level of p-YAP, elevated the epithelial markers and decreased mesenchymal markers (i.e., reversed the EMT) in high glucose stimulated HK-2 cells.

Conclusions: In conclusion, high glucose reduced the YAP nuclear translocation, thus more p-YAP was anchored in the cytoplasm and induced EMT of PTECs. Verteporfin could reverse the EMT, which suggested that Hippo pathway can regulate the EMT in PTECs. This study would provide a new potential therapeutic target for DN.

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FR-PO387

Blockade of RIPK3 Alleviates Renal Fibrogenesis Through TLR2/4 Signalling in Streptozotocin-Induced Diabetic Model

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Background: Current therapies for renal fibrosis are largely ineffective. Therefore, identification of novel therapeutic targets is essential. RIPK3 is identified as a crucial regulator of TLRs signalling activation, which has been well recognised to be involved in renal fibrogenesis. To date, the function of RIPK3 in renal fibrosis remains unclear.

Methods: C57BL/6 wild-type mice and C57BL/6 RIPK3 gene knock out (RIPK3-/-) mice were used in the study. streptozotocin (55 mg/kg/day) was administrated to induce diabetic model by i.p. for 5 consecutive days. After 24 weeks treatment, mice were sacrificed and urinary albumin creatinine ratio (UACR) was measured by ELISA. Kidney histological change and ECM deposition were assessed by PAS, picrosirius red staining and immunohistochemistry. Collagen IV, Fibronectin, α-SMA, TGF-β, TNF α, IL-1 β, TLR2. TLR4, MCP-1, F4/80 mRNA expression level were assessed by quantitative RT-PCR analysis.

Results: RIPK3 deletion reduced UACR compared to the increased level of diabetic group. Both Immunohistochemical staining and PCR revealed that the absence of RIPK3 decreased the diabetic induced collagen IV and Fibronectin within kidney cortex. In addition, diabetes induced the TLR2/4 signalling activation and resulted in an increase of MCP-1 and F4/80 gene expression. However, genetic ablation of RIPK3 decreased TLR2/4 mRNA expression levels and the downstream TNF α and IL-1 β transcription associating with less MCP-1 and F4/80 gene expression. Moreover, diabetes upregulated TGF-β and α-SMA mRNA expression within kidney, whereas this effect was blocked by RIPK3 deletion.

Conclusions: RIPK3 is crucial in renal fibrosis by mediating TLR2/4 signalling. Our data suggest that RIPK3 blockade may be a potential novel target in renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO388

Grem1 Plays a Vital Role in Nicotine Exacerbated Diabetic Nephropathy

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Background: Increasing evidences have demonstrated that cigarette smoking promotes the progression of diabetic nephropathy (DN), but the underlying molecular mechanisms are far from clear. Nicotine, a major component for smoking addiction, has been reported to be an independent component to cause kidney cell injury to accelerate the progression of DN. This study has been designed to evaluate the role of nicotine in DN and to explore the underlying molecular mechanisms.

Methods: *In vivo* studies, diabetic mice were developed through the administration of three doses of streptozotocin (STZ, 50 mg/kg body weight, intraperitonelly). These mice were fed with either nicotine (100 μg/ml) or vehicle (PBS) in their drinking water for 5 months. At the end of the experimental period, kidney function biomarkers (proteinuria, blood urea nitrogen [BUN]) were collected and kidneys were harvested for histological changes and molecular analysis (immunohistochemistry, real-time PCR, and Western blotting). The kidney transcriptomes of these mice were compared through RNA seq analysis, and the results were further confirmed by real-time PCR, Western blotting, and immunohistochemical studies. *In vitro* studies, human podocytes were treated with high glucose (30 mM) with or without nicotine (10 μM), followed by morphologic assay for apoptosis. The effect of high glucose with or without nicotine was also evaluated on podocytes-silenced for specific genes.

Results: *In vivo* studies, STZ-receiving mice displayed a higher level of blood glucose and associated kidney injury, however, nicotine further exacerbated this effect of hyperglycemia. Interestingly, nicotine alone didn't cause an over kidney injury. RNA seq analysis revealed that nicotine dramatically exacerbated the expression of Grem1, a DAN family member, which has been demonstrated to play a vital role in the pathogenesis of DN. *In vitro* studies, combined use of nicotine and high glucose displayed an increase in podocyte apoptosis as well as the expression of Grem1; while silencing of Grem1 decreased the number of cells with apoptosis.

Conclusions: Grem1 might play an important role in nicotine-exacerbated DN. Our study has highlighted novel molecular targets for the therapy and prevention of smoking boosted DN.

FR-PO389

Grem2 Mediates Podocyte Apoptosis in High Glucose Milieu

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Background: The DAN family members (Grem1, Grem2, Grem3, Cerberus, NBL1, SOST, and USAG1) are highly expressed during development where they have an important role in kidney formation and morphogenesis; in adults, however, increased DAN protein levels are often associated with severe disease-states, including renal fibrosis. Grem1, SOST, and USAG1 have been demonstrated to be upregulated and play a critical role in the progression of diabetic nephropathy (DN); other DAN family members have not been reported to be related to renal disease, and their expression in DN kidneys has not be yet investigated. In this study, we investigated the expression and the role of Grem2 in type 2 DN mice.

Methods: *In vivo* studies, 14-weeks-old BTBR ob/ob (a type 2 diabetic mouse model) and control (BTBR, wild-type) mice were evaluated for renal function biomarkers (proteinuria and blood urea nitrogen [BUN]). Kidneys were harvested and renal tissues were analyzed by real-time PCR, Western blotting, and immunohistochemistry studies. *In vitro* studies, human podocytes transfected with Grem2 plasmid were evaluate for apoptosis (morphologic assay and Western blotting). To evaluate the Grem1-mediated downstream signaling, the phosphorylation status of Smad2/3 and Smad1/5/8 was assessed; additionally, SIS3, an inhibitor for Samd3, and BMP-7, an agonist for Smad1/5/8 were used to treat the cells.

Results: *In vivo* studies, the diabetic mice showed elevated levels of and proteinuria BUN. Real-time PCR and Western blotting analysis showed an increased expression of Grem2 in diabetic kidneys. Immuno-histochemical studies showed enhanced Grem2 expression both by tubular and glomerular cells. *In vitro* studies, high glucose increased Grem2 expression in cultured human podocytes, and silencing of Grem2 partially suppressed high glucose-induced apoptosis. Overexpression of Grem2 promoted podocyte apoptosis morphologically as well as by an increased Bax/Bcl2 ratio. Overexpression of Grem2 increased the phosphorylation of Smad2/3 and decreased the phosphorylation of Smad1/5/8, while addition of SIS3 or BMP-7 attenuated Grem2-induced podocyte apoptosis.

Conclusions: High glucose increases Grem2 expression in kidney cells. Grem2 mediates podocyte apoptosis through Smads. Grem2 plays an important role for the progression of DN.

FR-PO390

Activation of Pro-Fibrotic Genes by Nicotine in a Mouse Model of Diabetes: Implications for Diabetic Nephropathy in Smokers

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Background: Tobacco use is a well-recognized, preventable risk factor for CKD progression, especially in diabetics; however, the mechanisms involved are not completely understood. We and others have demonstrated that nicotine acetylcholine receptors (nAChR) are present in rat, mouse, and human kidneys, and that the systemic administration of nicotine worsens the severity of renal injury in animal models of CKD. In these studies we hypothesize that siganling via the α7-nAChR promotes the gene expression of pro-fibrotic pathways in diabetic mice receiving nicotine.

Methods: Diabetes (DM) was induced by low dose STZ injection in male eNOS$^{-/-}$ mice (n=6 per group). After confirmation of diabetes nicotine was admnistered in the drinking water (Nic, 100 μg/mL) for 10 weeks. A group of mice was treated with the specific α7nAChR blocker IC200610 (NB, 2 mg/kg IP) 5 days a week for 10 weeks. An additonal group of mice double knockout for eNOS and α7nAChR was also made diabetic (DKDM) and treated with nicotine (Nic, 100 μg/mL). After euthanasia renal cortex mRNA expression for genes involved in fibrosis and inflammation was determined by RT-PCR.

Results: Diabetes resulted in increased expression of genes linked to fibrosis and inflammation (table). The administration of nicotine increased the expression of CTGF, COL1 and MMP2 three genes that have been linked to progression of CKD. The administration of a specific α7nAChR blocker or genetic deletion of α7nAChR reduced the expression of these genes suggesting that these effects are mediated via signaling activated by this receptor.

Conclusions: The administration of nicotine to diabetic mice results in increased expression of CTGF and MMP2 two genes involved in the pathogenesis of progressive CKD including diabetic nephropathy. In addition these effects appear to be mediated by the α7nAChR which could potentailly be a therapeutic target for diabetes with CKD who use nicotine containing tobacco products.

Funding: Other NIH Support - NIEHS

Gene expression in diabetic mice on nicotine

	FN	CTGF	CCL2	MMP2	MMP9	COL1	COL4	TGFβ
Control	1.0±0.3	1.1±0.4	1.1±0.3	1.0±0.2	1.0±0.5	1.0±0.1	1.0±0.2	1.1±0.3
DM	4.5±0.5*	1.9±0.1*,#	6.7±0.3*	2.8±0.1*,#	2.6±1.0#	2.2±0.4#	2.1±0.2*,#	2.0±0.2*,#
DM+Nic	4.3±0.7*	2.6±0.2*,#,$	6.0±1.1*	3.6±0.6*,#,$	1.6±0.2	3.5±0.6*,#,$	2.6±0.1*,$	2.1±0.1#,$
DM+Nic/NB	2.3±0.5*,$	1.0±0.1*,$	4.7±1.1*,$	2.7±0.3	1.0±0.1*,$	2.7±0.3	2.0±0.6	1.3±0.2*,$
DKDM+Nic	1.5±0.2*,$	0.75±0.1*,$	1.6±0.3*,$	1.8±0.3*,$	0.5±0.1*,$	1.0±0.4*,$	0.7±0.1*,$	0.7±0.1*,$

* P <0.05 vs Control, ** P <0.05 vs DM and DM+Nic, # P<0.05 DM (N=6 per group)

FR-PO391

Modulation of GSK-3β Expression by AMPK Ameliorates Diabetic Kidney Injury by Promoting IR Phosphorylation Cascade

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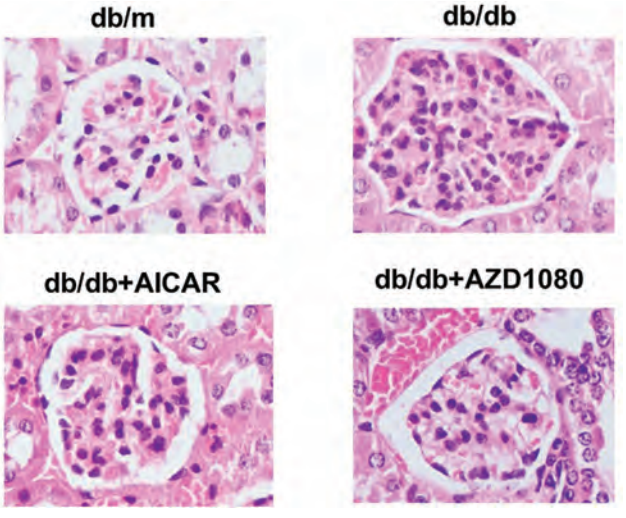
Background: Insulin resistance is a systemic disorder that affects many organs and insulin-regulated pathways. Insulin signaling to the glomerular podocyte is important for normal kidney function and is implicated in the pathogenesis of diabetic nephropathy (DN). It has recently been found that GSK-3β may play a role in the pathogenesis of diabetes and DN; however, the specific mechanism is still unknown. We aimed to investigate whether GSK-3β has a role in the amelioration of podocyte injury and insulin resistance, thus suppressing the progression of DN. Moreover, the molecular mechanisms responsible for the effects were examined.

Methods: Podocyte insulin responses were investigated with western blotting, cellular glucose uptake assays and fluorescent imaging of the insulin receptor signalling. Quantitative (q)RT-PCR was employed to investigate changes in mRNA. Cell viability and motility were detected by CCK-8 and wound healing assay. Db/db mice injected with different treatment were also generated. ELISA measurements were also used.

Results: Our results demonstrated that AMPK modulates podocyte IR level and enhances insulin-stimulated phosphorylation of PI3K/Akt cascades in high-glucose condition and diabetic db/db mice. Plus, AMPK prevented hyperglycemia-induced increase of GSK3β phosphorylation, ameliorated glucose uptake into podocytes, and impaired podocyte viability and motility. Moreover, treatments for modulation of key proteins in AMPK- PI3K/Akt -GSK3β signalling results in a reduction of proteinuria and significant improvement in renal function and pathological damage in db/db mice.

Conclusions: These findings evoke a novel therapeutic concept for DN, implying that the pharmacologic activation of AMPK might suppress the progression of DN and podocyte injury, also rescue podocyte insulin resistance. AMPK-PI3K/Akt- GSK3β pathway may be exploited as a therapeutic target for protection against podocyte injury and insulin resistance in DN.



Representative HE staining of diabetic kidney in each group

FR-PO392

Circulating Soluble Nogo-B Ameliorates Diabetic Glomerulopathy Partly by Modulating GSK3β/βcatenin Signaling

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Background: Early diabetic glomerulopathy (DG) is characterised by albuminuria, endothelial cell (EC) proliferation, EC glycocalyx disruption and podocyte loss. Nogo-B, expressed in glomerular EC and podocytes, is downregulated in diabetes. A 200-aminoacid N-terminus soluble Nogo-B (sNogo-B) is found in the circulation and (as Nogo-B) binds to its receptor NgBR promoting vascular integrity. Activation of GSK3β/βcatenin pathway promotes vascular stability; conversely, inactivation of GSK3β with βcatenin cellular accumulation, as seen in diabetes, promotes VEGFR2 signaling and ECs proliferation/vascular permeability. We investigated whether, in diabetes, sNogo-B overexpression modulates GSK3β/βcatenin and VEGFA signaling towards a stable glomerular capillary.

Methods: Adult DBA2J male mice were made diabetic with streptozotocin; sNogo-B overexpression was initiated after induction of diabetes by adeno-associated vector (AAV) (AAV driving the expression of green fluorescent protein-GFP served as control). Mice with glycemia >22 mM were considered diabetic. Mice were killed after 12-14 weeks of diabetes and kidney tissue collected for electron microscopy and immunofluorescence, respectively for podocyte number and EC proliferation/glycocalyx determination; renal cortex lysate was utilised for VEGFA/VEGFR2 phosphorylation levels (ELISA), and AKT, GSK3β/βcatenin signaling (western immunoblotting). Abuminuria was measured by ELISA.

Results: Diabetes (D) resulted in albuminuria, glomerular EC proliferation, EC glycocalyx disruption and podocyte loss when compared to non-diabetic (ND) mice (ND-GFP *vs* D-GFP, $p<0.01$); sNogo-B overexpression ameliorated diabetes-mediated albuminuria and vasculature anatomical alterations and was paralleled by inhibition of diabetes-mediated AKT^{ser473} and $GSK3\beta^{ser9}$ phosphorylation (D-GFP *vs* D-sNogo-B, $p<0.05$). βcatenin was highly expressed in kidney cortex lysate of D-GFP mice (ND-GFP *vs* D-GFP, $p<0.001$) and was downregulated in D-sNogo-B mice (D-GFP *vs* D-sNogo-B, $p<0.01$), an event paralleled by a normalisation of diabetes-mediated VEGFA/VEGFR2 receptor system activation (D-GFP *vs* D-sNogo-B, $p<0.04$).

Conclusions: sNogo-B overexpression in diabetic mice promotes a healthy vasculature *via* activation of GSK3β/βcatenin pathway; sNogo-B could represent a targetable pathway for the treatment of DG.

FR-PO393

Deacetylation of S6 Kinase (S6K) by High Glucose Drives Mesangial Cell (MC) Hypertrophy and Matrix Expansion in Diabetic Nephropathy (DN)

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Background: Hyperglycemia increases mTORC1-dependent S6K Thr-389 phosphorylation/activation to induce glomerular MC hypertrophy and matrix protein expansion in DN. S6K is acetylated in the C-terminal lysines (K484/485/493). We investigated the mechanism of S6K acetylation in relation to MC hypertrophy and fibronectin expression.

Methods: Human MCs in culture and streptozotocin (STZ)-induced diabetic rats were used. Activation/inactivation-specific phospho-antibodies, siRNA and plasmid-derived expression vector transfection and immunoblotting were employed.

Results: In MCs, 25 mM glucose (HG) decreased acetylation of multiple proteins including S6K concomitant with its increase in phosphorylation/activation. Consequently, HG increased phosphorylation of the S6K substrates rps6 and eEF2 kinase that resulted in dephosphorylation of eEF2. To determine the mechanism of S6K deacetylation, we considered the class I histone deacetylase-1 (HDAC1). Trichostatin-A (TSA), a pan HDAC inhibitor, blocked all of the HG-stimulated effects. HG increased the association of S6K with HDAC1. Expression of HDAC1 decreased the acetylation of S6K and increased the phosphorylation of S6K, rps6, eEF2 kinase, and dephosphorylation of eEF2, resulting in MC hypertrophy and expression of fibronectin, similar to HG. In contrast, siRNA against HDAC1 prevented these effects induced by HG. To study the precise mechanism, an acetylation mimetic triple mutant (TKA) was used. Expression of TKA blocked HG-stimulated phosphorylation of S6K, rps6, eEF2 kinase and inhibited the dephosphorylation of eEF2 resulting in attenuation of MC hypertrophy and fibronectin expression. In contrast, acetylation deficient mutant S6K (TKR) induced above phosphorylation events, and MC hypertrophy and fibronectin expression, similar to HG. Finally, in the renal glomeruli of STZ-induced diabetic rats, acetylation of S6K was significantly reduced concomitant with increased HDAC1, S6K activation, phosphorylation of rps6 and eEF2 kinase, dephosphorylation of eEF2, renal hypertrophy and fibronectin expression.

Conclusions: Our data for the first time show a role of S6K deacetylation in MC hypertrophy and matrix expansion, two pathologic features of DN. The results also furnish a molecular basis underlying the association between S6K and HDAC1 in DN.

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FR-PO394

DcR2 Interacts with Peroxiredoxin 1 and Accelerates Senescence of Renal Tubular Epithelial Cell in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD). The extent of tubulointerstitial lesions ultimate determines the rate of attrition of renal function, and premature senescence of RTECis a prominent renal histological change in DN. Decoy receptor 2 (DcR2) is a transmembrane receptor of cellular senescent marker, but the interaction proteins and the role of DcR2 are not clear.

Methods: 139 DN patients which diagnosed by renal biopsy were enrolled. Renal DcR2 and senescent markers, P16 and SA-β-gal were detected with immunostaining. The degree of cell senescence were evaluated after regulation of DcR2 expression. Co-IP combining with LC-MS/MS were screened the interaction proteins for DcR2 in renal tissue and high glucose (HG) induced-proximal tubular epithelial cells (PTECs). The interaction of DcR2 and PRDX1 was detected by Co-IP and pull down assay. Peroxidase activity of PRDX1 was assessed by the kits of ROS and specific 2-cys peroxidase activity. The level of PRDX1 phosphorylation was detected through WB.

Results: DcR2 was primarily expressed in renal proximal tubules, and co-expression with senescent markers P16 and SA-β-gal. Overexpression of DcR2 accelerate whereas knockdown inhibited the expression of P16 and SA-β-gal. Quantitative proteomics identified 135 differentially expressed proteins (DEPs) in renal tissue and 59 DEPs in HG. Peroxiredoxin 1 (PRDX1), an enzyme of oxidative stress, was screened not only in renal tissue but also in HG-induced cells. The interaction of DcR2 and PRDX1 was verified in vivo and in vitro. DcR2 can inhibited the peroxidase activity of PRDX1 through promote the phosphorylation of PRDX1.

Conclusions: DcR2 accelerates tubular cell senescence through interacting with a new partner PRDX1, and DcR2 can affect the peroxidase activity of PRDX1 through regulating the phosphorylation of PRDX1 in DN.

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FR-PO395

SMPDL3b Modulates Insulin Signaling in Lipid Raft Domains and Interferes with Diabetic Kidney Disease

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Background: SMPDL3b is a recently identified phosphodiesterase localized in lipid raft domains that regulates lipid composition and plasma membrane fluidity. As SMPDL3b is upregulated in diabetes while insulin receptor signaling is impaired, our study was aimed at testing the hypothesis that SMPDL3b affects the generation of sphingolipids involved in the regulation of insulin receptor signaling.

Methods: For *in vitro* studies, control and SMPDL3b overexpressing human podocytes were used. Cells were treated with insulin (0.1 and 1 nM, 30 min) or ceramide-1-phosphate (C1P; 100 uM, 1h) and analyzed by Western blotting or PCR. Lipidomic analysis was performed using LC-MS analysis and TLC plates. Co-immunoprecipitation experiments were performed using HEK293 cells. For *in vivo* studies, podocyte-specific *Smpdl3b* deficient diabetic db/db mice were produced using Cre-LoxP technology. Starting at 4 weeks of age, vital parameters (weight, glycemia, urine) were measured bi-weekly. For C1P replacement therapy, diabetic mice were IP injected with 30 mg/kg C1P daily for 28 days. Mice from all experiments were sacrificed for in-depth phenotypical analysis. All animal studies were performed in accordance with the NIH IACUC Guide. For statistical analysis One-Way ANOVA followed by Bonferroni's posttest or Student t-test were used.

Results: SMPDL3b binds to both IR isoforms (IRA and IRB) and, when in excess, competes with the binding of IRB to caveolin-1 and alters pro-survival insulin signaling in podocytes. *In vivo*, we demonstrated that kidneys of diabetic db/db mice are characterized by SMPDL3b excess and C1P deficiency, whereas podocyte-specific *Smpdl3b* deficient diabetic db/db mice show a normal C1P content and are protected from the development of diabetic kidney disease (DKD). Exogenous administration of C1P is sufficient to restore proper IR signaling *in vitro* and to protect from DKD *in vivo*.

Conclusions: Taken together, we identified new sphingolipid modulator of insulin signaling and demonstrated that replacement of deficient active sphingolipid species such as C1P may represent a novel approach to treat diabetic complications such as DKD.

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FR-PO396

LXR/mTOR/Nox4 Signaling Axes: Novel Therapeutic Targets in Diabetic Nephropathy

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Background: Podocyte injury has emerged as a key mediator in the initiation of Diabetic Nephropathy (DN). The molecular mechanism by which hyperglycemia induces podocyte injury is multi-factorial and not well defined. Recent studies have described the potentiality of defective autophagy mechanisms on the onset and development of diabetes. Our lab has described the importance of renal NADPH Oxidases (Noxs) in the progression of podocyte injury. Yet, a mechanistic pathway between Nox-induced ROS production and the alteration in autophagy has yet to be clarified. Liver-X-receptor (LXR) and the mTOR pathway have recently been linked to autophagy and oxidative stress. In this study we aim to assess the role of Nox/LXR/mTOR axes on autophagy and their possible links to podocyte depletion and injury.

Methods: Pharmacological means were utilized to alter the expression of Noxs, LXR and the mTOR signaling pathways, while podocyte depletion/loss, autophagy alteration and glomerular injury were assessed as the corresponding biological output both *in vitro* and *in vivo*.

Results: Our results reveal that high glucose (HG) induces defective autophagy in both podocytes and isolated glomeruli of type 2 diabetic mice. HG reduces LXR mRNA levels and protein expression and activates the mTORC1/p70S6kinase pathway. HG also increases the levels of Nox4 and Nox activity and induces ROS production. Activation of the LXR pathway using an LXR activator T0, decreases HG-induced Nox4 expression, Nox activity, inactivates the mTORC1 pathway, and restores autophagy protein levels. In parallel, inactivation of the mTORC1 pathway using low dose rapamycin, mimicked the effect of T0 on ROS production and podocytes injury but did not alter the LXR pathway, suggesting that mTORC1 is downstream of LXR and Noxs are the final common pathway altered in our experimental model. More importantly, our results display the role of Nox4 in autophagy, where inactivation of Nox4, using GKT, a potent Nox1 and Nox4 inhibitor, restores homeostatic autophagy levels, and reduces podocytes and glomerular injury.

Conclusions: Thus, LXR activation, mTOR and/or NADPH oxidase inhibition may represent a therapeutic modality for diabetic kidney disease.

FR-PO397

High Glucose–Induced Apoptosis and Necroptosis in Podocytes Is Regulated by UCHL1 via the RIPK1/RIPK3 Pathway

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Background: Depletion of podocytes plays a critical role in the pathogenesis of diabetic nephropathy (DN). Many investigations suggested its close association with apoptosis. However, the complex mechanism of podocyte loss in DN remains unclear. Recently, necroptosis has emerged as an important cell death model in cell injury related to many pathological conditions, which is regulated through the receptor interacting kinase 1/3 (RIPK1/RIPK3) pathway. It has been revealed that the molecular pathways to regulate apoptosis and necroptosis are closely related. Therefore, it is speculated that apoptosis and necroptosis may occur simultaneously during the process of podocyte injury in DN.

Methods: Immunofluorescence staining, trypan blue staining, Hoechst staining, TUNEL and ELISA were used to detect apoptosis and necroptosis of podocytes *in vitro and in vivo*. The ultrastructures of the two cell death patterns were observed under scanning electron microscope (SEM). After stimulation of podocytes with high glucose (HG), the expression of UCHL1 and RIPK1/RIPK3 pathway and the regulation effect of UCHL1 on apoptosis and necroptosis of podocytes were detected by western blot. The endogenous binding of UCHL1 with RIPK1 or RIPK3 and the ubiquitination of RIPK1 and RIPK3 proteins was detected by IP experiment.

Results: The present study demonstrated that necroptosis was involved in HG-induced podocyte injury both *in vitro* and *in vivo*. HG could induce both apoptosis and necroptosis in podocytes, which was dependent on HG concentration and treatment duration. This novel study explored the explicitly different morphological characteristics of apoptotic and necroptotic cells using SEM examination with TUNEL and Trypan blue double staining. The inhibition of apoptosis by z-VAD-fmk could enhance the necroptosis process, which was inhibited by Necrostatin-1(Nec-1). The present study also showed that ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) had a central role in regulating the two modes of cell death via mediating the ubiquitination states of the RIPK1/RIPK3 pathway.

Conclusions: These data suggested that necroptosis might be a major contributor to podocyte loss rather than apoptosis in HG treatment. The discovery of the novel function of UCHL1 may assist in developing strategies for treating podocyte damage induced by HG.

Funding: Government Support - Non-U.S.

FR-PO398

Amodiaquine and Chloroquine Attenuate Mitochondrial Abnormalities in Diabetic Tubulopathy Presumably by AMPK Phosphorylation

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Background: The activity of 5' AMP-activated protein kinase (AMPK), the major energy-sensing enzyme, was recently observed to be reduced in the kidneys of both diabetic mice and humans. Several previous studies showed that AMPK activators attenuate diabetic nephropathy, resulting in decreased albuminuria in diabetic mice. Chloroquine (CQ), an antimalaric drug, has also been considered an essential therapy in patients with systemic lupus erythematosus (SLE). It was reported that withdrawal of amodiaquine (AQ), a derivative of chloroquine is related to lupus flares after medication cessation. Although the mechanisms by which these agents act on SLE are unclear, a recent study reported that chloroquine increased AMPK phosphorylation in myotube cells. We investigated the effects of CQ and AQ on AMPK phosphorylation in renal tubular cells in a diabetic environment in vivo and in vitro. We also examined whether CQ- or AQ-mediated AMPK activity restoration attenuated diabetic tubulopathy by normalizing mitochondrial fragmentation.

Methods: Human renal proximal epithelial cells (HKC8) were incubated in high-glucose conditions. Diabetes was induced with streptozotocin in male C57/BL6J mice.

Results: Treatment with CQ or AQ abolished high-glucose-induced phospho-AMPK and phosph-PGC1α down-regulation in HKC8 cells. Improvements in functional mitochondrial mass and balanced fusion/fission protein expression were observed in HKC8 cells after treatment with CQ or AQ in high-glucose conditions. Moreover, decreased mitochondrial ROS production and reduced apoptotic and fibrotic protein expression were noted in HKC8 cells after treatment with CQ or AQ, even in high-glucose conditions. CQ and AQ treatment effectively mitigated albuminuria and renal histopathologic changes and increased AMPK activity in the kidneys of diabetic mice. Electron microscopy analysis showed that mitochondrial fragmentation was decreased, and 8-OHdG content was low in the renal tubular cells of the CQ and AQ treatment groups compared with those of the diabetic control group.

Conclusions: Our results suggest that CQ and AQ may be useful treatments for patients with diabetic kidney disease. This work was supported by a National Research Foundation grant of Korea (NRF-2016R1C1B1013814) funded by the Korea government.

Funding: Government Support - Non-U.S.

FR-PO399

Sirt6 Protects Podocytes from High Glucose-Induced Mitochondrial Dysfunction and Apoptosis Through AMPK Activation

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Background: Previous studies have shown that mitochondrial dysfunction plays an important role in podocyte injury. Sirt6 has been revealed with essential roles in the regulation of mitochondrial function. However, the pathological features and molecular mechanism of mitochondrial damage in podocytes under high glucose (HG) condition remains unknown. The present study aims to observe the changes of podocyte mitochondria under HG and to evaluate whether Sirt6 contributes to HG-induced podocytes apoptosis through modulating mitochondrial function.

Methods: In vivo study, transmission electron microscope (TEM) was used to identify ultrastructure changes of podocyte mitochondria in diabetic mice. Co-localization expression of Sirt6 and WT-1 was evaluated in glomeruli by double immunolabeling. Western blot was performed to assess Sirt6 and p-AMPK expression in glomeruli. In vitro study, conditionally immortalized human podocytes were exposed to HG (30mM) for 24 h. Mitochondria ultrastructure was observed by TEM. Mitochondrial number and ROS production were respectively evaluated by Mito Green and MitoSox Red staining. Mitochondrial membrane potential was determined by JC-1 staining. Flow cytometry was used to assess podocyte apoptosis. Western blot was performed to evaluate Sirt6 and p-AMPK expression.pcDNA3.1 SIRT6 was transfect to podocytes to evaluate the effect of Sirt6 over-expression on mitochondrial function and podocyte apoptosis under HG stimulation.

Results: Ultrastructural changes of podocytes in diabetic mice included mitochondria swelling, vacuoles formation, and mitochondrial cristae fracture. Double immunolabeling of Sirt6 and WT-1in glomeruli was obviously decreased in diabetic animals. In addition, p-AMPK expression was reduced in diabetic mice compared with controls. In cultured podocytes, TEM studies showed mitochondria swelling and cristae fracture under HG treatment. HG induced decrease in mitochondrial number and increase in mitochondrial ROS production. Furthermore, HG induced decreased mitochondrial membrane potential. All these changes were significantly alleviated by pcDNA3.1 SIRT6 transfection. Sirt6 overexpression also stimulated p-AMPK expression and alleviated HG-induced podocyte apoptosis.

Conclusions: These results indicate that Sirt6 could protect podocytes from high glucose-induced mitochondrial damage and apoptosis via AMPK activation.

Funding: Government Support - Non-U.S.

FR-PO400

Renoprotective Function of Liver Type Fatty Acid Binding Protein (L-FABP) in Diabetic Kidney Disease via Activation of Mitochondrial Function

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Background: Tubulointerstitial damage (TID) in diabetic kidney disease (DKD) is one feature of histopathology observed in the diabetic patients with early progressive renal decline. Therefore, TID is a therapeutic target in order to prevent the progression of DKD. Recently, TID in DKD is reported to be associated with renal mitochondrial injury. Renal liver type fatty acid binding protein (L-FABP) has an anti-oxidant effect as a scavenger of reactive oxygen species. However, the interaction between renal L-FABP and mitochondrial function has not been investigated yet. Therefore, the aim of this study is to reveal the renoprotective potential of renal L-FABP via activation of mitochondrial function in streptozotocin-induced DKD.

Methods: To evaluate the role of renal L-FABP, we used human L-FABP chromosomal transgenic (Tg) mice because L-FABP is not expressed in the kidneys of wild-type (WT) mice. The (Tg) mice and wild-type (WT) mice were divided into two groups: diabetic mice were injected with STZ; control mice were injected with a citrate buffer alone. At 19 weeks after these injections, the mice were killed and the kidney, and urine were isolated for analysis.

Results: The expression of renal L-FABP and the level of urinary L-FABP increased significantly in diabetic Tg mice compared to control Tg mice. Urinary albumin levels, the expression of α-smooth muscle actin in the interstitium and the level of renal oxidative protein were significantly lower in diabetic Tg kidneys compared with diabetic WT kidneys. The expression of mitochondrial superoxide dismutase 2 was significantly higher in diabetic Tg kidneys compared with diabetic WT kidneys. In the diabetic Tg kidneys, the expression of PPARγ co-activator 1α(PGC-1α) was significantly higher than that of diabetic WT kidneys.

Conclusions: In conclusion, renal L-FABP could activate mitochondrial function by acceleration of mitochondrial biogenesis due to rise of PGC-1α expression, and attenuate renal oxidative stress, and consequently, the renal fibrosis were prevented. Increase in renal L-FABP expression may be a promising treatment against TID in DKD.

FR-PO401

Disruption of Renal Tubular Mitochondrial Quality Control by KCa3.1 in Diabetic Nephropathy

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Background: Mitochondrial dysfunction is involved in the pathogenesis of diabetic nephropathy. Mitochondrial quality control is characterized by repairing of mitochondrial damage through mitophagy and fission/fusion. It has been shown that blockade of KCa3.1, a potassium channel, ameliorates diabetic renal fibrosis and KCa3.1 activation contributes to dysfunctional tubular autophagy in diabetic nephropathy through PI3K/Akt/mTOR signaling pathways. However, the role of KCa3.1 in mitochondrial quality control is not yet known. Therefore, the aim of the study is to identify the role of KCa3.1 in mitochondrial quality control in diabetic nephropathy.

Methods: In vitro human proximal tubular cells (HK2 cells) transfected with scrambled siRNA or KCa3.1 siRNA were exposed to TGF-β1 for 48h. Mitochondrial function and mitochondrial ROS (mtROS) production were assessed. In vivo, diabetes was induced in KCa3.1+/+ and KCa3.1-/- mice by streptozotocin injection. The pro-fission protein dynamin-related protein 1 (Drp1) and pro-fussion protein mitofusin 2 (Mfn2) as well as BCL2 interacting protein 3 (BNIP3) (a mitophagy regulator) were examined by western blotting in HK2 cells and mice kidneys.

Results: The in vitro results showed that TGF-β1 significantly inhibited mitochondrial ATP production rate, compared to the controls, which were significantly reversed by KCa3.1 siRNA in HK2 cells. KCa3.1 gene silencing inhibited TGF-β1-induced significant increase in MitoSOX Red fluorescence in HK2 cells. TGF-β1 significantly increased the expression of Drp1 and BNIP3 in HK2 cells, which were attenuated by KCa3.1 gene silencing. The expression of Mfn2 was not overtly apparent on TGF-β1 stimulation. Consistently, the in vivo results showed significantly increased Drp1 and BNIP3 expression in diabetic KCa3.1 +/+ mice, which were significantly reduced in diabetic KCa3.1-/- mice.

Conclusions: KCa3.1 mediates dysregulation of mitochondrial quality control in diabetic nephropathy.

FR-PO402

Urothelial-Specific Insulin Receptor Deletion Suppresses Host Defenses of the Kidney and Bladder

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Background: In people with diabetes mellitus (DM), urinary tract infection (UTI) is more common and has worse outcomes. With DM, UTI is more likely to cause acute kidney injury, which increases the risk of chronic and end-stage kidney disease. The mechanisms that predispose diabetics to UTI remain elusive. To investigate the significance of insulin signaling on kidney and urothelial host defense, we genetically deleted the insulin receptor (IR) in murine urothelium.

Methods: Urothelial-specific IR knock-out mice (IRKO) were generated by breeding homozygous mice for the floxed *Insr* gene (insulin receptor gene) with transgenic mice that have tamoxifen-inducible Cre recombinase under the Uroplakin 2 (Upk2) promoter. Littermates lacking the Upk2-Cre transgene served as controls (IRflox). To determine if urothelial-specific IR deletion impacts host defense, female mice were transurethrally infected with uropathogenic *E. coli* (UPEC). At 24, 48, and 72 hrs post infection, UPEC burden was enumerated in urine, bladder, and kidney. To assess why IRKO mice have increased UTI susceptibility, human urothelial cells were assayed *in vitro* using siRNA to silence IR and investigate if silencing IR disrupts urothelial barrier formation.

Results: PCR confirmed urothelial-specific Cre-LoxP recombination and IR transcript deletion in bladders of IRKO mice. Compared to IRflox, IRKO mice exhibit normal development, no evidence of hyperglycemia, and normal bladder/kidney histology. Following transurethral UPEC infection, the bladders of IRKO mice developed significantly pronounced and prolonged inflammation and edema. This was accompanied by significantly greater UPEC burden in the urine, bladder, and kidneys at all time points. siRNA-mediated *INSR* silencing in human bladder cells *in vitro* resulted in marked differences in urothelial proliferation and migration.

Conclusions: These results suggest that intact insulin signaling is critical for UTI defense. Also, they indicate that hyperglycemia alone does not explain increased UPEC susceptibility. Finally, they indicate that abnormal bladder defenses, including a reduced ability to regenerate an impermeable urothelial barrier, increases the likelihood for significant bladder and kidney infection. Additional studies are warranted to identify how IR deletion impacts urothelial defenses.

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FR-PO403

Genetic Regulation of Diabetic Kidney Disease Traits and Transcriptome Signature in Mice

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Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and end-stage renal disease. Thus far, the genetic factors contributing to hallmark features of DKD remain poorly understood. Our goal was to assess DKD and associated molecular markers in an intercross between two strains of mice differing in albuminuria on the background of the diabetes-inducing *Ins2*^{Akita} mutation.

Methods: We generated F2 mice from a cross between maternal CBA/J and paternal C57BL/6J-Ins2^{Akita} mice. We measured albumin-to-creatinine ratio (ACR) on 24-h urine from F2 mice at age 7 and 20 weeks. Kidney morphometry was quantified by light and electron microscopy at 20 weeks. We performed RNA sequencing on kidney cortex to identify transcripts associated with physiologic and structural traits. Linkage analysis identified causal loci of physiologic and molecular traits.

Results: We observed 20-fold variation in ACR among 87 diabetic F2 mice at age 20 weeks. Plasma glucose (p=1.7×10^{-6}), kidney weight (p=1.0×10^{-6}), glomerular volume (p=2.1×10^{-11}), glomerular basement membrane width (p=2.2×10^{-5}), total mesangial cell (1×10^{-2}) and total mesangial matrix (p=1.5×10^{-4}) increased significantly in diabetic F2 mice versus non-diabetic mice. We detected a significant quantitative trait locus for ACR on chromosome 4 (LOD=3.79, p=0.030) and a locus for volume fraction of mesangial cell and total mesangial cell on chromosome 14, LOD=3.79, p=0.031. We identified regulatory pathways enriched for oxidative stress (p=1.23×10^{-14}), fatty acid metabolism (p=6.86×10^{-11}) and mitochondrial function (p=4.51×10^{-12}) associated with ACR.

Conclusions: The study identified a genetic basis for increases in volume fraction of mesangial cell, total mesangial cell and ACR, and regulatory pathways associated with oxidative stress, fatty acid metabolism and mitochondrial function in DKD. The study provides further insight to the genetic determination of DKD traits.

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FR-PO404

Integrated Epigenetic Analysis for Kidney Function and Functional Decline Defines Novel Biological Pathways for Patients with Diabetic Kidney Disease

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Background: Poor metabolic control induces epigenetic changes, which play an important role in development and progression of diabetic kidney disease (DKD). Prior studies failed to integrate epigenetic information with genotype and transcriptomic data. Here we performed an integrated epigenetic, genetic and transcriptomic analysis in CRIC (Chronic Renal Insufficiency Cohort).

Methods: We analyzed genome wide cytosine methylation changes in blood samples of 473 patients with DKD from the CRIC. Subjects were matched for baseline features but showed differences in their kidney function decline. We adopted linear regression model adjusted for age, sex, batch, genetic background, hypertension, cell type heterogeneity and glucose control for eGFR and eGFR slope. To distinguish between genetically or environmentally driven methylation differences, we catalogued genotype-driven methylation changes by performing mQTL (methylation quantitative trait) analysis. To define genetically driven gene expression changes, we performed expression of quantitative trait analysis (eQTL). Bayesian co-localization analysis was adopted to identify causal genes by integrating GWAS, mQTL and eQTL datasets.

Results: We identified that methylation level of 2 probes significantly associated with baseline kidney function (eGFR). Methylation level of 9 probes significantly association with kidney function decline. We were able to replicate the association for 3 of the 11 probes in the ARIC (Atherosclerosis Risk in Communities Study) and FHS (Framingham Heart Study) cohorts. We found that methylation of 6 of the 11 loci were driven by genetic variation (mQTL SNP). To understand functional consequences of methylation changes, we integrated the results with RNA-seq data using expression of quantitative trait (eQTL) analysis. We found that the expression of (Lyzosome) LYZ significantly associated with the genetic variation and methylation differences. Transcript level of LYZ in the kidney also strongly correlated with kidney function.

Conclusions: We identified and replicated significant methylation changes associated with kidney function and functional decline. Integrated genetic, epigenetic and transcriptomic analysis defines genetically and potentially environmentally driven changes and novel biological mechanisms for DKD.

FR-PO405

Inhibition of P2X7 Receptor Delays the Progression of Diabetic Nephropathy and Represses Klotho Expression

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Background: Previous studies in our laboratory have suggested that P2X$_7$ could contribute to the progression of diabetic nephropathy and modulate klotho expression. Aim of this study was to investigate the role of P2X$_7$ knockdown in the onset of diabetic nephropathy and its possible relationship with klotho, in rats.

Methods: Seven-week-old male Wistar rats weighing 210g were all uninephrectomized; two-thirds were induced to diabetes with 60mg/kg streptozotocin i.v., and one-third received its vehicle (control rats). At 4th day of the fifth week of the protocol, half of the diabetic rats received a small interfering RNA targeting for P2X$_7$ mRNA, and the other half received its vehicle. Euthanasia was made at the eighth week.

Results: Diabetic animals reproduced all classic symptoms of the disease; besides, they showed reduced renal function and low NO bioavailability; also SOD1, SOD2 and catalase were increased, probably due to the oxidative stress factors which were elevated in this situation. Metabolic data of diabetic rats did not change by silencing P2X$_7$ receptor. For the other hand, silencing P2X$_7$ was able to increase plasma and membrane forms of klotho, which in turn could have contributed to balance oxidative and nitrosative profile, ultimately improving the renal function.

Conclusions: These findings suggest that the management of P2X$_7$ receptor can benefit the kidneys or perhaps even other organs involved in diabetic nephropathy. Maneuvers like silencing P2X$_7$ can be used as an adjuvant therapy in diabetes mellitus, improving the quality of life of these patients.

FR-PO406

Effects of Chronic Renal Impairment on Glucose Homeostasis: Role of Class II PI3K-C2β

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Background: Chronic kidney impairment may result in multiple metabolic derangements leading to insulin resistance and Type 2 diabetes. However the underlying mechanisms involved in the crosstalk between the kidney and insulin target tissues remains unknown. Therefore to help elucidate this we studied the effect of reduced kidney mass on whole-body glucose homeostasis in lean and obese mice.

Methods: Mice underwent unilateral nephrectomy (UniNX) or sham operation at 7-week old followed by either normal chow or high fat diet (HFD). 16 weeks after surgery, glucose homeostasis was assessed.

Results: Unexpectedly, despite mild proteinuria and uremia, glucose tolerance and insulin sensitivity were improved in UniNX animals both on normal and HFD without enhanced insulin secretion. This correlated with a significant increase in *in vivo* insulin stimulated-Akt signaling in metabolic tissues (liver, muscle and adipose tissue) both under normal and HFD in UniNX conditions. Furthermore, we observed a significant decrease of HFD-induced liver steatosis in UniNX animals. Taken together this unanticipated data show a beneficial impact of UniNX on glucose homeostasis. To get greater insight into the molecular mechanisms involved, we investigated the role of the class II PI3K-C2β, a lipid kinase previously reported as a potential drug target for insulin sensitization. We observed that class II PI3K-C2β inactivation positive effect was accentuated by UniNX with a significant improvement of glucose metabolism and a complete protection against HFD-induced obesity and hepatic steatosis. In conclusion this study highlights an unexpected beneficial synergistic effect of PI3K-C2β inactivation and UniNX to protect against obesity, insulin resistance and hepatic steatosis.

Conclusions: Taken together this data reveal the possibility that kidney donors taking PI3K-C2β inhibitors could be fully protected against obesity, insulin resistance and diabetes. This study could encourage living kidney donations in addition to improving our understanding of the molecular mechanisms involved in the crosstalk between the kidney and insulin target tissues.

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FR-PO407

Proximal Tubular Uptake of Free Fatty Acid (FFA) by Kidney Injury Molecule-1 (KIM-1) Mediates Tubulointerstitial Disease in Diabetic Mice

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Background: Diabetic kidney disease (DKD) is associated with tubulointerstitial damage which predicts progression of chronic kidney disease. KIM-1, a scavenger receptor, is the most upregulated proximal tubule protein in many forms of kidney injury.

Dysregulated lipid metabolism is a primary feature of DKD. We hypothesized that KIM-1-mediated uptake of FFAs contributes to tubulointerstitial damage in DKD.

Methods: Renal epithelial cells expressing KIM-1 (LLC-PK1 cells and mouse primary renal epithelial cells) were exposed to palmitate followed by measurement of FFA uptake, cell death and pro-inflammatory and pro-fibrotic effects *in vitro*. *In vivo*, two animal models were used to evaluate the role of KIM-1-mediated FFA uptake. A DKD model induced by unilateral nephrectomy, streptozotocin and high fat diet (UNx-STZ-HFD DKD) was studied in wild-type or KIM-1$^{\Delta mucin}$ (functional knockout of KIM-1 lacking a mucin domain) mice. A second new model was created whereby KIM-1 or KIM-1$^{\Delta mucin}$ was upregulated by aristolochic acid and the effect of subsequent injection of FFA was determined (AA-FFA model).

Results: FFA was taken up by the wild-type KIM-1 expressing cells but not by control or KIM-1$^{\Delta mucin}$ expressing cells, leading to cell death in cells expressing wild-type KIM-1. mRNAs of IL-1β and NLRP3 were increased after FFA treatment only in cells expressing wild-type KIM-1 but not controls. Conditioned media harvested from FFA-treated cells expressing wild-type KIM-1 stimulated greater αSMA expression in mouse fibroblasts, compared to media from KIM-1$^{\Delta mucin}$ cells. In the UNx-STZ-HFD DKD model, wild-type mice showed greater proximal tubular atrophy, macrophage infiltration, fibrosis and albuminuria when compared with KIM-1$^{\Delta mucin}$ mice. In the AA-FFA model, wild-type mice showed more macrophage infiltration, αSMA expression and loss of brush border when compared with KIM-1$^{\Delta mucin}$ mice.

Conclusions: KIM-1 mediates the proximal tubular uptake of FFA, which leads to cell death and pro-inflammatory and pro-fibrotic responses in diabetic mice. Our findings support the role of KIM-1 as a therapeutic target for DKD.

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FR-PO408

Diabetic Condition Induces Hypertrophy and Apoptosis in Parietal Epithelial Cells Through Mitotic Catastrophe

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Background: Podocyte hypertrophy and apoptosis are two hallmarks of diabetic glomeruli; however, little information is available about changes in parietal epithelial cells (PECs). We hypothesized that diabetes induces hypertrophy and apoptosis in PECs in a similar manner and causes damage. This study aimed to elucidate the effects of a diabetic condition on PECs in vitro and in vivo.

Methods: Conditionally immortalized mouse PECs were exposed to 5 mmol/L glucose (NG), 30 mmol/L glucose (HG), and angiotensin-II (AT-II) at the dosage of 10^{-6} mol/L or aldosterone at 10^{-7} mol/L. Hypertrophy and cell cycle analysis were assessed by flow cytometry. Podocyte apoptosis was ascertained by Annexin V/PI staining, Hoechst 33342 staining, and caspase 3/7 staining. For in vivo studies, streptozotocin-induced diabetic mice, db/db diabetic mice, and BTBR ob/ob mice were used as diabetic mouse models. Histomorphology of the renal tissue was observed using light microscopy and transmission electron microscopy (TEM). PEC apoptosis was assessed using the TUNEL assay and cleaved caspase-3 staining.

Results: In cultured PECs, HG induced hypertrophy, whereas AT-II and aldosterone failed to induce hypertrophy. Flow cytometry revealed that HG also induced PEC apoptosis in a dose-dependent manner and S-phase arrest of PECs, suggesting mitotic catastrophe of PECs. In TEM, PECs exhibited enlargement of both the cytoplasm and nucleus at the ultrastructural level in all diabetic mouse models. PAX 8 staining revealed PEC nuclear hypertrophy in diabetic mice, whereas the cell number of PECs remained unaltered, suggesting that PECs in diabetic condition underwent DNA replication with a mitotic defect. However, an increase in apoptotic PECs was not observed in diabetic glomeruli.

Conclusions: PECs in diabetic condition are in a state of dysregulation of proliferation similar to mitotic catastrophe. As PECs are considered a precursor of podocytes, this injury to PECs might impair glomerular regeneration. Nevertheless, further studies are warranted to elucidate the potential pathological role of morphological changes in PECs in diabetic kidney disease.

FR-PO409

ENaC and MARCKS Proteolysis in Diabetes Associated Hypertension

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Background: The majority of T2DM patients present with hypertension and diabetic nephropathy progresses more rapidly in hypertensive diabetic patients compared to those without hypertension. Thus, there is an urgent need to better understand the mechanisms contributing to diabetes associated hypertension in order to reduce morbidity and mortality in these patients. Proteolysis of both the epithelial sodium channel (ENaC) and the myristoylated alanine-rich C-kinase substrate (MARCKS) is necessary for high levels of ENaC activity.

Methods: Here we use salt-loaded db/db mice and control mice to test the hypothesis that increased proteolysis of ENaC and MARCKS plays an essential role in the pathogenesis of hypertension secondary to diabetes. Cleaved ENaC and MARCKS was assessed by Western blotting. Protease activity was measured by zymography and fluorometric assays. ENaC activity was assessed by electrophysiology. Blood pressure was measured by telemetry.

Results: Western blots using validated antibodies showed both ENaC and MARCKS proteolysis is increased in the diabetic db/db kidneys compared to kidneys from C57B6 wild-type mice. Western blot and zymography analyses showed increased expression and activity of proteases including cathepsins in the diabetic db/db kidneys compared to controls. ENaC activity was increased in split-open tubules from salt-loaded diabetic db/db mice compared to controls. Telemetry studies showed mean arterial pressure was increased in these diabetic db/db mice after salt-loading and the blood pressure was restored by daily injections with amiloride.

Conclusions: This project will contribute to our understanding of the protease-dependent regulation of ENaC and MARCKS in the development of diabetes associated hypertension and potentially lead to novel drug targets and therapeutics.

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FR-PO410

RNA Binding Proteins Tristetraprolin and Human Antigen R Mediate Diabetic Tubulopathy via Modulation of Inflammation and Apoptosis of Renal Tubular Epithelial Cells

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Background: Inflammatory components have been involved in diabetic tubulopathy, a key constituent of diabetic nephropathy (DN) pathology, with undefined molecular mechanisms. RNA binding proteins Tristetraprolin (TTP) and Human antigen R (HuR) have been implicated in inflammatory response in a variety of diseases and exert opposite modulatory effects on a number of inflammatory mediators. Nevertheless, their role in diabetic tubulopathy remains unknown. Evidence suggests that the expression and activity of TTP and HuR are regulated by phosphorylation that is catalyzed by a number of kinases, including GSK3β, a cell signaling transducer with a nephropathic action. The aim of this study was to examine the role of GSK3β -regulated TTP and HuR in diabetic tubulopathy by using an in vitro model of renal tubular epithelial cells (HK-2).

Methods: The mRNA or protein expressions were measured by qRT-PCR or immunoblotting. Apoptosis was analyzed by TUNEL staining. The subcellular localization of TTP, HuR and GSK3β was determined by immunofluorescence staining. GSK3β was silenced by RNA interference to examine the modulatory effect on TTP and HuR expression.

Results: After exposure of HK-2 cells to high ambient glucose (HG, 30Mm glucose), both mRNA and protein expressions of TTP were decreased, while those of HuR were increased, associated with an up-regulation of KIM-1 and TNF-α, loss of E-cadherin and augmented cellular apoptosis, implying that TTP and HuR were oppositely regulated upon high glucose-induced renal tubular cell injury. Tubular cell injury coincided with GSK3β hyperactivity, marked by GSK3β overexpression and suppressed phosphorylation of GSK3β at serine 9. Dual color fluorescent immunocytochemistry staining demonstrated that GSK3β is co-localized with TTP and HuR respectively in different subcellular compartments of HK-2 cells. Moreover, GSK3β seems to be essential for high glucose-induced TTP and HuR dysregulation, because silencing of GSK3β substantially reinstated TTP expression and offset HuR overexpression, concomitant with an improved cellular injury and apoptosis.

Conclusions: The GSK3β regulated RNA binding proteins TTP and HuR play a crucial role in mediating inflammation and apoptosis renal tubular cell injury in diabetes.

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FR-PO411

The Effects of Modulating Autophagy on Macrophages Adhesion and Migration in Diabetic Nephropathy

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Background: Macrophage infiltration is an important histopathological feature of various chronic renal diseases including diabetic nephropathy. This study aims to investigate the impact of macrophages adhesion and migration by modulating autophagy.

Methods: In vivo, rats were randomly distributed into control (NC) and diabetic nephropathy (DN) groups. The pathological changes in renal tissue were assessed, and expression of CD68, LC3, P62 were analysed. In vitro, RAW264.7 cells were divided into normal and high glucose (HG, 30mM) groups. The capacity for macrophage adhesion and migration and the expression of autophagy markers were observed with and without autophagy modulators (rapamycin, 3-methyladenine, chloroquine, and bafilomycin A1 for RAPA, 3-MA, CQ, BAFA). The numbers of autophagosomes and the process of degradation and fusion of autophagosome-lysosome were observed by electron microscopy.

Results: In vivo, renal injury is aggravated in diabetic rat compared with NC group. The expression levels of CD68 and P62 of renal tissues increased in DN group, while expression level of LC3 decreased. In vitro, HG or 3-MA reduce the numbers of autophagosomes with less expression of LC3 and Beclin-1, but increase expression of P62. HG or 3-MA promote the adhesion and migration capacity of macrophages. Moreover, CQ and BAFA inhibit the process of degradation and fusion of the autophagosome-lysosome as well as the expression of LC3 and Beclin-1. We notice an increase expression of P62 by CQ and BAFA stimulaion. These effects further facilitate the adhesion and migration capacity of macrophages. However, RAPA increases the numbers of macrophage autophagosomes, resulting in an increase expression of LC3 and Beclin-1, whereas a reduction expression of P62, which lead to inhibition of adhesion and migration of macrophages induced by HG ($P<0.05$).

Conclusions: Modulating the function of autophagy can affect the adhesion and migration capacity of macrophages in diabetic nephropathy.

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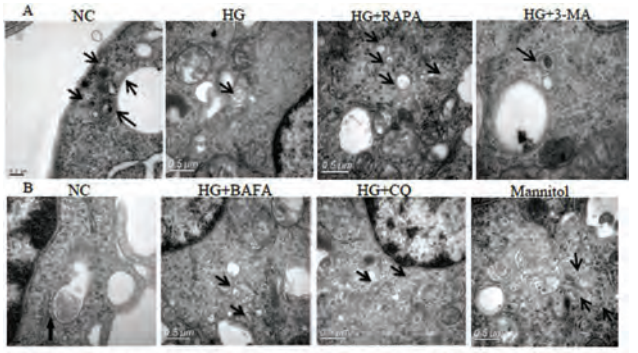

A: the change in the numbers of autophagosomes of macrophage; B: the change in degradation and fusion of autophagosome-lysosome.

FR-PO412

The Possible Mechanisms of Effects of NF-κB Inhibitor Parthenolide on Promoting Renal Tubules Albumin Reabsorption in Type 2 Diabetic Nephropathy

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Background: Increased albuminuria caused by albumin reabsorption reduction of renal tubules is highlighted as the cause of early stage of diabetic nephropathy. The underlying mechanism has not been fully figured out. We aimed to observe whether reducing inflammation thereby remodeling impaired insulin signaling could improve renal tubules albumin uptake in diabetic nephropathy.

Methods: 1)8-weeks db/m and db/db mice were used as control(C group) and diabetic nephropathy model(DN group). Parthenolide(PTN 1mg/kg) was used intraperitoneally every other day to db/db mice as treatment group(DN+PTN group). After 8-weeks treatment, urine, blood and kidney samples were collected. Expressions of NF-κB, insulin signaling protein pAKT/AKT and albumin receptors amnionless(AMN) and cubilin in kidneys were detected by immunohistochemistry and immunoblotting. 2)HKC cells were treated with TNF-α(25ng/ml), PTN(5μM) and insulin(100nM). Albumin uptake and expressions of NF-κB, pAKT/AKT, AMN and cubilin were tested by fluorometric assay and immunoblotting.

Results: 1)Compared with DN group, DN+PTN group showed decreased insulin resistance index levels($P<0.05$) and slightly reduced urine albumin creatinine ratio levels($P>0.05$). 2)NF-κB expression increased and phosphorylation of AKT decreased in DN group compared with C group ($P<0.05$). PTN reduced NF-κB expression and ameliorated decline of AKT phosphorylation($P<0.05$). Compared with C group, AMN and cubilin expressions decreased in DN group($P<0.05$), and PTN attenuated reduction of cubilin expression($P<0.05$). 3)Insulin promoted AMN and cubilin expressions and albumin uptake of HKC cells($P<0.05$). In TNF-α group, NF-κB expression increased and AKT phosphorylation decreased compared with insulin group($P<0.05$). In TNF-α+PTN group, PTN reduced NF-κB expression and AKT phosphorylation($P<0.05$). AMN and cubilin expressions decreased in TNF-α group($P<0.05$), and PTN attenuated reduction of cubilin expression($P<0.05$).

Conclusions: The study observed in diabetic nephropathy PTN could ameliorate insulin resistance and slightly reduce albuminuria. We found albuminuria with albumin receptors reduction was induced by inflammation impaired insulin signaling in renal tubules. PTN could reduce inflammation, remodel impaired insulin signaling, and then increase albumin uptake by ameliorating albumin receptors expressions.

FR-PO413

PKC-δ Reduced DUSP4 Expression Causing NOX4 and Progressive Diabetic Nephropathy

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Background: Diabetic nephropathy is characterized by the loss of an important epithelial cell called podocytes. Podocytes are specialized cells that have a critical role in maintaining the integrity of the glomerular filtration barrier. A promising insight in the initiation of glomerular pathology begins with the loss of expression of the dual specificity phosphatase 4 (DUSP4), known for its role in MAPK inhibition. We have observed that cultured podocytes exposed to high glucose (HG; 25 mM) concentrations and glomeruli of diabetic (*Ins2*$^{+/C96Y}$) mice exhibited significant reduction of DUSP4 which complied with glomerularsclerosis, podocyte foot process effacement and podocyte cell death. However, the exact mechanism of diabetes-induced DUSP4 reduction remained unknown but protein kinase C (PKC) activation has been shown to regulate DUSP expression in macrophages.

Methods: Non-diabetic (NDM) and diabetic (DM) mice with the deletion of DUSP4 (D4KO) and PKC-δ (*Prckd*$^{-/-}$) were used after 6 months of diabetes. Mouse podocytes were exposed to normal (NG; 5.6 mM) or high (HG; 25 mM) glucose levels for 72 hours with or without the overexpression of DUSP4 and PKC-δ adenoviral vector to evaluate the oxidative stress pathway. Human blood and kidney sample were collected to measure DUSP4 mRNA levels and estimated glomerular filtration rate using the CKD-EPI formula.

Results: By overexpressing the dominant negative form of PKC-δ specifically, we were able to reestablish DUSP4 expression levels in podocytes. In addition, decreased DUSP4 expression observed in renal cortex of DM mice were not seen in DM mice that did not possess the PKC-δ gene. Podocytes exposed to HG concentrations showed a 52% increase of NOX4 expression which was prevented with the overexpression of DUSP4. DM mice had a 30% increase in NOX4 expression in the glomeruli, which was exacerbated by 31% in DM mice with a specific deletion in DUSP4. Interestingly, in humans, decreased mRNA expression of DUSP4 in the renal cortex of diabetic patients correlated with eGFR level decline.

Conclusions: Reduction of DUSP4 expression induced by PKC-δ activation increased NOX4 expression and podocyte dysfunction in diabetic nephropathy.

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FR-PO414

Parkin Inhibits Accelerating Senescence of Renal Tubular Cells by Promoting GATA4 Degradation in Diabetic Nephropathy

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Background: Accelerating senescence of renal tubular epithelial cell (RTEC) plays a fundamental role in the pathogenesis of diabetic nephropathy (DN). Parkin, as an E3 ubiquitin ligase, can promote protein ubiquitination and degradation. Parkin gene mutation can accelerate neuron senescence in several neuropsychiatric disorders. GATA binding factor 4 (GATA4), as a substrate of E3 ubiquitin ligase, is a key regulatory factor for senescence phenotype. We investigated the role of Parkin in accelerating senescence of RTEC and its mechanism.

Methods: 149 cases of patients with DN diagnosed by renal biopsy were recruited in our study. Renal Parkin expression was detected by immunohistochemistry. In vivo, we generated Parkin overexpressed streptozotocin-induced DN mice. In vitro, knockdown and overexpression experiments were performed by parkin siRNA or Parkin overexpressed adenovirus in high glucose (HG) stimulated mouse primary RTEC.

Results: Expression of parkin was gradually decreased with development of tubulointerstitial injury and negatively correlated with renal tissue injury scores (tubular atrophy and interstitial fibrosis, renal interstitial inflammation score), renal function injury parameter Scr. Parkin positive tubular epithelial cell did not express senescent marker P16. Compared to wild type DN mice, parkin overexpressed DN mice had lower renal tissue injury scores and better renal function. P16 and GATA4 expression of renal tubules were inhibited in parkin overexpressed DN mice. In vitro, parkin overexpression inhibited HG-induced GATA4 expression and RTEC senescence, whereas parkin knockdown enhanced GATA4 expression in RTECs under HG conditions. Furthermore, we found parkin co-immunoprecipitated with GATA4. Parkin overexpression increased GATA4 ubiquitination under HG conditions, whereas parkin knockdown decreased GATA4 ubiquitination.

Conclusions: Parkin may inhibit HG-induced RTEC senescence by promoting GATA4 ubiquitination and degradation. Parkin is a potential anti-senescence factor in the development of DN.

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FR-PO415

ARF6: A Possible Molecular Target for Diabetic Kidney Disease?

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Background: Podocytes are key target cells that determine the progression of diabetic kidney disease (DKD), the leading cause of renal failure in the U.S. It is now clear that small GTPase proteins have quintessential roles that govern podocyte health – too much or too little GTPase activity can make the podocyte more susceptible to injury. We recently discovered that ADP-ribosylation factor 6 (ARF6), a Ras-family small GTPase protein, is present in human podocytes and involved in podocyte response to *in vivo* glomerular injury models; however, its role in DKD is unknown. Since ARF6 is involved in diverse cellular events (e.g. actin rearrangement or endocytic trafficking), we postulate that alterations in ARF6 activity might have injury-specific effects on kidney function and that glucose-induced activation of ARF6 in podocytes contributes to the progression of DKD.

Methods: We used an integrated genetic and pharmacologic approach by taking advantage of the CRISPR-Cas9 system to generate an ARF6-gene deleted mouse podocyte line as well as a selective ARF6 inhibitor, NAV2729 (R&D Systems). Mouse podocyte cell lines were cultured under normal glucose (NG, 5mM) or high glucose (HG, 25 mM) conditions for 48 hours.

Results: Podocytes cultured under HG conditions expressed significantly higher Arf6 mRNA and protein levels compared to podocytes cultured under NG conditions. Isolated podocytes from diabetic (Lepr$^{db/db}$) mice had increased ARF6 expression compared to control (Lepr$^{db/+}$) mice. Furthermore, we generated an ARF6-gene deleted mouse podocyte cell line in which we found that ARF6 knockout podocytes had augmented mitochondrial ROS production. To determine whether ARF6 might serve as a molecular target for pharmacologic inhibition in DKD, diabetic and control mice were treated with an ARF6 inhibitor (NAV2729) or vehicle (DMSO) at a dose of 60 mg/kg starting at 8 weeks of age. NAV2729-treated diabetic mice demonstrated significant improvement in the urine albumin to creatinine ratio (UACR) compared to diabetic mice treated with vehicle suggesting a nephro-protective effect of ARF6 inhibition.

Conclusions: These results suggest that ARF6 is an important protein involved in podocyte health. ARF6 expression is increased under diabetic conditions. Inhibition of ARF6 might prevent podocyte injury and DKD progression.

Funding: Private Foundation Support

FR-PO416

Inhibition of Vascular Endothelial Growth Factor Receptor-2 Phosphorylation by Calcium Dobesilate Requires Interaction with Heparan Sulfate Binding Site

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Background: Inhibition of vascular endothelial growth factor (VEGF) is a therapeutic option in diabetic microangiopathy. However, VEGF is needed at physiological concentrations for the maintenance of glomerular integrity. Since VEGF exerts its effects on endothelial cells via binding to (1) the VEGF-receptor and (2) to heparan-sulfate (HS) as co-receptor partial blockade of VEGF may be a possible strategy. We tested the hypothesis that the small molecule calcium dobesilate (CaD) (1) inhibits VEGF signaling in endothelial cells, (2) that this effect is mediated via interference between CaD and heparan-sulfate (HS) binding sites and (3) CaD ameliorates diabetic nephropathy (DN) in a diabetic mouse model via inhibition of VEGF.

Methods: In vitro, the effect of CaD on VEGF signaling in endothelial cells (EC) together with the role of heparin was analyzed by Western blotting. EC function was assessed by migration, proliferation and permeability assays. Streptozotocin-treated mice (STZ) were treated with CaD and functional parameters as well as renal histology and inflammatory cells infiltration (immunohistochemistry) were measured at 6 and 12 weeks of hyperglycemia.

Results: CaD inhibited $VEGF_{165}$-induced phosphorylation of VEGFR-2 kinase and suppressed the activity of VEGFR-2 mediated signaling cascades both in vitro and in diabetic animals. The effects of CaD in vitro were abrogated by exogenous heparin, suggesting the involvement of heparin-like domain in the interaction with CaD. $VEGF_{121}$, which does not bind to heparin, was not inhibited by CaD. CaD restored tight junction protein expression and decreased VEGF-induced migration, proliferation and permeability in endothelial cells. CaD ameliorated glomerular pathology, reduced albuminuria and inflammatory cells infiltration in STZ-treated mice and reduced VEGF signaling in diabetic kidneys.

Conclusions: Our results suggest that CaD inhibits VEGFR-2 phosphorylation through the interaction between CaD and HS binding sites both in cultured endothelial cells and in vivo. CaD is a partial VEGF inhibitor without the negative effects of complete VEGF blockade and could be useful as therapeutic strategy in diabetic nephropathy.

FR-PO417

The Use of Type 2 Hypoglycemic Agents in Type 1 Diabetic Animals: Unveiling Novel Signaling Pathways

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Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease. The AMPk activator, metformin, or the GLP1-agonist, liraglutide are hypoglycemic agents that are typically prescribed to type 2 diabetic patients. With their distinct mechanisms of action, these hypoglycemic drugs are utilized in our study to dissect the molecular pathway through which DN may ensue in type1 diabetes. Oxidative stress is known to be the unifying mechanisms that mediates the pathogenesis of DN, however, the role of the DUOX subfamily of enzymes, a poorly studied cellular source of reactive oxygen species (ROS), and their mechanism of action has not been previously characterized in DN. In this study, we aim to examine the expression of DUOXs in the diabetic renal system and reveal their crosstalk with AMPK/GLP-1 signaling in type 1 diabetic animals.

Methods: Monotherapy and combination therapy of metformin and liraglutide were used to assess their effects on glomerular injury in STZ-induced type-1 diabetic animals. ROS production, proteins and mRNA levels of DUOX, AMPK, mTOR, and autophagy markers were examined and correlated with morphological alterations observed histologically in addition to albuminuria.

Results: Our results showed that metformin or liraglutide monotherapy or their combination did not affect glycaemia. However, a decrease in albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis was evident, especially when the drugs were used in combination. Elevated ROS production correlated with NADPH oxidase activity in diabetic animals compared to non-diabetic animals. The administration of the metformin or liraglutide was shown to partially reverse DUOX-derived ROS production, the expression of fibronectin, COL IV, nephrin, DUOX1, DUOX2, AMPK, mTOR and autophagy markers LC3A and LC3B in the type 1 diabetic animals. An effect that was more pronounced when the drugs were used in combination.

Conclusions: These findings shed light on the crosstalk between the AMPK and GLP1 signaling pathways with the NADPH-oxidases and their role in restoration of autophagy, a potential reno-protective mechanism in DN.

FR-PO418

Renin Producing Cells in the Diabetic Kidney

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Background: Urinary renin is increased in patients with diabetes and models of diabetic kidney disease but its source is not clear. The intensity of renin staining in the collecting tubule is increased in the STZ model of diabetes and in Angiotensin (Ang) II-induced hypertension which could lead to RAS activation locally at this site. We examined the distribution of renin expressing cells using a renin reporter mouse made diabetic by STZ to trace the localization of renin lineage cells (RLC).

Methods: The Ren1d-Cre; mT/mG, a double transgenic reporter mouse model, expresses both Cre-recombinase from the endogenous renin locus (Ren1D) and the mT/mG cassette from the Rosa26 locus (mRenCre-mT/mG). The membrane-directed tomato protein (mT) is expressed ubiquitously and fluorescents in red, while the membrane-targeted green fluorescent protein (mG) is found only in those cells undergoing Cre-recombination. In RLC the mT/mG construct switches from red fluorescent to green fluorescent (mG), while all non-RLC remain mT positive. Ren1d-Cre;mT/mG were made diabetic using STZ. Animals were studied 11-12 weeks after STZ injection.

Results: In WT mice made diabetic by STZ, renin staining by immunohistochemistry was increased in the collecting tubule and by immunofluorescence aquaporin 2 (AQP2), a marker of principal cells, co-localized with renin protein. In the renin reporter mice AQP2 co-localized with green fluorescent protein (GFP+) reflecting that renin producing cells are or had been present at this site. A quantitative comparison of this GFP+ cells between kidney sections of STZ treated and untreated reporter mice, however, revealed no significant differences. Within the glomerulus, RLC were strongly present in parietal areas and within the glomerulus but no significant differences were found between diabetic and non-diabetic renin reporter mice.

Conclusions: In collecting tubules from diabetic mice there is an increased expression of renin which cannot be attributed to increased number of renin producing cells at that site. Alternative explanations such as increased uptake of filtered renin and impaired reabsorption mainly in the proximal tubule need to be considered as the source of collecting tubule renin.

Funding: NIDDK Support

FR-PO419

Inhibition of Glucose Transporters Ameliorates Fibrogenic Signaling in a Cellular Model of Diabetic Nephropathy

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Background: Diabetic Nephropathy (DN) is the leading cause of kidney failure. Prolonged exposure to elevated glucose strongly facilitates the progression of DN. Tubulointerstitial fibrosis is a key prognostic marker of DN. Approximately 90% of glucose in the glomerular ultra-filtrate is reabsorbed by the low affinity Na+/glucose co-transporter SGLT2. Following the advent of therapeutics targeting glucose uptake at this specific site, we propose a role for SGLT2 in regulating DN.

Methods: Primary PTEC were grown on collagen IV coated/uncoated culture dishes. On reaching 80% confluence, they were treated with D-Glucose at either 5.5 mM (normoglycaemic control), 25mM (hyperglycaemia) or 5.5 mM D-Glucose + 19.5 mM L-Glucose (osmotic control). Cells were treated with TGFβ1, 0.75ng/ml or vehicle. After 24 h, cells were lysed. Heparin pull down was applied to the media to isolate heparin-binding proteins. Dapagliflozin (0.1, 1 & 10μm) was administered to cells treated with high glucose in combination with TGF-β1. Western blot was then used to detect the level of Connective Tissue Growth Factor (CTGF) and EDA fibronectin protein.

Results: There was no obvious cytotoxic effect of any of the treatments. Western blotting demonstrated that primary PTEC secreted CTGF, mwt 36 & 38kDa. Neither TGF-β1 alone nor raised glucose induced a significant increase in CTGF; however the combination of both did ($p<0.05$ compared to all other treatments) at 24h. EDA+ fibronectin protein was unchanged. Dapagliflozin at all three concentrations significantly attenuated CTGF protein secretion, reducing the expression to approximately basal levels.

Conclusions: A combination of raised D-Glucose and TGF-β1, similar to that expected in DN, induced a significant increase in CTGF, an important pro-fibrotic marker. Dapagliflozin successfully reduced this outcome, thus confirming SGLT2 function. Interestingly, high glucose and TGF-β1 alone under these conditions did not produce a significant increase in CTGF, suggesting an additive effect in the upregulation of CTGF. Glucose-induced CTGF expression in vascular smooth muscle cells is associated with cellular damage and death. These phenomenon were not observed in our primary renal cells. This suggests a more precise controlled mechanism for glucose-induced CTGF in PTEC.

FR-PO420

Endoglin as Potential Target to Slow Down Progressive Diabetic Nephropathy via Inhibition of Fibrosis Formation

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Background: Diabetic nephropathy (DN) is a complication of diabetes, resulting in progressive decline of renal function and proteinuria. Progressive DN is histologically characterized by glomerular matrix expansion and interstitial fibrosis, in which TGF-β plays an important role. Endoglin, a co-receptor of TGF-β, mostly known for regulating endothelial cell functions, is also described in human fibrotic tissues such as liver, heart and intestine. To investigate the role of endoglin in progressive DN, we measured endoglin expression in biopsies of patients with DN and characterized the endoglin-expressing cell type in the interstitium. We also investigated the effect of endoglin knockdown on extracellular matrix production in kidney fibroblasts *in vitro*.

Methods: Kidney biopsy material of 11 patients with DN was collected. As control, tumor free tissue of 7 patients with a renal tumor was used. Sequential sections were stained for endoglin and Sirius Red. The positively stained interstitial area was quantified using ImageJ. Immunofluorescent double stainings for endoglin and CD31, CD68, vimentin or a-SMA were performed on biopsy material from a patient with and without DN. A human kidney fibroblast cell line (TK173) was transduced with a lentiviral vector expressing an shRNA against endoglin.

Results: Endoglin was significantly upregulated in patients with DN compared to controls ($p<0.001$). Also, the Sirius red-positive area was significantly increased in patients with DN ($p<0.001$). Immunofluorescence showed co-expression of endoglin with the endothelial marker CD31. Endoglin also co-localized with the myofibroblast marker a-SMA. Co-localization with fibroblast (vimentin) or macrophage (CD68) markers was not observed. In cell culture, endoglin knockdown in fibroblast resulted in reduced PAI-1, CTGF and fibronectin expression after stimulation with TGF-β ($p<0.05$).

Conclusions: Endoglin is upregulated in the interstitium of DN patients and is expressed in myofibroblasts. *In vitro*, endoglin is involved in TGF-β dependent matrix production. Therefore, endoglin might play a role in the development of fibrosis and thus the progression towards end-stage renal disease in DN.

FR-PO421

Inhibitor of Growth 2 Regulates the High Glucose Induced Cell Cycle Arrest and Epithelial-to-Mesenchymal Transition in HK-2 Cells

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Background: Cell cycle dysregulation has been linked to various kidney injuries in recent years; however, its involvement in the fibrosis of diabetic kidney disease (DKD) is far from being clarified. ING2 (inhibitor of growth 2) is the second member of the inhibitor of growth family and participates in the regulation of many cellular processes, yet the role of ING2 in the process of DKD remains largely unknown. In the present study, we aimed to investigate the involvement of ING2 in the cell cycle arrest and epithelial-to-mesenchymal transition (EMT) process in diabetic conditions and the underlying mechanism for it.

Methods: The human proximal tubular epithelial cells (HK-2) were stimulated with high glucose and diabetic mice were generated by streptozotocin injection. ING2 expression was detected by western blotting and immunofluorescent staining in vitro and immunohistochemistry staining in vivo. The expression of ING2 was silenced by siRNA transfection. Cell proliferation was analyzed by CCK-8 and EdU assay. Cell cycle arrest was measured by flow cytometry. The EMT markers were detected by qPCR and western blotting. The p53 activation by high glucose was proved by chromatin immunoprecipitation (ChIP) and the downstream p21 expression was detected by qPCR and western blotting.

Results: We first revealed that the expression of ING2 was increased both in diabetic mouse kidney in vivo and in high glucose stimulated HK-2 cells in vitro. ING2 downregulation ameliorated the reduced proliferation and cell cycle arrest induced by high glucose in HK-2 cells. Moreover, p53 was activated under hyperglycemia condition and ING2 knockdown suppressed p21 expression by reducing p53 acetylation and finally alleviated the expression of EMT markers in the high glucose stimulated HK-2 cells.

Conclusions: Our study demonstrated that cell cycle regulation is bound up with the EMT of high glucose cultured HK-2 cells, suggesting a novel function of ING2 as a potential therapeutic strategy targeting cell cycle arrest for the kidney fibrosis in DKD.

FR-PO422

Role of CD13 in Renal Proximal Tubular Handling of Albumin

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Background: Albuminuria, a complication of disease states that damage glomerular function such as diabetic nephropathy (DN), promotes renal damage by triggering pro-inflammatory and pro-fibrotic pathways leading to chronic kidney disease (CKD). Understanding how the kidney handles urinary albumin may thus be beneficial for identifying therapeutic mechanisms to limit disease progression. Urinary proteins are normally efficiently resorbed via the Megalin-Cubilin receptor complex and the neonatal Fc Receptor (FcRn) in the proximal tubule. CD13, a multifunctional cell surface molecule, negatively regulates clathrin-dependent endocytosis in various cell types. Like the albumin endocytic receptors, CD13 is expressed abundantly on the apical surface of proximal tubule epithelial cells. Here, we examined the role of CD13 in renal proximal tubular handling of albumin in two murine models of albuminuria as well as in unchallenged mice.

Methods: WT and CD13 KO C57/B16 mice were used for both a streptozotocin (STZ) induced DN model (50 mg/kg daily for 5 days) and albumin overload (AO) model (bovine serum albumin; increasing daily doses from 2 mg/g to 10 mg/g on day 5, final 10 mg/g dose on day 8). Urine and serum were collected at basal, 8, 12, 16, and 20 weeks post STZ-treatment in the DN model and day 8 in the AO model for ELISA analysis. Kidneys were collected for immunofluorescence, flow cytometry, and electron microscopy analysis. Relationship of CD13 to Megalin, Cubilin, and FcRn was analyzed by co-immunofluorescence of kidney sections and western blotting of brush border membrane fractions.

Results: Compared to WT, CD13 KO mice exhibited significantly decreased albuminuria in both 20 week STZ-induced DN and AO models, as well as increased cellular uptake of albumin in the proximal tubules even in unchallenged conditions. Furthermore, we identified possible mechanisms by which CD13 regulates albumin endocytosis, including 1) co-localization of CD13 and FcRn, 2) elevated levels of cubilin at the brush border of CD13 KO proximal tubules, and 3) maintenance of cristae integrity in CD13 KO mitochondria after 20 week STZ-induced DN.

Conclusions: Our results suggest that CD13 serves as a key mediator for albumin endocytosis in the proximal tubule and may be a potential therapeutic target for preventing albuminuria-induced damage in renal disease.

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FR-PO423

The iBEAT MRI Biomarker Panel: Prognostic Imaging Biomarkers for DKD

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Background: Advances in functional Magnetic Resonance Imaging (MRI) have provided novel renal imaging biomarkers that inform on parenchymal perfusion, oxygenation, filtration, fibrosis, inflammation, and tissue composition. We present a novel panel of MRI biomarkers designed to help predict DKD progression. The panel has been developed for iBEAT, a new cohort study in 500 patients with T2 diabetes and eGFR>30 mL/min, starting mid 2018. iBEAT is part of the BEAt-DKD project (www.beat-dkd.eu) funded by IMI-JU (No 115974).

Methods: iBEAT will collect MRI in 5 sites at 3 Tesla scanners of 2 vendors; studies will be uploaded into a central database. QC and MRI post-processing will be performed centrally, and MRI biomarkers will be integrated with clinical data, demographics, blood-, urine-, and biopsy biomarkers, endothelial function, and nuclear medicine gold-standards. The MRI protocol was developed through a 6-month process involving measurements on volunteers and a reference object developed by NIST.

Results: The iBEAT MRI panel characterizes both kidney parenchyma and general body composition. The latter includes liver fat (%, insulin resistance), pancreatic fat (%, insulin secretion), liver iron (mg/g, diabetes risk), visceral fat (mL, diabetes risk). Renal biomarkers cover three groups: (1) *Anatomical biomarkers* include kidney volume (mL, increased in hyperfiltration), renal sinus fat (mL, predictor of albuminuria), cortical volume (mL, surrogate for nephron number); (2) *Microstructure biomarkers* include T2* (ms, oxygenation), T1 (ms, fibrosis), T2 (ms, inflammation, oedema), blood volume (%, glomerular hypertrophy), tubular volume (%, tubular obstruction), fractional anisotropy (%, tubular dilatation, glomerulosclerosis); (3) *Dynamic biomarkers* include cortical and medullary perfusion (ml/min/g), filtration fraction (%, hyperfiltration), tubular flow (ml/min/g, concentrating capacity), GFR density (ml/min/g).

Conclusions: The iBEAT MRI biomarker panel is designed to capture DKD progression on the level of renal tissue dynamics, microstructure and anatomy, as well as broader risk factors for diabetes. The iBEAT study will determine the utility of these biomarkers for DKD prognosis, and whether they may become part of the clinical endpoint in future trial designs.

Funding: Commercial Support - European Federation of Pharmaceutical Industries and Associations

FR-PO424

Prognostic Imaging Biomarkers for Diabetic Kidney Disease (iBEAT): A BEAt-DKD Study

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Background: BEAt-DKD (Biomarker Enterprise to Attack DKD) is a public-private partnership committed to deliver more effective patient stratification, DKD prevention and management (www.beat-dkd.eu; IMI-JU No 115974). We report here on an early milestone in BEAt-DKD, the design and setup of a clinical study (iBEAT) to explore the utility of imaging biomarkers.

Methods: iBEAT was developed as a collaborative project with central coordination between sept 2016 and June 2018. iBEAT will be run by 7 core sites including 5 recruiting centres, one of whom is the coordinating site (Leeds), a central biobank (Lund), a data management centre (Lausanne), and an image processing and QA centre (Leeds)

Results: iBEAT is a 4-year prospective observational cohort study in 500 patients with Type 2 diabetes and eGFR>30mL/min, aiming to identify MRI & Ultrasound (US) biomarkers that can improve DKD prognosis. MRI and US will be collected at baseline only. Demographics, clinical, family and medication history, blood (70mL) and urine will be collected annually. Additional data will be collected by four sites to address ancillary objectives (100 patients per site): Kidney biopsies, digitalized and characterized by histology and EM (Bari); PET-based renal blood flow (Turku); glycocalyx and microvascular assessments (Exeter); 2-year follow-up MRI and US (Bordeaux). Biopsies and biofluids including urinary vesicles and sediment will be used for biomarker discovery using state of the art omics, and stored for validation studies. A parsimonious set of baseline biomarkers associated with eGFR (primary) and eGFR slope over time (secondary) will be identified.

Conclusions: iBEAT is the largest functional imaging biomarker study in DKD performed to date. The study will test the utility of imaging biomarkers for DKD prognosis, and may also help improve our understanding of disease pathogenesis.

Funding: Commercial Support - European Federation of Pharmaceutical Industries and Associations

FR-PO425

Magnetic Resonance Elastography (MRE) with Arterial Spin Labeling (ASL) Kidney Blood Flow for Noninvasive Evaluation of Diabetic Nephropathy

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Background: Noninvasive quantitative measurement of fibrosis in chronic kidney disease (CKD) would be advantageous diagnostically and therapeutically but standard radiologic imaging is too variable for clinical usage. Using MRE, by applying a vibratory force, shear waves are generated that can measure kidney parenchymal shear stiffness that may correlate with tissue fibrosis.

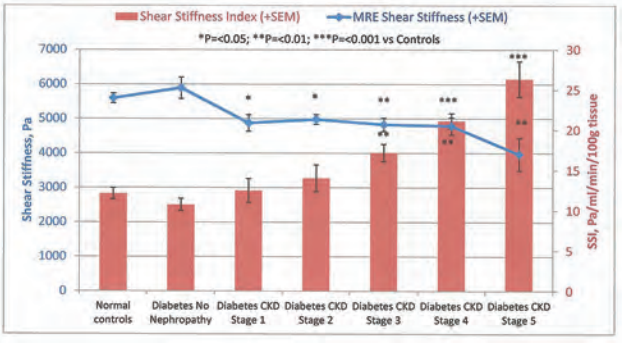
Methods: We used novel 3-dimensional MRE with ASL kidney blood flow rates to study 30 diabetic patients with stage 0 to 5 CKD compared to 13 control individuals without CKD.

Results: MRE cortical shear stiffness at 90 Hz was surprisingly decreased significantly below normal in diabetic nephropathy (DN) of stages 3-5 CKD. Likewise, cortical ASL blood flow decreased progressively from 480±136 ml/min/100g tissue in controls to 152±32 ml/min/100g in stage 5 CKD. Calculation of a surrogate filtration fraction (sFF = eGFR/ASL) decreased progressively from 0.21±0.07 in controls to 0.10±0.02 in Stage 4-5 CKD. To account for the effect of decreased blood flow which has been shown to decrease MRE kidney shear stiffness, we calculated a novel shear stiffness index normalized to blood flow (SSI = MR shear stiffness/ASL blood flow, Pa/ml/min/100g cortical tissue). The SSI increased progressively from 12±3 in the controls to 26±4 in stage 5 CKD. This significant increase of the SSI also correlated with the grade II-V interstitial fibrosis in DN graded 'blindly' by biopsy in 5 patients.

Conclusions: MRE coupled with ASL blood flow rates can noninvasively measure kidney tissue perfusion, quantitate a sFF proportional to measured filtration fractions, and calculate a novel shear stiffness index that correlates with the degree of kidney fibrosis in worsening diabetic nephropathy.

Funding: NIDDK Support, Other NIH Support - Harvard Catalyst Subaward

	Controls	DM, No Neph	DN, CKD1	DN, CKD2	DN, CKD3	DN, CKD4	DN, CKD5
ASL (ml/min/100g)	480±136	593±12	446±161	392±123	302±95***	229±7**	152±32**,+
sFF (eGFR/ASL)	0.21±0.07	0.18	0.31±0.10#	0.19±0.07	0.16±0.04$	0.10±0.02$	0.10±0.02+
Shear Stiffness, Pa	5592±693	5892±623	4876±589##	4978±447*	4829±1023&,&	4786±703&&	3968±942**
SSI (Pa/ml/min/100g)	12.1±3.2	10.8±1.1	12.5±3.7	14.1±5.2	17.2±5.6##	21.2±2.1###	26.4±4.4###



FR-PO426

Functional Magnetic Resonance Imaging (MRI) Is Promising in Predicting the Prognosis of Diabetic Kidney Disease (DKD): Confirmed by the Cohort Study

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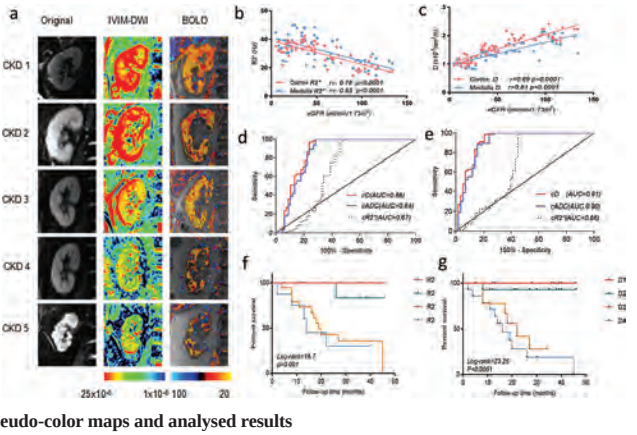
Background: DKD, the major cause of CKD and ESRD globally, which prognosis is determined by tissue hypoxia or fibrosis. However, assess the two aspects noninvasively is difficult. Whether functional MRI is available for predicting outcomings has not been proven.

Methods: we performed a corhort study in 67 DKD patients, measuring their renal oxygenation by blood oxygenation level-dependent(BOLD) MRI and fibrosis by intravoxel incoherent motion (IVIM) diffusion weighted imaging (DWI). 10 diabetes mellitus were recruited as control. The correlation were caculated by pearson linear analysis. Student's t-test and one-way ANOVA were used to assess the difference among groups. the area under the curve (AUC) were built to assess the discriminative accuracy of MRI values with GFR. finally, Kaplan-Meier analysis was used to evaluate the prognosis after follow up.

Results: Differences were discovered in MRI values between DKD groups and controls. There is strong positive corelation between cortex ADC (p<0.0001)or D value (p<0.0001)and GFR, but negative correlation found in cortex R2* (p=0.0008). AUC (identify with eGFR) of cortex D, was 0.86 (95% CI 0.79–0.93) stronger than the AUC of the cortex ADC (AUC: 0.84, 95% CI 0.77–0.92) or cortex R2* (AUC: 0.67, 95% CI: 0.57–0.77). A further increase in the AUC was obtained taking ECT-GFR as a standard. Follow-up period was 22.4±12.7 months, Kaplan-Meier curve according to cortex D over time showed a significantly different prognosis(Log-rank=23.26; P<0.0001), in contrast, that cortex R2* value is less accurate(Log-rank=16.7; p=0.001).

Conclusions: Cortex D value is in good agreement with the decline of renal function, Thus, cortex D value is an ideal biomarker for predicting the prognosis, cortex R2* is less accurate than cortex D but also helpful in judging prognosis.



Pseudo-color maps and analysed results

FR-PO427

Magnetic Resonance Imaging Allows a Novel Non-Invasive Functional and Pathophysiologic Assessment of CKD in Diabetic Nephropathy

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Background: Magnetic resonance imaging (MRI) has great potential to non-invasively assess functional and morphologic changes in the kidney that may improve diagnosis, prognosis and treatment in patients with chronic kidney disease (CKD). We investigated in diabetic nephropathy (DN) patients if non-contrast MRI using multiple techniques could differentiate a) CKD3-4 stages from healthy controls and b) CKD3 from CKD4 stages.

Methods: An interim analysis of the ongoing study evaluated 18 CKD4, 10 CKD3 patients with DN staged using measured GFR and 20 age- and gender-matched healthy controls. The MRI session included following techniques: R_2* for assessment of renal hypoxia, apparent diffusion coefficient (ADC) for fibrosis, arterial spin labelling (ASL) for cortical perfusion, renal artery blood flow (peak velocity maximum and minimum, mean arterial flow [MAF], renal artery resistive index [RARI), PC perfusion (MAF/kidney volume), and kidney volume corrected for body surface area (BSA).

Results: Several of these parameters (highlighted in the table) were highly sensitive and specific to differentiate healthy vs CKD3-4 and CKD3 vs CKD4. By multivariate analysis, the combination of mean arterial flow and R2* medulla showed a strong predictive ability to separate healthy from CKD patients.

Conclusions: A comprehensive non-contrast MRI protocol was developed, which as a single non-invasive tool could improve our understanding of the function and underlying pathophysiology of CKD including DN, obviating potential user-dependent errors and risky use of contrast agents. Longitudinal follow-up will assess whether these findings can identify patients at risk for progression of CKD.

Funding: Commercial Support - Antaros Medical AB, Astra Zeneca

	CKD3-4 vs Healthy				CKD3 vs CKD4			
Variable	**AUC**	**Sensitivity**	**Specificity**	**Cut-off**	**AUC**	**Sensitivity**	**Specificity**	**Cut-off**
R2* medulla (s^{-1})	0.80	0.67	0.80	25.6	0.57	0.65	0.60	24.8
ADC cortex ($mm^2s^{-1}x10^{-3}$)	0.73	0.68	0.78	2.35	0.64	0.78	0.80	2.32
ASL perfusion cortex (ml/100g/min)	0.91	**0.93**	**0.90**	161	0.64	0.65	0.70	60.0
Peak velocity max (cm/s)	0.70	0.71	0.80	48.7	0.81	0.67	0.80	44.5
Peak velocity min (cm/s)	0.96	**0.93**	**0.90**	12.6	0.91	**0.94**	**0.80**	8.33
RARI	0.96	**0.96**	**0.85**	0.73	0.68	0.61	0.80	0.84
Mean arterial flow (ml/s)	0.97	**0.89**	**0.90**	6.65	0.88	0.78	0.90	4.98
PC Perfusion (ml/100g/min)	0.93	**0.93**	**0.85**	380	0.85	**0.89**	**0.90**	328
Kidney volume (ml) corrected for BSA	0.81	0.75	0.75	60.4	0.51	0.50	0.50	51.9
Multivariable (mean arterial flow; R2* medulla)	0.99	**1.00**	**0.95**	7.55;26.9	NA	NA	NA	NA

FR-PO428

High Repeatability and Sensitivity of MR Imaging Biomarkers of CKD

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Background: New drug development tools are needed for monitoring response to therapy in chronic kidney disease (CKD) with increased precision and repeatability. We evaluated 18 CKD4 and 10 CKD3 subjects with type 2 diabetic nephropathy, and 20 age- and sex-matched healthy volunteers with a wide range of non-contrast magnetic resonance Imaging (MRI) techniques. Measured GFR (mGFR) was assessed using iohexol clearance. Half of the subjects were re-scanned after 2-4 weeks to assess repeatability.

Methods: MRI techniques included R_{2*} for assessment of renal hypoxia, apparent diffusion coefficient (ADC) for fibrosis, $R_1$for interstitial water balance, arterial spin labelling (ASL) for cortical perfusion, renal artery blood flow (peak systolic velocity, end diastolic velocity, mean arterial flow, and renal artery resistive index (RARI)), global perfusion (mean arterial flow/kidney volume), and kidney volume corrected for body surface area.

Results: see Table

Conclusions: Several MR parameters correlate strongly with mGFR indicating that these biomarkers are biologically relevant while providing additional information on pathophysiology. Given the known relationship between MRI biomarkers and mGFR plus the intra-subject CoV, the number of subjects needed to detect, e.g. a 2 ml/min/1.73m^2 change in mGFR can be calculated. To conclude, a 30 min non-contrast MRI protocol characterising important aspects of CKD with a high repeatability and sensitivity was identified. Repeatability data allows future CKD intervention studies to be correctly powered.

Funding: Commercial Support - Antaros Medical; AstraZeneca

	Healthy Controls	CKD Stage 3	CKD Stage 4	Correlation with mGFR (r)	p-value of correlation	Coefficient of variation
R2* cortex (s^{-1})	18.0 (1.4)	17.6 (1,9)	17.4 (1.4)	0.15	0.33	0.04
R2* medulla (s^{-1})	28.3 (3.1)	24.5 (3.6)	24.3 (3.9)	0.44	0.002	0.05
ADC cortex (mm^2s^{-1} x 10^{-3})	2.48 (0.17)	2.47 (0.17)	2.21 (0.24)	0.44	0.002	0.06
ADC medulla (mm^2s^{-1} x 10^{-3})	2.36 (0.17)	2.29 (0.21)	2.22 (0.22)	0.29	0.051	0.07
R1 cortex (s^{-1})	1.10 (0.17)	0.97 (0.23)	0.97 (0.18)	0.36	0.011	0.08
R1 medulla (s^{-1})	0.69 (0.03)	0.73 (0.04)	0.74 (0.09)	0.38	0.008	0.06
ASL perfusion cortex (ml/100g/min)	206 (65)	99 (63)	76 (59)	0.65	<.0001	0.28
Peak systolic velocity (cm/s)	54.3 (8.3)	60.7 (18.2)	42.1 (11.2)	0.35	0.015	0.09
End diastolic velocity (cm/s)	17.0 (3.9)	10.9 (2.4)	6.39 (2.26)	0.81	<.0001	0.11
RARI	0.68 (0.06)	0.81 (0.05)	0.84 (0.06)	0.79	<.0001	0.03
Mean arterial flow (ml/s)	0.43 (1.76)	6.31 (1.50)	4.15 (1.24)	0.86	<.0001	0.07
Global Perfusion (ml/100g/min)	436 (59)	346 (53)	248 (85)	0.76	<.0001	0.08
Kidney volume (ml)	66.5 (9.6)	56.6 (18.4)	52.5 (11.5)	0.448	0.001	0.06

mean (SD)

FR-PO429

Myocardial Flow Reserve Assessed by Cardiac 82Rb PET/CT Is Associated with Albumin Excretion in Patients with Type 1 Diabetes

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Background: To evaluate myocardial flow reserve (MFR) and coronary artery calcium (CAC) in persons with type 1 diabetes with or without albuminuria and in non-diabetic controls. MFR reflects the function of large epicardial arteries and myocardial microcirculation. CAC represents structural aspects of atherosclerosis. In addition we evaluated the association of MFR and CAC with retinopathy, another microvascular complication

Methods: Cross-sectional study in type 1 diabetes, stratified by normoalbuminuria (n=30) and macroalbuminuria (n=30), and in non-diabetic controls (n=30). MFR (pharmacological stress flow/rest flow) was evaluated by cardiac ^{82}Rb positron emission tomography/computed tomography.

Results: MFR was similar in patients with normomalbuminuria (NORMO) and controls (3.1 ± 0.8 vs. 3.0 ± 0.79; p=0.74). Patients with macroalbuminuria (MACRO) had lower (impaired) MFR compared to NORMO (2.1 ± 0.9 vs. 3.1 ± 0.8; $p < 0.0001$). The CAC score (median[IQR]) was higher in NORMO compared to controls (72[22-247] vs. 0[0-81], p=0.018), and comparable between MACRO and NORMO. MFR was comparable in patients with diabetes and simplex or no retinopathy (n=24 and n=12, 2.8 ± 0.84 vs. 3.3 ± 0.77, p=0.11), but lower in proliferative (n=24) compared to simplex retinopathy (2.1 ± 0.97 vs. 2.8 ± 0.84, p=0.02). The CAC score was comparable between groups of retinopathy.

Conclusions: Myocardial microvascular function was comparable in non-diabetic controls and patients with type 1 diabetes and normoalbuminuria; but impaired in the presence of microvascular complications (macroalbuminuria and proliferative retinopathy). Coronary calcification was elevated in diabetes, however not explained by albuminuria.

FR-PO430

Pulse Wave Velocity Is an Independent Risk Factor for Cardiovascular Events, Mortality and Decline in Renal Function in Patients with Type 1 Diabetes

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Background: The prognostic significance of carotid-femoral pulse wave velocity (cfPWV), the gold standard measure of arterial stiffness, remains to be determined in patients with type 1 diabetes (T1D). We investigated the predictive value of cfPWV for development of cardiovascular events (CVE), mortality and decline in renal function in T1D.

Methods: At baseline cfPWV was measured using the SphygmoCor device in 652 patients with T1D and various degrees of albuminuria, ranging from normo- (<30 mg/24h), micro- (30-299 mg/24) to macroalbuminuria (≥300 mg/24h. Endpoints were traced through National Registers and patient records until 31st December 2016 comprising: composite CVE, mortality, progression from normo- to micro/macroalbuminuria or from micro- to macroalbuminuria, and decline in estimated glomerular filtration rate (eGFR) ≥30%. Median follow-up ranged from 5.2 to 6.2 years. Slope estimates of eGFR and urinary albumin creatinine rate (UACR) were calculated for a median of 5.5 years. Adjustment included sex, age, mean arterial pressure, LDL cholesterol, smoking, HbA_{1c}, UACR and eGFR at baseline. Hazard ratios (HR) were calculated per 1 standard derivation (SD) increase in cfPWV.

Results: Of the 652 participants (56% male); mean±SD age was 54±13 years, cfPWV 10.5±3.38 m/s and eGFR 81±26 ml/min/1.73m^2. Median numbers of eGFR and UACR measures during follow-up were 6.0 and 17.0, respectively. After adjustment, higher cfPWV remained significantly associated with all endpoints: composite CVE (n=81; HR:1.31; p=0.045); mortality (n=48; HR:1.39; p=0.033); progression in albuminuria (n=31; HR:1.16; p=0.012); and decline in eGFR ≥ 30% (n=90; HR: 1.39; p=0.015). Higher cfPWV was associated with a steeper decline in eGFR and a steeper increase in UACR after adjustments (p≤0.009).

Conclusions: In patients with T1D, higher arterial stiffness was consistently associated with a higher risk of CVE, mortality and decline in renal function, independent of other risk factors. Measurement of cfPWV may have a promising role in risk stratification in T1D.

FR-PO431

Exome Wide Association Study Identifies a Rare Coding Variant in Cubilin Gene and Suggestive Variants in Additional Genes Associated with Albuminuria Among 33,985 Europeans with and Without Diabetes

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Background: Identification of rare coding variants associated with albuminuria may provide new options for preventing chronic kidney disease (CKD) and end-stage renal failure, especially in diabetic patients. With the increasing burden of CKD reaching about 15% in the US, efforts to identify underlying genetic factors for albuminuria have been limited, majority focusing just common variants.

Methods: We performed an exome-wide association study to identify coding variants in a two-phase (discovery and replication) approach employing 33,985 individuals of European ancestry (15,872 with and 18,111 without diabetes). Additive genetic models using linear regression on natural log transformed Albuminuria levels was performed for 263,894 single nucleotide polymorphisms (SNPs), adjusted for age, sex, and population substructure. Meta analyses conducted using fixed effects inverse variance method.

Results: We identify a rare (MAF: 0.8%) missense variant in Cubilin gene (*CUBN*, p=1.3 × 10^{-11}) associated with albuminuria in the combined European (EUR) meta-analyses. The rare *CUBN* variant had 3 times stronger effect in individuals with diabetes compared to those without ($p_{interaction}$: 5.4 × 10^{-4}, β_{DM}: 0.69, β_{nonDM}: 0.20) in the discovery meta-analyses. This *CUBN* rare variant is an independent signal for albuminuria after conditional analyses with the previously known albuminuria common SNP (LD: r^2 = 0.0002, D' = 1.0, $p_{condition}$: 8.5 × 10^{-7}). Gene-aggregate tests based on rare (MAF<0.01) and common variants suggest three additional genes associated with albuminuria (*HES1, CDC73,* and *GRM5*) after correction for multiple testing ($p_{bonferroni}$<2.7 × 10^{-6}).

Conclusions: The current study identifies a rare coding variant in the *CUBN* locus and suggestive variants in 3 other genes associated with albuminuria in individuals with and without diabetes, implicated in renal dysfunction. These highlight novel genes and pathways as potential targets towards diabetes related kidney disease prevention.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO432

TCF7L2 and ACE Polymorphisms Confer Genetic Susceptibility to Diabetes Mellitus Type 2/Diabetic Nephropathy in Chilean Patients

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Background: Diabetes mellitus type 2 (DMT2) is a chronic disease that is the leading cause of end-stage renal disease due to diabetic nephropathy (DN). A role in DN has been described for Gremlin (GREM1) and for an indel (I/D) in the Angiotensin-converting-enzyme (*ACE*) gene. Chile has the highest prevalence of DMT2 in Latin America, but the genetic susceptibility to develop DMT2 or DN remains undetermined. The aim of this work is to explore in a cohort of Chilean subjects, the association of polymorphisms in genes related to *GREM1* and *ACE* with DMT2 or DN.

Methods: A retrospective case-control study was performed in 140 control subjects and DMT2 patients without DN (n=80) or with DN (n=101), categorized as those with early DN (1-7 yrs after DMT2 diagnosis) and late DN (8-15 yrs after DMT2 diagnosis). The genotype in the following polymorphisms was determined: rs1129456 (*GREM1*), rs7903146 (*TCF7L2*), rs34231037 (*VEGFR2*), rs4819554 (*IL-17RA*), indel (18 pb) in the *VEGF* gene and the indel (~300pb) in the *ACE* gene. Allelic and genotypic frequencies were analyzed to determine Odds ratio (OR).

Results: The analysis showed that the T allele (*TCF7L2*) was associated with DMT2 (OR=1.53, IC 95%=1.08-2.18, p=0.009). Additionally, a significant association was identified between the D allele (*ACE*) and the development of DN (OR=1.62, IC 95%=1.06-2.47, p=0.01), as well as with an early development of DN (OR=2.22, IC 95%= 1.10- 4.46, p=0.01).

Conclusions: Our results demonstrate that particular variants in *TCF7L2* (T allele) and *ACE* (D allele) are highly prevalent in the study cohort (30-50%) and present a potential clinical value as risk alleles for DMT2 and DN of early development. TCF7L2 is a transcription factor controlling the GREM1 expression. Although the SNP in *GREM1* was not associated with DMT2/ DN, further studies are required to determine if the *TCF7L2* genotype is associated with GREM1 expression in the diabetic kidney. A larger study with multi-center individuals' recruitment is required to validate *TCF7L2* and *ACE* as genetic markers of susceptibility in the Chilean population, in order to consider them as input to design more effective strategies to prevent DMT2 and DN. *Grant FONDECYT Regular 116-0465*

Funding: Government Support - Non-U.S.

FR-PO433

Genome-Wide DNA Methylation Analysis for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is a serious complication of diabetes, characterised by progressive development of proteinuria and loss of renal function. Increasing evidence suggests that epigenetic alterations, including DNA methylation, are involved in the development and progression of DKD. This investigation compared methylation profiles from individuals with type 1 diabetes (T1D) and DKD to individuals with T1D and no evidence of renal failure, to identify potential methylation-based biomarkers of DKD.

Methods: Using the Zymo EZ DNA methylation kit to bisulphite treat the DNA and the Infinium HD Methylation Assay, MethylationEPIC BeadChips from Illumina, the methylation status of >850,000 CpG sites, gene bodies, promoters and CpG islands have been determined for 106 individuals with T1D. Of these, 66 individuals had DKD and 40 controls had no evidence of renal disease. Cases and controls for this analysis were matched carefully for ethnicity, sex, age (≤1 year), and duration of diabetes. We also considered 192 individuals with Illumina's HumanMethylation27K array data and 250 individuals with HumanMethylation450K array data for DKD. DNA obtained from each individual was treated consistently, with standard quality control applied.

Results: Methylation data was analysed using Genome Studio and Partek Genomics Suite v7.0. From the EPIC array, 891 CpG sites were identified as having significantly different levels of methylation in cases compared with controls, 9 of which had a significance level of p≤9.75x10^{-08}. Among the genes identified, several including *BCL2, CUX1, FKBP5, FBXO5, PRKAG2* and *PSD3* have been linked with T1D. High concordance (R^2=0.994) between duplicate samples (n=7) was observed. Across data from all arrays, top-ranked genes with differential methylation profiles included *CUX1, FKBP5* and *PRKAG2*.

Conclusions: We have previously reported *CUX1, FKBP5,* and *PRKAG2* genes associated with CKD, supported by changes in gene expression using RNA-Seq (Smyth *et al.,* Epigenetics, 2014). This project supports meta-analysis of independent cohorts across arrays and demonstrates blood-derived methylation signatures may serve as minimally invasive biomarkers of DKD.

FR-PO434

Gene Expression Profiles of Hyperfiltration in Early Diabetic Kidney Disease

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Background: Hyperfiltration (HF) is a state of high glomerular filtration rate (GFR) seen in early diabetic kidney disease. Prolonged HF damages glomeruli, eventually leading to a vicious cycle of fibrosis and an increased filtration load for remaining glomeruli. Previous definitions of HF based on GFR cut-points have not convincingly captured microstructural and gene expression signatures in individuals. We used novel methods of capturing individual HF to elicit morphometric and gene expression profiles from kidney biopsies.

Methods: 111 Pima Indians with type 2 diabetes had a research kidney biopsy between 2002-2007 and 9-29 iothalamate GFR and albumin-creatinine ratio (ACR) measurements between 1989 and 2017. Those with mean GFR <60ml/min/1.73m^2 or ACR >300mg/g around the time of biopsy were excluded. Subjects who had their highest ever recorded GFR measurement within two years of biopsy were categorized as having HF. Eigengene-based weighted gene co-expression network analysis modules were constructed from glomerular transcriptomes. Pathway analyses and downstream targets were identified.

Results: The interquartile range of GFR among HF subjects was 138.1-203.5. One module uniquely associated with HF. Individual genes of interest included KDR, ICAM2 and PECAM1. Main pathways included Hepatic Fibrosis and the Th2 Pathway. Downstream targets included angiogenesis and endothelial cell proliferation.

Conclusions: A new method of capturing individual HF in early diabetic kidney disease correlated with clinical and morphological data and yielded novel findings in gene expression analyses. These pathways may be potential targets for further research on diagnosis and treatment of HF.

Funding: NIDDK Support, Government Support - Non-U.S.

Summary statistics at the time of biopsy

	GFR peak >2 years prior to biopsy	GFR peak within 2 years of biopsy	GFR peak >2 years after biopsy	p-value (*=quadratic trend)
Number of subjects	27	32	27	
Age, years (standard deviation (SD))	47.8 (10.0)	44.8 (10.9)	45.0 (8.5)	0.30
Sex, % male	30%	16%	30%	0.15*
BMI, kg/m^2 (SD)	35.0 (7.1)	37.7 (9.4)	35.9 (8.0)	0.23*
Diabetes duration, years (SD)	17.3 (7.3)	15.2 (5.1)	12.8 (3.7)	0.004
GFR, ml/min (SD)	134.2 (40.7)	171.4 (43.1)	156.5 (38.6)	0.006*
ACR, mg/g (SD)	40.2 (44.7)	65.0 (62.4)	39.2 (48.5)	0.04*
Hemoglobin A1C, % (SD)	9.3 (1.7)	9.8 (1.8)	8.7 (1.9)	0.04*
Blood pressure, mm Hg (SD)	121.9/77.2 (11.0/5.6)	121.9/76.4 (10.2/5.3)	118.5/76.4 (9.1/6.2)	0.23/0.57
Glomerular volume, x10^6 µm^3 (SD)	2.21 (0.66)	2.63 (0.70)	2.18 (0.74)	0.01*
Podocyte numerical density, PCx10^3/glom (SD)	1.48 (0.68)	1.16 (0.68)	1.57 (0.83)	0.04*

FR-PO435

Genes Related to the Different Stages of Diabetic Kidney Disease: A Clariom™ D Assay in Patients with Biopsy Proven Diabetic Nephropathy

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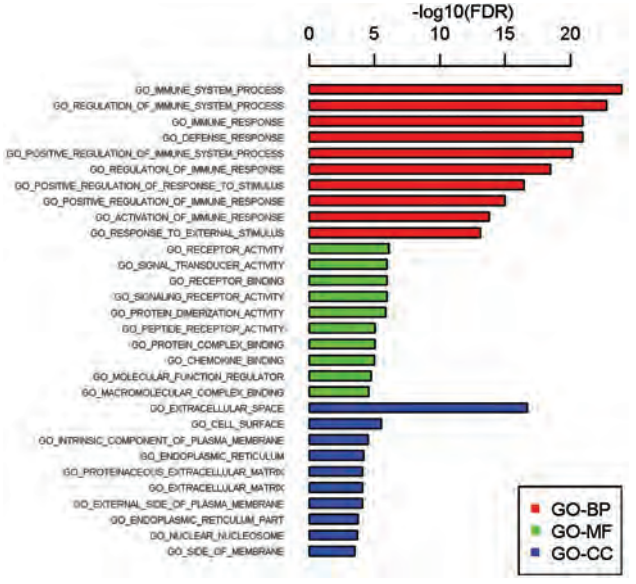
Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease. A great number of metabolites, cytokines, proteins and transcription factors play a role in the accumulation of extracellular matrix and mesangial proliferation in the glomerulus. The integrative analysis of the proteomic and transcriptomic features of bioptic samples among different categories of patients affected by diabetic nephropathy, especially based on the accurate classification of the histopathological changes in the glomerular and tubulointerstitial compartment, could lead to the identification of new early biomarkers.

Methods: Microarray data obtained from glomeruli isolated from normal kidneys (n = 2) and kidneys from patients with DN (n = 4) were used for the Clariom™ D Assay.

Results: Two patients were diagnosed as type IIb stage DN with moderate proteinuria, while other two patients were diagnosed as type IV stage DN with massive proteinuria. In the present study, differentially expressed genes (DEGs) between healthy controls and patients with different stages of DN were also analyzed. To investigate the function changes in the course of DN progression, GO enrichment and KEGG pathway analyses were performed for both up- and down-regulated DEGs. GO provides 3 structured networks of de ned terms to describe gene product attributes: cellular compartment (CC), biological process (BP) and molecular function (MF). Results show that signaling pathways are altered by the up-regulated DEGs (Fig1,2).

Conclusions: In conclusion, our transcriptome based analysis suggests that the association between gene expression and renal pathology is mediated by structural changes and that there may be differences in pathways that lead to protenuria.



GO term

FR-PO436

Integrating Plasma Proteomic with Tissue Transcriptomic Profiles in Early Diabetic Kidney Disease Identifies IFNG Activation as a Predictor of Disease Progression

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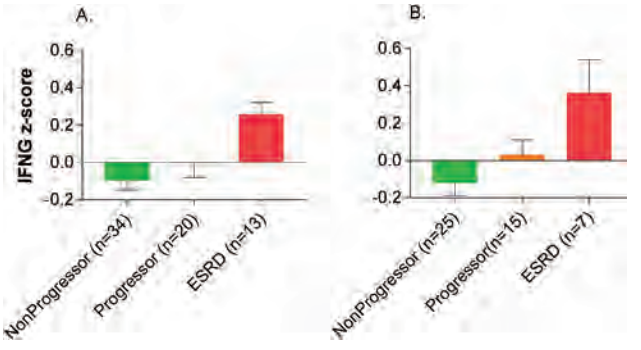
Background: Circulating proteins may act through their downstream signaling pathways in the kidneys to promote intrarenal impairment and progression to end-stage renal disease (ESRD) in persons with diabetic kidney disease (DKD).

Methods: Targeted plasma proteomics (SOMAscan) were obtained in (n=162) Pima Indians with type 2 diabetes and early DKD and compared to subsequent genome-wide transcriptomics of protocol kidney biopsies performed on average 2.3 years (n=74) and 11.2 years (n=57) later.

Results: 317 out of 550 plasma proteins were differentially expressed between 56 patients who progressed to ESRD and those who did not after a median follow up of 11 years (FDR<0.2). 114 genes in the glomeruli (Glom) (13 ESRD vs 54 of non-ESRD) and 182 in the tubulointerstitium (TI) (7 ESRD vs 40 non-ESRD) were differentially expressed (FDR<0.2). Interferon gamma (IFNG) was identified as the top ESRD-associated plasma cytokines and the top up-stream regulator of intrarenal ESRD-associated genes in both Glom and TI. An activation score (Z score) was generated for the IFNG signaling pathway based on the expression of IFNG downstream genes (Glom and TI). IFNG Z-scores in Glom and TI were inversely associated with measured GFR decline (r=-0.55 and -0.59, p<0.0001 respectively). Patients who progressed to ESRD had a significantly higher Z-score than those who did not (**Figure**). Circulating IFNG was associated with intrarenal IFNG pathway score in biopsies obtained 11.2 years later (r= 0.47 and 0.40, p<0.002, glom and TI respectively).

Conclusions: Increased circulating IFNG early in DKD precedes intrarenal IFNG pathway activation and subsequent clinical outcome a decade later, providing a strong rationale for targeting systemic inflammatory pathways in DKD progression.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim



Intrarenal IFNG pathway Z scores in Glom (A) and TI (B) are significantly higher in ESRD/ progressors compared to non progressors (median FU 11 ± 2.5 Years). Progressors were defined as measured GFR slope more than -3 mL/min

FR-PO437

Circulating MicroRNA Profiles and Risk of ESRD in Patients with Diabetes and CKD: An RNA-Sequencing Based Study

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Background: MicroRNAs (miRNAs) are endogenous, short non-coding RNA molecules that are involved in gene regulation and play important roles in the pathogenesis of various diseases including diabetic kidney disease (DKD). However, miRNA signatures associated with DKD has not been fully established.

Methods: Using High Throughput Genomics (HTG) edge sequence platform, the expression of 2,083 mature miRNAs were examined in baseline plasma specimens from 239 patients with type 1 diabetes (T1D) and CKD stages 3 & 4 to find miRNAs associated with progression to ESRD during 7-15 years of follow-up. The findings in T1D were validated using the same technology in the replication panel of 136 patients with type 2 diabetes (T2D) and the same CKD stages.

Results: Cox proportional hazard model analysis revealed that 15 miRNAs were strongly associated with renal function decline and time to ESRD in both T1D and T2D. Using Spearman's rank test, 3 candidate miRNAs were significantly associated with declining renal function after adjusting for age, sex, type of diabetes, duration of diabetes, HbA1c, eGFR and ACR (p<0.05). In pathway analysis, 6 KEGG pathways (Endocytosis, FoxO signaling, mTOR signaling, Neurotrophin signaling, Rap1 signaling and Ras signaling) were significantly enriched by genes targeted by all 3 miRNAs (P<0.01).

Conclusions: We investigated plasma miRNA profiles associated with ESRD in patients with diabetes using RNA-sequencing based platform. Our results suggest that these

miRNAs are associated with declining renal function in patients with diabetes and have potential to serve as circulating biomarkers, and possibly therapeutic targets for DKD.

Funding: NIDDK Support, Commercial Support - Novo Nordisk

FR-PO438

Urinary Exosomal CCL21 mRNA as Biomarker of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the common complications of diabetes characterized by variable histological changes and clinical course. Currently, renal biopsy and pathological assessment remains the standard approach in the diagnosis and prognosis of DN. Given the invasive procedures and unpredictable post-operative complications of biopsy, novel and noninvasive biomarkers are needed. We aimed to find noninvasive biomarkers reflecting the histological injury and progression of renal function in DN.

Methods: A screening cohort of 4 biopsy-proven DN patients and 4 diabetic patients with normal renal function(DM) and a validation cohort of patients with 28 biopsy-proven DN patients and 24 DM patients were enrolled in our study. We isolated exosomes from urine samples at the time of renal biopsy. Urinary exosomes was identified by Western blotting (using Alix, CD63 and CD9 as exosomal markers). Kidney histological damage of DN patients was scored according to Tervaet standard. Urinary exosome profile of the packing inflammatory response related genes were assessed and its correlation with clinic and histological injury parameters were analyzed.

Results: Known exosome markers including Alix, CD63 and CD9 were identified by Western blotting. Profile of the packing inflammatory related mRNA revealed CCL-21 was remarkably upregulated in urinary exosomes of DN patients compared with DM patients($p<0.05$). Validation study confirmed the findings and found the correlation of CCL-21 with levels of proteinuria ($r=0.590$, $p<0.05$) and eGFR ($r=0.591$, $p<0.05$). Furthermore, CCL21 was positively correlated with tubulointerstitial damage. DN patients with severe tubulointerstitial damge showed the highest expression of CCL-21 compared with DN patients with mild and moderate damage. Impressively, CCL21 showed good performance in discriminating patients with different levels of tubulointersitial inflammation.

Conclusions: In summary, urinary exosomal CCL-21 mRNA may be promising noninvasive biomarkers of diabetic nephropathy reflecting renal histological injury and renal function deterioration.

FR-PO439

Urine Synaptopodin Predicts Progression of Diabetic Nephropathy in Patients with Type 2 Diabetes

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Background: Synaptopodin, a protein that plays an important role in the maintenance of the structure of podocyte, is known as a marker that reflects the damage of glomerulus. Although some studies reported that urine synaptopodin was elevated in diverse kidney diseases, the clinical role of urine synaptopodin in the diabetic patients remains unclear. We hypothesized that urine levels of synaptopodin would be associated with severity and prognosis of diabetic nephropathy.

Methods: A total of 145 patients with type 2 diabetes and 25 healthy control subjects were enrolled. They were followed up with estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR) and urine protein-to-creatinine ratio. The participants with baseline eGFR less than 60 mL/min/1.73 m^2 were excluded. Urine levels of synaptopodin were assessed by enzyme-linked immunosorbent assays.

Results: The mean age of the study participants was 56.2 ± 10.5 years and their median follow-up was 36 (24–40) months. Urine synaptopodin levels, presented as urine synaptopodin-to-creatinine ratio, were significantly higher in patients with diabetes (256.0 [142.0–481.7] pg/mg) than healthy control (129.2 [96.5–289.1] pg/mg). Among diabetic patients, urine synaptopodin levels were increased according to albuminuria stages (normoalbuminuria, 234.3 [140.1–470.7] pg/mg; microalbuminuria, 258.3 [143.8–424.6] pg/mg; and macroalbuminuria, 341.8 [178.7–570.6] pg/mg). Urine synaptopodin in diabetic patients was not significantly correlated with baseline eGFR. However, urine synaptopodin was negatively correlated with changes of eGFR ($R = 0.209$, $p = 0.023$). Moreover, in the normoalbuminuric subgroup of diabetic patients, urine synaptopodin was significantly associated with changes of UACR ($R = 0.272$, $p = 0.045$). This finding was also valid after adjusting for age, sex, body mass index, glycated hemoglobin level, eGFR, and follow-up duration.

Conclusions: Our study presented that urine synaptopodin in patients with type 2 diabetes reflected the severity of diabetic nephropathy and predicted progression of the disease. These results suggest that urine synaptopodin would be a useful early biomarker for diabetic nephropathy.

FR-PO440

Urinary Excretion of Podocyte mRNA as a Risk Prediction Biomarker for Progression of Diabetic Nephropathy: 2-Year Follow-Up Study

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Background: Recent studies suggest that podocyte injury has already occurred at the early stage of diabetic nephropathy. Podocyte cell lineage-specific mRNA can be recovered from urine pellets. We previously reported that urinary excretion of podocyte mRNA could be an early diagnostic biomarker for diabetic nephropathy. Here, we examine whether it can be used as a risk prediction biomarker for progression of diabetic nephropathy.

Methods: For our previous study, outpatients at various stages of diabetes (n=83, normoalbuminuria group, n=31, microalbuminuria group, n=31, macroalbuminuria group) were enrolled from January to June 2015 and spot urine samples were collected. For the present study, we performed a prospective observational cohort study of these participants using data from a 2-year follow-up period (2015–2017). Renal outcome was defined as a decrease in the estimated glomerular filtration rate (eGFR) of >4% per year. Predictors used were baseline urinary excretion of podocyte mRNA (podocin/aquaporin 2 mRNA ratio), podocin mRNA/creatinine ratio (UPodCre), podocin/nephrin mRNA ratio, and albumin/creatinine ratio (UAlbCre). A logistic regression analysis was used to calculate the odds ratios (ORs) for eGFR decrease, with adjustments made for age, sex, duration of diabetes, body mass index, systolic blood pressure, eGFR, low density lipoprotein cholesterol, serum albumin, glycated hemoglobin, and usage of insulin or a renin-angiotensin system inhibitor.

Results: Of the 145 patients, 31 were excluded because of lack of follow-up or data. UPodCre and UAlbCre were significantly associated with decreased eGFR in univariable analysis [OR, 2.95 (95% CI, 1.18–7.34) and OR, 2.70 (95% CI, 1.67–4.36), respectively], and remained significantly associated with decreased eGFR in multivariable analysis adjusted for the above confounding factors [OR, 2.97 (95% CI, 1.07–8.27) and OR, 3.98 (95% CI, 1.94–8.15), respectively].

Conclusions: Urinary excretion of podocyte mRNA was independently associated with eGFR decline in addition to albuminuria in diabetic patients. Results from this and our previous study suggest that urinary excretion of podocyte mRNA could be used as early diagnostic and risk prediction biomarker for progression of diabetic nephropathy.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO441

Identification of New Protein Biomarkers for Diabetic Kidney Disease by Proximity Extension Assays

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Background: Diabetic kidney disease (DKD) is a complication of diabetes and the leading cause of kidney failure in developed countries. To treat DKD more effectively, it is essential to identify new drug targets and to judge the success of such developments using reliable markers. The olink proximity extension assay (PEA) allows measuring 92 proteins across 96 samples per panel simultaneously using only 1µl of plasma. To identify novel protein biomarkers for DKD the olink PEA was selected and evaluated in this study.

Methods: Plasma from DKD patients with different CKD stages (0,2,4) (n=62,mean age 70y) as well as healthy controls (n=9,mean age 62y) were used for protein profiling with the olink PEA. Plasma was obtained from informed and consenting donors. Here, two antibodies labeled with unique, partially complementary oligonucleotides bind pair-wise to the target protein. The formed double-stranded sequence is detected and quantified using RT-PCR. Relevant proteins were verified with ELISA for evaluation of the olink PEA.

Results: The CKD marker FGF23 showed higher expression in plasma of CKD4 patients (n=36,mean age 74y) than in CKD2 patients (n=20,mean age 69y) and CKD0 (n=6, mean age 61y) when measured with olink PEA. This was also seen in the FGF23 ELISA. Also markers as VCAM1 and PECAM1 had similar expression patterns in the olink PEA and ELISA measurements. Correlation analysis showed significant correlation between the 2 methods when FGF23 ($p<0.001$,$r=0.922$), VCAM1 ($p<0.001$,$r=0.84$) and PECAM1 ($p<0.001$,$r=0.851$) were compared. The olink PEA also identified other differentially expressed proteins in the observed groups. Even differences between CKD stages were detected. 48 proteins out of 192 proteins were significantly different among the groups (panel CV2 and 3). Stem cell factor (SCF) which contributes to renal fibrosis was significantly upregulated in plasma of CKD2 patients compared to CKD0 patients and even higher in CKD4 patients.

Conclusions: The olink PEA and ELISA showed similar patterns and correlated significantly for FGF23, VCAM1 and PECAM1 in plasma of DKD patients. Moreover, other proteins which were different between DKD patients with different CKD stages and control groups were identified. Therefore, the olink PEA might be a promising tool to identify novel biomarkers for possible new drug targets and treatment evaluation for DKD.

FR-PO442

High-Throughput Proteomic Search Reveals Novel Plasma Biomarkers of Time to ESRD in Type 1 Diabetes Patients with Persistent Proteinuria and CKD Stage 1-2

Jan Skupien,[1] Adam Smiles,[2] Andrzej S. Krolewski.[2] *[1]Jagiellonian University Medical College, Krakow, Poland; [2]Joslin Diabetes Center, Boston, MA.*

Background: The risk of end-stage renal disease (ESRD) reaches 30-50% in patients with type 1 diabetes and persistent proteinuria. An intensive research effort is needed to identify and evaluate interventions that improve prognosis in these patients. To better understand the disease process, identify novel drug targets and improve end-point definitions in clinical trials new biomarkers of renal function decline and ESRD risk are desperately needed.

Methods: We assayed baseline plasma specimens using an Olink proteomic platform (Uppsala, Sweden) in a group of 82 patients with type 1 diabetes and CKD stage 1-2 from Joslin Proteinuria cohort and replicated the findings in an additionally ascertained sample of

76 patients with similar baseline characteristics. Using an accelerated failure time survival regression model we sought association of 454 proteins with time to ESRD. Association was considered significant if false discovery rate-adjusted p-value <0.01 and a p-value <0.01 in the replication set.

Results: We identified 31 plasma proteins significantly associated with time to ESRD. The largest number of them represented tumor necrosis factor signaling pathway. All markers were associated with increased risk of ESRD, i.e. their higher concentration was associated with shorter time to ESRD. Most proteins were highly correlated and redundant as biomarkers. Three of them were independently associated with time to ESRD and are shown in the Table. Using these three proteins we estimated patients' time to ESRD. The median predicted time in patients with ESRD was 9.7 years (observed 8.2 years) and in those without ESRD the median predicted time was 15.8 years.

Conclusions: There are multiple novel biomarkers of fast progression to ESRD in patients with type 1 diabetes and proteinuria. These proteins should be further investigated for their biologic role and therapeutic potential. They may serve in the future for predicting time to ESRD in diabetic kidney disease.

Funding: NIDDK Support, Private Foundation Support

Multivariate predictive model of time to ESRD

Protein	Effect of doubling concentration on ESRD time	P-value
HAVCR1	-23.3%	<.001
WFDC2	-29.5%	0.001
PGLYRP1	-13.3%	0.049

FR-PO443

Pre-ESRD Determinants of Post-ESRD Mortality in Patients with Type 1 Diabetes (T1D)

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Background: We reported that in T1D patients the patterns of estimated glomerular filtration rate decline (eGFR slopes) preceding the onset of ESRD were linear but varied greatly among individuals. The slopes could be grouped to fast, moderate and slow (Skupien et al. *Diabetes Care*). In this study we investigated in the same cohort whether post-ESRD mortality was influenced by the pre-ESRD eGFR slopes. In addition we sought whether plasma concentrations of 568 proteins during pre-ESRD period were associated with post-ESRD mortality.

Methods: A cohort of 206 T1D patients who developed ESRD while attending the Joslin Clinic were matched against the United States Renal Data System and National Death Index registries to ascertain dates of starting dialysis, renal transplant and mortality. Plasma samples obtained from these patients when they had had CKD stage 2-4 were assayed on the SOMAscan proteomics platform. Relative concentrations of 568 proteins were measured. Cox proportional hazard model for time to mortality was used, and proteins with a p value of <0.005 were selected.

Results: There were 75 deaths while on dialysis during 441 person-years (py) of follow-up (17.0 deaths/100 py) and 40 deaths after transplant during 1204 person-years (3.3 deaths/100 py). Total mortality was 115 deaths during 1644 person-years (7.0 deaths/100 py) Patients with fast (< -10 ml/min/yr) and moderate (-5 -10 ml/min/yr) renal decline had a two times higher post-ESRD mortality than in those with slow (> -5 ml/min/yr) renal decline. This pattern was similar for mortality during time spent on dialysis and after receiving renal transplant (see Table). We identified 4 plasma proteins whose elevated level was associated with increasing risk of post-ESRD mortality: CCL3L1, CCL18, IL5RA, PRSS22 and 3 plasma proteins whose higher levels were associated with decreasing risk of post-ESRD mortality: VIP, IL11 and IFNL1.

Conclusions: Disease processes that determine post-ESRD mortality begin long before the onset of ESRD. The candidate proteins identified should be investigated further for their potential role as predictors and determinants of post-ESRD mortality.

Funding: NIDDK Support, Private Foundation Support

Mortality Rates (Deaths/100 Person-Years)

Pre-ESRD eGFR slope	Mortality during Dialysis	Mortality after Transplant	Total Mortality	p value compared to Slow
Fast Decline	18.3	4.6	8.7	0.0008
Moderate Decline	18.3	4.0	7.4	0.014
Slow Decline	13.3	0.6	3.9	

FR-PO444

DUPDN - Diagnostic Urinary Panel for Diabetic Nephropathy: A Model to Predict Progressive CKD

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Background: CKD in patients with diabetes is detected and monitored using eGFR and albuminuria. Both have limitations and a significant proportion of patients with type2 diabetes have CKD without albuminuria. We tested a panel of urinary biomarkers that reflect areas of injury and pathogenic mechanisms to develop a model to predict progressive CKD.

Methods: 400 patients with diabetes and CKD were recruited and 388 included in analysis. 50% of patients had ACR <3. A random urine sample was collected at baseline and analysed for a panel of biomarkers - ACR, inflammatory cytokines-IL1β, IL6, MCP1, Markers of proximal tubular injury/damage- NAG and RBP, NGAL, Fibronectin (Fn). Patients were followed for 5y. Logistic regression analysis was done to test the association of individual and combination of biomarkers with presence of CKD stage 3 or 4 aand progression to CKD st 3 or 4. ROC AUC results were obtained for each combination of biomarkers to measure their sensitivity and specificity to CKD stages and progression. A mixed model was used for the association of biomarkers with the trajectory of eGFR over 5y. Models with the same numbers of observations were compared using the AIC goodness-of-fit measure.

Results: Comparisons between CKD stages demonstrated significant differences in urinary RBP, NAG, MCP1, IL6. In multivariate analysis, at all levels of ACR, urinary RBP demonstrated better correlation with CKD stage 3 and 4 compared to ACR but this effect was not seen after adjusting for age, sex and race. Adjusted ACR predicted CKD stage 3 as well as any other combination of markers with AUC of 83%. For progression to stage 3 or 4 CKD, unadjusted and adjusted ACR was a poor predictor (With an AUC of 62-67%). Addition of RBP and MCP1 as covariates with adjustment for age, sex and race in patients with ACR of <3 improves the ROC AUC to 75%. Urinary Fn was raised in diabetic patients with early CKD compared to healthy controls. Using 1,243 observations of eGFR over 5y we arrived at 2 models with best AIC values: 1. where the eGFR gradient against time in yrs is associated with baseline ACR and RBP/Cre: 2. where the eGFR gradient against time in yrs is associated with baseline MCP1/Cre and RBP/Cre. This final model showed best AIC value.

Conclusions: Our study suggests that models that include RBP and MCP1 in addition to or instead of ACR improve prediction of future eGFR.

Funding: Private Foundation Support

FR-PO445

Plasma Lipids Are Associated with Diabetic Kidney Disease: A Study of Plasma Lipidomics in Type 1 Diabetes

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Background: The pathophysiology of diabetic kidney disease (DKD) is incompletely understood. The study aim was to perform lipidomics analyses to evaluate associations between plasma lipids and measures of DKD.

Methods: In total, the study comprised 668 patients with T1D with varying albuminuria status. Non-targeted lipidomics analyses were performed on plasma samples using ultra-high performance liquid chromatography quadrupole time-of-flight mass spectrometry. Cross-sectional associations between single lipid species and low eGFR or albuminuria were analysed. Longitudinal data on urinary albumin excretion (UAE) and estimated glomerular filtration rate (eGFR) were obtained from electronic records over a median of 5.5 years. eGFR slopes and hazard ratios for progression in albuminuria status (progression from normo- to micro/macroalbuminuria or from micro-to macroalbuminuria) were calculated. Adjustments included age, gender, HbA1c, systolic blood pressure, smoking, BMI, statin treatment, plasma triglycerides, total plasma cholesterol and baseline eGFR and/or UAE, where appropriate. Results were corrected for multiple testing.

Results: A total of 121 lipids from 4 different lipid classes (phosphatidylcholines (PCs), lysophosphatidylcholines (LPCs), triacylglycerols (TGs), and sphingomyelins (SMs)) were included in the analyses. In a crude model adjusted for baseline eGFR, PC(36:4) had the strongest association to eGFR decline ($p<0.01$) and 10 medium-and-short-chain TGs were weakly associated to eGFR decline ($p<0.10$). Among these lipids, the association between PC(36:4) and eGFR decline remained significant after adjusting for clinical variables (β=-0.08360; p=0.0004). Similar associations were seen in the cross-sectional analyses between lipids and eGFR. In cross-sectional analyses of macro- vs normoalbuminuria, PC, SMs and medium-chain-length TGs were decreased ($p<0.05$), however, no lipids were significantly associated with change in albuminuria status in longitudinal analyses.

Conclusions: Alterations in the plasma lipid levels were associated with decreased eGFR and macroalbuminuria in this T1D study cohort, indicating broad changes in the lipidome in individuals with DKD. Further, the PC(36:4) was discovered to have a significant association to future eGFR decline.

FR-PO446

Plasma Metabolomics Identifies Markers of Impaired Kidney Function: A Meta-Analysis of 1,984 Europeans with Type 2 Diabetes

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Background: There is a need for novel biomarkers and better understanding of the pathophysiology of diabetic kidney disease. The aim was to investigate the associations between plasma metabolites and measures of kidney function.

Methods: Blood metabolites (*n=235*) were measured by nuclear magnetic resonance spectroscopy (NMR) in 1,984 type 2 diabetes (T2D) cases among three independent Dutch studies (the Hoorn Diabetes Care System (DCS, *n=995*) cohort, the Maastricht Study

(MS, *n=848*) and the Cohort of Diabetes and Atherosclerosis Maastricht study (CODAM, *n=141*)) with mean ± SD age 59.7 ± 8.8. Linear regression based associations were tested between single plasma metabolites and estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) in each study. Covariate adjustments included age, sex, systolic blood pressure, body mass index, medication (lipid-lowering, glucose-lowering, anti-hypertensive), smoking, diabetes duration, HbA1c, and eGFR or UACR, where appropriate. A fixed effect meta-analysis of the 3 study sets was performed. A Bonferroni's correction of $p_{bonferroni} = 1.0 \times 10^{-4}$ was considered significant.

Results: After adjustment for multiple testing, 82 metabolites associated significantly with eGFR while two with UACR. Alteration of several lipoprotein subclasses of VLDL and HDL as well as amino acids (phenylalanine, isoleucine and glutamine) and glycoprotein acetyls were associated with lower eGFR. Higher UACR levels were significantly associated with glycoprotein acetyls and cholesterol esters in very small VLDL.

Conclusions: The current study identifies plasma metabolites associated with decreased eGFR and albuminuria among T2D cases of European origin. These findings implicate an involvement of lipid and amino acid metabolism in the pathogenesis of DKD.

Funding: Government Support - Non-U.S.

FR-PO447

A Biomarker of Type VI Collagen Formation Is Associated with Diabetic Kidney Disease and Is a Risk Factor for Mortality in Elderly Women

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Background: Diabetic kidney disease (DKD) is the leading cause of chronic dialysis and accounts for at large proportion of all cases of chronic kidney disease (CKD). Renal fibrosis is the hallmark of CKD and is caused by changes in the balance of extracellular matrix (ECM) remodeling. Type VI collagen is a crucial ECM molecule for the control of tissue organization. In this study, we investigated the association of PRO-C6 (collagen type VI formation) with DKD and with mortality in patients with DKD.

Methods: The study population included 5855 postmenopausal women from the Prospective Epidemiological Risk Factor Study (PERF) cohort. The women were examined at baseline (BL year, 2000) and serum PRO-C6 were measured. The dialysis, diagnosis and mortality information were extracted from Danish Health Registries at end of study (2015). DKD was defined as eGFR <60 ml/min/1.73m^2, dialysis, or a renal diagnose (ICD10). Healthy women were defined as women with no history of chronic diseases (ICD10 chapter II, IX, X, XI, XIII, XIV). Women with DKD were stratified into quintiles based on BL PRO-C6 levels and compared with an ANOVA test. Cox regression was used to explore the association with all-cause mortality with 15 years of follow-up.

Results: A total of 75 and 308 women were diagnosed with DKD and diabetes at BL, and 450 were healthy. Serum PRO-C6 levels were higher in women with DKD (mean=10.7 ng/ml (SD=3.7), p<0.0001) and diabetic (mean=8.7 ng/ml (SD=2.7), p=0.004) compared to the healthy group (mean= 8.0 ng/mL (SD=3.0)). Levels of PRO-C6 were higher in women with DKD compared to the diabetic group (p<0.0001). The women with DKD were older (age, 74.6) than the diabetic women (age, 71.3) (p<0.0001), but the effect of age did not affect the independent association of PRO-C6 with DKD. Finally, DKD women in the 5th quintile of PRO-C6 had an increased risk of all-cause mortality compared to women in the 3th quintile (HR=2.6 (95% CI=0.9-7.3), p=0.08). The borderline-significance was probably due to lack of power.

Conclusions: In this study, we demonstrated that PRO-C6, a biomarker of collagen type VI formation, was increased in serum of post-menopausal women with DKD compared to women with diabetes without kidney involvement and healthy women. In addition, PRO-C6 was associated with mortality in women with DKD.

FR-PO448

The Implications of Immunoglobulin G and Complement 3 in Differentiating Nondiabetic Renal Disease from Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus: A Single-Center Study in China

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Background: Heavy proteinuria caused by nondiabetic renal disease (NDRD) is common in type 2 diabetes mellitus (T2DM). The aim of this study was to investigate specific predictors for NDRD in addition to traditional indicators in T2DM.

Methods: A total of 341 patients with T2DM who underwent renal biopsy were retrospectively included. Eligible patients were divided into a nephrotic-range group (n=194) and a non-nephrotic-range group (n=147) based on proteinuria level. Risk factors for NDRD were evaluated using logistic regression, and the diagnostic implications of these variables were assessed by subgroup.

Results: Multivariate logistic regression indicated that reduced serum IgG (OR, 0.762; 95%CI, 0.628–0.924; *p*=0.006) was an independent predictor of NDRD in the nephrotic-range group. However, in the non-nephrotic-range group, increased C3 level was an independent risk factor for NDRD (OR, 1.313; 95%CI, 1.028–1.678; *p*=0.029). In the nephrotic-range group, the optimal cutoff value of IgG for predicting NDRD was 734.0 mg/dl, with 67.8% sensitivity and 74.8% specificity, and IgG ≤734.0 mg/dl was the best predictor of NDRD. In the non-nephrotic-range group, the optimal cutoff value of C3 for predicting NDRD was 122.0 mg/dl with low sensitivity (30.9%) but high specificity (97.8%).

Conclusions: At different levels of proteinuria, reduced IgG and increased C3 levels were independent indicators of NDRD in T2DM. Insights into these factors will help to advance the clinical management of NDRD.

FR-PO449

Cathepsin D: A Potential Biomarker for Diabetic Kidney Disease

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Background: Cathepsins are lysosomal proteases that play important roles in a wide range of physiological and pathological processes. Recent studies have suggested that dysregulation of cathepsin D (Cat D) can lead to development of fibrosis and induce apoptosis in the podocytes and tubular cells in acute kidney injury murine models. In the current study we analyzed if changes in Cat D are associated with the development and progression of diabetic kidney disease (DKD) in type I diabetic mouse models and in humans.

Methods: Cat D protein levels in urine were measured by liquid-chromatography mass spectroscopy in four diverse cohorts (CACTI, EDC, Finn-Diane, and Steno) with long-standing type I diabetes and normal kidney function (eGFR≥60ml/min/1.73m^2). Subjects were classified into slow decliners/controls with eGFR decline ≤1ml/min/1.73m^2/yr or rapid progressors/cases with eGFR decline of ≥3ml/min/1.73m^2/yr. Cat D activity in urine samples of patients with established kidney disease (eGFR<40ml/min/1.73m^2) and in type 1 DKD mouse model (Akita) was measured biochemically. Immunohistochemistry in mouse kidney tissues were performed with FFPE embedded kidney sections.

Results: Baseline mean eGFR and median ACR in controls (n=351) and cases (n=270) were 91.97 (sd 18.68) and 9.44 (IQR 30), and 98.37 (sd 25.44) and 33.49 (IQR 283.01), respectively. Cat D protein levels in urine were significantly elevated in cases as compared to controls [mean 1.18 au (1.07-1.3) in controls vs 1.56 au (1.37 to 1.57) in cases, p<001, FDR q=0.01). Immunohistochemical analysis identified predominant localization of Cat D to tubules in akita kidney sections and increased as compared to controls. Cat D activity was significantly elevated in urine (p<0.001) samples of of akita mice (n=6 each WT and akita, p<0.001) and in patients with established DKD (n=10 each control and DKD, p<0.0001). Cat D activity also correlated significantly (R^2: 0.855, p<0.0001) with albumin/creatinine in akita mouse urine.

Conclusions: The current data indicate that Cathepsin D may play vital role in the pathogenesis of diabetic kidney disease and its level as well as activity in urine can serve as biomarker of the diabetic nephropathy.

Funding: Private Foundation Support

FR-PO450

Plasma Endostatin and Kidney Outcomes in Patients with Type 2 Diabetes

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Background: Additional biomarkers are needed for prognostication of kidney function decline in patients with type 2 diabetes. There are limited data on the association of markers of endothelial dysfunction with longitudinal kidney function decline. We assessed the association of plasma endostatin, an inhibitor of angiogensesis, and kidney outcomes in two settings: a clinical trial and a contemporary clinical cohort.

Methods: We used banked plasma specimens from a nested matched case-control study (187 cases:187 controls) in the Action to Control Cardiovascular Disease (ACCORD) trial and a diverse cohort of patients with type 2 patients from the EMR and USRDS-linked Mount Sinai Bio*Me* Biobank (n=871). We measured endostatin in plasma specimens banked from the time of enrollment in ACCORD and Bio*Me* and examined its association with a composite kidney outcome of sustained 40% decline in eGFR or ESRD, as well as the clinical utility.

Results: Baseline eGFR was 90 ml/min/1.73 m^2 in ACCORD and 66 ml/min/1.73 m^2 in Bio*Me*. Baseline plasma endostatin levels were higher for participants that achieved the composite kidney endpoint (median 42 ng/ml in 187 ACCORD cases and 45 ng/ml in 121 participants reaching the endpoint in Bio*Me*) vs. those without the CKD endpoint in both cohorts (median 36 and 38 ng/ml, respectively). Each $\log_2$ increment in plasma endostatin was independently associated with the kidney outcome in both cohorts (adjusted OR 2.5; 95% CI 1.5-4.3 in ACCORD and adjusted HR 2.6; 95% CI 1.8-3.8). Participants in the highest quartile (>48 ng/ml in both cohorts) vs. lowest quartile of plasma endostatin (< 32 ng/ml in ACCORD and < 31 ng/ml in Bio*Me*) had approximately 4-fold higher risk for the kidney outcome (adjusted OR 3.6; 95% CI 1.8-7.3 in ACCORD and adjusted HR 4.4; 95% CI 2.3-8.5 in Bio*Me*). In Bio*Me*, at a predicted probability threshold of 30% using clinical variables (age, sex, BMI, history of CVD,CHF, baseline eGFR, baseline mean arterial pressure, and ACEi/ARB usage) plus endostatin, the NPV was 0.90 (95% CI 0.89-0.91) and the PPV was 0.45 (95% CI 0.37-0.54) for the outcome of composite kidney endpoint.

Conclusions: Higher baseline plasma endostatin associated with kidney outcomes during follow-up in patients with type 2 diabetes from two diverse cohorts.

Funding: NIDDK Support

FR-PO451

Serum Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Associates with Decline in Estimated Glomerular Filtration Rate (eGFR) Slope in a Phase 2 Study of Selonsertib in Diabetic Kidney Disease (DKD)

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Background: Circulating sTNFR1 is a promising biomarker of DKD severity and risk of progression. We investigated the disease associations and predictive effect of sTNFR1 in a Phase 2 study of selonsertib (SEL), a small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1), in DKD.

Methods: In this study, 333 patients with moderate-to-advanced DKD (UACR 600 mg/g for stage 3a, UACR 300 mg/g for stage 3b, UACR 150 mg/g for stage 4) were randomized 1:1:1:1 to receive SEL (2, 6, or 18 mg) or matching placebo (PBO) orally once daily for 48 weeks (W48). The analysis population (full analysis set) excluded 2 sites for technical deviations and patients with baseline eGFR 20 mL/min/1.73m^2. Serum sTNFR1 was measured at baseline (BL) and W48 by ELISA. Spearman correlation was used to assess association between markers, and a random slope model for differences in chronic eGFR slope (W4-W48) between treatments.

Results: Serum sTNFR1 was inversely correlated with eGFR at BL (N=261; r=-0.74; p<0.001) and at W48 (N=215; r=-0.75; p<0.001), in addition to change of sTNFR1 and change of eGFR at W48 (N=215; r=-0.35; p=0.0016). There was no significant relation between sTNFR1 and UACR at BL (N=261; r=0.12). We found a trend for a relatively lower increase in sTNFR1 from BL to W48 in the 18mg SEL group (median=0.12 ng/mL, Q1-Q3: -0.43 to 0.53 ng/mL; N=49) compared to PBO (median=0.31 ng/mL, Q1-Q3: -0.17 to 0.66 ng/mL; N=49). Applying a BL 4.3 ng/mL sTNFR1 cutpoint retrospectively (identified by Yamanounchi M, *et al. Kidney Int* 2017), 51% of our overall population were potentially at high risk for progression to end stage renal disease. The subgroup >4.3 ng/mL sTNFR1 had an apparent therapeutic benefit from SEL 18 mg compared to PBO when comparing eGFR chronic slope (W4 to 48) difference (p=0.029), however this was no different from the benefit shown overall (p=0.036).

Conclusions: Serum sTNFR1 was directly correlated with eGFR at BL and change at W48 in patients with moderate-to-advanced DKD. The subgroup with BL sTNFR1>4.3 ng/mL had similar treatment benefit to SEL compared to the overall trial population

Funding: Commercial Support - Gilead Sciences

FR-PO452

Serum Soluble CD163 Associates with Estimated GFR and History of Ischemic Heart Disease in Adults with Diabetes

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Background: CD163 is a scavenger receptor for haptoglobin-haemoglobin complexes that is expressed by monocytes/macrophages and undergoes ectodomain shedding into blood as soluble CD163(sCD163) in an inflammatory milieu. Activation of monocytes/macrophages is implicated not only in the pathophysiology of diabetes but also in the development of glomerular injury in diabetic kidney disease. The aim of this study was to determine the relationships between serum sCD163 and clinical/biochemical parameters in a cohort of diabetic patients with a broad range of renal functional parameters.

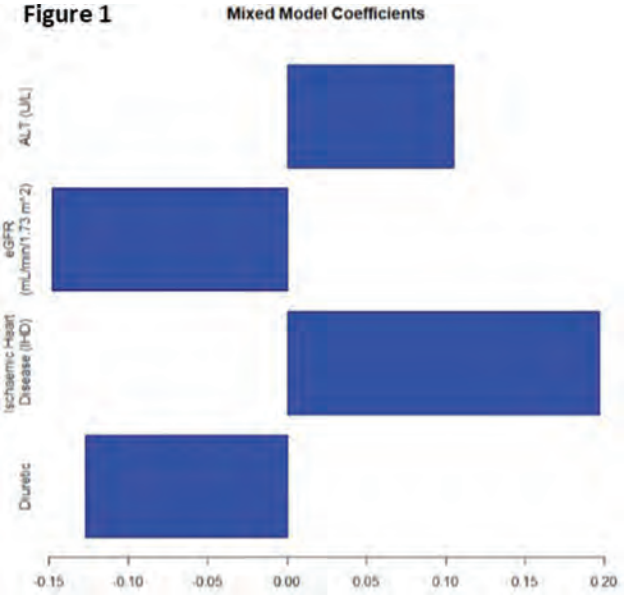
Methods: A total of 201 adults with diabetes (eGFR[CKD-EPI] range 10-143mL/min/1.73m^2) were recruited to a prospective cohort study. Subjects had serum collected at 1-4 timepoints(stored at -80^{o}C). Clinical, anthropometric and biochemical data were recorded at each timepoint. Serum sCD163 concentration was quantified using R&D ELISA(DY1607). To analyse the longitudinal relationships between relevant clinical/laboratory parameters and sCD163, a linear mixed model was fitted in R.

Results: Of 23 parameters included in the model, there were significant associations between serum sCD163 and eGFR, ALT, diuretic use and history of ischaemic heart disease(IHD). The highest value coefficients of association with serum sCD163 were for eGFR(negative) and IHD(positive) (Fig 1). Parameters for which no significant association was observed included BMI, HbA1c, urine ACR and lipids.

Conclusions: In adults with diabetes, serum sCD163 associated most closely with eGFR and IHD. Thus, variation in serum sCD163 among adult diabetic patients may reflect, in part, the role of monocyte/macrophage activation in renal and cardiovascular complications of diabetes.

Funding: Government Support - Non-U.S.

Figure 1 Mixed Model Coefficients



FR-PO453

Soluble Urokinase Plasminogen Activator Receptor Predicts Kidney Function Decline and Mortality in Patients with Type 1 Diabetes

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Background: Soluble urokinase plasminogen activator receptor (suPAR) is an important inflammatory biomarker. The predictive qualities of suPAR in relation to complications in patients with type 1 diabetes (T1D) are unknown. We investigated the prognostic ability of suPAR for the development of decline in renal function, end stage renal disease (ESRD), progression in albuminuric status and mortality in T1D.

Methods: 667 patients with T1D and various degrees of diabetic kidney disease were included in a prospective study. suPAR was measured with commercial ELISA kits. Patients were traced through the National Death Register, the National Health Register and electronic laboratory records. Endpoints were: eGFR-decline ≥30%, development of ESRD, progression to higher albuminuric status and mortality. Follow-up ranged from 5.2 to 6.2 years. Results were adjusted for sex, age, LDL cholesterol, HbA1c, systolic blood pressure, BMI, smoking status, urinary albumin excretion rate, eGFR, prescribed renin-angiotensin-aldosterone system inhibitors, and CRP. Hazard ratio (HR) is shown per doubling of suPAR and presented with 95% confidence interval (CI). Relative integrated discrimination (rIDI) was calculated to assess predictive contribution of suPAR to known risk factors.

Results: Of 667 participants, 368 (55%) were male; mean±SD age was 55±13 years and eGFR 88±25 ml/min/1.73m2. Median (interquartile range) of suPAR was 3.4 (2.7-4.5) ng/ml. There were 93 cases of eGFR-decline ≥30%, 26 cases of ESRD, 36 cases of progression in albuminuria and 58 deaths. Adjusted HR (95% CI) for the respective endpoints were 2.96 (1.70-5.16, p<0.001), 2.99 (0.75-11.9; p=0.12), 1.41 (0.60-3.35; p=0.43) and 4.42 (2.05-8.62, p<0.001). rIDI analysis showed contribution of 18.6% (p=0.009) for eGFR-decline, 5.5% (p=0.29) for ESRD, 1.1% (p=0.68) for progression in albuminuria and 23.8% (p<0.001) for mortality.

Conclusions: Higher suPAR level is independently associated with an increased risk of eGFR-decline and mortality in patients with T1D. In addition, it is a sizeable contributor in the risk stratification of the same based on rIDI. Our results suggest that suPAR may have an important role in identifying T1D patients at early risk of kidney function decline and death.

FR-PO454

Uric Acid Is an Independent Risk Factor for Decline in Kidney Function, Cardiovascular Event, and Mortality in Patients with Type 1 Diabetes

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Background: Previous studies have provided inconclusive results to the role of uric acid (UA) for risk prediction. Here we aimed to improve power and precision of the predictive value of UA for risk of decline in kidney function, cardiovascular event (CVE) and mortality in patients with type 1 diabetes (T1D).

Methods: UA was measured in 670 patients with T1D and various degrees of albuminuria, ranging from normo- (<30 mg/24 h) to macroalbuminuria (≥300 mg/24 h). Patients were traced through national registers to gather data on CVE and mortality. Endpoints: mortality, CVE and eGFR-decline of ≥30%. Median follow-up ranged from 5.1 to 6.2 years. Slope estimates of eGFR and urinary albumin excretion rate (UAER) were

calculated for a median of 5.5 years. We applied Cox regressions and linear regression models. Adjustment included sex, age, body mass index, HDL cholesterol, smoking, HbA_{1c}, mean arterial pressure, UAER, treatment with RAAS blockers and eGFR. Hazard ratio (HR) were calculated per doubling of UA and presented with 95% confidence interval (CI). Relative integrated discrimination (rIDI) was calculated to assess predictive contribution of UA to known risk factors.

Results: Of the 670 patients, 372 (55%) were male, mean ± SD age was 55±13 years and eGFR 82±26 ml/min/1.73m^2. Median (IQR) uric acid was 5.04 (3.87-6.22) mg/dl. Higher UA was associated with higher risk of decline in eGFR of ≥30% (n=89; HR: 3.14 (1.69-5.82), p<0.001), CVE (n=94; HR: 2.43 (1.31-4.52), p=0.005) and mortality (n=58; HR: 2.81 (1.23-6.43), p=0.014) in adjusted analyses. Adding UA to the adjusted model including conventional risk factors improved the rIDI by 12.8% for decline in eGFR of ≥30% (p<0.001), 8.7% for CVE (p=0.008) and 10.8% (p=0.040) for mortality. Higher UA was also associated with steeper decline in eGFR (p<0.0014) and steeper increase in UACR (p<0.0016) in adjusted analysis.

Conclusions: In T1D, higher UA is associated with higher risk of decline in kidney function, CVE and mortality, independently of other risk factors. Our results suggest that UA have a promising role in risk stratification among T1D.

FR-PO455

Diagnostic Efficacy of sPLA2R-Ab for Membranous Nephropathy in Diabetes Kidney Disease

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Background: The pathological types of diabetes kidney disease (DKD) are various, among which, membranous nephropathy(MN) accounts for a large proportion of non-diabetic renal diseases (NDRD). Serum anti-phospholipidase A2 receptor antibody(sPLA2R-Ab) is used for the diagnosis of MN, the diagnostic efficacy of sPLA2R-Ab for MN in DKD need to be further verified.

Methods: Screened on patients with type 2 diabetes mellitus who underwent a renal biopsy and had a valid sPLA2R-Ab test results, hospitalized in the general hospital of the people's liberation army of China between May 1st, 2016 and January 30th, 2018. Eligible patients were divided into two groups according to the pathological results: MN group and non-MN group. Patients'clinical characteristics and laboratory datas were collected.

Results: The study included 252 patients:59 (23.4%) in the MN group and 193 (76.6%) in the non-MN group. The baseline were compared between the two groups: age, history of diabetes, creatinine, GFR and blood pressure were statistically significant. MN group was older, lower blood pressure, shorter history of diabetes and better renal function than non-MN group. The positive value of SPLA2R-Ab was defined respectively as≥20, > 12, > 2: sPLA2R-Ab achieved a good diagnostic efficiency with sensitivity of 59.3%, 66.1% and 83.1%, specificity of 100%, 98.96% and 93.26%, positive predictive values of 100%, 95.12% and 79.0%, negative predictive values of 88.9%, 90.52% and 94.74%, and accuracy of 90%, 91.27% and 90.87% for MN in DKD respectively.

Conclusions: SPLA2R-Ab has a good diagnostic accuracy for MN in DKD, and the positive threshold may be reduced to 12, which can increase the accuracy of diagnosis.

Table1 The diagnostic efficacy of sPLA2R-Ab for MN in DKD

positive threshold	sPLA2R-Ab	renal pathological	renal pathological	Total
		MN	non-MN	
≥20	positive	35	0	35
≥20	negative	24	193	217
≥20	Total	59	193	252
>12	positive	39	2	41
>12	negative	20	191	211
>12	Total	59	193	252
>2	positive	49	13	62
>2	negative	10	180	190
>2	Total	59	193	252

FR-PO456

Urinary Biomarkers of Tubular Injury Predict Renal Progression and ESRD in Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Background: Diabetic kidney disease (DKD) typically evolves over many years. The diagnosis, evaluation and treatment are based mainly on biomarkers that assess kidney function. New potential tubular biomarkers in DKD could improve risk stratification and prediction.

Methods: A prospective cohort study, a total of 257 type 2 diabetic patients were included. The baseline values of urine albumin creatinine ratio (UACR), urine Cystatin-C to creatinine ratio (UCYS), urine angiotensinogen to creatinine ratio (UANG), urine NGAL to creatinine ratio (UNGAL) and urine KIM-1 to creatinine ratio (UKIM) were measured. The composite outcome was a rapid glomerular filtration rate (GFR) decline or incident of ESRD at 3 year follow-up.

Results: The median follow-up period was 40.8 monthsand the composite outcome were noted in 26.1%. Urine tubular biomarkers of UCYS, UANG, UNGAL and UKIM were significantly higher among patients with rapid GFR decline or new onset of ESRD. Using univariate followed by multivariate COX proportional hazard regression analysis, the number of patients reached the composite renal endpoint was higher among those in the highest quartiles of UCYS (HR 3.86, 95% CI, 1.95-7.66), UANG (HR 3.93, 95% CI, 1.95-7.88) UKIM (HR 3.41, 95% CI, 1.66-7.01) and UNGAL (HR 3.25, 95% CI, 1.58-6.71) than in those in the lowest quartiles. In addition, the highest quartile of UCYS, UANG, UKIM and UNGAL were associated with a 2.53 to 2.96-fold increased risk of rapid GFR decline or ESRD compared with the lowest quartile in adjusted models. All biomarkers predicted composite outcome with ROC for UACR = 0.731; 95% CI 0.65-0.81, UCYS = 0.64; 95% CI 0.56-0.72, UANG = 0.635; 95% CI 0.55-0.72, UKIM = 0.611; 95% CI 0.53-0.69 and UNGAL = 0.598; 95% CI 0.52-0.68. Highest ROC for integrated with UACR, UANG and UNGAL = 0.751; 95% CI 0.68-0.82.

Conclusions: The study supported that type 2 diabetic patients with high levels of urine tubular biomarkers (Cystatin-C, angiotensinogen, KIM-1 and NGAL) had more incidence of ESRD and rapid GFR decline. These tubular biomarkers may be independent predictors of the renal progression in DKD.

Funding: Government Support - Non-U.S.

FR-PO457

Clinical Value of Urinary C5b-9 Complement Complex in Overt Diabetic Nephropathy

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Background: Experimental studies support a role of complement activation through the lectin pathway in diabetic nephropathy (DN). We evaluated urinary levels of C5b-9 membrane attack complex (MAC) in patients with overt DN, tested associations with eGFR decline, proteinuria and inflammatory biomarkers.

Methods: This is a prospective observational cohort study of patients with overt DN followed for 2.1 years (1.6-2.8) from hospitals affiliated with the University of Montreal. We obtained repeated measurements of proteinuria, urinary MAC and inflammatory biomarkers expressed as urinary creatinine ratios. We also compare levels to patients with MGN, FSGS, AAV and IgAN.

Results: The diabetic cohort (n=83) was 80% male. The initial eGFR was 25 ± 9 mL/min/1.73m^2 with an eGFR decline of 2.9 ± 3.0 mL/min/1.73m^2/year. The median MAC-to-creatinine ratio was 1.89 (0.48-10.37) mg/mmol. The highest quartile was associated with a rate of decline in renal function of -5.1 ±mL/min/1.73m^2/year compared to -2.2 ± 2.6 (p < 0.001) (Figure 1). Urinary C5b-9 was also associated with inflammatory biomarkers and with the proteinuria (Spearman's rho 0.80, p<0.001). Furthermore, at comparable levels of proteinuria, the patients with DN in this study had similar or higher levels of urinary MAC than patients with other immunologic glomerulonephritis (n=62).

Conclusions: Complement MAC is present in the urine of patients with overt DN and higher levels correlate with a more rapid rate of renal function decline. At similar proteinurias, patients with DN had similar or higher levels compared to those with MGN, FSGS, AAV and IgAN. These findings support that urinary C5b-9 excretion in DN is not solely caused by a passive filtration of plasma C5b-9, but is locally expressed and implicated in the pathogenesis of DN.

Funding: Government Support - Non-U.S.

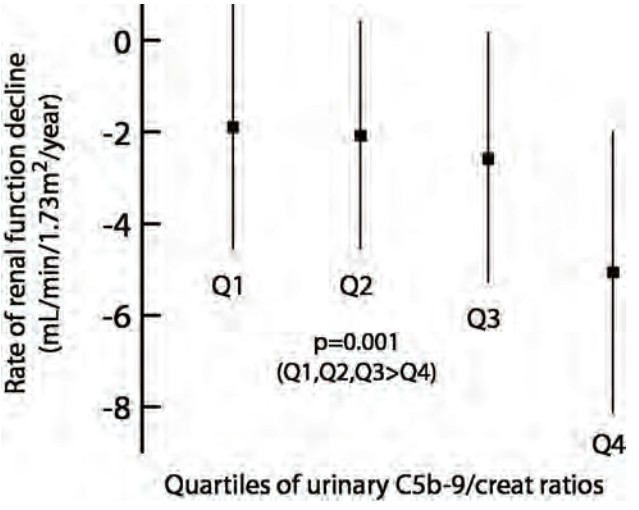

Figure 1. Rate of renal function decline according to urinary C5b-9 quartiles

FR-PO458

Associations of Urinary NGAL and RBP with Nephropathy and Their Roles in Normoalbuminuric Renal Insufficiency in T2DM

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Background: Diabetic nephropathy(DN)is an important complication of diabetes mellitus and has become the leading cause of end-stage renal disease (ESRD) worldwide. At present, the diagnosis of DN mainly depends on glomerular filtration rate (GFR) and albuminuria, but both of them have limitations. In addition, some patients follow a non-albuminuric pathway to renal impairment. The aim of this study was to investigate novel biomarkers in urine to reflect renal damage in T2DM.

Methods: This is a cross-sectional study recruiting 269 type 2 diabetic patients and 30 control subjects. Urinary neutrophil gelatinase-associated lipocalin (NGAL), retinol binding protein (RBP), plasminogen activator inhibitor-1(PAI-1), vascular cell adhesion molecule-1 (VCAM-1), E-cadherin, as well as urinary albumin excretion were measured in urine. Glomerular filtration rate (GFR) was estimated via CKD-EPI combined creatinine–cystatin C equation. The patients were further categorized based on urine albumin/creatinine ratio (UACR) or eGFR. Their correlations with UACR and eGFR were analyzed. Plasma TNF-α, IL-6, ET-1 and 8-OHdG was tested in patients with normoalbuminuria. The associations of TNF-α, IL-6, ET-1 and 8-OHdG with eGFR and urinary biomarker were analyzed. Sensitivity, specificity, and area under the curve (AUC) were calculated as measures of diagnostic accuracy.

Results: It was observed that the levels of urinary NGAL, RBP and PAI-1 were significantly elevated and correlated with UACR and eGFR in T2DM. In T2DM patients with UACR<30mg/g, plasma TNF-α, IL-6 and 8-OHdG were increased in patients with renal insufficiency, and plasma TNF-α and 8-OHdG were negatively correlated with eGFR. Urinary NGAL and RBP were statistically elevated in patients with renal insufficiency and inversely correlated with eGFR. In addition, urinary NGAL showed a positive correlation with plasma TNF-α and 8-OHdG, and urinary RBP showed a positive correlation with plasma 8-OHdG.

Conclusions: In conclusion, the results indicate that urinary NGAL, RBP and PAI-1 may serve as novel biomarkers for the diagnosis of nephropathy in T2DM and urinary NGAL and RBP may be promising biomarkers for diagnosing renal impairment in T2DM patients with normoalbuminuric.

Funding: Government Support - Non-U.S.

FR-PO459

Urine Metabolites Predict Kidney Function Decline in Type I Diabetic Subjects

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Background: Diabetes is the most common cause of chronic kidney disease (CKD) and end-stage renal failure. Albuminuria and eGFR are widely approved biomarkers to identify kidney disease progression. However, due to considerable heterogeneity not all subjects progress at the same rate. In the current study, we evaluated a set of urinary metabolites toward prediction of rapid progression of CKD in patients with type I diabetes.

Methods: We used a nested case-control study in four diverse cohorts (CACTI, EDC, FinnDiane, and Steno) with long-standing type I diabetes and normal kidney function. Subjects were classified into slow decliners/controls with eGFR decline ≤1ml/min/1.73m^2/yr or rapid progressors/cases with eGFR decline of ≥3ml/min/1.73m^2/yr. Thirty four urine metabolites were measured by gas chromatography-mass spectrometry. Logistic regression and Random Forest models were used to predict rapid eGFR decline. Area under the curve (AUC) were used to assess model performance.

Results: Baseline mean eGFR and median ACR in controls (n=340) and cases (n=212) were 91.97 (sd 18.68) and 9.44 (IQR 30), and 98.37 (sd 25.44) and 33.49 (IQR 283.01), respectively. Analysis with clinical variables revealed age, baseline ACR, and baseline eGFR to be significant predictors of rapid decline. Among the metabolites, three were univariately associated with rapid decline (FDR p=0.015, 0.025, 0.025). A model to predict eGFR decline using clinical variables had an AUC of 0.71 (95% CI 0.63-0.79); no significant improvements in AUC were observed with added metabolites. In a stratified analysis of eGFR≥60 ml/min/1.73m^2 and combined micro- and macroalbuminuria (MA+) group, metabolites significantly improved the AUC from 0.69 with clinical variables (0.45-0.84) to 0.76 (0.61-0.89) when combined with metabolites. Random Forest selected 6 metabolites as top 7 variables and the metabolites significantly improved the AUC from 0.61 (0.44-0.76) to 0.75 (0.61-0.89), 95% CI.

Conclusions: In subjects with albuminuria and normal eGFR (≥60 3ml/min/1.73m^2) clinical variables are not optimal to predict kidney function decline and urine metabolites may be useful as prognostic biomarkers for loss of renal function.

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FR-PO460

Developing Prognostic Models for Kidney Function Decline Based on Clinical and Metabolite Profiles in an Albuminuria-Stratified Analysis in the CRIC Cohort

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Background: There is significant heterogeneity in the rate of kidney function decline among Type 2 diabetics, signaling a critical need to better identify patients at high risk of rapid kidney function decline. We previously identified a metabolomic signature of chronic kidney disease (CKD) using cross-sectional analysis. Metabolomic analysis combined with novel statistical methods could provide clinically useful signatures of CKD using longitudinal cohorts.

Methods: We studied 1003 Type 2 diabetics with up to 10 years of follow-up. The median eGFR decline per year (-1.84 ml/min/1.73m^2/yr) cutoff delineated fast vs slow CKD progression. An untargeted flow-injection mass spectrometry method was used to assay an a priori 16-metabolite set, implicated in mitochondrial dysfunction in CKD. Models for fast vs slow decline were built with the 16-metabolite subset and standard clinical variables (e.g. age, race, HbA1c, MAP) as predictors. The accuracy (i.e. % of fast and slow decliners correctly identified by the model) of clinical-only, metabolite-only, and clinical-metabolite statistical models were compared using 5-fold cross-validation. Analyses were stratified by albumin/creatinine ratio (ACR): normal (ACR <30 mg/g), microalbuminuria (ACR 30-300 mg/g), macroalbuminuria (ACR >300 mg/g).

Results: There were significant differences in eGFR decline (p <0.001) between albuminuria groups: mean eGFR slopes (ml/min/1.73m^2/yr) were -0.43 in normo-, -1.47 in micro-, and -3.03 in macro-ACR groups. As expected, study entry eGFR, diabetes control (HbA1c) and blood pressure (MAP) were worse (p <0.001) as albuminuria increased. Predictive accuracy of models was 84% normo-, 64% in micro-, 82% in macro-groups. Given the high accuracy, we further investigated the models for the normo- and macro-groups. After adjusting for clinical variables, prognostic metabolites were (i) 2-methyl acetoacetate for normo-ACR and (ii) pyruvic and homovanillic acids for the macro-ACR groups.

Conclusions: The accuracy of the models differed by ACR level. Several a priori metabolites predicted CKD progression, and interestingly, prognostic metabolites varied by ACR status. Our findings suggest that metabolites may offer insights into CKD progression in Type 2 diabetes within albuminuria groups.

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FR-PO461

Validation of a Systems Biology Derived Urinary Metabolite Panel for Prediction of Albuminuria Response to Spironolactone Therapy in Type 2 Diabetes

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Background: The mineralocorticoid receptor antagonist spironolactone significantly reduces albuminuria in patients with diabetic kidney disease, albeit with a large between individual variability. We previously identified a panel of systems biology derived urinary metabolites for prediction of albuminuria response to spironolactone therapy.[1] Here we validate this metabolite panel in an external cohort.

Methods: Data and samples were used from a randomized placebo controlled double blind clinical trial.[2] Patients with diabetes, hypertension, and albuminuria (urine albumin-to-creatinine ratio ≥300 mg/g) who all received lisinopril 80 mg/day were randomly assigned to placebo (n=23) or spironolactone 25 mg/day (n=20) for 48 weeks. Urine samples were obtained at baseline, 24 and 48 weeks, and LC-MS metabolomics measurements were performed on the baseline samples. We used leave-one-out cross-validated optimism corrected ridge regression to predict albuminuria response to spironolactone.

Results: After 12 weeks of therapy, spironolactone reduced UACR relative to placebo by median -57%, with large variability (5th to 95th percentile -136% to +4%). A clear separation between the spironolactone and placebo arms was observed in the predicted treatment effect by the metabolite panel (Figure). The metabolite panel was able to predict albuminuria response to spironolactone (R^2 = 0.30, p-value <0.01).

Conclusions: We validated a previously identified panel of 18 urinary biogenic amines and organic acids to predict albuminuria response to spironolactone. These results suggest that this urinary metabolite panel may be used as a tool to tailor optimal therapy in diabetes and move in the direction of personalized medicine. **References** 1. Pena et al. Urinary Metabolomics Predict Albuminuria Response to Spironolactone Therapy in Type 2 Diabetes. J Am Soc Nephrol 27, 2016: 557A 2. Mehdi et al. J Am Soc Nephrol. 2009 Dec;20(12):2641-50

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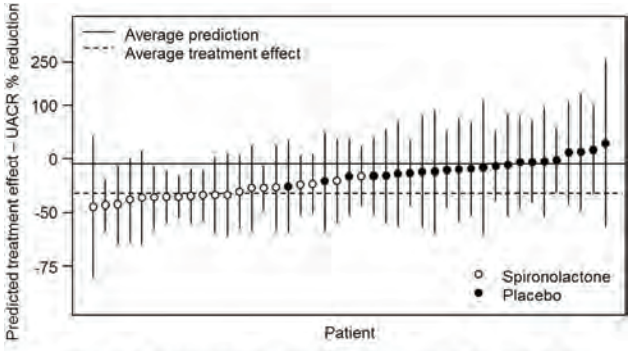

Figure. Prediction of spironolactone treatment effect on UACR by the metabolite panel. Data are presented as per-individual mean (95%CI) after 100 leave-one-out cross-validation runs.

FR-PO462

Increasing Baseline Albuminuria Is Associated with a Continuously Increased Risk of Cardiovascular (CV) and Renal Outcomes in the LEADER Trial

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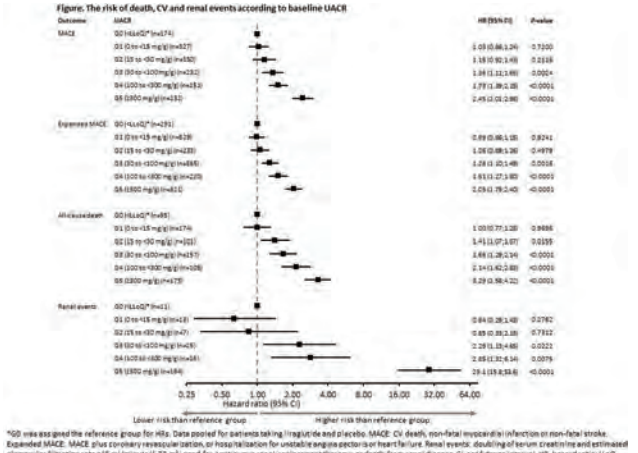
Background: Albuminuria is a known risk factor for CV disease, but the lower limit from which it is a risk factor is not well defined.

Methods: We assessed CV and renal outcomes by increasing levels of baseline urinary albumin-to-creatinine ratio (UACR) in the LEADER trial. LEADER was a randomized, double-blind, placebo-controlled CV outcomes trial of liraglutide up to 1.8 mg/day vs placebo added to standard care for 3.5–5 years in 9340 patients with type 2 diabetes and high risk for CV disease. We analyzed the risk of major adverse CV events (MACE), expanded MACE, all-cause death, and adjudicated renal events (doubling of serum creatinine and estimated glomerular filtration rate ≤45 ml/min/1.73 m^2; the need for continuous renal-replacement therapy; or death from renal disease) by baseline UACR irrespective of treatment group; UACR < lower limit of quantification (LLoQ) (G0; n=1598), 0 to <15 mg/g (G1; n=2905), 15 to <30 mg/g (G2; n=1196), 30 to <100 mg/g (G3; n=1609), 100 to <300 mg/g (G4; n=845), and ≥300 mg/g (G5; n=960).

Results: The risk of MACE, expanded MACE, all-cause death and renal events increased with increasing baseline UACR (Figure), statistically significant for all subgroups with UACR ≥30 mg/g compared to G0. Interestingly, in patients at the higher part of the normoalbuminuric range (G2), a trend towards increased risk for CV events and all-cause death was observed.

Conclusions: In LEADER, baseline UACR≥30 mg/g was associated with increased risk of death, and CV and renal events, emphasizing the importance of albuminuria as a modifiable risk factor.

Funding: Commercial Support - Novo Nordisk



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Association of Anthropometric Measures of Obesity and CKD in Elderly Women Admitted in a Tertiary Care Government Teaching Hospital

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Background: There is growing evidence which suggests that obesity is an important contributor to the development of CKD. However, the relationship between obesity and CKD is complex and not completely understood, and the best anthropometric index of obesity in predicting CKD is controversial. We carried out this study to determine the best anthropometric index of obesity in predicting CKD in a population of elderly women admitted in RCSM Government Medical College and CPR General Hospital, the only tertiary care government teaching hospital in the city of Kolhapur, India.

Methods: We carried out this study for the duration of 3 years from May 2015 to April 2018 at our institute. Anthropometric indices of obesity including body mass index (BMI), waist circumference (WC), waist-to-height ratio (WheiR) and waist-to-hip-ratio (WHR), were obtained in 1706 selected females. Biochemical measurements including blood glucose, lipid profile, and 2-h postprandial blood glucose were performed. GFR was estimated by using CKD-EPI equation. Adequate statistical tests were carried out and for all tests, a p-value <0.05 was considered statistically significant.

Results: The prevalence of CKD stage ≥ 3 was 36.64%. Overweight and obesity was found in 54.16% and 34.88% of participants, respectively. Increased central fat distribution, as defined by WheiR, WC and WHR, was found in 84.34%, 89.86% and 86.52% individuals, respectively. Univariate linear regression analysis showed positive correlations between CKD and age (p<0.001), BMI (p<0.0001), WC (p<0.0001), WHR (p<0.005), WheiR (p<0.0001), diabetes (p<0.005), as well as triglicerydes (p<0.003); however there was a negative correlation between CKD and HDL level (p=0.025). Multivariable analysis demonstrated that hypertension, diabetes, WC and WheiR were independent predictors of CKD. The area under the receiver operating characteristics curve was best for WheiR (0.638), followed by WC (0.619), BMI (0.603), and WHR (0.598).

Conclusions: Abdominal obesity is an important predictor of CKD. Of commonly used anthropometric parameters of obesity, WheiR ≥ 0.6 is particularly associated with CKD in elderly females. However, the value for these obesity indices is limited in screening CKD and further research in this regard is highly encouraged.

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Diabetic Retinopathy Is Associated with Renal Function Deterioration in Korean Population with Type 2 Diabetes

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Background: Although both retinopathy and nephropathy are major diabetic microvascular complications, a few studies have examined the relationship between retinal structural changes and renal functions in patients with diabetes. We investigated whether diabetic retinopathy (DR) status has adverse effects on kidney function in patients with type 2 diabetes.

Methods: We enrolled 2,139 patients with type 2 diabetes who had undergone fundus exam and serial renal function evaluation from August 2006 to February 2014. DR status was classified to no DR, non-proliferative DR (NPDR), and proliferative DR (PDR). Cox regression analysis was used to evaluate the hazard ratio for renal function decline according to DR status.

Results: The mean age of the study participants was 58.3±11.3 years and 1,124 (52.5%) were women. The mean follow-up period was 3.1±2.9 years. DR was associated with the change in estimated glomerular filtration rate (eGFR) and the development of renal dysfunction (decreased eGFR⟩20%) (no DR group 2.23±24.51; NPDR group -2.82±24.11; PDR group -4.82±46.63 mL/min/1.73m^2/year, P⟨0.001). After adjustments for other risk factors, DR was an independent predictor for renal function deterioration (HR 1.917, 95% CI 1.470–2.498, P⟨0.001). In addition, the progression of DR (new-onset DR or progression of DR status) was associated with the change in eGFR (no DR progression group 0.86±19.77, DR progression group -1.75±14.24 mL/min/1.73m^2/year; P⟨0.001). After adjustments for risk factors, however, DR progression was not an independent predictor for renal function deterioration (HR 1.374, 95% CI 0.748–2.523, P=0.305). On the other hands, DR was associated with the development of proteinuria during follow-up periods (no DR group 6.2%; NPDR group 17.5%; PDR group 30.1%, P⟨0.001). Progression of DR was also associated with the development of proteinuria during follow-up periods (no DR progression group 9.1%; DR progression group 17.1%, P=0.013). Multivariate analysis demonstrated that the status of DR as well as eGFR and HbA1c is an independent predictor for development of proteinuria.

Conclusions: Our findings showed a strong association between DR and progressive renal dysfunction after adjustment for traditional and non-traditional risk factors in Korean patients with type 2 diabetes.

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FR-PO465

Impact of Diabetic Retinopathy and Diabetic Kidney Disease on All-Cause and Cardiovascular Mortality

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Background: The relationship between diabetic microvascular complications including diabetic retinopathy (DR), and diabetic kidney disease (DKD), and mortality in populations are not clear.

Methods: We examined the association between DR, DKD and mortality among 2880 Chinese, Malay and Indian adults (aged 40-80 years) with diabetes who participated in the Singapore Epidemiology of Eye Diseases study (baseline, 2004-2011). Information on mortality was obtained by linkage with National Death Registry until May 2017. DR was ascertained from retinal photographs and DKD from estimated glomerular filtration rate (≤60 ml/min/1.73 m²). Associations of DR and DKD with each outcome separately and jointly were examined using multivariate Cox proportional hazards regression models.

Results: Over a median follow-up of 8.8 years, 580 deaths occurred (20.1%) of which 254 (8.8%) were due to CVD. DR and DKD were significantly associated with all-cause and CVD mortality separately and jointly. In joint models including both DR and DKD, 58.9% had neither DR nor DKD (DR^-DKD^-), 11.8% had DKD alone (DKD^+ DR^-), 21% had DR alone (DR^+ DKD^-), and 8.3% had both DR and DKD (DKD^+DR^+). Beyond the background risk (12% and 4.2% in DR^-DKD^-), excess risk of absolute all-cause and CVD mortality were 27.1%, 12.6% in DKD^+ DR^-, 6.5%, 5.2% in DR^+DKD^- and 5% and 5.3% in DKD^+DR^+. In multivariable models, compared to DR^-DKD^-, hazard ratio (95% confidence interval) of all-cause and CVD mortality were 1.89 (1.40-2.57), 2.26 (1.42-3.61) for DKD^+ DR^-, 1.38 (1.03-1.86), 1.64 (1.06-2.56) for DR^+DKD^-; 2.76 (2.05-3.72), 3.41 (2.19-5.32) for DKD^+DR^+. No significant interaction was observed between DR and DKD on additive or multiplicative scale for either outcome (all p>0.1).

Conclusions: Our results suggest that risks of all-cause and CVD deaths were significantly higher in those with DKD and DR, but DKD largely contributed to the excess risk. Our findings emphasize the need for assessing the presence of DR and DKD in diabetic populations to assess mortality risk associated with type 2 diabetes.

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FR-PO466

Non-Proteinuric versus Proteinuric Phenotypes in Diabetic Nephropathy: A Propensity Score Matched Analysis of a Nationwide, Biopsy-Based Cohort Study

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Background: Several cross-sectional studies have recently shown that a proportion of patients with type 2 diabetes mellitus develop loss of renal function without overt proteinuria or even without microalbuminuria, suggesting the existence of non-proteinuric phenotype of diabetic nephropathy. Their clinicopathological characteristics and renal prognosis, however, are scarce.

Methods: We retrospectively assessed patients with type 2 diabetes mellitus, who underwent clinical renal biopsy from Jan 1, 1985 to Dec 31, 2016 and had follow-up data until Dec 31, 2017, from the Japan's nationwide multicenter renal biopsy registry. Among 795 patients, we restricted 526 patients with reduced renal function (defined as estimated glomerular filtration rate <60 mL/min/1.73m²) and had a pathological diagnosis of diabetic nephropathy as the only glomerular disease diagnosis. 88 were non-proteinurics (urine albumin to creatinine ratio (UACR) <300 mg/gCre), and 438 patients were proteinurics (UACR ≥300 mg/gCre). For comparative analyses, we derived one-to-one paired cohorts of those without proteinuria versus those with proteinuria using propensity-score matching (matched by age, gender, and baseline eGFR). The primary endpoint was progression of CKD defined as new-onset ESRD, decrease of eGFR by ≥ 50%, or doubling of serum creatinine.

Results: In the matched analyses (82 patients in each group), patients with non-proteinuric diabetic nephropathy had lower systolic blood pressure and total cholesterol level, higher serum albumin level, and less frequent typical pathological lesions. After a median follow-up of 3.0 years (IQR 1.0-6.6) from the date of renal biopsy, 65 (40%) of the 164 matched patients had renal events. The 5-year CKD progression-free survival for all patients was 63.3% (95% CI, 53.3-71.7): 86.7% (95% CI, 72.5-93.8) for the non-proteinuric diabetic nephropathygroup and 43.2% (95% CI, 30.2-55.6) for the proteinuric diabetic nephropathygroup (log-rank test p<0.001). The lower renal risk in non-proteinuric diabetic nephropathy group was consistent across all subgroup analysis.

Conclusions: Patients with non-proteinuric diabetic nephropathy had lower blood pressure and less typical morphological changes, and were at lower risk of CKD progression.

FR-PO467

Histological Findings Associated with Proteinuria in Diabetic Nephropathy

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Background: Regardless of the causes of renal diseases, proteinuria is the strongest predictor of renal prognosis among clinical parameters. Diabetic kidney disease (DKD) patients are rarely examined by renal biopsy. Determination of the histological lesions that are responsible for proteinuria in DKD will be useful for the future research to identify the intervention to the specific lesions.

Methods: This is a serial cross-sectional study of 347 adults with biopsy-proven diabetic nephropathy (DN) from 1981 to 2014. Predictors were histological findings in renal pathology and outcome variable was proteinuria. DN was evaluated by two renal pathologists according to 9 glomerular lesions; mesangial expansion, exudative lesion, nodular sclerosis, microaneurysm, duplication of the basement membrane, perihilar neovascularization, glomerulomegaly, global sclerosis, and segmental sclerosis, 2 tubulointerstitial lesions; interstitial fibrosis tubular atrophy (IFTA) and inflammatory cell infiltration, and 2 vascular lesions; arteriolar hyalinosis and intimal thickening of large artery. In addition to histological findings, age, sex, body mass index, estimated glomerular filtration rate (eGFR), systolic blood pressure and use of renin-angiotensin system blockers were used for adjustment. Statistical analyses were performed using multivariate general linear model and two-way analyses of covariate and variance.

Results: Hypertension and diabetic retinopathy were observed in 65% and 46% of patients, respectively, with mean age of 58 ± 11. Median level of proteinuria at the time of renal biopsy was 0.50 g/day (25th and 75th percentile: 0.20 and 2.7 g/day) and mean eGFR was 62.4 ± 32.6 mL/min/1.73m². Twelve out of thirteen histological lesions were significantly correlated with each other and proteinuria levels. However, after multivariate adjustment nodular sclerosis and IFTA remained significant predictors for proteinuria levels. Two-way analyses of covariate and variance showed that IFTA and glomerular lesions had a synergetic effect on increased multivariate adjusted proteinuria levels.

Conclusions: Nodular sclerosis and IFTA were significant predictors of proteinuria levels and had a synergetic effect on increased proteinuria in DN patients. These two lesions might be relevant targets for developing new therapy in DKD patients.

Funding: Government Support - Non-U.S.

FR-PO468

Comparison of Renal Outcomes Between Diffuse and Nodular Diabetic Nephropathy: A Meta-Analysis

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Background: The diffuse (DIF) type and the nodular (NOD) type of glomerulosclerosis have long been recognized as the pathological characteristics of diabetic nephropathy (DN). However, the relationship between pathological changes and renal outcomes is not fully elucidated so far. The present meta-analysis was designed to compare the renal outcomes between the two pathological types of DN.

Methods: We reviewed relevant studies that compared the renal outcomes between DIF and NOD in Medline, Embase, Cochrane Library, CNKI and other sources from 1950 to 2015.

Results: Of 3615 citations identified, only four retrospective cohort studies involving 596 patients were included in the meta-analysis. Pooled analysis of relative risk (RR) in the fixed-effects model showed that NOD had higher risk for developing ESRD than DIF did (RR 1.86, 95%CI 1.28-2.70, P = 0.001, P for heterogeneity = 0.12, I^2 = 48%). The sensitivity analysis showed that the heterogeneity among studies was decreased when studies with type 1 diabetic patients were excluded (P for heterogeneity = 0.34, I^2 = 0%).

Conclusions: The present meta-analysis revealed that renal outcomes were closely related to pathological changes of DN, and NOD had higher risk for developing ESRD than DIF.

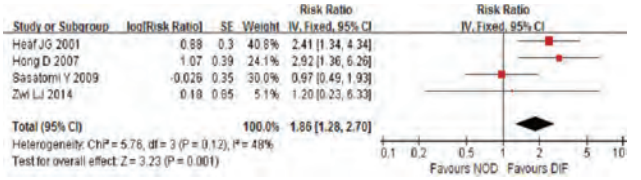

Fig. 1 Comparison of renal outcomes between the diffuse (DIF) type of diabetic nephropathy and the nodular (NOD) type

FR-PO469

Assessment of the Relationship Between the 2010 Pathologic Classification and Renal Outcomes in Patients with Diabetic Nephropathy: A Meta-Analysis

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Background: The pathologic classification for diabetic nephropathy (DN) established by the Renal Pathology Society in 2010 has received extensive attention. However, its relationship with renal prognosis requires further study.

Methods: Original cohort studies were identified by searching PubMed, Embase, the Cochrane Library, CNKI and other resource. Hazard ratios (HRs) were pooled using the RevMan 5.3 software.

Results: Of the 1549 relevant articles, six retrospective or prospective cohort studies with a total of 803 participants were finally included in the meta-analysis. The pooled HRs revealed that the risks for renal end-points of Class I and IIa were obviously lower than those of Class IIb, III and IV, and in turn, the risks of Class IIb and III were lower than that of Class IV. But there were no significant differences between Class I and IIa, and between Class IIb and III. The pooled HRs for tubular, interstitial and vascular changes showed that interstitial fibrosis and tubular atrophy (IFTA) and interstitial inflammation were significantly correlated to renal outcomes while arteriolar hyalinosis and arteriosclerosis were not (Table 1). Subgroup analyses and sensitivity analyses indicated that different types of diabetes generated heterogeneity.

Conclusions: The present meta-analysis revealed that 1) the glomerular classes were not completely associated with renal prognosis in that the renal outcomes were benign in Class I and IIa, moderate but similar in Class IIb and III and severe in Class IV; 2) the tubular and interstitial lesions were independent variables associated with renal outcomes while vascular changes were not.

Table 1 Results of statistical pooling

	N	HR (95%CI)	P-value	Heterogeneity	
				P-value	I2 (%)
Glomerular classes					
I vs IIa	206	0.39 (0.08, 1.87)	0.24	0.99	0
IIb vs IIa	266	2.64 (1.53, 4.54)	0.0005**	0.88	0
III vs IIa	422	3.06 (1.92, 4.89)	<0.00001**	0.23	30
IV vs IIa	272	7.54 (4.22, 13.45)	<0.00001**	0.68	0
III vs IIb	425	1.01 (0.53, 1.92)	0.98	0.05	59
IV vs IIb	256	2.98 (1.88, 4.71)	<0.00001**	0.67	0
IV vs III	417	2.11 (1.67, 2.68)	<0.00001**	0.63	0
Interstitial and vascular scorings					
IFTA	519	1.74 (1.37, 2.20)	<0.00001**	0.30	18
Interstitial inflammation	474	1.62 (1.09, 2.40)	0.02*	0.10	64
Arteriolar hyalinosis	519	0.81 (0.49, 1.35)	0.43	0.84	0
Arteriosclerosis	519	1.04 (0.61, 1.77)	0.88	0.63	0

Note: interstitial fibrosis and tubular atrophy, IFTA; *P<0.05, **P<0.01.

FR-PO470

Diabetic Fibrillosis, Not an Uncommon Entity: A Case Series

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Background: Diabetic Fibrillosis (DF) is a rare glomerular abnormality detected in electron microscopy as random nonbranching fibrillary deposits in mesangium. There are few case reports available related to this entity and we report a case series of this interesting association.

Methods: We reviewed all the cases of type 2 diabetic patients who underwent renal biopsy for various indications in last one year (April 2017 to march 2018). Cases which were reported as DF in electron microscopy were collected. Clinical course, investigation reports and biopsy findings were analysed.

Results: DF was reported in 5 (3.7 %) out of 134 cases of diabetic nephropathy. The mean age was 55.6±.6 years (46-65). All five had both hypertension and diabetes. Mean duration of diabetes was 12± 2.7years. All five had increased serum creatinine with mean of 6.9±3.5 mg/dl. Three patients had nephrotic and two had subnephrotic range proteinuria (mean 3±1.3 g/day). Autoimmune and myeloma workup was negative. Light microscopy showed diabetic nephropathy class IV with arteriolar hyalinosis in all 5 cases. The Immunofluorescence and congo red stain was negative in all. GBM thickening is seen in all cases with mean thickness ranging from 426 to 714 nm. Random non branching fibrillary deposition is seen in mesangium of all cases. No spherular microparticles or tubuloreticular inclusions were seen.

Conclusions: diabetic fibrillosis is not an uncommon entity with a prevalence of 3.7 % in our case series. The clinical significance of this entity is yet to be determined. The observations made in this series needs to be elicited with a larger series of cases to know the impact on long term kidney function.

FR-PO471

Renal Biopsy in Diabetic Patients: Preliminary Results of the Spanish Multicenter Study BIODIAB-GLOSEN-GEENDIAB

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Background: The diabetic patient with kidney disease has a high prevalence of non-diabetic nephropathy(NDN) and the renal and patient survival in relation to the presence of diabetic nephropathy(DN) or NDN has not been widely studied. The objectives of the study are: to determine the capacity of the clinical and analytical data in the prediction in the histological result(DN or NDN) and to find differences in renal and patient survival.

Methods: Spanish retrospective descriptive multicenter study of the pathological result of biopsies performed in diabetic patients in 2002-2014.

Results: 16 centers participated including 692 patients:511 men(73.8%), mean age of 62±12years, evolution of diabetes mellitus 10.5(3.7-15.3)years, serum creatinine 2,8±2,2mg/dl, glomerular filtration rate MDRD-4 of 37,7±26.8mL/min/1,73m^2, glycosylated hemoglobin 7±1,7% and proteinuria of 3.91(1.1-5)gr/24h. 40.6% of patients had DN,48.6%NDN and 10.8%ND plus NDN. The most frequent NDN was nephroangiosclerosis(12.7%). Multivariate logistic regression analysis: age(OR1,026,1,003-1,033,p=0.021), microhematuria(OR 1.523,1.047-2.214,p=0.028), creatinine(OR:1,149,1,045-1,164,p=0.004) and diabetic retinopathy (DR)(OR0.434,0.311-0.604p<0.001) were independently associated with NDN. We obtained the ROC curve model:(95% CI):0.683(0.636-0.731). 35.2%(n=184) of patients needed renal replacement therapy(RRT),47.3% of them presented DN,38.6% NDN and 14.1% DN and NDN. The overall mortality of the studied patients was 18.7%(n=98), of them 42% presented DN,46% NDN and 12% DN and NDN. In the analysis of survival with Kaplan-Meier curves: Patients with DN or DN+NDN presented worse renal prognosis than NDN patients(p<0.001). In the multivariate analysis of Cox adjusted by confusing variables, DN was confirmed as a risk factor for RRT.

Conclusions: The most frequent NDN is nephroangiosclerosis. Elder patients with microhematuria, worse renal function and absence of DR are high risk for NDN. DN has worse renal prognosis than NDN. The histological diagnosis of renal involvement in the diabetic can facilitate an effective treatment and an improvement in the renal prognosis.

Funding: Government Support - Non-U.S.

FR-PO472

Activation of the Free-Fatty Acid Receptor GPR40 Improves Anemia in Mouse Models of Kidney Disease via a Novel EPO-Independent Mechanism of Action

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Background: The prevalence of anemia increases with the progression of chronic kidney disease (CKD) and leads to reduced quality of life and increased cardiovascular risk. Yet, the use of erythropoiesis stimulating agents is associated with negative outcomes in CKD patients. Here we present an alternative pathway for the treatment of anemia secondary to kidney disease through activation of GPR40, in mediating *in vitro* stimulation of bone marrow cells, particularly the colony-forming-unit-erythrocytes (CFU-E) generation; and the anti-anemic effects of PBI-4050 in models of renal injury.

Methods: *In vitro*, murine bone marrow cells were assayed for CFU-E in the presence or absence of PBI-4050 (agonist of GPR40) and/or GW1100 (GPR40 antagonist). PBI-4050 was tested in ischemia-reperfusion (IR) AKI in WT mice. In addition, we used an adenine-induced CKD model whereby male wild type (WT) and GPR40$^{-/-}$ mice were fed a diet supplemented with 0.25% adenine for one week and treated for three weeks with PBI-4050 (200 mg/kg).

Results: PBI-4050 increased the formation of CFU-E in a GPR40 dependent manner as GW1100 blocked this increase. In addition, GPR40 antagonism led to a significant decrease in CFU-E counts. Furthermore, PBI-4050 showed comparable activity to EPO regarding CFU-E count. After 14 days following IR-AKI, PBI-4050 maintained hematocrit. In adenine-CKD mice, Hct, Hb and mean corpuscular volume were significantly decreased

in CKD-mice, while PBI-4050 maintained these levels and led to significantly higher plasma erythropoietin levels. In parallel, signs of anemia were present to similar degrees in both untreated WT and GPR40$^{-/-}$ mice. Interestingly, PBI-4050 treatment in adenine-fed GPR40$^{-/-}$ mice failed to improve Hct levels.

Conclusions: Taken together, our data suggest treatment of anemia through a novel alternative pathway which is EPO-independent. Treatment with PBI-4050 may provide therapeutic benefit by maintaining adequate Hct and Hb levels, while also improving renal and cardiovascular outcomes.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO473

Fludrocortisone Stimulates Erythropoietin (Epo) Protein Expression in the Distal Tubules of Mouse Kidney

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Background: Although normal plasma Epo concentration is very low, Epo mRNA was expressed in the kidney tubules under normal condition (Nagai, Yasuoka, et al, 2014). We further showed that fludrocortisone, an aldosterone receptor agonist, stimulated Epo mRNA expression in the distal nephron (Yasuoka, et al, ASN 2017). In this study, we investigated the localization of Epo protein-producing cells in the kidney and liver after fludrocortisone injection.

Methods: Fludrocortisone (2.5 mg/100 g BW) or Angiotensin II (0.5 μg/100 g BW) was once applied to mice (C57BL/6J, male, 10 weeks). After 2, 4, 6 and 72 hr, kidneys were examined by Western blot and immunohistochemistry using anti-Epo antibodies.

Results: Under normal (basal) conditions, Epo staining was widely found along the nephron (proximal tubules < thick ascending limbs < collecting ducts). Fludrocortisone significantly increased Epo production in the medullary thick ascending limb, and cortical and outer medullary collecting ducts, particularly in type A of intercalated cells after 4-6 hr. Western blot showed that Epo protein expression was increased by 5-fold in the kidney but not changed in the liver. Angiotensin II stimulated Epo mRNA expression in proximal and distal tubules but not in the interstitial cells. Epo staining decreased to the basal level after 72 hr, but was not detected in the interstitial cells.

Conclusions: Renin-angiotensin-aldosterone system regulates Epo production by the nephron.

Funding: Government Support - Non-U.S.

FR-PO474

Enarodustat (JTZ-951), an Oral HIF-PH Inhibitor, Stabilizes HIF-α Protein and Induces Erythropoiesis with Hardly Influence the Function of Vascular Endothelial Growth Factor

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Background: Renal anemia is principally caused by decreased erythropoietin (EPO) production in the kidney due to renal dysfunction. The production of EPO cannot be increased in response to hypoxia in the chronic kidney disease (CKD) kidney. The EPO production is regulated by hypoxia-inducible factor (HIF) -α, and it was hydroxylated by HIF-prolyl hydroxylase (PHD) and degradated by the ubiquitin-proteasome system. Several PHD inhibitors, including enarodustat are under clinical trials as treatment for renal anemia.

Methods: The enzyme inhibitory activity in human PHD enzymes was investigated by HTRF assay system. The expression of HIF proteins, EPO mRNA levels, and EPO proteins were evaluated by Western blotting, qPCR, and ELISA, respectively. Normal rats and 5/6-nephrectomized rats were used in *in vivo* experiment.

Results: Enarodustat had inhibitory effects on human PHD 1-3, but had no inhibitory effects on various receptors or enzymes. In Hep3B cells, enarodustat increased HIF-1α and HIF-2α protein levels, EPO mRNA levels, and EPO production. In normal rats, after a single oral dose of enarodustat, the plasma concentrations of enarodustat reached Cmax by one hour after administration, and then decreased rapidly. The liver and kidney EPO mRNA levels and plasma EPO concentrations also increased, and then both decreased by 24 hours. In 5/6-nephrectomized rats, repeated oral doses of enarodustat once daily showed the erythropoiesis stimulating effect in proportion to the doses from 1 mg/kg. The administration of enarodustat at the high dose (over 30 mg/kg) increased plasma vascular endothelial growth factor (VEGF), however, retinal VEGF mRNA levels and the retinal vascular permeability were not changed. Finally, we evaluated the effect of enarodustat in the colorectal cancer cell-inoculated mice model. Although enarodustat dosing at the high dose increased the plasma VEGF, it showed no effect on the tumor growth.

Conclusions: Enarodustat stabilizes HIF-α protein and induces erythropoiesis with hardly influence the unexpected function, and it is expected to become a new orally drug that can maintain the hemoglobin concentrations in CKD patients with renal anemia.

Funding: Commercial Support - Japan Tobacco Inc.

FR-PO475

A Dose-Dependent Biphasic Effect of HIF Stabilizer (MK-8617) on Renal Fibrosis

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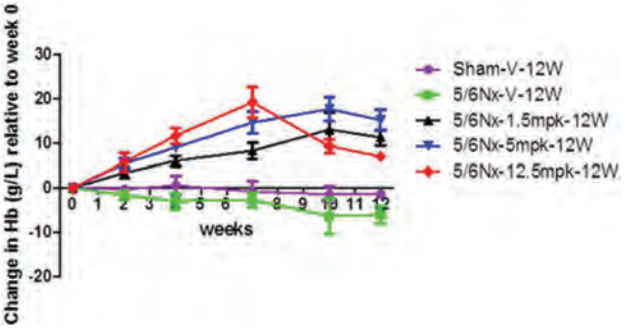
Background: HIF stabilizer is a novel drug for renal anemia. Previous clinical trials have demonstrated HIF stabilizer could elevate hemoglobin (Hb) levels effectively in CKD patients. As a critical transcription factor, HIF has been involved in regulating hundreds of genes, which raised too much concern by clinician for its potential adverse effect. Here we firstly demonstrated the dose dependent biphasic effect of MK-8617(HIF stabilizer, Selleck) on renal fibrosis.

Methods: CKD-anemia model was induced by in mice undergoing 5/6 nephrectomy (5/6Nx). 5/6Nx mice were treated with MK-8617 orally at low dose (1.5mg/kg/d, group A), middle dose (5mg/kg/d, group B) and high dose (12.5mg/kg/d, group C) for 12weeks respectively. The 5/6Nx mice not treated with MK-8617 served as Ctrl group.

Results: Hb level was significantly elevated in all three groups with MK-8617 treatment for 12 weeks compared with that in Ctrl group. However, Hb level in group C was lower than that of the other two groups. Compared with the Ctrl group, the Scr and BUN were significantly decreased in group A and B respectively. It is of note that there was no significant reduction of Scr and BUN in group C. The VEGF mRNA and protein expression were significantly increased in both remnant kidney and liver in mice with Group C, but not in group A & B. However, the number of glomerular endothelial cells was significantly decreased in group C. More impressively, mice in group C showed a serious renal fibrosis with macrophage infiltration, but in contrast, mice in group A & B showed the attenuation of renal fibrosis compared to the Ctrl group. Furthermore, we identified there was a transdifferention of macrophage to myofibroblast in group C.

Conclusions: Although the significant improvement of renal anemia with MK-8617 in 5/6Nx mice, the dose dependent biphasic effect on renal fibrosis has been found, which implied that cautious should be taken when long term use this kind of drug to treat renal anemia, specifically when the dose is high. And the exact mechanism is also to be clarified.

Funding: Government Support - Non-U.S.



FR-PO476

Hypoxia Increases Erythrocyte Death Rate and Oxidative Stress Induced by Indoxyl Sulfate

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Background: Prolonged intradialytic hypoxemia has been associated with higher erythropoietin requirements and poor clinical outcomes in dialysis patients. We analyzed the erythrocyte (RBC) response to indoxyl sulfate under hypoxic conditions.

Methods: RBC from 10 healthy subjects were incubated for 24h with buffer (CON-RBC) or IS (0.01; 0.09; and 0.17 mM) in normoxia (22% O_2) or hypoxia (5% O_2) conditions. Flow cytometry was used to determine: a) Eryptosis by phosphatidylserine exposure (PS) (by Annexin-Phycoerythrin) and intracellular Ca^{2+}influx (by Fluo-3AM), b) reactive oxygen species (ROS) production (by DCFH-DA probe) and reduced glutathione (GSH) content (by ThiolTracker Violet).

Results: Eryptosis increased in an IS dose-dependent manner in both normoxia and hypoxia, but the effect was more pronounced with hypoxia (Table 1). Similarly, IS exposure increased ROS production and decrease GSH content in an IS dose-dependent manner, and the response was also amplified by hypoxia (Table 1).

Conclusions: IS exposure increased eryptosis and oxidative stress and, this effect was amplified by hypoxia. These results suggest that the eryptotic effect of uremia may be aggravated by hypoxia. This may represent a novel mechanism in the development of renal anemia.

RBC incubation conditions / Analysis	NORMOXIA				HYPOXIA			
	CON-RBC	IS 0.01	IS 0.09	IS 0.17	CON-RBC	IS 0.01	IS 0.09	IS 0.17
PS (MFI)	4.8±1.7	8.2±2.4	14.5±4.2***	17.5±4.8***	11.5±2.6a	13.9±2.8b	17.3±2***c	27.5±4.5***d
Ca^{2+} (MFI)	37.5±9	45.7±11	57.5±12**	66.1±13***	49.5±10	57.1±13	67.5±10*	78.2±12***
ROS (MFI)	7.9±4	11.9±3.2	20.8±3.7***	24.9±2.6***	17±6.5a	23.5±8.5b	31.1±6.9***c	33.8±5.5***d
GSH (MFI)	13.7±1.5	12.5±1	13.4±0.6	11.7±0.7*	16.3±0.8a	13.5±1.2***	11.2±1.2***c	9.9±1***d

Mean Fluorescence Intensity (MFI); IS concentration in mM

*p<0.05; **p<0.01 correspond the difference in between CON-RBC vs different IS concentrations within each group Normoxia or Hypoxia.

a p<0.01 correspond the difference in between CON-RBC in Normoxia vs Hypoxia; b p<0.01 N-0.01; c p<0.01 N-0.09; d p<0.01 N-0.17 correspond the difference in between IS concentration in Normoxia vs Hypoxia

FR-PO477

Inflammation Contributes to Anemia of CKD Through Both Iron and HIF/EPO-R Pathways

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Background: Anemia of chronic kidney disease (CKD), originally thought to be due to impaired renal erythropoietin (EPO) synthesis as well as iron malabsorption, may also be due to EPO resistance, clinically associated with inflammation. The key pro-inflammatory cytokine Interleukin (IL-1) is normally controlled by a receptor antagonist (IL1Ra). IL1Ra-KO (RaKO) mice show arthritis and excessive inflammation. The aim of this study was to characterize the anemic state of RaKO mice with adenine induced-CKD.

Methods: Wild-type (WT) and RaKO mice were fed with 0.2% adenine or control diets, leading to 4 groups: WT, WT-CKD, RaKO, RaKO-CKD. Mice were sacrificed after 10 weeks. For a control model of anemia (CA), WT mice were bled every two days for a week.

Results: Higher levels of S-creat and histologic kidney inflammation were seen in RAKO-CKD Vs WT-CKD. Kidney IL-6 and phospho-STAT3 were increased in both CKD groups, especially in RAKO-CKD. Arthritis, associated with increased liver CRP, was more accentuated in RAKO-CKD Vs RaKO. Hct levels were decreased in CKD groups, especially in RAKO-CKD. The response to bleeding induced anemia (CA) included: no evidence for inflammation, low liver hepcidin, elevated renal HIF2 and increased EPO controlled bone marrow (BM) EPO-R and transferrin receptor (TFR). Serum iron and MCV levels were significantly reduced in both CKD groups and were even lower in RAKO-CKD Vs WT-CKD. Liver hepcidin mRNA levels were increased in RAKO-CKD in comparison to all other groups. Serum EPO levels were not increased. Renal HIF2 and BM EPO-R mRNA levels were significantly decreased in both CKD groups, especially in RAKO-CKD.

Conclusions: Exaggerated arthritis and inflammation were associated with higher degree of renal insufficiency and anemia in RAKO-CKD Vs WT-CKD. In addition to the well-known hepcidin mediated decreased iron absorption, the normal response to anemia induced hypoxia is deranged in CKD and even more accentuated when inflammation is increased in CKD-RaKO: renal HIF2 and EPO, BM EPO-R and TFR are not upregulated, which further exacerbate anemic tendency. Altogether, this supports the key role of inflammation in CKD-associated anemia. Novel treatments to reduce inflammation may attenuate the anemic state or increase the response to exogenous EPO.

FR-PO478

Hypervitaminosis A Contributes to Abnormal Iron Metabolism in CKD

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Background: Anemia is the major features of chronic kidney disease (CKD). Hepcidin (HAMP) is the principal iron regulatory hormone and its overproduction contributes to anemia. HAMP blocks iron fluxes to the blood by degradation of the iron exporter ferroportin (FPN) at the plasma membrane of macrophages. It has been reported plasma vitamin A and its metabolites, all-trans retinoic acid (ATRA), are increased in CKD patients. Several reports showed both hypervitaminosis A and vitamin A deficiency (VAD) results in iron deposition in the liver and reduces serum iron levels in rats, which suggests an inappropriate vitamin A levels may affect iron metabolism disorder. However, the molecular mechanism behind the regulation of iron metabolism by ATRA have been unclear. In this study, we investigated whether hypervitaminosis A can be involved in abnormal iron metabolism in CKD and its molecular mechanism.

Methods: Five-week-old male C57BL/6J mice were treated 5/6 nephrectomy operation to induce CKD and they were fed VAD diet for nine weeks. Iron deposition of tissues was evaluated by Berlin blue stain. Gene expressions were evaluated by RT-PCR, Western blotting.

Results: Berlin blue stain showed VAD diet did not affect hepatic iron deposition, but reduced hepatic HAMP protein levels in CKD mice. Furthermore, VAD decreased the expression of hepatic p-STAT3 protein, transcription factor which activates HAMP transcription, in CKD mice. In spleen, VAD inhibited iron deposition and increased FPN mRNA levels in CKD mice. To understand the more detailed mechanism of abnormal iron metabolism by hypervitaminosis A, we evaluated iron-related gene expression in response to ATRA *in vitro*. The expression of HAMP mRNA and protein were increased by ATRA in HepG2 cells. Ro 41-5253, RAR antagonist, reduced HAMP mRNA levels increased by ATRA in HepG2 cells. Both ATRA and TTNPB, RAR agonist, increased p-STAT3 protein levels in HepG2 cells. Finally, we investigated whether VAD-increased splenic FPN mRNA expression in CKD was not only via HAMP action but also a direct action of ATRA. Interestingly, ATRA reduced the levels of FPN mRNA and protein in Raw264 cells.

Conclusions: We suggest CKD-induced hypervitaminosis A may contribute to abnormal iron metabolism through the indirect regulation of hepatic HAMP and the direct regulation of splenic FPN.

FR-PO479

Ferric Carboxymaltose Restores Iron Status and Transiently Increases FGF23 in a Mouse Model of Iron Deficiency

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Background: Iron deficiency stimulates FGF23 transcription and cleavage, resulting in high circulating levels of total FGF23 (tFGF23) due to increased FGF23 fragments but relatively normal levels of biologically active intact FGF23 (iFGF23), and hence no hypophosphatemia. While this suggests that treating iron deficiency will decrease circulating levels of FGF23, recent publications have shown transient asymptomatic hypophosphataemia secondary to iFGF23 increase, in response to certain intravenous iron preparations such as ferric carboxymaltose (FCM).

Methods: We investigated whether treatment with FCM could impact FGF23 production in a mouse model of dietary iron deficiency. To induce iron deficiency, we fed 3 week-old C57BL6 mice an iron deficient diet (ID) for 3 weeks or a diet containing an adequate amount of iron (Ctr). Subsequently, six week old ID mice were treated with a single iv dose of 30mg/Kg FCM or saline vehicle (Veh). We then performed biochemical analyses of urine and serum from mice collected at different time points up to 2 weeks post injection.

Results: Compared to Ctr mice, six-week old ID animals showed evidence of iron deficiency anemia including low serum iron (23±6 vs 53±18 μg/dL), low red blood cells (7.9 ±0.3 vs 8.4±0.3 M/μL), and hemoglobin (10.0±0.2 vs 13.2 ±0.6 g/dL) ($p<0.05$, ID vs Ctr). FCM treatment rapidly increased serum iron levels 6 hours post-injection (290±21 vs 28±20 μg/dL) and hemoglobin (11.6±0.4 vs. 10.0±0.4 g/dL) after 48 hours ($p<0.05$, FCM vs Veh). As shown previously, tFGF23 was increased in ID animals (1013±143 vs 202±14 pg/mL) while iFGF23 was only slightly elevated (132±8 vs 82±5 pg/mL) ($p<0.05$, ID vs Ctr). FCM administration, led to a transient increase in tFGF23 (2448±269 vs 1343±256 pg/mL) and iFGF23 (193±13 vs 124±8 pg/mL) compared to iron deficient vehicle mice ($p<0.05$, FCM vs Veh). However, one week after FCM treatment, tFGF23 (378±76 vs 1142±186 pg/mL) and iFGF23 (112±7 vs 163±6 pg/mL) levels were corrected ($p<0.05$, FCM vs Veh), likely due to partial correction of iron deficiency.

Conclusions: Our data show that FCM administration to iron deficient mice corrects iron deficiency anemia and transiently increases iFGF23. The causes of this increase remain to be elucidated.

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FR-PO480

Role of Reduced [Ca2+]i in the Denser Bone Phenotype of Mouse Familial Hypocalciuric Hypercalcemia (FHH) Induced by Deleting the Gene Encoding Canonical Transient Receptor Potential 1 (TRPC 1) Channel

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Background: In reporting the 80% increased bone mass in FHH, we noted +/- mice have similar hypercalcemia (11 vs 10.7 mg %), calcitriol, & calcitonin as null, but no hyperparathyroidism (HPT) or hypocalciuria. We asked if gene dosage causes these & the bone phenotype. In parathyroid gland (PTG), renal cells & osteocytes from null mice, we found lower $[Ca^{2+}]_i$ & blunted response to CaSR agonists, shifting right Ca set point for PTH release. We tested the hypothesis that reduced $[Ca^{2+}]_i$ alters secretion of cytokines & phosphatonins to produce greater renal Ca & P retention & more bone mineral accretion.

Methods: We did metabolic studies in ♂ littermates of all 3 genotypes & measured blood chemistry as published & cytokines by mouse ELISA.

Results: At 6.5 mon, plasma leptin in null (2.34), but not +/- (1.78), was 75% higher than wild-type (wt) (1.3 ng/ml), compatible with known increased leptin secretion by low $[Ca^{2+}]_i$ in adipocytes. Given published positive feedback between PTH by PTG & leptin by adipocytes, the data suggest leptin could aggravate the HPT in null mice. Plasma adiponectin was reduced in null (5.36 vs 6.17 in +/- vs 6.39 μg/ml in wt), consistent with its known inhibition by low $[Ca^{2+}]_i$ & with the published hypocalciuric effects if downregulated. Indeed, despite hypercalcemia, urine Ca (50 in null vs 79 in +/- vs 84 μg/d in wt) & Ca clearance (0.68 vs 1.08 vs 1.25 μl/min) were lower in null. Consistent with the low $[Ca^{2+}]_i$ we found in osteocytes, FGF-23 was down in null (51% at 4 mon & 32 % by 5 mon). At 8 mon, P clearance was reduced in null (48 vs 60 in +/- vs 67 μl/min in wt). Thus, serum P was elevated in null (7.4 vs. 6.2 in +/- vs 6.3 mg % in wt). At 12 mon, urine P stayed 50% lower in null, consistent with the anti-phosphaturia of reduced FGF-23.

Conclusions: Our data support this model of bone phenotype in null mice. 1. Disturbed $[Ca^{2+}]_i$ homeostasis from losing both alleles shifts Ca set point to cause HPT. 2. Reduced $[Ca^{2+}]_i$ in adipocytes triggers leptin, aggravates HPT, & inhibits adiponectin. 3. Reduced $[Ca^{2+}]_i$ in osteocytes inhibits FGF-23. 4. In concert, these hypocalciuric & anti-phophaturic

factors promote renal Ca & P retention to favor bone formation, independent of any other renal & skeletal effects of TRPC1 deficiency.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO481

Cross-Talk Between Vascular and Bone Tissues: Does Vascular Calcification Induce Bone Loss?

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Background: Disturbances in bone homeostasis have been associated with development of vascular calcification. Results of epidemiological studies in general population and in CKD patients showed more severe progressive vascular calcifications were associated with greater bone loss and fractures. Our question was whether the presence of severe vascular calcification may have an impact on bone metabolism.

Methods: A novel model of isogenic aorta transplantation was used (ATX). Severe uremic vascular calcifications were induced in DA rats by 5/6 nephrectomy, high P diet and calcitriol. After 14 weeks the calcified abdominal aorta of the uremic rat was transplanted into a normal DA rat (n=16). Control groups were ATX of a normal aorta to normal rat (n=9) and age-matched rat (n=6). Rats were sacrificed 4 weeks after ATX and plasma biochemistry, bone and vessels were analyzed.

Results: The uremic donor rat suffered from severe kidney disease with disturbed mineral balance and its aorta had a high calcium content of 15.7±0.8 µg Ca/mg vs. none in the normal aorta. Control, normal ATX and calcified ATX rats had same levels of creatinine, Ca^{2+}, phosphate, PTH, FGF23 and sclerostin. The calcified ATX rats had significant changes in mRNA of several bone markers compared to normal ATX and control rats such as alkaline phosphatase (3.26±0.29 vs. 1.56±0.32 & 0.86±0.12, both p<0.001), sclerostin (3.60±0.68 vs. 1.41±0.34 & 1.04±0.27, both p<0.01), RUNX2 (1.53±0.09 vs. 0.80±0.18 & 0.44±0.11, p<0.01, p<0.001), Osteocalcin (0.54±0.06 vs. 0.92±0.14 & 1.19±0.06, p<0.05, p<0.001), RANKL (0.40±0.05 vs. 1.91±0.36 & 2.43±0.30, p<0.01, p<0.001), cathepsin K (2.36±0.24 vs. 1.19±0.23 & 1.01±0.07, p<0.01, p<0.001), beta catenin (3.15±0.25 vs. 1.28±0.26 & 1.03±0.13, both p<0.001), collagen I (8.50±0.93 vs. 4.06±2.02 & 3.25±0.88, p<0.05, p<0.001), osteopontin (1.46±0.18 vs. 0.69±0.17 & 0.49±0.06, both p<0.01). Finally, bone mineral density (BMD) was significantly lower in calcified ATX rats compared to normal ATX and control rats (1576±5 vs. 1592±5 & 1613±6 mg/cc, both p<0.05).

Conclusions: These novel findings indicate the existence of a tissue crosstalk between vessels and bone. The presence of vascular calcifications has an impact on several pathways in bone and decrease BMD. Vascular calcification does induce bone loss.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO482

The Phosphate Binding Therapy Fermagate Attenuates Vascular Calcification in Experimental Adenine-Induced CKD

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Background: Hyperphosphatemia, common in chronic kidney disease (CKD), is linked to vascular calcification (VC), which further increases cardiovascular risk. Some evidence suggests oral magnesium (Mg) inhibits VC. Fermagate is a calcium-free, magnesium-releasing phosphate binder that controls hyperphosphatemia. This study determined if fermagate treatment compared to untreated control could impact VC in the adenine-induced CKD rat model.

Methods: Male Sprague Dawley rats were fed a 0.25% adenine, 0.5% phosphate (PO_4) diet to induce CKD (creatinine >250 uM) over 4-5 weeks, then fed 0.5% PO_4 without adenine diet. At 6 weeks CKD, two dietary PO_4 regimens were tested: moderate PO_4 (0.75%P) diet (5g 8AM and 4PM ±fermagate (FER n=9) untreated control (CON n=6), 10g diet overnight, or a combination of high and low PO_4 (1-0.5%P): high (1%P 5g 8AM, 4PM ±fermagate) and 10g low (0.5%P) PO_4 diet overnight (FER n=8, CON n=10) with the same amount of daily dietary PO_4. Serum calcium (Ca), magnesium (Mg), PO_4, FGF-23, parathyroid hormone (PTH), vitamin D metabolome, and tissue Ca and PO_4 were determined.

Results: In both studies, fermagate increased serum Mg (203% 0.75%P, p<0.0001; 163% 0.5-1%P, p<0.0001, % control, 2-way ANOVA) and had lower levels of serum PO_4 (67% 0.75%P, p<0.001; 64% 0.5-1%P, p<0.001), and PTH (31% 0.75%P, p<0.001; 16% 0.5-1%P, p<0.001). The proportion of VC was significantly reduced in arterial tissues with fermagate treatment (79%/65% in CON vs. 35% FER(0.75%P) and 13% FER(0.5-1%P), respectively, p<0.001). This inhibition was also evident on a per animal basis (100%/70% CON had VC vs. 33% FER(0.75%P) and 13%(FER 0.5-1%P), p<0.05, respectively). Fermagate treatment did not significantly alter Mg levels in the vasculature tissue, serum Ca, FGF-23, or serum vitamin D metabolome.

Conclusions: These results demonstrate that fermagate effectively reduces the bioavailability of dietary PO_4, decreases serum PO_4, increases serum Mg, and effectively limits the development and progression of CKD-induced vascular calcification.

Funding: Commercial Support - OPKO Health: Renal Division

FR-PO483

TNAP Inhibition: A Novel Strategy to Prevent the Development of Vascular Calcification?

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Background: Vascular media calcification (VC) is frequently seen in chronic kidney disease patients. Pyrophosphate (PPi) is a well-known calcification inhibitor that binds to nascent hydroxyapatite crystals and prevents further incorporation of inorganic phosphate (Pi) into these crystals. However, the enzyme tissue non-specific alkaline phosphatase (TNAP), which is highly expressed in calcified arteries, degrades extracellular PPi into Pi ions, by which PPi loses its ability to block VC. Here, we aimed to evaluate whether a TNAP-inhibitor is able to prevent the development of arterial calcification in a rat model of warfarin-induced VC.

Methods: To induce VC, rats received a diet containing 0.30% warfarin and 0.15% vitK1 throughout the entire study and were subjected to the following daily treatments: (i) vehicle (n=10) or (ii) 10 mg/kg/day TNAP-inhibitor (n=10) administered via an i.p. catheter from start of the study until sacrifice at wk7. Calcium (Ca) and phosphorus (P) levels were determined in serum and urine samples being important determinants of VC. To evaluate osteo/chondrogenic switch of vascular smooth muscle cells (VSMCs), aortic mRNA expression of runx2, TNAP, SOX9, collagen1 and 2 was analyzed by qPCR. At sacrifice, VC was evaluated by measurement of the total Ca content in the arteries and quantification of the area % calcification on Von Kossa stained aortic sections.

Results: No difference in serum Ca and P levels was observed between both study groups. Warfarin exposure resulted in distinct calcification in the aorta and peripheral arteries in vehicle treated rats. Importantly, daily treatment with a TNAP-inhibitor significantly reduced VC as indicated by a significant decrease in calcium content in the aorta (mean ± SEM; vehicle 3.84±0.64 mg Ca/g wet tissue vs TNAP-inhibitor 0.70±0.23 mg Ca/g wet tissue) and peripheral arteries and a distinct reduction in area % calcification on Von Kossa stained aortic sections as compared to vehicle condition. TNAP-inhibitor treatment did not alter the mRNA expression of osteo/chondrogenic marker genes runx2, TNAP, SOX9, collagen1 and 2.

Conclusions: Treatment with a TNAP-inhibitor significantly reduced the development of VC in the aorta and peripheral vessels of warfarin exposed rats most probably by directly interfering with the apatite formation rather than promoting osteo/chondrogenic conversion of VSMCs.

Funding: Government Support - Non-U.S.

FR-PO484

Protein Bound Uremic Toxins Promote Vascular Calcification by Glucose Mediated Activation of Inflammation and Coagulation Pathways

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Background: Protein-bound uremic toxins indoxyl sulfate (IS) and p-cresyl sulfate (PCS) have been associated with cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). We aimed to provide direct evidence for a role of these toxins in CKD-related vascular calcification.

Methods: To induce CKD, rats were orally dosed with adenine sulfate for 10 days and continuously exposed to either vehicle, IS or PCS (150 mg/kg/day) until 7 weeks after CKD induction. Vascular calcification was assessed by measurement of arterial calcium content and through histochemical evaluation of Von Kossa stained sections. Quantitative mass spectrometric proteomics was further employed to investigate the mechanistic pathways underlying IS and PCS-mediated vascular calcification.

Results: IS and PCS exposure did not worsen renal function, fibrosis, or inflammation. Calcification in the aorta, carotid and femoral arteries was significantly increased by exposure to both toxins, for which serum levels similar to CKD patients were reached. Arterial calcification was not associated with changes in bone metabolism inherent to CKD. Unbiased proteomic analyses of arterial samples coupled to functional bioinformatics annotation analysis revealed that calcification events were likely associated with acute phase response signaling, coagulation and glucometabolic signaling pathways, while escape from calcification was linked with liver X receptors and farnesoid X/liver X receptor signaling pathways. Further metabolic linkage to these pathways also revealed that IS/PCS exposure engendered a pro-diabetic state, evidenced by elevated resting glucose and reduced glucose transporter (Glut1) transcript expression.

Conclusions: We demonstrate that both IS and PCS directly promote vascular calcification via activation of inflammation and coagulation pathways in the arterial wall which was strongly associated with impaired glucose homeostasis.

Funding: Government Support - Non-U.S.

FR-PO485

Calcium-Sensing Receptor Signal Modulation: Identification of CaRS875 as a Novel Phosphorlyation Site and the Contribution of Both Intracellular Domains to Homodimer Signaling

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Background: The calcium-sensing receptor (CaR) controls parathyroid hormone secretion and renal Ca^{2+} reabsorption and its function is inhibited by protein kinase C (PKC) phosphorylation on CaR^{T888}. However, the equivalent PKC site in metabotropic glutamate receptor-5 aligns instead to CaR^{S875}, not previously considered a PKC site. Thus, we examined whether a) CaR^{S875} represents a novel PKC site, b) mutation of CaR^{T888} can rescue loss-of-function (LOF) CaR mutants and c) whether one or both intracellular domains (ICD) of the CaR homodimer contribute to signaling.

Methods: The non-phosphorylatable mutation CaR^{S875A} was introduced into both wild-type human CaR and CaR^{T888A} to test whether this heightens signaling. Then CaR^{T888A} was introduced into two loss-of-function (LOF) mutants, CaR^{S170A} (extracellular domain, ECD) and CaR^{F801A} (intracellular domain, ICD) to determine a) whether it can rescue their lost function and b) whether its addition to both monomers enhances the benefit. If so then this would indicate that both ICDs of the dimer contribute to signaling.

Results: In HEK-293 cells, CaR^{S875A} exhibited significantly enhanced signaling vs wild-type CaR (EC_{50}, 3.4 ± 0.2 mM WT vs. 1.6±0.1 S875A; P<0.001) while the phosphomimetic CaR^{S875D} mutant reduced Ca^{2+}_o potency (4.7±0.2 mM S875D vs 3.4±0.2 WT; P<0.01). When combined with T888A, the Ca^{2+}_o responsiveness of the double mutant $CaR^{S875A/T888A}$ was further left-shifted relative to CaR^{T888A} alone (2.1±0.4 S875A/T888A vs. 2.6±0.1 T888A; P<0.01) demonstrating the sites' additive effects. Next, the LOF homodimers CaR^{S170A} (ECD) and CaR^{F801A} (ICD) exhibited no Ca^{2+}_o responsiveness up to 40mM, whereas co-mutation with T888A significantly rescued their Ca^{2+}_o responsiveness. It is known that heterodimerisation of CaR^{S170A} and CaR^{F801A} permits partial rescue of their function. However, additional co-mutation with T888A not only enhanced the rescue but gave maximal rescue when present on both monomers.

Conclusions: Thus, CaR^{S875} is a novel PKC site that, together with CaR^{T888}, shapes the CaR signalling that underpins Ca^{2+}_o homeostasis. Furthermore, removal of inhibitory signaling at CaR^{T888} can rescue both ECD and ICD loss-of-function mutants, and, both ICDs of the dimer contribute to CaR signalling.

Funding: Government Support - Non-U.S.

FR-PO486

INS-3001 Efficiently Inhibits Severe Vascular Calcifications by Direct Interference with Vessel Wall Calcification

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Background: Prevention/treatment of vascular calcification currently is based on controlling its most important risk factors. A new therapeutic approach with potential higher efficacy consists in the administration of molecules directly interfering with the calcification process in the vessel wall, such as INS-3001. This abstract reports about the administration of INS-3001 in a rat model of vitamin D-warfarin induced vascular calcifications (pooled data of 3 independent studies).

Methods: Calcification was induced in male rats (8 weeks) by warfarin (3mg/g diet) administration during 6 days and by 4 consecutive daily administrations of vitD3 (100.000 IU/kg) starting on day 1 of the warfarin administration. Rats were randomly assigned to different groups: vehicle, and INS-3001 groups of 12, 25, 2x25, 50 and 2x50 mg/kg/day. Treatment was administrated sc. for 7 days (starting together with vitD). Animals were sacrificed on the 8th day. Vascular calcification was evaluated on Von Kossa stained tissue sections of the thoracic/abdominal aorta and by measurement of the total Ca content of the thoracic/abdominal aorta and the carotid/femoral arteries by atomic absorption spectrometry.

Results: Mortality rate was 38% (15/40) in the vehicle group, similar -33% (4/12) and 44% (5/12)- in the 1x25 and 1x12.5 mg/kg/day dose groups, numerically lower -15% (3/19), 21% (4/19)- in the 2x50, 1x50 mg/kg/day dose groups and significantly lower 0% (0/18) in the 2x25 mg/kg/day dose group. In the abdominal aorta, significantly lower Von Kossa positivity (area%) was measured in the INS-3001 groups compared to the vehicle group (3±5%, 6±4%, 8±7%, 15±3%, 20±3% and 28±10% in respectively the 2x50, 50, 2x25, 25, 12.5 mg/kg/day and the vehicle group). Total Ca content of the abdominal aorta was also significantly lower in the INS-3001 (not the 12.5 and 25 mg/kg/day) groups compared to the vehicle group (2.8±3.7, 6.1±5.0, 7.4±6.9, 14.9±7.0, 15.6±9.4 and 14.9±7.5 mg/g tissue in respectively the 2x50, 50, 2x25, 25, 12.5 mg/kg/day and the vehicle group. Similar reductions in area% Von Kossa positivity and total Ca content were seen in the thoracic part of the aorta, and the arteria femoralis and carotis.

Conclusions: In conclusion, INS-3001 is a promising molecule for the treatment of CKD and non-CKD induced vascular calcifications.

Funding: Commercial Support - Inositec AG, Switzerland

FR-PO487

Identification and In Vitro Characterisation of a Novel Inhibitor of Vascular Calcification

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Background: Vascular calcification (VC) is the pathological deposition of calcium and phosphate minerals in the walls of the cardiovascular system. At present, there is no approved pharmacological treatment and affected individuals are left at great risk of experiencing cardiovascular events and death. Herein, we describe a new class of inhibitors of VC based on the previously reported inhibitor *myo*-inositol hexaphosphate (IP6), with improved drug-like properties.

Methods: Multi-step syntheses, starting from protected *myo*-inositol species, via selective PEGylation, phosphorylation or sulfation were employed to afford a library of novel IP6 derivatives. Activity was compared in a serum calcification propensity assay, and stability was monitored in serum. *In vitro* efficacy experiments were performed on primary human vascular smooth muscle cells (VSMCs), treated with either calciprotein particles (CPPs) (50 μg/mL) or calcification medium (2.7 mM calcium and 2.5 mM phosphate, CaP), respectively. Subsequently, calcification of the cell monolayer, cell viability and expression of cell markers were assessed.

Results: Synthesis and screening of twelve monodispersed PEGylated IP6 derivatives revealed IP4-di-PEG_2 (INS-3001) to be almost 10-fold more potent than IP6 in delaying serum calcification propensity, with activity in the low μM range. This activity was retained following 4 h incubation in fresh human serum. VSMC calcification was largely abolished by 1 μM INS-3001 in the CaP setup (Figure 1), and 30 μM INS-3001 in the CPP setup, respectively.

Conclusions: INS-3001 was superior to natural IP6 with regard to serum calcification propensity, *in vitro* stability and efficacy in cell culture models. Thus, the presented *in vitro* data provides support for the further development of INS-3001 as an inhibitor of vascular calcification.

Funding: Commercial Support - Janssen AG, Clariant International AG, Givaudan Schweiz AG, Government Support - Non-U.S.

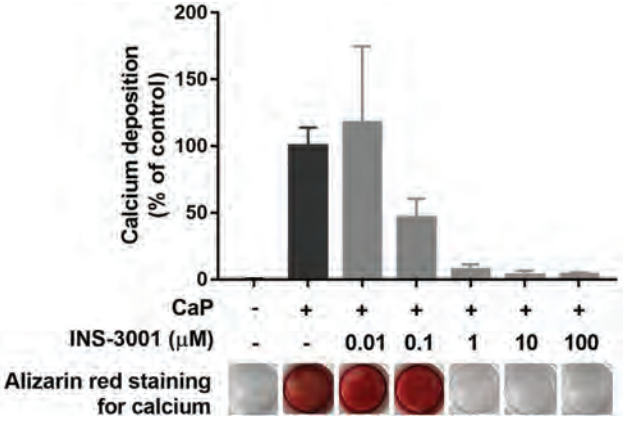

Figure 1 Reduction of VSMC calcification by INS-3001.

FR-PO488

Hyperphosphatemia Is a Negative Modulator of the Calcium-Sensing Receptor

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Background: Chronic kidney disease (CKD) is associated with hyperphosphataemia and secondary hyperparathyroidism (SHPT). The key controller of parathyroid hormone (PTH) secretion is the calcium-sensing receptor (CaSR), whose crystallised extracellular domain has revealed four putative phosphate-binding sites in its inactive conformation. Our aim was to determine whether extracellular phosphate, at concentrations found in CKD, can inhibit CaSR and increase PTH secretion, and thus potentially contribute to the aetiology of SHPT.

Methods: CaSR activity was measured as Ca^{2+}_i mobilisation (Fura-2) and extracellular signal-regulated kinase (ERK) phosphorylation in HEK-293 cells stably transfected with human CaSR. The HEPES buffer contained 0.5mM $CaCl_2$ with phosphate added as Na_2HPO_4 and KH_2PO_4 in a 4:1 ratio (pH 7.4). PTH secretion was measured in dispersed human parathyroid cells obtained ethically following neck surgery and in cultures of intact mouse parathyroid glands.

Results: Raising phosphate concentration from 0.8 mM (physiological) to 2 mM (CKD-like) inhibited CaSR-induced Ca^{2+}_i mobilisation (-52 ± 4%; P<0.001) and ERK activation

(-18 ± 3%; P<0.01). Raised phosphate concentration (2 mM) inhibited the maximal (E_{max}) Ca^{2+}_o response suggesting non-competitive antagonism (-32 ± 3%; P<0.001). Further, phosphate attenuated CaSR activity with an IC_{50} of 1.2 mM (95%CI 1.0 to 1.4). Mutation of $CaSR^{R62}$ (a putative phosphate-binding site) to alanine ablated this inhibitory effect. Finally, pathophysiologic phosphate concentrations elicited rapid (within minutes) and reversible increases in PTH secretion in freshly-isolated human parathyroid cells (+39 ± 10%, 0.8 vs 2mM, P<0.05; +58 ± 15%, 0.8 vs 3mM; P<0.001) consistent with a receptor-mediated action (with thanks to Ryan Mun). Similarly, in cultures of mouse parathyroid glands phosphate again elicited rapid, concentration-dependent increases in PTH secretion (by up to 180%, 3 vs 0.8mM).

Conclusions: Therefore CaSR is able to sense pathophysiologic deviations in phosphate concentration apparently via non-competitive antagonism at $CaSR^{R62}$ resulting in increased PTH secretion. This mechanism may help explain the contribution of hyperphosphatemia to SHPT.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support, Government Support - Non-U.S.

FR-PO489

Impact of Modifying Calcitriol Dosing on the Vitamin D Metabolome and Vascular Calcification in Experimental CKD

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Background: Calcitriol (CAL) and other vitamin D analogs are used to manage SHPT in CKD although treatment can result in PTH over-suppression and lead to vascular calcification (VC). This study sought to determine whether modifying CAL dosing frequency and magnitude could provide a better treatment profile (PTH, FGF23, VC) in experimental CKD.

Methods: Experimental CKD (e-CKD) was induced by 0.25% dietary adenine in adult male Sprague-Dawley rats (n=42). At 4 weeks (W), e-CKD rats were divided into 5 groups and treated with oral CAL as follows: 0ng/kg (e-CKD control, n=8), 5ng/kg x 4, q6h (n=9), 20ng/kg once daily (n=8), 20ng/kg x 4, q6h (n=9), or 80ng/kg once daily (n=8). After 3W treatment, rats were sacrificed, tissues and blood were collected and assessed for vitamin D metabolome, PTH, FGF-23 and VC. Sub-analysis according to PTH level: (i) over suppressed (OS), (ii) target, and (iii) mildly suppressed (MS) was performed.

Results: CAL treatment in e-CKD rats markedly increased the levels of 1,25-$(OH)_2D_3$ in a dose-dependent manner (4-6X). In contrast, both circulating 25-OH-D_3 and 24,25-$(OH)_2D_3$ fell significantly (10-30%), particularly at the higher CAL dose. Sub-analysis based on PTH suppression revealed a greater fall in 25-OH-D_3 and 24,25-(OH)2D3 levels in Target and OS groups compared to the MS and untreated e-CKD. Overall, in e-CKD, the CAL treatment induced markedly increased VC (94% in Tx vs. 29% of vessels in unTx) and FGF-23 (8-20 X increase in Tx vs. unTx) regardless of treatment profile.

Conclusions: CAL suppressed PTH early in e-CKD treatment as expected, but PTH became progressively refractory over the 3 weeks of treatment. Even in the absence of overt PTH over suppression, all animals in the CAL treatment group had significant vascular calcification. All CAL treatment groups induced similar changes in the circulating vitamin D metabolome, with increased 1,25-$(OH)_2D_3$ but decreased 25-OH-D_3 and corresponding 24,25-$(OH)_2D_3$. The CAL treatment induced varying alterations in the vitamin D metabolome which were reflected, in part, on how PTH levels were modified in response to CAL. These findings suggest that how calcitriol is administered as well as the level of PTH suppression should be re-examined to minimize VC in CKD.

FR-PO490

Significant Differences Exist in Intestinal Phosphate Absorption Between Species

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Background: The efficacy of a NaPi-IIb specific inhibitor was recently reported to be different between rat and human. In addition, intestinal phosphate absorption was previously reported to be different between rat and mouse. This study analyzed intestinal phosphate absorption in dog, monkey, and rat and also investigated the concentrations of phosphate and related hormones in serum. The results showed significant differences in the intestinal phosphate absorption between the three species.

Methods: Fecal and urinary phosphate excretion were compared in dog, monkey, and rat after paired feeding. Phosphate uptake by intestinal brush border membrane vesicles (BBMV) and the mRNA expression of NaPi-IIb, PiT-1, and PiT-2 were also evaluated in duodenum, jejunum, and ileum of each species. In addition, the ALP activity in each intestinal segment and the concentration of serum phosphate and FGF23 were measured.

Results: The intestinal phosphate absorption rate, as calculated from food intake and fecal excretion, was highest in dog out of the three species, as were urinary fractional excretion of phosphate and serum concentration of FGF23. Accordingly, phosphate uptake with BBMV and mRNA expression of NaPi-IIb were also highest in dog. Surprisingly, urinary phosphate excretion was lowest in monkey, and the intestinal phosphate absorption rate in monkey was by far the lowest out of the three species. Dog and rat showed positive correlations between phosphate uptake with BBMV and mRNA expression of NaPi-IIb in each intestinal segment. Although phosphate uptake in BBMV was high in monkey, mRNA expression of NaPi-IIb was not detected in any of the intestinal segments, and intestinal ALP activity was low.

Conclusions: These results suggest that, whereas NaPi-IIb is the major contributor to intestinal phosphate absorption in dog and rat, monkey phosphate degrades only slightly in the intestine, and its contribution to intestinal phosphate absorption might be through a sodium-dependent phosphate transporter other than NaPi-IIb. In conclusion, there are significant differences in intestinal phosphate absorption between dog, monkey, and rat. Further analysis is needed to elucidate the phosphate absorption in human.

FR-PO491

Oxidative Stress and Autophagy Are Involved in Matrix Vesicles (MV)-Induced Calcification of Recipient Vascular Smooth Muscle Cells (VSMC)

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Background: Oxidative stress is increased in patients with CKD and is associated with vascular calcification. Oxidative stress can also increase autophagy. We have previously demonstrated that cellular derived MV, but not media derived MV, increase calcification of recipient normal rat VSMC when endocytosed, in association with increased intracellular calcium and NOX production. We hypothesize that this increased oxidative stress in recipient VSMC cells may lead to inappropriate autophagy that induces vascular calcification and thus extends calcification lesions.

Methods: Cellular or media derived MV were co-cultured with recipient VSMC in the calcification inducing media (high phosphorus) and alteration of oxidative stress (ROS production) and autophagy were examined by confocal microscopy and Western blot, respectively. Calcification was determined by biochemical assay. In some experiments, inhibitors for autophagy (3-MA) and oxidative stress (NOX1/4 inhibitor GKT137831) were added to the MV-VSMC cultures.

Results: The addition of cellular MV, but not media MV, to recipient normal VSMC increased ROS production by 95% at 24 h and increased the expression of autophagy markers LC3II and Atg5 at 1 and 3 days during calcification. Pretreatment with GKT137831 significantly blocked cellular MV-induced ROS production in recipient VSMC. Furthermore, inhibition of autophagy with 3-MA decreased MV-induced calcification of recipient VSMC by 425%, a magnitude similar to the inhibition induced by blockade of NOX1/4 activity.

Conclusions: Cellular derived MV induced ROS production and increased autophagy in recipient VSMC during calcification (high phosphorus media). These results suggest that normal VSMC may endocytose cellular MV from calcifying VSMC leading to increased ROS and autophagy in the recipient VSMC, resulting in increased calcification.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support

FR-PO492

Effect of Advanced Glycation End-Products (AGE) Lowering Drug ALT-711 on a Rat Model of CKD-Mineral Bone Disorder (CKD-MBD)

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Background: Reduced bone quality is a key determinant of skeletal fragility in CKD. We hypothesized that the increased formation of AGEs that occur in advanced CKD due to oxidative stress may be responsible for the impaired bone fragility. To test this hypothesis, we evaluated the efficacy of an AGE breaker (ALT-711) on CKD-MBD and bone AGEs in a slowly progressive rat model of CKD, the Cy/+ rat.

Methods: We compared five groups of animals [1: Normal (NL); 2: CKD; 3:CKD+ALT-711; 4: CKD+ 3% calcium in drinking water (Ca, lowering PTH and reducing bone remodeling); and 5: CKD+ALT-711+Ca]. Treatment was started at 25 weeks of age (~50% kidney function) and ended at 35 weeks (~15% function). Blood, kidney weight, and heart weight were examined at sacrifice and aorta calcification determined biochemically. Bone AGE content was determined in demineralized femur shaft using fluorescence plate reader, normalized by collagen (hydroxyproline) content.

Results: As expected, there was progressive decline in kidney function over time in all 4 CKD groups compared to NL. The serum levels of calcium and FGF23 were higher, and phosphorus and PTH lower in CKD animals treated with calcium consistent with resolution of secondary hyperparathyroidism. The administration of ALT did not alter BUN, calcium, PTH or FGF23 levels but did reduce serum phosphorus levels in CKD animals. Heart weight and left ventricular mass index (LVMI) increased in all of the CKD animal groups compared to NL. Treatment with ALT-711, calcium, or ALT+Ca all reduced the heart weight and LVMI in CKD animals. There was increased vascular calcification in all of the CKD animal groups but no effect of ALT-711 treatment. Serum 8-OHdG levels (marker of DNA oxidation) was elevated in CKD compared to NL and not lowered by ALT-711. Bone AGE levels were increased in CKD compared to NL but not reduced by ALT treatment.

Conclusions: In a progressive rat model of CKD, there is increased AGE accumulation in bone. Starting treatment with an AGE breaker early in the course of CKD failed to improve bone AGE levels, but did reduce heart weight. Interestingly, there was also an interaction with secondary hyperparathyroidism in the pathogenesis of AGEs and response to ALT. Bone biomechanical testing is in progress.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support

FR-PO493

Specific Knockdown of WNT8b Expression Protects Against Phosphate-Induced Calcification in Vascular Smooth Muscle Cells by Inhibiting the Wnt/β-Catenin Signaling Pathway

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Background: In the last 10 years, the prevalence, significance, and regulatory mechanisms of vascular calcification have gained increasing recognition. The aim of this work is to study the action of WNT8b on the disease development of phosphate-induced vascular calcification through its effect on vascular smooth muscle cells (VSMCs) in vitro by inactivating the Wnt/β-catenin signaling pathway.

Methods: In order to find out the effect of WNT8b on the Wnt/β-catenin signaling pathway and vascular calcification in vitro, β-glycerophosphate (GP) induced T/G HA-VSMCs were treated with siRNA against WNT8b, LiCl (Wnt agonists), and both, respectively. The mRNA and protein levels of WNT8b, α-SMA, calcification associated molecules, the Wnt signaling pathway related molecules were determined by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and western blot analysis. TOP/FOP-Flash reporter assay was performed to detect transcription activity mediated by β-catenin.

Results: si-WNT8b reduced calcium deposition and activity of ALP, increased α-SMA level, and dropped BMP2, Pit1, MSX2, and Runx2 levels, while stimulation of LiCl worsened β-GP-induced calcium deposition, increased activity of ALP, reduced α-SMA expression level. si-WNT8b resulted in reductions in WNT8b, Fzd4, β-catenin, p-GSK-3β, and cyclin-D, whereas enhancement of p-β-catenin and GSK-3β, indicating si-WNT8b could alter the Wnt/β-catenin signaling pathway thus to hamper the vascular calcification in T/G HA-VSMC, which further demonstrated by TOP/FOP FLASH assay and detection of β-catenin expression level in the nucleus.

Conclusions: Taken together, we conclude that WNT8b knockdown abolishes phosphate-induced vascular calcification in VSMCs by inhibiting the Wnt/β-catenin signaling pathway.

FR-PO494

High Phosphate Diet Before Pregnancy Dysregulates Phosphate Metabolism in Neonatal Offspring Mice

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Background: Excess intake of dietary phosphate (Pi) increases fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) to maintain plasma Pi level. FGF23, is a potent phosphaturic factor, binds to α-klotho / FGFR complex in the kidney to promote excretion of Pi into urine. In addition, excess intake of dietary Pi also decreases in renal α-klotho expression. Downregulation or lack of α-klotho induces a premature aging-like phenotype such as ectopic calcification and osteoporosis resulted from hyperphosphatemia. Recent the theory of developmental origins of health and disease indicates that early exposure of dietary or environmental factors determines the risk of various diseases in adulthood. Thus, excess intake of dietary Pi during or before pregnant period may affect the gene expression of α-klotho or other Pi regulating factors related to future health risks in offsprings.

Methods: To investigate that, we used C57BL/6J female mice aged 8 weeks old. Mice were fed with either control Pi (CP) or high Pi (HP) diet for 21 days before pregnancy. At the end of diet control, they were mated with male mice and become pregnant. After the delivery, both groups were fed with CP diet. Neonatal offspring mice (at 3 weeks old when they were weaning) were subjected to analysis.

Results: As a result, although the no difference of Pi and calcium levels in breast milk between two groups, the offspring mice in HP diet group revealed plasma FGF23 concentration was significantly elevated, urinary Pi excretion tended to increase and urinary calcium excretion tended to decrease. Renal α-klotho mRNA expression level was not changed in the both groups. But interestingly, renal mRNA expression level of NaPi2c and CYP27B1, which are known to be suppressed by the FGF23/α-klotho signal was decreased in HP diet group. Femur mRNA expression level of Phex, which is known to FGF23 secretory suppression factor at the bone was increased in HP diet group. In addition, femur mRNA expression level of DNA methyltransferase (DNMT1) was significantly increased in HP diet group.

Conclusions: In conclusion, excessive dietary Pi intake before pregnant causes abnormal Pi metabolism, and it may be due to epigenetic modification through DNA methylation at bone.

Funding: Government Support - Non-U.S.

FR-PO495

Nox1 Induces Osteoblastic Transition of Vascular Smooth Muscle Cells and Contributes to Vascular Calcification in Early CKD Rats with Normal Serum Phosphorus

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Background: Vascular calcification (VC) is a major cause of mortality in patients with chronic kidney disease (CKD). While higher levels of serum phosphorus contribute to VC, but in early CKD patients with normal phosphorus have VC, and reduction of serum P by using various P binder is not effective in preventing VC progression in patients with CKD. So, we think some other factors contribute to VC, especially in Early CKD.

Methods: In CKD dialysis patients with VC (n=11) and dialysis CKD patients without VC (n=13), serum 8-OHdG was measured. We use CKD5 and early CKD rats to test the Vascular calcification and Nox1, we also use the serum of early CKD patients to incubate **primary VSMCs** , SM22α expression and RUNX2 expression, calcium deposition in primary rat VSMCs and Nox1 are measured.

Results: In a rat model for the stage 5 CKD (CKD5), robust increases of VC and 8-OHdG, significant reductions of smooth muscle 22 alpha (SM22α) expression, and an upregulation in RUNX2 expression in vascular smooth muscle cells (VSMCs) were demonstrated. Inhibition of 8-OHdG using MnTMPyP dramatically reduced these events without normalization hyperphosphatemia. In CKD patients with VC (n=11) but not in CKD patients without VC (n=13), 8-OHdG was significantly elevated. While the serum levels of calcium and phosphate were not altered in animal models in the early stage CKD (ECKD), 8-OHdG, VC, SM22α downregulation, RUNX2 upregulation, and NADPH oxidase 1 (NOX1) expression in VSMCs were all significantly changed. More importantly serum (10%) derived from patients with ECKD (n=30) or CKD5 (n=30) significantly induced SM22α downregulation, RUNX2 upregulation, NOX1 upregulation along with a robust 8-OHdG, and calcium deposition in primary rat VSMCs. These alterations were all reduced by MnTMPyP and a specific NOX1 inhibitor (ML171).

Conclusions: Collectively, we provide evidence for an important role of Nox1 in promoting VC development in early CKD patients, which was at least in part through induction of osteoblastic transition in VSMCs.

Funding: Government Support - Non-U.S.

FR-PO496

Polymer Characterization of VS-505, a Novel Non-Absorbed, Calcium- and Aluminum-Free Phosphate Binder

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Background: Inadequate control of phosphate in chronic kidney disease can lead to pathologies of clinical importance. VS-505 is a novel phosphate binder, which has been evaluated in hemodialysis subjects with hyperphosphatemia for 8 weeks (ClinicalTrials.gov Identifier #: NCT02469467) with the following results: (1) significantly reduced plasma phosphorus (Pi) in the treatment group (median Pi change -2.40 mg/dl), (2) no changes of iron parameters, and (3) no change of Ca levels, but a significant reduction in iPTH and CaxPi over the treatment period.

Methods: In this study, VS-505 was characterized by FT/IR spectroscopy (Fourier Transform Infrared), XPS (X-ray Photoelectron Spectroscopy), and ^{57}Fe Mössbauer spectroscopy. VS-505 is not soluble in regular NMR solution/solvent, and thus was analyzed by a 750 MHz solid-state NMR spectroscopy. In 5% EDTA, VS-505 was partially solubilized, and the solubilized material was analyzed by size exclusion chromatograph.

Results: VS-505 has a high density (1.95 vs. 1.27 g/cm^3 for sevelamer, by helium pycnometer) with a reduced pill size. When exposed to simulated gastric fluid, VS-505 exhibits a low swell volume (0.4 vs. 4 cm^3/ml/0.1 g for sevelamer), and low iron release (<3% Fe^{+3} vs. 53% for sucroferric oxyhydroxide) after 2 hr of incubation at 37°C. FTIR spectrum of VS-505 conforms with that of gum Arabic, indicating that gum Arabic is the main component in VS-505. Results from XPS show the presence of Fe, C and O in VS-505, devoid of chloride and other impurities. Mössbauer spectroscopy results indicate that all Fe atoms in VS-505 are in the high-spin Fe^{+3} state. Solid-state NMR results show significant differences in chemical shifts between gum Arabic and VS-505, implicating the presence of tight complex between iron ion and gum Arabic. Results from the size exclusion chromatograph with solubilized material in 5% EDTA indicate that gum Arabic in VS-505 maintains its original molecular weight with chelated iron ion.

Conclusions: The characterization shows that VS-505 is a stable complex with 30% iron ion chelated to 70% gum Arabic (by weight). While effectively binding phosphate, VS-505 releases <3% of its iron content in gastric fluid, and doesn't significantly affect blood iron parameters in both pre-clinical and clinical studies.

FR-PO497

Discovery of a Novel NPT2b Inhibitor That Inhibits Intestinal Phosphate Absorption in Mice and Rats

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Background: Hyperphosphatemia in CKD and ESRD contributes to bone, kidney and CV diseases. Inhibition of the intestinal phosphate (Pi) transporter, NPT2b, may be an approach to augment current therapies for hyperphosphatemia.

Methods: Utilizing radiolabeled Pi uptake assays in CHO cells over-expressing various Pi transporters, and a mouse model, we discovered a novel NPT2b inhibitor, LY3358966. Due to the insoluble nature of the compound at acidic and neutral pH, the sodium salt of the compound was formulated in PVP-VA for further characterization. An amorphous solid dose formulation suitable for clinical development was prepared by spray dry dispersion and incorporated into a capsule and further tested for activity in mice.

Results: LY3358966 inhibited Pi uptake in CHO cells over-expressing human, mouse and rat NPT2b with an IC50 of 32.4, 43.9, and 26.8 nM, respectively. Formulated in PVP-VA and dosed in water, the compound has desirable PK properties for a drug target found on the luminal surface of the small intestine, with low bioavailability, and very low serum free drug concentrations. LY3358966 acutely (15 min) inhibited Pi absorption in mice with an ED50 of 0.15 mg/kg and Emax of 73%. Four hours after dosing the inhibitor, the ED50 was 1.12 mg/kg and Emax was 79%. In contrast, it acutely inhibited Pi absorption with an ED50 of 0.051 mg/kg and an Emax of only 19% in rats. Importantly, a solid dose formulation of

LY3358966 incorporated into a capsule effectively inhibited Pi uptake in mice. Following three 10 mg/kg doses of LY3358966 and radiolabeled Pi, mouse feces were collected for 48 hours. Compared to placebo treated animals, there was a significant increase in radiolabeled Pi recovered in feces (8.6% of the dose, $p < 0.0001$).

Conclusions: LY3358966 is a potent NPT2b inhibitor with desirable PK properties that inhibits Pi absorption in mice when dosed in a solid dose formulation acceptable for clinical development. Using a pharmacological approach, we achieved an inhibition of Pi absorption in mice comparable to that reported in NPT2b knockout mouse models. The NPT2b inhibitor had less effect on acute Pi absorption in rats.

Funding: Commercial Support - Eli Lilly Co

FR-PO498

Stronger Phosphate Lowering Effects of a Novel PiT-1/PiT-2/NaPi-IIb Triple Inhibitor EOS789 in Hyperphosphatemia Than a NaPi-IIb Inhibitor

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Background: EOS789 is a novel inhibitor of the sodium-dependent phosphate co-transporters PiT-1, PiT-2, and NaPi-IIb, which play central roles in intestinal phosphate absorption.

Methods: The in vitro inhibitory activity and the in vivo potency of EOS789 were evaluated.

Results: The in vitro IC_{50} values of EOS789 on human or rat NaPi-IIa, NaPi-IIb, NaPi-IIc, PiT-1, and PiT-2 were between 1 and 10 μM, and its IC_{50} value on sodium-dependent phosphate uptake in rat small intestinal brush border membrane vesicles was 3.1 μM. The inhibitory effect of EOS789 on intestinal phosphorus uptake was evaluated in healthy rats by fecal phosphorus excretion rate. EOS789 dose-dependently increased the fecal phosphorus excretion rate and inversely decreased the urinary phosphorus excretion rate. The effects of EOS789 on serum phosphorus, FGF23, and intact PTH concentrations were evaluated in a hyperphosphatemia model of adenine-induced nephritis rats. After 14 days food admixture dosing of EOS789 with a dose between 0.015% and 0.5%, the serum phosphorus, FGF23, and intact PTH concentrations were decreased dose-dependently. Notably, EOS789 at the highest dose decreased these serum parameters to below their values in normal control rats. In addition, EOS789 exhibited a more potent effect on serum phosphorus than a NaPi-IIb-selective inhibitor in hyperphosphatemia rats. The effect of EOS789 on the progression of chronic kidney disease was also evaluated in chronic anti-Thy1.1 nephritis rats. During the experimental period, dietary dosing of EOS789 provided a sustained suppression of serum phosphorus, FGF23, and intact PTH. After 16 weeks of dosing, EOS789 significantly decreased serum creatinine concentration in parallel with suppression of fibrosis-related mRNA and pro-inflammatory cytokine mRNA expressions. In addition, EOS789 significantly ameliorated ectopic calcification of the thoracic aorta.

Conclusions: This series of data suggests that EOS789 has a robust lowering effect on serum phosphorus under hyperphosphatemic conditions, and that EOS789 treatment can ameliorate renal function deterioration and protect the cardiovascular system from ectopic calcification.

FR-PO499

Combination Treatment with Tenapanor and Sevelamer Synergistically Reduces Urinary Phosphate Excretion in Rats

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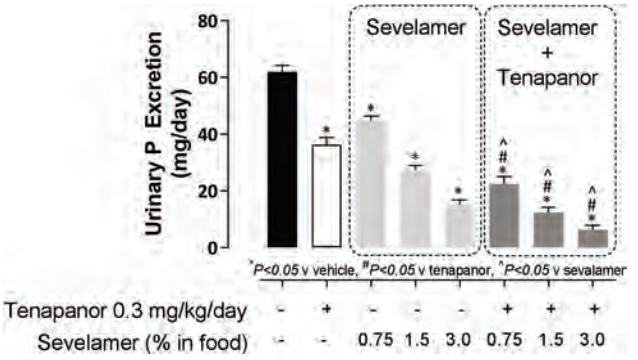
Background: Many chronic kidney disease (CKD) patients on dialysis fail to achieve target serum phosphate (P) levels, despite treatment with available P binding agents. Tenapanor is a first-in-class, minimally absorbed small molecule NHE3 inhibitor that reduces intestinal P absorption and is under investigation as a novel treatment for hyperphosphatemia in CKD patients on dialysis. This study evaluated the effect of tenapanor and varying doses of sevelamer carbonate administered alone and in combination on urinary P excretion, an index of intestinal P absorption, in rats.

Methods: Male Sprague Dawley rats were assigned to groups dosed orally with vehicle or tenapanor (0.3 mg/kg/day) and provided with a diet containing varying amounts of sevelamer (0-3% w/w) for 11 days. 24-hour urinary P excretion was measured over the final 4 days. The effect of the addition of tenapanor (0.3 mg/kg/day) or vehicle for 7-days on 24-hour urinary P excretion in rats (n=6/group) already on a stable dose of sevelamer (1.5% w/w) for 6 days was also assessed.

Results: In combination with tenapanor, sevelamer dose-dependently decreased urinary P excretion such that the combination effect was significantly greater than either tenapanor or the equivalent dose of sevelamer alone across all sevelamer dose levels (**Figure**). The BLISS statistical model of independence indicated that the drug combination interaction between tenapanor and sevelamer was synergistic. On a stable sevelamer dose (1.5% w/w) that reduced urinary P excretion by 42 ± 3% (*P<0.001*), the addition of tenapanor reduced residual urinary P excretion by 37 ± 6% (*P<0.05*).

Conclusions: The combination of tenapanor and sevelamer results in greater reductions in intestinal P absorption than when either agent is administered alone. Clinical evaluation of the potential for the combination of tenapanor and sevelamer to more effectively achieve serum P target levels in hyperphosphatemic CKD patients on dialysis is warranted.

Funding: Commercial Support - Ardelyx



FR-PO500

Effects of Ferric Citrate on Phosphate Metabolism in Alport Mice with CKD

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Background: The maintenance of phosphate (Pi) homeostasis depends on the absorption of Pi across the intestine, reabsorption by the kidney and resorption by the bone. The mechanisms however still remain unknown and the role of intestinal Pi transport is subject of ongoing debate. Hyperphosphatemia is a common occurrence and plays important roles in cardiovascular and metabolic bone disease. Normalizing the serum Pi by reducing the dietary Pi intake can resolve the biochemical changes which may improve the clinical outcomes in CKD. To investigate the role of intestinal Pi absorption, we studied the effects of the Pi-binder Ferric Citrate (FC) on reducing intestinal absorption of Pi in a mouse model of progressive CKD

Methods: 4-week old wild type (WT) and Col4a3 knockout (Alport, CKD) mice (n=6 to 8 per group) were fed with control diet (0.9% Pi, 0.6% Ca^{2+}) or control diet supplemented with 2% or 3% ferric citrate (FC) for 5 to 6 weeks. Tissues were harvested and serum biochemistry was measured at 9-10 weeks old mice. To determine the intestinal Pi transport mechanism in CKD, we isolated apical brush border membrane vesicles (BBMVs) from the ileum and studied sodium gradient dependent Pi (Na^+/Pi) transport and NaPi-2b protein abundance.

Results: Serum BUN and Pi were increased significantly in Alport CKD mice compared to WT. In parallel to Pi, serum FGF23 levels were markedly increased in CKD mice. Dietary FC administration in CKD mice significantly reduces the serum Pi levels along with a significant decrease in intact FGF23. In addition, serum calcium (Ca^{2+}) was reduced significantly in CKD mice compared to WT. FC diet improved Ca^{2+} levels in CKD mice. The excretion of Pi in the urine was increased in CKD mice compared to WT mice and in contrast, urinary Pi was reduced in both wild type and CKD mice fed with FC. BBMV Na^+/Pi cotransport activity was comparable between WT and CKD mice fed with control diet. However, BBMV Na^+/Pi transport activity was increased in both WT and CKD mice fed with FC diet. This was associated with a 2-fold increase in BBMV NaPi-2b protein abundance.

Conclusions: Our data indicates that, the administration of FC improved the dysregulated Pi metabolism in CKD. However, the resultant increase in NaPi-2b protein abundance suggest that FC or any other Pi binder needs to be administered at all times with the diet.

Funding: Commercial Support - Keryx Biopharmaceuticals Inc.

FR-PO501

Effects of Low-Dose Ferric Citrate on Hematologic and FGF23 Parameters in High-Hepcidin Murine Models with and Without CKD

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Background: Ferric citrate (FC) is an effective phosphate binder and iron supplement in CKD patients. FC-delivered iron is enterally absorbed, despite high hepcidin levels, but the specific absorption mechanism and its regulation remain unknown. We assessed the effects of FC in *Tmprss6* knockout (TKO) mice, a model characterized by high hepcidin levels and resultant iron-refractory iron-deficiency anemia, without or with the addition of adenine-induced CKD, which exacerbates anemia and iron restriction.

Methods: Wild-type (WT) and TKO mice were fed diets with or without 0.2% adenine for 6 weeks (to induce CKD), with or without 0.1% FC for the last 3 of the 6 weeks (corresponding to an adult human FC dose of ~2 tablets thrice daily). Blood and tissues were then collected for analysis.

Results: In the absence of CKD, TKO mice compared to WT mice had significantly higher serum hepcidin, lower liver iron, lower serum iron, lower hemoglobin, higher serum erythropoietin (EPO), higher bone and marrow *Fgf23* mRNA, and higher plasma C-terminal (total) FGF23, but no difference in circulating intact FGF23. In TKO mice, despite high serum hepcidin, FC administration significantly decreased serum phosphate, increased liver iron, increased serum iron, increased hemoglobin, decreased serum EPO, decreased bone and marrow *Fgf23* mRNA, and decreased plasma total FGF23. With adenine-induced CKD, TKO mice had the highest hepcidin levels. FC treatment caused no significant changes in serum phosphate, liver iron, or serum iron, but significantly increased hemoglobin, with a trend towards lower serum EPO. FC therapy significantly decreased bone *Fgf23* mRNA,

marrow *Fgf23* mRNA, and plasma total FGF23, but not intact FGF23. Despite the very high hepcidin levels, FC increased duodenal ferroportin protein in the CKD TKO mice.

Conclusions: In the high-hepcidin TKO mice, low-dose FC was sufficient to increase enteral iron absorption and ferroportin expression, improve the anemia of both iron deficiency and CKD, and decrease FGF23 expression. FC may decrease FGF23 expression through decreased enteral phosphate absorption, improved iron status, and/or decreased EPO levels. Although murine FC dosing needs to be optimized, the models of FC absorption despite high hepcidin levels will facilitate examination of the mechanisms involved.

Funding: Commercial Support - Keryx

FR-PO502

Vitamin D Increases Bone FGF23 Expression by Increasing Numbers of Early Osteocytes

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Background: Vitamin D directly stimulates osteoblast maturation and FGF23 expression. FGF23 is expressed in early osteocytes at the trabecular periphery. Whether the vitamin D-mediated increase in bone FGF23 expression reflects increased numbers of early osteocytes or an increase in per-osteocyte expression is unknown.

Methods: We evaluated markers of osteocyte maturity and FGF23 expression by immunohistochemistry (IH) and immunofluorescence (IF) and osteocyte apoptosis by TUNEL staining in iliac crest of 11 dialysis pts age 15.8±0.8 years who underwent bone biopsy before and after 8 mos of doxercalciferol (D) therapy. Bone protein expression was evaluated by Ariol scanning of IH. Numbers of FGF23-expressing osteocytes were counted and normalized by bone area. RNA was extracted from cores and evaluated by qRT-PCR.

Results: FGF23 co-localized with e11/gp38, a marker of early osteocytes (**Fig 1A**). Numbers of FGF23-expressing osteocytes correlated with FGF23 protein expression ($r=0.83$, $p<0.001$). Numbers of FGF23-expressing osteocytes increased by 226 (83, 440)% and FGF23 mRNA increased by 226 (124, 320)% in response to D. Expression of sclerostin, a mature osteocyte marker, increased in cortical bone in response to D ($p<0.05$). Osteocyte apoptosis was low at baseline but increased with D (**Fig 1B**).

Conclusions: The co-localization of FGF23 with e11/gp38 suggests that increased numbers of FGF23-expressing osteocytes reflect a D-mediated increase in early osteocytes. The tight relationships between FGF23 RNA message, FGF23 protein, and numbers of FGF23-expressing osteocytes suggest that D-mediated increases in FGF23 expression are due to increased numbers of FGF23-expressing osteocytes in CKD bone. Increased osteocyte apoptosis suggests that D is associated with increased osteocyte turnover. Further studies into altered osteocyte maturation, the effects of medications on osteocyte biology, and their implications for clinical bone disease in CKD patients are warranted.

Funding: Other NIH Support - NIAMS

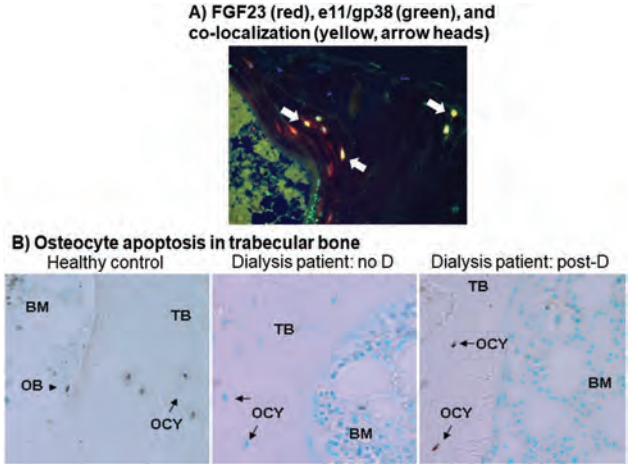

Figure 1

FR-PO503

Primary CKD Osteoblasts Are Resistant to the Pro-Maturation Effects of 1,25D In Vitro

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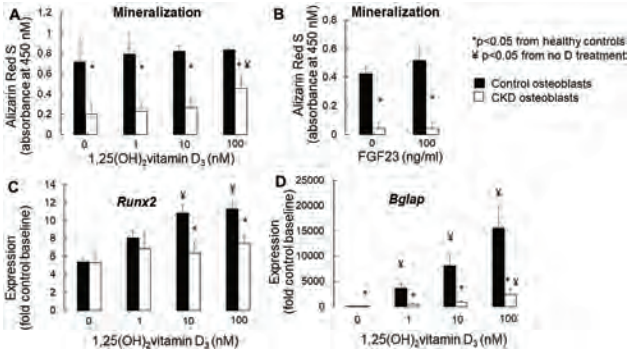
Background: Osteoblast maturation and bone mineralization are integrally linked processes. Pediatric CKD patients have a high prevalence of skeletal mineralization defects *in vivo* and primary CKD osteoblasts demonstrate intrinsic impairments in maturation *in vitro*. 1,25D simultaneously stimulates osteoblast maturation and bone FGF23 expression while overexpression of FGF23 in primary rodent osteoblasts impairs their maturation and mineralization. However, the independent effects of 1,25D and FGF23 on osteoblast differentiation in CKD are unknown.

Methods: To investigate this, primary osteoblasts from 6 adolescent dialysis patients and 3 healthy adolescent controls were grown to confluence and stimulated to mineralize in differentiation media for 2 weeks. Mineralization was quantified by staining cultures with 1% Alizarin Red S; gene expression was evaluated by qPCR in parallel cultures.

Results: Mineralization was greater in healthy control than in CKD osteoblasts. 1,25D increased mineralization of CKD osteoblasts (**Fig A**). FGF23 did not affect mineralization in either CKD or healthy control cultures (**Fig B**). *Runx2* (early osteoblast marker) expression was similar in healthy control and CKD osteoblasts at baseline and increased in both groups with time. 1,25D increased *Runx2* in control, but not CKD, osteoblasts (**Fig C**). Osteocalcin (*Bglap*) (mature osteoblast marker) expression was higher in control than in CKD osteoblasts at baseline. 1,25D stimulated *Bglap* in both groups (**Fig D**). FGF23 did not affect *Runx2* or *Bglap*.

Conclusions: These data suggest that CKD osteoblasts are resistant to the pro-maturation effects of 1,25D. This 1,25D resistance may contribute to the mineralization defects that persist in pediatric CKD patients despite current renal osteodystrophy therapies. The mechanism behind CKD osteoblast maturation resistance, which appears unrelated to exogenous FGF23, requires further evaluation.

Funding: Other NIH Support - NIAMS



Figure

FR-PO504

1,25-Dihydroxyvitamin D Stimulation Increases FGF23 Expression in Calcified Vessels Under High Phosphate Condition

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Background: Elevated fibroblast growth factor 23 (FGF23) is observed in patients with end stage renal disease (ESRD) or chronic kidney disease (CKD). Vascular calcification is also a commonly observed in patients with ESRD or CKD, which leads to increased cardiovascular events and mortality. Expression of FGF23 in bone is elevated by the factors as serum Pi, parathyroid hormone (PTH), and 1,25-Dihydroxyvitamin D, and is suppressed by dentin matrix protein-1 (DMP1). We hypothesized that 1,25-Dihydroxyvitamin D stimulates FGF23 expression in Pi-induced calcified vessels.

Methods: We performed aortic tissue culture in the medium with normal phosphate (0.9mM), high P (3.8mM)i, and high Pi with 1,25Dihydroxyvitamin D (1,25D) for 10 days, subsequently von kossa staining, quantification of calcium contents and gene expression of *Fgf23*, *Dmp1*, and other osteocyte/osteoblast marker; alkaline phosphatase (*Alp*), dickkopf-related protein 1 (*Dkk1*), and scrolostin, and immunostaining of FGF23 and DMP1 in the cultured aorta.

Results: Aortic ring cultured in the medium with high Pi and high Pi+1,25D showed calcium deposition and increased calcium contents significantly. Quantitative PCR demonstrated that increased*Alp*and *Dkk1*expression and unchanged *Sost* expression in high Pi+1,25D medium. Expression of FGF23 in aorta ring is not altered under the high Pi condition, but is increased under the high Pi+1,25D condition. DMP1 expression in aorta is increased under the high Pi condition while the up-regulation is attenuated under the high Pi+1,25D condition.

Conclusions: These results suggest that 1,25Dihydroxyvitamin stimulation increases FGF23 expression in calcified vessels under high phosphate condition.

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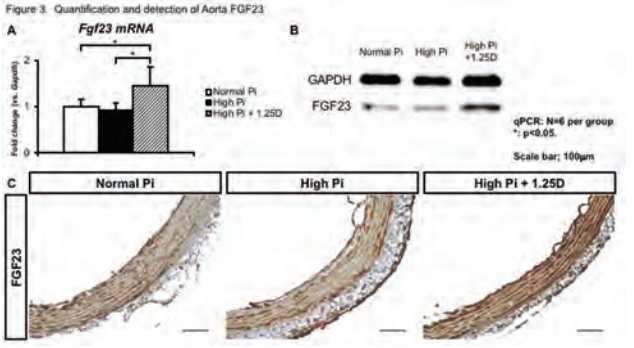

A. Quantification of *Fgf23*gene expression. B. Immunoblot image of FGF23 protein. C. Immunohistochmical images of FGF23 expression. Normal Pi; 0.9 mmol/L phosphate, High Pi; 3.8 mmol/L phosphate, High Pi+1.25D; 3.8 mmol/L phosphate and 100 nmol/L 1,25-Dihydroxyvitamin D_3.

FR-PO505

Osteocytes Are the Major Source of Circulating FGF23 During Acute Inflammation

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Background: Inflammation is a novel mechanism that stimulates fibroblast growth factor (FGF) 23 production in bone cells and extraosseous tissues, however the contribution of osteocytes to circulating FGF23 levels during acute inflammation is unknown.

Methods: To investigate the effects of inflammation on FGF23 production, wild-type (WT) mice and mice with a conditional deletion (cKO) of Fgf23 in osteocytes (Fgf23fl/fl;DMP1-Cre+) received a single injection of interleukin-1β (IL-1β) or saline (Ctr). We measured FGF23 mRNA and circulating intact and total protein (cFGF23 which includes intact and cleaved proteins) up to 6 hours post injection.

Results: In WT mice, injection of IL-1β increased circulating levels of intact and total FGF23 (12-fold and 62-fold, respectively, $p<0.001$ vs Ctr). IL-1β increased *Fgf23* mRNA expression by 60 fold in bone, 7 fold in spleen and by 300 fold in kidney ($p<0.05$ vs. Ctr), suggesting that extraosseous production of FGF23 may contribute to circulating FGF23 levels. In line with these findings, cKO-Ctr mice did not show a significant reduction in circulating FGF23 compared to WT-Ctr mice, suggesting that extraosseous FGF23 production is sufficient to maintain relatively normal circulating FGF23 levels. However, cKO mice showed a markedly reduced FGF23 secretion in response to IL-1β injection compared to WT- IL-1β mice for both intact (-80%) and total FGF23 (-92%, $p<0.001$). Consistent with these data, bone *Fgf23* mRNA and protein expression levels were also dramatically reduced by 80% ($p<0.01$) in cKO- IL-1β mice compared to WT- IL-1β. Finally, IL-1β treatment of primary osteocytes cultures from WT and cKO animals increased *Fgf23* mRNA expression and protein secretion by 10 fold in WT mice ($p<0.05$ vs. Ctr) but failed to increase FGF23 in cKO cultures.

Conclusions: These results suggest that *Fgf23* expression is increased in bone and extraskeletal tissues during acute inflammation, however osteocytes are the major secretory source for the circulating FGF23 protein.

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FR-PO506

Soluble Klotho Regulates TRPC6 Calcium Signaling via Lipid Rafts and Independently of FGFR-FGF23 Pathway

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Background: Membranous Klotho interacts with fibroblast growth factor receptor (FGFR) to form coreceptors for FGF23. The ectodomain of membranous klotho is shed (soluble klotho, sKL) and functions as a circulating endocrine or local paracrine factor. sKL protects the heart by inhibiting growth factor-stimulated, PI3K-dependent TRPC6-mediated Ca entry. Lipid rafts are membrane microdomain important in many cellular processes including growth factor signaling and membrane trafficking. We have shown that sKL binds to sialogangliosides of membrane lipid rafts to inhibit cardiac Ca signaling. Regulation of lipid raft formation and function may underlie pleiotropic actions of sKL. A recent X-ray crystal structure of sKL in ternary complex with FGFR and FGF23 suggests that function of sKL is mediated by FGFR and FGF23. The physiological circulating levels of sKL and FGF23 are ~30 pM and 2 pM (50 pg/ml), respectively. Yet many in vitro assays examining the function of sKL, FGF23, and FGFR based on formation of the ternary complex utilize supraphysiological levels of sKL and FGF23. For example, in cell proliferation assay based on sKL-FGF23-FGFR ternary complex, 100 fold higher sKL (3 nM) and 4,000 fold higher FGF23 (200 ng/ml = 4 nM) are commonly used. Here, we examine whether sKL can function independently of FGFR-FGF23.

Methods: Computer modeling of sKL structure with and without FGFR-FGF23. Whole-cell patch-clamp recording of TRPC6 channels in L6 myoblast cell line lacking endogenous FGF receptors.

Results: Computer modeling of sKL structure suggests potential binding sites for sialic acids of gangliosides in the absence of FGFR-FGF23. sKL inhibits TRPC6 channel in L6 cells. We identified amino acid sequence unrelated to sKL but structurally conserved for binding sialic acid known as carbohydrate binding motif (CBM). Purified recombinant CBM inhibits TRPC6 expressed in L6 cells and in HEK293 cells.

Conclusions: Our results support the hypothesis that sKL protects the heart by downregulating TRPC6-mediated calcium signaling in lipid rafts. sKL can exert actions independently of FGFR-FGF23 signaling pathway.

Funding: NIDDK Support

FR-PO507

Valsartan Mitigated CKD-MBD in Uremic Rats by Activation Klotho

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Background: Valsartan as the most commonly one of ARB drugs, can effectively lower blood pressure and remit the progression of chronic kidney disease. In addition, we also observed that the ARB drugs could ameliorate the calcium and phosphorus metabolism in patients. The main purpose of this experiment is to explore whether valsartan could mitigate calcium and phosphorus metabolism and secondary hyperparathyroidism and seek the underlying signal pathway in uremic rats.

Methods: Animal Experiment: The rats were divided into three groups: sham group, 5/6 nephrectomy group, 5/6 nephrectomy + calcitriol group. 1) Through serum biochemical tests, to detect the levels of BUN, Creatine, Ca and P in various groups and determine expression of Klotho, TGFβ1, iPHT in serum. 2) By HE, Masson staining of renal tussues, Observation of fibrosis and collagen deposition in parathyroid tissue and renal tissue. 3) Detection expression of Klotho, TGFβ1, iPHT in parathyroid tussue by Immunohistochemical staining. 4) Detection expression of AT1, Klotho, TGFβ1, iPHT, E-cadherin and α-SMA in renal tussue by Immunohistochemical staining. 5) Using PCR and Western-Bloting detect expression of Klotho, TGFβ1, E-cadherin and α-SMA in renal tussues.

Results: (1) Valsartan could effectively reduce the elevated creatinine, BUN, improve the calcium and phosphorus metabolism and lessen iPTH in the 5/6 nephrectomy rats; (2) Valsartan can distinctly reduce parathyroid hyperplasia and iPTH expression, increased Klotho expression in parathyroid tissue; (3) Valsartan might ameliorate kidney injury and fibrosis by light microscopy; (4) In renal tissue, Valsartan may induce Klotho and E-cadherin expression and reduce iPTH, TGFβ1 and α-SMA expression.

Conclusions: Valsartan could suspress parathyroid hyperplasia and ameliorate kidney injury and fibrosis in uremic rats. Valsartan might delay the progression CKD-MBD in ESRD by increasing the expression of Klotho, reducing iPHT, improving calcium and phosphorus metabolism.

Funding: Government Support - Non-U.S.

FR-PO508

Comparison of Four Commercially Available ELISA Kits for Serum and Urinary Klotho in Mice

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Background: Klotho is a transmembrane protein that serves as a co-receptor for fibroblast growth factor 23 (FGF23). Klotho is cleaved and released into body fluids, including serum, urine, and cerebrospinal fluid. Soluble Klotho has been implicated in diverse of biological activities and an increasing number of studies measured serum or urinary soluble Klotho levels using commercially available ELISA kits. However, the sensitivity and specificity of these kits have been poorly studied.

Methods: We assessed the diagnostic accuracy of 4 commercially available ELISA kits for soluble Klotho using serum and urine from 3-week-old *Klotho* homozygous knockout (*Klotho*$^{-/-}$), heterozygous knockout (*Klotho*$^{-/+}$), and wild type littermate mice. We measured serum soluble Klotho with 4 kits and urinary soluble Klotho with 2 kits following the instructions of manufacturers.

Results: *Klotho*$^{-/-}$ mice showed hyperphosphatemia, high 1,25-dihydroxyvitamin D, low PTH, increased fractional excretion of phosphate, and markedly elevated FGF23, as described previously. All 4 kits for serum soluble Klotho measurements appeared to be inaccurate, with false positive results with sera from *Klotho*$^{-/-}$ mice. As for urinary soluble Klotho measurements, we found that only a kit from Immuno-Biological Laboratories Co., Ltd. provided reasonable results. With this assay, mean±SD creatinine-adjusted urinary soluble Klotho levels in *Klotho*$^{-/-}$ mice, *Klotho*$^{-/+}$ mice, and wild type mice were 5±2, 218±38, and 290±149 pg/g creatinine, respectively ($P<0.001$).

Conclusions: These results indicate that appropriate choice of the assay is important for accurately measuring soluble Klotho levels. For validating the function of ELISA kits, measurement of target elements with specimens of knockout animals would provide valuable information.

FR-PO509

Sclerostin, a Potential Mediator in the Bone-Vascular Axis

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Background: The Wnt/β-catenin signaling, one of the most important bone anabolic pathways, might also be a major player in the crosstalk within the bone-vascular-axis. When pathologically disturbed, this axis results in the concomitant occurrence of disturbed bone metabolism and vascular calcification (VC). A hallmark of these VCs is the transdifferentiation of vascular smooth muscle cells (VSMCs) towards bone-forming (osteochondrogenic) cells. In the current study we investigated parameters related to the Wnt/β-catenin signaling cascade and its inhibitor sclerostin.

Methods: Rats were given 0.3mg warfarin/g diet to induce VC. Rats not receiving warfarin were included as controls. Rats were sacrificed at different time-points, i.e. after 4, 6, 8 and 10 weeks of warfarin treatment, to follow up the development of VC. At sacrifice; VC, aortic mRNA expression and immunohistochemistry, bone status and serum biochemistry were analyzed.

Results: Results showed a time-dependent increase in VC in warfarin-treated rats. Aortic calcium concentration significantly differed from controls in 4-wk treated rats (p=0.0286), reaching a 50-fold increase in 10-wk treated rats (p=0.0061). Furthermore, aortic mRNA levels of osteochondrogenic transdifferentiation markers (Sox9, p=0.0317 and Cbfa1, p=0.0635) and β -catenin (regulating target gene transcription, p=0.0159) were upregulated. Interestingly, this went along with an upregulation of aortic mRNA expression (p=0.0159) and protein levels of sclerostin, as well as serum levels of this protein which became significant (p=0.0381) in 10-wk treated rats compared to controls. Finally, a mild but significant (p= 0.0095) decrease in bone formation parameters was observed in 10-wk treated warfarin rats.

Conclusions: Our results support the hypothesis that VSMCs transdifferentiate towards osteochondrogenic cells and thereby also express genes/proteins associated with the Wnt/β-catenin signaling, including its inhibitor sclerostin. The latter thereby may act as a negative feedback protein to prevent excessive (vascular) calcifications, similar to its function in bone. Sclerostin might also spillover from the vessels to the circulation (high serum sclerostin levels) causing mild inhibition of bone formation.

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FR-PO510

Accumulation of Activated β-Catenin in Uremic Hyperparathyroid Glands

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Background: Parathyroid proliferation may become nodular mainly in cases of advanced uremic hyperparathyroidism. The ubiquitously expressed multifunctional protein β-catenin displays important functions in the canonical Wnt signaling pathway by regulating cell proliferation and differentiation. Activation of Wnt/β-catenin pathway leads to stimulate aerobic glycolysis, called Warburg effect, which is validated the dominant metabolic style in tumor tissue. While hyperplasic parathyroid glands display similar pathology characteristics of tumor, the aim of this study is to evaluate whether the Wnt/β-catenin signaling pathway is activated in hyperplastic glands from sHPT patients and if Warburg effect is activated by β-catenin pathway.

Methods: Serum iPTH levels were measured by radio-immunity method. Hyperplastic parathyroid glands from sHPT patients (n=36) were acquired from patients during the operation. Normal parathyroid tissue (n=3) was obtained from glands inadvertently removed in conjunction with thyroid surgery. Real time RT-PCR and immunohistochemistry were performed to detect PCNA and activated β-catenin, and glycolytic enzymes.

Results: 1. The average serum iPTH level was 1264.59±576.29 pg/ml of sHPT patients and 42.0±20.95 pg/ml of normal controls respectively. 2. HE staining revealed 5 diffuse hyperplasic glands and 31 nodular hyperplasic glands. 3. The mRNA and protein expression of PCNA was dramatically up-regulated compared to normal controls. 4. The expressions of activated β-catenin were increased in hyperplastic glands compared to normal glands. There was no difference between diffuse hyperplasic and nodular hyperplasic glands. Semiquantitative analysis didn't reveal association between β-catenin and iPTH level. 5. The expressions of glycolytic enzymes: HK2, PFK and LDH were not up-regulated in hyperplasic glands compared to the normal glands. Semiquantitative analysis didn't reveal associations between expressions of glycolytic enzymes and iPTH level.

Conclusions: Our results strongly suggest that modifications in the Wnt/β-catenin signaling pathway may be involved in the development of sHPT. However, aerobic glycolysis was not activated by β-catenin in hyperplasic glands. The precise mechanism is needed to be explored.

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FR-PO511

In Silico Model of PTH-Induced Self-Limiting Anti-Apoptotic Signaling Pathways in Osteoblasts

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Background: Cyclical and continuous stimulations of cell receptors result in differential responses with important clinical and therapeutic implications. An example of such differential response is seen in the anabolic and catabolic outcomes of intermittent and continuous elevations of parathyroid hormones (PTH), respectively, where chronic level of PTH, as seen in hyperparathyroidism, leads to catabolic effects on bone, whereas cyclical administration of PTH or analogs, as seen in osteoporotic therapy, stimulates osteoblastic activities resulting in anabolic gains. The goal is to develop an *in silico* model describing the proteasomal proteolysis mechanism limiting the anti-apoptotic effect of PTH in osteoblasts, in order to understand quantitatively the differential clinical responses.

Methods: We develop a model to describe the underlying PTH-induced intracellular osteoblastic signaling pathway, namely, Runx-2-CREB-Bcl-2 signaling pathway. The model incorporates multiple scale to capture scale differences between the anti-apoptotic and degradative enzymatic activities. The model is used to evaluate apoptotic activities under the conditions of continuously and intermittently elevated PTH, respectively.

Results: *In silico* result shows that continuously elevated PTH increases degradative enzymatic activities and blunt the anti-apoptotic effects associated with the Runx-2-CREB-Bcl-2 signaling pathway. The directional difference between CREB and Runx-2 equilibrates Bcl-2 level, thereby nullifying its anti-apoptotic effects on osteoblasts. Consequently, PTH-mediated osteoclastic activities via RANK-RANKL-OPG pathway exert catabolic loss. The model also predicts that intermittency of PTH increases CREB while only intermittently decreasing Runx-2, resulting in a net increase in Bcl-2. This, in conjunction with downstream inhibition of cytokine-mediated osteoblastic apoptosis, leads to anabolic gains. Employing global sensitivity analysis, different anti-apoptotic therapeutic directions are outlined.

Conclusions: There is a great need to understand the mechanisms underlying differential osteoanabolic and catabolic responses induced by intermittent and continuous levels of PTH, respectively, in order to provide new therapeutic options for patients. With our model, we can demonstrate importance of Runx-2-CREB-Bcl-2 signaling in limiting the osteoblastic apoptosis.

FR-PO512

Severe CKD, Even Without a High-Phosphorus Diet, Affects the Expression of Only CaSR, VDR, and Gcm2 in the Parathyroid Glands in Rats but Not of Other Key Genes Involved in Parathyroid Function

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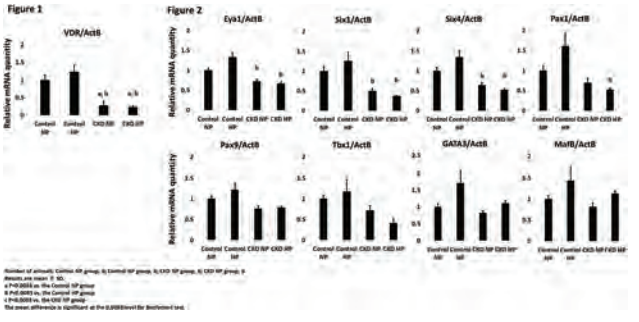
Background: Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD), which disrupts mineral homeostasis. It occurs during the early course of progressive renal insufficiency, and is associated with mortality and cardiovascular events. Downregulation of calcium-sensing receptor (*CaSR*) and vitamin D receptor (*VDR*) occurs throughout this process. Previously, we reported that glial cells missing 2 (*Gcm2*), which directly regulates *CaSR* and is related to hyper- and hypoparathyroidism, may be responsible for the reduction in mRNA and protein levels of *CaSR* (ASN 2017). However, as many other important genes regulate parathyroid function, we aimed to investigate the role of these genes in SHPT progression.

Methods: CKD was induced in rats with 0.75% adenine-containing diet. CKD and control rats were maintained for 2 weeks on diets with 0.7% (normal; NP) or 1.3% (high; HP) phosphorus. For gene expression analysis, quantitative real-time polymerase chain reaction (PCR) was performed with TaqMan probes. Protein expressions was analyzed by immunohistochemistry and Western blotting. DNA methylation analysis was performed by restriction digestion and quantitative PCR.

Results: *VDR* mRNA and protein expression levels were reduced in CKD rats fed NP and HP diets. There was no significant difference in the DNA methylation status of *VDR* promoters among the four groups (Figure 1) as same as *CaSR* (ASN 2017). There were no significant differences in the gene expression levels of *MafB*, *GATA3*, *Eya1*, *Tbx1*, *Pax1*, *Pax9*, *Six1, Six4* (Figure 2), although the Gcm2 gene and protein expression levels were significantly decreased.

Conclusions: CKD NP and HP rats showed significant reductions in *CaSR*, *VDR* and *Gcm2* gene and protein expressions. Our data suggested that compared with *CaSR* and *VDR*, *Gcm2* plays a major role in SHPT progression and may be an important therapeutic target for SHPT.



FR-PO513

Effect of Ovariectomy on the Progression of CKD-Mineral Bone Disorder (CKD-MBD) in Cy/+ Rats

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Background: There is increasing interest in sex as a biologic variable, yet studies have generally not examined the role of sex in the pathogenesis of CKD-MBD despite experimental and epidemiological evidence suggesting that estrogen is protective to kidney function and bone and thus CKD-MBD. In the Cy/+ rat model of CKD-MBD, a spontaneous genetic mutation causes progressive kidney function decline in males prior to 20 weeks of age, but kidney function is maintained in females past 80 weeks of age making it impractical to study these females as a model of CKD. Therefore, ovariectomy to mimic a post-menopausal state may accelerate the initiation of the CKD-MBD phenotype and enable the use of female Cy/+ rats in research.

Methods: Sixteen female Cy/+ rats were randomized to either ovariectomy (OVX) (n=8) or sham surgery (n=8) at 15 weeks of age. A casein-based diet was initiated at 24 weeks of age to promote kidney function decline as is done in studies with male Cy/+ rats. Blood was sampled at 10, 20, 25, 30, and 35 weeks of age, and analyzed for BUN, plasma phosphorus, and plasma calcium.

Results: Data collected on all n=16 through 25 weeks show that OVX rats have higher body weights ($p<0.0001$) (and lower uterine weights for n=4 that completed the 35 weeks of the study) confirming the success of the OVX procedure. Plasma phosphorus decreased over time in both groups ($p<0.0001$), but was not different between groups ($p=0.46$). Plasma calcium was not different between groups ($p=0.38$) and did not change over time ($p=0.57$). Plasma BUN decreased slightly over time in both groups ($p<0.01$) but remained in normal ranges, and there is no difference between OVX and sham ($p=0.23$). In n=2 OVX and n=2 sham that have completed the 35 weeks of the study, preliminary analysis shows no appreciable difference in BUN, phosphorus, or calcium between groups.

Conclusions: Analyses will continue through 35 weeks, however at 25 weeks of age, there is currently no indication that OVX accelerates kidney function decline in female Cy/+ rats. This is in contrast to Cy/+ male rats which can be phenotyped based on elevated BUN as early as 10 weeks of age, and by 25 weeks of age exhibit a ~50% reduction in kidney function (Moe et al. 2011).

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FR-PO514

Advanced Glycation End-Products (AGEs) Accumulation and Skeletal Complications in CKD Patients

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Background: Chronic kidney disease (CKD) has high rates of mortality related to uremic toxins and bone complications. Fractures risk is higher in CKD patients than general population and is dependent of cortical bone quality. We aim to investigate the relationships between advanced glycation end-products (AGEs) and bone in a cohort of patients at different stages of CKD.

Methods: 86 CKD patients (stages 3-4, N=26; hemodialysis, N=32; peritoneal dialysis, N=28) were included. AGEs levels were measured in serum (for glycated hemoglobin and pentosidine), skin (through AGE-Reader device), and cortical bone (by immunohistochemistry). Fracture risk was predicted using FRAX tool. Bone histomorphometry was performed to measure cortical porosity, thickness and volume.

Results: Age was 51±13 yrs., 48 (56%) male, 41 (48%) Caucasian and 16 (19%) diabetics; GFR was 6 (5-17) mL/min, body mass index (BMI) was 26±5 kg/m^2 and waist circumference 92±12 cm. AGEs levels in skin were 3.0±0.7 AU (reference: < 2.0 AU) and were positively correlated with age ($R=0.68$; $P=0.001$), glycated hemoglobin ($R=0.28$; $P=0.04$), risk for major osteoporotic fracture ($R=0.54$; $P=0.001$), hip fractures ($R=0.53$; $P=0.001$), Framingham risk ($R=0.53$; $P=0.001$). AGEs deposition in cortical bone were positively correlated with major osteoporotic fracture risk ($R=0.50$; $P=0.001$). Cortical thickness were negatively correlated with serum pentosidine ($R=-0.30$; $P=0.04$) and glycated hemoglobin levels ($R=-0.31$; $P=0.03$), Framingham Risk ($R=-0.33$; $P=0.02$), age ($R=-0.43$; $P=0.03$), BMI ($R=-0.43$; $P=0.03$), waist circumference ($R=-0.38$; $P=0.01$), and LDL-cholesterol ($R=-0.34$; $P=0.02$). Cortical porosity were positively correlated with cholesterol levels ($R=0.30$; $P=0.04$) and Framingham Risk ($R=0.32$; $P=0.03$).

Conclusions: AGEs were detected in cortical bone of CKD patients at different stages and correlates with their risk for major osteoporotic fractures; this risk was also related with AGEs accumulation in skin. Serum levels of pentosidine and glycated hemoglobin were associated to low thickness of cortical bone. Finally, there seems to be a relationship between poor quality of cortical bone and factors linked to cardiovascular disease.

Funding: Government Support - Non-U.S.

FR-PO515

PTH Suppression Normalizes CKD-Induced Elevations in Cortical Bone Perfusion in an Animal Model of Progressive CKD

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Background: Patients with chronic kidney disease (CKD) have accelerated bone loss, vascular calcification and abnormal biochemistries, together contributing to an increased risk of cardiovascular disease and fracture-associated mortality. Despite evidence of vascular pathologies and dysfunction in CKD, our group has shown that cortical bone tissue perfusion is higher in a rat model of high-turnover CKD. The goal of this experiment was to test the hypothesis that suppression of high turnover through calcium-induced suppression of PTH would normalize cortical bone vascular perfusion in the setting of CKD.

Methods: 35-week-old animals in one of three groups: normal (NL), Cy/+ (CKD), and Cy/+ treated with 3% calcium water (CKD+Ca) for 10 weeks (n=6/group) underwent intra-cardiac fluorescent microsphere injection to assess bone tissue perfusion.

Results: CKD animals had serum blood urea nitrogen (BUN) and PTH levels significantly higher than NL (+182% and +958%; $p<0.05$). CKD+Ca animals had BUN levels that were similar to CKD, while PTH levels were significantly lower and comparable to NL. Dynamic bone histomorphometry of the proximal tibia demonstrated that active remodeling surfaces were significantly increased in the CKD animals compared to normal (+88%); levels were normalized to NL levels by calcium supplementation. MicroCT analysis of the proximal tibia cortical porosity showed a trend toward higher values in CKD (+401%; $p=0.0962$) but not CKD+Ca (+111%; $p = 0.3787$) compared to NL. Both femoral cortex (+220%, $p=0.0083$) and tibial cortex (+336, $p=0.0009$) tissue perfusion were significantly higher in CKD animals when compared to NL; perfusion was normalized to those of NL in CKD+Ca animals.

Conclusions: These data demonstrate that the combination of bone remodeling suppression and serum PTH reduction normalizes cortical bone perfusion in the setting of CKD. Further work will focus on uncoupling the effects of PTH reduction and turnover suppression on cortical bone perfusion in the setting of CKD.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO516

Inflammation and Bone Loss in Patients with New Onset of Lupus Nephritis: The Pathways to Increased Osteoclastogenesis

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Background: The pathogenesis of lupus nephritis (LN) comprises immune complexes deposition, abnormalities of complement system,T,B and regulatory cells-TREG, unbalance of Th1/Th2 subsets and IL17. Bone loss is present in newly diagnosed LN patients without an expressive dose of corticosteroids. Some evidences indicate an increased osteoclastogenesis as the main disturb of the remodeling process. Although the pathways that lead to bone loss are not completely understood, some systems are involved such as RANK-L/OPG, Wnt/βcatenin and Th17/IL17. In this context osteoblasts seems to play a remarkable role in mediating the crosstalk between bone and immune systems as well as osteoclast response. Vitamin D (VitD) is well-known for its role in bone mineralization but studies have been revealing its anti-inflammatory actions such as redirecting Th1 to Th2 response, suppressing Th17 and stimulating TREG. This study aimed to determine the pathways involved in abnormal osteoclastogenesis observed in women at the diagnosis of proliferative LN as well as evaluating if vitD can reverse this response.

Methods: We cultured the human osteoblastic cell line hFOB 1.19. Once mature, we divided cultures into those supplemented with serum from healthy controls (n=15) and LN patients (n-15) instead of fetal bovine serum. Then 1,25-dihydroxyvitaminD was added in two subgroups at 10^{-9}M e 10^{-7}M while vitD was absent in one subgroup in both healthy and LN women. After 48h of vitD addition, hFOB cultures were trypsinized. Flow Cytometry and multiplex assays were performed to test CD166, CD54, RANK-L, OPG, CD14, TLR4, NFκB, SOST, DKK1, βcatenin, IL6, IL1β, TNFα, IL2, IL17A, IL17F, IL21 and IL22.

Results: There was a tendency of DKK1 to be higher in LN patients than healthy controls at baseline without vitD (668.6x460.4pg/mg, p0.07) but at vitD 10^{-7}M the difference became significant (673.0x456.6pg/mg, p0.02). Without vitD, OPG was higher in the healthy group than LN (298.7x 178.8pg/mg, p0.003).

Conclusions: Osteoblasts cultured with LN serum tend to have lower levels of OPG, which can corroborate to increased osteoclastogenesis by inhibition of RANK-L action. Although DKK-1, an inhibitor of wnt/βcatenin pathway, tend to be higher in osteoblasts cultured with LN serum, no difference was observed in βcatenin levels among the groups.

FR-PO517

Validation of a Small Caliber Bone Biopsy for the Diagnosis of Renal Osteodystrophy

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Background: Histomorphometric analysis of a transiliac bone biopsy is the gold standard for the diagnosis of renal osteodystrophy (ROD). This procedure is usually performed with an 8mm-diameter trephine. However, this procedure is progressively forgone due to its invasiveness and cost as well as to the increasing lack of experts able to carry it out. Our objective was to validate ROD diagnosis on halved bone samples, mimicking those obtained with a 4mm Jamshidi needle, a procedure of increasing popularity that has not been endorsed yet.

Methods: Fifty two bone biopsies performed in CKD patients with 8mm Meunier-Bordier trephines were included. Quantitative histomorphometric analysis of the complete bone samples was performed including assessment of bone mass (Bone volume, BV/TV,%), turnover (Bone Formation Rate, BFR, $\mu m^3/\mu m^2/d$, mineralizing surface, MS/BS,%, and Mineral Apposition Rate, MAR, μm/d), resorption (TRAP positive osteoclastic surface, OcS/BS, %), mineralization (osteoid surface, OS/BS %, osteoid thickness OTh, μm and Mineralization Lag Time, MLT, days). Each histological section was then divided lengthwise in two 4mm-wide hemi-biopsies. Histomorphometric analysis was repeated this time on one randomly chosen hemi-biopsy for each sample, blind form initial results. Diagnoses were classified as Osteitis Fibrosa (OF), Adynamic bone disease (ABD), Mixed uremic bone disease (MUO), Osteomalacia (OM) or other. Correlation of each parameter between the whole biopsy and the corresponding hemi-biopsy was studied using Pearson's test. Concordance between the ROD diagnosis obtained from the whole biopsy and the hemi biopsy was analyzed.

Results: Fifty two biopsies were analyzed including 39 OF, 3 ABD, 3 MUO, 3 OM and 4 Other. Correlations between whole 8mm-wide biopsies and the corresponding hemi-biopsies was for BV/TV, r=0.97, p<0.001, OS/BS, r=0.98, p<0.001, Oc.S/BS, r=0.98, p<0.001, and BFR/BS, r=0.93, p<0.001. Final diagnosis was concordant between the whole biopsy and the hemi-biopsies in 97% of cases.

Conclusions: Four mm wide bone biopsies allow for an accurate assessment of ROD in CKD patients. The replacement of Meunier/Bordier trephines with disposable Jamshidi-type needles could improve the procedure's feasibility at the patient's bedside, as well as decrease both its invasiveness and cost.

FR-PO518

Multiple Lower Doses of Zoledronate Reduces Skeletal Accumulation in the Setting of CKD

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Background: Chronic Kidney Disease (CKD) results in a dramatic increase in skeletal fracture risk. Bisphosphates (BP) are an effective and common treatment for reducing fracture risk but they are not recommended in advanced CKD. We have recently shown higher skeletal accumulation of zoledronate (ZOL) in the setting of CKD. This study aimed to test the hypothesis that more frequent, lower dose administration of ZOL would alter skeletal accumulation profiles in CKD.

Methods: At 25 weeks of age, normal (NL) and CKD (Cy/+) rats were divided into control groups (no dosing), a single dose of a fluorescent-tagged ZOL (FAM-ZOL), or ten weekly doses of FAM-ZOL each at $1/10^{th}$ the dose of the single dose group. A subset of CKD animals were provided 3% calcium (Ca) in drinking water to lower PTH and bone remodelling. At 35 weeks of age, serum, tibia, ulna, radius, vertebra, femora, and mandible were collected. Bulk fluorescence levels were assessed using Spectral CT and data compared using 2-way ANOVA.

Results: At 35 weeks of age, all CKD groups had significantly higher blood urea nitrogen (BUN) compared to NL. Parathyroid hormone (PTH) levels were 10-fold greater in CKD animals compared to NL; Ca supplementation normalized PTH levels to those of NL. At all skeletal sites assessed CKD and CKD+Ca animals had higher FAM-ZOL levels compared to NL (+89 to +167%). The vertebra, radius, and ulna all showed significant dosing effects with the multiple dosed animals accumulating 20-32% less FAM-ZOL than those given a single dose. At the distal femur, there was a significant interaction between factors, with CKD+Ca animals having a 40% reduction in FAM-ZOL retention with multiple FAM-ZOL doses versus a single dose.

Conclusions: More frequent, lower dose administration result in significantly less zoledronic acid accumulation compared to a single dose at multiple skeletal sites.

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FR-PO519

Effects of Fetuin-A-Containing Calciprotein Particle (CPP) on Posttranslational Modifications of Fetuin-A in HepG2 Cells

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Background: Fetuin-A is a liver-derived circulating glycoprotein that has potent calcification-inhibitory capacity. Under calcification stress such as CKD, fetuin-A prevent ectopic calcification by forming colloidal complexes that comprise calcium, phosphate and fetuin-A, termed fetuin-A-containing calciprotein particle (CPP). Recent reports suggest that CPP may have physiological and pathological functions including induction of inflammation. The objective of this study was to investigate the effects of CPP on fetuin-A expression in hepatocytes.

Methods: Synthetic CPP was prepared as previously reported. Because fetuin-A is posttranslationally modified, the molecular weight (MW) of fetuin-A is known to be approximately 60 kDa (fully modified fetuin-A: FM-Fet), which is much higher than deduced MW based on amino acid sequence. We focused on the effects of synthetic CPP on FM-Fet expression using the human hepatoma HepG2 cell line.

Results: CPP increased protein expression of FM-Fet in dose- (462% increase by 100 μg/mL CPP for 24hr) and time-dependent manner. However, CPP did not affect the mRNA expression of fetuin-A. Although we focused on the effects of CPP on degradation pathways of fetuin-A such as the lysosome and the ubiquitin-proteasome system, these pathways were not involved in CPP-induced FM-Fet expression. Since FM-Fet contains N-linked and O-linked glycosylation sites, cell lysates containing CPP-induced FM-Fet were incubated with N-glycosidase PNGase F (peptide-N-glycosidase F) and/or O-glycosidase. Treatment with N-glycosidase and/or O-glycosidase increased the considerable mobility of 60 kDa form of FM-Fet, suggesting that CPP modulate N- and O- glycosidations of fetuin-A. After HepG2 cells were pretreated for 30 min with or without 1 μg/mL brefeldin A, which blocks the transport of proteins from the endoplasmic reticulum to the Golgi complex, cells were incubated in 100 μg/mL CPP for 24 hr. Treatment with brefeldin-A inhibited CPP-induced FM-Fet expression concomitant appearance of approximately 50-55 kDa form.

Conclusions: CPP could upregulate posttranslational modifications of fetuin-A in HepG2 cells. These findings suggest a positive feedback loop between increased CPP which may reflect fetuin-A deficiency in advanced CKD and up-regulation of secreted fetuin-A.

FR-PO520

PPARγ Mediates Impaired Circadian Rhythmicity of Human Vascular Smooth Muscle Cells Cultured Under High Phosphate Environment

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Background: The onset of cardiovascular disease (CVD) in chronic kidney disease(CKD) patients often vary by time-of-day. Peroxisome proliferator-activated receptor γ (PPARγ) has been confirmed to play an important role in vascular smooth muscle cells (VSMC) by acting as a peripheral factor participating in regulation of cardiovascular circadian rhythms. It has been reported that hyperphosphatemia plays a vital role in abnormal cardiovascular circadian rhythms. Here we aim to investigate the role of PPARγ in the biorhythm regulation of human aortic vascular smooth muscle cells (HASMCs) under high phosphate environment in vitro.

Methods: The HASMCs were divided into (1) normal control group (1.0 mmol/L phosphorus), (2) high phosphorus group (2.5 mmol/L phosphorus), (3)PPARγ activator rosiglitazone group (10 μmol/L), and (4) high phosphorus(2.5 mmol/L phosphorus) + rosiglitazone group (10 μmol/L) (n=3). The timing of the beginning stimulated was counted as time 0. Thereafter, cells were collected every 4 hours for a total of 28 hours. The mRNA expressions of PPARγ, Bmal1, Per2 and Rev-erbα in different groups of cells at different time points were detected by quantitative polymerase chain reaction (qRT-PCR).

Results: The mRNA expressions of PPARγ and clock genes Bmal1, Per2, Rev-erbα showed circadian rhythm in control group of HASMCs. A high-phosphorus environment could inhibit the expression of above genes, thereby destroying the normal biorhythm of HASMCs. After activating PPARγ by rosiglitazone, the expression of clock genes were up-regulated, and the inhibited biorhythm of HASMCs by high-phosphorus environment could be reversed(Fig1).

Conclusions: Expression of PPARγ and clock genes Bmal1, Per2, Rev-erbα in HASMCs has circadian rhythm. High phosphorus environment destroys their normal biological rhythms by inhibiting PPARγ. We uncovered a vital role of PPARγ in vascular rhythms disorders under high phosphate environment, suggesting the new treatment target of CVD in CKD patients.

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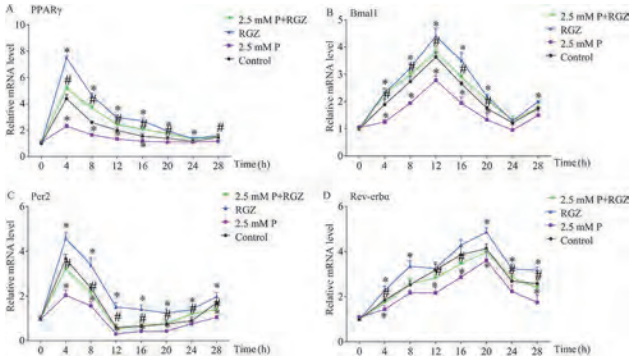

FR-PO521

NMR Metabolomic Profiling in Distinguishing Kidney Stone Formers from Controls

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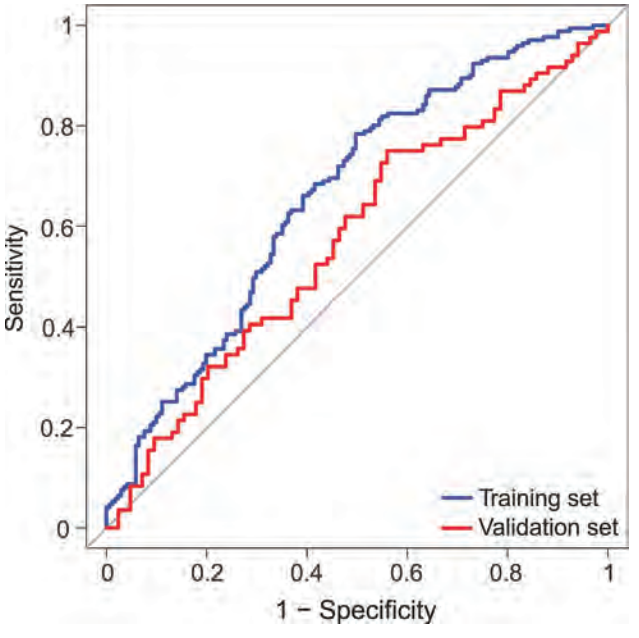
Background: NMR-based urine metabolomics has shown considerable potential in biomarker discovery. It is not fully understood why some individuals develop kidney stones and others do not. We hypothesized that certain urine metabolites can distinguish kidney stone formers from controls.

Methods: We used high resolution NMR spectroscopy to study urines of 255 adult first-time incident symptomatic stone formers (SF), and 255 age and sex-matched controls. This was split into a training dataset (2/3, n=171 SF/control each) and a test dataset (1/3, n=84 SF/control each). NMR spectra were normalized by total spectrum area. Sex and metabolites from NMR data were used in PLS discrimination analysis to fit a model that distinguishes stone formers from controls in the training dataset. Variables with VIP>0.8 were selected for inclusion and cross-validation was used to determine number of components in the final model.

Results: Among the 108 metabolites included in the final model, those with the strongest positive association with SF were 1,6-Anhydro-D-glucose, glucuronate, lactose and an unknown compound, while those with the strongest negative association were 2 unknown compounds and scyllo-inositol. The area under the curve for detecting stone formers with the metabolite panel was 0.66 in the training dataset and 0.57 in the validation dataset **(Figure).** Sensitivity and specificity were 78%/50% and 76%/36% in the training and validation sets, respectively.

Conclusions: This study found that a panel of urine metabolites could potentially discriminate those at risk for symptomatic kidney stones. Further studies are needed to identify the unknown compounds. Understanding the differential expression of these metabolites could shed new insights into the biology of kidney stone formation.

Funding: NIDDK Support



FR-PO522

Matrix Protein Differences Between Various Stone Types

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Background: Enrichment of highly anionic and highly cationic proteins was observed in calcium oxalate monohydrate (COM) stone matrix, but ittle is known about protein distributions other stone types. In this study, stone matrix proteins have been quantitatively identified in other stone types, including uric acid (UA), calcium oxalate dihydrate (COD), and basic calcium phosphate (BCP) using a previously reported method.

Methods: Stone matrix proteins were isolated from 11 COM stones (>60% COM content), 6 UA stone samples (>95% UA content), 6 COD stones (>50% COD content), and 5 BCP stones (>50% BCP content) by dissolution in sequential washes with an EDTA/SDS solution at pH=8 with dithiothreitol added. The solubilized proteins from each stone were concentrated and desalted by ultradiafiltration. Proteomic analysis was performed at the Medical College of Wisconsin Innovation Center using non-labelled, quantitative mass spectrometry methods and reported as spectral counts (SC), including only proteins with 2 or more peptide matches at >85% confidence, after removing keratin and redundant proteins.

Results: All samples contained >1,000 SC, but the total protein signal was slightly smaller in COM compared to other stone types. More than 400 unique proteins were identified in each stone type, but a smaller subset were both frequent and abundant in each stone type: 69 proteins in ≥7 of 11 COM stones (89% SC); 126 proteins in ≥4 of 6 COD stones (85% SC); 108 proteins in ≥3 of 5 BCP stones (92% SC), and 51 proteins in ≥4 of 6 UA stones (67% SC). Most abundant proteins were common between the different stone types, and all stone types were enriched in strongly cationic proteins. Calcium containing stones were also enriched in strongly anionic proteins, more prominently in COM compared to COD or BCP. UA stones exhibited a markedly different proteome compared to calcium stones, with fewer nuclear proteins and more inflammatory components.

Conclusions: Stone matrix proteins exhibit distinctly different patterns in each stone type, implying that unique crystal interactions with proteins and/or cell surfaces control their pathogenesis. The prominence of strongly anionic proteins in calcium stones, particularly in COM suggests that polyanion-polycation aggregation is a plausible mechanism for COM stone formation. Conversely, UA stone formation may be more dependent on inflammatory pathways, but the link to crystal aggregation is unkown.

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FR-PO523

Common CLDN2 Variants Are Associated with Kidney Stone Risk and Reduced Claudin-2 Expression in Human Tissue

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Background: The majority of calcium reabsorption in the proximal tubule (PT) occurs by an unknown route, although many studies suggest it is a passive process. The claudin family of proteins are tight junction proteins that in part modulate paracellular permeability and passive reabsorption in the kidney. The isoform claudin-2 forms cation-selective pores *in vitro* and is highly expressed in the PT. We previously showed that *Cldn2*$^{-/y}$ mice exhibit hypercalciuria and nephrocalcinosis, both of which are major risk factors for the development of kidney stones. We hypothesized that *CLDN2* polymorphisms would associate with susceptibility for nephrolithiasis. To date, genome-wide association studies of nephrolithiasis have excluded *CLDN2* from their analyses due to its location on the X chromosome.

Methods: Twelve SNPs in the *CLDN2* locus passed our inclusion criteria and were assessed by logistic methods for disease association in two separate patient populations. Meta-analysis of the 2 studies was subsequently conducted using METAL with a total of 11,130 kidney stone cases and 187,639 controls. Using the dataset from the Genotype-Tissue Expression (GTEx) project, we analyzed *cis*-acting eQTLs in the *CLDN2* locus. GTEx has insufficient kidney samples for eQTL analysis, but human kidney cortex and pancreas both exclusively express the same transcript (ENST00000540876.1). Thus, we analyzed pancreatic claudin-2 expression in association with *CLDN2* risk variants.

Results: Our findings show that 9 *CLDN2* SNPs were associated with nephrolithiasis with p-values of 0.0462-0.0055. Given our findings in *Cldn2*$^{-/y}$ mice, we predicted that *CLDN2* risk variants for kidney stones would lead to reduced claudin-2 expression. In 6 of the 7 *CLDN2* SNPs available for eQTL analysis using GTEx, nephrolithiasis risk alleles were strongly associated with decreased pancreatic claudin-2 expression.

Conclusions: Our present findings suggest that common *CLDN2* variants lead to reduced claudin-2 expression and thereby increase the risk for human kidney stone formation.

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FR-PO524

Urinary Stone Forming Crystals Activate Renal Medullary Epithelial Cells to Shed Extracellular Vesicles Containing Specific MicroRNAs and Proteins

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Background: The majority (~80%) of urinary stones are comprised of calcium oxalate (CaOx) and/or hydroxyapatite (HA). Our previous studies suggest that populations of urinary extracellular vesicles (EVs) and their contents differ in stone formers. This study was designed to examined whether CaOx or HA crystals activate human renal medullary epithelial cells (HRMdEC) to shed EVs containing specific microRNAs (miRNAs) and their target proteins.

Methods: HRMdEC grown in 6-well tissue culture plates were synchronized by incubation in RenaLife Basal Medium without fetal bovine serum for one hour before exposure to CaOx monohydrate (COM) or HA crystals (100μg/mL). Aliquots of medium (250μL) were collected at 0, 0.5, 1, 3, 6, 12, and 24 hour (h). Populations of EVs in medium were analyzed by digital flow cytometer. Cells were harvested at 24h to determine expression of miRNAs identified previously in the urinary EVs of stone formers and their target proteins using qPCR and Western blotting, respectively. Data were analyzed by Student's t-test or Wilcoxon rank sum test.

Results: The total number of EVs (exosomes and microvesicles) in the medium was significantly increased ($P<0.05$) by 3h and progressively increased out to 24h after addition of COM or HA crystals. Cellular expression of preselected miR-1299, miR-146b-5p and miR-483-5p were increased whereas miR-532-5p and 664a-3p were decreased significantly ($P<0.05$) in response to COM crystals. Expression of miR-146b-5p was increased whereas miR-532-3p was decreased significantly ($P<0.05$) in response to HA crystals. Cellular expression of miR-146-5p and miR-532-3p targeted matrix matalloproteinase-16 was increased significantly ($P<0.05$) following COM crystal treatment.

Conclusions: Exposure of cultured renal medullary epithelial cells to urinary stone forming crystals activates them to shed EVs and express specific miRNAs and target proteins. The response to COM crystals was more robust that to HA. Further analysis of intra- and inter-cellular signaling pathways via EVs and miRNAs could elucidate novel cellular mechanisms in early urinary stone pathogenesis.

Funding: NIDDK Support

FR-PO525

Specific Inflammatory and Renal Cellular Injury Markers Are Found in Urinary Extracellular Vesicles and Proteins Associated with Nephrocalcinosis and Stones in Type 1 Primary Hyperoxaluria Patients

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Background: Our previous study showed that specific inflammatory (MCP-1) and renal cell injury (NGAL) molecule associated urinary extracellular vesicles (EVs) were significantly lower in calcium oxalate (CaOx) stone formers compared matched controls. Primary hyperoxaluria type 1 (PH1) can cause nephrocalcinosis (NC), CaOx stones, and chronic kidney disease but specific populations of urinary EVs contribution in these disease processes are not well known.

Methods: Bio-banked urine from PH1 patients without (n=10) and with nephrocalcinosis (n=6) or stones (n=9) and age-/sex-matched (± 5 years) living kidney donors (n=25) was studied. All patients had an eGFR > 40 and no prior kidney or liver transplantation. Urinary EVs were analyzed by digital flow cytometry and analyzed as EVs/μL urine or EVs /mg creatinine. A customized protein array was used to identify specific proteins in urine.

Results: Compared to healthy controls, PH1 patients excreted significantly greater EVs and EVs with surface biomarkers of inflammation (ICAM-1, MCP-1, tissue factor, VCAM-1), renal injury (β2-microglobulin (β2-M), clusterin, KIM-1, Laminin α-5, NGAL), of glomerular origin (juxtaglomerular, mesangial, podocyte, and parietal cells), and of tubular origin (proximal and distal tubule, collecting duct) (all $P<0.05$). PH1 patients with NC had fewer total EVs than PH1 patients without NC or stones ($P<0.05$). PH1 patients with kidney stones had fewer total EVs, and subgroups of EVs with biomarkers of inflammation, renal injury, glomerular origin, specific renal tubular and papillary origin compared to PH1 patients without NC or stones (all $P<0.05$). Excretion of soluble urinary MCP-1, CRP, and osteopontin were all significantly lower in PH1 patients with NC compared to PH1 patients without either NC or stones, or patients with stones alone ($P<0.05$). A similar trend for decreased urinary excretion of soluble CD14, endoglin, E-selectin, ICAM-1, PDGFRβ, and osteoprotegrin was observed in PH1 patients with NC compared to the other groups.

Conclusions: This study suggests that inflammation-associated EVs and proteins released from specific populations of renal parenchyma of PH1 patients may contribute nephrocalcinosis and stone pathogenesis.

Funding: NIDDK Support, Private Foundation Support

FR-PO526

Characterization of Oxalobacter Formigenes-Derived Factors as Potential Novel Therapeutic Agents for Hyperoxalemia, Hyperoxaluria, and Related Kidney Stones

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Background: Most kidney stones are composed of calcium oxalate, and small increases in urine oxalate significantly enhance the risk for stone formation. Hyperoxaluria is a major risk factor for calcium oxalate kidney stones (COKS) and it has no specific therapy. The gut bacterium *Oxalobacter formigenes* (*Of*) induces colonic oxalate secretion and reduces urinary oxalate excretion via an unknown secretagogue. Given the difficulties with recolonization, *Of* alone is not therapeutically feasible and underscores the need to identify the secretagogue inducing colonic oxalate secretion. We previously identified *Of*-derived factors secreted in its culture conditioned medium (CM) that stimulate (>2.8-fold) oxalate transport by human intestinal Caco2-BBE (C2) cells, and reduce (>32.5%) urinary oxalate excretion in hyperoxaluric mice by stimulating (>42%) distal colonic oxalate secretion. The *in vivo* retention of biologic activity reflects the therapeutic potential of these factors and support the pursuit of their characterization.

Methods: Using Mass spectrometry we identified multiple protiens in a family of a regulatory protein as the major *Of*-derived factors, and we have obtained the crystal structures for 5 of these proteins.

Results: The identified proteins closely recapitulate the effects of the *Of*-derived factors and stimulate (1.4-2.4-fold) oxalate transport by C2 cells via PKA and stimulation of the oxalate transporters SLC26A6 and SLC26A2 similar to CM. We also identified 35-amino acid peptides (P8+9) within one of these proteins that significantly stimulate (>2.4-fold) oxalate transport by C2 cells. P8+9 peptides also stimulated oxalate transport by human sigmoid colon (1.8-fold) and ileum (2-fold) organoids (*ex vivo* intestinal epithelia models fully mimicking the *in vivo* physiological responses), strongly suggesting that P8+9 peptides will stimulate oxalate transport in human colonic and ileal epithelia *in vivo*.

Conclusions: We identifed *Of*-derived peptides with singificant potential to stimulate oxalate transport in human colonic and ileal epithelia *in vivo*. Future studies will evaluate the therapeutic potential of these peptides in reducing urine and plasma oxalate levels in hyperoxaluric and hyperoxalemic mice, respectively.

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FR-PO527

The Combination of Chlorthalidone and Potassium Citrate Is More Effective Than Either Agent Alone in Decreasing Calcium Oxalate Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

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Background: To study human idiopathic hypercalciuria (IH) we developed an animal model, genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that of human IH. All GHS rats spontaneously form calcium phosphate (CaP) stones while there is no stone formation in the founder rats. When the oxalate precursor, hydroxyproline, is added to the diet, only calcium oxalate (CaOx) stones form. Previously, we demonstrated that chlorthalidone (CTD) alone was superior to potassium citrate (KCit) alone or in combination with CTD, in reducing CaP stone formation. In the current study we tested the hypothesis that CTD and KCit combined would effectively reduce CaOx stone formation in GHS rats.

Methods: 113th generation GHS rats were fed a fixed amount of a normal Ca (1.2%) and P (0.65%) diet with 5% hydroxyproline added, housed in metabolic cages and divided into four groups. Diets were supplemented with KCl (4 mmol/d) as control, KCit (4 mmol/d), CTD (4-5mg/kg/d)+KCl, or KCit+CTD. Urine (u) was collected at 6,12, and 18 wks for analyses and kidney stone formation was determined by X-ray at 18 weeks.

Results: Compared to the KCl control, KCit reduced uCa (KCl= 17.2±0.3 mg/d, KCit=14.4±0.3), CTD reduced it further (CTD=13.0±0.6) and KCit+CTD reduced it even further (KCit+CTD=9.3±0.4). The combination of KCit+CTD decreased uOx compared to all other groups (KCl=3.4±0.2 mg/d, K Cit=3.5±0.2, CTD=3.5±0.1, KCit+CTD= 2.7±0.1). Compared to KCl (108.7±2.2 mg/d), KCit and CTD+KCit increased uCit (KCit=146.6±2.6, KCit+CTD=129.9±3.3). There were no significant differences in CaOx supersaturation (ss) in any group. CTD did not change uCaP ss (KCl= 4.3±0.3, CTD=2.3±0.2), while KCit alone, or in combination with CTD, increased it (KCit=10.3±0.6, KCit+CTD=11.5±0.9). Compared to KCl (stone formation with a range of 0-4: KCl=2.1±0.1), KCit did not alter stone formation (2.0±0.3), while there was less stone formation in rats fed CTD alone (CTD=1.6±0.2). The combination of KCit+CTD (0.8±0.2) resulted in significantly fewer stones than KCl, CTD or KCit alone.

Conclusions: Thus in GHS rats fed a diet that results solely in CaOx stone formation, the combination of KCit+CTD prevented stone formation better than either agent alone.

Funding: NIDDK Support

FR-PO528

Neutrophil Infiltration and NETosis in the Pathogenesis of Human Kidney Brushite Stones

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Background: The pathogenesis of kidney stones in humans is poorly understood. There are multiple types of kidney stones, and the role of inflammation in promoting specific stone types is not well established. Here, we applied a combination of unbiased omics and quantitative large-scale 3D imaging on kidney stones and papillae from two types of stone forming patients: calcium oxalate and brushite. Our goal was to uncover a specific inflammatory signature that could differentially associate with a specific type of stone disease and infer how they are formed.

Methods: Kidney stones were obtained from a well-characterized cohort of patients in a high volume clinic. Stones were further processed for label free quantitative mass spectrometry to quantify differentially expressed proteins. Papillary biopsies were obtained at the time of percutaneous nephrolithotomy and processed for histology and large scale 3D imaging. 3D tissue cytometry and analysis was done using Volumetric Tissue Cytometry and Analysis Software (VTEA).

Results: Brushite stones have differentially increased neutrophil proteins such as myeloperoxidase and elastase compared to calcium oxalate evaluated by LC/MS. To determine if this observation is driven by changes in the kidney papillae, we confirmed that the number (6.91 ±1.19% vs. 1.35 ± 0.28%; $p=3.2x10^{-5}$) and the density of neutrophils ($10.1x10^3$ ±$6.2x10^3/mm^3$ vs. $0.91x10^3$ ±$0.67x10^3/mm^3$; $p<0.05$) were increased in the papillae from brushite vs. calcium oxalate patients, respectively. To explain how neutrophil proteins are transitioning from the tissue to the stone matrix, we investigated whether Neutrophil Extracellular Trap (NET) formation, whereby neutrophils expel their DNA and their cytoplasmic content, is more common in brushite stones. Indeed, histone citrullination of neutrophils, a marker of NETosis, was increased in brushite compared the calcium oxalate papillae (1.3 ± 0.28% vs. 0.07 ±0.04%; $p<0.05$).

Conclusions: Our work supports that increased neutrophil infiltration and NETosis may be an important factor in the pathogenesis of brushite stones. We propose that metabolic changes or ascending infections could trigger a hyper-inflammatory response that leads to the release of NET proteins in the urine, which promote brushite stone formation.

Funding: NIDDK Support

FR-PO529

Inositol Phosphate Analogs as Inhibitors of Renal Calcium Oxalate Crystallization

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Background: Nephrocalcinosis and nephrolithiasis can be triggered by calcium oxalate (CaOx) crystallization, a main symptom in different forms of hyperoxaluria. To date, treatment options for pathologies involving renal CaOx crystallization are scarce, mostly aiming at slowing down disease progression, rather than directly targeting crystal growth and deposition. Inositol hexaphosphate (IP6) was previously shown to inhibit crystallization of calcium salts. Its clinical use, however, may be hampered by its low urine exposure following parenteral dosing. In this project, we aim at developing inhibitors against renal CaOx crystallization, based on IP6 analogs.

Methods: Potency of compounds to inhibit CaOx crystallization was assessed by light scattering measurements. Effects on the CaOx crystal morphology were characterized by light microscopy, followed by an automated image analysis and machine learning approach to classify different CaOx hydrate forms. *In vitro* cell experiments were performed using RPTEC human proximal tubular cells. Adhesion of CaOx crystals to a cell monolayer was determined by light microscopy and CaOx induced cellular toxicity *in vitro* was measured with a viability stain.

Results: In the initial screening of a small library of IP6 analogs, a subgroup of compounds that included IP5-mono-PEG_2 (INS-2001), showed inhibitory potential in the low micromolar range. Light microscopy experiments performed in human urine, confirmed the dose-dependent reduction in size of CaOx monohydrate crystals upon the addition of INS-2001. This compound also significantly reduced CaOx adhesion to renal epithelial cells at submicromolar concentrations. Additionally, protective effects of INS-2001 on CaOx induced cellular toxicity *in vitro* were observed.

Conclusions: The data generated with INS-2001 provide a starting point for further optimization of the IP6 analogs for treatment of renal CaOx crystallization. In subsequent steps, inhibitory effects of INS-2001 and related compounds on CaOx-induced fibrosis and inflammation *in vitro*, and *in vivo* efficacy will be characterized in depth.

Funding: Government Support - Non-U.S.

FR-PO530

Effect of Alanine Supplementation on Oxalate Synthesis

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Background: Alanine:glyoxylate aminotransferase (AGT) is the enzyme deficient in type 1 primary hyperoxaluria, which are a group of severe inherited kidney stone disorders characterized by an excessive endogenous synthesis of oxalate. The high Km of AGT for alanine (30 mM) and the lower level of alanine in human plasma (200-600 μM) suggest that AGT metabolic function, and therefore oxalate synthesis, could be improved by alanine supplementation. In support of this hypothesis, cells expressing normal or pathogenic variants of AGT and supplemented with L-alanine, have decreased synthesis of oxalate when incubated with an oxalate precursor, glycolate. In order to test whether L-alanine could improve AGT metabolic efficiency *in vivo*, we investigated the effect of L-alanine supplementation on the urinary excretion of oxalate in normal mice and mice deficient in AGT or Glyoxylate reductase (GR, deficient in primary hyperoxaluria type 2).

Methods: Wt, Gr Ko and Agt Ko mice were fed a low oxalate diet. Three 24 hr urines were collected in metabolic cages at baseline and after 1 week of equilibration with the low oxalate diet supplemented with 5-10% alanine. Plasma and liver alanine were measured by high-pressure liquid chromatography after extraction of the tissues. Urine oxalate was measured by ion chromatography coupled with mass spectrometry, urine creatinine was measured on a chemical analyzer. Statistical analysis was done with Student's paired t-test.

Results: Urinary oxalate was higher in Gr and Agt Ko compared with Wt mice at baseline (152 ±35, 215 ± 13 compared with 48 ± 5 μg oxalate/day, in GR KO, Agt Ko and Wt, respectively, $p<0.005$). Supplementation with L-alanine in the diet resulted in a 20-30% decrease in urinary oxalate in both Gr Ko and Wt animals (106 ± 20 and 36 ± 2 μg oxalate/day after supplementation, $p<0.002$ and $p<0.001$, respectively). There was no significant change in urinary excretion of oxalate in Agt Ko mice.

Conclusions: The urinary excretion of oxalate was decreased by dietary L-alanine supplementation in Wt and Gr Ko mice, which express functional Agt. These results suggest that L-alanine could prove useful as an adjunct therapy in PH2 and PH3, for which no specific treatment is currently available, and potentially idiopathic hyperoxaluria.

Funding: NIDDK Support

FR-PO531

The Role of the Microbiota in Mammalian Oxalate Metabolism

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Background: Kidney stones represent a disease of worldwide prevalence with significant public health implications. About 60–80% of stones are composed of calcium oxalate (CaOx); hyperoxaluria is a major risk factor for CaOx stones. Oxalate is an end-product of mammalian digestion and as with urea, must be excreted. We obtain oxalate from diet, or from endogenous production. Certain intestinal bacteria have the ability to degrade oxalate, protecting against oxalate nephropathy, including nephrolithiasis. To understand the role of the gut microbiome in oxalate metabolism, we compared conventional mice with germ-free mice (that lack a microbiota). In addition to the stress of endogenous oxalate production, we challenged groups with dietary and metabolic (via hydroxyproline (Hyp) supplementation) oxalate loads.

Methods: Conventional (CO) and germ-free (GF) mice were fed normal chow diets supplemented with either 1% Oxalate (Ox), 1% Hydroxyproline (Hyp) or were unsupplemented (NC) for 6 weeks (n=3-4/mice group). After 6 weeks, we obtained 48-hour urine collections for measurement of the oxalate/creatinine ratio (Uox/cr).

Results: In CO mice, Uox/cr increased with the Ox diet compared with NC (0.57 + 0.17 vs 0.16 + 0.05, p= 0.03 by Student's t test), but not with the Hyp diet (0.14 +0.03 vs 0.16 +0.05, p=ns). However, in germ-free mice, both dietary Hyp and Ox led to increased Uox/cr compared to NC diet (0.50 ± 0.04, 0.85 ± 0.11, vs. 0.31± 0.06, $p<0.05$ by ANOVA, respectively). Uox/Cr was lower in CO mice than GF mice when receiving Hyp (p=0.01, by Student's t test), Ox (p=0.06), and NC diets (0.06).

Conclusions: In conclusion, oxalate excretion was higher in the germ-free than in the conventional mice under all three dietary conditions (Ox, Hyp, NC), providing direct evidence that the normal gut microbiome plays a protective (symbiotic) role in oxalate metabolism. With the metabolic stress of the Hyp diet, the CO mice but not the germ-free mice could compensate. Since mice are not colonized with *O. formigenes,* this work indicates that other members of their microbiota have the functional capacity to alter oxalate metabolism.

Funding: NIDDK Support, Private Foundation Support

FR-PO532

Intermuscular Fat in Patients with CKD Inversely Correlates with Physical Activity and Mitochondrial Function

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Background: Patients with chronic kidney disease (CKD) have higher prevalence of sarcopenia, defined as reduction in muscle mass and/or muscle strength. Muscle quality (in particular, fat infiltration) may provide insight into the links between muscle metabolic health and physical functioning beyond traditional muscle mass assessment. We hypothesize that intermuscular fat is increased in patients with chronic kidney disease and it is inversely associated with physical activity and mitochondrial function.

Methods: In a cross-sectional study, we evaluated 51 subjects (20 with CKD stage 3-4, 15 with CKD stage 5 on hemodialysis, and 16 matched controls with no history of CKD). Intermuscular fat was evaluated in the quadriceps muscle using sequential thigh magnetic resonance images. Physical performance was measured using the six-minute walk test. Mitochondrial function was evaluated by measuring phosphocreatine (PCr) recovery after exercise using ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS). A longer PCR

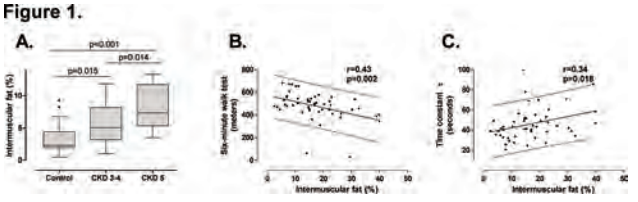
recovery results in a greater time constant tau (τ), which indicates worsening mitochondrial function.

Results: Groups were matched by gender, body mass index, and history of diabetes and hypertension. Patients with CKD stage 5 were younger than patients with CKD stage 3-4 (47.7±11.7 vs. 63.6±9.0) but had similar age compared to controls (46.9±9.5). Intermuscular fat was greater in patients with CKD stage 5 compared to patients with CKD stage 3-4 and controls (**Figure 1A**). We also found a negative correlation between quadriceps intermuscular fat and physical performance (**Figure 1B**). In addition, mitochondrial dysfunction (greater time constant τ) was associated with increased intermuscular fat (**Figure 1C**).

Conclusions: CKD is associated with greater intermuscular fat which associates with poor physical performance and impaired mitochondrial function. Future studies should evaluate the effectiveness of interventions that not only increase muscle mass but also improve muscle quality in patients with CKD.

Funding: NIDDK Support

Figure 1.



FR-PO533

Impaired Muscle Mitochondrial Energetics Is Associated with Poor Physical Performance and Reduced Objective Physical Activity in CKD

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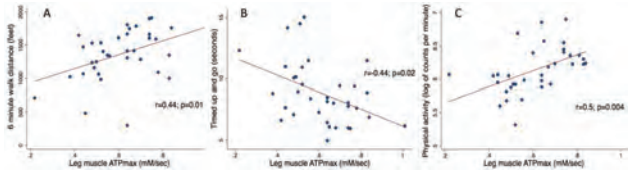
Background: Persons with chronic kidney disease (CKD) are at increased risk of impaired mobility function that is central to living independently. The abnormal uremic milieu of CKD may contribute to reduced ambulatory physical performance and sedentarism by impairing skeletal muscle mitochondrial metabolism.

Methods: We performed a cross-sectional analysis of 48 participants (37 with CKD not treated with dialysis and 11 matched, clinic-based controls without CKD) from the Muscle Mitochondrial ENergetics and Dysfunction (MEND) study. Persons were excluded from MEND if they used medications that influenced mitochondrial metabolism or had mobility disability. We measured mitochondrial capacity during the recovery from exercise of the tibialis anterior leg muscle as ATPmax using ^{31}Phosphorus magnetic resonance spectroscopy. We assessed ambulatory physical performance by the 6-minute walk and timed up and go tests and we quantified usual physical activity levels using digital accelerometry over a two-week period. Results were adjusted for age, sex, weight, diabetes, and leg muscle size.

Results: Among persons with CKD, the mean GFR was 36 ±15 ml/min; mean age was 62 ±15yr; 50% were female, and 30% had diabetes. After adjustment, patients with CKD had a 0.181mM/sec (1SD) lower muscle ATPmax compared with controls (95% CI 0.06-0.297 lower; P=0.003). Among those with CKD greater muscle ATPmax was associated with greater 6 minute walk distance **(A)**, faster timed up and go performance **(B)** and greater usual physical activity **(C)** (Figure).

Conclusions: CKD is associated with lower muscle mitochondrial capacity measured by ATPmax manifesting as poor ambulatory physical performance. Among CKD patients, mitochondrial capacity is associated with objective measurements of physical performance and activity.

Funding: NIDDK Support



FR-PO534

Factors Associated with Functional Impairment in Mild to Moderate CKD

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Background: Chronic kidney disease (CKD) is associated with functional impairment (reduced physical ability to perform normal activities and independently self-care) and may impact on quality of life. Additional factors related to functional impairment in CKD are less well described and may help identify those needing assessment and intervention. This study explored factors associated with functional impairment in people with mild to moderate CKD and comorbidities.

Methods: Data were analysed from 1013 patients at 5y follow up in the Renal Risk in Derby cohort study, comprising patients with CKD stage 3 at recruitment in primary care (baseline n=1741). Data included: age, sex, socioeconomic status (SES) based on index of multiple deprivation (IMD); comorbidities; renal function (estimated glomerular filtration rate (eGFR)); Karnofsky Performance Status (KPS). Functional impairment was defined as KPS score ≤70 (at best, unable to do active work or normal activities but can self-care; possible KPS score 0-100 in intervals of 10, lower score represents lower function). Binary logistic regression analyses assessed associations with functional impairment.

Results: Cohort characteristics were: median age 77y, 62% female, mean eGFR 54 ml/min/1.73m^2. 23% scored ≤70 on the KPS indicating low levels of functional impairment. On univariable analysis, functional impairment was associated with older age, lower SES, multiple comorbidities, and lower eGFR. In a multivariable model, these factors remained independently associated, and female sex became associated, with the outcome.

Conclusions: In addition to lower eGFR, older age, female sex, lower SES and multiple comorbidities were independent risk factors for clinician-assessed functional impairment in mild to moderate CKD. Persons with these risk factors should be considered for further functional status assessment and interventions to improve impairment.

Funding: Commercial Support - Roche Products plc, Private Foundation Support

		Univariable		Multivariable†	
		OR (95% CI)	p value	OR (95% CI)	p value
Age (y)		1.07 (1.05 - 1.09)	<.001	1.06 (1.03 - 1.08)	<.001
Sex (*vs* male)	Female	1.16 (0.86 - 1.57)	0.329	1.52 (1.09 - 2.11)	0.014
IMD national quintile (*vs* least deprived)	Most deprived	2.87 (1.61 - 5.11)	0.002	2.77 (1.50 - 5.10)	0.001
Comorbidities (*vs* CKD only or CKD plus 1 other)	CKD plus ≥2 others	3.95 (2.71 - 5.77)	<.001	3.19 (2.15 - 4.74)	<.001
eGFR (ml/min/1.73m^2)		0.97 (0.96 - 0.98)	<.001	0.98 (0.97 - 0.99)	0.003

†Adjusted for listed covariates. OR: odds ratio for functional impairment; CI: confidence interval.

FR-PO535

Association of Subjective Health Assessments with Frailty, ADLs, and iADLs in Advanced CKD

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Background: Subjective health measures (i.e., patient self-rated health (SRH) and the provider surprise question (SQ)) predict key outcomes such as mortality. How these measures relate to frailty and functional status has not been studied in chronic kidney disease (CKD).

Methods: We approached 293 and enrolled 271 outpatients ≥ 60 years of age with non-dialysis dependent CKD stage 4 or 5. Patients were assessed with the SRH questionnaire: "In general, would you say your health is: excellent, very good, good, fair, or poor." Providers completed patient assessments with the SQ using a 5-point Likert scale: "Would you be surprised if this patient died in the next 12 months?" Frailty was measured using Fried Frailty phenotype and the Clinical Frailty Scale. Activities of daily living (ADLs) and instrumental ADLs (iADLs) were assessed using Katz and Lawton measures. Correlations were evaluated using Spearman's rank correlation. We used cutoff responses of 'poor' or 'fair' for SRH and 1 or 2 (i.e., not surprised) for the SQ to determine test-characteristics.

Results: About 15% of patients were frail by both Fried Frailty phenotype and Clinical Frailty Scale and 8% and 29% of patients had at least 1 ADL or iADL deficit, respectively. Both SRH and SQ were fairly to moderately correlated with clinical frailty score, Fried Frailty phenotype, iADLs, and weakly correlated with ADLs [Table 1]. SRH (of excellent, very good or good) had a negative predictive value (95% confidence interval) of 0.92 (0.86 to 0.96), 0.92 (0.87 to 0.96), 0.96 (0.91 to 0.98), and 0.83 (0.76 to 0.89) for Fried Frailty phenotype, Clinical Frailty scale, ADL deficiency, and iADL deficiency respectively. SQ had a negative predictive value of 0.87 (0.82 to 0.91), 0.90 (0.86 to 0.94), 0.79 (0.73 to 0.84), and 0.95 (0.92 to 0.98) for Fried Frailty, Clinical Frailty, ADL deficiency, and iADL deficiency respectively.

Conclusions: Single question patient or provider subjective health measures are correlated with frailty and functional status. These measures also may serve as useful tools to rule out frailty and disability in this population.

Funding: Private Foundation Support

Spearman Rank Correlations Rho Values (95% confidence interval)

	Fried Frailty	Clinical Frailty Scale	ADL	iADL
Self-Rated Health	0.43 (0.32 to 0.52)	0.45 (0.35 to 0.54)	0.16 (0.04 to 0.26)	0.33 (0.23 to 0.44)
Surprise Question	0.31 (0.20 to 0.42)	0.45 (0.40 to 0.58)	0.23 (0.11 to 0.36)	0.40 (0.29 to 0.50)

FR-PO536

Profiles of Physical Activity in Hemodialysis Patients Randomized into the HDFIT Trial

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Background: Profiles of physical activity (PA) are poorly understood in dialysis patients. We characterized granular profiles of PA in hemodialysis (HD) patients.

Methods: PA was measured with the Actigraph (www.actigraphcorp.com) monitor over 1 week in patients treated with high-flux HD during the baseline period of the HDFIT randomized controlled study, which is a 6-month study of the impacts of modality (HDF vs HD) on PA levels (ClinicalTrials.gov: NCT02787161). Granular PA levels were captured in blocks including a HD period (Block A), 2-hour (hr) post-HD period (Block B; includes 30min data slices), and 2-to-24hr post-HD period (Block C; includes 4.5hr data slices) captured over 24hr periods relative to the start time of HD on dialysis days, and concurrent periods on non-HD days and the long interdialytic day.

Results: We recruited 195 HD patients from 13 sites during October 2016 to 2017. Patients were: age 53±15 years, 71% male, 59% white race, post-HD weight 76±16 Kg, 29% with diabetic nephropathy, 26% with hypertensive nephrosclerosis, and 16% with chronic glomerulonephritis. Patients took a mean of 4,725 steps/24hrs. On non-HD days and the long interdialytic day, patients took 1,387 and 1,105 more steps/24hrs vs HD days respectively (both p<0.001). During concurrent times to the HD session on non-HD days and the long interdialytic day, patients performed 1,351 and 1,082 more steps respectively (both p<0.001). Surprisingly, on HD days patients performed more steps in each 30 min slice during the 2hr post-HD period vs concurrent times on non-HD days and the long interdialytic day (all p<0.05). On non-HD days, patients performed more steps during the 2 to 6.5hr post-HD period (p<0.05).

Conclusions: Findings revel PA levels tend to be lower on HD days primarily due to sitting/lying during HD treatments, albeit patients had higher post-HD PA levels compared to concurrent times on non-HD days that may be related to transportation from the clinic. Offering intradialytic exercise programs could help increase PA during HD, potentially above sedentary levels (i.e. >5,000 steps/day or equivalents) with potential benefits as observed in the general population.

Funding: Commercial Support - Fresenius Medical Care and Pontificia Universidade Catolica do Parana

FR-PO537

Decline in Functional Status and Mortality in Patients on Hemodialysis: Results from the Japan Dialysis Outcome and Practice Patterns Study (J-DOPPS)

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Background: Poor functional status — the limitation in activities of daily living (ADL) — is strongly associated with adverse clinical outcomes among end-stage renal disease (ESRD) patients treated with hemodialysis (HD). Little is known in regard to the association of change in functional status and adverse clinical outcomes in this population. The current investigation tests the association of decline in functional status with all-cause mortality among HD patients using data from the Japan Dialysis Outcome and Practice Patterns Study (J-DOPPS).

Methods: We studied 817 ESRD patients on HD with repeat measures of functional status enrolled in the J-DOPPS. Information on age, sex, body mass index, smoke, dialysis vintage, comorbidities and laboratory data was collected. The assessments of functional status were conducted twice over a one-year baseline period (2012-2013), and functional status score was calculated based on Katz index and Lawton-Brody instrumental ADL scale. We classified patients into 2 groups based on having or not at least 1 point declined in functional status score during the baseline period. A Cox regression analysis was conducted to evaluate the association between the decline in functional status and the all-cause mortality during the follow-up period (2013-2015) with adjustment for potential confounders.

Results: Over this period, 163 (20.0%) patients showed decline in functional status score, and 44 (5.4%) patients died. Using Cox regression analysis adjusting for potential confounders including baseline functional status, the declined in functional status score was significantly associated with higher mortality (adjusted hazard ratio, 2.68; 95% confidence interval, 1.31-5.50).

Conclusions: Decline in functional status was strongly associated with mortality among patients treated with HD. These findings underscore the importance of interventions directed at preventing deterioration in functional status over time among HD patients.

Funding: NIDDK Support, Commercial Support - Kyowa Hakko Kirin, Government Support - Non-U.S.

Association between decline in functional status score and all-cause mortality

		All-cause mortality	
	N	Incidence rate (per 100 person years)	Adjusted HR (95%CI)
Functional status score			
not declined	654	2.2	Reference
declined	163	7.0	2.68 (1.31 – 5.50)

HR: hazard ratio; CI: confidence interval.

FR-PO538

Predictors of Mobility Impairment over Time in Incident Dialysis Patients

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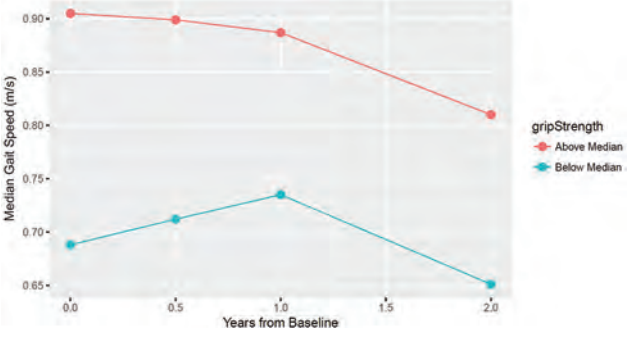
Background: Sarcopenia involves loss of muscle strength and/or mass that leads to loss in physical function (mobility impairment). Mobility impairment can be quantified by gait speed measures. In CKD, mobility loss is associated with hospitalizations, functional dependence and mortality. The trajectory of mobility over time in new dialysis patients is not well-characterized. We hypothesized that there are decreases in mobility over time in incident dialysis patients, independent of changes in muscle strength.

Methods: Gait speed was assessed in 195 subjects who were incident to outpatient dialysis by the 4-meter walk test at baseline, 6, 12 and 24 months. Maximum handgrip strength of 3 trials in both upper limbs was recorded at similar time points. Appendicular lean mass/ ht2 was measured by DXA. Mixed effects models were used to analyze changes in gait speed and identify predictors of change among covariates which included demographics, walking aids, self-reported health status, ESRD cause, time-varying muscle strength, baseline lean mass and physical activity.

Results: The mean age of the cohort was 54.3+/-13 years, with 53.3% male, 72.4% black and with a median of 93.7+/-72 days since dialysis start. There was an average decrease in gait speed of 0.023 m/s/yr. Lower grip strength at baseline was associated with lower gait speed trajectory over time (Figure). Age, use of walking aids, lower grip strength, diabetic nephropathy as cause of ESRD, self-reported poor ambulation and lower health utility were significantly associated with poor mobility over time in the adjusted mixed effects model (all p<0.05). Baseline lean mass or step counts did not affect these relationships.

Conclusions: There is loss of mobility with time in patients relatively new to dialysis. Loss of muscle strength is an independent risk factor for mobility impairment over time. Identifying risk factors for mobility loss may be used to target interventions like physical therapy, gait training and exercise.

Funding: NIDDK Support



Gait Speed Trajectory by Baseline Grip Strength

FR-PO539

The Effect of Exercise Intervention on Physical Activity in Patients with Non-Dialysis-Dependent CKD: A Systematic Review

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Background: As the population of chronic kidney disease (CKD) grows larger and older worldwide, frailty has become one of emerging problems that may affect the prognosis of patients with CKD and their quality of life. Many observational studies suggest that frailty should be a clinically-relevant mortality risk in both dialysis-dependent and non-dialysis-dependent (NDD) CKD. However, it is not well understood whether this vulnerable state is modifiable by lifestyle intervention, or exercise, in patients with NDD-CKD independent of diet and drug therapy. We performed a systematic review to evaluate the benefits and limitations of exercise intervention among patients with NDD-CKD on exercise tolerance.

Methods: We searched PubMed and the Japanese medical publication library "Ichushi" databases for randomized controlled trials (RCTs) or intervention trials targeting patients with NDD-CKD published until April 2017. Outcomes of interest included indices of exercise tolerance, such as VO_2 peak and 6-min walking test (6MWT). Two or three reviewers independently screened the title and abstract of extracted papers from the databases and reviewed the full-text of articles that met the prespecified inclusion and exclusion criteria. Data quality and risk of bias were evaluated by GRADE system. Any disagreements between the reviewers were resolved by discussion. Data syntheses and meta-analyses were performed using Review Manager version 5.3.

Results: After the full-text review of 50 selected articles, 14 RCTs and two intervention trials were included in meta-analysis. Four of them conducted resistance exercise, and others did aerobic exercise or exercise with reduced workload. Nine studies reported changes in VO_2 peak, six in 6MWT, and the rest measured other indices. Overall, VO_2 peak and 6MWT were significantly improved by 3.2 [inter quartile range (IQR): 1.5 – 5.0] mL/kg/min (N = 296, $I^2 = 0.67$) and 51 [22 - 80] m (N = 241, $I^2 = 0.27$), respectively. There was no report on adverse event regarding exercise intervention.

Conclusions: Moderate exercise intervention among patients with NDD-CKD is beneficial for exercise tolerance measured by VO_2 peak and 6MWT. These results should be verified by other objective indices for mobility and in other CKD populations especially with frailty.

FR-PO540

Physical Performance in Nocturnal Hemodialysis Patients: Systematic Review of the Literature

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Background: Hemodialysis (HD) pts have poor physical performance, leading to a diminished quality of life (QOL) and overall health. This low activity level can be explained by lack of energy due to insufficient metabolic clearance and shortage of time by time-consuming HD sessions. Nocturnal hemodialysis (NHD) improves metabolic control and results in largely increased spare time. Whether NHD stimulates pts to a more active lifestyle and increased muscle mass and strength, is unclear. Our aim is to investigate whether physical performance improves when pts switch from conventional HD to NHD.

Methods: A systematic literature search, with help of a specialized librarian, was conducted in multiple databases: MEDLINE, Embase, CINAHL, PhycInfo and Web of Science. Databases were searched until January 2018. Primary outcomes of interest were physical performance, activity, strength and muscle mass in NHD, either at home or in-center. Two reviewers performed data extraction and assessment of methodological quality independently, with the Newcastle-Ottawa scale.

Results: The search yielded 10 studies meeting the inclusion criteria including 2 RCTs. A total of 526 NHD pts were evaluated with a mean follow-up duration of 15,3 months. Physical performance was assessed with objective measurements in 7 studies: short-physical performance battery (1x), exercise spirometry (1x), 6-min walk test (6MWT, 1x), (skeletal) muscle mass using dual-energy X-ray absorptiometry (2x) and bioelectrical impedance analysis (BIA, 2x). In 5 studies physical performance was assessed subjectively, with a physical component score (PCS) of a QOL questionnaire. Of the objective outcomes, 3 studies found significant improvements in physical performance using exercise spirometry, 6MWT and BIA. Of the subjective outcomes, 2 studies showed a better PCS. The remaining 6 studies showed no improvement in physical performance nor PCS.

Conclusions: A limited amount of studies investigate whether physical performance improves after switching from CHD to NHD and a minority of these assess physical performance with objective measurements. As current literature regarding physical performance emphasizes the importance of physical activity on clinical outcomes, it is essential to conduct better research in larger study groups, to investigate whether NHD can improve physical performance of pts with ESRD.

Funding: Commercial Support - Baxter

FR-PO541

Physical Activity and Sedentary Behaviour in Hemodialysis: Preliminary Data from a Pilot Study

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Background: Dialysis patients have reduced moderate to vigorous physical activity (MVPA), defined as activities that use ≥3 metabolic equivalents (METS). This has been shown in both self-reported surveys and objective accelerometer studies. Less attention has been directed towards sedentary behavior (SB), which is characterized by low energy expenditure (≤ 1.5 METS). Furthermore, locations where MVPA or SB occur are largely unknown for dialysis patients. **Objective:** To determine the number of minutes per day of MVPA and SB for in-center hemodialysis patients using accelerometers and to identify locations where MVPA and SB occur using global positioning software (GPS).

Methods: We analyzed a cross-section of adult in-center hemodialysis patients at tertiary care dialysis program, recruited over a three-month period. Patients were fit with the Actigraph GT3X accelerometer and Qstarz BT-Q1000X GPS receiver and were instructed to wear these devices for ≥10 hours/day for ≥4 days/week. Minutes of physical activity at various intensities and SB were described as was time spent at each activity level across different locations.

Results: Overall, 50 patients consented to participate in the study; 47 were fit with both devices, and 37 met the minimum accelerometer wear time of ≥4 days/week. Mean age of the cohort was 61±15 years. Diabetes (46%), coronary artery disease (34%), and heart failure (21%) were highly prevalent. Among those who fulfilled valid days, median wear time was 755 minutes/day (IQR 720-794), median sedentary time was 544 minutes/day (IQR 487-583), and median MVPA time was 2 minutes/day (IQR 1-9). The cohort spent 73% (IQR 64-78) of their wear time in a sedentary state, and only 0.3% (IQR 0.1-1.2) in MVPA. Only three patients met Canadian guidelines for weekly MVPA (≥150 minutes/week in bouts of ≥ 10 minutes). The majority of SB occurred in the home, hospital, and during transport, whereas most MVPA occurred at home.

Conclusions: Hemodialysis patients exhibit substantial SB and minimal MVPA across a multitude of locations. The home environment may represent an ideal location for behavior interventions as the majority of SB and MVPA occurs at home. Further studies are needed to determine the effects of these behaviors on clinical outcomes as well as to determine barriers to MVPA and facilitators of SB.

FR-PO542

The Effect of Intradialytic and Home-Based Exercise on Physical Function and Quality of Life in Hemodialysis Patients

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Background: It's well established that hemodialysis (HD) patients are less active and have greater muscle atrophy compared to healthy people. Previous research has associated lack of physical activity with reduced physical function (PF) and quality of life (QOL) and increased mortality. Preceding research also states that HD patients' QOL may be negatively influenced by significant increases in intradialytic weight gain thus increasing the likelihood of a hypotensive event. HD patient's specifically cite sleep problems and fatigue as negative effects of hemodialysis on QOL. The aim of this study was to determine the effect of a 6-month physical exercise program on HD patients' PF and QOL.

Methods: HD patients (n=22) were enrolled in a larger volume control (VC) pilot trial with assessments at baseline (BL) and 6-months (6m). Nine HD patients were randomized into a volume control and exercise group (VCE). During regularly scheduled HD treatments, over the 6-month trial, VCE performed thrice weekly moderate intensity, progressive intradialytic cycling for 15-30 min per session. Additionally, VCE was given a progressive individualized home exercise prescription that consisted of total body resistance exercises and balance exercises, which the HD patients were asked to complete twice a week. Thera-bands of various resistance were given to perform the exercises at home. Before randomization, BL assessments were taken including; BP, short physical performance battery (SPPB), and self-reported Kidney Disease Quality of Life (KDQoL).

Results: SPPB total score did not improve BL to 6m between groups (VCE 9.4 to 10.1, VC 8.5 to 8.9; p=.71). The symptoms and sleep subsets, of the KDQoL, were significantly different between groups from BL to 6m (symptoms: VCE 73.2 to 85.0, VC 71.1 to 67.1; p=0.02, sleep: VCE 60.8 to 71.4, VC 58.5 to 50.9; p=0.02). Fatigue, part of the symptoms subset, was found to be reduced in VCE from BL to 6m (VCE 54.2 to 75.0, VC 51.7 to 40.0; p=0.05).

Conclusions: Despite no improvement in the SPPB between groups, specific QOL parameters such as sleep and fatigue improved significantly. These findings suggest novel benefits in QOL from an intradialytic cycling and home-based exercise program in HD patients.

Funding: Private Foundation Support

FR-PO543

Feasibility of Intradialytic Exercise in a Rural Community Hemodialysis Unit: Mixed Methods Analysis of Implementation

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Background: The use of leg cycle ergometers (LCEs) during hemodialysis (HD) has been shown to have a number of benefits including improved adequacy of HD and blood pressure reduction while also improving exercise capacity, physical function and quality of life in patients with end stage kidney disease. LCEs have been implemented at several dialysis centres in major Canadian cities, however no known location in British Columbia. Furthermore, a gap exists in the literature with respect to the feasibility of implementing such programs in small or rural HD centres. We examined the feasibility of implementing LCEs concurrent with HD in a rural community centre.

Methods: Study participants included patients and clinical care providers (CCPs) recruited from a remotely located community HD unit in northern British Columbia. Descriptive statistics were used to indicate frequency, intensity and length of cycle utilization. Barriers and facilitators to participation were captured in individual semi-structured interviews conducted with patient and CCPs at the end of the study period. Transcribed interviews were coded and analyzed using a theoretical framework scaffolded by constructs of acceptability and feasibility of implementation (O'Cathian et al. 2015).

Results: Of 14 eligible patients, 9 enrolled of which 6 actively participated in the study. Over 1 to 4 months patients used LCEs an average of 85% (63%-100%) of their dialysis sessions. Duration of LCEs use increased over time from a low of 15 minutes to an average of 1 hour (15-120 minutes) at an "easy" rate on the Perceived Exertion Scale with no adverse events reported. Thematic analysis of 14 interviews (9 patients; 5 CCPs) identified key elements for successful implementation: patient and CCP orientation and a structured

support process aided in acceptability, resulting in minimal disruption to workflow and generating motivation to participate and a positive patient and CCP experience.

Conclusions: Exercising during HD is acceptable, feasible, and safe when implemented in a rural community HD unit using a structured team-based approach. It does not add workload for clinical staff and can be incorporated in the workflow. Patients reported an overall positive experience and recommended the creation of an education tool to aid in recruitment.

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FR-PO544

Effect of Acute and Chronic Intradialytic Bicycle Ergometer Exercise on Nrf2 mRNA Expression in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have a constant state of oxidative stress, which results from an imbalance between reactive oxygen species production and endogenous antioxidant defense mechanisms, leading to increased cardiovascular risk. Physical exercise may reduce cardiovascular risk through its beneficial effects on nuclear factor erythroid 2-related factor 2 (Nrf2) expression that regulates several antioxidant genes. The aim of the present study was to verify the effect of acute and chronic intradialytic bicycle ergometer exercise on Nrf2 mRNA expression in HD patients.

Methods: Eleven HD patients were studied (7 men, 47.5 ± 6.7 yrs, 25.4 ± 12.3 months of dialysis, BMI of 23.7 ± 2.2 Kg/m^2). The physical exercise program was individualized and performed on an adapted stationary bicycle, consisting in heating (5 minutes), 35 minutes of aerobic training at target heart rate, and cool down (load reduction for 5 minutes). The acute effect (single session) was assessed after the first exercise session and the chronic effect after 3 months of the exercise program with 3 sessions per week. Peripheral blood mononuclear cells were isolated and processed for the evaluation of expression of Nrf2 and NAD(P)H:quinoneoxidoreductase 1 (NQO1) by quantitative real-time polymerase chain reaction.

Results: No significant changes were observed after a single exercise session in Nrf2 mRNA expression [from 0.38 (0.15 - 2.84) to 1.92 (0.65 - 2.48), p=0.21] or NQO1 mRNA expression [from 0.31 (0.16 -1.20) to 0.85 (0.43 - 1.98), p=0.17]. After 3 months of the exercise program there was a significant increase in Nrf2 mRNA expression [from 0.38 (0.15 -2.84) to 1.63 (0.64 - 3.25), p=0.04] and no significant change in NQO1 mRNA expression [from 0.31(0.16 -1.20) to 1.97 (0.45 - 3.88), p=0.17].

Conclusions: These results suggest that acute intradialytic bicycle ergometer exercise was unable to change Nrf2 but three months exercise program seems to modulate this transcription factor which could improve long-term endogenous antioxidant defense in HD patients.

Funding: Government Support - Non-U.S.

FR-PO545

Effect of Resistant Starch Supplementation on the Indole-3-Acetic Acid Levels and Aryl Hydrocarbon Receptor Expression in Hemodialysis Patients

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Background: Researchers have investigated the role of the gut microbiota in the pathogenesis of chronic kidney disease (CKD) and cardiovascular disease (CVD). The gut microbiota imbalance favors bacterial growth producing uremic toxins, such as indole-3-acetic acid (IAA). This toxin leads to inflammation and, the aryl hydrocarbon receptor (AhR) has been pointed as an important ligand of IAA, triggering inflammatory signaling responses. Thus, the use of prebiotics, such as resistant starch (RS), may be an effective non-pharmacological strategy to restore gut microbiota balance, reducing IAA levels and AhR expression, and consequently decreasing inflammation in CKD. The aim of this study was evaluate the effect of RS supplementation on IAA levels and AhR expression in hemodialysis patients (HD).

Methods: Randomized, double-blind, placebo-controlled clinical trial including 43 HD patients (53.4% male, 58.2 ± 9.5 years, 25.7 ± 3.8 kg/m^2, 37.5 ± 26.9 months of HD). The patients were supplemented with 16g/day of RS (HI-MAIZE 260) or placebo in the form of cookies (for consumption on the day of dialysis) and *sachet* (for daily consumption without dialysis) for 4 weeks. Blood samples were collected before and after the supplementation period. IAA plasma levels were measured by high performance liquid chromatography and, peripheral blood mononuclear cells were isolated and analyses of quantitative real time polymerase chain reaction was performed to evaluate the AhR mRNA expression.

Results: Thirty one patients completed the study, 15 in the RS group and 16 in the placebo group. No differences were found in IAA levels (2329.5 (1112-3451)mg/L vs 1667 (1191 - 2934)mg/L; p=0.16) or in AhR mRNA expression (1.08 ± 0.5 vs 1.12 ± 0.45, p=0.81) after RS supplementation. However, there was a positive correlation (r=0.48; p=0.03) between IAA and AhR at the baseline.

Conclusions: Although RS supplementation did not influence IAA levels or AhR expression, the positive association between this toxin and the AhR confirm a possible interaction between them. Future therapeutic strategies can be discovered in the sense of modulating this complex pathway.

Funding: Government Support - Non-U.S.

FR-PO546

Presarcopenia and Sarcopenia as Predictors of Hospitalization-Free Survival in Patients with CKD

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Background: Sarcopenia is defined as the degenerative loss of skeletal muscle mass, and strength associated with aging. In this article, we compared prevalence of sarcopenia using three different skeletal muscle mass indices in predialysis and dialysis patients with chronic kidney disease (CKD), and sought to the relationship with clinical outcomes.

Methods: 179 patients were recruited (114 male, 65 female, 103 predialysis, 76 dialysis) and followed prospectively for up to 3 years. Appendicular skeletal muscle mass (ASM) was measured by bioimpedance analysis (Inbody 620, In-body, Seoul, Korea). Weight (wt) adjusted, height square (ht^2) adjusted, or body mass index (BMI) adjusted ASM were assessed in all subjects. Hand grip strength and walking speed were measured. Frailty phenotypes were examed in all subjects. Sarcopenia was considered present when subjects had low handgrip strength accompanied by low adjusted ASM. Those who showed only low hand grip or muscle volume loss were categorized as presarcopenia.

Results: 9.5%, 4.5%, or 2.8% of the patients had sarcopenia, while 55.9%, 57.5%, or 58.7% of the patients were categorized as presarcopenic status according to three different indices (ASM/wt, ASM/ht^2, or ASM/BMI respectively). ASM/wt index showed significant correlation with age, handgrip strength, HOMA-IR and frailty score. During follow-up, 56 patients were hospitalized (cardiovascular 30.3%; infectious disease 23.2%). Multivariate cox proportional hazards models also demonstrated that the risk of hospitalization was significantly higher for CKD patients who were categorized as sarcopenic (hazard ratio [HR], 9.11 ; 95% confidence interval [CI], 2.295 – 25.182; P < 0.001) or presarcopenic (HR, 2.48 ; 95% CI, 1.180 – 5.230; P = 0.017) than normal status according to ASM/wt index

Conclusions: ASM/wt index showed best relationship with age, muscle strength, insulin resistance and frailty. Sarcopenia and presarcopenia defined using ASM/wt index predicted poorer hospitalization-free survival in patients with CKD. This work was supported by a National Research Foundation grant of Korea (NRF-2016R1C1B1013814) funded by the Korea government.

Funding: Government Support - Non-U.S.

FR-PO547

Relative Sarcopenia and Mortality and the Modifying Effects of CKD and Adiposity

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Background: Conventional definitions of sarcopenia based on lean mass may fail to capture low lean mass relative to higher fat mass, i.e., relative sarcopenia. The objective of this study is to determine the associations of sarcopenia and relative sarcopenia with mortality independent of co-morbidities, and whether chronic kidney disease (CKD) and adiposity alter these associations.

Methods: Dual energy X-ray absorptiometry (DXA)-derived appendicular lean mass index (ALMI, kg/m2) and fat mass index (FMI, kg/m2) were assessed in 14,850 NHANES participants from 1999-2006 and were linked to death certificate data in the National Death Index with follow up through 2011. Sarcopenia was defined using sex and race/ethnicity-specific standard deviation scores compared with young adults (T-scores) as an ALMI T-score < –2 and relative sarcopenia as fat-adjusted ALMI ($ALMI_{FMI}$) T-score < –2. Glomerular filtration rate (GFR) was estimated using creatinine- (eGFRCr) and cystatin C- (eGFRCys) based regression equations.

Results: Three (3.0) percent of NHANES participants met criteria for sarcopenia and 8.7% met criteria for relative sarcopenia. Sarcopenia and relative sarcopenia were independently associated with mortality (HR sarcopenia 2.89, 95% CI, 2.17 to 3.86; HR relative sarcopenia 2.62, 95% CI, 2.14 to 3.20). The corresponding population attributable risks were 6.2% (95% CI, 4.3% to 7.5%) and 25.8% (95% CI, 17.3% to 31.2%), respectively. The risk of mortality associated with relative sarcopenia was attenuated among persons with higher FMI (p for interaction <0.01) and was not affected by CKD status for either sarcopenia or relative sarcopenia.

Conclusions: Sarcopenia and relative sarcopenia are significantly associated with mortality regardless of CKD status. Relative sarcopenia is nearly 3-fold more prevalent amplifying its associated mortality risk at the population level. The association between relative sarcopenia and mortality is attenuated in persons with higher FMI.

Funding: NIDDK Support

FR-PO548

CKD and the Adiposity Paradox: Valid or Confounded?

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Background: Obesity is associated with decreased mortality risk in in patients with end-stage renal disease and mild to moderate chronic kidney disease (CKD), a phenomenon termed the obesity paradox. Indices of obesity, including Quételet's (body mass) index (BMI, kg/m^2) and % body fat (%BF) are confounded by muscle mass, while DXA derived fat mass index (FMI, kg/m^2) overcomes this limitation. We aimed to compare the associations between adiposity and mortality in persons with CKD using alternative estimates of adiposity, and to determine whether muscle mass, inflammation and recent weight loss modify these associations.

Methods: DXA-derived FMI, BMI, and %BF were calculated in 2,852 NHANES participants with CKD from 1999-2006, used to define obesity according to established cut-offs, and linked to death certificate data in the National Death Index with follow up through 2011. Cox proportional hazards models assessed associations between mortality and estimates of adiposity. Sequential models adjusted for percent weight change since the maximum reported weight and interactions with measures of inflammation and muscle mass.

Results: In adjusted models, obesity based on FMI (obese$_{FMI}$) was associated with lower mortality (HR 0.82, 95% CI, 0.70 to 0.97). As continuous variables, higher FMI, BMI and %BF were associated with lower mortality. The protective effect of obesity was less pronounced among those with higher lean mass. The prevalence of >10% weight loss was 20% in obese$_{FMI}$ participants, compared with 40.4% in the non-obese$_{FMI}$ participants. Prior weight loss was strongly associated with mortality, and the protective effect of obesity was no longer significant after adjustment for prior weight loss. Inflammation did not modify these associations.

Conclusions: These data demonstrated an apparent protective effect of high fat mass in CKD, particularly among persons with low muscle mass. The prevalence of prior weight loss was two-fold less among obese compared to non-obese persons and confounded these associations.

Funding: NIDDK Support

FR-PO549

Pre-ESRD 24 Hour Urine Creatinine Changes and Post-ESRD Mortality

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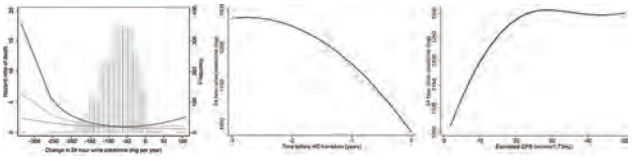
Background: Protein-energy wasting (PEW) is common in CKD and ESRD. The temporal dynamics of PEW in patients with progressive loss of kidney function, and its association with future outcomes, is unclear.

Methods: We examined changes in 24-hour urine creatinine (24hrUC; a surrogate of muscle mass) over the last 3 years prior to renal replacement therapy in a national cohort of 701 incident ESRD US veterans with 2 or more 24hrUC measurements. We estimated 24hrUC slopes in mixed effects models, and we examined their association with post-dialysis all-cause mortality using Cox models adjusted for confounders. To assess the temporal dynamics of pre-ESRD changes in 24hrUC and its association with changing eGFR, we separately fitted in mixed effects models penalized spline regressions of 24hrUC on time and on eGFR.

Results: Patients were 63±10 years old, 97% male, 35% African-American. Mean baseline eGFR and 24hrUC were 26±16 ml/min/1.73m2 and 1294±290 mg, respectively. The mean slope of 24hrUC vs. time was -77±45 mg/year. Decline in 24hrUC started to accelerate in the last 2 years prior to ESRD, and once eGFR was <25 ml/min/1.73m2 (Figure). 444 patients died (mortality rate 191/1000 patient-years, 95%CI: 174-209) over a median follow-up time of 3 years. More severe decreases in 24hrUC were associated with higher mortality (Figure).

Conclusions: Patients with advanced CKD lose an average of 6% of their muscle mass each year. Loss of muscle mass starts to accelerate once eGFR falls below 25 ml/min/1.73m2, and more loss of muscle mass is associated with higher mortality after ESRD transition.

Funding: NIDDK Support



FR-PO550

Change in Body Composition over Time and Its Association with Survival Among Patients on Hemodialysis

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Background: Patients with ESRD who have a higher body mass index have better survival, a phenomenon known as the obesity paradox. Accounting for body composition and for changes over time may help to elucidate this paradoxical association.

Methods: We leveraged repeated measures of body composition (at baseline, 12, and 24 months) by whole-body bioimpedance spectroscopy (BIS) from 286 prevalent ESRD patients from 7 dialysis facilities in the USRDS ACTIVE/ADIPOSE study to examine the obesity paradox. We performed BIS to estimate intracellular water as a proxy for muscle mass (ICW/m^2), extracellular water (ECW/m^2), and fat mass (FM/m^2). Death data were ascertained through linkage with the USRDS through June 2016. We used linear mixed models to examine change in body composition over time and Cox models with BIS-derived estimates as time-varying predictors to examine survival after adjusting for covariates.

Results: Results: Participants' mean age was 59 ± 15, and 66% were male. Over time, only ICW/m^2 declined (-0.08 95%CI -0.13, -0.04 L/m^2/year) and neither ECW/m^2 (0.02 95%CI -0.03, 0.06 L/m^2/year) nor FM/m^2 (-0.07 95%CI -0.20, 0.05 L/m^2/year) changed significantly. In survival analysis with body composition parameters as time-varying predictors, ICW/m^2 was associated with lower mortality (HR 0.67, 95%CI 0.49, 0.93). Higher ECW/m^2 was associated with higher mortality (HR 1.75 95%CI 1.19, 2.60). Fat mass was not associated with survival (HR 0.99 95%CI 0.93, 1.06).

Conclusions: In this cohort of participants with repeated measures of body composition, muscle mass declined over time. Higher muscle mass was associated with better survival, but higher fat mas was not associated with survival independent of muscle mass.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO551

Abdominal Obesity in Normal Weight versus Overweight and Obese Hemodialysis Patients: Associations with Nutrition, Inflammation, Muscle Strength, and Quality of Life

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Background: The biological basis of abdominal obesity leading to more severe outcomes in maintenance hemodialysis (MHD) patients with normal body mass index (BMI) is unclear. We compared the phenotype of abdominal obesity in different BMI categories of MHD patients.

Methods: We performed a cross-sectional study of 188 MHD patients (52.7% women; mean age, 69.4±11.5 years) with abdominal obesity in different BMI groups using WHO criteria. Appetite and dietary intake, body composition, handgrip strength, malnutrition-inflammation score (MIS), inflammatory biomarkers, adipokines and health-related quality of life (QoL) questionnaires were studied.

Results: According to multivariable analyses, abdominally obese patients with normal BMIs consumed less protein per day (p=0.04), had lower measurements of surrogates of lean (p<0.001) and fat mass (p<0.001), higher total cholesterol, TNF-α (p<0.05), and adiponectin to leptin ratios (p=0.003) compared to overweight and obese patients with abdominal obesity. Multivariable analyses showed no differences in handgrip strength among the study groups. The abdominally obese study participants with normal weight had significantly lower scores in role-physical (p=0.003) and pain (p=0.04) scales after multivariable adjustments.

Conclusions: Normal weight MHD patients with abdominal obesity exhibit a more proatherogenic profile in terms of inflammatory markers and adipokines expression, lower body composition reserves and lower physical ability compared to abdominal obesity patients with overweight and obesity. This at least partially explains the abdominal obesity paradox in MHD population in which worse clinical outcomes are seen in abdominally obese patients with normal BMIs, as opposed to overweight and obese patients who are also abdominally obese.

Funding: NIDDK Support

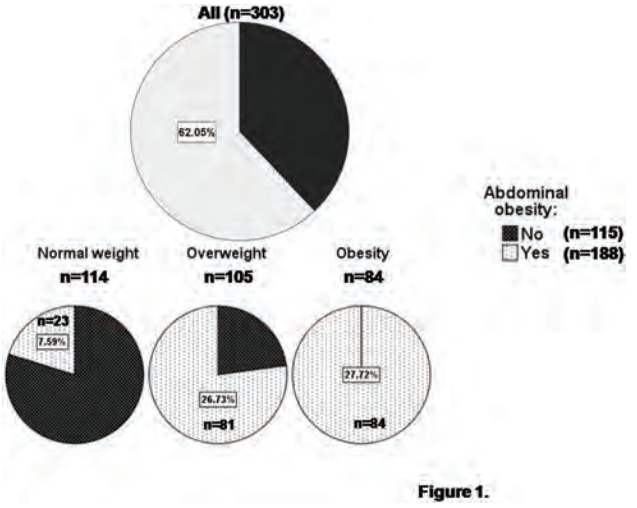

Figure 1.

FR-PO552

Effects of Body Fat Accumulation During PD on Mortality and Technique Failure: Is There a Difference by PD Duration?

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Background: Significant body fat accumulation is an inevitable but potentially serious problem in maintenance peritoneal dialysis (PD) patients. Whether excessive fat gain predicts long-term outcomes in these patients is still unknown.

Methods: In this prospective observational study of 296 patients, the association between excessive fat accumulation and patient survival and PD failure rates was analyzed. Patients were classified by dialysis duration at time of study enrollment into short- (<2years) and long-term (>2years) groups. Body weight (BW) and body composition analysis were measured twice, 12.8 ± 4.6 months apart. Excessive fat accumulation was defined as a 1-year change in body fat percentage (ΔPBF) over the highest quartile (5.0% for men, 5.4% for women).

Results: A substantial 1-year increase in BW and PBF were only observed in the short-term group (p<0.001, 0.027), whereas, in the long-term group, the changes were insignificant. In the short-term group, the ΔPBF was closely associated with unfavorable baseline metabolic profiles, including old age, diabetes, obesity, elevated blood pressure and edema. Accordingly, mortality rate in patients with excessive fat accumulation was significantly higher than in those without (P=0.007). The risk of technical failure was also increased with excessive fat gain. After adjusting for diabetes, obesity, and fluid status, it increased the incident risk of PD failure by 2.22-fold (95% CI 1.08–4.54). However, in the long-term group, fat gain did not impact on prognosis.

Conclusions: Excessive fat accumulation occurring primarily during the early period of PD was associated with baseline unhealthy metabolic profiles, higher mortality and PD failure rate independent of baseline obesity and fluid status.

FR-PO553

The Association Between Obesity and CKD in the Human Hereditary and Health in Africa Kidney Disease Research Network

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Background: There is very little existing data on the relationship between obesity and CKD in Africans. We estimated the prevalence of obesity among cases (eGFR<60ml/min/1.73m^2) and controls (eGFR>60ml/min/1.73m^2) in the Human Hereditary and Health in Africa Kidney Disease Research Network (H3A-KDRN) and determined the association between obesity (measured by body mass index (BMI) and waist circumference) and CKD.

Methods: In this case-control study, we estimated the prevalence of obesity in cases and controls using BMI ≥30kg/m^2 and waist circumference ≥88cm in women and ≥102cm in men as definitions for obesity. Using logistic regression, we estimated crude and adjusted prevalence odds ratios and 95% confidence intervals for CKD in the entire cohort.

Results: The prevalence of obesity using BMI was 28.2% in the cases vs 21.5% in the controls (p<0.0000001) while the prevalence of obesity by waist circumference was 22.8% in cases and 26.2% in controls (p<0.01). Cases with a higher BMI were more likely to have higher eGFR (p<0.001) while controls with a higher BMI had a lower eGFR (p<0.0001). Compared to those with normal BMI, underweight individuals were 1.43 times more likely to have CKD, OR=1.43 (95% CI 1.11, 1.83). Overweight OR =0.87 (0.77,0.99) and obesity class I OR=0.81 (95% CI 0.68,0.95) were both associated with lower odds of CKD in the crude analyses. After adjusting for age, gender, country, hemoglobin and ACR underweight OR=1.61(95% CI 1.31, 1.98), overweight OR=0.85 (95% CI 0.74,0.97) and class I obesity OR=0.82 (95% CI 0.68, 0.99) remained associated with CKD. Compared to those with a normal waist circumference (80-87.9cm in women and 94-101.9cm in men), individuals with a waist circumference of <80cm in women and <94cm in men were more likely to have CKD (OR=1.24, 95% CI 1.05,1.48) in the crude and some adjusted models OR=1.20 (95% CI 1.01, 1.44). No other waist circumference categories were associated with CKD.

Conclusions: The findings in this stud mimics the risk factor paradox for obesity. Underweight individuals were more likely to have CKD but obese and overweight were less likely to have CKD. We will need further prospective studies to determine if higher BMI is protective of CKD in Africans or if these findings are reflective of reverse causality.

Funding: NIDDK Support, Other NIH Support - NHGRI

FR-PO554

Effect Modification of GFR and BMI on Insulin Sensitivity Among Nondiabetic Patients

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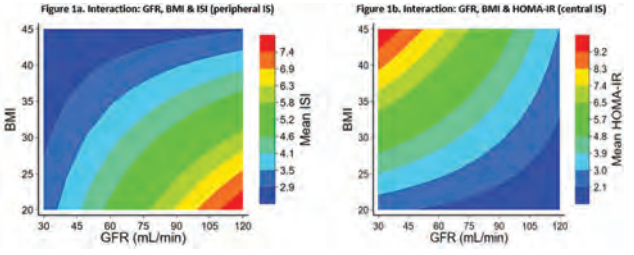
Background: Insulin resistance (IR) is highly prevalent in patients with CKD. The reason for this phenomenon is unknown. We studied the interaction between estimated glomerular filtration rate (eGFR) and body mass index (BMI) as determinants of peripheral and central insulin sensitivity (IS).

Methods: In a cross-sectional study of 150 patients, 56 CKD and 94 with normal GFR, we used hyperinsulinemic euglycemic glucose clamp to measure IS (peripheral or skeletal muscle IS) as insulin sensitivity index (ISI) and the homeostasis assessment of insulin resistance (HOMA-IR) (central or liver IS). eGFR estimated by CKD-EPI and body mass index (BMI) were estimated at baseline. Linear regression models with robust standard errors (to relax homoscedasticity assumptions) and interaction terms were used to investigate GFR and BMI as predictors of IS.

Results: The mean age was 53.9 (14.5) yrs; 50.7% were female and 36.7% African-American. Log ISI was positively correlated (r = 0.39, p < 0.0001) with eGFR and inversely correlated (- 0.30, p < 0.0001) with BMI. In multivariable models adjusted for age, sex and race, a 10 ml/min/1.73m2 increase in eGFR was associated with a greater increase in ISI among non-obese (0.48; 95% CI: 0.25, 0.70) compared to obese participants (0.18; 95% CI: 0.02, 0.35) (p-interaction = 0.04). Patients with low GFR had lower ISI (insulin resistant) even with normal BMI (Fig. 1a). Log HOMA-IR was inversely correlated with eGFR (r = - 0.49, p < 0.0001) and positively correlated with BMI (r = 0.52, p < 0.0001). HOMA-IR was higher for persons with lower GFR compared to higher GFR, at any BMI value. For example, at a BMI of 30 and a GFR of 30 ml/min/1.73m2, HOMA-IR was 4.8 compared to 1.2 at a GFR of 120 ml/min/1.73m2 (Fig. 1b).

Conclusions: GFR and BMI are both predictors of IS but the magnitude of the effect of BMI on IS varies across GFR levels and type of IS (peripheral versus central). The effect of BMI on central or liver IS (HOMA-IR) is more pronounced at lower GFR with small changes in BMI translating into greater variations in IS. Conversely, at low GFR, skeletal muscle IS is less affected by BMI.

Funding: Veterans Affairs Support, Private Foundation Support



FR-PO555

Density of Brown Adipose Tissue in Japanese Hemodialysis Patients: Association with Protein-Energy Wasting

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Background: Patients receiving chronic hemodialysis are on catabolic status in energy-consuming cycle, according to complex factors due to the pathogenesis of original disease, renal failure and dialysis therapy. Nutritional disorder in CKD patients with decreases of skeletal muscle and body fat has proposed to be called as Protein-Energy wasting (PEW) by International Society of Renal Nutrition and Metabolism (ISRNM). On the other hand, the pathogenesis of PEW is still unknown. In recent years, the importance of energy metabolism control via brown adipose tissue (BAT) gathers attraction, despite the difficulty in measuring its density. We have developed its portable measuring system, and investigated BAT densities and nutritional states in Japanese HD patients.

Methods: We assessed BAT densities in Japanese HD patients (66.5 ± 10.4 years) and healthy adults (65.3 ± 10.4 years) based on total hemoglobin concentrations in the supraclavicular region measured with near-infrared time-resolved spectroscopy. We also

assessed correlation between BAT densities and bioelectrical impedance analysis for the evaluation of body composition in HD patients.

Results: The BAT density in 33 HD patients was 75.6 ± 31.4 μM, which tended to be higher (p = 0.059) compared with 61.1 ± 4.3 μM in healthy subjects of the matched age over 40 years old. Furthermore, BAT density and body fat mass were negatively correlated in HD patients. BAT in healthy subjects were negatively correlates visceral fat area in previous studies. But in our study, despite the fact that the visceral fat area was significantly higher in HD patients, BAT tended to be higher in HD patients. The stimulation by cold and consequently increase in sympathetic nerve activity directly to BAT causes an increase in BAT density. It is known that muscle sympathetic nerve activity is elevated in patients with CKD complicated hypertension. It may be involved as a cause of increase in BAT density.

Conclusions: BAT may be one of the principal factors for malnutrition with energy-consuming cycles in HD patients.

FR-PO556

Glucose (Glu) Disposal in Diabetic (D) and Non-Diabetic (ND) Patients During Hemodialysis (HD)

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Background: It was the purpose to examine whether intra-venous (iv) Glu administered during HD caused a characteristic response suitable to detect impaired Glu tolerance in HD patients (pts) during routine treatment.

Methods: About 30 min into treatment (baseline T0), a 40% Glu solution (100.1±22.0 mL) was directly injected into the venous line of the extracorporeal circulation at a dose of 0.5 g/kg dry weight. Blood samples were drawn from the arterial line at T0, and 5, 10, 20, 30, 60 min after injection (T5, T10, T20, T30, T60). Glu (mmol/L) and insulin (Ins; mU/L) levels were measured. In addition, relative blood volume (RBV; %) was continuously measured by ultrasonic technique for quantification of osmotic volume effects.

Results: 25 ND and 9 D pts were studied (61±13 years, dry weight 80.6±17.6 kg, UF volume 2.47±0.92 L, 12 female). The increase and time course in Glu was largely comparable between D and ND pts; Ins significantly increased in ND pts only (Tab. 1). The RBV effect of Glu peaked around 6 min after injection and was 105.16±1.30 vs. 105.90±1.52% in ND and D pts, respectively, and also showed a comparable time course (Fig. 1).

Conclusions: In spite of significant difference in Ins secretion, infusion of Glu amount comparable to that of an iv Glu tolerance test did not produce major differences in Glu disposal during HD. It appears that Glu is removed faster by HD than it can be disposed in the large but slowly perfused Ins-dependent muscle and skin compartment. This may have implications for iv nutrition during extracorporeal treatments.

Funding: Clinical Revenue Support

Tab. 1

		T0	T5	T10	T20	T30	T60
Glu	ND	5.2±0.6	24.6±3.8	18.5±2.4	13.7±1.8	11.0±1.5	7.4±1.1
	D	7.5±2.4*	25.4±3.8	19.5±3.4	16.2±3.3	13.7±3.3	10.7±2.8*
Ins	ND	10.1±7.5	101.2±49.3	67.8±36.7	50.3±33.7	37.9±28.6	21.3±23.7
	D	8.0±3.5	14.2±7.6*	13.3±7.2*	15.5±8.9*	14.0±7.9*	11.0±6.0*

* p<0.05 ND vs. D

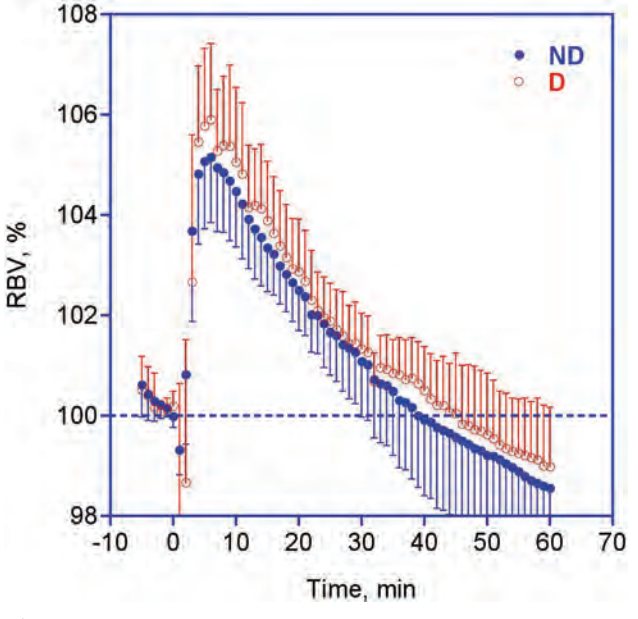

Fig. 1

FR-PO557

Lipoprotein Subfraction Analyses in a Cohort of the Palm Tocotrienols in Chronic Hemodialysis Study (PATCH)

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Background: Dyslipidemia (D) is one of the characteristics of end-stage renal disease patients who develop cardiovascular disease (CVD). The PATCH clinical trials [NCT02358967, NCT02913690] are double-blind one-year intervention trials (300 mg tocotrienols or placebo daily) in hemodialysis patients in USA, Malaysia and Bangladesh (currently some 400 patients are enrolled). A pilot study showed improvement in D with tocotrienols. The aim of this preliminary analysis is to evaluate and characterize lipoprotein subfractions in the PATCH Michigan cohort.

Methods: The Michigan cohort includes 138 patients enrolled across various dialysis clinics in Michigan (recruitment ends Dec 2018). Subject are 95% African Americans (Age 59 ± 13 yrs., 64% men, dialysis vintage 65±63 months). Blood was collected at baseline and plasma isolated for lipid determination and lipoprotein subfraction analyses using a gel-electrophoresis method (Quantimetrix Lipoprint™).

Results: Baseline plasma lipids (n=124) revealed HDL-C, LDL-C and Triglyceride (TAG) values (mg/dL) of 49±18, 79±39 and 95±51, respectively. The values were not influenced by the dialysis shift during blood collection. The percentage of large, intermediate and small HDL particles were 39.4±15.6, 46.9±9.5 and 13.6±8.4, respectively. The percentage of large, intermediate and small LDL particles were 15.0±4.3, 8.1±3.9 and 2.4±3.3, respectively. Eight percent of subjects were D (TAG 201±54, HDL-C 33±5, LDL-C 133±17 mg/dL), 48% were normolipemic [N] (TAG 64±25, HDL-C 61±18, LDL-C 55±23 mg/dL), while the rest had mixed D (TAG 110±36, HDL-C 40±11, LDL-C 96±38 mg/dL). Dyslipidemic subjects had significantly greater proportion of small HDL particles than N subjects (22.5%±4.5% vs 9.1%±6.9%), while large HDL (24.6%±8.9% vs 48.3%±13.9%) and intermediate HDL (52.9%±6.6% vs 42.4%±8.7%) were significantly lower. D subjects had significantly smaller LDL particle sizes compared to N subjects.

Conclusions: Changes in circulating lipoproteins reflect alterations in LDL and HDL particle sizes that can be readily detected. The role of these compositional changes in CVD in HDL patients is as yet, unresolved. (Supported by the Malaysian Palm Oil Board/ Government of Malaysia)

FR-PO558

Glycosylated Hemoglobin A1c as a Predictive Marker of Poor Sleep in ESRD Population

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Background: Patients on dialysis experience higher rates of sleep disorders compared to general population. Self-directed questionnaires can help to diagnose sleep disorders. We aim in this study to describe the epidemiology of sleep disorders in ESRD population and determine the clinical and laboratory biomarkers that can predict it.

Methods: We conducted a prospective cross-sectional study in ESRD patients on dialysis in the main dialysis unit in the state of Qatar. All adult patients on dialysis for at least one month were eligible. Enrolled patients underwent sleep disorder screening using the Pittsburgh Sleep Quality Index (PSQI), a validated questionnaire to measure the quality and patterns of sleep in adults. PSQI score ≥5 indicates poor sleep. Logistic and regression models were employed to evaluate the association between poor sleep scores and different commonly used clinical and laboratory markers.

Results: 253 patients on dialysis (62% on hemodialysis and 38% on peritoneal dialysis) were enrolled. 115 (44.6%) were male. Median PSQI score was 10 (interquartilerange(IQR): 6-18). Diabetic patients had significantly higher median score of PSQI of 10 (IQR: 7-18.75) compared to non-diabetics (Median 9, IQR: 5-16.5) (P=0.02). 84% of diabetics had PSQI ≥ 5 compared to 73% in non-diabetic (P=0.03). Using univariate linear regression model, PSQI scores correlated significantly with Hb1AC levels (β1= 0.9, P=0.006) (even after adjusting for BMI (β1= 0.6, P=0.03)). For every 0.9 unit increase in Hb1AC, the PSQI increases by 1. The receiver operating characteristic (ROC) using Hb1AC as a predictor for sleep disorder showed AUC of 0.65. Utilizing a cut-off value of 5.1, the predictive diagnostic utility of Hb1AC was 80% for sensitivity and 89% specificity. Univariate analysis of other clinical markers including hemoglobin level, anemia, PTH, KT/v, hypertension, and phosphorus revealed no statistical correlation with PSQI scores.

Conclusions: Our data shows high prevalence of sleep disorders in ESRD population and diabetic patients are at higher risk. Utilizing Hb1AC in diabetics with ESRD can predict patients at increased risk of sleep disorder. Our statistical models suggest that controlled diabetes is associated with better sleep quality, however, further investigational work is needed.

FR-PO559

Intra-Individual Variability in High Density Lipoprotein Cholesterol and Risk of ESRD: A Nationwide Population-Based Study

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Background: Recent studies demonstrated an association between low high density lipoprotein – cholesterol (HDL-C) and progression of chronic kidney disease (CKD). However, some of the results showed the inconsistencies between HDL-C and renal

function outcomes. We investigated the association between HDL-C variability and the risk of end-stage renal disease (ESRD).

Methods: Using nationally representative data from the Korean National Health Insurance System, 3 718 355 subjects who were free of ESRD and who underwent ≥3 health examinations during 2005 to 2010 were followed to the end of 2015. HDL-C variability was measured using the coefficient of variation (CV), standard deviation (SD) and the variability independent of the mean (VIM). The primary outcome was the development of ESRD, defined as a combination of the relevant disease code and the initiation of renal replacement therapy.

Results: There were 2095 cases of ESRD during a median follow up of 4.8 years. There was a graded association between a higher HDL-C variability and incident ESRD. In the multivariable adjusted model, the hazard ratios and 95% confidence intervals comparing the highest versus lowest quartiles of VIM of HDL-C were 1.60 (95% confidence interval, 1.39–1.84). The results were consistent when the variability of HDL-C was modeled using SD and CV and were independent of preexisting CKD.

Conclusions: Increasing HDL-C variability was associated with an increasing incidence of ESRD. This findings suggest that HDL-C variability is an important risk factor of CKD progression in the general population.

FR-PO560

The Impact of Onset Age on Metabolic Disorders in Urolithiasis

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Background: Urolithiasis is related with metabolic disease, such as hyperuricemia, diabetes, dyslipidemia and hypertension. We aim to explore the association between the metabolic diseases and the stone type, clinical and laboratory features, the onset age with urolithiasis patients.

Methods: Clinical data were retrospectively collected from 707 patients with urolithiasis surgery in Beijing Tsinghua Changgung Hospital from December 2015 to August 2017. Their demographic data, clinical manifestations, laboratory tests and examinations were analyzed retrospectively.

Results: (1) 446 males and 261 females (18 to 94 years old) from 28 provinces in China were included in our study. The urolithiasis patients with onset age > 30 years old are more likely common to diabetes mellitus, hypertension, gout, hyperlipidemia and metabolic syndrome. (2) The onset age of urolithiasis is positively associated with BMI (r=0.100, *P*=0.011), iPTH (r=0.089, *P*=0.049), TG (r=0.083, *P*=0.033), globulin (r=0.077, *P*=0.046) and IgG (r=0.077, *P*= 0.040), while it is negatively related to urine phosphorous (r=-0.109, *P*=0.027) and HDL-C (r=-0.099, *P*=0.010). (3) Correlation analysis showed that the level of TC and LDL-C were both positively associated with serum calcium, phosphorus, alkaline phosphatase (ALP), globulin and white blood cell (WBC) (*P*<0.05). The level of TG is positively associated with serum calcium, magnesium, 25-OH-VitD_3, while negatively associated with urine PH (*P*<0.05). HDL-C was negatively associated with urine uric acid (*P*<0.05). Fast glucose was positively associated with serum ALP, globulin and the count of urine bacterium (*P*<0.05). Serum uric acid was positively associated with serum calcium, phosphorous and urine phosphorus (*P*<0.05). (4) The incidence of urinary infection (70.3% vs. 62.2%, *P*=0.025) and amorphous calcium phosphate (1% vs. 0%, *P*=0.043) is significantly higher in patients with hyperlipidemia.

Conclusions: The urolithiasis patients with onset age > 30 years old are more likely associated with metabolic disorders and urinary infections. Elevation of serum lipid, glucose and urate acid may add risks to urolithiasis by impacting urine PH, calcium-phosphorus metabolism and infectious status.

Funding: Private Foundation Support

FR-PO561

Exosomal MicroRNAs Profiling in Obese Patient Using MicroRNA-Sequencing

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Background: Exosomal micro RNAs (miR) are valuable biomarker and regulate biological process of obesity. Bariatric surgery has beneficial effect on obese patients. However the mechanisms of this surgery are not clear. We investigated to identify exosomal miR signature associated with obesity and examine exosomal miR changes after bariatric surgery.

Methods: Healthy volunteers (HV, n=18) and non-diabetic obese patients (n=16) were enrolled prospectively. We assessed the miR profile of serum exosome from HV and obese patients using RNA sequencing (RNA-seq) cross sectionally. To evaluate the effect of bariatric surgery, we conducted exosomal miR analysis in 12 obese patients 6 months after surgery.

Results: RNA-seq analysis showed 224 obesity-related microRNAs. Using >2 and <-2-fold changes as cut-offs, we identified that the expression of 72 (up-regulation=57, down-regulation=15) exosomal miR in obese patients compared to HV (table 1). Biological pathway analysis was suggestive of modulation of signaling pathways including the Wnt pathway, fatty acid biosynthesis, AMPK signaling, p38 MAPK signaling, and AMPK signaling in exosome from obesity patients. Bariatric surgery induced weight reduction led to a marked change in the Wnt pathway and fatty acid biosynthesis pathway.

Conclusions: Obesity leads a different miR pattern in serum exosome compared to healthy volunteers. Weight loss after bariatric also induces changes in exosomal miR profiles.

Funding: Government Support - Non-U.S.

Top 5 list of exosomal micro RNAs from obesity compared to healthy volunteers

mature micro RNA	obesity/healthy volunteers fraction
hsa-miR-122-5p	11.8
hsa-miR-193b-5p	6.8
hsa-miR-4449	6.6
hsa-let-7a-3p	6.5
hsa-miR-1290	5.9
hsa-miR-26b-3p	5.9
hsa-let-7f-1-3p	5.9
hsa-miR-4461	-14.3
hsa-miR-6739-5p	-13.0
hsa-miR-1273a	-10.5

FR-PO562

Cognitive Impairments in Renal Transplant Recipients: Impact on Daily Life Functioning

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Background: After kidney transplantation, there is a heavy demand on the cognitive capacities of kidney transplant recipients (KTR) in order to increase survival chance with the donor organ. However, until now, it has been insufficiently examined to what extent cognitive functioning is affected in KTR. In this study, we aimed to examine the prevalence of cognitive impairment in KTR in the chronic stage. In particular, we assessed to what extent cognitive impairments affects daily life functioning post-transplant.

Methods: This study was conducted as part of the Transplantlines Biobank and Cohort Study at the University Medical Center Groningen. We included 120 KTR and 85 age, sex and education matched healthy controls (HC). Cognitive functions were assessed with tests measuring memory (15 Words Test (15WT), Wechsler Adult Intelligence Scale subtest Digit Span (Forward and Backward; DS FW, DS BW), Word Fluency (WF)), attention and mental speed (Trail Making Test part A (TMT-A)) and executive functioning (Trail Making Test part B (TMT-B), Dutch version of the Controlled Word Association Test (COWAT)). A questionnaire was used to examine participation in daily life (Utrecht Scale for Evaluation of Rehabilitation - Participation).

Results: Mean age of KTR was 56.9 ± 12.4 years, 69 were male, at a median time of 11 [1-41] years post-transplantation. KTR performed significantly worse on tasks measuring memory ($p < 0.01$ (15WT); $p < 0.001$ (WF); $p < 0.05$ (DS BW)), attention and mental speed ($p < 0.01$ (TMT-A) and executive functioning ($p < 0.001$ (TMT-B); $p < 0.001$ (COWAT)), compared to HC. Furthermore, daily life participation was significantly correlated with mental speed ($r = -0.36$, $p < 0.001$) and working memory ($r = 0.21$, $p < 0.05$).

Conclusions: This study shows cognitive impairments in multiple domains in KTR post-transplantation. Moreover, cognitive dysfunctioning interferes negatively with participation in everyday life. Administering early neuropsychological assessment in KTR is clinically highly relevant to detect cognitive impairments and to allow for timely counselling or treatment.

FR-PO563

Health-Related Hope, Disease Stage, and Disease Self-Management over a Very Wide Range of CKD Severity

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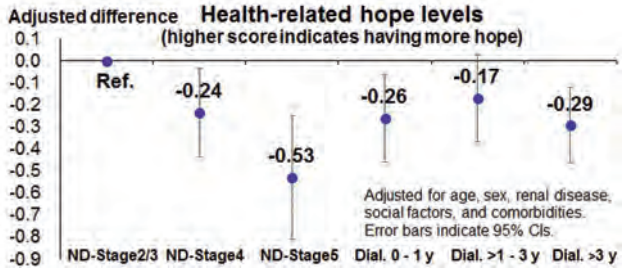
Background: Disease experience varies at different stages of CKD. Patients who experience hope might more effectively adjust to their health condition. The aims of this study were to quantify the associations of health-related hope with disease stage, and with psychological and medical indices of CKD self-management.

Methods: Data were collected from 461 adult CKD patients in Japan. The range of disease severity was very wide: Included were patients at stage 2-3 who were not receiving dialysis (ND stage 2-3) and those at ND stages 4 and 5. Also included were patients receiving dialysis. Health-related hope (HR hope) was measured with a recently developed 18-item scale focusing on how people experience their health and how healthcare affects hope. General linear models were used to examine the associations of HR hope with CKD stage, blood pressure (BP), and serum levels of phosphorus and potassium. The burdens of water and diet restriction were measured with the Kidney Disease Quality of Life questionnaire. Generalized ordered logit models were used to examine the associations of HR hope with the likelihood of reporting that water or diet restriction was burdensome.

Results: Patients at ND stages 4 and 5 had lower levels of HR hope than those at ND stage 2-3 (Figure). With ND stage 2-3 as the reference, patients at all further stages had lower levels of HR-hope. The lowest level of HR-hope was among patients with disease at ND stage 5. Higher levels of HR hope were significantly associated with lower likelihoods of reporting that water and diet restrictions were burdensome (adjusted OR 0.53 and 0.57 for water restriction and diet restriction, respectively). Higher levels of HR hope were also significantly associated with lower systolic BP (adjusted mean difference -5.8 mmHg). HR hope levels were not associated with diastolic BP or with serum levels of phosphorus or potassium.

Conclusions: Among CKD patients, higher HR hope is associated with less-severe disease, lower systolic BP, and lower perceived burden of water restriction and diet restriction.



FR-PO564

Exploring Beliefs about Treatment in Advanced CKD and Relationship with Well-Being and Outcome

Zoe C. Pittman,[1] Maarten W. Taal,[1] Christopher W. McIntyre.[2] *[1]Royal Derby Hospital, Derby, United Kingdom; [2]London Health Sciences Centre, London, ON, Canada.*

Background: The beliefs that individuals hold about treatments affect treatment adherence. We aimed to examine this in both dialysis and non-dialysis dependant CKD patients and to include reference to other aspects of a treatment.

Methods: The Beliefs about Medicines Questionnaire (BMQ) explores individuals' beliefs about the necessity and concerns of treatments. We adapted the BMQ for beliefs about dialysis, fluid restriction, medicines and dietary restrictions. Individuals from HD (29), PD (10), CKD 4/5 (5) and transplant (13) clinics completed all relevant BMQ questionnaires and the illness intrusiveness ratings scale (IIRS), PHQ-9 (cut point PHQ ≥ 10 for depression screening in dialysis), dialysis recovery time (DRT) and measures of treatment tolerability (TT) and burden (TB). BMQ outputs are reported as mean ± SD, necessity score (max 25) and necessity minus concerns score (N-C) (range ±20, 0 = balanced beliefs).

Results: Dialysis: necessity 11.2 ± 4.8 and N-C -3.7 ± 4.7. N-C correlated with renal replacement therapy vintage (r=0.332 p=0.045) and TT (r=0.478, p=0.003) but not with TB, DRT, IIRS or PHQ-9 or age. Dietary restriction: necessity 15.2 ± 4.7 and N-C -1.2 ± 4.0. N-C correlated with serum potassium (r=0.376 p=0.015) and phosphate (r=0.332 p=0.040) but not with number of phosphate binders. Medicines: necessity 12.5 ± 4.3 and N-C -4.5 ± 4.8. N-C correlated with serum phosphate (r=0.384, p=0.005) but not with total number of medications or binders prescribed. Fluid restriction: necessity 13.3 ± 4.1, N-C -1.3 ± 4.0. No correlations were seen, including with interdialytic weight gains or systolic blood pressure. There was variable but significant correlation between all N-C scales; Dialysis: Medicines (r=0.718), Diet (r=0.550), Fluid (r=0.588); Medicines: Fluid (r=0.416), Diet (r=0.601); Fluid: Diet (r=0.601).

Conclusions: Individuals have a sophisticated way of thinking about the treatments that they are prescribed. These beliefs are not dependent on knowledge but impact on behaviours that affect measurable outcomes such as serum potassium and phosphate. The variation in correlation between some scales suggest that these thought processes are related, however they are not fixed character traits, and therefore may be amenable to education that takes into account individual beliefs in order to address them directly.

FR-PO565

Illness Perceptions in Renal Disease Correlate with Well-Being Markers

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Background: Individuals' perception of their illness correlates with both mortality and quality of life in dialysis patients. Improved understanding of illness perception and its relationship with outcomes will allow improved targeting of information and education. We therefore examined illness perceptions in both advanced CKD and dialysis, and how these relate to other markers of wellbeing.

Methods: The revised illness perceptions questionnaire (IPQr) offers a robust mechanism for examining individual's perception of illness. Persons from HD (29), PD (10), CKD 4/5 (5) and transplant (13) clinics were recruited for a study of understanding and illness perceptions. Questionnaires included the IPQr, illness intrusiveness ratings scale (IIRS), PHQ-9 (cut point PHQ ≥ 10 for depression screening in dialysis), dialysis recovery time (DRT) and measures of treatment tolerability (TT) and burden (TB), including number of tablets (total (NT) and phosphate binders (NB)). Additional background data were collected.

Results: Mean±SD values for individual IPQr subscales (max allowed) were Chronicity (30) 17.15±2.74, Cyclical (20) 9.91±3.97, Consequences (30) 19.11±3.59, Personal Control (30) 17.95±3.83, Treatment Control (25), 14.98±3.24, Understanding (25) 12.98±3.95, Emotional response (30) 15.54±4.98. Subscale analysis did not show any effect from dialysis status, gender or dialysis vintage. There were no correlations with chronicity, treatment control or understanding. However, subscales did demonstrate correlation with: 1)Perception of negative consequences; Age (r=-0.411), PHQ-9 (r=0.289), IIRS (r=0.550), TT (r=0.376), TB (r=0.331) 2)Emotional response; Age (r=-0.305), PHQ-9 (r=0.476), IIRS (r=0.476), TT (r=0.419), TB (r=0.450), NB (r=0.292). 3)Increased perception of the cyclical nature of the condition; PHQ-9 (r=0.308), IIRS (r=0.359), TT (r=0.395), TB (r=0.298). 4)Perception of treatment control correlated with age (r=0.282).

Conclusions: This study shows that individuals' perceptions of the consequences and emotional burdens of kidney disease are high and correlate with depressive symptoms and measures of consequence such as illness intrusiveness, treatment tolerability and treatment burden. Perceptions did not differ with dialysis status or dialysis vintage, suggesting that this is not a treatment effect. Further work will look at other predictors and outcomes.

FR-PO566

Cancer Screening in ESRD Patients

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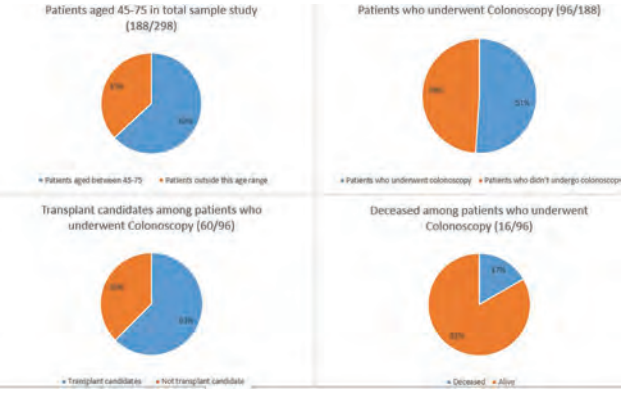
Background: As primary care physicians, we order health maintenance investigations as part of preventive work up which include cancer screening tests. ESRD patients form a special subset of population where regular cancer screening guidelines should not be applied as mortality is higher. The 2012 ASN 'choosing wisely' campaign recommended against regular cancer screening in ESRD patients. We initiated a project in our institution to assess the frequency of cancer screening tests- with focus on colorectal cancer screening in our ESRD population.

Methods: We did a retrospective study which included ESRD patients on hemodialysis (based on ICD codes) from a single center from 2012-2017 and excluded patients who had already received transplant or had prior malignancy. We had a total of 298 patients.

Results: Among the total 298 patients, 188 patients were between 45-75 year age group- out of which 96 patients (51%) underwent colonoscopy; out of 96 patients who underwent colonoscopy, 36 (37.5 %) were not transplant candidates and 16 (16.6%) died within the next 5 years. We also calculated Charlson comorbidity index of the patients to assess their 10 year survival likelihood.

Conclusions: Although patients who were undergoing transplant evaluation and patients with higher life expectancy had higher screening probability, the above numbers suggest that overscreening is still present. Hence, more individualized decision making including transplant likelihood and overall comorbidities of patients have to be considered before ordering cancer screening tests to avoid unnecessary cost and patient burden. These results can also help modify current practice- Providers can be alerted by EMR in ESRD population before ordering cancer screening tests to check if they will really benefit from them.



FR-PO567

Relationships Between Satisfaction Scores and Outcomes in Dialysis Patients

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Background: Patient satisfaction is an important aspect of the quality of care provided, yet the associations to outcomes are unknown. We determined correlations between Net Promoter Score (NPS) satisfaction survey scores and clinical outcomes in hemodialysis (HD) patients.

Methods: We used clinic level data from a large dialysis provider in 2015 and 2017. NPS index assesses consumer satisfaction with a company's services via their willingness to recommend it to others; scores range from -100 to 100. We calculated Pearson's correlation coefficient (R) between annual NPS and end-of-year quality metrics that include readmission and hospital day rates per patient year, as well as the percent (%) of patients: nonadherent with HD treatments, with arteriovenous fistula (AVF), with hemoglobin (HgB) ≥10.0 to ≤11.0g/dL, with albumin (Alb) ≥4.0g/dL, and with calcium (Ca) ≤10.0mg/dL & phosphate ≥3.0 to ≤5.5mg/dL & parathyroid hormone ≥150 to ≤600pg/mL for a composite mineral bone disorder (MBD) measure. NPS was further compared to an overall composite quality score that aggregated the above metrics and others (e.g. Kt/V). We also calculated R between changes in NPS and changes in quality metrics.

Results: We analyzed data from 2,287 in-center HD clinics. Mean NPS scores were 49.0 in 2015 and 61.3 in 2017. We found higher NPS was related to: a lower % of patients nonadherent with HD treatments (R= -0.19 in 2015 & -0.18 in 2017; both p<0.001), a higher % of patients with AVF (R= 0.11 in 2015 & 0.12 in 2017; both p<0.001), a higher % of patients with HgB ≥10.0 to ≤11.0g/dL (R= 0.09 in 2015 & 0.10 in 2017; both p<0.001), a

higher % of patients with MBD laboratories in goal range (R= 0.14 in 2015 & 0.16 in 2017; both p<0.001), and a higher overall composite quality score (R= 0.13 in 2015 & 0.15 in 2017; both p<0.001). NPS was not related to readmission and hospital day rates, or the % of patients with Alb ≥4.0g/dL. The 12.3-point increase in NPS from 2015 to 2017 was related to improvements in the overall composite quality score (R= 0.06; p=0.01).

Conclusions: NPS scores were related, albeit weakly, to several quality metrics including treatment nonadherence, AVF use, anemia and MBD laboratories, and overall composite quality scores. Increases in NPS over time were weakly related to better overall composite quality scores.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO568

Depressive Disorders Are a Risk Factor for Falls and Fall-Related Injuries Among Adults with Kidney Disease

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Background: Depressive disorders are common among patients with chronic kidney disease (CKD) and especially those who have advanced to end stage kidney disease (ESKD). In addition, depression and pharmacotherapy for depression have been associated with impaired gait and increased propensity for falls in older adults. Therefore, the purpose of this study was to determine the relationship between depressive disorders, falls, and fall-related injuries in a large cohort of US adults with CKD.

Methods: We analyzed the 2016 US Behavioral Risk Factor Surveillance System data using complex sample survey data analysis procedures in STATA software accounting for the multistage cluster study design.

Results: Among 354,829 adults, 16,675 (4.5%) reported CKD, 61,543 (16.8%) reported a history of a depressive disorder, 102,456 (28.5%) reported a fall, and 38.7% of those who fell reported a fall-related injury. Compared to adults without CKD or depression, adults with depression (OR=2.88, 95% CI=2.76-2.99), adults with CKD (OR=1.74, 95%CI=1.60-1.90), and adults with both CKD and depression (OR=4.17, 95%CI=3.69-4.71) had increased odds of suffering a fall. These results remained significant after accounting for demographic characteristics and comorbidities commonly associated with falls such as diabetes, arthritis, asthma, and cardiovascular conditions. Similarly, adults with depression (OR=2.02, 95%CI=1.90-2.14), CKD (OR=1.37, 95%CI=1.19-1.57), and CKD with depression (OR=2.89, 95%CI=2.47-3.38) had a higher risk of suffering an injury from a fall. Among only CKD patients, those who had been diagnosed with depression had higher odds of falling (OR=2.39, 95%CI=2.08-2.76) and suffering an injury (OR=2.11, 95%CI=1.72-2.59) even after adjusting for demographics and comorbidities commonly associated with falls.

Conclusions: Among adults with a self-reported diagnosis of CKD, depression is a risk factor for suffering a fall and fall-related injury. It is unknown if this increased propensity for falling is related to medications, depression, or an interplay of these and other factors. Given the high prevalence of depression within the CKD population, this relationship warrants further examination in order to prevent and decrease fall-related injuries in this population.

FR-PO569

Hospital Admission Rates Are Associated with Depressive Affect and Antidepressant Use in Dialysis Patients

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Background: Depression is a common mental health disorder and the leading cause of disability worldwide (WHO 2017). In the general population, antidepressant use has been associated with adverse drug events and frequent emergency room visits (Shehab N, et al. 2016). Little is known about the effects of antidepressant use, drug dialyzability, and associated outcomes in hemodialysis (HD) patients. We aimed to determine if hospitalization rates differ in HD patients by use of antidepressants and the presence of depressive affect (DA).

Methods: We analyzed data from a large dialysis provider on HD patients treated during 2016 to 2018. We stratified patients by antidepressant use and compared hospitalization rates per patient year (ppy). Furthermore, we captured data on patients who completed DA screening via the patient health questionnaire-2 (PHQ2) and compared hospitalization rates for those who were DA positive (PHQ2 score ≥3) or negative, and using an antidepressant or not.

Results: In a population of 268,443 HD patients, 26% of patients were using an antidepressant. Hospitalization rates were higher in those using an antidepressant versus patients not taking any antidepressants (2.18 vs 1.41 admissions ppy, respectively). Overall, there was a 75% response rate to the PHQ2 survey. Among those who completed the PHQ2, 9% were DA positive. Antidepressants were used by 41% of DA positive patients and 22% of DA negative patients. In DA positive patients, hospitalization rates were higher for those using an antidepressant versus patients not using antidepressants (2.66 vs 2.29 admissions ppy, respectively). Similarly, DA negative patients using antidepressants had higher hospitalization rates versus those not using antidepressants (2.4 vs 1.9 admissions ppy, respectively).

Conclusions: Findings indicate that patients taking antidepressants may have higher hospitalization rates when compared to those not taking any medication, irrespective of DA. Antidepressant-related hospitalization rates may be due to drug adverse events and could in part be confounded by indication. Treatment adherence and the presence of major depressive episodes are not addressed in this analysis. Further analyses are warranted.

FR-PO570

Association of Chronic Insomnia with Protein Energy Wasting in CKD

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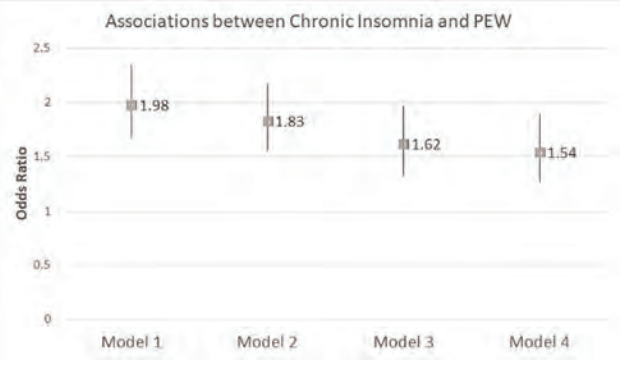
Background: Chronic insomnia is highly prevalent. Its effects on the sympatho-adrenal system could potentially cause multi-systems abnormalities. It is unknown if chronic insomnia plays a role in the development of protein energy wasting (PEW) in patients with chronic kidney disease (CKD).

Methods: In a national cohort of 229,236 CKD patients, we examined associations between chronic insomnia (defined as the presence of ICD9 codes 307.42, 307.49 and 780.52 and long-term use of insomnia medications) and PEW defined as the concomitant presence of serum albumin <3.8 g/dl or serum cholesterol <100 mg/dl, weight loss of 5% or more over 3 months, and neutrophil-to-lymphocyte ratio (NLR) >4.0. Associations were examined in crude logistic regression models (Model 1) and after adjustments for age, gender, race (Model 2), BMI, blood pressure, eGFR, chronic pain (Model 3), and comorbidities and socio-economic status (Model 4).

Results: 13,215 patients (5.8% of the cohort) had chronic insomnia and 1,412 (0.6% of the cohort) had PEW. 152 chronic insomnia patients (1.2%) vs. 1,260 patients in control group (0.6%) had PEW. Insomnia was associated with higher odds of PEW events in both unadjusted (Model 1) and in multivariable adjusted models (odds ratio in Model 4: 1.5 [95%CI: 1.3, 1.9], p<0.001), Figure 1. Results were consistent in subgroup analyses.

Conclusions: Chronic insomnia is associated with higher risk of PEW in CKD patients. Further studies are needed to determine underlying mechanisms of action and the effects of interventions.

Funding: NIDDK Support



FR-PO571

Hypokalemia: A Diagnostic Challenge

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Introduction: Hypokalemia, a very common clinical problem is generally due to decreased oral intake, urinary loss, gastrointestinal loss or transcellular shifts. Here we present a challenging case of refractory hypokalemia.

Case Description: A 72-year-old man with new diagnosis of prostate adenocarcinoma not yet on treatment presented with hematuria, new hypertension and hypokalemia. He denied poor oral intake, vomiting or diarrhea. He denied medications or herbal, dietary supplements. There was no family history of hypokalemia or hypertension. Laboratory: Serum Na 145mmol/L, K 2.0mmol/L, HCO3 34mmol/L, Plasma Renin 0.62ng/ml/hr, Aldosterone< 1ng/dl, Cortisol 38.8mcg/dl, ACTH 81pg/ml, Urine K 88.5mmol/L. Cystoscopy: large friable prostate, likely the cause of hematuria so palliative TURP was performed. Androgen deprivation therapy (Bicalutamide) was begun. Refractory hypokalemia persisted despite aggressive potassium replacement.

Discussion: In our patient, inappropriately high urine K, Hypokalemia and Chloride-resistant metabolic alkalosis and Hypertension suggested mineralocorticoid excess. However low plasma renin and aldosterone indicated pseudohyperaldosteronism. Differential diagnosis included Liddle's, Gellers syndromes, Syndrome of apparent mineralocorticoid excess or chronic licorice use, Cushing syndrome and Congenital adrenal hyperplasia. Patient's age and pertinent history excluded several of these leading us to a diagnosis of ACTH-dependent Cushing's syndrome. This was further confirmed by overnight dexamethasone suppression test. ACTH-dependent Cushing's syndrome could be due to Cushing's disease but MRI of brain was negative, making this unlikely. Ectopic ACTH producing tumor was felt more likely. A high grade prostatic adenocarcinoma with a neuroendocrine component was found in prostate tissue. The basic mechanism for hypokalemia is mineralocorticoid receptor (MR) activation by excess cortisol, leading to sodium reabsorption via ENaC. Treatment strategies focus on decreasing tumor burden and inhibition of MR or ENaC. Since some reports indicated spironolactone may

potentially promote prostate cancer, we instead recommended ENaC inhibitor triamterene. Chemotherapy (Etoposide/Carboplatin) was then initiated with resolution of hypokalemia after 5 days of treatment. He was off triamterene and potassium replacement by the end of 3rd cycle of chemotherapy.

FR-PO572

Hypokalemia as the Smoking Gun of Paraneoplastic Syndrome

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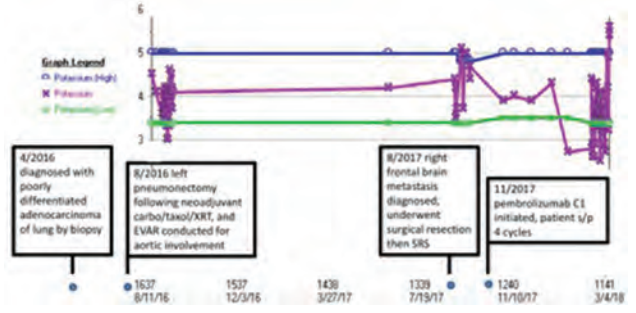
Introduction: Ectopic secretion of ACTH (EAS) is commonly associated with small cell lung cancer but rare with other lung cancers. The present case is that of an individual with EAS leading to hypokalemia in the setting of lung adenocarcinoma.

Case Description: A 66-year-old woman presents with metastatic lung adenocarcinoma (poorly differentiated) diagnosed 2 years prior to admission. She had been treated with carboplatin and taxol. She presents with hypokalemia (K 2.6mmol/L despite K supplementation of 80meq per day). Hypokalemia was noted at the time of carboplatin therapy but resolved following its discontinuation. Hypokalemia was noted again at the time of the diagnosis of brain metastasis. Other labs were notable for Mg 1.8mg/dL, bicarbonate 33mmol/L, pH 7.51, and WBC 34.4K/uL with neutrophil predominance. Urine K was 92mmol/L and transtubular K gradient ((urine K/plasma K)/(urine osm/plasma osm)) was 26.2. Plasma cortisol was 46.5ug/dL at 7pm when ACTH was 67pg/mL. Morning cortisol after 1mg and 8mg dexamethasone were 38.1ug/dL and 32.9ug/dL respectively. Urine free cortisol was 650mcg/24 hours. Renin and aldosterone levels were both below lower limits of assay detection. Brain MRI showed no pituitary pathology to suggest Cushing disease. She was thus diagnosed with EAS. The patient underwent bilateral laparoscopic adrenalectomy, and potassium normalized. She then pursued hospice care as there were no more chemotherapeutic options.

Discussion: Although rare among non-small cell lung cancer patients, 13 cases of EAS with non-small cell lung cancer had been reported as of 2012. Hypokalemia due to platinum-based chemotherapy tends to coexist with hypomagnesemia (platinum decreases Mg, which inhibits the Na+K+ATPase and K is lost in urine through potassium channels in the thick ascending limb). The patient had hypokalemia as well as leukocytosis at the time of diagnosis of brain metastasis. Trends in K and WBC over time may help predict progression of malignancy in the setting of EAS. Bilateral adrenalectomy represents an option for control of EAS, but expected survival post-operatively should be considered before proceeding.



FR-PO573

Abiraterone Induced Hypokalemia in Treatment of Castration Resistant Prostate Cancer

Waleed Asfar, Milos N. Budisavljevic, Andrew B. Elliott. *Medical University of South Carolina, Charleston, SC.*

Introduction: Abiraterone was approved in combination with prednisone for the treatment of metastatic Castration Resistant Prostate Cancer (CRPC) who recieved chemotherapy. In 2018 FDA expanded the indication to include chemotherapy naive patients. Most common side effects associated with abiraterone include fatigue, diarrhea, hypertension, elevated liver enzymes, and hypokalemia. Abiraterone inhibits CYP17A1, the rate limiting hydroxylase in androgen and steroids synthetic pathway. This causes ACTH level to increase, leading to secondary excess in mineralocorticoids. This secondary excess manifests as hypertension, hypokalemia, and fluid overload. Prednisone is co-administered to suppress the hypothalamic-pituitary-adrenal axis and diminish the symptoms of mineralocorticoid excess.

Case Description: We Describe a case of a 65 year old male with history of hypertension, dyslipidemia, hypothyroidism and prostate cancer. He was diagnosed with Prostate cancer in 2005 and recieved total prostatectomy. In 2012 he developed biochemical relapse and recieved radiation and androgen depreviation therapy. In 2015 he was found to have bone metastasis and recieved radiation therapy to the cervical spine and started on abiraterone and prednisone therapy early 2016. He was later found to have avascular necrosis of the left femoral head and decided to stop prednisone as he was worried about his bone health. He was found to have Hypokalemia and worsening control of blood pressure on follow up with primary care, his serum potassium was 2.5 with a serum bicarb of 25. He was started on oral potassium supplementation but his Hypokalemia persisted. He was seen by nephrology as an outpatient, his exam was significant for elevated BP and trace lower extremity edema. serum aldosterone to renin was low at 2.9. He was started on aldactone with improvement in his serum potassium on follow up.

Discussion: With the recent expansion of the FDA approval more prostate cancer patients will be treated with abiraterone, understanding the mechanism of action of abiraterone and resulting side effects is crucial as it can prevent dangerous arrhythmias and outcomes. Nephrology input is needed in manging these patient along with primary care. Patient with contraindications to steroids should be started on eplerenone or aldactone therapy.

FR-PO574

A Rare Mutation Causing Hypertension and Hypokalemia During Pregnancy

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Introduction: Geller syndrome is a rare autosomal dominant condition characterized by severe early-onset hypertension and hypokalemia in pregnancy due to a gain-of-function mutation that causes upregulated mineralocorticoid activity.

Case Description: A 42-year old woman presented to her obstetrician during her 29th week of pregnancy (G1P0) and was found to be hypertensive (172/109 mm Hg). Patient was diagnosed with hypertension in her late thirties which she initially managed with exercise but later required hydrochlorothiazide and atenolol for 3 years. Both were stopped when she became pregnant and she did not require initiation of any other agents. At week 29, patient presented to her obstetrician with hypertension. She was also noted then to have hypokalemia (2.9 mmol/L) and hypomagnesemia (1.4 mmol/L) both of which were repleted intravenously. Repeat labs three days later revealed a potassium of 2.9 mmol/L and a magnesium of 1.4 mmol/L. Nephrology was consulted for further evaluation. Patient denied using diuretics or any over-the-counter supplements. Lab work was notable for a trans-tubular potassium gradient (TTKG) of 6.7 consistent with renal potassium wasting. Extensive chart review was conducted including patient's routine labs prior to pregnancy. Potassium levels pre-partum were consistently around 4 mmol/L. Patient was treated with oral potassium and magnesium supplements with frequent labs and instructions to discontinue supplements after delivery of fetus. Repeat labs four weeks post-partum revealed potassium of 3.8 mmol/L and magnesium of 2.0 mmol/L. Blood pressure also improved to 144/86 mm Hg.

Discussion: Geller syndrome is a rare autosomal dominant condition in which a gain-of-function mutation causes upregulation of mineralocorticoid activity by progesterone during pregnancy. The progesterone-high environment of pregnancy, particularly in the second and third trimesters, is likely the reason our patient suddenly developed hypertension and hypokalemia at 29 weeks. Although genetic testing is still pending, we are fairly confident in our diagnosis particularly because our patient's blood pressure and potassium levels improved post-partum. It is important that clinicians are aware of this rare entity as treatment with aldosterone antagonists which theoretically sound ideal to treat hypertension with hypokalemia can in fact exacerbate the hypertension.

FR-PO575

Supratherapeutic Posaconazole: An Emerging Cause of Apparent Mineralocorticoid Excess (AME)

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Introduction: Apparent mineralocorticoid excess (AME) causes severe hypertension accompanied by metabolic alkalosis with hypokalemia. Substances which are well known to cause AME include glycyrrhizic and glycyrrhetinic acid found in licorice. These compounds competitively inhibit the enzyme called 11 Beta Hydroxysteroid Dehydrogenase type 2 (11β-HSD2). Lack of 11β- HSD2 caused higher cortisol available to bind the mineralocorticoid receptor, and results in ENaC-mediated Na reabsorption. Posaconazole, the broad-spectrum azole group antifungal agent, is commonly used for prophylaxis in patients with AML and severe neutropenia. Literature review revealed that posaconazole at supratherapeutic level can also inhibit 11β- HSD2 and cause apparent mineralocorticoid excess (AME).

Case Description: A 37 years old Caucasian female with refractory acute myelogenous leukemia (AML) with normal baseline blood pressure(100-120/65-80mmHg). She had neutropenia after third re-induction chemotherapy with G-CLAM regimen. She was then started on oral posaconazole 300 mg daily for fungal prophylaxis. One month later she then developed refractory hypokalemia with metabolic alkalosis and new onset hypertension (180/110mmHg). We were giving her potassium replacement 60-80 mEq/day, but her serum potassium level remained less than 3.3 mEq/L. Her serum cortisol level was 18.2 mcg/dL, plasma renin activity <0.167 ng/mL/h, plasma aldosterone level < 1ng/dL. Serum posaconazole level was 1800 ng/mL. Discontinuation of posaconazole, with documented normal therapeutic posacoanzole level, resulted in improvement of hypertension, refractory hypokalemia and metabolic alkalosis. All clinical features resolved within 2 weeks after discontinuation of posaconazole.

Discussion: We suggest that posaconazole level should be part of laboratory investigations in patients who are treated with posaconazole and have new onset of hypertension, hypokalemia and metabolic alkalosis. Posaconazole, at supratherapeutic level, inhibits 11 Beta Hydroxysteroid Dehydrogenase type 2 and causes apparent mineralocorticoid excess (AME).

FR-PO576

Urinary Exosome Analysis in a Case of Licorice-Induced Pseudoaldosteronism

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Introduction: Excessive licorice intake can cause a syndrome mimicking hypermineralocorticoidism. Glycyrrhizin, the active metabolite of licorice, inhibits 11bHSD2 that converts cortisol to inactive cortisone, resulting in epithelial Na^+ channel (ENaC) activation in principal cells. However, the contributions of other Na and Cl transporters including Na-Cl cotransporter (NCC) in distal convoluted tubules and the Cl/HCO_3 exchanger pendrin in intercalated cells remain unknown.

Case Description: A 74-year-old woman with type 2 diabetes was referred for muscle weakness, leg edema, and polyuria. She reported that she had been taking herbal medicine containing licorice (6 g/day). Her BP was 162/78 mmHg and work up revealed severe hypokalemia (1.9 mEq/L), mild hypernatremia (147 mEq/L), and metabolic alkalosis (pH 7.513, and HCO_3 43.2 mmol/L). Urinary potassium level was 84.0 mEq/gCr, indicating the urinary potassium loss. Serum magnesium level was 1.9 mg/dL. Her serum aldosterone level was below the detection limit (< 10 pg/mL) with low plasma renin activity (0.3 ng/mL/hour). Serum cortisol and adrenocorticotropic hormone were normal. Abdominal CT scan and Doppler ultrasound of renal arteries revealed no abnormality. She stopped taking licorice and received KCl 40 mmol of DIV and 24 mmol oral in first 24 hrs. However, hypokalemia persisted, and the patient received 25mg of spironolactone orally from day 3. On day 10, serum potassium returned to normal, and was discharged on day 13. To address the contribution of Na and Cl transport mechanisms in the distal nephron, we isolated exosomes from pre- and post-treatment urine samples. Comparison of the pre- and post-treatment samples revealed that active, cleaved form of ENaCγ was markedly increased, whereas uncleaved form was undetectable in the pre-treatment sample, consistent with the increased activity of ENaC. Of note, both pendrin and NCC levels were profoundly increased in the pre-treatment sample, and were reduced after the treatment. In contrast, NKCC2 levels were lower in the pre-treatment sample than in the post-treatment sample.

Discussion: These data indicate that not only ENaC but NCC and pendrin are involved in licorice-induced fluid and electrolyte abnormalities.

FR-PO577

Hypokalemic Tetraparesis as First Manifestation of MGRS

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Introduction: Renal potassium wasting is a frequent cause of hypokalemia; it can be consequence of medications, endogenous hormone production, inherited or acquired renal tubular defects

Case Description: A 50 y/o woman was admitted to our Hospital with limb weakness, muscle cramps progressing to tetraparesis, associated with severe hypokalemia (1,6 mEq/L). She denied diarrhea or vomiting; pharmacologic and past medical history were unremarkable. Labs showed normal renal function, hyperchloremic metabolic acidosis, urinary potassium wasting (88 mmol/24h) and alkaline urine. A diagnosis of hypokaliemic tetraparesis due to distal renal tubular acidosis (type 1 RTA) was made. IV NaHCO3 and KCl replacement resolved the tetraparesis. Further investigations were made: SPEP showed a IgMK monoclonal protein, ANA (1:640) and ENA-SSA were positive (689 U/ml) while antiDNAds were negative. At that time, she rejected a renal biopsy and any follow-up. Two months later, she was admitted to our Department with hypertension (170/90 mmHg) and swelling. Labs showed normal kidney function, hypokalemia, slightly increased CRP levels. Urinalysis revealed microscopic hematuria and proteinuria (3.6 g/24h). Serology revealed very low C3 and C4, positive ANA (1:320), ENA-SSA (314 U/ml), type 1 cryoglobulins (IgMk). Suspecting an MGRS, a renal biopsy was performed: light microscopy showed an MPGN pattern with coarse pseudothrombi and a diffuse interstitial infiltration of lymphomonocytes, kappa+. IF was coherent with serology, showing IgMK (+++) and C3 (++) subendothelial deposits, and kappa+ cytoplasmic droplets in proximal tubules. Type 1 cryoglobulinemia and kappa light chains induced chronic tubular interstitial nephritis (resulting in type 1 RTA) was diagnosed. After three courses of dexamethazone, rituximab and cyclophosphamide, microscopic hematuria disappeared, proteinuria improved to 0,15 g/24h and serum potassium levels persisted steady without potassium supplements

Discussion: We described an unusual presentation of MGRS, with severe hypokalemia due to diffuse tubular injury mediated by kappa light chain, followed by a full blown type 1 cryoglobulinemia. Searching for a monoclonal protein should be an essential part investigating an acquired tubular disfunction

FR-PO578

Neck Down Paralysis in a Young Male Triggered by High-Dose Steroids

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Introduction: Derangements in electrolyte homeostasis can result in a variety of clinical manifestations. Herein we present a unique case of sudden severe symptomatic hypokalemia in an otherwise healthy young male triggered by high dose steroid.

Case Description: A 30 year old caucasian male with no significant medical history was given intravenous high dose steroids for allergic skin rash in the ER. The next day he presented with sudden onset of bilateral upper and lower extremity weakness and palpitations. Vitals were normal except for tachycardia. Physical examination confirmed bilateral upper and lower extremity weakness with diminished reflexes. CBC and BMP were unremarkable except for potassium (K) 1.4 meq/L. EKG revealed atrial fibrillation. He was given IV and oral K replacement. Further workup showed TSH of 0.007mcU/ml(0.4-4.0) with free T4 of 4.28 ng/dl(0.7-1.9) and free T3 of 11.19 pg/ml(1.76-3.68). He was started on propranolol and methimazole. His symptoms completely resolved within twelve hours of treatment and he was discharged home in a stable condition.

Discussion: Hypokalemic periodic paralysis (HPP) is a rare autosomal dominant neuromuscular disorder with prevalence of 1 in 100,000. Male to female ratio is approximately 4:1. Genetic mutations have been identified that affect skeletal muscle sarcolemma calcium and sodium channels, resulting in inadequate depolarization. Acquired HPP has been described in association with hyperthyroidism and can be precipitated by administration of intravenous steroids as in our patient. Thyroid hormones increase tissue responsiveness to beta-adrenergic stimulation, resulting in increase sodium-potassium ATPase activity on skeletal muscle membrane resulting in hypokalemia. High dose steroid likely modulated the K lowering effect of thyroid hormones in our patient. It is important to differentiate thyrotoxic periodic paralysis (TPP) from HPP as the former requires administration of non selective beta blocker along with K replacement to ameliorate the acute attack whereas the latter corrects with K replacement alone.

FR-PO579

Symptomatic Hypophosphatemia from Parenteral Iron Administration

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Introduction: Fibroblast growth factor 23 (FGF23) plays a crucial role in phosphate and vitamin D homeostasis. Herein we present a case of severe symptomatic hypophosphatemia following the administration of intravenous (IV) ferric carboxymaltose likely triggerred by inappropriate FGF23 activity.

Case Description: A 31 year old female received two doses of IV ferric carboxymaltose for iron deficiency anemia. Four days later, she presented with numbness, tingling and muscle cramps. Evaluation revealed severe hypophosphatemia with serum phosphorus level of 1.0 mg/dl. Serum potassium, calcium, iPTH, 25 hyrdoxy, and 1,25 dihydroxyvitamin D levels were normal. A 24 hour urine collection revealed calcium of 27 mg (100 -250mg) and phosphorus of 1.8 g (0.4- 1.3 g) with a high fractional excretion of phosphorus >5%. Serum FGF23 level was inappropriately elevated at 97 RU/ml (44-215) for the degree of hypophosphatemia. Patient was given IV and oral phosphorus supplementation repeatedly without clinically significant improvement. Serum phosphorus levels were normalized with resolution of symptoms three weeks later.

Discussion: FGF23 is secreted primarily by bone, thymus, heart, brain and, in low levels, by several other tissues. It reduces serum phosphorus levels by decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased renal phosphate reabsorption. It also down regulates the gene transcription of 1α-hydroxylase thereby reducing the bioactive 1,25-dihydroxy vitamin D (1,25-2OH-VitD) further decreasing the phosphate reabsorption in the gut. Ferric carboxymaltose is a newer iron formulation increasingly prescribed due to its effectiveness and shorter infusion time. There have been reports of hypophosphatemia associated with use of IV iron preparations including saccharated ferric oxide and ferric citrate hydrate. Studies have shown that IV iron may reduce peripheral degradation, secretion, and clearance of FGF23 resulting in inappropriately elevated FGF23 levels. Data is scarce with use of IV ferric carboxymaltose and hypophosphatemia. Our case highlights the importance of understanding the side effect profile of commonly administered medications and formulations so that an early diagnosis could be established.

FR-PO580

A Case of Diabetic Ketoacidosis Concurrently with Severe Hypokalemia Induced by Distal Renal Tubular Acidosis Due to Toluene Intoxication

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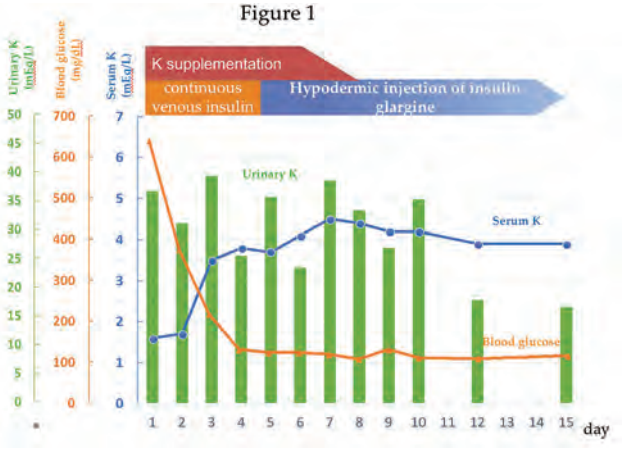
Introduction: Diabetic ketoacidosis (DKA) is a high anion gap metabolic acidosis due to excessive blood concentration of ketone bodies. Hyperkalemia is often accompanied with DKA because of extracellular potassium shift caused by lack of insulin action as well as reduced renal potassium excretion caused by acute prerenal kidney injury. Here, we report a case of DKA complicated by severe hypokalemia resulting from distal renal tubular acidosis type 1 (RTA-1) due to toluene intoxication.

Case Description: A 37-year-old male who had been treated with basal supported oral therapy for type 2 diabetes mellitus for 7 years experienced appetite loss. He took only isotonic drinks for 5 days and nausea and vomiting developed, followed by muscle weakness and difficulty of walking. He was referred to our hospital with his laboratory findings of hyperglycemia and high anion gap metabolic acidosis with ketonemia, which was diagnosed as DKA. In the meantime, normal anion gap metabolic acidosis was thought to be exist as well. In addition, he had severe hypokalemia and inappropriately high urinary excretion levels of potassium despite acute kidney injury due to volume depletion. He was treated with fluid resuscitation and continuous venous insulin infusion plus a large amount of potassium supplementation (Figure 1). After his general status improved, he stayed out of the hospital for trial. However, he came back in a haze with an odor of organic solvent and urinalysis revealed elevated levels of potassium and urinary hippuric acid concentration (23.65 g/L). Finally, he confessed to abuse of toluene for more than 20 years.

Discussion: It is known that toluene intoxication can be the cause of RTA-1 which gives rise to normal anion gap metabolic acidosis and hypokalemia. We should take toluene intoxication account if severe hypokalemia is accompanied with DKA.

Figure 1



FR-PO581

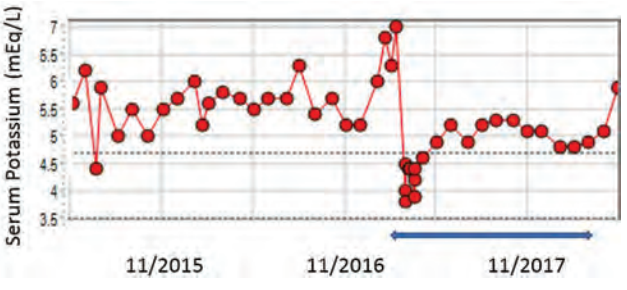
Use of Patiromer for Long-Term Management of Hyperkalemia in an ESRD Patient

Sylvester Barnes,[1,2] Julia Schneider,[1,2] David J. Leehey.[1,2] *[1]Hines VA, Hines, IL; [2]Loyola University Medical Center, Maywood, IL.*

Introduction: Hemodialysis patients generally undergo dialysis with a dialysate potassium concentration of either 2 or 3 mEq/L. Use of lower dialysate potassium concentrations (< 2 mEq/L) may lead to post-dialysis hypokalemia and an increased risk of arrhythmia. This leads to a dilemma when pre-dialysis hyperkalemia is not controlled despite use of a 2 mEq/L potassium dialysate. A possible solution is the use of potassium binding agents in order to decrease pre-dialysis serum potassium concentrations.

Case Description: A 60-YOM with ESRD due to IgA nephropathy was being maintained on hemodialysis on a MWF schedule for 4h each treatment using an AVF. He was very compliant with dialysis and with dietary restrictions. However he had persistent pre-dialysis hyperkalemia (peak K of 7 mEq/L and average around 5.5 mEq/L) despite use of a 2 mEq/L potassium dialysate. His Kt/V was 1.6. No access recirculation was present. He did not take RAAS inhibitors or other medications known to cause hyperkalemia. He had previously been prescribed maintenance sodium polystyrene sulfonate which was poorly tolerated. In February 2017 he was scheduled for laparoscopic cholecystectomy, and assistance was requested in lowering his serum potassium levels pre-operatively. He was begun on patiromer 8.4g every Saturday and Sunday which resulted in a marked decrease in his pre-dialysis serum potassium concentrations. He was subsequently maintained on patiromer for over one year (until March 2018) with no further episodes of hyperkalemia (see Figure; arrow depicts duration of patiromer therapy). At the patient's request the drug was then stopped, leading to an increase in pre-dialysis serum potassium level.

Discussion: Hyperkalemia can be a persistent problem for patients on chronic hemodialysis. Most guidelines recommend that very low potassium dialysates (< 2 mEq/L) be avoided. In this patient, use of patiromer twice weekly resulted in a long-term stable lowering of the pre-dialysis potassium concentration. To our knowledge this is the longest reported use of scheduled patiromer in a dialysis patient.



FR-PO582

Loquat Induced Severe Hyperkalemia Presenting as Secondary Hyperkalemic Paralysis and Cardiac Conduction Abnormalities

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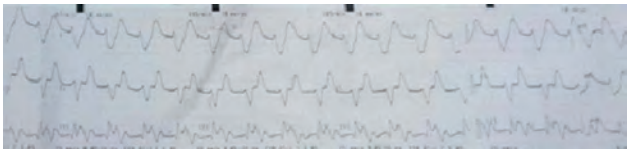
Introduction: Severe hyperkalemia is attributed to 3-5% deaths and a quarter of emergency dialysis sessions in ESRD patients. It generally manifests as cardiac abnormalities and rarely as secondary hyperkalemic paralysis. Missed dialysis sessions and dietary indiscretions to known potassium rich food are common causes. Loquat (Nispero, Eriobotrya japonica) is an often overlooked fruit for having moderate to high potassium content (266mg/100gram) that caused life threatening hyperkalemia in our patient.

Case Description: 27 year old male with ESRD secondary to diabetic nephropathy on thrice weekly maintenance hemodialysis for past 1.5 years presented in ER with restlessness, feeling of unease and weakness in limbs and inability to walk. There was no history of current or preceding fever and any such episode in the past. Examination revealed an alert yet restless individual, afebrile with pulse of 62 bpm and blood pressure of 90/60mmhg, flaccid paraparesis, hypotonia and diminished reflexes. His immediate EKG is shown in Fig. 1. Calcium gluconate was infused, transcelluar shifting measures were instituted and dialysis session of 4 hours was carried out within 30 minutes of presentation with constant cardiac monitoring. EKG changes necessitated repetition of calcium gluconate, thrice over an hour, changing serum calcium from 8.8 mg/dl pre-dialysis to 9.4mg/dl afterwards. Non hemolized and repeated samples confirmed pre dialysis serum potassium of 9.6mmol/L and post dialysis concentration of 5.2mmol/L. His symptoms improved after 80 mins of dialytic therapy. Patient was not on Beta blockers, ACE inhibitors or NSAIDs. The family and patient denied taking any unusual substance except for repeated large servings of loquat since his last dialysis session.

Discussion: Context specific and dietary education curtailing multicultural cuisines can prevent potassium catastrophes. In the ER, secondary hyperkalemic paralysis should be considered in differentials of acute paralysis. IV Calcium for myocardial stability is to be repeated judiciously unless pressing EKG changes vanish. Unambiguous EKG changes in pertinent clinical setting are sufficient in dialysis population to warrant urgent hemodialysis administration.



FR-PO583

SIADH as the Initial Presentation in Guillain Barre Syndrome

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Introduction: Guillain-Barre Syndrome (GBS) is an autoimmune disease damaging the peripheral nervous system that commonly presents as rapidly progressive symmetrical motor weakness. Autonomic dysfunction occurs in about 70% of GBS patients. Although there is a known association of SIADH in GBS patients, it usually occurs late in the disease course when there is maximal motor deficit. SIADH as an initial finding in patients with GBS is rare which is reported in this case.

Case Description: 72-year old female with history of dyslipidemia presented with subjective complaints of bilateral lower extremity weakness and difficulty ambulating. Her initial neurological exam was normal, with no deficits. She was found to have hyponatremia at 128 mEq/l that continued to drop to 115 mEq/l despite normal saline. Her serum Osmolality was 245 Osm/L, with elevated Urine Osmolality 702 Osm/L, suggestive of SIADH. Fluid restriction 1L daily was initiated, and her sodium continued to decline to 113 mEq/l. By day 6 she was found to have lower extremity weakness with strength 1/5. CSF analysis showed an albuminocytologic dissociation (total protein 288 & WBC 3) – suggestive of GBS. Therapeutic Plasmapheresis Exchange and oral Tolvaptan was initiated. Her sodium stabilized 134-137 mEq/l. With aggressive treatment and physical therapy, she regained her strength and walked without assistance at discharge.

Discussion: GBS commonly presents as progressive symmetrical muscle weakness with absent/decreased deep tendon reflexes. Incidence of SIADH in GBS is ~4.8%. Pathogenesis of SIADH in GBS is hypothesized to be: (1) Resetting of the osmoreceptor (2) Increased sensitivity of ADH at renal tubules. Hyponatremia in our case was present on admission prior to motor deficits from GBS. Urine and serum studies confirmed SIADH requiring tolvaptan. Her GBS was treated with plasmapheresis and her sodium stabilized only after treatment of the underlying GBS. Only 2 cases of GBS with SIADH at presentation have been reported. Observational and prospective studies have shown hyponatremia in GBS is associated with poor outcomes and increase mortality. Our case report emphasizes that SIADH may precede the development of profound motor deficit in GBS. Physicians should be aware of this rare presentation to prevent delays in treatment. Further studies are necessary to understand the cause behind SIADH in GBS and its impact on prognosis.

FR-PO584

Hyponatremia Due to Nivolumab-Induced Sequential Primary Adrenal Insufficiency and Hypothyroidism

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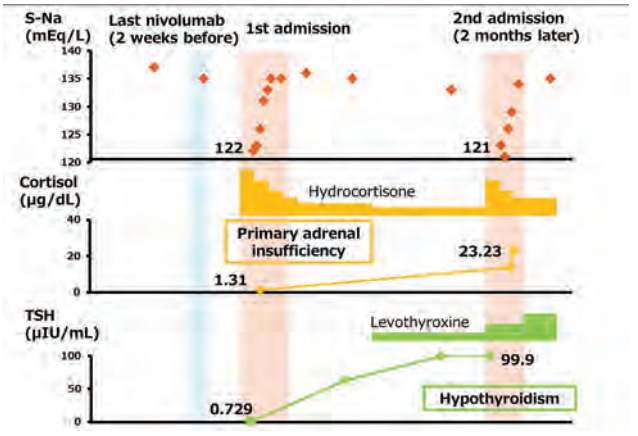
Introduction: Hyponatremia is the most common electrolyte disorders in lung cancer patients. Here we present a case of hyponatremia due to both primary adrenal insufficiency and hypothyroidism in a patient treated by nivolumab, a novel and increasingly used immune checkpoint agent.

Case Description: A 77-year old Asian man diagnosed as Stage IV non-small cell lung cancer on 6 courses of nivolumab for 4 months presented with 1-week general malaise. Laboratory test showed serum sodium (S-Na) 122 mEq/L. Cortisol, renin, aldosterone were 1.31 microg/dL, 1.1 ng/ml/hr and 23 pg/ml, respectively. Brain MRI denied hypophysitis. Positron emission tomography (PET) scan showed no adrenal metastasis but raised suspect of thyroiditis, though TSH was within normal limit. After treatment with hydrocortisone for primary adrenal insufficiency, S-Na was improved to 136 mEq/L. One month after discharge, laboratory follow-up revealed TSH of 62.7 micro IU/ml with low free T4 and T3. Levothyroxine was started but TSH remained high at 99.9 micro IU/ml. Two months after discharge he again presented with S-Na 121 mEq/L accompanied with loss of appetite. Laboratory test revealed cortisol 23.23 microg/dL, renin 7.5 ng/ml/hr and aldosterone 115 pg/ml. We increased both levothyroxine and hydrocortisone and S-Na returned to 135 mEq/L.

Discussion: Hyponatremia in lung cancer patients is commonly attributed to SIADH or hypovolemia. However, immune checkpoint agent including nivolumab can cause hypophysitis, primary adrenal insufficiency and hypothyroidism, or even more than one as in our patient. Any patient on a checkpoint inhibitor presenting with hyponatremia should undergo full work-up of endocrine disorders.



FR-PO585

A Rare Case of Hypophysitis Induced Hyponatremia

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Introduction: Immune checkpoint inhibitors are associated with a few electrolyte disorders. CTLA-4 antagonists are known to cause hypophysitis and as a result hyponatremia with an incidence of 3.2%. PD-1 inhibitors are not commonly associated with hyponatremia from hypophysitis. We report a case of hyponatremia associated with hypophysitis secondary to pembrolizumab therapy.

Case Description: A 69 year old male was diagnosed with non small cell lung cancer with metastatic lesions. Given the tumor was PDL1 positive, the patient was initiated on pembrolizumab therapy. 4 months into therapy, the patient was noted to have orthostatic hypotension and presented with a blood pressure of 90/50 mmHg and a sodium concentration of 125mmol/L. A trial of normal saline lead to improvement in blood pressure but worsening of hyponatremia to 123mmol/L. Serum osmolarity was 260mosm/Kg and urine osmolarity of 475mosm/Kg. Urine Na was 45mmol/L. An am cortisol repeated 3 times showed a very low value. ACTH was also suppressed. A thyroid panel revealed a low TSH and a low T4 level. FSH, LH and other hormones were in normal limits. An MRI of the brain did not show any pituitary lesions and a CT scan of the adrenals revealed no new findings. Given the hormonal abnormalities, a diagnosis of hypophysitis was made. This led to secondary adrenal insufficiency, hypotension and hyponatremia. The patient responded to corticosteroid therapy and Na improved to 133 mmol/L on discharge. The patient was also started on fludrocortisone and levothyroxine therapy.

Discussion: In contrast to CTLA4 antagonists, PD1 and PDL1 inhibitors are more commonly assocaited with thyroid and adrenalitis causing hyponatremia. Hypophysitis with PD-1 inhibitors is rare occuring <1% of patients. The mean onset of endocrine side effects is 9 weeks after initiation (range 5-36 weeks) of immunotherapy. Since the endocrine effects of immune checkpoint inhibitors are classified as toxic adverse events, it is recommended both discontinuation of the immune checkpoint inhibitor medication and 'high-dose' glucocorticoid treatment as in our patient. Our case highlights the potentially life threatening complication of checkpoint inhibitors and the urgent need for awareness amongsts hospitalists, nephrologists and oncologists for prompt recognition and treatment.

FR-PO586

Hyponatremia in Pregnancy and the Role of Renal Biopsy

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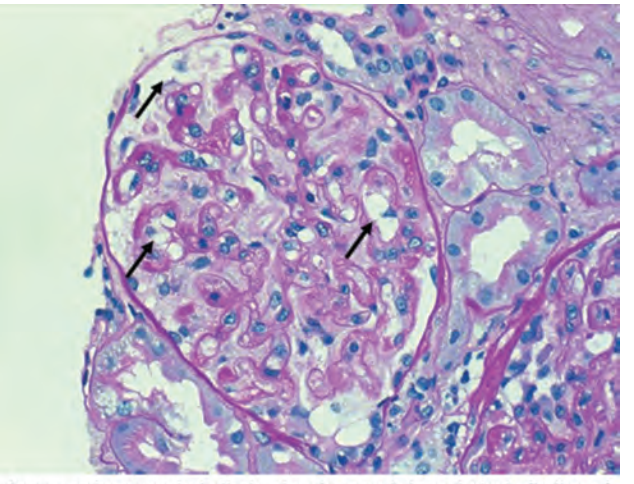
Introduction: Preeclampsia is a serious pregnancy complication that may mimic nephrotic syndrome. Severe hyponatremia in preeclampsia is rare and presents a unique clinical challenge as it increases the risk of seizures, mimicking eclampsia. It can also lead to several maternal and fetal adverse events.

Case Description: We report the case of a 35yo G1P0 female who presented at 21 weeks of gestation with anasarca and vomiting. The pregnancy was conceived via in vitro fertilization and was uneventful until the day of presentation. She was found to be hypertensive to 152/84mm Hg with 4+ proteinuria on urine dispstick. Her labs were significant for creatinine of 0.7 mg/dL, serum albumin of 2.5 g/dL, Na of 117 mmol/L, and proteinuria of 12.5 g/g. Serum osmolality was 233 mOsm/Kg, UNa was <20 mmol/L and UOsm was 235 mOsm/Kg. Severe hyponatremia was secondary to low effective circulating volume from hypovolemia in the setting of vomiting and anasarca, and improved with albumin infusions. The combination of severe hyponatremia and proteinuria prompted a renal biopsy to identify the underlying cause of nephrotic syndrome. The biopsy showed diffuse severe glomerular thrombotic microangiopathy with endotheliosis, consistent with preeclampsia. The pregnancy was terminated with normalization of Na levels within 3 days postpartum and reduction in proteinuria to 2 g/g within 2 weeks postpartum.

Discussion: This case is the earliest by gestational age at which preeclampsia-induced hyponatremia has been reported. The rarity of this complication, combined with the early gestational age of preeclampsia onset and the desire of the patient to maintain her pregnancy, necessitated a definitive diagnosis to explain her clinical picture. The renal biopsy proved critical in determining the diagnosis and best course of therapeutic action.



Arrows point to endotheliosis, the characteristic pathologic finding of preeclampsia. It is a variant of thrombotic microangiopathy with damaged swollen endothelial cells.

FR-PO587

Evaluating Preeclampsia as a Rare Cause of Severe Hyponatremia

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Introduction: During normal pregnancy, resetting of osmostat can take place resulting in decrease of plasma osmolality by about 10 mOsm/kg, and mild decrease in serum sodium concentration by 4-5 meq/L. This phenomenon has been associated with increased production of hCG. Preeclampsia is a multisystem disorder defined by hypertension and proteinuria, but not classically associated with severe hyponatremia. However, there are rare incidences where severe hyponatremia is a complication of preeclampsia that can result in serious complications such as convulsions and cerebral edema.

Case Description: The first case is about a 32-year old female of 27-week gestation who presented with preeclampsia with severe features. Due to worsening epigastric pain, HELLP syndrome and elevated blood pressure, patient had emergent C-section at 28-week gestation. Patient was also found to have severe hyponatremia with lowest serum sodium concentration of 120 meq/L on the day of C-section. She was initially treated with fluid restriction and diuretics; this resulted in overcorrection of sodium by 10 meq/L that was treated with hypotonic fluid and one dose of desmopressin. Gradually the correction of sodium slowed down and eventually corrected to 142 meq/L on the day of discharge. The second case is about a 29-year old female of 33-week gestation who also presented with preeclampsia with severe features. Due to breech presentation of the fetus and preeclampsia, patient had C-section at 34-week gestation. Patient initially had normal serum sodium concentration. Overtime sodium concentration decreased to 126 meq/L one day prior to C-section. Gradually, sodium improved appropriately with diuretics and fluid restriction to 136 meq/L 2 days after C-section.

Discussion: The pathogenesis of preeclampsia associated severe hyponatremia has been widely postulated. It is important to understand the etiology of severe hyponatremia based on history and physical exam, which can help guide treatment. The main mechanism

is yet to be understood. There is a theory that preeclampsia can stimulate non-osmotic release of ADH. Another theory suggests that defective placenta in preeclamptic patients is unable to produce enough vasopressinase that would rapidly inactivate ADH. Although the incidence of preeclampsia associated severe hyponatremia is reported rarely, it is a serious complication that needs to be addressed soon and managed promptly.

FR-PO588

Correction of Hyponatremia Using D5W Pre-Blood Pump on Patients on Continuous Renal Replacement Therapy: A Case Series

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Introduction: Patients with severe hyponatremia and renal failure who require continuous renal replacement therapy (CRRT) are at risk of overcorrection of their sodium (Na) level. Herein, we present three cases of using a calculated amount of dextrose 5% solution (D5W) pre-filter as pre-blood pump (PBP) to prevent overcorrection of hyponatremia.

Case Description: Case 1: 53 year old female with end-stage liver disease secondary to alcohol and lupus presented with abdominal pain and vomiting with serum Na level of 114 mEq/L, which was overcorrected to 138 mEq/L by day 2. She was initially treated with free water flushes via a nasogastric tube and peripheral D5W, which improved her serum Na to 129 mEq/L. On day 4, she was started on continuous venovenous hemofiltration (CVVH) for oliguric renal failure with replacement rate around 1.5 L per hour, and added D5W PBP at 35 ml/hr, to keep her serum sodium at 135 mEq/L on the following day. Achieved Na was around 135-137 mEq/L. Case 2: 39 year old male presented with alcohol withdrawal and hemorrhagic shock due to a variceal bleed. His admitting Na was 100 mEq/L, which corrected to 119 mEq/L by day 2. Patient was started on CVVH for acidosis, oliguric renal failure, and volume overload. Initial prescription was 2 L per hour replacement rate, D5W 500 ml per hour as PBP to aim for a goal Na of 112 mEq/l. The patient's Na level improved to 112-115 mEq/L by day 3-4. Subsequently, D5W PBP was slowly titrated downward to aim for slow correction of hyponatremia. Case 3: 45 year old male presented with acute alcoholic hepatitis, oliguric renal failure, and hyponatremia of 124 mEq/L. Patient was started on CVVH with D5W 100 ml per hour as PBP to achieve a goal Na of 131 mEq/L. In the next 24 hours, his Na was 127 mEq/L, and D5W was titrated downward with eventual slow correction of his hyponatremia.

Discussion: Slow correction of hyponatremia can safely be accomplished with the above calculation in patients with renal failure requiring CRRT using D5W PBP.

	D5W PBP (ml/hr)	Replacement Rate (L/hr)	Goal Na (mEq/L)	Achieved Na (mEq/L)
Patient 1	35	1.5	136	135-137
Patient 2	500	2	112	112-115
Patient 3	100	1.5	131	127

$$Rate\ of\ D5W\left(\frac{L}{hour}\right) = Replacement\ rate\left(\frac{L}{hour}\right)\left(\frac{140}{goal\ sodium} - 1\right)$$

FR-PO589

Syndrome of Inappropriate Antidiuresis (SIAD) in a Patient with Systemic Sclerosis: Cyclophosphamide (CYC) Use and Scleroderma Renal Crisis (SRC)

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Introduction: Hyponatremia is the most common electrolyte disorder and is often caused by SIAD, which can in turn be caused by the use of CYC, especially at moderate or high doses. To our knowledge, there has been only one reported case of hyponatremic hypertensive syndrome caused by SRC. The proposed mechanism is alteration of the osmoregulatory system, involving release of antidiuretic hormone (ADH) secondary to peripheral hyperstimulation of the renin-angiotensin system (RAS). We describe a case of SIAD associated with the use of low-dose CYC and aggravated after SRC.

Case Description: A 50-year-old male patient with a 2-year history of systemic arterial hypertension (controlled with losartan, 100 mg/day) presented with pulmonary interstitial disease and a 1-year history of progressive skin thickening. Skin biopsy showed sclerosing dermatitis, consistent with scleroderma. A mixed nucleolar and cytoplasmic reticular pattern of antinuclear antibodies was found. After an initial dose of CYC (500 mg), he developed asymptomatic hyponatremia (plasma sodium, 125-130 mEq/L). His condition was aggravated during an episode of hypertensive crisis and acute kidney injury, suggestive of SRC. During the hypertensive crisis, he presented to the emergency room with hypertension (200/120 mmHg), worsening of renal function (creatinine increasing from 1.0 to 1.5 to 2.5 mg/dl), and hyponatremia (Na, 121 mEq/L), as well as the following: plasma osmolality, 270 mOsm/kg; urine osmolality, 419 mOsm/kg; ADH, 1.5 pg/ml (reference: 1.0-13.3 pg/ml); schizocytes 0.6% (reference: absent); and lactate dehydrogenase, 259 U/L (reference: 135-220 U/L). Plasma sodium levels improved after blood pressure control with captopril (200 mg/day), fluid restriction and increased protein intake. There was also partial improvement of renal function (creatinine decreasing from 2.5 to 1.5 mg/dl).

Discussion: In this case, low-dose CYC use led to SIAD, with worsening of hyponatremia and increased plasma ADH, inconsistent with a hypo-osmolar state, in a patient whose condition was consistent with SRC. There was a significant increase in plasma renin activity, suggesting peripheral hyperstimulation of the RAS, which can deregulate the central osmoregulatory system.

FR-PO590

Osmotic Demyelination Syndrome Associated with Acute Severe Hypernatremia and Hyperglycemia

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Introduction: The association between hyponatremic osmotic disturbance and osmotic demyelination syndrome (ODS) are well-established and studied. It has been increasingly recognized that ODS can occur in the setting of hypernatremia. In case of hypernatremic ODS, there is no consensus on how rapid or slow to correct plasma sodium. We report a case of ODS accompanied by acute hypernatremia and hyperglycemia.

Case Description: A 63-year-old female with a history of hypertension and dementia was brought to the ER with coma. Laboratory data were significant for plasma sodium of 189 mEq/L, plasma glucose of 629 mg/dL, serum bicarbonate of 22 mEq/L, BUN of 63 mg/dL, and plasma osmolality of 412 mosmol/kg. Head CT did not reveal any abnormalities. She was diagnosed with hyperosmolar hyperglycemic syndrome (HHS) and hypernatremia, and was admitted to ICU. Since there were 2 target components of hypertonicity simultaneously, hypernatremia and hyperglycemia, a great attention was paid to lower the tonicity appropriately to avoid cerebral edema. The upper limit of a correction rate of plasma tonicity during correction of hyperglycemia was set as 3 mosmol/kg per hour and that of plasma sodium was 10 mEq/L per day according to clinical guidelines. Although those correction rates were strictly kept, her neurological symptoms were not improved significantly. Brain MRI was performed to ascertain more precise information on day 6, which was consistent with ODS. With continuation of those correction rates of plasma tonicity and plasma sodium, her neurological symptoms as well as ODS findings in MRIs were improved gradually. The patient was sent to a rehab facility with good condition on day 65.

Discussion: ODS usually occurs in patients with overly rapid correction of chronic hyponatremia. However, ODS also results from a rapid increase in tonicity in patients with acute hypernatremia or HHS. Since onset of hypernatremia is unclear in most of the cases, serial imaging with different modalities may be warranted for detecting subtle neurological findings associated with hypernatremia, such as cerebral edema or even ODS. Although the appropriate correction rate of plasma sodium with hypernatremic ODS is not known, this case suggests that adhering to clinical guidelines may improve the prognosis of it.

FR-PO591

Central Diabetes Insipidus in a Patient with Newly Diagnosed AML

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Introduction: Central diabetes insipidus (CDI) has been reported as both a rare complication of AML that may precede its diagnosis, and a may be a manifestation of its relapse. The exact mechanism by which diabetes insipidus and AML are connected remains elusive. The prevalence of cytogenic abnormalities in AML has been implicated as a possible cause. Here we describe a case of AML-induced CDI with monosomy 7 and without evidence on imaging of pituitary infiltration

Case Description: A 28 y/o woman was transferred from an outside hospital with significant leukocytosis (WBC 163,000) in the setting of a non-healing dental extraction and worsening odynophagia. She was found to have a new diagnosis of AML (diagnosed by peripheral blood smear and a deletion of D7S522 (7q31) locus via FISH) and a left neck soft tissue infection. The patient was started on the 7+2 chemotherapy protocol (Cytarabine and Idarubicin) on 4/17/18. The renal service was consulted for AKI in the setting of polyuria (approximately 2.5 to 3 liters per day). Labs were notable for a serum creatinine of 2.1 mg/dL, serum sodium of 152 meq/L, and urine osm of 190 mosm/L. She was started on ddAVP, and was continued for several days, over which time her urine output decreased, urine osmolality increased, with concomitant improvements in serum sodium and serum creatinine. Re-induction chemotherapy for persistent blasts was started 2 weeks later with clinical response over the next 10 days as evidenced by only 0.3% blasts. ddAVP was able to be discontinued as well at this point, as the resolution of the CDI coincided with the re-induction chemotherapy and subsequently confirmed low blast count and undetectable B cells

Discussion: A review of the literature reveals that CDI is a rare complication of AML, which can occur anytime during the course of AML. Although the exact mechanism connecting AML and CDI is unknown, some proposed theories include infiltration of hypothalamic pituitary stalk and abnormal expression of GP130 on neutrophils and platelets in patients with deletions on chromosome 7 or monosomy 7. The deficient GP 130 leads to abnormalities in glycosylation of neutrophils and platelets which can lead to CDI via two mechanisms: 1) decreased pre-pro-vasopressin which results in less active ADH production and 2) the dysfuctional platelets may affect ADH function and transport. Successful treatment of AML can rapidly reverse CDI.

FR-PO592

X-Linked Recessive Nephrogenic Diabetes Insipidus Cured with Bilateral Native Nephrectomy Following Living Donor Renal Transplant

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Introduction: X-linked recessive nephrogenic diabetes insipidus (X-NDI) is the most common subtype of congenital nephrogenic diabetes insipidus (CNDI) and is caused by mutations in the AVPR2 gene. This results in dehydration which increases the risk of urinary

tract damage. Current treatment for CNDI aims to reduce free water loss through low-solute diets, HCTZ and potassium-sparing diuretics, as well as NSAIDs. Diuretics enhance sodium and water reabsorption in the proximal nephron, and NSAIDs inhibit prostaglandin-meditated free water excretion. However, this treatment only reduces urine output by 25-50%, leaving a considerable aquaresis that impacts quality of life.

Case Description: A 19 year-old man with X-NDI with an AVPR2 mutation and neurogenic bladder underwent a Mitrofanoff procedure for neurogenic bladder at age 6. Despite intermittent catheterization several times a day, he developed recurrent UTIs, and eventually CKD IV secondary to chronic hydronephrosis. He had poor quality of life given need for q1-2 hr catheterizations with aprox. 600 cc of urine each time. Pre-transplant his creatinine baseline was 8.5 mg/dL. His medications included amiloride, HCTZ, and oxybutynin. He underwent a living related kidney transplant and was discharged on standard immunosuppression and antibiotics, amiloride, and HCTZ. He continued urinary catheterizations following discharge, with Cr stabilizing to a baseline of 1.7. His urine output continued at above 3L per day. He then underwent bilateral native nephrectomy in an attempt to cure his X-NDI and improve his quality of life. Labs following bilateral nephrectomy showed normal serum (289 mOsm) and urine (528 mOsm) osmolality with a urine output of 1.6L per day, and his Cr decreased to 1.1 mg/dL on discharge.

Discussion: Current research into new therapeutic strategies for X-NDI focuses on AVPR2 chaperones, methods to biochemically bypass the AVPR2 receptor, and existing drugs that affect AVPR2's signaling pathway. This case represents, to our knowledge, the first X-NDI patient cured with bilateral native nephrectomy following living related donor transplant for X-NDI complications. This suggests a role for renal transplantation and native nephrectomy as a definitive treatment of X-NDI and possibly CNDI, with a marked improvement in patients' quality of life.

FR-PO593

Hypophosphatemia and Phosphate Wasting Due to Oncogenic Osteomalacia in a Patient with Natural Killer T-Cell Lymphoma

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Introduction: Hypophosphatemia is common electrolyte disorder in hospitalized patients. Urinary phosphate wasting can be caused by oncogenic osteomalacia (OncOsteom), en entity characterized by production of phosphatonins, like fibroblast growth factor 23 (FGF-23). Mesenchymal tumors are the most common cause of OncOsteom and other malignancies are rarely associated. Here we present an unusual case OncOsteom in a patient with Natural Killer T-cell (NKT) lymphoma.

Case Description: A 33 year-old woman was admitted to the hospital with fever, chills, productive cough and myalgias. She had a remote history of mycobacterium *avium complex* infection and was actively being treated for hepatitis B virus with tenofovir and for hemophagocytic lymphohistiocytosis with etoposide. Upon arrival, the patient was normotensive but in respiratory distress. Examination showed sinus tachycardia and diffuse rales on lung auscultation. Laboratory data revealed serum electrolytes (mEq/L): Na 137, K 3.7, Cl 106, and CO_2 23. Others serum chemistries (mg/dL): creatinine 0.4, urea nitrogen 16, calcium 7.7 (serum albumin was 1.6 g/dL, corrected calcium 9.6) and phosphorus 1.5. Intravenous sodium phosphate was aggressively supplemented. Urine phosphate was 63 mg/dL, no glucosuria. Discontinuation of tenofovir did not lead to resolution of hypophosphatemia and the patient continued to require constant IV phosphate replacement for 12 additional days. A diagnosis of OncOsteom was entertained and a FGF-23 level was obtained and found to be elevated at 1940 RU/mL. A 1,25 (OH) vitamin D level was 48 ng/mL and 25 (OH) vitamin D was 8 ng/mL. A bone marrow biopsy was performed and the patient was diagnosed with NKT lymphoma. She continued to deteriorate clinically and expired 1 week later.

Discussion: Hypophosphatemia secondary to OncOsteom is an ominous disorder associated with significant morbidity. It is typically encountered in patients with mesenchymal tumors. Our case is the first reported in a patient with NKT lymphoma. The teaching point is that OncOsteom should be considered in cases of refractory urinary phosphate wasting in the presence of a lymphoproliferative disorder and measurement of FGF-23 level should be considered in those cases to reach a diagnosis.

FR-PO594

Case Report and Literature Review of Fanconi Syndrome Induced by Deferasirox in a Patient with Beta Thalassemia

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Introduction: Deferasirox (DFRA) is an oral iron chelating agent used to treat transfusion-related iron overload. Fanconi syndrome has been reported in less than 1% of patients receiving DFRA. There is a limited number of cases of Fanconi syndrome reported among patients with beta thalassemia treated with DFRA. Therapy with DFRA was permanently discontinued in all of the reported cases, except one in whom DFRA therapy was resumed after improvement of renal tubular function, resulting in recurrence of Fanconi syndrome. We report the case of a patient who developed Fanconi syndrome while receiving DFRA therapy who was rechallenged with the medication but has no signs of renal dysfunction after 6 months of therapy.

Case Description: A 25-year-old woman with medical history of beta thalassemia major and transfusion-related iron overload requiring iron chelation therapy, presented to the emergency department with generalized pain, nausea, and headaches for 24 hours. The patient had been receiving DFRA for 12 months prior to presentation. On admission, she was found to have hypophosphatemia (<1.0 mg/dL), hypokalemia (2.7 mEq/L), and non-anion gap metabolic acidosis (serum bicarbonate level 15 mEq/L). She was also found to have a urine pH of 5.5, glucosuria without hyperglycemia, and 100 mg/dL proteinuria based on urine disptick. Based on her clinical presentation, the patient was diagnosed with Fanconi syndrome. Her symptoms resolved within 1 week of discontinuing DFRA. Due to intolerance to alternative chelating agents, DFRA was restarted 1 year after Fanconi syndrome was diagnosed at 50% of the recommended dose and 3 months later, increased up to the full recommended starting dose. After 6 months of therapy, the patient has no symptoms or signs of Fanconi syndrome recurrence.

Discussion: As demonstrated in our case and prior reports in the literature, DFRA-induced Fanconi syndrome is reversible once DFRA therapy is discontinued. Plasmapheresis was attempted in one case, but did not significantly impact recovery time. Recovery can usually take several weeks to months. One case demonstrated the development of mild tubular damage after DFRA was restarted. Based on our case report, rechallenge with DFRA may be safe with close monitoring.

FR-PO595

Patiromer Associated Hypercalcemia

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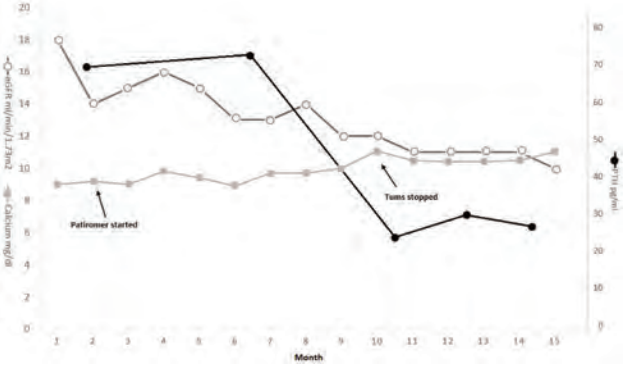
Introduction: Patiromer calcium sorbitex is a non-absorbable cation exchange polymer approved for management of chronic hyperkalemia in patients with chronic kidney disease. We report a case of hypercalcemia in a patient with chronic kidney disease stage 5 (CKD 5) treated with patiromer.

Case Description: A 75-year-old Caucasian male had Hypertension and CKD 5 (GFR of 10 ml/min/1.73m^2) secondary to biopsy proven Focal Segmental Glomerulosclerosis. He had chronic hyperkalemia despite discontinuation of RAAS inhibition. Patient was initiated on patiromer 8.4 grams daily. This has been continued for over a year now. Prior to patiromer's introduction, corrected calcium was in the 8.5 to 8.9 mg/dl range. Eight months into treatment with patiromer, calcium was between 10.5 to 11.1. iPTH was 23-29 pg/ml. 25-hydroxy vitamin D was low at 9ng/ml. TSH was normal and serum immunofixation was negative. Patient had been taking prn TUMS (calcium carbonate) otc for reflux symptoms that was discontinued upon discovery of hypercalcemia. However, hypercalcemia has persisted several months after discontinuation of TUMS.

Discussion: Patiromer binds free potassium and magnesium ions in the gut and releases calcium ions in exchange. This helps correct hyperkalemia in these patients without sodium loading, a problem with sodium polysterene sulfonate. Though 10% of the patients did develop hypomagnesemia (below 1.4mg/dL), significant hypercalcemia has not been reported in any clinical study or subsequently. The amount of calcium released from patiromer that may be systemically absorbed is modest and did not lead to significant hypercalcemia in clinical studies. However, patients with advanced CKD may be more vulnerable due to their limited ability to excrete calcium in the urine. Prolonged treatment with Patiromer may increase the risk of hypercalcemia as noted in our patient and should be monitored for, besides hypomagnesemia.



FR-PO596

SPECT/CT with Technetium 99m-Methyl Diphosphonate for the Diagnosis of Severe Symptomatic Hypercalcemia After Rhabdomyolysis Induced AKI in 2 Patients with Cirrhosis

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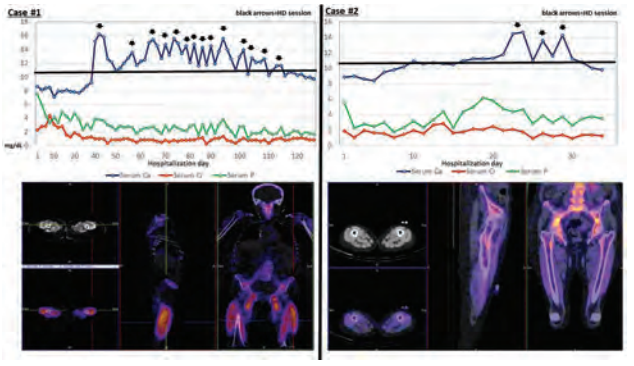
Introduction: Rhabdomyolysis induced acute kidney injury (RI-AKI) is often complicated by multiple electrolyte abnormalities. Hypercalcemia (HC) due to soft tissue mobilization of calcium deposits in the recovery phase of RI-AKI has been described yet severe HC is rare. We present two patients with cirrhosis who developed RI-AKI and severe HC, both with SPECT/CT deposit images

Case Description: Case 1: 56-yr-old female, primary biliary cholangitis Child-Pugh B cirrhosis who developed exertional RI-AKI that required hemodialysis (HD). She was

hypocalcemic during the oliguric phase; during the recovery phase developed severe HC (peak of 16.2 mg/dl) with neurological symptoms. She required intermittent 13 sessions of HD in addition to volume replacement, diphosphonates, and diuretics and recovered in 8 weeks. Plasma levels of 25-OH and 1-25(OH)2 vitamin D were low, iPTH appropriately suppressed. A SPECT/CT with $^{99}Tc^{m}$-methyl diphosphonate ($^{99}Tc^{m}$-MDP) demonstrated extensive soft tissue tracer accumulation (Fig1). Case 2: 65-yr-old female, Child-Pugh B cirrhosis secondary to hepatitis C, who developed exertional RI-AKI that required HD. Normocalcemic during the oliguric phase yet during the recovery phase developed severe symptomatic HC (peak 14.7 mg/dl), requiring 3 intermittent HD sessions. HC lasted for 2 weeks. Plasma levels of 25-OH and 1-25(OH) vitamin D were low, iPTH level appropriately suppressed and a SPECT/CT with $^{99}Tc^{m}$-MDP demonstrated soft tissue tracer accumulation. The evolution of serum calcium, phosphorus, and creatinine levels are showed in Fig1. Both patients had full renal and neurological recovery.

Discussion: SPECT/CT with $^{99}Tc^{m}$-MDP is a useful tool to identify soft tissue calcium deposits in patients with HC after RI-AKI. Intermittent HD is an effective treatment for severe HC. Since both of our patients were cirrhotic, we postulate that cirrhosis might be a risk factor for HC during the recovery phase of RI-AKI.



FR-PO597

Hypercalcemia in ESRD Patients Secondary to Immobilization: A Case Series

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Introduction: Immobilization is a well-known cause of hypercalcemia. However, there is scarce data available about hypercalcemia secondary to immobilization in end-stage renal disease (ESRD) patients as ESRD is often associated with hypocalcemia. We are presenting 3 cases of hypercalcemia in ESRD patients due to prolonged immobilization.

Case Description: 1: A 59-year-old man with the history of diabetes mellitus admitted for liver and heart transplant. Hospital course was complicated by sepsis, ventilator dependent respiratory failure (VDRF) and renal failure requiring hemodialysis (HD). He was initially hypocalcemic with elevated PTH and calcitriol was started. However, later he developed hypercalcemia with highest serum calcium level being 12.7mg/dl. Calcitriol was withheld and low calcium bath was used but hypercalcemia didn't resolve. Work-up came back negative [PTH-28 pg/ml, 25(OH)D-7 pg/ml and $1,25(OH)_2$ D-22 pg/ml]. 2: A 61-year-old man with the history of CHF and ESRD secondary to polycystic kidney disease on HD admitted with pericardial effusion. Hospital stay was complicated by hemothorax and VDRF. A few months later he became hypercalcemic with calcium level elevated up to 11.6 mg/dl. Work-up was negative [PTH-28 pg/ml, 25(OH)D-44 pg/ml and $1,25(OH)_2$ D-40 pg/ml]. 3: A 59-year-old lady with the history of atrial fibrillation, dilated cardiomyopathy, chronic heart failure and CKD admitted with CHF exacerbation. Hospital course was complicated by V. fibrillation arrest requiring AICD, renal failure requiring HD and VDRF. The patient remained ventilator dependent and developed hypercalcemia with a serum calcium of 11.2 mg/dl while on HD. Again, work-up was negative [PTH-74 pg/ml, 25(OH)D-26 pg/ml and $1,25(OH)_2$ D-24 pg/ml]. All of our patients had the extensive workup to rule out malignancy as a part of renal transplant evaluation and hypercalcemia was attributed to immobilization.

Discussion: Hypercalcemia due to immobilization is a result of diminished bone formation and increased bone resorption. Immobilization could be a common cause of hypercalcemia in ESRD patients than in the general population as ERSD is a low bone turnover disease and patients tend to be sicker. Immobilization should be considered a cause of hypercalcemia in ESRD patients especially when they are bed-bound and a conservative approach can be considered rather than an invasive or expansive approach of excluding malignancy.

FR-PO598

Successful Treatment of Tuberculosis-Associated Hypercalcemia with Denosumab in a Liver Transplant Patient with AKI

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Introduction: Denosumab, a human monoclonal antibody that inhibits RANKL, has recently been approved for treatment of malignancy-related hypercalcemia. To our knowledge, we present the first case of successful treatment of tuberculosis (TB)-associated hypercalcemia with denosumab.

Case Description: A 65-year-old African-American woman was admitted to the hospital with a 5-day history of vomiting. She also had a 3-month history of nonproductive cough. She underwent orthotopic liver transplantation for HCV-associated cirrhosis 8 months prior to admission and was maintained on tacrolimus, prednisone and mycophenolate mofetil. At presentation, she was found to have AKI with serum Cr 4.7 mg/dL (baseline Cr 2.2 mg/dL). Physical exam revealed bilateral crackles. Laboratory testing showed high serum Ca of 13 mg/dL. Phos was 4.4 mg/dL and PTH was suppressed at 7.8 pg/mL. She had elevated 1,25(OH)2 VitD (113 pg/mL) with low 25-OH-VitD level (14 ng/mL). Work-up confirmed the diagnosis of TB by demonstration of AFB in BAL. Liver biopsy also showed granulomas containing AFB. HyperCa showed only transient response to IV 0.9% NaCl. A high dose of steroids was not considered due to active TB. Zolendronic acid was not given due to potential AKI side effect. Thus, denosomab 120 mg SC injection was given. Ca started to decrease within 48 hours and normalized (Ca 10.2 mg/dL) on day 7 post-treatment with improvement in Cr of 2.1 mg/dL. However, asymptomatic hypoCa occurred on day 16 and reached nadir on day 27 (Ca 7.6 mg/dL). HypoCa subsequently improved with up-titration of Ca and active vitamin D supplements. At 4 months F/U, she remained normocalcemic (without Ca or Vit D supplement). PTH (47 pg/mL) and 1,25(OH)2 VitD (41 pg/mL) levels were normalized. 25-OH-VitD level increased to 19 ng/mL. Her Cr continued to improve (1.7 mg/dL).

Discussion: We report on the first experience in treatment of granulomatous disease-associated hypercalcemia with denosumab. Our patient had an improvement in hypercalcemia, however, hypocalcemia can occur following denosumab injection and requires close monitoring and treatment. Our patient developed asymptomatic hypocalcemia, which subsequently improved with up-titration of Ca and Vit D supplements. Further studies are needed to evaluate safety and efficacy in similar clinical scenarios.

FR-PO599

22q11.2 Deletion Syndrome Presenting with Chronic Hypocalcemia

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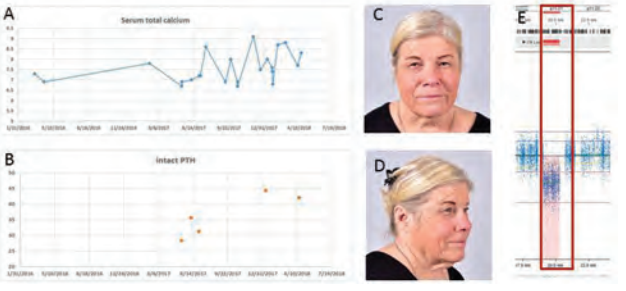
Introduction: 22q11.2 deletion syndrome, also known as DiGeorge syndrome, is a genetic disorder characterized with distinguishing facial features and congenital anomalies. Hypocalcemia can be seen in up to 50% of patients. However, it can be challenging to reach the diagnosis in adult patients who have no or mild congenital anomalies. Here we report one female who was diagnosed with 22q11.2 deletion syndrome after symptomatic hypocalcemia for more than 40 years.

Case Description: The patient was a 66 years old Caucasian female who was the product of an uncomplicated twin pregnancy. She had frequent ear infections and nasal speech requiring speech therapy during childhood. She completed a college education and denied history of developmental delay. She experienced seizures and muscles spasms at the age of 22 while in the military service. Hypocalcemia was diagnosed and she was treated with calcium and vitamin D supplementation. Since then, she has only had episodes of muscle spasms. Family history was significant for one son with hypocalcemia and another son who died from congenital heart disease at age 6 weeks. Since her transfer to our facility in 2016, she had fluctuating levels of total serum calcium (Figure 1A) with normal range intact PTH (Figure 1B). Urine calcium excretion was low. On physical exam, she had short stature with mild facial dysmorphism, including hypertelorism and square nasal root (Figure 1C and 1D). Chromosomal microarray showed 22q11.2 deletion (Figure 1E). Diagnosis was established and she received genetic counseling about the mode of inheritance and the possibility that her son had the same diagnosis. In follow up, she continues to have intermittent asymptomatic hypocalcemia despite supplementation of calcium.

Discussion: This case highlights the importance to consider 22q11.2 deletion syndrome in chronic hypocalcemia patients who have inappropriately normal or low levels of PTH. Chromosomal microarray is available to establish the diagnosis in most cases.



FR-PO600

A Case of Pseudohypoparathyroidism Presenting with Symptomatic Hypocalcemia After Acute Hepatitis Due to Epstein-Barr Virus

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Introduction: Pseudohypoparathyroidism (PHP) type 1b is characterized by isolated resistance to parathyroid hormone without the features of Albright hereditary osteodystrophy (AHO). In PHP type 1b, most cases are sporadic and the timing of development of symptomatic hypocalcemia is quite variable. The initial manifestations of hypocalcemia such as tetany, muscle cramps and convulsion usually occur in childhood or adolescence, but they may be delayed until adulthood. Here, we report a young adult case of PHP type 1b which presenting with hypocalcemic tetany after acute hepatitis due to Epstein-Barr virus infection.

Case Description: A 24-year-old man who had been previously healthy was admitted to the hospital because of nausea and appetite loss followed by tetany for three days. He had been well until two weeks prior to the admission, when he got a febrile pharyngitis with lymphadenopathy. The symptoms were improved by taking some antipyretics and antibiotics, however, general fatigue and appetite loss steadily developed with tetany and weakness. Laboratory test revealed significantly elevated transaminases which indicated acute hepatitis, as well as hypocalcemia, hyperphosphatemia and increased level of intact PTH. Head computed tomography showed bilateral basal ganglia calcification. On the basis of PTH-resistant hypocalcemia without the features of AHO, he was given diagnosis of PHP type 1b and started on calcium and calcitriol. He was symptomatically improved with treatment and his laboratory findings returned to normal range. At the same time, acute hepatitis, which had been proved to be caused by primary Epstein-Bar virus infection, recovered spontaneously.

Discussion: It is unknown what factor triggers symptomatic hypocalcemia in PHP type 1b. In our case, it was considered that decreased synthesis of 25-OH vitamin D in the liver due to acute hepatitis provoked PTH resistance followed by symptomatic hypocalcemia. PHP type 1b might be overlooked and should be taken into account if asymptomatic hypocalcemia is identified.

FR-PO601

A Rare Case of Hypoparathyroidism Complicating Pregnancy

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Introduction: Heterozygous activating mutations in the calcium sensing receptor (CaSR) which increase CaSR sensitivity to extracellular Ca cause autosomal dominant hypocalcemia (ADH). ADH results in hypocalcemia with low-normal parathyroid hormone (PTH) levels and is often diagnosed as hypoparathyroidism. This case describes the complicated course of a pregnant woman with ADH.

Case Description: A 31 year old female was diagnosed with autoimmune hypoparathyroidism at age 22 when she presented with paresthesias and cramping in both hands with a serum Ca of 5.5mg/dL, phosphate of 6.1mg/dL and PTH of 10pg/mL. Genetic testing for DiGeorge syndrome was negative. She had no family history of calcium or other electrolyte disorders. Her symptoms improved with oral Ca supplementation and calcitriol. Three years later a renal sonogram demonstrated medullary nephrocalcinosis. Her 24 hour urine Ca ranged 300 to 700mg and a thiazide (HCTZ) was added. Due to persistent hyperphosphatemia, the calcitriol was replaced by recombinant PTH. After starting HCTZ and recombinant PTH she developed symptomatic hypomagnesemia which persisted after stopping HCTZ. A 24hr urine magnesium (Mg) was 204mg. Her 24hr urine potassium was 140mEq while hypokalemic and off HCTZ. At age 29 she had a pregnancy complicated by exacerbation of hypomagnesemia and unexpected intrauterine fetal demise (IUFD) at 35 weeks. At the time, her serum Mg level was 1.3mg/dL. Other electrolyte levels were normal. A fetal ultrasound 10 days prior showed mild polyhydramnios and otherwise normal fetus. The cause of IUFD was uncertain but attributed to the hypomagnesemia. A year later she became pregnant again with exacerbation of hypomagnesemia. ADH was suspected and genetic testing was sent midterm. At 34 weeks she developed polyhydramnios, was induced, and delivered uneventfully. Two days post-partum, her newborn became bradycardic and seized with a serum Ca of 5.9mg/dL. PTH was 12pg/mL. Soon after, the mother's genetic testing confirmed a CaSR activating mutation consistent with ADH type 1.

Discussion: ADH should be considered in the differential for hypoparathyroidism as its diagnosis has significant genetic/family planning implications. Treatment of ADH (thiazides, recombinant PTH) may exacerbate renal Mg wasting associated with this disease, as does pregnancy. Calcilytics, allosteric antagonists of the CaSR, are an emerging therapy that may benefit patients with ADH.

FR-PO602

IV Iron Therapy Induced Acute Hypophosphatemia in CKD Patients

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Introduction: Intravenous (IV) iron-induced hypophosphatemia is a well-documented side effect in iron deficient patients. Single dosing studies suggest that decreases in serum phosphate are asymptomatic and fully reversible with phosphate repletion. Long term complications such as arrhythmias, muscular weakness, osteomalacia and bone fractures have also been documented. We report a case of hypophosphatemia with a newer formulation of IV iron: ferric carboxymaltose (FCM) induced severe acute hypophosphatemia.

Case Description: A 97 year old male with past medical history of atrial fibrillation, iron deficient anemia, hypothyroidism, chronic kidney disease III, and hypertension was referred to renal clinic for acute hypophosphatemia. The patient had been on oral iron supplementation for iron deficient anemia and it was not effective. He received IV FCM for iron deficient anemia twice in the previous month. The patient was sent to the emergency department after he was found to have a phosphate level of 0.8 mg/dL by routine lab work. Patient initially received both oral and intravenous phosphate repletion in the emergency department and subsequently received oral phosphate supplementation. However, the hypophosphatemia persisted in the presence of oral phosphate supplementation. Laboratory data showed calcium was 7.9 mg/dl, phosphate 1.5mg/dl, magnesium 2.1 mg/ml, intact parathyroid hormone 295pg/ml and 25-OH, vitamin D 30.8 ng/ml. His serum creatinine was at his baseline of 1.5-1.8 mg/dL. In addition, intact FGF23 level was found to be 1424 RU/ml (reference range < 180). Parathyroid scan showed no adenoma in parathyroid glands. Based on the above temporal association, patient was suspected of FCM induced, FGF23 mediated renal phosphate wasting. IV FCM was stopped and patient received oral active vitamin D, calcium and phosphate supplementation. The acute hypophosphatemia improved.

Discussion: This case highlights the association between FCM and low serum phosphate levels. Although there has been a growing body of literature on the association, many nephrologists may not be aware of the hypophosphatemic side effects of FCM. In the recently published phase 3 study of IV ferumoxytol versus FCM, hypophosphatemia was seen in 38.7% of the FCM group 2 weeks after treatment. In patients who receive IV FCM for iron deficient anemia, serum phosphate levels should be monitored.

FR-PO603

Hypomagnesemia: Beware of Zebras

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Introduction: Hypomagnesemia can be the initial and predominant manifestation of the rare17q12 deletion syndrome.

Case Description: A 62 year old male with 17 years history of severe hypomagnesemia of unclear etiology requiring daily IV and oral magnesium replacement and recent diagnosis of type 2 diabetes mellitus presented to our clinic for further evaluation. Patient experienced weakness, myalgia and cognitive deficits. Physical examination revealed macrocephaly along with brachydactyly of the hands and feet. He was found to have severe hypomagnesemia, hypocalcemia and hypokalemia with evidence for renal magnesium wasting requiring aggressive replacement with preserved renal function. Computed tomography scan of abdomen and pelvis showed bilateral kidney cysts. Because of the morphological and electrolyte abnormalities, chromosomal micro array was performed which showed a 1.5 mega-bases loss at chromosome 17q12 involving 20 genes. Per genetic analysist, patient's history, clinical findings and genetic analysis were consistent with17q12 deletion syndrome.

Discussion: Hypomagnesemia can be a presenting manifestation of 17q12 deletion syndrome also known as autosomal dominant tubulo-interstitial kidney disease sub type HNF-IB caused by a mutation in hepatocyte nuclear factor 1 beta. Classic features of 17q12 deletion syndrome are variable combinations of the following findings: structural or functional abnormalities of the kidney and urinary tract (80-85%), maturity onset diabetes of the young type 5 (MODY5) from beta-cell dysfunction (40%), and neurodevelopmental or neuropsychiatric disorders (50%). Renal abnormalities include tubular interstitial disease, characterized by reduced urine concentrating ability, hyperuricemia, hypomagnesemia, hypokalemia with bland urine sediment and tubular interstitial fibrosis on renal histology. Family members should be tested because of the autosomal dominant inheritance.

FR-PO604

Severe Hypomagnesemia as the Initial Indicator of HNF1β-Associated Renal Disease

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Introduction: Mutations in *HNF1*β (hepatocyte nuclear factor-1-beta) are known to cause Renal Cysts and Diabetes Syndrome (RCAD), so-named for two common clinical manifestations, maturity-onset diabetes of the young (MODY) and renal cystic disease. However, it has become increasingly recognized that HNF1β-associated disease can lead to a wide spectrum of clinical manifestations affecting multiple organ systems, with varying degrees of renal involvement. Due to the clinical heterogeneity, a high index of suspicion is required in making the diagnosis. Here, we present a case in which severe hypomagnesemia led to a diagnosis of RCAD.

Case Description: A 13-year-old Caucasian girl with newly diagnosed insulin-dependent diabetes mellitus presented with one month of intermittent lower abdominal pain, dysuria, and urinary frequency, and one day of paresthesias. On initial assessment, she appeared tired, but otherwise had an unremarkable physical examination. Laboratory studies revealed severe hypomagnesemia (0.6 mg/dL (normal range 1.5 to 2.2 mg/dL)) and hypocalcemia (ionized calcium of 0.75 mmol/L (normal 1.14 to 1.29 mmol/L)), as well as mild acute kidney injury (Creatinine 1.0 mg/dL) and metabolic alkalosis (bicarbonate 31 mmol/L and venous pH 7.5). Urinalysis revealed 3+ protein and 2+ glucose. Fractional excretion of magnesium was inappropriately elevated at 11%, and urinary calcium was undetectable. A renal ultrasound demonstrated a single 1.3 cm simple cyst in the right kidney. The patient received IV calcium and magnesium supplementation, and was ultimately transitioned to enteral magnesium oxide supplements. Subsequent genetic testing revealed a large deletion of chromosome 17q12. Upon retrospective chart review, it was found that at the time of her initial presentation with diabetes mellitus one month prior, the patient had mild hypomagnesemia and, unusually, a metabolic alkalosis.

Discussion: Mutations in *HNF1*β can lead to impaired magnesium handling in the distal convoluted tubule, but hypomagnesemia remains an under-recognized manifestation of HNF1β-associated disease. This case highlights that hypomagnesemia should be an indicator to test for mutations in *HNF1*β, particularly if present in conjunction with early-onset diabetes or urinary tract malformations.

FR-PO605

A Puzzling Case of Metformin (MF) Associated Lactic Acidosis (MALA)

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Introduction: MF, a biguanide used to treat type 2 diabetes mellitus, increases intestinal glucose utilization and lactate production. It inhibits the mitochondrial respiratory chain complex 1, which clears lactate by the liver and kidney. MF is highly cationic, not protein-bound and is eliminated unchanged by the kidneys. Its apparent volume of distribution (AVD) is enormous (up to 1000 L). MALA can occur with overdose or in cases associated with reduced kidney or liver function. The incidence of MALA without acute overdose is ~ 6.3 cases per 100,000 patient years. Normal therapeutic MF levels are 1-2 μg/mL and rarely exceed peak levels of 5 μg/mL, above which MF can cause MALA.

Case Description: A 70 year old female with a history of hypertension, type 2 diabetes mellitus and cerebral vascular accident, presented to the emergency room (ER) with a two day history of abdominal pain, nausea and vomiting. She was confused with Kussmaul breathing. Among her medications was MF/Januvia 1000/50 mg BID. Blood pressure was 98/59, pulse 96, RR 27, and temperature 89.4^{0}F. Initial arterial blood gas analysis revealed a pH of 6.88. Her serum bicarbonate was < 5 mmol/L, serum glucose 115 mg/dL and potassium 5.4 mmol/L. Initially her anion gap could not be calculated, but when her bicarbonate could be measured, it was as high as 52 mmol/L. Her admission serum creatinine was 8.1 mg/dL with a normal baseline (1 mg/dL). Her serum lactate was elevated at 33.8 mmol/L. A CT of her abdomen and pelvis did not show any acute pathology. She was immediately intubated, started on pressor support and bicarbonate infusion with continuous renal replacement therapy (RRT). Emergent exploratory laparotomy ruled out ischemic bowel. The patient had only 2-3 hrs of RRT because of repeat dialysis line clothing. In spite of this, her acid-base and electrolyte abnormalities spontaneously improved and RRT was discontinued. The patient was managed only with IV fluids, including dextrose/insulin, as a presumed enzymatic defect could not be excluded. Although the MF level was toxic (37 μg/mL), a prompt recovery ensued.

Discussion: Mortality from MALA is ~ 50%, and given MF's large AVD, an extended dialysis time (preferably hemodialysis) is required. Our patient had virtually no dialysis and her massive lactic acidosis corrected spontaneously over 2 days with only IV fluid therapy. The role of dextrose/insulin is unknown.

FR-PO606

Treatment of Severe Metformin-Associated Lactic Acidosis (MALA) with Continuous High Flux Hemodialysis and Tris-Hydroxymethyl Aminomethane (THAM)

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Introduction: Hemodialysis is the preferred modality for severe lactic acidosis due to MALA. We report a case of ingestion of 480 grams of metformin. After 33 hours of high flux hemodialysis (HFHD) his severe MALA was reversed by THAM. This is the first case report of the use of THAM to treat severe MALA not responding to HFHD alone.

Case Description: A 43-year-old suicidal man with type 2 diabetes ingested the largest reported dose of metformin, 480000 mgs. Initial serum potassium was 4.9 mmol/L, bicarbonate (HCO3) 16 mmol/L, anion gap 22, serum lactate 6.2 mmol/L, & an ABG showed a ph 7.16, pCO2 36, PO2 247 & HCO3 12 mmol/L. He was intubated for airway support & activated charcoal & polyethylene glycol given by NG tube. Repeat labs showed a potassium of 7.4 mmol/L, lactate of 6.6 mmol/L, & pH of 7.06. Emergent high flux HFHD was initiated. After 12 hours of dialysis the metformin dialyzer clearance was 416 ml/min which is significantly better than earlier reports of 68-228 ml/min. Due to a persistent lactate of 22.6 - 31.4 mmol/L we continued HFHD for a total of 33 hours. The next day the serum ph was only 7.11 and the serum HCO3 10' mmol/L. A dose of THAM was calculated as follows: THAM (ml of 0.3 mol/L solution) = lean body weight (kg) x base deficit (mmol/L). We chose 3 times the usual base deficit to increase serum HCO3 by 15 mmol/L rather than the usual 5. We gave 1280 ml of THAM over 12 hours, enough to increase the serum HCO3 by 15 mmol/L. Levophed & vasopressin for hemodynamic support were rapidly weaned. The serum lactate corrected dramatically after THAM from 31.4 to 6.2 mmol/L. In fact, over the next 24-hours, the serum lactate normalized along with pH & HCO3 levels.

Discussion: Our study is the first successful use of THAM with continuous HFHD in a patient with severe MALA complicated by anuria. THAM rapidly equilibrates into the intracellular space of liver, muscle & intestine. We hypothesize that the rapid increase in tissue pH inhibits lactate dehydrogenase & increases the activity of pyruvate dehydrogenase & pyruvate carboxylase leading to rapid inhibition of lactate production & enhanced metabolism of lactate. Our case supports the use of THAM to augment continuous HFHD for the correction of severe acidemia associated with MALA.

FR-PO607

Severe Lactic Acidosis in a Patient with Advanced Hepatic Malignancy Due to Warburg Effect

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Introduction: Lactic acidosis is one of the most common cause of metabolic acidosis in hospitalized pateints and is either due to overproduction or reduced metabolism of lactate. Impaired tissue oxygenation, either from decreased oxygen delivery or a defect in mitochondrial oxygen utilization usually causes increased lactate production. Causes of lactic acidosis can be divided into those associated with impaired tissue oxygenation as type-A and those without obvious systemic impairment in oxygenation as type B lactic acidosis. We report a case of severe type B lactic acidosis in a patient with extensive hepatic malignancy most likely from Warburg effect.

Case Description: 62 years old male with history of hypertension, hypothyroidism and advanced hepatic metastatic gall bladder cancer admitted to the hospital due to failure to thrive. On examination BP was 128/80mmhg, HR 90/min, temperature was 95.3F. Patient was lethargic, abdomen was soft, distended and multiple bulky masses were appreciated in the right upper quadrant. Labs revealed Na:134, K: 4.2, Cl: 94, bicarb <10, BUN 53mg/dl, creatinine 3.0mg/dl, anion gap 24. ABG showed pH 7.11, pCO2:9.7, HCO3: 3, lactate >22 suggesting severe high anion gap metabolic acidosis due to lactate. He also had evidence of tumor lysis syndrome with LDH 2331, uric acid 14.1, phosphorus 9.1. CAT scan of abdomen showed infiltrative tumor replacing majority of both hepatic lobes with some sparing of superior right hepatic lobe.

Discussion: Metabolic modifcation is a typical hallmark of cancer cells, despite presence of adequate oxygen, tumor cells generate energy from aerobic glycolysis instead od mitochondrial oxidative phosphorylation. This phenomenon is defined as "Warburg effect", this leads to increased glycolysis, accumulation of ATP and lactate production by tumor cells. Warburg effect confers advantage to cell growth by providing carbon sources that are required for rapid cell proliferation and also by decreasing reactive oxygen species. This effect is more commonly seen in hematologic malignancies like lymphoma and leukemia, but can rarely be seen in solid malignancies. Our patient had features of tumor lysis and severe type B lactic acidosis, by excluding other causes of type B lactic acidosis it was attributed most likely due to Warburg effect. In addition impaired hepatic and renal clearance of lactate contributed to very high lactate levels.

FR-PO608

Severe Chloride Deficiency Metabolic Alkalosis from Excessive Sweating

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Introduction: Most cases of chloride deficiency metabolic alkalosis are due to chloride loss from the gastrointestinal tract or the urine and secondary hyperaldosteronism contributes to hypokalemia.We are presenting a case of chloride deficient metabolic alkalosis from an unusual source.

Case Description: A 32 y/o man presented with generalized weakness, fatigue and failure to thrive since several days. He was severely volume depleted with hypotension and orthostatic BP changes, subjective weight loss and decreased skin turgor. Laboratory testing revealed a severe hypokalemic metabolic alkalosis with CO2 50 mmol/L, Chloride 70 mmol/L, sodium 126 mmol/L, potassium 2.1 mmol/L, magnesium 0.78 mmol/l BUN 18 mg/dl creatinine 0.7 mg/dl. A spot urine sodium was 10 mmol/L, Chloride <10 mmol/L and potassium 26 mmol/L. The patient had no nausea, vomiting or diarrhea and denied any use of diuretics. He had a history of multi substance abuse and incarceration and recently started working as a painter. The patient reported that painting under the hot roof in summer" was killing him". He had previous care in our institution because of cystic fibrosis. The patient's symptoms and metabolic abnormalities resolved with saline and the patient was discharged.

Discussion: Cystic fibrosis is an inherited disorder characterized by excessive chloride content in sweat with resulting pulmonary and gastrointestinal complications. Chloride deficiency metabolic alkalosis is a rare complication of cystic fibrosis precipitated by environmental stressors leading to excessive sweating, in this case by painting under a hot roof in summer.

FR-PO609

CVVH as Therapy for Severe Metabolic Alkalosis

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Introduction: Untreated severe metabolic alkalosis (pH>7.6) can lead to devastating clinical consequences such as seizures and coma. We describe the use of continuous veno-venous hemofiltration (CVVH) in the management of a patient with severe metabolic alkalosis.

Case Description: A 51-year-old male with advanced diffuse large B-cell Lymphoma was admitted for high-dose methotrexate infusion as part of his 6th cycle of chemotherapy (R-CHOP plus methotrexate). He received oral and intravenous sodium bicarbonate to maintain high urine flow rates (>100cc/hour) and a urine pH>7.5 to aid methotrexate excretion. He sustained an AKI (peak Cr of 2.5mg/dL; baseline 0.8mg/dL) two days after the infusion. Serum methotrexate levels, which were followed q12h were persistently high (>6umol/L) and isotonic sodium bicarbonate (250cc/hour) was continued. A week later, he developed altered mental status and respiratory failure requiring ventilator support. An arterial blood gas showed a pH of 7.60, pCO2 of 51mmHg and his HCO3 was 46mmol/L. He had received a total of 20L of isotonic sodium bicarbonate. His pH worsened to 7.69 on

the ventilator and we were consulted. We initiated CVVH on a citrate bath with a blood flow of 150mL/min and a replacement fluid rate at 800mL/min. Our aim was slow and steady correction of alkalosis - we achieved that over the next 12 hours with a drop in his pH from 7.69 to 7.52. CVVH was terminated after 24 hours. In the next few days, he was extubated and his mental status and renal function returned to baseline.

Discussion: Metabolic alkalosis has traditionally been treated with an acid such as hydrochloric acid (HCl) or an acid precursor such as ammonium chloride (NH4Cl). Issues with availability and the need for reconstitution and specific guidelines for administration (in the case of HCl) limit their use. CVVH is readily available and most ICUs can initiate CVVH within a few hours. There are no specific prescription guidelines to treat metabolic alkalosis. While conventional hemodialysis has been described as a treatment modality, effects of rapid correction of pH are unknown. We successfully achieved a gradual correction of alkalosis using a bicarbonate free bath with slow clearance parameters and constant monitoring. To our knowledge, this is one of the first cases describing the use of CVVH for correction of metabolic alkalosis in the setting of AKI.

FR-PO610

Autosomal Recessive Polycystic Kidney Disease (ARPKD) Presenting in Adulthood

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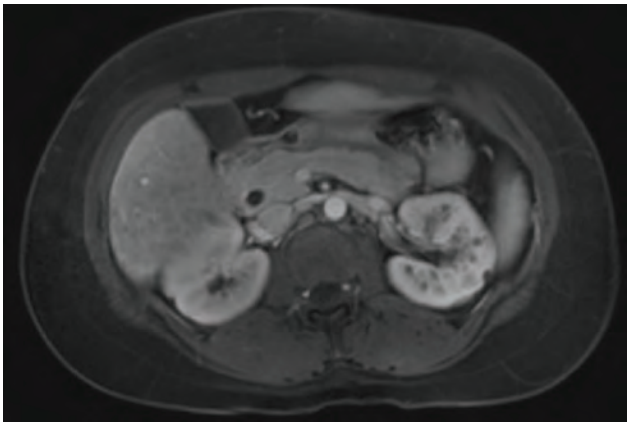
Introduction: ARPKD is characterized by multiple renal cysts arising from the collecting ducts, variable degree of progressive renal failure and congenital hepatic fibrosis. It is caused by mutations in PKHD1 gene located on chromosome 6p21. It is mostly diagnosed in infancy or childhood with only few cases being diagnosed as adults. Here we present a case of ARPKD that was diagnosed in adulthood.

Case Description: A 37-year-old female with past medical history significant for congenital hepatic fibrosis is referred to polycystic kidney disease clinic for evaluation of cystic kidney disease. Family history is significant for cystic kidney disease in two of her cousins (both on the paternal side). Neither of her parents had a history of kidney cysts. Her renal function was normal. Abdominal MRI revealed a cirrhotic liver with extensive fibrocystic changes and splenomegaly. It also showed several sub-centimeter cysts in both kidneys (Figure 1). Whole exome sequencing showed compound heterozygous variants of PKHD1; one, c.3761_3762delCCinsG is known to be pathogenic. The other, c.9107T>G, is a variant of unknown significance (VUS). This is a rare variant (2/100,000) which has previously been detected in at least 2 ARPKD patients, with clinical presentations of hepatic fibrosis.

Discussion: There are more than 750 different mutations described in PKHD1 gene. Most common amongst these is a missense mutation in exon 3. Our patient has a compound heterozygous mutation. The first allele had a mutation in exon 32. This involves deletion of two nucleotides and addition of a third nucleotide leading to a frameshift mutation which leads to a premature stop codon. This is a known pathogenic mutation. Less is known about the second variant, c.9107T>G although it has been described in ARPKD patients presenting with hepatic fibrosis and normal kidney function. Adult onset ARPKD is rare, and notable. The combination of hepatic fibrosis, splenomegaly and kidney cysts are consistent with ARPKD, although in this patient the liver findings dominate.



FR-PO611

Gastrointestinal Bleed in ESRD: An Unexpected Cause

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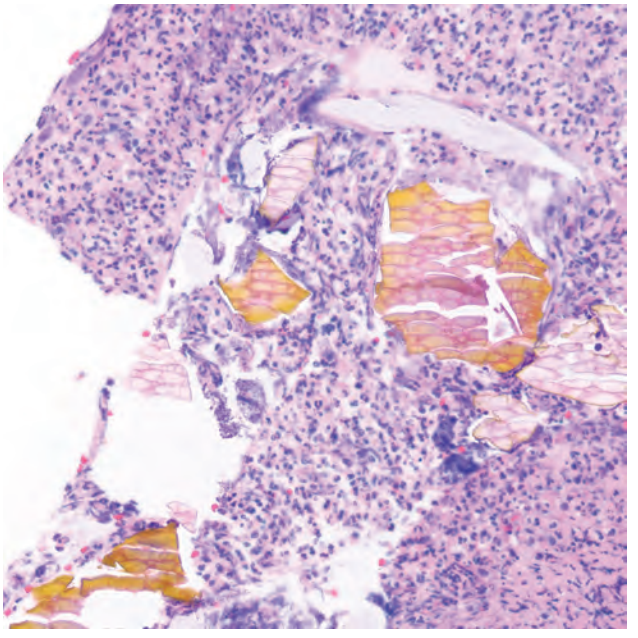
Introduction: ESRD patients have a fivefold higher risk of gastrointestinal (GI) bleed compared to those without CKD. Common causes include angiodysplasia, peptic ulcer disease, diverticular disease, ischemic colitis. A lesser known causes of GI bleed in this population is sevelamer induced GI ulcer.

Case Description: A 59-year-old African American man with type 2 diabetes mellitus, HTN, ESRD on hemodialysis, presented with severe headache and right sided weakness. He had intraventricular hemorrhage from severe hypertension. Routine labs showed hyperphosphatemia, so he was continued on sevelamer. On hospitalization day 20, he had multiple episodes of dark tarry stools with hemoglobin drop. Upper GI endoscopy revealed a large ulcer in the duodenum; he was started on pantoprazole. GI bleed recurred over the next weeks. A colonoscopy revealed a 3-5 cm segment of ulcerated and friable mucosa in the ascending colon. Biopsy of the colonic ulcer revealed presence of "fish scale" crystals previously associated with sevelamer, with inflammatory changes (Fig 1). A diagnosis of sevelamer induced colonic ulcer was made and sevelamer was stopped.

Discussion: Here we report 6 cases from our institution of GI ulcerations with deposition of sevelamer (Table 1). This is an underappreciated association and should be suspected in the right clinical scenario. Given the continued increase in use of sevelamer as a phosphate binder, it is important for the nephrologists to be cognizant of this entity.

Table 1

	Age (years)	Dialysis vintage (years)	Time on sevelamer (years)	Presenting symptoms	Location of lesion
Patient 1	59	5	5 years intermittent use	Melena, hgb drop	Ascending colon
Patient 2	58	7	5	Abdominal Pain, diarrhea	Transverse colon
Patient 3	50	3 (PD)	3	Sigmoid perforation	Sigmoid colon
Patient 4	56	2	2	Rectosigmoid colitis	Colon NOS (random biopsy)
Patient 5	75	3	2	Rectal ulcers, hematochezia	Rectosigmoid colon
Patient 6	69	3	3	Heme positive stools, anemia	Colon



Sevelamer crystals in biopsy from colon

FR-PO612

A Case of Early Onset Autosomal Dominant Polycystic Kidney Disease Caused by GANAB Mutation

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Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) typically results from mutations in the *PKD1* and *PKD2* genes, which code for polycystin 1 and polycystin 2 respectively. Mutations in these genes promote renal cystic dysplasia and are a significant cause of End-Stage Kidney Disease (ESKD). *PKD3* is related to *GANAB* gene mutation and represents mid- and late adulthood. We report a description of a case of ADPKD in a 12-year-old female with dual mutations in *PKD1* and *GANAB* genes and presented bilateral renal cysts in adolescence.

Case Description: A 12-year-old female presented to the local emergency room with persistent intense left flank pain. Dipstick showed large blood and abdominal CT showed 4 mm obstructing calculus in proximal left ureter, nephrolithiasis with minimal scaring in upper pole of left kidney, multiple bilateral renal cysts with the dominant on the left kidney at 2.8 mm. Non-calcified 2 mm right lower lobe pulmonary nodules was also identified. Renal function was preserved with BUN of 11 mg/dl and creatinine of 0.6 mg/dl, electrolytes were within normal range. The patient was treated with pain control medications and hydration with improvement and was referred to a nephrologist. Renal ultrasound (RUS) showed multiple bilateral cysts. The right kidney measured 10.5 cm x 4.9 cm x 4.8 cm and the left kidney measured 9.8 cm x 4.7 cm x 5.0 cm. Renal cysts were present bilaterally with some displaying thick internal septation. The largest cyst was present in the left kidney, measuring 3.3 mm. Using genomic DNA from the submitted specimens, the exonic regions and flanking splice junctions captured and sequenced by NGS and compared to the human genome build of non-mutated genes of interest. The results returned positive for *GANAB*, variant p.R61X generated nonsense mutation; and *PKD1*, variant p.P61L generated missense mutation. The *GANAB* mutation classified as pathogenic variant and the *PKD1* mutation classified as a variant of uncertain significance.

Discussion: The presented case is the first reported pediatric case with dual mutation (PKD1 and GANAB) and nephrolithiasis. The data present unreported novel *GANAB* mutations to expand the mutation spectrum reported by Porath et al., 2017. Knowledge of spectrum variety in pediatric patients with cystic kidney disease might direct early diagnostic and open prospective for gene therapy.

FR-PO613

Long Term Effect of High Dose Tolvaptan Treatment for Autosomal Dominant Polycystic Kidney Disease Patient

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Introduction: Based on the results of Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcome (TEMPO) 3:4 trial, tolvaptan was firstly approved by regulatory authority in Japan (March, 2014), as a therapy for Autosomal dominant polycystic kidney disease (ADPKD) patients. However, to date, the long term efficacy and safety of high dose tolvaptan is unknown. Here, we present a Japanese case with ADPKD, who have continued a high dose of tolvaptan (a total daily dose of 120 mg) for 9 years from the beginning of the TEMPO 3:4 trial.

Case Description: A 36-year-old man was diagnosed with ADPKD in 2008. His estimated glomerular filtration rate was 57.3 mL/ min/1.73 m^2 calculated as Japanese formul, and the total kidney volume (TKV) was 1499 mL.Tolvaptan was started at a dose of 60 mg/day (with 45 mg given in the morning and 15 mg in the evening), with weekly increase by 30mg/day, and finally to 120 mg/day divided into 90 mg in the morning and 30 mg in the evening. The rate of eGFR decline during tolvaptan treatment was - 3.01 mL/min/1.73 m^2 per year (57.3 mL/ min/1.73 m^2 before the treatment of tolvaptan; and 34.4 mL/ min/1.73 m^2 9 years later). The TKV increased by 6.17 %/year (1499mL before the treatment; and 2328 mL 9years later). During 9-year period, the patient has showed no tolvaptan-related adverse events, such as liver dysfunction, and hypernatremia, which were more common adverse events in tolvaptan group of the TEMPO 3:4 trial[9]. Tolvaptan treatment is continuing in this patient, and his condition is stable now.

Discussion: The *post hoc* exploratory analysis of the TEMPO3:4 trial also revealed that tolvaptan decrease the rate of eGFR by - 3.70 mL/min/1.73m^2 /year (n=151, 95% confidential interval:- 4.04 to - 3.36 mL/min/1.73m^2 /year) in the tolvaptan group and - 5.36 mL/min/1.73m^2 year (n=84, 95% confidential interval:- 6.19 to - 4.53 mL/min/1.73m^2 / year) in the placebo group, in ADPKD patients with CKD stage 33. In our patient, during 9-year period, the rate of eGFR decline was -3.01ml/min/1.73 m^2 /year, which was similar to the results of the previous study. Thus, high dose of tolvaptan treatment for the protection of kidney function could be maintained in longer term, even in patients with CKD stage 3.

FR-PO614

A Case of Autosomal Dominant Alport Syndrome Diagnosed by a Second Renal Biopsy

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Introduction: Typically, Alport syndrome is diagnosed by a renal biopsy and is characterized by Alport symptoms, including kidney disease, hearing loss, and eye abnormalities. However, symptoms and signs are characteristic of X-linked Alport syndrome that are not applicable to the autosomal dominant condition.

Case Description: A male patient experienced asymptomatic hematuria since childhood. His mother had chronic hemodialysis because of unknown renal disease. He received a renal biopsy at the age of 16 years; however, light and electron microscopic findings revealed minor abnormalities and the immunofluorescence staining of type IV collagen α5 chain was normal. Since then, he received conservative treatment ; however, hematuria and proteinuria tended to increase over time. Therefore, he received a second renal biopsy at the age of 23 years. While light microscopy revealed focal glomerulosclerosis in some glomeruli, electron microscopy revealed irregular thickening and thinning with a reticulated change in the glomerular basement membrane. Although renal biopsy findings suggested Alport syndrome, he reported no hearing loss or visual impairment. Therefore, genetic analysis revealed a single-base deletion of type IV collagen a3 chain [exon26 c.1826delC, p(Pro 609Leufs*138)], which, along with a family history, confirmed the diagnosis of autosomal dominant Alport syndrome. Currently, the patient is receiving conservative treatment, including renin–angiotensin system inhibitors.

Discussion: A renal biopsy cannot diagnose Alport syndrome at an early stage because of an unclear change in the basement membrane. Besides, autosomal dominant Alport syndrome lacks eyes and ears abnormalities, which delays the diagnosis unless positive suspicion. Recent advancements in sequence technology have revealed autosomal dominant Alport syndrome to be a relatively frequent disorder (19%–31% of Alport syndrome cases). Thus, in patients with family history of renal impairment, we should consider the possibility of autosomal dominant Alport syndrome, even if absence of Alport symptom except hematuria.

FR-PO615

A Case Report of a Novel Variant of X-Linked Alport Syndrome

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Introduction: X-linked Alport syndrome is a rare hereditary disorder caused by COL4A5 gene variants. We describe a case of a 28 year old Caucasian male with a family history of end-stage renal disease (ESRD) presenting with episodic gross hematuria and nephrotic range proteinuria. Renal biopsy showed focal segmental glomerulosclerosis with non-diagnostic ultrastructural findings. Next Generation Sequencing showed a COL4A5 missense likely pathogenic variant, substituting adenine for guanine at nucleotide 901(c.901G>A) of coding DNA predicting a glycine to serine substitution at amino acid 301 (p.Glyc301Ser).

Case Description: A 28 year-old Caucasian male with recent diagnosis of hypertension and a family history of ESRD presented with episodic gross hematuria and nephrotic range proteinuria (7.7g/g). Blood pressure was 146/92 mmHg. Physical examination was unremarkable with no lower extremity edema. All other laboratory testing and renal ultrasound was unremarkable. Renal biopsy showed FSGS with non-diagnostic ultrastructural findings (figure 2). NGS and Sanger Sequencing revealed a COL4A5 missense variant, substituing adenine for guanine at nucleotide 901(c.901G>A) of coding DNA predicting a glycine to serine substitution at amino acid 301 (p.Glyc301Ser).

Discussion: The pathogenicity for this novel missense variant is strongly suspected based on its location in a conserved GLY-Xaa-Yaa triple helical domain in the COL4A5 gene. Knebelmann et al first reported a similar missense variant substituting arginine for glycine at position 325 in a large kindred of X-linked Alport syndrome. The variant genotype has implications for individual prognosis. A study of 175 X-linked AS families showed that rate of progression of renal and extra-renal manifestations was associated with mutation type. Those with Gly-Xaa-Yaa variants reached ESRD at a median of 33 years versus 25 years for truncating mutations. Correct diagnosis allowed for appropriate genetic counseling and treatment, including ACE inhibitor therapy and the avoidance of immunosuppression. The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of the Army, the Department of Defense, nor the US Government.

FR-PO616

A New Pathogenic Stop Codon Variant in the COL4A5 Gene

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Introduction: X-linked Alport syndrome (AS) is a progressive form of renal failure caused by pathogenic variants in the *COL4A5*gene. More than 702 variants have been described and a further 400 are estimated to be known to individual laboratories but have not been published.

Case Description: We present the case of a 30 year-old man with a history of AS diagnosed at age 8 years (hearing loss, vision deficit, and proteinuria) who presented for discussion of inheritance patterns of his disease as part of family planning with his current partner. AS was biopsy-proven at age 14 years, which showed thinned and multi-laminated glomerular basement membranes. He experienced an acute decline in renal function at age 22 years, requiring dialysis for 2 years before undergoing a living-related renal transplant. He and his significant other have no known family history of chronic kidney disease. He notes a history of hypertension in his maternal grandfather. Since a pedigree was not possible, it was unclear whether he had X-linked, autosomal recessive, or autosomal dominant inheritance. Thus, the patient underwent sequencing of COL4A3, COL4A4, COL4A5, and COL4A6 genes to determine his specific mutation. A hemizygous stop codon variant was found in exon 52 of the COL4A5 gene, designated c.4829C>A, resulting in premature protein termination (p.Ser1610*) after TCA to TAA conversion. He was referred for genetic counseling.

Discussion: About 65% of AS cases are caused by COL4A5mutations and are inherited in an X-linked pattern. The patient's variant c.4829C>Aappears to be pathogenic in this given clinical context and has never been previously reported. The description and reporting of COL4A5 variants and clinical associations help to predict phenotype and understanding of collagen type IV biochemistry, which may ultimately inform therapy.

FR-PO617

Biallelic PKD1 Mutations in a Child with Aggressive Autosomal Dominant Polycystic Kidney Disease and Congenital Hepatic Fibrosis

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Introduction: Autosomal recessive polycystic kidney disease (ARPKD) is generally characterized by neonatal detection of enlarged kidneys and pulmonary hypoplasia. Autosomal dominant PKD (ADPKD) usually manifests in adulthood with hypertension and nephromegaly. Both have gastrointestinal manifestations - congenital hepatic fibrosis (CHF) is common in ARPKD, while ADPKD patients more typically have polycystic liver

disease. CHF has been rarely reported in cases of ADPKD, but specific modifier genes have not been identified. We report the case of a child with aggressive ADPKD and CHF in the context of a biallelic mutation of PKD1.

Case Description: We report the case of a term male infant of African descent presenting with neonatal nephromegaly, pulmonary hypoplasia and hypertension. ARPKD was suspected initially, but genetic testing did not identify a pathogenic mutation in PKD2 or PKHD1. Instead, two variants on the PKD1 gene were identified (c.11249G>A and c.6395T>G), one of which was previously unreported. His course was complicated by anemia, hypertension, respiratory insufficiency and progressive CKD. At 20 months of age, he became acutely ill with fever, ascites, and worsening abdominal distension and was diagnosed with spontaneous bacterial peritonitis. Liver imaging showed hepatomegaly with normal liver function tests. Renal function deteriorated, requiring hemodialysis and ultimately, nephrectomies. Kidney biopsy showed diffuse cysts involving all segments of the nephron, complete obliteration of the cortex and glomerulocystic changes. Liver biopsy demonstrated CHF, with diffuse ductal plate malformation, tortuous peripheral ductal profiles and expanded portal tracts. Doppler ultrasound did not reveal portal hypertension.

Discussion: Our patient has a previously unreported variant of PKD1, and biallelic or "double dominant" ADPKD. This case is significant due to his neonatal presentation, early deterioration of renal function, and CHF, all of which are unusual in ADPKD. This suggests that biallelic ADPKD has unique clinical characteristics. This case emphasizes the importance of considering a wider differential diagnosis when evaluating children with nephromegaly and cystic kidney disease; and the importance of monitoring for CHF and related sequelae, even in the context of ADPKD.

FR-PO618

Mutation in NOTCH2 Gene Causing Liver and Renal Failure in Newborn

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Introduction: Alagille syndrome is an autosomal dominant disorder known to cause a multi-organ dysfunction and often presents as neonatal liver disease. The majority of cases are related to the mutation of the JAG1 gene and only a small percentage, <1%, is due to mutation of the *NOTCH2* gene. We present a patient who was diagnosed with neonatal giant cell hepatitis and renal tubular dysgenesis later found to have *NOTCH2* gene mutation.

Case Description: The patient delivered at 39 weeks gestation via cesarean section due to being large for gestational age and appeared "swollen" on ultrasound. At 6 weeks of life, he was found to have elevated transaminases, hyperbilirubinemia, clay colored stools, rust colored urine and ascites. A liver biopsy was done and read as neonatal giant cell hepatitis with marked hemosiderosis, bile duct paucity, and acute microabscess. At 5 months of life, he was admitted for acute kidney failure when found to have oliguria, hyperkalemia, rising creatinine levels and coagulation levels indicative of disseminated intravascular coagulation. He underwent orthotopic liver transplantation at that time. A biopsy was done on the explanted liver and found hepatocellular necrosis with syncytial giant cell transformation and diffuse fibrosis with marked hemosiderosis which was highly concerning for possible embryonal hepatoblastoma versus neonatal hemochromatosis. He required a prolonged period of continuous renal replacement therapy and dialysis which prompted a fine needle biopsy of the kidneys revealing renal tubular dysgenesis. Repeated biopsy at the age of 4 years showed glomeruli with podocyte hypertrophy and fetal glomerular appearance. Whole exome sequencing was later done and revealed he had an unclassified variant detected of phenotype H2032N which is found in the *NOTCH2* gene and known to be linked to Alagille syndrome.

Discussion: Alagille syndrome is characterized by bile duct paucity but has the classical involvement of 5 main systems including: liver, dysmorphic facies, congenital heart disease, skeletal anomalies, and ophthalmic defects. Both the *JAG1* gene and the *NOTCH2* genes are involved with the Notch receptors. *JAG1* gene is responsible for up to 95% of cases while the *NOTCH2* gene is involved in <1% of cases. This case highlights the extensive multisystem involvement that can be seen in Alagille syndrome and the extremely rare presentation of the NOTCH2 gene mutation.

FR-PO619

C3 Gene Mutation Abnormality Associated with Atypical Hemolytic Uremic Syndrome in a Patient With Polycystic Kidney Disease

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Introduction: Atypical HUS (aHUS) is a disorder involving dysregulation of the serum complement system, resulting in endothelial cell injury and has been effectively treated with blockade of the complement system. The optimal therapy remains unknown, but advances in genetic testing help determine which patients would benefit from complement system blockade. We report a case of an aHUS patient that benefited from genetic testing after being on dialysis.

Case Description: 35-year-old female with a past medical history of obesity, gestational hypertension, history of a miscarriage, diabetes mellitus, and polycystic kidney disease presented with diarhea, acute renal failure, and uremic symptoms after eating uncooked meat. Her serum creatinine (sCr) was 11 mg/dL, platelet count 82 k/μL and labs concerning for microangiopathic hemolytic anemia. A kidney biopsy showed severe acute thrombotic angiopathy; extensive endothelial cell injury and prominent fibrinoid necrosis of vascular walls. There were mild chronic changes in the parenchyma including focal glomerulosclerosis, tubular atrophy and interstitial fibrosis. Genetic testing revealed a variant of unknown significance in the C3 gene. She required hemodialysis, and started on eculizumab, along with prednisone and plasmapheresis. A month later, her kidney function improved to be off dialysis and one year later her sCr is stable 3.0 mg/dl with continued use of eculizumab.

Discussion: Our case highlights the difficulty in recognition of mutations of complement cascade that can be trigged to cause thrombotic microangiopathy. We herein, present a case of atypical hemolytic uremic syndrome that is uncommonly associated with C3 gene mutation. Genetic susceptibility to aHUS has been well recognized with mutations in genes involving complement factor I, membrane cofactor protein, and CFH (complement factor H). These mutations affect the binding regions of C3b that interrelate with CFH, CD46, and complement receptor 1, with resultant dysregulation of the alternative complement pathway. Patients with C3 mutations usually progress to severe disease and ESRD within the first year following presentation. Therefore proper diagnosis and management (including the use of eculizumab) in this group of patients would have a great impact on prognosis of their renal disease.

FR-PO620

Atypical Hemolytic Uremic Syndrome (HUS): DGKE and Other Mutations in West Virginia Children's Hospital

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Introduction: HUS is a thrombotic microangiopathy (TMA) presenting with thrombocytopenia, anemia, and end organ involvement with normal ADAMTS13. Microvascular injury, platelet consumption and intravascular hemolysis lead to end organ damage. Renal biopsy is pathognomonic. Typical HUS presents acutely after E. coli (STEC) related bloody diarrhea with good prognosis despite severity. Atypical HUS (aHUS) has incidence projected at 0.53 per million. Here we focus on etiologies related to complement dysregulation. AHUS is a chronic and progressive disease leading to acute kidney injury (AKI), end stage renal disease (ESRD), and even death. Early treatment with complement blockade (Eculizumab) has improved prognosis. Although a rare disease, this reports 3 cases managed in our institution to highlight the varied presentation and management.

Case Description: Patient A had TMA at 8 months old with proteinuria and progressed to ESRD at 19 years. Renal biopsy showed chronic TMA. This patient received Eculizumab for 4 months after renal transplant. Patient B was diagnosed at 3 years old with acute gastroenteritis, neurologic symptoms, and nephrotic syndrome. Renal biopsy showed acute TMA. Symptoms resolved with Eculizumab. Patient C presented at 10 years old with abdominal pain, gross hematuria, and proteinuria. Renal biopsy showed IgA nephropathy and no TMA lesions. This patient improved without Eculizumab.

Discussion: Despite similarities in presentation, it is vital to differentiate aHUS from HUS as early treatment with Eculizumab is recommended in aHUS to prevent morbidity. Genetics will determine who benefits from this treatment. Mutation in CFH gene is a major cause in up to 25% of cases, has poor prognosis, and requires plasma treatment. Patient B had such treatment and did have a secondary mutation on CFH compared to patient C who did not require treatment. MCP mutations are generally known to be associated with glomerulopathies and have better prognosis. DGKE, a rarely reported mutation, presents in infancy with ESRD by age 20 years and is not known to respond to Eculizumab without a secondary mutation. Extending our review on prior and future cases will give more insight to this very rare disease.

Genetics of Cases

	Patient A	Patient B	Patient C
Major genetic mutation for gene mutation on Membrane cofactor protein (MCP, Complement factors I, B, H, CFHR4-6, Thrombomodulin, Diacydiacylglycerol kinase epsilon (DGKE)	Homozygous nonsense DGKE mutation(c.966G>A, p.Trp322StopiExon6	Heterozygous missense variant (c.1058C>T, p.Ala353Val) Exon 8 MCP/CD46. Homozygous polymorphism (IVS9-78 G>A) MCP intron	Heterozygous, missense variant (c.1058C>T, p. Ala353Val) Exon 8 MCP/CD46. Homozygous polymorphism (IVS9-78 G>A) MCP intron
Minor genetic mutation(s)	Heterozygous missense variant of PLG (c.112A>G, p.Lys38Glu) on Exon2, (c.1469G>A, p.ARg49 Gln) on Exon 12. Heterozygous MCP/CD46	Heterozygous for CFH C>T polymorphism	Heterozygous missense variant (c.754G>A, p.Gly252Ser) CFB exon

FR-PO621

A Case of Familial Infantile Nephrotic Syndrome Secondary to Membranous Nephropathy

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Introduction: Infantile nephrotic syndrome (NS) is defined as NS onset between 3-12 months of life. It is often caused by genetic alterations of proteins involved in forming the podocyte slit diaphragm and glomerular basement membrane. Over 95% of cases are autosomal recessive and can be attributed to mutations in NPHS1, NPHS2, NPHS3, WT1, and LAMB2. Biopsy findings are usually negative for immune deposition. In very rare cases membranous nephropathy causes infantile NS; however, there are no documented cases of dominant inheritance. We describe a case of familial infantile NS with a variable histologic phenotype and atypical inheritance pattern.

Case Description: A 9-month-old male presented with 2 weeks of diffuse swelling. He had massive proteinuria with a urine protein: creatinine ratio of 22.18. His renal function, complement levels, metabolic work-up and ANA were unremarkable. Family history included a half-brother (same mother) with steroid resistant NS who presented at 1 year of age and died of sepsis at 2 years of age 8 years prior to this case. The half-brother had a kidney biopsy revealing type III membranoproliferative glomerulonephritis but genetic

evaluation was not sent. Genetic evaluation on our current patient is pending; however, because of the biopsy findings of the half-brother, a biopsy was performed and consistent with membranous nephropathy. Immunofluorescence was positive for glomerular labeling of IgG (3+), IgA (2+), and C3 (4+). Additionally, glomerular capillary loops diffusely labeled with PLA2R (3+) antibody and tubular basement membranes labeled with IgG in a granular pattern. Patient currently maintains normal albumin levels on albumin infusions, furosemide, and ACE-inhibition.

Discussion: Infantile membranous nephropathy with tubular basement membrane antibodies is not currently reported in the literature. Some pediatric case reports exist but staining of the tubular basement membranes with IgG is typically in a linear pattern. The granular pattern seen in our patient is very unusual and usually seen in patients with SLE. Familial cases of these findings have not been reported. The presence of NS in half-brother suggests a dominant inheritance pattern and may suggest a novel gene mutation for infantile NS. The half-brother with a different histological pattern suggests a variable phenotype.

FR-PO622

Renal Manifestation in a Patient with Seckel Syndrome: An Interdisciplinary Challenge

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Introduction: Seckel syndrome (SCKL) ist the extremly rare manifestation of an proportionate dwarfism, presenting with microcephaly, osteodysplasia, bird head-like appearance and psychomotorical retardation. Approximately 20 cases worldwide are described. This genetically heterogeneous syndrome ist inherited autosomal-recessive and the gene located on chromosomal region 3q22.1-q24 (OMIM no. 210600). A renal manifestation is not described so far.

Case Description: We present the case of a 34 years old Lebanese woman diagnosed with Seckel syndrome in early childhood. Parents are first degree relatives. Intrauterine growth retardation was observed, several other family members are diagnosed with unclear dwarfism, but nobody else with Seckle syndrome. Birth weight was 1500 g (< 3rd percentile, gestational age 36 weeks). Besides the typical stigma of the syndrome, the patient did well and the family doctor in Lebanon was not seen on a regular basis. A chronic Hepatitis B infection remained clinically unapparent and was not treated. The family moved to Germany when the girl was 16 years old. The patient was first seen in our hospital at the age of 34 years presenting with a first transitorily ischemic attack and dexter hemiparesis. Further laboratory results revealed a so far unapparent chronic renal failure. Kidneys were dysplastic with volumina of 17 and 23 ml. Due to the low weight of 15.0 kg and a height of 107.6 cm, peritoneal dialysis was initiated by the paediatric dialysis department. Besides several internal, neurological and gynecological ailments such as progessive heart failure and dysmenorrhea, the patient remained under paediatric care due to the habit. Continuous cyclic peritoneal dialysis was continued for 5 years, the patient did well and was listed as kidney recipient with Eurotransplant. A second ischemic attack and severe heart failure with shortening fraction < 10% occured in April 2018 and the patient passed away few days later.

Discussion: Take-away lesson: Regardless the age, treatment of multi-morbid patients with rare diseases is an enormous interdisciplinary challenge. Preservation of quality of life has highest priority and needs individual definitions and solutions.

FR-PO623

A 5-Month-Old Female with One Week of Anuria

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Introduction: Anuric AKI is typically associated with worse outcomes than AKI with preserved urine volume. Anuria usually suggests obstruction, but it can also be seen in ATN or AIN. Acute vascular catastrophe can also cause anuria; however, it must affect both kidneys or a single functioning kidney.

Case Description: We present the case of a 5-month-old, ex-24-week female transferred to our PICU from an outside hospital NICU with anuria. Ten days prior to transfer the patient's creatinine had risen from 0.3 to 2.0 in five days with oliguria, and seven days prior to transfer the patient was noted to be anuric. A renal US demonstrated obliteration of the renal venous flow suggestive of thrombosis of the IVC and bilateral (BL) renal veins as well as high resistive flow in the main renal artery. Upon admission, the patient had a BUN of 219 mg/dl and creatinine of 6.8 mg/dl. She was placed on CRRT. A repeat US confirmed IVC and BL renal vein thrombi, so a heparin drip was started. Subsequent catheterization demonstrated BL renal artery thrombi as well, so the patient underwent mechanical thrombectomy of her IVC and right renal vein in addition to site-directed TPA to her IVC, renal veins, and renal arteries. Ultimately, anticoagulation was not sustainable due to the development of severe coagulopathy, so the decision to withdraw support was made. The etiology of this patient's BL renal artery thrombi is still unclear. Our patient had a normal hypercoagulability workup; however, she had multiple central venous lines placed, including a catheter placed immediately before her creatinine began to drastically rise. In addition, she had a known PFO. Therefore, the most likely etiology of in this patient was central-line associated thrombus formation.

Discussion: Renal vascular occlusion leads to renal infarct in hours as collateral vasculature can only maintain adequate perfusion for a short period of time. Therefore, early diagnosis and treatment is imperative. Treatment is controversial and depends on the acuity of the situation. Most patients are treated with systemic anticoagulation. In recent reports, supportive care is recommended for unilateral vascular occlusion without extension into the IVC where thrombolytic agents were used for bilateral cases. The long-term benefit of this approach is still unclear.

FR-PO624

LOANing a Kidney: Role of Whole Exome Sequencing (WES) in Diagnosis of Microscopic Hematuria in Potential Kidney Donors

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Introduction: Kidney donors with microscopic hematuria present a particular challenge to transplant clinics, with some advocating for donor kidney biopsies. Only those with no glomerular lesions by biopsy are deemed to be suitable donors. We used WES instead of a more invasive kidney biopsy to determine a donor's eligibility for transplant. Subsequent confirmatory testing in her sibling, the recipient, led to an unexpected finding.

Case Description: A 62-year-old French Canadian woman was referred to our transplant center for evaluation as a potential kidney donor to her 60-year-old younger sister with ESRD from biopsy proven FSGS. Years earlier, their mother had also developed ESRD of unknown etiology. Routine evaluation of the donor showed microscopic hematuria. Further inquiry revealed a long-standing history of microscopic hematuria in at least 3 other first degree family members. This prompted WES of the potential donor. An autosomal recessive homozygous variant (cA740G) in the INVS gene, associated with nephronophthisis was found. This variant was classified a variant of unknown significance (VUS). Her sister, the potential recipient, was also found to have the same homozygous mutation. However, in addition to his mutation, a likely pathogenic frameshift variant in the COL4A4 gene (P1235fs) was also found to be present. This led to a reformed diagnosis of autosomal dominant Later Onset Alport Nephropathy (LOAN) in the proposed recipient and cleared her sister for donation.

Discussion: COL4A4 mutations can differentiate the patients with familial microscopic hematuria into benign familial hematuria or LOAN presenting histologically as FSGS. About 25 % of patients above the age of 50 with COL4A3/A4 mutation, who are labelled as having thin basement membrane nephropathy, have been found to have proteinuria, hematuria, hypertension and progression to ESRD making this differentiation improtant. This case highlights the importance of WES in differentiating various familial microscopic hematuria syndromes and helps obviate the need for renal biopsies, especially in patients being considered for transplant.

FR-PO625

The Clinical Impact of Whole-Exome Sequencing by Japan's Initiative on Rare and Undiagnosed Diseases (IRUD) Project on Renal Genetic Diseases

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Introduction: There exist many patients who are suffering from rare, undiagnosed kidney diseases. In 2015, the Japan Agency for Medical Research and Development (AMED) launched the Initiative on Rare and Undiagnosed Diseases (IRUD). IRUD is a national project to analyze whole-exome sequence by using next-generation sequencer.

Case Description: Case 1: A 30-year-old woman, who was diagnosed with Retinitis Pigmentosa, developed renal dysfunction (serum creatinine level, 4.8 mg/dl). She had hypokalemia and metabolic acidosis, and her 31-year-old brother also had same symptoms and was receiving hemodialysis. Her brother was suspected of having Nephronophthisis and the genetic examination was performed but could not find the *NPHP* gene mutation. Therefore, we examined exome sequencing by IRUD. By genetic analysis, she had compound heterozygous missense variants in *ALMS1* gene c.[4331A>T];[7973C>G] which were also found in her brother, but it seemed atypical presentations as Alstrom syndrome because they did not show neither obesity nor type 2 diabetes. Case 2: A 57-year-old man, who was diagnosed with hematuria 37 years ago, developed proteinuria and renal dysfunction (serum creatinine level, 3.5 mg/dl). Her mother and younger sister also had hematuria and proteinuria and his three sons also had hematuria. From his family history of renal disease including women, Alport syndrome which is probably due to *COL4A3* or *COL4A4* mutation was suspected. Exome sequencing found deletion and missense variants in *COL4A4* gene c.[1323_1340del]; [2045A>G] in the patient. These mutations had not been reported so far as responsible genes in Alport syndrome.

Discussion: These genetic mutations found in the two cases were predicted to cause the phenotypes of diseases. Whole-exome sequencing by IRUD is a powerful tool for diagnosis of rare and atypical renal genetic diseases. Sharing and accumulating the genetic data of diseases will be important for further elucidation of the pathology.

FR-PO626

Proximal Tubule Histopathologic Variability in Renal Tubular Dysgenesis: A Case Report

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Introduction: Renal tubular dysgenesis (RTD) is a rare autosomal recessive disorder that presents with antenatal oligohydramnios and anuric renal failure, despite normal renal sonography. Mutations of 4 genes that code for integral proteins of the renin-angiotensin system (RAS) are responsible for RTD. The function of these proteins is necessary for proper fetal renal tubular development. The pathologic hallmarks of RTD include a

paucity of proximal tubules (PT) with aberrant developmental features, detectable by light microscopy and immunohistochemistry (IHC).

Case Description: A 32-week gestational age neonate delivered by urgent C-section for prolonged rupture of membranes and oligohydramnios had anuric renal failure since birth and severe hypotension refractory to vasopressors. Imaging revealed a normal renal sonogram and a large anterior skull ossification defect. Blood tests revealed markedly low renin activity, but normal cortisol, aldosterone, and angiotensin converting enzyme levels. Review of renal biopsy performed on DOL 20 revealed a paucity of PT. In contrast to prior reports, several developmentally mature PT were detected that stained positive with IHC targeted for PT-specific markers CD10 and CD15. Genetic confirmation was sought on DOL 23. The patient had a homozygous nonsense mutation in the *REN* gene, c.127C>T, which results in termination of coding of transcripts at the level of the pro-peptide of renin. This pathogenic mutation, which prevents any renin production, was previously identified and described in another patient with RTD.

Discussion: This case brings to question whether there exists a meager degree of biological redundancy in the fetal RAS that may obscure correlation of genotype and phenotype. For example in this case, might there be alternate enzymes (other than renin) capable of activating RAS? Recognition of the mild histopathologic variability in these rare cases supports early genetic testing for RTD in neonates with unexplained anuria. Furthermore, the finding of relatively mature PT in this case, associated with a mutation that prevents any renin production, suggests a greater complexity of the biology of the fetal RAS than currently appreciated.

FR-PO627

A Surprise Diagnosis: Oxalate Nephropathy

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Introduction: Hyperoxaluria can cause acute kidney injury (AKI) or chronic kidney disease (CKD) from oxalate crystal deposition. We present a surprising diagnosis of oxalate nephropathy in an elderly female.

Case Description: A 75-year-old female presented with dyspnea, weight gain, and edema. She had diastolic heart failure, CKD stage 3 attributed to insulin-requiring diabetes, and prior partial colectomy for ulcerative colitis. Furosemide was increased two weeks prior because of symptoms, but no other medication changes were noted. Admission serum creatinine was 8.1 mg/dl, (1.6 mg/dl baseline). AKI was attributed to cardiorenal syndrome, but she failed to improve with intravenous furosemide, and hemodialysis was started. Echocardiography showed mild left ventricular hypertrophy and atrial dilation, EF 60-65%, and grade 2 diastolic dysfunction. Protein and moderate blood were noted on urinalyis, but casts and crystals were not reported. Renal ultrasound found mild asymmetry in kidney size, few simple renal cysts, and hyperechoic cortices. Serum complement levels, anti-GBM, ANA, ANCA, urine protein electrophoresis and serum immunofixaton studies were normal. Kidney biopsy revealed acute tubular necrosis with prominent oxalate crystals, urine eosinophils, mild fibrosis, and interstitial changes consistent with oxalate nephropathy. The patient reported consumption of one gallon of iced tea daily for 20 years. While on hemodialysis, plasma oxalate was 15.4 micromol/L (normal <11) with urinary oxalate excretion of 11.4 mg/24 h (normal <40 mg/24 h). Calcium supplementation was started and she was instructed to maintain high water intake, avoid iced tea consumption, and begin a low oxalate, low vitamin C, calcium-enriched diet. The patient remains on hemodialysis post-discharge.

Discussion: Hyperoxaluria can be primary from enzymatic deficiency, or secondary from gastrointestinal disease, malabsorption syndromes, excessive vitamin C ingestion, and ethylene glycol toxicity. However, ingestion of oxalate-rich foods, including spinach, beets, rhubarb, peanuts, star fruit, and iced tea should also be considered. Despite documented excess dietary oxalate intake in individuals in the United States, reports speculate that oxalate nephropathy is under-recognized. Physicians should consider oxalate nephropathy in the right clinical scenario, in this case, excessive iced tea and underlying gastrointestinal disease.

FR-PO628

ESRD Secondary to Oxalate Nephropathy Post Whipple's Procedure: A Report of an Interesting Case

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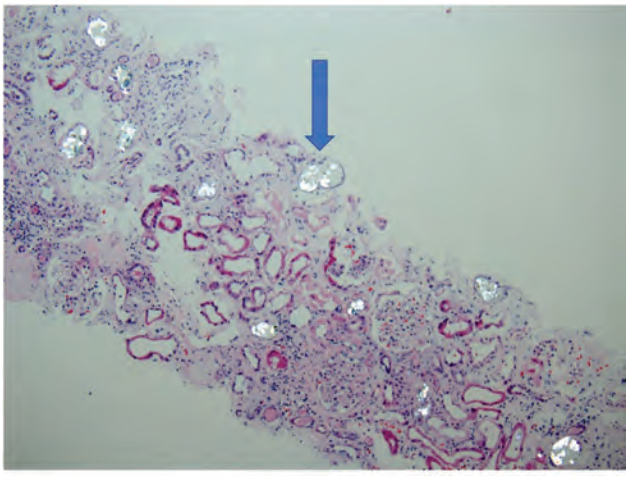
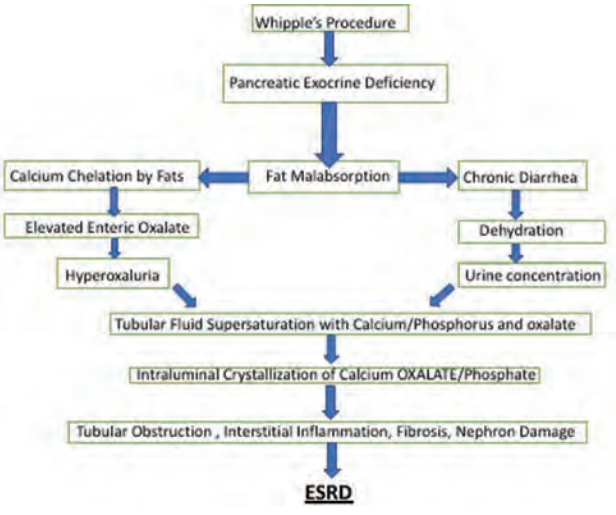
Introduction: HTN & DM are the two most common causes of ESRD. Secondary Oxalate Nephropathy is one of the rare causes of ESRD, We present an interesting case of ESRD secondary to oxalate nephropathy resulting from Pancreatic Exocrine deficiency.

Case Description: 77-year-old male with recently diagnosed HTN, presented to ER with generalized weakness, nausea, vomiting & swelling. Initial labs showed BUN of 109mg/dl, creatinine of 14.8 mg/dL. No recent IV contrast exposure, no NSAIDs use, no evidence of hematuria, had 0.5 g of proteinuria & negative urine eosinophils. Immune workup was negative. Renal ultrasound was negative for hydronephrosis. He was urgently dialyzed & later on underwent kidney biopsy which showed evidence of oxalate nephropathy & significantly advanced fibrosis. Patient had history of Whipple's procedure in 1996, he was not on any pancreatic enzyme supplementation. He had history of chronic recurrent diarrhea. His serum lipase was <10 U/L & serum Albumin was 2.8mg/dl. He was deemed ESRD & continued hemodialysis. He was started on pancreatic enzymes and his diarrhea improved.

Discussion: Our case represents one of the rare complications of pancreatic exocrine insufficiency resulting from Whipple's procedure. Pancreatic insufficiency is associated with fat malabsorption causing calcium chelation. Resulting Hyperoxaluria causes oxalate nephropathy. Our case presents a rare yet unfortunate long-term complication of pancreatic insufficiency post Whipple's procedure. Patients especially after Gut related surgeries should be monitored for any hyperoxaluria which can result in lifelong morbidity.



Oxalate Crystals Under Polarized Light in Renal Biopsy specimen



Mechanism of Oxalate Nephropathy

FR-PO629

Oxalate Nephropathy in Patient with Diabetic Kidney Disease

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Introduction: Secondary oxalate nephropathy is an uncommon condition that causes acute kidney injury with the potential for progression to end-stage renal disease. The diagnosis is based on high clinical suspicion and the findings from kidney biopsy.

Case Description: 54 year old female with significant past medical history for Diabetes mellitus type I since age of 10, proliferative diabetic retinopathy, diabetic kidney disease, CKD stage 3b, HTN. She presented into the ED with abdominal pain, nausea and vomiting for less than 1 week. Laboratory work showed severe deterioration of her kidney function BUN 129 mg/dl and serum creatinine of 10.4 mg/dl and severe anemia – hemoglobin 6.6 g/dl. Baseline creatinine of 1.82 mg/dl, eGFR 31 ml/min one month prior. Furosemide and Enalapril were discontinued, rehydration therapy was initiated in the next two days without significant improvement in renal function, The evaluation for secondary causes for worsening of the renal function were negative: C3 and C4, hepatitis status, free light chains, UA – bland sediment <5 RBC, 5-10 WBC, no casts, proteinuria +, 34 mg/24 h. The patient was started on hemodialysis. Because of relatively fast progression of the renal failure inconsistent with diabetic nephropathy a renal biopsy was performed. The histological findings were consistent with widespread tubular oxalate crystal deposition, diffuse and nodular diabetes glomerulosclerosis and severe arterial sclerosis. After that a detailed history of her dietary habits was taken. The patient acknowledge for recent change

in her diet habits including increased intake of green leafy vegetables, copious amount of green tea and almonds.

Discussion: A diet rich of oxalate can cause irreversible acute oxalate nephropathy, which can lead to ESRD in a patient with impaired renal function. Patients with predisposing conditions such as CKD and diabetic kidney disease are particularly at risk. Heightened awareness of the potential for acute oxalate nephropathy following a high green diet in susceptible individuals is needed to reduce the incidence of this preventable condition

FR-PO630

Acute Renal Failure Due to Dietary Hyperoxaluria

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Introduction: We present a case of rapid drop in GFR attaining CKD stage 5 from CKD stage 3 caused by excessive dietary oxalate intake.

Case Description: A 51-year-old male with the PMH of chronic kidney disease stage 3b, benign prostatic hypertrophy and kidney stones was admitted in February 2018 for unintentional weight loss, abdominal discomfort, and a creatinine of 6.9. Patient reportedly lost 14 lbs over 4 months. Detailed interviewing revealed a recent change in his diet. He was on a "Microbiome-intense diet" for two months in December 2017 to accompany his wife in her weight loss regimen. This diet included whole meals of raw fruits and vegetables, and later included eggs and cheese, as well as a lot of almonds, spinach, kale and berries. Pertinent positives on physical exam included BP of 100/60 mm Hg and dry mucous membranes. Labs: BUN 111, Creatinine 6mg/dL (baseline 2.0) and eGFR 8 mL/min/1.73m2. Chart review revealed a history of oxalate kidney stones in 2014 with high oxalate excretion. Prior CT abdomen/pelvis without contrast showed bilateral non-obstructing renal stones. Patient denied taking any herbal products, over the counter drugs including NDSAIDs, or any "diet pills". Family history was negative for renal stones. 24-hour urine collection for stone analysis demonstrated high urinary oxalate excretion. Renal biopsy showed chronic interstitial nephritis, with intraparenchymal deposition of oxalate and phosphate He was discharged with recommendations to stop the microbiome diet and restart potassium citrate.

Discussion: Oxalate is widely found in both plants and animals and is normally excreted by the kidneys.. Increased oxalate excretion in the urine causes supersaturation and deposition of calcium oxalate crystals in the renal tissue. The most common cause of hyperoxaluria is excessive oxalate absorption from the gastrointestinal tract, enteric hyperoxaluria from fat malabsorption or excessive endogenous oxalate production (primary hyperoxaluria). The diagnosis of dietary hyperoxaluria in this patient was suggested by the patient's extreme diet which altered the gut flora and consequently, the oxalate homeostasis. Most commonly implicated vegetables and fruits are peanuts, celery, carrots, parsley, beets, spinach, nuts and rubarb. As patient's GFR fell, his serum oxalate increased leading to more deposition.

FR-PO631

Gastrointestinal Bleeding Secondary to Gastric Mucosal Calcinosis in an ESRD Patient

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Introduction: Gastric mucosal calcinosis (GMC) is a pathological process of calcium salt deposition in normal tissues from prolonged periods of hypercalcemia or hyperphosphatemia. The gastric mucosa, kidneys and lungs are preferred sites for deposition. We describe a rare case of upper gastrointestinal bleeding (UGIB) secondary to GMC in a peritoneal dialysis (PD) patient.

Case Description: A 21 year old male with a history of ESRD secondary to anti-glomerular basement membrane disease on PD was transferred to our facility for work up of an UGIB. He has a complex cardiac history including congenital transposition of the great arteries requiring surgical repair in childhood and left ventricular thrombus on warfarin. He was listed for a combined heart-kidney transplant. He presented to the emergency department due to a syncopal episode which was attributed to hemorrhagic shock upon discovery of a hemoglobin 5.2g/dL from a baseline 9 g/dL and guaiac positive stools. His INR was 5.9 and his coagulopathy was reversed and transfused blood. An EGD demonstrated non-bleeding gastric ulcers which were biopsied. Pathology revealed diffuse calcification of the lamina propria with a mononuclear inflammatory infiltrate diagnostic of GMC. On review of his dialysis and bone mineral disease (BMD) history he a low average transporter without residual renal function on PD for 3 years. PD prescription was 10 hours of CCPD with 8 exchanges, fill volume of 1.8L of 2.5% dextrose dialysate per exchange, with a last fill of 1.5L of 2.5% dextrose. His last Kt/V was consistently > 1.7 for the last year. His serum calcium levels have been within goal but he has been hyperphosphatemic with average level of 8-9mg/dL and PTH 501 pg/ml attributable to noncompliance with multiple calcium and non-calcium binders. He had no signs of calciphylaxis. Despite these findings, he continues to do well post discharge.

Discussion: We report a unique case of GMC in the setting of hyperphosphatemia in an ESRD patient with a dialysis vintage of only 3 years and an adequate Kt/V. On literature review, there is no other reported cases of GMC in a PD patient and only one reported case in a hemodialysis patient. Our case also highlights the importance of recognizing GMC as an possible etiology of UGIB in ESRD patients, especially those with poorly controlled BMD.

FR-PO632

Spontaneous, Non-Traumatic Rupture of an Acquired Renal Cyst in ESRD Patient with Large Retroperitoneal Hemorrhage - A Case Report

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Introduction: Acquired Cystic Kidney Disease (ACKD) is asymptomatic in most patients. However, the renal cyst may be associated with back pain, infection, and malignant transformation. Cyst rupture and bleeding secondary to ACKD are considered unlikely because of reduced renal parenchymal blood supply in atrophic kidneys. We present a case of an End Stage Renal Disease (ESRD) patient with a previously unrecognized cystic condition who presented with extensive retroperitoneal hemorrhage.

Case Description: A 31-year-old male with the medical history of ESRD for 5 years due to hypertension and no history of smoking presented with acute onset of left flank pain. Patient denies any traumatic event prior to the onset of pain. Blood work showed a hemoglobin of 9.5 g/dl with normal coagulation profile and platelets. Imaging showed large heterogeneously attenuating, ruptured left renal/perinephric hematoma measuring 10x12x27 cm occupying most of the left retroperitoneal space and extending across the midline. There were multiple foci of active extravasation and no normal renal parenchymal tissue was visualized. (Figure-1). The patient had an emergent fluoroscopy guided coil and Gelfoam embolization of the superior and inferior pole left renal arteries with successful hemostasis. The patient remained hemodynamically stable for the rest of the stay.

Discussion: To our knowledge, it is the first reported case of ACKD associated massive hemorrhage. Although rare, hemorrhage due to ruptured renal cyst should be suspected when an ESRD patient presents with acute back pain and symptoms of shock. Screening for ACKD has been proposed but larger scale trials are required for consensus and guideline development.

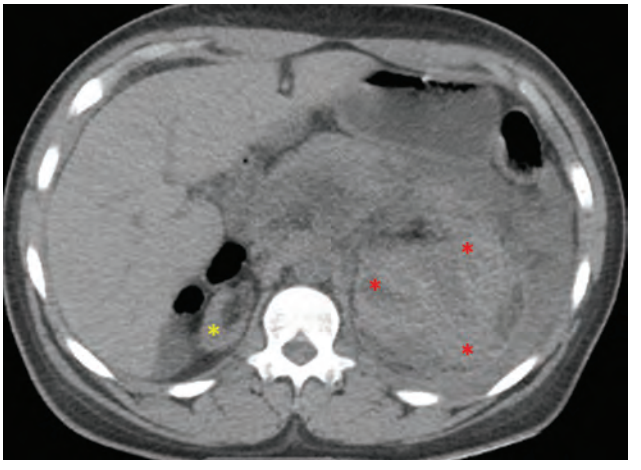


Figure 1: CT scan image. Red asterisk on the left of the patient indicating the area of retroperitoneal hemorrhage. Note right atrophic kidney (yellow asterisk).

FR-PO633

A Concrete Cause of Abdominal Pain

Jimmy D. Gentry, Peter Hanna, Rishi Naik, Lori Wanko, Edward Gould. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Sevelamer hydrochloride is a non-calcium based phosphate binder routinely used in the treatment of hyperphosphatemia in patients with impaired renal excretion of phosphorus. Sevelamer is commonly associated with mild gastrointestinal (GI) symptoms - most commonly, constipation, nausea and bloating. Here we describe a case of a more serious sevelamer concretion masquerading as a gastric malignancy in a patient presenting with abdominal pain.

Case Description: Our patient is a 48 year-old female with a history of hypertension, DM2, morbid obesity, and ESRD on hemodialysis three times a week, who presented with sharp left flank pain of two weeks duration as well as nausea and early satiety. A contrasted CT scan raised concern for invasive gastric malignancy. She underwent endoscopy with biopsy for diagnostic purposes. Visual examination revealed a discolored infiltrative mass. Histologic examination revealed irregularly shaped "fish-scales" consistent with sevelamer crystals and other debris all consistent with sevelamer concretion. After multidisciplinary discussion the decision was made to forego surgical removal and treat conservatively. Prior to presentation, she had been on 3200mg three times daily of sevelamer; this was discontinued with plan for repeat EGD to ensure resolution of the gastric mass and healing of the gastric ulcer.

Discussion: Resin-based phosphate binders such as sevelamer can crystallize leading to the formation of concretions. Since the first description of this in 2013 there have been seventeen reported cases of GI lesions attributable to sevelamer. Eighty-one percent of these were in the intestine and the most frequent presentation is GI bleeding. Pathology ranges from acute inflammation to chronic mucosal injury, strictures, ulcerations, and necrosis, many of which show sevelamer at least in close proximity to inflammation or ulceration on histology. Gastric involvement is rare, and when present is usually in the form of an ulceration. We could not identify previous reports of a gastric mass due to sevelamer. Given the frequency of sevelamer use, it is critical for clinicians to remain attentive to the

possibility of sevelamer concretions as a cause for GI symptoms and pathology in patients using it for phosphorous elimination.

FR-PO634

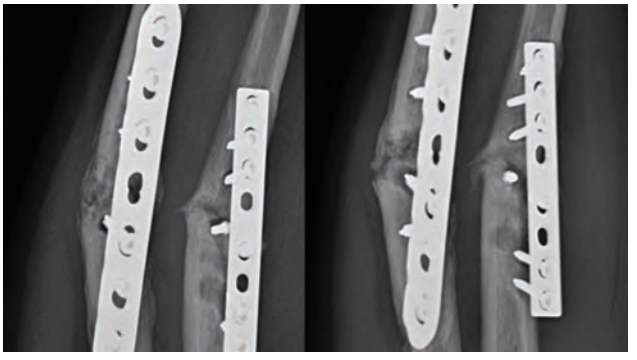
Normohormonal Primary Hyperparathyroidism Presenting as Fracture Non-Union

Amita Maibam, Madhumathi Rao. *University of Kentucky, Lexington, KY.*

Introduction: Primary hyperparathyroidism (PHPT) is a rare cause of poor fracture healing. We present a patient with osteopenia and fracture non-union with mild hypercalcemia in the setting of hydrochlorthiazide (HCTZ) treatment and normal intact parathyroid hormone (iPTH) level.

Case Description: A 54-year-old Caucasian female with history of hypertension, hypothyroidism and depression presented with progressive pain and deformity of the left forearm, 8 months after open reduction and internal fixation of fractures of left radius and ulna. X-ray showed fracture non-union (Figure:1, left); laboratory evaluation revealed mild hypercalcemia (10.5 mg/dl), non-suppressed iPTH (41 pg/ml), and elevated serum creatinine (1.3 mg/dl). Repeat serum calcium after stopping HCTZ, remained 10.5 mg/dl though iPTH increased to 64 pg/ml (range 14-66) Urine calcium was 851 mg/d and bone densitometry showed osteopenia of lumbar spine. A right inferior parathyroid adenoma was demonstrated on nuclear scan establishing a diagnosis of PHPT. The remainder of the work up for hypercalcemia was also significant for a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) confirmed by bone marrow aspiration. Patient underwent parathyroidectomy with prompt reversal of biochemical abnormalities. At 4 weeks after surgery, repeat calcium was 9.6 mg/dl and iPTH level 27 pg/ml; bone pain was improved, and forearm X-ray showed evidence of healing with new bone formation and reversal of cystic changes (Figure:1, right).

Discussion: Normohormonal PHPT accounts for about 5 % of parathyroid explorations and should be considered in patients with fracture non-union and should be corrected before any further orthopedic intervention is undertaken. Mild hypercalcemia in the setting of thiazide treatment and normal iPTH levels may confound the diagnosis and require a high degree of suspicion. The reported association between PHPT and MGUS was also notable in this patient.



Left Forearm XRAY showing fracture site before (left) and after (right) parathyroidectomy.

FR-PO635

Lytic Lesions in A Dialysis Patient: It's Not Always Cancer

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Introduction: Secondary hyperparathyroidism is a known complicaiton of end stage renal disease (ESRD). Increased production of parathyroid hormone (PTH) leads to excess osteoclast activity and fibroblast proliferation. In severe cases, patients are at risk of developing bone lesions called brown tumors.

Case Description: A 31 year old female with history of Hodgkins lymphoma treated with umbilical cord transplant and ESRD due to hypertension on dialysis for six years, presented for kidney transplant evaluation. She had no systemic complaints and an unremarkable physical exam. Laboratory values were significant for elevated PTH 1874 pg/ml. As part of her transplant evaluation, she underwent CT scan showing multiple bony lesions concerning for malignancy. PET scan confirmed FDG avid lytic lesions (Figure 1a). Biopsy of the right iliac crest (Figure 1b) revealed a giant cell rich lesion with osteoclasts and hemosiderin pigment deposition. Despite being medically managed with cinacalcet and doxercalciferol, the patient developed diffuse lytic bone lesions consistent with brown tumor of hyperparathyroidism.

Discussion: Brown tumor is a rare finding in ESRD patients and has an estimated incidence of 1.7 %. Clinically, they can be silent unless there is compression of surrounding structures. CT or PET imaging reveals the lesions, but histopathology is necessary to identify the giant cell granulomas with brown colored hemosiderin deposits from which the tumor gets its name from. Treatment begins with pharmacologic therapy to lower PTH, but can be ineffective, and parathyroidectomy and evaluation for kidney transplantation should be considered. This case underlines the importance of recognizing Brown tumor as a complication and important differential diagnosis of a patient with imaging showing lytic lesions. Prevention and early diagnosis are essential to reduce the prevalence of high turnover bone disease.

Figure 1a: PET scan demonstrating multiple FDG avid lytic lesions of the scapula, clavicle, sternum, femoral condyles, and right iliac crest. 1b: Right iliac crest histopathology with giant cell rich lesion comprised of osteoclasts, fibroblast like cells, and hemosiderin pigment deposition.

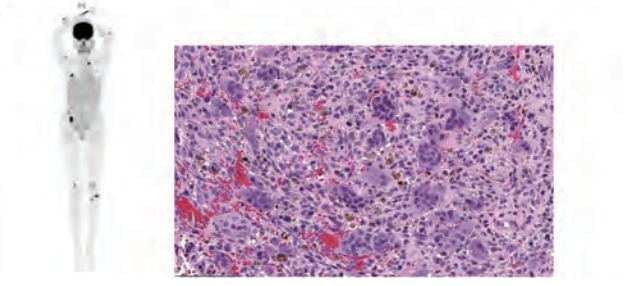


Figure 1

FR-PO636

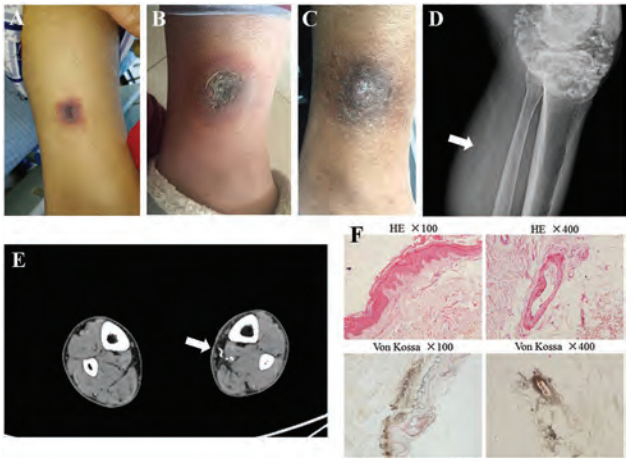
A Case Report of Early Calciphylaxis Based on Single Cutaneous Erythema and Literature Review

Yuqiu Liu, Haifeng Ni, Xiaoliang Zhang. *Institute of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, China.*

Introduction: We analyzed the clinical information of a patient with single cutaneous erythema leading to calciphylaxis, and reviewed literatures. Improve clinical understanding of calciphylaxis to reduce the occurrence of missed diagnosis and misdiagnosis.

Case Description: A 36-year-old male patient with hemodialysis for 5 years had focal purple-black skin changes in the left leg recently(Fig. A). Then the wound was enlarged and ulcerated with mild pain(Fig. B). X-rays showed the large vessel calcification(Fig. D). There was multiple subcutaneous small vessel calcification by further plain CT scanning of suspicious vessel calcification area. In particular, small blood vessels deep in the skin lesions were significantly calcified(Fig. E). Imaging evidence strongly suggests a diagnosis of calciphylaxis. A skin biopsy was performed on the rough skin of the patient's left lower leg. The pathology showed extensive calcium deposits in the subcutaneous soft tissue with calcification of the small vessel wall(Fig. F). The calciphylaxis was diagnosed and was still in the early stage of disease. After comprehensive treatment based on sodium thiosulfate for three months, the necrosis area was gradually scabbed and the wound healed(Fig.C).

Discussion: Calciphylaxis is a fatal vascular disease characterized by systemic arteriole calcification with endothelial destruction and thrombosis, resulting in peripheral tissue ischemic necrosis. This patient presented with a single, early-onset skin lesion and lacked typical skin lesions. Imaging examinations have a high guiding significance in the diagnosis of calciphylaxis in this case. Recently, the prevalence of calciphylaxis in dialysis patients has been increasing, and a combination of diagnostic techniques has helped early detection. Skin biopsy helps diagnose early and atypical patients, while imaging is a non-invasive test that can be used as an early screening and efficacy monitoring tool.



FR-PO637

Dramatic Improvement in Dialysis Related Tumoral Calcinosis Following Renal Transplantation

Win Win Moe, Kamal Nayyar, Ruby Zhao, Nobuyuki (Bill) Miyawaki, James Drakakis. *NYU Winthrop Hospital, Mineola, NY.*

Introduction: Tumoral calcinosis (TC) is an uncommon and serious complication of dialysis. It is usually associated with high serum calcium and phosphorus product. Management of this ectopic calcification syndrome involves dietary phosphorus restriction,

non-calcium based binders, low calcium dialysis, and parathyroidectomy. Here, we present a case of extensive TC which failed to respond to conservative measures in a patient on long-standing dialysis, only clinically and radiographically improved after a successful renal transplant.

Case Description: A 56 year old male with history of HIV on HAART therapy with resultant end-stage-renal-disease (ESRD) on dialysis for 8 years, presented with hip pain and difficulty ambulating. CT scan revealed abundant metastatic calcium deposition within the adductor compartment of the right thigh, enlarging within the vastus intermedius and iliopsoas tendon and invading the femur. Biopsy revealed benign fibrous tissue and marked granular calcification. He was initially on hemodialysis (HD) but later switched to peritoneal dialysis (PD) due to limited vascular access. While on PD, clearances were sub-optimal and phosphorus ranged 8-10 mg/dL. PTH was elevated (300-400 pg/mL) despite attempts to suppress with calcimimetic. He then switched back to an intense HD regimen via a femoral dialysis catheter and was given low calcium dialysate and sodium thiosulfate. However, he did not improve and a request for medical urgency to receive compassionate points on the deceased donor wait list was filed. Shortly after, he received a functioning kidney transplant and imaging began to show resolution. In fact, a CT scan done 3 years later revealed the deposition to be 2.9 x 1.0 x 3.2 cm, compared with14 x 14 x 10 cm at time of initial diagnosis.

Discussion: There is known morbidity associated with extraosseous tumoral calcification associated with ESRD, often carrying with it a poor prognostic significance. Several medical and surgical (i.e, parathyroidectomy) treatment options are available, but responses may be limited. Renal transplantation has been described as being useful to treat TC and several cases of complete dissolution have been reported. This case similarly illustrates success after kidney transplantation and highlights the need for awareness in diagnosis and urgency to help facilitate an effective treatment strategy.

FR-PO638

Calciphylaxis Patient Characteristics and Outcomes: Case Series of 7 Patients

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Introduction: Calcific uremic arteriolopathy (CUA) also known as calciphylaxis is a rare, life-threatening ischemic small-vessel vasculopathy, primarily a complication of advanced CKD or ESRD. The pathogenesis involves intimal hypertrophy and medial calcification, resulting in endovascular fibrosis and thrombosis of small arteries and arterioles. We reviewed historical cases to assess patient characteristics, treatment modalities employed and clinical outcomes.

Case Description: We present 7 cases of calciphylaxis diagnosed between 2013 and 2017. Median age at time of diagnosis was 57.7 (42-76), 57% were male, 57% were Caucasian, 71% smokers, and 100% obese. Patients had been on dialysis for an average of 5.2 years prior to diagnosis. Only 1 patient was on peritoneal dialysis; the rest were on in-center hemodialysis (3 days/week). Comorbid conditions included DM (4/7), HTN (4/7), concomitant anticoagulation with warfarin (2/7), vitamin D analogue (4/7), oral calcium supplements (2/7), and calcitriol (2/7). Calciphylaxis was confirmed by skin biopsy in 7 cases. Mean calcium, phosphorus and PTH levels were 9.15, 5.6, and 322.9, respectively. All patients received sodium thiosulfate 25 mg 3 days/ week, along with increased daily dialysis (average of 5.2 treatments/ week for 4.3 hours over 7.2 months). 5/7 patients were reported to have complete resolution after an average of 7.64 months. One patient continues to receive treatment. Two patients died, including one patient who chose to discontinue dialysis 3.8 years after diagnosis, and the second patient did not tolerate sodium thiosulfate (metabolic acidosis and hypotension) and died from sepsis 8 days after diagnosis. Complications of sodium thiosulfate included metabolic acidosis (6/7), hypotension (4/7), and hypocalcemia (2/7).

Discussion: Previously reported risk factors include high BMI, female sex, DM, PD, higher serum calcium, phosphorus, and parathyroid hormone, and combined therapy with calcium salts and vitamin D, cinacalcet, warfarin and calcitriol. Mortality rate is reported at 27% at 6 months after CUA diagnosis, and 45% at 12 months. Data on the dose and duration of increased intensity dialysis as well as treatment are lacking, and while CUA is associated with a high rates of mortality, we have a 71% survival rate with emphasis on maximizing dialysis (daily).

FR-PO639

Penile Calciphylaxis: A Clinico-Radiologic Diagnosis

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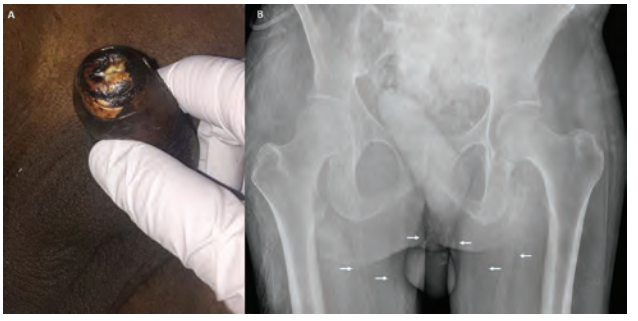
Introduction: Calciphylaxis, also known as calcific uremic arteriolopathy (CUA) is a rare and serious disorder typically seen in ESRD patients that presents with skin ischemia and necrosis and histologically characterized by calcification of dermal arterioles. While most lesions occur on the lower extremities followed by the lower abdomen, rare sites such as breast and penis have been reported. Herein, we present a case of penile calciphylaxis that was diagnosed clinically.

Case Description: A 34-year-old man with end-stage renal disease (ESRD) secondary to diabetes mellitus, on hemodialysis for 2 years was seen for worsening pain and blackening of the skin in the penile region that started a month ago. He denied having any fever, painful urination, discharge from the urethra or unprotected sexual intercourse in the recent past. Physical examination revealed mild edema and superficial necrosis of the foreskin and glans penis [Figure 1A]. Laboratory data demonstrated a high blood urea nitrogen of 100 mg/dL, serum creatinine 12.2 mg/dL, parathyroid hormone (PTH) 400 pg/mL and calcium-phosphorus product of 111 mg/dL. He was not on therapeutic anticoagulation and work up for hypercoagulable disorders was negative. Plain radiographs of the pelvis demonstrated widespread vascular calcification [Figure 1B], suggestive of CUA.

Discussion: High calcium-phosphate product, elevated PTH, hypoalbuminemia, diabetes, obesity, warfarin use, female sex and protein C or S deficiency are among the risk factors for CUA and skin biopsy is the gold standard of diagnosis. However, biopsy is not typically recommended for penile lesions because of the risk for progression of necrosis and therefore, penile CUA essentially remains a clinico-radiologic diagnosis. Treatment includes aggressive risk factor control, intensification of hemodialysis regimen, supportive wound care and administration of intravenous sodium thiosulfate with dialysis, all of which we instituted in our patient. The prognosis remains poor despite treatment and the main cause of mortality in these patients is sepsis.



FR-PO640

Non-Uremic Calciphylaxis: Early Diagnosis of a Rare Entity and Successful Treatment with Sodium Thiosulfate

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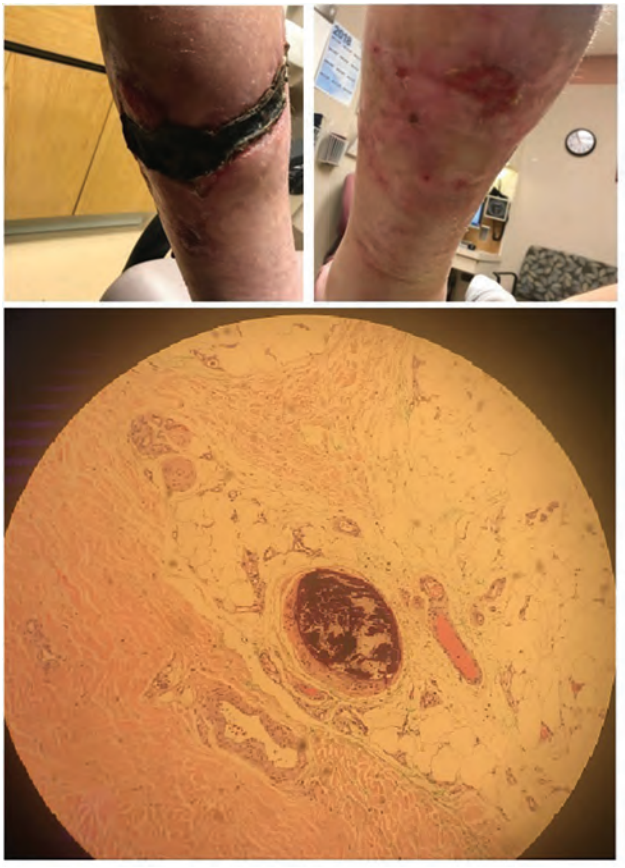
Introduction: Calciphylaxis is a rare cutaneous disease, with varied lesions: from bullae to necrotic ulcers. Pain out of proportion to clinical examination is a distinct finding. Key finding is Vitamin K deficiency, contributing to progressive microvascular calicifcation and microthrombi. Diabetes, liver cirrhosis and patients on warfarin are Vitamin K deficient.

Case Description: A 64 yo male with DM2, HTN and cirrhosis was referred to the Nephrology Clinic for evaluation of AKI, hematuria, nephrotic range proteinuria. Kidney biopsy showed Nodular Diabetic Nephropathy, secondary IgA nephropathy (liver cirrhosis) and ATN. His Ca was 9.6 mg/dl, Phos 4.1 mg/dl, vitamin D 15ng/dl, and PTH 129 pg/ml. Three months after initial evaluation, measured GFR (Iohexol) was 19 ml/min/1.73m^2 and he presented with left lower extremity, painful, necrotic ulcers. Despite surgical debridement, lesions increased in size and he developed new lesions on the right leg. Skin biopsy via telescoping technique showed intraluminal occlusion of small and medium sized vessels with calcified appearing material consistent with calciphylaxis. Sodium thiosulfate was started at 12.5 g twice/week, it was increased to 25 g twice/week and that dose was kept for 7months. Patient lesions improved and thiosulfate was discontinued.

Discussion: This illustrates the importance of an early diagnosis and treatment of non uremic calciphylaxis with attention to “at risk” patients: liver cirrhosis, in our case. The patient is currently been referred for simultaneous liver-kidney transplantation.



Top Left: **Lesion at presentation**Top Right: **Lesion resolved**

Bottom: **H&E**, shows **calcification and fibrointimal hyperplasia**

FR-PO641

A Case of Delayed Onset Hungry Bone Syndrome After Subtotal Parathyroidectomy in ESRD Patient with Secondary Hyperparathyroidism

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Introduction: Hungry bone syndrome (HBS) is an important postoperative complication of parathyroidectomy done for severe hyperparathyroidism of renal origin; occuring in 27.8 to 72% of cases. It is marked by hypocalcemia (most severe in the first 24-48 hrs) associated with hypophosphatemia, hypomagnesemia and elevated Alkaline phosphatase. We are reporting a case where hungry bone syndrome is seen to develop more than one week post-op, and did not respond to standard management despite normal magnesium and Phosphorus levels.

Case Description: 52 yr old male with ESRD on HD underwent subtotal parathyroidectomy for management of severe secondary hyperparathyroidism (PTH 2024 pg/ml) in spite of high dose of cinacalcet and calcitriol. Post -op PTH dropped to 63.5 pg/ml. The lowest reading of Ca was 8.2mg/dl in the immediate post-op period and was treated with Ca and vitamin D analogs as per standard guidelines. Two weeks later patient reported symptoms of tetany on dialysis and serum Ca was 6.8 mg/dl. Serum Phos remained 3.3 -4.5mg/dl range and ALP 282 u/l with a normal Magnesium. Calcium was persistently low despite treatment with IV calcium ; requiring a prolonged hospital stay.

Discussion: HBS is characterised by prolonged and severe postoperative hypocalcemia and hypophosphatemia as a result of extensive and accelerated remineralisation of bone following sudden decrease of parathyroid hormone. This syndrome should be anticipated when there is evidence of severe parathyroid bone disease with marked elevation of serum ALP and PTH levels. Other factors that predict the development of HBS include old age, high BMI, and high pre-op BUN. HBS is seen within 24 hrs of a total parathyroidectomy in patients with SHPT. The post operative fall in serum calcium has been strongly correlated with the severity of bone disease which can be diagnosed only with pre-operative bone biopsy not by serum chemistries. This case shows that patients might develop severe hypocalcemia in the later time despite a normal serum calcium postoperatively. We recommend, patients undergoing total parathyroidectomy should have their serum calcium and phosphate levels closely monitored in the following 2 weeks to safeguard against the development of severe and symptomatic hypocalcemia and to provide guidance on the intensity of calcium supplementation.

FR-PO642

Hyperparathyroidism Induced Erythropoietin Resistance After Successful Renal Transplantation

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Introduction: Resistance to erythropoietin (EPO) in the CKD-ESRD population is pervasive. Common causes include iron deficiency, chronic inflammation, medications and hyperparathyroidism. Most if not all of these conditions resolve after successful renal transplant. Post-transplant anemia can occur due to multiple factors including immunosuppressant medications, dapsone, TMP-SMX, RAAS antagonists, and viral infections (CMV, Parvovirus). We report a case of hyperparathyroidism-induced EPO resistance in a patient which was successfully treated with subtotal parathyroidectomy three-years after her transplant.

Case Description: A 36-year-old woman with a history of ESRD secondary to hypertension underwent a successful deceased donor kidney transplant managed with tacrolimus, mycophenolate mofetil and prednisone complicated by refractory anemia and hyperparathyroidism. Three years post transplantation with baseline creatinine of 1 mg/dL, she continued to require 40,000 units of subcutaneous epoetin alfa twice weekly for refractory anemia. Her hemoglobin oscillated between 6 – 7 g/dL during this time. She underwent an extensive workup that included: multiple iron panels all with >20% saturation, negative parvovirus PCR, and a bone marrow biopsy that showed mild hypocellularity. Her blood pressure management did not include ACEi/ARBs. Her initial immunosuppressive regimen included sirolimus; her anemia, however, persisted after switching to tacrolimus. Her NT-PTH was noted to be consistently above 1750 pg/mL and subsequently referred for parathyroidectomy following a sestamibi scan demonstrating multigland hyperplasia. One month following her parathyroidectomy, her anemia resolved completely and was able to stop epoetin alfa injections.

Discussion: Although hyperparathyroidism is a known cause of EPO resistance in the CKD-ESRD population, it is thought to contribute minimally to the overall burden of EPO resistance. This case highlights that isolated hyperparathyroidism in the absence of other common causes for EPO resistance (iron deficiency, medications, infection/inflammation) can cause severe EPO resistance, and must be addressed when evaluating anemia in renal transplant patients despite stable creatinine.

FR-PO643

Laparoscopic Gastric Sleeve Surgery in a Patient on Peritoneal Dialysis

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Introduction: The high prevalence of obesity along with its potential resulting conditions make obesity a major public health concern. Morbid obesity is a limiting factor for a dialysis patient to obtain a kidney transplant. While an obese patient may elect to undergo bariatric surgery to induce weight loss, there is little data on this type of surgery involving a PD patient. We present a rare case of a patient with end-stage kidney disease (ESKD) on PD who underwent laparoscopic gastric sleeve surgery while maintained on PD.

Case Description: A 66-year-old morbidly obese female patient with ESKD on PD underwent laparoscopic gastric sleeve surgery. Prior to her surgery, she was 124 kg and was on continuous cyclic peritoneal dialysis (CCPD) for 9 hours with 4 cycles of 3000 mL 2.5% dextrose solution with 500 mL icodextrin last fill. Her adequacy prior to surgery was residual renal (RR) Kt/V 0.45 and PD Kt/V 1.56 for a total of 2.01. She cycled the night before her surgery and did not do a last fill. She received clindamycin 600 mg IV perioperatively (allergy to cefazolin) and post operatively, she held PD the first night, then initiated 1000 mL 2.5% dextrose for 6 cycles over 12 hours. At day 5 post operatively, it was increased to 1500 mL for 6 cycles over 12 hours due to low drain alarms. After 3 weeks, it was increased to 2500 mL alternating 1.5% and 2.5% dextrose for 4 cycles over 9 hours. Her adequacy 4 weeks postoperatively was RR Kt/V 1.03, PD Kt/V 1.11, and total 2.15. Two months postoperatively she was 113 kg.

Discussion: One particularly interesting observation regarding this case is the fact that the patient's RR Kt/V improved after her surgery also leading to an increase in her total adequacy. This case illustrates how PD patients undergoing bariatric surgery can successfully be maintained on PD post-operatively without having to transition temporarily to hemodialysis and without sacrificing renal adequacy. Being allowed to continue PD as opposed to hemodialysis allows for the patient to avoid potential complications involved with a catheter and leads to a goal weight suitable for transplantation.

FR-PO644

Rapid Diagnosis of Fungal Peritonitis in a Peritoneal Dialysis Patient using a Multiplex PCR-based Identification Panel

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Introduction: Fungal peritonitis can be difficult to detect using conventional culture methods and delayed diagnosis can lead to significant morbidity and mortality. The FilmArray® blood culture identification panel (BCID; BioFire Diagnostics, LLC.) is an US FDA approved test for rapid identification of common bacterial and fungal pathogens in positive blood culture broths. We present a case of peritoneal dialysis (PD) peritonitis

with Candida albicans that was detected using the BCID panel prior to conventional fungal culture results.

Case Description: The patient is a 50-year-old female with history of end stage renal disease (ESRD) secondary to membranoproliferative glomerulonephritis on PD for 7 years. She was admitted with abdominal pain and cloudy PD fluid concerning for peritonitis. She had been discharged ten days prior after being treated for Clostridioides difficile colitis. She reportedly had a breach in aseptic techniques while performing PD exchanges since her hospital discharge. On presentation, her PD effluent had 5,150 white blood cells (WBC/μL) with 94% polymorphonuclear (PMN) cells. She was started on empiric intraperitoneal antibiotics as well as oral fluconazole for prophylaxis for fungal peritonitis. Initially, her WBC count in the PD fluid and clinical condition improved and PD fluid cultures were negative. However, on the 5th hospital day she had worsening symptoms and increasing WBC count in the PD fluid. The BCID panel was able to detect Candida albicans on a PD fluid sample that was saved at the time of her presentation. Treatment was escalated to intraperitoneal antifungal therapy, and subsequent PD fluid cultures confirmed Candida Albicans peritonitis. Her PD catheter was eventually removed on the 7th day of her hospitalization and she was switched to hemodialysis.

Discussion: Rapid diagnosis of fungal peritonitis in PD patients can lead to life saving therapy and definitive PD catheter removal. In this case, initial conventional PD fluid cultures were non diagnostic, but the BCID enabled rapid identification of a Candida albicans infection. This case illustrates a potential use and supports future studies on rapid PCR based diagnostic techniques for diagnosing PD peritonitis.

FR-PO645

A Rare Presentation of an Unusual Fungus: Trichoderma Peritonitis

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Introduction: Peritoneal Dialysis (PD) can be an attractive modality for end stage renal disease (ESRD) patients. It does, however, require patients be responsible enough to safely perform their own dialysis care, otherwise they can develop peritonitis. Often there is a bacterial source, however, in rare cases fungal infections are seen and in these cases, mortality is higher. Trichoderma is an opportunistic fungus normally found on decaying wood, and it's presence in humans is especially rare and mainly limited to case reports, most of which surfacing in the last 10 years. This likely reflects the increasing number of relatively immunocompromised patients on PD and recent improvements in identifying pathogens. Presented is a rare case of PD associated Trichoderma peritonitis.

Case Description: A 48 year old Hispanic male with past medical history of diabetes mellitus, hypertension, and 1.5 years of PD presented to his nephrologist's office with decreased appetite, abdominal pain, and cloudy effluent from his PD catheter. He was on his 3rd week of treatment with vancomycin and meropenem for gas gangrene diabetic foot ulcer infection. Intraperitoneal vancomycin was initiated for presumed PD peritonitis. PD effluent studies showed 1984 WBCs and mold culture growth, indicating fungal infection. He was immediately admitted for PD catheter removal, anti-fungal therapy with amphotericin B, and hemodialysis preparation with a tunnel catheter. Cultures finalized during his admission showed Trichoderma species susceptible to voriconazole, which he was switched to and discharged with a 1 month course.

Discussion: Peritonitis is a feared complication in PD patients as it can permanently ruin PD access as well as quickly develop into florid sepsis and death. This is especially true in fungal peritonitis cases, where all cause mortality is worse compared to bacterial counterparts. Nephrologists must remain vigilant in monitoring for signs and symptoms of peritonitis (mainly abdominal pain, fever, and cloudy effluent) at every office visit and maintain a low threshold for treatment and admission. Risk factors specifically for fungal peritonitis include: HIV co-infection, recent treatment with antibiotics, or recent abdominal surgery/peritonitis. It is imperative when fungal peritonitis is diagnosed the catheter is removed and strong antifungals are started until susceptibilites are returned.

FR-PO646

Spontaneous Rupture of Peritoneal Dialysis Catheter with No Drainage Problem

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Introduction: Background: Spontaneous rupture of the intraperitoneal portion of peritoneal dialysis (PD) catheter is a rare complication and usually presents with drainage failure and PD related infection. Here we present a case of PD catheter rupture who presents with peritonitis; however, intact out- and in-flow.

Case Description: Case report: A 32-year female with end stage renal disease due to hypertension on PD for 5 years presented with 2 days of mild grade fever, nausea, abdominal pain and cloudy peritoneal fluid. She was managed on CCPD with a two-cuff coiled Tenckhoff catheter. She practiced daily exit site care using topical exsept and alternative gentamicin/bactroban cream. She had 2 episodes of exit site infections with pseudomonas and coagulase negative staphylococcus, respectively 3 years prior to presentation but no peritonitis. On examination, she was afebrile, tachycardiac and had diffuse abdominal tenderness; however, no findings of exit site infection. PD fluid revealed 12,000 WBC/μl with 98% neutrophils and culture grew Pseudomonas aeuroginosa. CT scan done for abdominal pain showed discontinuity of the PD catheter within the anterior abdominal wall soft tissue. Later, fluoroscopic study with gastrograffin confirmed the fracture site in subcutaneous fat with pooling of contrast around the site and drainage of a portion of contrast into peritoneal cavity suggestive of a track. Of note, the patient had an episode of exit site trauma with mild bleeding 8 months prior to the presentation but no infection. Since then she had intermittent issues with long drain time (about 30 minutes) which improved somewhat with laxatives. In addition, she maintained good solute and volume clearance throughout this period. Finally, she underwent surgical removal of the fractured catheter and found to have abscess around the fracture site which was evacuated. The patient had an uneventful recovery and PD was resumed successfully with a new catheter after few months.

Discussion: Conclusion: This is a rare case of PD catheter rupture which likely occurred slowly over time allowing the formation of a soft tissue track and uninterrupted PD therapy but with long drain time. This case highlights the need to be vigilant about these rare events even with mild catheter flow issues.

FR-PO647

Physical Examination of the Hemodialysis Vascular Access: An Unforgettable Tool

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Introduction: Hemodialysis (HD) access failure is an important cause of morbidity and mortality in HD patients. We present a case of false-negative fistulography in an end stage renal disease patient presenting with life-threatening hyperkalemia.

Case Description: A 66-year-old man on chronic HD for 5 years via right brachiocephalic fistula presented with one day of profound weakness. There were no missed HD sessions and no major dietary indiscretions by history. Initial labs showed serum potassium of 8.7 mmol/L (non-hemolyzed), serum bicarbonate 23 mmol/L, glucose 98 mg/dL. EKG showed widened QRS complex and he promptly received intravenous calcium gluconate and insulin. On physical exam his fistula was well-developed and had a harsh, pulsatile bruit. He underwent an emergent, 4-hour HD session with 2K dialysate, blood flow of 400 mL/minute, and dialysate flow of 800 mL/min. Labs 4 hours after HD showed serum potassium 6.1 mmol/L. Reflux fistulography showed no stenosis at the anastamotic segment. Given recurrent hyperkalemia despite an additional 3.5 hours of HD the following day, the case was reviewed with Interventional Radiology and variable contrast densities were noted along different fistula segments. Repeat fistulography via retrograde access was obtained, during which a wire and catheter were advanced across the anastomosis, placing the catheter retrograde in the brachial artery prior to infusing contrast. A hemodynamically significant anastomotic and juxta-anastomotic narrowing was identified and successfully treated with angioplasty. Back pressure generated by reflux angiography masked the stenoses that were apparent when retrograde approach was utilized. After another 4-hour HD session, the patient's hyperkalemia resolved.

Discussion: Thorough assessment of the HD vascular access includes both physical and radiological data. Retrograde arterial catheterization and angiography in a dialysis access circuit provides better physiologic imaging when stenosis is suspected at the anastomosis and/or juxta-anastomotic segment. This case illustrates the importance of correlating clinical and physical examination data with subtle angiographic findings and raises awareness among nephrologists of potential pitfalls in the diagnosis and management of HD access failure with important patient safety implications.

FR-PO648

Arteriovenous Fistula (AVF) Pseudo-Stenosis

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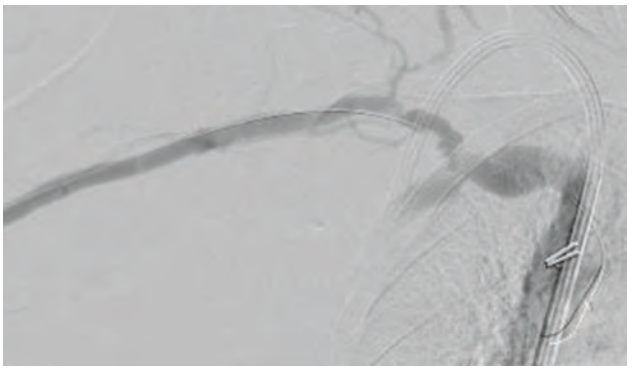
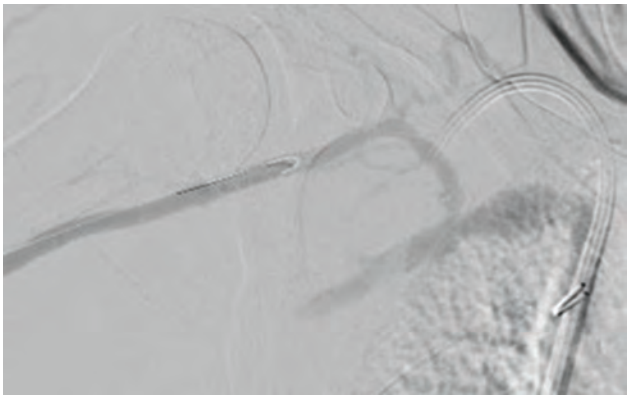
Introduction: Pseudo-stenosis of an AVF has not yet been described in the literature, though it has been noted in the coronaries. It is the false visual appearance of stenosis seen during interventions involving the use of guidewire.

Case Description: Patient 1. 81-year-old male with a brachio-basilic AVF was referred for a fistulogram for high venous pressures noted during dialysis. A fistulogram with guidewire insertion and contrast injection showed multiple areas of apparent stenosis of the basilic vein. After retraction of the guidewire and repeat contrast injection, these areas of apparent stenosis were no longer observed. Patient 2. 83-year-old male with a brachio-cephalic AVF was referred for a fistulogram because of arm pain. A fistulogram with guidewire insertion and contrast injection showed high-grade stenosis at the cephalic arch which was sucessfully dilated with a balloon. Distal to the area of stenosis, the cephalic vein appeared tortuous with multiple areas of stenosis seen while the guidewire was in place (Fig1). Once the guidwire was removed and contrast re-injected, these areas of apparent stenosis were absent (Fig2).

Discussion: Pseudo-stenosis (accordion effect) is well-described in the coronary arteries and is characterized by pseudo-narrowing of the coronary vessels which disappears after guidewire withdrawal. Although the exact mechanism is unclear, the theory is that advancing a guidewire, thereby shortening a tortuous artery, induces folds of the vessel wall which creates the false impression of narrowing. This phenomenon has not previously been reported in an AVF. It is important to recognize this phenomenon to avoid unnecessary interventions.





FR-PO649

Airway Compromise and Failed Extubation Due to Central Venous Stenosis in a Hemodialysis Patient

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Introduction: Central Venous Stenosis (CVS) in hemodialysis (HD) patients is common and is not always easy to manage. We encountered a patient who presented with a unique complication of central venous stenosis.

Case Description: 57 Yr old Female pt with HIV and ESRD on HD for more than eight years via left AV fistula presented to the hospital for large bloody bowel movement and hypotension (80/50). She was given a liter of fluid and three units of red blood cells with improvement of blood pressure to (110/70). She was admitted to floor and started on maintenance IV fluids at 75cc/hr. Dialysis was held for two days due to stable labs, clinical euvolemia and borderline blood pressures. Pt developed shortness of breath, difficulty breathing and got intubated. During intubation it was noted that pts airway was swollen, angioedema was clinically diagnosed and started on Rx. Chest x ray did not show any fluid in the lungs and she continued to remain clinically euvolemic other than swollen face and left arm. No precipitant for angioedema could be found and the swelling did not resolve with medical treatment. CT scan of the chest was performed which showed subcutaneous edema throughout the neck bilaterally (left greater than right), subcutaneous edema of upper chest wall, mucosal edema of base of tongue and supraglottic larynx, Extensive collateral venous vessels in left anterior upper chest with narrowing of brachiocephalic vein. Angiogram showed occlusion at the level of left brachiocephalic vein which was difficult to open. Left arm AV fistula doppler showed wide patency with flow of 2.4 Liter per min. Pt was trached and weaned off ventilator after aggressive removal of volume with help of midodrine and cold dialysate. However she could not be decannulated due to persistence of edema from CVS. After 8 months of hospital stay she was sent to hospice care.

Discussion: Our patient developed upper airway edema secondary to CVS and high flow AV fistula on the same side. The volume resuscitation she received for GI bleed resulted in worsening airway edema leading to intubation. Once intubated the positive pressure in the chest cavity will decrease venous return worsening the airway edema leading to failed extubation. CVS should be considered as potential cause of airway edema and failing extubation in hemodialysis patients.

FR-PO650

Potential Anaphylactic Shock Related to Tunneled Hemodialysis Catheter Material

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Introduction: We report a most concerning case of likely allergic reaction related to tunneled dialysis catheter (TDC) polyurethane material, manifesting with anaphylactic shock and culminating in the patient's death.

Case Description: The index case of a 57-year-old male veteran with end-stage renal disease, diabetes mellitus, obesity, and sleep apnea had been receiving in-center maintenance hemodialysis for nine years. Due to an interval left arterio-venous upper extremity fistula malfunction, he received a tunneled dialysis catheter (TDC) [major manufacturer; 23 cm, 14.5 French dual-lumen catheter] in the right internal jugular position. Of note, this was his first catheter access. Shortly after TDC placement, he complained of diffuse and severe itching; however, no hives or respiratory difficulties were observed. Approximately 12 hours after TDC placement, he presented for his scheduled chronic dialysis. Immediately after start (1-2 min), he complained of intolerable whole body itching and requested termination of treatment; blood was not returned. Diffuse swelling of the tongue and face was observed with almost immediate full-blown hemodynamic collapse and cardiovascular arrest. A prolonged resuscitation attempt failed. Subsequent autopsy revealed severe cardiomegaly and atherosclerosis, but no clear or competing immediate cause of death. An extensive investigation of dialysis machine and water supply ruled out bacterial or chemical contamination. No other patients experienced any problems in the unit. Aside from the catheter use in this patient, there was no technological change in the facility (filter, sterilization) and his dialysis prescription was unchanged. An institutional Root Cause Analysis was also performed, which failed to disclose any other competing cause for cardiovascular arrest.

Discussion: To our knowledge, this is the first report of possible anaphylactic shock related to TDC polyurethane material. Diffuse itching soon after TDC placement (not related only to insertion site) should raise clinical suspicion and may indicate risk of hemodynamic collapse after blood starts flowing through the catheter. Also it is important to consider other entities that may cause allergic reaction that has not been discovered in this setting and possible differences in cleaning of VA dialysis machines vs other outpatient units to see differences arise.

FR-PO651

Volume of Distribution in a Severely Underweight Female Is Better Approximated by Ideal Body Weight Than Actual Body Weight

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Introduction: Guidelines recommend that patients treated with continuous renal replacement therapy (CRRT) be delivered an effluent dose of 20-25 mL/kg/hr. There is debate, especially at the extremes of BMI, as to whether actual, adjusted, or ideal body weight (IBW) should be used in these dose calculations.

Case Description: The patient is a 50 year-old woman with a history of anorexia who was admitted with altered mental status. Initial vital signs were significant for weight of 27 kg, BMI 10.1 kg/m2, and BP 70/34 mmHg. Labs showed lactate 21 mg/dL, bicarbonate (HCO_3^-) 2 mmol/L, and creatinine 2.1 mg/dL. Arterial blood gas (ABG) showed an initial pH 6.55, PCO_2 32 mmHg, and calculated HCO_3^- 3 mg/dL. Protocolized sepsis management was initiated, and she was intubated. Shortly thereafter, she became anuric and was initiated on CRRT. The initial dialysate dose, prescribed using actual weight, was 800 ml/hr. Labs 2 hours later revealed pH 6.84, pCO_2 10 mmHg, and calculated HCO_3^- 3 mg/dL. The dialysate dose, recalculated using her IBW of 58 kg, was increased to 1750 ml/hr. Six hours later, pH was 6.83 with calculated HCO_3^- 3 mg/dL. Lactate remained elevated at 20 mg/dL. Her CRRT prescription was changed to 1500 mL/hr of dialysate with 250 mL/hr of post-filter concentrated bicarbonate solution (6 ampules in 1 L of water or 300 mEq/L of sodium bicarbonate). After 4 hours, pH was 7.39, pCO_2 was 15 mmHg, and measured serum HCO_3^- was 9 mg/dL. Sodium had risen from 143 to 147 mmol/L. Notably, lactate remained elevated at 18 mg/dL. When using appropriate formulas to estimate the expected rate of change in sodium and bicarbonate and comparing to the observed changes, the effective volumes of distribution were those of a typical patient with a weight in the range of 55 – 70 kg, in line with her IBW. Ultimately the patient was found to be surreptitiously taking metformin (later confirmed with serum testing). Her acidosis resolved with 48 hours of CRRT and she was transferred to the floor the next day.

Discussion: This case illustrates the challenges of dosing CRRT in severely underweight patients and suggests that IBW, rather than actual body weight, gives a better approximation of the volumes of distribution of sodium or bicarbonate and therefore may be more appropriate for dosing of CRRT.

FR-PO652

Does a Very High Nephrocheck Level (Above 10) Predict the Need of Early RRT?

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Introduction: Studies have shown that elevated levels of TIMP-2 (tissue inhibitor of metalloproteinase) and IGFBP7 (insulin-like growth factor binding protein) predict AKI early on compared to other biomarkers, and early intervention can prevent AKI or its progression. It is, however, unknown if elevated levels of these biomarkers can predict the need for RRT. We present two cases of high Nephrocheck levels (above 10) who required RRT within 24 hours.

Case Description: (1) 51 y/o woman with a PMH of DVT and DM-2 was transferred to our hospital with complaints of nausea, dizziness, and abdominal pain. She was found to have wide complex tachycardia; she was subsequently cardioverted and started on amiodarone, as well as lidocaine drip. 2D Echo showed an EF of 10% with SBP in the 80s. Emergent cardiac catheterization did not reveal any CAD; an IABP was placed and the patient was transferred to our facility for ECMO placement. Her BUN/Cr initially was 20/0.91 which increased to 33/3.3. Nephrocheck was performed showing a level of more

than 10; her Cr worsened the following day and the patient became anuric; CVVHD was started. (2) 52 y/o woman with a PMH of sickle cell disease and asthma was transferred to our hospital for further management of septic shock. On admission, her Cr was 1.5 which worsened to 2.3. Nephrocheck was done showing a level of more than 10; the patient was placed on HD shortly thereafter.

Discussion: Nephrocheck has a high negative predictive value, ruling out potential AKI if the value is negative; however, it has a low positive predictive value. A high Nephrocheck level is indicative of significant kidney injury; however, no studies have been done, thus far, examining the correlation between a high Nephrocheck level predicting the need for early or late RRT. Both of our patients with Nephrocheck levels above 10 required RRT within 24 hours of admission. Therefore, Nephrocheck can be used an early surrogate marker of kidney injury, seen prior to elevations in serum Cr; this data can be helpful to triage the patients with severe AKI requiring RRT.

FR-PO653

Hemodialysis for Urea Cycle Disorder Associated Hyperammonemia - Does It Have a Role?

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Introduction: Hemodialysis for hyperammonemia is rarely performed. We report a patient who presented with acute encephalopathy, nausea and vomiting associated with elevated levels of serum ammonia and normal hepatic workup and responded only to hemodialysis.

Case Description: A 20 year old Caucasian male with no significant past medical history presented with nausea, vomiting and altered mental status of one day duration. On admission, his vitals were stable and examination was unremarkable except for disorientation. Laboratory work-up revealed normal CBC and BMP and liver function tests except for elevated serum ammonia at 144 mmol/L (normal11-32mmol/L): Head CT, EEG and CSF fluid analysis were negative. Further liver work up including hepatitis panel, HIV screen, alfa-feto-protein, calcinoembrionic antigen, smooth muscle ab, alpha-1 antitrypsin, anti-mitochondrial ab, antinuclear ab, ceruloplasmin level, hemochromatosis panel, liver ultrasound and a liver biopsy was normal. On admission, patient was started on intravenous fluids, vitamin B12, lactulose, rifaximin and protein restriction, but failed to respond and serum ammonia levels trended up to 275 mmol/L on day 3. He was initiated on hemodialysis and underwent a total of 2 dialysis sessions with reduction in ammonia levels to <9umol/L and improvement in mentation by day 5. The urine organic acid gas chromatography test showed highly elevated orotic and uracil levels suggesitive of a urea cycle defect, possibly OTC (ornithine transcarbamylase deficiency), citrullinemia, argininosuccinic aciduria, argininemia or Hyperammoninemia-Hyperornithinemia-Homocitrullinuria syndrome. Genetic testing was negative for the most common mutations but did not rule out a urea cycle defect. The patient was discharged on L carnitine, lactulose and a low protein diet and has not had a recurrent episode of hyperammonemia till last follow-up.

Discussion: Serum Ammonia is a small molecule, with a molecular weight less than that of urea and as such its clearance by a dialyzer membrane is greater than the clearance rate for urea. Hemodialysis can be effectively utilized to treat hyperammonemia associated with urea cycle defect in medically refractory cases.

FR-PO654

Back from the Cold!

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Introduction: Continuous Renal replacement therapy (CRRT) can modulate core body temperature through modulation of the replacement fluid temperature. Although this has been theorized to be helpful in hypotension, there are no guidelines for a temperature setting during CRRT. We present a case where maintaining an optimal temperature during CRRT was of paramount importance to the overall patient management.

Case Description: A 32-year-old African American male presented to the emergency room with recurrent syncope and was notably pale and lethargic on arrival. Lab tests revealed hemolytic anemia with hemoglobin of 3.3 g/dL, LDH of 991 U/L, haptoglobin of 1 mg/dL, positive C3 and total bilirubin of 4.3 mg/dL. A peripheral smear showing severe anemia, prominent agglutination and several granulocytes containing intracytoplasmic cryoglobulins was conclusive for cold agglutinin disease. Although steroids and plasmapheresis were started, patient's condition worsened with the development of multiorgan failure, shock and oliguric renal failure from acute tubular necrosis. We instituted emergent initiation of CRRT for correction of malignant hyperkalemia and acidosis in the setting of hemodynamic instability. Patient underwent 5 days of CRRT with concomitant plasmapheresis. To assist with the overall therapeutic warming strategy, the Replacement fluid was heated on an external heating device and via the CRRT machine to the maximum temperature of 38 C. He improved significantly with resolution of acidosis, and electrolyte derangements; he ultimately required rituximab to truncate the autoimmune hemolytic anemia. A repeat cold agglutinin assay confirmed IgG+ cold agglutinin disease with a positive Mycoplasma IgM thought to be the likely trigger of the autoimmune hemolytic anemia.

Discussion: This case provides a unique perspective on temperature control during CRRT. Typically, cooling of dialysate or replacement fluid is used to bolster blood pressure in times of hemodynamic shock. In this setting, the reverse was utilized as a therapeutic benefit. While often overlooked as a part of the routine CRRT order set, this case highlights the important impact that temperature modulation can have on overall patient management, and should be carefully considered when approaching the CRRT prescription.

FR-PO655

Emergent Hemodialysis: Not Only for AKI

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Introduction: Severe hypothermia, i.e. core body temperature <28°C, is associated with a mortality rate of 50% despite optimal medical care. Commonly used external and internal rewarming techniques may not be effective in achieving the desired core body temperature, and more invasive rewarming modalities i.e. extra corporeal membrane oxygenation (ECMO) and cardiopulmonary bypass (CPB) are not available in all institutions. Hemodialysis (HD) is a safe, effective, and readily available option for the emergent management of hypothermia when conventional techniques have failed.

Case Description: A 78-year-old woman found unconscious, was airlifted to our institution with severe hypothermia (core body temperature of 28°C). She was unresponsive, requiring intubation for airway protection. Initial vital signs included BP 167/87 HR 40 RR 18 T 28°C. External rewarming with thermal blankets, and internal rewarming with 40 °C NS infusion resulted in increase in core body temperature from 28°C to 31°C over 5 hours. The patient remained unresponsive and bradycardic. Nephrology was consulted for role of extracorporeal renal replacement therapy in the setting of persistent hypothermia. We initiated hemodialysis via a right femoral HD catheter, with HD blood flow (Qb) of 300 ml/min, dialysate flow (Qd) 600 ml/min, and dialysate temperature of 37°C. The achieved Qb was 250 ml/min. The patient's core body temperature was monitored via bladder probe, and rose from 32°C to 36.5°C after 3 hours of treatment i.e. hourly increase of 1.5°C. She regained consciousness soon after HD was completed, and was extubated. Frostbite lesions were evident in fingers and toes, although no other sequela of hypothermia persisted. No further complications, including electrolyte abnormalities, developed during, and after rewarming with HD.

Discussion: Hemodialysis is an effective therapeutic option to improve core body temperature, after external and internal rewarming techniques have failed. The rate of core body temperature increase can be closely monitored, and the ability to adjust the dialysate temperature offers the advantage to achieve a safe rate of correction (0.5 to 2°C). Timely rewarming can minimize duration and severity of adverse events including bradycardia and QT prolongation, which may result in a cardiac arrest if untreated. Furthermore, possible electrolyte derangements are simultaneously addressed with HD.

FR-PO656

Adverse Events During Hemodialysis in HeartWare LVAD Recipients

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Introduction: Over the past decade, implantable left ventricular assist devices have become an acceptable alternative to support patients with advanced heart failure, either as a bridge to transplantation or as destination therapy for patients who are not candidates for heart transplantation. As the number of LVAD implantation increases, greater number of LVAD recipients requiring long term renal replacement therapy, usually chronic hemodialysis (HD), will be seen. This is due to common simultaneous chronic kidney disease in patients with heart failure, but more frequently due to irreversible acute kidney injury occurring in the peri-implantation period. We looked at 92 HD sessions in HeartWare LVAD recipients between 2015 and 2017 and assessed adverse events requiring early termination of HD sessions.

Case Description: Between 2015 and 2017 at the University of Maryland Medical Center, 7 patients required HD after LVAD implantation. These 7 patients had a total of 92 HD sessions during their hospitalizations. The average age of the patients was 46 +/- 11.9 years old. Two patients had ESRD and were on HD prior to LVAD implantation. The remaining 5 patients had CKD but were not on HD. The pre-LVAD creatinine average for all 7 patients was 2.55 +/- 1.8. After LVAD implantation, all of the patients were initially on continuous renal replacement therapy before being transitioned to HD. During HD all patients were on midodrine, vasopressors, or fludrocortisone to help increase blood pressure. There were 7 HD sessions that required early termination due to symptomatic hypotension (3), asymptomatic hypotension (2), sinus tachycardia and cramping and discomfort. The average duration of all HD sessions was 172 minutes and the average duration of HD sessions that were terminated early was 148 minutes.

Discussion: 7 out of 92 sessions required early termination and the most common reasons (5 out of 7) were related to hypotension. Complications related to blood pressure was also found to be the most common reason for termination of HD in a previous study of HD sessions in Heartmate LVAD patients. As a result of continuous-flow technology, in most LVAD recipients, there is an absence of pulse, precluding the standard assessment of blood pressure and making assessment of blood pressure during dialysis difficult. There needs to be more research on how to address this in addition to how to optimize and change LVAD settings during HD sessions.

FR-PO657

Full Vessel and Empty Chambers: Volume Management in a Patient with Total Artificial Heart

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Introduction: Total Artificial Heart (TAH) is a pulsatile device that is FDA approved as a bridge to transplant among individuals with biventricular failure. Renal failure requiring renal replacement therapy (RRT) is seen in 15 to 20% of these patients. Given the mechanical constraints of these devices, volume management in dialysis dependent patients is challenging as they are prone to deleterious effects of volume overload and contraction.

We describe the use of blood volume monitor as a tool to guide ultrafiltration management in a patient with TAH.

Case Description: A 50 year-old male with non-ischemic cardiomyopathy was admitted with decompensated biventricular failure and acute kidney injury (AKI) requiring RRT. He was evaluated for advanced heart failure therapies. His hospital course was prolonged with multiple cardiac and medical complications warranting percutaneous cardiac support devices. He was eventually listed for heart-kidney transplantation and underwent TAH implantation as a bridge to transplant. The ventricular chambers of the TAH have limited pre-load capability, thus 6 to 7 days a week of dialysis therapy has been a requirement to avoid volume overload. Similarly, excess ultrafiltration can also lead to unstable hemodynamics. Four months post-operatively the patient remained on a step-down inpatient unit, without invasive hemodynamic monitoring capabilities, while awaiting organ transplantation. It was difficult to maintain an adequate fluid balance without additional hemodynamic monitoring. In addition to fill volumes reported on the patient's TAH monitor, (Companion 2 Driver- SynCardia) blood volume monitoring with the Crit-line III™ was utilized for real time fluid management. Each dialysis treatment was 3-3.5 hours duration with ultrafiltration of 2-3 liters per session. The average blood volume change was between -7 to 8%, allowing safe ultrafiltration without untoward hemodynamic instability.

Discussion: A clinical trial for TAH as destination therapy is currently underway and more widespread adoption of TAH is likely. Understanding the mechanics and hemodynamic effects of TAH is important for nephrologists caring for dialysis dependent patients. This index case describes the feasibility and utility of employing a blood volume monitor to assist in safe volume management.

FR-PO658

Intraperitoneal Filling Transiently Decreases Hepato-Splanchnic Perfusion During Regular Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is considered a hemodynamic more tolerable treatment mode compared to hemodialysis (HD). However, during PD intra-abdominal pressure (IAP) reaches values close to intra-abdominal hypertension (IAH, defined as IAP>12 mmHg) known to cause local venous congestion. It was the aim to investigate whether a standardized PD filling reduced hepato-splanchnic blood flow (Qh).

Methods: Measurements were done during a peritoneal equilibration test (PET) with 2L of 2.27% glucose dialysate. Subjects remained fasting and assumed a supine body position throughout the duration of the study. Data were obtained in the drained state at baseline (T0), immediately after instillation of dialysate (T1), as well as 2 h after instillation (T2). IAP was measured by Durand's approach. Qh was determined from kinetics of indocyanine-green (ICG) dye venously injected and transcutaneously measured by pulse-dye-densitometry (DDG-2001, Nihon-Kohden, Japan). Mean arterial pressure (MAP) and total peripheral resistance (TPR) were derived from continuous arterial pulse analysis (Finometer, Finapres Medical Systems, The Netherlands). Plasma glucose (G) and insulin (I) concentrations were measured by standard techniques. Variables obtained at T0, T1, and T2 were compared by non-parametric Friedman-test.

Results: Ten patients (58.6±14.8 years; 87.5±18.8 kg dry body mass; 172±9 cm; 8 male; 8 non-diabetics) were studied after a 13.9±4.3 h fasting period. IAP increased after filling and remained elevated (Tab. 1). Qh fell by about 13.4±17.6% at T1 but returned close to baseline values at T2. MAP increased at T1 and T2. TPR (in peripheral resistance units, PRU) remained unaffected.

Conclusions: The increase in IAP during PD causes a small and transient decrease in Qh. The subsequent rebound coincides with the absorption of glucose and is likely due to the vasodilatory effects of glucose and insulin which appears to compensate for the pressure induced flow congestion in the splanchnic circulation.

Table 1

	IAP, mmHg	Qh, L/min	MAP, mmHg	TPR, PRU	G, mmoL/L	I, mU/L
T0	6.9±3.2	1.25±0.57	106.2±17.7	1.13±0.33	5.8±1.5	13.9±17.3
T1	10.2±3.1***	1.05±0.38*	111.9±20.5*	1.07±0.26	—	—
T2	10.6±3.0***#	1.21±0.48*	110.1±17.7*	1.08±0.25	6.9±2.2*#	16.5±18.2*#

*p<0.05, **p<0.01, ***p<0.001

FR-PO659

Prevalence and Prognosis of Coexisting Frailty and Cognitive Impairment in Continuous Ambulatory Peritoneal Dialysis Patients: A Prospective Cohort Study from a Single Center in China

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Background: The aim of this study was to investigate the prevalence of coexisting frailty and cognitive impairment as well as its association with clinical outcomes in continuous ambulatory peritoneal dialysis (CAPD) patients.

Methods: Patients on CAPD from January 1, 2014 and December 31, 2016 were recruited. Frailty was assessed by clinical frailty scale (CFS), and cognitive function was assessed by the Montreal Cognitive Assessment (MoCA). All patients were followed up until cessation of PD or December 31, 2017.

Results: A total of 880 CAPD patients were recruited, with a median vintage of PD 24.9 (6.0-52.4) months. The mean age was 48.5±14.6 years, 352 (40%) patients were female and 147 (26.7%) patients with diabetic nephropathy. Coexisting frailty and cognitive impairment was present in 205 (23.3%) patients. Pathway models showed that CFS score was negatively associated with MoCA score (β=-0.14, P<0.001); diabetes mellitus and cardiovascular disease are positively associated with CFS score (β=0.14, p<0.001; β=0.12, P<0.001) while negatively associated with MoCA score (β=-0.14, p<0.001; β=-0.08, P<0.01); serum albumin was negatively associated with CFS score (β=-0.09, P<0.01) while positively associated with MoCA score (β=0.05, P<0.05). Coexisting frailty and cognitive impairment was associated with increased mortality (HR 2.34; 95% CI 1.16-4.72; P<0.05) and had higher peritonitis rate (0.22 vs. 0.11 episodes per patient year, P<0.05).

Conclusions: Coexistence of frailty and cognitive impairment was common in CAPD patients, which increased the risk of adverse outcomes. A significant relationship between frailty and cognitive impairment was demonstrated.

Funding: Government Support - Non-U.S.

FR-PO660

Peritoneal Dialysis in the Elderly: An Opportunity Not to Miss

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Background: End Stage Renal Disease (ESRD) prevalence is steadily increasing in the United States with 700,000 patients currently requiring some form of renal replacement therapy, with a steeper increase in prevalence in the older population (age > 65 years). The rate of peritoneal dialysis (PD) utilization in the US is low at 7% of the ESRD population. The aim of this study is to find the rate of utilization of PD in older patients and examine the outcomes of PD compared to hemodialysis (HD) in old patients segmented into chronological age groups in order to study modality-based survival as age advances.

Methods: We utilized the United States Renal Data System (USRDS) to track the survival of patients with ESRD who started dialysis between 2001-2014. Survival of patients on PD and HD was compared in three age groups: age 65-74, age 75-84, and age >85. Comparisons of PD and HD were adjusted for sex, year of initiation of dialysis and number of comorbidities, and mortality rates were calculated.

Results: A total of 743,229 patients were analyzed in the 3 different age categories. Prevalence of PD use was lower as age progressed, with 6%, 4%, and 3% of patients using PD in the three age groups: 65-74 (N=21,776), 75-84 (N=11,978), >85 (N=2,426), respectively, (Table 1). PD was associated with lower mortality compared to HD across all age groups after adjustment for sex, race and number of comorbidities, (Table 2).

Conclusions: PD is underutilized in the older population but overall is associated with a lower mortality in these patients. Despite comorbidity adjustments, it is possible that PD patients are inherently healthier than HD patients. However, the results of this study should encourage providers to strongly consider PD as an option in older patients.

Table 1: Patient demographics taken from USRDS on dialysis, separated into three ascending age brackets: 65-74 years, 75-84 years, and >85 years.

	Age 65-74	Age 75-84	Age >85	p-value
Mean Age	69.4	79.1	87.6	< 0.001
Total N	362,925	299,452	80,852	< 0.001
% Female	45.7%	45.8%	46.3%	< 0.001
Race				
• Caucasian	69.22%	76.53%	79.51%	< 0.001
• Black	24.49%	18.19%	15.38%	< 0.001
• Asian	3.31%	3.33%	3.79%	< 0.001
• other	2.99%	1.95%	1.32%	< 0.001
Modality				
• % HD	94%	96%	97%	< 0.001
• % PD	6%	4%	3%	< 0.001

Table 2: Hazard Ratios for ESRD patients on peritoneal dialysis compared to hemodialysis in three ascending age brackets: 65-74 years, 75-84 years, and >85 years.

Age	HR (PD/HD)	CI (95%)	p-value
65-74	0.89	0.88-0.91	< 0.001
75-84	0.94	0.92-0.96	< 0.001
>85	0.91	0.87-0.96	< 0.001

FR-PO661

Prevalence and Outcome Impact of Depression and Frailty Among Peritoneal Dialysis Population in a Local Dialysis Centre

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Background: Depression and frailty are increasingly being recognized as contributing factors to the adverse clinical outcome of peritoneal dialysis (PD) patients. Depressed patients have multiple physical and psychological symptoms, and have poor adherence to dialysis and medical therapy. Frailty refers to a state of increased vulnerability caused by decline in physical reserve and function, and is caused by malnutrition, chronic inflammation, and repeated infection. However, the interaction between depression and frailty in PD patients remains uncertain. We determine the prevalence of depression and frailty in prevalent PD patients. We further dissect the internal relationship between depression and frailty, and their relative contribution to the adverse clinical outcome in PD patients.

Methods: This is a prospective observational study. We recruited 267 prevalent PD patients between 2015 and 2016. Depression was identified by Patient Health Questionnaire (PHQ-9). Frailty was identified by a validated Frailty Score. All cases were followed for one year. Outcome measures included number and duration of hospitalisation, peritonitis rate, and all-cause mortality.

Results: Of the 267 patients, 197 patients (73.8%) were depressed, and 157 (58.8%) were frail. There was a substantial overlap between depression and frailty. Although depression and frailty were associated the number and duration of hospitalisation by univariate analysis, the association became insignificant after adjusting for confounding factors by multivariate analysis. Both depression and frailty were associated with one-year mortality by univariate analysis, but only frailty was an independent predictor of patient survival by multivariate analysis (adjusted hazard ratio 1.424, 95% confidence interval 1.011-2.005. p = 0.043).

Conclusions: Depression and frailty were common among Chinese PD patients. Frailty, but not depression, was an independent predictor of one-year mortality. Further studies are needed to determine the benefit of treatment for frailty in PD patients.

Funding: Government Support - Non-U.S.

FR-PO662

Factors Affecting Selection of Dialysis Modality in Elderly Patients with CKD: Prospective Cohort Study of Korea

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Background: Several factors associated with dialysis modality selection have been reported in many studies. However, the factors affecting selection of dialysis modality in elderly patients with chronic kidney disease is not known. We investigated which factors are associated with selection of dialysis modality in elderly patients compared to younger patients.

Methods: This study included 2,238 incident dialysis patients from a multicenter prospective cohort study in Korea from August 2008 to July 2015 (NCT00931970). We surveyed demographic, referral, dialysis planning, socioeconomic, and clinical data. Using multivariate regression analyses, variables significantly associated with the chosen dialysis modality were analyzed. The differences in the factors were compared between elderly (≥65 years) and younger (<65 years) groups.

Results: Of the enrolled patients, 1,537 (68.7%) and 701 (31.3%) selected hemodialysis (HD) and peritoneal dialysis (PD) respectively. The percentage of HD was higher in elderly patients compared to younger patients (82.3% vs. 62.2%, p<0.001). In elderly group, patients choosing PD was younger than patients choosing HD (70.4±4.4 vs. 72.2±5.4, p<0.001). Patients with planned dialysis (p<0.001), employed status (p=0.042), married status (p=0.023), and congestive heart failure (p=0.003) were more common in elderly PD patients. However, patients with tumor were more common in elderly HD patients. Multivariate analysis showed that planned dialysis (p<0.001) and congestive heart failure (p=0.003) were independent factors for selecting PD and tumor (p=0.01) was for selecting HD in elderly group. In younger group, planned dialysis (p<0.001), employed status (p<0.001), and independent economic status (p=0.043) were revealed as the independent factors for choosing PD whereas peripheral vascular disease (p=0.019) and tumor (p=0.02) were independent factors for choosing HD.

Conclusions: As age of patients with chronic kidney disease increases, HD was more frequently selected modality than PD. Dialysis planning and specific comorbidities were associated with selection of dialysis modality in elderly patients. However, elderly patients were less affected by socioeconomic status compared to younger patients.

FR-PO663

Barriers and Facilitators to Home Dialysis in Older Veterans: Perspectives from Patients and Caregivers

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Background: Home-based dialysis - hemodialysis (HD) or peritoneal dialysis (PD) – often confers greater survival and quality of life, and lower morbidity than in-center hemodialysis for patients with end-stage renal disease (ESRD). However, home dialysis is underutilized, especially among older adults. To understand this underutilization, we assessed barriers and facilitators to home dialysis from the perspectives of older Veterans and their caregivers.

Methods: Semi-structured telephone interviews were conducted and audio-recorded separately with Veterans receiving home dialysis through VA and their informal caregivers in five VA facility-based programs during 2017-2018. Transcribed interviews were analyzed using content analysis to identify themes emerging from the data.

Results: Out of 82 Veterans on home dialysis (78 PD, 4 HD), 63 (77%) had informal caregivers. We interviewed 20 Veterans (24% participation rate) and their 20 caregivers (32% participation rate). Most Veterans were male (100%), white (77%), with an average age of 64 years. Most caregivers were female (95%), white (78%), with an average age of 63 years. Most Veterans (54%) believed that they needed their caregiver to assist in performing home dialysis. Key patient-level barriers included unsuitable home environment, lack of self-efficacy in administering home dialysis treatments, and physical disability. Important facilitators included having sufficient space at home, knowledge/training on performing home dialysis, and caregiver support. Significant caregiver-level barriers included unsuitable home environment, lack of self-efficacy in administering home dialysis treatments, and competing job duties. Common facilitators included personal devotion to the Veteran, knowledge/training of the home dialysis procedure, and VA dialysis staff support. Veterans and caregivers similarly supported interventions to foster home dialysis, including telemedicine applications and paid stipends for caregivers.

Conclusions: Informal caregivers play a key role in supporting home dialysis for older adults. Interventions should address both patient and caregiver barriers to increase use of home dialysis.

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FR-PO664

Association Between Receiving Public Assistance and Long-Term Peritoneal Dialysis Outcomes in Adults

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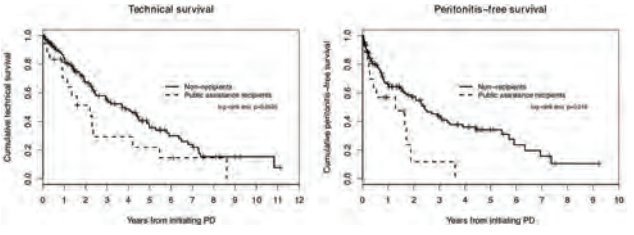
Background: Public assistance (PA) in Japan is available as part of the financial support system for the poor. With the increasing number of elderly people living in households, the number of elderly people receiving PA has increased. Although the role of peritoneal dialysis (PD) is substantial in the treatment of end-stage renal disease (ESRD) in the elderly, the effects of the long-term PD on PA recipients remain unknown.

Methods: We reviewed medical records for 147 patients who had initiated PD between 2005 and 2018 at Kawasaki Saiwai Hospital and had remained in care at a related facility. We examined patient characteristics, including age, sex, ESRD etiology, and serum creatinine and albumin levels at the PD induction. Data on PD prescription and the method of connection were also collected. The long-term technical survival and peritonitis-free survival rates were calculated using Kaplan–Meier method, and predictors of technical and peritonitis-free survival were determined using Cox regression analysis.

Results: PD was initiated in 88 males and 59 females, of which 18 received PA. At the induction, mean patient age was 63.1 years and mean estimated glomerular filtration rate (eGFR) was 5.9 ml/min/1.73m^2. In the Kaplan–Meier analysis, the overall median time for technical survival was 1158 days: 806 days for the recipients and 1357 days for non-recipients. Although there was no statistical difference in the technical survival rate between the two groups, the outcome appeared to be unfavorable in the PA recipients. The peritonitis-free survival was significantly shorter in the PA recipients than in the non-recipients. In Cox regression analysis, PA was associated with short technical [HR 2.16; 95%CI 1.06–4.40] and peritonitis-free survival [HR 3.13; 95%CI 1.55–6.34] after adjustments for age, sex, estimated GFR at the induction, the presence of diabetes, connection method, and the presence of people living together.

Conclusions: Receiving PA was associated with unfavorable technical survival outcomes and significantly poor peritonitis-free survival outcomes.



FR-PO665

Quality of Life and Emotional Distress Changes Between Peritoneal Dialysis Patients Versus Hemodialysis Patients and Their Families

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Background: In Japan, hemodialysis (HD) is the most popular modality for the end stage renal disease (ESRD) patients. While, the number of peritoneal dialysis (PD) patients accounts for 2.8%. We investigated the reason of low PD penetration through the prospective assessment of quality of life(QOL) and emotional distress(ED) of patients and their families.

Methods: Fifty one incident patients (31 PD, 20 HD) were recruited. The SF-36 and CES-D were assessed in all patients and their families at the start of dialysis and every year for 2 years.

Results: The background characteristic was similar between two groups. The CES-D in PD was not changed, but was significantly increased in HD at 2 years. As for families, the CES-D results showed the same trend as patient's. Summary of physical components and role of social components (RS) in SF-36 at 2 years in PD but not in HD revealed significant improvement,. The summary of mental components (MC) were not changed in both groups. But MC in PD were significantly higher than that in HD at 2 years. The summary of RS was significantly improved at 2 years in PD and retained higher than that in HD. In the family's test, all SF-36 scores were not changed in PD, but MC was decreased in HD, followed significant lower at 2 years than in PD.

Conclusions: In this study, PD provided better QOL and ED due to preservation of residual renal function and lesser hospital visiting. However, HD is more prevalent in Japan instead of burdening the families. It might be considered that most Japanese tend to or depend on others and select HD modality. Moreover, ESRD patients were not well educated according to PD. Finally, it is important to inform patients of PD where PD provides better QOL and better effect on emotional change.

table 1: QOL and ED change

		PD (n=31)			HD (n=20)		
		at baseline	after 12 months	after 24 months	at baseline	after 12 months	after 24 months
Patient	CES-D	11.9 ± 6.8	12.6 ± 7.5	13.8 ± 9.3	13.8 ± 9.3	13.4 ± 4.5	16.4 ± 6.2*
	Physical component summary	38.2 ± 15.0	43.5 ± 13.0	45.8 ± 10.6*	32.1 ± 9.8	31.6 ± 12.9	25.8 ± 14.6* ,†
	Mental component summary	47.8 ± 8.8	49.1 ± 8.1	51.8 ± 8.1	51.6 ± 4.7	52.4 ± 8.9	50.8 ± 7.4
	Role of social role component summary	39.9 ± 13.0	43.3 ± 2.0	47.3 ± 10.5*	39.3 ± 12.2	38.4 ± 10.1	36.1 ± 10.8
Family	CES-D	8.6 ± 3.6	9.2 ± 3.2	8.8 ± 3.0	8.3 ± 2.2	8.6 ± 2.9	10.3 ± 3.2*
	Physical component summary	49.0 ± 9.7	50.5 ± 10.5	48.0 ± 10.2	58.1 ± 6.4	57.8 ± 5.0	58.2 ± 5.0
	Mental component summary	50.2 ± 9.3	54.6 ± 7.3	52.3 ± 6.3 †	48.9 ± 9.9	49.5 ± 9.8	45.8 ± 11.3
	Role of social role component summary	44.6 ± 14.5	41.8 ± 13.7	42.7 ± 12.9 †	51.2 ± 11.1	44.2 ± 12.5	39.0 ± 11.6*

*: p<0.05 vs at baseline, †: P<0.05 vs group HD

FR-PO666

Estimating Total Small Solute Clearance in Patients Treated with Continuous Ambulatory Peritoneal Dialysis Without Urine and Dialysate Collection

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Background: Higher total (kidney plus dialysis) clearance of small solutes is associated with lower mortality in peritoneal dialysis (PD) patients. Measurement of total clearance (mCL) is recommended to monitor and adjust dialysis dose, but is difficult and prone to errors due to the requirement for timed fluid collections. We hypothesized that equations (eCl) could be developed to estimate mCl using serum concentrations of endogenous filtration markers.

Methods: Using 2/3 of the participants in the Guangzhou PD Study (N=980), we used linear regression to develop eCl equations. Reference tests were mCl for urea nitrogen (mCl_{UN}, ml/min) and average mCl for UN and creatinine (mCl_{UN-Cr}, ml/min/1.73 m^2). Index tests were various eCl equations using UN, creatinine, low-molecular-weight-proteins (LMWP) [beta-trace-protein (BTP), beta-2-microglobulin (B2M), cystatin C], demographic variables and body size. We validated the equations in the remaining 1/3 of the cohort (n=322) and refitted equations in the combined dataset. We analyzed the predictive value of the equations to detect a weekly total standard Kt/V (mCl_{UN} per week indexed for total body water) >1.7 using receiver-operating-characteristic curve.

Results: Mean age of the cohort was 50±15 years, 53% were male; mCl_{UN} was 6.9±1.8 ml/min, mCl_{UN-Cr} 7.5±2.8 ml/min/17.3 m^2. Creatinine but not UN contributed to eCl (Table). LMWP did not improve accuracy for mCl_{UN} (range 87.6-88.6%). BTP and B2M improved accuracy for mCl_{UN-Cr} (range 81.6-82.0 vs. 79.7%), however, differences were small. The area-under-the-curve for predicting a weekly kt/V >1.7 was similar for all equations (range 0.791-0.802).

Conclusions: Total small solute clearance can be estimated moderately well [TMC1] in CAPD patients from serum concentration of creatinine and demographic variables without urine and dialysate collection. Equations to estimate total clearance need to be evaluated in other cohorts.

Funding: Commercial Support - Siemens, Dialysis Clinic Inc., Private Foundation Support

Table: Performance total clearance estimating equations in the entire dataset (n=980)

Markers	Co-Variables	RMSE (95%-CI)[a]	ΔRMSE[b]	Accuracy (95%-CI)[c]
Equations estimating mCl_{UN}, ml/min		ml/min	%	%
Creatinine	Age, Sex, Height, Weight	0.205 (0.192, 0.219)	-	87.6 (85.5, 89.5)
BTP	Creatinine, Age, Height, Weight	0.202 (0.188, 0.216)**	1.5	88.4 (86.4, 90.3)
B2M	Creatinine, Age, Height, Weight	0.202 (0.188, 0.218)**	1.5	87.6 (85.5, 89.6)
Cystatin C	Creatinine, Age, Height, Weight	0.203 (0.189, 0.217)	1.0	87.6 (85.4, 89.6)
B2M-BTP	Creatinine, Age, Height, Weight	0.201 (0.187, 0.215)**	2.0	88.6 (86.5, 90.5)
BTP-Cystatin C	Creatinine, Age, Height, Weight	0.201 (0.187, 0.216)**	2.0	88.3 (86.1, 90.3)
B2M-Cystatin C	Creatinine, Age, Height, Weight	0.202 (0.188, 0.217)**	1.5	87.8 (85.7, 89.9)
Equations estimating mCl_{UN-Cr}, ml/min/1.73 m^2		ml/min/1.73 m^2	%	%
Creatinine	Age, Sex	0.239 (0.223, 0.259)	-	79.7 (77.2, 82.0)
BTP	Creatinine, Age, Sex	0.233 (0.213, 0.253)**	2.5	81.6 (79.2, 84.1)*
B2M	Creatinine, Age, Sex	0.232 (0.213, 0.252)**	2.9	82.0 (79.6, 84.4)**
Cystatin C	Creatinine, Age, Sex	0.234 (0.216, 0.253)**	2.1	80.9 (78.5, 83.4)
BTP-B2M	Creatinine, Age, Sex	0.231 (0.211, 0.251)**	3.3	81.7 (79.2, 84.2)*
BTP-Cystatin C	Creatinine, Age, Sex	0.232 (0.213, 0.252)**	2.9	81.6 (79.3, 84.0)*
B2M-Cystatin C	Creatinine, Age, Sex	0.232 (0.213, 0.253)**	2.9	82.0 (79.5, 84.3)**

All associations of filtration marker and clearance are linear except for BTP (two-slope polynomial, breakpoint at 10 mg/l for mCl_{UN} and 10.5 for $-Cl_{UN-Cr}$).
Abbreviations: RMSE=root-mean-square-error; 95%CI=95%-confidence interval; mCl_{UN}= urea nitrogen clearance in ml/min; B2M=beta-2-microglobulin; BTP=beta-trace-protein; mCl_{UN-Cr}=average of urea nitrogen and creatinine clearance in ml/min/1.73 m^2. Bias (difference between mCl and eCl) not included because it is expected to be zero.
[a] RMSE from a linear regression model with the measured clearances and the filtration markers on natural logarithmic scale, co-variables on raw scale
[b] ΔRMSE expresses the reduction of the RMSE of the model compared to the model only containing creatinine in percent.
[c] Accuracy is defined as the percentage of estimated clearances within ±2.0 units of the measured clearances
* p<0.05, ** p<0.01 compared to the model only containing creatinine.

FR-PO667

Factors Associated with Peritoneal Membrane Permeability in Patients Starting Peritoneal Dialysis

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Background: Peritoneal membrane transport characteristics vary in peritoneal dialysis (PD) patients and have been related to patient and technique survival.

Methods: Data from PD patients from 10 PD units in Greece were retrospectively analyzed. Patients with a history of early catheter dysfunction or leakage were excluded. 163 patiens (100 male and 63 female) were finally included, whose first PET test was performed within 2 months after PD catheter insertion. Patients were divided into 4 sub-groups according to 4 hr D/P creatinine ratio; fast as 1SD above mean, average fast as between mean and mean+1SD, average slow as mean-1SD and slow as below 1SD from the mean. Ordinal regression analysis was performed to identify risk factors for faster membrane permeability.

Results: The median age of the study group was 58.2 (range 21-88) years. The etiology of ESRD was unknown in 26.5%, diabetes mellitus in 19.5%, hypertension/nephrosclerosis in 18%, glumerolonephritis in 17.2%, polycystic kidney disease in 10.5%. Gender and BMI did not differ significantly between sub-groups of patients (p>0.05). In univariate analysis age (p=0.02), the history of diabetes mellitus (p=0.03) and lipidemia (p=0.03), as well as hemoglobin (p=0.03) and albumin concentrations (p=0.01) were significantly different among the four sub-groups. In multivariate analysis only the presence of diabetes mellitus (OR=1.98, p= 0.045) and hemoglobin levels (OR: 0.76, p=0.01) were independently associated with higher membrane permeability.

Conclusions: Diabetes mellitus and anemia are independent predictors of membrane transport characteristics in patients starting PD.

FR-PO668

Risk Factors for Loss of Residual Renal Function During the First Year of Chronic Automated Peritoneal Dialysis (APD) in Children

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Background: In chronic dialyzed patients, preservation of residual renal function is associated with better survival, lower morbidity, and greater quality of life. The aim of this study was to assess risk factors for loss of residual renal function (RRF) in children during the first year of chronic automated peritoneal dialysis (APD).

Methods: The study group included 56 children (33 boys and 23 girls, median age 9.58 years) with end-stage renal disease (ESRD) at Children's Hospital of Fudan University from Jan 2008 to Dec 2015 who commenced APD as the initial method of renal replacement therapy for at least 12 months with significant initial residual renal function (daily diuresis more than 100ml/m^2/day). Patient characteristics and potential risk factors of developing oligoanuria (under 100 ml/m^2/day) including gender, BMI and age at APD, etiology of ESRD, baseline daily diuresis and residual glomerular filtration rate (rGFR), PD fluid volume, glucose load, ultrafiltration, peritoneal permeability, dialysis adequacy, blood pressure, biochemical parameters, medications used and dialysis-related peritonitis frequency were analyzed.

Results: 1. Mean diuresis before initiation of APD was 692.0±315.9 (mL/m^2/day) and mean rGFR was 7.48±2.93 (mL/min/1.73 m^2). An average decline of daily urine volume was 376.2±354.6 (mL/m^2/day) in the first year of APD and 23 (41.14%) children became oligoanuria. 2. Risk factors associated with loss of RRF: Children who lost RRF during the first year frequently exhibited a lower baseline rGFR (P=0.02), were exposed to higher dialysate glucose (P<0.001), higher PD fluid volume (P=0.002) and achieved higher daily ultrafiltration volume (P<0.001). The use of RAS antagonists (ACEI/ARB) tended to increase the risk of becoming oligoanuria (P=0.003).

Conclusions: The important risk factors for rapid RRF loss in children during the first year of chronic APD include lower baseline rGFR, higher glucose load, higher PD fluid volume, higher ultrafiltration and administration of RAS antagonists.

FR-PO669

Simultaneous Optimization of Ultrafiltration and Solute Transport in Automated Peritoneal Dialysis (APD)

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Background: In a recent study we found that the treatment with APD could be improved in terms of shorter treatment times and markedly (> 20%) lower glucose absorption using optimized bi-modal treatment regimens, combining cycles with a high glucose concentration and cycles using low or no glucose.

Methods: We further explored this novel concept *in silico* by using a sparse linear regression model with constraints to find the shortest possible treatment time given a set of clinical treatment goals. We created optimal regimes giving the same Kt/V urea and/or weekly creatinine clearance and UF as a standard (6 × 2 L 1.36%) and an adapted (2 × 1.5L 1.36% + 3 × 3L 1.36%) regime.

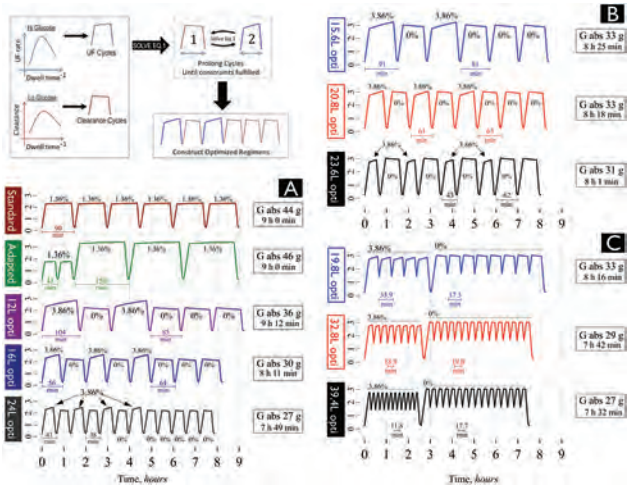
Results: Compared to the non-optimized (standard and adapted, see Figure A) regimes, optimized regimes for creatinine (35 L/week; see Figure B and C) and UF (0.5 L/day) demonstrated marked reductions (up to 40%) in glucose absorption (G abs), having a similar sodium and phosphate removal (see Table). Optimizing for urea Kt/V (1.40 / week; PD-only; see Figure A) and UF (0.5 L/day) leads to a slightly lower creatinine and phosphate removal but leads to a shorter treatment time. Larger fill volumes of 1200 mL/m^2 (UF cycles) and 1400 mL/m^2 (Clearance cycles) can be applied to shorten the total treatment time.

Conclusions: These simulations suggest that great reductions in treatment time and in glucose absorption are possible using a novel optimization technique for APD prescription. Further studies are needed to evaluate the feasibility of these novel regimens.

Funding: Private Foundation Support

Regime	Sodium Removal (mmol/d) †	Urea Kt/V †	Phosphate Clearance (L/w) †
Standard 6 x 2 L 1.36%	53	1.38	29
Adapted APD	54	1.40	31
Optimized 12 L ‡	51	1.40	30
Optimized 23.6 L *	59	1.56	30
Optimized 32.8 L *	55	1.64	31

† PD only. ‡ optimized for urea Kt/V and UF, see text. * optimized for creatinine clearance and UF, see text.



Optimized APD

FR-PO670

A Time-Varying Analysis: The Relationship Between Serum Uric Acid and Residual Renal Function Loss in CAPD Patients

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Background: Residual renal function(RRF) is significantly associated with mortality and quality of life in peritoneal dialysis(PD) patients. A number of studies demonstrated that pre-dialysis serum uric acid(UA) was predictor of RRF loss in PD patients. However, the relationship between serum uric acid and RRF loss in patients over time are unknown.

Methods: This is a single-center, retroperspective cohort study. Total 201 CAPD patients who started PD between January1, 2008 and April 30, 2016 at the third affiliated hospital of Sun-Yat Sun University were eligible for the study with follow-up through December 31, 2016. Urine volume, biochemical and therapeutic information was collected within 1 month of PD commencement and at every 3-month intervals thereafter. Cox proportional hazard regression models and penalized splines analysis were employed to analyze the association between uric acid and RRF loss and to identify independent risk factors of RRF loss.

Results: During the period of first five years in PD, 86 patients became anuria. Multivariate Cox regression analysis showed that uric acid, 5-year peritonitis rate, ultrafiltration and phosphorous were independent risk factors of RRF loss while KT/V urea was a protective factor. Using Cox proportional hazard regression models and penalized splines analysis, when compared to patients with UA 403-455umol/L, patients with UA>455umol/L (HR=1.99, 95%CI 1.021-3.345; p<0.05) or UA<403umol/L (HR=2.12, 95%CI 1.005-3.611; p<0.05), UA levels conferred a higher risk of RRF loss, while it showed a U-shaped relationship between continuous UA levels and RRF loss.

Conclusions: A U-shaped relationship between UA levels and RRF loss was found in patients over time. Uric acid, 5-year peritonitis rate, ultrafiltration, phosphorous, and KT/V urea were independent risk factors for RRF loss in CAPD patients.

FR-PO671

Early Complications of Urgent-Start Peritoneal Dialysis

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Background: Urgent-start peritoneal dialysis (PD) would be an effective option for patients need unplanned dialysis. However, the early catheter-related complications in urgent-start PD have not been well investigated and the previous results were inconsistent.

Methods: In this retrospective study, end stage renal disease (ESRD) patients were included if they were over 18 years old and received regular PD in our PD center between 1 March 1996 and 30 September 2016. Urgent-start PD was defined as initiation of PD within 2 weeks of catheter insertion. The time from placement-to-PD was determined by the nephrologists based on the clinical condition of each patient. Patients were divided into two groups according to whether PD was started urgently or not. The outcome was mechanical and infectious complications and technique survival in the first 6 months.

Results: A total of 667 patients (203 urgent-start, 464 conventional-start) were included. The mean age of the study patients was 59.6±15.4 years old, and 49.8% of the patients were female. Diabetes was the primary cause of ESRD (36.1%) and was followed by glomerulonephropathy (25.6%) and hypertension (20.5%). The time from catheter insertion to PD initiation was 8.1±4.5 and 18.6±12.7 days in urgent-start and conventional-start PD group, respectively. Compared with conventional-start patients, urgent-start patients had lower serum albumin, Kt/v, Ccr and eGFR levels at the start of PD, and otherwise there was no significant difference between the two groups. The rate of mechanical complications at 1 month, 3 months, and 6 months after PD commencement was 9.4%, 16.7%, and 18.2% in the urgent-start PD group, respectively. The rate of infectious complications at the same time points was 11.8%, 13.8%, and 20.7% in the urgent-start group. Technique survival was 96.9% and 98.4% in urgent-start and conventional-start PD group, respectively. There was no difference in the rate of mechanical and infectious complications and technique survival between urgent- and conventional-start PD patients at either time point.

Conclusions: Urgent-start PD patients had similar rates of catheter-related complications and technique survival compared with conventional-start PD patients.

FR-PO672

Low-Volume Tidal Peritoneal Dialysis Is a Preferable Mode in Patients Initiating Urgent-Start Automated Peritoneal Dialysis

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Background: To evaluate the safety of low-volume tidal peritoneal dialysis (TPD) and intermittent peritoneal dialysis (IPD) in end-stage renal disease (ESRD) patients initiating automated peritoneal dialysis (APD) after an acute catheter insertion.

Methods: Clinical outcomes of patients who received either TPD or IPD using an APD system were compared in a randomized, open-label, prospective control study in a single-center setting. From May 2011 to May 2013, 49 patients were enrolled and 27 patients received low-volume TPD treatment whereas 22 patients underwent low-volume IPD right after Tenckhoff catheter insertion. The incidence of complications during the 14-day APD treatment were observed. After APD treatment, all the patients were transferred to continuous ambulatory peritoneal dialysis (CAPD) and followed up for 2 years.

Results: The IPD group demonstrated a significantly high incidence of catheter-related complications than the TPD group after adjusting for age, gender, baseline diabetes, systolic blood pressure, and body mass index. However, the short duration of APD treatment with either IPD or TPD mode did not affect the long-time technical survival.

Conclusions: In patients immediately after catheter insertion, low-volume TPD mode demonstrated a lower incidence of catheter-related complications compared to IPD. However, definitive conclusions about TPD benefit cannot be made, owing to early termination of the trial.

Characteristics	TPD (n=27)	IPD (n=22)	*p*-Value
Female, n (%)	16(59.3)	16(72.7)	0.325
Age（Y）	38.9 ± 15.1	41.7 ± 17.1	0.542
BMI (kg/m^2)	21.6 ± 3.0	21.8 ± 3.2	0.914
SBP (mmHg)	157 ± 25	157 ± 33	0.981
DBP (mmHg)	92 ± 16	90 ± 18	0.556
Causes of CKD			
Chronic glomerulonephritis	21	11	0.042
Diabetes kidney disease	1	8	0.007
Other diseases	6	3	0.139
Concentration of hemoglobin (g/L)	85.7 ± 2.2	88.6 ± 3.4	0.105
Serum Creatinine (μmol/L)	757.8 ± 51.1	761.6 ± 50.4	0.591
Serum Albumin (g/L)	31.2 ± 1.1	31.6 ± 1.1	0.536
Serum Potassium (mmol/L)	4.02 ± 0.12	4.05 ± 0.13	0.917
Serum Calcium (mmol/L)	2.14 ± 0.03	2.10 ± 0.06	0.035
Adjusted Serum Calcium (mmol/L)	2.46 ± 0.05	2.41 ± 0.06	0.544

Patient characteristics at baseline.

Complications (events, %)	TPD (n=27)	IPD (n=22)	*p* Value
Suction pain	0 (0)	4 (18.2)	0.021
Catheter migration	2 (7.4)	2 (9.1)	0.831
Omental wrapping	0 (0)	6 (27.3)	0.004
Pericatheter leak	**0 (0)**	**0 (0)**	**-**
Peritonitis	1 (3.7)	1 (4.5)	0.882
Exit-site infection	**0 (0)**	**0 (0)**	**-**
Wound bleeding	4 (14.8)	1 (4.5)	0.238
Inguinal hernia	**0 (0)**	**1 (4.5)**	**0.263**
Reoperation (patients, %)	0 (0)	7 (31.8)	0.002

The incidence of complications during 2-week APD treatment.

FR-PO673

Clinical Outcomes Associated with Peritoneal Dialysis Catheter Placement by Interventional Radiology

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Background: Fluoroscopy-guided peritoneal dialysis (PD) catheter insertion by interventional radiologist (IR) has been reported as an appropriate alternative to surgical insertion to increase access to PD. The objective of this study was to report clinical outcomes and complications associated with PD catheter insertion by IR.

Methods: We conducted a single-center retrospective study of all patients who had PD catheter insertion by IR from January 2014 to January 2018. The primary outcomes were to report the complications related to catheter insertion within the first 3 months and the number of active PD patients at 3 months. Secondary outcomes were to evaluate the impact on the prevalent number of PD patients and on the waiting time for PD catheter insertion.

Results: 56 patients with a median age of 55 years old (20-85) were included in this study. Patients with severe obesity (IMC>35), polycystic kidney disease and previous major surgery were not eligible for IR and were referred for laparoscopic insertion. Among these 56 patients, 1 had kidney transplantation, 1 had renal recovery and 2 were deemed unable to learn the procedure. Therefore, 52 completed the training and began PD. Among these 52 patients, 49 (94%) were on active PD at 3 months (catheter removed due to an acute intestinal perforation post-insertion (n=1), refractory peritonitis (n=1) and a pleural leak (n=1)). Within 3 months, catheter malposition occurred in 12 (21%) patients but only 3 of them needed surgical or IR repositioning. Three patients (5%) experienced peri-catheter leaks where PD was successfully restarted after temporary cessation for 4 weeks. Finally, 1 patient developed peritonitis and 1 had exit site infection that were successfully treated with antibiotics. Since the introduction of this technique, the number of prevalent PD patients in our center increased from 60 to 84 while the average time for PD catheter insertion has decreased from 4.5 to 1.5 months.

Conclusions: Insertion of PD catheter by IR is associated with a low complication rate while it improves access to PD therapy. Its use should therefore be encouraged as an alternative to surgical placement in most patients.

FR-PO674

Peritoneal Dialysis After Renal Transplant Failure: A Different Beast Altogether

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Background: The number of patients starting dialysis after graft failure (DAGF) has been steadily increasing in the United States. This population differs significantly from those with native End Stage Renal Disease (ESRD) and little is known about the outcomes of DAGF patients on peritoneal dialysis (PD). We undertook this study to examine characteristics and survival of DAGF patients on PD compared to the native ESRD population on PD.

Methods: We analyzed the United States Renal Data System (USRDS) to assess characteristics and survival of DAGF and native ESRD patients on PD. Mortality rates were compared after adjustment for age, sex, number of comorbidities, and year of dialysis initiation.

Results: A total of 7.46% of DAGF and 7.09% of native ESRD patients used PD (p=0.01) and a total of 108,194 patients on PD were analyzed (Table 1). The mean age for DAGF patients on PD was significantly lower than native ESRD patients on PD (p<0.001). DAGF patients on PD were more likely to be employed than their counterparts with native ESRD (p<0.001). Those with DAGF had higher mortality than those with native ESRD (Table 2). This trend was even more significant after adjustment for age, sex, number of comorbidities, and year of dialysis initiation (p<0.001).

Conclusions: DAGF patients on PD have much worse outcomes compared to their native ESRD counterparts. The results of this study should encourage providers to consider DAGF PD patients as a high risk group and focus on risk reduction. Further research regarding the timing and cause of mortality in DAGF population on PD is needed.

Table 1. Patient demographics obtained from USRDS separated into Native ESRD patients on PD and DAGF patients on PD

Characteristic	All Patients on PD	Native ESRD patients on PD	DAGF Patients on PD	p Value
N	108,194	105,952	2,242	0.01
% Utilizing PD of the total ESRD population	7.10%	7.09%	7.46%	0.01
Mean Age	57.40	57.82	37.49	<0.001
% Female	49.98%	44.84%	51.38%	<0.001
Race				
• Caucasian	70.81%	70.85%	68.87%	<0.001
• Black	21.43%	21.37%	24.53%	<0.001
• Asian	4.79%	4.78%	5.04%	<0.001
• Other	2.97%	2.99%	1.56%	<0.001
No. of Comorbidities				
• 0	53.39%	53.23%	61.24%	<0.001
• 1	25.86%	25.91%	23.42%	<0.001
• 2	10.39%	10.43%	8.74%	<0.001
• 3+	10.35%	10.43%	6.60%	<0.001
% Employed	25.55%	25.47%	29.26%	<0.001
Albumin Level				
• % less than 2g/dL	1.09%	1.09%	1.12%	0.001
• % 2-3 g/dL	13.79%	13.73%	16.73%	0.001
• % > 3g/dL	61.56%	61.59%	59.72%	0.001

Table 2. Unadjusted and Adjusted (for age, sex, number of comorbidities and year of initiation) Hazard Ratio of Mortality for DAGF patients compared to native ESRD patients on PD

	HR (DAGF / Native ESRD)	CI (95%)	p Value
Unadjusted	1.37	1.29-1.45	<0.001
Adjusted	3.49	3.28-3.71	<0.001

FR-PO675

Bedside Peritoneal Dialysis Catheter Repositioning - A Novel Technique

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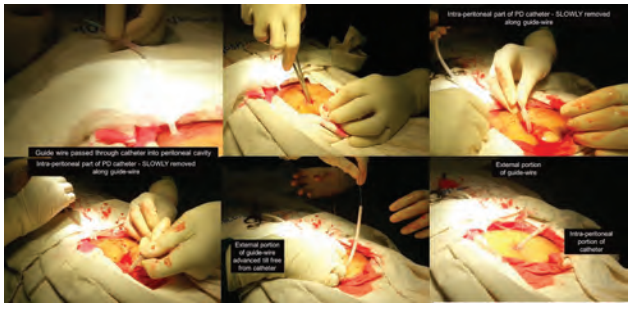
Introduction: Malfunction of peritoneal dialysis (PD) catheters usually need surgical repositioning, requiring anaesthesia, operating time, longer hospital stay and surgical expertise. This novel technique obviates need for surgical intervention.

Case Description: The abdomen is scrubbed and cleaned. PD catheter distal to exit site is meticulously cleaned, titanium adaptor and transfer set removed, the former soaked in povidone-iodine. A guidewire is passed through catheter into peritoneal cavity. A 5mm incision is made over previous healed incision scar. Soft tissue is dissected until deep cuff is visible. With blunt dissection, cuff is gently separated from subcutaneous tissue where it had become anchored. Taking care to retain guide wire's position inside peritoneum, intra-peritoneal part of PD catheter is removed. External portion of guidewire is advanced through PD catheter till free from catheter. Proximal end of guidewire is in peritoneum

and distal end free. PD catheter is searched for occluding clots, and if present, are gently milked out and catheter flushed with saline. A dilator is advanced along guidewire to ensure adequate space for PD catheter at linea alba. Peel-away sheath and dilator are then advanced into peritoneum. The dilator and guide wire are removed leaving only sheath in place. The catheter is then re-introduced into peritoneum through the sheath, which is separated leaving catheter in place. Peritoneal cavity is filled with PD fluid and good inflow and outflow are ensured. Subcutaneous tissue and skin are closed in layers. In the 18 patients so far. we have had an immediate technical success of 100% and a month later 12 catheters were functioning well (66.67%). Six months later, the catheters remained functional except in one patient who died due to heart disease.

Discussion: This novel technique allows for preservation of the catheter, exit site and tunnel. This reduces costs and duration of hospital stay and does not require specialized surgical expertise, operating room time or a dedicated anaesthetist.



Steps of repositioning

FR-PO676

Percutaneous Re-Positioning of Peritoneal Dialysis Catheter Accidentally Placed in the Pre-Peritoneal Subcutaneous Space Leaving the Tunnel and Exit-Site Intact - A Novel Idea

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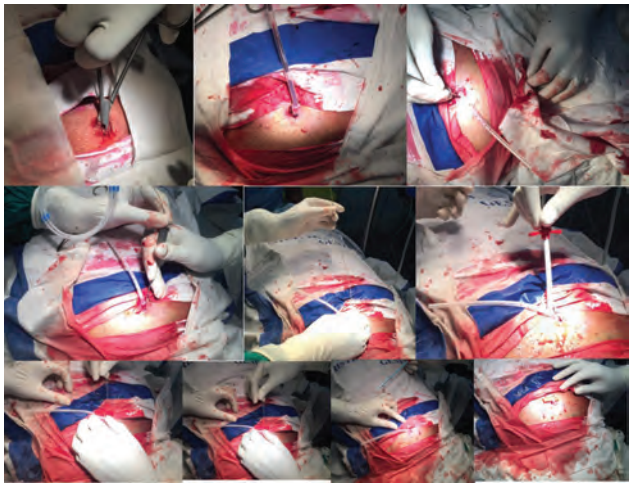
Introduction: Percutnaeously placement of peritoneal dialysis (PD) catheters may be accidenatly be placed in the pre-peritoneal subcutanous space if the introducer needle does not pierce the peritoneal membrane in the initial part of the procedure. If this happens, the catheter insertion has to be redone either percutaneously or surgcially. The catheter often has to be replaced as part of it has been externalized and is unsterile.

Case Description: 70 year old man with end stage renal disease underwent bedside PD catheter insertion. Unfortunately, the cathteter was accidetally placed in the pre-peritoneal subsutaneous space. The inflow and outflow of PD fluid was present as the pre-peritoneal subcutaneous space had expanded with the PD fluid, but was slow. The problem was identified on CT scan and PD catheter re-insertion was planned. A week later, a novel technique was attempted in which the exit site and tunnel were untouched. The skin and subcutanousl sutured over the origical catether insertion site were undone and the deep cuff of the catheter was dissected and the intrabdominal part of the cathteter was exteriorized. A veress needle was advanced till it reached the peritoneal space, the position of which was confirmed using a guidewire. The track was dilated using a peel-away sheath-dilator assembly. The dilator was removed and the intra-abdomina portion of the catheter was slid in. The wound was closed in layers after ensuring good inflow and outflow. Peritoneal dialysis exchanges were begun the same day.

Discussion: Compared to using a new PD catheter and tunnel, this novel technique allows for a simple bedside repositioning technique, saving time, operating room time, reducing hospital stay and possibly avoiding unnecessary hemodialysis.



Steps of procedure

FR-PO677

Long-Term Outcomes in Peritoneal Dialysis Patients Who Initiated Immediately After Catheter Insertion Using Percutaneous Catheter Placement Method

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Background: The aim of this study was to evaluate the long-term outcomes in peritoneal dialysis (PD) patients who initiated immediately after catheter insertion using percutaneous catheter placement method without a break-in procedure.

Methods: We conducted a retrospective study including all incident PD patients in our hospital who began PD therapy between January 2002 and December 2017. PD catheter (swan neck or non-swan neck) were used and inserted by a nephrologist using percutaneous catheter placement method with guidewire. PD therapy initiated immediately after catheter insertion without a break-in procedure. Demographic and clinical data including ESI, peritonitis, pericatheter leakage, and catheter dysfunction during the study period were collected. Event-free survival rates of clinical events and patient survival rates were calculated using Kaplan-Meier analysis.

Results: One-hundred thirty seven patients began PD during the study period, and 127 of these patients were included in the final analysis. During the follow-up period, 83 patients were withdrawn from PD. Reasons for discontinuing PD were transfers to hemodialysis(42.3%), kidney transplantation (18.8%), follow-up loss(21.7%), or death(17.6%). The survival rates were 96.7%, 94.3%, 91.3%, 91.3% and 86.8% at 1, 2, 3, 4 and 5 years after PD initiation, respectively [Fig. 1]. In the Cox multivariate model, DM was related to patient survival. The technique survival rates were 90.9%, 83.7%, 81.2%, 73.5% and 69.6% at 1, 2, 3, 4 and 5 years after PD initiation, respectively [Fig. 1]. The risk factor for technique survival was catheter migration (95% CI 0.113-0.701, p=0.006). Event-free survival rates of variable clinical events were shown in Fig 1.

Conclusions: Our study showed that long-term outcomes including patient survival rates and event-free survival rates were comparatively high in PD patients who initiated immediately dialysis after catheter implantation using percutaneous method

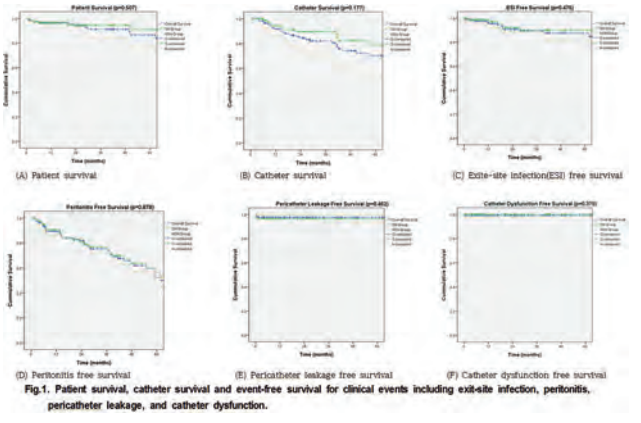

Fig.1. Patient survival, catheter survival and event-free survival for clinical events including exit-site infection, peritonitis, pericatheter leakage, and catheter dysfunction.

FR-PO678

Laparoscopic Peritoneal Dialysis Catheter Insertion Using Nitrous Oxide Under Conscious Sedation

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Background: The conventional laparoscopic peritoneal dialysis catheter implantation using carbon dioxide (CO2) for peritoneal insufflation necessitates general anesthesia (GA) due to CO2-induced peritoneal pain. However, end stage kidney disease (ESKD) patients are not generally ideal candidates for GA. Using nitrous oxide (N20) as an insufflation agent offers several advantages, including PD catheter insertion under regional anesthesia.

Methods: We performed a retrospective cohort study in ESKD patients who underwent laparoscopic PD catheter insertion with N2O under regional anesthesia from Jan 1, 2008 to May 31, 2018. Patient demographics, treatment outcomes and adverse events were collected from our electronic databases.

Results: There were 152 patients, mean age was 68.2 ± 13.2 years; 41.5% women. Most common cause of ESKD was diabetic nephropathy (25.6%). Only 2 patients had unsuccessful catheter insertion due to extensive intra-abdominal adhesions. One patient required unexpected hospitalization due to intraoperative bleeding requiring a blood transfusion. Mean follow up was 26.6±23.1 months. One-year and 2-year catheter survival rates were 90.1% and 84.9%. Mean catheter survival was 51.0 ± 7.6 months.

Conclusions: Laparoscopic implantation of PD catheter with N2O insufflation and local anesthesia is feasible and can be performed safely in end-stage renal failure patients.

FR-PO679

Bedside Peritoneal Dialysis Catheter Insertion Program at the University Health Network – An Improvement Initiative to Grow PD Prevalence

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Background: Peritoneal dialysis (PD) is underutilized in many jurisdictions, despite known societal and individual benefits, cost efficiency, and safety. One identified cause is lack of timely access to PD catheter insertion, which lends itself to quality improvement and innovation.

Methods: At the University Health Network at the University of Toronto, we sought to initiate a nephrologist-led bedside PD catheter insertion program directed at late presenting ESKD patients, beginning in January 2013, with appropriate support from a nursing education and infrastructure perspective. This included the implementation of a "Dialysis Start Unit" for patients needing Intermittent Peritoneal Dialysis while waiting for training with a nursing educator, as well as a dialysis catheter coordinator who was involved in both the bedside and surgical PD insertion programs. Specifically, the program aimed to help grow the PD program, while maintaining literature standards for catheter function, adverse events, and technique survival.

Results: The nephrology division at UHN has been able to create sustainable growth at a rate of 35% in its PD population using a safe, resource conscious, and effective way. This growth has come with no cost by way of patient adverse events or sacrifice of technique survival. Indeed, PD catheter failure rates have been consistently falling with more experience within the program, and within the last 2 years have been well below the accepted literature standards of 25%, at a rate of 5-7%. This is in keeping with available evidence that operator expertise, experience and interest have a large bearing on the success of any insertion technique. The rise in PD population was also accompanied by stability of home hemodialysis (HHD) and in-centre intermittent hemodialysis (IHD) numbers, while continuing to have a sustained rise in PD patient numbers.

Conclusions: Using a well-coordinated multi-disciplinary initiative to insert PD catheters at the bedside, the nephrology division at UHN was able to increase PD prevalence in a safe manner, which can be replicated in a similar context using similar resources and planning

FR-PO680

Abdominal Rectus Thickening as a Predictor of Peritoneal Catheter Primary Dysfunction

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Background: Percutaneous insertion of peritoneal dialysis (PD) catheters by nephrologists are an effective alternative to open surgical techniques. Complications following PD catheter insertion requiring manipulation or replacement are about 20%. Previous studies show that ultrasound measurements of skin depth to the peritoneum with values> 5.5 cm ($p < 0.001$) are associated at percutaneous DP catheter dysfunction.

Methods: We conducted a cross-sectional study of 46 patients who had their first percutaneous peritoneal dialysis (PD) catheter and had a primary PD catheter dysfunction (PDC) defined as PD catheter removal when the PDC never worked due to a problem related to the catheter. They were divided into 2 groups: Group A patients who presented DPC dysfunction (20 patients) and Group B without DPC dysfunction (26 patients). We perform ultrasound measurement of the abdominal wall to all patients after DPC was inserted. We mesured distance from the surface of the skin to the parietal peritoneum (SPP) and the thickness of the rectus abdominis (RAT) in centimeters (cm) in the sagittal plane, on the medial border of the rectus abdominus muscle at the level of the umbilicus, just above the scar of the procedure. Body mass index (BMI), central obesity (CO) was calculated.

Results: The mean age was 44.3 years (SD +/- 13.6). The BMI of Group A 24.9 kg / m2 (SD +/- 5.5) and Group B 24.4kg / m2 (SD +/- 4.1), central obesity (OC) of group A 93.6cm (SD +/- 16.8) and Group B 90.5 cm (SD +/- 11.2), SPP Group A 2.7 cm (SD +/- 0.94), Group B 2.2 cm (SD +/- 0.7), Group A RAT 1,005 cm (SD +/- 0.2), Group B 0.7cm (SD +/- 0.15). Of the 46 patients, 43% (20) had primary PDC dysfunction (group A). The RAT $\geq$ 1 cm was the only variable that was significantly associated with the primary dysfunction of the PD catheter (RR: 6.8, IC 95% 2.7-16.0) OR: 100, (IC 95% 10.23 .977.1, $p < 0.0001$), a sensitivity of 80%, specificity 96%, PPV of 94% NPV of 86%, with an AUC 0.86.

Conclusions: It was also observed that 94.4% (17) of patients with CO who did not have primary PDC dysfunction had a RAT <1 cm. No significant association was observed between primary PDC dysfunction and other risk factors, such as age, BMI, CO and SPP. The RAT $\geq$ 1cm is an very good predictor of the risk of primary dysfunction of the PD catheter.

FR-PO681

Comparison of Different Techniques for Peritoneal Dialysis Catheter Insertion: A Systematic Review and Network Meta-Analysis

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Background: Peritoneal dialysis (PD) is one of the important treatment methods of end-stage renal disease (ESRD). Various techniques had been applied to the PD catheter insertion, including open surgery, laparoscopy and percutaneous techniques. However, the best technique, regarding both the catheter survival and catheter related complications, is still controversial. Previous studies did not compare the three techniques at the same time. Therefore, we did a systematic review and network meta-analysis to identify the best insertion method.

Methods: We systematically searched PubMed, Embase, Cochrane library, CNKI, WanFang and VIP database for randomized controlled trial, case-control study and cohort study until December 2017. Quality assessment and data extraction were conducted by two reviewers independently. We performed a direct meta-analysis and Bayesian network meta-analysis to pooled odds ratios (OR) or weighted mean differences (WMD) with 95% credible intervals (CrI) with random effects model. The node-splitting method was used to assess the inconsistency. We estimated the potential ranking probability of treatments by calculating the surface under the cumulative ranking curve for each intervention. Meta data is analysed by Addis software version 1.16.5.

Results: Forty studies involving 6494 patients were included (10 RCTs and 30 retrospective studies). The surface under the cumulative ranking curve (SUCRA) ranking from the network analysis showed that laparoscopy had the lowest occurrence of PD catheter displacement and obstruction, followed by percutaneous insertion and open surgery. Percutaneous insertion had the lowest occurrence of hernia, exit-site and tunnel infections. Open surgery had the lowest incident of bleeding.

Conclusions: Considering about the dysfunction of PD catheter, laparoscopy may be the best technique for PD catheter insertion. Different technique has the advantage of their own and more RCTs with larger sample size, comparing laparoscopy and percutaneous insertion directly are needed in the further.

FR-PO682

Stakeholder Priorities for Remote Management in Peritoneal Dialysis

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Background: Remote management (RM) technologies alert and enable health care providers to manage a range of health-related changes including remote follow-up, where appropriate. In this study, an Advisory Group including patients, social workers, nurses, nephrologists, alongside researchers, developed and reviewed interviews and responses from patients, care partners and clinicians on using remote management (RM) technologies that may influence priorities for patient care and engagement in peritoneal dialysis (PD) treatment for kidney failure.

Methods: Thirty semi-structured phone interviews were conducted in the United States and United Kingdom between October 2017 and January 2018. These aimed to assess effects of RM on PD treatment from patients', care partners' and clinicians' perspectives. NVivo11 was used to organize and analyze the data to identify remote management priorities. Sample quotes illustrating the variations in perspectives among the three groups are shown in Table

Results: Sample quotes illustrating the variations in perspectives among the three groups are shown in the Table. Clinicians tended to view RM as a tool with the potential to significantly change management and delivery of PD care while patients and care partners frequently perceived RM as having some benefits but not necessarily addressing some of the more immediate needs with their care.

Conclusions: There were variations in aspects of RM that were most valued by patients, care partners and clinicians. Opportunities for further technological innovations might exist in addressing patient and care partner priorities for PD care.

Table: Sample quotes on priorities for remote management and PD care

Clinician	"[RM enables us] to better understand how each of them dialyze, to be able to identify problems and to change how we manage our day... not necessarily burden families with unnecessary phone calls" "I really enjoy this because it [RM] does allow us to sort of dissect out all the important components of their prescription and then to discuss them with the family and give them some visual information as well to sort of compliment what we're telling them..." "...in that first phase there's a potential to be more gradual about introducing the treatment and more responsive to problems that the patient's experiencing, anticipating those sorts of problems. I think that's the potential benefit of remote technologies"
Patient	"It would be great if, ya know, you had your blood pressure cuff and that information could also be directly transmitted so you don't have to actually enter anything." "And the Smart machine tells you, it tells me when my treatment is going to be over, which is really good, I never knew with the other machine.." "...my car was going to be towed and he banged on my door and I couldn't even go to the door, you know and I realize I couldn't disconnect when I'm in dual mode... I'm on there nine hours, it's a long time to be trapped"
Care Partner	"If the RM enables us to individualize the treatment of care I would say maybe that would be a benefit..." "It [RM] does kind of cut down on the requirements for me to make sure that we are relaying all of his vitals and input and output for treatment." "..just maybe being able to, like, message, like, last night my husband was having some issues with severe itching so be able to maybe message the team and say 'hey he's having this, do we need to do something different, is this normal?'"

FR-PO683

Comparison of Hospitalization Rate in Automatized Peritoneal Dialysis Patients with and Without Remote Management Program in Colombia

Angela S. Rivera,[3] Mauricio Sanabria,[2] Jasmin Vesga,[1] Adriana M. Suarez,[1] Alfonso Bunch.[1] *[1]RTS, Bogota, Colombia; [2]RTS Baxter, Bogota, Colombia; [3]Baxter, Bogota, Colombia*.

Background: The remote monitoring technology specifically designed to be integrated into APD systems (such as ShareSourceä, Baxter Healthcare) gives both patients and their clinical team a powerful tool that can enhance communication, potentially improve adherence to the treatment, optimize fluid balance; and address potential complications of therapy in near real-time. The purpose of this study was to compare the hospitalization rate in incident adult patients in Automated Peritoneal Dialysis (APD) with and without HomeChoice Claria® & Shaaresource®.

Methods: Multicenter observational retrospective cohort study in incident adult patients in Automated Peritoneal Dialysis (APD) with HomeChoice Claria and Sharesource®, enrolled between October 1st, 2016 to October 31th, 2017 with follow up of 1 year, in 46

renal clinics of the Renal Therapy Services (RTS) Colombia network. For the analysis, descriptive statistics and incidence rate were used

Results: 954 patients were evaluated, 56.6% were men, the mean age was 59.63 years (SD = 16.12). See table 1 We found a decrease statistically significant in days and hospitalization rate with the monitoring program for APD patients. Details are presented in table 2 y 3

Conclusions: A remote monitoring program for APD patients may be easily and efficiently implemented in healthcare settings improving clinical outcomes.

Funding: Commercial Support - Baxter Healthcare Corporation

Table1. Baseline clinical and demographic characteristics

Variables	With Claria N= 90 % N	Without Claria N= 864 % N
Age [mean;SD] year	56.83 17.14	59.92 15.99
Male	58.89 53	56.37 487
History Diabetes Mellitus	38.89 35	46.30 400
Charlson Index >= 4	13.33 12	13.43 116
Educational level		
None	8.89 8	17.13 148
Elementary school	23.35 21	41.09 355
High School/Technical diploma	50.00 45	33.8 292
University degree	17.78 16	7.99 69

Table 2. Hospitalization rate

Year	N	Person-Time (Years)	Events	Rate	95% CI		P
2017 without Claria	864	604.18	484	0.80	0.73	0.87	0.0159
2017 with Claria	90	71.7	41	0.57	0.41	0.77	

Table 3. Hospital days rate

Year	N	Person-Time (Years)	Days	Hospital days Rate	95% CI		P
2017 without Claria	864	604.18	4357	7.21	6.99	7.42	0.0000
2017 with Claria	90	71.7	394	5.49	4.96	6.06	

FR-PO684

Impact of Peritoneal Dialysis (PD) Remote Monitoring on PD Services

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Background: Remote monitoring to manage renal patients is increasing. HomeChoice Claria with Sharesource™ (Baxter Healthcare Ltd) is a web-based, two-way connectivity platform enabling remote monitoring of automated peritoneal dialysis (APD). We introduced it in 10/2015 and reviewed it's impact after 12-months.

Methods: 48 patients were studied; median age 62.8 years (24 – 90), 30 males. Patients and clinical information were identified from the electronic patient records system and medical records. We investigated the number of patient on PD, months on treatment, outpatient attendances, remote consultations, home visits and staff travel. We also looked at take-up/ drop-off rates. Continuous variables were analysed by the independent samples t-test.

Results: Average number of patients on active PD increased by 14%, patient months on treatment increased by 12% as patients spent 4 months longer on treatment on average. Outpatient attendances increased by 34%. 60 remote consultations were performed, averaging 0.2 remote consultations/ patient/ month. The number of home visits per month increased by 41% and the visits per patient increased by 29%. The mean nurse mileage/ month increased by 57% and mileage/ patient/ month increased by 43% in 2015/16 (Results shown in Table 1). There was a net loss of 9 patients 12 months prior to implementation and a net gain of 2 patients 12 months after implementation.

Conclusions: More service was delivered with the same number of nursing staff. There was a rise in PD-related OP attendances per patient, mean home visits/ month and mileage/ patient in 2015/6; this may be due to increased visit for educational purposes during system exchange as data collected across the year showed a reduction. Further study involving longer period of observation is needed to validate the result.

Summary of results

	Pre ShareSource (01/10/14 – 30/09/15)	Post ShareSource (01/10/15 – 30/09/16)	p-value
No. patients on active PD (mean)	21.5	24.5	0.05
Number of months on treatment (mean)	32.8	36.8	0.001
Outpatient attendances/ month (mean)	61.6	82.3	0.08
No. home visits/ month (mean)	11.3	15.8	0.03
No. visits/ patient (mean)	0.5	0.7	0.42
Mileage/ patient/ month (mean)	6.4	9.2	0.07
Nurse mileage/ month (mean)	139	217.8	0.02
PD related blood tests/ month (mean)	36.8	36.1	0.89
PD catheter removal	9	6	
Net take on drop on-off rate	-9	+2	

FR-PO685

Cost Consequence Analysis of a Remote Monitoring Program to Improve Clinical Practice of Automatized Peritoneal Dialysis in Colombia

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Background: To estimate from the payer perspective, the cost and clinical consequences of a Remote Monitoring (RM) standardized program, supported in *Claria Sharesource* technology, to improve the clinical practice and control of incident patients in automatized peritoneal dialysis (APD) currently treated in the Renal Therapy Services (RTS) setting in Colombia.

Methods: A one year Markov analytic model, structured in five health states, was used to project costs and clinical outcomes from a cohort of 100 APD patients with and without RM. Real world outcomes required as model inputs such as rates of hospitalization, peritonitis, technique failure and mortality were estimated from retrospective patient level registries and RTS medical records. Renal care ambulatory costs were estimated from referent national tariffs. Inpatient care costs were obtained from administrative database in a referent health care provider. Model results were reported as the RM incremental effect in: overall direct costs, patient months in control, one year persistence in APD, hospitalization episodes, days of hospitalization, peritonitis episodes, technique failure episodes and death episodes. Both deterministic and probabilistic sensitivity analyses were done to analyze the effect of information uncertainty in the model results.

Results: *In comparison with APD without RM, the implementation of a standardized RM program in 100 APD patients during one year resulted in*: Overall savings USD $ 16,169; 73 additional patient months in control; 25 hospitalization episodes avoided; 243 hospitalization days avoided; 17 peritonitis episodes avoided; 7 technique failure episodes avoided; 7 death episodes avoided and 13 additional patients persisted in APD technique after one year. *Deterministic sensitivity analysis*: RM tariff, hospitalization rate and hospitalization episode costs were the most sensitive drivers of model results. *Probabilistic sensitivity analysis:* With 66% of chance, the RM standardized program was a cost-saving dominant intervention.

Conclusions: From the payer perspective, RM is a cost saving dominant alternative, improving patient time in control, burden of hospitalization, risk of complications, persistence in APD technique and mortality.

Funding: Clinical Revenue Support

FR-PO686

Associations Between Use of a Patient Portal with Hospitalization Rates and Modality Failure in Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) patients often have their clinical status assessed monthly, which limits the clinicians view of the patients' health state. A large dialysis provider has recently constructed a connected health program for PD patients to enter their clinical parameters or complaints daily. This portal provides automated alerts to clinicians for abnormal findings, as well as non-adherence with reporting. We analysed outcomes for hospital admission rate and modality failure in patients who were using the portal versus those who were not.

Methods: We included data from 5549 active PD patients who were introduced to the patient portal prior to Sep 30, 2017 and had <=10 hospitalizations days in Sep 2017. Patients who documented data for ≥20 treatments during Sep 2017 were considered "the engaged group" (n=1199). The remaining 4350 patients who did not document any treatment data on the portal were considered "the non-engaged group." Patients who documented data on >0 and <20 treatments were not included in this analysis. Patients were followed 6 months starting Sep 30, 2017 up until the earliest of discharge from the clinic (including death), switch from PD to hemodialysis (HD) or end of follow-up. We compared the percent of patients who switched modality from PD to HD using Chi-square test without accounting for the length of follow-up. We compared the hospital admission rate during follow-up period using Poisson regression model adjusted for prior hospitalizations.

Results: We observed that patients in "the engaged group" had a 20% lower risk of hospitalization compared to the "non-engaged group" (Relative Risk=0.8, p<0.001). We found no significant difference in modality changes from PD to HD between groups (11% engaged patients vs 13% non-engaged patients, p=0.11).

Conclusions: Consistent documentation of treatment data in the patient portal was associated with lower hospital admission rates among PD patients suggesting that better patient engagement as well as more real-time clinician involvement may impact patients' hospitalization rates. However, observations may be confounded by indication of portal use, which could represent a more adherent group of patients. Further analysis is needed to confirm these findings.

FR-PO687

Role of Peritoneal Phosphorus Transport in Peritoneal Dialysis Regimen for the Management of Hyperphosphatemia

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Background: The ratio D/P-Creatinine (DP-Cr) obtained by the peritoneal equilibrium test (PET) is the most widely used parameter to characterize the type of peritoneal membrane transport, and it is used to determine the dialysis regimen for ultrafiltration (UF). It has been suggested that net UF influences the final clearance of solutes, so guiding ultrafiltration by D/P-Phosphorus (DP-P) instead of DP-Cr could have some added value in the management of hyperphosphatemia. The objective of this study is to define if there is a correlation between DP-P and DP-Cr, and if these are related to the clearance of phosphorus (P) and creatinine (Cr).

Methods: Retrospective analysis of PET performed in our center in 2016-2017. DP-Cr and DP-P were calculated, and in patients with 24h effluent sample the day of the PET, it was also analyzed weekly Kt/V-urea, and peritoneal Cr and P clearance (CrCl and PCl). Statistical analysis was done using t-Student test for independent data and Pearson correlation coefficient, establishing a significance level of $p<0.05$.

Results: 68 PET were analyzed in 54 patients, mean age 60.4 years (SD 17), predominantly men (69% vs 31%). The mean plasma P, DP-Cr and DP-P were respectively 4.5 mg/dL (SD 1.2), 0.74 (SD 0.12) and 0.71 (SD 0.17). The correlation coefficient DP-P/DP-Cr showed a significant relationship ($r=0.84$, $p<0.001$), which was maintained when analyzing patients according to phosphorus levels: DP-P/DP-Cr with P<5 mg/dL ($r=0.81$); and P≥5 mg/dL ($r=0.93$) ($p<0.001$). Patients in DP-P ≥50th percentile had P levels of 4.2 (± 1.05), and those in <50th percentile had levels of 4.88 (± 1.38) ($p <0.031$). Moreover, in patients with 24h effluent analyzed the day of the PET (n=35), the average PCl and CrCl was 4.1 and 2.85 ml/min, with statistical significant correlation ($r=0.92$, $p<0.001$). However, in these patients no relationship was found between DP-Cr and CrCl ($r=0.068$, $p=0.7$), nor between DP-P and PCl ($r=0.052$, $p=0.7$).

Conclusions: The DP-P/DP-Cr high correlation suggests that both parameters could be useful to classify the type of peritoneal transport. However, although patients with higher DP-P had better control of hyperphosphatemia, thus suggesting a direct positive relationship between DP-P and PCl, our data showed no correlation between them.

FR-PO688

Tissue Sodium Stores in Peritoneal Dialysis Patients

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Background: A remarkable amount of sodium (Na^+) is stored in the tissue without commensurate water retention, particularly in the skin and muscle. Using ^{23}Na-magnetic resonance imaging (MRI), elevated tissue Na^+ content was found in hemodialysis patients. Peritoneal dialysis (PD) patients generally have higher residual kidney function than HD patients, yet the effectiveness of PD in tissue Na^+ removal has not been evaluated.

Methods: We examined tissue Na^+ levels in 10 PD patients. PD patients were matched with healthy controls by age, race, gender and body mass index (BMI). All study subjects underwent ^{23}Na-MRI to quantify Na^+ levels in lower leg muscle and skin.

Results: We studied 10 PD patients and 41 controls. PD patients had significantly higher skin and muscle Na^+ levels compared to controls (figure 1). In PD subjects, skin Na^+ level was inversely correlated to ultrafiltration volume, a marker of Na^+ removal adequacy (figure 2).

Conclusions: Our data suggest that PD patients have elevated tissue Na^+ stores. The mechanisms by which this abnormality develops and its consequences should be further examined.

Funding: Commercial Support - Baxter Healthcare Corporation

Characteristics of the study population

	Patients on PD (n=10)	Controls (n=41)	P value^
Age (years)	55 [48.8, 61.5]	51 [45, 59]	0.55
Male	3 (30)	23 (56.1)	0.14
African American	4 (40)	23 (56.1)	0.25
Caucasian	5 (50)	18 (43.9)	
BMI (kg/m^2)	23.6 [21.9, 17.9]	27.6 [25.4, 31.4]	0.07
Creatinine (mg/dL)	10.3 [7.2, 13.3]	0.9 [0.8, 1.1]	<.001
Urine output (mL/day)	100 [50, 520]		

Continuous variables are presented as median [interquartile range], categorical variables are presented as n (%).

Figure 1. Skin and muscle sodium levels in PD patients and healthy controls

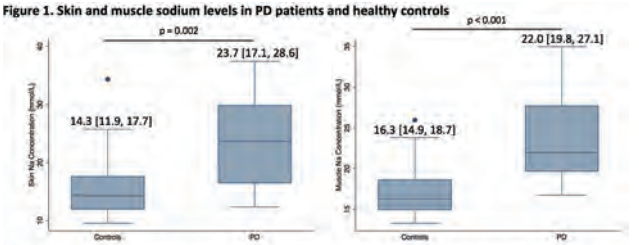
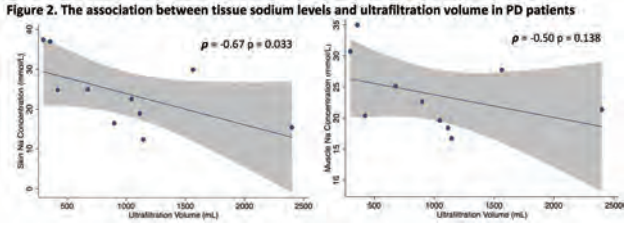


Figure 2. The association between tissue sodium levels and ultrafiltration volume in PD patients



FR-PO689

Comparison of Low and Standard Dose Adrenocorticotropic Hormone (ACTH) Stimulation Test in the Diagnosis of Adrenal Insufficiency in Peritoneal Dialysis Patients

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Background: Adrenocorticotropic hormone (ACTH) stimulation test is the current standard for diagnosing adrenal insufficiency (AI). The low dose (1 μg) ACTH stimulation test (LDT) has been introduced to detect incomplete impairment of adrenal function with partial corticotropin deficiency, which might be masked by the conventional supraphysiological dose (250 μg) of ACTH employed in the standard dose ACTH stimulation test (SDT). Indeed, several studies have shown an increased sensitivity of LDT over SDT in chronic ill patients with secondary AI. This study aims to investigate the diagnostic value of low and standard dose ACTH stimulation tests for identifying AI in patients on peritoneal dialysis (PD).

Methods: A total of 60 prevalent PD patients were enrolled and underwent LDT and SDT using doses of 1 μg and 250 μg synthetic ACTH, respectively. The two tests were performed in random sequence with minimum one week interval and a cut-off level of peak serum cortisol for AI was <18 μg/dL in both tests. Surveys of AI-associated symptoms and laboratory test were performed.

Results: Overall, 22 (36.7%) patients in the LDT and 8 (13.3%) patients in the SDT showed an insufficient increase of cortisol to ACTH stimulation and were categorized as having AI. In the LDT, no remarkable difference in presence of symptoms associated with AI was observed between the AI patients and non-AI patients. Laboratory findings were not different between the two groups, either. However, the patients who were diagnosed with AI by the SDT complained fatigue (62.5% vs. 15.4%, P=0.009) and constipation (50.0% vs. 13.5%, P=0.031) more frequently compared with the patients without AI. The adequacy of dialysis (Kt/V) was significantly lower in patients diagnosed with AI by the SDT than non-AI patients (1.64±0.21 vs. 1.99±0.37, P=0.019).

Conclusions: Adrenal response to ACTH was diminished in low dose compared with standard dose and the use of LDT diagnosed more adrenal abnormalities than SDT in PD patients. However, the clinical significance of identifying AI patients using the LDT was not observed in those patients.

FR-PO690

Hyperosmolality in Peritoneal Dialysis Increases Plasma Arginine Vasopressin Levels

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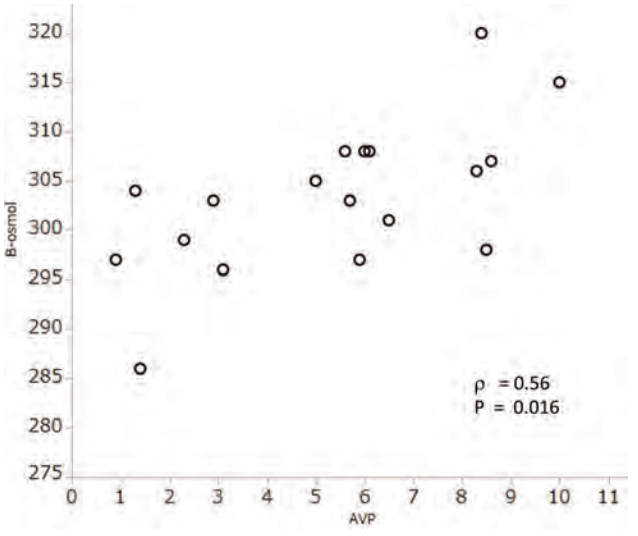
Background: Fluid retention is common in peritoneal dialysis (PD) patients. Arginine vasopressin (AVP), an antidiuretic hormone, promotes fluid retention and stimulates thirst. Consequently, AVP is important for fluid management in PD patients. Although several studies have reported an increase in plasma AVP levels in hemodialysis patients, the dynamics of plasma AVP levels in PD patients has not yet been clarified.

Methods: We measured plasma AVP levels and osmolalities in 20 PD patients aged 48-79 years-old over 2-145 months of PD duration. Blood volumes were evaluated by bioelectrical impedance analysis.

Results: Plasma AVP levels (5.5 ±0.6 pg/mL) and osmolality (303.4 ±1.6 mOsm/kgH_2O) increased significantly in PD patients. In addition, a positive correlation was observed

between plasma AVP levels and osmolality, and a small increase in plasma glucose levels (138.5 ±11.0 mg/dl) was observed in PD patients.

Conclusions: Several studies have shown that PD solution increases plasma glucose levels. Therefore, we considered that PD-induced hyperglycemia may cause an increase plasma osmolality and AVP levels. To the best of our knowledge, this is the first report to demonstrate an increase in plasma AVP level in PD patients. These findings provide novel insights into the fluid management of PD patients.



FR-PO691

Use of Raman Spectroscopy Analysis to Evaluate the Molecular Composition of Spent Peritoneal Dialysate and Urine over Time

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Background: Common indices to assess peritoneal dialysis (PD) adequacy – Kt/V urea and creatinine clearance – may not reflect clearance of other small and middle-molecular weight molecules that may be more important in the pathogenesis of uremia and patient outcomes. These indices may not reflect changes in residual renal function, peritoneal membrane integrity, local/systemic inflammation, patient metabolism, or mineral/electrolyte balance. Identification of other potentially important molecules in both spent dialysate (SD) and urine (UR) may provide better measures of treatment adequacy. However, analysis of these potentially-important molecules, with current technology (chromatography, mass spectroscopy), is time-consuming, expensive, and unlikely to be widely available in clinical settings.

Methods: We used novel methods, based on Raman spectroscopy and computational analysis, to study the molecular composition of SD and UR collected periodically from 15 PD patients over a two-year period of observation. Raman spectra were generated by irradiation of SD and UR samples at 785 nm, corrected for incident (background) radiation and then computationally normalized. The spectra of SD and UR samples from PD patients were compared to analytical standards, to unused dialysate fluid (SD samples) and urine (UR) collected from consented, healthy volunteers. Quantification of prominent spectral peaks (urea, creatinine, glucose, for example) was achieved by comparison with analytical standard calibration curves.

Results: As expected, spectra of SD and UR differed significantly. Of note, SD spectra among 15 patients also differed significantly from one another, as did UR spectra. For individual patients, both SD and UR spectra varied over time, reflecting changes in types of molecules being dialyzed and/or excreted in urine. Variations in either SD or UR spectra were not well-correlated to Kt/V urea or creatinine clearance. Prominent spectral peaks representing collagen and nucleic acids in some SD specimens may signal changes in peritoneal membrane integrity; this requires further analysis.

Conclusions: Changes in the molecular composition of peritoneal dialysate and urine over time can be identified using computational Raman spectroscopy. This method may yield a viable tool for assessing the clinical effectiveness of the peritoneal dialysis therapy.

FR-PO692

Time-Course Changes in the Levels of Biomarkers in Peritoneal Dialysis Effluent Among Patients Using New Neutral Fluids

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Background: Recently, new neutral peritoneal dialysis fluid (PDF) contained bicarbonate 25mEq/L and lactate 10mEq/L (Bic/Lac PDF), instead of lactate 40mEq/L contained neutral fluid (Lac PDF), was available in Japan. The levels of biomarkers in PD effluents are used as the indexes of peritoneal deterioration associated with PD. However, there are few reports evaluating time-course changes in biomarker levels according to dwell time using Bic/Lac PDF.

Methods: Six stable PD patients were included (72±6 y/o, male 83%, PD duration 52.8±32.8 months). We compared the levels of CA125, IL-6, FDP, VEGF, and TNF-α in PD effluents between Bic/Lac PDF and Lac PDF after a dwell time of 2, 4, 6, and 8 hours.

Results: The levels of CA125 and IL-6 after the dwell time of 2, 4, 6, and 8 hours were as follows; CA125: Bic/Lac PDF, 13.2±6.5, 21.3±10.9, 26.8±14.2, and 33.6±19.1 U/mL; Lac PDF, 10.5±3.6, 16.6±5.6, 21.5±8.0, and 27.4±10.5 U/mL, and IL-6: Bic/Lac PDF, 10.1±7.8, 16.9±9.0, 23.4±10.3 and 33.2±11.9 pg/mL; Lac PDF, 12.1±6.9, 21.1±11.6, 29.4±16.2, and 43.2±23.6 pg/mL, respectively. The levels of FDP also showed increasing trends over time. The levels of VEGF and TNF-α in some samples were below the detection limits up to a dwell time of 6 hours.

Conclusions: The levels of biomarkers in PD effluents are greatly affected by PDF dwell time. Time-course changes in the levels of biomarkers are similar between two PDF.

Funding: Commercial Support - Baxter Healthcare

FR-PO693

T Regulatory Cells in Peritoneal Dialysis: Effect of the First Dialysis Session

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Background: T Regulatory (Treg) cells are a subpopulation of T cells that modulate the immune system, maintain tolerance to self-antigens, prevent autoimmune disease and regulate key immune responses across a variety of disease settings. In the literature, contrasting results have been reported about the influence of dialysis on Treg cells, in chronic kidney disease stage G5 patients that show activated but impaired immune system. Moreover the influence of dialysis on T cells needs further investigation. The aim of this study is to evaluate the influence of the first peritoneal dialysis (PD) treatment on Treg cells subset.

Methods: A total of 13 patients that have to start PD were enrolled. Treg were studied by flow cytometry with: CD3(PerCP); CD4(FITC); CD25(PECy7); CD127(PE) and FOXP3(APC) antibodies. Time point: T0 (before the first dialysis treatment); T1 (after 1 month). We performed Wilcoxon for dependent samples to compare the mean delta percentage difference between T0 and T1(100*(T1-T0)/T0).

Results: Treg cells (either considered as CD25+FoxP3+ or as Foxp3+) analyzed as percentage of lymphocytes showed a statistically significant increase during time (median=35.92; p=0.0425 for CD25+FOXP3+ and median=30.85; p=0.0479 for FOXP3+); Splitting Foxp3+ cells into CD25Hi, CD25Int and CD25Lo, showed an increment during time of Foxp3+CD25hi population (median=53.85; p=0.0215) while the other two populations remained unchanged (median=23.81 and median=15.38 respectively; p>0.05), as well as T lymphocytes (median=-6.58; p>0.05).

Conclusions: The study analyzed for the first time T cells variation before and after the first PD treatment. PD treatment improves T cells status by increasing Treg percentage, and Treg expressing CD25 after one month of treatment, while it does not influence other cells populations.

FR-PO694

miRNAs and Hyalinizing Vasculopathy in Peritoneal Dialysis Patients

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Background: Peritoneal membrane is conditioned by lesions appearing at long-term for dialysis purposes. Among these lesions, Hialynazing Vasculopathy has received less attention than others, and mechanisms causing this damage are incompletely studied although it is regularly found at advanced peritoneal stages. miRNAs are important regulators of cell biology. A miRNA transcriptomic study is an appropriate approach to independently (non-hypothesis driven) explore molecular mechanisms involved in this pathology.

Methods: We studied 7 patients affected by peritoneal vasculopathy and 4 patients without it. Total RNA was extracted from FFPE peritoneal tissue, small RNA libraries were prepared and sequenced.

Results: 20 miRNAs differentially expressed between groups were found (Table, up/down in vasculopathy). Remarkably, 9 of them belong to a cluster of miRNA loci separated by less than 10 kb in chromosome 14 (marked in Table). We also detected messenger RNAs which were differentially expressed, and positive correlations between miRNAs and these messenger RNAs were found

Conclusions: GO enrichment performed based on coding genes shown as differentially expressed, revealed differential enrichment in proteins with hydrolase activity and proteins with RNA and protein binding functions. Differential enrichment was also observed in proteins involved in translation processes with sub-localizations mainly exosomal vesicles and extracellular space besides of cytosol sub-localisations probably related with translational processes. Enrichment analysis of metabolic pathways reveals enrichment in enzymes involved in three pathways; Aminoacyl-tRNA biosynthesis, N-Glycan biosynthesis and Galactose metabolism. The impact of these new findings in terms of gene function will be discussed.

Funding: Government Support - Non-U.S.

Coordinates	logFC	Name	UP/Down	FDR	Targets
chr14_101040068_101040148	inf	hsa-mir-376a-2-5p	UP	0,000777221	No
chr2_35471404_35471486	inf	hsa-mir-548ad-3p	UP	0,0460239	1717
chr14_101056218_101056300	4,23946	hsa-miR-323b-5p	UP	0,00191471	998
chr14_101029633_101029714	4,02943	hsa-miR-494-5p	UP	0,000777221	712
chrX_134541340_134541437	3,20755	hsa-mir-542-5p	UP	0,000777221	1047
chr14_101062049_101062118	3,19646	hsa-miR-377-3p	UP	0,000777221	635
chr14_101042976_101043062	3,04605	hsa-mir-1185-1-3p	UP	0,0415403	1717
chr14_101065446_101065537	2,69693	hsa-miR-412-3p	UP	0,0377543	2888
chr14_101059754_101059838	2,46522	hsa-miR-154-5p, hsa-miR-154-3p	UP	0,000777221	165/83
chr14_101065597_101065667	2,35251	hsa-miR-369-5p	UP	0,0377543	294
chr1_1167862_1167952	2,13423	hsa-miR-200a-3p	UP	0,0182197	110
chrX_8126964_8127061	2,11956	hsa-miR-651-5p	UP	0,0444497	3719
chr11_111513438_111513515	1,70316	hsa-miR-34C-5p, hsa-miR-34a-5p	UP	0,040268	319/184
chr11_104252590_104252651	1,60367	hsa-mir-7641	UP	0,0336975	No
chr9_28888878_28888955	-2,58201	hsa-mir-873-3p	DOWN	0,00706994	4301
chr8_14853437_14853510	-2,49557	hsa-miR-383-5p.1,hsa-miR-383-5p.1,	DOWN	0,037625	235/223
chr14_101030051_101030129	-inf	hsa-mir-1193	DOWN	0,00509868	No
chr2_176600979_176601052	-1,64322	hsa-mir-1246	DOWN	0,00706994	No
chr9_40929009_40929092	-1,49387	hsa-mir-1299	DOWN	0,0443131	5405
chr10_98924498_98924568	-inf	hsa-miR-6507-5p, hsa-miR-6507-3p	DOWN	0,000777221	No

FR-PO695

Predictors of Icodextrin Induced Hyponatremia

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Background: Icodextrin (ICO) is a polyglucose peritoneal dialysis (PD) solution used in the long dwell. It is known to produce a mild dilutional hyponatremia due to its absorption and metabolism to maltose. In our program, many patients are treated with a single ICO dwell overnight as part of an incremental PD approach. We hypothesized that these patients are more likely to develop ICO induced hyponatremia due to decreased peritoneal clearance of maltose.

Methods: We performed a cross sectional analysis of our prevalent PD patients treated with ICO to determine the predictors of a significant (≥ 5 mmol/L) drop in serum sodium (Na) after ICO initiation. From our electronic database, demographic and biochemical information was abstracted. Serum Na values immediately before and a minimum of two weeks post ICO initation were compared.

Results: 107 of 193 prevalent patients had at least once ICO exposure and 98 patients had pre/post Na values and were included. Predictors of a significant drop in Na are shown in the table. When age and modality were entered into a regression model, the adjusted OR for hyponatremia with single ICO exchange was 1.88 (CI 1.16 to 3.13, P=0.01) compared with a single ICO and full CAPD or CCPD.

Conclusions: We conclude that use of a single overnight ICO exchange is associated with a significantly higher risk of hyponatremia than when ICO is used as part of a full CAPD or CCPD regime. This suggests that peritoneal clearance of maltose is important in attenuating the apparent drop in serum sodium with ICO. Further prospective studies are needed to validate this concept.

Characteristic	Delta Na ≥ 5	Delta Na <5	p value
N	35	63	
Age in years	66.3 ± 11.7	61.6 ± 14.2	0.08
Men	21 (60%)	39 (38.1%)	0.85
Modality			0.03
Single	13 (37.1%)	9 (14.3%)	
CAPD	8 (22.9%)	18 (28.6%)	
CCPD	14 (40.0%)	36 (57.1%)	
DM	21 (60.0%)	38 (60.3%)	0.98
D/P Cr	0.78 ± 0.07	0.79 ± 0.08	0.88
rGFR	5.1 ± 2.9	5.7 ± 3.8	0.36
PCR	0.83 ± 0.2	0.82 ± 0.19	0.86
Weight	75.9 ± 17.4	78.0 ± 19.2	0.58
Pre K	4.3 ± 0.5	4.3 ± 0.7	0.70

FR-PO696

Body Mass Index Trends in Patients Undergoing Peritoneal Dialysis for Decades and Their Effect on Patient Survival: Analysis of Data from an ESRD Registry (1985–2014) in Korea

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Background: Significant increases in the prevalence of obesity have been observed among patients with end-stage renal disease (ESRD). However, the changes in body mass index (BMI) status in prevalent Korean patients undergoing peritoneal dialysis (PD) over the recent decades and their impact on patient survival remains unknown.

Methods: Among 80,674 patients from the ESRD registry of the Korean Society of Nephrology. Prospective cases for Our analysis were outpatients ≥ 18-years-old who underwent maintenance peritoneal dialysis between 1985 and 2015. Among the possible (10,495) cases identified, cases with sufficient data was not measured were excluded. After screening, our analysis was based on the data of 6,095cases. BMI divided the entire patient population into quartiles. As a result, BMI was divided into <21.19 in group 1, 21.19 to 23.18 in group 2, 23.18 to 25.71 in group 3, and >25.70 in group 4. Among the 6,095 cases included in our analysis, 2,229 (36.7%) all-cause deaths was recorded over the follow-up period, Kaplan-Meier survival curves confirmed increase in all-cause mortality among BMI. We additionally analyzed these patients by dividing them into diabetic and non-DM patients.

Results: The log rank of the Kaplan-Meier survival curves according to the BMI Group was 19.53 and the P-value was 0.001. Cox proportional hazards model, Even after adjustment for potential confounders, the all-cause mortality HR was 1.29 (95% CI, 1.10–1.551; $P = 0.001$) in quartile 3 and 1.36 (95% CI, 1.14–1.59; $P< 0.001$) in quartile 4 respectively. However, There was no statistical significance between quartile 1 and quartile 2(HR, 1.17; 95% CI, 0.99–1.37; $P = 0.055$). In diabetic patients which were adjusted for several parameters that was important to mortality, meaningful values were seen in group 4 and mortality was 1.45 times higher in patients with BMI 25.7 or higher in diabetic patients 1.45 (95% CI 1.20-1.76 p-value<0.001).

Conclusions: In the Korean PD patients BMI elevation is significantly correlated with increased mortality of CAPD patients. In particular, the high BMI of DM CAPD patients increases mortality

FR-PO697

A Single Center Validation Study of a Korean Version of the SARC-F for Patients on Peritoneal Dialysis

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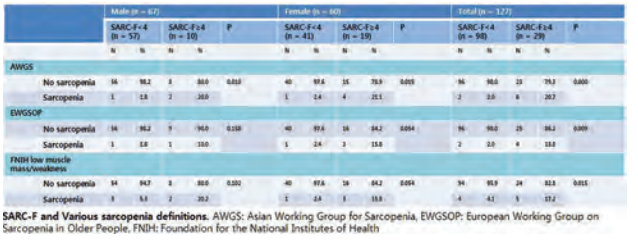
Background: The SARC-F is a simple screening tool for sarcopenia, consisting of 5 questions covering strength, assistance in walking, rising from a chair, climbing stairs, and falls. Given most of those on peritoneal dialysis (PD) have low muscle mass and poor physical function, it is worth examing an usefulness of SARC-F for them. This study aimed to **validate the Korean version of SARC-F** for patients **on PD**.

Methods: The Korean version of SARC-F, which was introduced from a previous study validating it in community-dwelling older adults, was tested in regular visiting 127 outpatients on PD (men 52.8%, women 47.2%). **Validity was analyzed by standard criteria based on the Foundation for the National Institutes of Health, Asian and European Working Group**. The subjects were divided into two groups according to SARC-F score (<4 and ≥4) and its correlation with multiple factors including age, KT/V, residual renal function, skeletal muscle mass, handgrip strength, etc. was inspected by sex.

Results: The prevalence of sarcopenia in men and women according to SARC-F was 14.9% and 31.6%, respectively. **For men**, SARC-F showed low sensitivity and low positive predictive value (PPV) [33.3%-66.7%, 10.0%-20.0%, respectively], but **high specificity and high negative predictive value (NPV) [85.9%-87.5%, 94.7%-98.2%, respectively]**. Similary, **for women**, SARC-F showed low sensitivity, low PPV and **high NPV** [50.0%-80.0%, 5.3%-21.1%, **97.6%**, respectively], although specificity was relatively lower than men [69.0%-72.7%]. The SARC-F<4 group had less muscle mass and poorer hand grip strength.

Conclusions: As the **specificity and NPV of Korean version of SARC-F were high**, it is useful, particularly for men on PD, to **rule out** sarcopenia in a simple way. Regarding the lower specificity for women, it is suggestive that applying a **different cut-off value according to sex** is necessary. The **sensitivity was too low to screen** the sarcopenic patient on PD, and hence, further attention for screening sarcopenia would be required.



SARC-F and Various sarcopenia definitions. AWGS: Asian Working Group for Sarcopenia, EWGSOP: European Working Group on Sarcopenia in Older People, FNIH: Foundation for the National Institutes of Health

	Sensitivity			Specificity			PPV			NPV		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
AWGS	66.7	80.0	75.0	87.5	72.7	80.7	20.0	21.1	20.7	98.2	97.6	98.0
EWGSOP	50.0	75.0	66.7	86.2	71.4	79.3	10.0	15.8	13.8	98.2	97.6	98.0
FNIH low muscle mass/weakness	40.0	75.0	55.6	87.1	71.4	79.7	20.0	15.8	17.2	94.7	97.6	96.0

SARC-F Validated Against Different Sarcopenia Definition

FR-PO698

Comparison of the Risk of Fracture in Peritoneal Dialysis Patients with Sarcopenia Using the FRAX

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Background: For chronic patients with chronic diseases such as peritoneal dialysis, the rate of sarcopenia is high. This sarcopenia increases the risk of dying by causing heart failure, fractures, infection, frailty, and resistance to insulin. This study was initiated because of the lack of evidence of a risk of fractures in patients with peritoneal dialysis.

Methods: : We studied 146 patients on peritoneal dialysis. For the diagnosis of sarcopenia, we measured muscle mass (measured using a bioimpedance analysis), muscle strength (measured using a handgrip strength), and physical performance (measured using a gait speed). Sarcopenia was diagnosed on the basis of the European Working Group on Sarcopenia in Older People (EWGSOP). The risk of fracture was measured using the fracture risk assessment tool (FRAX) after measuring the femoral neck bone mineral density. The FRAX is computerized algorithm that determines fracture probability in individuals by integrating important individual clinical risk factors for fracture and mortality.

Results: The mean age was 57.7 ± 11.8; There are 63 men and 83 women. There were 101 patients with continuous ambulatory peritoneal dialysis and 45 patients with automated peritoneal dialysis. A total of 45 patients were sarcopenia (30.8 %), of which 21 were men and 24 were women. There was no difference between the two groups of dialysis duration (1713.4 ± 1621.6 days vs 1804.3 ± 1917.4 days, p=0.761). Differences in values of the 10-year probability of fractures were seen depending on the presence of sarcopenia. The risk of 10-year of major osteoporotic fractures was low in a group that did not have sarcopenia (4.3 ± 3.0 % vs. 6.9 ± 5.9, p = 0.021). And the risk of 10-year of hip fractures was also lower in the group without sarcopenia (1.3 ± 2.0 vs 2.3 ± 1.5, p=0.022).

Conclusions: In peritoneal dialysis patients, the risk of fractures increases if they have sarcopenia. In peritoneal dialysis patients, it is desirable to reduce the risk of fractures by preventing sarcopenia.

FR-PO699

A Study Based on Bioelectrical Impedance Analysis on the Weight Gain in Peritoneal Dialysis: Fat or Muscle?

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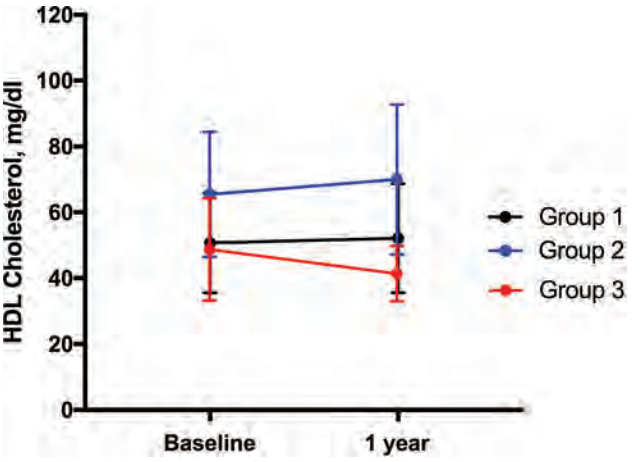
Background: Patient weight gain after the beginning of Peritoneal Dialysis (PD) is a well-known phenomenon, yet whether this is resultant from increased overhydration, fat or muscle mass is not well established. Bioelectrical Impedance Analysis (BIA) can assess both nutritional status and tissue hydration in these patients.

Methods: This is a cross-sectional study that included 44 incident patients on PD. A subset of 20 patients underwent BIA at baseline and 6 months after PD initiation for the following variables: fat mass (FM), muscle mass (MM), phase angle (PA), extracellular/total body water ratio (ECW/TBW). Weight, body mass index, fasting glucose, total and HDL cholesterol, albumin, creatinine and FM/MM behavior during study period were also evaluated.

Results: Patients aged 52±17 years (43% men, 30% diabetic). There was an increase in weight gain (p<0.001), with no significant increase in fasting glucose, total and HDL cholesterol. Serum albumin reduced from 3.7±0.5 to 3.5±0.6g/dl (p=0.024). Fat increased from 19±6 to 21±7kg (p=0.041), with no increase in MM (from 23±4 to 24±5kg p=0.142), PA (from 4.4±2.5 to 3.5±5.6° p=0.914), and ECW/TBW (from 0.40±0.01 to 0.40 ±0.02, p=0.667). There were 3 distinct behaviors: Group 1: increased FM/decreased MM (N=7); Group 2: decreased FM/increased MM (N=6); Group 3: increased FM and MM (N=6). Groups were similar by age, gender, albumin and presence of diabetes, albeit group 2 presented higher HDL cholesterol at 1 year (p=0.049), independent of statin prescription. [Figure 1]

Conclusions: PD is associated with weight gain, which is mostly due to a FM component. Intriguingly, some patients presented reduced FM and increased MM, and exhibited high levels of HDL cholesterol. Further studies are necessary to establish a link between weight gain, body composition and cardiovascular risk in PD patients.



FR-PO700

Elevated Serum Uric Acid Is Associated with Greater Skeletal Muscle Mass in Patients on Peritoneal Dialysis

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Background: Serum uric acid (UA) has been identified as a good nutritional marker in hemodialysis patients, but was little investigated in patients on peritoneal dialysis (PD). The aim of this study was to investigate the relationship between uric acid and skeletal muscle mass (SMA) in PD patients.

Methods: This is a cross-sectional study. The patients who performed multi-frequency bioelectrical impedance (BIA) from January 1, 2013 to December 31, 2016, and with SUA values were enrolled. Collected data included demographic characteristics, clinical and laboratory measurements. Skeletal muscle mass was measured by BIA. The relationship between SUA and the skeletal muscle mass was tested by multiple linear regression models.

Results: A total of 734 prevalent PD patients (57.4%male) were enrolled, with a mean age of 48.3±14.2 years, a mean SMA of 27.0±5.5kg and a mean serum UA of 6.8±1.3mg/dl. Compared with participants in lowest quartile of UA, those participants in highest quartile showed a higher SMA(28.22±5.88 vs. 25.97±4.70, p =0.015). When examined as a continuous variable in multiple linear regression models, serum UA was positively associated with skeletal muscle mass in total patients [standardized coefficients (β) 0.453; 95% confidence interval(CI) 0.145 - 0.760, p = 0.004]. And gender-stratified analysis shows that the association exists both in male (β 0.433; 95% CI 0.010 - 0.856, p= 0.045) and female patients (β 0.486; 95% CI 0.032 to 0.940, p= 0.036). Furthermore, a significant association was found between the highest or the second highest quartiles of UA and skeletal muscle mass in fully adjusted models in PD patients(β 1.952; 95% CI 0.801 -3.102, p= 0.001; β 1.453; 95% CI 0.305-2.600, p= 0.013, respectively).

Conclusions: The elevated serum UA was associated with a greater skeletal muscle mass in PD patients, and uric acid could be a potential nutritional marker in PD patients.

Funding: Government Support - Non-U.S.

FR-PO701

Home-Based Aerobic and Resistance Exercise Training on Peritoneal Dialysis Patients: A Randomized Controlled Trial

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Background: Muscle wasting, common and progressive in uremic patients, is associated with a high probability for morbidity, lower health-related quality of life (HRQOL), and mortality. However, potential effect of aerobic and resistance training on peritoneal dialysis (PD) patients has not been fully elucidated. This randomized, controlled study investigated whether a home-based exercise program for PD patients would improve their physical function, PD-related parameters and HRQOL.

Methods: 47 PD participants (mean age, 64 years; mean PD vintage, 3.8 years; 35 men) were randomly assigned to home-based training (n = 24) or usual care (n = 23). Participants were included if they started PD more than 3 months prior to baseline assessment. Patients were excluded if they had unstable medical conditions. Home-based-exercise patients were instructed to perform aerobic exercise at 40–60% of the peak oxygen uptake (VO_{2peak}) thrice weekly, and resistance training at 70% one-repetition maximum twice weekly for 12 weeks. Exercise capacity was assessed by VO_{2peak} estimated from incremental shuttle walking test and handgrip and quadriceps strength. In addition to evaluation of PD-related parameters, HRQOL was assessed by the Kidney Disease Quality of Life-Short Form questionnaire.

Results: 44 participants completed the study (home-based training, n = 22; usual care, n = 22). Analyses of covariance, adjusted for baseline values, revealed significant differences between home-based training and usual care in VO_{2peak} (12.5 ± 3.6 to 13.1 ± 4.2 mL/kg·min versus 11.9 ± 2.8 to 11.2 ± 3.1 mL/kg·min; P = 0.02) and serum albumin (3.46 ± 0.49 to 3.51 ± 0.44 g/dl versus 3.55 ± 0.41 to 3.42 ± 0.47 g/dl; P = 0.03). Moreover, compared to usual care group, exercise group showed significant improvements in HRQOL scores of physical role functioning (P = 0.02) and role/social component summary (P < 0.01), as well as non-significant improvements in kidney disease component summary (P =0.06), bodily pain (P = 0.07), and vitality (P = 0.06). There were no reported adverse events as a result of the intervention.

Conclusions: A 12-week home-based aerobic and resistance exercise improved aerobic capacity, serum albumin and HRQOL in PD patients. The present study demonstrated for the first time, the efficacy of home-based training in PD patients.

FR-PO702

Roles of Matrix Metalloproteinase (MMP)-2 and MMP-9 in Arteriovenous Fistula (AVF) Development

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Background: Collagen is one of the most abundant vascular extracellular matrix components, and collagenolytic MMP-2 and MMP-9 are key regulators of vascular remodeling. MMP-2 and MMP-9 are known to stimulate the proliferation of vascular endothelial cells (ECs) and smooth muscle cells (SMCs) and cause collagen disruption. These properties may respectively promote the formation of neointimal hyperplasia (NH) and alter the ability of the AVF wall to expand in patients with chronic kidney disease (CKD). Thus, we investigated the effect of CKD on MMP-2 and MMP-9 expression, and their roles in AVF development.

Methods: Human vascular ECs and SMCs were cultured in serum obtained from CKD patients or non-CKD control subjects and then quantified for MMPs by western blot. We used a modified low-dose adenine diet to induce CKD in Wistar rats. Baseline femoral venous MMPs were quantified and femoral AVFs were created in CKD rats and non-CKD rats. Baseline vascular compliance was measured and carotid-jugular AVFs were created in global MMP-2 or MMP-9 knockout (KO) mice on C57BL/6 background, with C57BL/6 mice serving as wild-type (WT) controls. AVFs from both animal models were harvested for histology.

Results: Compared to non-CKD serum, CKD serum enhanced MMP-2 (1.3-fold) and MMP-9 (20-fold) protein expression in cultured ECs. Similar trends were found for SMCs. When compared to non-CKD rats, CKD rats had higher baseline venous MMP-2 (3-fold) and MMP-9 (4-fold), and smaller AVF vein lumen area 4 weeks after creation. Baseline carotid arteries from the MMP-2 KO mice and MMP-9 KO mice had higher compliance when compared to WT mice. The percent open lumen area of the AVF veins at 1 week after creation was larger in the MMP-2 KO mice (39% ± 6%) and MMP-9 KO mice (47% ± 3%) vs. the WT mice (11% ± 2%).

Conclusions: Our animal studies showed that MMP-2 and MMP-9 were strong impediments to AVF development. Therapeutic approaches of inhibiting these molecules may enhance AVF maturation in CKD patients.

Funding: NIDDK Support

FR-PO703

Preexisting venous Medial Matrix Metalloproteinase (MMP)-2 and Arteriovenous Fistula (AVF) Maturation: Findings from the Hemodialysis Fistula Maturation (HFM) Consortium Study

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Background: AVF maturation requires adequate outward remodeling (luminal expansion) and limited inward remodeling (neointimal hyperplasia) to facilitate increases in AVF diameter and blood flow. MMP-2 and MMP-9 are critical for vascular remodeling in other settings. Inhibition of MMP-2 and MMP-9 reduces neointimal hyperplasia following vascular injury or graft implantation in animals with normal renal function. However, the clinical relevance of MMP-2 and MMP-9 in AVF diameter (a net result of luminal expansion and neointimal hyperplasia) and blood flow remains unclear.

Methods: We prepared histological slides of venous samples from 100 randomly selected patients at the time of AVF creation in the HFM Study. The protein expression levels of MMP-2 and MMP-9 were quantified by immunohistochemistry and ImageJ, and reported as a percentage of the total medial area. We then investigated the statistical associations of MMP-2 or MMP-9 levels with AVF diameter and blood flow assessed using duplex ultrasound at 6 weeks after AVF creation.

Results: Venous medial MMP-2 (Fig. 1) and MMP-9 expression varied widely among patients. We found a negative association of venous medial MMP-2 with the 6-week AVF diameter (Δ diameter = –0.23 mm; 95% CI, –0.44 to –0.02; p=0.029) and a trend for AVF blood flow (Δ flow = –39 ml/min; 95% CI, –106 to –29; p=0.26), per 10% increase in MMP-2. No association was found between MMP-9 and the 6-week AVF diameter or blood flow.

Conclusions: Preexisting venous medial MMP-2 expression was associated with impaired AVF maturation in this subset of HFM patients. More rigorous validation of this observation using a larger cohort is necessary.

Funding: NIDDK Support

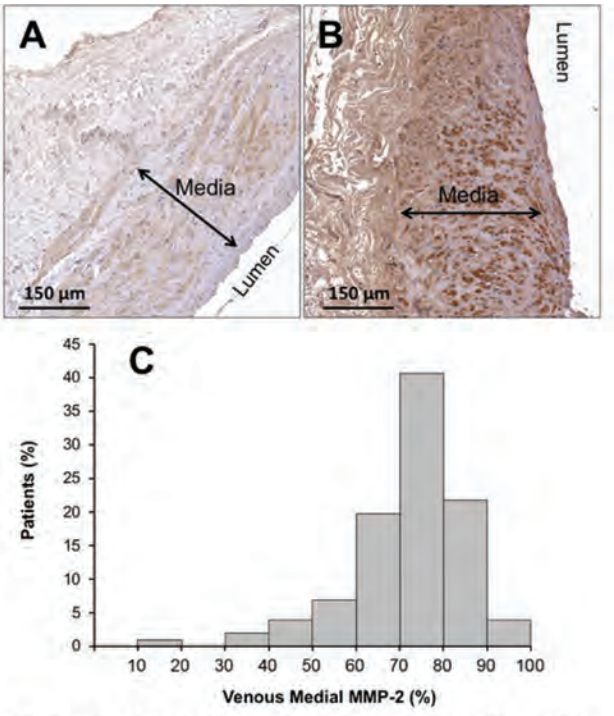

Fig. 1. Representative immunohistochemistry images of MMP-2 (rust color) show **(A)** a patient whose venous medial layer had low MMP-2 quantity (50% of area stained positive of MMP-2), and **(B)** a different patient whose venous medial layer had substantially more MMP-2 (93%). **(C)** Distribution of MMP-2 in 100 patients.

FR-PO704

Transcriptomics of Human Arteriovenous Fistula Failure Uncovers an Unexpected Source of Inflammation

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Background: Improving arteriovenous fistula (AVF) outcomes requires a better understanding of the biology underlying maturation or failure. Unfortunately, our current knowledge of the biological processes associated with maturation relies on assumptions and extrapolation from other vascular pathologies, which overlooks the uniqueness of AVF remodeling.

Methods: In this study, we used an unbiased "omics" approach based on high-throughput RNA sequencing of human pre-access veins and fistulas to uncover novel molecular targets associated with nonmaturation. We obtained native vein and juxta-anastomotic AVF tissues from patients undergoing two-stage upper arm AVF surgeries at a single center. Paired venous samples from both stages were used to study the vein to AVF transformation at the transcriptomics level.

Results: We discovered a unique molecular signature of pro-inflammatory genes (*CSF3R, FPR1, S100A8, S100A9,* and *VNN2*) that was upregulated in native veins that failed vs. matured (FDR<0.05), and whose expression co-localized to smooth muscle cells in the media. Furthermore, expression of *S100A8* and *S100A9* was significantly associated with postoperative intimal hyperplasia (IH) and the product of medial fibrosis x IH (R^2 0.10-0.15, P<0.05). We revealed the drastic vascular transformation that occurs during early remodeling at the molecular level, with >9,500 genes differentially expressed between native veins and AVFs in paired tissue samples.

Conclusions: In conclusion, this work demonstrates the importance of the subclinical inflammatory status of the pre-access vein in AVF nonmaturation, and identifies calprotectin (S100A8/A9) as a potential therapeutic target to prevent this complication. Our transcriptomics data underscores the complexity and uniqueness of vascular remodeling after fistula creation.

Funding: NIDDK Support

FR-PO705

Endothelial-to-Mesenchymal Transition in Neointimal Hyperplasia of a Mice Model of Arteriovenous Fistula

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Background: To date, arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. However, for the matured AVF, the 2-year patency without intervention was only 30-50%. In addition, frequent interventional procedures were required to maintain AVF patency, which causes immense suffer to patients. As such, medical treatment to prevent AVF stenosis is desired. Stenosis of AVF resulted from the process of neointimal hyperplasia, signifying thickening of subintima caused by proliferation of cells express α-smooth muscle actin (α-SMA) and vimentin. The pathogenic role of neointimal hyperplasia in AVF stenosis has been confirmed by multiple studies, however, understanding of its molecular mechanism is still suboptimal. Endothelial-to-mesenchymal transition (EndMT) is the process that endothelial cells transform to mesenchymal cells, which had been demonstrated in pathogenic fibrogenesis of cardiovascular diseases. This study tries to demonstrate EndMT in a mice AVF model.

Methods: Chronic kidney disease (CKD) in mice is induced by diet containing 0.2% adenine. After 10 days of adenine diet, CKD was confirmed by elevated serum creatinine and surgical creation of AVF was performed. Murine AVF model is created by aortocaval puncture to form AVF between abdominal aorta and inferior vena cava (IVC). The successful creation of AVF was confirmed by doppler ultrasound during surgery. Six weeks after AVF creation, the mice were sacrificed and AVF was resected. The specimens were stained for α-SMA and vascular endothelial-cadherin (VE-cadherin) to show the expression of both endothelial and mesenchymal features of the proliferated intima.

Results: After 10 days of adenine containing diet, serum creatinine increased significantly from 0.25 mg/dL to 0.73 mg/dL. Immediately after AF creation, doppler ultrasound showed increased blood flow and exaggerated pulsation wave form of the IVC proximal to AVF site. The IVC wall adjacent to AVF site showed proliferated intima, which stains positive for α-SMA. Co-staining the same area showed that the proliferated intima expressed both α-SMA and VE-cadherin, which indicated possible EndMT.

Conclusions: This pilot study provided preliminary evidence of the presence of EndMT in AVF mice model, which may underly the pathogenic stenosis of human AVF. However, more evidence is still required to confirm EndMT in AVF and its molecular pathway.

FR-PO706

The Role of PDE5A Inhibition in Arteriovenous Fistula Remodeling

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Background: Impaired outward vascular remodeling along with neointimal hyperplasia (NH) are thought to be the major underlying causes of arteriovenous fistula (AVF) maturation failure. We hypothesize that a selective phosphodiesterase type 5A (PDE5A) inhibitor, sildenafil, administered before and after AVF creation can be used to improve vascular outward remodeling. The aims of this study are to evaluate in a rat AVF model, the effect of PDE5A inhibition on: 1) venous and arterial diameter 2) venous blood flow and 3) venous NH formation.

Methods: Sildenafil was administered to 12-16-week-old Sprague-Dawley rats two weeks prior to AVF (Femoral vein to artery) creation and continued until sacrifice at 7 days. Venous blood flow was measured using transonic perivascular flow probes and the diameters of the AVF venous and arterial segments were measured at a point proximal and a point distal to the anastomosis using the microscopic ocular micrometer (Fig. 1A), at the time of sacrifice. Morphometric analysis of the AVF vein was also carried out to assess the changes in NH development.

Results: When compared to control group, a significant increase in venous and arterial diameter was observed in the sildenafil treated group in proximal and distal regions, at 7days after AVF creation. Furthermore, increased venous blood flow was also observed in sildenafil treated AVFs. However, no significant difference in the NH development was observed between the two groups.

Conclusions: Sildenafil administered before and after AVF creation, improves venous blood flow and the outward expansion in AVF vessels without affecting the level of NH at 7 days. These observations suggest that, outward expansion of venous limb of the AVF can preserve the luminal caliber and allow proper maturation of AVF, in the presence of NH formation. Therefore, targeting mechanisms that enhance outward vascular remodeling could be a potential therapeutic approach for treating AVF maturation failure.

Funding: Veterans Affairs Support

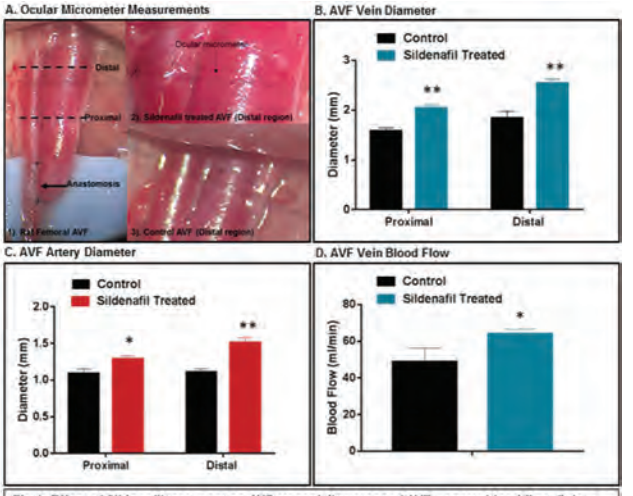

Fig 1: Effect of Sildenafil treatment on AVF vessel diameter and AVF venous blood flow, 7 days following AVF creation in rats.
A) Representative regions of interest for the measurement of the diameter of AVF vessels. Note the significant increase in venous diameter at the distal region of the sildenafil treated AVF, compared to the control. Average diameter of vein (B) and artery (C) in sildenafil treated rats (n=6) compared to control rats (n=4). (D) Comparison of average venous blood flow in Sildenafil treated rats (n=6) and control rats (n=3). *P<0.05 and **P<0.005.

FR-PO707

Neutrophil Activation Status Was Associated with the Degree of ºArteriovenous Fistula Stenosis in Chronic Hemodialysis Patients

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Background: Although arteriovenous fistula (AVF) dysfunction is a major cause of morbidity in hemodialysis (HD) patients, detailed pathogenesis of AVF stenosis is still under investigation. Leukocytes have been shown to play an important role in the development AVF stenosis. However, prior reports have focused on monocyte lineage cells, and little is known about the possible role of neutrophils. We aimed to evaluate the association between AVF stenosis and neutrophil activation status by measuring circulating levels of neutrophil elastase (NES), lactoferrin, and angiogenin, which are markers of neutrophil activation and inhibition, respectively.

Methods: A total of 69 patients were included who received HD with native AVF for more than 3 months. Patients with recent history of infection, antibiotics, or AVF intervention were excluded. Degree of AVF stenosis was expressed by the percent of the greatest stenotic diameter to the widest adjacent vessel diameter by ultrasound

Results: The pre-dialysis circulating NES and lactoferrin levels were not significantly different between HD patients and control (healthy and CKD stage 3), although angiogenin level was significantly higher in HD population. The degree of AVF stenosis was positively correlated with NES (r=0.360, p=0.002) and lactoferrin (r=0.352, p=0.003) levels. Patients with AVF stenosis (stenosis > 50%) were older (65.9±9.7 vs 58.0±13.7, p=0.004), had longer duration of AVF use (52.9±45.8 vs 39.5±46.0 month, p=0.019), higher hsCRP (0.34±0.35 vs 0.15±0.17 mg/dl, p=0.029), and higher NES (421.0±254.2 vs 192.2±136.3 ng/ml, p<0.001) and lactoferrin (279.4±127.4 vs 144.0±68.9 ng/ml, p=0.001) levels compared with the other group. There was no significant difference in gender, presence of diabetes, angiogenin, and other biochemical measurements including albumin, calcium, phosphorus, iPTH, and cholesterols according to the degree of AVF stenosis. In multivariable analysis, however, only age and duration of AVF use were statistically significant factors for AVF stenosis.

Conclusions: Circulating levels of NES and lactoferrin, indirect markers of neurophil activation, were associated with the degree of AVF stenosis. Larger scales of long-term prospective studies are needed to show whether they could be used as independent predictors of at-risk AVF.

FR-PO708

The Role of Heme-Degrading and Heme-Binding Proteins in Decreasing Thrombosis

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Background: Induction of the heme-degrading enzyme, heme oxygenase-1 (HO-1), protects against dysfunction and closure of an arteriovenous fistula (AVF) and other types of vascular injury. Thrombosis contributes to AVF dysfunction and closure, and to certain types of vascular and renal injury. The present study examined whether HO-1 induction or administration of its products reduces thrombosis in vivo.

Methods: We employed the murine clot model induced by infra-renal ligation (L) of the inferior vena cava (IVC). Clot size is assessed in this model by determining the clot

weight/clot length ratio. Our prior studies in this model demonstrated that HO-1 is induced, and that clot size is increased in HO-1$^{-/-}$ mice as compared with HO-1$^{+/+}$ mice.

Results: Clot size in the IVCL model was significantly reduced in mice treated with hemin (an inducer of HO-1) as compared with saline on day 1 (1.13±0.54 vs 2.92±0.21), day 2 (1.72±0.26 vs 3.58±0.36), and day 3 (1.70±0.47 vs 3.29±0.24) after IVCL. These beneficial effects of hemin were accompanied by reduced expression of proinflammatory and thrombogenic genes. We confirmed marked induction of HO-1 mRNA and protein and HO activity in the IVC in hemin-treated mice. HO-1 upregulation in the IVC by adeno-associated viral delivery also reduced clot size in the IVCL model. Biliverdin, a product of HO activity, reduced clot size on day 2 after IVCL, as did another product of HO activity, carbon monoxide, delivered as CORM-3. The constitutive HO isoform, HO-2, did not exhibit the anti-thrombotic efficacy of HO-1 as clot size was not increased in HO-2$^{-/-}$ mice as compared with HO-2$^{+/+}$ mice. Analysis of the clot model further demonstrated that the heme-binding protein, hemopexin (HPX) was induced in the IVC, and that clot size was increased in HPX$^{-/-}$ mice as compared with HPX$^{+/+}$ mice.

Conclusions: HO-1 and its products are markedly effective in inhibiting thrombosis, whereas such efficacy is not exhibited by HO-2. The beneficial effect of HO-1 in reducing AVF closure and vascular injury likely reflects, at least in part, its inhibitory effect on thrombogenesis. HPX is identified as a novel inhibitor of thrombogenesis in the IVCL model.

Funding: NIDDK Support

FR-PO709

Role of Mevalonate Pathway on Vascular Access Failure in Maintenance Hemodialysis

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Background: We have reported the effectiveness of statins against vascular access (VA) dysfunction. Despite statin administration, there was no difference in serum cholesterol levels between the statin users and the non-users, suggesting that the VA protective role of statin is different from the cholesterol lowering effect. In recent years, Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) were found as a new pathway associated with arteriosclerosis. The turbulence of intravascular blood flow triggers the YAP/TAZ pathway, which enhances gene expressions correlated with inflammation and fibrosis, resulting in arteriosclerosis. Mevalonate acid (MA) activates this pathway and statins are known to inhibit the MA production. Therefore, we hypothesized that VA protective effect of statin could be inhibition of YAP/TAZ pathway via MA reduction.

Methods: Patients on maintenance hemodialysis and people with stage 4 or 5 chronic kidney disease were enrolled in this study. The serum MA levels were measured using an enzyme cycling method. Gene expressions of connective tissue growth factor (CTGF) and cysteine-rich angiogenic inducer 61 (CYR61) in the peripheral blood mononuclear cells were evaluated using real-time PCR.

Results: Serum MA levels in patients with CKD and maintenance hemodialysis increased compared to healthy subjects (6.6±0.7, 8.8±0.6, and 4.6±0.8 μg/dL, respectively). Among hemodialysis patients, serum MA levels were higher in patients with VA dysfunction than without dysfunction (9.2±0.6 vs 6.6±0.7 μg/dL, p=0.07). Moreover, serum MA levels in patients who required VA angioplasty more than a year showed a higher value than those without repeated angioplasty (9.4±0.9 vs 8.7±0.7 μg/dL, p=0.60). These data suggest that serum MA levels associate with an increased risk of VA dysfunction. Serum MA levels were lower in statin users compared to non-users (7.4±1.1 vs 9.4±0.6 μg/dL, p=0.10), indicating that statin could decrease serum MA levels. Lastly, CTGF and CYR61 gene expressions were decreased in statin users compared to non-users (0.13±0.02 vs 0.17±0.01, 0.48±0.05 vs 0.67±0.11, respectively), implying that statin inhibits the YAP/TAZ pathway.

Conclusions: Statin treatment could be effective on VA dysfunction through lowering MA and YAP/TAZ suppression.

Funding: Private Foundation Support

FR-PO710

Zinc Deficiency Is a Risk for Vascular Access Failure in Hemodialysis Patients

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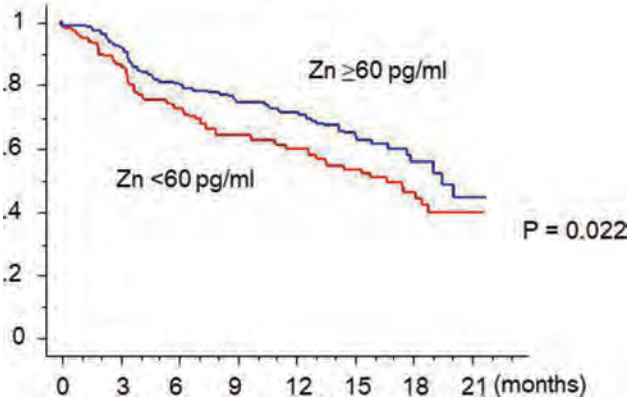
Background: Vascular access (VA) is essential for the hemodialysis (HD) patients. Percutaneous transluminal angioplasty (PTA) is an effective therapy against VA failure, however, re-failure of VA is often occurred even after PTA. Zinc plays a role in endothelial cell function, and Zinc deficiency can effect vascular dysfunction. To investigate the association of Zinc deficiency with VA failure, serum Zinc and the patency of VA following PTA were examined.

Methods: Blood samples were taken from 337 HD patients at PTA against VA failure. Serum Zinc, factors related to mineral-bone metabolism (Ca, iP, PTH-intact [iPTH], ALP), 8-hydroxy-2'-deoxyguanosine (8OHdG) as a maker of oxidative stress, inflammation (CRP, interleukin-6, tumor necrosis factor-α), and uremia (BMI, albumin, urea nitrogen, Hb) were measured. The end point of study was VA failure (re-vascularization or re-operation) during the observational period after PTA. Cox proportional hazards models for the end point was used.

Results: During follow-up period (median 367 days), re-vascularization was performed in 67 participants and re-operation in 69. The median of serum Zinc was 63 pg/ml (IQR 56 to 74), and 130 (38.6%) participants had Zn deficiency (<60 pg/ml). The participants with VA failure had lower Zn (p=0.03), higher iPTH, and a tendency to high 8OHdG compared with the participants without VA failure. There was no difference in the other factors. The Kaplan-Meier analysis showed that the participants with Zn deficiency was associated with higher incidence of VA failure (Figure 1). Cox regression analysis also revealed that Zn deficiency (adjusted hazard ratio 1.51, 95% CI 1.06 to 2.13, p=0.022) was a risk for VA failure.

Conclusions: Zinc deficiency was an independent risk for VA failure. Zinc might be associated with the maintenance of VA patency in HD patients.

Figure 1.
Patency of vascular access



FR-PO711

Increased Monocyte-to-High-Density Lipoprotein Ratio Is Associated with Recurrent Vascular Access Stenosis

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Background: Previous studies indicate that increased monocyte count and decreased high-density lipoprotein (HDL) cholesterol levels are associated with chronic kidney disease, and increased risk for cardiovascular diseases, indicating its possible role in pro-inflammatory and pro-oxidant states. We tried to investigate the clinical significance of circulating monocyte count-to-serum HDL cholesterol ratio (M/H ratio) in predicting recurrent vascular access stenosis after angioplasty in hemodialysis patients.

Methods: M/H ratio at access creation and prior to angioplasty was measured in a total of one-hundred and fifty hemodialysis patients in Incheon St. Mary's hospital from July, 2006 to September, 2017. The impact of M/H ratio in predicting recurrent access stenosis was evaluated retrospectively by using Kaplan-Meier, Cox regression, and ROC curve analyses.

Results: The patient group comprised of 67% male and 58% diabetes, aged 62±14 years old (n=150). Baseline M/H ratio at access creation was not different between those with vascular access stenosis (n=71) and those without stenosis (n=79) (10.74 vs. 12.42, p = 0.11). Among patients with vascular access stenosis, there also was no difference in baseline M/H ratios between those with recurrent stenosis (n=33) and those without recurrence (n=38) (9.98 vs. 11.4, p = 0.24). However, pre-angioplasty M/H ratio increased significantly when compared to that of baseline (10.75 vs. 17.95, p < 0.001). Delta M/H ratio, as defined by a difference between baseline and pre-angioplasty ratios was calculated and mean delta M/H ratio was 1.9. Increased delta M/H ratio (delta M/H ratio greater than or equal to 1.9) was associated with recurrent stenosis (HR 4.16, CI 1.43-12.12, p = 0.009). Moreover, increased delta M/H ratio was clinically significant in predicting recurrent vascular access stenosis (AUC 74%, p = 0.001).

Conclusions: Increased delta M/H ratio may play a role in pro-inflammatory and pro-oxidant environment and predispose vascular access for recurrent stenosis after angioplasty.

FR-PO712

Artery to Fistula Diameter Ratio as a Predictor of Early Re-Occlusion of Immature Arteriovenous Fistulas After Percutaneous Transluminal Angioplasty

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Background: Percutaneous transluminal angioplasty (PTA) is widely performed for arteriovenous fistula (AVF) that fails to mature after initial formation. We observed that some immature AVFs re-occlude earlier than others. We sought to investigate the predictors for early post-intervention failure of immature fistulas after the primary PTA.

Methods: We retrospectively reviewed the records and angiographic images of patients who had immature fistulas and thereby received PTA between years 2013 to 2017 at our center. We investigated the short-term post-intervention outcomes of the patients within 90 days post PTA. Patients who had re-occlusion within the period were defined as early failure group and the rest as patent group. We investigated factors associated with early failure.

Results: There were 80 eligible patients with 22 brachiocephalic (BC) and 58 radiocephalic (RC) AVFs. The median age of the patients was 64 years [range, 38-87]. There were 51 (63%) males and 29 (36%) females. Among the 58 RC AVFs, 10 (17%) patients had early failure. Logistic regression analysis showed that larger artery to fistula (A/F) diameter ratio was the sole independent predictor of early failure after primary PTA (odd ratio 2.29 [1.023-5.147], P= 0.044).

Conclusions: Although further studies in a larger scale are required to confirm the clinical significance, larger A/F diameter ratio was a potential predictor of early re-occlusion in immature fistulas after primary PTA.

Funding: Government Support - Non-U.S.

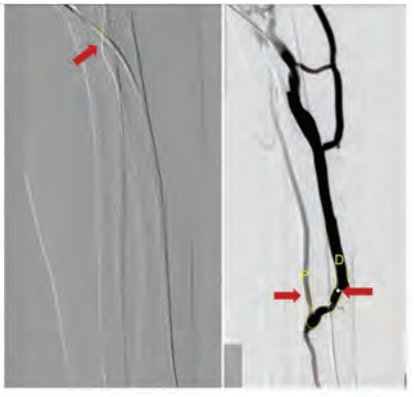

Figure 1. Measuring diameters of vessels using The Cardiovascular Angiography Analysis System. (A) The diameter of catheter (red arrow) was used for calibration reference. (B) A/F ratio was measured by ratio of diameter of radiocephalic artery (red arrow and yellow letter P) and AVF vessel (red arrow and yellow letter D).

FR-PO713

Comparison of the Outcomes of Upper Arm Arteriovenous Fistula and Forearm Arteriovenous Graft

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Background: Forearm arteriovenous graft (AVG) and upper arm arteriovenous fistula (AVF) are secondary choices when forearm AVF fails or the vascular quality is poor because of the increased hemodialysis duration or primary disease, such as diabetes. In this study, we compared the outcomes of upper arm AVF and forearm AVG in our dialysis center.

Methods: Patients underwent upper arm AVF or forearm AVG in our hospital from October 2014 to December 2017 were enrolled. The primary and secondary patency, complications were compared between the two groups. Kaplan-Meier survival curves and univariate Cox proportional hazard models were used.

Results: There were 116 (55.2%) patients underwent AVF and 94 (44.8%) patients underwent AVG, respectively. The characterizations of the patients, including age, gender, primary renal disease, comorbidities, hemodialysis duration and previous fistulation history were similar between the two groups. The primary patency of AVG *vs.* AVF were 83.5% *vs.* 93.1%, 75.8% *vs.* 91.4%, 60.3% *vs.* 75.3%, 42.1% *vs.* 56.6%, 31.6% *vs.* 57.1% at 3, 6, 12, 24, 36 month after the surgery, respectively; however, no significant differences were observed between the two groups (P=0.13). Compared with AVF, AVG has higher secondary patency (P=0.03), which were 94.7% *vs.* 93.1%, 95.6% *vs.* 91.4%, 85.7% *vs.* 80.4%, 73.6% *vs.* 66.0%, 68.4% *vs.* 57.1% at 3, 6, 12, 24, 36 month after the surgery, respectively. The incidences of complications were higher in AVG than AVF, including thrombosis (23.3% *vs.* 13.4%), stenosis (50.0% *vs.* 21.2%), infection (2.4% *vs.* 0.5%) and steal syndrome (2.4% *vs.* 1.7%). In all kinds of comorbidities, fistulation history was correlated with reduction of primary patency (HR: 0.42; 95% CI: 0.26 to 0.67) and secondary patency (HR: 0.44; 95% CI: 0.28 to 0.69) in AVF group but not in AVG group.

Conclusions: Forearm AVG has superiority in secondary patency than upper arm AVF. AVG has more complications than AVF. Upper arm AVF may be recommended to increase primary patency and reduce complications.

Funding: Government Support - Non-U.S.

FR-PO714

Use of Smaller Vessels to Create an AVF Increases the Need for Interventions to Promote Its Maturation

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Background: Preoperative vascular mapping using ultrasound (US) is often used to aid in the creation of an arteriovenous fistula (AVF). Current vascular access guidelines recommend minimal arterial and venous diameters of 2.0 mm and 2.5 mm, respectively, to optimize *overall* (assisted and unassisted) AVF maturation. However, the relationship of preoperative US measurements with *unassisted* AVF maturation (successful use without a prior intervention) has not been evaluated.

Methods: We reviewed the clinical, demographic, and preoperative mapping ultrasound information of 189 hemodialysis patients from a large dialysis center who received new upper extremity AVFs from 2010-16. We then evaluated the association of preoperative US measurements of venous diameter, arterial diameter, and brachial blood flow with two AVF outcomes: unassisted AVF maturation and overall AVF maturation.

Results: The mean age of the study population was 53 years. 58% of the patients were male, 81% were black, 57% were diabetic, and 48% were obese. 74% of the AVFs were located in the upper arm. Progressive increases in preoperative arterial diameter, venous diameter and brachial artery blood flow were each associated with corresponding increases in unassisted AVF maturation. Incremental increases in preoperative arterial diameter and blood flow were likewise associated with progressive increases in overall AVF maturation. In contrast, there was no significant association between preoperative venous diameter and overall AVF maturation (**Table 1**). Finally, the proportion of AVFs requiring assisted maturation was 52, 32, 31, and 22% when the preoperative arterial diameter was < 3, 3-3.9, 4-4.9, and ≥ 5 mm, respectively.

Conclusions: Preoperative arterial diameter and blood flow are associated significantly with both unassisted and overall AVF maturation. Preoperative venous diameter is associated with unassisted, but not with overall, AVF maturation. Use of smaller vessels to create an AVF increases the need for interventions to promote its maturation.

Funding: NIDDK Support

Arterial Diameter	<3 mm	3-3.9 mm	4-4.9 mm	≥ 5 mm	P value
Unassisted Maturation, %	32	39	57	70	0.0007
Overall Maturation, %	68	57	83	90	0.0005
Venous Diameter	<3 mm	3-3.9 mm	4-4.9 mm	≥ 5 mm	P value
Unassisted Maturation, %	34	44	66	61	0.01
Overall Maturation, %	68	68	83	82	0.18
Brachial Artery Blood Flow	<40 mL/min)	40-79 mL/min	≥ 80 mL/min		P value
Unassisted Maturation, %	33	53	68		0.004
Overall Maturation, %	57	75	95		0.0002

Table 1. Preoperative arterial diameter, venous diameter, and brachial artery blood flow and their associated AVF outcomes.

FR-PO715

Sirolimus Treated AV Fistulae: Maturation Profile and Impact of Processes of Care

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Background: An arteriovenous fistula (AVF) is clinically mature if it can be reproducibly cannulated with 2 large-bore needles and has enough blood flow to support adequate hemodialysis. This analysis relates to AVF maturation data from patients (pts) who received intraoperative sirolimus delivered perivascularly at and around the AVF anastomosis from a collagen membrane (Drug product Vascular Therapies, Cresskill, NJ). The 7 center Hemodialysis Fistula Maturation (HFM) Study (n=602) recently reported impact of care processes on AVF maturation outcomes (Allon AJKD 2018)

Methods: Data for sirolimus treated AVF is from 30 Phase 2 + 22 open label pts. (from an ongoing US multicenter Phase 3 study NCT 02513303) undergoing surgery for a first, single stage upper extremity AVF. Mature AVF is defined as ability to use the AVF for 3 consecutive 2-needle dialysis sessions with a mean flow of ≥300 mL/min for pts on dialysis or vein diameter of 6 mm and blood flow of ≥500 mL/min on ultrasound for patients not on dialysis.

Results: 52 pts; 51 ESRD, 1 CKD, 67% Male, mean, age 56±17y, 42% diabetic; 65% forearm AVF. Table compares metrics of AVF that matured without (Gp1) and with (Gp 2)

supplementary procedures (SP) which included balloon PTA, vein elevation and exclusion of collateral vein(s)

Conclusions: 1. Excluding the 6 AVF that thrombosed early, all (100%) remaining 46 sirolimus treated AVF matured into a useful fistula (HFM: 77.6%) 2. 38/46 (83%) of sirolimus treated AVF matured after a median of 48 days (HFM: 125 days) 3. The median time of 121 days to maturation for the 8/46 (17%) AVF which required supplementary procedure(s) for maturation was roughly 2.5 times > than Gp 1. 4. For 83% of sirolimus treated AVF's (Gp1) the ONLY metric influencing use of the AVF for dialysis was the anatomical and functional readiness of the fistula for cannulation. 5. For the 17% AVF that required supplementary interventions (Gp2), optimizing processes of care should help in reducing time to first AVF use.

Funding: Commercial Support - Vascular Therapies, Inc. Cresskill, NJ

Table

		Median Days (Interquartile Range; IQR)			
	N	Surgery to Maturation	Surgery to SP	SP to Maturation	Maturation Success
Group 1	38	48 (38,56)			100%
Group 2	8	121 (104,127)	59 (51,72)	40 (17,47)	100%
Total	46[b]				

* 6/52 (11.5%) AVF thrombosed within 2 weeks and are excluded from this analysis

FR-PO716

Risks and Benefits of Antiplatelet Agents and Anticoagulants on Preventing Vascular Access Dysfunction in Hemodialysis Patients

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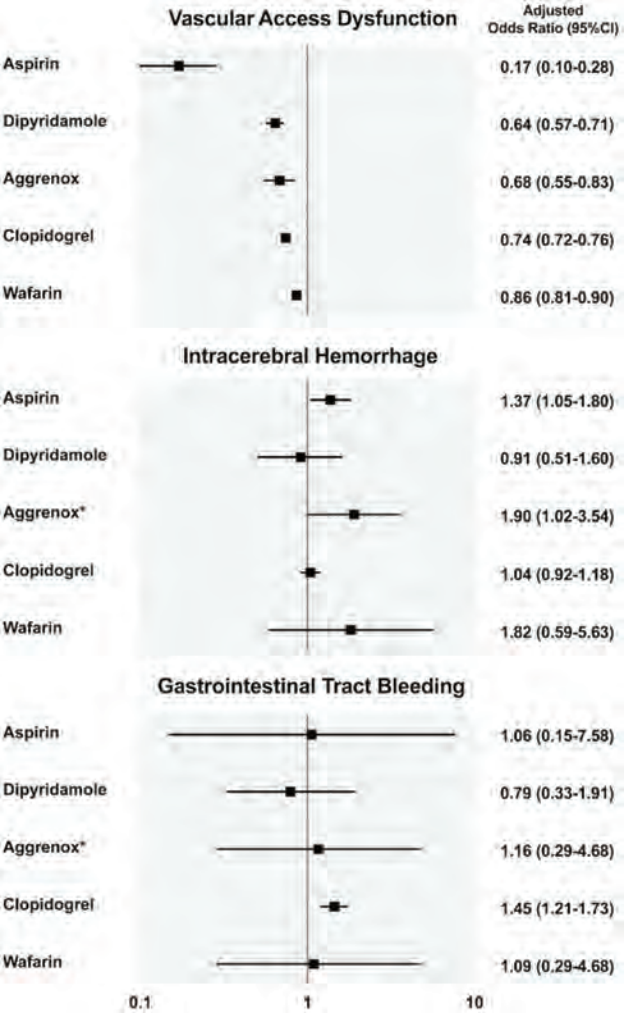
Background: Dialysis adequacy is one major determinant of survival for patients with end-stage renal disease. Good vascular access is essential to achieve adequate dialysis. This study evaluated the impact of different drugs on the vascular access dysfunction rate of an arteriovenous fistula or arteriovenous graft and the rate of major bleeding in hemodialysis patients

Methods: Patients with end-stage renal disease registered in the Taiwan National Health Insurance program from January 1, 1997 to December 31, 2012. A total of 95,992 patients were enrolled in our study. Vascular access dysfunction, defined as the need of thrombectomy or percutaneous angioplasty. Major bleeding, defined as emergent department visits or hospitalization with a primary diagnosis of gastrointestinal bleeding or intracerebral hemorrhage. Adjusted odds ratio between person-quarters with or without antiplatelet or oral anticoagulant using were calculated using logistic regression and inverse probability treatment weighting.

Results: The odds ratio of vascular access dysfunction was 0.17 (0.10-0.28) for aspirin, 0.69 (0.67-0.71) for clopidogrel, 0.62 (0.55-0.71) for dipyridamole, 0.62 (0.50-0.77) for Aggrenox, and 0.86 (0.81-0.90) for warfarin. The highest odds ratio for intracerebral hemorrhage was 2.55 (1.36-4.79) in patients using Aggrenox. The odds ratio for gastrointestinal bleeding was 1.53 (1.28-1.83) for clopidogrel, 1.11 (0.09-13.4) for aspirin, 0.90 (0.38-2.17) for dipyridamole, 1.22 (0.29-5.16) for Aggrenox, and 1.27 (0.79-2.03) for warfarin.

Conclusions: Antiplatelet and anticoagulant agents might reduce vascular access dysfunction rate. The gastrointestinal bleeding rate was increased in clopidogrel using group. Aggrenox might increase the intracerebral hemorrhage rate and should be used with caution.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



FR-PO717

Effect of Aspirin Resistance and Mean Platelet Volume on Vascular Access Failure in Hemodialysis Patients

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Background: Maintaining patency of vascular access in hemodialysis patients is important because it is a life-saving vessel. We investigated the effect of aspirin resistance and mean platelet volume (MPV) on vascular access(VA) failure in hemodialysis (HD) patients.

Methods: We enrolled 163 maintenance HD patients. Aspirin resistance was defined as aspirin resistance unit (ARU) >550. VA failure was defined as thrombosis or a decrease of greater than 50% of normal vessel diameter which was angiographically documented reduction with ≥ 50 % luminal diameter accompanied by abnormal clinical findings.

Results: 163 patients showed a mean age of 57.6 ±12.0 years and 79 were male (48.5 %). Mean dialysis duration was 50.1 ± 52.1 months. Aspirin resistance was observed in 17 out of 109 patients who measured the value. During a follow-up period of 34 months, 65 VA failures occurred out of all subjects while 41 events among the failures occurred in a patient group who measured aspirin resistance. There was no significant difference between the two groups according to aspirin resistance in the cumulative event rate of VA failures (57% vs. 38.2%, log-rank test, p=0.051). Mean MPV was 9.15 ± 0.05 fl. The 163 patients were grouped according to half-tile values of MPV (9.08 fl) at baseline and ones with higher MPV levels (n=82) had exhibited lower levels of platelet count (p=0.002), albumin (p=0.009). The Kaplan-Meier curve showed significant difference between two groups in cumulative events of VA failure (54.1% vs 35.3%, p=0.018). In multivariate analysis, MPV (HR 1.794; 95% CI1.066-3.020; p=0.028), platelet count (HR 1.003; 95% CI 1.001-1.006; p=0.01) and smoking (HR 1.894; 95% CI 1.019-3.519; p=0.043) were independent predictive factors of VA failure.

Conclusions: High MPV was associated with increased risk of VA failure. However, aspirin resistance showed a weak relationship with VA failure. MPV may be a potential marker for prediction of VA survival in HD patients.

FR-PO718

Intermittent Pneumatic Compression Devices Assists in Vascular Access Selection: A Hierarchical Regression Model Study

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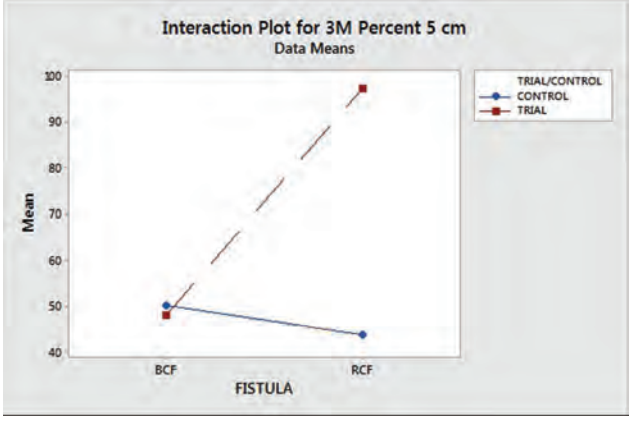
Background: Arteriovenous fistulas (AVF) are the preferred type of vascular access for hemodialysis patients. Among AVF, radiocephalic fistulas (RCF) are recommended. RCF placement has dropped in the USA to low rates. The aim of the present study is to determine if the use of a novel intermittent compression device can assist in vascular acces fistula selection.

Methods: After AVF creation, an intermittent pneumatic compression device enabling 60 mm Hg of cyclic compression was worn proximal to AVF intermittently for 6 hours daily for 3 months. Patients in the treatment group (n=41) wore the device. Twenty-four (n=24) had BCF, while seventeen (n=17) had RCF. Controls (n=12) used a sham device. Vein size was measured at baseline and at 3 months by duplex. Percentage increase was tested for significance. Hierarchical regression models were developed to model vein size dilation based on factors such as patient group, fistula type (BCF or RCF), the interaction between patient group and fistula type, and patient demographics.

Results: The interaction effect between patient group and fistula type was found to be significant. In a stepwise regression procedure, the first term enteresd in the model is the *interaction* between patient group and AVF type. At a proximal distance of 5 cm and 10 cm, the interaction term was highly significant ($p < .01$). Vein size increase is affected by patient group (treatment vs. control) as well as the type of fistula created for vascular access. The type of fistula created for vascular access, has an interaction effect with patient-group type (treatment vs. control) in affecting vein size dilation

Conclusions: The use of a novel, pneumatic compression device has significant impact on the recommended guidelines for vascular access selection. For patients who use the non-invasive device, a larger vein size dilation is achieved with a radiocephalic fistula. Novel, pneumatic devices may assist in RCF placement in the future.



Hierarchical regression modeling at 5 cm of fistula

FR-PO719

Correspondence of Low Wall Shear Stress and Cephalic Arch Stenosis in Brachiocephalic Arteriovenous Fistula Access

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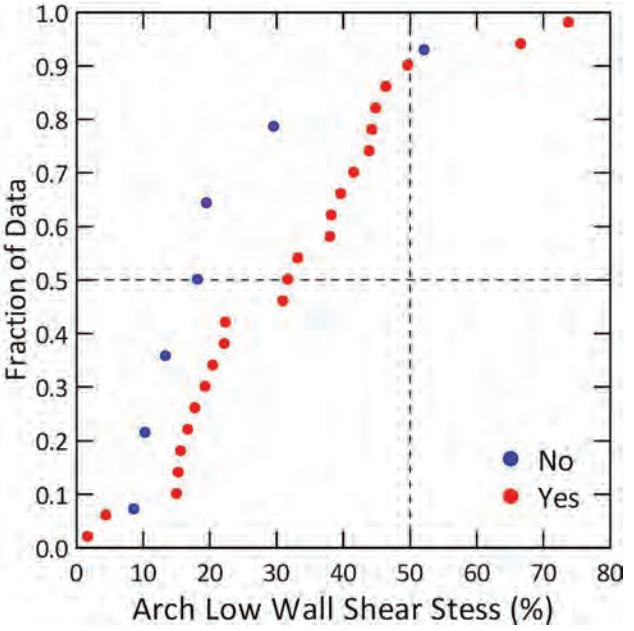
Background: An arteriovenous fistula (AVF) is the optimal access for hemodialysis. A brachiocephalic fistula (BCF) is often placed, but cephalic arch stenosis (CAS) commonly develops leading to failure. We hypothesized that a contribution to AVF failure is low wall shear stress (WSS) (less than 0.076 *Pa*), resulting in neointimal hyperplasia and venous stenosis. The aim of this study was to determine the correspondence of low WSS and the development of CAS in a large cohort followed longitudinally.

Methods: 39 subjects with ESRD and a primary BCF were followed from time of placement for three years or until the time of CAS. A venogram, Doppler, and blood viscosity were performed at time of AVF maturation (3 months), then annually up to three years or to time of CAS. Geometric measurements of venous diameter, radius of curvature, and arch angle were made. Computational modeling determined the location and percent low WSS in the arch. The relationship between WSS at three months and location of CAS was estimated by correlating computational modeling and quadrant location of CAS. Correspondence was examined using Chi-square.

Results: 32 subjects developed CAS by three years as shown by dots in the Figure. Of these, 25 subjects (red dots) displayed correspondence between low WSS at three months and CAS, whereas 7 subjects did not (blue dots) ($p=0.0015$). Most subjects with correspondence had low WSS areas evident in greater than 20% of the arch ($p=0.0006$). Venous diameter, radius of curvature and arch angle at three months did not predict CAS($p>0.05$).

Conclusions: The presence and magnitude of low WSS in the cephalic arch is a factor associated with the development of CAS. Determination and attenuation of low WSS at 3 months may help to prevent the development of CAS which is difficult to treat once it develops.

Funding: NIDDK Support



FR-PO720

A Computational Fluid Dynamics (CFD) Approach to Optimize Arterio-Venous Fistula (AVF) Anastomotic Hemodynamics with Ôan External Support Device (VasQ™)

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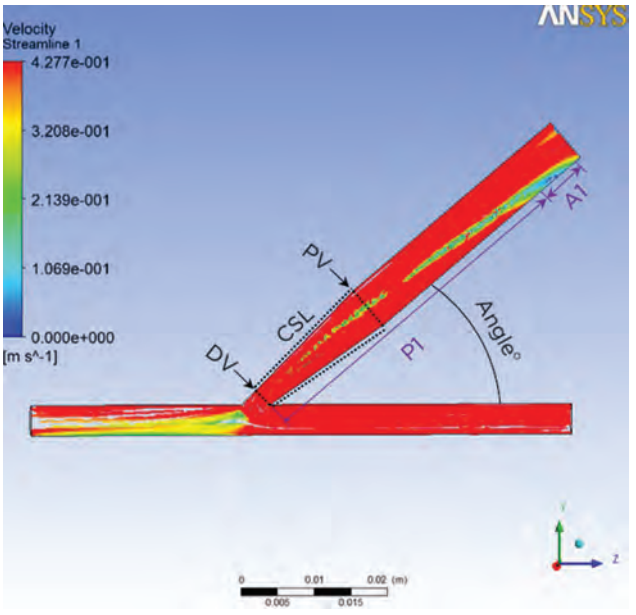
Background: The complex AVF geometry induces hemodynamic changes in the juxta-anastomotic region (JAR). Multidirectional flow and oscillating wall shear stress (WSS) along the venous wall invoke undesirable inward vein remodeling through aggressive development of neointimal hyperplasia. A CFD model was utilized to study the effect of geometric parameters on hemodynamic profiles to inform optimal design of the VasQ™ device.

Methods: A fully developed 3D end-to-side AVF CFD model was evaluated through a range of artery and vein diameters (2.9-8mm) and flow volumes (40–1100 ml/min) assuming steady, laminar, Newtonian flow. 2D velocity streamline patterns were analyzed. Geometric parameters controllable by external scaffold were optimized for minimizing multidirectional flow along the venous wall (A1) and maximizing its distance from anastomosis (P1). Parameters included anastomotic angle (20°-60°), Proximal Vein (PV)/Distal Vein (DV) diameter ratio (conical shape) (1.2-2) and conical segment length(CSL) (15-25mm). Each parameter was analyzed by fixing all model values excluding the tested one.

Results: Improved flow patterns (small mean λ value; λ =A1/P1) were observed for anastomotic angle between 40°-50° (0.92±0.2) compared to angle between 20°-30° (2.3±1.7) and 60° (1.74±1.3). Optimal PV/DV (conical shape) was 1.5 (0.23±0.07) with higher λ values for PV/DV lower or higher than 1.5. λ values of 0.2±0.8, 0.27±0.05 and 0.35±0.06 for CSL of 25mm, 20mm and 15mm accordingly.

Conclusions: Improved unidirectional flow pattern directly correlated to uniform WSS in the JAR were observed for anastomotic angle between 40°-50°, conical vein shape with 1.5 PV/DV and CSL of 25mm in multiple configurations. These conclusions were the basis for designing VasQ™.

Funding: Commercial Support - Laminate Medical Technologies



Tested geometrical parameters

FR-PO721

New Approach for Assessing Vascular Stiffness in Patients with Hemodialysis

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Background: It is known that increased vascular stiffness, as measured by pulse wave velocity (PWV), can predict cardiovascular events in hemodialysis (HD) patients. Additionally, the measurement of static intra-access pressure ratio (SIAPR), using transducer on HD machines, is preferred vascular access surveillance method. However, little is known about the clinical usefulness of SIAPR in predicting the degree of vascular stiffness.

Methods: A total of 209 patients on maintenance hemodialysis were evaluated between January 2014 and February 2018 at three hospitals. Brachial-ankle pulse wave velocity (baPWV) and SIAPR were measured in HD patients. After that, we performed echocardiography at study enrollment and investigated cardiovascular (CV) events after study enrollment, respectively.

Results: Patients with arteriovenous (AV) graft and AV fistula was 172 and 37, respectively. Among AV fistula group, SIAPR was significantly negative correlation with baPWV (ß = - 0.16, p =0.04). The area under the receiver operating (ROC) curve for SIAPR value to predict CV events was 0.09 (95% confidence interval [CI]; 0.86 - 0.95, $p < 0.001$). A SIAPR value of 0.09 was selected as the cut-off value for CV events. baPWV (222.7 ± 418.1 vs. 2010.2 ± 511.4 cm/s, $P = 0.04$) and the proportion of left ventricular diastolic dysfunction (86% vs. 25%, $p = 0.01$) was significantly higher in patients with a SIAPR value ≤ 0.09 than with a SIAPR value > 0.09. Kaplan-Meier analysis revealed that cumulative incidence of CV events was significant higher in patients with a SIAPR value ≤ 0.09 ($p.= 0.04$). Among AV graft group, there were significantly negative correlation between SIAPR and baPWV. When a SIAPR value of 0.15 was selected as the cut-off value for CV events, similar trends were observed.

Conclusions: SIAPR was significantly associated with baPWV and left ventricular diastolic dysfunction in HD patients. Additionally, lower value of SIAPR could predict cardiovascular events.

FR-PO722

Adjunctive Use of Color-Coded Digital Subtraction Angiography During Percutaneous Transluminal Intervention of Hemodialysis Vascular Access

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Background: Parametric color-coding of digital subtraction angiography (DSA) has been successfully used in interventional neuroimaging and diagnostic imaging for peripheral arterial disease. We aimed to examine the utility of color-coded DSA for quantitative hemodynamic analysis in percutaneous transluminal angioplasty (PTA) of hemodialysis access.

Methods: This is a prospective, single center study. DSA acquisitions were post-processed into color-coded images. Regions of interest (ROI) were selected for each image. Hemodynamic parameters including time-to-peak (TTP) contrast opacification, contrast transit time (TT) and contrast decay time were obtained. These parameters were compared pre-and post-PTA.

Results: DSA of 16 patients who underwent PTA were included. 9 interventions were performed on arteriovenous fistulas and 7 on arteriovenous grafts with median access age of 3.5 ± 3.1 years (interquartile range 1.8-6.7). All patients had improvement in percentage of stenosis post PTA with a mean difference of 39.71 ± 16.25% ($p<0.01$). TTP improved significantly following PTA, with mean reduction of 0.35 ± 0.65 seconds (s) ($p<0.01$) and 0.60 ± 0.83s ($p<0.01$) for pre- and post- stenosis ROIs respectively. Mean reduction in contrast transit was 0.23 ± 0.53s ($p=0.04$). Receiver operator characteristics analysis showed that 10% contrast decay time at 0.05s correlated with access flow of 800cc/min with sensitivity of 0.91 and specificity of 0.5 (area under the curve 0.89, 95% confidence interval 0.71 – 1.0).

Conclusions: Adjunctive usage of parametric color-coded DSA could provide hemodynamic information, which may be useful for decision-making during PTA of hemodialysis access.

FR-PO723

Timing of Vascular Access Creation in Hemodialysis Patients

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Background: Late referral for vascular access creation in Chronic Kidney Disease (CKD) patients who opted for hemodialysis (HD) may lead to high central venous catheter (CVC) rates. In contrary, too early referral potentially leads to unnecessary vascular access interventions. The aim of the present study was to analyze timing of vascular access creation in patients starting HD.

Methods: We conducted a retrospective, observational study in stage 4 and 5 CKD patients from a single center in the Netherlands, referred for first vascular access creation between 2009 until 2011. Patients were divided in three groups: (too) early, optimal or (too) late vascular access creation. Early was defined as vascular access surgery ≥6 months prior to start HD. Optimal was defined as starting HD with an adequate vascular access and surgery was within 6 months prior to start. Late was defined as starting HD with a CVC. Patient characteristics as well as vascular access interventions were recorded.

Results: Forty-two patients were included (age 68±11y; 50% male; eGFR 11±3ml/min/1.73m^2). Mean time from vascular access surgery to initiation of HD was 338±470 days. Vascular access creation was early in 60% (n=25), optimal in 29% (n=12) and late in 12% (n=5). Forty-four percent of the patients in the early group (n=11; 26% of all included patients) never started HD after a mean follow-up of 8 ±0.7 years (7 patients died, 2 had stabilized kidney function, 1 underwent pre-emptive kidney transplantation, and 1 was lost to follow up). Overall, in 45% (n=19) of patients a surgical and/or endovascular intervention was performed before initiation of HD. Of the 11 patients that never started HD an intervention was performed in 36% (n=4). All patient in the early and optimal group had an adequate vascular access at start of HD. Higher age and high eGFR were associated with late vascular access creation.

Conclusions: In this study, the majority of patients started HD with an adequate vascular access. However, in a substantial proportion of patients interventions were needed prior to start HD, also in the subgroup of patients that never started HD during follow up. More studies are warranted to investigate the optimal timing of vascular access creation aiming at adequate vascular access at time of start HD on the one hand and avoiding too early referral resulting in unnecessary interventions on the other hand.

FR-PO724

Evolution of Vascular Access in the First Year of Dialysis in the Irish Health System: A National Cohort Study

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Background: Although the arteriovenous fistula (AVF) confers superior benefits over central venous catheters (CVC), utilisation rates remain low among prevalent haemodialysis (HD) patients. The goal of this study was to determine the type and frequency of vascular access provision in the first year of dialysis and identify factors associated with conversion to AVF.

Methods: Data was obtained from the *National Kidney Disease Clinical Patient Management System* which tracks all patients with end stage kidney disease (ESKD) in Ireland. All adult patients who began HD in 2015 and 2016 and treated for at least 90 days were included. Data was captured on demographics factors, primary cause of ESKD (P-CKD), comorbid conditions, and biochemical indicators at day 90 (D90). Univariable and multivariable Cox regression quantified the risk of conversion from CVC to AVF with follow-up to D360 expressed as hazard ratios (HR), censored at change in modality and death.

Results: The study cohort included 610 patients, mean age 61.7yr (±15.8), 65% men and 76.7% were using a CVC for dialysis at D90. At D90, the likelihood of CVC varied significantly across HD centres (from 63 % to 91%, P<0.001) and these differences persisted when adjusting for case-mix. From D90 to D360, rates of AVF increased modestly from 23% to 41%, P<0.001 with a corresponding fall in CVC rates from 77% to 59%, P<0.001. Factors associated with conversion from CVC to AVF included age [HR, 0.45, (0.21- 0.96) for age > 78 vs < 60 years (ref)]; P-CKD-hypertension [HR, 0.19 (0.05- 0.72) and P-CKD-unknown [HR 0.25, (0.10- 0.61) vs P-CKD-polycystic kidney disease (ref)], increasing BMI, [HR1.05 (1.02- 1.08)] per unit increase, and HD centre (Figure 1).

Conclusions: CVCs remain the major type of vascular access in Irish HD patients with only a modest rise in AVF provision observed during the first year. Substantial centre

variation exists at dialysis initiation and continues throughout the first year which is not fully explained by patient-level factors.

Funding: Government Support - Non-U.S.

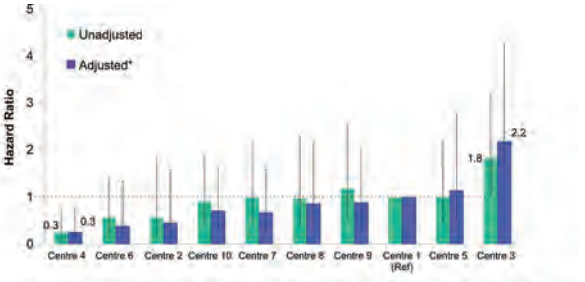

Figure 1. Hazard Ratio for Conversion from CVC at Day 90 to AVF at Day 360 by Primary Centre
*Model adjusted for age, gender, primary cause of ckd, comorbidities and primary HD centre

FR-PO725

Improving Rate of Access Placement for Inpatients with eGFR Less Than 20 mL/min/1.73 m2

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Background: The most common form of renal replacement therapy in the US is hemodialysis (HD) which requires Arterio-Venous (AV) access placement. Challenges with obtaining timely permanent AV access include late referral to nephrology and vascular surgery, patient non-compliance, and lack of effective patient pathways. Baseline data at our institution for inpatients with eGFR < 20 ml/min, revealed there was a greater prevalence of patients without permanent AV access for HD initiation compared to national data. Using Quality Improvement (QI) methodology and interventions, we aimed to improve AV access creation in this population.

Methods: Over a three month period on five medicine teaching services, residents were given a protocol to order venous mapping, consult nephrology and vascular surgery for all patients with an eGFR<20 ml/min. The vascular team established care and scheduled outpatient appointments for permanent HD access. The nephrology fellows scheduled follow up appointments and conducted post-discharge physician phone calls. Baseline data was collected on patients with an eGFR< 20 ml/min who were discharged without initiation of HD including readmitted patients over a 3 month period.

Results: The study population had a greater rate of AVF/AVG present at 62% compared to the baseline data at 23% and did not significantly alter the length of stay (Table 1).

Conclusions: Hospitalizations are stressful and making decisions regarding long term care can be difficult. Follow-up physician phone calls allowed care teams to speak to patients when they were more receptive and motivated to make healthcare decisions. This improved patient compliance and follow-up rates, and resulted in timelier AV access rates without adversely affecting length of stay. Study limitations included the time-intensive nature of care coordination, lack of a transitions of care coordinator and the structure of patient capture. We conducted a successful QI intervention in a limited pilot project. Creating an effective patient pathway for inpatients with advanced CKD can increase rates of AV access placement without significantly increasing length of stay.

Vascular Access Rate and Length of Stay

Transitions of Care Category	Baseline Data N=22	Study Population N=27
AVF/AVG Present	23%	62%
Average Length of Stay	8.31 days	8.4 days

FR-PO726

Outcomes of Coordinated Late Vascular Access Creation

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Background: Guidelines recommend timely pre-dialysis access creation to reduce incident catheter utilization which is associated with higher risk of hospitalization, procedures, mortality and cost. The process to achieve this goal is ambiguous and access coordination could be valuable, especially if the creation is late. Our program utilizes a hemodialysis (HD) access coordinator working closely with nephrologists and surgeons. This study analyzes how this system affects the outcomes of late access creation in our patient population.

Methods: Prospectively collected data from an electronic access database and the medical records of patients undergoing HD access creation between 2011-2017 prior to HD initiation from a single hospital system were analyzed.

Results: A total of 130 patients between the age of 22 to 89 years at the time of access placement had 146 accesses created. Seventy-eight (60%) were male, 52 (40%) female, 52% Caucasian and 42% African American. At time of access creation, median age was 60.5 and 56.5 years and median eGFR was 13.5 and 15.5 ml/min per 1.73 m^2 in the AVF and AVG group, respectively. A total of 131 AVF and 15 AVG were created. Seventy six patients started HD with a median time after creation of 109 and 131 days for non-diabetics and diabetics, respectively. At this time, 54 (42%) patients remain pre-HD-18 (33%) with failed access and 6 (11%) have died with a functioning access. Access success rate in those who initiated dialysis was 63%. HD was initiated with a catheter in 36% (46% in females vs. 30% in males). The average time to an interventional procedure after creation was shorter in non-diabetics (153 days) vs diabetics (197 days) and shorter in AVF (184 days) vs AVG (219 days). Interestingly, non-diabetics and patients under the age of 70 had a higher rate of access failure.

Conclusions: Nationally, 60-80% of incident HD patients have a catheter with fewer than 15% access placed less than 3 months prior to HD initiation. In our program, access placement occurred 3.5-4.5 months prior to dialysis initiation, later than recommended 6 months and at a very low eGFR. Despite that, our incident catheter rate was about half the national average. Our data emphasizes the importance of access coordination in order to reduce the incident catheter use and unnecessary access creations.

FR-PO727

Patient Centered Care: The Effect of an Integrated Nephrology-Vascular Surgery-Ultrasound Clinic on Arteriovenous Fistula Use

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Background: Arteriovenous fistula (AVF) is the preferred form of vascular access for hemodialysis due to their association with lower rates of complication and lower cost of maintenance. Multiple teams are involved throughout the course of AVF creation but they are often not seeing the patient simultaneously. We hypothesize that an integrated, multidisciplinary clinic including nephrologists, vascular surgeons, and an ultrasonographer will improve initiation of hemodialysis using AVF.

Methods: The study population included adults at least 18 years old who received an AVF between March 2013 and March 2016 at Kaiser Permanente San Francisco (KPSF), during which an integrated clinic was formed. This cohort was retrospectively compared to KPSF patients who received an AVF between March 2009 to March 2012. Subjects were excluded if they had a prior AVF placed in the previous 12-24 months, history of renal transplant, death before AVF use, or lost to follow up. The final analytic cohort included 233 patients. Chi-square tests and t-tests were used to compare the demographic (age, race, gender) and clinical characteristics (diabetes mellitus, HbA1c, estimated glomerular filtration rate, peripheral vascular disease, and tobacco smoking status) by integrated vs the non-integrated clinic. Chi-square tests and logistic regression were used to compare clinical outcomes of patients in integrated clinic compared to patients in the non-integrated clinic.

Results: There were 118 patients in the integrated clinic (mean age 70.4±13.7 years, 30.5% women) and 115 patients in the non-integrated clinic (mean age 66.2±13.1 years, 40.9% women). Enrollment in the integrated clinic significantly improved initiation of dialysis using an AVF (48.3% versus 33.9%; odds ratio, OR, 1.8; p=0.03). The integrated clinic also significantly decreased initiation of dialysis using a central venous catheter (CVC) (35.6% versus 51.3%; OR 0.5, p=0.02).

Conclusions: An integrated, multidisciplinary AVF surveillance clinic increases initiation of hemodialysis using AVFs and decreases initiation of hemodialysis using CVCs.

FR-PO728

Clinical Outcomes and Economic Impact of Starting Hemodialysis with a Catheter (CVC) vs a Permanent Access After Pre-ESRD Arteriovenous Fistula (AVF) Creation

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Background: Patients progressing to ESRD frequently have an AVF placed pre-ESRD, but may initiate HD with a CVC if the access is not yet suitable for use. Little is known about the clinical outcomes and economic impact of such patients initiating HD with a CVC vs a permanent access.

Methods: We identified 205 patients who received an AVF pre-ESRD between 2006 and 2012, and started hemodialysis within 2 years. Of these, 91 initiated HD with a CVC and 114 with a permanent access. We compared these two groups in terms of demographics, co-morbidities, the frequency of percutaneous access procedures, surgical access procedures, total access procedures, hospitalizations due to catheter related bacteremia (CRB), and annual cost of vascular access management from ESRD to the end of patient follow-up.

Results: The groups initiating HD with a CVC vs a permanent access were similar in terms of age, sex, race, diabetes, vascular disease, and heart failure. As compared to patients initiating HD with a permanent access, those initiating with a CVC had a 61% greater annual frequency of percutaneous access procedures, a 41% greater frequency of surgical access procedures, a 55% greater frequency of total access procedures, and a 5-fold higher frequency of CRB hospitalizations (Table 1). Patients initiating HD with a CVC incurred a median annual cost of access management that was $2,930 higher ($5,478 [2,011-12,497) vs $2,548 [924-6717], p<0.001).

Conclusions: Among patients with pre-ESRD AVF creation, those initiating HD with CVC had substantially more frequent percutaneous, surgical, and total access procedures, as well as CRB hospitalizations. The annual cost of access management was substantially higher in those initiating HD with a CVC vs a permanent access.

Frequency of post-ESRD access procedures and CRB hospitalizations in patients starting HD with permanent access vs a CVC after pre-ESRD AVF surgery.

	Permanent access	Catheter	p-value
N of patients	114	91	
Years of follow-up, median [IQR]	4.6 [2.1-6.7]	4.7 [2.2-7.5]	0.82
All percutaneous procedures per pt-yr	0.82 (0.75-0.90)	1.32 (1.22-1.43)	<.001
All surgical procedures, per pt-yr	0.34 (0.29-0.39)	0.48 (0.42-0.55)	0.001
All access procedures per pt-yr	1.16 (1.07-1.25)	1.80 (1.68-1.93)	<.001
CRB hospitalisation per 100 pt-yr	7.22 (1.14-3.87)	10.00 (7.29-13.37)	<.001

FR-PO729

Incremental Costs of Arteriovenous Fistula (AVF) Non-Use Among US Hemodialysis Patients

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Background: Despite the importance of vascular access (VA) for adequate hemodialysis (HD), few studies have examined the real world costs related to AVF maturation and use. We used national Medicare claims data to examine per patient VA costs over a 3 year period based on AVF use for dialysis among a cohort of dialysis patients.

Methods: We conducted a retrospective observational study using USRDS data for all incident Medicare patients who initiated dialysis from 2010-2011 and initiated dialysis with a mature AVF (n=2,704) or initiated dialysis with a CVC and underwent AVF creation in the next 6 months (n=3,901). Using a multidisciplinary expert panel, we identified VA-related diagnostic, imaging, endovascular, surgical, infection, hospitalization and anesthesia codes to calculate total VA costs paid by Medicare. *Annualized per patient per year (PPPY) costs* were calculated from the AVF creation date with costs censored at death or change in renal replacement modality. VA costs were calculated from the AVF creation date and were compared based on whether the AVF was successfully used for dialysis, as defined by the presence of at least one monthly ESRD billing claim in which AVF was recorded as the VA in use.

Results: Regardless of timing of fistula insertion, AVFs that were not successfully used for dialysis resulted in incremental VA-related costs to Medicare of more than $20,000 PPPY in the first year after AVF creation, compared to AVFs that were successfully used. Incremental VA-related costs were also observed in the second and third year following AVF creation. In aggregate, annualized VA costs for three years after AVF creation are more than three times as high for patients whose fistula does not mature compared to those whose fistula matures.

Conclusions: Improvements in processes of care and technologies to enhance AVF maturation and use for dialysis as well as better patient selection should result in less morbidity with the potential for significant cost-savings.

Funding: Commercial Support - Proteon Therapeutics Inc

Table1. Vascular access-related per patient per year costs (± SD) from AVF creation based on AVF use and non-use in year 1

	Patients initiating with mature AVF			*Patients initiating with CVC and subsequent AVF creation*		
	All AVFs N=2704	**AVFs used N=2493**	**AVFs never used N=211**	**All AVFs N=3901**	**AVFs used N=2117**	**AVFs never used N=1784**
Year 1	$11,433±$22,347	$9,883±$14,340	$30,687±$60,013	$19,512±$70,235	$11,371±$16,046	$32,405±$104,035
Year 2	$4,759±$12,322	$4,600±$12,100	$13,686±$17,432	$6,966±$23,295	$5,826±$19,805	$17,000±$33,334
Year 3	$5,416±$16,660	$5,250±$16,792	$20,384±$26,045	$7,709±$23,306	$6,364±$19,314	$20,254±$42,393
Yrs 1-3	$9,126±$21,740	$7,699±$13,284	$29,710±$59,969	$17,462±$70,200	$9,351±$17,421	$31,630±$103,941

FR-PO730

Procedural Burden Following Arteriovenous Graft Placement Among Incident Hemodialysis Patients in the United States

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Background: We previously reported that half of patients required interventional procedures for successful maturation of arteriovenous fistula (AVF), with additional post-maturation burden of 0.40 and 0.52 procedures per person-year (ppy) for those with natural and assisted maturation, respectively (p<0.0001). Herein, we sought to determine the procedural burden during 'maturation' and maintenance phases of newly placed arteriovenous grafts (AVG).

Methods: Using data from the United States Renal Data System (USRDS), patients new to HD from 7/1/12 to 12/31/14 with initial billing codes for AVG placements (since HD start) from 7/1/12 to 12/31/15 were included. Successful maturation was defined as first documentation of AVG use in CROWNWeb monthly data. Patients were followed until 12/31/2016, or 1 year post-AVG placement.

Results: Among 258,731 incident HD patients, there were 23,629 first-time AVG placements. Of these, 59.9% were successfully utilized, 28.7% had no recorded use, and 11.3% were lost to follow-up (Table). Of successfully utilized AVG, 18.2% required interventions during the maturation phase, for 0.31 procedures per person (pp), while 43.3% of unsuccessful AVG underwent intervention, for 1.03 pp (p<0.0001). Following successful first use, those with assisted maturation underwent 2.05 ppy, while those without assistance demonstrated 1.59 ppy (p<0.0001).

Conclusions: Surprisingly, AVG utilization following placement was lower than anticipated. Interventions on AVG were common for both maturation and maintenance. While the maturation procedural burden for AVG compares favorably with AVF, the maintenance phase procedural burden is much higher, implying potential logistic and cost advantages of AVF over AVG.

Funding: NIDDK Support

Procedural Burden Before Recorded Successful Use				
	Failed Maturation	**Successful Maturation**	**P**	**Total**
Patients	6,792	14,164		20,956
Patients with Interventions	2,938	2,580		5,518
Interventional Procedures	6,985 (1.03 pp)	4,330 (0.31 pp)	<0.0001	11,315
Diagnostic Fistulogram Only	1,197 (0.18 pp)	703 (0.05 pp)	<0.0001	1,900
Any Therapeutic Intervention	5,788 (0.85 pp)	3,627 (0.26 pp)	<0.0001	9,415
Angioplasty	2,067 (0.30 pp)	1,123 (0.08 pp)	<0.0001	3,190
Thrombectomy	2,892 (0.43 pp)	2,067 (0.15 pp)	<0.0001	4,959
Thrombectomy only	522 (0.08 pp)	334 (0.02 pp)	<0.0001	856
Percutaneous thrombectomy	2,030 (0.30 pp)	1,473 (0.10 pp)	<0.0001	3,503
Revision + Thrombectomy	340 (0.05 pp)	260 (0.02 pp)	<0.0001	600
Revision	470 (0.07 pp)	195 (0.01 pp)	<0.0001	665
Stent	359 (0.05 pp)	242 (0.02 pp)	<0.0001	601

Procedural Burden After Recorded Successful Use (Maintenance Phase)				
	Natural Maturation	**Assisted maturation**	**P**	**Total**
Patients	11,584	2,580		14,164
Patients with New Interventions	6,221	1,605		7,826
Interventional Procedures	15,303 (1.59 ppy)	4,337 (2.05 ppy)	<0.0001	19,640
Diagnostic Fistulogram Only	1,860 (0.19 ppy)	483 (0.23 ppy)	<0.0001	2,343
Any Therapeutic Intervention	13,443 (1.40 ppy)	3,854 (1.82 ppy)	<0.0001	17,297
Angioplasty	4,754 (0.62 ppy)	1,288 (0.96 ppy)	<0.0001	6,042
Thrombectomy	7,647 (1.00 ppy)	2,275 (1.70 ppy)	<0.0001	9,922
Thrombectomy only	845 (0.11 ppy)	234 (0.17 ppy)	<0.0001	1,079
Percutaneous thrombectomy	6,340 (0.83 ppy)	1,927 (1.44 ppy)	<0.0001	8,267
Revision + Thrombectomy	462 (0.06 ppy)	114 (0.08 ppy)	<0.0001	576
Revision	275 (0.04 ppy)	63 (0.05 ppy)	<0.0001	338
Stent	767 (0.10 ppy)	228 (0.17 ppy)	<0.0001	995

FR-PO731

The Repeatability of AVF Mean Blood Flow in Temperate and Sub Saharan Environments

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Background: We have previously demonstrated a 70% difference between Dialysis AVF blood flow in the UK and Sudan, the Sudan mean being greater than the UK mean [(1)]. The study has recently been extended to 4 renal centres in Sudan.. A recent 7 centre study in the USA has published the mean AVF blood flow at 6 weeks maturation [(2)]. We have characterised UK and USA environments as temperate and the Sudan environment as sub Saharan.

Methods: AVF blood flow was measured with a Duplex device in all centres. Clinical indications were used in the USA study to eliminate failing or failed AVF from the study of mature fistulae.. The incidence of failing AVF in each cohort in the UK and Sudan was studied using a new device Bluedop ™ [(1)]

Results: The results are tabulated below. Additional data was recorded including patient Age, Gender and AVF location.

Conclusions: Conclusion: A number of explanations for the elevated Sub Saharan mean Blood Flow results have been explored. Mean annual temperature appears to be a possible cause, Published values for minimal seasonal ambient temperatures show Khartoum is approximately 14 degrees C warmer than London thoughout the year. USA ambient temperatures have not been studied. Deep Infra Red studies have been shown to speed AVF maturation. It should also be noted that although AVF failure rates were comparable in Sudan and the UK, that active intervention was not available in Sudan. (1) Environmental and Patient Specific Factors associated with AVF Blood Flow. ASN Abstracts New Orleans, November 3rd 2017 (2) Relationship Between Clinical Processes and Arteriovenous Fistula Cannulation and Maturation: A MultiCenter Cohort Study, AJKD, published online, doi: 10.1053/j.akjd.2017.10.027

Funding: Commercial Support - Bluedop Medical Ltd

Means/Ratios	Age ± 1sd	female/male	forearm	avf flow+/-	n
Sudan 1 & 2	43 ±16.1	30.3 %	37.3 %	1797 ± 843	45
Sudan 3 & 4	47 ±14.6	32.3 %	35.4 %	1614 ±699	66
UK 1 &2 & 3	66 ±13.3	42.1 %	41.2 %	1062 ±543	58
USA 1 to 7	55 ±13.8	28.5 %	21.4 %	1031 ±613	430

Results Table

FR-PO732

Outcomes of Expanded Polytetrafluoroethylene Vascular Grafts as Dialysis Access in Chinese Population: A Retrospective Study

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Background: With the increased prevalence of end stage renal disease and extended life expectancy of hemodialysis patients, more and more patients had limited quality and availability of superficial vessels for fistula. It is recommended to apply expanded polytetrafluoroethylene (ePTFE) vascular grafts if native fistula is not possible. The aim of our study is to analysis the outcomes of arteriovenous graft (AVG) in our dialysis center.

Methods: It was a retrospective study enrolled all the patients who underwent AVG from October 2014 to December 2017 in our dialysis center. The demographic characteristics, dialysis duration, laboratory tests, location and configuration of AVG, operation outcome,as well as the patency rate were analyzed.

Results: A total of 222 patients with the mean age of 60.5±13.9 were included in this study. 56% of the study population was female. The most common comorbidities were hypertension (84%) and diabetes (49%). All the grafts were successfully implanted. The follow-up period ranged from 3 to 40 months. The configurations of the grafts were 73% loop and 27% straight, and 57% of them were implanted in forearms. There was no operation-related mortality. However, 3 early failure were noted. The primary and secondary patency rates were 81% and 98%, 63% and 92%, 49% and 82%, 30% and 63%, at 6, 12, 24, 36 months after the surgery, respectively. The primary and secondary patency of grafts in forearm was markedly better than those in upper arm. Comorbidities and configurations were not correlated with patency. There were 160 postoperative complications developed in 96 patients during the study period, including thrombosis (74), proximal vein stenosis (72), infection (11), bleeding with hematoma (1), steal syndrome (1), and pseudoaneurysm (1).

Conclusions: AVGs implanted in forearm has superior primary and secondary patency than in upper arm. We recommended using ePTFE grafts as an alternative in patients with poor autogenous vascular conditions.

Funding: Government Support - Non-U.S.

FR-PO733

A Prospective Outcome Analysis of the Early Cannulation Graft ACUSEAL® versus the Standard Expanded Polytetrafluoroethylene (ePTFE) Graft in Hemodialysis (HD) Patients

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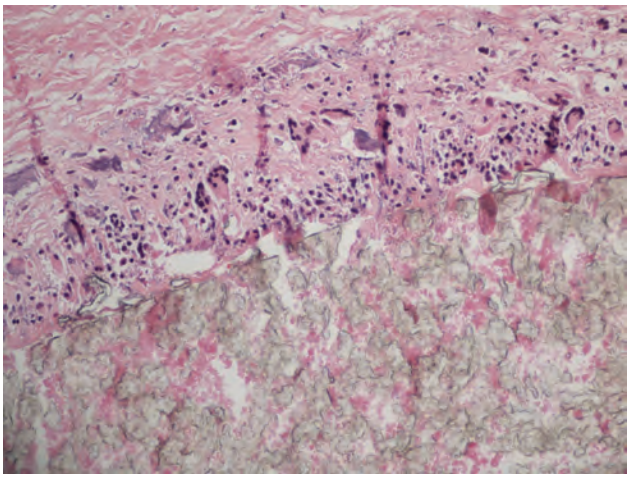
Background: Our objective was to prospectively compare survival, assisted primary (APR) and secondary (SEC) patency rates of the early cannulation ACUSEAL® and standard ePTFE arteriovenous grafts (AVG) for HD access.

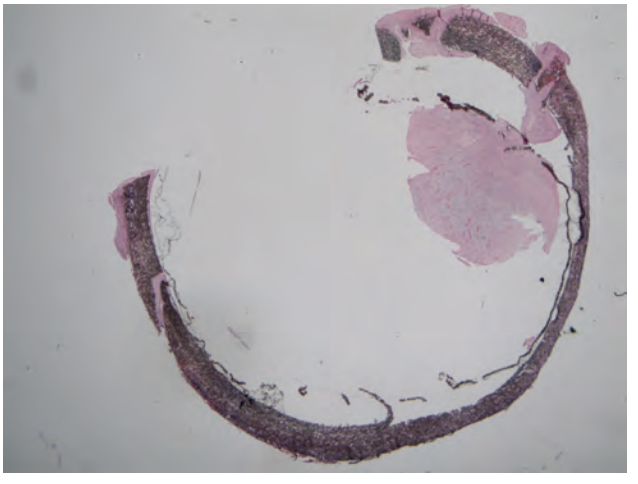
Methods: Incident patients requiring implantation of an AVG for HD initiation or therapy continuation were enrolled between December 2014 and December 2017. Outcome measures were APR, SEC survival, APR and SEC patency rates of these AVG.

Results: A total of 146 HD patients had AVG implanted, 63 were ACUSEAL® and 83ePTFE. For ACUSEAL® APR survival was 190 days and APR patency rate was 31%, 12%, 6% in 12, 24 and 36 months. For ePTFE grafts APR survival was 537 days(p=0.001) and APR patency rate 56%, 43% and 30%. Whereas, SEC survival was 596 days for ACUSEAL® and 1,365 days for ePTFE(p=0.04) while SEC patency was 72%, 49%, 34% and 80%, 70% και 57% in 12, 24 and 36 months, respectively. Wall destruction and lumen stenosis were common findings in removed ACUSEAL®AVG.

Conclusions: The advantage of early cannulation of ACUSEAL® AVG seems to be partly neutralized by the inferior clinical outcomes seen by this graft compared to those of ePTFE AVG. Prospective randomized trials are needed to confirm these preliminary results



Foreign-body giant and mononuclear cell Inflammatory infiltrate penetrating the inner and intermediate graft layers



Polypoid granulation tissue causing wall, layer separation and luminal stenosis

FR-PO734

The Effect of Citrate Dialysate on Clot Formation and Anemia in Hemodialysis Patients

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Background: Citrate anticoagulation in renal replacement therapy is increasingly becoming a favorite choice to prevent extracorporeal circuit clotting. The use of citrate rendered the reduction of heparin in conventional hemodialysis. This is a study to test the effect of citrate on heparin avoidance and other parameters such an ESA dose, anemia, adequacy of dialysis, and inflammatory cytokines compared to acetate dialysate.

Methods: Sixty one chronic HD patients were switched from acetate to citrate dialysate and treated in 3 phases, with each phase lasting for four weeks. These phases comprised 50% and 25% heparin reduction and heparin free treatments. Visual clotting score, as graded by a visual analog scale, ESA doses and laboratory data including pre- and post-HD ionized calcium levels,IL-6 and hs-CRP were measured

Results: Except for two episodes of clotting, the dialyzers could be used thoroughly throughout the citrate phases. The mean visual clotting scores for all three study periods were comparable. Hemoglobin decreased slightly in phase 2 (9.68±1.88 VS 9.06±1.60 g/dL, p=0.001, pre and post protocol) despite constant ESA dose. There were no significant differences in electrolytes, adequacy of dialysis, and inflammatory cytokine levels, as measured by IL-6 and hs CRP between acetate and citrate dialysis. The post protocol level of iCa^{2+} paradoxically rose after HD in most sessions. We observed no adverse events during citrate dialysis.

Conclusions: During periods of citrate dialysis in chronic HD patients, heparin can be avoided while maintaining balanced electrolyte levels and adequacy of dialysis and hemoglobin. No significant adverse events, including hypocalcemia, were found.

Funding: Government Support - Non-U.S.

FR-PO735

The Total IV Iron Burden and Insulin Sensitivity in ESRD

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Background: Systemic iron overload has been strongly associated with increased incidence of diabetes in non-CKD patient populations. Despite the high prevalence iron overload in hemodialysis (HD) patients due to frequent IV iron infusion, there are no studies to evaluate the association between total accumulative IV iron dose and insulin sensitivity.

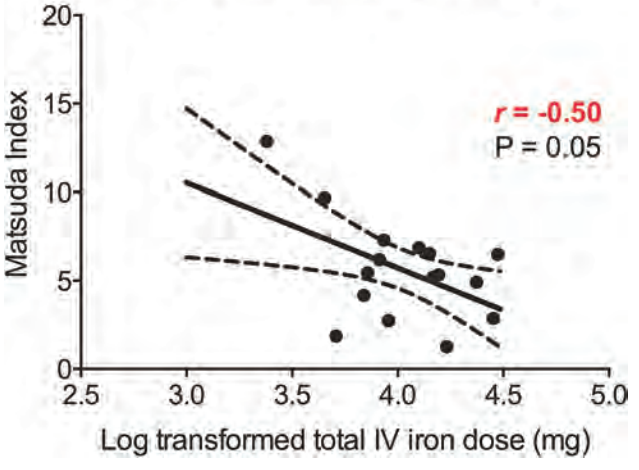
Methods: We performed an observational pilot study of prevalent hemodialysis patients at University of Utah (N=16). Patients with history of dementia, chronic hepatitis, steroid use, malignancy, thalassemia, hemochromatosis, sickle cell disease, hospitalization or IV antibiotic use within one month of screening were excluded. The total accumulative dose of IV iron for the entire duration of dialysis was calculated for each participant. All 16 participants underwent 3-hour oral glucose tolerance test to calculate whole-body insulin sensitivity (Matsuda Index, MI). The total accumulative IV iron dose was log transformed to enable parametric analysis with Pearson correlation coefficient to evaluate its association with MI.

Results: The study group was diverse (8 Hispanics, 4 Whites, 1 Asian, and 3 mixed), with 9 men and 7 women. Half of the group had diabetes. The mean±SD values for age, dialysis duration, systolic blood pressure, hemoglobin, and albumin were 52±14 years, 7.4±5.8 years, 142±28 mmHg, 10.6±1.9 g/dL, and 3.9±0.2 mg/dL, respectively. The median (IQR) transferrin saturation and ferritin were 28 (21, 39)% and 652 (300, 971) ng/mL. The median (IQR) total IV iron dose over the mean HD duration was 10,825 (6,986, 16675) mg (range of 2,400 to 29,748 mg). The insulin sensitivity as assessed by MI showed a *significant inverse relationship* with the total IV iron dose (r = -0.50, Figure 1).

Conclusions: This is the first study to evaluate the association between IV iron therapy and insulin sensitivity and to suggest a possible role of IV iron therapy in metabolic risk in HD patients. Larger studies are required to confirm the result and to further investigate the underlying mechanisms.

Funding: Private Foundation Support

Figure 1. Correlation between the total IV iron dose and insulin sensitivity



FR-PO736

Comparison of Measured and Prescribed Dialysate Sodium in Three Brands of Dialysate Acid Concentrate

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Background: There is ongoing controversy regarding the optimal dialysate sodium concentration (DNa). This issue is further complicated by differences between prescribed and measured DNa. These differences are higher in facilities utilizing Fresenius K2 dialysate delivery machines, dialysate concentrates mixed on site, and a centralized delivery system. These differences may reflect errors in the DNa acid dialysate concentrate, abnormal pressures in the distribution loop, or machine malfunction. The present study was conducted to assess the measured DNa in three brands of dialysate acid concentrate.

Methods: We measured DNa in two lots of Diasol, NaturaLyte and Rockwell acid concentrates, delivered from individual jugs by Fresenius T-machines. We used a single lot of pre-mixed bicarbonate concentrate. The prescribed DNa was 140 mEq/L. We sampled acid concentrates on a single day. We measured DNa on three consecutive days by both direct and indirect ion selective electrode method. We computed least square means of measured DNa concentrations from linear mixed models.

Results: The least square mean DNa concentrations are shown in the Table. There were no statistically significant differences between prescribed and measured DNa observed with different brands of dialysate acid concentrates, measurement method, lot and day of measurements (p=0.3 for each).

Conclusions: There were no significant differences between the prescribed and measured DNa in any of the three pre-mixed dialysate acid concentrates. The significant differences between prescribed and measured DNa previously reported may reflect errors in mixing dialysate concentrates on-site or pressure abnormalities in the delivery loop.

Funding: Clinical Revenue Support

	Least square means (95% CI) of measured DNa with prescribed DNa of 140mEq/L	
	Indirect ISE (n=18 samples each)	Direct ISE (n=18 samples each)
Diasol	139.7 (136.9, 142.4)	139.3 (136.6, 142.1)
NaturaLyte	141.7 (138.3, 143.8)	140.4 (137.7, 143.2)
Rockwell	140.5 (137.8, 143.2)	138.3 (135.6, 141.1)

FR-PO737

Effect of a Hemodialysis Treatment on Platelet Function Using PFA-100

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Background: Platelet dysfunction is well known to be present in patients with end-stage renal disease (ESRD). Various tests have been used to assess platelet function in patients with ESRD, but few studies involve the platelet function analyzer (PFA-100). PFA-100 is more accurate in assessing platelet function compared to prior methods such as skin bleeding time and platelet aggregation. The purpose of this study was to show the effect of a hemodialysis (HD) session on platelet function in a patient with ESRD on chronic HD.

Methods: The study enrolled 16 patients undergoing chronic HD three times a week from a single unit. Exclusion criteria were hemoglobin < 9 mg/dL, thrombocytopenia and the use of antiplatelet agents. Blood was drawn prior to and after HD after the long interdialytic period, and sent for PFA-100 analysis. Heparin was held during the treatment. PFA -100 measured both the collagen /epinephrine (COL/EPI) and collagen/ ADP (COL/ADP) closure times in seconds.

Results: Pre-HD, 11 (69%) started with an abnormal COL/EPI of which none normalized. Of the 5 patients that started with a normal COL/EPI, 1 developed an abnormal COL/EPI post-HD. Pre-HD, 11 (69%) started with an abnormal COL/ADP of which one normalized. Of the 5 patients that started with a normal COL/ADP, 4 patients developed an abnormal COL/ADP post-HD. Overall post-HD, there was an increase in COL/EPI closure time in 11 (69%), no change in 2 (12%), and decrease in 3 (19%) patients. There was an increase in COL/ADP in 12 (75%), no change in 1 (6%), and decrease in 3 (19%) of patients. Only one patient who originally had an abnormal PFA test, had normalization of the PFA- 100 after a HD treatment.

Conclusions: This study found that the majority of regularly dialyzed patients in our population had abnormal platelet function as measured by the PFA -100 analyzer after the long interdialytic interval. Only one patient had normalization a abnormal PFA-100 after a HD treatment. Most patients appeared to have worsening of platelet function as indicated by a longer closure time. This could be due to an interaction with the dialyzer membrane. Our findings don't support a common practice of performing a HD treatment prior to surgical procedures in order to help avoid bleeding complications. This study involved a small cohort of patients from a single HD unit, a larger multi-centered trial is warranted to confirm results.

FR-PO738

Hemodialysis (HD) Using Molecular Hydrogen-Enriched Dialysate Generates Greater Amount of Exhaled Hydrogen Than Conventional HD, Decreases Plasma Glucose, and Increases Serum LDL-C in One Session

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Background: Novel hemodialysis using molecular hydrogen-enriched dialysate (Hydrogen HD) is reported to improve the prognosis of patients on chronic dialysis. To investigate whether or not this effect is derived from the hydrogen infused through dialysate, we aimed to investigate the difference of exhaled hydrogen concentration between novel Hydrogen HD and conventional HD. We also investigated the effect of Hydrogen HD on glucose and lipid metabolism.

Methods: We investigated the exhaled hydrogen concentration (ppm) of patients undergoing Hydrogen HD and conventional HD and compared the concentrations between the two groups. The subjects are eight adult HD inpatients in our hospital that gave written informed consent to go through Hydrogen HD and conventional HD. Exhaled hydrogen concentration were monitored at 0h, 0.5h, 1h, 2h after the start of HD, at the end of HD, and 0.5h after the end of HD (6 points). Exhaled hydrogen was calculated as AUC. Plasma glucose and lipid profile were also investigated before and after the each session of HD. Statistical analyses were performed by Wilcoxon signed rank test using JMP. The ethics committee in our hospital approved this study.

Results: The patients' characteristics were as follows; age 74 (63-79) y.o., sex F/M 3/5. Total exhaled hydrogen in Hydrogen HD was 502 (261-1541) ppm*hour and that in conventional HD was 45 (11-149) ppm*hour (p=0.0078). Serum LDL-C changes from 75 (39-102) to 78 (43-105) in Hydrogen HD significantly (p= 0.0156) and from 79 (45-105) to 78 (49-103) in conventional HD (n.s.). Plasma glucose changes from 142 (111-168) to 117

(99-144) in Hydrogen HD significantly (p=0.0078) and from 144 (111-184) to 129 (105-166) in conventional HD (n.s.).

Conclusions: Exhaled hydrogen in hemodialysis treatment using molecular hydrogen-enriched dialysate is significantly greater in amount than that in conventional HD. Overflowed molecular hydrogen from exhaled gas is the clue that the beneficial effect of this novel HD is based on the infused molecular hydrogen from dialysate. Hydrogen HD decreases plasma glucose and increases serum LDL-C in one session.

Funding: Commercial Support - Otsuka pharmaceutical Co.

FR-PO739

Effect of Statins on Life Prognosis in Japanese Patients Undergoing Hemodialysis

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Background: Although large-scale studies have not proved the benefits of statin use in patients undergoing maintenance hemodialysis, recent studies suggest that statins could be useful to reduce the risk of cardiovascular events and all-cause mortality in specific groups of patients undergoing hemodialysis. The aforementioned large-scale studies included a small percentage of Asians, and few studies have investigated the effects of statins in Asians undergoing dialysis. We investigated the benefits of statins in patients undergoing maintenance hemodialysis at a large single center in Japan.

Methods: We obtained demographic, clinical, and hemodialysis data pertaining to all patients who underwent maintenance hemodialysis at the Nagasaki Renal Center between July 2011 and June 2012. Data were based on the patients' birth month. Patients were followed-up until September 2017.

Results: We studied 339 patients among which 51 (15.0%) were prescribed statins. The mean duration of observation was 3.7±2.0 years, 43% were women, and the mean hemodialysis vintage was 90±96 months. During the follow-up, 194 patients (57%) died. Among those who died, 43% (n=23) had been prescribed statins and 61% (n=171) had not been prescribed statins. After propensity score matching based on age, gender, dialysis vintage and time, diabetes mellitus, ischemic heart disease, dry weight, left ventricular ejection fraction, and serum albumin, an intergroup comparison between those who received statins and those who did not (44 patients in each group) showed significant differences in the survival rate based on the log-rank test, P=0.03. Although causes of death did not differ between groups, there were fewer causes of death from cardiovascular events, infections, and cancer in the group prescribed statins.

Conclusions: Our results suggest that statins may improve life prognosis in Japanese patients undergoing maintenance hemodialysis. Although potential residual confounders could not be excluded, statins may have an effect in reducing cardiovascular events, infections, and cancer. Further studies are required to prove this hypothesis.

FR-PO740

Erythropoietin-Stimulating Agent Dose Not Associated with Patient Transition to Nocturnal In-Center Hemodialysis

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Background: Nocturnal dialysis (ND) can support longer sessions with better clearances of uremic toxins, compared to traditional in-center hemodialysis (HD). It has been suggested that patients with improved clearances may have improved responses to erythropoietin-stimulating agents (ESAs). We compared use of ESAs for ND patients before and after they initiated ND treatment.

Methods: We identified ND patients at a medium-sized dialysis organization to be those HD patients for whom ≥80% of dialysis sessions were ND sessions—starting at 6:30pm or later and lasting ≥5 hours—over the 3 months after their first ND session (≥20 sessions total) during 2010-16. Outpatient dialysis session and administered ESAs data were extracted for these patients within 12 months of ND transition (pre and post). Epogen units administered per month before December 2012 (when the organization switched to Aranesp) were converted to approximately equivalent Aranesp mcg/month dosages to support a single measure of ESA use per patient-month. Descriptive analyses of ESA use were performed for all months with ≥7 sessions (i.e., still in care). The effects of post-transition ND care status on ESA use were estimated using a generalized linear model (GLM) with a Gaussian distribution and random intercepts and slopes; standard errors were clustered at the patient level.

Results: We identified 64 ND patients (4.7% of 1,357 eligible patients in care), with 354 pre-transition patient-months (3,974 sessions) and 496 post-transition patient-months (5,841 sessions). Across descriptive analyses and GLM analyses accounting for patient-level clustering, we found no statistically significant differences in ESA use post-transition. We estimated ESA use levels of 158.3 mcg/month post-transition versus 147.1 pre-transition (p=0.24) in descriptive analyses, and our GLM point estimate associated with post-transition was +5.5 mcg/month (p=0.69).

Conclusions: After transitioning to ND, patients may not experience any change in their ESA use. Further studies are needed to more fully assess any changes in patients' anemia management, including iron use; these analyses should also account for potential differences in Kt/V, hemoglobin, and other lab results.

FR-PO741

Effects of Glucose-Containing Dialysate During Hemodialysis

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Background: When hemodialysis is performed using glucose-free dialysate, glucose is released into the dialyzer and hypoglycemia may occur. Repeated occurrence of hypoglycemia increases the risk of cognitive decline and reduces the quality of life of patients. In this study, we aimed to compare the incidence of hypoglycemia and biochemical changes in patients with hemodialysis using glucose-containing dialysate and glucose-free dialysate.

Methods: All patients were dialyzed with glucose-free dialysate and changed to glucose-containing dialysate. We measured the levels of albumin, BUN, creatinine, total cholesterol, triglyceride, C-reactive protein, calcium, phosphorus, SPKt/V and URR 3 months before and after dialysate change. Two hours after the start of dialysis, blood glucose level was measured. When the blood glucose level was less than 90 mg/dl, 100 ml of 50% dextrose fluid was administered and the number of times was recorded.

Results: A total of 53 patients participated in the study. When comparing before and after dialysis solution change, no statistically significant differences were found in albumin(g/dl)(3.53±0.36 vs 3.54±0.34; p-value 0.87), BUN(mg/dl)(60.02±19.07 vs 60.46±16.26; p-value 0.87), creatinine(mg/dl)(9.42±2.66 vs 9.36±2.68; p-value 0.95), total cholesterol(mg/dl)(148.83±33.39 vs 147.19±30.44; p-value 0.56), triglyceride(mg/dl)(113.57±75.55 vs 117.34±78.40; p-value 0.65), C-reactive protein(mg/dl)(0.38±0.63 vs 0.37±0.60; p-value0.61), calcium(mg/dl)(9.63±9.31 vs 8.35±0.58; p-value 0.61), phosphorus(mg/dl)(4.77±1.43 vs 5.03±1.31; p-value 0.18), SPKt/V(1.57±0.23 vs 1.59±0.24; p-value 0.40) and URR(71.74±10.36 vs 73.26±5.01; p-value 0.49). The mean number of dextrose fluid administration was statistically significant(0.16±0.27 vs 0.03±0.08; p-value 0.00).

Conclusions: Hyperglycemia is known to increase the production of free radials and to induce oxidative stress. However, in our study, with glucose-containing dialysate, the deterioration of inflammatory markers associated with oxidative stress was not observed, the incidence of hypoglycemia was reduced, and the dialysis efficiency remained similar. It is believed that the use of glucose-containing dialysate will be more beneficial to the patient.

FR-PO742

Accuracy of Dialysate Sodium from Dialysate Conductivity Compared to Measured Sodium: A Quality Assurance Study

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Background: Dialysate sodium is traditionally set at a constant with the intention of providing isonatric dialysis. A dialysate sodium higher than plasma levels can result in transfer of sodium to the patient, while a lower sodium can lead to cramps and hypotension. Modulations of dialysate sodium are done by changing dialysate conductivity, since sodium is the primary driver of conductivity. Recent studies have suggested that the agreement between dialysate conductivity and measured dialysate sodium is imperfect. This quality assurance study was designed to examine the bias between machine reported conductivity and measured dialysate sodium and determine the factors associated with the bias, if present.

Methods: We conducted patient-free dialysis sessions using 3 different dialysis machines (Gambro Artis, Bellco Formula and Fresenius 4008) with varying sodium and potassium baths. Machine reported conductivity was recorded at time 0, 1hour, 2 hour, and 4 hours. Concurrently, dialysate samples were sent for measurement of sodium (indirect ion selective [ISE] method) and other electrolytes. A total of 46 sessions with different sets of dialysate sodium (135 mEq/L or 140 mEq/L) and K baths (2 mEq/L or 3mEq/L) were analyzed.

Results: At all 4 time points, the measured dialysate sodium was significantly higher than the set dialysate sodium. At T0, the difference was 6.11 ± 1.62 mEq/L (mean +/- SD) with similar results noted for all time points. The difference between measured and set dialysate sodium was higher for 3K (6.48 ± 1.85 mEq/L) bath than 2K bath (5.58 ± 1.07 mEq/L) (p=0.003), but not different whether set sodium was 135 or 140 (p = 0.80). There also was a difference between the 3 models of HD machines tested; model one: 6.23 ± 1.36 mEq/L; two: 4.80 ± 1.93 mEq/L; three: 7.10 ± 1.10mEq/L; p=0.0035.

Conclusions: Our analysis shows that, for 3 common dialysis machine models, there is a significant difference between the ordered dialysate sodium (I.e. conductivity) and the measured dialysate sodium. The bias persists throughout session time, and a range of common sodium and potassium baths. It is large enough to have clinical implications.

FR-PO743

Evaluation of Albumin Loss During Hemodialysis with Theranova® Medium Cut-Off (MCO) Dialyzer: Six Months Follow-Up

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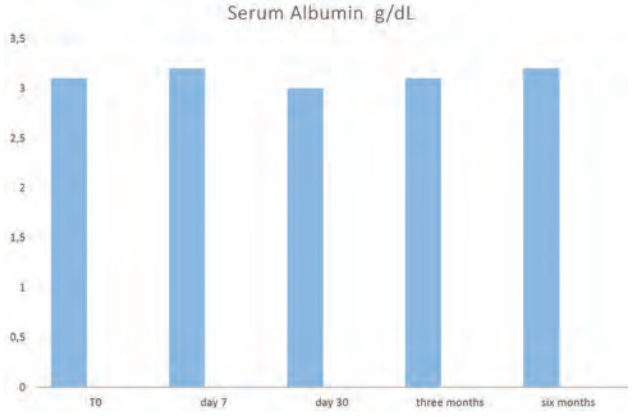
Background: Theranova® medium cut-off (MCO) dialyzer is an innovative membrane designed to expand the spectrum of medium molecules removal, beyond standard high-flux dialysis, using conventional hemodialysis (HD) infrastructure. It represents a novel method to remove uremic toxins in an increased range of molecular weight (MW).

Methods: The purpose of this observational study was to evaluate the safety of treatment in terms of albumin removal, evaluating the albumin concentrations in plasma and dialysate. Six patients on chronic HD were observed for a period of six months. Each patient was treated with Theranova® 400 filter (PAES/PVP membrane, 1.7 m2 surface area, Baxter) in dialysis bicarbonate 4 h Qd 500 ml/min. Pre-treatment patient albuminemia and protein loss at the end of the treatment (dialysate sample) were assessed at the first treatment, one week, one month, three and six months after.

Results: Serum levels of predialitic albumin remained constant throughout the observation period (figure). Protein loss in each hemodialysis session was similar or lower than in HD bicarbonate treatments with high flux membranes, previously tested (3.7 ± 2.2 g).

Conclusions: In addition to a high efficiency in low and medium MW uremic toxins removal, in this study Theranova medium cut-off filters demonstrated not to cause an increased protein loss in comparison with a standard high flux dialyzer



FR-PO744

The Role of Neutrophil/Lymphocyte Ratio as a New Paradigm to Determine Hemodialysis Initiation

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Background: There are still much controversies about the timing of initiation of the dialysis in patients with chronic kidney disease (CKD) although absolute and relative indications have been well established. This study underwent to evaluate whether neutrophil/lymphocyte ratio (NLR) could be used as an important index of dialysis initiation by comparing the other clinical presentations and biochemical findings.

Methods: We retrospectively evaluated the medical records of patients to start chronic maintenance hemodialysis from January 2011 to December 2016 in our institutions. We compared laboratory findings of the last 3 months with those of just before timing of dialysis initiation. Patients with acute infection, using steroid or immunosuppressive agent use, and undergoing acute hemodialysis for acute kidney injury were excluded.

Results: Total 300 patients were included. The mean age was 61 years old. The mean estimated glomerular filtration rate (eGFR) by MDRD was 5.93 ± 2.78 (ml/min/1.73m^2) at the time of hemodialysis, whereas it was 7.86 ± 3.28 (ml/min/1.73m^2) 3 months before hemodialysis ($p<0.001$). The mean NLR significantly increased from 2.50 ± 1.02 to 4.32 ± 2.08 ($p<0.001$) in this duration. We found significant correlations between NLR and hemoglobin ($r=-0.523$, $p<0.001$), serum albumin level ($r=-0.685$, $p<0.001$), serum phosphorus level ($r=0.465$, $p<0.001$), total CO_2 level ($r=-0.361$, $p<0.012$), and CRP level ($r=0.458$, $p<0.001$). In addition, patients undergoing planed dialysis through prepared arm vascular access showed significantly lower NLR than those of emergency dialysis requiring Perm-cath or temporary catheter (3.58 ± 1.55 vs.4.75 ± 2.23, $p<0.001$) although eGFR was not different between two groups. Lower hemoglobin, total CO_2, albumin, sodium and calcium level was shown in patients undergoing emergency dialysis, compared with patients using planned arm vascular access ($p<0.001$, $p=0.002$, $p<0.001$, $p=0.006$, and $p=0.002$, respectively).

Conclusions: In conjunction with many other components, NLR might be used valuable marker in CKD patients when clinician consider the initiation of renal replacement therapy or prepare vascular access.

FR-PO745

Quantification of Lipoteichoic Acid, Biofilm Morphology, and Microbiology in Hemodialysis (HD) Patients with Catheters

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Background: Lipoteichoic acid (LTA) is a Gram-positive bacteria cell wall component that is shed and induces inflammation through toll-like receptor 2. Currently, there are no non-invasive approaches to assess biofilm burden within a dialysis access. The purpose of this study was to characterize LTA concentrations in HD patients with central venous catheters (CVCs) compared to arterio-venous grafts (AVGs), and arterio-venous fistulas (AVFs) and to evaluate biofilm distribution and microbiology in pulled CVCs.

Methods: Eligible patients were adults with indwelling CVC, AVG or AVF being used for HD at the time of sample collection with no concurrent treatment for infection. Venous blood samples were collected prior to dialysis initiation, at 30 minutes, 2 hours and end of treatment (EOT). Catheter aspirate was also collected. LTA concentrations were measured by ELISA. In an ongoing sub-study, catheters that were pulled by clinical decision were evaluated by scanning electron microscopy (SEM) for biofilm surface area and the tip, mid-section and hub were cultured and bacterial species determined by MALDI-TOF.

Results: LTA profiles were measured in 17 CVC, 15 AVG and 16 AVF patients. Unexpectedly, LTA was detectable in serum from all access types at baseline and increased significantly over the dialysis session at each time point measured compared to baseline ($p<0.012$ for all comparisons). Catheter aspirate LTA concentration significantly correlated with serum concentrations at 2 hours and EOT (r^2 0.34 and 0.30, respectively $p=0.02$) The rate of change from baseline to EOT was highest in patients with CVCs but was not statistically significantly different from AVF and AVG. Among catheters pulled (n=4) large plaques of biofilm were observed on all sections examined by SEM. *Staphylococcus sp.* including *epidermidis, caprae, hominis, lugdenisis* were most abundant, however, *Candida albicans* was also cultured from some external hub and external/internal tip sections.

Conclusions: LTA was detectable in the serum of HD patients across access types and large increases during dialysis sessions were observed. Further study of the relationship of serum LTA to biofilm surface area and biomarkers of inflammation are warranted to understand the extent to which access type contributes to inflammation in HD patients.

Funding: Private Foundation Support

FR-PO746

Calcium Mass Balance During Hemodialysis: A Comparison of Different Dialysate Calcium Concentrations Including Citrate-Acid Calcified Dialysate

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Background: Bone and mineral disorders are still cause of morbidity and mortality among chronic kidney diseases, even though adjustments made in therapy and techniques. The optimal dialysate calcium (dCa) and magnesium (dMg) is debated in hemodialysis as international guidelines differ. Citric-acid dialysate may affect Mg and Ca removal during dialysis. The aim of this study was to compare the mass balances in calcium (CaMB) and magnesium (MgMB) between bicarbonate/acetic-acid dialysate with dCa1.50 (dAcetCa1.50) and dCa1.25 (dAcetCa1.25), as well with citric-acid dialysate with dCa1.50 (dCitCa1.50) and dMg of 0.5 mmol/l.

Methods: Twenty patients were enrolled in this 4-week prospective multicenter randomized cross-over trial where they received a baseline week (dAcetCa1.50), followed by the randomized sequence of dAcetCa1.25 or dCitCa1.50 for one week and the alternate treatment was provided after a washout week with dAcetCa1.50. Spent dialysate was collected from the outlet of the dialysis machine in a fractionated way.

Results: Eighteen patients completed the study, one session was excluded due to unclear dialysate. CaMB was in general positive during dAcetCa1.50 and negative during dAcetCa1.50 and dCitCa1.50. MgMB was negative during all different treatments There was an inverse correlation for pre-dialytic serum ionized calcium (iCa) with CaMB in dAcetCa1.50 (r; p-value) (-0.687; 0.002) and in dCitCa1.50 (-0.725; 0.001). This was also found for total calcium in dAcetCa1.50 (-0.579; 0.012) and dCitCa1.50 (-0.708; 0.001), and corrected total calcium in dAcetCa1.50 (-0.687; 0.002) and dCitCa1.50 (-0.725; 0.001).

Conclusions: Our study shows that whereas dAcetCa1.50 leads to net gain of calcium by the body during dialysis, net loss occurs during dCitCa1.50, with levels comparable to dAcetCa1.25. Given the strong dependence of CaMB on pre-dialytic iCa, the introduction of dCa solution with 1.375 mmol/l may be relevant for individualizing CaMB during dialysis. Major losses of Mg occur during the use of conventional dialysis solutions.

Funding: Commercial Support - Fresenius Medical Care

Total mass balances per dialysate

	N	dAcetCa[.50 (A)	N	dAcetCa[.25 (B)	N	dCitCa[.50 (C)	N	p-value	Post-hoc A-B	A-C	B-C
CaMB (mmol/ treatment)	18	5.67 [0.59; 9.54]	17	-2.4 [-6.19; 1.78]	17	-2.00 [-5.26; -0.18]	16	<.001	<.001	<.001	0.906
MgMB (mmol/ treatment)	18	-5.06 [-6.04; -3.12]	17	-4.00 [-6.17; -3.29]	17	-4.40 [-6.00; -3.49]	17	0.204			

Data are presented as median [25th; 75th percentile].

FR-PO747

Reduction in Mean Patient Body Weights and Blood Pressures Were Observed During a Fluid Management Quality Improvement (QI) Project Utilizing Relative Blood Volume Monitoring (RBV-M)

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Background: A one-year fluid management QI project utilizing RBV-M was conducted at 20 Renal Research Institute clinics. A retrospective database analysis of the QI project was conducted to assess changes in body weight and blood pressure in hemodialysis (HD) patients.

Methods: Patients included in this analysis received HD in the month before QI initiation (Pre-QI) and QI end. RBV-M was used to monitor relative blood volume during hemodialysis with Crit-Line® Monitors (CLM-III, CLM-IV, or CLiC). All available PreHD- and PostHD- body weights (wt) and PreHD- and PostHD- systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were averaged monthly for each patient. A subgroup analysis of patients with Pre-QI hypertension was conducted for patients with PreHD-SBP ≥ 140 mmHg and/or PreHD-DBP ≥ 90 mmHg during Pre-QI. Paired t-tests were utilized to test for difference between Pre-QI and QI month 12 (M12).

Results: In total, 651 patients were included in the analysis and 473 had Pre-QI hypertension. Mean PreHD-wt decreased from 84.06 to 83.27 kg (-0.79 kg, p<0.0001) and PostHD-wt from 81.71 to 80.96 kg (-0.75 kg, p<0.0001) from Pre-QI to M12. Mean PreHD-SBP decreased from 152.04 to 149.92 mmHg (-2.12 mmHg, p=0.005) and mean PostHD-SBP decreased from 139.32 to 137.09 mmHg (-2.23 mmHg, p=0.003) from Pre-QI to M12. Mean PreHD-DBP decreased from 80.07 to 78.70 mmHg (-1.37 mmHg, p=0.002) and PostHD-DBP decreased from 73.69 to 72.41 mmHg (-1.28 mmHg, p=0.001) from Pre-QI to M12. On average, in the subgroup of patients with hypertension during Pre-QI, PreHD-SBP decreased from 161.54 to 156.55 mmHg (-4.99 mmHg, p<0.0001) and PostHD-SBP decreased from 145.56 to 141.56 mmHg (-4.00 mmHg, p<0.0001).

Conclusions: A QI project on fluid management utilizing RBV-M was associated with reductions in patient body weights and blood pressures. Most patients had Pre-QI hypertension (73%). These patients had an average decrease in PreHD-SBP of 4.99 mmHg and may be a population that could particularly benefit from a QI initiative on fluid management.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

FR-PO748

Impact of PEAK Methodology on Interdialytic Weight Gain: A Multi-center Experience

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Background: Hemodialysis (HD) patients who experience larger interdialytic weight gains (IDWG) are at increased risk of cardiovascular and all-cause mortality. Diastolic dysfunction, associated with fluid overload is reported in a significant numbers of dialysis patients directly reducing survival. In addition reports suggest that IDWG > 4% increases the risk of death substantially. This risk prompted us to focus quality improvement activities on the IDWG of chronic patients on HD.

Methods: PEAK methodology based on six sigma and lean processes was introduced incrementally into each of the 15 DaVita KSA clinics included in this study. During the implementation period the teams were provided with education about PEAK and supported to hold daily reviews of the current status, then to discuss ideas and action plans to implement patient centered strategies to promote compliance. The percentage of patients showing ≥ 4% IDWG on each treatment day during the 9 month study period was counted. The data included all prevalent and incident patients with valid data reported in the electronic medical records system (n=1472). Average data were calculated for each treatment week and month. Results were compared at 3, 6 and 9 months using Chi² test.

Results: The percentage of patients not achieving IDWG in each of the clinics at the start of the study period ranged from 20.5%-66.1%. Improvement in IDWG was observed in 11 of 15 and 12 of 15 clinics after 3 and 6 months, respectively. After 9 months, the percentage of patients not achieving target IDWG ranged from 15.6%-63.7% and had decreased by 36% of the initial value for the whole population. At the end of the study the percentage of patients not achieving target had decreased in all 14 clinics.

Conclusions: By implementing the PEAK methodology and encouraging team focus on this defined outcome, all clinics that implemented the program achieved a decrease in average IDWG in their patient populations.

Funding: Commercial Support - DaVita

Percentage of patients with IDWG ≥ 4% over 9 months observation period (whole population)

Initial IDWG ≥4%	3 months		6 months		9 months	
	% of patients	P initial vs. 3 months	% of patients	P initial vs. 6 months	% of patients	P initial vs. 9 months
37.7%	34.4%	NS	33.5%	NS	28.9%	P < 0.001

FR-PO749

The Swelling of the Median Nerve Is the Independent Risk Factor for Carpal Tunnel Syndrome in Patients with Short-Term Hemodialysis

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Background: A carpal tunnel syndrome (CTS) is a frequent complication of long-term hemodialysis. 20% to 50% of the patients dialyzed for 10 years or longer are reported to have CTS. However, risk factors for CTS in short-term hemodialysis have been less known. In this study, we investigated whether the swelling of median nerve could be a risk factor for CTS in patients with relatively short-term hemodialysis (mean duration of hemodialysis: 4.03 years).

Methods: The study included 43 patients (23 male & 20 female) on maintenance hemodialysis and 97 healthy controls. We diagnosed the CTS by nerve conduction study (NCS) and clinical symptom. The cross-sectional area (CSA) of median nerve was measured at the wrist (CSA–W) and forearm (CSA-F) by ultrasonography. The wrist to forearm ratio (WFR; CSA-W/CSA-F) was calculated for each arm. The degree of swelling of median nerve was assessed by the WFR.

Results: The mean duration of hemodialysis (n=43) was 4.02 ± 3.30 years. The WFRs in hemodialysis patients were higher than those in healthy controls (1.37 ± 0.45 vs. 1.21 ± 0.25, P = 0.021). We classified into patients with CTS (n=19) and without CTS (n=24). There were no significant differences in age, sex, duration of hemodialysis, the cause of renal failure, β2-microglobulin, and adequacy of dialysis (Kt/V) between patients with CTS and without CTS. The WFRs in patients with CTS were higher than those in patients without CTS (1.5 ± 0.5 vs. 1.2 ± 0.2, P = 0.001). We performed ROC analysis to investigate the best cut-off value of WFR for predicting the CTS in all study subjects (n=43). The AUC of the WFR was 0.825 (95% CI: 0.678-0.923). The best cut-off value of the WFR was > 1.25 with a sensitivity of 84.2% and specificity of 70.8%. In multivariate analysis, the patients with WFR > 1.25 were 6.3 times more likely to have the CTS compared with patients WFR (HR: 6.30, 95% CI: 1.45-27.5, P = 0.014)

Conclusions: This study demonstrated that the swelling of median nerve was the independent risk factor for the CTS in patients with relatively short-term hemodialysis.

FR-PO750

Development of a Microparticle-Based Bio-marker of Hemodialysis Induced Vascular Injury

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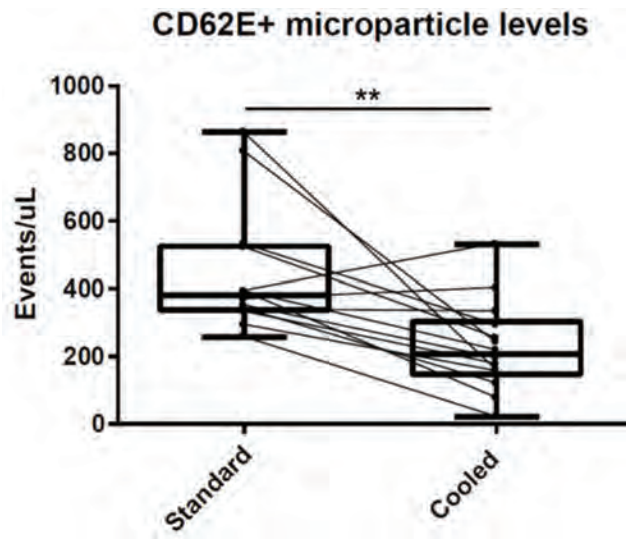
Background: Hemodialysis (HD) is a treatment option that is associated with complications such as microvascular dysfunction and damage to vulnerable vascular beds. This damage has been observed through gold standard imaging techniques such as Echo, CT, MRI, and PET, however there are no reliable blood based bio-markers available to identify this injury that might be suitable to use in general clinical practice. We therefore investigated the use of blood vessel and circulating blood cell derived microparticles as an indicator of vascular damage in a cohort of HD patients under standard treatment condition and a state of reduced circulatory stress (using dialysate cooling).

Methods: An assay was created to assess the level of endothelial, platelet, erythrocyte, and leukocyte derived microparticles. By utilizing Nanoscale Flow Cytometry (Apogee A50), we measured microparticle levels within plasma samples obtained from patients receiving standard hemodialysis treatment (36.5 degrees Celsius, n=31) and 16 of the same patients receiving cooled dialysate treatment (35 degrees Celsius). Microparticles were enumerated at pre, during, and post treatment.

Results: CD31+/CD62E+ microparticles (derived from activated endothelium) correlated with ultrafiltration rate (as the primary driver of HD-based circulatory stress) (R^2=0.1720, p<0.05). There was no relationship between erythrocyte, leukocyte, and platelet derived microparticles and ultrafiltration rate. Furthermore, we observed that 86% of patients experienced a reduction in CD62E+ (e-selectin) microparticle levels when administered cooled dialysate treatment in comparison to standard treatment (Figure, **p<0.01).

Conclusions: The use of microparticles as a bio-marker of HD induced ischemic injury shows promise and warrants further refinement and investigation to identify and risk assess patients receiving HD, as well as monitoring response to efforts to individualize and optimize HD treatment.



FR-PO751

Hospitalizations for Cryptococcal Meningitis in End-Stage Kidney Disease (ESKD) Patients Without HIV: National Estimates 2006-15

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Background: While cryptococcal meningitis (CM) has been reported in HIV-negative persons with ESKD, its epidemiology is poorly described

Methods: Using the National Inpatient Sample, a national all-payer database, we estimated CM hospitalizations among persons with ESKD from 2006-15. Using ICD9 codes, we identified patients with ESKD on dialysis (CKD-G5D), and transplanted (CKD-T), CM (in first 5 discharge diagnoses, to improve specificity), and HIV. We evaluated in-hospital mortality in CKD-G5D and CKD-T patients without HIV using logistic regression models, adjusted for demographics and *a priori* comorbidities (age, sex, diabetes, liver disease, heart failure, lung disease, rheumatic disease).

Results: We estimated 1855 hospitalizations of ESKD patients with non-HIV CM from 2006-15, with409 (95% CI:317-502) on dialysis, and 1446 (95% CI:1212-1680) with kidney transplant. The number of hospitalizations increased from 2006-2007 to 2008-2009, especially in the CKD-T population, and has remained steady since then (Figure). In-hospital mortality was higher for patients with CKD-G5D compared to CKD-T:21% (95% CI 12.3-29.9%) vs. 9% (95% CI 2.0-16.0%), respectively. Adjusted odds -ratio for death in CKD-T vs.CKD-G5D was 0.39 (95% CI [0.16-0.96]).

Conclusions: ESKD patients without HIV are at risk for cryptococcal meningitis, and nephrologists should be aware of this risk. Mortality among those on dialysis is significantly higher than among those with a kidney transplant, perhaps reflecting underlying severe comorbidities causing the immune suppression among affected dialysis patients.

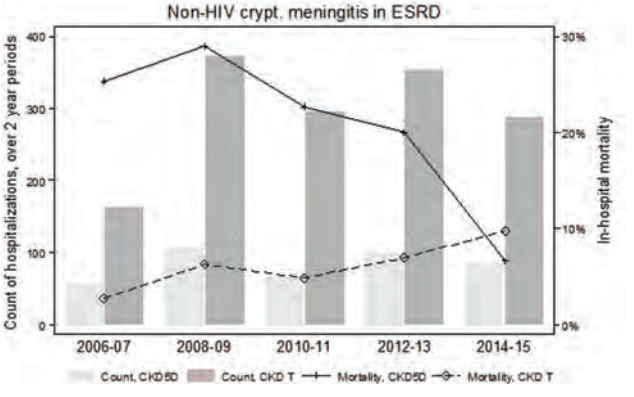

Figure.

FR-PO752

Hemodialysis Transportation Modality and Their Effects on Treatment Adherence

Candace D. Grant, James Drakakis, Naveed N. Masani, Nobuyuki (Bill) Miyawaki. *NYU Winthrop Hospital, Mineola, NY.*

Background: A common reason for nonadherence to hemodialysis (HD) treatments is difficulty with transportation. Health disparities occur in groups of people that experience suboptimal health care based on their social, economic, and/or environmental disadvantage. The modality used for transportation is dependent on a patient's socioeconomic status and can be related to health disparities. Identifying how transportation modality affects adherence to HD regiments can hopefully lead to improved strategies in HD transportation and improve clinical outcomes for all HD patients. We examined transportation modality and HD treatment adherence.

Methods: We reviewed the electronic charts of patients enrolled at our outpatient HD units. We identified 306 eligible patients that had documented transportation modality as well as health insurance information. HD compliance was calculated for the group between April 2014 to April 2018. The modes of transportation were designated as self/family (SF), ambulance/ambulette (AMB) and Taxi/AbleRide (TX). Health insurance was divided into three groups: Medicare (MCR), Medicaid (MCD) and private insurance/self-pay (PVT).

Results: The study population was 53% white, 57% male with a median age of 66 years. 59%, 18% and 23% of the patients had MCR, MCD, or PVT for insurance respectively. Patients with more than one mode of transportation (n=20) had an average compliance of 91.27% versus 90.95% with only one mode (n=286). Of the patients with only one mode of transportation, the average compliance was 91.78%, 90.39%, and 88.21% for travel by SF, AMB, and TX, respectively. HD compliance by primary insurance varied at 92.3%, 91.8% and 86.7%, for PVT, MCR and MCD, respectively ($P<0.01$). When comparing compliance of different transportation modes within the designated insurance groups, there was a significant difference between the modes of transportation at 90.3% and 85% for SF and combined AMB/TX respectively, ($p<0.05$).

Conclusions: Our findings suggest that health insurance and transportation modality both play a significant role in HD treatment compliance. Patients on MCD experience more health disparities that can interfere with HD regiment complaince. Further prospective studies are required to explore this relationship and why MCD insured patients would experience lower HD compliance when relying on commercial sources for transportation.

FR-PO753

Screening for Obstructive Sleep Apnea in Hemodialysis Patients Using the Crit-Line Monitor

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Background: Obstructive sleep apnea (OSA) is common among end-stage renal disease patients. The absence of airflow leads to a decrease in arterial and peripheral blood oxygen saturation (SO_2). A saw-tooth pattern of SO_2 is considered as a sign of OSA. The Crit-Line monitor (CLM) is being used in hemodialysis (HD) centers. Our goal was to investigate if CLM can be used to identify sleep-related breathing disorders

Methods: Prospective, observational study done in chronic HD patients. Subjects were studied twice and equipped with a WatchPAT device (FDA approved device for OSA) and videotaped and CLM data was recorded. The degree of similarity between SO_2 from WatchPAT and CLM was determined by cross-correlation analysis

Results: We studied 14 patients (age 55.4±10 yrs, 64% males, BMI 25.6±6.8 kg/m^2) with a total of 27 visits. We identified a saw-tooth pattern in the SO_2 signals in 9 sessions (Fig 1). The cross-correlation coefficient between CLM and WatchPAT for SO_2 was 0.93±0.11 for 9 visits. Prolonged desaturation (>3% points from baseline) episodes occurred in 5 visits, with 4 showing SO_2 saw-tooth patterns. Fig.2 shows the SO_2 signals from CLM and WatchPAT for one of these visits. Cross-correlation coefficient is 0.89±0.10 for these 5 visits, and 0.53±0.23 for visits without saw-tooth pattern

Conclusions: While there was a high degree of correlation between the SO_2 from the CLM and the WatchPAT device, the CLM captures a higher-resolution. CLM provides richer information and reveals SO_2 nuances (such as the signature SO_2 saw-tooth patterns) better than the WatchPAT device. It is ought to be possible to use the CLM for screening for sleep apnea as well as other blood oxygenation disorders. Further validation is required (e.g. comparison to polysomnography)

Figure 1.

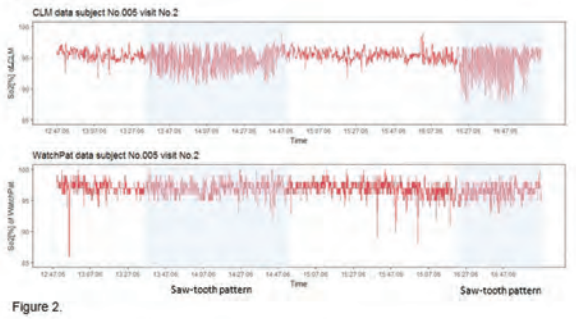
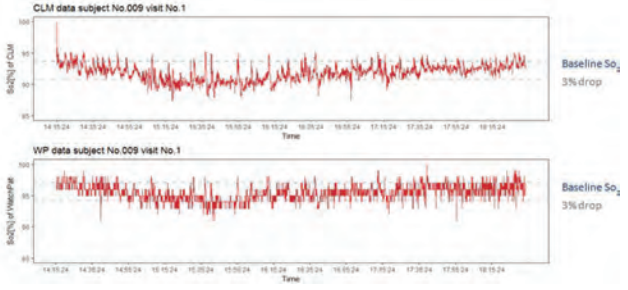


Figure 2.



FR-PO754

Determination of Calf Normalized Resistivity at 50 kHz in the General Population

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Background: We have developed 5 kHz calf normalized resistivity (CNR_5) method to identify degrees of fluid status in dialysis patients. However, the 50 kHz BIA method have been used in clinical studies for many years. The aim of this study was to evaluate whether 50 kHz CNR (CNR_{50}) could be used to determine fluid status by comparing CNR_5 and CNR_{50} chosen randomly from a general population.

Methods: Subjects from a general population were studied once. Calf multi-frequency bioimpedance spectroscopy measurements (Hydra 4200) was performed in the supine position. Further measurements included body height, weight and calf circumference. Resistances at 5 kHz (R_5) and at 50 kHz (R_{50}) respectively were extracted from the raw data. Calf resistivities (Rho_5 and Rho_{50}) were calculated based on resistances and average cross-sectional areas over a calf length measurement of 10 cm. CNR_5 and CNR_{50} were obtained by normalizing calf resistivities with body mass index (BMI).

Results: Ninety-one subjects (sex: 49 f, age: 57±10 year, BMI: 27.9± 4.7 kg/m^2) were evaluated. Although calf R_{50} (R^2=0.89, p<0.0001), Rho_{50} (R^2=0.9, p<0.0001) and CNR_{50} (R^2=0.91, p<0.0001) highly correlated with CNR_5, Rho_5 and CNR_5 respectively, the values of R_{50} (36.6±6.0, Ohm), Rho_{50} (352.9±60.6, Ohm*cm) and CNR_{50} (13.0±2.5, 10^{-2} *Ohm*m^3/kg) were significantly lower than in R_5 (48.1±7.2, Ohm), Rho_5 (464.9±79, Ohm*cm) and CNR_5 (17.1±3, 10^{-2} *Ohm*m^3/kg) respectively (Fig.1 and Fig.2). Bland-Altman analysis showed that the differences between CNR_5 and CNR_{50} was 4.08±0.95 10^{-2} *Ohm*m^3/kg (Fig.3). The difference between CNR_5 and CNR_{50} was weakly (R^2=0.13) but significantly (p<0.001) associated with subject age (Fig.4).

Conclusions: Values of 50 kHz data R_{50}, Rho_{50} and CNR_{50} were lower than that of 5 kHz data with BIA respectively, presumably because a 50 kHz current passes into part of the intracellular space, while this does not occur measurably with 5 kHz current. This difference offers the practicability of using the CNR_{50} range in healthy subjects, as a criterion of normal fluid status.

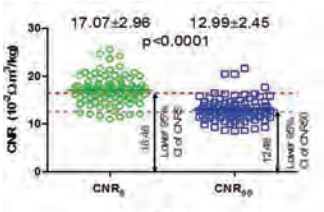

Fig.1

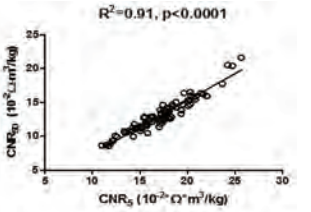

Fig.2

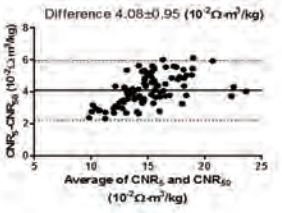

Fig.3

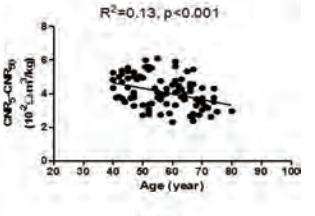

Fig.4

Figures

FR-PO755

Effects of Medium Cut-Off (Theranova) Dialyzer on Hemodialysis Patients: A Prospective, Cross-Over Study

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Background: Recent data suggest that expanded hemodialysis (HDx) enabled by middle cut-off membrane promotes greater clearance for large middle molecules implicated in inflammation and immune function modulation.

Methods: In prospective, open-label, controlled, crossover pilot study, 20 prevalent hemodialysis (HD) patients were studied for 6 months in two dialysis treatments as follows: one MCO (Theranova) dialyzer and one high-flux dialyzer.

Results: In table 1, we present the baseline characteristics of HD patients. Hemoglobin, ferritin, transferrin, calcium, phosphate, parathyroid hormone and 25(OH) vitamin D levels were similar with MCO and high-flux HD. In addition, we did not find any albumin loss in the two treatment groups. Also, dialysis adequacy was similar in MCO and high-flux HD treated patients. Interestingly, the cumulative number of episodes of infection, confirmed clinically and treated with antibiotics) was significantly lower in HDx (# 6), compared with high-flux HD patients (# 20) (Figure 1), while number of hospitalizations did not change.

Conclusions: In conclusion, our pilot study demonstrates that Theranova dialyzer has a good tolerance profile and, intriguingly, reduces the cumulative number of infections in HD patients.

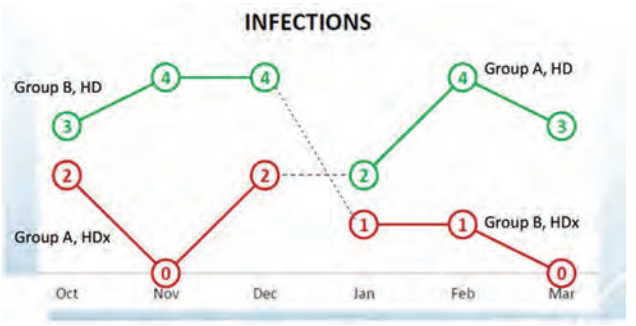
Funding: Commercial Support - Baxter

Table 1. Baseline characteristics of patients

Characteristic	All patients (n=21)
Male sex	16 (76)
Age, y	71 ± 13
Dialysis vintage, mo	27 [15-37]
Access	
Fistula	8 (38)
Central venous catheter	13 (62)
Hypertension	18 (86)
Diabetes	10 (48)
Dyslipidaemia	15 (71)
BMI, kg/m²	23,9 ± 2,9
Smoker	
Current smoker	3 (14)
Ex-smoker	4 (19)

Note : Values for categorical variables are given as count (percentage); values for continuous variables, as mean ± standard deviation or, in the case of non-normally distributed data, median [interquartile range]

Abbrevations: BMI, body mass index.



FR-PO756

Impact of Bemiparin, a Low Molecular Weight Heparin, in the Oxidative Stress of Patients in Chronic Hemodialysis

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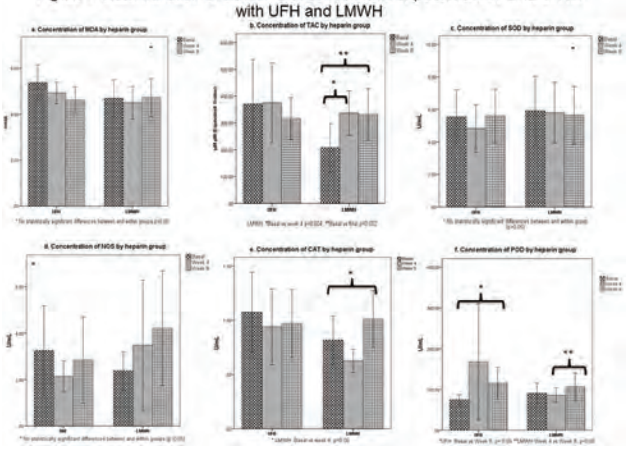
Background: Patients in hemodialysis (HD) has increased oxidative stress (OS), what it produces endothelial damage secondary to the generation of reactive oxygen species (ROS), and consequently progression of cardiovascular disease (CVD). It has been observed, that the use of low molecular weight heparin (LMWH) could decrease the OS in this patients. We evaluated the effect of bemiparine a LMWH on the OS of patients in chronic HD.

Methods: Randomized, open, single-blind controlled clinical trial in chronic HD patients: group with UFH (n=19) as standard anticoagulation during HD and group with LMWH (n= 19). The OS markers were measured basal, at 4 and at 8 weeks: malondialdehyde (MDA), total antioxidant capacity (TAC), Superoxide Dismutase (SOD), Nitric Oxide synthase (NOS), Catalase (CAT) and Peroxidase (POD). Student's t-test, one-way ANOVA were performed.

Results: The mean age of the study groups was 33.5± 4.4 years. The comparison between groups did not present statistically significant differences in markers of OS. While, the intragroup comparison group with LMWH, was statistically significant differences in the levels of TAC (basal vs intermediate and, basal vs final); CAT (Intermediate vs final) and POD (intermediate vs final); while, the group with UFH showed statistically significant differences ($p \leq 0.05$) in the levels of POD (basal vs final), see Figure 1. None of the groups presented events of thrombosis or hemorrhagic complications.

Conclusions: There was a prospective increase in the concentration of OS markers in the LMWH group, what it demonstrates that the continuous use of LMWH participates in the antioxidant defense against the generation of ROS and the OS of patients with CKD in HD. It is necessary to evaluate the long-term use of LMWH on oxidative stress markers and evaluate the possible benefit of it use in the reduction of cardiovascular mortality.

Figure 1. Determination of oxidative stress markers in patients with CKD in HD with UFH and LMWH



FR-PO757

Safety and Efficacy of Heparin During Dialysis in the Context of Systemic Anticoagulant and Antiplatelet Medications

Steven M. Brunelli,[1,2] Dena E. Cohen,[1,2] Gilbert Marlowe,[1,2] Daniel Liu,[2] Levi Njord,[2] David B. Van Wyck,[2] George R. Aronoff.[3] *[1]DaVita Clinical Research, Minneapolis, MN; [2]DaVita Institute for Patient Safety, Denver, CO; [3]DaVita Kidney Care, Denver, CO.*

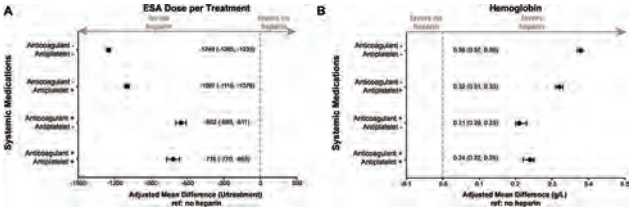
Background: Heparin is widely used to prevent coagulation during hemodialysis (HD). Although systemic anticoagulants and antiplatelet agents are commonly prescribed in the HD population, the safety and efficacy of heparin in the presence versus absence of these medications is unclear.

Methods: This retrospective, longitudinal, time-updated cohort study considered adult patients receiving in-center HD (Aug 2015 – Jul 2017). Study data were derived from deidentified patient electronic health records. For each calendar month, patients were ascribed a 3-part exposure status (use of heparin, systemic anticoagulant, systemic antiplatelet agent). Outcomes included anemia measures, peri-treatment bleeding and clotting, and hospitalization for gastrointestinal (GI) bleeding. Within each systemic medication exposure category, associations of heparin use (vs. non-use) were examined using adjusted general linear, negative binomial, or Poisson models.

Results: Across all systemic medication exposures, heparin use (vs. non-use) was associated with significantly lower erythropoiesis stimulating agent (ESA) dose and higher hemoglobin values; slightly lower intravenous (IV) iron dose; and similar serum ferritin and transferrin saturation. Heparin use was also associated with lower rates of clotting during treatment. Heparin use was not associated with excess risk of hospitalization for GI bleeding, or with peri-treatment bleeding episodes. Associations with respect to ESA, IV iron, hemoglobin, and clotting were approximately 2-fold more potent in the absence of a systemic anticoagulant; the presence of a systemic antiplatelet agent did not impact these associations. Neither systemic medication type influenced associations between heparin use and peri-treatment or GI bleeding.

Conclusions: Heparin use was safe and effective regardless of systemic anticoagulant and antiplatelet agent status. Clinical judgment must be applied to assess bleeding risk in individual patients; however, the decision to withhold heparin should not solely be based upon the concurrent use of systemic anticoagulant or antiplatelet agents.

Funding: Commercial Support - This was a research project conducted by the DaVita Institute for Patient Safety and supported by DaVita Kidney Care



FR-PO758

Decreasing the Incidence of Catheter-Related Blood Stream Infections in Hemodialysis Patients: A Quality Improvement Program

Wisam H. Al-Badr, Mahmoud M. Shaheen, Hany A. Salama, Mahmoud A. Ahmed, Hany Elshiekh, Ibrahim A. Jubran, Saad S. Alobaili, Abdulkareem Alsuwaida. *DaVita-Saudi Arabia, Riyadh, Saudi Arabia.*

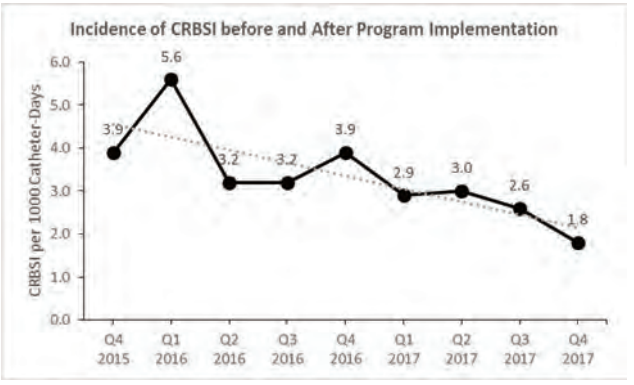
Background: Hemodialysis patients dialyzing with a central venous catheter are at risk for developing catheter-related bloodstream infections (CRBSI), which are associated with substantial morbidity. In 2009, the US Centers for Disease Control and Prevention (CDC) sponsored a collaborative project to reduce CRBSIs in outpatient hemodialysis facilities. The aim of our study was to evaluate the impact of applying the CDC program on the occurrence of CRBSI in an outpatient hemodialysis population.

Methods: All cases of CRBSI that occurred among patients treated at 20 outpatient dialysis centers operated by DaVita-Saudi Arabia (Oct. 2015 to Dec. 2017) were recorded. The quality improvement project, which involved adopting the CDC Dialysis BSI Prevention Collaborative Interventions was initiated in April 2016. Interventions used included the CathAway protocol, ideal catheter lock, standardization of antibiotic therapy, training protocols, closed audits for catheter care, and maximal barrier precautions at the time of catheter insertion. The rate of CRBSI was calculated monthly as the incidence of CRBSI per 1000 catheter-days.

Results: During the studied period, the monthly CRBSI incidence decreased from 5.6 per 1000 catheter-days in the first quarter 2016 to a nadir of 1.8 during the last quarter 2017. There was also a substantial decrease in the mean monthly incidence of CRBSI from 5.1 ± 3.8 among 1477 patients in 2016 to 2.7 ± 0.86 among 2255 patients in 2017.

Conclusions: The most effective strategy for prevention of CRBSIs is reducing the use of catheters. However, given the reality that catheter use cannot be eliminated, adoption of CDC-recommended programs may reduce the rate of CRBSI.

Funding: Commercial Support - DaVita



FR-PO759

Characteristics of Hospital Acquired Central Line Associated Bloodstream Infection (CLABSI) in Hemodialysis (HD) Patients in a Single Tertiary Medical Center in Hawaii

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Background: Hospital acquired CLABSI is one of an important complication of dialysis catheter and is associated with high morbidity and mortality in HD patients. We studied baseline characteristics of HD patients who developed hospital acquired CLABSI as part of our institutional quality improvement project.

Methods: We identified index patients through the hospital database based on CDC definition of CLABSI. We studied the hospital acquired CLABSI patients who had HD catheter presented at the time of CLABSI diagnosis between 1/1/12 and 12/31/17. We studied baseline characteristics, hospital-related factors, and mortality rate associated with CLABSI.

Results: Of the 13 patients, 46% were male and median± SD age was 66±11.28 years old. Asian is the most prevalent (46%) followed by mixed race (31%). There were no Caucasian patients in the cohort. More than half had diabetes. Infection (46.2%) was the most common admitting diagnoses followed by cardiovascular diseases (30.1%). The majority of patients had ESRD (69.2%) followed by AKI on CKD (23.1%), and AKI (7.7%) and two-third of the patients infected tunneled HD catheter (TDC) and the remaining one-third had non-TDC. A quarter of patients (23%) was in ICU when CLABSI was diagnosed. Only 38% of blood cultures were drawn from peripheral sites and central line. Up to 31% had an early CLABSI occurred within 7 days after HD catheter placement. Gram positive cocci is the most common pathogens (54%), followed by gram negative bacilli (31%), anaerobe (8%), and fungus (7%) and 85% of cases were managed by infectious disease physicians. Median length of hospital and ICU stays were 21 and 17 days, respectively. In-hospital mortality rate was 15.4%.

Conclusions: Our patients are elderly with diabetes mellitus being the major co-morbidities. There are unexplained racial disparities of races given no Caucasian patients in our cohort. The majority of hospital acquired CLABSI occurred in ESRD patients and the prevalence of infected TDC was greater than that of non-TDC. A third of patients developed CLABSI within 7 days of HD catheter placement therefore strict measures should be employed during this phase to prevent early HD catheter infection.

FR-PO760

ESRD and a Risk of Tuberculosis: A Nationwide Population-Based Cohort Study

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Background: The converging epidemics of tuberculosis (TB) and end-stage renal disease (ESRD) have generated a significant public health burden and difficulties in controlling TB, although the relationship between these conditions remains poorly understood. This nationwide propensity score-matched cohort study aimed to assess the rateof developing TB among patients receiving dialysis for ESRD.

Methods: The Korean national health insurance database was used to identify patients receiving dialysis for new-onset ESRD during 2004–2013, who were matched to an equivalent number of non-dialysis subjects. We also collected data from the KNHIS National Sample Cohort (NSC), which is stored in the same database. The KNHIS-NSC included approximated 1,000,000 individuals (2.2% of the total Korean population) and was created by sampling the records of the National Health Information database. The incidences of active TBin the dialysis and control cohorts during 2004–2013 were identified using International Classification of Disease, tenth revision (ICD-10) codes (A15–19, U88). The diagnosis of active TBwas then confirmed based on simultaneous prescriptions for ≥2 anti-tuberculosis drugs during a 30-day period. The incidences of TB in the ESRD and control cohorts were calculated for 2004–2013, and multivariable Cox proportional hazards modelwas used to evaluate the ESRD-related risk of developing TB.

Results: During 2004–2013, 59,584 patients received dialysis for newly diagnosed ESRD, which was associated with a significantly higher risk of TB than among the controls (incidence rate ratio: 4.80). The cumulative TB incidence was significantly higher in the dialysis cohort than in the control cohort (p<0.0001; log-rank test), and subgroup analyses revealed similar results for both hemodialysis and peritoneal dialysis (both p<0.0001; log-rank test). However, there was no significant difference in the risk of TB between the hemodialysis and peritoneal dialysis subgroups(p= 0.67; log-rank test). The ESRD cohort had an independently elevated risk of TB (hazard ratio: 4.39, 95% confidence interval: 3.60–5.37).

Conclusions: Similar to the findings of previous studies, we found that patients receiving dialysis for ESRD had an elevated risk of TB. These results highlighted the need of detailed and well-organized guidelines for TB screening among patients with ESRD.

FR-PO761

Effect of Vancomycin on Plasma Concentration of Uremic Solutes

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Background: Many uremic retention solutes are products of gut bacterial metabolism. Protein-binding renders these solutes poorly dialyzable. In a prior study we observed that a single dose of 250 mg of vancomycin, given by mouth, resulted in a significant (40%) decrease in the plasma concentration of indoxyl sulfate and p-cresyl sulfate over a period of one week. In this study we compared the changes in plasma concentration of a panel of protein-bound uremic retention solutes in response to the once-weekly oral administration of 250 mg of vancomycin or placebo over a period of 8 weeks.

Methods: Eight subjects with chronic, stable ESRD on thrice-weekly hemodialysis via AV fistula in the River Renal Dialysis Unit in Bellevue Hospital, were randomized to two groups, utilizing a single-blinded procedure. Baseline plasma samples were collected prior to the initial dose of vancomycin or placebo and at weeks one, two, three, four, and eight. Uremic retention solutes were measured by MS-HPLC.

Results: Six of the eight uremic retention solutes (Table 1) demonstrated a significant decline in concentration over the eight week period of once-weekly vancomycin administration. The magnitude of the decline makes it more likely that gut production was reduced rather than renal excretion increased. Solute concentrations remained unchanged over the same period of placebo administration.

Conclusions: The significant decline in the plasma concentrations of multiple uremic retention solutes provides evidence of the importance of the gut microbiome in the generation of these solutes. The reduction in concentrations of indoxyl sulfate, p-cresyl sulfate, and kynurenic acid, recognized as likely uremic toxins, suggests that altering the gut microbiome might provide a valuable therapeutic strategy in the management of ESRD.

Funding: Private Foundation Support

Linear Trends in Solute Concentrations Over 8 Weeks

Solute	Placebo	Vancomycin	Change	p-value
Hippuric acid	3.50	-26.60	-30.10	0.026
Phenyl Acetyl Glutamine	1.63	-21.78	-23.41	0.002
p-Cresyl Sulphate	4.58	-6.88	-11.46	0.005
Indoxyl Sulphate	0.15	-4.56	-4.71	0.053
Kynurenine	0.03	-0.15	-0.18	0.015
Kynurenic Acid	0.03	-0.08	-0.11	0.005
Phenyl Sulphate	0.14	-1.67	-1.81	NS
Indole-3-Acetic Acid	0.08	-0.24	-0.32	NS

FR-PO762

The Amino Acid Losses Are Equal Between Pre and Post On-line HDF Under the Same Dialysis Dose (Kt/V)

Shunichiro Urabe,[1] Motoko Kato,[1] Emi Hiyama,[1] Asami Kurii,[1] Toru Hyodo,[2] Makoto Kitamura,[3] Miho Hida,[3] Yasuhisa Kurata,[3] Kenichi Kokubo.[4] [1]*Eijin Clinic, Hiratsuka, Japan;* [2]*Eijin Clinic and Cambodian Association of Nephrology, Hiratsuka, Japan;* [3]*Kurata Hospital, Hiratsuka, Kanagawa, Japan;* [4]*Kitasato University School of Allied Health Sciences, Sagamihara, Japan.*

Background: We analyzed the amino acid losses that occur on performing pre-dilution on-line HDF (Pre-HDF) and post-dilution on-line HDF (Post-HDF) because the amino acid kinetics of HDF has been unknown until now.

Methods: We compared the total amino acid, total non-essential/essential/branched-chain amino acid amount into the total waste fluid, and Kt/V (urea) between 9 patients undergoing Pre-HDF (7 males, 4 diabetic, mean age: 72.4±2.1 years) and the same patients receiving Post-HDF. The mean blood flow rate in the former and latter was 222.2±24.8 and 200.0±0.0 mL/min, respectively. The dialysate flow rate was 328.7±48.6 and 556.0±0.0 mL/min, respectively. The replacement fluid flow rate was 251.3±27.4 and 44.0±0.0 mL/min, respectively. The replacement fluid volume was 56.7±6.2 and 10.0±0.0 L, respectively.

Results: In the Pre-HDF group, the total and total non-essential amino acid losses (4814.3±1055.6 and 3058.4±632.0 mg, respectively) were not significantly different from in the Post-HDF group (5257.3±698.9 and 3421.9±446.8 mg, respectively) (p = 0.180 and 0.116, respectively). In the former, the total essential amino acid (1755.9±503.3 mg) was

not significantly different from in the latter (1835.3±351.0 mg) (P=0.401) and also in the former, the branched-chain amino acid (780.2±224.2 mg) was not significantly in the latter (816.4±210.1 mg) (P=0.139). In the Pre-HDF group, the urea and Cr reduction rates were 69.5±7.4 and 63.2±6.7%, respectively. In the Post-HDF group, the values were 70.9±4.4 and 64.8±3.9%, respectively. The values showed no significant differences between the Pre-HDF and Post-HDF group (Urea: P=0.354, Crea: P=0.309). The Kt/V (urea) values in the former and latter were 1.46±0.28 and 1.45±0.19, respectively; there was no significant difference (p=0.862).

Conclusions: Under the same dialysis dose of Kt/V for urea, the amino acid losses were same between Pre-HDF and Post-HDF, suggesting that the moderate volume Post-HDF (replacement fluid volume: around 10.0 L) is as favorable as the Pre-HDF as a blood purification method from the viewpoint of nutrition.

FR-PO763

Safety and Effectiveness of Sucroferric Oxyhydroxide in Dialysis Patients: 24-Month Interim Analysis of the VERIFIE Study

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Background: Sucroferric oxyhydroxide (SFOH) is an iron-based phosphate binder (PB) for the treatment of hyperphosphatemia in dialysis patients (pts).

Methods: VERIFIE is a non-interventional prospective, multicenter, European cohort study evaluating the real-world safety and effectiveness of SFOH. This interim analysis was performed 24 months after first-patient, first-visit.

Results: 1075 pts (mean age 61.5 yrs; 66.7% male) were included in the safety analysis set, with 1023 pts in the full analysis set to evaluate SFOH effectiveness. Prior PB use was reported for 58.9% of pts at study entry, while 40.1% received concomitant PBs during the study. The mean observation period was 186 days. In total, 378 (35.2%) pts reported ≥1 adverse drug reaction, the vast majority of which were gastrointestinal-related (**Panel A**). 263 (24.5%) pts withdrew from the study during the observation period. No statistically significant changes in serum ferritin, TSAT or hemoglobin were observed from baseline (BL) to Month 18. Mean daily dose of SFOH during observation period was 1144.3 mg (2.3 pills/day). Overall, serum phosphorus (sP) levels decreased significantly from 6.3 mg/dL at BL to 5.4 mg/dL at Months 6, 12 and 18 with SFOH therapy ($p \leq 0.0001$). The % of pts achieving sP control (≤5.5 mg/dL) from BL to Month 6 increased across all participating countries (**Panel B**).

Conclusions: The safety profile of SFOH was comparable to that observed in the Phase 3 study; no new safety signals were identified. SFOH effectively reduced and maintained sP levels, with a relatively low pill burden.

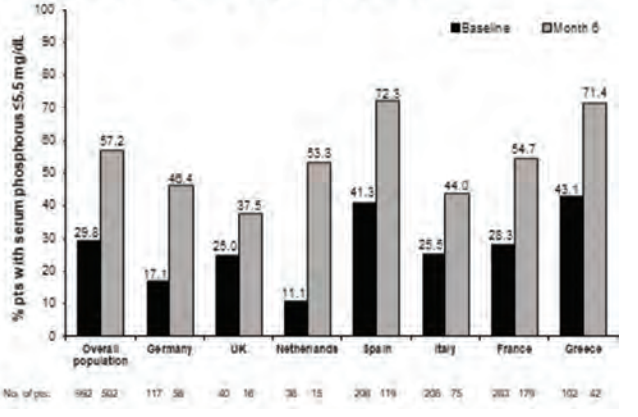
Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma

A: Key safety and effectiveness outcomes

Parameter	Safety analysis set (N=1075)
Adverse drug reactions, n (%)	378 (35.2)
Serious adverse drug reactions, n (%)	26 (2.4)
Gastrointestinal adverse drug reactions, n (%)	312 (29.0)
Diarrhea	118 (11.0)
Discolored feces	114 (10.6)
Mean (SD) serum phosphorus, mg/dL	**Full analysis set (N=1023)**
BL (n=992)	6.3 (1.5)
ΔBL to Month 6 (n=492)	−0.9 (1.7)*
ΔBL to Month 12 (n=180)	−1.0 (1.6)*
ΔBL to Month 18 (n=67)	−1.0 (2.0)**

*p<0.0001, **p=0.0001 for change from baseline (t-test)

B: % pts with sP control (<5.5 mg/dL) at baseline and Month 6 by country (full analysis set; N=1023)



FR-PO764

Changes in Serum Magnesium During Hemodialysis in Three Facility Settings

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Background: A quality improvement project monitored serial serum magnesium (sMg) after a manufacturer changed dialysate magnesium (dMg) content. Three Medical Directors decided to order facility-wide post-dialysis sMg in addition to pre-dialysis sMg. Only 60-75% of sMg diffuse during hemodialysis (HD) due to sequestration by albumin a.k.a. the Gibbs-Donnan effect.

Methods: All maintenance HD patients in three outpatient units were included and sMg were tested with the monthly blood draws for December, 2017. Facility A utilized a dMg of 1.0 mEq/L which is most commonly used by DCI, a non-profit dialysis provider. Facility B also utilized dMg of 1.0 mEq/L but routinely gave oral magnesium supplements to target pre-dialysis sMg of ~2.0 mEq/L. Facility C utilized a dMg of 1.6 mEq/L with a citrate-based bath for over three years.

Results: The facilities (A-B-C) had varying levels of pre-dialysis sMg with A having levels consistent with other DCI facilities at ~1.8 mEq/L.; B had higher pre-dialysis sMg of ~2.0 mEq/L consistent with its target; and C also had elevated pre-dialysis sMg consistent with prior reports at dMg ~1.5 mEq/L. At dMg = 1.0 mEq/L A (representing usual care) had ~10% decline of sMg post-dialysis compared to ~17% decline in B, which started with higher pre-dialysis sMg. The sMg was unchanged in C with no net removal at dMg of 1.6 mEq/L. Results are summarized in the table.

Conclusions: Serum magnesium did not fully equilibrate with dialysate consistent with the Gibbs-Donnan effect. Net sMg removal increases with higher sMg levels at dMg of 1.0 mEq/L; At dMg of 1.6 mEq/L, sMg is maintained at ~2.1 to 2.2 mEq/L with no net dialytic magnesium removal. These findings illustrate what could be expected in a comparative effectiveness study comparing dMg at 1.0 vs. 1.5 mEq/L.

Pre- & Post-HD Magnesium Under 3 Different Settings

Facility	Dialysate Mg	Oral Mg Supplement	N	Pre-HD Mg	Post-HD Mg	% Change
A	1.0 mEq/L	No	52	1.79 ± 0.25	1.61 ± 0.10	-10%
B	1.0 mEq/L	Yes	131	2.07 ± 0.27	1.71 ± 0.12	-17%
C	1.6 mEq/L	No	42	2.15 ± 0.31	2.15 ± 0.19	0%

Mg = Magnesium; Note: Pre-HD & Post-HD serum magnesium shown as mean +/- standard deviation, in mEq/L.

FR-PO765

High Risk of Pyogenic Spondylitis in CKD Patients: Its Characteristics and Incidence

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Background: Pyogenic spondylitis is a rare but life- threatening disease. Mortality has been reported to be approximately up to 11% with the incidence of 2.5 - 7.4/100,000 population per year, particularly more in elderly people or compromised hosts. CKD patients often have infectious complications. However, little information is available regarding the incidence of this disorder in CKD patients. In this study, we examined to clarify the incidence and characteristics of pyogenic spondylitis in CKD patients.

Methods: A retrospective observational study was conducted in our hospital. Fifty-seven patients (45 CKD patients without HD (eGFR < 60ml/min/1.73m^2) [ND] and 12 HD patients [HD]) were diagnosed to have pyogenic spondylitis between January 2012 and October 2016. We investigated age, disease background, affected site, causative microorganism, therapy, hospitalization period, mortality rate, causes of death in ND group and HD group.

Results: Median of age in all patients was 79 years old (IQR: 72-86): 54% were male, 30% had diabetes and 21% were HD patients. In-hospital mortality was 23%, and average hospitalization period was 55 days. Staphylococci species were the most frequent pathogen (49%). Comorbidities are diabetes (30%), ischemic heart disease (17.5%), peripheral vascular disease (11%), and cerebral vascular disease (10%). There was no significant difference in hospitalization period and mortality rate between ND and HD group. The rate of pyogenic spondylitis caused by Staphylococci tended to be higher in HD group(P=0.056). Fifty percent of pyogenic spondylitis developed due to infection of AV fistula (AVF), and the causative microorganism of all cases due to infection of AVF was Staphylococci.

Conclusions: Mortality of pyogenic spondylitis is high in CKD patients. Bacteremia caused by blood access infection is a risk factor of pyogenic spondylitis and more attention should be paid to infection of AVF.

FR-PO766

Long Term Effects of Expanded Hemodialysis (HDx) on Clinical and Laboratory Parameters in a Large Cohort of Dialysis Patients

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Background: Expanded hemodialysis (HDx) enabled by medium cut off membrane provides clearance of large middle molecules which have been linked to inflammation, immune modulation and atherosclerosis. The long term effects of HDx on serum levels of small solutes and albumin has not been investigated in large cohort of patients.

Methods: Multicenter prospective study in prevalent hemodialysis patients, older than 18 years old; enrolled from September 1 to November 30 of 2017, and converted to HDx using Theranova 400 (3 sessions per week, 4 hours per session, same heparin dose). Albumin assay used was bromocresol blue with laboratory reference values between 3,5 gr/dl – 5,1 gr/dl Measurements were done at baseline, week 2, and month 1,2,3,4,5,6; descriptive statistics and ANOVA were used.

Results: We analyzed data on 524 patients, 61.6% (n=323) men, mean age 60.1 years (SD=15.3), dialysis vintage was 5.4 years (SD=5.01). We did not observe clinically significant differences in laboratory variables after 6 months of intervention with expanded hemodialysis; details are presented in Table 1. We found an initial small decrease in serum albumin level which stabilized and within the normal range per our laboratory references. See Table 1 Dialysis performans adequacy (Kt/V) was achieved. No clinically significant differences in laboratory values at 6 months with HDx was observed (Table 2).

Conclusions: The expended hemodialysis (HDx) shows a very good safety and performance profile during the first three months of use.

Funding: Commercial Support - Baxter Healthcare Corporation

N = 524

	Albumin g/dl (mean +/-SD)	Difference g/dl	Difference %	95% CI Difference %
Baseline	4.05 +-0.32			
Week 2	3.98 +- 0.32	- 0.07	- 1.7	-1.2 to -2.2
Month 1	3.97 +- 0.31	- 0.08	- 1.9	-1.4 to -2.4
Month 3	3.93 +- 0.29	- 0.12	- 2.9	-2.2 to -3.4
Month 6	3.95 +- 0.33	- 0.11	-2.4	-1.9 to -3.4

*Change from baseline with ANOVA (p<0.0001)

N = 524

	Hemoglobin g/dl (mean +/-SD)	Phosphorous g/dl (mean +/-SD)	ktv (mean +/-SD)
Baselilne	11.93 +- 1.63	4.73 +- 1.41	1.61 +- 0.34
Month 1	11.76 +-1.67	4.55 +- 1.38	1.68 +- 0.36
Month 2	11.90 +- 1.69	4.60 +- 1.28	1.72 +- 0.35
Month 3	11.76 +-1.64	4.67 +- 1.41	1.70+-0.34
Month 4	11.72 +-1.62	4.62 +- 1.41	1.68+-0.33
Month 5	11.83 +-1.59	4.59 +- 1.39	1.67+-0.33
Month 6	11.75 +-1.61	4.70 +- 1.45	1.68+-0.33
P value*	0.2666	0.3575	0.0002

*ANOVA

FR-PO767

In-Vivo Dialysis Kinetics of 300 mL/min and 500 mL/min Dialysate Flows

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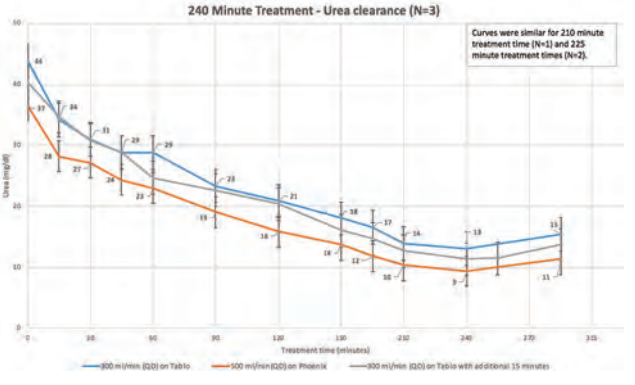
Background: Conventional dialysate flow rates (Q_D) are typically 500-800ml/min with the intent to maximize urea removal during hemodialysis. We previously conducted kinetic modeling of 300 ml/min compared to 500 ml/min (Q_D) and concluded that lower Q_D would be expected to provide adequate hemodialysis. Little is known about the kinetics of dialysis with a 300 ml/min (Q_D) since the bulk of literature focuses on (Q_D) above 500ml/min. We present in-vivo kinetic testing of hemodialysis patients with 500ml/min and 300ml/min (Q_D) and evaluate the differences in kinetic curves.

Methods: The study group included 6 patients undergoing chronic hemodialysis via a fistula (n=4) or graft (n=2). Mean age was 58 years; mean weight was 85kg. We performed a prospective, open label, randomized, cross-over evaluation of in-vivo kinetics of serum urea, phosphorus, and other solutes at variable (Q_D). All patients participated in 2 complete dialysis sessions in each of 3 treatment conditions: 1. 500ml/min (Q_D), 2. 300ml/min (Q_D), and 3. 300ml/min (Q_D) with extended time.

Results: The mean urea kinetic curves with (Q_D) 300ml/min and 500ml/min mirrored each other in all 6 patients. The figure displays data for the 3 patients with 240 minutes prescriptions. The inverted curves include an initial steep decline and gradual trough at the end of hemodialysis treatment; the curves conclude with a slight rebound curve within an hour post treatment. Mean serum beta$_2$ microglobulin, bicarbonate, potassium, phosphate, and sodium all followed similar kinetic curves during Q_D 300ml/min and 500ml/min.

Conclusions: With a fixed dialyzer size and blood flow rate, solute kinetics of 300 ml/min (Q_D) are similar to those of a 500 ml/min (Q_D).

Funding: Commercial Support - Outset Medical, Inc



FR-PO768

Neutrophils to Lymphocytes Ratio Prior to Death in Hemodialysis Patients: Results from the Global MONDO Initiative

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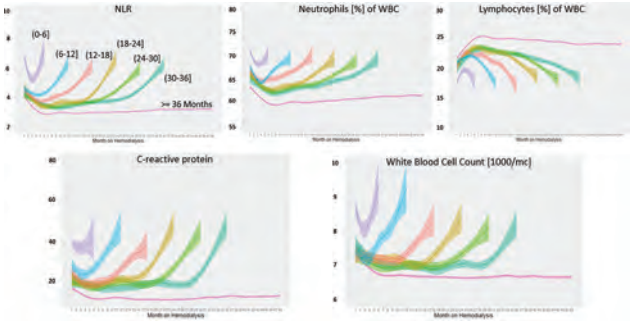
Background: Among patients(pts) with end stage renal disease (ESRD), chronic inflammation is highly prevalent and associated with adverse clinical outcomes including CVD and death. Understanding the dynamics of readily available inflammatory markers (NLR,CRP,WBC) across different survival time is an essential way to explore patient- and process-related factors that contribute to adverse outcomes.

Methods: MONDO Initiative is a global retrospective cohort study that contained data of 150k+ pts with in-center HD from 41 countries&6 continents. Adult pts who died within the first 36 months (mos) on HD were stratified into 6 groups, pts died from 0-6, 6-12,12-18,18-24,24-30 and 30-36 mos after HD initiation. Pts who survived 36+ mos were chosen as the control group. Monthly average of NLR, CRP, Neutrophils, Lymphocytes, WBC were obtained, cubic spline function were applied to access the trends and rate of changes for each of the parameters of interest. Additionly, subgroup analysis were performed to explore the sex and regional differences.

Results: 18,276 incident HD pts were included, 2,068 died within 6 mos,1,231 died 6 -12 mos,971 died 12 -18 mos,792 died 18-24 mos,721 died 24-30 mos, 648 died 30-36 mos, and 12,295 survived 36+ mos. For pts who with shorter survival time, NLR, Neutrophils, Lymphocytes, WBC&CRP were observed to be higher at HD initiation. Additionaly, all the inflammatory markers were declined after the HD initiation and reached nadir from 3-0 mo, vary by pts' survival time. All the markers with an accrelated trend mos before death. For pts who survived 36+ mos, NLR, CRP and WBC seem to be stable after they reached the nadir. No sex and regional differences were observed.

Conclusions: Understanding the dynamics of readily available inflammatory markers is an important way to explore patient- and process-related factors that contribute to outcomes. NLR variations over survival time may have a prognostic impact.



FR-PO769

Are Cytokines and Body Composition Surrogate Markers for Outcomes in Hemodialysis Patients?

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Background: Obesity has been linked to better outcomes in hemodialysis (HD) patients (pts). Persistent inflammation, an important contributor to wasting, is associated with increased levels of tumor necrosis factor-alpha (TNF-α), hepcidin (Hpc) and soluble CD-163 (sCD163). TNF-α is a pro-inflammatory adipokine, sCD163 is a marker of macrophage activation and Hpc is the main regulator of hepcidin-ferroportin axis, all relevant inflammatory mediators. Our aim was to identify potential targets to minimize inflammation in HD pts.

Methods: Prospective cohort study with 160 prevalent HD pts. Baseline demographic data, blood biochemistry, serum inflammatory markers, comorbidities, anthropometric parameters and multifrequency bioimpedance were evaluated.

Results: In our cohort, 91 pts were male, mean age was 67 years, 40% had diabetes (DM) and average time on HD was 92 months. During the follow up (39±16 months), 38 pts died of cardiovascular (CV) events. Charlson comorbidity score was 4.4±2.3 and body index mass was 26.3±4.6 kg/m^2. Pts were divided in two groups, according to their lean mass (LM): 51% had LM≥27%; no differences seen in age and time on HD between the two groups. Pts with LM≥27% had lower TNF-α (p=0.004), sCD163 (p=0.047), Hpc (p=0.038), hospital admissions (p=0.048) and had higher serum albumin (p=0.008). In a Kaplan Meier test, pts with higher LM had a better survival (139 vs 117 months; log rank 5.1; p=0.024). TNF-α was positively correlated with ferritin (p=0.005); sCD-163 was negatively correlated with serum albumin (p=0.02) and positively with CV events (p=0.025). Hpc was positively correlated with ferritin (p=0.018) and with cardiac failure (p=0,005) and negatively with triglycerides (p=.005). In a Cox hazards model, LM <27% was an independent predictor of mortality (HR=2.82; p=0.021; IC 95% 1.2-6.8), adjusted for age and DM.

Conclusions: We observed an association between a higher LM and better clinical outcomes and attenuation in inflammatory markers. Further studies of whether interventions that optimize body composition and interfere with the inflammatory profile of HD pts will improve survival are warranted.

Funding: Commercial Support - Davita

FR-PO770

Immunogenicity and Safety of a Single Booster Dose of Heplisav-B in Patients Undergoing Hemodialysis

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Background: Patients with end-stage renal disease (ESRD) undergoing hemodialysis have a greater risk of hepatitis B virus (HBV) exposure, a lower seroprotection response to primary HBV vaccination, and experience a more rapid decline in antibody to HBV surface antigen (anti-HBs) levels compared with healthy subjects. Anti-HBs levels should be assessed annually, and a booster provided if levels decline to <10 mIU/mL. Heplisav-B® is a TLR9-agonist-adjuvanted HBV vaccine with higher protection rates than commonly used alum-adjuvanted HBV vaccine (Engerix-B®), particularly in populations known to be hyporesponsive. This phase 3, randomized, open-label study assessed the immunogenicity of a single booster dose of Heplisav-B in patients with ESRD receiving hemodialysis who had previously received HBV vaccinations.

Methods: Adult patients with or without seroprotection from at least 1 HBV vaccine series (prior responders and prior nonresponders, respectively) and with anti-HBs levels <10 mIU/mL were randomized 1:1:1 to receive a booster vaccination of Heplisav-B, Engerix-B, or Fendrix (not available in the US). Seroprotection rates (SPRs) (proportion of patients with anti-HBs ≥10 mIU/mL) were assessed at week 4. Here we report the comparison between Heplisav-B and Engerix-B.

Results: A total of 76 prior nonresponders (Heplisav-B, n=38; Engerix-B, n=38) and 28 prior responders (Heplisav-B, n=16; Engerix-B, n=12) were enrolled. Among prior nonresponders, a single dose of Heplisav-B induced a higher SPR at week 4 compared with a double dose of Engerix-B (42.1% vs 18.9%); treatment difference was 23.2% (95% CI: 1.4, 43.1). Among prior responders, SPRs at week 4 were comparable (Heplisav-B: 80.0% vs Engerix-B: 90.9%; treatment difference: –10.9% [95% CI: –41.3, 23.5]). In a post hoc analysis based on criteria established in prior phase 3 trials, the SPR at week 4 with Heplisav-B group was significantly higher than with Engerix-B among prior nonresponders. Adverse events (AEs), serious AEs, and deaths were comparable between groups.

Conclusions: A single booster of Heplisav-B provides better protection against HBV than a double dose of Engerix-B with a comparable safety profile in patients undergoing hemodialysis who were nonresponders to prior HBV vaccination. **Acknowledgement:** Writing assistance, funded by Dynavax Technologies, provided by Caroline Walsh Cazares, PhD, of JB Ashtin.

Funding: Commercial Support - Dynavax Technologies

FR-PO771

Successful Hepatitis B Seroconversion Using Intradermal Engerix-B in Hemodialysis Patients Unresponsive to Two Courses of Standard Double-Dose Intramuscular Vaccine - Real World Experience

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Background: Double dose intramuscular (DDIM) hepatitis B vaccination of nonimmune incident hemodialysis patients remains standard of care. Given best case reported seroconversion rates of only 70 percent in this population following a standard DDIM regimen, a significant number of hemodialysis patients are deemed non-responders, remain at risk for infection and ultimately require cohorting away from isolation rooms when an actively infected patient is present. Multiple protocols have been recommended to convert these non-responders including administration of a single DDIM booster dose, repetition of an entire DDIM series or conversion to an intradermal delivery protocol. We report our experience with short-term intradermal hepatitis B vaccination in 28 patients who failed to respond to two courses of standard DDIM hepatitis B vaccination.

Methods: Non-responder patients were defined as those with an anti-HBsAg titer < 10 mIU/mL 30 days after receiving two DDIM series consisting of Engerix-B (GlaxoSmithKline) 40 mcg at months 0, 1, 2 and 6. All non-responders subsequently received 5-10 mcg intradermal Engerix-B every two weeks for a total of 8 doses. An anti-HBsAg titer > 10 mIU/mL at one year after completion of intradermal dosing was considered a successful response.

Results: Twenty-five of 28 (89%) patients unresponsive to two courses of DDIM Engerix-B responded to intradermal dosing with a mean anti-HBsAg titer of 258 mIU/mL at 1 year. Twenty of the 25 patients who seroconverted responded with a titer > 30 mIU/mL. No significant differences in age, race, gender, dialysis access type, comorbidities, nutritional parameters, bone mineral markers, dialysis adequacy, or dialysis vintage were noted between the two groups. There were no reports of adverse events associated with intradermal dosing.

Conclusions: Intradermal dosing of Engerix-B to hemodialysis patients unresponsive to two courses of DDIM vaccination is highly effective in achieving a sustained serologic response. The practice of administering a second DDIM vaccination series to non-responder hemodialysis patients should be abandoned and replaced with an intradermal Engerix-B dosing regimen.

FR-PO772

HCV in Hemodialysis Patients: Where Is the Difference?

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Background: Several authors have described worst outcomes in HCV patients (pts) due to cardiovascular (CV) diseases, cirrhosis and hepatocarcinoma. Though, outcomes in HD pts are controversial. The aim of this study was to identify HCV+ pts characteristics affecting long term survival in HD.

Methods: Pts from Fresenius Medical Care Argentina database were included and classified as HCV+ when HCV antibodies were detected by ELISA and then followed until death, transplant or lost to follow-up. Differences in baseline labs were compared and all-cause, CV and liver mortality were analyzed using uni and multivariate Cox models.

Results: 35,707 incident pts were included. Age 57.1±16.9 yrs, gender 57.7% male, DBT 16.5%, CVD 12%, neoplasia 1.1%. HCV+ prevalence 5.9% (2121). Mean follow-up time 3.45 ± 3.2 yrs CI [3.42 - 3.48]. HCV+ pts were younger (52.3 ± 15 vs 57.4± 17 yrs), had higher Hb (9.98 ± 2.1 vs 9.28 ± 1.9 mg%), higher ferritin (543 ± 646 vs 469 ± 521 ng/ml), higher Ca (8.94 ± 1.1 vs 8.59 ± 0.9 mg%), higher albumin (3.69 ± 0.5 vs 3.61 ± 0.6 g/dl), lower CRP (11.9 ± 21 vs 18.8 ± 36 mg/l), higher liver enzymes (AST 32.5 ± 28 vs 21.4 ± 24, ALT 34.6 ± 41 vs 22.2 ± 58, ALP 377.7 ± 438 vs 256 ± 236 IU/l) and lower total cholesterol (163.5 ± 44 vs 172.8 ± 51 mg%). Surprisingly, unadjusted Cox models showed advantage in HCV+ for all-cause mortality (n=35,707, events 15,839 RR 0.87 p < 0.0001, CI [0.82-0.93]) and CV mortality (n=35,707, events 2,545 RR 0.31 p < 0.0001, CI [0.24-0.39]) but no difference for liver mortality. After adjustment to case-mix, nutritional and inflammation markers, survival advantage disappears for all-cause (n=4,283, events 1,227 RR 1.17 pNS) and CV mortality (n=4,283, events 470 RR 1 pNS).

Conclusions: In our study HCV+ pts showed lower CRP and higher Hb levels, as well as lower all-cause and CV mortality. Lower CRP levels were previously reported associated with disturbance in production of CRP[1]. Higher Hb levels were published related to increased production of EPO in the liver[2]. Even paradoxical unadjusted effect of HCV+ was reported[3], it's not in accordance with several studies and may be related to ameliorated inflammatory response. In fact, adjusting to inflammatory markers vanished this effect. Prospective, controlled trials may be needed to identify HCV effect on HD patients [1]Braz J Med Biol Res. 2005;38:783-8 [2]Blood Purif 2011;32:69–74 73 [3]J Bras Nefrol 2010;32(4): 335-339

FR-PO773

Procalcitonin as a Predictor of Sepsis in Patients with ESRD

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Background: Procalcitonin is a helpful biomarker in the diagnosis of sepsis in critically ill patients, especially in identifying occult bacterial infections. Procalcitonin levels rise 3-6 hours after onset of sepsis, and peak at 24-48 hours. It has been found that renal clearance of procalcitonin is low, and the use of procalictonin in kidney disease has not been widely studied.

Methods: A Retrospective chart review of patient admitted with diagnosis of Sepsis and End Stage Renal disease was reviewed for 57 months. All patients with end stage renal disease and sepsis with procalcitonin measured at admission or during hospitalization were included. We used two-way ANOVA table to explore the relationships between procalcitonin, lactic acid levels, hemodialysis, and cultures.

Results: Of 362 patients, 190 were male and 172 were female with ages ranging from 30-100 years. 158 of 362 patients were on hemodialysis. 210 of 362 had procalcitonin levels measured during hospitalization. Procalcitonin of these patients ranged from less than 0.05 to 235.94 ng/mL. 148 of 362 patients had lactic acid measured, with 62 having lactic acid ≥ 2 mmol/L. Of the 362 patients, 41 had positive cultures. By using our method of statistical analysis, we found that only age was statistically significant, with a P-value 0.0107, meaning that procalcitonin levels were increased with increasing age. We also found that lactic acid and culture growth when compared with procalcitonin levels, were not statistically significant, with P-values of 0.4095 & 0.9148, respectively.

Conclusions: Procalcitonin's role has not been well studied in patients with end stage renal disease on hemodialysis, although it has been found that it is the best predictor of infection in hemodialysis patients. Previous studies have found that higher cutoff levels of procalcitonin should be used to rule in or rule out infection, and it has been found that a procalcitonin of ≥0.5 ng/mL can be used to rule in infection in patients on hemodialysis. Our study looked at patients with end stage renal disease on hemodialysis and sepsis comparing procalcitonin, lactic acid and culture growth. We found that lactic acid and culture results were not statistically significant, meaning that those values may be negative despite positive procalcitonin levels. Therefore, clinical judgment should be used when a patient has sepsis.

FR-PO774

Analysis of Infection Rate According to Natural Killer Cell Activity in Hemodialysis Patients

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Background: Natural killer (NK) cells are lymphocytes of innate immune system that play a key role in host defense against diverse range of pathogens. NK cell deficit has been suggested in patients undergoing hemodialysis (HD) with conflicting results regarding their activity and impaired antimicrobial activity in host defense. Aim of this study was to determine the susceptibility to bacterial infection according to NK cell cytotoxic activity in HD patients.

Methods: Clinically stable HD patients without active malignancy or immunosuppressive medications were enrolled (N=204). NK Vue™ assay (ATGen Co. Seoul, Korea), that uses serum of ex vivo stimulated whole blood to detect interferon (IFN)-γ secreted from NK cells, was used to assess NK cell activity. This NK cell activity was consecutively assessed at six-month intervals from 2015 to 2017. We further investigated the incidence of major infections requiring intravenous antibiotics or hospitalization according to NK cell activity during the study period.

Results: Mean patient age was 61.4 ± 13.8 years and 58.8% were male. During the study period, a total of 214 major infections occurred. Mean baseline NK cell activity was 586.2 ± 540.7 pg/mL. Decreases in NK cell activity were significantly correlated with incidence of major infections. Furthermore, mean changes in NK cell activity were significantly different between periods at which infections have occurred and those periods free of infections, -71.7 ± 875.7 pg/mL and 110.5 ± 846.0 pg/mL, respectively (P=0.016). In univariate logistic analysis, older age [odds ratio (OR): 1.018; 95% CI, 1.004-1.032, P=0.010], higher serum C-reactive protein (CRP) [OR: 1.052; 95% CI, 1.010-1.096, P=0.014] and decreased NK cell activity [OR: 0.975; 95% CI, 0.955-0.995, P=0.017] were associated with higher incidence of infection. After adjusting for age, sex and CRP, decreased NK cell activity was independently associated with higher incidence of infection. [OR: 0.976; 95% CI, 0.956-0.996, P=0.019] Increases in CRP was not significantly correlated with decreases in NK cell activity (R=-0.056, P=0.189).

Conclusions: Our results show higher incidence of infection during period of greater decrease in NK cell activity from baseline. NK cell activity could thus be a useful marker to predict risk of infection in HD patients.

FR-PO775

Short-Chain Fatty Acids Increase CD25HighCD127Low-Regulatory T-Cells in Patients with ESRD

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Background: Patients with End Stage Renal Disease (ESRD) suffer from an elevated systemic inflammation, which can lead to an increased morbidity and mortality. Previous data obtained from the EAE mouse model of MS, revealed the potential of disease amelioration by short-chain fatty acids. This clinical improvement was accompanied by increased frequency of regulatory T-cells (Treg). We hypothesized that the elevated systemic inflammation of patients with ESRD could be reduced though a dietary supplement with a short-chain fatty acid.

Methods: ESRD patients and healthy volunteers supplemented their diet with a daily dose of 2 x 500 mg propionic acid (PA) for 30 days. PBMCs were isolated at day 0, 15, and 30 of the PA supplement and 60 days later for a follow-up after PA supplementation. The baseline status and possible physiological oscillations in cell numbers were assessed through sampling at days -60, -45, and -30. We established a 12 color flow cytometry panel to quantify Tregs, and characterized them with respect to their developmental and gut homing phenotype through expression of CCR7/CD45RA and CCR9/β7 integrin, respectively. We also analyzed changes in functional activity of antigen-specific memory/effector T cells by stimulation with recall antigens. Here, we used stimulation with Tetanus/Diphteria vaccine and subsequent evaluation by 13 parameter flow cytometry.

Results: We observed a gradual and significant expansion in the frequencies of $CD25^{high}CD127^{low}$ Tregs in the ESRD patients and healthy volunteers already at day 15 of PA supplementation. At day 30, an increase of 20-35% as compared to Treg baseline counts was observed in both study groups. Treg numbers returned to baseline values after discontinuation of the PA supplement. Despite significant expansion of Tregs during PA diet, the responsiveness and functionality of effector T cells remained stable as demonstrated by the stable frequencies of antigen-specific T effector cells upon ex vivo stimulation.

Conclusions: Our data revealed that dietary supplements with short-chain fatty acids might have a beneficial effect on the elevated systemic inflammation of ESRD patients. The effect can be achieved through an expansion of circulating Tregs without affecting the antigen-specific memory response.

Funding: Government Support - Non-U.S.

FR-PO776

HBV Vaccination Non-Responders with ESRD Demonstrate Available Cellular Memory Immunity Against Hepatitis B Vaccine

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Background: In the compromised immune system of patients with end-stage renal disease (ESRD) undergoing hemodialysis, the adequacy of host protection upon hepatitis B vaccination is crucial. Whereas seroconversion rates to hepatitis B (HBV) vaccine in this population is known to be lower than the general population, the cellular immune response to the vaccine in hemodialysis patients remain under study. Here, we functionally analyze and quantify HBV surface antigen (HBsAg)-specific T cells in patients with ESRD vaccinated against HBV with HBsAg vaccine. Cellular immunity against HBsAg and its correlation with humoral response were explored in 35 patients with ESRD undergoing hemodialysis and 13 healthy controls (HC).

Methods: Patients were divided according to their Hepatitis B vaccine titers into three groups: High responders (HR), Low-responders (LR), Non-responders (NR). Using multi-parameter flow cytometry HBsAg-specific T cells were quantified and functionally analyzed according to expression of activation markers CD40L and/or CD137 and cytokine release upon stimulation with HBsAg overlapping peptide pools. We also performed immunophenotyping of B cells, dendritic cells and regulatory T cells.

Results: HBsAg-specific CD4+T cells were detected not only in LR (88.8%) and HR (100%) but also in almost all NR; 78.6% of NR demonstrated HBsAg-specific memory T-cell response. Counts of HBsAg-specific CD4+CD40L+ T cells were significantly higher in HR compared to NR ($p<0.001$). No difference in cytokine release between the groups was. A correlation between vaccine-specific CD4+ T cell response and humoral response was identified ($r=0.7537$, $p=0.0021$). No significant difference was found in the number of myeloid and plasmacytoid dendritic cells between patients with ESRD of different titer groups. Interestingly, they were significantly higher in HR than in HC ($p<0.05$). A significantly larger Naïve B cell (IgD+CD27-) population was found in HR and HC compared to NR ($p<0.05$).

Conclusions: Our results show that HBV-specific memory T cells producing effector cytokines are detectable in humoral non-responders and might provide antiviral effects in case of HBV exposure in ESRD patients.

Funding: Government Support - Non-U.S.

FR-PO777

The Clinical Utility of Routine Screening of Multi-Drug Resistant Organisms in Hemodialysis Outpatients

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Background: Hemodialysis (HD) outpatients are routinely screened for Methicillin Resistant Staphylococcus Aureus (MRSA) and Vancomycin Resistant Enterococcus (VRE) despite limited information on effective MRSA/VRE control in outpatients. Yet, MRSA/VRE colonized patients are not subject to different care in the community. HD patients would be empirically treated for MRSA if clinically appropriate, regardless of their colonization status. Patients may have negative experiences from swab collection +/- cohort.

Methods: We aimed to assess the clinical utility of the current practices by evaluating a) the MRSA/VRE infection rates and b) the estimated costs of such practice for the local HD patients. We evaluated the 12-month-data on access related infection (bacteremia and exit site infection) in the two typical HD units, using a provincial renal database. We reviewed 1) the prevalence of MRSA/VRE access infections, 2) the relationship between colonization and infection in this cohort, and 3) the costs of routine screening and contact precaution practices for the provincial HD cohort.

Results: There were 52 access related infections (among 43/410 HD patients) (2016). 40/52 (77%) infections were not caused by MRSA or VRE (Figure 1). The prevalence rates for MRSA and VRE were 10-25% and 3-5% in both units. There was poor correlation between colonization and infection. The annual cost of provincial screening practice (2,200 prevalent and 600 incident HD patients) was estimated to be over 120,000 Canadian dollars.

Conclusions: We provide additional evidence demonstrating little clinical utility for routine MRSA/VRE screening in HD outpatients, which leads us to advocate for practice re-evaluation.

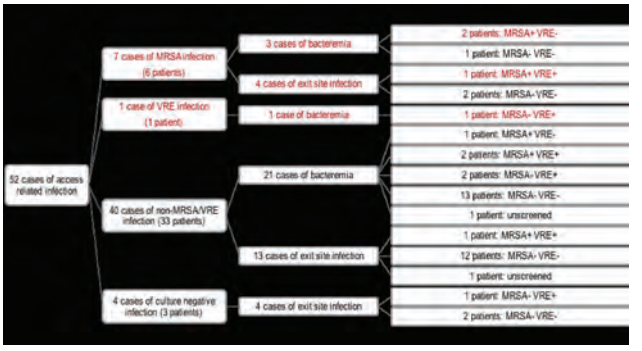

Figure 1. Number of MRSA/VRE infections among the 52 access related infections in the study HD units

FR-PO778

Routine Screening for Staphylococcus aureus in Haemodialysis Patients – Is It Worthwhile?

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Background: *Staphylococcus aureus* (*S. aureus*) is common in haemodialysis (HD) patients, with manifestations varying from asymptomatic colonisation to bacteraemia. This has led to the development of guidelines for routine screening for both methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA and MRSA). We aimed to establish the effectiveness of screening and de-colonisation for *S. aureus* in a cohort of HD patients.

Methods: We screened all HD patients at a UK satellite unit between September 2009 and July 2010 for *S. aureus* carriage. Screening was at 0, 1, 2, 3, 6 and 9 months with nasal, groin and HD line site swabs, cultured on chromogenic agar. Isolates were characterised by antibiogram. Eradication with Chlorhexidine solution was given to all carriers. A further course of eradication therapy was given to those in whom repeat swabs were positive. Due to limited capacity, not all patients with MRSA were isolated in side rooms. Universal precautions were used in all cases. Clinical and demographic data were collected from patient records.

Results: 82 patients were included. 68% were male; median age was 68.5 years (range 57-78). 42% were carriers of *S. aureus*; 80% had MSSA, 20% had MRSA. 15/28 MSSA carriers underwent successful eradication; of these 8/15 re-acquired MSSA. 3/7 MRSA carriers underwent successful eradication, all three re-acquired the same strain of MRSA. MRSA antibiograms were identical in 2/7 patients. These patients dialysed on separate days, making transmission between them unlikely. All other MRSA strains had different antibiograms.

Conclusions: Our data show that *S. aureus* colonisation is common in HD patients. We found that, despite treatment, eradication is often short-lived or unsuccessful. We believe that *S. aureus* is often re-acquired from non-clinical areas such as hospital transportation, the home environment and perhaps close relatives/friends. We question the benefit of routinely screening for *S. aureus*, given the poor de-colonisation and high re-acquisition rates. The antibiotic resistance profile showed that there was no evidence of cross-transmission within the unit and in the absence of facilities to segregate colonised patients, we have shown that universal infection control measures are sufficient to prevent spread between patients.

FR-PO779

Vitamin D and Risk of Infection in Long-Term Dialysis Patients: A Systematic Review and Meta-Analysis

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Background: Infections are common and can be fatal in patients undergoing long-term dialysis. Current studies have shown conflicting evidence associating infection with vitamin D, which have not been systematically reviewed in this population

Methods: We searched PubMed, Web of Science, Cochrane Library, Embase databases and three Chinese databases, from inception through December 2017, for interventional (non-randomized or randomized controlled trials, RCTs), cohort and case-controlled studies on levels of serum 25-hydroxy vitamin D (25(OH)D); or use of vitamin D [supplemental nutritional vitamin D or vitamin D receptor activator (VDRA)] and infection (any infection, infection-required hospitalization or infection-related death, or composite), in long-term dialysis patients. We conducted a meta-analysis on the relative risk of infection and level of 25(OH)D or use of vitamin D.

Results: Of 2,440 reports identified, 17 studies met inclusion criteria, all with moderate quality, with 6 cohort studies evaluating 25(OH)D serum concentrations (N=5,714) and 11 (2 RCTs and 9 observational studies) evaluating the use of vitamin D (N=92,309). The risk of composite infection was 39% lower (relative risk [RR] 0.61, 95% CI 0.41-0.89) in those

with high/normal levels of 25(OH)D than in those with low levels. Compared to those who did not use vitamin D, the pooled adjusted risk for composite infection was 41% lower in those who used vitamin D (RR 0.59, 95% CI 0.43-0.81).

Conclusions: High/normal serum levels of 25(OH)-vitamin D and use of vitamin D, particularly VDRA, were each associated with a lower risk of composite infection in long-term dialysis patients.

Funding: Government Support - Non-U.S.

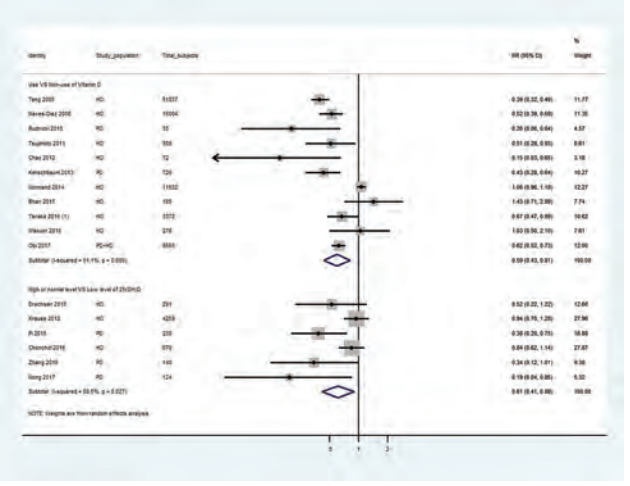

Figure: Forest plot depicting the meta-association between use and non-use of Vitamin D, and high/normal vs. low level of 25(OH)D, and risk for infection-related outcomes

FR-PO780

Vaccinations for Patients with ESRD: Crossroads Between Nephrology and Primary Care

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Background: A subset of patients with end-stage renal disease (ESRD) who receive maintenance hemodialysis consider their nephrologist as their primary care provider (PCP). Preventive measures such as vaccinations markedly reduce mortality among these patients, yet their vaccination rates fall far below recommended. We aimed to (1) determine whether there is a difference in rates of compliance with recommended vaccinations between ESRD patients with PCPs (PCP group) and those without PCPs (No PCP group), and (2) identify differences in the characteristics between the PCP and No PCP groups.

Methods: We performed a cross-sectional survey of adult patients with ESRD in two outpatient dialysis centers affiliated with the University of Florida. A survey instrument was used to conduct one-to-one interviews. We used the Advisory Committee on Immunization Practices (ACIP) guidelines to determine eligibility for various vaccinations. We used X^2 or *t*-test to compare various characteristics.

Results: The mean age of the 132 study participants was 57.8 ±14.7 years. Sixty-six (50%) were male, 81 (61.3%) were African American, and 118 (89.4%) reported having a PCP. The PCP group had significantly higher rates of influenza vaccination (89.8% vs. 71.4%, p=0.046), pneumonia (75% vs. 42.9%, p=0.012), and tetanus (Tdap) (96.4 vs. 78.6%, p=0.006). The rates of vaccination for human papillomavirus (HPV), hepatitis B, and shingles were also higher among the PCP group but did not reach statistical significance. The PCP group was older than the no PCP group (mean age 58.9 vs. 47.9 years, p=0.008) with higher education level; none of the patients without PCP had higher education while 54.2% of those with PCP had undergraduate or graduate education; p<0.001). Men were more likely not to have a PCP (p=0.024), but no difference was observed among races.

Conclusions: This study suggests that among ESRD patients receiving hemodialysis, having a PCP is associated with higher rates of recommended vaccinations and that female gender, advanced age, and higher education level are associated with higher likelihood of having a PCP. These findings could have important implications for optimizing the preventive care of these patients. Future studies are needed to explore whether increasing the number of patients with a PCP will portend salutary impact on their care.

FR-PO781

Recent Trends in Emergency and Observation Room Admissions Among Medicare Dialysis Patients

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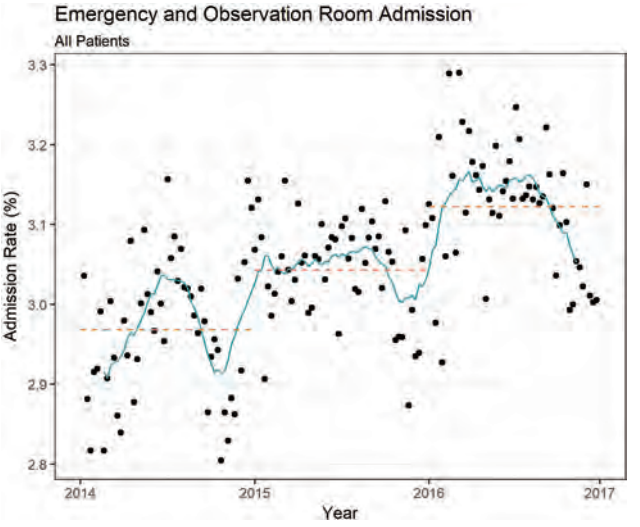
Background: Among dialysis patients, emergency room (ER) and observation room (OBS) admissions - excluding those resulting in transfer to inpatient care - may reflect several factors, including morbidity and insufficient availability of outpatient clinic appointments. We assessed trends in ER/OBS admissions among Medicare dialysis patients in 2014-2016.

Methods: We analyzed Medicare limited data sets. For each calendar week (Monday to Sunday) in 2014-2016, we identified all Medicare Parts A and B beneficiaries with ≥1 outpatient dialysis treatment. We excluded patients hospitalized on Sunday and not discharged before the end of the day. During the next week, we calculated the percentage of patients with ≥1 ER/OBS admission not resulting in transfer to inpatient care. We fit an ARIMA(1,0,0)x(0,1,0) model to the time series of admission percentages and used a likelihood ratio test to assess whether a secular trend remained after accounting for serial correlation and seasonality. We analyzed the aggregate population and strata defined by age, race, sex, concurrent Medicaid enrollment, US Census Division, and dialytic modality (hemodialysis, peritoneal dialysis).

Results: The average number of Medicare dialysis patients per week was more than 286,000. As displayed in the figure, the mean percentage of dialysis patients with ≥1 ER/OBS admission each week was 2.97% in 2014, 3.04% in 2015, and 3.12% in 2016 ($P < 0.001$, from test of secular trend). The percentage of dialysis patients with ≥1 ER/OBS admission each week increased significantly ($P < 0.05$) in every stratum. Strata with the highest mean percentages of dialysis patients with ≥1 ER/OBS admission each week in 2016 were ages 20-34 years (5.14%), ages 35-44 years (4.04%), and Medicaid enrollees (3.83%).

Conclusions: Utilization of emergency and observation room care is increasing among Medicare dialysis patients.

Funding: Commercial Support - NxStage Medical, Inc.



FR-PO782

Discrepant Associations of Hemodialysis Intensity and Survival in the Facility and at Home

Eric D. Weinhandl,[1,2] Kristine Kubisiak,[1] Debabrata Ray,[1] Allan J. Collins.[1,2] *[1]NxStage Medical, Inc., Victoria, MN; [2]University of Minnesota, Minneapolis, MN.*

Background: Incremental hemodialysis (HD) has recently garnered interest. Mathew *et al* (*Kidney Int*, 2016) reported that in US incident patients on in-center HD, adjusted hazard ratios (AHRs) of death for 2 vs. 3 and ≥4 vs. 3 sessions/week were 0.88 (95% confidence interval, 0.72-1.08) and 1.56 (1.21-2.03), respectively. These data may reflect either the relative efficacy of twice-weekly HD as an initial prescription or residual confounding. We assessed whether these associations could be replicated among in-center hemodialysis (IHD) and home hemodialysis (HHD) patients.

Methods: We used data from the United States Renal Data System. We identified adult patients who initiated HD in 2011-2015, and we retained patients with an initial HD prescription of 2 to 7 sessions/week and 2-8 hours/session, according to form CMS-2728. We followed patients until death, but for a maximum of one year. Using Cox regression, we assessed associations of HD frequency, HD hours per week, and HD product (frequency^2 × hours/session) separately among IHD and HHD patients, with adjustment for demography, vascular access type, and disease severity, including estimated glomerular filtration rate.

Results: We identified 503,678 IHD patients and 2849 HHD patients. With IHD (vs. HHD), the percentage of patients prescribed 2 sessions/week was 1.1% (vs. 1.1%), the percentage of patients prescribed ≥4 sessions/week was 0.5% (vs. 59.7%), mean HD hours per week were 11.4 (vs. 14.0), and mean HD product was 34 (vs. 62) points. With IHD, the AHRs of death for 2 vs. 3, ≥4 vs. 3, and ≥4 vs. 2 sessions/week were 0.84 (0.80-0.89), 1.05 (0.96-1.14), and 1.24 (1.12-1.38), respectively; with HHD, the AHRs were 0.83 (0.39-1.76), 0.63 (0.52-0.75), and 0.76 (0.36-1.61), respectively. With IHD, the AHR of death for each additional HD hour per week was 1.012 (1.008-1.016); the corresponding AHR for HHD was 0.967 (0.943-0.993). Finally, with IHD, the AHR of death for each 10-point increment in HD product was 1.039 (1.028-1.051); the corresponding AHR for HHD was 0.946 (0.915-0.979).

Conclusions: Associations of HD frequency, HD hours per week, and HD product are almost entirely discrepant with IHD and HHD. In the facility, lower HD frequency and fewer HD hours are associated with better survival. In the home, higher frequency and greater HD hours are associated with better survival.

Funding: Commercial Support - NxStage Medical, Inc.

FR-PO783

Predictors of Hyperkalemia-Related Emergency Department Encounters Among Patients Receiving Hemodialysis Care

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Background: Almost 10% of emergency department (ED) visits among dialysis patients are for conditions that could potentially be managed in an outpatient setting such as hyperkalemia. We used population-based data to identify factors that place hemodialysis patients at increased risk of hyperkalemia-related ED events.

Methods: We identified all chronic hemodialysis patients age ≥18 years from March 2009–March 2015 within southern Alberta, Canada. We used a nested case-control design to identify differences between patients with and without hyperkalemia-related ED events (defined by ICD-10 related codes and/or serum K^+ ≥6mmol/L). Cases were matched to controls based on dialysis site type (satellite or in-centre) and time period. Clinical and dialysis-specific variables were measured 2-4 weeks prior to outcome dates. We assigned a random date within each control's period on hemodialysis to serve as a proxy for an outcome date. Potential predictors included demographic/clinical characteristics, prior health system use, and dialysis run sheet variables. Conditional logistic regression models were used to identify significant predictors of hyperkalemia-related ED events.

Results: Of 2012 patients on chronic hemodialysis, 129 had 180 hyperkalemia-related ED events (cases) within the study timeframe. Controls were matched to cases at a ratio of ~3-to-1 (508 controls). In bivariate analysis, cases were younger, had higher levels of comorbidity, higher acute care use in the prior 6 months, and received more intensive dialysis treatment (e.g. higher ultrafiltration (UF) volume, cumulative duration of dialysis) in the weeks prior to an ED event. Multivariate modeling identified the following predictors of hyperkalemia-related ED events: ED use in prior 6 months (OR: 2.70; 95% CI: 1.69-4.33), dialysate potassium concentration ≤3.0mmol/L (2.95; 1.28-6.77), average UF volume>2.5L per dialysis session (2.73; 1.59-4.71), >15 hours of cumulative dialysis time in the prior week (5.84; 2.32-14.70), dialysis access via fistula (1.79; 1.20-2.66).

Conclusions: We identified a number of predictors that place patients at greater risk of presenting to the ED with hyperkalemia. Identification of such patients may allow for targeted strategies for preventive care, thus avoiding unnecessary acute care use and cost while improving patient quality of life.

FR-PO784

Predicting Who Needs Urgent Dialysis Prior to Ambulance Transport to the Emergency Department

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Background: Chronic hemodialysis patients who require ambulance transport to the emergency department (ambulance-ED) may subsequently need urgent dialysis. However, little is known about predictors of urgent dialysis based on patient factors identified prior to ED transport. The purpose of this study was to develop a risk prediction model for urgent dialysis after ambulance-ED based on patient characteristics identified at the time of paramedic assessment.

Methods: We analyzed a cohort of incident thrice-weekly hemodialysis patients between 2009-2013 (last follow-up of 2015) who experienced one or more ambulance-ED events. Chief complaint, vital sign parameters and time from last dialysis to ambulance dispatch was assessed for all patients at the time of paramedic assessment prior to ED transport. Urgent dialysis was defined as a need for dialysis within 24 hours of an ambulance-ED in a monitored setting or among patients with an initial ED potassium of >6.5 mmol/L. Associations with urgent dialysis were analyzed using logistic regression. A risk prediction model was created and internally validated.

Results: Among 197 patients, there were 624 ambulance-ED events and 87 episodes of urgent dialysis. Weakness as a presenting complaint (OR 4.62, 95% CI 1.23-17.29), >24 hours since last dialysis (OR 2.09, 95% CI 1.15-3.81), and triage vitals (heart rate <60 beats/minute (OR 3.06, 95% CI 1.09-8.61), systolic blood pressure >160 mmHg (OR 2.37, 95% CI 1.32-4.25), respiratory rate ≥20 breaths/minute (OR 2.00, 95% CI 1.06-3.75) and oxygen saturation <90% (OR 3.04, 95% CI 1.55 – 5.94)) were associated with an increased need for urgent dialysis after ambulance-ED. A risk prediction model incorporating these variables had very good discrimination (C-statistic: 0.81, 95% CI 0.76-0.86). The negative predictive value for not needing urgent dialysis was 93.6% using the optimal cut point (≥15% predicted probability). Of the patients who were predicted to need urgent dialysis but were transported to a dialysis incapable facility, 31% required a second transport for urgent dialysis.

Conclusions: We created a risk prediction model for urgent dialysis after ambulance-ED based on patient characteristics at the time of paramedic assessment. This model has the potential to guide dialysis patient transport to dialysis-capable facilities when needed.

FR-PO785

Cumulative Time in Hospital After Initiation of Dialysis: A Cohort Study

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Background: Chronic dialysis patients are at risk for frequent and prolonged hospitalizations. Less is known about predictors of cumulative time in hospital after initiation of dialysis, including each subsequent hospitalization. Having an awareness of the predictors of cumulative hospital time is important for informed decision making between patients and providers prior to initiation of dialysis.

Methods: We analyzed a cohort of incident, chronic dialysis patients from 2009-2014 (last follow-up of 2015) at a tertiary care center. Baseline characteristics including demographics, comorbidities, frailty status (assessed using the clinical frailty scale; CFS rated from 1: very fit to 7: severely frail) and laboratory parameters were captured in all patients at dialysis initiation. The primary outcome was cumulative time in hospital (proportion of time in hospital/total follow-up time and inclusive of the time in hospital after dialysis initiation for inpatient dialysis starts). Generalized linear models were used to fit a negative binomial distribution of cumulative time with total time of followup as the offset.

Results: A total of 647 patients were included in the study. Mean age was 62 ± 15 years, 90% were caucasian and the majority (63%) were male. Diabetes (48%), coronary artery disease (30%), congestive heart failure (22%), and cancer (11%) were prevalent at dialysis initiation; a smaller proportion (5%) had underlying liver disease. The median CFS score was 4 (IQR 2.5) corresponding to "vulnerable but not frail". Median days in hospital for the cohort was 13 (IQR 41) and cumulative hospital time was 3% of total follow-up time (48/1704 years). In an adjusted model, the percent change in the incident rate of cumulative days in hospital was 22% for each 1 point increase in frailty severity. Other factors associated with higher cumulative time included age (IRR 1.02, 95% CI 1.01-1.03 per year), liver disease (IRR 2.07, 95% CI 1.07-4.02), malignancy prior to dialysis initiation (IRR 1.78, 95% CI 1.09-2.90) and low albumin (IRR 0.93, 95% CI 0.91-0.96 per each g/L decrease in albumin).

Conclusions: Demographics, comorbidities, frailty status and laboratory parameters are associated with a higher cumulative time in hospital after dialysis initiation. This information may be used to better inform patients of their risk of hospitalization after starting chronic dialysis.

FR-PO786

B-Line Score Is Predictive of Repeat Acute Care Utilization in Hemodialysis Patients

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Background: ESRD is burdensome both for patients and healthcare systems because of high acute care utilization. Hemodialysis (HD) patients present to an emergency department (ED) an average of 3 times per year and are hospitalized an average of twice per year with readmission rates of 30%. Readmissions are particularly taxing on hospitals as they are not reimbursed by Medicare. Cardiovascular disease, due in large part to visits for fluid overload (FO), drives these high rates of acute care utilization. The standard of care for assessment of FO remains physical exam despite its poor accuracy. 28-point B-line score (BLS) has emerged as a quantitative marker of FO, outperforming the physical exam. The goal of this study was to determine if BLS is predictive of hospital readmissions or ED revisits.

Methods: A convenience sample of patients with ESRD presenting to a large urban tertiary care ED was enrolled consecutively. Patients were excluded if they were not chronically on HD or were unable to consent. BLS was obtained after enrollment, prior to their first HD session at our center. The patients were followed for 30 days to determine the rate of readmissions and 60 days to determine the rate of ED revisits. Presence of FO was determined by the treating nephrologist or on chart review. Visits for FO were determined by discharge diagnosis.

Results: Of 101 patients enrolled, median age was 60, 51% were male, 84% identified as Black or African American. Comorbidities included 65% diabetic, 27% coronary artery disease, 33% airways disease, 40% systolic heart failure, 75% diastolic heart failure. Median dialysis vintage was 33 months. Access type was 54% arteriovenous fistula, 29% graft, and 17% catheter. ESRD vintage was 33 months. Residual renal function was minimal. 62% of patients had FO on arrival and 27% of visits were for FO. 45% of patients had an ED revisit within 60 days. Median BLS for patients with a 60-day ED revisit was significantly higher than those without (64 vs 29, p=0.001). Median BLS for patients with a 30-day readmission was also higher (57 vs 32, p=0.12).

Conclusions: BLS for patients with a 60-day ED revisit or 30-day readmission was higher than patients without revisits or readmissions. BLS is a useful metric in the ED for determining whether patients with ESRD on HD are likely to have repeat visits.

FR-PO787

Correspondence Between Causes of Recurrent Hospitalizations Among Hemodialysis Patients

Scott Sibbel, Adam G. Walker, Francesca Tentori, Steven M. Brunelli. *DaVita Clinical Research, Minneapolis, MN*.

Background: Despite targeted efforts, hospitalizations represent a major burden for end-stage kidney disease patients, with an average of 1.7 admissions per patient-year and

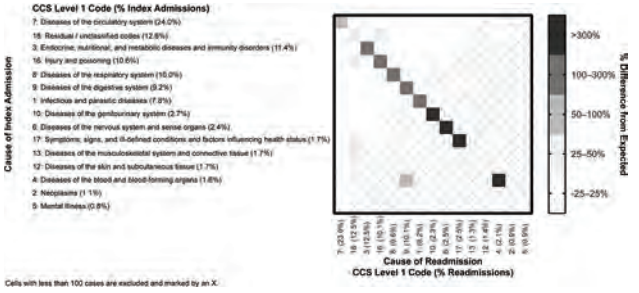
30.7% of patients being readmitted to the hospital. There is a need to identify factors that drive hospitalization risk in this population. We evaluated cause of initial admission and readmission among patients receiving in-center hemodialysis at a large dialysis organization (LDO) in the US.

Methods: Using Medicare claims we identified all patients with at least one index hospitalization ≥ 1 day during 2014. Readmissions were defined as hospitalizations that occurred within 30 days after index admission. Cause of hospitalizations were determined by primary ICD-9 diagnosis code and were classified using the clinical classification system (CCS). The relationship between causes of index hospitalization and readmission were determined through cross-tabulation of the percent difference between observed (O) and expected (E) readmissions accounting for background admission rate (O-E/E*100).

Results: During the study period the overall probability of readmission was 31.5%. Diseases of the circulatory system were the most common cause for both hospitalizations and readmissions. Overall, the probability of readmissions did not vary greatly by cause of index admission (28.8%-35.8%) and the leading cause of readmission was the same as that of the index hospitalization.

Conclusions: We found that the cause of readmission was closely related to the cause of prior hospitalization in a large sample of US dialysis patients. Despite potential misclassification of readmission cause, these results raise the possibility that the clinical issue was not fully addressed during the index admission. Further studies are needed to identify clinical practices that may help reduce readmission rates.

Funding: Commercial Support - DaVita Inc



FR-PO788

Lower Rates of Hospital Admissions During a Fluid Management Quality Improvement (QI) Project Utilizing Relative Blood Volume Monitoring (RBV-M) - A Retrospective Database Analysis

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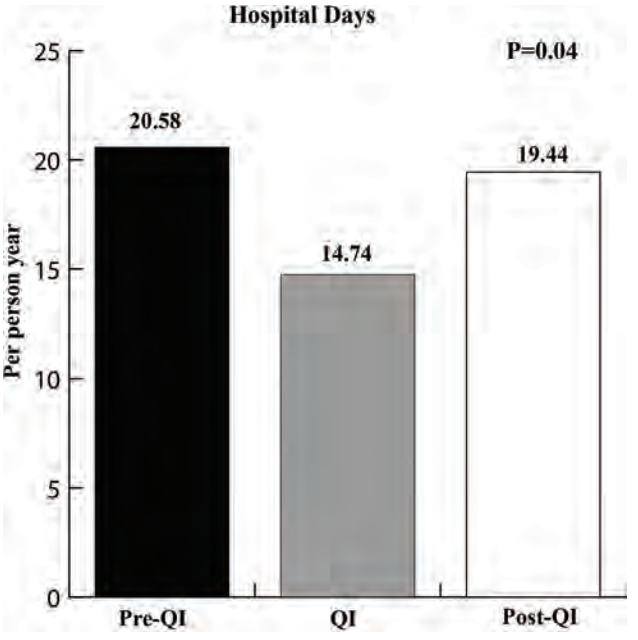
Background: Hemodialysis (HD) patients experience high rates of hospitalization and mortality, especially in the first 90 days of dialysis. A clinic-wide fluid management QI project was conducted at 9 dialysis facilities utilizing RBV-M. The aim of this retrospective analysis was to assess hospital admissions among incident HD patients during the QI project compared to incident HD patients not participating in the QI project.

Methods: Incident patients in their first 90 days of HD were analyzed. The analysis included 3 periods: before the QI start (Pre-QI); during the QI project (QI); and following the end of the QI project (Post-QI). RBV-M was conducted using Crit-Line® monitors. Hazard ratios were modeled using all hospital admissions during the first 90 days of dialysis. Poisson regression was used to compare hospital days across 3 periods.

Results: 1068 adult incident HD patients (Pre-QI: 501, QI: 376, Post QI: 191) who started HD between 2009 and 2017 were analyzed. There was a difference in hospital admission rates among the 3 periods (P=0.02). Compared to the QI period, the Pre-QI period had a 20% increased rate of hospitalization (HR= 1.2, 95%CI: [0.99,1.47]) and the Post-QI period had a 40% increased rate (HR= 1.4, 95%CI: [1.11,1.84]). Fewer hospital days were observed for the QI period (P=0.04) compared with the non-QI groups, with 5.84 (P=0.01) less hospital days per person-year (PPY) and 4.7 (P=0.12) less hospital days PPY compared with Pre-QI and Post-QI, respectively (Figure).

Conclusions: The use of RBV-M as part of a QI on fluid management was associated with a decreased rate of hospital admissions and fewer hospital days among incident HD patients during the first 90 days of dialysis.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group



FR-PO789

Early Readmissions Are More Common After Long Hospitalizations Among Hemodialysis Patients

Adam G. Walker, Scott Sibbel, Francesca Tentori, Steven M. Brunelli. *DaVita Clinical Research, Minneapolis, MN.*

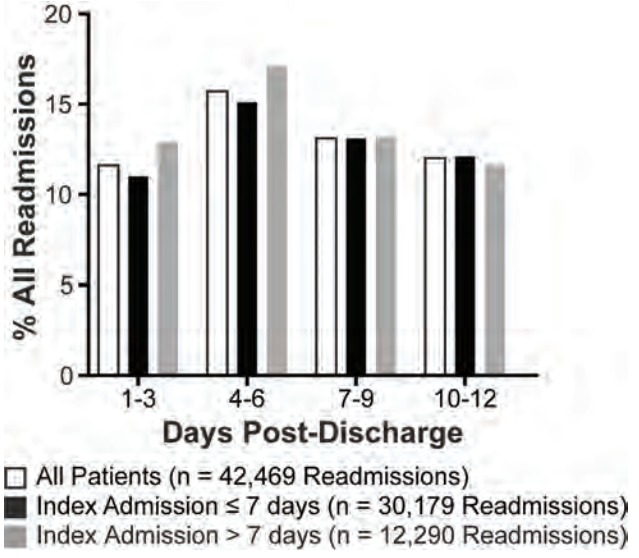
Background: Approximately one-third of dialysis patients who are hospitalized will be readmitted post discharge. In this study, we characterized patterns of readmissions by length of index hospitalizations.

Methods: Patients included in this analysis were Medicare beneficiaries, receiving in-center hemodialysis at a large dialysis organization (LDO,) and had a qualifying index hospitalization lasting ≥ 1 day during the study period (2014). Hospitalizations were considered readmissions if they occurred ≤ 30 days post-discharge from the index admission. Causes of hospitalizations were determined by primary ICD-9 diagnosis code.

Results: The mean length of stay for index admissions was 7.1 ± 9.5 days (median 4 days). The longest index hospitalizations were those due to infectious and parasitic disease and the shortest were related to endocrine, nutritional, metabolic diseases and immunity disorders. The overall probability of readmission was 31.5%; 27.6% and 52.4% of all readmissions occurred within 6 ("early readmissions") and 12 days post-discharge, respectively. Patients with index hospitalization duration > 7 days had a higher probability of readmission overall (34.7% vs. 30.3 %) and of early readmission (30.0% vs. 26.1%) compared to those with shorter index hospitalizations.

Conclusions: These results suggest that patients with longer hospitalizations are more vulnerable to readmissions overall and to early readmissions, likely due to the severity of disease. This was particularly common among patients admitted for infections. These results raise the possibility that the clinical issue was not fully addressed during the index admission or shortly after discharge. There is a need to identify clinical practices that may help reduce readmission rates.

Funding: Commercial Support - DaVita Inc



FR-PO790

Recent Trends in Hospital Admissions Among Medicare Dialysis Patients

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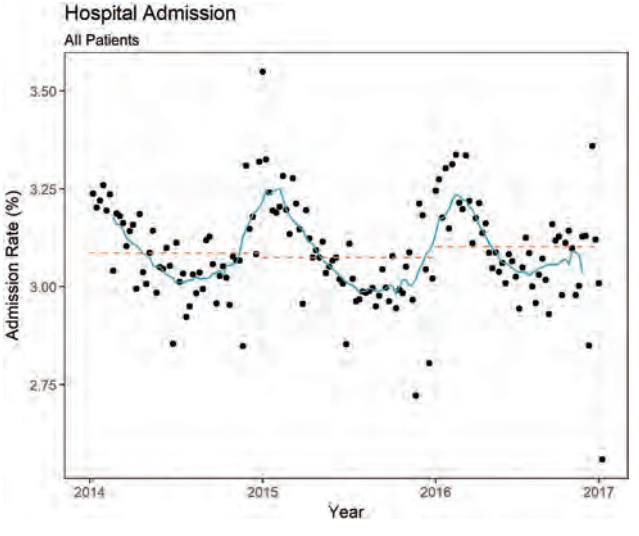
Background: Hospital admissions not only reflect the morbidity of dialysis patients, but also account for more than one-third of Medicare Parts A and B expenditures among patients (USRDS Annual Data Report, 2017). We assessed trends in hospital admissions among Medicare dialysis patients in 2014-2016.

Methods: We analyzed Medicare limited data sets. For each calendar week (Monday to Sunday) in 2014-2016, we identified all Medicare Parts A and B beneficiaries with ≥1 outpatient dialysis treatment. We excluded patients hospitalized on Sunday and not discharged before the end of the day. We calculated the percentage of patients with ≥1 hospital admission during the next week. We fit an ARIMA(1,0,0)x(0,1,0) model to the time series of admission percentages and used a likelihood ratio test to assess whether a secular trend remained after accounting for serial correlation and seasonality. We analyzed the aggregate population and strata defined by age, race, sex, concurrent Medicaid enrollment, US Census Division, and dialytic modality (hemodialysis, peritoneal dialysis).

Results: The average number of Medicare dialysis patients per week was over 286,000. As displayed in the figure, the mean percentage of dialysis patients who were newly hospitalized each week was 3.09% in 2014, 3.07% in 2015, and 3.10% in 2016 ($P = 0.90$, from test of secular trend). This percentage increased significantly ($P < 0.05$) among ages 20-34 years (3.47%, 3.58%, and 3.70% in 2014, 2015, and 2016, respectively), ages 35-44 years (2.93%, 2.98%, and 3.09%), Medicaid enrollees (3.33%, 3.33%, and 3.39%), and West South Central residents (2.91%, 2.92%, 3.00%). In other strata, secular trends were not significant ($P > 0.05$).

Conclusions: Between 2014 and 2016, the risk of hospital admission among all Medicare dialysis patients was stable, although a secular trend of increasing risk was evident in young adult and dual-eligible patients.

Funding: Commercial Support - NxStage Medical, Inc.



FR-PO791

Using Artificial Intelligence to Help Predict Imminent Hospitalizations in Patients with ESRD

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Background: Patients with end-stage renal disease are hospitalized two times per year on average; approximately 35% have a re-admission within 30 days of discharge (USRDS 2017). The cost of hospitalizations represents about one-third of the total Medicare spending for patients on dialysis. We developed a model to predict which patients treated at a large dialysis provider are at imminent risk of hospitalization to highlight patients who might benefit from additional interventions.

Methods: We built a machine learning model using over 1500 variables to predict the probability that a patient would be admitted within 7 days of the current outpatient dialysis treatment. Some of the variables in the model include treatment vital signs, administered medications, lab values, prior hospitalizations, demographics, comorbidities, lifestyle, and free-text clinical notes. Training data was extracted from patients treated at a large dialysis provider between January 2016 through May 2017. The results shown below are from unseen test data with 200,000 patients in June 2017.

Results: Approximately 2.7% of patients are hospitalized weekly. Results from the test data show the model has an area under the receiver operating curve (AUROC) of 0.78, sensitivity of 69%, and specificity of 72%. The confusion matrix for test data is shown in Table 1. Top variables for predicting hospitalization are related to prior hospitalizations, the content of free-text clinical notes, serum albumin, blood pressure, interdialytic weight gain, and hemoglobin.

Conclusions: This work demonstrates that data routinely collected during dialysis treatments can be used to predict imminent hospitalization. We are currently pilot-testing this model to determine if surfacing the results of these real time artificial intelligence-based machine learning algorithms to the local care team can help patients avoid hospitalizations and lead to improved patient outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

Confusion matrix for test data (n = 200000)

		Actual admit in 7 days	
		Positive	Negative
Predicted admit in 7 days	Positive	1.8%	27.2%
	Negative	0.8%	70.2%

FR-PO792

Prior Hospitalization Burden and the Relatedness of 30-Day Readmissions in Patients Receiving Hemodialysis

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Background: Thirty-day readmissions are common in patients receiving hemodialysis and costly to Medicare. Because patients on hemodialysis have a high background hospitalization rate, thirty-day readmissions might be less likely related to the index hospitalization or to the quality of post-discharge care than in patients with other conditions.

Methods: We evaluated whether prior hospitalization burden was associated with increased 30-day readmissions unrelated to the index hospitalization in adults with Medicare receiving hemodialysis in the United States from 1/1/2012-12/31/2013. We categorized a hospitalization, 30-day readmission pair as "related" if the principal diagnoses came from the same organ system. Using multinomial logistic regression, we estimated the likelihood that an index hospitalization was followed by a related or unrelated 30-day readmission.

Results: The adjusted probability of an unrelated 30-day readmission after any index hospitalization was 19.1% (95% CI: 18.9%, 19.3%) in patients with 0-1 hospitalizations in the prior year, 22.6% (95% CI: 22.4%, 22.8%) in patients with 2-4 hospitalizations, and 31.2% (95% CI: 30.8%, 31.5%) in patients with 5 or more hospitalizations. Cardiovascular index hospitalizations had the highest adjusted probability of a related 30-day readmission: 10.4% (95% CI: 10.2%, 10.7%), 13.6% (95% CI: 13.4%, 13.9%), and 20.8% (95% CI: 20.2%, 21.4%) respectively. Conversely, renal index hospitalizations had the lowest adjusted probability of a related 30-day readmission, 2.0% (95% CI: 1.8%, 2.3%), 3.9% (95% CI: 3.4%, 4.4%), and 5.1% (95% CI: 4.3%, 5.9%) respectively.

Conclusions: High prior hospitalization burden increases the likelihood that a patient receiving hemodialysis experiences a 30-day readmission unrelated to the index hospitalization. Healthcare payers such as Medicare should consider incorporating clinical relatedness into 30-day readmission quality measures.

Funding: NIDDK Support, Other NIH Support - National Institute of Aging

FR-PO793

Hospital-Acquired Anemia in Hemodialysis Patients: Opportunities for Improvement

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Background: Anemia is a significant comorbidity in end-stage renal disease (ESRD) patients. Hospital-acquired anemia (HAA) is well-described in non-ESRD patients, where

it correlates with increased morbidity and mortality. Little is known about the development of HAA in hospitalized ESRD patients and potential modifiable factors.

Methods: We used retrospective chart review to compare hemoglobin (Hgb) on admission, at its lowest (nadir) and on discharge in 52 adult patients with ESRD admitted over a three month period to our medical center. Inclusion criteria were age > 18 years and admission between December 1st 2016 and February 28th 2017, as well as a billing code of ESRD (N18.6). Exclusion criteria were: bleeding-related admission, multiple admissions over the observation period, admission longer than 30 days, peritoneal dialysis. We analyzed change in hemoglobin from admission to discharge or admission to nadir and factors that were associated with the changes. Total diagnostic blood volume refers to the total amount of blood drawn by phlebotomy during the stay.

Results: The mean Hgb on admission was 10.6 (+/-1.5) g/dL and the mean discharge Hgb was 9.6 (+/-1.7) g/dL. The mean lowest Hgb was 9.0 (+/- 1.6) g/dL. Total diagnostic blood volume for the admission was significantly correlated with Hgb change from admission to lowest (0.578, p<0.001); 23% of patients required blood transfusions. Age, sex, comorbidities, admission diagnosis and access type were not associated with the change in Hgb, while length of stay and total diagnostic blood volume were associated with a Hgb drop from admission to nadir. We propose a definition of HAA for the ESRD population to include a Hgb decrease from admission to discharge of 1.5 g/dL or greater or need for transfusion.

Conclusions: Hospitalized ESRD patients showed significant decrease in hemoglobin during inhospital stay that correlated most closely with length of stay and total diagnostic blood volume. Strategies to minimize phlebotomy volume in this vulnerable population need to be tested.

Funding: NIDDK Support, Private Foundation Support

FR-PO794

Determinants of Dialysis Facility Hospital Readmissions

Ziad M. Ashkar. *Lafayette General Health, Lafayette, LA.*

Background: Hospital readmissions are common, costly, and potentially avoidable. In ESRD, factors including anemia, CHF, cardiovascular disease, malignany, vascular access and low albumin were associated with readmissions. No studies have looked into dialysis units specific determinants of dialysis facility readmission rate. The purpose of this study is to identify unique dialysis facility determinants of hospital readmissions.

Methods: Observational retrospective, cross-sectional design. Data are obtained from CMS Dialysis Facility Compare, release date April 2018. Dialysis facility readmission rate was used as outcome variable. (defined as a percentage of hospital discharges). Multilinear regression with cluster by network was then done, with number of dialysis stations, % of patients with hemoglobin<10g/dl, % with KT/V>=1.2, % with AV Fistula in use, % with catheters more than 90 days, % with Calcium > 10.2mg/dl, phosphorus < 3.5 mg/dl and >7mg/dl

Results: For each increase in number of dialysis stations, there is a 6.3 % increase in dialysis facility readmission rate (DFR). For each increase in % patients with Hb < 10g/dl, there is a 3.8 % increase in DFR. Each increase in % with KT/V>=1.2 is associated with 13.5 % decrease in DFR. There are no associations with the other variables.

Conclusions: Using data from dialysis facility compare, hemodialysis clinics with KT/V>=1.2 are associated with significant decrease in dialysis facility readmission rates. Increase in dialysis stations and increase in percent with hemoglobin < 10g/dl are associated with increase in readmission rates. Strategies targeting adequate clearance and anemia management will likely have significant impacts towards decreasing hospital readmissions in individual dialysis facilities. More studies are needed to understand drivers behind increase in station numbers and readmissions in dialysis.

Multilinear regression determining Dialysis Facility Readmission Rate.

	coefficient	p value
Dialysis stations	0.0628	0.008*
% Hb<10	0.038	0.002*
%KT/V>=1.2	-0.135	0.014*
%AV fistula in use	-0.035	0.112
%catheter>90 days	0.032	0.24
%Ca>10.2	-0.03	0.779
%Pi<3.5	0.06	0.103
%Pi>7	-0.006	0.819

FR-PO795

Post Hoc Ergo Propter Hoc: A Multilevel Strategy to Reduce 30-Day Readmissions in Patients on Dialysis

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Background: Patients with end-stage renal disease (ESRD) requiring dialysis are twice as likely as the general population to be readmitted within 30 days of hospital discharge. Inpatient care costs account for approximately 40% of total Medicare expenditures for dialysis. As of 2017, outpatient dialysis facilities have been penalized by the Centers of Medicare and Medicaid (CMS) for excessive readmissions as the standardized readmission ratio (SRR) became part of the ESRD quality incentive program. Our study examines the effect of a multi-level strategy to reduce readmission rates.

Methods: Washington University owns and operates 2 out-patient ESRD facilities in the city of St. Louis, with a census of approximately 400 patients. Using 2014-2017 data as our benchmark, we examine the impact of a dedicated transitional care nurse (TCN) and communication improvements (between the inpatient nephrology service and dialysis facilities) on readmission rates. The role of the TCN is to reconcile patient's hospitalization with their outpatient care plan and bridge the gap from hospital to home. The TCN commenced work in the 3rd quarter of 2017.

Results: Admission and 30 day readmission data are outlined below in table 1. Admissions and readmissions have been decreasing over the past 3 years. 30 day readmissions reduced since introduction of readmission prevention strategy. An influenza outbreak was responsible for the increased number of admissions in the first quarter of 2018. The TCN was able to see approximately 50% of patients within 48 hours of discharge and the patient's nephrologist saw 90% of patients within one week of discharge.

Conclusions: This study highlights the ongoing difficulty dialysis units have with reducing readmission rates. We show that increased patient engagement with a TCN in the first 48 hours post discharge and improved structured communication between in patient nephrology services and dialysis facilities has led to reduced rates of readmissions.

Funding: Private Foundation Support

Table 1

	Pre intervention			Intervention				
	2014	2015	2016	2017 (1st quarter)	2017 (2nd quarter)	2017 (3rd quarter)	2017 (4th quarter)	2018 (1st quarter)
Admissions (n)	713	889	634	148	135	126	125	151
Readmissions (%)	32	34	31	32	30	26	23	22

FR-PO796

In-Hospital Hemodialysis Services Provided by Tele-Nephrologists Using the NxStage System One S

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Background: Telemedicine has recently permeated into the nephrology space allowing ESRD patients in rural hospitals without access to traditional hemodialysis (HD) to receive dialysis care without transfer to larger healthcare systems. We report 5 months of experience using non-traditional dialysis machines (Nxstage System One S) in providing hemodialysis to patients remotely monitored by tele-nephrologists in rural hospitals.

Methods: A retrospective, descriptive study of patients receiving tele-nephrology consultation and chronic dialysis services between January 2018 and May 2018 in rural community hospitals across the U.S. Consultations were requested by the on-site physicians and were performed by reviewing the patient's hospital EMR and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope. Tele-nephrologists ordered HD using Nxstage System One S technology and Certified Clinical HD Technicians per standard nephrology practice. Hemodialysis treatment data was captured electronically and extracted into Excel for analysis

Results: A total of 6 rural hospitals across the U.S, provided 145 HD treatments to 51 ESRD patients (25 females, 26 males; average age 64.9 (22-88 years) during the first 5 months of 2018. HD prescription details with average blood flow (Qb), dialysate flow (Qd), dialysate volume, duration, flow fraction, and fluid removal (UF) rates are listed in Table 1. Average pre-systolic BP (SBP) was 134 and post- SBP -131 with low SBP- 109. For those with pre- SBP 100-130, and pre-SBP>130, 18% and 3% respectively had intradialytic drop to SBP<90. 7% of treatments utilized a 1 K bath, 44% - 2 K bath, and 48% - 3K bath. Average hours in between subsequent HD sessions was 47.

Conclusions: Hemodialysis services provided by NxStage System One S in ESRD patients in rural hospitals is effective and safe. This low dialysate volume platform is performed at similar frequencies and UF rates as traditional dialysis platforms (high dialysate volume) without high rates of hypotension.

Table 1 HD NxStage prescription

duration	Qb	Qd	volume dialysate	FF	UF volume	UF ml/hr	UFR	pre-wt
209 min.	365 ml/min	300 ml/min	61 L	82%	1581 ml	803	10.1 ml/hr/kg	85.4 kg

FR-PO797

Factors Affecting Sudden Death in Hemodialysis Patients: Ten-Years Outcome of the Q-Cohort Study

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Background: Sudden death is a serious problem in hemodialysis patients. However, the precise incidence rate of sudden death and its risk factors remain unclear.

Methods: A total of 3,506 Japanese HD patients aged ≥18 years were prospectively followed for 10 years. Sudden death was defined as sudden and unexpected natural death within 24 hours. Multivariate-adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) of each risk factor of sudden death were calculated using a Cox proportional hazards model.

Results: During a follow-up period, 1,748 patients died from any causes and 227 of them (13%) were attributed to sudden death. In multivariable-adjusted Cox analysis, male sex (hazard ratio [HR] 1.65; 95% CI 1.19–2.30), age (HR 1.44; 95% CI 1.26–1.65 for every 10-years increase), presence of diabetes (HR 2.45; 95% CI 1.82–3.29), history of

cardiovascular events (HR 1.85; 95% CI 1.38–2.46), cardiothoracic ratio in chest X-ray (HR 1.21; 95% CI 1.07–1.39 for every 5-percentage-point increase), serum levels of phosphate (HR 1.15; 95% CI 1.03–1.30 for every 1-mg/dL increase), and C-reactive protein (HR 1.11; 95% CI 1.03–1.20 for every 1-mg/dL increase) were independent predictors for developing sudden death. In subgroup analysis, shorter dialysis session length (<5 hours) was associated with an increased risk of sudden death in male group (HR 1.51; 95% CI 1.03– 2.21; p for interaction 0.01) or elderly group (≥ 65 years) (HR 2.45; 95% CI 1.82–3.29), and lower serum calcium level was a significant predictor for sudden death in female group (HR 1.88; 95% CI 1.36–2.63 for every 1mg/dL decrease; p for interaction <0.001).

Conclusions: The present study demonstrated the lower occurrence rate of sudden death compared to previous reports, but elucidated its specific risk factors, related to atherosclerosis, vascular calcification, left ventricular hypertrophy, and chronic inflammation, in hemodialysis patients.

FR-PO798

Characteristics of Sudden Cardiac Death in Our Hemodialysis Unit

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Background: In hemodialysis (HD) patients sudden cardiac death (SCD) accounts for one out of every four deaths. It is complicated to determine how unexpected death is on ESRD patients whose illness is chronic and have a high comorbidity. Our aim was to study mortality in our dialysis unit, focusing on SCD.

Methods: Retrospectively, we collected mortality data for ten years. Clinical, biochemical (analytical closer to the date of death) and causes of death were analyzed. SCD was defined as an unexpected circulatory arrest or an unwitnessed, unexpected death in patients known to be well within the past 24 h.

Results: 215 deaths were reviewed. First cause of death was cardiovascular disease (CVD) (54 p, 25%), the second SCD (42p, 19%). Risk factors for SCD at univariate study are showed in Table 1. In the logistic regression analysis, SCD was associated with: lack of AF (p0,05, HR0,27,CI 0,107-0,67), higher potassium levels (p0,02, HR1,64,CI 1.0,7- 2,4), higher albumin levels (p0,02,HR2,CI 1,1-3,8) and lower CRP levels (p:0,01 HR0,99,CI 0,98-0,99).

Conclusions: SCD was the second cause of death in our HD patients and was not associated to traditional risk factors. There was no relationship between SCD and previous diagnosis of CVD, malnutrition and inflammation nor structural heart disease (AF). High value of serum potassium was the only risk factor associated to SCD that we can modify.

	SCD	NO SCD	p
N	175	42(19,5%)	
Age, y	68,5±10,5	70,3±11,3	NS
Males	55,8%	57,2%	NS
Diabetic Neph.	37%	18,9%	0,03
Death at home	72,5%	4,5%	0,00
ICCIs	4,8±1,9	5,2±2,1	NS
Vintage (m)	52,8±42	59,3±65	NS
Atrial fibrillation (AF)	19,1%	37,6%	0,02
Cholesterol	124,5±31	112,9 41	0,05
Albumin	3,1±0.7	2,6±0,64	0,00
Hemoglobin	11±2,1	10,1±1,7	0,03
CRP	47±59	112±102	0,00
Ferritin	332±263	684,7±833,7	0,00
Transferrin	164,3±49,8	130,7±41	0,00
Sodium	136,6± 3,8	136±4,6	NS
Potassium	4,8± 0,9	4,3±1	0,00
Bicarbonate	25,6±3,6	25±4,4	NS
Phosphate	4,1± 1,8	4,5±1,7	NS

FR-PO799

Plasma Syndecan-1 in Hemodialysis Patients Associates with Survival and Reduced Volume Status

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Background: Syndecan-1, a transmembrane heparan sulfate proteoglycan, associates with renal and cardiovascular functioning. We earlier reported syndecan-1 to be involved in renal tubular regeneration. We now examined plasma values of syndecan-1 in a hemodialysis cohort and its association with volume, inflammatory and endothelial markers in addition to outcome parameters.

Methods: Eighty-four hemodialysis patients were evaluated for their plasma syndecan-1 levels by ELISA before, 60, 180 and 240 minutes after starting dialysis. Patients were divided into sex-stratified tertiles based on predialysis plasma syndecan-1 levels. We studied the association between plasma levels of syndecan-1 and volume, inflammation and endothelial markers and its association with cardiovascular events and all-cause mortality using Kaplan-Meier curves and cox regression analyses with adjustments for gender, age, diabetes and dialysis vintage.

Results: Predialysis syndecan-1 levels were two-fold higher in males compared to females (P=0.0003). Patients in the highest predialysis plasma syndecan-1 tertile had a significantly higher ultrafiltration rate (P=0.034) and lower plasma values of BNP (P=0.019), pro-ANP (P=0.024) and endothelin (P<0.0001) compared with the two lower predialysis syndecan-1 tertiles. No significant associations with inflammatory markers were found. Cox regression analysis showed that patients in the highest syndecan-1 tertile had significantly less cardiovascular events and better survival compared with the lowest syndecan-1 tertile (P=0.02 and P=0.005, respectively).

Conclusions: In hemodialysis patients, higher plasma syndecan-1 levels were associated with lower concentrations of BNP, pro-ANP and endothelin, and with better patient survival. This may suggest that control of volume status in hemodialysis patients allows an adaptive tissue regenerative response as reflected by higher plasma syndecan-1 levels.

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FR-PO800

Gender Differences in Three-Year Clinical Outcomes in Japanese Dialysis Patients

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Background: A recent Dialysis Outcomes and Practice Patterns Study (DOPPS) has shown a male-to-female mortality ratio one-to-one, notwithstanding women's statistically longer life expectancy in the general population (Hecking et al., 2014). This finding contrasts with the recent report that Japanese women on dialysis treatment have more favorable longevity (Jap. Soc. Dial. Ther., 2009). Accordingly, we further investigated clinical procedures and outcomes in order to clarify the gender differences in Japanese patients on chronic dialysis treatment in order to establish an optimal dialysis modality.

Methods: Subjects were patients in 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) from October 2011 to September 2013. We excluded 129 from the study because their three-year outcome data was unavailable. Thus, 1,395 subjects were enrolled in the study. Three-year mortality was analyzed by multivariate logistic regression model adjusted by age, gender, body mass index (BMI), diabetes mellitus, C-reactive protein, serum albumin, use of statin, history of cardiovascular disease (CVD) and malignancy. Three-year mortality and CVD events were studied separately in women and men with or without CVD at baseline.

Results: Overall, 458 (32.4%) of 1,395 test subjects were women. Women had lower rates of diabetes mellitus (Women 49.8% vs Men 56.0: P=0.028) and history of CVD (38.2% vs 49.8: P<0.001). Age (mean ± SD, 68.2 year ± 12.7 vs 67.7 ± 12.8: P=0.51) and BMI (23.3 ± 5.3 vs 23.5 ± 3.9: P=0.30) were similar in both sexes. Female gender (adjusted odds ratio 0.66: 95% CI 0.47-0.91) was a positive and history of CVD (OR 1.85: 1.37-2.51) was a negative independent predictor of three-year mortality.

Conclusions: Women on chronic dialysis treatment had a lower mortality risk than men. However, women with CVD comorbidity had a higher mortality rate which cancelled out the survival advantage. These data suggest that the dialysis modality for women with a risk of CVD needs to be modified.

Three-year outcome in subgroups (N=1395)

	Women CVD+ N=175	Women CVD- N=283	Men CVD+ N=467	Men CVD- N=470	P value
Age, year: Mean (SD)	71.5 (11.3)	66.2 (13.2)	70.6 (11.6)	64.9 (13.3)	0.05
All-cause mortality: N (%)	50 (28.6)	26 (9.2)	140 (30.0)	83 (17.7)	<.001
CVD mortality: N (%)	31 (17.9)	11 (3.9)	75 (16.4)	35 (7.5)	<.001
Cardiac mortality: N (%)	26 (15.0)	9 (3.2)	53 (11.6)	29 (6.2)	<.001
CVD event: N (%)	69 (43.1)	43 (15.8)	201 (48.8)	107 (24.9)	<.001

FR-PO801

Estimating the Fraction of First-Year Hemodialysis Deaths Attributable to Potentially Modifiable Risk Factors: Results from the DOPPS

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Background: Despite recent improvements in survival on chronic hemodialysis (HD), mortality soon after HD start remains high. We aimed to identify potentially modifiable risk factors with the greatest impact on early HD mortality.

Methods: The analysis included 15,891 incident HD patients (<60 days on HD) from 21 countries in phases 1-5 (1996-2015) of the Dialysis Outcomes and Practice Patterns Study (DOPPS). Using adjusted Cox regression, we estimated the fraction of deaths in the first year of HD attributable to potentially modifiable risk factors at study entry (the attributable fraction, AF) by comparing predicted survival based on risk factors observed vs. counterfactually set to reference levels.

Results: Of 12 risk factor chosen based on known mortality associations, the highest AFs were observed for catheter use (22%), serum albumin <3.5 g/dL (19%), and serum creatinine <6 mg/dL (12%). Risk factors with an AF of 5-9% were lack of pre-HD nephrology care, lack of residual urine volume, SBP out of range 130-160 mm Hg, phosphorus out of range 3.5-5.5 mg/dL, hemoglobin out of range 10-12 g/dL, and WBC count >10,000/μL. The AFs for ferritin >800 ng/mL, serum calcium out of range 8.4-9.5 mg/dL and PTH out of range 150-300 pg/mL were <3%. Overall, 65% (95% CI 59-71%) of deaths were attributable to these 12 risk factors. The AF for CRP was 21% in facilities where it is routinely measured.

Conclusions: A substantial proportion of first-year HD deaths could potentially be reduced by successfully modifying a few risk factors. Highest priority targets should include decreasing catheter use and avoiding or treating malnutrition/inflammation whenever possible.

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Table. Attributable fractions for risk factors for 1-year mortality

Risk Factor	% pts	HR (95% CI)	AF (95% CI)
Catheter use	57%	1.52 (1.37-1.71)	22% (17-27%)
Albumin < 3.5 g/dL	51%	1.51 (1.35-1.68)	19% (14-24%)
Creatinine < 6 mg/dL	43%	1.32 (1.18-1.48)	12% (7-16%)
Lack of pre-ESRD care	26%	1.38 (1.24-1.56)	9% (6-12%)
No residual urine volume	32%	1.32 (1.18-1.50)	9% (5-12%)
SBP > 160 mm Hg	27%	0.87 (0.78-0.99)	8% (4-12%)
SBP < 130 mm Hg	23%	1.51 (1.35-1.70)	
Phosphorus > 5.5 mg/dL	39%	1.20 (1.06-1.36)	7% (2-11%)
Phosphorus < 3.5 mg/dL	13%	1.12 (0.96-1.31)	
Hemoglobin > 12 g/dL	9%	1.04 (0.87-1.27)	6% (1-11%)
Hemoglobin < 10 g/dL	50%	1.14 (1.02-1.29)	
WBC count > 10,000/µL	19%	1.30 (1.17-1.46)	5% (3-8%)
Ferritin > 800 ng/mL	8%	1.35 (1.14-1.63)	2% (1-4%)
Calcium > 9.5 mg/dL	13%	1.09 (0.92-1.27)	< 0%
Calcium < 8.4 mg/dL	38%	0.96 (0.86-1.08)	
PTH > 300 pg/mL	39%	0.88 (0.76-1.01)	< 0%
PTH < 150 pg/mL	33%	0.92 (0.77-1.04)	
All risk factors			65% (59-71%)

Cox model stratified by DOPPS phase and country, adjusted for all risk factors, plus age, gender, black race, BMI, and 12 comorbidities

FR-PO802

Poor Immune Response to Influenza Vaccine Is Associated with Increased Mortality in Hemodialysis Patients

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Background: Immune response reflects an individual's immune status. Hemodialysis (HD) and renal transplantation (TX) are associated with the state of immune dysfunction. The aim of our study was to assess natural levels of pneumococcal IgG (pne-IgG, patients unvaccinated against pneumococcus) and hemagglutination-inhibition antibodies (HIA, post influenza vaccine) in HD and TX patients. We tried to determine the factors influencing the immune status and the relationship of the immune response to mortality.

Methods: A total of 99 HD and 64 TX patients who have never received a pneumococcal vaccine were vaccinated against influenza in seasons 2015/16 and 2016/17. Their pne-IgG, pre- and post-vaccine HIA titre, iron status, C-reactive protein (CRP), albumin and 25-OH vitamin D were measured at baseline and after one year. Total follow-up was 30 months. To identify variables associated with mortality, univariate Cox regression analyses were performed with mortality as a dependent variable, and age, gender and the above mentioned markers as predictors. Markers with $p<0.1$ (post-vaccine rise in HIA, CRP, albumin, age) were subsequently included into a multivariate Cox regression model.

Results: Pneumococcal IgG levels and percentage of seroprotective HIA were comparable in HD and TX groups and between the two consecutive years (Table 1). Mortality was higher in the HD, in which 30 patients died, while only one death was recorded in TX. According to the multivariate Cox regression model (adjusted R^2 0.246, $p<0.0001$), the predictors of death were low postvaccination HIA titre ($p=0.019$), and high CRP ($p=0.003$).

Conclusions: The immune response to the influenza vaccine and the natural production of pne-IgG are comparable in HD and TX patients. Besides dependence on HD, significant independent predictors of mortality in HD population are low antibody response to influenza vaccine and high CRP.

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	HD 2015/16	HD 2016/17	TX 2015/16	TX 2016/17
Pneumococcal IgG (mg/L)	72 (43-125)	62 (35-108)	54 (34-88)	66 (32-104)
A H1N1 SPpost (%)	93	89	91	80
A H3N2 SPpost (%)	82	88	83	77
B SPpost (%)	91	68	87	75

Data are medians (interquartile ranges), unless stated otherwise; Mann-Whitney and $\chi 2$ test; A H1N1, A H3N2, B are influenza virus strains, SPpost is post-vaccine seroprotection rate; differences among groups were not statistically significant.

FR-PO803

Association of Fruit and Vegetable Intake with All-Cause Mortality in Hemodialysis Patients (DIET-HD): A Prospective Cohort Study

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Background: Higher fruit and vegetable intake is associated with lower vascular and all-cause mortality for the general population. However, whether fruit and vegetable consumption benefits patients treated with haemodialysis is uncertain. We evaluated the association of fruit and vegetable intake with mortality outcomes in adults on hemodialysis.

Methods: The DIET-HD study was a prospective cohort study involving 9757 adults treated with hemodialysis. Fruit and vegetable intake was measured using the GA²LEN food frequency questionnaire. Cox regression analyses adjusted for sociodemographic and clinical variables and clustered by country were conducted.

Results: During a median follow up of 2.7 years (18,666 person-years), there were 2087 deaths, of which 958 were vascular deaths. Overall, higher combined intake of fruit and vegetables was associated with lower risks of non-vascular and all-cause mortality. The risk for vascular mortality was lower with the highest tertile of intake although the 95% confidence interval included the possibility of a null effect. With reference to the lowest tertile of intake (0 to 5.5 servings per week), the adjusted hazards ratios (95% confidence interval) for the middle (5.6 to 10 servings per week) and highest (>10 servings per week) tertiles were 0.88 (0.76-1.02) and 0.77 (0.66-0.91) for non-vascular mortality; 0.90 (0.81-1.00) and 0.80 (0.71-0.91) for all-cause mortality ; and 0.95 (0.81-1.11) and 0.84 (0.70-1.00) for vascular mortality.

Conclusions: Higher consumption of fruit and vegetables is associated with lower risk of mortality in hemodialysis patients.

FR-PO804

Variability of Pre-Dialysis Serum Sodium, a Risk Factor of Survival in Hemodialysis Patients: Results from the Global MONDO Initiative

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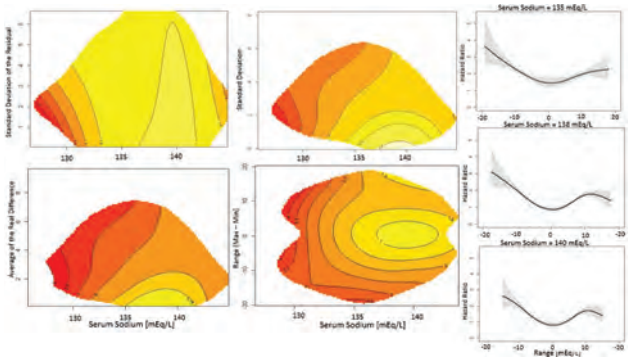
Background: Variability of laboratory parameters and serum sodium (SNa) observed to associated with adverse physical conditions in chronic hemodialysis (HD) patients (pts) [Nakazato Y et al]. SNa, the main determinant of plasma osmolality, play a key role in fluid shifts between the extra-& intracellular compartments. Variability SNa, denoted as the measured-to-measured variation, affects the stability of cell volume.

Methods: All adult incident pts with more than 5 SNas during the first year on HD were included, outcomes were recorded over a 2 yrs period. Average baseline SNa as well as variabilities were computed by standard deviation (SD) of the residual, SD, relative range (the difference between the largest and smallest), average real variability (ARV). Cox proportional models with bivariate spline functions were applied to study the joint effects of SD of residual, SD, ARV and relative range of SNa, respectively. Cox proportional models with multiple adjustments were also used to further evaluate the adverse effect of SNa variability.

Results: Out of 30,174 pts (EU:15,660, Asia:8,749,US:2,691,UK:2,282, South America:791) were included, 7,021 (23.3%) died. Hyponatremia (SNa<=135) was the most prominent predictor of increase mortality. For pts with SNa>135, we didn't observe an association between SD residual and mortality. Increased risk of death with higher SD and ARV appeared to be present at all levels of SNa. A more pronounced effect of relative range

was observed compared to SD and ARV. More significant effect was observed with the maximal SNa happened before the minimal SNa [Figure 1]. Cox proportional model with adjustments also yield the same results.

Conclusions: Given the positive association between mortality and hiher SNa range,S, ARV regardless of the SNa level, these measures constitute novel prognostic indicators in HD therapy.



FR-PO805

Incidence and Mortality of Cancers Among ESRD Patients Receiving Hemodialysis or Peritoneal Dialysis: A National Cohort Study in Korea

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Background: Patients with end-stage renal disease (ESRD) have a higher-than-normal cancer risk. However, the incidence and mortality of cancers in ESRD patients receiving hemodialysis (HD) or peritoneal dialysis (PD) have been rarely studied for Korean populations.

Methods: We analysed data from the National Health Insurance Service (NHIS) of Korea to identify the incidence and mortality of cancers in ESRD patients receiving HD or PD. The study population was all ESRD patients starting maintenance dialysis between 2006 and 2014. They were followed from initiation of dialysis until death, discontinuation of dialysis, or the end of 2015. Cox proportional hazard regression models was used to identify the risk factors for cancer in ESRD patients.

Results: Of 17,140 ESRD patients, 4,258 (24.8%) had been newly diagnosed with cancer. The incidence of any cancer was higher for certain subgroups: older age, DM, hypertension, stroke, and coronary artery disease. In age-, gender-, and 1:2 propensity score-matched general population, 24.7% had been newly diagnosed with cancer. Rate of cancer in HD patients was 1.06 times higher than in the general population (95% CI 1.025-1.110, p=0.0014), while PD patients did not differ from general population (HR 0.897, 95% CI 0.765-1.051, p=0.1782). There were no significant differences in rates of cancer (HD vs. PD, 24.9% vs. 21.7%), the time from start dialysis to diagnosis of cancer (HD vs. PD, 4.49±3.00 vs. 3.68±2.92 years), and mean age at diagnosis of cancer (HD vs. PD, 64.44±12.14 vs. 60.23±13.20 years) between patients on HD and PD. Figure-1 showed the overall survival curves of cancers after newly diagnosed in ESRD patients and general populations.

Conclusions: These results suggested that the frequency of cancer is higher in ESRD patients on HD, not PD, than in the Korean general population.

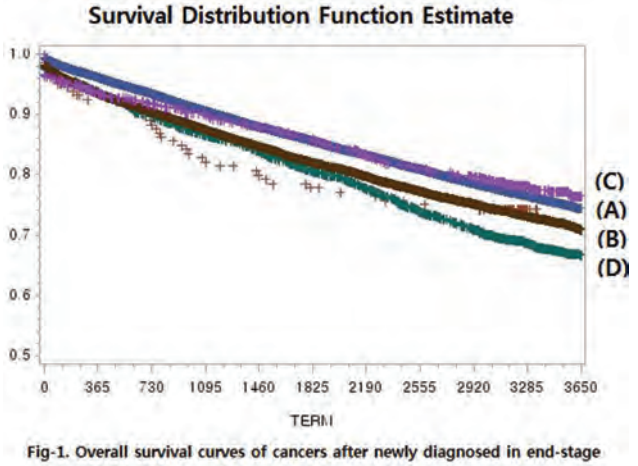

Fig-1. Overall survival curves of cancers after newly diagnosed in end-stage renal disease patients and general populations. (A) General population, (B) Hemodialysis, (C) Peritoneal dialysis, (D) Switched modality group

FR-PO806

Effects of the Specific Oriented Care in Hemodialysis Incident Patients (SOCHIP) Program on Key Performance Indicators and Early Mortality

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Background: An increased risk of early mortality exists for patients (pts) starting chronic hemodialysis (HD) therapy. In the French NephroCare (NC) centers a Specific Oriented Care for HD Incident Patients (SOCHIP) program has been implemented.

Methods: The SOCHIP program started in October 2015. One nurse was in charge to recover monthly the Key Performance Indicators (KPIs) for all incident HD pts during the first 4 months. The prescriptions of pts out of target were reviewed monthly. We have retrospectively calculated monthly the % of pts in target before and after the implementation of the SOCHIP program.

Results: Respectively, 816 (SOCHIP-) and 666 (SOCHIP+) pts have been analyzed (age:68,4 and 68,7 yo; % females: 35 and 31,3; Charlson Index:5,1 and 5,2). At M4 the % of pts in target has been significantly increased for effective treatment time (≥720 minutes/week; 33 versus 43%, p=0,0007), the processed blood volume (240 liters/week; 20,0 versus (vs) 43,8%, p<0,0001), KT/V (≥1.4; 37,5 vs 56,4%, p<0,0001) the HyS (<13% (females) and <15% (males); 38,7 vs 65,9%, p<0,0001), the hemodynamic status (BCM® + predialysis systolic blood pressure <160 mmHg; 53,2 vs 65,7%, p<0,0001), albuminemia (≥35g/l; 51,6 vs 59,4, p=0,094). There was no significant changes of the % of patients in target for the vascular access (AV fistula; 54,0 vs 49,2%), hepatitis-B protection (Ac antiHbs+ or complete immunization record in E5; 96,7 vs 98,0%), Hemoglobine (≥10g/dl ou between 10 et 12g/dl if EPO; 52,8 vs 54,8%) and mid-week phosphatemia (<1,65 mmoles/l or >0,75 mmoles/l if Pi-binders prescription; 67,9 vs 69,4%). The crude mortality has significantly decreased from 30,1 to 22,4 for 100 patient/years p=0.0002).

Conclusions: These data show that the SOCHIP program has allowed to improve the % of pts in target for 6 out of 10 usual KPIs. The KPIs improvement parallels the improvement of the early mortality. Other parameters included in the SOCHIP program have not been evaluated (early access to cardiologist and diabetologist). Moreover, the significant increase of pts in target for albuminemia suggests that the early access to the dietitian has been improved by the SOCHIP program. We can conclude that a specific program for incident HD patient improves the % of pts in target of most of the KPIs and may improve the early mortality in this setting.

FR-PO807

Estimated Glomerular Filtration Rate (eGFR) at Initiation of Hemodialysis and Long Term Mortality

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Background: The results of the Initiating Dialysis Early and Late (IDEAL) study suggested that patients with stage V CKD, randomized to late initiation of Hemodialysis (HD) had similar mortality to those who started early. However, more than 3/4th of patients assigned to the late arm received dialysis earlier than planned. Moreover, IDEAL study population was very different from that of the United States and had close nephrology followup. We used a propensity score based analysis of the USRDS database to examine how the eGFR at the time of initiation of dialysis affects total and cardiovascular (CV) mortality in the US population in a real word setting.

Methods: Patients ≥18 years old who initiated in-center HD between 2006 and 2014 were included. 676,196 patients were categorized based on the tertiles of MDRD eGFR levels prior to initiation of HD, into late (eGFR <8.7), intermediate (eGFR 8.7 to <13.0) and ≥ and early start (eGFR >13.0 ml/min) groups. Associations between eGFR groups and 10-year all-cause and CV mortality were assessed using KM curves and multivariable Cox proportional hazards models with propensity-score weighted regression.

Results: Mean age was 64±15 years. Elderly, Caucasians, males and those with diabetes or heart failure were more likely to be initiated on HD early. Compared to the late start group, the intermediate and early start had a 42% and 93% increased risk of 10-year all-cause mortality, respectively (HR=1.42; 95%CI: 1.41-1.43 and HR=1.93; 95%CI: 1.91-1.94 respectively). This association was attenuated, but remained significant when adjusted for multiple covariates (adjusted HR=1.13; 95%CI:1.12-1.14 for intermediate and HR=1.37; 95%CI: 1.36-1.39, for early start respectively). The 10-year CV mortality was similarly increased with early dialysis (adjusted HR=1.13; 95%CI: 1.12-1.15 and HR=1.40; 95%CI: 1.38-1.42, for late and early start respectively). This association was robust and consistent across multiple sub-groups and sensitivity analyses.

Conclusions: Our results demonstrate that early initiation of dialysis is associated with increased toal and cardiovascular mortality. This increased mortality is not completely accounted for by co-morbidities in the early initiation group. The mechanistic basis of these observation requires further study.

Funding: Other NIH Support - Rajesh Mohandas K08HL130945

FR-PO808

Planned Initiation of Hemodialysis Alleviates the Survival Disadvantage of Hemodialysis over Peritoneal Dialysis

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Background: Since the discovery of initial survival disadvantage of hemodialysis (HD) over peritoneal dialysis (PD), selection bias has been questioned when making this comparison. To minimize the bias, patients with planned initiation of HD have previously been chosen for comparison, but the results were inconclusive. Here, with a different definition for planned initiation, we tested the hypothesis that the dialysis modality had no effect on the one-year mortality rate in incident dialysis patients.

Methods: A total of 45,825 incident dialysis patients with maintenance dialysis for more than 3 months in Taiwan between 2007 and 2011 were enrolled. Planned initiation of HD was defined as the initiation of HD through peripheral vascular access at an outpatient clinic (planned-HD), and the one-year mortality rate was compared between HD and PD groups in cohorts by planned initiation of HD and propensity score matching using Cox model.

Results: In all, 39,635(age 64±14y, F:48%, DM:60%), 9,184(age 65±13y, F:46%, DM:57%), and 6,190(age 55±15y, F:51%, DM:44%) incident dialysis patients were enrolled in HD, planned-HD, and PD groups, respectively. During the observation period, the death was reported for 4,453, 812, and 342 patients, respectively. HD group had a higher one-year mortality rate than PD group after either adjusting the baseline clinical characteristics (age, sex, socioeconomic status, urbanization, hypertension, diabetes, cardiac disorder, ischemia stroke, gout, peripheral vascular diseases, and Charlson score) [adjusted hazards ratio (95% confidence interval) 1.17 (1.04–1.30)] or propensity score matching [1.23 (1.07–1.42)]. However, this survival disadvantage disappeared when the planned-HD group was compared with the PD group after either adjusting the baseline clinical characteristics [0.96 (0.85–1.10)] or propensity score matching [0.99 (0.85–1.16)].

Conclusions: The initial survival disadvantage of HD over PD can be alleviated by planned initiation of HD in the dialysis population in Taiwan.

Funding: Government Support - Non-U.S.

FR-PO809

Serum Globulin and All-Cause Mortality in Hemodialysis Patients

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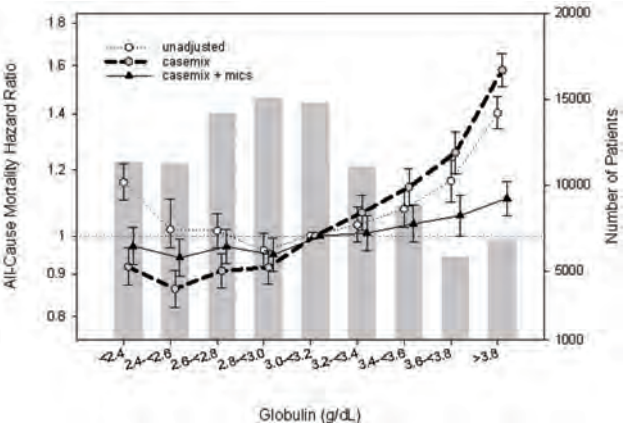
Background: Nutritional status and inflammation are significant markers for mortality and morbidity, especially in hemodialysis patients. While there is much evidence to support the association between albumin levels and nutritional status and inflammation, less is known about the associations between globulin levels and mortality risk in hemodialysis patients.

Methods: We retrospectively examined a cohort of 104,164 incident hemodialysis patients treated by a large dialysis organization from 2007 to 2011 whose first patient quarter (dialysis start + 91 days) globulin measurements were obtained during treatment. Patients were grouped into 9 globulin categories. Using Cox models, we explored the association between serum globulin levels and all-cause mortality from the time of dialysis initiation with adjustments for case-mix variables and laboratory markers of malnutrition inflammation complex syndrome (MICS), including albumin.

Results: Mean patient age was 63±15 years; 44% were female, 31% were African American, and 58% were diabetic. Mean globulin level was 1.16±0.31 g/dL. Compared to the reference group of 3.0-<3.2 g/dL, patients with lower globulin (<2.8 g/dL) and higher globulin (≥3.8 g/dL) had higher mortality risk in the unadjusted model. After case-mix adjustment, compared to the referent, patients with lower globulin had lower mortality risk while higher globulin still had higher mortality risk. After adjustment for MICS covariates, the associations were attenuated; however, patients with globulin >3.8 g/dL still had a higher mortality risk compared to the referent [figure1].

Conclusions: Among incident hemodialysis patients, higher globulin level is associated with higher mortality risk, independent of other markers of malnutrition and inflammation, including albumin.

Funding: NIDDK Support



FR-PO810

Comparison of All-Cause Mortality Between Maintenance Dialysis and Cancer Patients

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Background: Mortality risk is high in dialysis patients. Yet, the mortality risk in dialysis compared to other diseases like cancer is poorly understood. We conducted a population-based cohort study using healthcare databases from Ontario, Canada, to examine survival probabilities for all-cause mortality in maintenance dialysis patients compared to patients with common cancers (women: breast, colorectal, lung, or pancreas; men: prostate, colorectal, lung, or pancreas) from 1997 to 2015.

Methods: We used the Kaplan-Meier product limit estimator to determine the cumulative probability of survival for all-cause mortality. Additional analyses examined the risk of mortality adjusting for clinical characteristics and trends in survival probability using Cox proportional hazards regression.

Results: 33,500 maintenance dialysis patients and 532,452 cancer patients (median follow-up 4.4 years). In males, dialysis had worse 5-year survival (50.8%, 95% confidence interval [CI]: 50.1, 51.6%) compared to prostate (83.3%, 95% CI: 83.1, 83.5%) and colorectal cancer (56.1%, 95% CI: 55.7, 56.5%) but better survival than lung (14.0%, 95% CI: 13.7, 14.3%) and pancreas cancer (9.1%, 95% CI: 8.5, 9.7%). In females, dialysis had worse 5-year survival (49.8%, 95% CI: 48.9, 50.7%) compared to breast (82.1%, 95% CI: 81.9, 82.4%) and colorectal cancer (56.8%, 95% CI: 56.3, 57.2%) but better survival than lung (19.7%, 95% CI: 19.4, 20.1%) and pancreas cancer (9.4%, 95% CI: 8.9, 10.0%). After adjusting for clinical characteristics, similar results were found. Survival significantly improved across eras (1997-2001, 2002-2006, 2007-2011, 2012-2015) for all cancer types ($P<0.01$) but no significant change was observed in dialysis patients (females, $P=0.89$; males, $P=0.48$) (**Figure**).

Conclusions: Survival in dialysis patients was lower than patients with several types of common cancers. Unlike cancer patients, the prognosis of patients on dialysis has not improved over time. Results highlight the need to develop and test interventions to improve survival in maintenance dialysis patients.

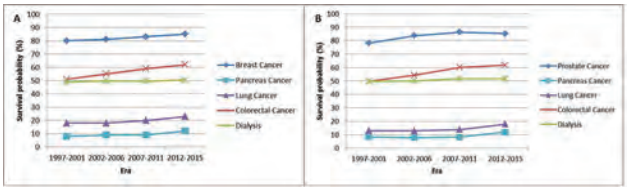

Figure. 5-year survival probabilities for all-cause mortality by era of cohort entry for women (A) and men (B)

FR-PO811

A Simple Vitality Question, Its Correlates, and Clinical Outcomes in Patients Receiving Hemodialysis: The Japanese Dialysis Outcomes and Practice Pattern Study

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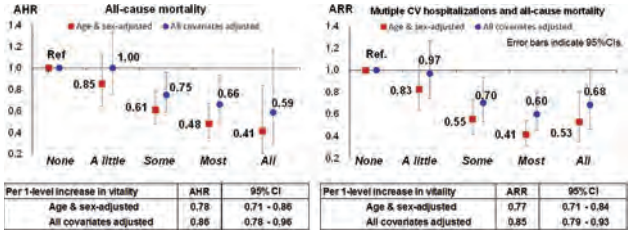
Background: The lack of an assessment of vitality in daily practice may be partially due to inadequate understanding of lack of vitality and the lack of a concise method of assessing it. The aim of this study was to examine the predictability of a simple 1-item vitality question and its correlates.

Methods: This was a cohort study involving hemodialysis patients who participated in the Japan Dialysis Outcomes and Practice Pattern Study (phase 3 to 4 [2005–2011]). Predictor was one-item vitality measured via the 12-item Medical Outcomes Study Short Form survey version 2.0, using a 5-level Likert scale. Outcomes were all-cause mortality and a composite of multiple cardiovascular hospitalization and all-cause mortality. A pooled ordered logit model was fitted to examine correlates of 1-item vitality. Cox and mixed-effects Poisson regression models were fitted for mortality and composite outcomes, respectively.

Results: 3,667 patients were analyzed. Decrease in vitality category was associated with tachycardia (≥ 100 vs. 60 to < 70 beats/min) and benzodiazepine, hypnotics, or antidepressant use. In contrast, increase in vitality was associated with increase in single-pool Kt/V, serum albumin, and BMI. Compared with the lowest vitality category, the second highest and middle categories were negatively associated with all-cause mortality (Figure; adjusted hazard ratio [AHR] 0.66, 95% confidence interval [95% CI] 0.47–0.93 and AHR 0.75, 95% CI 0.59–0.96, respectively). A one-category increase in vitality was consistently associated with lower mortality (AHR 0.86, 95% CI 0.78–0.96). The associations between 1-item vitality and multiple cardiovascular hospitalization and mortality were similar to those between vitality and mortality.

Conclusions: 1-item vitality predicted all-cause mortality and a composite of multiple cardiovascular hospitalization and all-cause mortality, and correlates with some modifiable factors, including vital signs. Dialysis staff should consider asking this simple question in daily practice to improve patient quality of life and outcomes.

Funding: Commercial Support - Kyowa Hakko Kirin



Per 1-level increase in vitality	AHR	95% CI
Age & sex-adjusted	0.78	0.71 - 0.86
All covariates adjusted	0.86	0.78 - 0.96

Per 1-level increase in vitality	ARR	95% CI
Age & sex-adjusted	0.77	0.71 - 0.84
All covariates adjusted	0.85	0.79 - 0.93

FR-PO812

Epilepsy and All-Cause Mortality Among ESRD Patients in the US Renal Data System, 2013-2014

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Background: Despite the long-appreciated association of seizures with uremia, there are few national data regarding the prevalence and outcomes of ESRD patients with epilepsy compared to those without epilepsy.

Methods: We assessed claims-based diagnoses of epilepsy, baseline characteristics, anticonvulsant drug prescriptions and outcomes by comparing ESRD patients with and without epilepsy in the USRDS. Study population comprised of prevalent US ESRD patients with continuous Medicare Part A, B, and D coverage from Jan. 1, 2013 to Dec. 31, 2014. Epilepsy was defined as one claim with an International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) code for *epilepsy* or two claims with ICD-9-CM codes for *seizures* at least 30 days apart from Jan. 1, 2013 to Dec. 31, 2014. The outcome was all-cause mortality from Jan. 1, 2015 to July 31, 2016. We used modified Poisson regression with a robust variance estimator to estimate risk ratios and 95% confidence intervals for the association between epilepsy status and mortality. Final models were adjusted for sociodemographics, ESRD treatment history, and comorbidities.

Results: Of 195,319 ESRD patients in the cohort, 15,233 patients (7.8%) were classified as having epilepsy. Of ESRD patients with a claims-based diagnosis of epilepsy, 80.4% filled an anticonvulsant or hydantoin prescription compared to 31.6% of patients without epilepsy. 19 anticonvulsant medications were prescribed. Levetiracetam and Phenytoin were the most commonly prescribed anticonvulsant drugs without another indication such as pain. 20.1% of patients died during the 19-month follow-up period: 27.9% of patients with epilepsy and 19.4% of patients without epilepsy (p <0.0001). After adjustment for confounders, the estimated mortality risk among those with epilepsy was 1.14 (95% CI: 1.11, 1.18) times that among those without epilepsy.

Conclusions: ESRD patients have a high prevalence of epilepsy and many are treated with anti-convulsant drugs such as Levetiracetam and Phenytoin. ESRD patients with epilepsy had an increased risk of death compared to those without epilepsy. Given the high epilepsy prevalence among the ESRD population, continued efforts are needed to identify appropriate treatment/medication selection and to prevent premature mortality among ESRD patients with epilepsy.

Funding: NIDDK Support

FR-PO813

All-Cause Mortality in Relation to Intradialytic Relative Blood Volume and Central-Venous Oxygen Saturation Among Hemodialysis Patients

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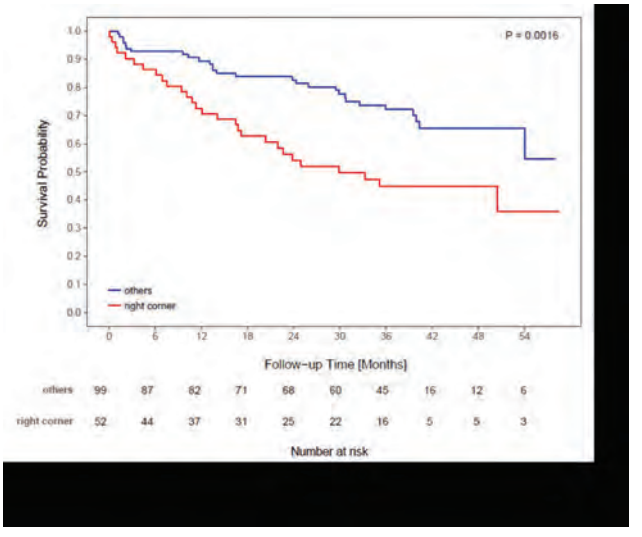
Background: Relative blood volume (RBV) and central venous oxygen saturation ($ScvO_2$) monitoring is increasingly adopted. We previously identified that at higher $ScvO_2$ levels, that RBV had only a small effect on mortality risk, whereas at lower $ScvO_2$ levels, RBV tends to drive mortality risk. In this study, we further explored the association between RBV and $ScvO_2$ values on all-cause mortality.

Methods: This is a retrospective multicenter cohort study of HD patients with central-venous catheter (CVC) as vascular access from 17 Renal Research Institute clinics from January 2012 to June 2017 where the Crit-Line® Monitor (CLM) is used. The CLM allows for monitoring of extracorporeal hematocrit (Hct) and $ScvO_2$. The patients were stratified into 2 groups depending on their RBV and $ScvO_2$ at 3 hours (mean values between minutes 170 and 190) into HD.

Results: We included 151 patients with a total of 3,937 HD treatments. The median follow-up time was 2.8 years. The patients were stratified into 2 groups, 52 patients with their RBV larger than 91.74% and $ScvO_2$ lower than 56.72% at 3 hours into HD were labeled right corner patients (based on the position from our last study [1]). The results indicate a significantly increased mortality in patients with lower $ScvO_2$ and higher RBV levels compared to others (Figure 1 KM plot). Multivariate Cox analysis with different levels of adjustments corroborated the higher hazards ratios for all-cause mortality in these patients.

Conclusions: We found that patients with lower $ScvO_2$ and higher RBV levels had higher mortality. These findings may be related to patients' volume status and cardiac function. **References** Hanjie Zhang et. al. Association of intradialytic relative blood volume and central-venous oxygen saturation with mortality among hemodialysis patients. ERA EDTA 2018 abstract.

Funding: Commercial Support - Fresenius medical care north america



FR-PO814

Association Between Reduction of Extracellular Volume by In-Center Short Daily Hemodialysis and Survival

Ana Beatriz L. Barra,[1] Ana P. Silva,[1] Eufronio D'almeida,[1] Marcos Sandro F. Vasconcelos,[1] Jorge P. Strogoff-de-Matos.[2] *[1]Fresenius Medical Care, Rio de Janeiro, Brazil; [2]Universidade Federal Fluminense, Niteroi, Brazil.*

Background: Overhydration (OH) is associated with a higher mortality risk in maintenance hemodialysis. A better management of OH through daily hemodialysis (DHD) could improve survival.

Methods: Retrospective analysis of patients on hemodialysis 3 sessions/week for >3 months who shifted to in-center short DHD (≥ 5 sessions / week) between 2012 and 2016 at 23 dialysis units in Brazil. Hydration status was evaluated before and 6 months after initiating DHD by bioimpedance spectroscopy. Pre-dialysis hydration state was considered adequate when OH ≤15% of extracellular volume. For survival analysis, data were censored 2 years after initiating DHD.

Results: A total of 208 patients were included in the analysis (56±16 years old, 64% males, 38% diabetics, 56% on dialysis 6 sessions/week, treatment time was 12.5±1.8 h/week. After 6 months on DHD, 177 patients were re-evaluated. OH was reduced from 13.9% (IQR 5.4 – 22.3%) to 8.9% (IQR 0.4 – 15.9%), P<0.0001, the rate of patients with OH>15% dropped from 47% to 29% (P= 0.0005) and pre-dialysis systolic blood pressure fell from 139±21 mmHg to 134±21 mmHg (P= 0.029). The 2-year survival rate was 76%, with no difference according to the OH status before DHD initiation (P= 0.92). However, survival was higher for patients reached OH ≤15% after the beginning of DHD than those with OH >15% (83% vs. 70%; P= 0.02). In a Cox regression model, after adjustment for

demographic, clinical and laboratory variables, OH ≤15% persisted associated with a lower mortality risk (hazard ratio 0.40 [95% confidence interval 0.18 – 0.90]).

Conclusions: Moving from standard hemodialysis to short DHD was associated with a better control of excessive extracellular volume and blood pressure. Patients who reached OH ≤15% after initiating DHD presented a lower risk of death.

FR-PO815

Weight loss Increases Risk of Cardiovascular Events and Mortality in Incident Dialysis Patients

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Background: Protein-energy wasting is a common and established risk of cardiovascular events and mortality in dialysis patients, while obesity is associated with a greater survival as well known "reverse epidemiology". Recent study suggested that short-term weight loss was more associated with worse outcome. Here we explored if weight loss just before initiation of dialysis could predict CVD events and mortality among incident dialysis patients.

Methods: In an ongoing prospective cohort study, 175 incident Japanese dialysis patients (113 males, age 59 ±11 years) were enrolled and followed for a median of 55.2 months (range 1-112 months). Laboratory biomarkers were determined at baseline. We defined [dry weight of the first month of start dialysis therapy] – [body weight at 6 months before start dialysis therapy] as the delta body weight (DBW), patients with over 5kg weight loss during this term as weight loss and patients with under 5kg weight loss or weight gain as stable weight, respectively.

Results: In Spearman rank test, DBW negatively correlated with body weight (rho=-0.15, P=0.042), abdominal circumference (rho=-0.21, P=0.007), serum CRP (rho=-0.17, P=0.032) and cardiothoracic ratio (rho=-0.20, P=0.013), while there was no correlation between DBW and body mass index (BMI). In Kaplan-Meier curves, the CVD death was associated with weight loss (Log rank 5.91, P = 0.015). And the duration from start of dialysis therapy to the first CVD events was significantly shorter in patients with weight loss (Log rank 10.74, P = 0.001). In Cox hazard model, after adjustments for age, gender, and BMI, the weight loss had a significantly increased relative risk of CVD deaths (2.89, 95% CI; 1.05-9.22, P = 0.0385).

Conclusions: In Japanese incident dialysis patients, short-term weight loss just before initiation dialysis therapy associated with increased risk of CVD deaths and events. These results may suggest that we should pay attention to lean losing weight rather than physical status.

FR-PO816

Association of White Blood Cell Count with Survival in Incident Hemodialysis Patients

Tiffany Zai,[1] Christina Park,[1] Jui-Ting Hsiung,[1] Melissa Soohoo,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh,[1] Elani Streja.[1] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

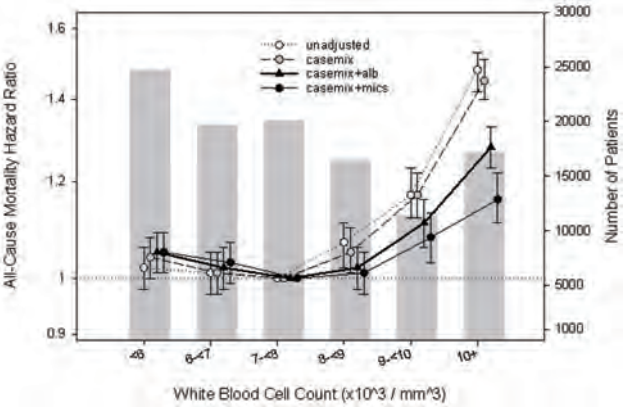
Background: Higher white blood cell counts (WBC) have been shown to be strongly and independently associated with all-cause mortality in maintenance hemodialysis (HD) and incident peritoneal dialysis patients; however, the association between WBC count and mortality in incident HD patients has been understudied.

Methods: We retrospectively examined a cohort of 109,767 incident HD patients receiving treatment within a large dialysis organization from 2007-2011, with available WBC measurements during the first 91-days of dialysis. Patients were grouped into 6 WBC categories. Using Cox models, we examined the association between WBC count and all-cause mortality with hierarchical adjustments for case-mix variables, albumin and additional laboratory markers of malnutrition and inflammation (MICS).

Results: Mean patient age of the cohort was 63±15 years; 44% of patients were female, 32% were African American, and 58% were diabetic. Mean WBC count was 7.82±2.68 $x10^3/mm^3$. Compared to the reference group of WBC 7.0-<8.0 $x10^3/mm^3$, we observed a J-shaped association between WBC and mortality. Patients with low WBC (<6.0 $x10^3/mm^3$) had a higher risk of mortality (hazard ratio (HR): 1.04 [95% CI: 1.00, 1.08]), and patients with greater WBC (>9.0 $x10^3/mm^3$) had the highest risks of mortality in case-mix adjusted models. After further adjustment for albumin and MICS covariates, associations were modestly attenuated; however, patients with WBC >9.0 $x10^3/mm^3$ still had a higher mortality risk compared to the referent [figure1].

Conclusions: Among incident HD patients, higher WBC count is associated with higher mortality risk, independent of other markers of malnutrition and inflammation, including albumin. These data suggest that WBC count may need closer monitoring in patients who are new to dialysis, but further studies are needed to examine this relationship.

Funding: NIDDK Support



FR-PO817

Intradialytic Relative Blood Volume Changes and All-Cause Mortality Among Hemodialysis Patients

Priscila Preciado,[1] Hanjie Zhang,[1] Stephan Thijssen,[1] Jeroen Kooman,[2] Frank van der Sande,[2] Peter Kotanko.[1] *[1]Renal Research Institute, New York, NY; [2]Maastricht University Medical Centre, Maastricht, Netherlands.*

Background: Adequate volume control is a major challenge in hemodialysis (HD) patients, as both fluid overload and depletion are associated with increased mortality. Ultrafiltration is the only means for fluid removal in anephric patients. Whenever the ultrafiltration rate (UFR) exceeds the plasma refilling rate, the blood volume declines and hypotension may ensue. Relative blood volume (RBV) monitoring during HD is used as a means to tailor UFR. Our goal was to explore the association between intradialytic RBV levels and all-cause mortality in maintenance HD patients

Methods: We conducted a retrospective analysis of data from HD patients dialyzed in 17 Renal Research Institute clinics between 1/2012 and 12/2016. A 6-months baseline period preceded a follow-up. Censoring events were change in treatment modality, transfer to another clinic, and study end. RBV was measured using the Critline monitor. RBV was assessed after 25%, 50%, 75% and 100% of the elapsed treatment time. The relationship between mortality and RBV at these four time points was analyzed using Cox proportional hazards models with spline terms

Results: We studied 842 patients with a total of 28,119 HD treatments (mean age 61.0±14.8 years, 50% whites, 62% males, 56% had diabetes mellitus, 22% had congestive heart failure). Median follow-up time was 30.8 months. The mortality rate was 11.5/100 patient years. We identified specific intradialytic RBV levels after 25%, 50%, 75% and 100% of the elapsed dialysis treatment time that were associated with a significantly lower all-cause mortality **[Fig 1].**

Conclusions: We showed in a large cohort of HD patients that specific RBV levels are associated with better outcomes. These findings corroborate the notion that RBV monitoring has the potential to improve outcomes. Prospective studies are warranted to explore if active attainment of these RBV levels translates into improved patient outcomes.

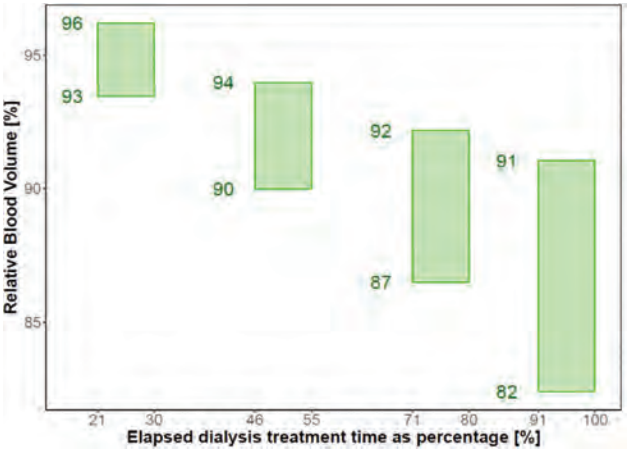


Fig 1. Intradialytic RBV ranges associated with hazard ratios significantly below 1.0 for all-cause mortality.

FR-PO818

Synergic Impact of BMI, Diabetes, and Age on Long-Term Mortality in Incident Japanese Hemodialysis Patients: A Cohort Study of the Large National Dialysis Registry

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Background: In general Japanese with diabetes, leanness has been associated with an increased risk of all-cause mortality. However, it currently remains unclear whether BMI and age influence the prognosis of diabetic patients who start hemodialysis.

Methods: Study design: Cohort study. Participants: Data from the national dialysis registry in 2007, including 35,415 patients on incident hemodialysis and 6,061 patients aged ≥20 years with BMI data. Predictor: Patients were divided into 6 categories according to baseline BMI levels (Leanness: <18.5, Normal: 18.5-25, Obesity: ≥25) and the presence or absence of diabetes. Outcomes: All-cause mortality during a 5-year follow-up. Measurements: Hazard ratios were estimated using Cox's model for the relationships between diabetes, BMI categories, and all-cause mortality, and adjusted for potential confounders including sex, age, systolic BP values, a previous history of cardiovascular disease, and so on. Patients with normal BMI levels without diabetes were set as our reference category. We also examined the effects of age on these relationships.

Results: Among 3239 and 2822 patients with or without diabetes, 993 and 887 patients died of all-cause mortality, respectively. Cox's regression analysis showed that leanness, but not obesity, was independently associated with an increased risk of all-cause death in patients with and without diabetes. When patients were divided into two groups: younger and older than 60 years, the risk of all-cause death in the younger group was markedly increased among lean diabetic patients as well as among those with a normal BMI and diabetes, but not obesity. However, in the older group, the risk of death among diabetic patients with a normal BMI was not significantly different from that among those without diabetes. In diabetic patients of the older group, only leanness was associated with an increased risk of mortality.

Conclusions: Among incident Japanese hemodialysis patients, leanness, but not obesity, increases the risk of all-cause mortality. Particular attention must be paid to the markedly high mortality rate in lean diabetic patients regardless of age. Furthermore, diabetes may be associated with mortality in patients younger than 60 years with a normal BMI.

FR-PO819

A Higher Mortality Rate in Afebrile Bacteremia in Chronic Hemodialysis Patients

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Background: Body temperature (BT) has received little attention as a prognostic factor in hemodialysis patients. Some previous studies reported that fever in initial bacteremia is associated with better survival. Therefore, we aimed to analyze the difference in hospital mortality between febrile and afebrile chronic hemodialysis (CHD) patients with bacteremia and investigated positive blood culture rate according to the C-reactive protein (CRP) level.

Methods: The blood culture data in CHD patients from 2006 to 2014 were collected and the bacteremic events were assigned to either "febrile group" or "afebrile group" based on the BT measured on the day of blood culture. Fever was defined as a tympanic temperature > 37.5 degrees Celsius or an axillary temperature > 37.0 degrees Celsius. Empirical antibiotics were administered immediately after blood culture. Laboratory values were considered only for the day of blood culture sampling. The primary outcome was in-hospital mortality rate, the length of ICU stay and the length of hospitalization.

Results: From a total of 1556 blood cultures, 190 bacteremias were identified excluding cases of immunosuppressive agents or anti-cancer drug use and cases of delayed blood culture. Both the febrile group (n=162) and afebrile group (n=28) showed no difference in baseline characteristics. With regard to primary outcome, in-hospital mortality rate was higher in the afebrile group (41.4% vs. 6.1%) and the interval from admission to blood culture was longer in the afebrile group (3 hours v. 1 hour). The major reason for blood culture in the afebrile group was a high CRP level. Assessing the positive blood culture rate according to the CRP level in all the 1556 cultures, we found that the rate was 5.7 % (34/600) in patients with CRP levels <5mg/dL, 15.1 % (44/292) in those with CRP levels between 5 and 10 mg/dL, and 23.8 % (158/664) in those with CRP levels >=10 mg/dL.

Conclusions: An afebrile state with bacteremia in CHD patients was associated with a higher in-hospital mortality rate. Therefore, a prompt blood culture and empirical antibiotics administration should be considered in CHD patients with high CRP levels irrespective of fever.

FR-PO820

Long-Term Blood Pressure Variability Better Predicts All-Cause Mortality in Hemodialysis Patients than Intradialytic Blood Pressure Variability

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Background: Blood pressure variability (BPV) is a potential prognostic predictor for all-cause mortality. Here we conducted a retrospective cohort study to compare the affecting factors and prognostic ability of long-term BPV with intradialytic BPV in hemodialysis(HD) patients.

Methods: We included 611 HD patients, collected their baseline characteristics including one-year blood pressure, and followed up for 40 months. Long-term BPV was assessed by pre-dialysis SBP residual metric, while intradialytic BPV was assessed by intradialytic absolute SBP residual.

Results: Long-term BPV showed a correlation with intradialytic BPV (Spearman r from 0.5997 to 0.6883). According to logistic regression, both long-term and intradialytic BPV were associated with age, vascular access type, dialysis time, dialysis vintage, pre-dialysis blood pressure and serum albumin(Alb), while only intradilytic BPV was affected by body mass index (Fig 1 A-D). High long-term BPV but not intradialytic BPV was associated with high all-cause mortality (p= 0.0047 and 0.3682, respectively)(Fig 1 E-F). According to receiver operating characteristic (ROC) curve with mortality as dependent variable, long-term SBP residual metric showed a stronger prognostic ability than intradialytic BPV (area under curve [AUC] 0.679 *vs.* 0.568, p=0.0381), which was more significant in patients with blood pressure≥140/90mmHg (AUC 0.713 *vs.* 0.556, p=0.0191)(Fig1 G-H). After complete adjustments, long-term BPV remained significantly associated with all-cause mortality (hazard ratio 1.628 per quartile; 95% confidence interval, 1.086 to 2.441).

Conclusions: Our results implied an advantage of long-term BPV in predicting all-cause mortality in HD patients, suggesting long-term BPV as an additional target of blood pressure management.

Funding: Government Support - Non-U.S.

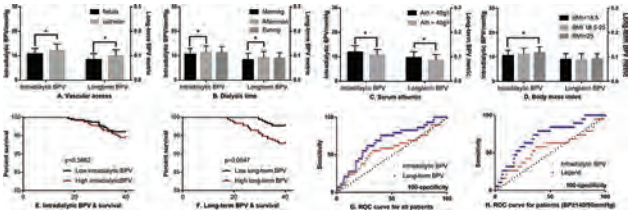

Fig 1. Affecting factors and prognostic ability of intradialytic and long-term BPV

FR-PO821

Predialysis Hyponatremia and Post-Dialysis Elevation in Serum Sodium Concentration During Hemodialysis as Significant Predictors of Mortality in Patients Undergoing Hemodialysis

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Background: Previous studies have reported that hyponatremia is associated with increased mortality in hemodialysis (HD) patients. However, there have been few reports on studying the fluctuation of serum sodium (Na) concentration during HD (ΔNa: postdialysis Na – predialysis Na) in HD patients. We conducted this cohort study using a nation-wide registry of patients with end-stage renal disease in Japan to examine the association of predialysis hyponatremia and ΔNa during HD with mortality.

Methods: We identified 178,114 patients from a nation-wide database of HD patients receiving thrice-weekly HD in Japan. The study outcome was 2-year all-cause mortality and baseline Na levels were categorized into quintiles. We examined the association of serum Na concentration and ΔNa with the mortality using a Cox proportional hazards model.

Results: During a 2-year follow-up period, 25928 patients died from any cause. Each 1-mEq/L decrement in pre-dialysis Na concentration was associated with increased risk of all-cause death (Hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.05-1.06). In contrast, higher ΔNa level was associated with higher all-cause mortality (HR for 1 mEq/L increment in ΔNa, 1.02; 95% CI, 1.01-1.02). The combined association of tertiles of predialysis Na concentration and ΔNa with all-cause mortality showed the highest mortality (HR 1.09, 95% CI 1.05–1.13) in subjects with the lowest Na concentration (Na ≤136 mEq/L) and the highest ΔNa level (ΔNa >4 mEq/L) compared with those (reference) with intermediate predialysis Na concentration (137–140 mEq/L) and the lowest ΔNa level (ΔNa ≤2 mEq/L).

Conclusions: Lower predialysis Na concentration and higher ΔNa are associated with an increased risk of death in HD patients.

FR-PO822

Blood Pressure Variability along Hemodialysis: Is It Related to Mortality?

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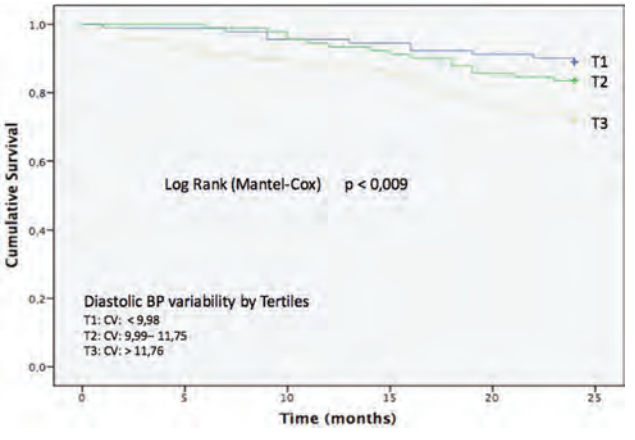
Background: Recent studies, link Hemodialysis systolic blood pressure (BP) variability and mortality. However BP variability can be seen with different (BP) components, including systolic and diastolic as well as predialysis, intradialytic, and postdialysis BP. Aims: To analyze BP variability in different measurements along Hemodialisys (HD) session and verify which of them predict mortality in incident patients.

Methods: Retrospective analysis of 277 incidents patients on conventional HD. BP records were collected throughout the hemodialysis sessions from the beginning of treatment. BP variability was calculated using the coefficient of variation (CV). Demographic and clinical data were analyzed during a 24 month follow-period as well as mortality rate. Survival analisys (Cox proportional hazards) was carried out by stratifying patients in tertiles of BP variability.

Results: 277 incident HD patiens (186 M, 91 F). Age (yr): 65,1 ± 13,1. Sex (%men): 67,1. Diabetes (%): 45,8. Hypertension (%): 95. Systolic preHD BP (mmHg): 137,6 ± 14,5 CV: 11,5 ± 3,7, Diastolic preHD BP (mmHg): 73,3 ± 6,8. CV:12,1 ± 7,7. Systolic postHD BP(mmHg) : 137,2 ± 14,7. CV: 11,2 ± 3,05. Diastolic postHD BP: 73,5 ± 6,5. CV: 13,5 ± 14,5. We observed 51 deaths (18,4%) during the follow-up period. Higher Diastolic post hemodialisys blood pressure variability (DBPV) was associated with an increased risk of death, as shown in the table below (Fig1). Survival analysis (Kaplan-Meyer) shows significative differences between tertiles of DBPV (p<0.009) (Fig2).

Conclusions: In our study we observed and increased risk of mortality in patients with higher diastolic blood pressure variability, especially those with greater variability post hemodialysis.

Risk Factor	Parameter estimate	P-Value	Hazard Ratio (HR) (95% CI for HR)
Diabetes Mellitus	-0,128	0,880	0,872 (0,489-1,554)
Age	-0,011	0,289	0,990 (0,971-1,010)
Male Sex	0,104	0,734	1,037 (0,567-1,896)
DBPV post HDT1	Reference	Reference	Reference
DBPV postHD T2	0,413	0,313	1,511 (0,678-3,368)
DBPV post HD T3	0,996	0,009	2,708 (1,286-5,703)



FR-PO823

The Impact of Sunlight Exposure on Mortality of ESRD Patients: A Bi-Directional Case-Crossover Study in the Korean Nation-Wide ESRD Cohort

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Background: Recent data suggest that reduced sunlight exposure is associated with increased mortality in the general population. To date, the association between sunlight exposure and mortality in dialysis patients has not been examined.

Methods: Among 134,478 dialysis patients in the Korean end-stage renal disease (ESRD) cohort from 2001 to 2014, 31,291 patients were enrolled from seven metropolitan cities, and data were analyzed using bi-directional case-crossover design. We examined the association between short-term sunlight exposure and mortality in ESRD patients. We adjusted for temperature, humidity, and daily concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particle matter (PM_{10}) as confounders.

Results: The characteristics of the study population included age (65.6 ± 12.26 (mean ± standard deviation [SD]) years), sex (male, 59.96%; female, 41.04%), comorbidity (diabetes, 53.58%; hypertension, 40.5%), and kidney dialysis type (hemodialysis, 73.02%; peritoneal dialysis, 26.98 %). The mean ± SD follow-up time was 4.68 ± 4.37 years. The daily sunlight exposure was significantly decreased in the case group compared with the control group (P=0.004). Sunlight exposure was associated with all-cause death overall (ORs [95%CI]: 0.99 [0.98-0.99], P=0.042) in a fully adjusted model. Patients with diabetes (ORs [95%CI]: 0.98 [0.97-0.99], P=0.016) or aged higher than 75 years (ORs [95%CI]; 0.97 [0.96 – 0.99], P=0.020) had higher risks of mortality than patients without diabetes or aged below 75 years, respectively.

Conclusions: These findings suggest that sunlight exposure is inversely correlated with all-cause mortality in dialysis patients, especially in high-risk patients with diabetes and older adults.

FR-PO824

Association Between Endothelin-1 Levels and Mortality Among Hemodialysis Patients

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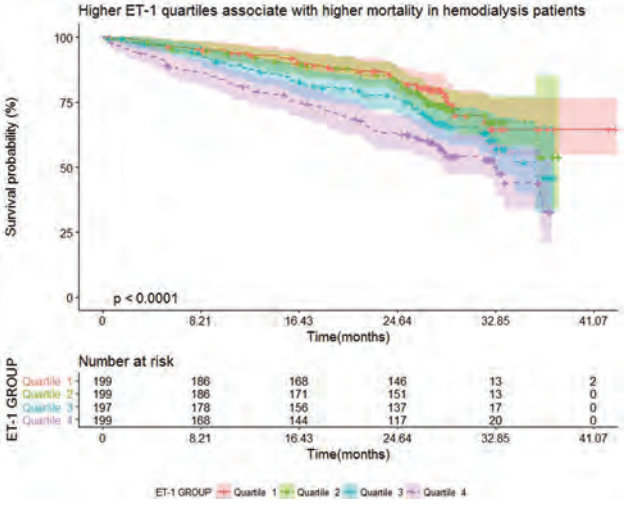
Background: Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor peptide implicated in the pathogenesis of hypertension, heart failure, and CKD. The association of endothelin with adverse outcomes in individuals with end stage renal disease on hemodialysis is unclear.

Methods: We measured pre-dialysis plasma levels of ET-1 in 794 individuals with ESRD on maintenance hemodialysis from the DaVita BioReg Biorepository, a prospective cohort study of prevalent hemodialysis patients. ET-1 was measured with a commercially available ELISA, with CV's of 7.3% from blind split replicate samples. Unadjusted and adjusted proportional hazards regression models were fit to exam the association of ET-1 with all- cause mortality.

Results: Mean age was 60, 41.4% were women, and median vintage was 37.2 months. Median (IQR) endothelin-1 concentration was 2.02 (1.56 – 2.71) pg/mL. ET-1 levels were positively correlated with pre-dialysis blood pressure (r=0.13, p<0.001), weight difference before and after dialysis (r=0.119, P<0.001) and longer dialysis vintage (r=0.084, P=0.019). In multivariable proportional hazards models adjusted for age, race, sex, BP, BMI, vintage, laboratory variables, and dialysis access, higher ET-1 levels were associated with a 37% higher risk of all-cause mortality (hazard ratio 1.37; 95% confidence interval, 1.23 to 1.53; $P < 0.001$) during median 27.8 months of follow-up time.

Conclusions: Higher pre-dialysis plasma ET-1 levels are associated with an increased risk of death. The mechanisms underlying this association and its potential therapeutic relevance merit further investigation.



FR-PO825

Beta-2 Microglobulin Levels and All-Cause Mortality: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Background: Dialysis-related amyloidosis due to beta-2 microglobulin (β2M) accumulation among hemodialysis (HD) patients is now uncommon due to HD delivery improvements. The impact of β2M levels and other middle molecules on other adverse

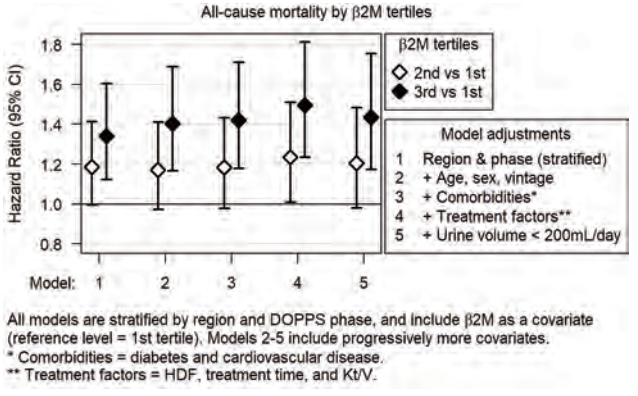
events among HD patients remains unclear. We sought to identify patient factors that may affect β2M level and estimate the effect of β2M on mortality.

Methods: Facilities in DOPPS phases 4-6 were included in this study if ≥50% of patients had β2M levels reported in ≥50% of follow-up rounds. Cox regression was used to estimate the association (hazard ratio [HR]; 95% CI) between β2M, categorized in tertiles, and all-cause mortality, adjusting for demographic factors, comorbidities, HD treatment factors, and stratified by study phase and region (Japan vs. Europe).

Results: We identified 5366 patients from 77 HD facilities in Japan (n=3837), France, Italy, and Spain (n=1529). Median (IQR) values of β2M (mg/dL) were 2.58 (2.17-3.00) in Japan and 2.55 (1.98-3.21) in Europe. In cross-sectional, unadjusted analysis, patients in the upper β2M tertile had longer dialysis vintage, greater likelihood of urine volume <200mL/day, lower prevalence of diabetes, higher serum phosphorus, and higher C-reactive protein, relative to the lower β2M tertile. Little association was observed between β2M and HD treatment time. Compared with the lower β2M tertile, the adjusted HR for mortality was 1.20 (0.98-1.48, 95% CI) for the middle tertile and 1.44 (1.17-1.75, 95% CI) for the upper tertile (Figure).

Conclusions: β2M is positively associated with mortality, controlling for several potential confounders. Interventions targeting greater β2M clearance during HD therapy may be an effective therapeutic strategy to improve outcomes among these patients.

Funding: NIDDK Support, Commercial Support - The DOPPS Program is supported by Amgen, Kyowa Hakko Kirin, Baxter Healthcare. Additional support for specific projects and countries is provided by AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Keryx, Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Proteon, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN) in the United Kingdom, and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Dr. Muenz directly., Private Foundation Support, Government Support - Non-U.S.



FR-PO826

Polyvascular Disease and Cardiovascular Risk in Hemodialysis Patients: Ten-Year Outcomes of the Q-Cohort Study

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Background: Patients with polyvascular disease (PVD), which indicates co-existing arteriosclerotic disease on multiple vascular beds, have been identified to be a high-risk group of recurrent ischemic events in a community setting. However, the impact of PVD on the risk of cardiovascular events has not been evaluated previously in a hemodialysis population.

Methods: A total of 3,504 hemodialysis patients were prospectively followed for 10 years. PVD were defined as prior cardiovascular disease plus co-existing vascular diseases in one or more vascular beds. We examined the relationship between PVD and the occurrence of composite end point of ischemic events, including cardiovascular death, non-fatal coronary artery disease, stroke, and critical limb ischemia.

Results: The proportion of participants with PVD was 5.7% (n=200) at baseline. During follow-up period (median: 106.6 months, interquartile range: 50.1–121.8 months), 1,316 patients experienced at least 1 or more events of cardiovascular death (n=620), non-fatal coronary artery disease (n=456), stroke (n=524) or critical limb ischemia (n=257). In multivariable analysis, PVD was the most powerful predictor for ischemic events exceeding the contribution of presumed risk factors such as diabetes, aging and hypertension. Compared to the group without injured vascular beds, the risk of the events significantly elevated with the increase in the number of injured vascular beds (hazard ratio [HR] 1.71, 95% confidence interval [CI] 1.52–1.92 in the group of single vascular bed lesions, and HR 2.16, 95% CI 1.78–2.67 in the group of polyvascular bed lesions).

Conclusions: This study clearly demonstrates that PVD is the most powerful predictor for future incidences of ischemic events in hemodialysis patients.

FR-PO827

An Inverse Association of Proteinuria with Mortality in Incident Hemodialysis Patients

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Background: Proteinuria is a potent predictor of mortality. However, in patients with severely reduced kidney function, a few studies from the CKD Prognosis Consortium and Veterans Affairs showed a J-shaped association between proteinuria and mortality. To our knowledge, no studies have explored this association in incident dialysis patients.

Methods: We examined data from 1380 Japanese incident dialysis patients (mean age 67 years). Baseline data were collected just before or during the hospitalization at which dialysis was initiated. The associations of dipstick proteinuria (negative/trace, 1+, 2+ and ≥3+) with all-cause mortality and cardiovascular disease (CVD) mortality were quantified in Cox models after accounting for potential confounders such as age, cause of CKD, and history of CVD.

Results: Proteinuria ≥3+ was the most prevalent category (n=765 [55.4%]), followed by 2+ (430 [31.2%]), 1+ (137 [9.9%]), and negative/trace (48 [3.5%]). Patients with lower proteinuria were likely to be older and have a history of CVD, compared to the patients with higher proteinuria. During a mean follow-up of 3.3 years, there were 352 deaths (129 due to CVD). Patients with lower proteinuria had a higher risk of mortality, with unadjusted hazard ratios 3.86 (2.55-5.85) for negative/trace, 1.62 (1.16-2.26) for 1+, and 1.35 (1.07-1.71) for 2+ (Model 1 in Table). Although attenuated, this pattern remained significant after accounting for potential confounders (p for trend ≤0.001 and adjusted hazard ratio 2.60 [1.62-4.17] for negative/trace in Model 4 in Table). This association was consistent for CVD and no-CVD mortality, even when restricting to adults aged ≥70 years, or further adjusting for cardiac ejection fraction.

Conclusions: We documented a progressive inverse trend of proteinuria with mortality among incident dialysis patients, with a strikingly high risk of mortality in persons with negative/trace proteinuria. Our study highlights the prognostic value of predialysis data and suggests that absence of proteinuria as a potential indicator of the highest postdialysis mortality risk.

Funding: Private Foundation Support

Table. Hazard ratios (95% CI) of all-cause mortality according to dipstick proteinuria categories

	Proteinuria (dipstick)				
	negative/trace (n=48)	1+ (n=137)	2+ (n=430)	3+ (n=765)	P for trend (n=1380)
All-cause mortality (n = 352)	26 deaths	44 deaths	119 deaths	163 deaths	
model 1	3.86 (2.55-5.85) **	1.62 (1.16-2.26) **	1.35 (1.07-1.71) *	ref	<0.001
model 2	3.07 (2.02-4.65) **	1.37 (0.98-1.92)	1.23 (0.98-1.58)	ref	<0.001
model 3	2.84 (1.86-4.33) **	1.32 (0.93-1.86)	1.27 (1.00-1.61)	ref	<0.001
model 4	2.60 (1.62-4.17) **	1.35 (0.95-1.93)	1.25 (0.97-1.62)	ref	0.001

* P < 0.05, ** P < 0.01

FR-PO828

Low Eosinophil Count and Decrease in Eosinophil Count During the First 6 Months After Hemodialysis (HD) Are Associated with High Mortality

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Background: Eosinophilia has been recognized to occur in HD patients, however its causes and clinical significance are still uncertain. Eosinophils are traditionally known as the moderator of allergic reactions, however they have now emerged as one of the most important immune-regulating cells, and an increase in eosinophil count is also reported to be a predictor of vascular disease in the general population. Associations of eosinophil count (EOS) and its changes with mortality in dialysis patients are still unknown.

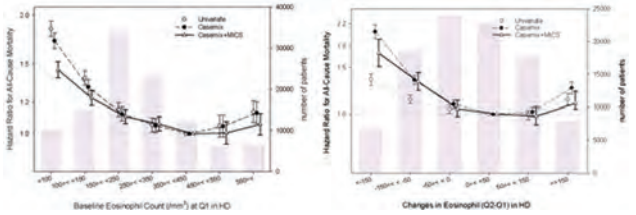
Methods: In a cohort of 107,056 incident HD patients treated by a large dialysis organization during 2007-2011, we examined the relationships of baseline EOS (Q1-average within 3 months of HD transition) and 6-month changes in EOS (Q2-Q1) with mortality using Cox proportional hazards models. Three adjustment models were used including case-mix variables and markers for malnutrition and inflammation.

Results: Baseline EOS and fraction during Q1 were 231 (interquartile range: 155-339) /mm^3 and 3.2% (2.2-4.6). Eosinophilia (>350/mm^3) was observed in 23.4% of patients. There was a gradual increase in mean EOS after the initiation of dialysis. The 6-month mean and percent changes in EOS were 5.1 (-53 to 199) /mm^3/quarter and 0.11 (-0.22 to 0.28) %/quarter, which did not parallel with the changes in WBC count. In fully adjusted models, mortality risk was highest in subjects with lower baseline EOS (<150/mm^3), and also slightly higher in patients with higher levels (>550/mm^3) resulting in a reverse J-shaped relationship. Compared to the group with stable EOS (change: -50 to <50/mm^3/quarter), both decrease or increase in EOS was associated with higher all-cause mortality risk. Case-

mix-adjusted HR [95% CI] 2.05 [1.93-2.18] in the decrease group and 1.25 [1.19-1.32] in the increase group, respectively. [Figure]

Conclusions: Low baseline EOS and a 6-month EOS decrease following dialysis initiation were associated with higher all cause mortality risk.

Funding: NIDDK Support



FR-PO829

Syncope and Collapse Is Associated with an Increased Risk of Cardiovascular Disease and Mortality in Patients Undergoing Dialysis

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Background: Patients undergoing dialysis have a higher risk of cardiovascular disease and mortality than the general population. Syncope and collapse (SC) is often observed in patients before and after dialysis sessions. However, the epidemiology of SC is undetermined and the association between SC and cardiovascular outcomes in a dialysis population has not been discussed. This study explored the impact of SC on cardiovascular events and mortality.

Methods: This study retrospectively examined data of patients undergoing dialysis from population-based medical registries between 1998 and 2011. Patients undergoing dialysis who have SC (N = 3876) were selected as the study cohort and those without SC who were propensity score-matched at a 1:1 ratio were included as controls. Major adverse cardiovascular events (MACEs), included acute coronary syndrome (ACS), arrhythmia or cardiac arrest, stroke, and overall mortality, were evaluated and compared in both cohorts.

Results: In 2011, the incidence and prevalence rates of SC were 7.05% and 10.8%, respectively, in the dialysis population. The mean follow-up periods until the occurrence of ACS, arrhythmia or cardiac arrest, stroke, and overall mortality in the SC cohort were 3.51 ± 2.90, 3.43 ± 2.93, 3.74 ± 2.97, and 3.76 ± 2.98 years, respectively. Compared with the patients without SC, those with SC had higher incidence rates of ACS (30.1 vs. 24.7 events/1000 people/year), arrhythmia or cardiac arrest (6.75 vs. 3.51 events/1000 people/year), stroke (51.6 vs. 35.7 events/1000 people/year), and overall mortality (127.7 vs. 77.9 deaths/1000 people/year). The SC cohort also had higher risks of ACS, arrhythmia or cardiac arrest, stroke, and overall mortality (adjusted hazard ratios: 1.28 [95% confidence interval (CI) = 1.11–1.46], 2.05 [95% CI = 1.50–2.82], 1.48 [95% CI = 1.33–1.66], and 1.79 [95% CI = 1.67–1.92], respectively) than did the non-SC cohort.

Conclusions: SC was significantly associated with cardiovascular events and overall mortality in the patients on dialysis. SC may serve as a prodrome for cardiovascular comorbidities, thereby assisting clinicians in identifying high-risk patients.

FR-PO830

Elevated Levels of Soluble ST2 but Not Galectin-3 Are Associated with Increased Risk of Mortality in Patients with Hemodialysis

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Background: Soluble ST2 (sST2) and galectin-3 has been proposed as novel biomarkers of cardiac fibrosis and heart failure, and may also predict cardiovascular event and mortality. However, there are limited data on the association between sST2 and galectin-3 and clinical outcomes in patients with end-stage renal disease. To determine this, we examined associations of sST2 and galectin-3 with all-cause mortality and cardiovascular events in patients with hemodialysis (HD)

Methods: This study included maintenance HD patients 18 years or older who consent to preserve their serum to the Bio Bank at our institution between March 2014 and March 2015. The primary outcome was all-cause mortality. The secondary outcome was composite of the cardiovascular event (CVE) and mortality. We used Cox proportional hazards regression analysis to evaluate associations between sST2 and galectin-3 levels and clinical outcomes. Patients were followed for CVE and mortality through March 2018.

Results: A total of 296 patients were analyzed in this study. Mean age was 57 ± 13 years, 52.9% were male. The mean serum level of sST2 was 24.81 ± 12.43 ng/ml and mean serum level of galectin-3 was 35.50 ± 9.91 ng/ml. Serum sST2 concentration was significantly associated with higher mortality (hazard ratio [HR], 1.043; 95% confidence interval [CI], 1.017 – 1.070; P = 0.001) and composite outcome including CVE and mortality (HR, 1.022; 95% CI, 1.003 – 1.040; P = 0.022) after adjustment for confounding factors. However, serum galectin-3 level was not independently associated with mortality nor composite outcome after adjustment.

Conclusions: Elevated levels of sST2 is independently associated with increased risk of adverse clinical outcomes in patients with HD.

FR-PO831

Racial and Sex Disparities in Mortality in Incident ESRD Patients

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Background: End Stage Renal Disease (ESRD) is a global public health problem; and is characterized by high morbidity and mortality. Although mortality in patients is highest during the first year of dialysis, differences in mortality across five different races among men and women is not well studied.

Methods: We evaluated 944, 650 adult patients who initiated dialysis between 1/1/2005 and 12/31/2014 from the United States Renal Data System (USRDS). Using adjusted logistic multivariate regression models adjusted for major cofounders, we examined the effect of race and sex on all cause mortality after dialysis initiation.

Results: Mean age of the study population was 65±14 years. Of the study cohort, 56% were male. 53% were White, 28% were Black, 14% were Hispanic, 4% were Asian, and 1% were Native American. Of those who started dialysis, 77% initiated with a catheter. Overall, 30% did not receive pre-dialysis nephrology care. One-year mortality was 24% and 90-day mortality was 9%. In adjusted analyses, as compared to Whites, one-year mortality was lower among Blacks (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.72-0.74]), Hispanics (OR, 0.64; CI, 0.63-0.65), Asians (OR, 0.55; CI, 0.53-0.56), and Native Americans (OR, 0.67; CI, 0.63-0.71). Females were less likely to die within one year after initiating dialysis than were males (OR, 0.98; CI, 0.97-0.99). Other significant predictors of mortality included absence of predialysis nephrology care, use of central venous catheter as dialysis access, older age, poor functional status, serum albumin < 3.5 mg/dl, and comorbidities (congestive heart failure, cancer, and chronic obstructive pulmonary disease).

Conclusions: Among incident dialysis patients; as compared to White patients, Black patients are 27% less likely, Hispanic patients 36% less likely, Asians patients 45% less likely, and Native Americans are 33% less likely to die within one year. Females have lower mortality than males. Biological factors associated with these disparities need to be explored further to understand the reasons behind the survival advantage among minorities and women.

FR-PO832

Impact of Transferrin Saturation on All-Cause Mortality in Patients on Maintenance Hemodialysis

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Background: To evaluate iron status, transferrin saturation (TSAT) and serum ferritin levels are commonly used. TSAT provides an assessment of how much transferrin has bound iron, whereas serum ferritin is a marker used to reflect body iron storage. Our aim was to evaluate the prognostic importance of TSAT in Japanese patients on maintenance hemodialysis (MHD).

Methods: A total of 398 MHD patients were recruited and divided into 3 groups according to baseline TSAT of <20%, 20–40%, and >40%. The mean duration of the study was 52.2 ± 16.3 months. The primary endpoint was all-cause mortality, and the secondary endpoint was cardiovascular (CV) mortality.

Results: A total of 130 patients died during a mean follow-up duration of 52.2 ± 16.3 months. There were no differences in the proportion of patients on erythropoiesis-stimulating agents or iron supplements among the 3 groups. During a mean follow-up duration of 52.2 ±1 6.3 months, 130 patients died of CV causes (n = 63, (15.8%) and infection (n = 47, 11.8%). Compared with the reference group (TSAT 20–40%), patients with TSAT <20% had significantly higher all-cause mortality rates (6.44 vs. 9.55 events per 100 patient-year, p = 0.0452). Kaplan-Meier analysis also showed that all-cause mortality rates were significantly higher in patients with TSAT <20% compared to the other two groups (p =0.0353).

Conclusions: Low TSAT was a significant independent risk factor for all-cause mortality in a cohort of Japanese MHD patients. These findings suggested that the adverse clinical outcomes in patients with low TSAT can be partly attributed to iron-deficiency anemia.

FR-PO833

Modelling Survival in Dialysis Patients to Improve Their Access to Life Insurance for Loan

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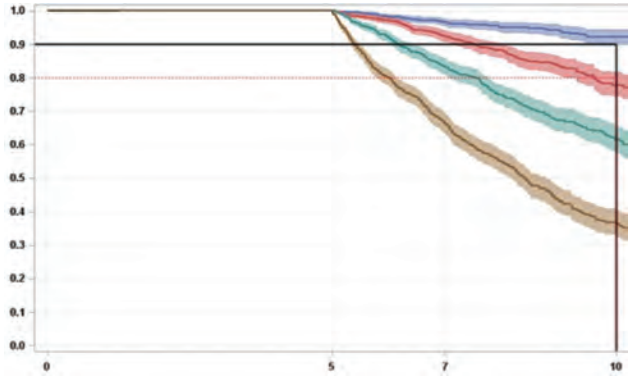
Background: "AERAS convention" (Access to Loan for People with Increased Health Risk Agreement) aims in France to provide insurance companies with evidence-based data to improve their assessment of risk for patients with chronic diseases.Data from the French REIN registry were used to predict survival for ESRD patients who frequently face the highest difficulties to borrow money due to high (often precluding) life insurance premiums, especially for those under dialysis.

Methods: The study included a cohort of 27952 patients who started a replacement therapy between 2002-1-1 and 2016-12-31 at the age of 25 to 60 yo. We focus here on 10-years survival conditionally on being alive and not previously transplanted at 1, 3 or 5 years. A Cox model was used to build multivariate risk functions for each conditional time points, taking into account updated data from the closest annual follow-up. A 10-year survival threshold significantly greater than 90% with an unilateral alpha risk of 2.5% was considered as a proxy for considering a potential access to loan without major life insurance premiums.

Results: Age, albuminemia, diabetes, number of cardio-vascular comorbidities, respiratory insufficiency, dialysis modalities and placement on the waiting list were significant and independent predictors of 10-years survival, with varying HRs and ß coefficients with conditional time points (e.g. 1, 3 or 5 years from dialysis start). C-indexes were greater than 0.6 and discrimination was good, as illustrated by quartile-stratified 10-years survival conditionally on being alive and not previously transplanted at 5 years (Figure 1). More than a quarter of patients who were 25 to 65 yo at start of dialysis and respectively alive after 1, 3 and 5 years of dialysis are predicted with 10-year survival greater than 90%.

Conclusions: ESRD registries indeed provide useful personalized tools to improve access to loan for many patients with ESRD, thus contributing to their social and professional integration of these patients, and finally to their quality of life.



FR-PO834

Cause of Death in Patients on Renal Replacement Therapy Varies Across Australia, New Zealand, and Malaysia - Results from the Study of Heart and Renal Protection-Extended Review (SHARP-ER)

Ben Talbot,[1] Louisa Sukkar,[1,3] Brendan Smyth,[1,3] Min Jun,[1] Meg J. Jardine,[1] Alan Cass,[4] Robert J. Walker,[2] Christina A. Reith,[5] Hooi L. Seong,[6] Martin P. Gallagher.[1] *[1]The George Institute for Global Health, The University of New South Wales, Sydney, NSW, Australia; [2]University of Otago, Dunedin, New Zealand; [3]Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia; [4]Menzies School of Health Research, Darwin, NT, Australia; [5]CTSU, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; [6]Sultanah Aminah Hospital Johor Baru, Malaysia, Johor Bahru, Malaysia.*

Background: The mortality rate among dialysis patients is high with regional variability. The Study of Heart and Renal Protection-Extended Review (SHARP-ER) comprised extended 5-year follow up of eligible participants in Australia, New Zealand and Malaysia alive at the end of SHARP (a randomised double-blind trial of simvastatin and ezetimibe vs. placebo in chronic kidney disease). We compared survival and cause of death between countries in dialysis patients in the SHARP-ER cohort.

Methods: Eligible participants in Australia, New Zealand and Malaysia alive at the end of SHARP were identified and extended 5-year follow up data collected. Cause of death was determined using registry data (national death index in Australia and New Zealand and national death registry in Malaysia) for participants receiving chronic dialysis (haemodialysis or peritoneal dialysis) at the beginning of the extended review period. Multivariate survival analysis and multinomial logistic regression were conducted to assess for differences.

Results: The cohort comprised 1136 participants in total. Of these, 526 were receiving chronic dialysis and were included in the analysis. During the 5 year follow up 203 died (38.6%). Median age was lowest in Malaysia (56.2 years [50.4-63.8]), followed by New Zealand (60.4 years [55.5-67.3]) and Australia (66.1 years [55.3-75.8]). Treating country did not significantly affect survival following adjustment for age, gender and dialysis modality. Cardiovascular disease was the most common cause of death (New Zealand 52.4%, Australia 43.2%, Malaysia 32.6%). Infectious causes of death were significantly more common in Malaysia versus Australasia (Australia and New Zealand combined; RR 4.56, p=0.002, 95% CI 1.75-11.85) following adjustment. Crude rates of infectious death by country were: Malaysia 31.8%, New Zealand 9.5%, Australia 6.8%. Peritoneal dialysis was also associated with an increased risk of infectious death (RR 3.64, p=0.017, 95%CI 1.26-10.48) following adjustment.

Conclusions: In the SHARP-ER cohort, survival on dialysis was comparable between Australia, New Zealand and Malaysia but causes of death differed. This suggests a need for region specific interventions.

Funding: Government Support - Non-U.S.

FR-PO835

Prevalence of Oral Mucosal Lesions in Hemodialysis Patients and Association with Mortality: A Prospective Cohort Study

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Background: Oral mucosal lesions are highly prevalent and frequently severe for adults treated with longterm hemodialysis. We aimed to evaluate the prevalence of mucosal lesions and association with mortality among hemodialysis patients.

Methods: The ORAL-D study was a multinational cohort study that involved a comprehensive, standardized oral and dental examination among 4726 patients with ESKD disease treated with haemodialysis in Europe and South America. We evaluated oral mucosal lesions assessed by trained dentists according to standard WHO guidelines. The association between mucosal lesions and all-cause and cardiovascular mortality was estimated using a Cox proportional hazard regression model. Analyses were adjusted for sociodemographic and clinical variables. The primary outcome was all-cause mortality.

Results: 70 participants (1.7%) had mucosal ulceration, 147 (3.5%) presented white stain, 169 (4%) red stain, 85 (2%) neoformation, and 331 (7.9%) had petechial lesions. Overall, 207 (4.9%) had geographical tongue and 450 (10.7%) had a fissured tongue. Oral candidiasis was observed in 192 (4.6%) participants and 21 had oral herpetic lesions. 401 participants (9.5%) had a cancer-related mucosal lesion and 213 participants (5%) an infection-related lesion. During a median 3.47 (1.55-5.78) months of follow-up, there were 2114 deaths including 1013 cardiovascular deaths. In unadjusted survival analyses, the proportion of patients who died was higher among those with red stain, fissured tongue, and petechial lesions. Similarly, the estimated proportion of patients who had a cardiovascular death was higher among those with red stain, fissured tongue, petechial lesions, neoformation and oral candidiasis. When adjusting for clinical and sociodemographic factors, only the presence of oral candidiasis was significantly associated with an increased risk of all cause (adj HR 1.37, 95% CI 1.00-1.86) and cardiovascular mortality (adj HR 1.64, 95% CI 1.09-2.46). This association was confirmed in competing risks analysis and using a shared frailty model to account for clustering by country.

Conclusions: There is generally limited evidence of an independent association between oral mucosal lesions and mortality outcomes among hemodialysis patients.

FR-PO836

Outcomes of Treatment of Myeloma in Patients Requiring Renal Replacement Therapy – A Single Centre Experience

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Background: Renal impairment is a complication of multiple myeloma (MM). The incidence of renal impairment at diagnosis of MM is 20-50%; about 10% of these present with acute kidney injury requiring renal replacement therapy (RRT). Treatments including Bortezomib have improved prognosis with full or partial recovery of renal function; however they cause side effects e.g. peripheral neuropathy. We reviewed outcomes of MM treatments in patients requiring RRT over an 11 year period.

Methods: Patients diagnosed with MM requiring RRT between January 2007 - December 2017 were identified. Patient data was obtained from electronic records.

Results: 29 patients met the inclusion criteria. Median age 64 years (range 45-86); 59% were male; 72% were Caucasian. Median follow up time was 33 months (range 8-96 months). 65% (N=19) were treated with first line chemotherapy including Bortezomib; of these 84% showed complete (21%), or partial (63%) response to therapy. 1 year survival was 89% (N=19), 5 year survival 71% (N=14). Complications were thrombosis (11%), neuropathy (53%) and infection requiring hospital admission (42%). 37% recovered enough renal function to cease RRT. 35% (N=10) did not have Bortezomib as part of initial treatment. Of these 50% responded to therapy; all with partial response, none with complete response. 1 year survival was 90% (N=10), 5 year survival was 50% (N=10). Complications were thrombosis (20%) and infection requiring hospital admission (20%). No patient experienced neuropathy. Only 10% recovered sufficient renal function to stop RRT. Patients who gained dialysis independence had significant reduction of free light chains after 2 chemotherapy cycles (median 85%, range 61%-99%). Those who were still on RRT had more variation in change in free light chains ranging from -99% to +63%.

Conclusions: Our study coincides with the introduction of Bortezomib as first-line treatment in 2010. In our cohort, Bortezomib resulted in increased rates of response to first line therapy, greater likelihood of dialysis independence and improved overall survival. However, more side effects were associated with Bortezomib. As has been shown in patients with renal amyloid (Rezk et al, Kidney International 2017), reduction of free light chains post chemotherapy can be used as a predictor for dialysis independence and our results support this.

FR-PO837

End-of-Life Care Among Patients with ESRD Who Undergo a Lower Extremity Amputation

Catherine Butler,[1] Susan M. Hailpern,[4] Margaret Schwarze,[6] Ronit Katz,[1] Manjula Kurella Tamura,[3] Maria E. Montez-Rath,[5] Yoshio N. Hall,[7] William Kreuter,[1] Ann M. O'Hare.[2] *[1]University of Washington, Seattle, WA; [2]VA Puget Sound Health Care System, Seattle, WA; [3]Stanford University, Palo Alto, CA; [4]Medicine, University of Washington, Kidney Research Institute (retired), Seattle, WA; [5]Stanford University School of Medicine, Palo Alto, CA; [6]UW School of Medicine and Public Health, Madison, WI; [7]University of Washington-Kidney Research Institute, Seattle, WA.*

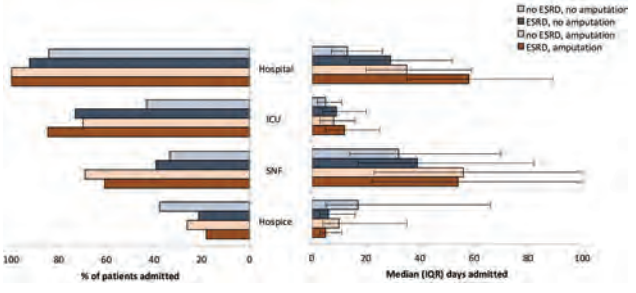
Background: Patients with ESRD have a high incidence of lower extremity amputation and limited post-operative long-term survival, but little is known about the relationship between amputation and patterns of their end-of-life care.

Methods: We used Medicare claims to compare patterns of amputation and health care utilization in the last year of life among 754,762 patients with ESRD registered in the USRDS and 958,412 Medicare beneficiaries without ESRD who died between 2002 and 2014.

Results: During the last year of life, 8.2% of Medicare beneficiaries with, and 0.9% of those without ESRD underwent at least one lower extremity amputation. After adjustment for differences in patient characteristics, patients with ESRD were more likely to have undergone at least one amputation (relative risk (RR) 2.30, 95% confidence interval (CI) 2.24-2.35) and multiple amputations (RR 3.65, 95% CI 3.36-3.97) within a year of death. During their last year of life, patients with ESRD who underwent amputation were more likely to be admitted to the hospital, ICU, and/or to a SNF and less likely to be enrolled in hospice than other patients (figure). During this time, they spent a median of 58 days admitted to a hospital (vs. 35 days for patients without ESRD who underwent amputation, 29 days for patients with ESRD who did not undergo amputation, and 13 days for patients without ESRD who did not undergo amputation), 12 days admitted to an ICU (vs. 8, 9, and 5), 54 days admitted to a SNF (vs. 56, 39, and 32), and 5 days enrolled in hospice (vs. 10, 6, and 17).

Conclusions: Almost one in ten patients with ESRD undergo an amputation in the last year of life. These patients spend prolonged periods of time in acute and subacute care settings towards the end of life, but receive relatively little hospice care. These findings argue for more work to understand the end-of-life experience of these patients and suggest opportunities to improve care.

Funding: NIDDK Support



Percentage of patients admitted and median days spent in each care setting in the last year of life

FR-PO838

Regional Factors Associated with Hospice Use in the US Hemodialysis Population

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Background: Hospice use remains underutilized in the US ESRD population. We explored patient, hospice, and community factors at the county level for hospice use in a contemporary cohort of hemodialysis (HD) patients.

Methods: All deaths in patients on HD from 2014-2015 in the USRDS database were obtained. Hospice use was based on the death form hospice indicator or at least one Medicare hospice charge the year of death. Number of Medicare-certified hospices, their profit status, and regional characteristics at the County level were obtained from publically available databases and linked to the patient by County. Univariate comparisons and Multivariables Logistic Regression models were used.

Results: Of 140,729 deceased patients, 25% utilized hospice at the time of death. Those who utilized hospice were older at the time of death, predominantly White (74%), and non-Hispanic (89%). In logistic regression analyses, men were 11% less likely to utilize hospice than women, Hispanics were 12% less likely to use hospice than non-Hispanics, and Blacks were 33% less likely to utilize hospice than Whites. Those who utilized hospice were 3% more likely to have a Medicare certified hospice within their county. The number of hospices within county of residence and non-profit status were positively associated with hospice use. Residing in the Northeast region of the US and higher % of Medicare recipients eligible for Medicaid in the county were negatively associated with hospice use. Other socio-economic factors and intensity of care measures did not appear to be associated with hospice use.

Conclusions: Patient demographics associated with hospice use are consistent with published research. We also found that the region in the US, number of hospices in the county of residence and the composition of Medicare recipients in the county appear to also be associated with hospice use in a contemporary HD cohort.

Characteristics of patients by hospice status at time of death

Characteristics	No hospice N = 105,375 (75%)	Hospice N = 35,354 (25%)
Mean age at death, years (SD)	67 (13)	73 (12)
Male	57%	55%
White	63%	74%
Black	32%	22%
Hispanic	12%	11%
Region *	–	–
NW	73%	27%
NE	78%	22%
S	75%	25%
W	73%	27%

All p-values <0.0001.

* row % within each region; all others are column %.

FR-PO839

Postoperative Outcomes in Chronic Dialysis Patients: A Meta-Analysis of 37 Studies and 75,428 Patients

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Background: Chronic dialysis patients frequently undergo major surgery, but their absolute and relative risk of postoperative complications is unclear. The aim of this study was to estimate the risks of fatal and non-fatal postoperative outcomes in chronic dialysis patients undergoing non-transplant surgery.

Methods: Two authors performed a systematic review of observational studies indexed in Embase and MEDLINE till July 2017 that reported postoperative outcomes in chronic dialysis and non-dialysis patients undergoing major, non-transplant surgery. Summary level data on study characteristics, type of surgical procedure, patient demographics and comorbidity were extracted. The primary outcome was death(30-day or in-hospital mortality); secondary outcomes were myocardial infarction and sepsis. Random effects meta-analysis was performed to derive summary risk estimates and meta-regression was performed to explore heterogeneity.

Results: 37 studies involving 75,428 chronic dialysis and 9,624,178 non-dialysis patients undergoing orthopedic, vascular, cardiothoracic, general and urological procedures were included. Summary, unadjusted risk estimates showed increased risks of postoperative mortality (7.2% vs. 0.2%, OR 5.61, 95%CI 4.5-7.0, $I^2$90%), myocardial infarction (1.1% vs. 0.3%, OR 3.3, 95% CI 2.3-4.7, $I^2$74%) and sepsis (6.3% vs. 0.6%, OR 3.6, 95% CI 2.4-5.3, $I^2$96%) in dialysis patients compared to non-dialysis patients irrespective of discipline. Adjustment for age and comorbidity attenuated the risks of postoperative death (OR 3.1, 95% CI 2.9-3.3 $I^2$90%), myocardial infarction (OR 1.8, 95% CI 1.3-2.3, $I^2$0%) and sepsis (OR 2.6, 95% CI 2.3-2.9, $I^2$70%). Weighted univariate metaregression showed a significant association between individual study reported mortality odds ratios and differences in age (slope 0.099, p<0.01), cardiac disease prevalence (slope 0.002, p<0.01) and diabetes prevalence (slope 0.49, p<0.01) between dialysis and non-dialysis patients.

Conclusions: Chronic dialysis patients have substantially increased risks of both fatal and non-fatal postoperative complications across all surgical disciplines. This heightened risk is attributable not only to their dialysis dependency, but also to their older age and higher comorbid illness burden.

Funding: Government Support - Non-U.S.

FR-PO840

The Association Between Race/Ethnicity and Mortality Is Modified by BMI

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Background: African-Americans (AA) and Hispanics have better survival rates once on hemodialysis (HD). This phenomenon is known as "racial paradox". Besides, obese HD patients might have a survival benefit, too. Therefore, we aimed to examine if BMI is an effect modifier of the race/ethnicity-mortality association.

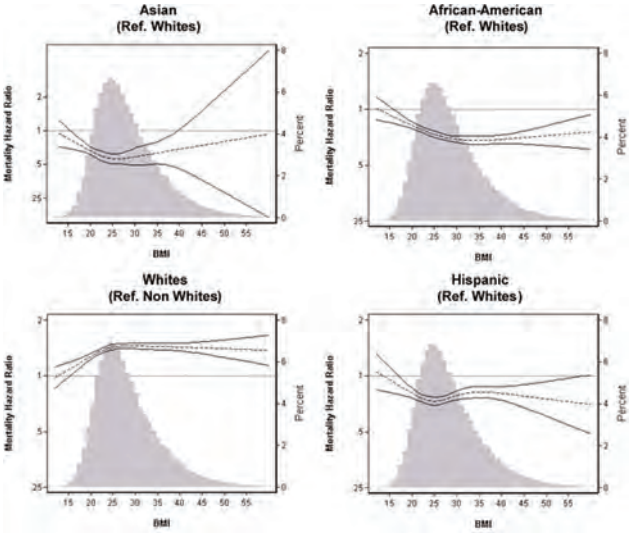
Methods: We retrospectively examined a cohort of 140,817 HD patients from a large dialysis organization in 2007 to 2011 who had known race/ethnicity and recorded BMI value. Patients were grouped according to their self-identified race/ethnicity. We explored the effect modification of BMI on the association between AA vs White, Hispanic vs. White, Asian vs. White and White vs non-White and all-cause mortality with adjustments for case-mix variables and laboratory markers of malnutrition and inflammation by using restricted cubic spline models, which splined the impact over continuous BMI.

Results: The cohort consisted of 29% AAs, 3% Asians, 14% Hispanics, 50% Whites and 3% others with a mean age of 64±15 years and mean BMI value of 28.2±7.3 kg/m^2. We found a survival benefit of both AA and Hispanic patients when compared to White patients.

This survival benefit was more observed in those with higher BMI and attenuated for low BMI patients. We observed a similar trend for Asians (reference Whites), however it did not reach statistical significance for higher BMI values. For Whites, the mortality association mirrored the findings in non-Whites. [figure1].

Conclusions: Among HD patients, BMI is an effect modifier of the race/ethnicity-mortality association.

Funding: NIDDK Support



FR-PO841

Normothermic Ex-Vivo Kidney Perfusion Restores the Gene Expression Profile of Marginal Kidney Grafts Subjected to Warm Ischemia

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Background: Normothermic ex-vivo kidney perfusion (NEVKP) results in improved marginal renal graft function compared to static cold storage (SCS) post-transplantation. To determine the mechanisms responsible for the beneficial effects of NEVKP, we investigated gene expression profiles of donation-after-cardiac-death (DCD) grafts stored with NEVKP or SCS to that of unmanipulated naïve-kidneys.

Methods: Kidneys from Yorkshire pigs were removed following 30-min of warm ischemia modelling DCD. Grafts were stored in SCS or NEVKP for 8hr prior to heterotopic autotransplantation. On POD3, grafts were collected and microarray analysis was performed.

Results: During NEVKP storage, DCD-grafts demonstrated favorable perfusion characteristics including lactate clearance, decreasing intra-renal resistance, and urine production. NEVKP resulted in improved graft function compared to SCS post-transplant with decreased peak serum creatinine (POD1: 4.0+/-1.15mg/dL vs POD3: 12.0+/0.78mg/dL, n=5, p<0.01) and higher creatinine clearance (POD3: 39.6+/-11.8mL/min vs 2.6+/-0.9mL/min, n=5, p<0.01). Transcriptomic analysis demonstrated significant differences in the expression of 27 genes in NEVKP grafts compared to naïve-kidneys (Table 1, ≥±2-fold change, n=3, FDR q<0.20). In contrast, 668 genes were differentially expressed between grafts stored with SCS and naïve-kidneys (Table 2, ≥±2-fold change, n=3, FDR q<0.20).

Conclusions: NEVKP of DCD kidney grafts resulted in a gene expression profile more closely resembling naïve kidneys. Conversely, grafts stored with SCS demonstrated increased expression of genes related to inflammation, apoptosis, and repair.

Top 10 Upregulated Named Genes (NEVKP vs naive kidney)		Downregulated Named Genes (NEVKP vs naive kidney)	
Name	Fold Change	Name	Fold Change
PCNA-associated factor	8.1	cytochrome P450 2A19	-12
olfactomedin 4	7.74	Kruppel-like factor 9	-3.43
collagen, type III, alpha 1	5.47	calsequestrin 2	-3.06
ubiquitin-like with PHD and ring finger domain	5.05	cytochrome P450, family 4, subfamily A	-2.98
annexin A1	4.47	ATP-binding cassette sub-family A	-2.87
lectin, galactoside-binding, soluble, 1	4.47		
kinetochore-associated protein 1-like	4.45		
ATPase family, AAA domain	3.98		
collagen, type V, alpha 2	2.51		
centromere protein W	2.41		

Table 1: Differential expression between NEVKP grafts and naïve kidneys

Top 10 Upregulated Named Genes (CS vs naive kidney)		Top 10 Downregulated Named Genes (CS vs naive kidney)	
Name	Fold Change	Name	Fold Change
lithostathine-like	16.16	cytochrome P450 2A19	-23.78
NAD(P)H dehydrogenase, quinone 1	14.9	placenta expressed transcript protein	-10.57
retinol binding protein 4, plasma	13.72	CCL16 chemokine (C-C motif) ligand 16	-9.57
TTK protein kinase	12.26	apolipoprotein D	-8.03
centromere protein F, 350/400kDa	11.89	uromodulin	-7.65
cytoskeleton associated protein 2	11.01	sialic acid acetylesterase	-7.11
kinesin family member 23	10.14	adhesion G protein-coupled receptor E2-like	-6.28
versican	10.05	alkylglycerol monooxygenase;	-6.16
ADAM-like, decysin 1	9.69	C-type lectin domain family 18 member A	-6.1
PCNA-associated factor	9.2	CYP2D25 vitamin D3 25-Hydroxylase	-6.05

Table 2: Differential expression between CS grafts and naïve kidneys

FR-PO842

Dextran-Based and Albumin-Based Perfusates in Normothermic Ex Vivo Kidney Perfusion

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Background: Kidney transplantation is the definitive treatment for end-stage renal disease. Transplantation is superior to the alternative, dialysis, in survival, quality of life, and cost-savings. However, the gap between kidney donation and demand for donor kidneys is growing, and improved utilization of renal grafts, especially extended criteria donors, is necessary. Normothermic *ex vivo* kidney perfusion (NEVKP) is a novel method for graft preservation; it maintains metabolism, allows assessment, and allows therapeutic interventions. Currently many NEVKP systems use perfusates composed of a combination of physiological saline, red blood cells, and supplemental source of oncotic pressure and nutrients. Our study examines the effect of dextran-40 based perfusate compared to albumin based perfusates in NEVKP.

Methods: We establish a NEVKP model using porcine kidneys extracted with 10 minutes of warm ischemia perfused using cardiopulmonary bypass equipment. Donor kidney is perfused at normothermia and 60mmHg arterial pressure. Perfusate is composed of donor whole blood and a modified plasmalyte solution containing either 8% dextran-40 or 8% bovine serum albumin. Glucose and insulin are infused.

Results: Dextran and albumin produced similar intra-renal resistance during 12 hours of perfusion. However, dextran based perfusate shows improved urine production rates and urine quality (lower pH, lower/undetectable glucose and calcium) and lower plasma and tissue inflammatory markers (plasma interleukin-6 2.45±0.88ng vs 5.24±0.52ng, plasma tumor necrosis factor-α undetectable in dextran perfusates vs 0.55±0.14ng, tissue expression of toll like receptor-4 77% higher in albumin perfusate group tissues). Neither perfusate groups significantly increase plasma kidney injury molecule-1 (KIM-1), however both perfusate groups show lower tissue KIM-1 compared to tissue from start of perfusion.

Conclusions: With improved perfusion characteristics and reduced inflammatory profile, we believe a dextran based perfusate is superior to albumin based perfusates in NEVKP and that our system provides a viable platform for *ex vivo* preservation of porcine kidneys and further study of different interventions during *ex vivo* kidney perfusion.

FR-PO843

Proteomics Analysis Reveals Novel Molecular Mechanisms Associated with Normothermic Ex-Vivo Perfusion

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Background: Normothermic ex-vivo perfusion (NEVKP) is associated with significantly improved graft function following transplantation in comparison to static cold storage (SCS); however, the molecular mechanisms underpinning this improvement remain unclear. We hypothesized that NEVKP induces key alterations in the renal proteome compared to SCS, enabling us to characterize the molecular mechanisms that lead to superior graft function in this setting.

Methods: Porcine kidneys were removed following 30 minutes of warm ischemia, before being subjected to either SCS or NEVKP (n=5, each group) for 8 hours prior to autotransplantation. Kidney biopsies were collected at time zero, upon reperfusion, and at POD3. We conducted an unbiased proteomics analysis by LC-MS/MS on Q-Exactive-Plus mass spectrometer. Subsequent analyses were performed using MaxQuant, Perseus, pathDIP, mirDIP, NaVIGaTOR and Cytoscape.

Results: Renal function was significantly improved with NEVKP in comparison to SCS with decreased peak serum creatinine on POD1, and higher creatinine clearance on POD3. We detected 6354 proteins in total (FDR <0.01), with 71 proteins identified as significantly differentially expressed between experimental groups and time points (2-way ANOVA, p<0.05). Pathway enrichment analysis demonstrated that proteins increased in SCS compared to NEVKP kidneys mediated inflammation, antigen presentation, extracellular matrix production and fibrosis (e.g. THBS1, XRCC6, TMCO1, JUN, CD40). We identified microRNAs predicted to regulate these SCS-dominant proteins (e.g. miR-129, miR-206). In contrast, proteins increased in NEVKP compared to SCS were mostly metabolic, mediating energy production through TCA cycle (ACO2, COX4I1, ATP5J2, ETFB, MPC2, NDUFAF7). These proteins were predicted to be regulated by miR-203 and miR-199, and the transcription factor ZNF143.

Conclusions: NEVKP may thus repair grafts by diminishing inflammatory/fibrotic signals and altering metabolism via the TCA cycle. Conversely, proteins enriched in SCS kidneys are associated with fibrogenic and inflammatory pathways. Our findings may yield novel therapeutic targets to attenuate injury associated with warm ischemia.

Funding: Private Foundation Support

FR-PO844

RNA-Seq Analysis of Human Renal Allograft Biopsies Reveals Key Mediators of Interstitial Fibrosis/Tubular Atrophy

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Background: Interstitial Fibrosis/Tubular Atrophy(IFTA) is the final common pathway of most progressive renal diseases and is a potent predictor of renal outcome in both native and transplanted kidneys. IF/TA is a major cause of late allograft loss; however, our understanding of the molecular mechanisms underpinning this complex process remains incomplete.

Methods: We performed RNA-Seq gene expression profiling on renal tissue from transplanted patients undergoing a clinically indicated biopsy (n=21). IF/TA was determined from the renal biopsy report, and by quantitative morphometric analysis. Bioinformatic analysis was performed by DESeq2 to obtain differentially expressed (DE) genes. Ingenuity Pathway Analysis and MatInspector were employed to identify the key pathyways & transcription factors related to the dysregulated genes. NetworkAnalyst was used to generate a gene-protein interaction network.

Results: We identified 671 DE genes (381 upregulated, 236 downregulated; FDR<0.1) between severe and mild/moderate IF/TA in our cohort. Pathway analysis revealed that B-Cell development, NRF2-mediated oxidative stress response & superoxide radical degredation comprise the top canonical pathways associated with the perturbed genes in our dataset. Pivotal upstream regulators are associated with lymphoid cell development (SPI1), proteasomal degradation (BACH1,LONP1) & regulation of antioxidant proteins (NFE2L2). In silico cell-type enrichment analysis reveals enhanced transcriptional signatures from CD19+ B-Cells, Dendritic cells & CD4+ T-cells in the expression profiles of patients with severe IF/TA. DE genes were validated using external datasets prior to generating a gene-protein interaction network. Zero & first order interactions were examined. Significant gene modules detected in the networks relate to oxidative stress and mitochondrial function, T & B-Cell signalling, ECM-Receptor interaction, scaffolding proteins & chemokine signalling pathways.

Conclusions: Our dataset reveals novel molecular signatures and transcriptional regulators central to IF/TA using systems biology tools. These data underscore a prominent role of inflammation and oxidative stress in the development of IF/TA and reveal novel potential mediators of this process.

FR-PO845

Proteomics of Microdissected Glomeruli and Tubulointerstitium Reveals Compartment-Specific Alterations in the Extracellular Matrix of Kidney Allografts with Antibody-Mediated Rejection

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Background: Kidney transplantation is the optimal treatment for end-stage kidney disease, but most grafts fail prematurely. Antibody-mediated rejection (AMR) is responsible for >50% of graft loss. AMR is caused by antibodies against HLA and non-HLA antigens, which are directed against proteins in the two main compartments of the kidney: glomeruli and tubulointerstitium (TI). We hypothesized that renal AMR is associated with compartment-specific proteome alterations that may uncover the mechanisms of early antibody-mediated injury.

Methods: We performed laser capture-microdissection to isolate glomeruli and TI from paraffin-embedded kidney biopsies, and subjected samples to proteome analysis on Q-Exactive mass spectrometer. We compared 8 biopsies with pure AMR with 23 matched 'non-AMR' biopsies with cellular rejection (ACR) or acute tubular necrosis (ATN). Biopsies were for-cause and scored using Banff criteria-2017.

Results: Biopsies were performed early post-transplant; none of them had marked fibrosis. AMR biopsies were C4d+ and had no chronic lesions. We identified 2026 proteins in glomeruli and 2426 in TI. Podocyte-specific proteins were exclusively found in the glomeruli (NPHS1, PTPRO), and tubular proteins were found only in TI (CUBN, UMOD), indicating compartment-specific enrichment. 141 proteins were differentially expressed in AMR vs. non-AMR glomeruli (73 up- and 68 downregulated) and 123 in TI (15 up- and 108 downregulated). Proteins involved in HLA-mediated antigen presentation were increased in both AMR compartments. Interestingly, proteins significantly decreased in both compartments in AMR (e.g.LAMC1, COL1A1, NID1) belong to basement membranes and processes such as integrin signaling, collagen, extracellular matrix (ECM) and cytoskeleton. Levels of collagens, laminins, and other ECM proteins directly correlated (R>0.7; p<0.05), suggesting co-regulation in renal AMR.

Conclusions: Basement membranes are often remodeled in late chronic AMR and are the targets of non-HLA antibodies, suggesting that these proteomic changes may represent early, important alterations in AMR. Targeting early ECM remodeling in AMR may represent a new therapeutic opportunity.

FR-PO846

The Difference of IgA1 O-Glycosylation Between IgA Nephropathy Transplant Recipients and IgA Deposition Donors

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Background: IgA nephropathy (IgAN) is most common primary glomerulonephritis, and recurrence of IgAN after renal transplantation is frequent. On the other hand, IgA deposition (IgAD) from donor kidney without any manifestation of renal disease is often observed. The reason why IgA depositionD does not progress to IgA nephropathyN is not clear. In this study, we firstly analyzed the frequency of IgAD in living renal transplant donors, and we secondarily evaluated the IgA1 *O*-glycan structure in IgAN recipients, IgAD donors, and non-IgAD healthy donors (healthy donors).

Methods: We investigated *O*-glycan structure of IgA1 hinge region in 25 IgAN recipients, 17 IgAD donors, and 26 normal healthy donors matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Results: In *O*-glycans analysis using MALDI-TOF-MS, GalNAc and Gal content in HR of IgAN recipients were significantly decreased than IgAD donors and healthy donors. However, in all patterns of *O*-glycans, there was no significant difference between IgAD donors and healthy donors.

Conclusions: This is first report to compare the *O*-glycans structure in IgAN recipients and IgAD donors using MALDI-TOF-MS. Our result indicated that the decreased number of GalNAc and Gal content in HR could play pathogenic role in IgAN.

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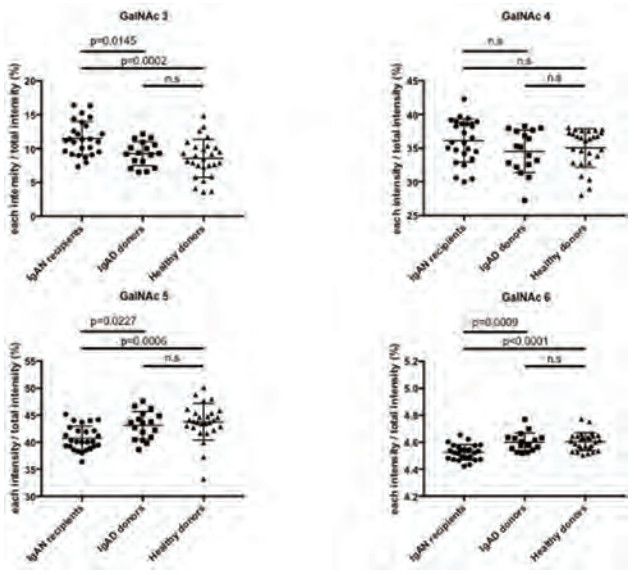
		IgAD donors N=21(13.0)	non-IgAD healthy donors N=140(87.0)	p-value
IgAN relation	related	8/28 (28.6)	20/28 (71.4)	0.0073
	non-related	13/133 (9.8)	120/144 (90.2)	
Donor age		56.1(12.1)	59.0(9.4)	0.2204
Donor sex F/M		16/5(76.2/23.8)	96/44(68.6/31.4)	0.4792
eGFR(ml/min/1.73m2)		76.9(12.4)	78.1(13.3)	0.7026
mGFR(ml/min/1.73m2)		100.0(17.7)	97.9(17.7)	0.6805
sBP(mmHg)		127.8(12.4)	121.4(18.4)	0.9216
dBP(mmHg)		77.6(11.7)	74.2(12.3)	0.8634



FR-PO847

Kynurenine 3-Monooxygenase Is a Key Mediator in the IDO Signaling Pathway for Prevention of Rejection in Experimental Kidney Transplantation

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Background: Indoleamine 2,3-dioxygenase (IDO) degrades tryptophan to kynurenine (KY), and the IDO-transprotein prevents rejection (RJX) in rat kidney transpants (KTx). KY is the substrate for KYnurinase (KYase), KYamiotransferase II (KAT), and KY 3-monooxygenase (KMO), each of which may generate immunosuppressive KYs, including the product of KMO, 3HK. Thus, in pig KTx we showed loss of graft KMO expression in RJX. 3HK is toxic to Tcells and neurons, yet tubular cells with elevated KMO appear normal, suggesting lineage specificity to 3HK toxicity. In this work, we further gauged the effect of RJX on enzymes degrading KY and studied the in vitro effects of 3HK on cultured kidney and Tcells.

Methods: Yorkshire pigs underwent allogeneic (Allo) or auto renal transplants (Auto [control for ischemia]) as we described (Trans Immun, 42:40, 2017). Allos had SLA testing and received mismatched kidneys. All pigs had R UNx before closure (control tissue). 72 hr post-op all grafts were taken and probed for IDO and tandem enzymes (qPCR, immunohistochemistry (IHC), and HPLC for IDO activity). 3HK cytotoxicity and cell proliferation was assessed using human primary kidney cortical endothelial (Endo) and epithelial (Epi) cells, and human peripheral blood Pan-T cells (Tcells).

Results: Allografts showed acute RJX (Banff 1-3), a 6X increase in IDO mRNA and 19.5X increase in IDO activity vs Auto. When compared to R UNx, KMO, KYase and KAT all showed a near 50% reduction in Autos, a change attributed to ischemia. However in rejecting Allos vs Autos, there was an over 90% reduction in KMO mRNA with no additive effect on KYase or KAT. IHC of kidney showed dramatic reductions in KMO protein in Epi and Endo cells. 3HK inhibited proliferation of active Tcells and promoted Tcell injury and death. The same and higher concentrations of 3HK had no effect on cortical Epi and Endo cells.

Conclusions: The loss of KMO, KYase and KAT from ischemia may partially explain RJX in the face of elevated IDO levels. The dramatic decline in KMO in RJX vs the other enzymes may exacerbate the process. 3HK destroys Tcells without affecting Epi or Endo cells. These data suggest that KMO is a key player mediating RJX in the IDO pathway and that the loss of 3HK from reductions in KMO may favor Tcell proliferation and promote RJX.

Funding: Private Foundation Support

FR-PO848

Dimethyl Fumarate Ameliorates Tacrolimus-Induced Nephrotoxicity in Rats

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Background: Tacrolimus (TAC) is an important maintenance immunosuppressive drug that is widely used for organ transplant. However, patients treated with TAC are at high risk of developing organ injuries such as kidney and pancreas, especially kidney is more susceptible to TAC. TAC causes renal dysfunction or failure not only on donor kidneys but also on native kidneys. The incidence is 52%, 40% and 59% in patients after kidney, liver and heart transplants, respectively. Despite the tremendous efforts to reduce TAC-induced kidney injury, satisfactory therapies have not been established because the exact pathogenesis has remained unclear. There are increasing evidences that oxidative stress is involved in both TAC-induced kidney and pancreas injuries. Dimethyl fumarate (DMF), which has recently been approved by FDA for the treatment of relapsing forms of multiple sclerosis (MS) and relapsing-remitting MS patient, is a modifier of the nuclear factor-2-keap1 pathway that induces antioxidative and antiapoptotic effects. In the present study, we investigated the effects of DMF on TAC-induced kidney and pancreas injuries.

Methods: Male Sprague-Dawley rats at 9 weeks of age were divided randomly into four groups; low-salt (LS) diet (group LS), LS+DMF (group DMF), LS+TAC (group TAC), or LS+TAC+DMF (group TAC+DMF). DMF at a dose of 50 mg/kg·BW or vehicle was gavaged once a day. TAC at a dose of 1.5 mg/kg·BW or vehicle was subcutaneously injected once a day.

Results: At 15 weeks of age, significantly elevated levels of serum creatinine and urea nitrogen were detected in group TAC. Group TAC+DMF showed significantly lower levels of them than group TAC. Both Masson's Trichrome staining and immunohistochemical collagen1 staining of rat kidney showed consistent results with renal function. On the other hand, intraperitoneal glucose tolerance test, HOMA-IR and HOMA-β showed significantly impaired glucose tolerance and β cell function in group TAC, which could not be improved by DMF.

Conclusions: DMF ameliorated kidney injury but not pancreas injury in the TAC-induced rat model. This provides a novel approach for preventing TAC-induced nephrotoxicity in patients after organ transplant. Our data also indicates that TAC-induced kidney and pancreas injuries may have different pathogenic mechanisms. We expect to further investigate the pathogenic mechanisms of TAC-induced organ injuries.

FR-PO849

The Potential Role of IL-33/ST2 Pathway in Renal Allograft Rejection

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Background: Interleukin (IL)-33 is one of IL-1 family cytokine that has pleiotropic effects, such as inflammation promotion and immune response regulation. Recent studies showed that IL-33 and its receptor, growth stimulation gene-2 (ST2) are biomarkers in heart allograft rejection. However, there is no studies about their role in renal allograft rejection. Moreover, its response according to rejection type remain unclear. We that IL-33 and ST2 expression differently express according to rejection type in renal allograft rejection.

Methods: Serum and kidney biopsy tissue were obtained from healthy controls and kidney transplanted recipients with acute antibody mediated rejection (AAMR), acute cell mediated rejection (ACMR), and chronic antibody mediated rejection (CAMR). We compared the expression of IL-33 and ST2 between 4 groups. To test the suppressive effect of anti-ST2 monoclonal antibody (anti-ST2 Ab), mixed lymphocyte reaction and chemotaxis assays by Boyden chambers were performed. We also evaluated the change of expression of IL-33/ST2 in dose of the anti-ST2 Ab (0.5 and 1 μg/ml).

Results: In comparison with the ELISA, ST2 level was higher in rejection group than in control group. The level of IL-33 was too low to be analyzed. Immunohistochemical analysis demonstrated that IL-33 and ST2 elevate in kidney tissue with rejection, especially in acute rejection. However, the expressions of IL-33/ST2 were no difference between AAMR and ACMR. In response to anti-ST2 Ab, primary human renal proximal tubular epithelial cells, which was stimulated by recipients' serum, showed a decrease in fibronectin and IL-33/ST2. IL-8, pro-inflammatory cytokine, was also decreased after treatment with anti-ST2 Ab by each group. In vitro validation, anti-ST2 Ab caused decreases in proliferation of lymphocyte and the level of IL-8. These decreases were significantly at high concentrations. We found that anti-ST2 Ab was able to significantly decrease chemotaxis.

Conclusions: Expressions of IL-33 and ST2 are higher in acute rejection than chronic rejection. Pro-inflammatory cytokines associate with IL-33/ST2 pathway during rejection. Blocking of the IL-33/ST2 axis may contribute to protect the allograft rejection.

FR-PO850

Effect of Klotho on Autophagy Clearance in Tacrolimus-Induced Renal Injury

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Background: Recently, we showed that tacrolimus-induced renal injury is closely associated with impairment of autophagy clearance, and Klotho deficiency aggravates tacrolimus-induced renal injury. In this study, we evaluated the effect of Klotho treatment on autophagy clearance in tacrolimus-induced renal injury.

Methods: We evaluated the effect of Klotho on tacrolimus-induced renal injury in an experimental mouse model and in vitro by treatment with tacrolimus and/or recombinant mouse Klotho.

Results: In vivo and in vitro studies showed that tacrolimus treatment impaired lysosomal acidification and decreased cathepsin B activity, expression of lysosome-associated membrane protein 2, and transcription factor EB (TFEB), a master regulator for lysosomal biogenesis. These results were improved by Klotho treatment. Moreover, addition of bafilomycin A1, an inhibitor of lysosomal function, abolished the protective effect of Klotho, indicating that the protective effect of Klotho was closely associated with lysosome function. Klotho induced nuclear translocation of TFEB through inhibition of phosphorylation of glycogen synthase kinase 3β (GSK3β) by confirming using CHIR99021, a GSK3β inhibitor.

Conclusions: Collectively, our data suggest that Klotho improves autophagy clearance via activation of lysosomal function in tacrolimus-induced nephrotoxicity.

FR-PO851

Self In Vivo Production of a Synthetic Biological Drug, Anti-IL-2Rα/IL-10 Fusion Protein Using Minicircles in Skin Allograft Model

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Background: Anti-IL-2Rα monoclonal antibodies are typically used to prevent acute rejection in patients after transplantation. Minicircle DNA, one of the most remarkable gene therapy technologies of late, has the advantage of being small in size, non-viral, and free of unwanted immune responses such as no bacterial backbone. The aim of this study was to investigate the therapeutic effects of anti-IL-2Rα and IL-10, anti-inflammatory cytokine, in vitro and in vivo using a minicircle vector system.

Methods: Minicircle DNA was prepared by inserting the sequences for Basiliximab (anti-IL-2Rα) and IL-10 into the parental plasmid and removing the bacterial backbone. After minicircle DNA administration, protein production for anti-IL-2Rα and IL-10 was determined in HEK293T cell line and mice, and the therapeutic effect was evaluated in skin allograft rejection model.

Results: Minicircle DNA was transfected into the HEK293T cells and observed up to 30 days and detected the protein production in the conditioned media. In mice, in vivo imaging was used to confirm that DNA expression persists for up to 30 days after single administration. The produced protein was maintained in the blood for up to 10 days. Anti-IL-2Rα/IL-10 fusion protein increased survival effect more than single protein expressing anti-IL-2Rα or IL-10 in the skin allograft rejection model.

Conclusions: Anti-IL-2Rα/IL-10 fusion protein, which is synthesized in the body using minicircle DNA, has demonstrated an effective therapeutic effect on acute rejection after transplantation. We also demonstrated the potential of the minicircle DNA as a powerful biological agent to induce immune tolerance of grafts by combining various therapeutic target designs.

FR-PO852

Accelerated Cellular Senescence Associated with CFHR3-1 Variants Influences Graft Survival in IgA Nephropathy Transplanted Patients

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Background: The deletion of complement factor H-related genes 1 and 3 (CFHR3-1Δ) has been associated with a decreased risk of IgA nephropathy (IgAN) and is in linkage disequilibrium (LD) with the SNP rs6677604 ("A" allele), which can be used as a proxy to detect it. We hypothesized that CFHR3-1Δ is also implicated in the processes that influence graft survival in recipients with IgAN and tested whether cellular senescence is involved in mediating the damage.

Methods: A total of 67 biopsy-proven IgAN patients who received a renal transplant at the Kidney Transplant Center of the Department of Emergency and Organ Transplantations (D.E.T.O), University of Bari between 1993 and 2017 where included in the study. The region in CFHR3-1 encompassing the SNP rs6677604 was amplified using PCR and sequenced by Sanger. Immunohistochemical expression of p16INK4A was performed on paraffin-embedded kidney transplant biopsies of 8 patients (4 with rs6677604-AA vs 4 with rs6677604-GA), and quantified using the Aperio Positive Pixel Count Algorithm. Masson's trichrome staining and quantification of positive area was performed. Clinical data at baseline and during the follow-up were recorded. An eGFR < 60mL/min/1.73m2 (MDRD equation) was considered as main outcome at a univariate and multivariate analyses.

Results: The rs6677604-A allele was found in 22 (32.8%) patients (genotype rs6677604-AG) whereas 45 (67.2%) carried the GG genotype. These two groups had no difference as for demographic features, donor and transplant-related variables (incidence of delayed graft function and acute rejection episodes). Patients with the rs6677604-GG had a worse outcome during a mean follow-up of 69 ± 62 months at univariate (P=5.81E-05) and multivariate analysis (HR 30.8; 95% IC 3.3-285.5; P=0.003). Graft biopsies in this group featured a significantly higher expression of the senescence marker p16INK4a (P=0.001) in tubular epithelial cells showing increased levels of fibrosis (P=0.005).

Conclusions: These findings suggest that CFHR3-1Δ and its proxy rs6677604 are associated with long term graft function in transplant recipients with IgAN nephropathy through mechanisms involving accelerated cellular senescence.

FR-PO853

Extracellular Vesicles (EVs) Induce Tubular Epithelial Cells (TEC) Inflammaging in Antibody-Mediated Rejection (AMR)

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Background: Recent data suggest a strong correlation between chronic kidney disease development and activation of accelerated senescence processes known as "inflammaging" in tubular epithelial cells (TEC). However, the role of TEC inflammaging and its mediators in kidney transplantation remains incompletely understood.

Methods: Renal biopsies of 10 transplanted patients with Acute and Chronic AMR were collected. Serum samples (5% for 24h) and EVs isolated from the same patients ($5E^{+4}$EVs/cells target for 24h) were incubated with primary culture of TEC (3th passage); p21 and p53 gene levels were measured by qPCR to assess TEC senescence. IHC staining for markers of inflammaging ($p16^{INK4a}$ and Klotho) were performed on paraffin tissue of the same patients.

Results: Pre-implantation biopsies did not showed signs of TEC Inflammaging. TEC from patients with Chronic AMR expressed significant levels of $p16^{INK4a}$ indicating occurrence of senescence phenotype, compared with Acute AMR ($p<0.05$). *In vitro*, the exposure of TEC to serum of Acute and Chronic AMR patients induced senescence by up-regulating of p21 and p53 gene levels, compared to basal condition ($p<0.05$). Interestingly, EVs isolated from the AMR patients induced senescence *in vitro* promoting a significant increase in p21, p53 and cyp1b1 gene level, and a down-regulation of klotho gene ($p<0.05$).

Conclusions: Our data demonstrated that TEC inflammaging induced by EVs might represent a new pathogenetic mechanism involved in acute and chronic AMR and could be identified as a potential new therapeutic target to counteract accelerated aging in kidney transplantation.

FR-PO854

The (R)-Enantiomer of the 6-Chromanol Derivate SUL-121 Counteracts Renal Vasoconstriction by Antagonism of the A1-Adrenoceptor

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Background: In kidney transplantation, impaired graft perfusion associates with decreased graft survival. Disturbed adrenergic signal transduction during rewarming is an important factor limiting renal perfusion. Recently, we developed a class of 6-chromanol based SUL-compounds which maintain mitochondrial function and limit reactive oxygen species (ROS) during cooling and metabolic stress. Here, we investigate the effects of SUL-121 on vascular function of porcine kidneys.

Methods: Porcine kidneys were collected at a local slaughterhouse and immediately flushed with UW with heparin, placed on ice and transported to the laboratory. The effects of SUL-121 and its enantiomers *(R)*-SUL-150 and *(S)*-SUL-151 on renal perfusion pressure was assessed in an isolated kidney perfusion system. In addition, rings from isolated intrarenal arteries were used to measure constriction responses to various agonists after pre-incubation with SUL-compounds. Receptor binding and intracellular calcium transients were assessed in α_1 adrenoceptor transgenic CHO cells. Molecular docking simulation was performed in an α_1 adrenoceptor flexible homology model using Induced Fit software.

Results: Addition of SUL-121, SUL-150 but not SUL-151 caused a decrease (-11±1, -13±2 and -1±1 mmHg, respectively) in renal perfusion pressure. Pre-incubation with SUL-121 and SUL-150 competitively inhibited contraction responses to the α_1 adrenoceptor agonist phenylephrine (pA_2 5.37±0.03). SUL-151, other 6-chromanols and their metabolites were without effect. Contraction responses to histamine and U46619 were not influenced by SUL-150. Phenylephrine-induced calcium signalling was similarly inhibited by SUL-150 in transgenic CHO cells (pA_2 5.31±0.03). SUL-150 effectively displaced radiolabelled prazosin in a competitive binding assay. Simulation of molecular docking demonstrated shared binding characteristics of SUL-150 and prazosin.

Conclusions: SUL-150, the *(R)*-enantiomer of SUL-121, is an antagonist of the α_1 adrenoceptor with ligand-receptor interactions similar to prazosin. Considering the improvement of renal perfusion through adrenergic antagonism in addition to previously reported beneficial effect on mitochondrial function and ROS production, we propose SUL-150 as a novel and unique protectant in kidney transplantation.

Funding: Commercial Support - Sulfateq B.V., Groningen, Netherlands

FR-PO855

Effect of Deceased Donor Inflammatory Pathways on Chronic Renal Graft Dysfunction

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Background: In deceased donor (DD) renal transplantation an inflammatory activity is established prior to nephrectomy. It produces macrophage infiltration and has been associated with the onset of fibrosis. Adenosine exerts its anti-inflammatory activity mainly through the A2A receptor. Monocytes and macrophages release TNF-α which induces A2A activity and mediates renal interstitial fibrosis through an increase in TGF-β1 and macrophage M2 switching. The aim of this study is to determine the effect of DD inflammation on chronic renal graft dysfunction.

Methods: Samples of pre-implantation renal tissue, 17 from living donor (LD) and 40 from DD were analyzed by Real-time PCR with the TaqMan® OpenArray® and western-blot.

Results: Infiltration of macrophages in DD kidneys was significantly greater than in LD. The expression of TNF-α, TGF-β1 and A2A was also higher than in LD and correlated positively with each other. A2A receptor also correlated with: pro-fibrotic markers such as α-SMA, fibronectin, vimentin, and collagen; the enzyme adenylate cyclase and the M2 macrophage marker CD163, C/EBPβ and IL-10, which are most expressed in DD kidneys. Western-blot results show PKA and CREB activation and increased CD163 and A2A protein translation.

Conclusions: TNF-α-mediated inflammation in DD kidneys is associated with the increase/activation of anti-inflammatory factors such as TGF-β1 and adenosine receptor A2A. Our results indicate that the activation of this pathway induces PKA-mediated CREB phosphorylation, which in turn stimulates transcription of C/EBPβ and promotes the induction of factors that could lead to fibrosis in the renal graft via M2 macrophages.

Funding: Government Support - Non-U.S.

FR-PO856

Tacrolimus Results in Increased CTGF Expression by Human Proximal Tubule Cells and Is Associated with Donor ABCB1 3435C>T Genotype

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Background: Clinical studies have demonstrated the importance of genetic variation in *CYP3A5* and *ABCB1* for tacrolimus disposition and suggested a role in the development of renal fibrosis associated with long-term tacrolimus treatment. Our aim was to explore the implications of tacrolimus exposure in a model of human proximal tubule cells incorporating genetic variation in *CYP3A5* and *ABCB1* on the expression of profibrotic cytokine CTGF and correlate these findings with CTGF expression in kidney allograft biopsies.

Methods: We selected 8 clones of human conditional immortalized PTC (ciPTC) with 4 different combinations of *CYP3A5 (rs776746)* and *ABCB1 (rs1045642)* genotypes. Cells were incubated with vehicle, 50 ng/ml and 300 ng/ml tacrolimus (in vivo concentration range). Quantitative RT-PCR and western blot were performed to study CTGF expression. In addition, CTGF staining was performed on protocol biopsies with a known pharmacogenetic background derived from 21 allograft recipients over a period of 2 years.

Results: CTGF mRNA and protein expression increased with tacrolimus concentration (CTGF vs. β-actin vs. vehicle at 50ng/ml: + 34.1% (95% CI: 22.3 - 45.9) and at 300 ng/ml: +45.0% (95% CI: 35.2 - 54.8); p<0.001). Subgroup analysis demonstrated 46% higher protein expression in *CYP3A5 *3/*3* allele carriers vs. **1* allele carriers (p=0.047) and more than 2-fold higher CTGF expression in *ABCB1 3435 TTs*, while in the genetic *CC/CT* counterparts CTGF expression decreased (p=0.01). Immunohistochemical studies of protocol biopsies demonstrated a 37.1% increase in tubular cell CTGF staining between 3 to 24 months in kidneys from *3435 TT* genotype donors, while in *CC/CT* donor grafts the percentage of CTGF positive tubuli remained stable (p=0.015).

Conclusions: Tacrolimus exposure in human PTCs results in a concentration-dependent increase in CTGF expression. Tacrolimus exposure for 72 hours resulted in increased CTGF expression in PTC derived from *CYP3A5 *3/*3* allele carriers, and in particular with the *ABCB1 3435TT* genotype. Immunohistochemical studies on protocol biopsies confirm increasing CTGF expression over time in donor kidneys with the *ABCB1 3435TT* genotype.

Funding: Government Support - Non-U.S.

FR-PO857

A Biomarker of Collagen Type VI Formation Is Associated to Allograft Outcome in Kidney Transplant Recipients

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Background: A careful evaluation of kidney transplant recipients is important for a successful allograft outcome. Non-invasive biomarkers are needed to predict immediate and long-term kidney function after transplantation. Preliminary findings have identified PRO-C6, a non-invasive biomarker of collagen type VI formation related to burden of kidney fibrosis, as a good prognostic marker for kidney function loss and mortality in chronic kidney disease patients.

Methods: Here we evaluate the prognostic potential of PRO-C6 in kidney transplant recipient by measuring PRO-C6 in plasma of 219 patients before transplantation, and 1 day, 3 months and 12 months after transplantation, by means of an ELISA developed at Nordic Bioscience.

Results: Levels of the serum PRO-C6 decreased significantly from baseline (median, 95% CI: 50.7, 46.7-53.5) to day 1 (median, 95% CI: 34.8, 31.1-38.3) and further decreased at month 3 (median, 95% CI: 14.2, 12.7-14.5), but not significantly from month 3 to month 12 (median, 95% CI: 13.5, 12.7-14.5). PRO-C6 correlated with plasma creatinine before transplantation (rho =0.43, p<0.0001), 1 day after rho for PRO-C6 vs plasma creatinine was 0.67, p<0.0001, at 3 months after rho for PRO-C6 vs measured GFR was -0.58, p<0.0001, and at 12 months after rho for PRO-C6 vs measured GFR was -0.57, p<0.0001. PRO-C6 measured either before transplantation and at day 1 after transplantation could identify patients who required dialysis one week after transplantation (delayed graft function) (AUC: 0.679, p<0.0001; and AUC: 0.860, p<0.0001, respectively). PRO-C6 measured 1 day after transplantation identified patients who still required dialysis three months after transplantation (AUC: 0.789, p<0.0001). Plasma creatinine measured one day after transplantation did not have any prognostic ability to identify patients with no graft function after 3 months. PRO-C6 measured 1 day after transplantation was also associated to the time needed to reach a 50% reduction in plasma creatinine after transplantation (HR per doubling of PRO-C6: 0.659 (0.548-0.792), p<0.0001).

Conclusions: PRO-C6 measured in plasma was associated with delayed graft function and no function at 3 months after transplantation and it can potentially be used to identify the patients at risk of graft function loss.

Funding: Commercial Support - Nordic Bioscience

FR-PO858

Liposomal Delivery Improves the Efficacy of Prednisolone to Reduce Renal Inflammation in a Mouse Model of Acute Renal Allograft Rejection

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Background: Allograft rejection remains one of the main obstacles in kidney transplantation. Although treatment with high doses of corticosteroids is often efficacious, systemic exposure and activation of the glucocorticoid receptor (GR) results in substantial side effects. In this study we used a mouse model of acute renal allograft rejection to investigate whether liposomal encapsulation could facilitate local delivery of prednisolone to the allograft and enhance its therapeutic effect.

Methods: Male BalbC^{HanZtm} recipients received a kidney transplant from male C57BL/6J^{HanZtm} donors (n=10 per group). Recipients were injected daily with 5 mg/kg cyclosporine A and received either 10 mg/kg prednisolone (P), or liposomal prednisolone (LP) intravenously on day 0, 3, and 6, or no additional treatment (NA). Functional MRI was performed at day 6 (N=6) to study graft perfusion and organs were harvested at day 7 for FACS- and qPCR analysis.

Results: MRI analysis revealed better allograft perfusion upon LP treatment, as compared to NA treatment (428.3±114 vs 218.5±117 ml/min*100g, p<0.05) while P vs NA treatment showed no significant improvement. FACS analyses of allografts revealed a reduced number of CD45+ leukocytes in LP vs P or NA treatment (5,3 and 6,6 fold decrease, p<0.05), less CD3+ T cells in LP vs NA (3,7 fold decrease, p<0.05), and less F4/80+ macrophages in LP vs P and NA (4,3 and 4,2 fold decrease, p<0.05). Upon LP treatment, the expression of the GR responsive gene *Fkbp5* was upregulated in the allograft, as compared to P and NA treatment (3,7 and 4,4 fold change, p<0.05). This was also observed in the spleen, but not in the heart, a non-target organ.

Conclusions: Liposomal delivery results in a higher local bioavailability of prednisolone, increased perfusion and a reduced cellular infiltrate in the transplanted kidney, compared to conventional prednisolone. Future clinical studies should reveal if treatment with LP results in improved efficacy and reduced side effects in patients with renal allograft rejection.

Funding: Commercial Support - Enceladus Pharmaceuticals B.V., Private Foundation Support

FR-PO859

Variability in Outcome in Patients with DSAs Is Modulated by the Expression of HLA Antigens on the Allograft Endothelium

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Background: The development of *de novo* donor-specific antibodies (DSAs) is associated with antibody-mediated rejection and allograft failure. However, some patients with DSAs escape graft rejection. We hypothesized that DSA-mediated injury is modulated by 1) the variability in expression of HLA-II antigen subtypes (DR, DP and DQ) on a within-patient basis and 2) the variability in HLA antigen expression on a between-patient basis.

Methods: We measured *in vitro* HLA-I and II (DR, DP and DQ subtypes) antigen expression on 2 glomerular endothelial cell lines and on blood outgrowth endothelial cells (BOEC) from patient's collected PBMCs (n=12). Endothelial cells were treated following a time-course of IFN-g for 10 days to induce HLA-II expression. HLA antigen expression was assessed by flow cytometry over time. Unstimulated cells were used as controls.

Results: Across all individuals, the maximal percentage and the standard deviation of HLA-positive cells varied substantially (97±3 vs. 96±3 vs. 89±9 vs. 44±37% for HLA-I vs. –DR vs. –DP, vs –DQ respectively, $p<0.001$) as well as the time of incubation to reach maximal expression (5±2 vs. 4±1 vs. 6±2 vs. 9±1days, $p<0.001$). Maximal MFI also varied between HLA subtypes (98±49 vs. 12±8 vs. 10±6 vs. $4\pm3x10^3$, $p<0.001$) as well as the time to reach this maximum (4±1 vs. 6±2 vs. 8±2 vs. 10±1days, $p<0.001$). Repeated experiments on the same individuals showed little variation between experiments (mean SD 12±8 vs. 7±5 vs. 6±4 vs. 1±1, $p<0.07$), indicating that the variability was not due to inter-assay variation.

Conclusions: Among HLA-II subtypes, the DR antigen seems to be the most inducible, whereas DQ has a lower and more variable expression. The use of BOEC is breaking new in the analysis of HLA antigen expression *in vitro*. A better understanding of the expression of DSA ligand could be instrumental in our understanding of antibody-mediated rejection.

FR-PO860

MHC Class II Ligation on Glomerular Endothelial Cells Upregulates Adhesion Molecules and Chemoattractants

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Background: Microvascular injury and leukocyte margination across endothelial cells are key pathologic processes in kidney allograft rejection. The mechanisms of glomerular endothelial cell injury and leukocyte infiltration remain unclear. We hypothesize MHC class II ligation on glomerular endothelial cells will result in upregulation of adhesion molecules and chemoattractants.

Methods: A Bl/6 mouse glomerular endothelial cell (MGEC) line was stimulated with IFNγ to upregulate MHC class I and II; then incubated with anti-MHC class II antibodies or plasma from balb/c mice sensitized with Bl/6 splenocytes. Expression of adhesion molecules were assessed by flow cytometry. Gene expression was measured by RT2 profiler and Taqman RT PCR. Cytokine expression was analyzed in culture supernatants with LegendPlex.

Results: MGEC stimulated with IFNγ upregulated gene expression of TRAIL, RANTES, MCP-1, caspase1, beta2microglobulin, Vcam1, IL-6 and Icam1 (**A**). IFNγ stimulation of MGEC increased surface expression of MHC class I, MHC class II, VCAM1, and ICAM1; but not P-selectin **(B)**. Subsequent ligation with MHC class II antibody transiently increased surface expression of P-selectin at 6 hours; while sensitized plasma resulted in a greater increase in P-selectin, which persisted at 24 hours (**C**). MGEC secretion of chemoattractants (MCP-1 and RANTES) increased with IFNγ stimulation and was further enhanced with MHC II ligation (**D**). Adhesion molecules and MHC co-localize on the cell surface (**E**).

Conclusions: MHC II crosslinking on MGEC resulted in an upregulation of P-selectin as well as chemoattractants. MHC molecules and adhesion molecules are co-localized on the endothelial cell surface. Future studies will examine therapeutic targets, such as inhibitors of mTOR (inhibition of ICAM1 clustering) and Nox4 (TRAIL pathway).

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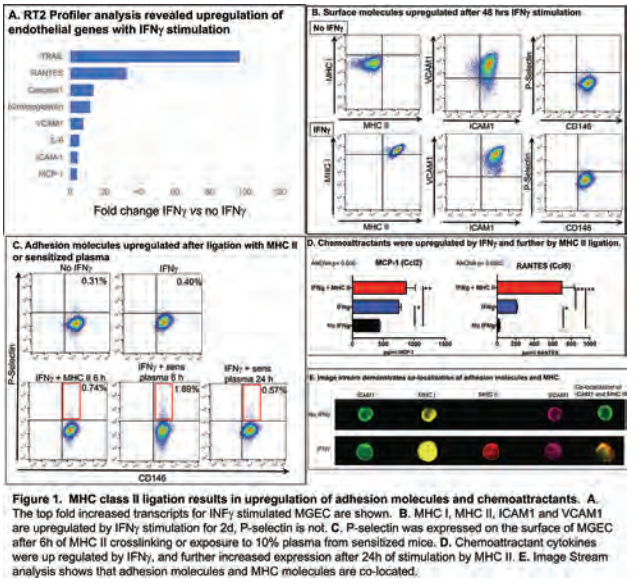

Figure 1. MHC class II ligation results in upregulation of adhesion molecules and chemoattractants. A. The top fold increased transcripts for INFγ stimulated MGEC are shown. **B.** MHC I, MHC II, ICAM1 and VCAM1 are upregulated by IFNγ stimulation for 2d, P-selectin is not. **C.** P-selectin was expressed on the surface of MGEC after 6h of MHC II crosslinking or exposure to 10% plasma from sensitized mice. **D.** Chemoattractant cytokines were up regulated by IFNγ, and further increased expression after 24h of stimulation by MHC II. **E.** Image Stream analysis shows that adhesion molecules and MHC molecules are co-located.

FR-PO861

B Cell Deficiency in a Rat Kidney Transplant Model Reduces Glomerular Basement Membrane Duplication in Early Transplant Glomerulopathy

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Background: B cells play core roles in the humoral response and are able to contribute to cellular immunity, but the specific role of B cells in early transplant glomerulopathy (TG) remains unclear. We hypothesize B cell deficiency will attenuate the pathology of TG.

Methods: A rat kidney transplant model was used with 4 treatment groups: **Syngeneic** (Lewis to Lewis), **Allogeneic** (Fisher to Lewis), **Sensitized** (Fisher to Lewis 3 weeks following donor blood transfusion), or **Allogeneic B cell deficient ($B^{-/-}$)** recipients (Fisher to $B^{-/-}$ Lewis). All animals were harvested at 3 or 6 months. The following 5 parameters were measured by electron microscopy: duplication of glomerular basement membrane (GBM), total length of GBM, diameter of endothelial cell (EC), height of EC, and layers of peritubular capillary basement membrane (PTCBM). The ratio of GBM injury and mean data was determined among these groups.

Results: At 3 months after transplant, GBM duplication was reduced between $B^{-/-}$ recipients and sensitized recipients (10.2±0.8% versus 6.5±0.7%; p=0.01). The percent of GBM with duplication was reduced at 6 months after transplant in $B^{-/-}$ recipients compared to allogeneic and sensitized recipients ($B^{-/-}$:8.5±1.1%, allogeneic:17.2±0.8%, sensitized:32.6±3.3%; $p<0.001$) (Figure 1). The mean maximum diameter and the mean height of EC demonstrated no differences among allogeneic, sensitized, and $B^{-/-}$ recipients in both 3 and 6 months samples. PTCBM multilayering was also similar among allogeneic, sensitized, and $B^{-/-}$ recipients in both 3 and 6 months samples.

Conclusions: B cell deficiency in this model reduces the duplication of GBM in early TG. The GBM injury occurs before obvious EC injury and PTCBM multilayering. Future studies of B cell directed interventions are needed in TG.

Funding: Other NIH Support - This project was supported by the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR000427, and the KL2 training Award (KL2TR000428).

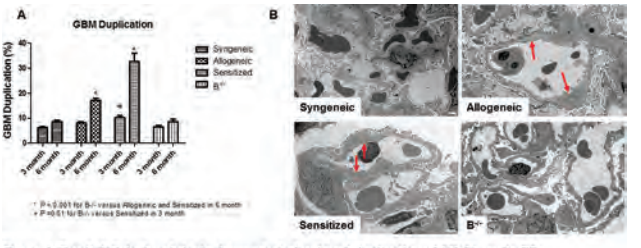

Figure 1. B cell deficient recipients demonstrated reduced duplication of GBM in early TG.
(A) Electron microscopy showed reduced duplication of GBM in $B^{-/-}$ recipients at 3 and 6 months.
(B) Representative photos of pathology at 6 months is shown. Areas of GBM duplication are highlighted with red arrows.

FR-PO862

An Optimized Protocol to Quantify Signaling in Human Transitional B Cells by Phospho Flow Cytometry

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Background: Phospho flow cytometry is a powerful technique to analyze signaling in rare cell populations. This technique, however, requires harsh conditions for cell fixation and permeabilization, which can denature surface antigens or antibody-conjugated fluorochromes. These are among several technical limitations which have been a barrier to quantify signaling in unique B cell subsets. One such immature subset, transitional B cells (TrBs), may play a role in suppressing solid organ transplant rejection, graft-versus-host disease, autoimmunity, and even the immune response to malignancy. Here we sought to optimize a protocol for quantification of signaling in human TrBs compared with mature B cell subsets.

Methods: TrBs were defined by surface marker expression as $CD19^{+}CD24^{hi}CD38^{hi}$. Key parameters optimized included antibody clone selection, sequence of surface epitope labeling in relation to paraformaldehyde-based fixation and methanol-based permeabilization, photomultiplier tube (PMT) voltages, and compensation. Special attention was paid to labeling of CD38 with regard to these parameters, and an optimized protocol enabled reliable identification of TrBs, naïve ($CD24^{+}CD38^{+}$), early memory ($CD24^{hi}CD38^{-}$), and late memory ($CD24^{-}CD38^{-}$) B cells.

Results: Phospho flow cytometry enabled simultaneous quantification of phosphorylation among at least three different signaling molecules within the same sample. Among normal donors, transitional B cells exhibited diminished mitogen activated protein kinase/extracellular signal-regulated kinase and Akt phospho signaling upon nonspecific stimulation with phorbol 12-myristate 13-acetateand ionomycin stimulation.

Conclusions: We optimized an effective protocol to quantify B cell subset signaling upon stimulation. Such a protocol may ultimately serve as the basis for assessing dysfunctional B cell signaling in disease, predict clinical outcomes, and monitor response to B cell-directed therapies.

FR-PO863

Utility of Immunoglobulin/T-Cell Receptor Gene Rearrangements As a Tool for Early Detection and Monitoring of Post-Transplant Lymphoproliferative Disorder in Renal Transplant Recipients

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a well-known complication post-transplant and contributes significantly to the morbidity and mortality seen in transplant recipients. A key limitation in the management of this dreaded disease involves its early detection and subsequent monitoring. A potential solution involves Ig/TCR gene rearrangement analysis. This molecular clonality analysis technique is based on the principle that, all cells of a malignancy have a common clonal origin and demonstrate clonally rearranged Ig or TCR genes. The diagnosis of malignant B- and T-cell proliferations is therefore supported by the finding of Ig/TCR gene clonality, whereas reactive lymphoproliferations show polyclonally rearranged Ig/TCR genes. We report our experience with two renal transplant recipients with PTLD whereby Ig/TCR gene rearrangements may play a role in the surveillance of this lymphoproliferative disorder.

Case Description: The 2 patients reported underwent cadaveric renal transplantation with subsequent development of PTLD. Both had reduction in immunosuppressants with rituximab therapy, following diagnosis of PTLD. One of the patients went on to CHOP chemotherapy and even lost her renal allograft secondary to PTLD involvement. Both patients were in clinical, hematological and radiological (PET scan) remission at the point of performance of Ig/TCR gene rearrangements. In these two pediatric renal transplant recipients with PTLD, it was noticed that there were Ig/TCR gene rearrangements detectable in their peripheral blood suggestive of clonal remnant of their PTLD.

Discussion: Lymph node/tissue biopsies remain the gold standard for the diagnosis of PTLD. Transplant recipients could not and should not be subjected to infinite repeated biopsies or expensive imaging studies (e.g. PET-CT scans) for the purpose of monitoring for the development of PTLD in view of inherent risks associated with biopsies and radiation risks, respectively. Our case report suggests the potential utility of Ig/TCR gene rearrangements as a non-invasive tool for early detection and monitoring of PTLD. Further large prospective trials are required to validate the above proposal.

FR-PO864

Multiplexed Immunofluorescence to Investigate the Immune Response to BK Virus in Kidney Transplant Recipients

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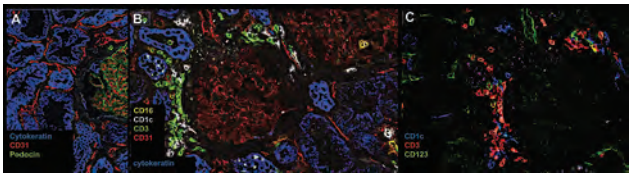
Background: BK virus nephropathy is a complication in renal transplant that leads to allograft dysfunction or failure. Acute inflammation, tubular atrophy, and interstitial fibrosis are seen in both BKVN and acute rejection making it challenging to differentiate. Previous studies have characterized the immune response on histology, but the identification and characterization of infiltrating cells was limited due to constraints of traditional immunohistochemistry. Multiplexed immunofluorescence allows a more comprehensive understanding of the spatial relationships of immune cell phenotypes and ongoing signals within the kidney microenvironment.

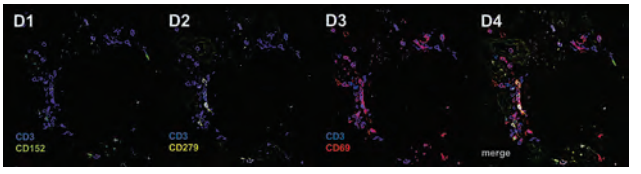
Methods: Using CO-detection by inDEXing (CODEX), the expression of 50 markers for identifying renal structural elements, immune cell subsets, and immune function were evaluated on a single tissue section of a pediatric kidney transplant recipient.

Results: See images and caption for results.

Conclusions: CODEX is a novel technique in characterizing the immune repertoire in BKVN and visualizing renal histology. Predominant immune infiltrate in BKVN consists of T cells, plasmacytoid and myeloid dendritic cells, and sparse NK cells, which have not been previously described. A majority of CD3 T cells in BKVN appear to be activated and a minority expressing markers of exhaustion and inhibition. Comparing the immune repertoire of BKVN and acute rejection is an important and clinically significant future direction.



A) Renal tubules with cytokeratin, endothelial cells and blood vessels using CD31, and glomerular podocytes using podocin. B) Co-localization of CD3 T cells (green), CD1c myeloid dendritic cells (white), CD16 NK cells (yellow). C) Infiltration of interdigitating plasmacytoid dendritic cells (green) and myeloid dendritic cells (blue) in a cluster of T cells (red).



D) Functional analysis of CD3 T cells (blue) show co-expression of markers of inhibition with CD152/CTLA4 (green), exhaustion with CD279/PD1 (yellow), activation with CD69 (red), D4 shows a merge of all markers.

FR-PO865

Inhibition of Cyclophilin A and Large T Antigen Interaction Reduces Polyomavirus BK Replication

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Background: Specific treatment for polyomavirus BK (BKV) infection in kidney transplant recipients remains unsolved. We previously demonstrated that cyclophilin A (CypA) was crucial for BKV replication. The aim of this study was to assess the impact of interaction of CypA and BKV large T antigen (TAg) on BKV replication.

Methods: HRPTEC or HK-2 were used in this study.

Results: The immunoprecipitation (IP) revealed an interaction between TAg and CypA. Similarly, the ELISA assays using purified TAg and CypA confirmed a binding between CypA and TAg. Atomic force microscope (AFM) revealed a binding between TAg and CypA. This binding was reduced if the TAg-coated probe was pretreated with anti-TAg blocking antibody. Immunocytochemistry (IHC) also verified nuclear colocolization of CypA and TAg expression. Both N-terminus (DN-CypA) and C-terminus (DC-CypA) failed to colocalize with nuclear TAg expression. The IP assay confirmed a failure of DN-CypA binding to TAg. Overexpression of DN-CypA in the CypA-knockdown cells reduced BKV replication, confirming that the N-terminus of CypA binding to TAg is crucial for viral replication. Overexpression of CypA but not DN-CypA enhanced TAg-induced promoter activity of BKV. Overexpression of CypA in the NFATc3-knockdown cells still enhanced viral replication, indicating a NFATc3-independent pathway. Addition of Debio-025 caused a reduction in BKV replication. IHC showed that Debio-025 caused a reduction of nuclear CypA expression. Immunoblotting assay confirmed a dramatic reduction of CypA in the nuclear fraction by addition of Debio-025. Mutant CypA proteins at six different functional residues in the enzyme pocket of CypA (possible functional sites of Debio 025) did not affect TAg and CypA interaction detected by the IP assay and the ELISA assay. In vivo, following BKV injection, BKV copies in the kidneys were reduced in the CypA-knockout mice or in the Debio-025-treated mice, when compared with those in the wild-type mice or non-treatment controls.

Conclusions: Nuclear translocation of CypA and interaction with nuclear TAg, both of which depends on N-terminus of CypA is essential for BKV replication. Blockade of the CypA-dependent NFAT-independent pathway by Debio-025 suppressed BKV replication. As no anti-BKV treatment is satisfactory so far, alisporivir that has no immunosuppressive effect can be potentially applied for anti-BKV treatment.

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FR-PO866

Efficacy and Safety According to Dose of Valganciclovir for Cytomegalovirus (CMV) Prophylaxis in Transplantation: Network Meta-Analysis Using Recent Data

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Background: Valgancivlovir is used to prevent post-transplant CMV infection among kidney transplantation patients. However, the dose of drug being used still remains controversial since the continuous use of such drug decrease kidney functions and induces leukopenia in some of the cases. Accordingly, the purpose is to measure the appropriate dose of the drug required for preventing CMV using network Meta analysis

Methods: We searched the Cochrane Central Register, OVID MEDLINE, EMBASE, and Pubmed until April 15, 2017. We reviewed the reference lists of relevant reviews, registered trials, and relevant conference proceedings. Definition of low dose valganciclovir group is 450mg and standard dose one is 900mg. Studies evaluating among valganciclovir 900 mg, 450 mg and controls were evaluated. We performed direct and indirect network meta-analysis using Bayesian models and generated rankings of the different dose of valgaciclovir agents by generation mixed treatment comparison (GeMTC).

Results: Twenty-four studies involving 3,730 participants were eligible. As a result of analyzing among three groups, following completion of the research, the analysis revealed that the glomerular filtration rate, graft loss, tacrolimus level, antibody mediated rejection, fungal, and *Candida* infection rates were not different among groups. Compared with control, there was no difference between low dose 0.79 [95% Crl, 0.50-1.40] and standard dose 1.0 [95% Crl, 0.61-1.60] groups when CMV incidence was compared. In the Rank probabilities table, the best order for lowering the CMV event was as high as dose of 450mg (71.1%). Incidence of leukopenia showed a significant difference, but there was no statistical significance in the low dose group 1.5 [95% Crl, 0.99-2.20] compared with the control group, but 4.3 times higher in the high dose group 4.3 [95% Crl, 2.69-7.10], which was 2.9 times higher in the low dose group and the high dose group 2.9 [95% Crl, 1.88 -4.67].

Conclusions: The use of valganciclovir did not show any difference in other side effects, but the use of low doses of leukopenia significantly reduced side effects. The incidence of CMV was not different among the three groups, but the tendency was also decreased at low dose.

FR-PO867

Cytomegalovirus Serostatus and Living Donor Kidney Transplant Outcomes in the Era of Routine CMV Prophylactic and Preemptive Therapy

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Background: The impact of CMV serostatus on living donor kidney transplant outcomes in an era when CMV prophylactic and preemptive strategies are used routinely has never been examined.

Methods: Using UNOS/OPTN data, adult patients with first living donor kidney transplant between 2010 and 2015 were stratified into 4 groups: D-/R-, D+/R-, D+/R+, and D-/R+. Death-censored graft survival, all-cause mortality and cumulative incidence of rejection at 1-year were examined using D-/R- as a reference group.

Results: A total of 28,730 recipients were included: 4,972 (17.3%) in D+/R-, 7,404 (25.8%) in D-/R-, 10,233 (35.6%) in D+/R+, and 6,121 (21.3%) in D-/R+ group. In the multivariable analysis, D+/R- was associated with an increased risk of graft failure (HR=1.18, P=0.049) when compared to D-/R-. There was also an increased risk of graft failure in D+/R+ when compared to D-/R- (HR=1.09, P=0.021). CMV serostatus did not have any statistically significant effects on all-cause mortality or acute rejection at 1 year.

Conclusions: In living donor kidney transplantation, CMV mismatch (D+/R-) is not an independent risk factor for patient mortality in the era of effective prophylactic and preemptive strategies. D+/R- and D+/R+ serostatus have a slightly negative impact on graft survival. These findings can be informative and used for patient counseling before undergoing living donor kidney transplantation.

CMV Serostatus	Graft failure		Mortality, all cause		Acute rejection at 1-year	
	HR (95% CI)	P-value	HR (95% CI)	P-value	OR (95% CI)	P-value
Main cohort						
D-/R-	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
D+/R-	1.18 (1.00-1.38)	0.049*	1.08 (0.92-1.27)	0.327	1.04 (0.97-1.11)	0.254
D+/R+	1.09 (1.01-1.18)	0.021*	1.05 (0.98-1.12)	0.197	0.96 (0.85-1.07)	0.444
D-/R+	1.04 (0.99-1.10)	0.118	1.03 (0.98-1.08)	0.302	1.04 (0.92-1.18)	0.545

*P-value < 0.05

FR-PO868

The Outcomes of Kidney Retransplantation After Graft Loss Due to BK Virus Nephropathy

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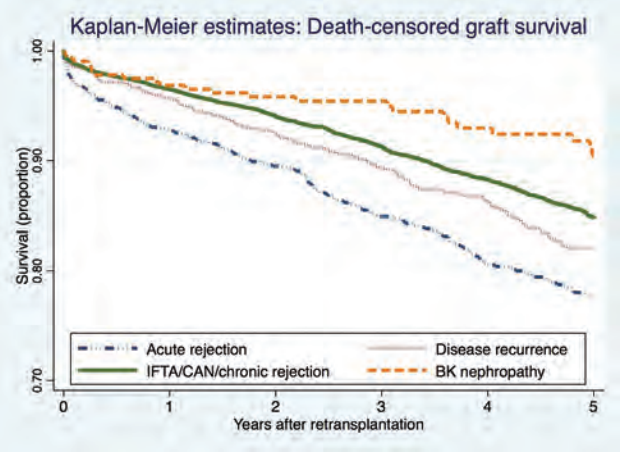
Background: Existing literature on outcomes of kidney retransplantation in patients with previous graft failure due to BK virus nephropathy (BKVN) is scarce.

Methods: Using UNOS/OPTN data, we analyzed adult patients who received their second kidney transplant between 2005 and 2015.

Results: 321 out of 15,724 patients lost their first graft to BKVN (BK-group) with a median follow-up time of 4.2 years. Of these 321 patients in BK-group, 54 patients underwent preemptive second kidney transplantation. Retransplant occurred at a median of 2.2 years after graft failure. Patients in BK-group were twice more likely to receive basiliximab when compared to patients who lost their first graft due to other causes. One-year acute rejection rate in BK-group was 15%. As of March 3, 2017, 264/321 grafts were still functioning with 6 grafts that failed due to BKVN. Kaplan- Meier death-censored graft survival rates at 1, 3, and 5-year after retransplantation in BK-group were 96.9%, 95.4%, and 90.5%, respectively, which were comparable to other causes of graft loss (and perhaps superior to patients who lost their first graft due to acute rejection) [Figure 1]. Patient survival in BK-group was similar to other causes of graft loss. The log-rank test was not performed due to unbalanced sample sizes across the groups.

Conclusions: Retransplantation after graft loss due to BKVN appears to be associated with good outcomes. However, the clinical interpretation of this study is limited by the lack of information on viral clearance and transplant nephrectomy prior to retransplantation.



FR-PO869

Impact of Antiviral Dose Adjustments on Risk for Breakthrough CMV Viremia After Kidney Transplantation

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Background: CMV infection continues to cause significant morbidity in kidney transplant recipients in the modern era of transplantation. CMV seronegative patients with CMV seropositive donors are at highest risk for complications, including invasive disease and loss of allograft function. Inadequate drug dosing is associated with breakthrough viremia and drug resistance. We sought to evaluate whether drug dosing was associated with CMV viremia.

Methods: We reviewed CMV PCR testing results from 1297 adult kidney transplant recipients (excluding multiorgan transplants) between the years 2013-2017. We performed chart review to obtain antiviral prophylaxis regimens prior to viremia, and assessed sCr and calculated GFR at regimen start. Adequacy of dose adjustment for renal insufficiency was determined based on the package insert for valganciclovir to determine whether there was an association between antiviral dosing and breakthrough CMV viremia.

Results: We identified 14 seronegative kidney transplant recipients who developed CMV viremia during the first year after transplantation. 9 had received basiliximab (64%) and 5 (36%) antithymocyte globulin. 3 patients experienced biopsy-proven rejection (2 ACR and 1 AMR) prior to CMV viremia. The median time to viremia was 75 days (range 62-178). 5 patients (36%) were not taking valganciclovir at the time of viremia detection, while 9 patients (64%) were on valganciclovir. 8 of the 9 (89%) patients on valganciclovir were on dose-adjusted regimens at the time of viremia, correct according to the Valcyte package insert, at doses ranging from 450 mg once daily to 450 mg 3x/week.

Conclusions: Despite appropriate valganciclovir dose-adjustment, breakthrough CMV viremia occurred. This suggests that renal impairment is associated with CMV infection either because standard dose adjustments are inadequate, impaired drug absorption, or exacerbation of impaired CMV immune response. This suggests a role for therapeutic drug monitoring, and for the need for more effective antiviral prophylaxis medications. Future

studies will evaluate patterns of drug dosing associated with CMV viremia in seropositive transplant recipients. Immunologic analysis will be performed to identify patients lacking effective CMV-specific immune response in need of prolonged antiviral prophaylaxis.

FR-PO870

The Molecular Profile in Kidney Allograft Highlighting Subclinical Acute Rejection (SAR): Towards a Targeted Treatment

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Background: SAR diagnosed by protocol biopsy is an independent risk factor for chronic allograft injury. We organized a molecular study on 24 AB0 compatible cadaveric kidney transplant recipients with standard immunological risk who received protocol biopsy in the first post-transplant year. Aim of our study was to identify specific gene expression changes that characterize SAR and to highlight specific therapeutic interventions based on the molecular fingerprints.

Methods: Total RNA was extracted from archival FFPE renal tissue samples of 12 patients with SAR scored by 2 pathologists according to the updated Banff criteria and a control group of 12 patients with normal histological findings in protocol biopsies performed at 3- and 12-months post-transplant. All patients had a stable renal function (mean serum creat < 1.65 mg/dL). The cRNA fragments were hybridized on GeneChips Agilent. Genome-wide gene expression profiles were generated and bioinformatic analysis was done with Genespring. A false discovery rate (FDR) <0.02 and fold change > 2 were applied. Canonical pathways and biological functions were explored using Ingenuity pathway analysis (IPA) software. Real Time PCR was used for validation of the identified transcripts.

Results: We identified 1849 genes aberrantly modulated in SAR biopsies, 184 were down-regulated and 1257 up-regulated. Three-dimensional Principal Component Analysis showed a different spatial distribution between the SAR patients and control Patients. The most significant canonical pathways were *Natural killer cell signalling (p=0.00413)*, Wnt/β-catenin pathway (p=0.03) *Role of cytokines in mediating communication between immune cells* (p=0.04). The top selected networks highlighted several modulated genes involved in Acute Kidney Injury and candidate transcripts were validated by qRT-PCR.

Conclusions: Our data demonstrates a specific fingerprint associated with SAR characterized by various genes involved in molecular inflammatory processes and crosstalk between immune cells. These results suggest the possibility of early recognition and targeted treatment before chronic allograft disease.

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FR-PO871

Urinary Exosomal MicroRNA as a Non-Invasive Biomarker for the Diagnosis of Acute Rejection in Kidney Transplant Recipients

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Background: Acute rejection (AR) is the main obstacle to the graft survival after kidney transplantation. Urinary exosome is a promising source of biomarker for various kidney diseases, but few studies determined the clinical relevance of urinary exosomal microRNA in kidney transplant recipients. The purpose of this study was to investigate the profiles of urinary exosomal microRNAs to discover novel biomarkers of AR in patients who underwent kidney transplantation.

Methods: urinary exosomal microRNAs from 108 kidney transplant recipients were extracted. The candidate microRNAs for the diagnosis of AR were selected based on Nanostring analysis of urinary exosomal microRNAs, meta-analysis and the review of literature. The levels of candidate microRNAs were further confirmed by quantitative real-time polymerase chain reaction. The diagnostic value of final candidate microRNAs was determined in independent validation group.

Results: Nanostring analysis found that the expressions of 14 microRNAs were significantly altered in patients with AR compared to those with stable graft function. Meta-analysis and the review of literature revealed 10 and 7 additional candidate microRNAs of AR, respectively. Quantitative real-time polymerase chain reaction confirmed that a total of 7 microRNAs maintained their differential expressions, and 4 microRNAs (hsa-miR-21-5p, hsa-miR-30a-3p, hsa-miR-4488, and hsa-miR-4532) were chosen as final candidate microRNAs of AR by forward stepwise logistic regression model. The combinations of the levels of these 4 microRNAs effectively discriminated patients with AR from other patients in validation group, with an AUC value of 0.790.

Conclusions: This study demonstrated that the profiles of urinary exosomal microRNAs are altered in kidney transplant recipients having AR, and these differences could be potential non-invasive biomarkers for the diagnosis of AR.

Funding: Government Support - Non-U.S.

FR-PO872

Involvement of Genetic Variation and Related Gene Expression Changes on Acute Rejection in Renal Transplant Recipients

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Background: Acute rejection (AR) is one of the major risk factors for renal allograft loss. The effect of genetic factors on the transplant outcomes has been clear. However, the correlation between genetic variation and acute rejection remains undetermined.

Methods: We collected blood samples from recipients with biopsy-proven AR (n = 81) and with stable graft function (n = 48). Gene expression data was pooled from RNA microarray and RNA sequencing. Integrative analysis combining genome-wide association studies (GWAS) and expression quantitative trait loci (eQTL) was used to identify single nucleotide polymorphisms (SNPs) for acute rejection.

Results: In eQTL analysis, we detected potential 35,465 SNPs, which correlated with RNA expression. We analyzed AR-related SNPs in GWAS with covariate adjustment, and detected 140 overlapped SNPs in integrative analyses of eQTL and GWAS. The corresponding genes of these SNPs were matched with genes whose expression level differs between patients with AR and stable graft, and three loci were finally mated. One locus encompasses *PFDN6*, which involves the activation and development of lymphocyte. Two other loci encompasses *ZSCAN10* and *HEBP2*, which involves the DNA binding transcription factor activity and microtubule dynamics, respectively.

Conclusions: Our integrated analysis of GWAS and eQTL helps to find relevant genes, which had both biological and clinical significance, and identify three novel acute rejection susceptibility loci in renal transplant recipients.

FR-PO873

Differential Expression of Plasma miRNA in Acute Transplant Rejection

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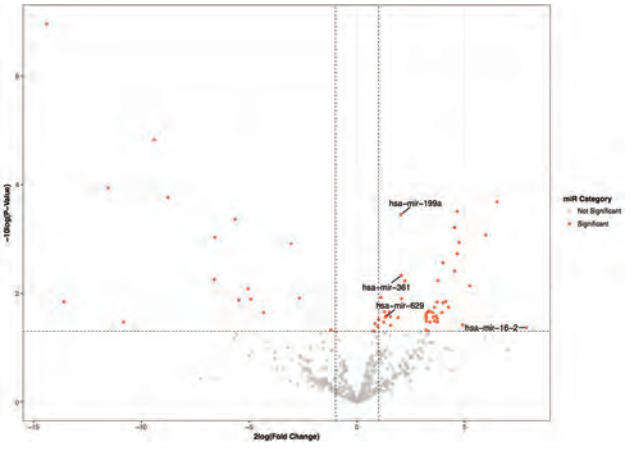
Background: Transplant rejection remains a major clinical problem in nephrology. miRNAs, negative epigenetic regulators of gene expression at the posttranscriptional level, are involved in various conditions including kidney disease. We performed next-generation sequencing (NGS-)based miRNA profiling of plasma to discover a miRNA signature of acute graft rejection in kidney transplant recipients.

Methods: 6 stable (STA, 4 male, 46 ± 8 years) and 4 patients with biopsy-proven acute rejection (AR, 1 male, 44 ± 10 yrs) within the first 3 months after transplantation were studied. AR was defined as a rise in creatinine ≥ 0.3 mg/dl and a score ≥ Banff 2 on biopsy. STA patients had normal biopsies and stable creatinine levels. NGS was performed on isolated miRNA from EDTA plasma. Obtained read counts were normalized for library size, log2 transformed and subjected to differential miRNA expression analysis (*limma*-package BioConductor). Support Vector Machine (SVM) classification was applied to build and cross-validate (i.e. leave-one-out method) a predictive model for graft rejection.

Results: 68 miRNA (26 novel) were differentially expressed in AR vs STA ($p<0.05$) with 16 miRNA being downregulated and 52 miRNA upregulated (Fig1). The SVM classification model revealed a signature of 4 miRNAs (miR-16-2, miR-361, miR-629 and miR-199a) that could predict AR with 90% accuracy, and a positive and negative predictive value of 100% and 86%, respectively.

Conclusions: We found a novel and unique plasma signature of 4 miRNA in AR patients. Prior to clinical implementation, prospective validation in an independent cohort with sensitivity and specificity analysis is mandatory. In addition, study of the involved miRNA and their mRNA targets can offer more insights into underlying disease mechanisms.

Funding: Government Support - Non-U.S.



Volcano plot: plasma miRNA expression profiles AR vs STA

FR-PO874

Reduced Early Acute Rejection with Depleting Induction and Steroid Minimization Maintenance in Pediatric Kidney Transplant Recipients

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Background: Prolonged steroid exposure in pediatric kidney transplant recipients (PKTRs) can result in adverse effects. Recent studies indicate steroid minimization (SM) is effective compared to steroid based (SB) regimens, but outcomes data in PKTRs are limited. Subclinical rejection is prevalent in PKTRs, and is associated with poor outcomes.

Methods: We hypothesized that SM with depleting induction would decrease risk of acute rejection (AR) during the first post-transplant year in PKTRs compared to a SB regimen with non-depleting induction. A single-center, retrospective cohort study was performed on PKTRs from 8/2011 to 8/2017. The primary exposure was the immunosuppression regimen. Biopsies were performed for surveillance at 3- and 6-months post-transplant, and as indicated for allograft dysfunction. The primary outcome was AR by 1 year, including borderline, cellular, and antibody mediated. Secondary outcomes included allograft function, calcineurin inhibitor nephrotoxicity (CNIT), viral infections, and neutropenia.

Results: The cohort included 63 PKTRs; 21 and 42 patients on the SM and SB regimens. The median age at transplant was 12.9 years. The cohort included 37% black and 71% deceased donor PKTRs. Overall, 32% of PKTRs had AR by 1 year post-transplant, with 80% of those detected on surveillance biopsy. By Kaplan-Meier analysis, PKTRs on SM had significantly less AR than those on the SB regimen (Figure 1, log rank p = 0.02). There was no significant difference in mean eGFR at 1 year in the SM vs SB groups. There were also no differences in the rate of CNIT, BK nephropathy, CMV viremia, or neutropenia. PKTRs in the SM group had a lower incidence of EBV viremia (33% vs 69%, p = 0.01).

Conclusions: The incidence of AR in the first year post-transplant was significantly reduced in PKTRs undergoing a SM regimen. Further study is needed to determine the effect of SM on long term outcomes in PKTRs.

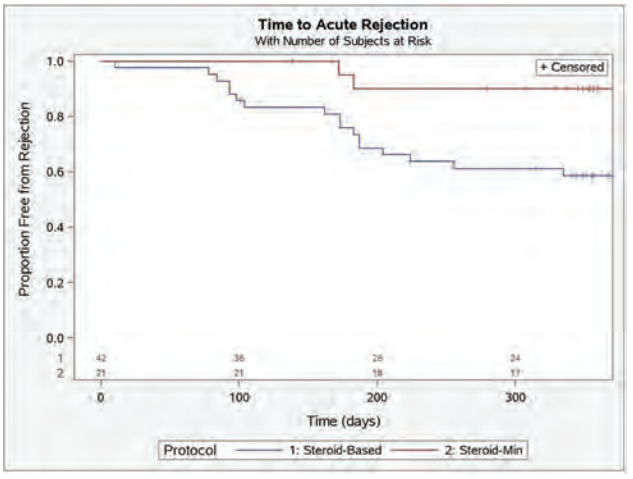

Figure 1

FR-PO875

Molecular Assessment of Pre-Implantation Transplant Kidney Biopsies

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Background: Deceased-donor (DD) kidneys are at higher risk for ischemia/reperfusion injury leading to increased inflammatory mediators compared to living donors (LD). We investigated the association between intragraft molecular gene expression profiles and clinical outcomes including delayed graft function (DGF) and allograft function.

Methods: The study included 48 pre-implantation kidney biopsy samples (29 LD and 19 DD). Patients were grouped on the basis of cold ischemia time (CIT) < 16 or > 16 hrs and presence of poor clinical/histological markers (final donor serum creatinine > 1.9 mg/dl, donor age > 60 yo, glomerulosclerosis/interstitial fibrosis/vascular sclerosis > 10%). The gene expression profiles were assayed using Affymetrix HuGene 1.0 ST arrays.

Results: DD pre-implantation biopsies showed increased expression of injury and repair (IRIT), gamma interferon and rejection (GRIT), cytotoxic T cell (CAT) and constitutive macrophage (CMAT) associated pathogenesis based transcripts (PBTs) compared to LD biopsies. CIT did not affect intragraft gene expression profiles. Biopsies with poor clinical/histological markers had increased expression of NKAT and endothelial cell associated transcripts (ENDAT). DGF occurred in 47% of DD patients but intragraft gene expression profiles were similar to patients who did not develop DGF. Patients with lower eGFR (<50 ml/min) at 1 year had increased expression of CAT, NKAT, CMAT and B cell associated transcripts at their pre-implantation biopsies compared to patients with higher eGFR (> 50 ml/min).

Conclusions: Pre-implantation DD biopsies showed increased expression of transcripts associated with increased immune activity. This is exacerbated if the donor had any poor clinical/histological markers, but not with increased CIT. Molecular analysis of pre-implantation biopsies did not differentiate patients based on DGF status but did show association of specific PBTs with better allograft function at 1 year

Pathogenesis Based Transcripts	DD vs LD	CIT > 16 hours vs. < 16 hours	Poor clinical/histological markers vs. better clinical markers	DGF vs. No DGF	eGFR < 50 ml/min vs. eGFR > 50 ml/min
IRIT	0.019	0.76	0.05	0.67	0.39
GRIT	0.008	0.74	0.63	0.21	0.35
CAT	0.01	0.86	0.46	0.58	0.02
BAT	0.37	0.54	0.11	0.69	0.029
NKAT	0.21	0.49	0.045	0.47	0.047
CMAT	0.009	0.84	0.79	0.60	0.047
ENDAT	0.34	0.21	0.013	0.42	0.25

Figure

FR-PO876

CYP4F11 - A Potential Marker of Accommodation in ABO-Incompatible Renal Transplant Biopsies

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Background: Recipients of an ABO incompatible transplant have circulating anti-AB antibodies, A and/or B antigens expressed on endothelium and usually C4d deposition on the endothelium, yet this seldom leads to antibody-mediated rejection. It has been hypothesised that this is related to upregulation of complement regulator and/or anti-apoptotic transcripts. We sought to identify differentially expressed genes between ABO-incompatible (ABOi) and ABO-compatible (ABOc) surveillance biopsies with normal histology.

Methods: RNA sequencing was performed to identify differentially expressed genes between 4 ABOi and 4 ABOc surveillance biopsies with normal histology. Differential expression was validated using RNA from formalin-fixed paraffin-embedded tissue from 14 ABOi and 80 ABOc renal transplant patients, using a Nanostring nCounter custom panel.

Results: RNA sequencing identified a number of differentially expressed genes. None of the complement regulator and/or anti-apoptotic genes were upregulated in ABOi samples. Eighteen genes considered the top hits in sequencing analysis were validated using a Nanostring nCounter custom panel. The only differentially expressed gene that was confirmed was CYP4F11, which was reduced in ABOi biopsies (p=0.001, Mann-Whitney test) (See figure 1).

Conclusions: Genes classically hypothesised to be up-regulated in ABOi transplants were not found to have differential expression. Expression of cytochrome p450 4F11 isoform (CYP4F11) is reduced in ABOi patients. Most of the substrates of cytochrome p450 4F isoforms are eicosanoids, which play important roles in the inflammatory response. Down-regulation of CYP4F11 in ABOi transplants may be be playing a role in accommodation to the anti-A or B antibodies and the presence of complement on the endothelial cell surface..

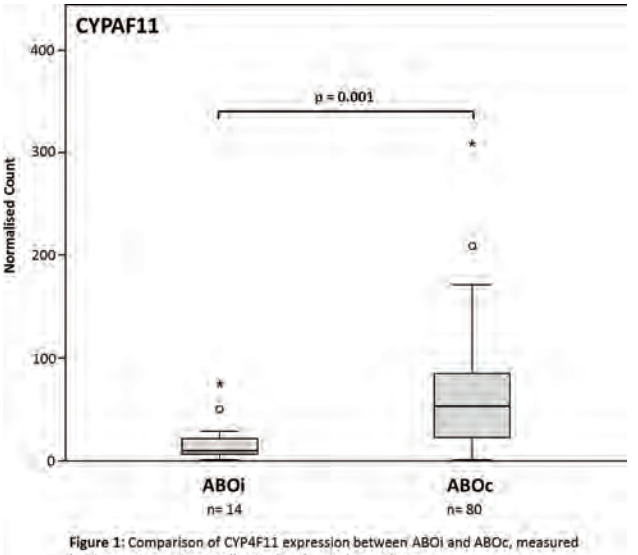

Figure 1: Comparison of CYP4F11 expression between ABOi and ABOc, measured by Nanostring and normalised using the nSolver software.

FR-PO877

C4d Positive Renal Transplant Biopsies with No Other Evidence of Rejection: A Transcript Expression Investigation Using NanoString nCounter Technology

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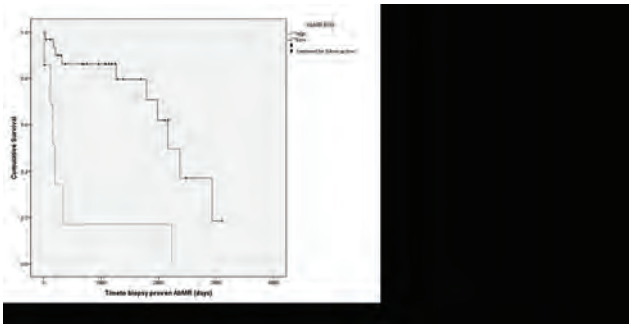
Background: Immunohistochemical staining for C4d in peritubular capillaries has been part of antibody-mediated rejection (AbMR) definition in the Banff Classification for Allograft Pathology since 2003. However, with limited sensitivity and specificity, the clinical significance of C4d-positive biopsies without evidence of rejection (C4d+ WER) is unknown. We investigated the molecular significance of C4d positivity in such biopsies from both ABO-compatible and incompatible renal transplant patients.

Methods: RNA was extracted from formalin-fixed paraffin-embedded renal transplant biopsies (n=125) and gene expression analysis of 35 AbMR-associated transcripts carried out using the NanoString nCounter system.

Results: AbMR-associated transcripts were significantly increased in samples with AbMR or suspicious for AbMR. A subgroup of 17/35 transcripts that best distinguished AbMR from C4d-negative biopsies without evidence of rejection was used to study C4d+ WER samples. There was no differential expression between C4d negative and C4d positive biopsies WER from both ABO incompatible and compatible transplants. The geometric mean of 17 differentially expressed genes was used to assign the C4d+WER biopsies a high- or low-risk score for AbMR. Follow-up biopsies showed AbMR within 1 year of initial biopsy in 5/7 high-risk patients but only 2/46 low-risk patients. In multivariate logistic regression analysis, elevated transcript levels in a C4d+ WER biopsy were associated with increased odds for biopsy-proven AbMR on follow-up (p=0.032, odds ratio 16.318), whereas factors including DSA status and time from transplant to biopsy were not.

Conclusions: Gene expression analysis in C4d+WER samples has the potential to identify patients at risk of imminent AbMR.



FR-PO878

C3 Deposition on Biopsy Is an Independent Risk Factor for Allograft Failure in Transplant Glomerulopathy

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Background: Transplant glomerulopathy (TG) is a well-established cause of renal allograft loss, but the prognostic significance of complement activity in TG remains unclear. We hypothesized patients with evidence of complement-mediated allograft injury are at higher risk of graft failure.

Methods: Kidney transplant recipients who received a biopsy diagnosis of TG (cg score≥1a) between 2011-2014 and had immunofluorescence (IF) performed were eligible for the study. Primary outcome was allograft failure (re-transplant, return to dialysis or death).

Results: Of the 111 patients included in the study, 72 (65%) had allograft failure, with a median follow-up of 3 years. Patients with C3 deposition vs. no C3 deposition had a higher rate of allograft failure (78 vs. 55%, respectively). Adjusted multivariate analysis demonstrated an increased risk of graft failure in patients with C3 deposition vs. no C3 (HR 1.37, 95% CI 1.12-1.69, P=0.002); this was not observed for C4d and C1q (Fig 1). Chronicity score was also associated with allograft loss (HR 1.26, 95% CI 1.13-1.42, P=0.0001). C3 positive vs. negative patients did not differ with respect to cause of ESRD, induction or maintenance immunosuppression, donor type, PRA or presence of Class I or II donor-specific antibodies.

Conclusions: In this cohort of patients with TG, C3 deposition was independently associated with increased risk of allograft failure. Other complement products were not found to be significant in predicting allograft loss. Future studies are needed to validate these findings, but our results suggest that IF should routinely be performed on transplant biopsies, as C3 deposition may indicate TG patients who are at higher risk for allograft loss.

Funding: Other NIH Support - KL2TR002374 and UL1TR000427

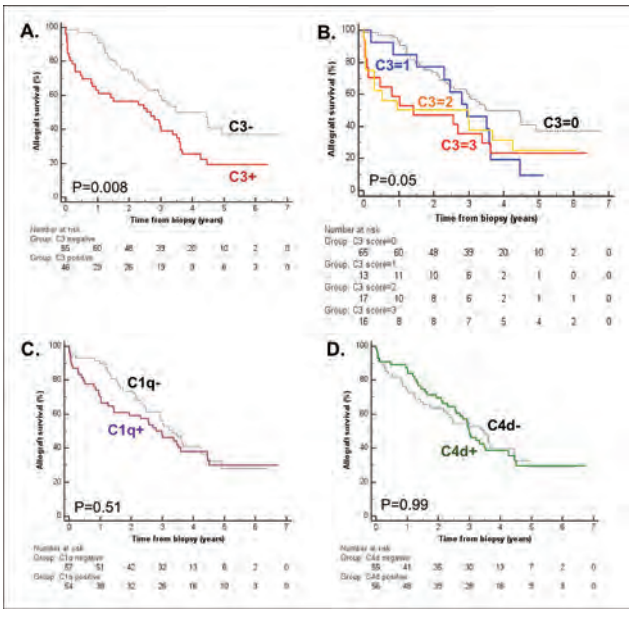

Fig 1: C3 is associated with decreased allograft survival

FR-PO879

C4d Staining Following Thymoglobulin Treatment for Acute Cellular Rejection

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Background: Rejection is an important cause of allograft failure in kidney transplant recipients (KTRs). Treatment is guided by histologic and biochemical findings indicating cellular and/or humoral origin. C4d staining is one of the diagnostic criteria for antibody mediated rejection (ABMR). At our center we observed an increase in C4d staining on some biopsies following thymoglobulin treatment for acute T-cell mediated rejection (TCMR).

Methods: We performed retrospective review of all KTRs at our pediatric center from January 2013 to April 2018 who received thymoglobulin treatment for acute TCMR and who had a follow-up biopsy within 45 days of diagnosis. Patients who had C4d staining or other histologic evidence of ABMR on initial biopsy were excluded. We evaluated C4d staining on repeat biopsy and compared patients who did not have existing or de novo donor specific antibodies (DSAs) within 12 months of diagnosis to those who did.

Results: 14 KTRs received an average of 12.7mg/kg of thymoglobulin over 4-14 days. Mean time between TCMR diagnosis and follow-up biopsy was 14.9 days. 8 patients remained negative for DSAs during the defined peri-rejection period. Of the 6 patients found to have positive DSAs, 1 showed persistence of known chronic class II DSAs and 5 developed de novo DSAs (4 within 6 weeks of TCMR diagnosis and 1 at 7 months). Post-thymoglobulin C4d staining increased in all 6 DSA-positive patients but only 3/8 (37.5%) of DSA-negative patients (p=0.03). Histologic evidence of ABMR (capillaritis) on follow-up biopsy was seen in two patients with de novo DSAs.

Conclusions: Positive C4d staining can be seen following thymoglobulin treatment of rejection even in the absence of DSAs. C4d staining increased following thymoglobulin therapy in all patients with DSAs, sometimes before the DSA was detectable. These findings may indicate thymoglobulin enhancement of complement activation by DSAs, non-DSA ABMR, or independent in situ complement activation facilitated by the polyclonal xenoantibody preparation.

C4d staining following thymoglobulin treatment of TCMR

C4d Staining	Negative DSA (n=8)	Positive DSA (n=6)
Negative or Nonspecific Glomerular and Tubular	5	0
Glomerular without PTC	1	3
PTC	1	1
Diffuse (Glomerular & PTC)	1	2

PTC, peritubular capillaries

FR-PO880

Causes of Living Donor Rejection: A Single Center Experience

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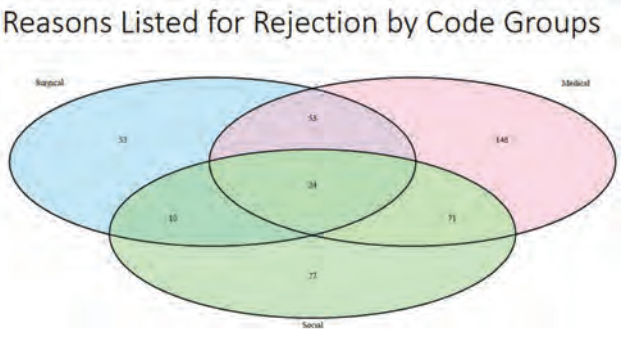
Background: Living donor kidney transplantation (LDKT) is the preferred treatment for end stage kidney disease because it leads to better survival than either dialysis or deceased donor transplantation. Yet, the rate of LDKT has not grown despite high numbers of potential donors. Understanding the reasons that potential donors are rejected is key to developing effective interventions to increase LDKT.

Methods: In this single center retrospective observational study from UCLA Medical Center, both a transplant nephrologist and a transplant surgeon reviewed the medical records of all potential living donors presented to the living donor selection committee from 2009 to 2014 and coded the reasons they were rejected as donors. Reasons were categorized as medical, surgical, social, or "other".

Results: Out of 1370 patients, 55% (760) were accepted as potential donors, 16% (225) required further workup, and 29% (385) were denied as donors. 84% (323) of those rejected were rejected for multiple reasons (Figure). The top 3 most common reasons for rejection were medical: young age, family history of diabetes, and obesity. The top social reason was a prior history of psychiatric illness other than depression, and the top surgical reason for rejection was evidence of a renal lesion.

Conclusions: Most potential donors were denied for multiple reasons. Effective interventions to increase the rate of acceptance of potential donors will need to be multi-faceted since addressing just a single cause for rejection is unlikely to clear a potential donor for donation.



FR-PO881

Does Non-Adherence Predict the Futile Treatment of Severe Acute Kidney Transplant Rejection?

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Background: To treat or not to treat-- that is the question a clinician faces when a patient presents with renal failure in the setting of non-adherence and is found to have acute rejection. Potent rejection therapy, with its associated risks and cost, should arguably be withheld if treatment is to be futile. In this study we aimed to identify clinico-pathologic characteristics, with particular interest on non-adherence, that are associated with futile treatment. We defined futile treatment as graft loss occurring within 6 mos of acute rejection treatment.

Methods: The study included patients >=18y with biopsy-proven acute rejection and received maximal rejection therapy with a lymphocyte-depleting agent, with/without AMR treatment. Patient/transplant characteristics, adherence status and outcomes were collected via chart review. Descriptive statistics were utilized to compare groups. The outcome was all-cause graft loss within 6 mos of acute rejection treatment. Multivariable poisson regression with robust variance analysis was utilized to quantify the association of predictors with the outcome.

Results: 115 patients were included in the study, 46% of which were non-adherent. Non-adherent patients were younger (36 vs 46 y), more likely to be on steroid withdrawal (32 vs 16%), attained a lower nadir SCr (1.2 vs 1.8 mg/dL) and rejected later (65 vs 19 mos from transplant). There was no difference in eGFR at presentation or Banff grade on biopsy. Overall, 31% of patients lost their grafts within 6 mos of acute rejection, with a higher percentage in the non-adherent group (42% vs 23%, p=0.03). In adjusted analysis, non-adherent patients had an increased RR of graft loss within 6 mos of acute rejection (RR 1.9, p<0.01). Other predictors of futile treatment included eGFR <=10 at presentation and >5% interstitial fibrosis on biopsy. Age, race, Banff grade, presence of concomitant AMR and type of lymphocyte depleting agent used were not significantly associated with the outcome.

Conclusions: Patients who are non-adherent are at 2-fold higher risk for futile treatment of acute rejection despite lymphocyte depletion. Other risk factors include severe renal dysfunction on presentation and the presence of interstitial fibrosis. In such patients, withholding potent rejection therapy should be considered, and ESRD planning should be initiated.

FR-PO882

Treatment of Biopsy-Proven Borderline Rejection in Kidney Transplant Recipients

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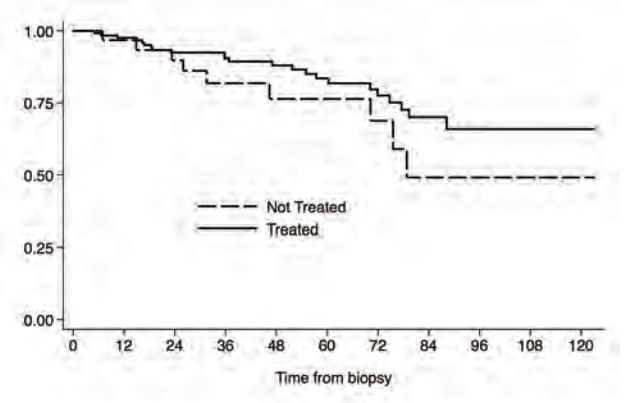
Background: Borderline cellular rejections are now the most common type of rejection found after kidney transplantation. Most centers either treat borderline rejection episodes with a pulse of high dose corticosteroids or do not provide any additional immunosuppression.

Methods: We identified 161 consecutive patients (50.6 ± 14.8 yrs, 62% male) who had a borderline rejection on allograft biopsy with no prior evidence of biopsy proven acute rejection between 2008 – 2015 at our center. While the majority of patients received our protocol of high dose corticosteroids, we identified 29 patients who did not receive any additional immunosuppression. We compared improvement in renal function over 4 weeks after the rejection episode for those who were treated versus those who were not.

Results: Recipients who were treated were significantly younger (55.7±12.7 vs 49.4±15.1 years p=0.03) than recipients who were not treated but were similar with respect to gender distribution, time from transplant to biopsy (347.7±486 vs 264.1±481.9 days, p=ns), and the creatinine at the time of biopsy (2.29±0.95 vs 2.57±1.48 mg/dL, p=ns). There was no difference in the decrease in serum creatinine at 4 weeks (0.31±0.55 not treated vs 0.59±1.28 mg/dL treated, p=ns) and 90 days (0.48±0.2 not treated vs 0.64±1.1 mg/dL not treated) following the biopsy between the two groups. While there were a higher number of graft failures among patients who were not treated (28.1% vs 18.2%, p=ns), this difference was not significant. [figure1]

Conclusions: The treatment of isolated borderline rejections with high dose pulse steroids did not improve short term outcomes in this single-center retrospective study. The higher rate of graft failure in the nontreated arm is however concerning and more studies are needed to understand the optimal management strategy for biopsy proven borderline rejections.



Time from biopsy to graft failure

FR-PO883

Adenovirus Allograft Nephropathy Mimicking Acute T Cell Rejection

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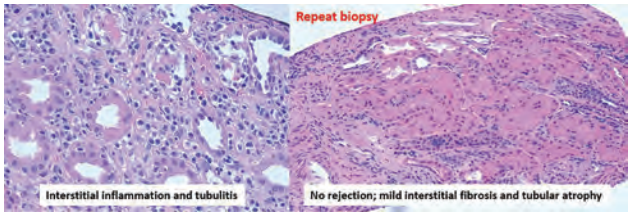
Introduction: Adenovirus is associated with significant morbidity and mortality in renal transplant recipients and may even lead to the loss of allograft. Adenovirus nephropathy can be confused with acute cellular rejection as illustrated in our case. As the management of these two entities is completely different, clinical correlation is crucial.

Case Description: A 33-year-old African American woman with a history of ESRD status post deceased donor kidney transplantation was admitted for acute kidney injury (AKI) with a Scr of 8mg/dL (baseline 1.3). Her pre-transplant CPRA was 29%, received Alemtuzumab for induction immunosuppression (IS) followed by mycophenolate mofetil, tacrolimus and prednisone for maintenance. Her post-transplant course was complicated by BK viremia that resolved with reduction in IS. This time, BK virus serology was negative and she was given methylprednisolone 1 gram/day for 3 days for suspected rejection. She later developed fever and hematuria and clinically deteriorated despite receiving broad-spectrum antibiotics. Blood cultures remained negative. Allograft biopsy demonstrated severe interstitial inflammation with T cells, mononuclear cells and plasma cells with severe tubulitis [Figure]. Immunohistochemistry staining was negative for adenovirus but serum adenovirus PCR was positive with 10 million copies/ml. Her respiratory status worsened and CT scan of the chest showed tree-in-bud nodular opacities. Adenovirus PCR was positive in BAL and in the urine suggestive of adenovirus

pulmonary and renal allograft involvement. Mycophenolate was held and she received treatment with intravenous immunoglobulin and cidofovir. Patient clinically improved and Scr was 1.5mg/dl at discharge. A repeat biopsy at follow-up visit was negative for rejection, showed mild interstitial fibrosis and tubular atrophy with no glomerulosclerosis [Figure].

Discussion: High index of suspicion for adenovirus infection is required in renal graft dysfunction, especially in the setting of hematuria. Histology can mimic acute rejection, which creates a diagnostic dilemma. Tissue adenovirus immunostains, though usually reliable, may not be always positive like in our case.



FR-PO884

The Role of Plasma Donor-Derived Cell-Free DNA in Minimal Invasive Graft Monitoring

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Background: After transplantation, cell-free DNA derived from the donor organ (ddcfDNA) can be detected in the recipient's circulation. We aimed to investigate plasma ddcfDNA kinetics in renal transplant recipients thereby evaluating the role of this biomarker in graft monitoring.

Methods: From 107 renal transplant recipients, plasma samples were collected longitudinally from day 1 until 3 months after transplantation within a multicenter set-up. Cell-free DNA from the donor was quantified in plasma as a fraction of total cell-free DNA by next generation sequencing using a targeted, multiplex PCR based method for the analysis of single nucleotide polymorphisms.

Results: Slope normalization analysis was performed in 42 patients that met predefined criteria for stable graft recipients. After an exponential decrease in ddcfDNA, a mean stable baseline level of 0.455% + 0.427 (2 SD) was reached on average 9.85 (± 5.6 days) after transplantation. In the entire cohort, patients that were not stabilized by day 10 (n = 37) had higher individual baseline ddcfDNA values (p = 0.007) and higher ddcfDNA fractions on day 1 (p = 0.0002). Sixteen recipients exhibited abnormal non-exponential ddcfDNA kinetics in the early post-engraftment phase; and this was associated with the occurrence of an early adverse event including a urinary tract infection, a surgical adverse event or episode of hydronephrosis that required treatment, a BKV or CMV infection episode or prerenal acute kidney injury (p=0.0012). From day 10 onwards, increases of ddcfDNA% above the baseline value of 0.882% (mean+2 SD) were significantly associated with the occurrence of episodes of acute rejection (p = 0.017), acute tubular necrosis (p = 0.011) and pyelonephritis (p = 0.032).

Conclusions: Within 10 days after transplantation, plasma ddcfDNA fractions decrease to a stable baseline level. From day 10 onwards, increases of ddcfDNA% are associated with graft injury related to acute rejection, acute tubular necrosis or pyelonephritis.

Funding: Government Support - Non-U.S.

FR-PO885

Donor-Derived Cell-Free DNA in Renal Transplant Recipients with Delayed Graft Function

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Background: Delayed graft function (DGF) is a major barrier to improved outcomes after kidney transplantation (KTx) with no definitive tool available to assess severity or chances for recovery. Donor-derived cell-free DNA (dd-cfDNA) was previously validated to discriminate active rejection in KTx pts but its characteristics have not been defined in those with/at risk for DGF. This report describes dd-cfDNA levels in a cohort of KTx pts with suspected DGF.

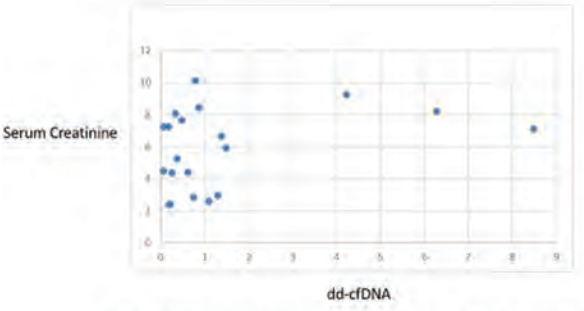
Methods: dd-cfDNA samples of KTX pts with suspected DGF at three centers were obtained between Days 1-16 post-tx as part of the Donor-derived Cell-free DNA in Blood for Diagnosing Acute Rejection in Kidney Transplant Recipients (DART) study. Similar clinical data were collected at each sample visit during this early post-tx period as was collected during later visits per DART protocol.

Results: dd-cfDNA samples were obtained from 17 KTx pts with suspected DGF. All received a deceased donor KTx (mean CIT 23 ±9 hours; mean KDPI 64 ±17). Mean dd-cfDNA level was 1.47% (SD 2.25%) in samples collected Days 1-16 post-tx and 0.60% (SD 0.99%) in samples collected at Months 1-24 post-tx. By comparison, the mean level in a reference cohort without DGF from DART was 0.34% (SD 0.58%) in samples collected 30 or more days post-tx. No obvious correlation was seen between Scr and dd-cfDNA in samples from Days 1-16 (Fig. 1) or in Months 1-24 (Fig. 2).

Conclusions: dd-cfDNA levels are higher early post-tx in suspected DGF samples vs. later time points and in those without DGF. Larger studies with long-term follow-up are needed comparing dd-cfDNA levels directly in pts with vs. without DGF after KTx. This may allow for more accurate assessment of dd-cfDNA patterns related to DGF severity/recovery.

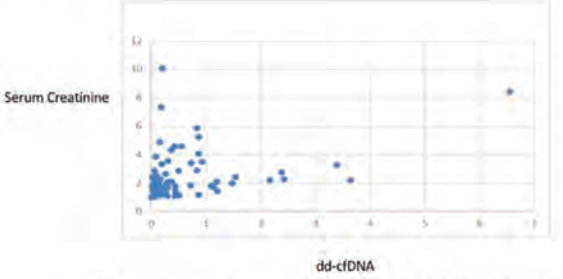
Funding: Commercial Support - CareDx

Figure 1



No obvious correlation between Scr and dd-cfDNA levels in all samples collected between Day 1 and Day 16 post-transplant

Figure 2



No obvious correlation between Scr and dd-cfDNA levels in all pooled samples collected between Visit 1-Visit 11 (Month 1-Month 24) post-transplant

FR-PO886

The Association Between Location of Eplet Mismatches, De Novo Donor Specific Antibodies, and Acute Rejection in Simultaneous Pancreas-Kidney Transplant Recipients Using Novel Machine Learning Methods

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Background: To determine the association between HLA class and location of eplet mismatches with de novo donor specific antibodies (dnDSA) and acute rejection in simultaneous pancreas-kidney (SPK) transplant recipients.

Methods: The cohort consisted of SPK recipients (n=170) transplanted in New South Wales, Australia between 2005 and 2017. Using machine learning models (random forest), we determined the association between the number and location of class specific eplet mismatches, and adverse allograft outcomes (dnDSA formation and acute rejection (acute cellular (ACR) and (antibody-mediated (AMR)). One hundred times 5-fold cross validation was conducted using R.

Results: The cohort included 93 (55%) males, with mean age at transplant of 38.7 years (SD 7.0) and median follow up time of 5.0 years (IQR: 2.1, 7.1). The median total number of class I and II eplet mismatches were 17 (IQR: 13-22) and 34 (IQR: 22-47), respectively. The most important (highest Mean Decrease Accuracy) class I eplet mismatches for predicting dnDSA and any acute rejection corresponded to locations 102HV, 149TAH, 152RE, 163RW, 21H, 44RM, 44RMA and 82LR; and for class II mismatches at 76L. For the prediction of class I and II dnDSA, the median AUC and balanced error rate from the

location of class I eplet mismatches were 57.8% (SD: 3.5%) and 47.0% (SD: 1.6%); and for class II were 53.5% (SD: 2.6%) and 50.9% (SD: 2.5%), respectively. The median AUC and balanced error rate for predicting any acute rejection from class I eplet locations were 54.3% (SD: 2.7%) and 50.2% (SD: 2.7%); and for class II were 56.7% (SD: 3.3%) and 43.9% (SD: 2.7%), respectively.

Conclusions: In this cohort of SPK recipients, the location of class I mismatches best classify recipients with dnDSA and any acute rejection.

FR-PO887

Comparison of Banff Allograft Injury Scores of Patients with De Novo Donor-Specific Antibodies (DSAs) to Patients with Preformed DSAs

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Background: We aimed to compare histological features of rejection in patients with preformed and de novo DSAs and its association with clinical outcomes

Methods: This is a prospective study including 681 non-HLA-identical patients who received a kidney tx between 1/2009 and 12/ 2014 at our center. Protocol testing for DSA via LABScreen single antigen beads was done before and at 1, 3, 12 months, and then annually after kidney tx or when clinically indicated. Tx kidney biopsies are performed as clinically indicated

Results: 114 (17%) patients had preformed DSA. During a median 3.8 (2.4-5.3) years of follow-up, de novo DSA developed in 92 patients (13%) at a median of 1.24(0.71-2.35) years after kidney tx. While there was no difference in patient survival, de novo DSA group had significantly lower graft survival (63.8% vs. 88.6%, P<0.001), higher antibody-mediated rejection (ABMR) (13.04% vs. 6.14%, p=0.001), transplant glomerulopathy (16.6% vs. 9% vs. 4.7%, P=0.004) and T cell mediated rejection (14.13%vs. 2.63%, p=0.001) compared to patients with preformed DSA. ABMR developed at a median 0.39 years (0.13-1.4) in pre-transplant DSA patients and at 1.25 years (0.25-3.31) in de novo DSA ones. When comparing the Banff allograft injury scores in 16 pre DSA and 34 de novo DSA biopsies, mean total acute Banff allograft injury score (g+ i+t+ptc+v, 6.29±3.57 vs. 4.19±3.39, p=0.046) was statistically significantly higher in the de novo DSA. The rest of acute and chronic allograft injury scores were not significantly different

Conclusions: Development of de novo DSA after kidney tx is associated with higher total acute allograft injury score, rejection episodes, and lower allograft survival compared to preformed DSA.

Banff Scores

	Pre Transplant DSA	De novo DSA	P
g(mean, SD)	0.52±0.77	0.51±0.76	0.87
i(mean,SD)	1.05±1.07	1.65±1.23	0.09
t(mean, SD)	0.57±0.69	1.11±1.15	0.14
ptc(mean,SD)	0.84±0.89	0.90±1.08	0.95
v(mean, SD)	0.15±0.37	0.18±0.39	0.86
g+i+t+ptc+v(mean, SD)	4.19±3.39	6.29±3.57	0.046
ct(mean, SD)	1.26±0.99	1.00±0.89	0.36
ci(mean, SD)	1.05±0.97	0.74±0.87	0.24
cv(mean, SD)	0.31±0.47	0.39±0.62	0.84
ct+ci+cv(mean, SD)	7.31±3.30	8.71±4.71	0.30
c4d(mean, SD)	1.05±1.39	1.16±1.28	0.74

FR-PO888

Long Term Follow Up for Antibody Mediated Rejection of Kidney Transplant Due to Angiotensin II Type 1 Receptor Antibodies

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Background: A new appreciation for the contribution of non-HLA antibodies (Abs) in kidney transplantation (K-TXP) has arisen as a result of reports of antibody mediated rejection (ABMR) without HLA Abs. Abs directed against the angiotensin II type 1 receptor (AT1R-Ab) have received greater scrutiny because of the existence of a commercially available assay. Studies on the treatment and long term follow up of AT1R-Ab mediated ABMR are lacking

Methods: Among K-TXP patients with positive (≥17 Units/ml) or borderline (10-17 Units/ml) AT1R-Ab, we retrospectively identified those with biopsy proven ABMR by Banff 2017 and had negative or low level HLA Abs at the time of rejection

Results: 14 patients were identified. Patients' characteristics are shown in table 1. Median time of follow up from ABMR is 24 months. Median time from transplant to ABMR is10 months. With regards to treatment, 9 received plasmapheresis and intravenous immunoglobulins +/- high dose corticosteroids (HDCS), 1 received HDCS, and 1 received HDCS and thymoglobulin. Of treated patients, 6 responded. One lost allograft due to recurrence of ABMR. Of all patients, 10 had follow up biopsy. 5 had improvment in histological findings, and the other 5 developed transplant glomuerlopathy. Of the 3 who did not receive any treatment, 1 progressed to allograft loss, 1 had resolution on follow up biopsy, and 1 remained with elevated but stable serum Creatinine. Of the 11 who received treatment, 9 had evidence of reduction in AT1R-Ab titer. Of the three who did not receive treatment, 1 had improvement in AT1R-Ab titer

Conclusions: AT1R-Ab mediated ABMR is seen in HLA sensitized and non sensitized patients. Conventional ABMR treatment reduces AT1R-Ab titer in most patients but not all achieve clinical response. As with HLA antibodies, AT1R-Ab may lead to transplant glomerulopathy

Table 1

Mean age at current transplant (yr)	40.8 +/- 3.8
Number of males	11/14
Number with previous K-TXP	8/14
Deceased donor K-TXP	9/14
Mean number of mismatches in ABCDRDQ	4/10
Number with HLA sensitization at transplant	8/14
Number with HLA DSA at transplant	6/14
Number with positive or borderline AT1R-Ab at transplant	13/13, one unavailable
Induction immunosuppression with thymoglobulin	14/14
Maintenance immunosuppression at time of ABMR	14/14 tacrolimus, mycophenolate, and prednisone

FR-PO889

ABO Incompatible Kidney Transplantation Without Use of Anti-CD20 Antibody or Splenectomy: Experience from Northern India

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Background: ABO-incompatible (ABOi) renal transplants help in crossing an important immunological barrier against kidney transplantation, thereby meeting the unmet demands of renal transplants. The study was conducted to assess ABOi transplant without the use of Anti CD20 antibody or splenectomy and compare their outcomes with ABO compatible (ABOc) transplants.

Methods: The study period was from January 2014 to February 2018. 290 patients were divided into two groups: ABOi (n=33) or ABOc (n=257) living renal donors. In ABOi cases, plasmapheresis and low dose intravenous immunoglobulin (100 mg/kg) was given till isoagglutinin titer were <1:8. All patients received induction immunosuppression: Thymoglobulin (1 mg/kg/day for 3 days) for all ABOi and ABOc with HLA mismatch > 3/6 and Basiliximab in ABOc with HLA mismatch < 3/6. In ABOi, titers were monitored post-operatively and plasmapheresis was done if they increased to >1:8 in first week and >1:16 in second and third week post transplant. Patient and allograft survival; 1, 3, 6, 12, 24, and 36-month renal function; infectious complications; and incidence of rejection were measured.

Results: 30.3% of the ABOi recipients and 22.17% of ABOc recipients were females. Median isoagglutinin titer at start was 1:32 (1:1 to 1:256). Mean number of plasmapheresis required were 3. In ABOi group, Mean±SD creatinine levels were 1.37±0.41 mg/dL at 1 month, 1.29±0.31 mg/dL at 12 months, and 1.36±0.39 mg/dL at 36 months. In ABOc group, Mean±SD creatinine levels were 1.26±0.41 mg/dL at 1 month, 1.26±0.44 mg/dL at 12 months, and 1.28±0.45 mg/dL at 36 months. In the ABOi group, there were 6 episodes of acute antibody mediated rejection (AMR) and 1 patient had acute cellular rejection (ACR), which were successfully treated (3 AMR and 4 ACR were observed in the ABOc group). Two patients succumbed to fungal sepsis in the ABOi group.

Conclusions: Successful ABOi renal transplantation is possible without the use of splenectomy or Anti-CD20 treatment but AMR episodes as well as fungal sepsis are significantly high.

Table 1: Patient characteristics of ABO incompatible (ABOi) and compatible (ABOc) transplant groups

		ABOi (n=33)	ABOc (n= 257)
Donor	Age (Mean ± SD) in years	47.12±12.15	48.96±13.78
	Females	51.51%	80.54%
Recipient	Age (Mean ± SD) in years	42.93±11.71	41.31±12.94
	Females	30.30%	22.17%
Serum Creatinine (Mean ± SD) in mg%	At discharge	1.39±0.59	1.31±0.51
	At 1 month	1.37±0.41	1.26±0.41
	At 3 months	1.27±0.33	1.26±0.46
	At 6 months	1.29±0.36	1.27±0.47
	At 12 months	1.29±0.31	1.26±0.44
	At 24 months	1.31±0.38	1.27±0.44
	At 36 months	1.36±0.39	1.28±0.45
Graft survival at 1 year		84.84%	98.44%
Patient survival at 1 year		84.84%	98.44%
Rejection episodes	AMR	18.18%	1.16%
	ACR	3.03%	1.55%
Infections	UTI in first 12 weeks	3.03%	3.50%
	Parvovirus	0%	1.16%
	Fungal septicemia	6.06%	0.77%
	CMV	3.03%	3.11%

FR-PO890

CD19+ Cell Behavior in the 12 Months Following a Single Dose of Rituximab in Patients with Humoral Rejection: Clinical and Histological Outcomes

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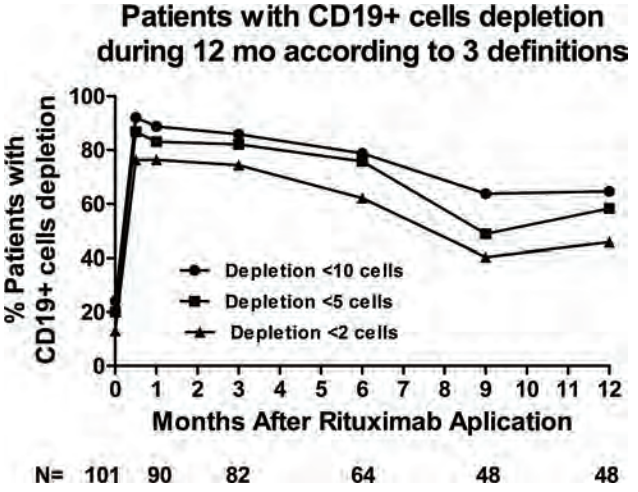
Background: Treatment of antibody mediated rejection (AMR) commonly includes rituximab (RTX). It has been suggested that a single dose of RTX is enough to deplete CD19+ cells. Aim: to analyze CD19+ cell behavior during the 12 months following a 500 mg dose of RTX and its correlation with clinical and histological outcomes.

Methods: Prospective cohort study of 122 kidney transplant recipients with biopsy proven AMR who received a single dose of RTX 500 mg as part of standard AMR treatment between 2012 and 2018. Peripheral CD19+ cells were measured at baseline, 15, 30, 90, 180, 270, and 360 days after RTX infusion, and correlated this data with clinical and histological outcomes.

Results: 122 patients were included. Mean age was 35±13 y, 56.6% female, median time to rejection was 6y post-transplant. Treatment included PE and IVIG in 75%, 21% also received Bortezomib. All patients received 500 mg of RTX and were followed for a median of 21mo (0.1-83). Median allograft survival after AMR was 5.5y. CD19+ cell depletion (<10 cells) at 1mo was associated with less IFTA at follow-up biopsy (p=0.01) and improvement of proteinuria at last follow-up (p=0.05). Early CD19+ cell repopulation was associated with higher graft loss and dead (p=0.03). Persistent CD19+ cell depletion (<10 cells) at 12mo was associated with better graft and patient survival (0.04).

Conclusions: A single dose of RTX achieved CD19+ cell depletion in more than 80% of patients, which lasted at least 6 mo. CD19+ cell depletion is associated with improvement of proteinuria and less IFTA; and the persistence of CD19+ cell depletion at 12mo improves graft and patient survival.



CD19+ cell depletion patterns.

FR-PO891

High Level of HLA-DP Expression in Kidney Donors Is Associated with a Reduced Graft Survival

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Background: HLA-DP mismatch between kidney allograft donors and recipients has increasingly been recognized as risk factor for adverse long-term outcome following transplantation. Current matching algorithms do not account for HLA-DP mismatch. The single nucleotide variant rs9277534 in the 3′ UTR of DPB1 is associated with HLA-DPB1 expression levels.

Methods: We made use of the iGeneTrain consortium and genotyped 477 first kidney transplant recipients and respective deceased donors from two centers in Vienna and Prague. HLA eplet mismatch was calculated for the HLA-A, -B, -C, -DP, -DQ, and -DR loci. The median follow-up time of the cohort was 6.5 years. Kaplan-Meier analysis and a Cox PH model were used to assess the association of rs9277534 with death censored graft loss.

Results: The rs9277534 variant influencing HLA-DPB1 expression levels is associated with graft loss after kidney transplantation. Kaplan-Meier analysis (figure 1) showed that presence of one or two copies of a 'G' allele at rs9277534 in the donor was associated with an elevated risk for graft loss. This association remained significant in a multivariable Cox model after adjustment for donor age and full HLA eplet mismatch (HR of rs9277534: 2.05 CI: 1.15 – 3.67).

Conclusions: Presence of the high expression variant in kidney allograft donors is associated with a reduced graft survival.

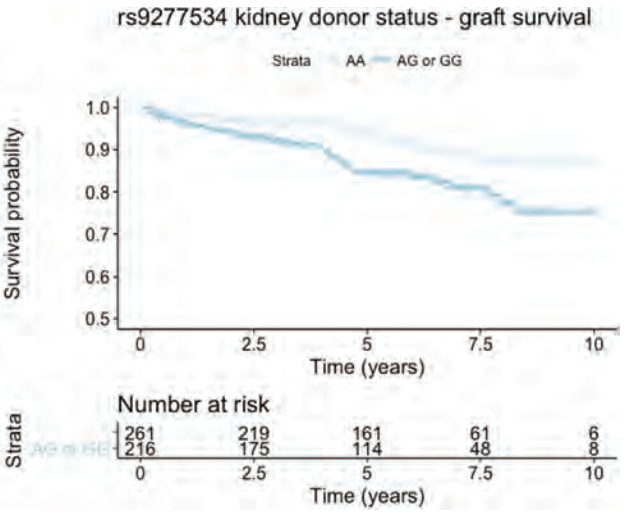

Figure 1: KM plot relating kidney allograft donor status of the rs9277534 variant influencing HLA-DPB1 expression with death censored graft loss after transplantation.

FR-PO892

Biopsy Guided Evaluation in Patients with Renal Impairment Awaiting Liver Transplantation - How Kidney Biopsies Save Organs

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Background: After the introduction of MELD score in liver allocation, the number of simultaneous liver-kidney transplantations (SLKT) significantly increased therefore contributing to the shortage of allografts for patients waitlisted for kidney transplantation. We analyzed the data in our high-volume transplant center with a stable number of SLKT and reviewed our biopsy-guided kidney allocation policy in pts with renal dysfunction undergoing liver transplantation (LT).

Methods: We analyzed LT and SLKT performed in UH Merkur, Croatia from April 2007 to April 2018. As significant renal impairment at time of enlisting we defined serum creatinine higher or equal to 2 mg/dL, renal replacement therapy (RRT) or pathologic proteinuria higher than p/c 1 g/g.

Results: In total 1056 LT and 19 SLKT were identified. 129 pts fulfilled the criteria for renal impairment given above. There were 95 male pts (73,6%). 13 patients had ESRD receiving RRT prior to referral for LT and were automatically enlisted for SLKT. From those 13, in 2 pts SLKT was performed because of primary hyperoxaluria. In evaluation of other pts with renal dysfunction 22 renal biopsies were performed under US guidance after correction of coagulation parameters. There were no major complications of biopsies. Other 94 pts were diagnosed with acute kidney injury/hepatorenal syndrome (AKI/HRS). The most common pathohistological diagnosis was IgA nephropathy (63,6%), followed by ATN (18,2%) and diabetic nephropathy (9,1%). The cut-off for SLKT was more than 40% interstitial fibrosis and tubule atrophy (IFTA), or more than 30% of globally sclerosed glomeruli (GS) on biopsy. Based on biopsy results additional 6 pts were enlisted for SLKT. None of the patients with presumed AKI/HRS who received only LT and survived for more than one-month post-LT required RRT at one-month post-LT.

Conclusions: We believe that kidney biopsy is a useful and safe tool to avoid kidney graft wasting when evaluating enlistment for SLKT. We enlist a patient for SLKT if IFTA is higher than 40% or GS more than 30%. A separate indication for SLKT are metabolic diseases. In decompensated liver cirrhosis HRS develops and makes evaluation of kidney recovery potential speculative. In our experience, percutaneous kidney biopsy in pts with advanced liver disease was not linked to adverse events and is a safe procedure in experienced centers.

FR-PO893

Proteomic Analysis of Perfusate from Machine Cold Perfusion of Transplant Kidneys: Comparison Between Circulatory and Neurological Death

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Background: Renal donation after circulatory death (DCD) is associated with increased of delayed graft function (DGF) events shortly after transplant and with a decrease in renal function at 1 year compared to donation after neurological death (DND). Machine cold perfusion has been suggested to reduce incidence of DGF and improved long and short-term function in marginal kidneys and those obtained from DCD donors. We compared several early biomarkers of renal injury in perfusate of kidneys from DCD and DND.

Methods: Perfusates from DCD and DND were collected (n=25) at the beginning (T0) and at the end (T1) of perfusion and analyzed by Luminex technology for neutrophil

gelatinase-associated lipocalin (NGAL), Cystatin C, Kidney Injury Molecule-1 (KIM-1), Monocyte chemoattractant protein-1 (MCP-1), and trefoil factor 3 (TFF3).

Results: Donor kidneys characteristics are resumed in **Table**. The highest levels of early biomarkers of renal tubular injury were seen for the DCD compared to DND kidneys for all markers except for MCP-1, the key chemokine that regulate migration and infiltration of monocytes/macrophages (**Figure**). No differences are reports for DGF of recipients.

Conclusions: Comparison of the perfusates from the different types of kidneys has allowed us to identify increased levels of biomarkers, representatives of increased acute tubular damage, that will be useful in future research into improving DCD kidneys outcome.

Funding: Clinical Revenue Support

Table

	DND n= 11	DCD n= 14	p-value
Donor Age (yrs±SEM)	59.9±1.4	61.9±2.3	n.s.
Donor Gender (M:F)	8:3	12:2	n.s.
Donor baseline serum creatinine (mg/dl±SEM)	0.7±0.07	0.9±0.13	n.s.
Machine cold perfusion (min±SEM)	184±29	215±29	n.s.
Machine cold perfusion flow (ml/min±SEM)	47.4±5.3	59.9±7.9	n.s.
Cold ischemic time (hours±SEM)	14.3±1.1	9.8±0.8	0.013
Delayed graft function	2	2	n.s.

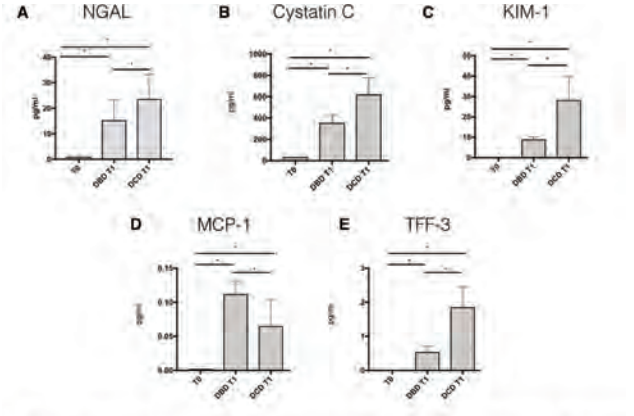

Figure. Levels of markers of kidney injury. (A) neutrophil gelatinase-associated lipocalin (NGAL); (B) cystatin C,(C) Kidney Injury Molecule-1 (KIM-1), (D) Monocyte chemoattractant protein-1 (MCP-1) and (E) trefoil factor 3 (TFF3) for DBD (n=11) and DCD (n=14) transplant kidneys. * Represents p<0.05 using ANOVA.

FR-PO894

Urinary RANTES, IL-4, and IL-6 as Potential Prognostic Markers of Early Renal Outcome in Living Donor Kidney Transplantation

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Background: Changes in intrarenal immunologic micromilieu has been shown to affect the renal outcome in kidney transplantation. Recent studies have shown that some cytokines and chemokines may have potential as non-invasive diagnostic markers that detect early injury after kidney transplantation. This prospective study aimed to investigate the diagnostic value of urinary cytokines and chemokines after living donor kidney transplantation as prognostic markers of early renal outcome.

Methods: Serum and urine samples were serially collected from kidney transplant patients at the following time points; during transplantation, 8 hours, 24 hours, 72 hours, 1 week, 3 months, and 1 year after transplantation. Cytokines and chemokines including regulated on activation, normal T cell expressed and secreted (RANTES), fractalkine, interleukin (IL)-10, IL-4, IL-6, monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF) were measured in 64 patients. Patients were divided into either the good prognosis group (eGFR at post-transplant 3 months ≥ 60ml/min/1.73m^2 or eGFR change ≥ -5 between post-transplant 3 and 12 months) or the poor prognosis group (eGFR at post-transplant 3 months < 60ml/min/1.73m^2 or eGFR change < -5 between post-transplant 3 and 12 months). T-test and one-way or two-way ANOVA tests were used for statistical analysis.

Results: The median age of patients was 42.3 years and 70.3% were male. Urinary RANTES ($P < 0.001$) and urinary IL-4 ($P < 0.05$) at 24 hours after transplantation were higher in the good prognosis group. When patients were divided by eGFR change between 3 months and 1 year after transplantation, urinary IL-6 at 3 months after transplantation ($P < 0.05$) was higher in the good prognosis group. There were no differences in serum cytokines or chemokines between groups.

Conclusions: Our study showed the potential clinical value of urinary RANTES and IL-4 measured at 24 hours after transplantation as well as urinary IL-6 at 3 months after transplantation as non-invasive predictors of early renal outcome after living donor kidney transplantation.

FR-PO895

Plasma Fibroblast Growth Factor 21 Plasma Concentration in Patients After Kidney Transplantation

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Background: Fibroblast growth factor 21 (FGF21) is a protein hormone involved in the regulation of energy expenditure. The results of clinical studies suggest that plasma FGF21 concentration increases with the progression of chronic kidney disease. The aim of the present study was to analyze the effect of successful kidney transplantation on plasma FGF21 concentration and to study the factors related to plasma FGF21 concentration in patients long-term after kidney transplantation.

Methods: Forty patients with chronic kidney disease (CKD) 5 or 5D before kidney transplantation [27 women and 13 men aged 47.0 (39.3 - 54.0)], 180 patients long-term after kidney transplantation [70 women and 110 men aged 52 (47,4 – 54)] and 50 healthy subjects [28 women and 22 men aged 50.0 (47.6 - 58.0)] were enrolled into this study. In CKD patients, plasma FGF21 concentrations were measured four times (immediately before and 14 and 30 days, and 6 months after kidney transplantation). In patients long-term after kidney transplantation and in healthy subjects, this measurement was made once.

Results: In patients before kidney transplantation plasma FGF21 concentration were significantly higher than in healthy subjects [1013.0 pg/ml (744.4-1635.7 pg/ml) vs 256.0 pg/ml (219.0 – 332.0 pg/ml); $p < 0.001$]. At 14, 30 days and 6 months after kidney transplantation, a significant decrease of plasma FGF21 was observed [1013.0 pg / ml (744.4 - 1635.7 pg / ml); 322.5 pg/ml (199.0 - 546.8 pg/ml); 367.5 pg/ml (289.3 - 483.5 pg/ml); 363.5 pg/ml (293.5 - 508.2 pg/ml) ($p < 0.001$), respectively]. In patients long-term after kidney transplantation, a negative correlation was found between plasma FGF 21 concentration and estimated glomerular filtration (eGFR) ($R = -0.165$, $p < 0.05$) and a positive correlations between plasma FGF21 concentration and HOMA ($R = 0.185$, $p < 0.02$), BMI ($R = 0.148$, $p < 0.05$) and serum triglycerides concentration ($R = 0.362$, $p < 0.001$).

Conclusions: 1. In patients after kidney transplantation a decrease of plasma FGF 21 concentration was found. 2. Plasma FGF21 concentration in patients long-term after kidney transplantation is related to the degree of impairment renal function and metabolic status.

Funding: Government Support - Non-U.S.

FR-PO896

Oxalate Nephropathy Due to Enteric Hyperoxaluria in the Renal Allograft: A Case Series

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Background: Secondary hyperoxaluria due to enteric causes is an underrecognized cause of renal allograft injury and loss. We present a single center case series of oxalate nephropathy in kidney transplant (KTx) patients due to enteric hyperoxaluria (EH).

Methods: Cases of oxalate nephropathy based on pathological description from 2008 to 2018 were ascertained. Cases of primary hyperoxaluria were excluded. Clinical risk factors for EH, serum and urine oxalate levels around the time of the biopsy, treatment, and allograft outcomes were analyzed.

Results: Fifteen cases of oxalate nephropathy were identified. Median follow-up was 3.0 years (range 0.4 to 8.6 years). Median time from transplant to allograft biopsy showing oxalate nephropathy was 104 days (range 14 days to 8.6 years). The most common pre-Tx risk factors for EH included short bowel syndrome (27%) and gastric bypass (13%). Post-Tx risk factors included chronic diarrhea (33%) and frequent antibiotic use (27%) with presumed altered gut flora. Median serum oxalate was 13.4 umol/L (range 2.7 to 37.5 [normal 0.4 to 3]) and median 24-hour urine oxalate was 97.7 mg/24 hours (range 40.5 to 121.2 [normal 9.7 to 40.5]). The predominant treatment was a low oxalate diet, increased oral fluids (93%), coupled by dietician counseling (87%) and calcium supplementation (93%). At last follow-up, 6 patients had GFR<45ml/min, 4 had GFR<30ml/min and 4 were on dialysis. [Table1]

Conclusions: Enteric causes of hyperoxaluria in KTx patients can be attributed to pre and post-transplant risk factors. Oxalate nephropathy due to EH in KTx patients is an important cause of allograft failure and warrants a standardized approach for early detection and treatment approach tailored for patients' unique risk factors.

Table 1: Summary of identified renal transplant oxalate nephropathy cases.

Case	Risk Factors	Management	HD at Time of Biopsy	GFR at Last Follow-up
1	Crohn's disease, short bowel syndrome	IVF, low oxalate diet, calcium, pyridoxine	No	27
2	Chronic diarrhea, diabetic gastroenteropathy, vitamin C, frequent antibiotic use for recurrent UTI	Hydration, low oxalate diet, calcium	No	24
3	High oxalate diet, frequent antibiotic use for recurrent UTI	Hydration, low oxalate diet, calcium, potassium citrate	Yes, DGF	36
4	Gastric bypass, diabetes, chronic diarrhea	Hydration, low oxalate diet, calcium	No	47
5	Short bowel syndrome	Hydration, low oxalate diet, calcium	No	17
6	Frequent antibiotic use, diabetes	None	Yes, DGF	32
7	Chronic diarrhea, diabetic enteropathy	Hydration, low oxalate diet, calcium, GI consult, cholestyramine	No	HD
8	Short bowel syndrome	Hydration, low oxalate diet, calcium, potassium citrate, GI consult	No	25
9	Cholestasis, diabetes	Hydration, low oxalate diet, calcium	Yes, DGF	38
10	Chronic diarrhea, diabetes	IVF, low oxalate diet, calcium, probiotic, GI consult	No	32
11	Chronic diarrhea, diabetes	Low oxalate diet, calcium	No	HD
12	Chronic pancreatitis, diabetes	Hydration, low oxalate diet, calcium, potassium citrate, pyridoxine, pancreatic enzymes	No	32
13	Bowel resections, gastric bypass, diabetes	Intensified HD, low oxalate diet, calcium	Yes, primary non-function	HD
14	Diabetes, frequent antibiotic use for recurrent UTI	Hydration, low oxalate diet, sodium citrate	No	HD
15	Gastric bypass, chronic diarrhea	Hydration, low oxalate diet, calcium, potassium citrate, probiotic, changed MM to azathioprine	No	35

Delayed graft function (DGF); Gastroenterology (GI); hemodialysis (HD); intravenous fluids (IVF); mycophenolate mofetil (MM); urinary tract infection (UTI)

FR-PO897

Glomerular Neovascularization in Renal Allograft: Clinical and Pathological Significance

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Background: An extra efferent arteriole is often observed in the glomerular vascular pole. This morphological change is referred to as polar vasculosis (PV). PV has been associated with glomerular hypertrophy and is considered as a sign for detecting early recurrent diabetic nephropathy after renal allograft. We have often noted PV even in cases without diabetic nephropathy after renal allograft; however, its significance remains uncertain. In the present study, we examined the clinical and pathological significance of PV in renal allograft.

Methods: This study included 9,004 renal biopsy specimens obtained from January 2007 to December 2017 at the Tokyo Women's Medical University.

Results: PV was identified in 186 biopsies obtained from 165 patients. We excluded 44 biopsies from 36 patients because of transmitted PV, which was detected in pre-transplantation biopsy. We identified 142 biopsies from 129 patients as the PV group. In addition, we identified 130 control renal allograft recipients who were matched according to their age and post-transplantation period. We obtained the clinical information of 48 and 116 patients in the PV and control groups, respectively. In the PV group, the mean age was 49.0 ± 14.0 years, and the mean post-transplantation period was 1850.1 ± 2235.7 days. In the pathological findings, a significant correlation was observed among glomerulomegaly, focal segmental glomerulosclerosis lesion, mm score, ah score, and aah score in Banff score ($P < 0.05$). The clinical findings revealed a significant correlation between the tacrolimus trough level at two weeks post-transplantation and the systolic blood pressure ($P < 0.05$).

Conclusions: This findings of this study indicated that polar vasculosis is associated with calcineurin inhibitor toxicity along with glomerular hypertrophy.

FR-PO898

Validation of a Cellular Assay for Detection of Over-Immunosuppression in Kidney Recipients: An Interim Report

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Background: The transplantation community lacks a clinical tool to diagnose over-immunosuppression, resulting in major clinical side effects. Recently, our laboratory has unveiled an association between the cytokine secretion of intermediate CD14+CD16+ monocytes stimulated *in vitro* with Epstein-Barr Virus (EBV) peptides and the status of over-immunosuppression in a prospective, longitudinal cohort of kidney recipients. We are now validating the test in a large cross-sectional cohort.

Methods: We recruited 120 unsensitized kidney recipients, isolated their peripheral blood mononuclear cells at 2 timepoints (3mo interval) and stimulated the cells with EBV peptides overnight. Staining for viability, CD14 and CD16 and tumor necrosis factor (TNF-α) was performed to quantify cytokine secretion of intermediate monocytes by flow cytometry.

Results: We report interim results of the first 24 patients. Mean±SD age was 56±13 years and mean glomerular filtration rate was 46±15 mL/min/1.73m². Median time (25-75th percentiles) post-transplant was 2 (1 – 8) years. Patients were treated with prednisone, mycophenolate and tacrolimus. Eleven patients received induction therapy. There were 15 controls and 9 cases, including 7 opportunistic infections, 1 recurring bacterial infections and 1 *de novo* neoplasia, events which happened on mean of 1.4±2.0 months after blood was withdrawn for the assay. Mean TNF-α-positive cells on the first sample was 70±20% for the controls and 53±15% for the cases. All but one patient who scored below the previously established threshold (<73% TNF-α) were confirmed on the second sample. AUC of the ROC curve was 0.83±0.09 ($p<0.01$). Preliminary values of sensibility, specificity, positive and negative predictive values were 89% (8/9), 60% (9/15), 57% (8/14) and 90% (9/10) respectively.

Conclusions: These interim results seem to confirm that over-immunosuppressed patients have lower intermediate monocyte response to EBV peptides. Furthermore, they show high sensibility and negative predictive value, similar to the derivation cohort. This assay could allow ruling out over-immunosuppressive state in the clinical setting.

FR-PO899

Mammalian Target of Rapamycin (mTOR) Inhibitor Might Augment Klotho Levels of Kidney Transplant Recipients

Yukiko Hasuike,[1] Kosuke Mizusaki,[1] Tomoko Kimura,[1] Yasuyuki Nagasawa,[1] Takahiro Kuragano,[1] Yusuke Yamada,[2] Michio Nojima,[2] Shingo Yamamoto,[2] Masaharu Ishihara.[1] *[1]Div Kidney and Dialysis, Dep Internal Medicine, Hyogo College of Medicine, Nishinomiya City, Japan; [2]Dep. Urology, Hyogo College of Medicine, Nishinomiya, Japan.*

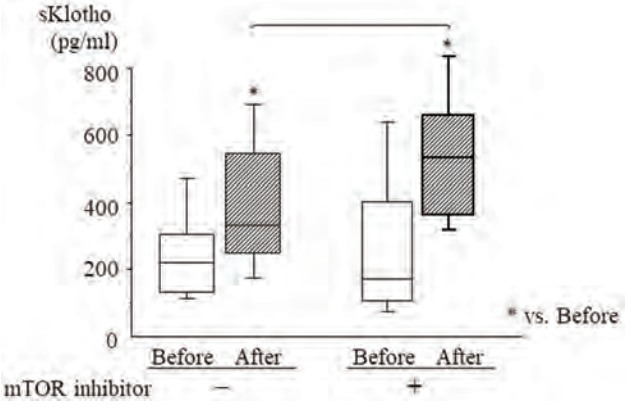
Background: α-Klotho, an anti-aging kidney-secreted hormone, exists in several forms including the membrane and a soluble form (sKlotho). sKlotho level of chronic kidney disease (CKD) patients is reduced. sKlotho administration attenuated renal fibrosis and dysfunction. It was reported that mTOR inhibitor reduce interstitial fibrosis and glomerular sclerosis of kidney transplantation (TPL) recipients, however, the mechanism is unclear. We investigated the influence of mTOR inhibitor on sKlotho of CKD patients before and after TPL.

Methods: This was a retrospective, observational study of kidney TPL recipients who were treated in Kidney Transplant Center of Hyogo College of Medicine (from 2001 July to 2016 October). Blood samples were collected before and 1-year after TPL and stored until assay. Serum sKlotho and fibroblast growth factor (FGF)-23 concentrations were measured using human ELISA, respectively. Several factors related to CKD (Ca, iP, intact parathyroid hormone, and $1,25(OH)_2$vitamin D) were examined.

Results: The CKD patients (n=36) were participated. Median age and vintage of participants was 37.0 (IQR, 27.5-50.5) y.o. and 4.6 (1.0-8.8) years. In this study, 75.0% (n=27) of kidney TPL were living donor, 8.3% (n=3) were received preemptive TPL, and 36.1% (n=13) were administrated mTOR inhibitor (everolimus). Comparing before and after TPL, sKlotho level was significantly increased ($p<0.001$) and FGF23 level was decreased ($p<0.001$). After TPL, sKlotho level of participants with mTOR inhibitor was significantly higher than that without mTOR inhibitor, 537 (367-659) pg/ml vs 332.4 (250-550) pg/ml ($p=0.026$, Figure 1). There was no significant difference of the other parameters between before and after TPL.

Conclusions: Administration of mTOR inhibitor might augment Klotho level of CKD patients after TPL.

Figure 1.



FR-PO900

Clinicopathologic Characteristics of Kidney Allografts with Donor-Derived Diabetic Nephropathy

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Background: The general consensus is that donor kidneys with biopsy proven diabetic nephropathy (DN) should be discarded, although data regarding outcomes of these cases is lacking. In this study, the clincopathologic characteristics of allografts with moderate to advanced donor-derived DN was examined.

Methods: Retrospective analysis (between 06/2011 to 01/2017) of all kidney transplant recipients with biopsy proven class II or III DN within the first six months post-transplantation was performed. For each patient, all biopsies were reviewed to assess progression/regression in disease. Glomerular changes were classified based on Tervaert

pathologic classification. Associated clinical data were extracted from electronic medical records, including donor information.

Results: Fifteen recipients received donor kidneys with DN from 11 donors. All but one donor had confirmed history of long-standing diabetes, while 47% of recipients had history of diabetes. Nine grafts had class III, two had class IIb, and four had class IIa donor-derived DN. Mean clinical follow up time was 13.2 months (range 3-30 months). Four grafts (27%) failed within the first year, three of which were due to primary non-function and one showed slow graft function without need for dialysis but had subsequent rapid deterioration within 9 months. Two failed grafts had class IIb and two had class III DN, while none of the class IIa grafts failed. Two of the failed grafts had contralateral sister kidneys that demonstrated good renal function. Of the functional grafts, four (36%) experienced delayed graft function. Average creatinine at latest follow up for functional grafts was 1.4 mg/dL, and none experienced rejection episodes. No significant histologic progression/regression in DN class was observed, and no histologic findings on initial biopsy were significant for predicting graft failure.

Conclusions: Despite the high incidence of failed grafts, 73% of recipients in this cohort experienced successful transplantation using kidneys with moderate to advanced donor-derived DN. Although no histologic findings were statistically significant for predicting graft failure, the grafts that failed showed either class IIb or III DN and not class IIa DN, suggesting that kidenys with class IIa DN may be safe to use.

FR-PO901

Plasma Cell Infiltrate in Allograft Rejection in Kidney Transplant Recipients

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Background: Allograft rejection has always been the chief obstacle to renal outcomes in kidney transplant recipients. We aimed to evaluate the different kidney allograft rejection phenotypes between acute cellular rejection with and without plasma cell infiltrate.

Methods: We conducted a hospital-based study including 1237 kidney transplant recipients between Jan 1, 2002 to Dec 31, 2017 in a tertiary medical center. Of them, we assessed patients who received renal biopsy and biopsy samples showed allograft rejection, which was defined by the renal function deterioration and histopathological lesions. The primary outcome of interest included kidney allograft loss and reinitiation of dialysis, graft histology, the severity of microvascular invasion and tubulitis.

Results: In our study, 1237 patients were included in the main analyses, of whom 293 (23.7%) had acute biopsy-proven rejection. We evaluated distinct patterns of kidney allograft rejection: T cell rejection and antibody mediated rejection with and without plasma infiltrates. Risk of failure to achieve graft function returning to to baseline after 6 month rescue therapy was highest in rejection with plasma cell infiltrate (hazard ratio [HR], 2.00; 95% confidence interval [CI], 1.142–3.307; $P = 0.0105$), followed by antibody rejection without plasma cell infiltrates (HR 1.25), compared with T cell mediated rejection without plasma cell infiltrate.

Conclusions: In our study, we found that allograft rejection with plasma cell infiltrates were associated with poor renal outcomes compared to those without plasma cell infiltrates. Therefore, nephrologists and renal pathologists need to be aware of this entity and arrange more aggressive management to salvage kidney allografts.

FR-PO902

Safety and Efficacy of Management of Refractory Cytomegalovirus Infection in Kidney Transplant Recipients Treated with Foscarnet and Conversion from Antimetabolite to mTOR Inhibitor

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Background: Cytomegalovirus (CMV) infection is a frequent complication after kidney transplantation and it is associated with graft dysfunction and increased mortality. Foscarnet may be an alternative to ganciclovir-resistant or CMV refractory infections. As additional therapies, there are limited published studies assessing the conversion from antimetabolite (mycophenolate or azathioprine) to mTOR inhibitor (mTORi) to avoid recurrence.

Methods: We retrospectively evaluated the adverse events and outcomes of the treatment of refractory CMV with foscarnet from January 1, 2010 to April 30, 2018 and we analyze the outcomes of the group of patients who were submitted to conversion from antimetabolite to mTORi.

Results: We evaluated 28 patients with refractory CMV treated with foscarnet; 89.3% received thymoglobulin as induction therapy and, as a maintenance therapy, 46.4% started with azathioprine and 53.6% with mycophenolate. The first episode of CMV occurred, on average, 40 days after transplantation. The average duration of therapy with ganciclovir was 98 days and 34.9 days with foscarnet. The UL97 mutation was present in all cases and the UL54 mutation was in 28.7%. After treatment with foscarnet, 17.8% had CMV recurrence. During treatment, 92.8% had antimetabolite discontinued, 64.3% were converted to mTORi. There were 19 recurring cases of CMV, 7 of them (36.8%) after conversion to mTORi against 12 cases (63.2%) in patients that not received mTORi. About the adverse effects to foscarnet, hypomagnesemia is the most common (82.1%), followed by hypophosphatemia (57.1%) and leucopenia (46.4%). There were 4 graft rejections and 3 deaths.

Conclusions: Prolonged use of ganciclovir with doses not adjusted for renal function as well as the immunological status of the transplanted patient are considered the main risk factors for resistance to ganciclovir therapy. Foscarnet seems to be an effective alternative in the control of viremia and treatment of CMV invasive disease. However, adverse events should be monitored cautiously, avoiding unfavorable outcomes for the graft. Preliminary data show that the conversion from antimetabolite to mTOR inhibitor is effective to avoid recurrence of CMV episodes.

FR-PO903

The Rate of Cytomegalovirus Infection and Disease in Renal Transplant Patients

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Background: Cytomegalovirus (CMV) is a common opportunistic pathogen in renal transplant recipients (RTR) and is known to cause significant morbidity and mortality. To prevent CMV infection and disease, this single center academic institution utilizes both valganciclovir prophylaxis and continued monitoring through the outpatient transplant refill and mailing program (RAMP). The purpose of this study is to determine the incidence of CMV infection and disease in RTR who received valganciclovir and were enrolled in RAMP.

Methods: This is a retrospective, single center, cohort study of adult RTR between 2014-2016. Patients were eligible if enrolled in RAMP, >18 years old, and able to take oral valganciclovir. The primary endpoint was the incidence of CMV infection or disease in the first year post-transplant. The secondary endpoint was the dose of valganciclovir at various time intervals post-transplant for a subgroup of 100 patients (including all patients with infection and disease).

Results: A total of 418 RTR of CMV high risk (Donor+/Recipient-) and intermediate risk (D+/R+, D-/R+) were included. Most were male (59%) and of Hispanic (38%) or Caucasian (26%) descent. Their mean age was 51 years old (range 18 to 81). Of the 418 patients, CMV infection occurred in 15 (3.6%) and disease occurred in 2 (0.48%), with the majority of these cases occurring in the D+/R- group (11/17). For the subgroup of 100 patients evaluated for valganciclovir dosing, 50% of patients were dosed higher and 20% were dosed lower than recommended at hospital discharge. At weeks 4, 8, and 12 post-transplant 54-58% received lower and 12-20% received higher dosing than recommended.

Conclusions: The incidence of CMV infection and disease was lower than what is reported in the literature, with the highest prevalence in the D+/R- group. A combination of outpatient monitoring through RAMP and aggressive upfront dosing, followed by subsequent dose reductions in the outpatient setting likely contributed to the low rate of CMV infection and disease.

FR-PO904

Clinical Significance of Using the Banff 2017 Polyomavirus Nephropathy Classification in Kidney Transplantation: A Single Center Experience

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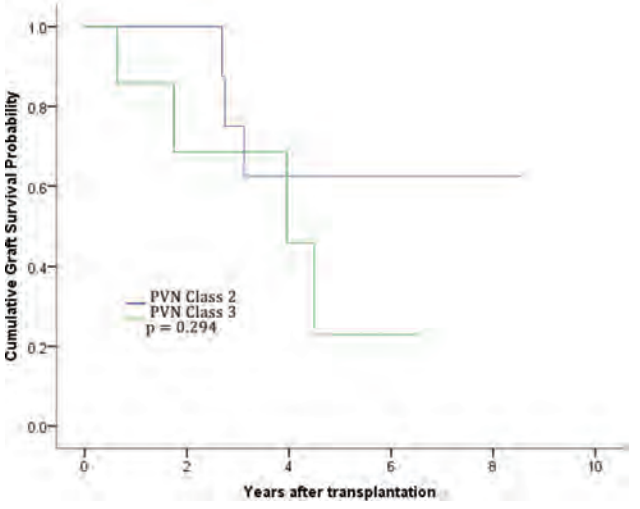
Background: BK virus is a known cause of BK polyomavirus nephropathy (PVN) and renal allograft failure. The 2017 Banff PVN classification is based on intrarenal polyoma viral load and Banff interstitial fibrosis score. The aim of this study is to examine the clinical significance of using PVN classes and its correlation with allograft survival.

Methods: This is a single-center retrospective analysis of all patients with BK viremia (BKV) > 10,000 copies/ml from 2009 to 2017 who underwent for-cause renal allograft biopsy. Patients were histologically classified into Banff Class 1, 2 or 3. Kidney function was compared between groups. A Kaplan-Meier analysis was performed to compare renal allograft survival differences among the groups using log rank test.

Results: BKV was identified in 122 patients (88 male and 34 female). Renal allograft biopsy was performed in 61 patients (50%). Seventeen patients (27.9%) had only PVN, and another 17 patients (27.9%) had only acute cellular rejection (ACR), whereas concomitant PVN and ACR were found in 4 patients (6.6%). The remaining 23 patients (37.7%) had neither PVN nor ACR. There was no statistically significant difference in clinical, demographic and laboratory parameters between the PVN groups. Out of 17 patients with PVN, one patient had class 1 (5.8%), 9 had class 2 (52.9%) and 7 had class 3 (41.2%). The single patient with class 1 PVN was excluded from the analysis. There was a trend toward better graft survival in PVN class 2 compared to class 3 (figure 1), but it failed to reach statistical significance.

Conclusions: Allograft survival was not statistically different between PVN class 2 and 3 although a non-significant trend towards worse graft survival was seen in PVN class 3.



Survival Curves

FR-PO905

BKV Clearance Time Correlates with the Exhaustion State and T-Cell Receptor Repertoire Shape of BKV-Specific T-Cells in Renal Transplant Patients with Severe BKV Infection

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Background: Reactivation of the BK polyomavirus is known to lead to severe complications in kidney transplant patients. The current treatment strategy relies on decreasing the immunosuppression to allow the immune system to clear the virus. Recently we demonstrated a clear association between the resolution of BKV reactivation and reconstitution of BKV-specific CD4+ T-cells. However, the factors determining the duration of the clearance of the viral infection remain unknown.

Methods: Here we apply a combination of in-depth multiparametric flow cytometry and CDR3 beta chain receptor repertoire analysis of BKV specific T-cells to a cohort of 5 kidney transplant patients with BKV reactivation. In this manner we were able to track the TCR repertoires at single clone levels during the clinical course of BKV infection.

Results: The number of BKV-specific T-cells in peripheral blood did not affect the duration of BKV infection. In contrast, the diversity of the T-cell receptor repertoire as well as exhaustion status of BKV-specific T-cells correlated with the duration of viral clearance. This duration was further found to be independent of hyperexpanded, immunodominant BKV-specific T-cell clones and of the overall magnitude of cellular immunity. Rather, the diversity of BKV-specific TCR repertoire in peripheral blood: high diversity of the repertoire and lack of PD1 and TIM-3 exhaustion markers on BKV-specific T-cells is associated with short remission time.

Conclusions: Our data demonstrate that the quality (exhaustion status and shape of the repertoire) rather than quantity of BKV-specific T-cells determines the remission time after BKV reactivation.

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FR-PO906

BK Virus Seroprevalence in Donors and Kidney Transplant Recipients and Their Correlation with Development of BK Virus Infection in the Post-Transplant Period

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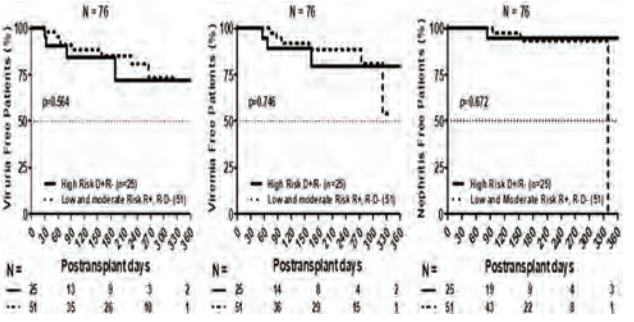
Background: BK virus (BKV) nephritis is a common cause of allograft dysfunction, which is related to the level of immunosuppression. Since no specific antiviral treatment is available, predictive markers that could help clinicians personalize the level of immunosuppression given to a specific patient are needed. Aims: to evaluate BKV seroprevalence in kidney donors and recipients as a predictive factor of BKV viruria, viremia and BKV nephritis in the post-transplant period.

Methods: BK-IgG ELISA qualitative test (MyBioSource Inc, San Diego, CA), was measured in 169 pts (81 donors and 88 recipients) before kidney transplantation. 76 recipients were followed post-transplant with BKV-PCR in blood and urine at 1, 3, 6, 9, and 12 months after transplantation. In addition, protocol biopsies at 3 and 12 months, and for-cause biopsies due to allograft dysfunction were performed.

Results: 58% of donors and 62.5% of recipients were seropositive prior to transplantation. Mean follow-up of transplant recipients was 198 days. They were divided into high risk (D+/R-, n=25) and moderate/low risk (D-/R+, D+/R+ and D-/R-, n=51). Viruria, viremia and BK nephritis developed in 16%, 12%, and 4% in the high risk, and 15.7%, 11.7%, 5.8% in the moderate/low risk group, respectively (p=0.9). Time to development of viruria, viremia, and BKV nephropathy was evaluated with the Kaplan-Meier in both groups and no statistically significance was observed [Figure 1].

Conclusions: BKV seroprevalence in Mexican population was 58.0% in donors and 62.5% in kidney transplant recipients. No correlation was observed between pretransplant serological status of donor and/or recipient and the post-transplant development of BKV viruria, viremia, and nephritis.



FR-PO907

Plasma Cell Neoplasms After Renal Allograft: A Single-Center Experience

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Background: Plasma cell disorders (PCD) are B-cell neoplasms that develop as a consequence of dysregulated B-cell clonal proliferation. The various types of PCD include monoclonal gammopathy of unknown significance (MGUS), multiple myeloma (MM) and monoclonal gammopathy of renal significance (MGRS). PCD and their complications can impact graft survival and other outcomes following kidney transplantation (KT). This underscores the need to investigate the natural history of PCD after KT.

Methods: Retrospective chart review was done at our institution in patients >18 years who had KT between 2008 and 2017 to identify those developing PCD after KT. Patients with a PCD before KT were excluded from the study.

Results: Of the 711 patients who received KT, 12 (1.68%) developed PCD. Three patients developed MM, 2 developed MGRS and 7 had MGUS in the post-transplant course. The study population was predominantly male (75%). Patients in the MM group were younger (mean age 54 years, range 47-67) than those in the MGUS (mean age 57, range 39-69) and MGRS groups (mean age 80 years, range 74-86) at the time of transplant. The mean time from transplant to PCD was 2.9, 3.2 and 4.6 years respectively in the MGRS, MGUS and MM groups. Mean follow up of survivors in the study was 5.9 years. Epstein Barr virus (EBV) positivity was noted in all 3 MM patients but in 50% of MGRS and 28% of MGUS groups. The mean creatinine at last follow up was higher (2 mg/dL) in MM subjects and was similar (1.7 mg/dL) in the MGRS and MGUS groups. Induction and maintenance immunosuppressive regimens used were similar in three groups. One MM patient died 3 years after diagnosis but all other patients were alive with a functioning graft at last follow up.

Conclusions: We found an incidence of new PCD after KT of 1.68% over a 10-year period after KT, which is similar to the incidence of post-transplant lymphoproliferative disorder (1.5%-2%). The risk of developing MM may be higher in patients who are transplanted at a younger age though the time from transplant to diagnosis may be longer than other types of PCD. EBV status at KT may influence development of MM post-transplant suggesting a role of immunosuppression. These findings merit further examination in a larger study.

FR-PO908

Mutational Signature of Urothelial Carcinoma After Kidney Transplantation as Revealed by Whole-Exome Sequencing (WES)

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Background: Urothelial carcinoma (UC) has the characteristic of high degree molecular heterogeneity. In Taiwan, UC is the most common cancer after kidney transplantation(KT). Mutational profiles by WES could help in identifying not only UC-specific genes but also novel genes for disease specific therapeutic target and outcomes. We perform WES of UC developed after KT in an effort to discover the molecular genetics of UC.

Methods: Formalin-fixed paraffin-embedded archival samples of UC from 6 kidney transplant patients in our center were obtained. Patients with UC diagnosed before the transplant surgery were excluded. All patients were sporadic, without any family history of UC. For control group, we selected 5 hemodialysis patients with UC diagnosed after the commencement of dialysis treatment. DNA was extracted for WES analysis.

Results: Missense mutations were the most common type of somatic mutation (Figure 1a, 2). The A:T→T:A transition was the most significant nucleotide changes (Figure 1b).

Our WES data was matched with the Cosmic, Intogen, and TCGA database for onco-driver genes. We newly identified five genes, including *GNAQ, MLLT10, SEPT6, SLC34A2, NTRK3*, which comprised of 25% of mutations specifically in our patients (Figure 2).

Conclusions: The finding of A:T→T:A transition as the most significant nucleotide changes was different from TCGA cohort, as about 51% of their mutation resulted in TpC>T or G. Our results suggest that the genetic mutation in our cohort might be associated with aristolochic acid (AA) exposure, which is the one of the risk factor for renal failure and UC development. This preliminary data provides clues for understanding the mutational landscape of UC developed after KT.

Figure 1a The Numbers of Non-Silent Somatic Mutation

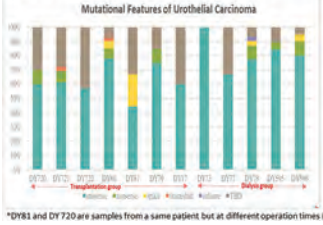
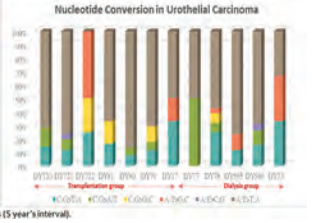
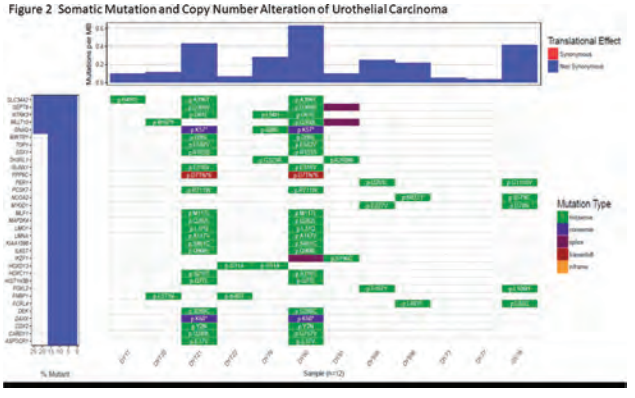


Figure 1b Nucleotide Conversion in Urothelial Carcinoma



*DY81 and DY 720 are samples from a same patient but at different operation times (5 year's interval).

Figure 2 Somatic Mutation and Copy Number Alteration of Urothelial Carcinoma



FR-PO909

Predictive Role of Histological and Immunological Parameters in ABMR in a Cohort of Renal Transplanted Patients

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Background: In clinical practice, the diagnosis of antibody-mediated rejection (ABMR) is based on three main components: specific histological lesions, presence of peritubular capillaries C4d and of circulating anti-HLA donor specific antibodies (cDSA). Our study aims to evaluate the concordance between histological and immunological diagnostic elements of ABMR and their predictive role on renal transplant (RTx) prognosis.

Methods: Among the 486 RTx patients transplanted from deceased donors in our Unit (2004-2015), 115 patients were submitted to renal biopsy (RBx) on clinical indications and evaluated for tissue C4d and cDSA (Luminex). Follow-up time was 3.7±2.7 yrs. According to histological lesions, RBx were categorized in: ABMR (hABMR), T-cell mediated rejection (hTCMR) or other lesions (hO). In addition, a categorization according to C4d positivity (C4d+/C4d-) and presence of cDSA at RBx (cDSA+/cDSA-) was made. In the relationship between histological and immunological elements, we considered 4 groups: cDSA-/C4d- (gr-A); cDSA-/C4d+ (gr-B); cDSA+/C4d- (gr-C); cDSA+/C4d+ (gr-D).

Results: Among the 115 RBx, 20%, 21% and 59% were respectively hABMR, hTCMR and hO. Compared to others, hABMR had higher PRA at RTx (p=0.03), higher Prot-U at RBx (p=0.01), more prevalence of C4d+ and cDSA+ (both p <0.0001) and shorter follow-up after RBx (p=0.03). In hABMR, 17.4% and 8.7% were in gr-A and gr-B, 30.4% and 43.5% in gr-C and gr-D (p<0.0001); in hTCMR, 95.8% and 0% were in gr-A and gr-B, 4.2% and 0% in gr-C and gr-D (p<0.0001); in hO, 80.9% and 2.9% were in gr-A and gr-B, 14.7% and 1.5% in gr-C and gr-D (p<0.0001); hABMR, C4d+ and DSA+ were singularly associated with graft loss, but among them h-ABMR was the only independent predictive factor for graft loss (HR 2.64 - p=0.01). Kaplan Meier analysis showed a worse graft outcome in hABMR compared to other histological diagnoses (p<0.001). h-ABMR had also higher graft loss discriminative power than C4d+ and cDSA+ (AUC 0.70, p<0.001). No discriminative informative advantages were found considering together h-ABMR and/or C4d+ and/or cDSA+.

Conclusions: Our data suggest that the histological evaluation of RTx is an unavoidable test for the diagnosis of graft dysfunction and represents the best prognostic parameter.

FR-PO910

Outcomes of Two Diarrhea-Causing Infections in Kidney Transplant Recipients

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Background: Diarrhea caused by infection from *Clostridium difficile* (*CD*) or Norovirus (NV) is a common complication in immunosuppressed kidney transplant recipients (KTRs). There is limited data comparing the outcomes of these infections in KTRs. Comparing the outcomes of these two prevalent infections may inform preventive and therapeutic strategies in patient management.

Methods: We examined KTRs transplanted at our center between 01/01/1994 to 12/31/2014 who suffered from *CD* or NV infection-related diarrhea. Those who suffered *CD* or NV infection were matched with controls randomly selected from surviving recipients without these infections to that point in time with a 5:1 ratio. Outcomes examined include number of *CD* or NV infections, interval from transplant to infection, and graft failure.

Results: Of 4941 kidney transplants performed during the study period, 294 developed primary *CD* and 64 developed NV. Mean interval from transplant to infection was 1401±1621 days for *CD* infection and 1355±1357 days for NV infection. Polycystic kidney disease, diabetes, and glomerulonephritis were more common in the *CD* group compared to NV (p<0.05). Median uncensored graft survival following infection was 456 days for *CD*, 541 days for NV, and 1276 days for controls. Cox proportional hazard regression demonstrated that those with *CD* had higher risk of graft failure than controls (HR 2.43, 95% CI 2.07 to 2.87, p<0.01). Graft failure in the *CD* group and NV group were higher than for the control group at different times (Table 1).

Conclusions: Both *CD* and NV infection are associated with deleterious effects on kidney graft survival. Prevention and early management of these infections may prolong graft survival.

Funding: Private Foundation Support

Table 1. Graft failure in CD, NV, and control study groups.

	Graft failure by 6 months of infection	*Graft failure by 12 months of infection*	*Graft failure by 36 months of infection*	*Graft failure by 5 years of infection*
CD	21%	30%	47%	60%
NV	5%	10%	30%	44%
Control	3%	6%	20%	32%

FR-PO911

Presence of Anti-HBs Confers Protection Against Hepatitis B Virus Infection in HBsAg-Negative and Anti-HBc-Positive Patients Undergoing Kidney Transplantation

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Background: The American Gastroenterological Association (AGA) and European Association for the Study of the Liver (EASL) recommend that hepatitis B surface antigen (HBsAg)-negative and hepatitis B core antibody (anti-HBc)-positive patients who receive immunosuppression should be monitored for hepatitis B virus (HBV) infection regardless of hepatitis B surface antibody (anti-HBs) status. However, anti-HBs may provide protection against HBV infection. To investigate whether the presence of anti-HBs in addition to anti-HBc confers protection, we classified HBsAg-negative kidney transplantation (KT) patients into 4 groups according to anti-HBc and anti-HBs status, and compared the HBV infection rate between the anti-HBc(+)/anti-HBs(+) group and the other 3 groups.

Methods: In this single-center retrospective study, we classified 1,959 patients into 4 groups: anti-HBc(-)/anti-HBs(-) (n=356), anti-HBc(-)/antiHBs(+) (n=652), anti-HBc(+)/anti-HBs(-) (n=142), and anti-HBc(+)/anti-HBs(+) (n=809).

Results: HBV infection was noted in 31 patients (1.6%) after KT. There was a significant difference in HBV infection rate between anti-HBc(+)/anti-HBs(+) (1.2%) and anti-HBc(+)/anti-HBs(-) (5.6%) (p<0.001), but not between anti-HBc(+)/anti-HBs(+) and anti-HBc(-)/anti-HBs(-) (1.1%) or anti-HBc(-)/anti-HBs(+) (1.4%). There was a significant difference in HBV infection rate according to anti-HBs titer, but no difference according to the donor viral profile. Hepatic failure occurred in 1 anti-HBc(+)/anti-HBs(-) patient and 1 anti-HBc(+)/anti-HBs(+) patient, both of whom died. Hepatocellular carcinoma was noted in 4 anti-HBc(-) patients, but not in anti-HBc(+) patients.

Conclusions: The presence of anti-HBs confers protection against HBV infection. The EASL or AGA guidelines may be modified to indicate that monitoring should be performed for HBV infection after KT in HBsAg(-)/anti-HBc(+)/anti-HBs(-) patients, but not in HBsAg(-)/anti-HBc(+)/anti-HBs(+) patients.

FR-PO912

The Risk of Hepatitis B Virus Reactivation with Rituximab Desensitization in HBsAg-Positive Kidney Transplant Recipients

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Background: Rituximab, as a powerful immunosuppressive agent, is used for ABO mismatched Kidney transplantation (KT) or flow cytometry positive patients. Because rituximab has elevated risk for hepatitis B virus (HBV) reactivation, antiviral prophylaxis is

recommended for positive hepatitis B surface antigen (HBsAg(+)) recipients. The purpose of this study was to evaluate whether treatment with an antiviral agent is enough for preventing HBV reactivation in HBsAg(+) patients who had KT with rituximab desensitization.

Methods: The 128 patients who underwent KT from 2009 to 2016 identified as HBsAg(+) before KT in a single center were retrospectively analyzed. They were divided into two groups according to whether rituximab was used or not (29 patients in Rituximab(+) group, 99 patients in Rituximab(-) group). HBV reactivation was diagnosed by an increase in HBV DNA more than 2 $\log_{10}$ international units/mL or a detectable HBV DNA level when previously undetectable HBV DNA. In addition, HBV reactivation was compared between 500 mg and 200 mg in rituximab(+) group.

Results: Reactivation of HBV DNA was detected in 4 among 29 (13.79%) HBsAg(+) patients in rituximab(+) group and 20 among 99 (20.20%) HBsAg(+) patients in rituximab(-) groups (P=0.592). The 4 patients with HBV reactivation in rituximab(+) group had already taken antiviral agents since KT (Table1). LFT elevation was detected in 2 of the 4 patients that HBV DNA was reactivated. The elevated LFT or reactivated HBV DNA was spontaneously resolved without change of antiviral agents. The Number of HBV DNA reactivation was not lowered according to changing rituximab dose from 500 mg (1/8, 12.50%) to 200 mg (3/21, 14.29%) in rituximab(+) group.

Conclusions: When HBsAg(+) patients received KT, the use of Rituximab may not increase HBV reactivation. It is suggested that the usage of antiviral agents is efficient prophylaxis for HBV reactivation of HBsAg(+) recipients who had KT with rituximab desensitization.

Table 1. Time of DNA reactivation after KT in the 4 patients with HBV reactivation in rituximab(+) group (by year)

	Antiviral agent	Time of DNA reactivation after KT				
		0-1 year	1-2 year	2-3 year	3-4 year	4-5 year
Patient 1	entecavir			v		
Patient 2	entecavir		v			
Patient 3	entecavir				v	
Patient 4	telbivudine				v	

FR-PO913

HIV-Infected Kidney Allograft Recipients Managed with Anti-Thymocyte Globulin Induction

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Background: Reconsiderations of the risks involved in using immunosuppressive therapy in patients with HIV have resulted in a welcome foray into providing kidney allografts to HIV-infected patients. Anti-thymocyte globulin (ATG) induction reduces acute rejection but its use in HIV-infected kidney transplant recipients is limited. We assessed the long-term outcomes of HIV-infected kidney transplant recipients at our center managed with ATG induction.

Methods: Single center chart review of HIV-infected kidney allograft recipients between 2006 and 2016 who received induction immunosuppression with ATG. Maintenance immunosuppression included tacrolimus and mycophenolate with or without corticosteroids. Infection prophylaxis included clotrimazole, valganciclovir and co-trimoxazole. Primary outcome measures were patient and graft survival. Patients who did not meet their primary outcomes were censored at their last follow up.

Results: Twenty-nine HIV-infected patients (34% female, 66% black, 83% early corticosteroid withdrawal) underwent deceased (n=24) or living donor (n=5) kidney transplantation. Median (IQR) age was 54 years (50-59). CD4+ T-lymphocyte count was 455 (392-508). Graft and patient survival were 96.6% and 96.6% at 12 months respectively (Fig. 1). At 12 months post-transplantation, acute rejection-free survival was 96.4% and infection-free survival was 55.2%. Sustained HIV viral suppression was observed in 69% of patients. Ten patients (34%) developed 11 malignancies during their follow up.

Conclusions: Induction immunosuppression with anti-thymocyte globulin is associated with excellent clinical outcomes in HIV-infected kidney allograft recipients.

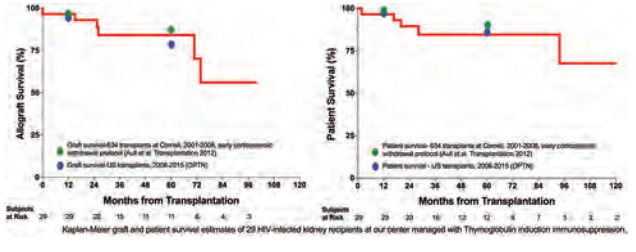

Figure 1. Kaplan-Meier graft (Left) and patient survival (Right) estimates of 29 HIV-infected kidney recipients at our center managed with Thymoglobulin induction immunosuppression.

FR-PO914

Clinical Experience of Prevalence and Prophylaxis for Latent Tuberculosis Infection in Living Donor Kidney Transplant Recipients

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Background: Latent tuberculosis infection (LTBI) is a risk factor of active tuberculosis (TB) in kidney transplant recipients (KTRs). Transplant-associated TB poses a significant risk for both graft loss and patient death. Current guideline recommends LTBI prophylaxis in KTRs. The aim of this study was to assess the property of current LTBI prophylaxis.

Methods: We investigated 404 living donor KTRs between November 2013 and December 2017. We analyzed Data including QFT, TST, chest radiography, past TB history, post-transplant TB incidence, and current practice of LTBI prophylaxis. LTBI was diagnosed to one of following criteria: (1) positive result in tuberculin skin test (TST) or interferon-gamma release assays (IGRA) by QuantiFERON-TB Gold In-Tube test (QFT); (2) the old healed TB sequelae in chest radiography without TB treatment history; (3) previously insufficient TB treatment history; (4) contact history with active pulmonary TB patient within a year. Initial prophylactic agent for LTBI was isoniazid 300mg per day.

Results: The mean follow-up period of the patients 25.6 ± 14.2 months. QFT was positive in 37.6% (n=152), while TST was only positive in 13.1% (n=30). Additionally, only seven patients (1.7%) among patients with negative QFT were positive TST. On the other hand, there was no tuberculosis outbreak in living donor kidney transplant recipients during followed-up period. A total of 137 subjects were prescribed INH. Of them, 37 patients (27%) underwent adverse events, with the most common adverse event being hepatotoxicity, most occurring within three months.

Conclusions: Careful surveillance in KTRs needs at early period of INH prophylaxis. High incidence of adverse events of INH prophylaxis including hepatotoxicity suggests to need additional strategies to reduce that in LTBI prophylaxis.

FR-PO915

High Plasma Cadmium and Late Graft Failure in Renal Transplant Recipients

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Background: Although short-term outcome after kidney transplantation has strongly improved, late graft failure remains a major distress for both patient and physician, and its etiology is poorly understood. This urges the identification of new treatable risk factors for late graft failure. In the general population, substantially increased plasma cadmium levels contribute to progressive renal function loss. Since renal transplant recipients (RTRs) only have one functioning kidney which is also exposed to noxious factors during transplantation, we assumed that RTRs are more susceptible to cadmium nephrotoxicity. Therefore, we hypothesized that higher plasma cadmium levels, even below the normal range, are associated with an increased risk of graft failure in RTRs.

Methods: The study was conducted in the TransplantLines Food and Nutrition Biobank cohort study. Plasma cadmium was measured using inductive coupled plasma mass spectrometry (ICP-MS). All RTRs (age>18 years) had a functioning graft for more than one year. Cox regression analyses were used to investigate prospective associations of cadmium with graft failure.

Results: We included 706 RTRs (age 53±13 years; 56.8% males at mean 5.4 (1.9-12.0) years after transplantation). Mean plasma cadmium levels were 0.70 ± 0.13 µg/L (normal range <5 µg/L) and eGFR was 45.0 ± 18.7 ml/min/1.73m^2 (normal range 90 – 120 ml/min/1.73m^2). During follow-up for 4.9 (3.3-5.5) years, 80 (11.3%) RTRs developed graft failure. In univariable analysis, increased plasma cadmium levels were associated with increased risk of graft failure (hazard ratio (HR) 2.49 [95%CI 1.73-3.58], P < 0.001). In multivariate analysis, after adjustment for age, sex, proteinuria, primary renal disease, time since transplantation, acute rejection, cold ischemia time, HLA mismatches, deceased donor status, BMI, systolic blood pressure, plasma glucose, diabetes, smoking, and alcohol use, the association of cadmium with graft failure remained (HR 2.23 [1.39-3.57], P = 0.001).

Conclusions: We conclude that cadmium levels are associated with an increased risk of graft failure in RTRs. Interventions aiming at reducing bodily cadmium concentrations, e.g. chelation therapy, seem warranted to improve long-term graft survival after renal transplantation.

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FR-PO916

Evaluating the Functional Response of a Barrier-Free Glomerulus-on-a-Chip System to Injury: A Novel Tool for Renal Personalized Medicine

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Background: With increasing rates of renal failure, there is an urgent need of implementing new strategies for understanding glomerular pathophysiology and for developing efficient patient-specific drug screening tools. To this regard, we recreated an in vitro 3D multicellular platform that allows fluid perfusion and proper interactions between podocytes and glomerular endothelial cells (hGEC). This glomerulus-on-a-chip system can be used to study the complex architecture and function of the glomerular filtration barrier (GFB).

Methods: Human amniotic fluid derived podocytes (hAKPC-P), human immortalized podocytes (iPod), primary human podocytes (pPod) and human fibroblasts (negative control) were seeded on microfluidic chips (Organoplates™) with hGEC. Immunofluorescence was performed for podocyte, endothelial and GBM markers. Barrier selective-permeability was investigated. Feasibility of the system for high throughput screening and disease modeling was evaluated by measuring permselectivity following Puromycin Aminonucleoside (PAN) injury or culture with serum from FSGS (focal segmental glomerular sclerosis) and membranous nephropathy (MN) patients.

Results: We have developed an innovative, barrier-free, glomerulus-on-a-chip system. hAKPC-P, iPOD and pPOD formed a slit diaphragm-like structure expressing nephrin and podocin. CD31-expressing hGEC formed capillary-like structures. De-novo deposition of GBM components such as collagen IValpha3,4,5 and laminin alpha5 was confirmed for hAKPC-P and pPOD but not iPOD. Albumin permselectivity was confirmed on chips with hAKPC-P, pPOD and less efficiently for iPOD while use of fibroblast lead to marked albumin leakage. Permselectivity was impaired following PAN administration as confirmed by our experiments. In the presence of MN serum (but not from healthy controls or FSGS) IgG-mediated injury to the barrier caused albumin leakage, suggesting an MN specific mediated damage.

Conclusions: We have successfully developed a glomerulus-on-a-chip system that closely mimics the GFB and provides a powerful tool for studying renal regenerative, disease mechanisms and toxicity effects. In conclusion, this system will increase our ability to individualize treatments and drug susceptibility, thus ultimately benefiting patients affected by renal failure.

Funding: Private Foundation Support

FR-PO917

Dynamic Chromatin Accessibility at Poised Developmental Enhancers of Nephron Progenitors

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Background: Remodeling of chromatin accessibility at dynamic lineage-specific enhancers has emerged as a key mechanism in the control of cell fate in health and disease. Recent studies defining the gene regulatory network of nephron progenitor cells (NPC) have identified cis-acting modules bound to the master transcription factors (mTF) Six2, Osr1, and Wt1. However, it is unclear how these combinatorial factors gain access to chromatin to define enhancer function. In this study, we mapped the chromatin landscape of NPC to determine accessibility of developmental enhancers to mTFs during the NPC lifespan.

Methods: Self-renewing young (E13.5, E16.5), and differentiating old (P0 and P2) $Six2^{+}/GFP^{+}$ NPCs were subjected to genome-wide ATAC-seq to map open chromatin regions, i.e., accessible enhancers. Chromatin states (poised, active, repressed) of enhancers were determined by ChIP-seq of H3K4me1, H3K27ac, and H3K27me3, respectively. Enhancer access and chromatin states were integrated with genome-wide mTF binding (ChIP-seq) and gene expression (RNA-seq).

Results: We examined 80 poised NPC genes that bind the three mTFs and show >4-fold increase in mRNA expression during NPC lifespan. mTFs occupancy corresponded to K4me1-marked (poised) chromatin regions in young NPC and to K4me1/K27ac-marked active enhancers in old NPC. Surprisingly, activation of differentiation poised enhancers (and gene transcription) correlated with progressive reduction in the size of open chromatin regions and thus to accessible cis-acting elements. In comparison, NPC lacking the H3K27 methyltransferases, Ezh1 and Ezh2, displayed persistent open chromatin at poised enhancers.

Conclusions: Progressive restriction of access to dynamic developmental enhancers may act as a gateway to fine-tune the timing of differentiation gene expression and cessation of nephrogenesis. Targeted epigenome editing of developmental enhancers may be a useful strategy to manipulate NPC fate and lifespan.

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FR-PO918

Comprehensive Analysis of Chromatin Signature and Transcriptome Uncovers Functional lncRNAs Expressed in Nephron Progenitor Cells

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Background: Emerging evidence from recent studies has unraveled the roles of long noncoding RNAs (lncRNAs) in the function of various tissues. However, little is known about the roles of lncRNAs in kidney development. In our present study, we aimed to identify functional lncRNAs in one of the three lineages of kidney progenitor cells, i.e., metanephric mesenchymal (MM) cells.

Methods: MM cells were purified by FACS from *Cited1*$^{nuc\text{-}TagRFP\text{-}T}$ mouse embryonic kidneys, and comprehensive analyses of the chromatin signature and transcriptome were conducted by RNA-seq and ChIP-seq.

Results: We found seventeen lncRNAs that were expressed specifically in MM cells with an active chromatin signature, while remaining silenced in a bivalent chromatin state in non-MM cells. Out of these MM specific lncRNAs, we identified a lncRNA, Gm29418, in a distal enhancer region of Six2, a key regulatory gene of MM cells. We further identified three transcript variants of Gm29418 by Rapid Amplification of cDNA Ends (RACE), and confirmed that the transcription-start-sites (TSSs) of these variants were consistent with the result of Cap Analysis Gene Expression (CAGE). In support of the enhancer-like function of Gm29418 on Six2 expression, we found that knock-down of Gm29418 by two independent anti-sense locked nucleic acid (LNA) phosphorothioate gapmers suppressed Six2 mRNA expression levels in MM cells. We also found that over-expression of Gm29418 led to an increase in Six2 mRNA expression levels in a mouse MM cell line.

Conclusions: In conclusion, we demonstrated in our present study that a comprehensive analysis of chromatin signature and transcriptome can be a powerful tool in screening lncRNAs in various tissues, which led us to identify a lncRNA, Gm29418, in renal progenitor cells that has an enhancer-like function on a key regulatory gene, Six2.

Funding: Private Foundation Support

FR-PO919

Netrin-1 Directs Neurovascular Patterning Required for Proper Kidney Development

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Background: Proper kidney development requires the coordinated growth and differentiation of multiple cell types. Alterations to nephron number and function can have significant health consequences. While advances have been made in elucidating how nephron progenitors form, differentiate, and interact with the adjacent stroma and collecting duct system, almost nothing is known about how the neural and vascular systems influence these processes or even how they become established in the fetal kidney. This is a significant void in our understanding, given the critical importance of vascular perfusion and innervation for mature organ formation and function.

Methods: To this end, we have interrogated the function of netrin-1 in the developing kidney. Netrin-1 is an axon guidance cue which also regulates vessel pathfinding. Netrin-1 (*Ntn1*) is highly expressed by the stromal progenitors. We conditionally deleted *Ntn1* in these cells and examined the resulting phenotypes with light-sheet and confocal microscopy in addition to standard histological techniques.

Results: *Ntn1* loss results in abbarent neural and vascular networks. Normal patterning is disrupted, leading to localized networks which are in excess or deficient. Additionally, ectopic neurovascular tracts are found on the outside surface of the kidney which can infiltrate and severely disrupt local tissue morphology. Mutant kidneys are hypoplastic with an extension of nephron progenitor lifespan by ~2 days. Deletion of *Unc5c*, a known receptor for netrin-1 which is expressed by the nephron progenitors, does not result in any obvious developmental defects. Therefore, we predict the hypoplastic and progenitor phenotypes we observe are due to a disruption in signals that the nerves/vessels supply to nephron progenitors and the branching collecting duct system, rather than a direct action of netrin-1. Consistent with congenital renal defects having ongoing effects into adulthood, we find that mutant adult kidneys show focally dilated and vacuolated tubules indicative of tubular injury, as well as abnormal glomerular histology.

Conclusions: These studies have provided novel insights into the establishment of neurovascular networks in the developing kidney and the implications for adult function. Such findings will help inform efforts to engineer kidneys de novo, where establishing proper kidney filtration will be essential.

FR-PO920

Stromal Prorenin Receptor (PRR) Is Critical for Normal Kidney Development

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Background: The transcription factor Foxd1, a specific marker of kidney stromal cells, is critical for normal kidney development. Global loss of the PRR, a receptor for renin and prorenin, is lethal in mice, indicating its essential role in embryonic development. Here, we investigated the role of the PRR in Foxd1+ stromal progenitors in mice.

Methods: *Foxd1-eGFP-Cre*$^{+}$ mice were crossed with *PRR*$^{flox/flox}$ mice. The resulting *Foxd1*$^{Cre+}$/*PRR*$^{flox/flox}$ mice represent deletion of the *PRR* in Foxd1+ stromal progenitors (*cKO*). Control mice consisted of *Foxd1*$^{Cre-}$/*PRR*$^{flox/flox}$ littermates (*Con*). Molecular marker analysis was performed by immunohistochemistry in kidneys on E17.5. Glomerular number was counted at P0 from 3 consecutive H&E-stained sections/kidney adjacent to the longitudinal midplane. Conscious systolic, diastolic and mean tail-cuff arterterial blood pressure (BP) was measured in heterozygous (*Foxd1*$^{PRR+/-}$) (*Het*, n=3) and *Con* (n=3) mice at 2 months of age using a Visitech BP2000 system (Visitech Systems, Apex, NC).

Results: *cKO* mice showed neonatal mortality. Although kidney weight did not differ in surviving *cKO* mice on P0, the number of glomeruli per kidney section was reduced in *cKO* compared with *Con* (39±3.7 vs. 68±2.3, p<0.001). Immunofluorescence showed reduced expression of stromal markers Foxd1 and Meis1, expansion of Six2+ nephron progenitors, reduced expression of Jag1, lack of WT1+ glomeruli in more differentiated nephrons, decrease in the expression of renin and of α-SMA in the developing interstitium in *cKO* kidneys. *cKO* mice had fewer and thinner intrarenal arteries and arterioles. Systolic, diastolic and mean BP did not differ in *Het* and *Con* mice (124±3.5 vs. 133±11, p=0.4; 69±3 vs. 68±5, p=0.9; 88±3 vs. 92±7, p=0.6).

Conclusions: We conclude that stromal PRR restricts excessive expansion of nephron progenitors, thereby promoting nephron differentiation. In addition, stromal PRR is crucial for the differentiation of renin-positive cells as well as smooth muscle and the proper formation of the renal arterial tree.

FR-PO921

DNMT1 in Six2 Progenitor Cells Is Essential for Transposable Element Silencing and Kidney Development

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Background: In mammalians cytosine methylation (5mC) is erased in the embryo and reestablished during development and differentiation. De novo DNA methyltransferases such as Dnmt3a and 4b plays key role in establishing methylation, while Dnmt1, a hemimethylase copies methylation during cell division. Much attention has been placed on promoters and enhancer methylation as they play role in gene expression regulation.

Methods: We performed genome methylation analysis by reduced representation of bisulfate sequencing (RRBS) during kidney development. We examined the renal phenotype of mice with genetic deletion of Dnmts and Tets in the Six2+ population which can differentiate nephrons in mice.

Results: Differential methylation of enhancer regions was the most prominent when kidneys of newborn and adult mice were compared. Mice with conditional deletion of Dnmt3a, 3b, Tet1 and Tet2 showed no significant renal abnormalities. In contrast, Six2^{Cre}/Dnmt1$^{fl/fl}$ mice died within 24hrs of birth and had small kidneys. Surprisingly, the greatest methylation difference in Dnmt1 knock-out mice was observed on transposable elements (TE). RNA sequencing also detected the expression endogenous retroviruses indicating the release of silencing of TE. In addition, Dnmt1 KO kidneys expressed high levels of genes that exclusively expressed in early embryos. The re-expression of ERV was not tolerated by the cells and induced the expression of endogenous RNA sensing pathways and interferon response and ultimately resulting in cell death.

Conclusions: Our results showed that Dnmt1-mediated DNA methylation is essential for kidney development by preventing the demethylation of TEs and dedifferentiation of progenitor cells.

Funding: NIDDK Support

FR-PO922

Modulation of Lef/Tcf Activity in Response to Differential β-Catenin Levels Underlies Nephron Progenitor Differentiation

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Background: The Wnt9b ligand and β-catenin are required for both nephron progenitor cell (NPC) self-renewal and differentiation (Carrol et al., 2005; Park et al., 2007; Karner et al., 2011). Though high Wnt pathway activity stimulates NPC commitment, stabilized β-catenin binds to enhancers regulating both self-renewal and NPC differentiation targets, with opposing transcriptional outcomes (Park et al., 2012). How different levels of β-catenin result in distinct outcomes for NPCs remains to be determined.

Methods: To investigate the molecular mechanism behind Wnt/β-catenin-driven NPC self-renewal and differentiation, we modeled the two processes *in vitro* in NPEM culture medium (Brown et al., 2015) which enables NPC expansion when supplemented with low levels of CHIR99021 (CHIR), a β-catenin agonist, and NPC differentiation with elevated CHIR levels. Gene expression and epigenetic profiles were determined by bulk RNA-Seq and ATAC-Seq, followed up with immunohistochemistry on key targets-of-interest. To directly map genomic targets of Lef/Tcf factors and β-catenin, we performed ChIP-Seq on NPCs under expansion and differentiation conditions.

Results: RNA-Seq and immunohistochemistry data suggests differential expression levels of Lef/Tcf factors between NPC cultured in low and high levels of CHIR. In the high CHIR condition, the transcriptional repressor *Tcf7l1* is down-regulated, while the activators *Tcf7* and *Lef1* are up-regulated. ATAC-Seq analysis showed strong enrichment of Tcf/Lef footprint in open chromatin regions specific to high CHIR condition, suggesting a role of β-catenin in activating relevant enhancers. Direct ChIP-Seq for Lef/Tcf factors showed a rapid replacement of Tcf7l1/Tcf7l2 repressors by Tcf7/Lef1 activators at enhancers for differentiation target genes on stabilization of β-catenin.

Conclusions: We propose a model wherein Tcf7l1/Tcf7l2 repressors maintain NPC self-renewal state by silencing enhancers involved in differentiation and β-catenin stabilization triggers a switch promoting the engagement of Tcf7/Lef1 activators. This state is reinforced by a positive feedback loop where *Lef1* is a target of itself. Given the widespread role of Wnt signaling in stem/progenitor cell programs, these findings are likely to have broader significance beyond the mammalian kidney.

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FR-PO923

SIX2+CITED1+ Human Nephron Progenitors: Novel Insights of Wilms Tumor Biology

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Background: Wilms tumor (WT) accounts for 95% of renal malignancies in children and is characterized by uncontrolled proliferation of nephron progenitors (NP) without generation of functional nephrons. Due to inability of isolating these human NP, little is known about WT formation and specifically the involvement of NP in tumor progression. Using our validated Smartflares technique we isolated NP expressing SIX2 and CITED1 (the master genes regulating nephrogenesis) from WT samples and from human fetal kidneys (hFK) and compared them in terms of gene expression by RNA-seq. We also performed in vivo and in vitro experiments to study regulation of self-renewal *vs* differentiation of NP.

Methods: WT (#3) and hFK (#3) samples were digested to single cell suspension, incubated with Smartflare-probe and SIX2+CITED1+ cells were immediately sorted and processed for RNA-seq. Using a nephrogenic specific media, we established conditions for long-term culture of NP cells and study in vitro mechanism of self-renewal *vs* differentiation of NP from both WT and hFK. We also transplanted NP in vivo to study tumorogenesis.

Results: We confirmed expression of SIX2+CITED1+ cells in WT samples within the blastema and ~ 9% of the total population was expressing these markers (while ~0.2% was present in hFK). WT-NP present a similar pattern of expression of developmental genes as hFK-NP but increased expression of EYA1, SALL4 and decreased expression of LEF1 and FOXD1 suggesting their self-renewal state. WT-NP showed, as expected, upregulation of pluripotency genes (OCT-4, NANOG) and modulation of cell cycle regulators indicating their shorter G1 phase (typical of pluripotent/cancer stem cells). WT-NP presented modulation of integrin signaling, which plays an important role in exit to differentiation during nephrogenesis. WT-NP and hFK-NP were cultured in vitro for more than 28d maintaining expression of SIX2 and CITED1. Modulation of integrin outside-in signaling reduced SIX2 and CITED1 long-term in vitro and reduced tumor growth in vivo.

Conclusions: This work represents the first characterization of SIX2+CITED1+ cells from WT and suggests the importance of matrix-cell interaction in development and tumor formation. These studies can help to increase our knowledge on human nephrogenesis and the development of new strategies aimed at halting tumor progression.

Funding: Private Foundation Support

FR-PO924

TAZ Plays an Important Role in Maintenance of Podocyte Viability

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Background: TAZ (also known as WWTR1), a paralogue of YAP, is an important nuclear effector of the Hippo signaling pathway. TAZ shares 45% amino acid identity with YAP and they share some redundant roles in some organ development, but they also differ in some functions. TAZ is highly expressed in kidney, especially in renal proximal tubule cells. TAZ global knockout causes early mortality in a subset of homozygous mice, while bilateral kidney cysts and a pulmonary emphysema-like phenotype presented in the surviving adult mice. YAP is highly expressed in the nucleus of podocytes, and podocyte-specific deletion of YAP causes FSGS and progressive renal failure. The goal of these studies was to determine whether TAZ also plays a physiologic role in podocytes.

Methods: Mice with podocyte-TAZ deletion (TAZ^{podKO}) were generated by crossing TAZ$^{flox/flox}$ mice with podocin-Cre recombinase transgenic mice. Urinary albumin excretion and kidney histology and podocyte number per glomerulus were evaluated in TAZ^{podKO} and WT mice. Immunoblotting analysis of isolated glomerulus lysates of TAZ^{podKO} or TAZ^{podWT} mice were performed. In cultured mouse podocytes, cell morphology and cell lysates were evaluated after silencing TAZ with specific siRNAs.

Results: 41.7% of TAZ^{podKO} mice develop mild proteinuria at age of 3-4 weeks (n=36), with a urine albumin/creatinine ratio of 89.57 ± 12.67 vs 27.86 ± 1.55 (µg/mg, n=7). At 9 weeks of age, compared to TAZ^{podWT} mice, the glomeruli of TAZ^{podKO} mouse kidney had focal sclerosis and significant podocyte loss (WT1+ cells: 13.23 ± 0.699 vs. 17.85 ± 0.608 (n=13). There was increased YAP expression and nuclear localization in the TAZ^{podKO} mice compared with TAZ^{podWT} mice. Glomeruli of TAZ^{podKO} mice had increased cleaved-caspase 3 and decreased Bcl2 expression. In cultured podocytes, silencing TAZ by siRNA altered cell morphology and F-actin distribution, up-regulated of cleaved-caspase 3 and inhibited Bcl2 expression.

Conclusions: This study demonstrates that TAZ expression plays an important role in maintenance of podocytes, which cannot be compensated by its paralogue YAP.

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FR-PO925

Clathrin-Dependent Nephrin Endocytosis Mediated by Y1139RSL Motif Is Essential for Glomerular Slit Diaphragm Formation

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Background: Nephrin is critical to the glomerular slit diaphragm. The cytoplasmic tail of human nephrin contains a YxxØ-type motif Y^{1139}RSL & genetic variation of this motif in human cases supports its potential importance. A c.C3418T nucleotide change, resulting in p.R^{1140}C, has been implicated as causal for congenital nephrotic syndrome (CNS) in one of the first reported patients, & was found as a single allele in siblings with CNS.

Methods: We generated expression plasmids for human (hs) nephrin (hs-Nephrin-WT), hs-Nephrin-Y^{1139}F mimicking non-phosphorylated tyrosine, or hs-Nephrin-Y^{1139}A disrupting YxxØ endocytic motif. We transfected these into a human podocyte line, which were used for coimmuprecipitations (CoIP), clathrin-coated vesicle & endocytic assays. In zebrafish, we depleted endogenous nephrin by morpholino (dr-Nephrin-MO) injections & performed rescues with RNA derived from the aforementioned hs-Nephrin plasmids. We assayed for edema, a phenotype previously shown in nephrin morphants, & for glomerular organization imaged by single plane illumination microscopy & electron microscopy.

Results: In podocytes, Hs-Nephrin CoIP with clathrin & the adaptor complex AP-2; residue Y^{1139} was phosphorylated. The Y^{1139}F substitution increased clathrin-dependent nephrin endocytosis & reduced the steady-state abundance & stability of nephrin at the podocyte plasma membrane. By contrast, the Y^{1139}A substitution had the opposite effects. Zebrafish embryos depleted of nephrin exhibited pericardial & yolk edema, curvature of the body axis, & amorphous glomerular & podocyte foot process organization. Co-injecting the hs-Nephrin-Y^{1139}F transcript with dr-Nephrin-MO partially rescued the phenotype & improved defects in glomerular & foot process organization, similar or superior to hs-Nephrin-WT. By contrast, morphants injected with hs-Nephrin-Y^{1139}A failed to rescue, having phenotypes similar to dr-Nephrin-MO alone.

Conclusions: The Y^{1139}RSL motif is a structural element for clathrin-dependent nephrin endocytosis & functions as a phosphorylation-sensitive signal essential for the slit diaphragm formation. We propose that the Y^{1139}RSL-mediated endocytosis helps to maintain asymmetric distribution of nephrin in specialized membrane domains leading to podocyte differentiation & formation of the slit diaphragm.

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FR-PO926

Role of the Circadian Clock in the Timing of Branching Morphogenesis and Kidney Development

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Background: Kidney development is guided by a complex array of molecular signals that guide precise arrangement of ~1 million nephrons. Developmental errors such as renal hypodysplasia are a leading cause of pediatric kidney failure. Extremely rapid and stereotypic branching of the ureteric tree during early kidney development gives rise to a stochastic branching pattern but with a much slower, controlled and constant tip doubling rate during the second half of development (JASN 2015;26(10):2414). We also found that iron deficiency has a profound effect on nephron number and branching morphogenesis. Because core circadian clock transcription factors bind heme, we hypothesized that this timer plays a role in the timing of kidney development.

Methods: We studied the roles of circadian clock regulators Clock and Bmal1 during kidney development by quantitating branching parameters in global knockout and in conditional mutants. We also measured continuous circadian clock gene expression in developing kidneys using luminescence microscopy. Mice also were mated for a 1-hour time period at "lights on" and subsequently RNASeq was performed from embryonic days 18.0 to 20.0 (E18.0 to E20.0) at exact 4-hour intervals to measure gene expression patterns. Relevant genes were mapped to specific nephron structures and compared to adult kidneys.

Results: Luminescence studies confirmed the activity of an autonomous peripheral clock in the developing kidney. Oscillatory expression of core clock genes became measurable by E18.5. Quantification of branching parameters showed decreased nephron number in Bmal1-/- kidneys at E14.5 and at E19.5 (mean glomerular number [SD] 664±103 vs. 956±84, p> 0.05). Moreover, when pregnancies were timed strictly, RNASeq analysis identified 6,949 transcripts with significant rhythmicity between days E18.0 and E20.0 (p<0.05). Many genes were kidney-specific and known to regulate cell cycle and core developmental processes.

Conclusions: While known to regulate renal processes in the adult, we found that circadian regulators also provide a critical timing mechanism during kidney development by controlling gene expression. These regulators are required during a critical developmental window. Investigation of circadian-regulated pathways may uncover new targets that can be exploited to prevent disease or aid kidney development.

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FR-PO927

Genetic Regulation of Intermediate Mesoderm Specification

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Background: The kidneys are derived from the intermediate mesoderm (IM), yet the pathways that determine the precise dimensions of the IM in the early embryo are poorly understood. We have found that the bHLH transcription factor Hand2 limits the size of the pronephron by refining IM dimensions. In *hand2* mutants, the IM is expanded, and the IM is diminished when *hand2* is overexpressed. The *hand2*-expressing portion of the posterior mesoderm lies laterally adjacent to the IM, and a set of venous precursors arises at the interface between these two territories. *hand2* promotes venous precursor development while suppressing IM formation in this region. Furthermore, Hand2 and the similarly localized zinc-finger transcription factor Osr1 have functionally antagonistic influences on both kidney and vein development.

Methods: Our studies of *hand2* and *osr1* provide valuable entry points for the identification of additional factors that regulate IM specification. How do *hand2* and *osr1* coordinate the development of the IM and venous progenitor populations? Do *hand2* and *osr1* impact the same genes as they execute these functions? To address these questions, we aim to identify additional genes in the *hand2* and *osr1* pathways.

Results: Preliminary analysis has revealed a potent role for bHLH transcription factor Twist1a in modulating IM and vessel precursor formation. Furthermore, to identify genes regulated by *hand2*, we have evaluated expression profiles from wild-type, *hand2* loss-of-function, and *hand2* gain-of-function embryos. Additionally, to increase the sensitivity of our investigation, we have compiled expression profiles from sorted *hand2*-expressing cells in wild-type and *hand2* loss-of-function embryos. We are currently analyzing our most intriguing candidate genes, including *twist1a*, through loss-of-function, gain-of-function, and genetic epistasis experiments to determine their roles in IM formation and their genetic interaction with *hand2* and *osr1*; updated findings will be presented.

Conclusions: Together, our studies will elucidate the roles of *hand2* and *osr1* in defining the boundaries of the IM by balancing formation of the kidney and vein lineages.

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FR-PO928

Transcription Factor 21 Is Required for Branching Morphogenesis and Regulates the GDNF-Axis in Kidney Development

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Background: The definitive mammalian kidney develops through reciprocal inductive signals between the metanephric mesenchyme (MM) and ureteric bud (UB). Transcription factor 21 (Tcf21) is highly expressed in cells of the MM including Six2+ condensing mesenchyme (CM) and Foxd1+ stromal mesenchyme (SM). *Tcf21* knockout (KO) mice die in the perinatal period with severe renal hypodysplasia. In humans, Tcf21 levels are reduced in renal tissue from stillborn infants with renal dysplasia. However, molecular mechanism(s) to explain these renal defects are not yet known.

Methods: We utilized systemic and conditional *Tcf21 k*nockout mouse models and employed immunohistochemistry, in-situ hybridization, RT qPCR and kidney explant studies.

Results: Tcf21 null kidneys show very abnormal UB branching and arrested mesenchymal-to-epithelial transition, reminiscent of human CAKUT. These changes are accompanied by decrease in *Gdnf* mRNA levels and protein and by low *Ret* and *Wnt11* mRNA levels starting at embryonic day (E)12.5. In contrast, global deletion of *Tcf21* does not attenuate the expression of members of the retioic acid and fibroblast growth factor signaling pathways, nor does it reduce expression of inducers of *Gdnf* (e.g. Osr1, Eya1, and Pax2). The stromal factor Bmp4, a potent inhibitor of Gdnf, is increased in kidneys from *Tcf21* KO mice, offering a potential mechanism. Under the hypothesis of pleiotropism, we dissociated Tcf21's effects in distinct cell lineages of the MM by studying the kidney phenotype of selective removal of *Tcf21* from the renal stroma (Tcf21$^{fl/fl}$;FoxD1-Cre strain) and from the CM (Tcf21$^{fl/fl}$;Six2-Cre strain). Absence of *Tcf21* from the stroma leads to low Gdnf and abnormal UB branching at E14.5 and results in paucity of collecting ducts and severe urinary concentrating defect at 4 wks of life. In contrast, deletion of *Tcf21* from the CM leads to abnormal glomerulogenesis and proteinuria but has no obvious effects on Gdnf expression or the development of the collecting ducts.

Conclusions: Taken together, our data illustrate distinct roles of Tcf21 in the stromal mesenchyme and cap mesenchyme in kidney development and support a model whereby Tcf21 regulates key molecular pathways required for branching morphogenesis. Direct genetic targets for Tcf21 in the kidney have not yet identified.

Funding: Other U.S. Government Support

FR-PO929

Developmental Loss of Intercalated Cells increases but Pharmacological Carbonic Anhydrase Suppression Decreases Pyelonephritis Susceptibility

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Background: We had previously shown that carbonic anhydrase (CA) 2 knockout mice (*Car2*$^{-/-}$) have an intercalated cell deficiency and are susceptible to pyelonephritis. However it was not known whether this pyelonephritis risk is due to systemic absense CA, renal absence of CA, decreased CA activity or developmental depletement of intercalated cells. We hypothesized that the pyelonephritis susceptibility in *Car2*$^{-/-}$ *mice i*s secondary to intercalated cell deficiency

Methods: We compared pyelonephritis susceptiblity following transplantation of *Car2*$^{-/-}$ kidneys into wild type mice (isolated renal *Car2* absence), transplantation of wild type (WT) kidneys into *Car2*$^{-/-}$mice (nonrenal Car2 absence) and transpantation of control WT kidneys into WT mice. To determine whether pharmacological suppression of CA results in a similar pyelonephritis risk to developmental intercalated cell absence, we identified the dose of acetazolamide that suppressed renal carbonic anhydrase activity then compared pyelonephritis risk in treated versus untreated C57Bl/6J WT mice. Experimental pyelonephritis was induced by transurethral inoculation of uropathogenic E.coli (UPEC).

Results: Results are presented in Figure 1: Compared WT donor/WT recipient, the *Car2*$^{-/-}$donor/WT recipient, but not the WT donor/*Car2*$^{-/-}$recipient group had higher kidney (A) but not bladder (B) bacterial burdens at 24-hours post UPEC inoculation. Both 50 mg and 100 mg of acetazolamide given intraperitoneally suppressed CA (C) and increased urine pH (D). There was no difference between kidney (E-F) or bladder (G) bacterial burdens at 24 hours between acetazolamide treated and control mice. Mice treated with acetazolamide had lower kidney (H-I), but not bladder (K) bacterial burdens at 6-hours.

Conclusions: Developmental absence of intercalated cells is responsible for the pyelonephritis risk in *Car2*$^{-/-}$mice. Surprisingly acetazolamide appears to be protective against pyelonephritis, at least at an early time point.

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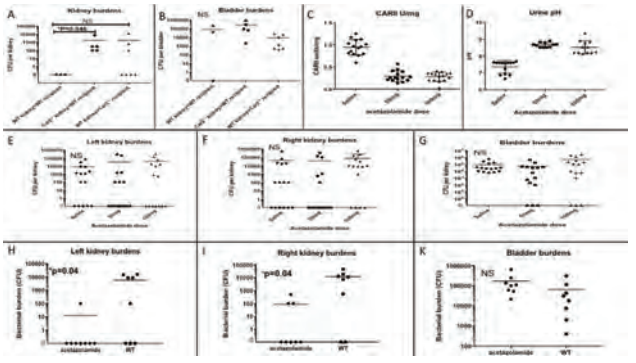

FR-PO930

Homeogene Emx1 Is a Required Downstream Component of the Mecom-Tbx2 Genetic Pathway That Regulates Pronephros Distal Segment Formation

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Background: Vertebrate kidneys contain nephron functional units where specialized cell types are organized into segments with discrete physiological roles. Many gaps remain in our understanding of how segment regions develop. To date, several studies have identified key signaling molecules and transcription factors that are essential for segment patterning in the pronephros, which has been speculated to offer a primitive blueprint for nephron segmentation in other kidney forms. *empty spiracles homeobox gene 1* (*emx1*) encodes a homeodomain transcription factor that is expressed in renal progenitors during early stages of pronephros development, and numbers among those genes that have been implicated to act downstream of retinoic acid (RA) signaling during segmentation.

Methods: Here, we used reverse genetics approaches to study the role of *emx1* during nephron formation. We discovered that *emx1* is required to regulate the balance of distal segment domains within the distal pronephros, and then performed a suite of genetic epistasis and expression studies to elucidate its relationship with other essential segment patterning components.

Results: *emx1* deficiency altered distal segment domains without changes in cell turnover or physical traits like cell size and morphology. In exploring further how Emx1 influences nephron pattern, we found that RA, which induces proximal and represses distal fates during early intermediate mesoderm development, negatively regulates *emx1* expression. Next, through a series of epistasis studies, we found that Emx1 acts downstream of a genetic cascade involving the essential distal segment genes Mecom and Tbx2. Finally, we determined that Emx1 restricts the expression boundary of *irx3b* to control distal segment territories.

Conclusions: Taken together, our work reveals how *emx1* is a necessary component of the pronephros genetic segmentation network, which has broad implications for understanding the regulatory cascades that orchestrate vertebrate nephron patterning.

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FR-PO931

Morphogenesis and Function of the Nephron-Collecting Duct Connection

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Background: A correct morphogenesis of the connection between nephrons and collecting ducts (CD) profoundly impacts the ability of the renal system to regulate the water-salt and acid-base balances in adults. However, the origin of the nephron-CD connection has yet to be established.

Methods: These observations were based on the morphology and computer-assisted tubular tracing on LM and EM serial sections.

Results: The present study showed that the nephron-CD connection was initiated by fusion of cells arising from the renal vesicle (RV) and the terminal tip of the ureteric bud (UB). One terminal tip often connected with two nephrons at different developing stages. A lumen in the nephron-CD connection was observed early at the S-shaped body stage, where the opening to the tip consisted mainly of distal tubule cells mixed with a few tip cells. With nephron development, the nephron-CD connection elongates with tip and RV cells, and the connection is then composed of cells expressing Na^+-Cl^- co-transporters, H^+-ATPase, and AQP2, with a similar distribution as in the adult kidney. AQP2 and H^+-ATPase, was constantly expressed at the UB trunk, increasingly expressed at the UB neck, while the expression was undetectable at the UB tip.

Conclusions: The study suggests that the nephron-CD connection is initiated by cell-cell fusion between RV and UB tip cells, then it elongates with participation of UB tip and neck cells, and finally it matures into the connecting tubule as the glomerulus develops.

FR-PO932

Loss of Dicer Activity in the Peri-Wolffian Duct Stroma Leads to Increased Rates of Vesicoureteral Reflux

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Background: Vesicoureteral reflux (VUR) is associated with urinary tract infections, hypertension, and reflux nephropathy, a leading cause of pediatric end-stage renal disease. Formation and location of the vesicoureteral junction is determined largely by the induction site of the ureteric bud from the Wolffian duct, which depends mostly on signals from the surrounding stroma. VUR appears heritable, but no single genetic mutation causes most known cases of VUR. miRNAs are small, noncoding RNAs, processed by Dicer, that regulate gene expression post-transcriptionally. We hypothesize that miRNAs are necessary for vesicoureteral junction development and prevention of VUR.

Methods: We generated a transgenic mouse model with loss of Dicer in the peri-Wolffian duct stroma (Tbx18cre; Dicer$^{Fl/Fl}$). We performed euthanized cystograms and 3D reconstructions of the ureters and bladder on mutants and controls (Tbx18Cre negative littermates). We performed whole mount Calbindin immunostaining at E11.5 to assess the ureteric bud induction site.

Results: Euthanized cystograms demonstrated significantly higher rates of VUR in the mutant mice compared to control [40% (6/15) of Dicer mutants as opposed to 3.8% (2/52) of controls ($p < 0.01$)]. 3D reconstructions showed lower ureteral insertions into the bladder and shorter intravesicular tunnel lengths on the side of VUR in mutants compared to control mice and non-refluxing mutant ureters ($p < 0.05$). Calbindin immunostaining reveals a cranially shifted ureteric bud induction site in E11.5 mutants compared to controls ($p < 0.05$).

Conclusions: These data suggest for the first time that miRNAs have a role in preventing VUR. This appears due to a requirement for miRNAs in peri-Wolffian duct stroma for normal ureteric bud induction and subsequent ureter insertion into the bladder. Future work will assess molecular mechanisms by which deletion of miRNAs in the peri-Wolffian duct stroma leads to VUR and elucidate which miRNAs in the peri-Wolffian duct stroma are critical for normal ureteric bud induction.

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FR-PO933

Role of Fgfr2 in DNA Damage in Bladder Urothelium After Cyclophosphamide Injury

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Background: Stimulation of fibroblast growth factor 2 (Fgfr2) (IIb isoform) by keratinocyte growth factor (KGF), reduces injury in many epithelial cells. Deletion of Fgfr2IIIb prolongs cyclophosphamide (CPP)-induced bladder urothelial injury. Our purpose was to identify roles for Fgfr2 in bladder urothelial repair after CPP- injury.

Methods: We first subjected wildtype mice to a 150 mg/kg intraperitoneal (IP) dose of CPP to characterize the injury/ repair and to determine expression of Fgfr2 after injury. To determine roles of Fgfr2 in CPP-induced injury, we used a Tamoxifen inducible ShhCre line to knockout *Fgfr2* in all urothelial layers (*ShhcreFgfr2KO*), and subjected Cre-negative and

knockout mice to IP CPP. We performed general histological staining, *in situ* hybridization, and immunostaining.

Results: In controls, we observed major loss of urothelium, hemorrhage, and inflammation 1-day post CPP. We noted urothelial hyperplasia from 3-10 days post injury. *In situ* hybridization showed increased *Fgfr2* expression at 1 and 3 days post injury in control urothelium. We also observed evidence of DNA damage by γH2AX immunostaining in control urothelium at 3-7 days, which was reduced by 10 days. In the knockout studies, we observed significant decreases in weight at 1 and 3 days post-CPP in *ShhcreFgfr2KO* vs. Cre-negative mice. We noted similar urothelial loss, hemorrhage and inflammation 1-day post CPP in Cre-negative and mutant bladders. At 3 days post injury, *ShhcreFgfr2KO* bladders had ongoing marked hemorrhage and inflammation with reduced uroplakin staining vs. Cre-negative mice. While mutants and Cre-negative mice had expansion of Keratin 14 (Krt14)-positive presumptive progenitor cells across basal layers 3 days-post CPP, Cre negative mice had 6-7 urothelial cell layers while *ShhcreFgfr2KO* had only 3-4 cell layers. Also, mutants had many (mostly Krt14+) cells that were hypertrophic with enlarged nuclei (suggesting a cell cycle block). Furthermore, mutants had 2-fold increases in γH2AX+ nuclei vs. Cre negative mice.

Conclusions: Together, Fgfr2 appears dispensable for Krt14+ progenitor cell expansion after CPP-injury, but appears required for DNA repair and proliferation/cell cycle progression/differentiation of Krt14+ progenitors. Administration of KGF to wildtype bladders injured by CPP may enhance DNA repair.

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FR-PO934

Comprehensive Gene Expression Analysis for Pax2 Related Genes with Existing FANTOM Database

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Background: Pax2 is essential transcriptional factor for kidney development. Pax2 homo knockout mouse shows kidney agenesis and neonatal lethal. In human, PAX2 mutation is major causative genes for Renal coloboma syndrome (RCS), which is characterized by kidney hypoplasia or dysplasia and abnormality of the optic nerve. It is reported that Pax2 involved in ureteric bud branching via the regulation of Gdnf expression. Pax2 is known to involve both gene expression and suppression through epigenetic mechanism, apart from the role of transcriptional factor. In this study, using gene expression of mouse embryonic kidney from FANTOM database, comprehensive analysis for the genes which involved to Pax2 were evaluated. Furthermore, the role of PAX2 gene during human kidney development is not clear. Gene expression analysis in the kidney lineage cells differentiated from human induced pluripotent stem cells(iPSC)was performed.

Methods: To evaluate Pax2 related genes in mouse, we extracted gene expression data during kidney development (from embryonic day 14.5 to neonatal day 30). In the view of embryonic time course and organs, the correlation to Pax2 gene expression was evaluated. To evaluate PAX2 related gene in human, human iPSCwas differentiated into kidney lineage cells with reported methods (Taguchi, et al. Cell Stem Cells 2014). Some markers for kidney lineage cells were checked by immunocytochemistry and qPCR. Gene expressions of extracted candidate genes from mouse database were confirmed using the kidney lineage cells differentiated from human iPSC.

Results: About 180000 promoter expression data during mouse kidney development were extracted. The correlation to Pax2 promoter for time course and organswas evaluated. 3646 genes and 135 genes were extracted respectively. 18 genes, including some known essential genes for kidney development were overlapping. Human iPSC was differentiated to kidney lineage cells and checked PAX2 and other kidney lineage markers by immunocytochemistry and qPCR.A part of 18 genes were confirmed by qPCRin human differentiated kidney lineage cells.

Conclusions: Comprehensive analysis using FANTOM databaseis useful for identification of Pax2 related genes during kidney development.

FR-PO935

Effect of Hypoxia on Subpopulations of Cells During Kidney Development

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Background: During early developmental stages, embryonic kidneys are not fully vascularized and exposed to hypoxic condition (HC). HC is known to influence cell proliferation and survival, ureteric bud (UB) branching and vascularization of the developing kidney. We aimed in our present study to gain further insight into the effect of HC on different subpopulations of cells in embryonic kidneys at early developmental stages.

Methods: E11.5-13.5 embryonic kidneys were obtained from *Hoxb7*^{Venus}, *Foxd1*^{GFP}, *Six2*^{EGFP},*Cited1*^{RFP}mice and cultured under either HC or normal condition (NC) for up to 120h. Cell viability and gene expression pattern of Hoxb7^{+}, FoxD1^{+}, Six2^{+}and Cited1^{+}cells were analyzed by flow cytometry and q-RT-PCR, respectively. UB branching morphogenesis was analyzed under confocal microscopy to generate 3D images for measurements of organ volume, branching generations, branching length and diameter by using a gradient vector based software (TreeSurveyor).

Results: We found that HC reduced overall cell viability after 24, 48, 72, 96 and 120h. However, as compared to Foxd1^{+}stromal cells and Six2^{+}metanephric mesenchymal (MM) cells, Hoxb7^{+}UB cells and Cited1^{+}MM cells were less susceptible to HC and showed reduced cell death after 48, 72, and 96h. HC increased the number of branching generations in E12.5 and E13.5 kidneys after 24h and decreased at 48 and 72h, while E11.5 kidneys were not affected. HC further increased the length and diameter of UB branches in E13.5 kidneys at 24h but not at 48 and 72h. HC increased HIF1a mRNA levels in E12.5 kidneys at 48h and 72h, but normalized at 96h. HC also upregulated the mRNA levels of angiotensinogen at 24h, 48h and 72h, renin and angiotensin receptor 2 at 72h, while angiotensin receptor 1 was unchanged.

Conclusions: We conclude that HC imposes different effects on different subpopulations of cells in embryonic kidneys at different developmental stages. Studies are ongoing to further characterize the effects of HC on different subpopulations of cells during kidney development.

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Transcription Factor HNF-1β Regulates Axonal Guidance Genes During Kidney Development

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Background: Mutations of the transcription factor hepatocyte nuclear factor 1β (HNF-1β) represent the most common genetic cause of congenital anomalies of the kidney and urinary tract (CAKUT). HNF-1β plays essential roles in kidney development through the regulation of branching morphogenesis, nephrogenesis, and nephron patterning. However, the molecular mechanisms whereby mutations of HNF-1β cause CAKUT remain incompletely understood. Here, we used chromatin immunoprecipitation and deep sequencing (ChIP-seq) to identify novel transcriptional targets of HNF-1β in the developing mouse kidney.

Methods: Chromatin was extracted from wild-type E14.5 mouse metanephroi, immunoprecipitated with an anti-HNF-1β antibody, and sequenced using next-generation sequencing. HNF-1β binding sites were mapped to the mouse genome, and nearby genes were identified. The functions of HNF-1β target genes were determined using Ingenuity Pathway Analysis (IPA). The expression of HNF-1β target genes in wild-type and HNF-1β-deficient mIMCD3 cells was measured using RNA-seq.

Results: ChIP-seq identified 8,490 HNF-1β binding sites in chromatin from E14.5 mouse kidneys, including peaks at known HNF-1β developmental genes, such as Wnt9 and Pax8. 6,104 binding sites were novel and were not previously detected by ChIP-seq in mIMCD3 cells. IPA analysis of HNF-1β target genes revealed that axonal guidance was the highest scoring canonical pathway. HNF-1β binding sites were identified near 63 axonal guidance genes, including netrins (Ntn4), netrin receptor (Unc5c), semaphorins (Sema4a, Sema3g, Sema3d, Sema6a), and ephrins (Eph4b). RNA-seq analysis showed altered expression of core axonal guidance genes in HNF-1β-deficient cells compared to wild-type cells, suggesting that they were directly regulated by HNF-1β.

Conclusions: HNF-1β regulates the transcription of axonal guidance genes in the developing mouse kidney. In addition to their roles in axonal guidance, netrins, semaphorins, and ephrins are essential for branching morphogenesis in epithelial organs such as the lung. Dysregulation of axonal guidance genes may underlie branching defects in HNF-1β mutant kidneys.

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FR-PO937

ZEB2 in Renal Stromal Progenitors Regulates Nephrogenesis and Nephron Endowment in Mice

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Background: ZEB2 is a SMAD-interacting transcription factor that is mutated in Mowat-Wilson syndrome, a congenital disorder with renal anomalies. ZEB2 is highly expressed in developing kidney stromal progenitors and is a target gene for FOXD1, a transcription factor and an early marker for renal stromal progenitors. FOXD1 regulates nephrogenesis and nephron endowment during kidney development while *Foxd1* knockout mice have aberrant ZEB2 expression. However, the role of ZEB2 in nephrogenesis and nephron endowment is not known.

Methods: We analyzed the nephrogenesis and nephron endowment in *Zeb2* stroma-specific conditional knockout mice *Zeb2*$^{flox/flox}$;*Foxd1Cre*$^{+}$ (*Zeb2* cKO) and their wild-type littermate controls. Glomerular numbers were quantified by direct counting using kidney histology and nephrin immunostaining. Nephron progenitors were analyzed using SIX2, WT1 and PAX2 markers. Nephrogenesis was analyzed by immunostaining using nephron morphogenesis markers Jagged1, megalin, uromodulin, pan-cytokeratin and Dolichos Biflorus Agglutinin (DBA). Cell proliferation in developing kidney was analyzed by phospho-Histone H3.

Results: We found that *Zeb2* cKO had significantly less glomerular numbers at newborn and 3 weeks old compared to wild type littermate controls ($p<0.01$). Immunohistochemical analysis showed that newborn *Zeb2* cKO kidneys have fewer SIX2+ nephron progenitors compared to wild type littermate controls. This result was also confirmed by WT1 and PAX2 immunostaining. Jagged1, megalin, and uromodulin staining demonstrated abnormal nephron structure in *Zeb2* cKO kidneys. Pan-cytokeratin and DBA staining showed defective ureteric branching morphogenesis. Newborn *Zeb2* cKO mice also have reduced cell proliferation in the nephrogenic zone as compared to wild type littermate controls.

Conclusions: ZEB2 in renal stromal progenitors regulates SIX2+ nephron progenitor self-renewal and differentiation. Loss of *Zeb2* in renal stromal progenitors leads to abnormal nephrogenesis, low nephron endowment and congenital renal anomalies.

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FR-PO938

Abcg2-Expressing Endothelial Cells Contribute to Kidney Postnatal Vascular Growth and Maintenance

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Background: Tissue blood vessels are lined by endothelial cells (EC) with heterogeneous states of proliferative potential. Several groups have recently identified resident vascular endothelial stem cells (VESC) and confirmed their critical role in vascular growth as they are highly proliferative, give rise to clonal endothelial colonies and are able to form vessels upon in vivo transplantation into sites of ischemia and hypoxia. Many other tissue resident stem cells express the ATP-binding cassette family drug transporter, *Abcg2*. We examined if *Abcg2*-expressing EC contribute to development of the kidney vasculature.

Methods: We crossed *Abcg2CreERT2* knock-in mice, which faithfully express Cre in *Abcg2*-expressing cells, with *ROSATdTomato* transgenic reporter mice to make Abcg2TT mice. TdTomato labels *Abcg2*-expressing cells and their progenies upon tamoxifen injection. We performed lineage tracing studies by injecting Abcg2TT mice at postnatal day 0 (neonate) or 42 (adult). Flow cytometry analysis of TdTomato+ EC was performed at days 1, 7, 21 and 56 post-tamoxifen in neonates, and days 1, 42 and 84 post-tamoxifen in adults. MACS-sorted EC from transgenic mice one day after tamoxifen injection were plated on OP-9 cultures and examined for the presence of endothelial colonies after 14 days.

Results: In neonates, 8.3±1.7% of total EC expressed TdTomato one day after tamoxifen injection. After 7 days, this population contributed to 36.0±11.1% of all kidney EC. In adult mice, 2.9±1.3% of total EC was labeled one day after a single tamoxifen injection. This population contributed to 15.4±2.9% of total kidney EC after 84 days. BrdU labeling studies are currently examining whether the turnover of kidney EC during these stages of development are derived from this population. The frequency of colony formation of TdTomato labeled EC is significantly higher than non-labeled EC.

Conclusions: Neonate and adult murine kidney blood vessels contain *Abcg2*-expressing EC that contribute to kidney vessel growth during development and maintenance of kidney vessel homeostasis in vivo. Thus, *Abcg2*-expressing EC may represent kidney VESC.

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FR-PO939

The Role of Mir218 in the Function of the Renal Vasculature

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Background: Vascular density is critical to normal kidney function. Reduced renal capillary number is associated with hypertension, chronic kidney disease, and kidney failure. Endothelial progenitor cells play a pivotal role in the construction of endocapillaries as well as their repair following ischemic injury. The function of endothelial progenitor-derived cells is dependent on cellular programs regulated by select microRNA. Mir218 directs retinal endothelial cell migration and motor neuron development. The role of mir218 in the function of the renal vasculature is widely unknown.

Methods: With CRISPR/Cas9 gene editing, we created an animal model, with germ-line miR-218-2 deletion (miR218-/-). These miR218-/- mice were subjected to bilateral renal ischemia-reperfusion injury (IRI) for 26 minutes, or sham surgery at 3 months of age and then evaluation the kidney function at 48 and 96 hours. Immunofluorescence staining of CD31 was assessed for the vascular density in this context.

Results: Following renal-specific ischemia/reperfusion injury, miR218-/- mice (n=6) were slow to recover renal function after 48 and 96 hours. There was a 20% of miR218-/- mice suffered fulminant renal failure and died within 96 hours. In miR218-/- mice, a lower vascular density in kidney with reduced renal capillary number were identified by CD31 staining.

Conclusions: With CRISPR/Cas9 gene editing approach to knock out miR-218-2 in the regulation of endothelial cell migration, we demonstrate for the first time the critical role of mir218 in the function of the renal vasculature.

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FR-PO940

Single Nucleus RNA-Seq from Fresh and Frozen Adult Mouse Kidney Offers Major Advantages over Single Cell RNA-Seq

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Background: Single-cell sequencing methods (scRNA-seq) have emerged as powerful tools for identification of cell types and states in kidney. However, generating a healthy single cell suspension is one of the biggest challenges to the field, limited by stress artifacts, RNA degradation and dissociation bias. We tested the hypothesis that single nucleus RNA-seq (snRNA-seq) is a superior approach.

Methods: We created 3,796 single cell transcriptomes from mouse kidney using the Dropseq platform, and single nucleus transcriptomes using the protocols from sNuc-Dropseq (2,951 nuclei), DroNc-seq (2,739 nuclei) and 10x Chromium (2,027 nuclei). We applied unbiased computational approaches to compare the gene expression and cell composition for each kidney cell type across different platforms. Finally, we aligned the cell types from snRNA-seq techniques to uncover the variations in gene expression within the shared subpopulations across techniques.

Results: 12 clusters were identified in the scRNA-seq dataset with most clusters from tubule and no cells at all from glomerulus. One cluster specifically expressed genes that were previously defined as artifactual dissociation-induced stress response genes induced by the cell dissociation protocol. By contrast, snRNA-seq from all platforms captured a diversity of kidney cell types including glomerular podocytes, mesangial cells and endothelial cells. The artifact cell cluster was not observed in the snRNA-seq datasets since the procedure is carried out on ice. Integrated analysis revealed that all snRNA-seq techniques can detect the same kidney cell types but DroNc-seq can capture more transcripts at the same sequencing depth over other snRNA-seq techniques. We also demonstrate that snRNA-seq is feasible on snap frozen tissue.

Conclusions: snRNA-seq provides substantial advantages over scRNA-seq in kidney, including the absence of dissociation-induced transcriptional artifacts, better representation of glomerular cell types (reduced dissociation bias) and the ability to perform snRNA-seq on archival, frozen samples.

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FR-PO941

Single-Nucleus Transcriptome Sequencing of Fetal Kidney Cells Identifies a Transient Pro-Angiogenic Signature in Developing Podocytes

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Background: The renal corpuscle is composed of cell types including parietal epithelium, podocytes, mesangium, and endothelium. How this critical structure is generated from its constituent precursor cells during development is not well understood. Transcriptional profiling of the developing human kidney can provide novel insights into developmental processes.

Methods: Nephrogenic zone and renal corpuscles from 13 to 16 week human fetal kidneys were profiled by single nuclear Drop-seq and cell clusters were resolved using Pagoda2. To better understand nephron development, we performed trajectory analysis using Monocle. Specific predictions of genes identifying specific cell types and developmental transition were validated by in situ hybridization and immunohistochemistry. A specific hypothesis formulated on the transient production of secreted factors by podocytes co-regulating vascular and mesangial cell types was explored in vitro.

Results: SnDrop-seq identified 12 different nephrogenic clusters that were identified by known markers. Novel gene expression was discovered and validated in our analysis. Computational ordering of transcriptomes along a developmental trajectory revealed that a novel transient expression signature was present within precursors progressing to the podocyte lineage prior to expression of mature markers. Anatomical and *in vitro* characterization of these genes support an angiogenesis-promoting function within this transient population.

Conclusions: Previous studies have established that cell signaling including VEGF signaling is required for glomerular vascularization *in vivo*, however attempts to recapitulate this process *in vitro* have failed. Our findings provide insight into a critical spatiotemporal program that aids in the formation of the primary filtration unit in the kidney. Our findings provide new insight into human glomerular developmental programs and highlight novel targets-of-interest to explore in human kidney disease.

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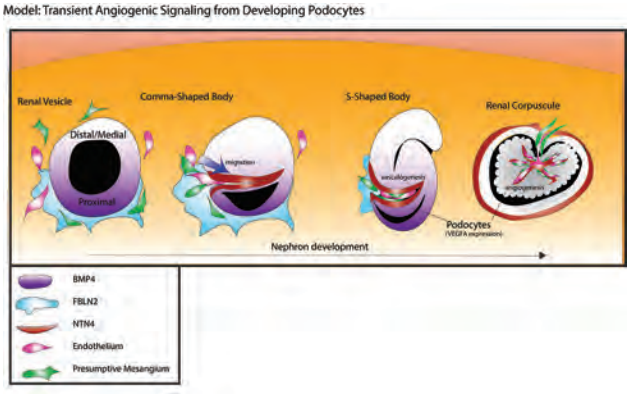

FR-PO942

Single Cell RNA-Seq Identifies Molecular Fingerprints of Endothelial Cell Subpopulations in Kidney

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Background: The kidney consists of functionally and anatomically discrete vascular plexus, and correspondingly distinct endothelial cell (EC) subpopulations. The precise targeting of renal vascular plexus in treatment requires a comprehensive understanding of the molecular characteristics of EC subpopulations. This study aims to distinguish renal EC subpopulations through dissection of their molecular fingerprints using single cell RNA-Seq (scRNA-Seq) analysis.

Methods: The BTBR mouse was perfused with magnetic Dynabeads that were subsequently trapped in glomeruli. The kidneys were enzymatically digested and glomeruli containing Dynabeads were removed. The cell suspension was further incubated with Pecam1 antibody and Pecam1$^+$ single cells were FACS sorted onto a 384-well plate. Single EC cDNA library was generated and RNA-Seq was performed on Illumina HiSeq 2500. Unsupervised clustering of EC subpopulations was performed with BackSPIN analysis.

Results: Pecam1 antibody selection of renal cell suspension produced a rather purified EC population, with ~80% successfully sequenced single cells being ECs. The ECs were clustered into 3 major subpopulations: the big vessel ECs (~30% of total ECs), peritubular capillary ECs (~36%), and glomerular ECs (~34%). These subpopulations displayed distinct molecular fingerprints. In particular, the glomerular and peritubular ECs showed differential gene expression patterns in vascular endothelial growth factor receptors, angiopoietin receptors, adrenomedullin system, caveolae-associated proteins, endocytic transport proteins, etc. The recent whole kidney scRNA-Seq analysis (Park et al, Science 2018) provided us an overall picture of the renal single cell population but limited resolution in ECs (Pecam1$^+$ ~1% of total cell population, peritubular ECs ~10% of EC population). In contrast, a dedicated EC scRNA-Seq may facilitate balancing various EC subpopulations in a single study and revealing in-depth definition of EC subpopulations in kidney.

Conclusions: The renal EC subpopulations display certain distinct gene expression patterns as revealed by scRNA-seq, which underscores the potential of selecting specific mechanisms for targeted vascular therapies in renal diseases.

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FR-PO943

Single Cell Transcriptional Profiling of Kidney Organoids Identifies a Novel Gene Activation Signal in Human Glomerular Disease

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Background: Proposed mechanisms for podocyte (PC) compensation in kidney disease include dedifferentiation and non-PC transdifferentiation. Identifying genes expressed during PC development may reveal novel aspects of pathogenesis and progression of glomerular disease. Analysis of developing human kidneys is limited by availability and relative rarity of PCs in tissue. Kidney organoids generated from human stem cells offer a novel *ex vivo* system to explore gene expression during PC development.

Methods: We generated kidney organoids from human stem cells and performed single cell RNA sequencing. Over 10,000 transcriptomes were combined and clustered using an unsupervised algorithm. Single cell transcriptomes from organoids and developing human kidneys were combined to create developmental trajectories for multiple cell lineages originating from central progenitors. Genes expressed uniquely in cell clusters were identified and expression was quantified in bulk transcriptomic data from microdissected glomeruli isolated from humans with kidney disease (ERCB) and analyzed relative to eGFR and proteinuria.

Results: Cell clustering revealed two putative groups of PCs. Trajectory analysis confirmed both groups mapped to the same cell lineage expressing *NPHS2* but separated along the spectrum into early and mature. Early and mature clusters uniquely expressed 69 and 169 genes respectively. The cumulative expression score for the early (but not mature) PC gene set was significantly upregulated ($p<0.01$) in diseased glomerular tissue relative to living donors. Intriguingly, the early PC set contained genes previously unrecognized as being involved in kidney disease including *LYPD1* and *PRSS23*, each of which correlated with proteinuria and inversely correlated with eGFR.

Conclusions: Developing PCs in kidney organoids express a group of genes that are not expressed in later stage PCs. Expression of these genes in the human adult glomerulus is associated with the presence of kidney disease, suggesting reactivation of a developmental transcriptional program in cells in the glomerulus. This approach identifies the beneficial role of single cell transcriptional profiling of kidney organoids in identification of novel biomarkers of kidney disease.

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FR-PO944

High-Throughput Analysis of Single Cells in Immunofluorescent Kidney Sections

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Background: Immunofluorescence staining is a standard method for analyzing histological, physiological and pathophysiological markers in a variety of cell types and compartments of kidney tissue. However the final quantification of image data is still often performed by manual counting, a time consuming and potentially biased process.

Methods: With the open source software Fiji and R we are able to automatically analyze a variety of markers in complete kidney sections. Following the automatic acquisition of high-resolution sections our batch-processing is able to classify and detect up to 100.000 nuclei per kidney section by marker-controlled watershed with a systematic error rate below 5%. This approach largely eliminates personal bias, reduces analysis time and enables semiautomatic tissue compartmentation for stereometric analysis. By thresholding and segmentation of additional channels cells can be classified as marker-positive. Parallel documentation and a database creation with nuclear characteristics, spatial parameters and marker-positivity enable complete reproducibility and verification of the results in the original image.

Results: We used our approach to quantify renin-abundancy in a previously described triple-transgenic mouse with an inducible Gs alpha knockout (Lachman et al., 2017, JASN). This evaluation correlated to the counting of renin-producing cells by kidney FACS ($p<0.001$, Pearson). Furthermore we successfully quantified proliferation (PCNA) and apoptosis (TUNEL)-staining in a mouse model of serum induced kidney damage with our analysis algorithms. We could also asses the differential activation of TGF-beta signaling pathway in kidney compartments in an animal model of STZ-induced diabetic nephropathy by quantifying nuclear pSMAD.

Conclusions: Our novel quantification approach is easily implementable, versatile and generates high amounts of data. The systematic nature of methodic errors combined with high cell count in complete sections and the absence of personal bias results in advantages towards manual quantification. While the high number of nuclei assessed per sample is comparable to FACS, our approach requires less tissue, avoids artifacts related to organ disintegration and provides a spatial resolution of the data sets.

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FR-PO945

Spatial and Sex-Related Cell Diversity in the Adult Mouse Kidney Through scRNA-Seq Profiling

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Background: Applying single cell RNA Sequencing (scRNA-seq) methodology to adult mouse kidneys facilitates examination of the gene expression profiles of individual kidney cell-types in high resolution. Recent studies have shown the power of this approach for adult mouse whole kidney (Han et al., *Cell*; Park et al, *Science*). By incorporating zonal dissection of tissue samples and both sexes, we are generating a high resolution map of kidney cell types that integrates spatial organization and sex-related differences.

Methods: We profiled adult kidneys from two male and female wildtype C57B6/J strain mice. Prior to tissue dissociation, kidneys were dissected along the corticomedullary axis (CMA) to isolate pieces containing exclusively cortex, outer medulla or inner medulla/papilla. Tissue dissociation at 12 C utilized cold active proteases to reduce stress responses. scRNA-seq profiling used 10XGenomics Chromium platform. PCA and identification of variably expressed genes executed with Seurat v2.3 package in RStudio.

Results: We obtained 38,039 transcriptional profiles from four mice representing all expected cell types of the adult kidney, though podocytes were underrepresented. Initial analysis has focused on identifying lineage, zonal and sex differences. We observe expected zonal clustering for known cell types. Although within specific lineages distributed along the CMA, we find regional diversity in profiles and can identify cell types excluded from published scRNA-seq studies. A marked sex diversity was observed in specific cell populations, confirming and extending known sex-related differences in kidney gene expression. Our zonal analysis also facilitates mapping regional diversity amongst the associated cell populations (eg. vascular, mesenchyme, immune-related).

Conclusions: These data generate a solid foundation for building a high resolution map of cell diversity in the adult male and female mouse kidney. We will discuss our progress towards this goal and review new insights that have come from scRNA-seq analysis of specific kidney lineages.

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FR-PO946

Transcriptome Analyses of Altered Mouse Kidney Development Following Maternal Interleukin-6 Exposure During Gestation

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Background: Children born to obese mothers have higher incidence of renal anomalies. Obesity is characterized by systemic inflammation. IL-6, an inflammatory cytokine, can cross the placental barrier, and is elevated in the amniotic fluid of obese women. Increasing evidence suggest that epigenetic mechanisms and microRNA (miRNA) interact in a bidirectional manner, a potential key mechanism for environmental effects on development. We hypothesized that renal development would be affected by elevated levels of maternal IL-6 brought about by epigenetic changes that alter both miRNA and RNA expression.

Methods: Pregnant C57BL/6 mice received either normal saline or IL-6 (10 pg/g BW) intraperitoneally on alternate days from E12.5. Fetal kidneys (E20.5) were removed from uterine horns by dissection and fixed in 10% formalin or used to isolate DNA and total RNA. LC-MS analysis of hydrolyzed DNA was performed to evaluate for methylation changes. TruSeq RNA Libraries (saline n=5, IL-6 n=5) were subjected to miRNA- and RNA-seq on an Illumina platform. Reads were mapped to the mouse reference genome and analyzed by miRDeep2.pl and Tuxedo Suite for miRNA-seq and RNA-seq, respectively.

Results: Maternal IL-6 administration resulted in decreased renal cortical parenchyma (358.4±74.3μm) compared with control (453.9±80.5μm, n=5, p=0.04). LC-MS analysis found a 10% increase in methylated cytosine in the IL-6 group suggesting epigenetic modifications in fetal kidney DNA. These modifications correlated ($q<0.05$) with 58 and 2087 differentially expressed (DE) miRNAs and RNAs, respectively. Stringent target prediction (score>90) identified 1350 mRNA regulated by the 58 miRNA of which 196 (9.4%) were present in the list of 2087 DE genes. Nephrotoxicity, as predicted by Ingenuity Pathway Analysis, associated with *Renal Necrosis/Cell Death* (p=1.5E-11, 104 genes) and *Renal Damage* (p=1.2E-8, 52 genes). We have identified the *STAT3* (p=3.2E-06, 20 genes), *NRF2-Mediated Oxidative Stress Response* (p=3.5E-06, 37 genes) and *Glucocorticoid Receptor Signaling* (1.9E-05, 53 genes) pathways for further analysis and confirmation.

Conclusions: Our model of maternal IL-6 administration has allowed us to better understand the role of environment mediated changes on epigenetics and global gene expression in kidney development.

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FR-PO947

Amphiregulin Mediated Cellular Reprogramming Modulates Inflammation and Tissue Remodeling Following Kidney Injury

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Background: Acute Kidney injury (AKI) is a major cause of mortality and morbidity. There is a growing evidence of interaction between tissue-resident immune cells and epithelial progenitor cells that participate in the process of regeneration. Recent studies indicate that Amphiregulin (AREG), a member of epidermal growth factor (EGF) family, also secreted by immune cells and has been shown to modulate both host immunity and tolerance mechanism. We hypothesize that AREG, produced by Regulatory T Cells (Tregs) promotes tissue repair and regeneration. In this study, we investigated differential effects of AREG towards promoting tissue homeostasis and regeneration using both *in vivo* and *in vitro* models.

Methods: Murine ischemia-reperfusion injury (IRI) and Endotoxemic renal injury models were developed to investigate a therapeutic effect of AREG. The protective effect of cytokine treatment both before and after the injury was examined. The structure and function of the kidney were probed using flow cytometry, intravital microscopy, histology, immunohistochemistry, quantitative gene expression and biochemical analysis. Kidney organoids and tubular epithelial cell line were used to probe the efficacy of AREG under *in vitro* conditions.

Results: Our findings showed that treatment with AREG immediately after injury not only enhanced the expansion of Tregs but also accentuates the suppressive function of Tregs, thus preventing kidney damage and preserving renal function in murine models. On the other hand, impediment of EGFR signaling resulted in increased fibrosis and deterioration of kidney function. Experiments using kidney organoids showed that addition of exogenous AREG attenuated cell death in an *in vitro* model of injury. Interestingly, direct addition of AREG to proximal tubular epithelial cell culture resulted in the development of cellular plasticity. Furthermore, AREG knockout mouse model was used to elucidate the role of AREG mediated regeneration in AKI.

Conclusions: This study addresses the application of AREG in immunomodulation and renal regeneration as a therapeutic approach for renal injury and sheds light on the mechanisms enforced by immune cells in the switch of maladaptive repair to successful regeneration.

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FR-PO948

c-Myc Is a Modulator of Pkd1 Gene and Polycystic Kidney Disease Progression

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common disorders associated mainly with Pkd1/Pc1 mutations. Orthologous Pc1 dosage-reduced and -increased mouse models develop renal tubular cysts. A causal connection between c-Myc-targeted overexpression and PKD was determined from transgenic SBM mice that closely resemble ADPKD and orthologous mouse models. Using these mouse models, we investigated for a clear regulatory interplay and signaling crosstalk between c-Myc and Pkd1 or Pc1.

Methods: Kidney tissues of SBM and four Pc1-dosage models were analyzed for molecular expression at mRNA levels by qPCR, at protein levels by WB and for cellular expression by IHC. Pkd1 gene regulation was assessed *in vivo* using genome ChIP analysis. Direct causal connection was interrogated by *in vivo* genetic interactions.

Results: We showed that renal regulation in four Pc1 dosage-reduced and -increased mouse models converge toward stimulation of c-Myc expression along with β-catenin (~5-10-fold) in tubular epithelial cells as in ADPKD renal tissues. This systematic increase defined c-Myc as a key *Pkd1* node in cystogenesis and confered the high relevance of the SBM transgenic mice for further analysis. Enhanced c-Myc in SBM transgenic mice led conversely to striking upregulation of *Pkd1*/Pc1 expression (~10-fold) and β-catenin activation, uncovering reciprocal crosstalk between c-Myc and Pc1. In adult SBM kidneys, c-Myc ChIP analysis showed strongly enriched binding on *Pkd1* promoter associated with RNA pol II, consistent with *Pkd1* upregulation during cystogenesis. Similar c-Myc direct binding also at birth uncovered an equivalent role on *Pkd1* regulation during renal developmental program, suggesting a role in condensing metanephric mesenchymal stem cells as for c-Myc. These data revealed an inter-regulatory network of c-Myc and Pc1 in normal physiologic and PKD conditions and shed light on PKD1 upregulation in the face of human ADPKD mutation. Genetic ablation of *c-Myc* in Pc1-reduced and -increased mouse models significantly attenuates cyst growth, proliferation and PKD progression, providing evidence that c-Myc is a Pkd1 causal cystogenic factor.

Conclusions: Together our data determined a dual role for c-Myc, as a major contributor in a feed-forward regulatory *Pkd1*–c-Myc loop mechanism and in Pc1-induced cystogenesis that may also prevail in human ADPKD.

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FR-PO949

A RhoA-YAP-c-Myc Signaling Axis Promotes the Development of Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disorder caused by mutations in *PKD1* or *PKD2* and affects 1 in 500-1000 humans. Limited treatment is currently available for ADPKD and there is great interest in identifying molecular targets and/or pathways for the development of mechanism-based therapeutics. In mammals, the Hippo signaling pathway comprises several tumor suppressors (NF2, Sav1, Mst1/2, Lats1/2, etc.) acting through a kinase cascade to affect the phosphorylation and cytoplasmic retention of the oncoproteins YAP/TAZ, transcriptional coactivators of the TEF/TEAD family transcription factors to transactivate growth-promoting genes. In this study, we investigated the function and regulation of the Hippo signaling pathway in ADPKD.

Methods: We performed gene set enrichment analysis of YAP/TAZ/TEAD target genes after global gene profiling on human *PKD1* polycystic kidney cysts compared to minimally cystic tissues using Affymetrix cDNA arrays, analyzed various genetically engineered mouse models with kidney cystogenesis, and searched for kinase inhibitors that promoted tubulogenesis in 3D-cultured *Pkd1* mutant mouse kidney inner medullary collecting duct (mIMCD3) cells through an unbiased kinase inhibitor screen.

Results: Our results showed that YAP/TAZ were activated in human ADPKD kidney cysts compared to minimally cystic tissues. While transgenic overexpression of YAP promoted proliferation and tubule dilation in mouse kidneys, loss of YAP/TAZ or their transcription target c-Myc suppressed cystogenesis in a mouse ADPKD model resulting from *Pkd1* deficiency. Through the comprehensive kinase inhibitor screen, we identified a signaling pathway involving the RhoGEF LARG, the small GTPase RhoA and the RhoA effector Rho-associated kinase (ROCK) as a critical signaling module between PKD1 and YAP. Further corroborating its physiological importance, inhibition of RhoA signaling suppressed cystogenesis in 3D culture of *Pkd1* mutant kidney cells as well as *Pkd1* mutant mouse kidneys in vivo.

Conclusions: Taken together, our findings shed light on the mechanisms underlying ADPKD pathogenesis and implicate the RhoA-YAP-c-Myc signaling axis as a critical mediator and potential drug target in ADPKD.

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FR-PO950

Reconstitution of ADPKD Cyst Formation in 3D Culture Reveals a Role for YAP 1 in Cyst Lumen Size

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Background: Proximal tubule cells grown in 3D culture, initiate cyst emergence with uniformly small lumens upon expression of CDH8. Prior studies indicate that cyst expansion in ADPKD results from increased proliferation from increased YAP1 signaling. We tested the hypothesis that YAP1 action is sufficient to cause enlarged cyst lumens in 3D culture and YAP1 interference by AMOTL1 decreases lumen size.

Methods: Immune-blots were carried out on lysates of confluent PKD Q4004X and HmPKT cells using antibodies for SAV1, MST1/2, MOB1, p-MOB1 (thr 35), LATS1, YAP/TAZ, p-YAP (ser 127) and p-YAP (ser 397). HK2 cells were transduced with lentivirus bearing constitutively active *YAP1-5SA* and grown in 3D culture. Cyst emergence was activated by cell transduction with adenovirus bearing *CDH8*. Separately, PKD Q4004X cells were transduced with lentivirus expressing *YAP1-5SA* or *AMOTL1 (S262E)* and grown in Matrigel for 14 days. Cysts were imaged and analyzed with Image J.

Results: Cyst epithelia had lower expression of SAV1, MST2, LATS1, YAP1 and TAZ and reduced ratio of p-YAP (ser 127) over YAP1. These cells also showed increased levels of p-MOB1 and p-YAP (Ser 397). HK-2 cells transduced with lentivirus expressing YAP1-5SA formed normal tubule arrays in 3D culture. However, when cyst emergence is activated by microinjected CDH8 expressing adenovirus, large lumen cysts are formed. In separate experiments, PKD Q4004X cells were grown in Matrigel for 14 days to allow for cyst formation. PKD Q4004X cells transduced with YAP1-5AS or AMOTL1 (S262E) were compared to control PKD Q4004X cells. After 14 days, samples were fixed, stained and imaged to determine cyst size using ImageJ. PKD Q4004X cells had an average maximum area of 177.89 ± 7.16 μm^2 . PKDQ 4004X cells transduced with AMOTL1 (S262E) had an average area of 122.77± 6.03 μm^2 ($p<0.01$). PKDQ4004X cells transduced with YAP1-5SA had an average area of 6619.66 ± 773.78 μm^2 ($p<0.01$).

Conclusions: 1) Cystogenesis can be reproduced by the combined activation of CDH8 and YAP1. 2) CDH8 expression initiates decreased cell-cell adhesion that is sufficient for cyst emergence. 3) YAP1 expression in the absence of CDH8 activation does not promote cyst formation. 3) Cyst size in ADPKD cells can be inhibited by AMOTL1 and increased by YAP1. 4) Overall, YAP1 activation following cyst emergence is necessary for increased lumen size in ADPKD.

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FR-PO951

Bile Acid Receptor Agonists and Metformin Slow Cyst Growth and Correct Perturbed Energy Metabolism in PKD1-Null Kidney Cells

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Background: Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in polycystin-1 (PKD1) or polycystin-2 (PKD2), presents with progressive development of renal cysts and eventual end-stage kidney disease. PKD1-null cells have increased proliferation and decreased AMP-activated kinase (AMPK) activity, along with dysregulated cellular metabolism. Bile acid receptor agonists, INT-777 and INT-767, promote a shift from glycolytic to fatty acid oxidative metabolism and regulate several key signaling pathways, including inflammation, fibrosis and the AMPK and extracellular signal-regulated kinases (ERK) pathways. Here we sought to determine whether these agonists alone or in combination with the AMPK activator metformin, may be effective as novel therapeutics for ADPKD by correcting dysregulated metabolism and slowing cyst growth in PKD1-null cells in vitro.

Methods: Using PKD1-null kidney epithelial cells, we examined AMPK and ERK pathway markers and levels of key glycolytic enzymes by immunoblotting, which were correlated with effects of various treatments. 3-D cultures were used to assess cyst growth after treatment with INT-767 or INT-777 alone or in combination with metformin. Seahorse assays were performed to evaluate cellular metabolic phenotypes under different conditions.

Results: INT-767 treatment of PKD1-null cells activated the AMPK and inhibited the ERK pathways and expression of the key glycolytic enzyme PDK1. INT-767 also reduced glycolytic fluxes while significantly increasing mitochondrial oxidative respiration as compared with control cells. INT-777 treatment also increased fatty acid oxidation in PKD1-null cells. Both INT-767 and INT-777 inhibited cystogenesis of PKD1-null cells in 3D cultures. Moreover, combination INT-767 or INT-777 treatment with metformin, another potential therapeutic for ADPKD, achieved much better control of cyst growth than either drug alone.

Conclusions: The bile acid receptor agonists INT-767 or INT-777 in combination with the AMPK activator metformin appear to have a synergistic effect on slowing cyst growth and correcting perturbed energy metabolism in PKD-deficient ADPKD kidney epithelial cells. These beneficial effects may potentially occur via activation of the AMPK pathway and will be explored further using in vivo ADPKD mouse models.

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FR-PO952

New Organoid Model for ADPKD Reveals Pkd2 Loss Disrupts Apical Junctional Complex and Master Scaffold Ezrin

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive cystogenesis, resulting in end stage renal disease. This common monogenetic disorder is attributed to loss of function mutations in the genes, *PKD1* and *PKD2*, that encode for transmembrane proteins, polycystin 1 and 2. Hallmark components of cystogenesis, including increased proliferation, changes in apicobasolateral compartmentalization, and a secretory phenotype, suggest a defect in the organization of renal epithelial cells following *PKD1/2* loss.

Methods: Immunofluorescent morphometric analysis of nephrectomized kidney tissue from ADPKD patients recently revealed significant changes in the morphology of the apical compartment, demarcated by zonula occludens 1 (ZO-1), in small, emerging cysts, when compared to normal tubules. Additionally, transepithelial electrical resistance assays using inducible *Pkd2* Cre (*Pkd2 Pax8 rtTA TetOCre +mTmG*) primary cells suggest that inactivation of *Pkd2* results in a decrease in resistance, indicating disruption of junctional integrity.

Results: While many pathways have been implicated in the complex progression of cystogenesis, these results suggest disruption of the apical junctional complex (AJC), may be responsible for changes in the organization and compartmentalization of apical proteins and signaling. Using a new in vitro tubule model system designed to investigate the initiation of cyst formation directly following the loss of functional polycystin 2 (PC2), we have demonstrated that loss of PC2 results in a decrease in master scaffold of apical compartment organization, ezrin. Furthermore, an inducible *Pkd2* Cre mouse model demonstrates that ezrin loss can be recapitulated in vivo following inactivation of *Pkd2* with doxycycline. Human ADPKD cystic tissue exhibits a decrease in ezrin protein abundance relative to normal kidneys and aberrant localization in cyst walls.

Conclusions: Therefore, the initiation of cystogenesis in ADPKD may be dependent on PC2's regulation of the AJC and master scaffold, ezrin, highlighting a novel function of PC2 in renal epithelial cells.

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FR-PO953

Mitochondrial Morphological Abnormality in Cyst Epithelial Cells of Autosomal Dominant Polycystic Kidney Disease Patients

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Background: Recent studies reported that polycystin-1 affects mitochondrial function directly or indirectly and facilitates pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). However, it is not confirmed in the kidney of ADPKD patients.

Methods: We conducted multi-center study, collected the kidney tissues from 20 ADPKD patients (this study was approved by the research ethics committees of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo. No.11560-(2)). By transmission electron microscopy, mitochondrial morphology was assessed in the kidney from ADPKD patients or ADPKD model animals. Quantification of mitochondrial morphology was done using ImageJ software.

Results: In cyst epithelial cells with cuboidal shape, mitochondria are abundant. In contrast, in the cyst epithelial cells, which reduce their height, the number of mitochondria was decreased, and subsequently, mitochondria are almost gone in the cyst epithelial cells with flat shape. The mean volume of the cyst epithelial cells of ADPKD patients (mtADPKD) were about 1.2 times larger than in the tubules of normal human control (mtCON). Mitochondria of mtCON exhibited a wide variety of morphologies (elongated and fragmented), however that of mtADPKD showed almost uniform with round shape. In addition, mtADPKD showed indistinct cristae formation. These characteristics of abnormal mitochondrial shape are the same with that observed in the cyst epithelial cells of *$Pkd1^{flox/flox}$:Ksp-Cre* mice and *$Pax8^{rtTA}$;TetO-Cre;$Pkd2^{lox/flox}$* mice but different from that of *Cy/+* rat.

Conclusions: Our results indicate that mitochondria in the cyst epithelial cells of ADPKD patients swollen with indistinct cristae formation and this might be the characteristics of polycystin-1 or polycystin-2 dysfunction in the kidney of ADPKD patients. Mitochondrial dynamics serves a variety of different functions, including cell proliferation. Similar mitochondrial morphological change was observed in cancer cells and which might reflect pathological derangements characteristic of ADPKD has marked similarities to those of solid tumors.

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FR-PO954

CaSR Activation Corrects the Impaired Mitochondrial Energy Status in Human Cell Models of ADPKD

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Background: Clinical and fundamental research data suggest that reduced resting cytosolic calcium (Ca^{2+}) concentration and increased level of cAMP are two of the most proximal events in the pathogenesis of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Reduced cellular free Ca^{2+} found in ADPKD, can on the other hand affect mitochondrial function and ATP production and, interestingly, a relationship between mitochondria and renal polycystic diseases have been suggested. CaSR is a G protein coupled receptor, which plays an essential role in regulating Ca^{2+} homeostasis whose activation is associated with an increase in intracellular Ca^{2+} and decrease in cAMP. We have recently reported (Di Mise et al, Sci Rep, 2018) that selective CaSR activation reduces intracellular cAMP and mTOR, and increases intracellular Ca^{2+}, reversing the principal ADPKD dysregulations. Here, the effect of CaSR activation on mitochondrial energy status is investigated.

Methods: Control human conditionally immortalized Proximal Tubular Epithelial cells with stably down-regulated PKD1 (ciPTEC-PC1KD) were used as experimental tools.

Results: The investigation of the bioenergetics status in ciPTEC-PC1KD revealed a multilevel inhibition of the mitochondrial ATP production by oxidative phosphorylation (OXPHOS) in ciPTEC-PC1KD compared with wt cells, specifically at complex I, complex II and complex IV levels. Interestingly, ciPTEC-PC1KD have significantly lower mitochondrial Ca^{2+} levels (88.05 2.6%), associated with a severe deficit in mitochondrial ATP production (38 ± 4%), with respect to wt cells, secondary to the OXPHOS impairment. Notably, selective CaSR activation with the calcimimetic NPS-R568 increases mitochondrial Ca^{2+} content close to the levels found in resting wt cells, and fully recovers the cell energy deficit associated to the PC1 silencing.

Conclusions: Together these data indicate that, besides reversing altered intracellular Ca^{2+}, cAMP and mTOR, selective CaSR activation in PKD1 deficient cells corrects mitochondrial energy status that, in ADPKD, is known to facilitate cyst formation. These findings identify CaSR as a potential therapeutic target.

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FR-PO955

Connective Tissue Growth Factor Is Regulated by TGF-β2 and ERK via Smad2/3 in Autosomal Dominant Polycystic Kidney Disease

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Background: In autosomal dominant polycystic kidney disease (ADPKD), the mechanism of pericystic fibrosis is not elucidated. Connective tissue growth factor (CTGF) plays an important role in the renal fibrosis. Also, It is known that ERK phosphorylates the linker region of Smad3 to enhance and activity of ERK is increased in ADPKD. Here, we study whether CTGF is regulated by TGF-β and ERK via Smad2/3 signal pathway in ADPKD.

Methods: To examine the expression of CTGF and phosphorylation of Smad2/3, we performed immunohistochemistry(IHC) and Western blot of ADPKD kidney tissues and isolated cyst cells. To investigate whether Smad2/3 signal pathway was involved in the upregulation of CTGF and the role of ERK in Smad2/3 pathway, we treated A83-01, which blocked phosphorylation of Smad2/3, and ERK inhibitor, PD98059, into cyst cells. Next, we performed ELISA and RT-PCR to examine which TGF-β induced Smad2/3 pathway in ADPKD.

Results: In kidney tissues and isolated cyst cells of ADPKD patients, we found that expression of CTGF and phosphorylation of Smad2/3 were increased. The expression of CTGF and nuclear localization of phospho-Smad3 were reduced on treatment of A83-01. Thus, Smad2/3 pathway induced the expression of CTGF. We found that TGF-β2 was secreted and mRNA of TGF-β2 was increased in cyst cells. On the treatment of TGF-β2, phosphorylation of Smad2/3 and expression of CTGF were increased. When we treated ERK inhibitor, PD98059, it was found that nuclear phospho-Smad2/3 was reduced in nuclear/cytosol fractionation and immunofluorescence. Next, we study whether PC1 repressed TGF-β2 via AKT. IMCD cells expressing PC1 showed that secretion and mRNA of TGF-β2 were reduced. After treatment AKT inhibitor, the secretion and mRNA of TGF-β2 were increased indicating PC1 downregulated TGF-β2 via AKT.

Conclusions: Taken together, our results suggested that CTGF was regulated by TGF-β2 and ERK via Smad2/3 signal pathway in pericystic fibrosis of ADPKD.

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FR-PO956

Dysregulated 4E-BP1 Pathway in Polycystic Kidney Disease

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Background: Unchecked proliferation of cystic epithelial cells is a major contributor to cyst growth in PKD. The 4E-BP1 pathway is a crucial checkpoint in translation and cellular proliferation, regulated by multiple stimulatory factors like PKCα, ERK, and AKT. The aim of this study was to 1) determine whether the 4E-BP1 pathway is dysregulated in human $PKD1^{-/-}$ cells, 2) examine the effects of an AKT and mTOR insensitive 4E-BP1 (F113A) on protein translation, proliferation, and 3) assess the feasibility of *in vivo* gene therapy of F113A 4E-BP1 adeno-associated virus (AAV9) in neonatal and adult mice.

Methods: Immunoblot, proliferation, and luciferase assays were performed on human epithelial cells from normal renal cortical tubular epithelium ($PKD1^{+/+}$) and ADPKD cyst-lining epithelium ($PKD1^{-/-}$) transfected with pCAG-TdTomato or pCAG-F113A. AAV9 F113A, and AAV9-TdTomato vectors were prepared and administered from D3 and to D17, or D120 to D180.

Results: There was increased phospho (p4E-BP1) species and increased pPKCa(3.6±0.2 vs 0.6±0.0DU***), pERK(3.6±0.2 vs 0.5±0.2DU***), and pAKT(0.6±0.1 vs 0.2±0.1DU*), in $PKD1^{-/-}$ vs. $PKD1^{+/+}$ cells respectively. *In vitro*, F113A expression reduced p4E-BP1 S65 (1.4±0.2 vs 0.02±0.01DU***), reduced cyclin D1 (0.65±0.04 vs 0.51±0.10DU*) and increased autophagosome marker, LC3-II, (0.02±0.00 vs 0.31±0.13DU*) expression in $PKD1^{-/-}$ cells. Stimulation with insulin resulted in maintained p4E-BP1 suppression with F113A in $PKD1^{-/-}$ (2.1±0.3 vs 0.2±0.1DU***). F113A also reduced cap-dependent protein translation (by 37%**), and 72hr proliferation (250±4 vs 180±5 480/528nm O.D***). In neonatal and adult mice, administration of AAV9 resulted in detectable F113A RNA in the heart, kidney, and liver, and reduced p4E-BP1 S65 expression in the heart (2.0±1.3 vs 0.6±0.4DU*). *p<0.05, **p<0.01, *** p<0.001 vs to control.

Conclusions: In PKD, a setting of cystic tubular epithelial hyperproliferation, the 4E-BP1 pathway is dysregulated with increased phosphoregulation of 4E-BP1 by multiple overactive kinases such as; PKCa, ERK, AKT. *In vitro*, F113A expression in $PKD1^{-/-}$ cells, results in hypophosphorylated 4E-BP1 species, reduced cap dependent protein translation, reduced proliferation, and increased autophagosomes. F113A gene therapy to counter the dysregulated 4E-BP1 pathway in *in vivo* models of PKD is feasible to inhibit a pathway seemingly integral to the pathobiology of PKD.

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FR-PO957

Polycystin-1 Signaling Is Regulated by a Stachel-Like Sequence

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Background: Polycystin-1 (PC1) is involved in modulation of G protein signaling, but the regulatory mechanism is unknown. Similar to the Adhesion class of GPCRs, PC1 undergoes auto-catalyzed cleavage at a GPS motif present within its conserved GAIN domain that generates noncovalently-associated extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. Adhesion GPCR signaling can be regulated by residues in the extracellular stalk (the so-called 'Stachel sequence') of the CTF that are exposed upon removal of the NTF. We hypothesized that PC1-mediated signaling is regulated by a Stachel-like sequence within the N-terminus of its CTF.

Methods: Full-length (FL) or CTF forms of PC1 with wild type or mutant stalk sequences (i.e., deletion, ADPKD-associated missense, or alanine substitution) were transiently expressed in HEK293T cells. Activation of a co-transfected NFAT promoter-luciferase reporter and levels of total and surface-expressed protein were compared between mutant and wild type PC1.

Results: FL PC1 activated the NFAT reporter in a dose-dependent fashion, while the CTF demonstrated an inverse dose relationship possibly dependent on its % surface expression. Deletion of the entire stalk region from CTF eliminated NFAT reporter activation, which was not solely due to reduced total protein or surface expression levels. Alanine-scanning of the CTF stalk sequence resulted in a range of effects on NFAT activity, from abolishment to augmentation, which were not entirely consistent with changes in mutant CTF expression characteristics. ADPKD missense mutations in the CTF stalk abolished NFAT activation with varying effects on total or surface protein expression. The same ADPKD mutations when engineered into FL PC1 also inhibited NFAT reporter activation, but had differing effects on GPS cleavage and cell surface expression.

Conclusions: The CTF may be the 'native form' of PC1 responsible for signaling to the NFAT reporter, whose signaling ability is dependent on the presence of the extracellular stalk. Mutation analyses implicate specific residues within the stalk that are critical for NFAT activation, which are likely involved in intramolecular interactions with membrane-embedded portions of the CTF. These observations are consistent with an adhesion GPCR-like and a stalk/Stachel sequence-dependent mechanism for PC1-mediated signaling.

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FR-PO958

Protection Effect of Klotho on Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: ADPKD is the most common hereditary renal disorder. Klotho is a protein with a single transmembrane domain, which is mainly expressed in the kidney

and acts as a co-receptor for fibroblast growth factor 23 (FGF23). The membrane bound extracellular domain of Klotho (soluble α-Klotho) can be cleaved and released into the blood stream. The soluble a-Klotho levels in ADPKD patients was decreased. However, the mechanisms for the downregulation of Klothos and its roles in regulating cyst development remain unknown.

Methods: To evaluate a potential role of Klotho in cyst pathophysiology, we investigated the expression of Klotho in cystic kidneys from ADPKD patients and *Pkd1*$^{flox/flox}$ conditional knockout mice by using immunohistochemistry staining, western blot and qRT-PCR. A recombinant mouse Klotho was used to evaluate its effects on cyst growth *in vivo*.

Results: We found that the expression of Klotho in the kidneys from ADPKD patients and Pkd1 knockout mice was decreased in addition to the decrease of the soluble a-Klotho levels in the serum of ADPKD patients. We further found that the methylation on the promoter of *Klotho* was increased in the genome of ADPKD patients and *Pkd1* mutant mice, which provided a mechanism for the downregulation of Klothos in ADPKD by the upregulated DNA methyltransferases (DNMTs). Treatment with the recombinant mouse Klotho delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/ body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in *Pkd1* mutant mice (all $p < 0.01$). Klotho treatment decreased the activation and phosphorylation of Akt, ERK, Rb, S6, and STAT3, whereas it increased the expression of p21. Since Klotho overexpression mice is normal and the average lifespan is about 20-30% longer that the wild type mice, overexpression or treatment with Klotho should not only protect renal function but also has less side effect.

Conclusions: The expression of Klotho was not only deceased in the serum of ADPKD patients but also in the kidneys from ADPKD patient and *Pkd1* knockout mice, which was regulated by the DNMTs mediated methylation on the promoter of *Klotho*. Treatment with the recombinant Klotho may be a viable new therapy for ADPKD.

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FR-PO959

Homeostasis of Phosphate Kinase PIPKIγ and Phosphatase INPP5E Modulates the Ciliary Accumulation of Polycystin2 in ADPKD

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Background: Primary cilia defects lead to a panel of genetic human disorders, collectively termed as ciliopathies. Polycystin2 as a transmembrane protein functions to interact with PKD1 and maintains normal orientationof tubular architecture. Mutations in either PKD1 or PKD2 causes autosomal dominant polycystic kidney disease (ADPKD), which is also considered to be among the ciliopathy diseases. The function of phosphoinositides in mediating acute response, and acting as constitutive signals to help define organelle identity, are also emphasized by various human diseases. Recently, several studies implicated the involvement of PI species in ciliopathies. Also, Homeostasis of Phosphoinositide PI(4)P and PI(4,5)P2 functions significantly in cilia, and mutations in the phosphatases INPP5E can significantly increase ciliary PI(4,5)P2. But the relationship between regulated homoeostasis of PIs and ciliopathy proteins still remain to explore in the future.

Methods: Cell culture and transfection of DNA constructs and siRNA Immunofluorescence microscopy Immunoprecipitation and pull-down assay

Results: Phosphatidylinositol phosphate kinase PIPKIγ and phosphatase INPP5E cordinate to regulate homeostasis of PI(4)P and PI(4,5)P2 in cilia. Recently, we discovered In INPP5E knock-out MEF cells, endogenous ciliary pool of polycystin2 is significantly increased, while PIPKIγ depletion can partially reduce the accumulation of polycystin2. Also, in GANAB cell which always exhibits the absent ciliary localization of polycystin2, after knocking down INPP5E, we also observed increased PC2 accumulation. To verify this observation, we treated GANAB cell with the INPP5E inhibitor and found similar ciliary accumulation of PC2 after 24h treatment. As mutations in INPP5E increased ciliary PI(4,5)P2, we hypothesized that the enriched PI(4,5)P2 promoted PC2 accumulation. By overexpressing PIPKIγ kinase domain or its activator protein HYLS1 in GANAB cells, the increased PC2 signal in cilia also convinced our hypothesis.

Conclusions: By activating PIPKIr or inhibiting INPP5E, we found enriched PI(4.5) P2 is associated with ciliary PC2 accumulation. As reduced level of PC2 can always lead to kidney disease ADPKD, increased dosage of ciliary PC2 by PI(4,5)P2 may provide some new targets to understand the relationship between PIs and kidney diseases and also new methods for studying ADPKD.

FR-PO960

Polycystin 1 (PC1) and NPHP1 Interact with Ciliary LKB1 to Regulate Inflammation, Providing New Insights into the Pathophysiology of Ciliopathy Phenotypes

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Background: Peritubular inflammation and fibrosis are key aspects of the renal ciliopathies nephronophthisis (NPH) and autosomal dominant polycystic kidney disease (ADPKD). In addition, macrophages drive cyst growth in the latter. Yet, the mechanism, how mutations in *NPHP* or *PKD* genes cause inflammation, is unknown.

Methods: Biochemistry, expression screens, molecular biology, imaging, transgenic animal models, immune phenotyping.

Results: We find that loss of *Lkb1* in the kidney results in an NPH phenotype. LKB1 interacts with NPHP1 and PC1 to regulate CCL2 expression through an intra-ciliary mechanism. Loss of *Lkb1* or *Pkd1* in the kidney leads to increased numbers of CCR2 positive mononuclear phagocytes. Simultaneous targeting of *Ccl2* or the essential cilia protein *Kif3a* in *Pkd1* mutant mice prevents CCL2 expression, macrophage expansion and leads to an ameliorated phenotype.

Conclusions: Our findings describe a novel physiological role for PC1 and NPHP1 as gatekeepers of peritubular immune cell numbers and explain how disturbance of this function results in an essential pathological process driving these entities.

Funding: Government Support - Non-U.S.

FR-PO961

Deletion of Ift-A Gene, Thm1, Differentially Affects Cystic Kidney Disease in Pkd1 and Jck Mouse Models

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Background: Primary cilia are signaling organelles that are built and maintained by intraflagellar transport (IFT) complexes B and A. The role of primary cilia in renal cystic disease is poorly understood. Ciliary dysfunction causes renal cystic disease, yet ablation of cilia via Ift-B gene deletion and pharmacological shortening of cilia attenuated renal cystic disease in *Pkd1* conditional knock-out (cko) and *jck* mutant mice, respectively. Such results suggest that cilia-mediated signaling within a renal cystic disease background may be pro-cystogenic. In contrast to deletion of an Ift-B gene, which often results in cilia loss, deletion of an Ift-A gene causes shortened cilia with protein accumulation in bulbous distal tips and can have opposing effects on signaling. Thus we examined the effect of Ift-A deficiency on a renal cystic disease background.

Methods: Using the ROSA-Cre^{ERT} recombinase, *Thm1* was deleted together with *Pkd1* in mice at 5 weeks of age, and in *jck* mutant mice at perinatal and postnatal (4 weeks) ages.

Results: *Thm1* deletion attenuated *Pkd1* cko renal cystic disease, decreasing BUN, cell proliferation, and P-STAT3 and P-ERK levels in *Thm1;Pkd1* dko kidneys relative to *Pkd1* cko kidneys. In contrast, *Thm1* deletion caused a combinatorial effect in *jck* mice. While *jck* mice showed renal cysts of collecting duct and Loop of Henle tubular origins, perinatal deletion of *Thm1* in *jck* mutants caused additional cysts of proximal tubular origin, and increased BUN. Deletion of *Thm1* at 4 weeks of age in *jck* mutants did not affect proximal tubules, but did increase cell proliferation and BUN in *Thm1*; *jck* double mutant females. Renal P-STAT3 and P-ERK levels correlated with disease severity in all mutants. Additionally, primary cilia were elongated in *jck* mice, and *Thm1* deletion in *jck* mice caused elongated cilia with IFT81 accumulation at the distal tips.

Conclusions: Attenuated renal cystic disease in *Thm1;Pkd1* dko mice suggests that *Pkd1* renal cystogenesis requires Ift-A, while the combinatorial effect in *Thm1*;*jck* double mutant kidneys suggests independent cyst-promoting roles for *Thm1* and *jck*. The contrasting effects of *Thm1* deletion in *Pkd1* and *jck* mutants may reveal divergent mechanisms underlying *Pkd1* and *jck* renal cystogenesis.

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FR-PO962

Targeting Axoneme Polyglutamylation as a Potential Therapeutic Approach for ADPKD Treatment

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorders, causing uncontrolled growth of cysts in kidney eventually leading to kidney failure. Primary cilia, the non-motile sensory devices on most cell surfaces, have been suggested as the key organelles in the pathogenesis of ADPKD. Proper targeting/maintenance of Polycystin 1(PC1)/ Polycystin 2(PC2) heterodimer on cilia surface are critical for cilia as mechano-sensor. Dysfunctional polycystins would compromise cilia-dependent signaling in maintaining normal nephron structure and lead to cystogenesis. Recently, accumulating evidence suggest a link between the level of functional Polycystins and disease severity, indicative of a dosage model of cystogenesis in ADPKD. Theoretically, restoring the functional level of cilia polycystins is a promising therapeutic strategy to delay or even prevent the cystogenesis. However, perusing this strategy is impeded by the lack of understanding of how the ciliary targeting/maintenance of polycystins is controlled.

Methods: 1. Immunoprecipitation and GST pull-down. 2. MDCK cyst formation in 3D culture. 3. Immunofluorescence microscopy. 4. Live-cell imaging. 5. Western blotting. 6. Bio-ID.

Results: Axoneme polyglutamylation is specifically regulated by a Joubert syndrome protein ARL13B and tuned by the balance of glutamylases TTLL5/6 and deglutamylase CCP5. ARL13B interacts with RAB11 effector FIP5 to promote the ciliary import of glutamylases. Hypoglutamylation caused by a deficient FIP5-regulated trafficking impairs the proper anchoring of PC2 in cilia. Remarkably, depletion of CCP5 effectively promotes hyperglutamylation and restores the ciliary PC2 in *GANAB*$^{-/-}$ cells. By implementing axoneme polyglutamylation as readout, we initiated a preliminary imaging-based drug screen. We identified several hits which could induce axoneme hyperglutamylation and increase PC2 dosage and, importantly, suppress MDCK cyst formation in 3D culture, implicating the therapeutic potential of targeting axoneme polyglutamylation for ADPKD.

Conclusions: 1. ARL13B-FIP5-regulated ciliary import of glutamylases is essential for axoneme polyglutamylation. 2. Axoneme polyglutamylation anchors ciliary PC2. 3. Restoring ciliary polycystins by increasing axoneme polyglutamylation could be a potential therapeutic approach for ADPKD treatment.

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FR-PO963

Genomic Background of Adults with Suspected Ciliopathy on Renal Biopsy

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Background: In adult patients, ciliopathy is often difficult to make a precise diagnosis based on clinical features, because they usually have no specific findings such as retinitis pigmentosa or liver dysfunction. Furthermore, it is impossible to make a definitive genetic diagnosis by renal biopsy. Therefore, genetic testing is crucial for precise diagnosis and clinical management of the patients and their families.

Methods: We investigated 17 adult patients who were suspected ciliopathy by renal biopsy. Their pathological findings were tubular dilatation or thickening and lamellation of tubular basement membranes. All patients had no extrarenal findings (retinitis pigmentosa and liver function disorder) and no family history of ciliopathy. Comprehensive genetic testing was performed using capture-based next-generation sequencing for 69 genes that cause nine types of hereditary cystic kidney diseases (autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, nephronophthisis, Joubert syndrome, Meckel syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, autosomal dominant tubulointerstitial kidney disease, etc.).

Results: Median age at renal biopsy was 55 (17–84) years old and seven patients (41%) were male. Through our analysis, two patients had homozygous full gene deletions of *NPHP1*. Additionally, compound heterozygous mutations in *NPHP3*, *NPHP4* and *CEP164* were found in each one patient. The patients who had pathogenic mutations were significantly younger than those without mutations (median, 26 years old vs 68 years old, $P = 0.045$, Mann-Whitney U test), and no mutations in the known genes were detected in those aged ≥50 years ($n = 9$).

Conclusions: In the adult patients suspected of ciliopathy by renal biopsy, 29% were genetically diagnosed as nephronophthisis by our comprehensive genetic testing. Additionally, older patients tend not to have any pathogenic mutations in the known genes.

Funding: Government Support - Non-U.S.

FR-PO964

Deletion of Cep164 in the Collecting Duct Causes Polycystic Kidney Disease-Like Phenotype

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Background: Nephronophthisis is an inherited cause of polycystic kidney disease that represents the most common cause of end-stage renal failure in the first three decades of life. Although all known genes associated with the disease phenotype localize to the cilia, the underpinning pathomechanisms remain largely unknown. We recently reported that mutations in *centrosomal protein 164*(*CEP164*) gene, cause nephronophthisis with extrarenal manifestations in humans. In order to study the function of Cep164 in mouse we generated a Cep164 transgenic mouse model.

Methods: Targeted *Cep164* ES cells were obtained from KOMP and injected into blastocysts to generate the *Cep164*$^{-/-}$ mice. Collecting duct-specific deletion of *Cep164* was achieved by crossing *Hoxb7-Cre* mice with *Cep164*$^{loxP/loxP}$ mice. Immunofluorescence staining was used to study the expression of ciliary proteins both in celture and in the kidney. Gross morphological characterization and tissue histological analysis of mutant mice was performed on E9.5 embryos, P7, P14 and P21 animals.

Results: Whole body deletion of *Cep164* resulted in mid-gestational lethality in mice. Molecular analysis revealed that the mutant animals lacked primary cilia and had impaired hedgehog signaling. To circumvent embryonic lethality, Cep164 was deleted from the kidney collecting duct using Hoxb7-Cre mice. Deletion of *Cep164* abolished cilia in the collecting duct cells of *Hoxb7-Cre*;*Cep164*$^{loxP/loxP}$ mice. The mutant kidneys developed normally until P7, after which they underwent a rapid cyst formation in the collecting ducts, which led to widespread structural damage, kidney failure and mortality by P21. Morphological and molecular analysis demonstrated that the rapid cyst growth was caused by uncontrolled cell proliferation in the collecting duct epithelium. Treatment with cyclin-dependent kinase inhibitors mitigated the rapid cyst growth in *Hoxb7-Cre*;*Cep164*$^{loxP/loxP}$ mice.

Conclusions: Our data demonstrate that abrogation of Cep164 leads to severe developmental abnormalities in early mouse embryogensis due to defective ciliary signaling. Conditional ablation of Cep164 in the collecting duct results in massive cyst growth in postnatal kidneys, resembling the pathogenesis of autosomal polycystic kidney disease. Together, Cep164 mouse represents a novel genetic model of autosomal recessive polycystic kidney disease.

Funding: NIDDK Support

FR-PO965

Consequences of Centrosome Numerical Aberrations in Cystic Kidney Disease

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Background: The centrosome and primary cilium act together as a cellular "hub" to regulate several important developmental signaling pathways. Defects in centrosome biogenesis can result in numerical aberrations in centrosome-cilium number, resulting in cells that either lose these structures or assemble too many. Importantly, numerical aberrations in centrosomes have been reported in various types of cystic kidney disease including ADPKD, nephronophthisis, and cystic kidneys of ciliopathy patients. What remains unknown are the consequences of centrosome numerical aberrations during embryonic kidney development, adult kidney homeostasis, and after renal injury.

Methods: To ablate centrosomes we utilized mice harboring a conditional allele of Cep120 (Cep120^{fl}), which we previously showed is essential for centrosome formation. To increase centrosome number, we used a transgenic mouse with a conditional overexpression allele of the kinase Plk4 (Tg::mChPlk4), known as the master regulator of centrosome duplication. Cep120^{fl}or Tg::mChPlk4 mice were crossed with Six2-Cre or Hoxb7-Cre animals to cause ablation/amplification of centrosomes in the metanephric mesenchyme or ureteric bud epithelium, respectively. Finally, these mice were mated with Slc34a1-Cre^{ERT}or Ksp-Cre^{ERT}to induce overexpression/loss of centrosomes in fully developed kidneys.

Results: Increasing centrosome number perturbed mitotic spindle morphology, ciliary assembly, and signaling pathways essential for growth of renal progenitors. This resulted in defective branching morphogenesis, renal hypoplasia, and rapid cystogenesis after birth. Moreover, centrosome amplification sensitized kidneys in adult mice, causing cystogenesis following ischemic renal injury. In contrast, loss of centrosomes did not have an adverse effect on progenitor cell proliferation, nor caused renal hypoplasia. In fact, loss of centrosomes resulted in enlarged kidneys that became rapidly cystic. Remarkably, loss of centrosomes during kidney homeostasis did not affect overall kidney function, nor cause cyst formation.

Conclusions: Our results highlight the heterogeneity of response to centrosomal numerical aberrations in different renal cells types and developmental stages. These results indicate that the underlying signaling changes are likely to be different, and suggest that therapeutic strategies will have to be developed separately for each case.

Funding: NIDDK Support

FR-PO966

Structure-Function Analysis of Inversin in Proximal Ciliary Patterning and Ciliary Transport

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Background: The proximal end of the primary cilium contains the inversin compartment (IC), comprised of four interacting ciliopathy proteins, inversin (INVS), NEK8, ANKS6 and NPHP3. Mutations in these proteins give rise to a multiorgan malformation syndrome, with L-/R-asymmetry perturbations, congenital heart defects and polycystic kidney disease. The most upstream factor in the IC is inversin, which is necessary for IC localization of the other proteins. The goal of this study is (1) to identify the structural determinants of inversin, necessary and/or sufficient for IC reconstitution and (2) to analyze ciliary length and intraflagellar transport (IFT) phenotypes in presence or absence of IC proteins.

Methods: CRISPR/Cas9-mediated gene knockout Lentiviral and retroviral transduction Immunofluorescence microscopy Immunoprecipitation Western-blot Live fluorescence cell imaging Kymograph analysis

Results: Immunofluorescence for FLAG-antigen revealed proximal ciliary localization only of FLAG-tagged full-length inversin and C-terminal truncations (INVS[745-1065] and INVS[554-1065]), but not N-terminal truncations INVS[1-553] and INVS[1-744]. Furthermore, only full-length inversin, and none of the partial add-backs were capable to localize NEK8 and ANKS6 to the IC. These results suggest that the ciliary signal sequence of inversin lies in its C-terminal domain, but the full-length protein, including the N-terminal ANK-repeat domain is required to assemble the other proteins in the IC. Moreover, we analyzed ciliary length and IFT-B particle velocities in CRISPR/Cas9-knockouts and full-length add-backs of IC proteins. Loss of inversin led to a >30% decrease in ciliary length and of IFT-B particle velocity, while a lentiviral full-length INVS add-back completely rescued both knockout phenotypes. An identical phenotype was observed with NPHP3, while NEK8 knockout revealed ~30% ciliary length increase and acceleration in IFT-B transport velocity.

Conclusions: As ciliary lengthening control and IFT particle velocity are physiological readouts for ciliary function, our results indicate that inversin is necessary and sufficient for ciliary homeostasis. The similar behavior of inversin and NPHP3 knockout phenotypes suggests that inversin may function through NPHP3, while NEK8 may play an independent role as a kinase.

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FR-PO967

Stat3 Activation Is Elevated in Pre-Cystic Kidneys of Thm1 Conditional Knock-out Mice

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Background: Primary cilia are sensory organelles that mediate signaling pathways. Dysfunction of cilia leads to renal cystic disease. Multiple cellular and signaling aberrations contribute to renal cystogenesis, while the initiating molecular mechanisms remain unknown. In mice, perinatal global deletion of the ciliary gene, *Thm1,* causes renal cysts beginning at postnatal day (P) 15.

Methods: To identify molecular events that initiate renal cystogenesis in *Thm1* conditional knockout (cko) mice, we performed RNA sequencing on kidney RNA lysates of pre-cystic P9 and cystic P42, *Thm1* cko mice and control littermates. We reasoned that genes with significantly altered expression at both P9 and P42 would represent early initiation events leading to cystogenesis.

Results: *Endothelin 1, Egr2, Fos, Jun, Stat3,* endothelial *Vcam1,* immune genes, *Complement C3* and *Adcy7,* were upregulated at P9 and further upregulated at P42. Western blot analysis showed increased P-STAT3 at P10, and upregulation of multiple components of STAT and EDN1-MAPK signaling pathways at P42. Immunohistochemistry revealed more intense nuclear localization of P-STAT3 in epithelial cells of non-dilated and dilated tubules at P20, and in cyst-lining epithelial cells and interstitial cells at P42. To study the connection between primary ciliary dysfunction and upregulated STAT3 signaling, we have generated *Thm1* knock-down human renal 293T clonal cell lines. These cell lines show shortened primary cilia with IFT81 accumulation in a bulb-like structure at the distal tip, indicative of a retrograde ciliary protein trafficking defect.

Conclusions: Our data reveal upregulated Stat3 activation in pre-cystic *Thm1* cko kidneys and suggest that simultaneous alteration of gene expression and signaling in renal epithelial, vascular and immune cells may potentiate renal cyst initiation. We are examining mechanisms by which *Thm1*-deficient cilia cause increased Stat3 activation and are inhibiting Stat3 pharmacologically in *Thm1* cko mice. This may reveal initiating mechanisms underlying *Thm1*-deficient renal cystogenesis.

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FR-PO968

Collecting Duct-Specific Deletion of the Transcription Factor Grainyhead-Like 2 (Grhl2) Aggravates Cyst Growth in Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a genetic disorder characterized by the development of cysts as a result of abnormalities in proliferation, apoptosis and dedifferentiation of the renal epithelium. The transcription factor Grhl2 is highly expressed in the collecting duct cells of the kidney and controls epithelial barrier function in the mouse kidney. The collecting duct is known to be an important source of cysts in PKD, but whether Grhl2 is involved in cyst formation and growth is not known.

Methods: To investigate the role of Grhl2 in PKD pathogenesis, we first examined GRHL2 protein expression in kidney samples from patients with autosomal dominant PKD (ADPKD). We then studied the effects of a collecting duct-specific Grhl2 deletion on a mouse model with slowly progressive PKD caused by overexpression of the human MYC proto-oncogene. We compared renal phenotypes of HoxB7-Cre; R26StopFLMYC; $Grhl2^{flox/flox}$ mice and HoxB7Cre; R26StopFLMYC mice using functional, histological assays and gene expression profiling.

Results: Analyses of patient samples with ADPKD (n=6) revealed that GRHL2 protein was downregulated by 65% in collecting duct-derived cyst-lining epithelia when compared with its expression in healthy collecting ducts (n=4). HoxB7Cre; R26StopFLMYC mice developed slowly progressive bilateral polycystic kidneys that mimicked human ADPKD. Collecting duct-specific deletion of Grhl2 in the kidneys of HoxB7Cre, R26StopFLMYC mice (HoxB7-Cre; R26StopFLMYC; $Grhl2^{flox/flox}$) markedly accelerated PKD progression, led to a more aggressive bilateral cystic kidney disease, and caused early lethality. Proliferation and apoptosis rates of cyst-lining epithelia were found to be significantly higher in HoxB7Cre; R26StopFLMYC; $Grhl2^{flox/flox}$ mice compared with HoxB7Cre; R26StopFLMYC mice. Furthermore, a genome-wide analysis of differentially regulated genes in HoxB7Cre; R26StopFLMYC; $Grhl2^{flox/flox}$ mice compared with HoxB7-Cre; R26StopFLMYC mice identified deregulation of genes involved in cell-cycle regulation and epithelial cell polarity.

Conclusions: Our data indicate a role for Grhl2 and its target gene program in the progression of collecting duct-derived cyst formation in PKD. Targeting Grhl2 activity may constitute a novel strategy to limit cyst progression.

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FR-PO969

Cyst Growth in the Anks6pR823W Model of ADPKD Is Reduced by the Anks3I454E Mutation

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Background: The $Anks6^{R823W}$ mutation in rats causes an ADPKD-like phenotype with massive renal cyst growth leading to kidney failure and death. Previously we demonstrated that this mutation prevents the Anks6-SAM domain from binding to the Anks3-SAM domain and disrupts the spatial expression of both proteins. Since Anks6-Anks3 binding prevents Anks3-Anks3 SAM domain interactions it is possible that increased formation of Anks3 homopolymers is part of the pathological process. Thus, we created a rat with an $Anks3^{I454E}$ mutation in the SAM domain where Anks3 can no longer bind to itself but can interact with Anks6.

Methods: The $Anks3^{I454E}$ mutation was generated using CRISPR-Cas9 in Sprague Dawley rats. Clinical parameters in 24-h urine and blood plasma were determined to evaluate renal function. Histological analysis and western blots were performed by standard techniques. These rats were crossed into the TGR-CMV-$Anks6^{pR823W}$ line and the kidneys of the offspring investigated at 2 and 4 weeks. Cysts were counted and scored using a 4 point scale.

Results: No histological abnormalities were observed in the kidneys of $Anks3^{I454E/I454E}$ rats up to 1 year of age. There was an increase in urine osmolarity and a decrease in the concentration of plasma parameters in these rats, probably due to increased water reabsorption in the kidney, supported by an increase in aquaporin 2 expression. In TGR-CMV-$Anks6^{pR823W}Anks3^{WT}$ rats, cyst growth started within the first 10 days after birth leading to massive kidney hypertrophy. In both the 2 and 4 week old TGR-CMV-$Anks6^{pR823W}$ carrying the $Anks3^{I454E}$ mutation there was a significant reduction in the kidney to body weight ratio and cyst score with the largest reduction in $Anks3^{I454E/I454E}$ rats versus TGR-CMV-$Anks6^{pR823W}Anks3^{WT}$ rats (2 weeks: kw/bw p=0.0003, cyst score p=0.0001; 4 weeks: kw/bw p=0.0086, cyst score p=0.0001).

Conclusions: 1) The disruption of Anks3-Anks3 binding via the SAM domain is not pathological in rats and causes increased water reuptake in the kidney. 2) The disruption of Anks3-Anks3 binding in the $Anks6^{pR823W}$ rat model of ADPKD significantly reduces the rate of cyst growth and this effect is increased in $Anks3^{I454E}$ homozygous versus heterozygous rats. *This study was supported by the grant of the NIH (5RO1DK100482) to JB and SH.*

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FR-PO970

Biallelic ANKS6 Variants Causing Late Onset Ciliopathy with CKD in Adulthood

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Background: The progressive and irreversible conditions summarized under the term "Chronic kidney diseases" (CKD) are a heterogeneous group of disorders with significant health and economic effects. Affected individuals and their nephrologists are often unaware of underlying causes. Diagnostic tools used in clinical practice, such as kidney biopsy do not always yield to a definitive diagnosis. High-throughput sequencing methods have advanced our ability to identify the underlying molecular etiology in families with unknown origin of CKD.

Methods: Whole exome sequencing (WES) was performed in two sisters from a non-consanguineous family of German descent who presented with CKD onset in mid-adulthood (>30 years of age). DNA was extracted from whole blood, enriched, and sequenced on a HiSeq2500. In addition patient-derived fibroblasts from skin biopsies were cultured for performing functional studies via immunoblotting.

Results: WES detected two disease associated variants c.[934G>C;938A>C], p.[(A312P);(D313A)]) and c.1973-3C>G in the *ANKS6* gene in both affected siblings. Segregation testing by Sanger sequencing confirmed compound heterozygosity. The ciliary protein ANKS6 localizes to the proximal compartment of the cilium, where it regulates ciliary signaling. Mutations in *ANKS6* are known to cause Nephronophthisis-related ciliopathies in humans, including laterality defects and congenital hepatic fibrosis. Renal biopsy of both patients showed tubulointerstitial fibrosis and glomerulosclerosis. Careful clinical examination does not reveal any extra-renal findings in both affected individuals. Interestingly, immunoblotting studies from patient-derived fibroblasts show a nearly complete loss of the ANKS6 protein and suggest an effect on gene dosage for both the missense and the splicing variant.

Conclusions: In summary, we confirmed the diagnosis of an ANKS6-associated Nephronophthisis which is typically syndromic and juvenile-onset in two adults with CKD onset in mid-adulthood, highlighting the extreme heterogeneity of CKD. Offering genetic testing to families with renal disease of unknown origin can improve our knowledge of the clinical course in CKD entities, leads to a better understanding of pathophysiological mechanism and may help to develop novel therapeutic strategies, possibly also of relevance to the broader field of kidney diseases.

FR-PO971

The Exhaustive Screening Tool Is Superior to the Simplified Version to Identify Pediatric Patients with a Pathogenic HNF1β Genotype

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Background: Pathogenic genotypes involving hepatocyte nuclear factor-1 beta (HNF1β) are now recognized as the most frequent cause of monogenic congenital anomalies of the kidney and urinary tract (CAKUT), a leading cause of paediatric-onset chronic kidney disease (CKD). Identifying these patients is challenging due to the substantial phenotypic heterogeneity across age groups. We sought to characterize the paediatric phenotype of HNF1β disease and to assess the utility of established screening tools (exhaustive or simplified) for pediatric patients with renal cysts.

Methods: Between 2011 and 2018, 45 patients with renal cysts from our institution were tested for mutations in the gene HNF1β.

Results: Testing was positive in 17/39 (44%) unrelated kindreds (total, 21/45 patients) with median age at diagnosis of 6.1 years (range 0.1-17.3). A heterozygous deletion encompassing the entire HNF1β gene was detected in all but 2/17 kindreds that had either a gene duplication or a point mutation, respectively. Analysis of the three multiplex kindreds revealed significant intrafamilial phenotypic heterogeneity. The most common clinical features included hypomagnesemia (53%, 9/17), neurodevelopmental problems (43%, 9/21), hyperuricemia (50%, 4/8), hyperparathyroidism (33%, 3/9), and pancreatic hypoplasia (14%, 3/21). Clinical features commonly reported in adults were rare: no patients with hypokalemia or early-onset gout, and two patients with either maturity-onset diabetes of the young (MODY) or unexplained elevated liver enzymes. The exhaustive screening tool identified all affected patients but required testing 80% of the patients who tested negative (19/24). In contrast, the simplified screening tool called for genetic testing for only 4/45 patients, all of whom ultimately tested positive.

Conclusions: We observed that patients harboring a HNF1β mutation display variable phenotypic penetrance and expressivity. This heterogeneity was even noted among members of multiplex kindreds. A comparison of the simplified and exhaustive screening tools applied to pediatric patients with renal cysts reveals that the latter is more sensitive to identify patients with pathogenic HNF1β genotypes.

FR-PO972

ADTKD-HNF1B Has a Slow-Progressive Phenotype in Childhood—with the Exception of Very Early Onset Cases: Results of the German Multicenter HNF1B Childhood Registry

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Background: *HNF1B* nephropathy is part of the autosomal dominant tubulointerstitial kidney disease spectrum (ADTKD) and affects pediatric patients with bilateral (cystic) dysplasia. The clinical variability, the absence of genotype-phenotype correlations, and limited long-term data render counseling of affected families difficult.

Methods: Longitudinal data of 62 children with ADTKD-*HNF1B* was obtained in a multicenter approach. Genetic family analysis was performed in 30/62 cases.

Results: 87% of ADTKD-*HNF1B* patients had bilateral dysplasia, 74% visible bilateral and 16% unilateral renal cysts at the end of observation. Cyst development was non-progressive in 72% with a mean GFR loss of -0.33 ml/min/1.73qm per year (±8.9). In patients with an increase in cyst number, the annual GFR reduction was -2.8 ml/min/1.73qm (±13.2), in the total cohort -1.0 ml/min/1.73qm (±10.3). A subset of ADTKD-*HNF1B* patients differs from this group and develops ESRD at very early ages < 2 years. Hyperuricaemia (37%) was a frequent finding at young age (median 1 year), whereas hypomagnesemia (24%), elevated liver enzymes (21%) and hyperglycaemia (8%) showed an increased incidence in the teenaged child. Genetic analysis revealed no genotype-phenotype correlations but a significant parent-of-origin effect with a preponderance of 78% of maternal inheritance in dominant cases.

Conclusions: In most children, ADTKD-*HNF1B* has a non-progressive course of cyst development and a slow-progressive course of kidney function. A subgroup of patients develops ESRD at very young age < 2years requiring special medical attention. Patients will be annually followed in the registry and new patients can be included at any time.

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FR-PO973

Clinical Characteristics of HNF1B Related Disorders in Japanese Population

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Background: Hepatocyte nuclear factor 1β (*HNF1B*) gene is located at chromosome 17q12 and is known as the causative gene for the renal cysts and diabetes syndrome (RCAD). It is also well known that various phenotypes of congenital anomalies of the kidney and urinary tract (CAKUT) or Bartter-like electrolyte abnormalities can be caused by *HNF1B* variants. In addition, 17q12 deletion syndrome shows multi-system disorders as well as RCAD.

Methods: We conducted gene screening for cases with RCAD, CAKUT and Bartter-like syndrome cases. As a result, 31 cases were detected heterozygous variants or whole gene deletions in *HNF1B* (heterozygous variant: 18 cases and deletion: 13 cases). All cases with deletion were diagnosed with 17q12 deletion syndrome confirmed by MLPA or array CGH. A retrospective review of clinical data was conducted for these cases.

Results: Most cases had morphological abnormalities in the renal urinary tract system. Diabetes developed in 11 cases (38%). Hyperuricemia and hypomagnesemia were associated with 5 cases (17%) and 12 cases (41%), respectively. Pancreatic malformations were detected in 6 cases (21%). Nine patients (31%) had liver abnormalities. When data were classified by mutation types, the eGFR (estimated glomerular filtration rate) levels were significantly lower in the patients who carried heterozygous variants compared with those in the patients who carried deletions (median: 37.9 ml/min/1.73 m^2 vs 55.9 ml/min/1.73 m^2, p=0.0264). Patients who carried deletions had higher frequencies of hypomagnesemia (p=0.0005) and neurological complications (p=0.0064) than those who carried variants.

Conclusions: We presented the clinical characteristics of *HNF1B* related disorders. To predict the renal prognosis or onset of extra renal complications, accurate genetic diagnosis at an early age is important. *HNF1B* related disorders show various clinical symptoms and should be noted for accurate diagnosis.

FR-PO974

Extracellular Vesicle Induction of Cortical Collecting Duct Cell Growth

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Background: Tuberous sclerosis complex (TSC), a genetic tumor suppressor syndrome, is caused by inactivation of either *TSC1* or *TSC2* genes. Renal manifestations include early onset chronic kidney disease, angiomyolipomata and multiple patterns of renal cystic disease. The mechanism of cystogenesis has been assumed to be somehow linked to the *PKD1* gene that is adjacent to the *TSC2* gene, though the precise mechanism remains unclear.

Methods: We used transgenic animals with aquaporin-2 promoter driven Cre recombinase and renin-1c promoter regulated Cre recombinase to specifically inactivate the Tsc2 and Tsc1 genes in principal cells (*Aqp2CreTsc2*) and renal pericytes (*Ren1cCreTsc1*), respectively. We also used CRISPR/CAS9 technology to disrupt the *Tsc1* or *Tsc2* gene in a principal cell line and used ultracentrifugation to isolate extracellular vesicles. Conditioned media or isolated extracellular vesicles were used in cell culture studies with M1 intercalated cell line as a target. We measured the phosphorylation of S6 expression as a read out.

Results: Both animals develop renal cystic disease, by far more prominently in the renal cortex, and the cysts highly expressed pS6. Cystic epithelium was predominantly type A intercalated cells, and principal cells seemed to drop out with time in the *Aqp2CreTsc2* renal cysts. The cysts in both animals continued to express tuberin and hamartin, and we noted extracellular vesicles in some of the smaller cyst lumens of perfused animals. Using a tissue culture model we found that principal cell extracellular vesicles activated intercalated cell mTORC1 activity, and this was exaggerated if either the Tsc1 or Tsc2 gene was disrupted.

Conclusions: We demonstrate that mice with principal cell specific *Tsc2* inactivation and mice with renal pericyte *Tsc1* inactivation develop cortical cystic disease comprised of type A intercalated cells. The cystic epithelium appears to have an activated mTORC1 axis, though still express hamartin and tuberin. Cell culture experiments suggest a role for extracellular vesicles in this growth activation signal.

Funding: Other U.S. Government Support

FR-PO975

Manifestations of Renal Disease in Adult Patients with Tuberous Sclerosis Complex–Reference Center Experience

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Background: Renal involvement is a considerable cause of mortality and morbidity in tuberous sclerosis complex (TSC) patients and include angiomyolipomas (AMLs), cysts and malignant tumors. Surgical treatment of life-threatening bleeding from AMLs additionally impairs kidney function, while treatment with mammalian target of rapamycin inhibitor (mTORI) is effective in preventing bleeding complications and preserving renal function. However, data concerning proteinuria, albuminuria and hypertension in TSC patients, as possibly modifiable risk factors of chronic kidney failure (CKF) is limited.

Methods: The initial assessment was performed in 32 TSC patients admitted to reference academic TSC center from 03/2016 to 01/2018. Study group consisted of 15 men and 17 women in the mean age of 32±11.6 yrs. Prevalence of renal manifestations, CKF, hypertension, proteinuria (urinary protein-to-creatinine ratio;uPCR) and albuminuria (urinary albumin-to-creatinine ratio;uACR) were studied.

Results: TSC renal manifestations were: AMLs (29/32; 91%), cysts (17/32; 53%) and renal cell carcinoma (1/32; 3%). 25% patients were previously nephrectomised due to complications related to AMLs. eGFR<60 mL/min was found in 19% individuals. The incidence of proteinuria (uPCR>150mg/g), albuminuria (uACR>30mg/g) and hypertension were 41%, 44% and 34%, respectively. TSC patients after nephrectomy in comparison with non-nephrectomised patients had statistically significant decline of kidney function-higher

creatinine level (1.48±0.52mg/dL vs 0.97±0.63mg/dL) and lower eGFR (52.5±21.4mL/min vs 93.67±30.91mL/min) and also higher albuminuria (uACR 346.7±677.6mg/g vs 49.41±90.27mg/g);($p<0.05$). The differences in prevalence of hypertension (50% in patients after nephrectomy vs 29% in non-nephrectomised;$p=0.397$) and quantity of proteinuria (uPCR 579.3±1003.2mg/g vs 263.8±516.7mg/g;$p=0.25$) were insignificant.

Conclusions: The incidence of renal manifestations was consistent with previous reports. Adult TSC patients have relatively high prevalence of CKF as well as its potentially modifiable risk factors, hypertension, proteinuria, albuminuria. The previous nephrectomy seems to have a significant impact on kidney function, that supports the invaluable role of pre-emptive treatment of AMLs with mTORI to prevent need of surgery.

FR-PO976

Renal Involvement in Tuberous Sclerosis Complex

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Background: Tuberous sclerosis complex (TSC) is a rare, genetic disorder caused by alterations in tumor suppresor proteins such as hamartin or tuberin leading to uncontrolled activity of the mTOR pathway and, consequently, to the development of the tumors, known as hemartomas. TSC manifestation is multisystemic including renal, cardiac, pulmonologic, neurological, cutaneous lesions and can differ depending on disease related genetic variants. Mutations of at least two different genes, the TSC1 gene or the TSC2 gene, are known to cause TSC. We analyzed clinically or genetically diagnosed TSC with different TSC gene mutations and disease manifestations, focusing on renal findings: renal cysts (RC), angiomyolipomas (AML) or renocellular carcinoma (RCC).

Methods: A retrospective data analysis of the clinical and radiographic (CT or MRI) records of the patients with TSC was made.

Results: 25 patients (14 children and 11 adults), 13 females and 12 males were included. Diagnosis was genetically confirmed in 56% patients, with TSC2 and TSC1 genes 64,3%, 35,7% respectively. All patients had more than one organ involvement. Renal lesions were seen in 72 % of patients with an average age at diagnosis 25,3 years (2 – 60 y). AML occurred in 72,2%, bilateral RC - in 44,44%, while no RCC was observed. Both cysts and AML were significantly more frequent and more numerous in *TSC2* comparing with *TSC1*. Bilateral renal cysts were presented in 50% of all AML cases. TSC2 gene mutation was not more common in patients with combination of AML and renal cysts than in those with AML as would be expected. Two patients with bilateral AML underwent nephrectomy before systemic disease was suspected. Disease progression correlated with the age ($p<0.05$). Everolimus was introduced in 4 patients, 1 of them had TSC, 2 patients had TSC2 mutations and 1 was not genetically confirmed. Response to the treatment was successful in 89% at 6 months period and did not differ between different mutation types ($p<0.01$).

Conclusions: Renal involvement is high and significantly associated with genotype, TSC2 mutation has more severe manifestation. Everolimus showed effectiveness in reducing angiomyolipoma in all types of mutations.

FR-PO977

Metformin Ameliorates Kidney Injury of Tsc1ptKO Mice Through AMPK/AKT Pathway

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Background: As an intractable branch among chronic kidney diseases, tuberous sclerosis complex (TSC) in kidney usually expresses kidney enlargement, increasing cysts, interstitial fibrosis and serious damage on renal function. One of the critical mechanism underlies TSC is aberrant down-regulation of 5'AMP-activated protein kinase (AMPK) phosphorylation. Indicated by several researches, metformin showed excellent functions in reducing inflammation and inhibiting proliferation through AMPK phosphorylation, as well as decreasing the level of interstitial fibrosis. Therefore, we investigated whether metformin could induce the amelioration of kidney injury in TSC.

Methods: Firstly, we established the *Tsc1* knockout in proximal tubule ($Tsc1^{ptKO}$) mice model, which caused striking kidney growth. Then we performed metformin by intraperitoneal injection in $Tsc1^{ptKO}$ mice by 1 week of age for 1-3 weeks every day.

Results: We observed that metformin significantly reduced kidney growth in $Tsc1^{ptKO}$ mice by 4 weeks of age, with obvious shrunken kidneys size, decreased amount and size in cysts as well as obvious decline in proteinuria and serum creatinine level. Besides, immunochemistry showed metformin inhibited proliferation and induced apoptosis of proximal tubular epithelial cells in $Tsc1^{ptKO}$ mice, meanwhile reduced inflammation and interstitial fibrosis. The above alterations were induced by apparent AMPK phosphorylation under the influence of metformin, which was confirmed by immunoblotting and immunochemistry.

Conclusions: Altogether, these results proved the amelioration effect of metformin on the kidney injury of $Tsc1^{ptKO}$, which provides an innovative idea for clinical treatment on TSC and related kidney diseases.

FR-PO978

Proliferation of Intercalated Cells in Cystic Epithelium of Principal Cell-Specific Tsc1-KO Mice

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Background: Tuberous sclerosis complex (TSC) is a genetic disorder caused by inactivation of either TSC1 or TSC2 genes and affects multiple organs. In the kidney, TSC presents with development of angiomyolipomas and renal cysts, which lead to renal failure. Despite our knowledge regarding its genetics, little is known about the promotion of cyst growth and enlargement in TSC.

Methods: Mice with principal cell specific inactivation of Tsc1 (Tsc1 floxed mice crossed with Aqp-2-promoter driven cre mice) develop an increasing number of cortical cysts as they age.

Results: Single and double immunofluorescence labeling studies demonstrated that cyst epithelium is predominantly comprised of A-intercalated (IC) cells, as shown by strong expression of apical H^+-ATPase and pro-renin receptor (PRR). Cyst formation in Tsc1-KO mice is preceded by extensive areas of proliferation in the cortical collecting ducts (CCD), which are exclusively comprised of mitotically active (PCNA-positive) A-intercalated cells. This is distinct from a mouse model of ADPKD (Pkd1-KO mice), in which CCD-derived cystic epithelium contains numerous principal cells. Expression of Foxi1 transcription factor, a master regulator of intercalated cells and their acid base transport machinery, robustly increased in kidneys of young Tsc1-KO mice. Kidney cysts show mTORC1 activation in intercalated cells as determined by phosphorylation of p70-S6 kinase 1 (S6K1). Kidney cysts from humans with TSC display a similar preponderance of intercalated cells in their epithelium.

Conclusions: We propose that the robust proliferation and propagation of A-intercalated cells is crucial to kidney cystogenesis in Tsc1-KO mice. We further propose that unlike cysts in PKD, which respond to AVP antagonism by reduction in their fluid secretion and size, TSC1 cysts, which hardly contain any principal cells will be resistant to AVP antagonists. We suggest that the pathogenesis of kidney cyst formation and fluid secretion into the cyst in TSC is distinct from PKD, is associated with proliferation of intercalated cells and gradual disappearance of principal cells in cyst epithelium, is independent of AVP-receptor/ADH axis and is energized by H^+-ATPase and Pro-renin Receptor.

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FR-PO979

The C-Term of Human Fibrocystin Regulates STAT3-Dependent Transcription

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is the rare but severe form of PKD characterized by early fibrocystic renal alterations and congenital hepatic fibrosis. The disease is mainly caused by mutations in *PKHD1*, encoding the 4,074aa transmembrane protein Fibrocystin (FC). The molecular mechanisms leading to ARPKD and Fibrocystin's cellular function are poorly understood. Experimental and clinical data suggest that there may be partial overlap with pathomechanisms of autosomal dominant PKD.

Methods: We evaluated effects of the C-term of human FC on STAT3-dependent transcription and the SRC-STAT3 axis by applying standard techniques such as immunoprecipitation, immunochemistry and luciferase reporter assays.

Results: We identify a link of human FC to the regulation of STAT3-dependent transcription with activation of factor STAT3 in cyst-lining epithelial cells of ARPKD patient kidneys. Strikingly, a C-terminal truncation of FC negatively regulates SRC- and JAK2-dependent STAT3 activity and can be found in a common protein complex with SRC and JAK2. C-terminal FC also modulates SRC-dependent STAT3-activation after SRC-activation by forskolin-induced increased intracellular levels of cAMP. Mutation analyses point to a role of C-term FC in the activation of SRC.

Conclusions: This data is in accordance with recent observations that showed a beneficial effect of both SRC and STAT3 inhibitors in orthologous and non-orthologous rodent models of PKD. We present insights into potential molecular mechanisms by providing evidence for a regulation of the SRC-STAT3-axis by human C-terminal FC.

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FR-PO980

Human Urine Derived Renal Epithelial Cells Provide Insights into Kidney Specific Alternate Splicing Variants in NPHP3

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Background: The majority of multi-exon genes undergo alternative splicing to produce different mRNA transcripts and this may occur in a tissue-specific manner. Assessment of mRNA transcripts isolated from blood samples may sometimes be unhelpful in determining the pathogenicity of putative splice-site variants affecting kidney specific mRNA transcripts.

Methods: Here we present data demonstrating the power of using human urine derived renal epithelial cells (hUREC) as a source of kidney RNA. We report clinical and molecular genetic data from 3 affected cases from two families all with end stage renal disease by 15 years of age.

Results: In both families, heterozygous variants which are predicted to affect function in NPHP3 were found on one allele, in combination with a synonymous SNV (c.2154C>T; p.Phe718=, 18 base pairs from the exon-intron boundary within exon 15 of NPHP3. The only mRNA transcript amplified from wild type whole blood showed complete splicing out of exon 15. Urine samples obtained from control subjects and the father of family 2, who carried the synonymous SNV variant, were therefore used to culture hUREC and allowed us to obtain kidney specific mRNA. Control kidney mRNA showed normal splicing of exon 15 whilst the mRNA from the patient's father confirmed evidence of a heterozygous alternate splicing of exon 15 of NPHP3.

Conclusions: Analysis of RNA derived from hUREC allows for a comparison of kidney specific and whole blood RNA transcripts and for assessment of the pathogenicity of putative splice variants leading to end stage kidney disease.

FR-PO981

CD206 Positive Renal Resident Macrophages Are Associated with Cyst Progression in a Juvenile-Induced Cilia Mutant Mouse Model

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Background: Polycystic kidney disease (PKD) is one of the most common inherited genetic renal diseases. Abnormalities in the structure or function of primary cilia are one cause of kidney cyst growth in animal models of PKD and human patients, but the mechanism of how primary cilia regulate cystogenesis is largely undefined. Recent data suggests that macrophages are associated with cyst formation in PKD; however, the contribution of specific macrophage subsets in promoting renal cyst formation and how this is related to ciliary dysfunction and cyst progression is unknown.

Methods: To address the involvement of cilia and macrophage subtypes in cyst formation, our lab utilized an inducible cilia deletion mouse model by conditionally disrupting the *Ift88* gene. Macrophage populations were analyzed in both wild type and cilia mutant backgrounds as well as in human autosomal dominant PKD (ADPKD) patients with end-stage renal disease via immunofluorescence microscopy and flow cytometry at different time points following cilia loss.

Results: Our mouse data indicate that there is a predominant subset of renal resident macrophages expressing CD206 in juvenile WT mice and that the number of CD206+ macrophages decreases rapidly as the mice mature into adulthood. However, in conditional cilia deficient mice, induction of cilia loss in juvenile stages leads to persistently elevated numbers of CD206+ macrophages compared to control mice. Moreover, our data show that in the juvenile period the severity of cyst formation is associated with the time of cilia deletion. Early induction of cilia loss (e.g. P3), coincides with greater number of CD206+ macrophages and increased cyst severity compared to induction at later ages (e.g. P7). Preliminary analysis of kidneys from ADPKD patients shows increased numbers of CD206+ macrophages compared to normal human kidneys.

Conclusions: These data suggest that CD206+ macrophages are involved in renal cystogenesis in human patients and mouse models of renal cyst formation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO982

Clinical and Radiologic Features of Older-Age ARPKD Patients

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Background: Autosomal recessive polycystic kidney disease (ARPKD) presents classically in pediatric age, affecting primarily kidney and liver and constituting a frequent cause of ESKD in children. While its manifestations are well characterized and quantified in pediatric population, they are not so well established in adults.

Methods: To assess the disease burden in older patients (pts), we retrospectively analyzed the biometric, clinical, laboratorial and radiologic features in a case series of 12 ARPKD individuals with ≥16 years of age.

Results: This study included 7 male and 5 female pts, with median age of 22 years (19.0-34.5). Mean height and body mass index were 172.0±10.5 cm and 21.3±2.8 kg/m^2 in males and 160.2±6.4 cm and 20.9±3.9 kg/m^2 in females. Half of the pts were hypertensive, evenly distributed among the 6 cases in renal replacement therapy (RRT) and the 6 pts not in this therapy. RRT was initiated at 17.5±8.1 years, including 5 kidney transplants and 1 hemodialysis. Two pts (16.7%) developed nephrocalcinosis, 1 of them with associated nephrolithiasis. One pt underwent unilateral nephrectomy prior to kidney transplantation. Total kidney volume (TKV) was calculated in 8 pts for whom computed tomography or magnetic resonance imaging was available, showing a mean value of 575.6±540.4 mL. TKV did not correlate with RRT requirement (p=0.49). The 2 pts with shrunken kidneys were in RRT. Post-transplant native TKV (3-9 years of follow-up) displayed a trend of lower values compared to kidneys of nontransplanted pts [115.1 mL (50.5-337.8) *vs* 535.4 mL (396.2-1387.0); p=0.07]. Most of the 12 cases developed liver and/or portal hypertension-related manifestations, including hypersplenism (66.7%), esophageal varices (50%), Caroli syndrome (25%), and need of liver transplantation (8.3%). One pt died due to rupture of a basilar artery dolichoectasia, however no episodes of cholangitis were observed.

Conclusions: In addition to findings expected in older ARPKD pts, our analyses revealed relevant complementary information and brought interesting insights into ARPKD clinical reality. Our data suggest absence of growth deficit and lower frequencies of hypertension and cholangitis in older pts than reported for younger or broad-age pt populations. Moreover, kidney size tends to decrease after transplantation, reproducing findings obtained in autosomal dominant PKD.

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FR-PO983

A Cross-Sectional Characterization of Young Adult ARPKD Patients – Data from the ARegPKD Cohort Study

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Background: Autosomal recessive polycystic kidney disease (ARPKD) shows pronounced phenotypic variability. Although the classic phenotype is a severe disease of early childhood, a substantial number of ARPKD patients nowadays reaches adulthood and a minor proportion of patients is diagnosed with ARPKD in adulthood. Knowledge about clinical courses of adult patients suffering from ARPKD is scarce.

Methods: A cross-sectional analysis was performed on data sets of 45 adult patients with documented visits after their 18th birthday deriving from the international ARPKD cohort study ARegPKD.

Results: Median age at analysis was 21.4 (18.0-29.0) years, age at diagnosis 0.5 (-0.2-25.0) years. 53.3 % of patients are male. *PKHD1* was sequenced in 22/45 patients with a variant detection rate of 78%. One quarter of patients showed prenatal abnormalities. Most frequent symptoms at primary manifestation were extended abdomen with palpable tumor, arterial hypertension and urinary tract infection. One patient suffered from gastrointestinal bleeding at primary manifestation. 22 patients received 34 transplanted organs (median age at first transplantation 14.7 (2.4-42.8) years), with 7 patients receiving at least two transplantations. More than half of the young adults showed hepatomegaly, one third showed splenomegaly. Complications due to portal hypertension in form of varices were observed in one quarter of patients. 84.4% of patients received antihypertensive medication. At the timepoint of analysis renal function of native kidneys lies within CKD stages 1 to 3 in more than 50% of patients, 40.5% of patients received renal replacement therapy in their history.

Conclusions: Although ARPKD is classically a severe pediatric hepatorenal disorder, more and more patients reach adulthood. We describe a well-phenotyped cohort of young adult ARPKD patients setting a basis for the identification of clinical complications evolving in adulthood.

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FR-PO984

CRISPR-Mutant Organoids Identify Cystogenic Signal Pathways in the Early and Late Stages of Polycystic Kidney Disease

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Background: Human pluripotent stem cell (hPSC)-derived nephron organoids have significant potential for the development of targeted therapies for polycystic kidney disease (PKD). Previously, we generated heterozygous and homozygous *PKHD1* mutant hPSCs by CRISPR/Cas9 genome editing to establish autosomal recessive PKD (ARPKD) models in human cells. Following standardization to isogenic controls, here we identify cystogenic signal pathways of ARPKD for the potential development of novel therapeutics.

Methods: Following an identical differentiation protocol, nephron organoids were generated from heterozygous (*PKHD1*+/-, isogenic control) and homozygous (*PKHD1*-/-) mutants in 3D culture. Organoids were treated with and without forskolin, a cAMP inducer, and cyst formation was evaluated by bright field and fluorescent microscopy. Cell proliferation was assessed by Ki67 positivity in proximal (LTL+) and distal (CDH1+) tubule cells. RNA was isolated from organoids on differentiation day 35. RNA was amplified, fluorescently labeled, hybridized to a microarray (Toray, 3D-Gene® Human mRNA Oligo chip 25k), and signal pathway analysis was conducted using Metacore™.

Results: Gene expression analysis identified 1056 genes that differed by > 2-fold between heterozygous and homozygous mutants cultured without forskolin, the latter manifesting tubular dilatation (early cystic phase). Pathway analysis identified 50 signal pathways specific to the homozygous mutant in this early cystic phase ($p<0.01$), including the Rho kinase pathway known to induce loss of cellular polarity in PKD. Treatment with forskolin induced large cysts (late cystic phase) limited to homozygous mutants, which

display 1876 genes differing by > 2-fold compared to similarly treated isogenic controls. 96 signal pathways were identified as specific in the late cystic phase of the disease and included proliferative transcriptional phenotypes.

Conclusions: The CRISPR approach enabled generation of isogenic controls which differentiated into nephron organoids following an identical protocol. Global gene expression analyses identified 50 and 96 specific signal pathways in the early and late cystic phases of PKD, respectively, in comparison to an isogenic control. These signals may identify novel therapeutic targets for PKD at different stages of the disease.

Funding: NIDDK Support, Private Foundation Support

FR-PO985

Post-developmental Inactivation of Pkhd1 Results in Liver Cysts in Mice

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Background: Autosomal recessive polycystic kidney disease (ARPKD), caused by recessive mutations in the *PKHD1* gene, is a rare congenital disease characterized by diffusely cystic kidneys and hepatic fibrosis. We recently found genome-wide significant enrichment of adult heterozygous *PKHD1* carriers in our cohort of genetically unresolved autosomal dominant polycystic kidney and liver disease (ADPKD/ADPLD). ADPKD/ADPLD cysts originate when over time somatic second hit mutations in scattered cells result in the cellular recessive genotype. In order to explore the hypothesis that, like ADPLD cysts, cysts in *PKHD1* carriers could result from post-developmental biallelic loss, we used the Cre;Lox system to inactivate *Pkhd1* post-developmentally in mouse liver.

Methods: Using a $Pkhd1^{flox}$ allele, originally used to generate the $Pkhd1^{del3\text{-}4/del3\text{-}4}$ mouse model, we generated the following mice; $Pkhd1^{fl/fl}$;UBC-Cre (experimental, n=13) and $Pkhd1^{fl/+}$;UBC-Cre (littermate controls, n=12). All mice were induced with Tamoxifen at postnatal day 28 for 5 days and aged to 17 weeks. Liver and kidney histology was examined for cystic disease.

Results: Histological analysis performed on experimental (n=8) livers demonstrated polycystic livers with minimal pericystic inflammatory infiltrate, while "control" livers were normal. Anti-cytokeratin 19 (CK19) staining demonstrated the cysts were of biliary origin, consistent with both ARPKD and ADPKD mouse models, with significant increase in the CK19+ cell area percentage [6.1% (n=8) vs. 0.5% (n=8)] and cystic index [15.6% (n=8) vs. 3.0% (n=8)]. The mean liver weight to body weight ratio (LW/BW) for the $Pkhd1^{fl/fl}$;UBC-Cre animals was 5.8 ± 0.8% (n=13) versus 4.3± 0.6% (n=12) (P<0.0001). These data are comparable to $Pkhd1^{del4/del4}$, and within range of the ADPKD mouse model $Pkd1^{fl/fl}$;UBC-Cre with the same age and induction regime. Female mice had the most profound effect (LW/BW, 6.2± 0.4% vs. 3.8± 0.2%, n=5 females each). The $Pkhd1^{fl/fl}$;UBC-Cre kidneys appeared histologically normal.

Conclusions: Post-developmental inactivation of *Pkhd1* results in cystic liver disease indicative that *Pkhd1* after development is required for biliary epithelial homeostasis. This finding supports investigation of whether the human polycystic liver disease seen in *PKHD1* carriers may indeed fit the ADPKD/ADPLD mechanistic paradigm.

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FR-PO986

Pkd1-Pkhd1 Interaction During Embryonic Development via a Mitochondria-Dependent Mechanism

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Background: PKD occurs in autosomal dominant or recessive forms, caused by mutations mainly in *PKD1* (PC1) *or PKHD1* (FC) respectively. PC1 cleavage at the GPS motif is required for efficient ciliary trafficking and is frequently disrupted by *PKD1* mutations. Non-cleavable PC1 in $Pkd1^{V/V}$ knockin mice sufficiently maintains kidney structure during embryonic development, yet rapid cystogenesis in distal tubules (DTs), but not proximal tubules (PTs), ensues postnatally. The pancreas remains intact throughout the lifespan. *Pkhd1* mutants display negligible renal and pancreatic disease but show increased dilation in the renal DTs and pancreas in adult stages with heterozygous *Pkd1* deletion; yet early-onset cystogenesis was not detected.

Methods: We performed genetic studies using $Pkd1^{V}$ and *Pkhd1* mutant alleles to test for their interaction during development and the role of PC1 cleavage. To examine the role of *Pkhd1* in the interaction, we analyzed biochemical, morphological and subcellular characteristics of mutant kidneys by western blot, scanning electron and immunofluorescent microscopy.

Results: When combined with *Pkhd1* hypomorphic or null mutation, $Pkd1^{V/V}$ mice developed rapid renal cystic dilation, progressing from PTs to DTs, during embryonic development and die perinatally. Pancreas is also severely dilated with a single central lumen. Mitochondrial structural defects were observed in *Pkhd1* mutant kidneys. A FC C-terminal fragment translocated into mitochondria in cultured renal epithelial cells. Deleting this FC region caused PT cystic dilation and enhanced DT dilation in early postnatal $Pkd1^{V/V}$ mice.

Conclusions: *Pkhd1* inactivation triggers severe early-onset renal and pancreatic cystogenesis in the absence of PC1 cleavage. *Pkd1* and *Pkhd1* interact for regulating proper tubular structure of the two major organs during embryonic development. This interaction operates for uncleaved PC1 at a non-ciliary site and involves FC's C-terminus. *Pkhd1* mutation may confer a strong procystic state that significantly contributes to early-onset kidney and pancreas disease through its C-terminus by a mitochondria-dependent mechanism.

Funding: NIDDK Support

FR-PO987

Mice Lacking Pkhd1 Exons 3-67 Develop Biliary but Not Renal Abnormalities

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Background: Autosomal recessive polycystic kidney disease (ARPKD; OMIM 263200) is caused by mutations in *PKHD1* and is characterized by cysts/dilations in kidney collecting ducts, liver biliary cysts and portal fibrosis. While orthologous mouse models of ARPKD reproduce the liver phenotype, the kidney disease is mild, of low penetrance and strain-dependent. It was suggested that *Pkhd1* alternative splicing could compensate for the lack of full-length *Pkhd1*. Here we tested if genomic deletion of most of the *Pkhd1* locus could exacerbate the renal pathology.

Methods: We had previously generated two *Pkhd1* mouse models: $Pkhd1^{flox3\text{-}4}$, with loxP sites flanking exons 3-4; and $Pkhd1^{flox67HA}$, with loxP sites flanking the last exon (67). We bred mice carrying $Pkhd1^{del3\text{-}4/del67}$ alleles to Ddx4-Cre mice, a transgenic line with cre activity in embryonic germ cells of males and females. Starting with 6 independent $Pkhd1^{del3\text{-}4/del67}$ vs. Ddx4-Cre crosses, we obtained 9 heterozygous $Pkhd1^{del3\text{-}67}$ mutants, and started 4 independent founder lines, which were bred separately to homozygosis, generating a total of 28 $Pkhd1^{del3\text{-}67/del3\text{-}67}$ (4 to 12 per founder) with overlapping phenotypes. Subsequent generations were allowed to interbreed across founder-lines. A total of 84 $Pkhd1^{del3\text{-}67/del3\text{-}67}$ were harvested between 30 and 440 days at approximately 10-day intervals, and two animals were allowed to age to 620 days. Animal body, liver and kidney weights were measured; kidneys and livers were visually inspected. In a subset of samples we measured eye weight and embedded kidney, liver and eyes for histological analysis.

Results: None of the animals had abnormal kidney size or macroscopic appearance, and histologic analysis confirmed absence of dilated tubules. In contrast, all analyzed animals had some degree of liver pathology, characterized by biliary cysts, duct proliferation and variable degrees of periportal fibrosis and cholangitis. Large coledochal and pancreatic cysts, and ascitis were occasionally observed. Additional phenotypes included ophthalmic pathology.

Conclusions: Compensation by alternative splice variants cannot explain the mild kidney phenotype in orthologous ARPKD mouse models. Further studies are required to determine if *Pkhd1* or other sequences in the deleted genomic region are responsible for the additional unexpected phenotypes.

Funding: NIDDK Support

FR-PO988

Adult Inactivation of Pkhd1 Results in Liver Cysts in an ARPKD Mouse Model

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Background: Autosomal recessive polycystic kidney disease (ARPKD; OMIM 263200) is a severe disease of infancy and childhood caused by mutations in *PKHD1*. A common feature of both human disease and orthologous mouse models is biliary duct cysts with portal tract fibrosis, usually attributed to ductal plate malformation, a developmental disorder. According to this model, immature biliary ducts fail to remodel/involute during embryogenesis, leading to congenital fibrosis and biliary cysts. In this study we tested if adult loss of *Pkhd1* could result in biliary cysts and portal fibrosis in mature livers.

Methods: The $Pkhd1^{Tm1Ggg}$ ($Pkhd1^{flox3\text{–}4}$) mouse line was crossed to FLPeR mice expressing the FLP1 recombinase (stock 003946, Jackson Laboratories) to remove the neomycin cassette, since previous studies determined that uninduced mice developed liver lesions over time. The resulting $Pkhd1^{delneo.flox3\text{–}4}$ was bred to C57/BL6 tamoxifen-Cre (stock 004682, Jackson Laboratories). A set of 53 $Pkhd1^{delneo.flox3\text{–}4}$ mice with or without transgene cre expression (cre negative: 8 females and 8 males; cre positive: 15 females and 22 males) was induced at 40 days of age by one intraperitoneal injection of 0.2 mg/g tamoxifen and harvested between ages 100 and 328. An additional set of 29 mice was aged without being induced with tamoxifen (cre negative: 4 females and 7 males; cre positive: 9 females and 9 males). Animal body, liver and kidney weights were measured, and the kidney and livers were visually inspected. A subset of samples was embedded for histological analysis.

Results: Uninduced animals and induced cre negative mice had normal kidney and macroscopically normal liver morphology up to 300 days of age. Cre positive animals had enlarged livers with visible cysts starting on day 200 (n=7), progressively more affected with age. Expression of cre recombinase was a statistically significant determinant of liver cystic phenotype (p<0.001) in induced mice. No obvious kidney cysts were detected in any mice, and there was no statistical significance in kidney/body weight between induced animal with or without cre expression.

Conclusions: Adult inactivation of *Pkhd1* mimics germline inactivation in causing an ARPKD liver phenotype in a mouse model. This suggests that additional mechanisms, independent of ductal plate remodeling and involution, may play a role in the ARPKD polycystic liver.

Funding: NIDDK Support

FR-PO989

Fibrocystin-Deficient MDCKII Cells: Defective Control of Cell Adhesion and Polarity Blocks Epithelial Morphogenesis

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Background: Mutations of the *Pkhd1* genecause autosomal recessive polycystic kidney disease (ARPKD). *Pkhd1* encodes fibrocystin/polyductin (FPC), a very large, ciliary type I membraneproteinof mostly uncharacterized function, which is suggested to affect adhesion signaling of cells. Contributions of altered epithelial cell interaction to the disease process of ARPKD are not understood. Here, we propose a model wherein inadequate control of cell adhesion and centrosome positioning prevent formation (and homeostasis) of correctly polarized epithelia.

Methods: Based on *Pkhd1* silencing, we analyze FPC function in cells with renal collecting duct characteristics, Madin-Darby canine kidney cells (MDCKII). Cells are studied on micro-pattered chips in 3D cell culture conditions allowing analysis of polarity, lumen formation and ciliogenesis in epithelial spheroids. Quantitative automated image processing is applied to analyze z-stacks of 5-color fluorescence images. To determine critical differences in cell adhesion parameters, MDCK cells are studied also on chips in their 1-/2-cell stages. Activation of adhesion signaling is addressed based on phosphorylation of the FAK/Src axis.

Results: Using defined adhesion conditions, we quantified the impact of FPC deficiency on size / density of adhesion sites, cell shape characteristics and initiation of an apical surface. Effects on apicobasal polarity and lumen formation correlate significantly with positioning of centrosomes in 1-/2-cell stages, and activation of adhesion signaling. FPC-deficient cells reveal defects in the formation of correctly polarized epithelial spheroids, which are restored upon transient reduction of actomyosin contractility during the critical early phase of the morphogenesis assay.

Conclusions: Altered adhesion sensing and interaction of FPC-deficient epithelial cells lead to impaired epithelial morphogenesis and by implication homeostasis, which are suggested to lie at the heart of progressive epithelial defects in ARPKD. Closely controlled cell-based models with selective genetic alterations provide the means for a better molecular understanding and furthermore options to test pharmacological correction of epithelial defects.

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FR-PO990

Nuclear Complexes Containing FPC-CTD/Mcm3/Mcm5/STAT1 Define a Myc-Regulatory Pathway in Mouse with Implications for Renal Cystogenesis

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Background: ARPKD (MIM 263200) typically results from mutations in *PKHD1*. The intracellular C-terminal domain (FPC-CTD), encoded by exon 67, undergoes regulated membrane-release (Kaimori, 2007). Using single particle EM, we have shown that affinity-captured, natively-formed FPC-CTD nuclear assemblies integrate into DNA networks in ring-shaped structures reminiscent of known DNA-binding proteins (Harafuji, 2016). The current study was designed to examine FPC-CTD binding partners and their nuclear function.

Methods: Stable cell lines expressing V5-tagged FPC-CTD were generated; cell lysates fractionated on glycerol gradients; and immunoprecipitation (IP) were performed. Proteins were identified by mass spectrometry (IP-MS) and interactions confirmed by co-IP. Kidneys from ARPKD patients as well as the *Pkhd1*^{cyli}, *Pkhd1*^{del67}, *Pkhd1*$^{del3\text{-}67}$, *Cys1*^{cpk} mouse models were examined by RT-PCR, immunohistochemistry, and IB. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays were conducted using the *Myc* P1 promoter.

Results: IP-MS identified 34 proteins, including four members of the minichromosome maintenance protein complex (Mcm3, Mcm5, Mcm6, Mcm7). IP confirmed FPC-CTD-Mcm3, FPC-CTD-Mcm5, and Mcm5-STAT1 interactions. In FPC-CTD stable cell lines, *Myc* is upregulated. FPC-CTD binds to the P1 promoter (ChIP) and enhances *Myc* P1 promoter activity (luciferase assay). When compared to controls, we observed *Myc* overexpression in human ARPKD and *Cys1*^{cpk} cystic kidneys, but not in *Pkhd1*^{cyli}, *Pkhd1*^{del67}, or *Pkhd1*$^{del3\text{-}67}$ kidneys, none of which express cystic disease.

Conclusions: Trudel (2015) has proposed that *Myc* overexpression defines a causative pathway in renal cystic disease. In this study, we show that: 1) *in vitro*, FPC-CTD upregulates *Myc* expression; and 2) FPC-CTD nuclear complexes contain Mcm3/Mcm5. Mcm5 interacts with STAT1, which transcriptionally represses *Myc* expression (Ramana, 2000). Our data suggest a reciprocal mechanism in which FPC-CTD activates, while STAT1 represses *Myc* expression. This model may explain the lack of *Myc* upregulation in mouse kidneys with reduced or absent FPC-CTD. Given that the mouse and human FPC-CTD share only 41% identity, we speculate that there are species-specific differences in *Myc* translational regulation.

FR-PO991

Urinary Metabolic Profiling by NMR Spectrometry Associates with eGFR in a Cohort of Patients with ADPKD

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Background: With the advent of therapeutic options to slow the rate of disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD), there is an unmet need for biomarkers to select those at high-risk of rapid progression in the early stages of their disease. This study explored changes in the urinary metabolome associated with different chronic kidney disease (CKD) stages or estimated glomerular filtration rate (eGFR) in ADPKD, which is a first step towards identifying markers for early risk stratification.

Methods: Quantitative metabolic profiling (^{1}H NMR-spectrometry) was performed on spot urine samples obtained from 338 ADPKD patients with various CKD-stages, 84 healthy controls and 42 chronic, non-ADPKD, renal disease patients. Uni- and multivariate analyses were used to detect differences between the groups and associations between metabolic profiles and eGFR (CKD-EPI equation). Findings were validated in an independent cohort of 163 ADPKD patients.

Results: Twenty-nine urinary metabolites were quantified from the spectra. Logistic regression reliably distinguished ADPKD patients from healthy controls (AIC(DF 30,392)=185.7, $p=6\times10^{-46}$, $pR^2=0.70$; cross-validated AUC of 0.947 for CKD stage 1 in ADPKD). In patients with ADPKD, six metabolites were significantly decreased and seven significantly increased as compared to healthy controls, while metabolic profiling did not discriminate ADPKD from other renal diseases with comparable eGFRs. Sixteen metabolites correlated with eGFR in ADPKD patients, with the metabolite with the highest negative correlation having a pearson correlation coefficient of -0.72 ($p=5\times10^{-55}$) and the highest positive correlation of $r=0.66$ ($p<2\times10^{-16}$). A multiple linear regression model for eGFR was constructed based on all metabolite levels ($F(30,308)=39.95$; $p=5\times10^{-87}$, $R^2=0.79$). A much simpler model, however, based on the ratio of the two metabolites with the highest correlation only also served as a good predictor for eGFR ($F(2,336)=536.2$; $p=1\times10^{-71}$, $R^2=0.615$). Using the later model, the results were validated in a separate cohort ($F(30,133)=6.293$; $p=6\times10^{-14}$, $R^2=0.578$).

Conclusions: Quantitative NMR profiling enabled identification of urinary metabolic markers that distinguished ADPKD patients from healthy controls and markers that were also significantly associated with eGFR.

FR-PO992

Kidney-Targeting Nanoparticles for Drug Delivery in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive kidney cyst growth and leads to ESRD. Currently, one drug, tolvaptan has been recently FDA-approved to decrease cyst expansion, although repurposed drugs such as metformin and rapamycin used for diabetes and immunosuppression, have also been proposed. Unfortunately, these drugs suffer from short half-life, poor bioavailability, and adverse side effects. To mitigate these limitations, we describe the development of kidney-targeting multimodal micelles (KMs) that accumulate in the kidneys and can deliver therapy for ADPKD via oral administration.

Methods: KKEEE$_3$K is synthesized on an automated peptide synthesizer, and conjugated to DSPE-PEG2000. Metformin, cy7, and peptide amphiphiles are purified by HPLC and mass spectrometry. Upon micelle construction, nanoparticles were characterized by dynamic light scattering, transmission electron microscopy (TEM), and zeta potential. To assess therapeutic efficacy in vitro, mouse cortical collecting duct cells were treated with metformin-KMs and AMPK activation measured by immunoblotting against phospho-AMPK and ENaC current. Towards oral delivery of nanoparticles, KMs were encapsulated into chitosan nanocapsules to enhance mucoadhesion and passage through the GI tract.

Results: KMs and non-targeting (NT) micelles were found to have an average diameter of 15.0 and 12 nm, and zeta potential -7.8 and -1.4 mV, respectively. To test therapeutic effciacy, mouse cortical collecting duct cells incubated with 300 uM metformin-KMs showed enhanced activation of phospho-AMPK and decreased ENaC current compared to metformin-NT micelles or free metformin. Chitosan nanocapsules were developed by ionic gelation using sodium tripolyphosphate. TEM images showed chitosan particles were between 20-150 nm in diameter, which is large enough to encapsulate KMs. Current work includes investigating additional factors affecting chitosan particle size, stability, and mucoadhesive strength, such as deacetylation, molecular weight, and tri-methylation of chitosan, and assessing metformin-KM release kinetics, adhesion to CaCo-2 cells, and in vivo therapeutic studies in ADPKD mouse models.

Conclusions: Our approach is the first nanomedicine effort for ADPKD and will provide many new insights as well as potentially establish a novel therapeutic for ADPKD.

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FR-PO993

Kidney-Specific Targeting Using PLGA Nanoparticles in Polycystic Kidney Disease Mice

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Background: Drugs that slow cystogenesis in murine models may not show similar results in clinical trials, possibly due to the smaller dose used in humans to avoid systemic side effects. One way to improve the efficiency of the drugs in the kidney, without increasing the drug dose/risk for adverse effects, is kidney-specific drug delivery. Polymeric nanoparticles (NP) can encapsulate drugs and they are small enough in size which can freely filter through the glomerulus and be reabsorbed in the tubules, without potentially being taken up by extra-renal organs. The purpose of this study is to determine the bio distribution of NP in polycystic kidney disease (PKD) mouse.

Methods: Fluorescent coumarin-6 encapsulated poly(lactic-co-glycolic acid) (PLGA) biodegradable polymer nanoparticles were prepared by a double emulsion method with an average size of 124 ± 26nm, confirmed by scanning electron microscopy (SEM). PLGA-NP was administered via tail vein injection at the concentration of 50mg/kg to adult Pkd1 mice with moderate kidney cyst formation and control mice with no kidney cyst. Mice were sacrificed at 1, 4, 24, 48 and 72 hours after injection. Kidney, liver, heart, lung, and spleen were harvested and fixed for immunofluorescence and transmission electron microscopy (EM).

Results: Kidneys from both PKD and control mice revealed strong green fluorescent staining in the proximal tubules and in the arterial endothelium at 1 to 4 hour after injection, retaining its fluorescence at 24 hours and fading at 72 hours. There was PLGA-NP uptake in kidney cystic structures for both proximal and distal tubular cysts. PLGA NPs were present in the liver, heart, lung, and spleen early after the NP injections (1 to 4 hours) but diminished over time. The overall intensity of NP's in the extrarenal organs were significantly lower compared to the kidney. EM of kidney harvested at 24 hours revealed an intact NP structure in the cytosolic compartment of the tubular epithelium.

Conclusions: PLGA-NP in PKD mice were predominantly reabsorbed in the kidney tubules and cystic epithelia compared to extra-renal organs including the liver. PLGA-NP may have a role in kidney-specific drug delivery in PKD.

Funding: NIDDK Support

FR-PO994

A Bioinformatics Analysis of Gene Expression in Experimental Alport Syndrome Reveals an Fstl1 Signature in the Kidney

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Background: Alport syndrome (AS) is a rare inherited form of chronic kidney disease characterized by progressive nephropathy and the development of end stage renal disease. It is caused by mutations in the Col4a3, Col4a4, and Col4a5 genes. The goal of my studies is to better understand the pathogenesis of AS in the kidney.

Methods: We performed studies using a well-characterized experimental murine model of AS. Global gene expression profiling of renal cortical mRNA samples was performed in male Col4a3-/- mice and Col4a3+/+ control mice at 4 and 7 weeks of age to identify early differentially expressed genes. We performed a cluster analysis and constructed a heat map on the microarray studies at 4 and 7 weeks of age. Studies using HK2 cells were conducted to analyze inflammation and apoptosis related to a protein of interest and its cognate receptor. Finally, using a transgenic mouse model with a reduction in our protein of interest we performed UUO at 7 weeks of age.

Results: The microarray analysis revealed that only 5 genes were differentially expressed in the kidneys of male Col4a3-/- mice at 4 weeks of age compared to Col4a3+/+. Amongst these genes was Follistatin-related protein 1 (FSTL1). We used search tool for the retrieval of interacting genes/proteins to predict protein-protein interactions (PPIs) thereby identifying a functional protein association network for FSTL1. The network included 39 proteins. Cluster analysis of the cognate genes from the FSTL1 protein network showed marked upregulation of gene expression at 7 weeks of age. FSTL1 increased NFκB mediated luciferase activity, caspase 3 activation and PARP cleavage in HK2 cells. These effects were due, at least in part to TLR4 receptor activation. The RT-qPCR analysis of mice that were subjected to UUO surgery showed an increase in FSTL1 expression as well as an increase in the expression of FSTL1's cognate receptors compared to sham controls.

Conclusions: Our microarray and bioinformatics analyses identified early upregulation of FSTL1 in the kidneys of Col4a3-/- mice. A FSTL1 gene signature, based on predicted PPIs, emerged in the kidneys by 7 weeks of age. FSTL1 elicited an inflammatory response and activated apoptosis in HK2 cells. These findings support the hypothesis that FSTL1 may be a novel determinant of kidney injury in mice with experimental AS.

FR-PO995

Sparsentan, a Dual Angiotensin II Type 1 (AT1) and Endothelin Type A (ETA) Receptor Antagonist, Prevents Renal Disease in COL4A3 -/- Autosomal Alport Mice

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Background: Strain-mediated induction of endothelin (ET-1) in glomerular endothelial cells activates ET_A receptors on mesangial cells, initiating invasion of glomerular capillaries by mesangial filopodia. The filopodia deposit matrix in the glomerular basement membrane resulting in stimulation of NFκB activity in podocytes and expression of pro-inflammatory cytokines, culminating in glomerulosclerosis and interstitial fibrosis. Both ET_A receptor blockade and angiotensin-converting enzyme (ACE) inhibition have been shown to ameliorate these events in Alport mice. Therefore, we explored the ability of sparsentan to improve nephropathy in this model.

Methods: Alport mice were treated once daily with sparsentan (60 or 200 mg/kg given orally; n=3–4/group) or vehicle (n=4) from 3–7 weeks of age. Blood pressure (BP) and urinary protein/creatinine ratio (UP/C) were determined at the end of the study, together with determination of fibronectin and collagen 1 protein (COL1) immunohistochemistry (IHC) in kidney sections as an assessment of glomerulosclerosis and tubulointerstitial fibrosis.

Results: BP was not significantly different in Alport mice treated with sparsentan compared to vehicle at 7 weeks of age. Sparsentan led to significantly lower UP/C (60 mg: 5.6±3.0 mg/mg, n=4, $P<0.05$; 200 mg: 0.8±1.4 mg/mg, n=3, $P<0.01$) compared to vehicle-treated Alport mice (34.1±17.4 mg/mg, n=4). The percentage of sclerotic glomeruli, determined from fibronectin IHC was lower ($P<0.01$) in Alport mice that received sparsentan at 60 mg/kg (3.5±1.6%) or 200 mg/kg (1.4±1.3%) compared to vehicle-treated mice (39.0±19.5%). COL1 immunoreactivity was absent in sparsentan-treated Alport mice, similar to wild-type mice. In contrast, vehicle-treated Alport mice had a COL1 score of 2.5±0.6 (arbitrary units).

Conclusions: This preclinical study demonstrates that sparsentan, a dual ET_A and AT_1 receptor antagonist provides nephroprotection in Alport mice, in both glomerular and tubulointerstitial compartments. A further preclinical study is under way to explore the activity of sparsentan compared with ACE inhibition, the current standard of care in Alport renal disease.

Funding: Commercial Support - Retrophin, Inc., San Diego, CA

FR-PO996

Transcriptome-Based Discovery of Lysine Deacetylase Inhibition as a Novel Treatment Approach to Alport Syndrome

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Background: Alport syndrome (AS) is a hereditary progressive disorder caused by mutations in type IV collagen genes. It is characterized by early proteinuria and activation of the renin-angiotensin system (RAS). Few effective treatment approaches to AS are currently available. Therefore, we applied a drug repurposing strategy to examine a novel therapy.

Methods: RNA expression profiling of kidney cortices from *Col4a3*$^{-/-}$ (KO) and wild-type (WT) mice on a 129/SvJ background was performed at 4 and 7 weeks of age. A disease progression signature composed of differentially expressed genes was used to query the Connectivity Map (CMAP). CMAP identified vorinostat, a lysine deacetylase inhibitor, as a potential therapy. KO mice were treated with vorinostat (50 mg/kg/day in DMSO by oral gavage) from 4 to 7 weeks of age. Mice were euthanized at 7 weeks of age for kidney function, structure, inflammation, and fibrosis analyses. Separate groups were followed for assessment of lifespan. Finally, angiotensin II-stimulated human proximal tubule epithelial (HK-2) cells were treated with vorinostat (5 μM) and used to assess mechanisms of drug action.

Results: Vorinostat increased the acetylation of lysine in the kidney. This was associated with a significant increase in survival (n = 19/group) and a trend toward decreased serum creatinine and proteinuria (n = 6-10/group). Vorinostat had no effect on glomerulosclerosis, but significantly reduced urinary excretion of NGAL, a marker of tubular injury. mRNA for cytokines and kidney injury markers including *Fn1*, *Havcr1*, and *Tnf* were reduced in the kidneys of treated mice (n = 6/group). Kidney tissue protein analysis showed lowered αSMA and proinflammatory cytokine expression. Pilot mechanistic studies revealed that vorinostat exerts its beneficial effects, at least in part by, dampening mitogen-activated protein kinase (MAPK) signaling and subsequent activator protein 1 (AP-1) transcription factor activation.

Conclusions: CMAP analysis identified vorinostat as a novel therapy for AS. Testing of the putative therapy showed that it exerts renoprotective effects and extends the lifespan of KO mice. Future studies will provide more insight into the molecular mechanisms of vorinostat through assessment of lysine acetylation, and MAPK and AP-1 signaling pathways in the progression of AS nephropathy.

Funding: Government Support - Non-U.S.

FR-PO997

Urine and Blood Biomarkers Correlate with Rate of eGFR Decline in Alport Syndrome

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Background: Alport syndrome (AS) is a genetic condition leading to progressive glomerular disease and hearing loss in many affected individuals. This natural history study was performed to identify novel predictors of kidney function decline in patients with AS in order to populate future clinical trials with individuals at greatest risk of progressive kidney disease.

Methods: ATHENA (NCT02136862) was a non-interventional, global, multicenter study enrolling patients with CKD due to AS. Urine and plasma renal biomarkers and estimated GFR (eGFR) were assessed at baseline and every 12 weeks thereafter for up to 2 years. Pearson correlations of the GFR slope (provided at least 3 time points) with each baseline biomarker were derived. Statistical significance was based on FDR adjusted p-value <0.02.

Results: 165 individuals were enrolled (33.9% male, 64.8% X-linked, age mean 44.8 years, 83% white). Baseline mean eGFR was 63.9 (SD 21.6) ml/min/1.73m^2 and 24 urine protein was 1844mg (SD 2608). The median slope of eGFR was -2.35 ml/min/year. Higher serum albumin, protein, and CO2 correlated with a less negative slope of decline in eGFR. Higher urine albumin/cr ratio, urine protein/cr ratio, chloride, cholesterol, LDL cholesterol, and NGAL correlated with a more negative slope of decline in eGFR.

Conclusions: A number of urine and blood biomarkers correlate with short term rate of decline in eGFR in patients with AS. Multivariable models to predict slope of GFR decline using demographic and baseline biomarker data are in progress.

Funding: Commercial Support - Regulus Therapeutics

Correlation between baseline biomarker and slope of GFR

Biomarker	Correlation	FDR p-value
U Alb/Cr ratio	-0.40	<0.001
U Microalb/Cr ratio	-0.36	<0.001
U Prot/Cr ratio	-0.35	<.001
NGAL	-0.30	0.002
CO2	0.28	0.002
LDL Cholesterol	-0.29	0.002
Total Protein	0.28	0.002
Total Cholesterol	-0.27	0.005
Albumin	0.25	0.008
Chloride	-0.25	0.008
Cystatin c	-0.24	0.012

FR-PO998

Glomerular Endothelial Cell Identity and Contribution to CKD in Alport Syndrome

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Background: Many studies suggest that glomerular endothelial cell (GEC) injury plays a key role in the development of chronic kidney disease, but whether they contribute to pathogenesis and progression of Alport syndrome (AS) is not clearly established. In AS, a hereditary CKD characterized by the mutations in the collagen IVα3α4α5 protein, the major constituent of the glomerular basement membrane (GBM), we found morphological and biological alterations in GEC very early during disease progression and before the onset of heavy proteinuria. Thus, we hypothesized that in our model of CKD, GEC damage plays a key role.

Methods: To investigate our hypothesis we generated GEC specific (Tek-Cre driven) *td*Tomato reporter AS mice, harvested their glomeruli by the sieving method and isolated GEC by FACS. GEC were characterized and studied by flow cytometry analysis, PCR and WB at different time points along disease progression. GEC transcriptome profiling was performed by NGS on Illumina HiSeq 4000 and further analyzed by alignment of reads to Genecode M16 mouse genome. Differential gene expression analysis was performed post RUV normalization by BIOBASE and Ingenuity Pathway Analysis tools.

Results: We identified two unique subsets of endothelial cells within the glomerulus of WT mice, and for the first time also in AS mice, which might present different functional roles during AS progression. We showed a significant increase in endothelial fenestration size, loss of glycocalyx integrity and alteration of VEGF signaling in GEC, early during progression and before the onset of proteinuria in AS mice. In addition, we identified differentially expressed genes involved in the angiogenic, stress response and metabolic regulatory pathways such as VEGF, PPAR, and FATp4.

Conclusions: In sum, our data indicate that GEC injury is an important early event that sets the stage for further progression and onset of proteinuria in Alport mice. Characterization of the transcriptional profile of GEC in AS mice could lead to the development of targeted new therapies for the treatment of CKD.

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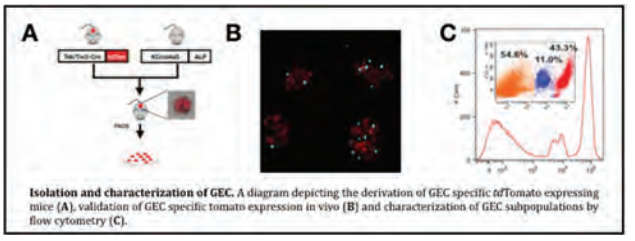

Isolation and characterization of GEC. A diagram depicting the derivation of GEC specific *td*Tomato expressing mice (**A**), validation of GEC specific tomato expression in vivo (**B**) and characterization of GEC subpopulations by flow cytometry (**C**).

FR-PO999

Factors Regulating the Severity in Male X-Linked Alport Syndrome: Study of 367 Cases

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Background: X-linked Alport syndrome (XLAS) is a hereditary disease caused by mutations of *COL4A5* gene. Affected males generally develop end-stage renal disease (ESRD) in early or middle adulthood. It has been reported some factors such as genotype or ACEI treatment affect renal prognosis. However, comprehensive analysis for the influence of factors regulating the severity using large-scale data has not been reported.

Methods: We conducted a retrospective study of 367 male patients in 231 families who were genetically diagnosed with XLAS at our institute. We collected clinical data from medical records and constructed renal survival curve. These curves were compared depending on the following differences in clinicopathological or genetic features; presence of hearing loss, findings of α5 staining positivity on glomerular basement membrane, treatment with ACEI/ARB and genotype. Regarding genotype, renal survival curve was constructed on not only each mutation type but also dividing all genotypes into two groups of truncating and non-truncating variants.

Results: The median age of our cohort was 12yrs. 149 cases reached ESRD and the median renal survival period was 33yrs. Ocular changes were detected in 6.1% and hearing loss was 34%. There was a significant difference in the median renal survival period between cases with (27yrs, n=94) and without hearing loss (55yrs, n=134) (P=0.0116), α5 staining positive (>60yrs, n=54) and negative (28yrs, n=75) (P=0.0052), treated by ACEI/ARB (43yrs, n=112) and not treated (28yrs, n=72) (P=0.0079). The median renal survival period of each mutation type was 18yrs (nonsense mutation, n=29), 21yrs (large rearrangement, n=14), 25yrs (splicing variant, n=57), 26yrs (small rearrangement, n=62) and 40yrs (missense mutation, n=196). In addition, there was a significant difference between cases with truncating (20yrs, n=102) and non-truncating variants (39yrs, n=241) (p<0.0001).

Conclusions: It was shown that the renal prognosis of male XLAS was regulated by various factors. In particular, treatment with ACEI/ARB dramatically improved renal prognosis. In addition, we also showed that the strong genotype-phenotype correlation was observed not only among mutation types but also, and for the first time, between cases with truncating and non-truncating variants.

FR-PO1000

Angiotensin-(1-7) Attenuates Renal Injury in Experimental Alport Syndrome

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Background: Angiotensin-(1–7) [Ang-(1–7)] antagonize the actions of the renin-angiotensin-aldosterone system via the Mas receptor and thereby has a renoprotective effects. Previously, murine recombinant angiotensin-converting enzyme (ACE) 2 has been reported to have renoprotective effects in experimental Alport syndrome but the effect of direct administration of Ang-(1-7) has not been studied.

Methods: To examine the effects of Ang-(1-7) on Alport syndrome, Col4a3 knockout mice, a model of Alport syndrome were used. Mice were divided into three groups: saline-treated wild type mice group, saline-treated Col4a3 knockout mice group, and Ang-(1-7) treated Col4a3 knockout mice group. Ang-(1–7) was continuously infused (25 μg/[kg×h]) using osmotic mini-pumps.

Results: Col4a3 knockout mice revealed increased α-smooth muscle actin (SMA) and fibronectin expression which attenuated by Ang-(1-7) treatment. Messenger RNA (mRNA) expression of α-SMA, fibronectin and Collagen I were suppressed by Ang-(1-7) treatment. Ang-(1-7) treatment alleviated the transforming growth factor (TGF)-β/Smad signaling. Ang-(1-7) attenuated protein expression of ED-1 and heme oxygenase-1, indicating the attenuation of renal inflammation. mRNA expression of inflammatory cytokine, TNF-α, MCP-1 and adhesion molecule ICAM-1, VCAM-1 were also decreased by Ang-(1-7) treatment. The ratio of cleaved caspase 3 to caspase 3 was increased in Col4A3 knockout mice kidney which was decreased by ang-(1-7) treatment, indicating attenuation of apoptosis by ang-(1-7). Lastly, ang-(1-7) influenced the alter the ACE2-Ang-(1-7)-Mas receptor axis, as it downregulated angiotensin-1 receptor and upregulated ACE2 and Mas receptor.

Conclusions: Thus, treatment with ang-(1-7) alter the ACE2-Ang-(1-7)-Mas receptor axis in the kidneys of Col4a3 knockout mice and attenuates the progression of Alport syndrome nephropathy.

FR-PO1001

Quality of Life Changes as Measured with SF-36 in Patients with Alport Syndrome: Results from the ATHENA Natural History Study in Alport Syndrome Patients

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Background: Alport Syndrome (AS) is a rare genetic disorder caused by mutations in genes coding for type IV collagen (COL4) α3, α4 and α5 proteins leading to hematuria, renal failure, hearing loss and eye involvement. CKD is associated with progressively worse quality of life (QOL) scores. The presence of a progressive genetic disease can also impact QOL. QOL in patients with AS has not previously been reported.

Methods: ATHENA (NCT02136862) was an international multi-center observational cohort study designed to characterize the progression of renal dysfunction in subjects with AS. Patients were followed for up to 24 months with serial evaluations. An SF-36 questionnaire was completed at baseline and every 24 weeks. The change in SF-36 score over time was modeled using mixed model repeated measures. The models incorporated baseline score, time in weeks, and subgroup indicators.

Results: 165 patients were enrolled. The study population is described elsewhere. For the entire cohort, the baseline score for physical component summary was 52.5; mental component summary was 49.7. Five domains decreased ($p<0.05$) during the study: general health, role limitations due to physical health, mental health, role limitations due to emotional problems and social functioning. The mental component summary was lower in females, those with X-linked mutations, and eGFR>60ml/min/1.73m^2. These three groups were more likely to have domain scores decrease with time. The only significant domain difference between subgroups was general health which was lower in females and those with eGFR>60 ml/min/1.73m^2.

Conclusions: In patients with AS, QOL scores using the SF-36 are low and decrease with time. Lower baseline eGFR is associated with lower QOL. Women, those with X-linked mutations and with eGFR>60 ml/min/1.73m^2 showed significantly greater decreases in QOL scores over time.

Funding: Commercial Support - Regulus Therapeutics

FR-PO1002

Identification of Novel Secretion-Defective Mutations of Type IV Collagen α5 Genes by Split NanoLuc-Based α345(IV) Trimer Formation Assay

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Background: Alport syndrome (AS) is a hereditary glomerular disease caused by a mutation in type IV collagen α3, α4, or α5 (α3/α4/α5(IV)), components of the glomerular basement membrane (GBM). Several hundred different mutations have been found in AS patients and the phenotype differs depending on the mutation. Generally, immunostaining of renal *biopsy* specimens for type IV collagen is useful for predicting prognosis; however, its invasiveness and incompleteness on the prediction accuracy are clinically problematic. Here, by utilizing the cell-based system to assess α345(IV) trimer formation (Omachi K., *et al., Cell Chemical Biology* **2018**), we evaluate the capability of α345(IV) trimer formation of several α5 missense mutants that are clinically relevant but poorly understood.

Methods: Split nanoLuc-fusion α3/ α5 and α4 were transfected into HEK293T cells, and luminescence was assessed in the cell lysate for intracellular trimer and in culture media for secreted trimer. Scatterplot analysis of the intracellular/secreted RLU ratio from cells expressing the WT or several α5 missense mutants classifies the character of mutants.

Results: Trimer formation assay revealed that *G509R, G805R, G953V, G1000V, G1030S, G1140V, G1143S* α5 mutants have normal properties of intracellular trimerization (>98%) and extracellular secretion (>65%). Scatterplot analysis showed that most of the mutants (*G509R, G805R, G953V, G1143S*) with mild phenotype (no obvious proteinuria) showed the similar pattern as the WT, while some mutants (*G1000V, G1030S, G1140V*) exhibited secretion-dependent defect. Particularly, *G1140V* with severe phenotype (obvious proteinuria) showed significantly increased intracellular accumulation of trimer (>130%).

Conclusions: Trimer formation assay reveals that three α5 mutants (*G1000V, G1030S, G1140V*) had defect in secretion. Because patient with *G1140V* mutation had relatively severe clinical phenotype, our system may, at least in part, reflect genotype-phenotype correlation. Further phenotypic characterization would also be needed for *G1000V* and *G1030S* mutations. Moreover, because adjacent mutations *G1140V* and *G1143S* had severe and mild phenotypes, respectively, structure and molecular bases on differential phenotypes is now under investigation.

Funding: Government Support - Non-U.S.

FR-PO1003

Human NOS1AP Recessive Mutations Impair Podocyte Filopodia Formation and Cell Migration and Cause Steroid-Resistant Nephrotic Syndrome Through CDC42 Dysregulation

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. Mutations in >39 genes provide a monogenic cause in up to 29.5% of SRNS cases (*JASN* 26:1279, 2015) with defined pathomechanisms (*NDT* 31:1802, 2016) including dysregulation of the small GTPase CDC42 (Ashraf *Nat Commun* 2018, in press).

Methods: Whole exome sequencing (WES) was performed in ~500 SRNS subjects to discover a novel genetic cause. IF was performed on rat kidney sections. In a human podocyte cell line, we performed active-CDC42 ELISA, live cell imaging as well as shRNA-mediated downregulation and cDNA over-expression of *NOS1AP*.

Results: We identified homozygous recessive mutations in 2 unrelated children with SRNS in *NOS1AP* (c.428G>A; p.C143Y and c.345-3T>G; p.I116Afs*4). *NOS1AP* encodes an adaptor protein that interacts with nitric oxide synthase (NOS) and with NOS effectors through its phospho-tyrosine binding domain (PTB) (*Neuron* 28:183, 2000). The C143 residue within the PTB is conserved to *C. elegans* and in 85/101 human PTB sequences and registered strong *in silico* conservation scores. The c.345-3T>G coding change is predicted to reduce splicing, cause skipping of exon 5, and result in the truncation p.I116Afs*4. Both mutations are not observed, even heterozygously, in the gnomAD Genome Aggregation Database. NOS1AP is expressed selectively in podocytes, not endothelial or mesangial cells, of rat kidney glomeruli. Transfection of wild-type *NOS1AP* induced filopodia in 58% of immortalized human podocytes, while *NOS1AP* constructs containing SRNS subject mutations failed to generate filopodia. *NOS1AP* shRNA-mediated knockdown reduced podocyte migration. This was rescued by wild-type *NOS1AP* over-expression but not by *NOS1AP* mutants. Active CDC42 levels, which promote filopodia and migration (*Curr Opin Cell Biol* 36:103, 2015), were induced by wild-type *NOS1AP* but not by patients' mutants. Induction of filopodia by *NOS1AP* over-expression was inhibited by CDC42 chemical inhibitor CASIN.

Conclusions: We discovered recessive *NOS1AP* mutations as a novel monogenic cause of SRNS, leading to podocyte dysfunction through CDC42 dysregulation.

Funding: NIDDK Support, Private Foundation Support

FR-PO1004

2,4-Dihydroxybenzoic Acid Improves Survival and Demonstrates a Renoprotective Effect in a Podocyte-Specific Coq8b-Knockout Mouse Model of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease (ESRD) within the first three decades of life, requiring dialysis or transplantation for survival. Human mutations in the *COQ8B* gene (known also as *ADCK4* - aarF domain containing kinase 4) cause SRNS (Ashraf *JCI* 123:5179, 2013). To study the function of *COQ8B* in podocytes we generated a podocyte specific *Coq8b*-knockout mouse model

Methods: *Nphs2.Cre* mice were crossed with *Coq8b$^{lox/lox}$* mice, to generate podocyte specific *Coq8b* knockout mice (*Coq8b$^{\Delta Podocyte}$*) on a C57BL/6 background. Treatment with 2,4-dihydroxybenzoic acid (2,4-diHB) at 25 mM in the drinking water was started at 3 months of age. Kidneys were harvested for histological and ultrastructural analysis at 9 months in the untreated cohort and at 13 month in the cohort under treatment. Blood and urine were collected monthly for metabolic studies

Results: *Coq8b$^{\Delta Podocyte}$* mice displayed onset of proteinuria at 4 months. Non-treated *Coq8b$^{\Delta Podocyte}$* mice displayed a significant reduction in survival (40% alive) being moribund at 12 months of age progressing to ESRD (n=15). In contrast, *Coq8b$^{\Delta Podocyte}$* mice treated with 2,4-diHB (n=12) showed significantly improved survival (100% alive), comparable to their untreated *Coq8b$^{\Delta Podocyte}$* and wild type littermates. Histological analysis of *Coq8b$^{\Delta Podocyte}$* kidneys at 9 months demonstrated severe global and focal segmental glomerular sclerosis (FSGS) with extensive interstitial fibrosis and tubular atrophy. Electron microscopy studies revealed severe foot process effacement and disturbed podocyte cell morphology. In contrast, treatment of *Coq8b$^{\Delta Podocyte}$* mice with 2,4-diHB significantly reduced the levels of proteinuria and prevented the development of FSGS as well as foot process effacement maintaining normal renal function in treated mice at 13 months (n=12)

Conclusions: Our data demonstrate that 2,4-diHB, metabolite that functions to bypass the hydroxylation step mediated by Coq7 of the CoQ_{10} biosynthesis pathway efficiently ameliorates proteinuria and prevents FSGS in *Coq8b$^{\Delta Podocyte}$* mice. Further, our study reveals a potential novel treatment option in 2,4-diHB for human SRNS caused by dysfunction in the CoQ_{10} biosynthesis pathway

Funding: Other NIH Support - DK076683

FR-PO1005

GAS2L2 as a Candidate Gene for Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) inevitably progresses to end-stage renal disease (ESRD) within the first three decades of life requiring dialysis or transplantation for survival. To date discovery of more than 50 different monogenic causes of SRNS has helped to elucidate the pathogenesis of SRNS.

Methods: To identify novel mongenic causes of NS, we performed whole exome sequencing, homozygosity mapping, and targeted exon sequencing. To investigate molecular mechanisms of a newly identified monogenic cause of NS *in vitro*, we generated immortalized human podocyte cell lines with stable knockdown of the *GAS2L2* gene.

Results: By next-generation sequencing, we identified a homozygous recessive missense mutation in a region of high evolutionary conservation (*Drosophila melanogaster*) within the GAS2 domain of *GAS2L2* gene (c.817C>T, p.Arg273Cys) in a patient with early onset NS. *GAS2L2* is a known linker between actin filaments and microtubules. We show that GFP-*GAS2L2* localizes to the cytoskeleton filaments and that knockdown of *GAS2L2* results in severe defect of podocytes migration rate.

Conclusions: We discovered a recessive mutation of *GAS2L2* as a likely novel monogenic cause of early-onset SRNS. We propose that the disease phenotype is caused by defect of crosstalk between actin filaments and microtubules.

Funding: Other NIH Support - DK076683

FR-PO1006

Recessive Mutations in the Kirrel Gene in Human Nephrotic Syndrome (NS)

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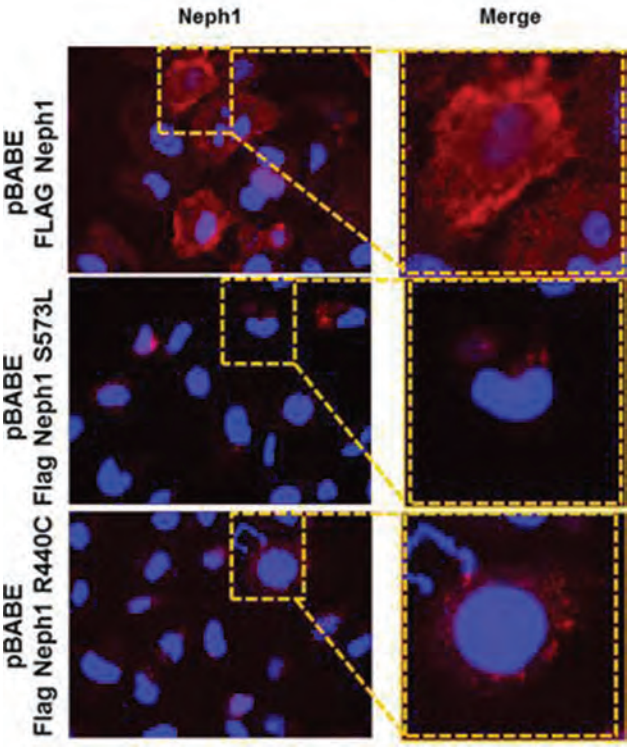
Background: Steroid-resistant nephrotic syndrome inevitably progresses to end-stage renal disease within the first three decades of life requiring dialysis or transplantation for survival. Podocyte proteins Neph1 and Nephrin form a critical structural framework of a functional glomerular filtration barrier. While many mutations in the Nephrin gene have been described, there are no reports of human mutations in the *Neph1/Kirrel* gene associated with the NS.

Methods: To identify novel monogenic causes of NS, we performed whole exome sequencing. To investigate the molecular mechanisms of a newly identified monogenic cause of NS *in vitro* we generated stable podocyte cell lines expressing human wild-type and mutant Neph1. IF studies were performed for localization defects for *Neph1* mutants. *Neph1* knockdown in podocytes using specific shRNA was performed to evaluate the effect of *Neph1* depletion on cell proliferation and migration.

Results: Using next-generation sequencing, we identified two homozygous recessive missense mutations in two unrelated families with NS, which were in a region of high evolutionary conservation (*Danio rerio*). Immunofluorescence studies revealed that unlike WT *Neph1*, both *Neph1* mutants failed to localize at the podocyte cell membrane (**Fig 1**). Additionally, we find an increased accumulation of these proteins in endosomes suggesting defective localization, which may contribute to the disease phenotype. Further, these mutant cell lines formed impaired tight junctions as evaluated by the permeability assay using labeled BSA.

Conclusions: This is the first report showing mutations in the *Kirrel* gene in FSGS patients.

Funding: NIDDK Support



IF showing reduced localization of mutant Neph1 proteins at the podocyte cell membrane

FR-PO1007

Mutations of NEK3, PREX1, or TIAM1 Are Novel Causes of Nephrotic Syndrome

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Background: Nephrotic syndrome (NS) is a heterogeneous group of disorders characterized by gross proteinuria with hypoalbuminemia and edema. The identification of >55 single-gene causes provided new insights into the pathogenesis of NS, linking Rho-like small GTPases to podocyte function.

Methods: We performed whole exome sequencing (WES) to identify novel monogenic causes of NS in >1,000 individuals with NS.

Results: We identified 4 different recessive mutations in 3 different genes *NEK3*, *PREX1* and *TIAM1* in 4 unrelated families with NS. Specifically, in a family of two siblings (F754) with steroid-sensitive NS, we identified a homozygous truncating mutation, N209Kfs*21 in *NEK3* (*NIMA Related Kinase 3*), which is known to be activated by prolactin stimulation, leading to phosphorylation of the GEF-VAV2 and thereby activation of the Rac1-GTPase. Accordingly, by coimmunoprecipitation, we demonstrated that NEK3 interacts with VAV1, VAV2 and EDH2 proteins. The mutated NEK3 protein showed stronger binding affinity with VAV1 but abrogated the interaction with EHD2. Coimmunofluorescence staining of NEK3 in developing rat kidney sections (P1) showed that NEK3 localizes to the cytoplasm of podocytes. Additionally, we discovered mutations in *PREX1* (family F1070, M1546T [Hom], conserved to *D. rerio*) and *TIAM1* (family F1287, R23C [het] and A163V [het], both conserved to *D. rerio*; family F1, p.R23C [Hom]). We thereby identified *PREX1* and *TIAM1* as two novel GEFs for Rac1 that are relevant for podocyte function.

Conclusions: We have identified mutations of *NEK3*, *PREX1* and *TIAM1* as novel causes of NS. Our findings confirm that Rho-like small GTPase signaling in podocytes can cause NS.

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FR-PO1008

Mutations in 4 Diaphanous Related Formins as Novel Causes of Nephrotic Syndrome

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Background: Nephrotic Syndrome (NS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. Identification of >55 monogenic genes that cause NS if mutated (Vivante et al, *Nat Rev Nephrol*, 12:133, 2016), has rendered first insights into disease mechanisms of NS. Diaphanous Related Formins (DRF) regulate actin polymerization and bundling, and have a role in directing microtubules, filopodia and lamelipodia formation. Mutations in the DID domain of the Formin gene, *INF2*, have been shown to cause NS (Brown, Nat Gen, 42:72, 2010).

Methods: To identify novel monogenic causes of NS we performed whole exome sequencing (WES) in a worldwide cohort of ~600 individuals with NS.

Results: In 5 unrelated patients with early onset NS, we discovered recessive mutations in the following 4 DRF encoding genes: A homozygous mutation in *DIAPH1* (individual B1678, p.Gln1098Leu). Gln1098 is part of the DIAPH1 actin nucleating domain, FH2. A hemizygous mutation In *DIAPH2* (B2506, p.Arg1075Trp). Arg1075 is part of the basic region ('RRKR' sequence) of the DAD domain and is critical for auto-inhibition by binding to the DID domain. From the crystal structure of mDia1 we predict that the mutation would interrupt the DID-DAD interaction. In *DIAPH3* we found mutations in two individuals with NS (A1938 p.Thr431Ala, homozygous, and F983 p.Asn346Ser; p.Arg28His compound het.). Thr431 is located in a loop between alpha helix 1 and alpha helix 2 of the predicted dimerization domain. In the crystal structure, Asn346 is in the DID domain and within the DAD-binding site, thus the Asn346Ser substitution is predicted to alter DID-DAD binding. Furthermore, we found a mutation in *DAAM2* (individual B1068, Ala335Gln, homozygous). Ala335 is located in the DID domain of DAAM2. All mutations are deemed disease causing by SIFT, MutTaster and PolyPhen2 prediction programs. All variants are absent hemizygously or homozygously from the gnomAD database.

Conclusions: We here discovered mutations in the DRF encoding genesDIAPH1,2,3 and DAAM2 as 4 potential novel monogenic causes of NS. Crystal structure analysis predicts disruption of the interacting domains DIA- DAD and of the interaction of FH2 with actin as the underlying mechanisms.

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FR-PO1009

Recessive Mutations of LAMA3 Cause Nephrotic Syndrome

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Background: Integrin α3β1 represents the major podocyte integrin heterodimer. *Itga3* knock out mice have severe defects in podocyte growth and differentiation, and in glomerular basement membrane organization (Kreidberg Development 122:3537, 1996), and *ITGB4* mutation causes nephrotic syndrome (NS) in humans. In the glomerular basement membrane, integrin α3β1 is the main receptor for laminins, which are heterotrimers composed of laminin subunits α5 (*LAMA5*) or subunits α3 (*LAMA3*), β2 (*LAMB2*) and g1 (*LAMC1*). Monogenic mutations in two laminin genes have been identified to cause NS in humans, including *LAMA5* (Braun NDT, in press 2018) and *LAMB2* (Zenker Hum Mol Genet 13: 2625, 2004). In additional *LAMA3* knock out mice have abnormal glomerulogenesis (Abrass KI 70:1062, 2006).

Methods: To identify additional monogenic causes of NS, we performed whole exome sequencing in a cohort of 600 families with pediatric NS under a recessive model.

Results: In 3 families, in whom mutation in the 55 known monogenic genes of NS were excluded, we identified 3 different homozygous mutations in the gene *LAMA3* as likely causative for NS. In family B149 with congenital NS, we detected the mutation p.S1359A (homozygous, conserved to *X.tropicalis*). In A2069 2 siblings with steroid dependent NS, we detected the mutation p.T2527I (homozygous, conserved to *G.gallus*). In A2563 with steroid sensitive NS, we detected homozygous truncation mutation p.E1354*.

Conclusions: We here identified *LAMA3* as a new candidate gene for pediatric NS.

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FR-PO1010

Rare Variants in PLCG2 in a Large Cohort of Multi-ethnic Children With Nephrotic Syndrome

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Background: We have previously shown that variants in *PLCG2* are associated with the development of SSNS in a cohort of South Asian children. PLCγ2 is an essential signaling component of leukocyte driven adaptive immunity and inflammation. Therefore, we hypothesized that *PLCG2* variants are associated with pattern of response to corticosteroid therapy in NS and variability in prevalence of NS across ancestries/ethnicities.

Methods: We performed high throughput next generation targeted sequencing of *PLCG2* in a multi-ethnic cohort of 583 children with the nephrotic syndrome. Identified variants that are likely to have effects on gene function (missense, stop codon, frameshift, and obligatory splice site variants) were compared with presumed controls in the gnomAD database. Additionally, we analyzed specific *PLCG2* variants and their association with steroid therapy response (SSNS vs SRNS) and ancestry (European, African, Asian) in our cohort.

Results: We identified 10 distinct variants that are associated with NS in our multi ethnic cohort, most of which were associated with SSNS (majority with $p<0.001$). One of the variants (N174H) is novel, i.e. absent from all public databases. Seven of the variants are predicted to be pathogenic by *in silico* analysis and one occurs at an obligatory splice site (Q838). The variants associated with SSNS are grouped tightly in the EF-hand domain that is predicted to affect calcium binding and in the autoregulatory region, a region that is linked to increased PLCγ2 activity and inflammation. Variant burden was associated with disease in patients with European or Asian ancestry but not in those of African ancestry.

Conclusions: Rare variants in *PLCG2* are associated with NS and may predict the pattern of response to therapy. The clustering of variants in specific PLCγ2 regulatory domains suggests that these variants are important in the pathogenesis of NS and pattern of response to therapy. Furthermore, this data indicates that SSNS-associated variants in PLCG2 may alter calcium-dependent inflammation signaling.

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FR-PO1011

ER Stress Induced by Dysregulated PI3K/AKT/mTOR Signaling Drives Increased Apoptosis in Podocytes Expressing the Human FSGS-Causing ANLN R431C Mutation

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Background: We previously reported that mutations in *ANLN* cause familial forms of focal segmental glomerulosclerosis (FSGS). Anillin is a F-actin binding protein that modulates podocyte cell motility and interacts with the phosphoinositide 3-kinase (PI-3K) pathway through the slit diaphragm adaptor protein CD2A-associated Protein (CD2AP). However, it is unclear how $ANLN_{R431C}$ causes the FSGS phenotype. We hypothesized that the R431C mutation exerts its pathogenic effects by uncoupling ANLN from CD2AP and inducing aberrant PI3K/AKT signaling.

Methods: To understand the cellular effects of $ANLN_{R431C}$, we performed *in vitro* functional assays using human podocyte cell lines stably expressing $ANLN_{WT}$ or $ANLN_{R431C}$.

Results: We found that $ANLN_{R431C}$ increased cell migration ($p=0.001$), enhanced cellular proliferation ($p=0.001$), and apoptosis ($p=0.029$) relative to $ANLN_{WT}$ cells. Biochemical characterization of these dysregulated phenotypes revealed hyperactivation of the PI-3K/AKT/mTOR/Rac1 signaling axis and activation of mTOR-driven ER stress in $ANLN_{R431C}$ podocytes. Podocyte hypermotility, hyperproliferation, and ER stress-induced apoptosis were ameliorated by inhibition of mTOR, GSK-3b, Rac1, or calcineurin (Cn). Additionally, we found that endogenous ANLN and mTOR expression are regulated by the Cn/NFAT pathway suggesting that the benefits derived from calcineurin inhibition in FSGS may be due, in part, to the suppression of endogenous anillin and mTOR protein levels.

Conclusions: The $ANLN_{R431C}$ mutation causes multiple derangements in podocyte function through hyperactivation of PI-3K/AKT/mTOR/p70S6K/Rac1 signaling. These studies illustrate that rational therapeutic targets for familial FSGS can be identified through biochemical characterization of dysregulated podocyte phenotypes.

Funding: NIDDK Support

FR-PO1012

Splicing Assay with Hybrid Minigene: Assessing Pathogenicities in COL4A5 Intronic Mutations

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Background: X-linked Alport syndrome is a congenital renal disease caused by mutations in *COL4A5*. In recent years, splicing is focused on as the origin of pathogenicity and the target of treatment. But the effect and mechanism of aberrant splicing caused by intronic mutations of *COL4A5* are not fully established. To assess the splicing abnormalities arising from intronic mutations of *COL4A5*, we conducted this research.

Methods: We conducted functional splicing assay with hybrid minigene for 7 intronic mutations in *COL4A5* (1 was found in our case and 6 were in reported cases shown on the Human Gene Mutation Database). In addition, we conducted *in silico* analysis using HSF (http://www.umd.be/HSF3/HSF.shtml) and SVM-BP finder (http://regulatorygenomics.upf.edu/Software/SVM_BP/) to predict and assess the mechanisms for aberrant splicing.

Results: The minigene assay showed exon skipping by 4 variants, exon skipping+10bp insertion by 1 variant and no change by 1 variant. For 1 variant, it was difficult to assess the splicing pattern by some reason and our assay did not work. Among 3 of them, the patients' transcript analyses were conducted and the results were completely consistent with our *in vitro* assay results. *In silico* analysis revealed that in 3 variants, polypyrimidine tracts were weakened and in 2 variants, dramatic change in splicing regulation elements binding sites were observed.

Conclusions: Our splicing assay with hybrid minigene make it possible to assess whether the mutation cause aberrant splicing. In addition, *in silico* tools can assess the mechanisms for causing aberrant splicing. Our findings may help the discovery of treatment strategy.

FR-PO1013

Genomic Analysis of Focal Segmental Glomerulosclerosis in Thailand

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Background: Focal segmental glomerulosclerosis (FSGS) has currently been found to be caused by mutations in at least 62 genes. Recently, next generation sequencing has provided a robust tool to identify its causative genes. Mutational spectra of various populations are usually different. We sought to identify causative variants in Thai patients with FSGS.

Methods: Patients aged one year or older with biopsy-proven FSGS without clinical and laboratory evidence of secondary causes were included in this study. DNA samples, pedigree and clinical information were obtained. Mutation analysis was performed by whole exome sequencing (WES) method. Patients were screened in 62 known genes formerly reported to cause FSGS. Exome data were interpreted using Variant Interpreter and the American College of Medical Genetics and Genomics (ACMG) criteria. Patients without causative mutations identified by WES will be analyzed by trio study to determine pathogenicity in variant of uncertain significance. New gene may also be discovered by trio study.

Results: WES identified the pathogenic variants in two out of 24 unrelated patients (8.3%) with biopsy-proven FSGS. A novel c.905del (p.G302Vfs*23) in exon 15 of the *COL4A4* gene resulting in frameshift was detected in one patient. Mutations in *COL4A4*, encoded collagen type 4 alpha 4, are responsible for autosomal dominant Alport's syndrome, revealing the fact that this patient was previously misdiagnosed as idiopathic FSGS. Another patient harbored a novel c.357+1G>A mutation in exon 3 in the *ZMPSTE24* gene, which encoded zinc metallopeptidase. *ZMPSTE24* mutations are found to be associated with mandibuloacral dysplasia, an autosomal recessive musculoskeletal disorder in which some patients developed FSGS. In addition to FSGS, our patient also had jaw malocclusion. Although we could identify only one mutant allele in *ZMPSTE24* in the patient, it remains possible that the other mutant allele could not be detected by WES.

Conclusions: Using WES, we successfully identified disease-causing variants in only 4.2% of patients with FSGS. To date, this is the first study in Thailand for genetic approach toward diagnosis of FSGS which could provide more accurate disease management and counseling. An appropriate testing algorithm is needed for developing future Thai guideline.

FR-PO1014

Genetic Alterations in Familial Focal Segmental Glomerulosclerosis

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Background: The phenotypic variability observed in focal segmental glomerulosclerosis (FSGS) patients bearing mutations in the same gene suggests that modifier genes may impact renal presentation and outcomes. We investigated genetic alterations observed in inherited adult FSGS patients.

Methods: We analyzed 172 unrelated patients with biopsy proven idiopathic FSGS including familial (n=46) and non-familial (n=126) cases. Genetic sequencing, either whole exome sequencing (n=32) or a targeted gene panel (n=14), was performed on these 46 index patients with family history of kidney disease. Variants were included if: minor allele frequency <0.01 (recessive) or <0.001 (dominant); loss of function mutation or missense with CADD score ≥15; not seen as homozygotes in any control databases; amino acid residue conserved through evolution in multicellular organisms. Variant interpretation was done using the ACMG guideline.

Results: The median age of onset [29 (12-48) vs 35.5 (3-73) years] was significantly earlier in patients with familial FSGS compared to non-familial cases (p=0.004). The median follow up in months after diagnoses was similar between familial [38 (2-276)] and non-familial [42 (1-235)] cases (p=0.86). During follow-up, ESRD progression was higher in familial cases (21/46, 45.7%) compared with non-familial cases (22/126, 17.5%) (p<0.001). We identified a pathogenic genotype in 26 out of 46 familial cases. Thirteen individuals were explained by heterozygous (7/46, 15%) or homozygous/hemizygous/compound heterozygous (6/46, 13%) collagen IV gene (*COL4*) mutations. Thirteen individuals (13/46, 28%) were explained by mutations in the documented or recently proposed FSGS genes with or without a concurrent *COL4* mutation [*NPHS2* hom (n=2), *NPHS2* hom/*COL4A5* hem (n=1), *ADCK4* hom (n=2), *NUP107* hom (n=1), *SCARB2* hom (n=1), *TRPC6* het (n=1), *LMX1B* het (n=1), *ARHGAP24* het/*COL4A3* het (n=1), *ABCA6* hom/*COL4A4* het (n=1), *LAMA5* hom/*COL4A4* het (n=1), *PALLD* hom/*COL4A5* het (n=1)].

Conclusions: Collagen IV gene mutations explain a significant fraction of familial FSGS in our population. In a limited number of patients with parental consanguinity carrying pathogenic genotype in podocyte-related genes, *COL4* mutations were also found. Further analysis of the phenotype in patients with this co-inheritance could shed light on variations in phenotype in familial FSGS.

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FR-PO1015

Loss of Podocyte-Specific SGPL1 Results in Albuminuria and Focal Segmental Glomerulosclerosis in Hypertensive Mice

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Background: Steroid-resistant nephrotic syndrome (SRNS) often manifests as focal segmental glomerulosclerosis (FSGS), has no efficient treatment, and carries a high risk of relapse after transplant. Inactivating SGPL1 mutations cause a familial form of SRNS, but the cellular and molecular mechanisms are unknown. SGPL1 encodes sphingosine phosphate lyase (SPL), an enzyme responsible for the irreversible degradation of sphingosine-1-phosphate (S1P). S1P is a bioactive lipid that ligates to a family of G protein-coupled receptors (S1PRs) whose signaling regulates cell survival, migration and immune cell trafficking. Because whole body SGPL1 knockout mice die in the perinatal period, and most monogenic causes of SRNS result from recessive or dominant mutations in genes localized to the podocyte, we focused on podocyte-specific SGPL1.

Methods: We generated conditional knockout mice lacking SGPL1 expression in podocytes (SPL^{Podo_KO}). Hypertension was induced in wild-type (WT) and SPL^{Podo_KO} mice by nephrectomy, implanted osmotic minipumps releasing angiotensin II (AngII, 1.2 μg/kg/min), and 1% NaCl in the drinking water. Blood pressure was measured by tail-cuff, 24-hr-urine was collected, and kidneys harvested at 4 weeks for histology. SPL-deficient cultured human podocytes were generated by CRISPR/Cas9, assayed for S1P levels, and treated with AngII. Autophagy was assayed by Western blotting of LC3A-I and -II.

Results: SPL^{Podo_KO} mice had no spontaneous phenotype. Compared to WT mice (n=6), hypertensive SPL^{Podo_KO} mice (n=8) had elevated albumin-to-creatinine ratio (ACR g/g) (2.7+/-1.8 vs 0.5+/-.1 at 2 wks and 8.1+/-5.7 vs 1.93+/-3.7 at 4 wks; both P<0.05). In addition, the % glomerulosclerosis in hypertensive SPL^{Podo_KO} was more than double than WT mice (1.51+/-0.71% vs 0.70+/-0.21%; P<0.05). In vitro studies revealed undetectable SPL expression and activity and sphingolipid accumulation in SGPL1-KO vs WT human podocytes. In addition, SGPL1-KO human podocytes showed increased autophagy with AngII exposure, indicating increased sensitivity to injury.

Conclusions: We found that SPL^{Podo_KO} mice are profoundly sensitive to glomerular stress, indicating a prominent role for this signaling pathway in FSGS. Therapeutic targeting of S1P signaling, such as with the S1PR antagonist FTY720, which is already FDA approved for use, may be beneficial.

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FR-PO1016

Modeling of FSGS in Podocin R138Q Knock-in iPSC-Derived Human Organoids

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Background: The recent development of iPSC derived human kidney organoids has opened the possibility to study human kidney physiology and pathophysiology in a differentiated, three-dimensional human experimental system in vitro. Organoids are an attractive approach to study genetic causes of human kidney diseases, such as FSGS. However, due to the fact that organoids are thought to represent second trimester human kidneys and due to lack of vascularization and urine flow, whether they can be used as a model system of human kidney diseases remains uncertain.

Methods: To explore whether FSGS can be reproducibly modeled in human iPSC-derived organoids, we generated CRISPR/Cas9-engineered podocin R138Q knock-in iPSCs and developed a protocol for their successful differentiation into human kidney organoids. The human podocin R138Q mutation was chosen in this proof-of-concept study because this variant causes FSGS with early disease onset and rapid progression to end-stage renal disease in patients and homologous R140Q causes FSGS in knock-in mice.

Results: Here we present a thorough characterization of R138Q organoids at the structural, molecular, cellular and pathophysiological level. We also present data on the phenotypic changes resulting from the treatment of organoids with pharmacologic agents.

Conclusions: We conclude that using iPSC-derived organoid technology is a promising tool for modeling human kidney disease, as it empowers ongoing drug discovery for genetically defined FSGS.

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FR-PO1017

A Novel Heterozygous Missense Mutation of Wilms' Tumor 1 May Cause FSGS Through Dysregulated Expression of ARHGAP24

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Background: Mutations of the transcriptional regulator Wilms' Tumor 1 are most commonly associated with syndromic disease but some mutations have been shown to cause renal-limited disease. We previously reported a novel heterozygous missense mutation (Exon 9; p.R458Q) of Wilms' Tumor 1 that caused non-syndromic autosomal dominant FSGS in two Northern European kindreds. We now report a second novel WT1 mutation (Exon 8; p.R443G) as a cause of non-syndromic autosomal dominant FSGS in a 3-generation kindred from North-Central India.

Methods: Direct sequencing, lentivirus-mediated WT1 expression, immunoblot, immunofluorescence imaging, electrophoretic mobility shift assay (EMSA) and apoptosis assays.

Results: A novel heterozygous missense mutation of WT1 (Exon 8; p.R443G) was identified by direct sequencing of the proband and an affected cousin in a North-Central Indian kindred with non-syndromic FSGS. An autosomal dominant pattern of inheritance was suggested by male-to-male transmission across three generations of the family. Substitution of the highly conserved arginine residue at position 443 was considered damaging by *in-silico* prediction. The R443G mutation impaired DNA-binding by EMSA and distorted the secondary structure of the transcription factor DNA-binding domain by *in-silico* modeling. WT1 was previously identified as a potential regulator of *ARHGAP24*; a known FSGS gene that regulates podocyte cytoskeletal dynamics and survival through modulation of Rac1 activity. ARHGAP24 protein expression was significantly upregulated in $WT1_{R443G}$ podocytes (p=0.003; n=3) relative to $WT1_{WT}$ podocytes. Consistent with the increase in ARHGAP24 expression, $WT1_{R443G}$ podocytes exhibited decreased motility (p=0.01; n=3) and increased apoptosis (p=0.04; n=5) accompanied by a significant decrease in STAT3 phosphorylation at Ser727 (p=0.02; n=3); a Rac1-mediated prosurvival post-translational modification. These findings suggest that WT1 functions as an inhibitor of *ARHGAP24* expression and the R443G mutation impairs this inhibitory effect.

Conclusions: The novel $WT1_{R443G}$ mutation causes non-syndromic FSGS. The mutation induces an upregulation of *ARHGAP24* expression and increases podocyte apoptosis probably through decreased Rac1-mediated prosurvival signaling.

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FR-PO1018

The LMX1βR246Q Mutation Induces Podocyte Injury Through Dysregulation of Cholesterol Transport Gene Expression

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Background: We previously reported a heterozygous missense mutation of the LIM Homeobox Transcription Factor 1 Beta (LMX1β) as a cause of nail-platella-like renal disease (NPLRD) in two families with hereditary FSGS. Currently, there are no targeted therapies for $LMX1\beta_{R246Q}$-induced glomerulopathy. We hypothesized that $LMX1\beta_{R246Q}$ disrupts the expression of disease-relevant molecular targets within key signaling pathways that may be amenable to pharmacotherapy. To test this hypothesis, we performed an unbiased, whole-transcriptomic analysis in our established $LMX1\beta_{WT}$ and $LMX1\beta_{R246Q}$-overexpressing podocyte lines to uncover potential therapeutic targets.

Methods: We conducted RNA-seq, qPCR, immunoblot, cholesterol efflux assays and apoptosis assays in our established $LMX1\beta_{WT}$, $LMX1\beta_{R246Q}$- and VIVIT overexpressing podocytes to evaluate the effect of the $LMX1\beta_{R246Q}$ mutation on cholesterol transport gene expression, cholesterol efflux and viability.

Results: Using RNA-seq, we determined that $LMX1\beta_{R246Q}$-overexpressing podocytes express significantly reduced levels of ATP-binding Cassette Transporter Family A1 (*ABCA1*) and *ABCG1* relative to $LMX1\beta_{WT}$-overexpressing podocytes. These results were confirmed by qRCR. Protein expression of ABCA1 and ABCG1 was similarly reduced. Consistent with these findings, $LMX1\beta_{R246Q}$-overexpressing podocytes displayed significantly increased lipid droplet accumulation, decreased basal and Apo-AI-stimulated cholesterol efflux and increased apoptosis relative to $LMX1\beta_{WT}$-overexpressing podocytes. Evaluation of the putative promoter regions for ABCA1 and ABCG1 revealed no LMX1β binding sequences (i.e. FLAT-E or FLAT-F) but did reveal multiple candidate NFAT binding sequences. $LMX1\beta_{R246Q}$-overexpressing podocytes displayed decreased NFAT4 expression and ABCA transporter expression was decreased in VIVIT-overexpressing podocytes.

Conclusions: The $LMX1\beta_{R246Q}$ mutation may cause FSGS, in part, through the dysregulation of NFAT-dependent lipid trafficking gene expression. This study provides the first demonstration of a potential role for impaired lipid trafficking in the pathobiology of familial FSGS and suggests that lipid depleting therapies may have a role in the treatment of some forms of familial FSGS.

Funding: NIDDK Support, Private Foundation Support

FR-PO1019

Interstrain Variation in Severity of Nephropathy and Immunoglobulin Levels in HIV-1 Transgenic Mice

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Background: We studied the genetic and immunological determinants of nephropathy in HIV-1 transgenic (Tg) mice, a model that displays the clinical and molecular signatures of collapsing FSGS. On the FVB/NJ background over 80% of the Tg-FVB mice develop significant glomerulosclerosis; however F1 hybrids with other inbred strains of mice demonstrate variable penetrance from completely resistant to highly sensitive.

Methods: Tg-FVB mice were crossed with 12 different inbred strains of mice to generate F1 hybrids. At 8 weeks of age, we evaluated the severity of nephropathy by histology, analysis BUN, and serum IgA and IgG. Urine was analyzed for proteinuria, hematuria and NGAL.

Results: Three stains (A/J, C3H/HeJ, and DBA/1J) were highly sensitive to the Tg resulting in severe glomerulosclerosis, 4 strains (129S1/SvImJ, C57BL6/J, C57BL6/NJ, and CAST/EiJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 5 strains (CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HlLtJ and WSB/EiJ) had intermediate glomerulosclerosis. Preliminary analysis of the laboratory strains of mice indicated that the MHC haplotype b was associated with limited to no glomerulosclerosis. The glomerulosclerosis score correlated with the presence of casts, interstitial fibrosis and tubular atrophy, interstitial inflammation, proteinuria, elevated plasma BUN, and decreased plasma IgG concentrations. To determine if there were baseline differences between the 12 wildtype F1 hybrid mice, IgA, IgG and BUN plasma concentrations were determined. Significant differences were observed in the BUN (ANOVA p-value = 0.014), IgG (ANOVA p-value = 0.016), and highly significant differences were observed in plasma IgA (ANOVA p-value = 0.0022), between the groups of mice. No kidney pathologywas observed in the wildtype F1 hybrid mice.

Conclusions: Our data demonstrates differences in the immunoglobulin levels and BUN in the steady state of 12 different F1 wildtype strains of mice. The MHC b haplotype was associated with reduced penetrance of nephropathy. Future studies will include additional inbred stains of mice and GWAS analysis, to confirm findings and identify additional immunological and genetic influences.

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FR-PO1020

Precise Modeling of NUP93 Highlights Downstream Pathways

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Background: Variants in nuclear pore complex components, including *NUP93*, cause steroid resistant nephrotic syndrome (SRNS), but underlying mechanisms are not understood. *NUP93* null mutations are likely to be lethal. Genetic validation and investigation requires tools to link genetics to cellular function. Conventional methods in immortalized podocytes fail to model non-null variants under physiological promotors, and are limited by transfection resistance. To better mimic human disease we applied CRISPR/Cas9 to model a *NUP93* variant.

Methods: Lentivirus was used to generate human podocytes constitutively expressing Cas9 and introduce guide sequences. Motility was assessed by scratch assay. 150 bp PE polyA RNA-Seq (HiSeq4000) was analysed in R, fitting a quasi likelihood generalised linear model with edgeR.

Results: Lentiviral podocyte CRISPR is efficient, disrupting 43% of alleles, 98% after single cell selection. We modeled a homozygous mutation in exon 13 of *NUP93*, identified

in a child with SRNS. Edited podocytes had NUP93 protein but reduced motility. We performed RNA-Seq on NUP93, wildtype and two Wilms Tumor 1 (WT1) podocyte lines. WT1 requires cofactor translocation; the WT1 transcriptomes clustered, but were distant from NUP93, suggesting NUP93 is not essential for WT1 function. Comparing NUP93 to wildtype, 3011 genes were significantly differentially expressed. Gene ontology analysis highlighted cell cycle, proliferation and interferon signalling. Highly overexpressed genes included *ID2*, which regulates proliferation and is repressed by SMAD4. Since NUP93 facilitates SMAD4 nuclear transport, this suggests a pathway.

Conclusions: Lentiviral CRISPR efficiently induces mutation in immortalized podocytes, providing a new technique for genetic manipulation of this cell line. Using this approach we modeled human SRNS disease due to aberrant NUP93 and highlight potential downstream targets.

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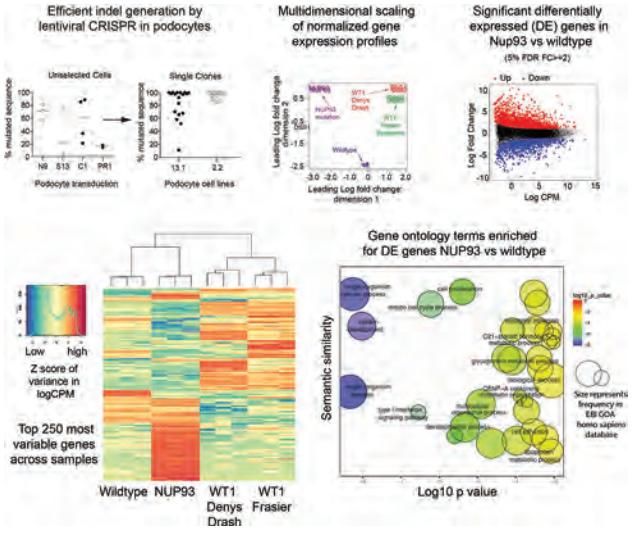

FR-PO1021

Ablation of PFN1 Expression Causes Proteinuric Disease

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Background: Understanding the pathobiology of glomerular diseases is paramount as it accounts 80% of end stage kidney disease cases in the US. Recent reports have identified human mutations in INF2 to cause proteinuric disease leading to loss of F-actin stress fiber formation in podocytes. Our study focused on an INF2 interactor Profilin 1(PFN1), a protein involved in the elongation of F-actin fibers. Despite the discovery of reduced PFN1 expression in microdissected Diabetic Kidney Disease(DKD) patient glomeruli, the function of PFN1 in podocytes is unknown. To investigate the role of Pfn1 in podocytes we studied diabetic mice, generated podocyte specific Pfn1 knockout mice and used CRISPR-Cas9 to knockout PFN1 in cultured human podocytes.

Methods: Glomeruli from the DKD model, db/db, were isolated using dynabeads. Analysis for RNA and protein were performed. Podocyte specific *Pfn1* knockout mice were generated and phenotyped. Purified primary podocytes were isolated from *Pfn1*KO mice by breeding to the Terminator mouse. CRISPR-Cas9 mediated PFN1 knockout (*PFN1*KO) cultured human podocytes were generated and analyzed.

Results: Pfn1 expression is reduced in glomeruli from db/db mice compared to controls. To understand the role PFN1 in podocytes, podocyte specific *Pfn1* knockout(*Pfn1*KO) mice were generated. *Pfn*1KO mice demonstrated progressive albuminuria starting at 3 weeks($p<0.05$) and severe kidney failure ($p<0.05$) leading to morbidity and mortality by ($p<0.05$) by 9 weeks of age. Histological analysis revealed increased mesangial expansion (PAS staining, $p<0.05$) and progressive interstitial fibrosis/proteinaceous casts (Trichrome Staining, $p<0.05$) by 6 weeks of age. Ultrastructural analysis revealed podocyte foot process effacement and vacuole-like structures which was recapitulated by similar structures in *PFN1*KO cultured human podocytes. Primary mouse *Pfn1*KO podocytes and *PFN1*KO cultured human podocytes revealed a significant reduction in ability to spread and migrate ($p<0.05$).

Conclusions: Our data suggest that loss of podocyte *Pfn1* expression is sufficient to cause podocyte injury, identifying PFN1 as an essential regulator of podocyte function and maintenance. These data support further identification of PFN1 regulatory targets in podocytopathies.

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FR-PO1022

Elucidating Transport Kinetics of Risk-Variant APOL1 Through the Secretory Pathway Helps to Understand Molecular Mechanism of Kidney Cell Toxicity

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Background: APOL1 is an innate immunity factor circulating on HDL particles, forming cation specific channels in African trypanosomes that lead to ionic imbalance and osmotic lysis. When endocytosed by the parasite, APOL1 undergoes a necessary acidification followed by neutralization upon recycling to the plasma membrane. G1 and G2 variants of APOL1 protect against human-infective trypanosomes but increase the risk of kidney disease. Within a human cell, APOL1 traffics along the secretory pathway, which is acidified at the golgi followed by neutralization at the plasma membrane. We show that the trafficking kinetics of G2 and non-risk G0 are similar as they travel along the secretory pathway. We also find that APOL1 is membrane-bound within the cell and is not secreted out.

Methods: Stably transfected FlpIn Trex HEK 293 cells were generated expressing the cDNA of APOL1 variants under a tet-inducible promoter. Soluble proteins were separated from membrane-bound proteins through subcellular fractionation. Cells were collected at different time points to analyze intracellular APOL1 localization. Organelles were separated using mechanical lysis and sucrose gradient ultracentrifugation. Protein co-localization with organelles was analyzed via Western blot. Toxicity was measured by quantifying LDH release. Culture media was immunoprecipitated to pull down APOL1.

Results: Subcellular fractionation showed APOL1 co-localizing in membrane-bound fractions. Sucrose gradient separation of organelles revealed that the majority of G0 and G2 APOL1 localized to the plasma membrane within 10 hours of induction of expression. Unlike G0, the G2 variant leads to cell swelling followed by cell lysis. No APOL1 secretion was detected in the media of cells expressing any of the variants.

Conclusions: We report that there is no secretion of G0 or G2 APOL1 into the media, indicating that the toxicity is related to intracellular localization of G2. There appears to be no distinction between G0 and G2 APOL1 in relation to their trafficking through the secretory pathway to the plasma membrane. However while both associate with the membrane fraction, G2 is toxic to cells but G0 is not, hinting to a hypothetical chaperone or regulatory mechanism that G2 evades, allowing for ion channel formation.

FR-PO1023

A Modifier Genetic Screen for APOL1 in Drosophila Nephrocytes Identified Potential Therapeutic Targets That Rescue the Renal Toxicity of APOL1

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Background: African Americans are at higher risk for developing chronic kidney diseases due to APOL1 risk alleles (RA), but the treatment is lacking. We generated a *Drosophila* model of APOL1 nephropathy by expressing APOL1-G1 in nephrocytes, which share striking similarities with podocytes. APOL1-G1 expression in nephrocytes led to loss of renal function and cell death, providing a platform to identify genes that modifies APOL1 renal toxicity.

Methods: We designed and performed a modifier genetic screen for APOL1 in *Drosophila*, by crossing thousands of transgenic RNAi lines to a master line that carries four transgenes: a nephrocyte-specific driver (Dot-Gal4), a nephrocyte function readout (MHC-ANF-RFP), a marker (Hand-GFP) and the UAS-APOL1-G1 over a balancer chromosome. We examined and compared the effects of silencing each individual gene in nephrocytes, with or without APOL1-G1. We also used a human kidney cell line to validate our findings.

Results: We identified ~20 genes (out of ~1000) that could modify the APOL1-G1 toxicity in nephrocytes. Silencing of these genes alone in nephrocytes did not generate a phenotype, but the toxicity was increased in a synergistic manner together with APOL1-G1, suggesting that these genes could antagonize APOL1-G1 toxicity when over-expressed. We therefore generated transgenic lines to over-express these genes in nephrocytes. We discovered that two of these genes, when over-expressed with APOL1-G1, could rescue the functional defects of nephrocytes caused by APOL1-G1 expression. We further tested these two genes in a human kidney cell line, and found that they encode proteins that co-localize and directly bind to APOL1. Furthermore, expression of these two genes in human kidney cells significantly rescued the cell death caused by APOL1-G1 expression.

Conclusions: Our findings suggest that the *Drosophila* genetic screen can be used to identify modifier genes for APOL1 renal toxicity. Our data suggest that an evolutionarily conserved genetic network mediates the renal toxicity of APOL1-RA. Using *Drosophila* genetic screen and cultured human kidney cells, we discovered two genes that antagonize the renal toxicity of APOL1-G1 in both fly nephrocytes and human kidney cells, as potential therapeutic targets for APOL1 nephropathy.

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FR-PO1024

pH-Dependent Channel Formation by APOL1: Gateway to Toxicity?

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Background: African variants of apolipoprotein L-I (APOL1) are strongly associated with kidney disease among African Americans. APOL1 variants are cytotoxic when expressed in human cells, a property which is associated with the formation of pH-dependent cation fluxes across the plasma membrane. This cation flux is likely mediated by APOL1 itself as recombinant APOL1 forms pH-gated cation-selective channels in planar lipid bilayers that are similarly affected by pH. Here we show that APOL1 of baboons also forms a cation-selective conductance in planar lipid bilayers, but that this conductance is largely unaffected by pH. We identify two human APOL1-specific residues - tyrosine-351 and glutamate-355 - that combine to produce channel closure at acidic pH and opening at neutral pH.

Methods: We utilized human-baboon APOL1 chimeras and site-directed mutagenesis to identify residues involved in pH gating. Recombinant proteins were produced in *E. coli* and incorporated into planar lipid bilayers using established techniques.

Results: Similar to baboon APOL1, a human-baboon APOL1 chimera containing the C-terminal 46 residues of baboon APOL1 produced channels that remained open at acidic, as well as neutral pH. This effect could be entirely replicated with the single change of tyrosine-351 for its baboon-specific counterpart glycine, but was only partially recapitulated by the more conservative tyrosine-351 for phenylalanine substitution. A single substitution of human APOL1 glutamate-355 for the uncharged glutamine also abrogated pH gating.

Conclusions: We propose that under acidic conditions the bulky side-chain of Tyr-351 is positioned to effect channel closure. Upon pH neutralization Glu-355 becomes negatively charged, allowing for displacement of Tyr-351 and for channel opening to occur. Investigations are currently underway to determine if mutation of channel gating behavior affects the toxicity of APOL1 when expressed in human cells.

FR-PO1025

Changing the Channel: Mutational Analysis of APOL1 Reveals Structural Insights Impacting G1 and G2 Associated Kidney Disease

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Background: The human innate immunity factor Apolipoprotein L-1 (APOL1), is a cation selective channel that protects against African Trypanosomes. The channel has two putative transmembrane domains, requires acidification for activation, and opens upon subsequent neutralization. Natural variants of APOL1, G1 and G2, have been recognized as risk factors for kidney disease. Investigating the structure of APOL1 would assist in identifying mechanisms of channel formation responsible for kidney cell toxicity caused by the G1 and G2 variants.

Methods: Recombinant APOL1 (rAPOL1) was purified from *E. coli* BL21-DE3-RIPL cells expressing the pNIC-28 vector. The effects of single and multiple amino acid substitutions were first tested for trypanolytic activity, followed by channel formation and ion selectivity in planar lipid bilayers. Blue Native PAGE of APOL1 expressing FlpIn TREX 293 cells along with SDS-PAGE of rAPOL1 was performed to visualize oligomers of the APOL1 channel. Protease protection assays of rAPOL1 channels in LUVs were used to ascertain orientation and channel transmembrane domains via silver stain and mass spectrometry.

Results: At acidic pH, rAPOL1 G0 is a non-ideal cation channel. Substituting amino acids in the second predicted transmembrane domain not only inhibited *in vitro* trypanolytic activity, but also altered channel conductance and cation selectivity. Changes in the leucine zipper motif at the C-terminus abolished rAPOL1 activity *in vitro* and in planar lipid bilayers. Mutations within the C-terminus, that retain trypanolytic activity, indicate that rAPOL1 is an oligomer as a functional channel. Furthermore, oligomers of APOL1 have been visualized by Blue Native PAGE from the TREX 293 cells upon release from the ER. Fragments of the digested rAPOL1 channel protected by LUVs designate orientation and transmembrane regions.

Conclusions: These findings reveal that APOL1 requires oligomerization to form a functional channel, which is driven by residues in the C-terminus. In addition, we identified specific amino acids in the second transmembrane domain that govern cation selectivity.

FR-PO1026

APOL1 (G0) Confers Protection from HIVAN by Facilitating Parietal Epithelial Cell (PEC) Transition to Podocytes (PD)

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Background: The majority of HIV infected Africans carrying APOL1 risk alleles develop HIVAN if not treated with antiviral therapy. On the contrary, HIV infected Africans as well as Caucasians carrying APOL1 wild-type (G0), rarely develop HIVAN. We hypothesize that APOL1G0 facilitates PDs renewal by PECs, thus allowing replenishment of HIV-induced podocyte loss, whereas, PECs expressing APOL1G1 or APOL1G2 are not able to complete the transition and accumulate into Bowman's space.

Methods: To aim transition (differentiation) to PDs, immortalized human PECs were incubated in special media for 14 days. PEC- transduced with either Vector or HIV (NL4-3) were assayed for APOL1 expression. To determine the role of APOL1, differentiated PECs were transduced with Vector, APOL1G0, APOL1G1, or APOL1G2 lentivirus. After 48 hours, cellular lysates were probed PEC (PAX2 and Claudin 1) and PD (CD2AP, WT1, α-actinin, and podocalyxin) markers. To determine the role of APOL1-miR193a axis, cellular lysates of above-mentioned transduced cells were assayed for miR193a expression and PEC/PD markers. To confirm the disruption of APOL1-miR193a axis, HEKs (human embryonic kidney cells with undetectable APOL1 expression) were transfected with Vector, APOL1G0, APOL1G1, or APOL1G2 plasmids followed by evaluation of miR193a expression and PEC/PD markers. Human renal biopsy specimens and renal cortical sections of 4-week and 8-week old HIV transgenic mice (Tg26) expressing APOL1G0, APOL1G1, and APOL1G2 were graded for the severity of renal lesions.

Results: HIV induced the expression of APOL1 in PECs. The induction of APOL1 in undifferentiated PECs and HEKs down-regulated miR193a expression but stimulated the expression of PD markers. APOL1G1 and APOL1G2 in differentiated PDs as well as in differentiated PECs down-regulated PD markers but upregulated the expression of miR193a. Renal biopsy specimens of HIVAN patients displayed accumulation of PECs in Bowman's space with the expression of occasional PD markers. Tg26: APOL1G0 mice displayed minimal accumulation of PECs in Bowman's space as well as minimal renal lesions vs. TG26: APOL1 G1/G2 mice.

Conclusions: APOL1G0 prevents the development of HIVAN through facilitating PECs transition to PDs.

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FR-PO1027

Role of Epigenetics in Parietal Epithelial Cell Transition

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Background: APOL1 is a minor component of circulating lipid-rich multiprotein complexes in certain primate species including humans. It is expressed in liver, pancreas, kidney, brain, macrophages, and endothelial cells. In kidneys, APOL1 protein is expressed in podocytes, tubular, and vascular smooth muscle cells. Parietal epithelial cells (PECs) do not express APOL1 under a normal physiologic state. We hypothesize that epigenetic factors have a potential to induce APOL1 expression in PECs for their participation in PDs renewal in adverse milieus

Methods: Immortalized human PECs (at 33°C) were transduced with either vector (V) or HIV (NL4-3) (n=4); PECs were incubated in media containing variable concentration of IFN-γ (0, 5, 10, and 20 nM) for 48 hours (n=4); PECs were treated with either buffer, azacytidine (5 μM, a demethylating agent), or SAHA (10μM, a histone deacetylation inhibitor) for 48 Hours (n=4). Protein blots were probed for APOL1, DNMT 1-3, HDAC 1-4, $H3K27me^3$, $H3K4me^3$, $H3K8/9^{ac}$, and reprobed for β-actin. cDNAs were amplified for *DNMT1-4*, *HDAC1-4*, and *APOL1* with specific primers. RNAs were assayed for miR193a. To confirm histone acetylation at miR193a gene promoter, ChiP assay was carried out. To confirm binding of miR193a to APOL1 gene promoter, RIP-ChIP assay was performed. To measure methylation of CpG islands at miR193a gene, Bisulphite sequencing was carried out in PECVs and PECHIVs.

Results: Both HIV and IFN-γ induced APOL1 expression in PECs. PECHIV and IFN-γ-treated PECs showed 2- to 2.5-fold decrease in miR193a expressions, respectively; as expected, inhibition of miR193a in PECs also resulted in the induction of APOL1expression. The treatment of PECs with either azacytidine or SAHA induced the expression of APOL1 as well as decreased (3-fold) miR193a levels. HIV and IFN-γ enhanced the expression of DNMT3b, HDAC4, $HK4me^3$, and $H3K27me^3$, but down-regulated the expression of $H3K8/9^{ac}$. ChIP assay revealed histone methylation at 27 lysine residues. RIP-ChIP assay

confirmed binding of miR193a on APOL1 gene promoter. Bisulphite-sequencing displayed enhanced methylation of CpG islands at miR193a gene in PECHIVs.

Conclusions: Epigenetic factors play a role in the induction of PECs expression of APOL1 through modulation of miR193a expression in adverse milieus.

Funding: NIDDK Support

FR-PO1028

Community-Based Evaluation of APOL1 Genetic Testing in African Americans: National Stakeholder Meeting and Return of Results Recommendations

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Background: African Americans (AA) are 2-4 times more likely to develop ESRD, compared to whites. Apolipoprotein L1 (*APOL1*) high-risk variants have been associated with greater risk of developing non-diabetic ESRD among African Americans (AAs), incident CKD, proteinuria, and transplant failure compared to those with wild type *APOL1*. Currently there is a lack of national guidelines for genetic testing for *APOL1* in transplantation and general clinical care.

Methods: We convened a national meeting of stakeholders (researchers, clinicians, patients, family members, community members, national advocacy and professional organizations, and NIH representatives) to develop guidance for policy-makers and clinicians regarding *APOL1* genetic testing in transplantation and general clinical care. We identified areas of consensus, disagreement, and needed research. Participants received educational information, *APOL1* research updates, results of stakeholder interviews and of community deliberative groups. Participants discussed *APOL1* relevant policy concerns regarding genetic testing.

Results: After 2 days of discussion, draft conclusions regarding *APOL1* were developed, including: 1) AA should be informed about *APOL1* risk; 2) *APOL1* testing should be integrated into renal transplant programs; 3) routine use of *APOL1* testing in general clinical care is not recommended, because it is not actionable; 4) research is crucial to ensure better understanding of *APOL1* risk; and 5) AA community involvement in the development of policies and educational materials about *APOL1* risk and testing is recommended to ensure testing policies address community preferences. Areas with lack of consensus included: 1) whether transplant programs should require *APOL1* testing of living donors; 2) whether transplant recipients should be told the *APOL1* status of transplanted kidneys; and 3) access to *APOL1* testing in general clinical care.

Conclusions: Draft conclusions from a national stakeholder meeting regarding *APOL1* risk indicate consensus regarding informing the AA community regarding *APOL1* genetic testing in transplantation, but lack of consensus regarding using *APOL1* testing to determine eligibility for transplant donation or in general clinical care, given current research knowledge.

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FR-PO1029

Loss of Function of EMP2 Does Not Cause Glomerular Disease in Mice

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Background: Mutations in the human gene Epithelial Membrane Protein 2 (EMP2) have been linked to childhood-onset nephrotic syndrome (OMIM#615861) with expression reported within podocytes. In mice, the Emp2 gene is necessary for embryo implantation and placental angiogenesis. Its gene product, a tetraspan integral membrane protein, affects various cell behaviors including cell adhesion and migration. To further understand its role in glomerular disease, we studied Emp2 expression and generated cell-specific Emp2 knockout (KO) mice.

Methods: Emp2 mRNA was profiled in various tissues using qRT-PCR analysis. We created a conditional floxed Emp2 allele carrying a lacZ cassette that allows whole-mount β-galactosidase (β-gal) histochemical analysis of Emp2 expression. We created podocyte-specific knockout and null Emp2 mutant mice by breeding floxed Emp2 animals with Nphs1-Cre and EIIa-Cre driver strains, respectively. Emp2 mutant mice were assessed for proteinuria and renal histology.

Results: Based on qRT-PCR analysis, Emp2 expression was highest in lungs, but is expressed in multiple other organs including the kidney. β-gal staining reveals that Emp2 is present in the vasculature. In the kidney, β-gal staining is found in large caliber vessels but is surprisingly absent in glomeruli. By 3 months of age, mice lacking Emp2 within podocytes or globally do not exhibit proteinuria or renal abnormalities.

Conclusions: In contrast to previous reports, we did not observe significant Emp2 expression in podocytes or within the glomerulus. Emp2 deficiency in mice did not cause overt kidney disease. Our data demonstrate a vascular pattern of expression throughout multiple tissues. These findings suggest that Emp2 may have a key endothelial function, which would explain reports implicating Emp2 in placental vascular development and tumor angiogenesis. Our findings do not support a causative role for EMP2 mutations in patients with childhood-onset nephrotic syndrome.

FR-PO1030

Exome-Wide Association Study for C3 Glomerulopathies

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Background: C3 glomerulopathies (C3Gs) include a spectrum of rare diseases such as C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), which share phenotypic similarities and underlying genetic commonalities. Mutations in components of the complement pathway have been implicated, but the genetic underpinnings are largely unknown. The aim of this study is to use whole-exome sequencing to improve understanding of the genetic architecture of C3G.

Methods: We performed a case-control exome-wide collapsing analysis using 282 case subjects with C3Gs [C3GN, DDD, and immune complex-mediated MPGN] and 9,825 control subjects with no known kidney diseases. To identify risk signals, we tested all protein-coding genes for an excess of ultra-rare genetic variation among the cases, compared with control samples. We tested multiple models, including loss-of-function variants and non-benign nonsynonymous variants. We also applied regional intolerance model based on missense tolerance ratio (MTR).

Results: In multiple model, patients with C3G had a higher frequency of loss-of-function variants and non-benign nonsynonymous variants in *Complement Factor H* ($P = 6.51 \times 10^{-07}$), *C3* ($P = 1.04 \times 10^{-04}$) in the dominant models and *C5* ($P = 0.0279$) and *CFB* ($P = 0.0279$) in the recessive models. Rare putatively pathogenic variants were detected mainly among C3GN cases. In addition, we identified many signals that did not reach exome-wide significance but represent interesting candidate genes for C3Gs.

Conclusions: We identified excess ultra-rare variation in several known C3G genes under both dominant and recessive models. These data suggest that exome sequencing can discover rare risk alleles for C3Gs enhancing the established gene-mapping paradigms.

Funding: NIDDK Support

FR-PO1031

Kank1 Knockout Fish Causes Proteinuria

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Background: Kank family consists of Kank1-4 and contains KN motif, coiled-coil domains, and ankyrin-repeats. Kank1 protein is mostly located in the cytoplasm and is thought to play a role in organizing actin cytoskeleton. Recently, Kank1 is reported to be associated with nephrotic syndrome.

Methods: The expression pattern of Kank1 protein was examined in human frozen kidney sections. Since Kank1 is a conserved gene between human and zebrafish, kank1 knockout zebrafish has been used in this study. The mutant kank1 zebrafish line has a C to T point mutation in exon 3 of kank1 gene, which results in a premature stop codon from CAA (Q) to TAA. By utilizing kank1 knockout zebrafish embryos, we examined its phenotype and performed a functional assay by injecting fluorescent-conjugated dextrans.

Results: Kank1 protein was localized in the podocytes and the proximal tubules. Genotyping of zebrafish embryos from kank1 heterozygous parents was performed by polymerase chain reaction method. The phenotype of kank1 knockout embryos at 4 days per fertilization (dpf) was comparable with that of wild-type embryos. The morphology of pronephros in kank1 knockout embryos was also comparable with that in wild-type embryos under Periodic acid–Schiff stain. However, there was an uptake of both 500-kDa fluorescein isothiocyanate and 10-kDa rhodamine dextrans in the proximal tubules of kank1 knockout embryos at 3.5 dpf while there was only an uptake of 10-kDa rhodamine dextran in the those of wild-type embryos.

Conclusions: Knockout of kank1 in zebrafish might be related to the disturbed filtration barrier in the pronephros and support the human data in nephrotic syndrome.

FR-PO1032

TRPC6 Overexpression Mice Produced Proteinuria with Downregulated Podocyte Genes

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Background: Mutations in transient receptor potential channel-6 (TRPC6) can cause autosomal dominant FSGS. We have previously identified novel p.R68W TRPC6 gain-of-function mutation. We aim to study the disease-causing mechanism of p.R68W mutation.

Methods: Wild type (OE^{wt}) and p.R68W (OE^{mut}) TRPC6 were overexpressed in FVB/N mice by pronuclear microinjection. The albumin:creatinine ratios were obtained. Podocyte gene expressions were measured by reverse-transcription PCR and western blot analysis. Podocyte ultrastructural changes were assesssed by transmission electron microscopy and transgene localization was performed by immunogold staining. Statistical analysis was performed using Mann-Whitney U test.

Results: Over one third of both groups of overexpression mice had albuminuria, and lower body weights compared with control mice from 6 month. Interestingly, OE^{wt} were significantly lighter compared with OE^{mut} since 6.5 month. Kidney electron microscopy slices demonstrated extensive podocyte foot process effacement in both OE mice. Immunogold staining revealed TRPC6 in OE^{wt} mice localized predominantly in the central cytoplasmic areas, whereas in OE^{mut}, TRPC6 occurred predominantly at the peripheral and central parts of the foot processes. Quantitative PCR data showed that nephrin and podocin expressions were decreased in OE mice compared to wild-type, and to a greater degree in the OE^{wt} compared to OE^{mut}.

Conclusions: Our work suggests p.R68W mutation may affect TRPC6 intracellular trafficking and its interactions with the slit diaphragm proteins in the podocytes.

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FR-PO1033

Targeting MTAP-Deficient Cells in Advanced Renal Cell Carcinoma

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Background: The metabolic enzyme methylthioadenosine phosphorylase (MTAP) has been reported to function as a tumor suppressor and the lack of this gene was found in approximately 58% of kidney cancer (or renal cell carcinoma, RCC) cases. However, the mechanisms of how MTAP regulates RCC progression still remain unknown.

Methods: Tissue microarray and immunohistochemistry (IHC) were performed to analyze the correlation between MTAP expression and IGF-1R phosphorylation in RCC. A phospho-receptor tyrosine kinase array screen was utilized to assess RCC signaling pathway activity. Genetic manipulations were achieved by siRNA knockdown, CRISPR/Cas9 and ectopic expression approaches. In addition, we used an IGF-1R inhibitor, linsitinib, to suppress type 1 Insulin Growth Factor 1 Receptor (IGF-1R) signaling. *In vitro* and *in vivo* tumor suppressive activities of MTAP were confirmed by MTT, colony formation, migration assays and *in vivo* subcutaneous implantation. MTAP-regulated gene expression and signaling were determined by qRT-PCR and Western blots.

Results: We found a decrease of protein-methylation level concomitant with an increase in tyrosine phosphorylation in MTAP-knockout cells. We next performed a receptor tyrosine kinase array screen and identified IGF1R as the top-one candidate with upregulated tyrosine phosphorylation in response to MTAP loss. Western blots showed an elevation of IGF1R phosphorylation and its signaling after MTAP knockout. IHC staining on a tissue microarray has also confirmed an inversely association between IGF-1R phosphorylation and MTAP expression. We noticed a decrease of cell viability, migration, invasion and colony-forming capabilities in MTAP-knockout RCC cells after linsitinib treatment. Surprisingly, RCC cells were more sensitive to this inhibitor in response to MTAP loss, suggesting that MTAP-deficient become addicted to IGF1R activity.

Conclusions: IGF-1R signaling is a driver pathway conferring aggressive nature to MTAP-deleted renal cell carcinomas.

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FR-PO1034

Stromal Signaling Promotes ccRCC Tumor Growth Through FOXD1 Overexpression

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Background: Clear cell renal cell carcinoma (ccRCC) is the 8th most common cancer in the U.S.. Although tyrosine kinase inhibitors (TKIs) have improved survival in patients, many patients are not responsive to TKI are in need of more options. The tumor microenvironment (TME) in ccRCC is not well understood and may be a potential target. The transcription factor FOXD1 has been shown to be upregulated in lung, breast, and kidney cancer. Functionally, FOXD1 regulates epithelial-stromal signaling in the developing kidney. We hypothesize that FOXD1 overexpression in ccRCC would promote tumor growth through stromal signaling.

Methods: The relevancy FOXD1 was first determined through RNA-seq and staining analyses. ccRCC tumor microarrays (TMAs) were stained for FOXD1, PECAM, aSMA, PDGFRb, and NG2. A Kaplain-Meier survival analysis for FOXD1 expression was performed using data from The Cancer Genome Atlas (TCGA). A potential FOXD1 binding site analyses using the TRANSFAC FOXD1 binding site matrix was performed. Binding site were compared to previously reported FOXD1-/- RNA-microarray data to determine direct binding targets. Results were confirmed by qPCR in renal proximal tubule cells (RPTECs) after transfection with a FOXD1 adenovirus. SLIT2 was found to be a functionally relevant target in kidney cancer and was assessed for its role in fibroblast signaling through scratch assays, 3D migration assays, and multiplex proximity ligation assays. Knockdown of FOXD1 in the 786-O cell line followed by qPCR, western blot, and migration analyses.

Results: 65% of TMA samples stained positively for FOXD1. FOXD1 expression within the cancer cells correlated with stromal PDGFRβ expression ($p<4.5x10-6$). FOXD1-high ccRCC patients had a worse survival outcome (FOXD1 low= 2830 days; FOXD1 high= 1913 days). FOXD1 binding site analysis, RNA-microarray, and qPCR found FGF1, SLIT2, and Decorin to be potential secreted signaling molecules repressed by FOXD1. Scratch assays on fibroblasts showed that SLIT2 reduced PDGFBB-induced cell migration ($p<0.27$). Additionally, 3D migration co-culture with 786-O cancer cells determined a repulsive effect of SLIT2 in 3D culture as well (5μm p=1.34x10-4; 50μm p=1.64x10-2).

Conclusions: FOXD1 is an important prognostic marker for aggressiveness in ccRCC. The importance of fibroblast recruitment by cancer cells in ccRCC is still not known.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO1035

Birt Hogg Dubé Syndrome (BHD) and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome (HRLCC): An Effective Multidisciplinary Approach to Hereditary Renal Cancer Predisposing Syndromes

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Background: BHD and HLRCC are rare hereditary disorders caused by germline *FLCN*and *FH*mutations respectively. BHD is characterized by skin fibrofolliculomas, lung cysts, spontaneous pneumothorax and Renal Cell Carcinoma (RCC). HLRCCis characterized by skin piloleiomyomas, uterine leiomyomas and RCC. BHD and HLRCC are autosomal dominant disorders and have estimated cumulative risk of RCC 16% with life-long screening recommended. We aimed to assess adherence to surveillance guidelines in an Australian BHD and HLRCC cohort and to describe disease characteristics.

Methods: All patients with a diagnosis of BHD or HLRCC at RBWH 01/01/2014-31/12/2017 were included (HREC/17/QRBW/276). All patients were initially assessed and counselled by a Clinical Geneticist and then referred to an Adult Nephrologist. Baseline and incidental clinical variables were extracted and analysed.

Results: 40 patients were identified (18 BHD, 22 HLRCC) with a median age of 49.5years. The median and cumulative follow up were 1year and 76years respectively. Surveillance renal MRI occurred in 32/40 patients on annual basis. Of 8/40 without surveillance imaging 4 were yet to have imaging, 3 were lost follow up and 1 patient had logistic difficulties. RCC was diagnosed in 8/40 patients: 2/18 with BHD were diagnosed with RCC aged 73 and 77 both prior to commencement of surveillance. 6/22 patients with HLRCC were diagnosed with RCC (2/22 during surveillance) and 4/22 prior to commencement of surveillance (11-43 years). Amongst BHD patients, cutaneous fibrofolliculoma was noted in 8/18 patients, lung cysts in 3/18 patients, spontaneous pneumothorax in 3/18 patients, and past parotid oncocytoma in 2/18. Amongst those with HLRCC, cutaneous leiomyoma were noted in 15/22, cutaneous leiomyosarcoma in 1/22 and uterine fibroids in 10/16 female patients.

Conclusions: Evidence-based RCC screening in BHD and HLRCC cohort is feasible and able to identify incident renal lesions. Multidisciplinary patient management enables expedited genetic counselling, diagnosis, longitudinal screening and RCC management. The success of this clinical model warrants consideration of undertaking longitudinal screening of BHD and HLRCC patients by nephrologists.

FR-PO1036

Efficiency and Safety of mTOR Inhibitors for Tuberous Sclerosis Complex-Associated Renal Angiomyolipoma

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Background: Kidney involvement is the most important cause of morbidity and mortality in adult patients with tuberous sclerosis complex (TSC). mTOR inhibitor Everolimus (EVE) is the only pathogenic treatment approved. Since TSC is a rare genetic disease, long-term experience with EVE is still limited.

Methods: TSC patients treated with EVE for renal angiomyolipoma (AML) at increased bleeding risk without immediate surgery indication were followed prospectively. Kidney CT or MRI (same modality throughout the study for each patient) was done at baseline and annually thereafter. Treatment response was evaluated as percentage of reduction of sum of volumes of all target AML identified at baseline. Adverse events (AE) were graded according to the CTCAE v3.0.

Results: Between January 2015-May 2018 17 patients (12F, 5M), mean age 34.8±7.5 years (17-61), started treatment with EVE. Baseline diameter of the biggest AML was 7.7±2.8 cm (3.8-12), 7 patients had a history of spontaneous AML bleeding with 4 of them suffering total one-sided nephrectomy. Baseline eGFR was 78.8±36.1 ml/min/1.73 m^2 CKD-EPI (9-126): 5 patients had stage 2 CKD, 1 patient stage 3, 2 patients stage 4 and 1 patient stage 5. Initial EVE dose was 10 mg/day, with dose adjustments according to target trough level (5-15 mcg/l) and tolerance. Total treatment period was 23.4±11.4 months (5-45). 69.2% of patients had a more than 30% response after 12 months and the proportion of patients with response ≥50% increased over time. No patient had new bleeding episodes, neither increase in AML volume or new AML (Table 1). All patients experienced AE, the most frequent one being dyslipidemia in 16 patients. The severity of AE was grade 1 or 2, with maximum incidence during the first 12 months, with no need for permanent treatment withdrawal.

Conclusions: Treatment of TSC-associated renal AML with EVE is efficient and well tolerated. mTOR pathway regulates many major cellular processes, so AE to EVE

are frequent. Since this is a life-time treatment, careful surveillance is essential to rapidly identify and treat these AE.

Patients treated (n)	AML response rate (%)			
	<15	15-29	30-49	≥50
Treatment ≥12 months				
13	1	3	3	6
Treatment ≥24 months				
8	1	1	1	5
Treatment ≥36 months				
2	0	1	0	1

FR-PO1037

Outcomes of Arterial Embolization in Treating Renal Angiomyolipomas: A Single Center Experience

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Background: Selective arterial embolization (SAE) of renal angiomyolipoma (AML) is associated with parenchymal loss and contrast exposure. The aim of this study was to evaluate the baseline characteristics and the change in glomerular filtration rate (GFR) in patients with AML following SAE.

Methods: This study included all AML cases that were treated with SAE procedure at our center from 2004 to 2017. Data on demographics, tumor size, and other laboratory values were collected. Serum creatinine and calculated GFR were assessed immediately prior and 3 months after SAE procedure. GFR was calculated using CKD-EPI formula.

Results: Our cohort included 44 patients who underwent SAE. The indications for SAE included back pain, hematuria and retroperitoneal hemorrhage. Baseline characteristics were: age (mean ± SD) 47± 16.5 years; 77% females; 68% whites; and 36% were hypertensive. Acute kidney injury (AKI) was encountered in 4 patients (9%) following the SAE procedure. The (mean ± SD) serum creatinine increase from 0.97 ± 0.48 to 1.17 ± 0.88 mg/dl (p=0.008) after SAE procedure. The GFR dropped from 86.7 ± 25.8 to 79.7 ± 28.8 ml/min after procedure (p= 0.001). Post SAE GFR correlated with the tumor size (p= 0.047). Further, patients who developed AKI was found to have larger AML as compared to those with no AKI (16.8 vs 7 cm; p<0.0001).

Conclusions: Following the embolization of renal AML, there was a statistically significant decrease in GFR. Further, tumor size was associated with post procedure GFR and AKI incidence. Although the decrease in GFR could be in part attributed to the partial parenchymal loss and contrast exposure, its clinical significance is yet to be elucidated.

Baseline Characteristics and changes in GFR & Creatinine after AML Embolization

	Large (Tumor size >4cm) N=40	Small (Tumor Size >4cm) N=4	p-Value
Age Mean ± SD	47.1 ± 16.7	46.3 ± 17.1	0.84
Female	30 (75%)	4 (100%)	0.26
Race- White	27 (67.5%)	3 (75%)	0.90
Hypertension	16 (40%)	0 (0%)	0.11
Symptoms- Pain	14 (35%)	1 (25%)	0.69
Symptoms- Hemorrhage	26 (65%)	3 (75%)	0.69
Acute Kidney Injury	4 (10%)	0 (0%)	0.51
	Pre-Embolization	Post-Embolization	p-Value
Serum Creatinine, Mean(SD)	0.97 (0.48)	1.17(0.88)	0.0080
GFR CKD Epi, Mean (SD)	86.7 (25.8)	79.7 (28.8)	0.0019

FR-PO1038

Trans-Ethnic Genome-Wide Association Study of Kidney Function Identifies Novel Loci Influencing the Risk for Kidney Stone

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Background: Genetic variants in the *UMOD* and *RGS14* genes are associated with kidney function and the risk of kidney stone. We hypothesized that additional kidney function loci influence the risk of kidney stone.

Methods: We performed trans-ethnic meta-analysis of genome-wide association studies of estimated glomerular filtration rate (eGFR) in 312,468 individuals of diverse ancestry, followed by fine-mapping of regions informed by functional and regulatory annotations. Variants driving eGFR association signals were queried in 452,264 UK Biobank participants of European descent for association with ICD clinical code of calculus of kidney or ureter. Associations were validated in an independent sample of 20,339 individuals of diverse ancestry (44% European ancestry) with self-reported diagnosis and history of kidney stones.

Results: We identified 93 loci attaining genome-wide significant evidence of association with eGFR ($p<5x10^{-8}$), of which 20 were novel. After adjusting for multiple testing, five eGFR loci were associated with an ICD-code diagnosis of kidney stone in the UK Biobank. These included the two loci previously associated with kidney stones (*UMOD*, rs77924615, $p=1.6 \times 10^{-16}$ and *RGS14*, $p=2.0 \times 10^{-8}$), a novel eGFR locus *CERS2* (rs267738, $p=1.6 \times 10^{-5}$), and two known eGFR loci: *CYP24A1* (rs17216707, $p=9.0x10^{-10}$), and *PRKAG2* ($p=2.4 x10^{-5}$). The association of the *CERS2* variant with kidney stone replicated in the independent multi-ethnic study ($p=0.008$).

Conclusions: Several genetic variants associated with eGFR also confer risk for kidney stone, supporting shared genetic factors for kidney function and stone formation.

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FR-PO1039

Autosomal Dominant Tubulointerstitial Kidney Diseases: A Single Center Five-Year Cohort

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Background: In patients with chronic kidney disease of unknown cause, certain aspects of clinical history, urinalysis and renal ultrasound might point to hereditary chronic interstitial nephritis (CIN). Recent sequencing technologies, such as *Next-Generation Sequencing* (NGS), have been used to identify and characterize different genetic kidney diseases, difficult to diagnose up until recently. The authors present this single center cohort of patients with identified mutations in genes responsible for autosomal dominant tubulointerstitial kidney diseases (ADTKD) in the last 5 years.

Methods: Over the last five years, when patients with CKD of unknown cause presented with a phenotype suggestive of CIN, NGS study of the *UMOD*, *REN* and *HNF1B* genes was performed, if negative, variable number tandem repeat (VNTR) mutations of the *MUC1* gene were researched, if negative, multiplex ligation-dependent probe amplification (MLPA) was performed to find further mutations of the *HNF1B* gene.

Results: In the past five years, our department has identified ADTKD in 22 patients. Mutations identified included *UMOD* gene in 2 families (c.1463G>A (p.Gly488Asp); c.628G>A (p.Gly210Ser)) and 1 patient (c.859T>C (p.Cys287Arg)), *MUC1* gene in 4 families, *REN* gene in 1 patient with two variants one of them not described yet (c.29G>A e c.338C>T), and *HNF1*β gene in 2 patients.

Conclusions: A suggestive phenotype includes bland urinalysis, hyperuricemia without proportion to the CKD stage, anemia not proportional to the CKD stage, hypercalemia, acidemia, urinary concentration defects, normal to low blood pressure and medullary renal cysts. Although some clinical manifestations might suggest a specific gene, many clinical aspects of different gene mutations might have a similar phenotype. NGS technology is promising in improving the approach to patients with hereditary CKD, and has allowed us to diagnose several patients with CKD of unknown cause. The availability, celerity and cost-effectiveness of this approach make it advantageous over the sequential study of each gene with Sanger sequencing technique. The generalization of these technologies to identify genetic diseases requires consistent identification of phenotypes and integration of data obtained. Therefore, the creation of diagnostic panels is crucial to increase diagnostic accuracy.

FR-PO1040

BM-Transplant Mouse Model of MPO-ANCA-GPA

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Background: Granulomatosis with polyangiitis is an ANCA-vasculitis characterized by necrotizing granulomatous inflammation and small vessel vasculitis. Pathogenic mechanisms involved in the development of GPA remain poorly understood. Therefore, we sought to develop a reliable murine GPA model.

Methods: MPO-knockout mice (n=8) previously immunized with mouse MPO were exposed to lethal irradiation, followed by transplantation of MPO-expressing bone marrow ($1.5x10^7$ BM cells); resulting in circulating anti-MPO antibodies and MPO^+ neutrophils. Lipopolysaccharide (LPS, 5μg) was administered by intratracheal instillation 3 weeks after BM transplant; mice were euthanized one week after.

Results: Engraftment of MPO-positive BM in combination of IT LPS resulted in the development of typical pulmonary and kidney ANCA-associated lesions in various phases of evolution, i.e., lung granulomatous lesions and vasculitis in addition to necrotizing crescentic glomerulonephritis (Figure 1).

Conclusions: A reproducible mouse model of MPO-ANCA-GPA is reported. Our results demonstrate that: 1) LPS functions as synergistic pro-inflammatory factor for facilitating anti-MPO induced pulmonary granulomatosis and 2) The effect of long-term exposure to anti-MPO-ANCA resulted in lung and kidney inflammatory lesions of different ages of evolution, closely mimicking human disease.

Funding: Other NIH Support - *

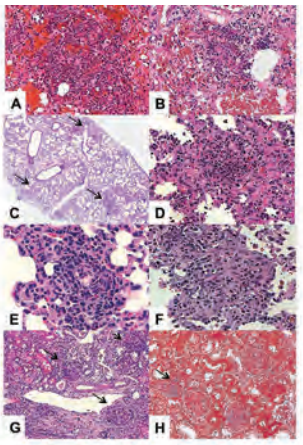

FIGURE 1. Pathology findings. A) Alveolar capillaritis with pulmonary hemorrhage. B) Necrotizing vasculitis. C) Granulomatous parenchymal nodules. D) Acute granuloma with intense neutrophilic infiltration. E) Later stage granuloma demonstrating necrotic debris and adjacent band of macrophages. F) Chronic fibrotic granuloma. G) Acute glomerular crescents. H) Chronic segmental glomerulosclerosis (Masson trichrome).

FR-PO1041

The Investigation on the Production of Anti-Neutrophil Cytoplasmic Antibodies in Chronic Bronchitis Rat

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Background: The purpose of this study was to investigate the possibility of the production of Anti-Neutrophil Cytoplasmic Antibodies(ANCA) in the rat model of chronic bronchitis with a long-term and recurrent infection.

Methods: The chronic bronchitis model was designed by double stimulation with smoke and lipopolysaccharide(LPS). Rats were divided into four groups, including healthy control rats (group N), group with chronic bronchitis(group CB), group with healthy rats stimulated with PBS and Phorbol-12-mytistate-13-Beetate(PMA)(group N/PBS+PMA), group with chronic bronchitis stimulated with LPS and PMA(group CB/LPS+PMA). Immunological markers, which include Citrullinated Histone H3(CitH3), myeloperoxidase anti-neutrophil cytoplasmic antibodies(MPO-ANCA) and proteinase 3 anti-neutrophil cytoplasmic antibodies(PR3-ANCA) were measured by enzyme-linked immune sorbent assay(ELISA) at different timepoint after each stimulation. The pulmonary and kidney tissue samples were taken for histopathology. All of related parameters indicators were measured and compared by optimal statistical methods.

Results: (1) The rat models of chronic bronchitis were established and verified by histopathology. (2)With multiple and recurrent stimulation with LPS and/or PMA, the serum levels of CitH3 and MPO-ANCA were found increased gradually. (3)Compared to those in group N, group CB and group N/PBS+PMA, the serum levels of CitH3 in group CB/LPS+PMA were found increased significantly. (4)The serum levels of MPO-ANCA in group N/PBS+PMA and group CB/LPS+PMA were higher than those in group N and group CB. (5)The serum levels of CitH3 in rats were positively correlated with the serum levels of MPO-ANCA(r=0.490, p=0.024). (6)In group with CB/LPS+PMA, mild renal pathology changes could be observed with inflammatory cells infiltration, while no significant functional changes were detected.

Conclusions: With a rat model of chronic bronchitis, recurrent infections combined with multiple stimulation with PMA, MPO-ANCA could be produced.

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FR-PO1042

Urinary CD163 Levels Reflect Crescentic Glomerulonephritis in ANCA-Associated Vasculitis

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Background: Early recognition of renal flares in ANCA-associated vasculitis (AAV) can be challenging, particularly among patients with persistent or recurrent urinary abnormalities. Kidney biopsies are therefore often needed to detect active vasculitis. Urinary soluble CD163 (usCD163) has been shown to reflect early renal disease. Animal studies demonstrated that increased usCD163 reflects early stage necrotizing and crescentic glomerulonephritis (GN). However, this needs confirmation in humans to establish its role as a marker of active renal AAV. Also, it is unknown whether tubulointerstitial and/or vascular damage can affect usCD163 levels. Therefore, we analyzed usCD163 in relation to histologic data on kidney biopsy.

Methods: Thirty-two patients with AAV underwent a kidney biopsy because of suspected renal vasculitis (de novo, n=13; renal flare, n=19); concurrently, urine samples were collected. None of the patients were receiving immunosuppressive treatment before biopsy. usCD163 was analyzed by ELISA and corrected for creatinine excretion. Kidney tissue samples were classified according to the ANCA GN classification and scored for tubulointerstitial and vascular damage.

Results: Increased usCD163 levels were found in 27 (90%) out of 30 patients with crescentic GN but not those with normal kidney tissue (n=2) or controls (n=6), underlining usCD163's specificity; median usCD136 levels did not differ between de novo and relapsing patients (302 versus 521 ng/mmol, P=0.1). In patients with crescentic GN, usCD163 correlated with the number of affected glomeruli (R^2=0.61, P<0.001), but no differences were found according to ANCA GN class. Neither tubulointerstitial nor vascular damage affected usCD163 levels. Patients classified as sclerotic class however, progressed more often to the composite endpoint of CKD5, ESRD, and death as compared to those classified as focal, crescentic, and mixed class (n/N= 6/11 and n/N=3/18; P<0.05). No association between usCD163 and the composite endpoint were found.

Conclusions: usCD163 is linked to crescentic GN in de novo patients with AAV, as well as during relapses. Both tubulointerstitial and vascular damage do not affect usCD163 levels, suggesting that usCD163 specifically reflects crescentic GN and should be used as a marker of active renal disease in AAV.

FR-PO1043

Familial Goodpasture's Disease Associated with a Deletion in COL4A3: A Potential Clue to Etiology

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Introduction: Goodpasture's (GP) or anti-glomerular basement membrane (GBM) disease is characterized by glomerulonephritis (GN) and/or alveolar hemorrhage. It is caused by antibodies that bind the non-collagenous domain (NC1) of the collagen IV α345 network in the GBM and alveolar basement membranes. Antibodies bind to α3 and α5 NC1 monomers but not native α345NC1 hexamers, indicating that a perturbation of the quaternary structure of the hexamer is required for eliciting an autoimmune response. We describe a case of familial GP disease associated with a structural alteration in the α345NC1 domain.

Case Description: The index patient was affected at the age of 45 years by alveolar hemorrhage and renal failure due to GN with linear IgG deposits in the GBM and circulating anti-GBM antibodies. Her son developed the same clinical phenotype at the age of 24 years. Genetic analysis revealed a heterozygous 18 base pair deletion in both subjects in the region of the *COL4A3* gene coding for the NC1 domain. The deletion contains the stop codon and leads to an elongated collagen α3NC1 domain, which substitutes 8 additional amino acid (AA) residues for the very last C-terminal AA.

Discussion: *COL4A3* mutations typically cause autosomal Alport's or thin basement membrane disease, yet there was no evidence for this in our patients. Anti-GBM antibodies behaved like in classical GP cases. They reacted with dissociated, but not native α345NC1hexamers, and bound to the wild type α3NC1 monomer at both EA and EB epitopes. Analysis of the 3D model of the α345 hexamer revealed that the mutant extension of 8 polar and hydrophobic residues is located proximal to the EA and EB epitopes. Potentially, the extension can fold into the crevice between both epitopes and lead to conformational changes that impact epitope presentation. The epitope structure may be altered to include residues of the extension or rendered accessible by the antibody. In conclusion, this is the first report of a *COL4A3* mutation associated with GP disease. The occurrence of this mutation in two family members, with autoantibodies against the α3NC1 autoantigen, indicates that it plays a key role in disease etiology. The association of this mutation with disease may be a clue to the etiology of both familial and sporadic cases of GP disease.

FR-PO1044

Significance of Glomerular Fibrinoid Necrosis in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) represent a group of severe diseases with frequent kidney involvement and poor renal prognosis. Risk factor for progression to ESRD include creatinine at presentation, presence of globally sclerosed glomeruli and arteriosclerosis. The 2010 histologic classification of AAV includes 4 classes (focal, crescentic, mixed and sclerotic), based on the rate of globally sclerosed glomeruli, cellular crescents and normal glomeruli. To our knowledge, the prognostic value of glomerular fibrinoid necrosis (FN) quantification in AAV has not been evaluated.

Methods: We retrospectively studied 45 consecutive renal biopsies with diagnosis of AAV (01/2010-5/2015). Conventional stains were used to assess the percentage of glomeruli showing FN, cellular crescents, global sclerosis and presence of vascular FN. For 31 patients, follow-up data were available for clinicopathological correlations

Results: Fibrinoid necrosis was observed frequently in our cohort (91%), involving an average of 22% (SD±20.5) of the glomeruli. When different histological classes were analyzed, percentage of FN was higher in crescentic (biopsies with >50% of the glomeruli showing cellular crescents) compared to other categories (**Figure 1**). The presence of >20% of the glomeruli showing FN was not correlated with a worse renal survival at any time of the follow up. No significant correlation was found between percentage of

glomerular FN and gender, ethnicity, age, ANCA levels (ELISA), eGFR at diagnosis and presence of vascular FN. The distribution of glomerular FN was the same in different vasculitis (granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis).

Conclusions: FN is seen in the presence of active crescentic lesions and is less likely observed in biopsies with advanced chronicity. Higher percentage of FN is not associated with worse renal prognosis, suggesting an active inflammatory process, potentially reversible after adequate therapy.

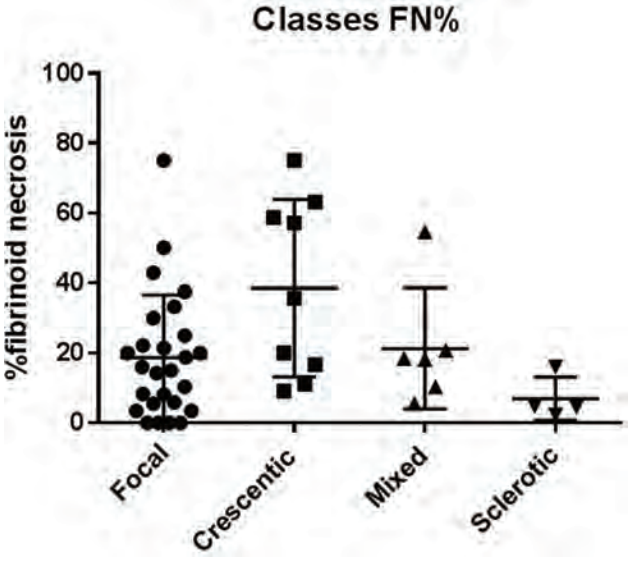

Figure 1. Distribution of percentage FN in different classes of AAV.

FR-PO1045

Transcriptional Dysregulation in Low Density Granulocytes from Patients with ANCA Vasculitis

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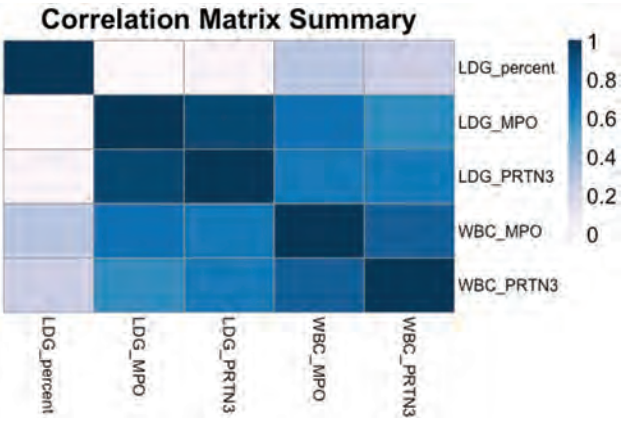
Background: ANCA vasculitis is characterized by elevated expression of autoantigen genes, *MPO* and *PRTN3*; however, the source and implications of the elevated expression are unresolved.

Methods: We isolated monocytes, neutrophils, and an enriched fraction of PBMC from 30 healthy controls (HC) and 75 patients. PBMC from 8 HC and 18 patients were sorted for CD15+ and CD15+/CD10+ cells. Low density granulocytes (LDG) were enriched from PBMC of 28 HC and 67 patients. Gene expression was measured by quantitative RT-PCR. LDG were immunophenotyped by flow cytometry for cell surface markers.

Results: Expression of *MPO* and *PRTN3* was significantly elevated in active patients compared to controls in neutrophils (2.6 and 3.6-fold) and in an enriched PBMC fraction (7 and 15.8-fold). Based on the greater fold-change expression in the PBMC fraction we sorted PBMC into CD15+ and CD15+/CD10+ cells. The nuclear morphology of the CD15+ cells is consistent with immature progenitor granulocytes, while the CD15+/CD10+ cells had segmented nuclei of mature neutrophils. We purified LDGs containing both CD15+ and CD15+/CD10+ cells. *MPO* and *PRTN3* expression in LDGs were elevated in active patients compared to controls (9.3 and 16.5-fold), and correlated with expression in total leukocytes (WBC). LDG heterogeneity was analyzed by flow cytometry and the percentages of cell populations were compared to autoantigen gene expression. The percent of LDGs in PBMC and the percent of CD15+ cells in the LDG population showed weak correlations with *MPO* and *PRTN3* expression (r^2<0.09) (Figure).

Conclusions: The frequency of LDGs or CD15+ cells explains less than 10% of the variation in *MPO* and *PRTN3* expression suggesting transcriptional dysregulation, not an increase in neutrophil progenitors, drives increased expression.

Funding: NIDDK Support



Heatmap represents the correlation coefficients (color scale shown at right) for pairwise comparisons.

FR-PO1046

Immunoproteasome-Deficiency Attenuates Antibody-Mediated Podocyte Injury

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Background: Membranous nephropathy (MN) is an autoimmune disease characterized by subepithelial immune complex deposition and podocyte injury. Persistent podocyte injury during MN is associated with the upregulation of the ubiquitin-proteasome system (UPS), wherein the immunoproteasome is responsible for enhanced protein degradation and for generating peptides for MHC class I presentation. Here we address the impact of immunoproteasome-deficiency on the development of antibody-mediated podocyte injury.

Methods: Anti-podocyte nephritis (APN), a model for MN, was induced in global-β5i and podocyte-specific β5i deficient mice as well as littermate controls. As clinical parameters urine albumin/creatinine and BUN were measured. Morphological analysis of the kidney was obtained *via* PAS staining. Proteasomal function and activity of isolated glomeruli were analyzed via Western Blot and proteasomal activity assays.

Results: The development of proteinuria during APN was attenuated in global- and podocyte-specific β5i deficient mice compared to wildtype littermates. Western blot analysis revealed the upregulation of the standard proteasome in β5i deficient mice during APN. This was also shown in the upregulation of the chymotrypsin-like activity (the major proteasomal activity) in the β5i deficient mice.

Conclusions: Immunoproteasome-deficiency protects against antibody-mediated podocyte injury in mice. This can be explained by the upregulation of the standard proteasome, which leads to a different quantity and quality of peptide generation.

Funding: Government Support - Non-U.S.

FR-PO1047

The Effect of B Cell Targeted Therapies on Autoantibodies and Excessive Neutrophil Extracellular Trap Formation in Systemic Lupus Erythematosus Patients

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Background: Systemic lupus erythematosus (SLE) is a severe systemic autoimmune disease characterized by immune-complexes (ICx) which cause inflammation and damage. Effective targeting of autoantibody secreting cells could be key to reset autoimmunity. Functionally, SLE-specific ICx are important triggers of neutrophil extracellular trap (NET) formation. A consortium was formed to study B-cell targeted therapies, including RTX, Bortezomib (BTZ) or combination of RTX + Belimumab (BLM). The present study aimed to investigate the effects of these therapies on relevant autoantibody levels and excessive NET formation.

Methods: This study involved three cohorts of severe SLE patients that were eligible to experimental treatment with RTX (n=16), BTZ (n=12) or RTX+BLM (n=16). A cross-sectional cohort of 35 SLE patients served as a control cohort. A panel of SLE relevant autoantibodies against dsDNA, histones, nucleosomes and C1q were measured by ELISA. NET formation was quantified by a novel highly-sensitive assay using 3D confocal microscopy (Kraaij et al. 2016).

Results: Comparing three regimens, RTX+BLM resulted in the strongest significant reduction on anti-dsDNA, anti-Histone and anti-Nucleosomes antibodies compared to a smaller decrease by RTX and BTZ. Interestingly, RTX+BLM specifically decreased anti-C1q antibodies, which were not targeted by RTX or BTZ. ICx-mediated NET formation was only significantly decreased with a median of 75% [53 – 85%] after RTX+BLM

(p=0.0002). Successful seroconversion of autoantibodies associated with decreased NET formation (p=0.02). The latter phenomenon was further corroborated in an independent cohort of SLE patients, where excessive NET formation associated with the presence of three or more autoantibody specificities (p=0.02), and specifically with the presence of anti-C1q antibodies (p=0.03).

Conclusions: In this reverse, translational study of B-cell targeted therapies, we demonstrate that anti-C1q autoantibodies were derived from Blys-dependent proliferating plasmablasts because they were only susceptible to RTX+BLM therapy. Moreover, therapeutically narrowing of the autoantibody repertoire decreased immune-complex mediated NET formation.

FR-PO1048

Efficiency and Safety of Thalidomide Combined with Dexamethasone in Patients with Proliferative Glomerulonephritis with Monoclonal IgG Deposit

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Background: To evaluate the efficacy and safety of thalidomide combined with dexamethasone (TD) in patients with proliferative glomerulonephritis with monoclonal IgG deposits(PGNMID).

Methods: We retrospectively analyzed the clinical data of 12 patients diagnosed with PGNMID from December 2015 to November 2017 in Jinling Hospital, who received TD regimen, and 32 PGNMID patients treated with non-TD regimen from 2011 to 2016.

Results: There are 4 males and 8 females with a median age of 48.5(27,63) yr taking the regimen of TD. With a mean follow-up of 7.5 mo, 6(50%) patients achieve renal response, including 2(16.7%) patients achieving complete response and 4(33.3%) patients achieving partial response, median time of response was 5.5 mo. 5(83.3%) patients got hematological response, in which 1(16.7%) patients obtain complete response, 2(33.3%) patients obtain very good partial response and 2(33.3%) patients obtain partial response. After treatment, serum albumin improved(P=0.002), serum creatinine kept stable(P=0.79), urine protein decreased(P=0.099), and no patient progressed to ESRD. One patient got histopathological recovery. During the secondary renal biopsy, the monoclonal IgG3 and κ light chain deposited in kidney disappeared completely, and glomerular nodular changes also improved. There was no statistical difference in clinical data between the two groups except for gender. With a mean follow-up of 19.2 mo in non-TD group, 5(15.6%) patients achieve renal response, including 3(9.4%) patients achieving complete responseand 2(6.3%) patients achieving partial response. The renal response rate was lower than those in TD group (P=0.045). 3 (33.3%) patients got hematological response. Serum creatinine in the last follow-up were worse than the baseline(P=0.046), albumin (P=0.005) and proteinuria (P=0.044) were improved, and 8(25%) patients progressed to ESRD with an average time of 25.2 mo. The common side effects of TD group were numbness (50%), edema (50%) and sleepiness (50%), but most of the patients were tolerable through symptomatic treatment and drug reduction.

Conclusions: The TD regimen is effective for PGNMID patients. Side effects are common but most of the patients can tolerate it.

FR-PO1049

Suboptimal Dosing of Initial Eculizumab Therapy in aHUS?

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Background: Atypical hemolytic uremic syndrome (aHUS) is caused by dysregulation of the alternative complement pathway. With the introduction of the complement inhibitor eculizumab the prognosis of aHUS patients has significantly improved. Initiation of eculizumab immediately at disease onset is advised to prevent persistent kidney injury. For complete blockade of the terminal complement pathway eculizumab trough levels of 50-100 µg/ml are recommended. However, recent data suggested that the advised treatment protocol may be insufficient: low eculizumab levels in the induction phase were followed by eculizumab levels exceeding the recommended trough levels in the maintenance phase. (Volokhina, 2017).

Methods: We have extended previous observations and evaluated all adult aHUS patients who were treated with eculizumab in our center from 2013 to 2018.

Results: Eculizumab was used as induction therapy 23 times in 19 adult aHUS patients. Eculizumab trough levels after the first dose were measured in 12 patients. Five patients did not maintain eculizumab levels of >50 µg/ml after the first dose. This was paralleled by incomplete complement blockade. After the second infusion target levels were attained in all patients. No differences in gender, body-weight, CRP, creatinine-protein ratio and the presence of edema at presentation were found between the patients who did and did not reach target level. Eculizumab levels after the second dose increased far above target range and resulted in near complete blockade of the classical complement pathway (measured with Wieslab® Euro Diagnostica complement system screen) in all patients (reference value 69-129%, complete deficiency <1%) (Figure).

Conclusions: After the first dose of eculizumab trough levels were not reached in 41% of the patients. Subsequent eculizumab levels exceed the recommendation. Our results suggest that the current induction protocol is insufficient: the first dose should be increased or the interval shortened, later doses may be reduced.

Funding: Commercial Support - Health insurance association, The Netherlands, Government Support - Non-U.S.

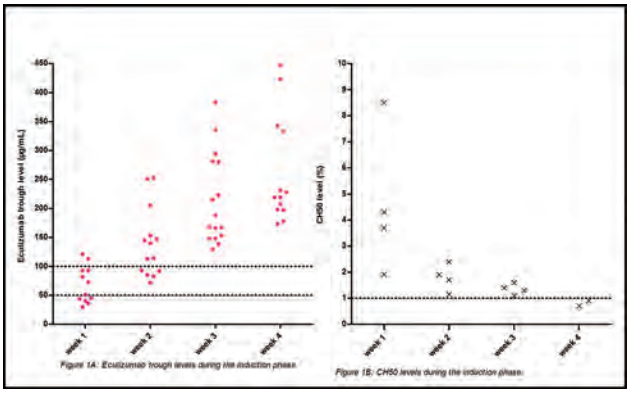

Figure 1A: Eculizumab trough levels during the induction phase. Figure 1B: CH50 levels during the induction phase.

FR-PO1050

The Study on the Mechanism of SOCS1/STAT1 Regulate Renal Inflammation in Mesangial Proliferative Glomerulonephritis Models

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Background: Glomerulonephritis (GN) is characterized by intraglomerular inflammation and is a major cause of end-stage renal disease. Inflammation plays a crucial role in the progress of mesangial proliferative glomerulonephritis (MsGN). The suppressor of cytokine signaling (SOCS) proteins which are inhibitors of cytokine signaling pathways unveiled an important mechanism for the negative regulation of the cytokine-induced JAK/STAT pathway. This study examined whether SOCS1 can regulate renal inflammation in MsGN models.

Methods: In Vivo: Rat (Thy 1.1 GN) and mouse (Habu GN) mesangial proliferative nephritis models were established. The expression of SOCS1, MHC class II, STAT1, inflammatory cells and cytokines were analyzed in MsGN modes. In Vitro: IFN-γ-stimulated mouse mesangial cells(MMCs)were transfected with SOCS1 plasmids. Meanwhile, we used STAT1 inhibitor fludarabine in IFN-γtreated MMCs. The expression of MHC class II, STAT1 and cytokines were analyzed.

Results: Thy1.1 GN recapitulates the main features of human mesangial proliferative glomerular diseases, was generated. In addition, mouse GN was induced with Habu snake venom (HV). The number of macrophages and CD4 T cells increased significantly in glomeruli of MsGN models. Expression of IFN-γ, TNF-α, IL-12A and IL-12B increased significantly in the course of Thy 1.1 and Habu nephritis. MHC class II is expressed in mesangial cells of MsGN models. SOCS1 protein also showed a significant decrease and P-STAT1 increased significantly at early stage in MsGN models. It suggested that SOCS1/STAT1 participate in MsGN model progression. STAT1 inhibitor decreases renal inflammation and ameliorates glomerular lesions in Habu GN. The overexpression of SOCS1 repress MHC class II and STAT1 phosphorylation which is induced by IFN-γ in mesangial cells. STAT-1 inhibitor could inhibit IFN-γ-induced CIITA promoter activity and MHC class II significantly.

Conclusions: This study emphasizes the pivotal role of the SOCS1/STAT1 axis in regulating inflammation in mesangial proliferative glomerulonephritis. In addition, it demonstrates that SOCS1 is a critical regulator of cellular sensitivity to IFN-γ-induced CIITA and MHC class II expression in mesangial cells. The negative feedback between the expression of SOCS1 and inflammation may play an important role in the mesangial proliferative glomerulonephritis.

Funding: Government Support - Non-U.S.

FR-PO1051

Evolution of Autoantibody Function in C3 Glomerulopathy

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Background: Autoantibodies play an important role in the pathogenesis of C3 Glomerulopathy (C3G). Binding of either C3 nephritic factors (C3Nef) or Factor B autoantibodies (FBAA) to the alternate complement (AP) pathway's C3 convertase (C3C) stabilizes this critical enzyme, prolonging its half-life and preventing normal regulation of the AP. The stabilizing characteristic of these antibodies are well described. Little is known about their correlation with disease natural history. Further characterization of C3G disease related autoantibodies has the potential to influence patient management algorithms.

Methods: Our study cohort included 8 C3G patients (drawn from the University of Iowa's C3G Natural History Study) in whom at least 3 squential draws were available (4 FBAA and 4 C3Nef). Comprehensive biomarker studies and autoantibody kinetic studies (SPR) were performed across multiple times points of disease course. Comparisons were made between C3C t ½, comprehensive biomarker assays and measures of clinical activity.

Results: FBAA kinetics were independent of FBAA titer or complement biomarker, and tended to be static over time. In contrast, the C3C stabilizing kinetic of C3Nef were more variable over disease course - tending to trend downward. In one patient, the C3Nef stabilization of C3C dropped by factor of 4 (211 minutes to 49.5 minutes over a 6 yr period

- with 5min being normal). This change was associated with a normalization of a previously undetectable C3.

Conclusions: Point assessments of C3Nef are insufficient to fully characterize the function of this autoantibody. C3Nef kinetics evolve over disease course and are associated with changes in both biomarkers of complement dysregulation and clinical activity. This preliminary data prompts a number of interesting hypotheses, not the least of which is the concept that C3Nef functional testing may be a way to detect "windows" of relative disease quiescence in given patients.

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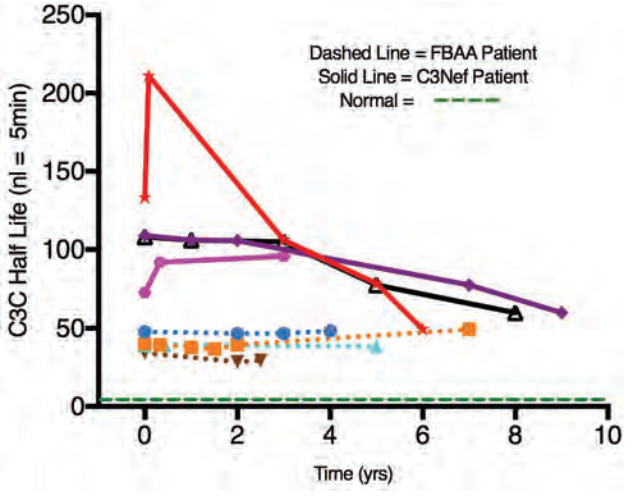

FR-PO1052

Complement and Cytokine Characterization of C3GN

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Background: The complement pathway is an innate immune defense mechanism, when uncontrolled can cause damage to host tissues including the kidney upon uncontrolled activation of the alternative complement pathway (ACP). C3GN is characterized by deposits in the glomerulus made up entirely of complement C3 protein without the presence of immunoglobulins.

Methods: We determined the cytokine and complement profiles derived from the plasma of 40 C3GN cases, and 15 healthy controls (HC), utilizing the Luminex assay.

Results: Analysis of the plasma from 40 C3GN patients compared to HC revealed significant decreases in the complement pathway proteins C3 (424±336 vs 673±118 μg/ml), C4 (233±71 vs 392±115 μg/ml), C4b (10.9±4.3 vs 15.9±3.1 μg/ml), C5 (15.8±8.3 vs 24.3±6.4 μg/ml), CFH (247±60 vs 285±44 μg/ml), and Properdin (19.2±5.3 vs 25.2+5.6 μg/ml). In-depth analysis of the plasma derived from C3GN patients identified significantly low C3 levels (2*SD below Average HC) in 21 patients, in which 72% of these had significantly low levels of plasma C5. Key components of the ACP are CFH and properdin, and we only identified 10 patients with significantly low levels CFH (7 associated with low plasma C3), and 11 with significantly low levels properdin (8 associated with low plasma C3). Global cytokine analysis in C3GN plasma determined significant increases in proinflammatory cytokines TNFα detected in 100% of C3GN patients (17.9+8.9 pg/ml) and IL-1α detected in 82% of C3GN patients (80.3±80.1 pg/ml) compared to HC ((100%) 7.2+3.6 and (40%) 29.7+29.9 pg/ml, respectively). Cytokine analysis demonstrated bi-modal patterns with increased percentage of C3GN patients having elevated levels of pro-inflammatory cytokines, IL-6 and IL-12p40 was more prevalent in the plasma of C3GN patients (45% and 50% respectively), compared to HC (26% and 26% respectively)

Conclusions: The plasma of C3GN patients demonstrates activation of the ACP and elevated levels of proinflammatory cytokines that are associated with stimuli know to activate the ACP. Our data set is being expanded to include additional samples and will be correlated with the clinical status of patients. In-depth profiling of immunological markers and the specific relationships will able to design a panel specific to individual complement associated glomerular pathology.

FR-PO1053

C3 Glomerulopathy: Pattern of Injury and Response to Treatment

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Background: C3 glomerulopathy refers to those renal lesions characterized histologically by predominant C3 accumulation within the glomerulus with absent or scanty immunoglobulin deposition, and pathogenetically by aberrant regulation of the alternative pathway of complement. Objectives:To describe the evolution of renal involvement and the response to treatment with 1year follow- up.

Methods: Observational study case series type. The data were extracted from NefroRed©, a platform that contains the socio-demographic, anthropometric, clinical and laboratory data of 1340 patients with kidney biopsies from 2007-2015. It was selected for the study those patients that showed the pattern of glomerulonephathy and C3 deposits only or predominant. The primary endpoint for subjects enrolled was change in proteinuria and serum creatinine over treatment period. Patients will be subclassified into three groups, those who had been treated with mycophenolate mofetil (MMF), Cyclophosphamide (CP) and those who had anti-complement therapy with eculizumab (ECZ). Statistical analysis descriptive.

Results: 34 patients with C3 glomerulopathy were identified. Pathological lesion: 80% membranoproliferative glomerulonphritis, 6.7% GSFS, 6.7% mesangial proliferative, 6.7% membranous. Clinical preentation: 86.67% Nephrotic Syndrome, 26.67% nephrytic syndrome, 13% renal insuficiency, 53.33% Hypertension. 15 patients received active treatment with CP, 12 with MMF and 3 with eculizumab.

Conclusions: The scope of the study is limited largely because of the rarity of these disorders. There was not a response to ECZ. The treatment with MMF improved proteinuria but not renal function. The CP improved proteinuria and creatinine. Reports suggest that a in our population the cyclophosphamide is more effective. Formal trial of comprising a greater number of well-characterized patients is warranted.

Comparison of the CrSr and Proteinuria between MMF, ECZ and CP

SrCr	Baseline	12 months	p-value
MMF	1.52 CI 0.74	1.21 CI 0.38	NS
ECZ	3.01 CI 2.07	1.83 CI 0.47	NS
CP	1.53 CI 0.95	1.10 CI 0.42	<0.05
Prot	Baseline	12 months	p-value
MMF	1677.42 CI 1031.83	1212.42 CI 717.24	<0.05
ECZ	1266.33 CI 1735.97	1162.67 CI 1382.19	NS
CP	2624.00 CI 1882.23	2098.44 CI 1608.42	<0.05

MMF: Mofetil Mycophenolate; CP: Cyclophosphamide; ECZ: Eculizumab; SrCr: Serum Creatinine; NS: Not Significant.

FR-PO1054

Comparison Among Dominant C1q Positive Cases Including C1q Nephropathy Classified by Immunofluorescence

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Background: Although the disease entity of C1q nephropathy was first described by Jennette and Hipp in 1985, the characteristics of the heterogeneous phenotypes and the pathogenic role of C1q for the disease progression has not been elucidated yet. We analyzed dominant C1q positive renal biopsy specimens to speculate the significance of C1q localization.

Methods: A total of 1763 consecutive patients performed renal biopsy at Kyoto University Hospital from 1982 through 2001 were investigated. We analyzed 34 cases (1.9%) with dominantly C1q-positive staining excluding lupus nephritis, IgA nephropathy, and membranous nephropathy. Next, we classified these patients into three groups; C1q mono-dominant (mC1q) group (n=3) with no immunoglobulin deposition and C1q co-dominant group (total n=31) with IgG (cC1q-IgG) (n=19) or IgM (cC1q-IgM) (n=12).

Results: Precise pathological analysis showed in mC1q group, minor glomerular abnormality in light microscopy (LM), with mesangium localization of C1q with C3d positivity in immunofluorescence microscopy (IF). Apparent electron dense deposit (EDD) and foot process effacement were observed in electron microscopy (EM). CC1q-IgG group revealed variety of glomerulonephritis pattern frequently showing capillary wall involved glomerular lesion such as double contour, subendothelial deposit and crescent formation with high frequency of global sclerosis. C1q localized in capillary wall and mesangium accompanying IgG, and IgM in all cases and additional IgA in 15 cases with strongly positive C3c and C3d in IF. CC1q-IgM group exhibited focal segmental sclerosis and double contour in LM. C1q was positive in mesangium colocalized with IgM and C3d in all but C3c in some in IF. EDD was negative in all 6 cases in EM. Laboratory data revealed cC1q-IgG group included relatively severe cases in creatinine level and hematuria compared with the other two groups.

Conclusions: The hypothesis of glomerular injury through activation of complement system might be applicable via immune complex formation in cC1q-IgG group, directly in mC1q group and not applicable in cC1q-IgM group. The analysis of dominant C1q-positve renal biopsy specimens include several diseases in these case series raises the possibility that current category of C1q nephropathy indicates some specific condition of existing diseases.

FR-PO1055

Fibrillary Glomerulonephritis: Clinical Features and Outcomes in an Ethnically Diverse Urban European Population

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Background: Fibrillary glomerulonephritis (FGN) is a rare glomerular lesion characterised by the presence of 20nm fibrillary deposits on electron microscopy (EM). It is usually associated with poor renal outcomes. The largest case series to date describe North American populations.

Methods: We performed a retrospective case note review of patients with FGN, identified through the renal histology database at our tertiary referral hospital in the UK from 2001-17. EM has been performed routinely on all native biopsies since 2014.

Results: We identified 19 patients with FGN. 7 had a second histological lesion present including: IgA disease (2), vasculitis (4) nodular glomerulosclerosis (1). The median age at presentation was 58 (47-72) years, with a female preponderance (1.7:1 F:M). 83% were Caucasian. There were no strong associations with systemic disease. At presentation, median eGFR was 44 (20-68) ml/min and urine albumin:creatinine ratio 264 (80-351) mg/mmol. Hypertension (35%), proteinuria (88%), haematuria (71%) and hypercholesterolaemia (71%) were common while nephrotic syndrome was rare (11%). 38% patients received immunomodulatory therapy: corticosteroids (n=6), mycophenolate mofetil (n=2), azathioprine (n=1), cyclophosphamide (n=1). After median 44 (22-49) months follow-up, 47% patients were clinically stable, 6% had progressive CKD, 35% had progressed to end stage renal disease (ESRD) and 12% had died. Of those patients receiving immunomodulatory therapy, n=3 were stable, n=2 progressed to ESRD and n=1 had died. Renal insufficiency and significant proteinuria at diagnosis were risk factors for poor renal outcomes. Patients with FGN alone had significantly better renal outcomes than those with a second histological lesion; 75% of patients with vasculitic lesions progressed to ESRD.

Conclusions: Diagnosis of FGN has become more common with routine use of EM. FGN was more common in Caucasian patients, even in an ethnically diverse population. In contrast to previous studies, there were no strong associations with systemic disease. The efficacy of immunomodulatory therapy is difficult to evaluate in a small sample size. Significant proteinuria and renal insufficiency were poor prognostic indicators. Renal outcomes were better than in published case series; longer follow-up is required to determine the significance of this observation.

FR-PO1056

ABIN1 Contributes to Glomerulonephritis via Induction of IP-10 Expression and Activity

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Background: Our research to define genetic risks of glomerular inflammation identified variants in TNIP1 as risks for development of lupus nephritis. TINIP1 encodes ABIN1, a physiological inhibitor of NF-κB and MAPK-mediated inflammation. We reported that loss of ABIN1 function in podocytes (ABIN1[D485N]) exacerbates immune-mediated podocyte injury and enhances podocyte cytokine and chemokine production in vivo and in vitro, leading to enhanced neutrophil recruitment and activation. The NF-κB-mediated chemokine IFN-γ-inducible protein 10 (IP-10) had a > 20-fold increase in gene expression in podocytes with loss of ABIN1 activity. The current study tested the hypothesis that IP-10 contributes to ABIN1-mediated podocyte injury and glomerular inflammation.

Methods: In vitro exocytosis (flow cytometry for granule markers CD66b and CD35) and chemotaxis (transwell migration assay) of primary human neutrophils was measured following incubation with recombinant IP-10 w/wo a known activator FMLF. Urinary IP-10 levels were measured by ELISA 24 h following administration of nephrotoxic anti-GBM antibody in WT and ABIN1[D485N] mice. Proteinuria was measured 24 h following administration of anti-GBM in WT and ABIN1[D485N] mice w/wo pre-treatment with neutralizing IP-10 antibody.

Results: Recombinant IP-10 did not activate neutrophil chemotaxis alone, but significantly primed the response to FMLF. IP-10 activated neutrophil exocytosis alone and also primed the FMLF response. Urinary IP-10 levels were significantly higher in ABIN1[D485N] mice than WT mice 24 h-post anti-GBM administration. Anti-GBM-induced proteinuria was inhibited by pre-treatment with IP-10 antibody in WT and ABIN1[D485N] mice.

Conclusions: Our data suggest that genetic disruption of ABIN1 in podocytes results in enhance production of IP-10 during experimental glomerulonephritis and that IP-10 production regulates neutrophil activation and contributes to glomerular damage leading to proteinuria. Our data provide clinical relevance for the finding that IP-10 is a urinary biomarker for lupus nephritis (LN). The use of IP-10 neutralizing antibody for treatment of ulcerative colitis and rheumatoid arthritis, suggests a new therapeutic approach for patients with LN associated with variants for TNIP1 or other NF-κB or MAPK regulatory genes.

Funding: Other NIH Support - NIAMS, Clinical Revenue Support

FR-PO1057

Elevated Levels of Urinary Extracellular Vesicle Fibroblast-Specific Protein 1 in Patients with Active Crescentic Glomerulonephritis

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Background: Extracellular vesicles (EVs), including exosomes, are present in a variety of bodily fluids, including urine. We previously reported that large numbers of fibroblast-specific protein 1 (FSP1)-expressing cells accumulate within damaged glomeruli and that urinary FSP1 could potentially serve as a biomarker of ongoing glomerular injury. However, the precise mechanism by which urinary FSP1 is secreted is unknown.

Methods: To address that issue, we collected urine samples from 37 patients with various types of glomerular disease (6 with ANCA-associated nephritis, 11 with IgA nephropathy, 11 with membranous nephropathy, 6 with minimal-change disease and 3 with lupus nephritis), purified the urinary EVs using total exosome isolation regent, and characterized the vesicles using Nanosight, western blotting and immunoelectron microscopy. We measured FSP1 levels in total urine and EVs fraction with sandwich ELISA. FSP1 level associated with crescentic formation were evaluated by receiver operating characteristic (ROC) curve analysis.

Results: Deemed to be mainly exosomes, based on their size distribution, the vesicles contained FSP1. Moreover, a portion of these FSP1-positive EVs were also positive for podocalyxin. ELISAs showed that FSP1 levels in urinary EVs correlated positively with rates of biopsy-proven cellular crescent formation ($r = 0.562$, $P < 0.001$) and total crescent formation ($r = 0.448$, $P = 0.005$) among total glomeruli. FSP1 levels in urinary EVs were significantly higher in patients with cellular crescents affecting 20% or more of their glomeruli than in those with fewer affected glomeruli ($P = 0.003$). FSP1 level in EVs for predicting cellular crescent formation affecting more 20% was 2.4 ng/mL, with an area under the ROC curve were 0.88 (95%CI, 0.693 to 1.070). FSP1 levels in urinary EVs also correlated positively with total urinary FSP1 levels ($r = 0.834$, $P < 0.001$) in patients with at least one cellular crescent.

Conclusions: These data suggest that a portion of urinary FSP1 is secreted as microvesicles originating from podocytes, and that FSP1 levels in urinary EVs reflect active and ongoing glomerular injury, such as cellular crescent formation.

FR-PO1058

Deficiency for the Chemokine Receptor CCR2 Protects from Glomerular Injury and Interstitial Fibrosis in Adriamycin-Induced Glomerulosclerosis

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Background: Glomerulosclerosis and tubulointerstitial fibrosis are hallmarks of chronic kidney injury leading to end-stage renal disease. Inflammatory mechanisms contribute to glomerular and interstitial scaring including chemokine-mediated recruitment of leukocytes. In particular, accumulation of chemokine receptor CCR2 expressing macrophages promotes renal injury and fibrotic remodeling in diseases like glomerulonephritis and diabetic nephropathy. However, whether CCR2 plays a functional role in the initiation and progression of primary glomerulosclerosis induced by podocyte injury remains unclear.

Methods: To explore potential pro-inflammatory and pro-fibrotic functions of CCR2 in focal segmental glomerulosclerosis (FSGS) we analyzed adriamycin-induced nephropathy, a murine model of FSGS, in BALB/c wild-type and *Ccr2*-deficient mice.

Results: In adriamycin-induced FSGS progressive glomerular scaring and reduced glomerular nephrin expression was paralleled by induced glomerular expression of the CCR2 chemokine ligand CCL2. In comparison to wild-type, *Ccr2*-deficient mice with adriamycin nephropathy showed reduced albuminuria and preserved renal function. Whereas the extent of glomerular podocyte and endothelial cell injury was similar, glomerular sclerosis and glomerular macrophage infiltration were reduced in *Ccr2*-deficient mice. Moreover, *Ccr2* deficiency decreased tubular damage, interstitial leukocyte infiltration, renal inflammation and renal expression of extracellular matrix molecules. Consistently, tubulointerstitial fibrosis, accumulation of αSMA-positive myofibroblasts and renal fibroctyes were reduced in *Ccr2*-deficient kidneys.

Conclusions: Our data indicate that the chemokine receptor CCR2 contributes to glomerular scaring and interstitial fibrosis in FSGS by facilitating glomerular and tubulointerstitial infiltration of macrophages, renal inflammation, and renal accumulation of fibrocytes. Thus, CCR2 is an important mediator of glomerular injury and progression of FSGS. CCR2 targeting therapies may represent a novel approach for its treatment.

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FR-PO1059

The Acute-Phase Protein α1-Acid Glycoprotein Ameliorates Proteinuria Through Maintaining Renal Endothelial Barrier Function and Modulating Macrophages Polarization in Proteinuric Kidney Disease

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Background: Proteinuria is the hallmark of progressive chronic kidney disease (CKD). It is highly desired to develop an effective strategy that prevents glomerular filtration barrier injury and renal inflammation which can cause proteinuria. The acute phase plasma protein, α_1-acid glycoprotein (AGP) is a component of glomerular endothelial barrier and contributes to maintaining an intact barrier. In addition, we have previously showed that AGP has anti-inflammatory action via up-regulating CD163 in macrophage. The purpose of this study is to evaluate the renoprotective effect of exogenously administered-AGP against adriamycin-induced nephropathy (AN), a model of chronic proteinuric renal disease.

Methods: AN-mice were created by the administration of 15mg/kg of adriamycin. AGP was administered to AN mice (*iv*) from day 1 to day 5. Mice were sacrificed on day 7 or 21. Renal function, structural injury and inflammation were evaluated. The renal glomerular distribution of exogenous administered AGP was examined by immunostaining using anti-AGP antibody. To investigate the effect of AGP on macrophage polarization, *in vitro*experiments were performed using PMA-differentiated THP-1 cells.

Results: AGP administration ameliorated AN-induced proteinuria, histological changes and macrophage infiltration in renal tissue. We also found the decreased distribution of endogenous AGP on the glomerulus in AN-mice, but this decrease was recovered by the administration of exogenous AGP. In kidney of AGP-treated mice, increased mRNA expression of CD163, M2 macrophage marker, and decreased mRNA expression of iNOS,

M1 macrophage marker, were observed. To confirm this finding in vitro, we investigated the effect of AGP on THP-1-derived macrophage polarization. The data showed that AGP treatment significantly increased CD163 mRNA expressions, while it decreased iNOS mRNA expression, suggesting that AGP could be able to modulate the macrophage phenotype to anti-inflammatory potential.

Conclusions: AGP ameliorates proteinuria through maintaining renal endothelial barrier function and modulating macrophages polarization.

FR-PO1060

Classic IL-6R Signaling in CD4+ T Cells Directs Nephritogenic Th17 Responses and Enhances Treg Function

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Background: Th17 cells are central pathogenic mediators of glomerulonephritis (GN), while regulatory T cells (Tregs) mediate protection. The pleiotropic cytokine IL-6 was shown to modulate the function of both cell populations, but many aspects in this process remain unclear. These include the mode of IL-6 signaling responsible (classic, alternative or cluster), whether IL-6 effects are mediated in a cell intrinsic fashion or indirectly and finally the functional importance of T cell subtype specific IL-6R signaling for GN.

Methods: Selective abrogation of classic IL-6 signalling on T cells was achieved by generating quadruple transgenic $CD4^{Cre}$xIL-$6Ra^{fl/fl}$ mice, harbouring flourochromes under control of the Foxp3 (FIR) and IL-10 promoters (Tiger). The NTN model of crescentic GN was studied in these mice and in $Rag1^{-/-}$ recipients after transfer of different $CD4^+$ T cell populations.

Results: $Rag1^{-/-}$ recipients of IL-6R deficient $CD4^+$ T cells showed significantly and selectively reduced splenic and renal Th17 responses. In line, renal neutrophil recruitment was substantially diminished. Surprisingly, however, the course of NTN was not ameliorated. As one possible explanation, we found reduced Treg infiltration into recipient kidneys of IL-6R deficient $CD4^+$ T cells. Additional studies in $CD4^{Cre}$xIL-$6R^{fl/fl}$xFIRxTiger mice revealed, that production of anti-inflammatory IL-10 by $Foxp3^+$ Tregs and $Foxp3^-$ Tr1 cells, was not affected by absence of IL-6R signaling. In a next step, we transferred Treg depleted $CD4^+$ T cells into $Rag1^{-/-}$ mice and again studied NTN. Also in this setting, Th17 responses were strikingly reduced by lack of IL-6R signaling in $CD4^+$ T cells. Importantly, however, in the absence of Tregs in both groups, NTN was significantly ameliorated in recipients of IL-6R deficient $CD4^+$ Teff.

Conclusions: Our data indicate, that classic IL-6R signaling on T cells, induces nephritogenic Th17 reponses and aggravates crescentic GN. Surprisingly, however, classic IL-6R signaling also enhances Treg function via currently undefined pathways. Given the impact on potential IL-6R directed therapies, the underlying molecular mechanisms clearly need to be defined by further studies.

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FR-PO1061

Kidney-Targeted Autoimmunity Exposed in Human Immune System Mice

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Background: Lupus and anti-GBM nephritis are paradigmatic systemic and organ-specific autoimmune diseases, respectively, in which kidney and other organ injury is induced by pathogenic autoantibodies. Gene-environment interactions are implicated in disease induction, yet mechanisms by which this occurs in man are poorly understood. We explored the utility of an in vivo human immune system model (HuHSC-NSG) to study autoimmune regulation by inhaled crystalline silica, an environmental exposure compellingly linked to multiple human autoimmune diseases with a prominent humoral component.

Methods: Conditioned immunodeficient NOD-scid-gamma (NSG) mice were intravenously injected with CD34+ human hematopoietic stem cells (HSC) from two different donors and monitored for reconstitution with a human immune system. Three months after engraftment, mice were exposed to crystalline silica (Si) or vehicle (V, saline) by oropharyngeal aspiration. Tissue was collected 1-3 months post-aspiration. Chimerism was determined by flow cytometry, and lung pathology and lymphocytic infiltrates were scored by investigators blinded to experimental conditions. Serum autoantibodies that bound DNA or the NC1 domain of the alpha3 chain of collagen IV were measured using enzyme linked immunosorbent assay. Data are reported as mean±SD.

Results: HuHSC-NSG mice (n=29) demonstrated mean spleen chimerism of 57.6±28.4%, with the human CD45+ subset composed of 70.7±18.6% B cells and 19.4±20.1% T cells. Si-exposed subjects developed significantly greater lung injury and inflammation than did their V-exposed counterparts, with composite lung pathology score 2.8±2.2 vs 0.7±1.7, Si vs V, $p<0.05$. Focal infiltrates of human CD45+ leukocytes were observed in Si-exposed lungs. All mice developed circulating human IgM and IgG, and a subset had detectable circulating human anti-DNA or anti-alpha3(IV)NC1 collagen autoantibodies.

Conclusions: NSG mice reconstituted with a human immune system develop Si-induced lung injury and circulating autoantibodies with specificities relevant to human antibody-mediated nephritis. This model should be useful in studying gene-environment interactions that promote pathogenic autoimmunity in humans, without putting volunteers or patients at risk.

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FR-PO1062

Treatment of Glomerulonephritis Using Drugs Targeting Folate Receptor Expressing Activated Macrophages

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Background: Macrophages are linked with the irreversible scarring that leads to end-stage renal disease. Since activated macrophages highly express a functional folate receptor β (FRβ), targeting this population of macrophages with folate-linked drugs could increase selectivity in the treatment of inflammatory diseases.

Methods: Accordingly, we synthesized and investigated the biologic activity of a novel folic acid-aminopterin conjugate (FA-AMT) designed to intracellularly deliver AMT specifically via the FR. The anti-inflammatory activity of FA-AMT was evaluated in a model of severe, macrophage-mediated anti-glomerular basement membrane glomerulonephritis in WKY rats.

Results: Toxicity assessment demonstrated that FA-AMT is not toxic (its maximum tolerated dose was 40-fold higher compared to unmodified AMT). We found that treatment with FA-AMT significantly attenuated kidney injury and preserved normal renal function. Glomerular proliferation, necrotizing lesion, crescent formation, tubulointersititial injury (TIN), and the number of tubular casts, a good indicator of chronic TIN injury, were markedly reduced in the FA-AMT-treatment group compared with the control group. FA-AMT reduced glomerular macrophage infiltration (52%) and decreased M1 macrophage phenotype without affecting M2 macrophages. Notably, interstitial macrophage accumulation that predicts progression of kidney injury was decreased in rats treated with FA-AMT. The expression of CCL2 and the pro-fibrotic cytokine TGF-β were reduced in nephritic glomeruli with FA-AMT treatment. Importantly, in rats treated with FA-AMT there was a significant reduction in the deposition of type I, III, and IV, collagens. Staining with specific anti-FRβ antibody showed no expression of this receptor in normal kidneys, however, in nephritic kidneys FRβ was mainly expressed on macrophages present in the crescents and also on macrophages within the glomerular capillaries. Notably, in rats treated with FA-AMT, the expression of FRβ was decreased and correlated with less macrophage infiltration and reduced crescent formation.

Conclusions: These findings suggest that targeting kidney activated macrophages attenuates inflammation and prevents progression of kidney injury and that because this is a FR-restricted specific treatment systemic immunosuppression can be prevented.

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FR-PO1063

KLF4 on Macrophages Attenuates TNF-α Mediated Kidney Inflammation and Fibrosis in Autoimmune Nephritis

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Background: The Kruppel-like factor (KLF) family of transcriptional regulators play complex roles in the pathogenesis of kidney disease. We recently found that activating type 1 angiotensin receptors in macrophages upregulates KLF4 and paradoxically limits renal fibrosis. As KLF4 attenuates NF-kB-dependent vascular injury, we directly investigated the role of macrophage KLF4 in renal inflammation and fibrosis using the murine nephrotoxic serum nephritis (NTS) model. As KLF4 suppressed TNF-α in intra-renal macrophages in our studies, we additionally probed the contribution of macrophage TNF-α to NTS progression.

Methods: Mice with floxed alleles for the genes encoding KLF4 or TNF-α were bred with LysM-Cre mice to yield KLF4 or TNF "MKO" mice with macrophage-specific deletion of KLF4 or TNF-α, respectively. NTS was induced in KLF4 MKO, TNF MKO, and wild-type (WT) littermate control mice by IV injections of sheep IgG followed 5 days later by sheep anti-mouse GBM serum.

Results: At day 14 NTS, KLF4 MKO mice compared to WTs had augmented glomerular matrix deposition (44.4 ± 3.3 vs 33.7 ± 2.5%; P = 0.04), urinary albumin/Cr ratios (7.7 ± 0.8 vs 5.3 ± 0.6 mg/mg; P = 0.05), and renal NGAL mRNA (1.3 ± 0.1 vs 1.0 ± 0.2 au; P = 0.03). KLF4 MKO kidneys also showed increased mRNA levels for collagen 1 (1.9 ± 0.2 vs 1.0 ± 0.3 au; P = 0.01), fibronectin (1.7 ± 0.2 vs 1.0 ± 0.2 au; P = 0.03), and the fibrosis mediators TGF-β (1.4 ± 0.1 vs 1.0 ± 0.2 au; P = 0.03) and PAI-1 (1.4 ± 0.1 vs 1.0 ± 0.2 au; P = 0.03). CD11b+ Ly6Chi inflammatory macrophages isolated directly from NTS kidneys of KLF4 MKO animals had 50% higher TNF-α expression than WTs (1.5 ± 0.1 vs 1.0 ± 0.1 au; P = 0.04). To explore whether macrophage KLF4 protects the kidney by suppressing TNF-α, we repeated our NTS studies in TNF MKO mice and WT controls. At day 14 of NTS, TNF MKOs compared to WTs had reduced glomerular matrix deposition (33.2 ± 0.6% vs 43.8 ± 1.6%; P < 0.01), urine albumin/Cr ratios (3.6 ± 0.4 vs 4.7 ± 0.3 mg/mg; P = 0.04), and mRNA levels for NGAL (0.5 ± 0.1 vs 1.0 ± 0.2 au; P = 0.02), collagen 1(0.5 ± 0.2 vs 1.0 ± 0.2 au; P = 0.04), aSMA (0.3 ± 0.1 vs 1.0 ± 0.2 au; P < 0.01), and PAI-1 (0.6 ± 0.1 vs 1.0 ± 0.1 au; P < 0.01).

Conclusions: KLF4 activation on macrophages mitigates renal injury and fibrosis during NTS by inhibiting production of macrophage-derived TNF-α.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO1064

Characterisation of a Novel P2X7 Deficient Rat and Differential Requirement for P2X7 for Release of IL-1β from Bone Marrow Derived Cells In Vitro

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Background: P2X7 is an ionotropic receptor activated by extracellular ATP and expressed on immune cells including macrophages and dendritic cells. P2X7 may have an important role in kidney disease. However, the specific role of P2X7 in different cell types is controversial. We characterise a novel P2X7 knockout (KO) rat and define the role of P2X7 in IL-1β production in bone marrow derived macrophages (BMDM) and dendritic cells (BMDC).

Methods: A P2X7 KO rat was created using zinc finger nucleases. Cells and tissues were used for extraction of protein and mRNA for Western blot and PCR. P2X7 function was assessed using uptake of Yo-pro1 dye in response to ATP and by stimulating cells with LPS 1μg/ml followed by ATP 5mM, and measuring IL-1β production. When P2X7 antagonist or caspase-1 inhibitor was used this was added 30 mins prior to LPS.

Results: No P2X7 protein was detected in P2X7 KO rat cells or tissue. BMDM and BMDC from WKY WT but not P2X7 KO rats formed pores and took up Yo-pro1 following ATP stimulation. As expected, WKY WT BMDM produced significant IL-1β when stimulated with LPS plus ATP compared to LPS alone. In contrast, BMDM from P2X7 KO rats did not produce IL-1β (Figure 1A). However, both WKY WT and P2X7 KO BMDC were able to cleave IL-1β following stimulation with LPS alone, Use of a P2X7 antagonist (A438079) confirmed this was P2X7 independent (Figure 1B). IL-1β release was independent of K+ efflux from cells, but was inhibited by a caspase-1 inhibitor.

Conclusions: This is the first description of a novel P2X7 KO rat showing it is a true knockout. BMDC (but not BMDM) do not require a second signal via P2X7/ATP to produce active IL-1β. IL-1β is a powerful pro-inflammatory cytokine and is thought to play a role in human and experimental glomerulonephritis; understanding how different cell types use different pathways to produce IL-1β will improve our understanding of the pathogenesis of kidney diseases.

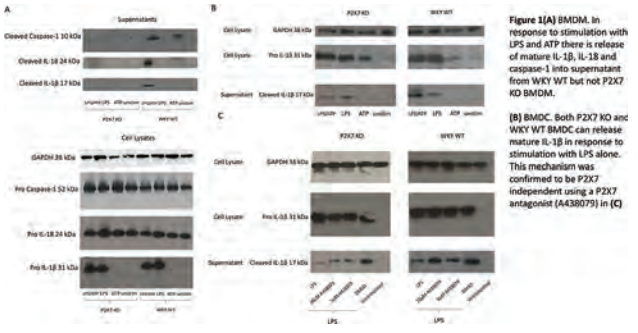

Figure 1(A) BMDM. In response to stimulation with LPS and ATP there is release of mature IL-1β, IL-18 and caspase-1 into supernatant from WKY WT but not P2X7 KO BMDM.

(B) BMDC. Both P2X7 KO and WKY WT BMDC can release mature IL-1β in response to stimulation with LPS alone. This mechanism was confirmed to be P2X7 independent using a P2X7 antagonist (A438079) in **(C)**

FR-PO1065

Neuraminidase Activity Mediates IL-6 Secretion from Activated Lupus Mesangial Cells Through TLR4 and MAPK p38

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Background: Glycosphingolipid (GSL) levels and the activity/levels of the enzyme neuraminidase (NEU), which mediates GSL catabolism, are elevated in the kidneys and/or urine of lupus mice and human patients with nephritis compared to their non-nephritic counterparts and healthy controls. We recently demonstrated that NEU activity mediates IL-6 secretion from mesangial cells (MCs) in response to activation by heat aggregated IgG (HA-IgG) and lupus serum. Our previous results demonstrated that NEU1 and NEU3 staining partially overlapped with IgG deposits in cell cultures of primary MCs stimulated with HA-IgG and in renal sections of kidneys from nephritic lupus mice. Both Fcγ receptors (FcγRs) and TLRs can mediate immune complex activation of cells, are expressed by MCs, and were shown to be involved in progression of lupus nephritis. In this study, we examined the role of FcγRs and toll like receptors (TLRs), and downstream signaling pathways in NEU-mediated secretion of IL-6 by activated lupus prone MCs.

Methods: Cell surface receptors and MAPK pathways were identified by treating MC cultures with antibodies and inhibitors, respectively, prior to activation with HA-IgG or lupus serum. Phosphorylation of p38 was analyzed by western immunoblot. Cellular localization of NEUs and TLR4 was performed by immunofluorescence. Screening of cytokines secreted by MCs was performed using a 20-plex Luminex cytokine array. Levels of individual cytokines were quantified by ELISA.

Results: Blocking TLR4 significantly inhibited, while blocking FcγRs had no effect on, NEU-mediated IL-6 secretion by activated MCs. Preliminary results show overlap between TLR4 and NEU1 at the plasma membrane of MCs. An inhibitor of the p38 MAPK pathway significantly blocked NEU mediated IL-6 secretion. Phosphorylation of p38 was increased following activation of MCs with HA-IgG or lupus serum and was blocked when NEU activity was inhibited or NEU1 expression was reduced. Although several cytokines were secreted in response to activation by both HA-IgG and lupus serum, only IL-6 and IP-10 (CXCL10) were blocked when NEU activity was inhibited.

Conclusions: Together our results suggest that NEU specifically mediates secretion of IL-6 and IP-10, two cytokines important during early development of lupus nephritis, from activated lupus prone MCs through a TLR4-p38 MAPK pathway.

Funding: Other U.S. Government Support

FR-PO1066

Patient Derived Endothelial Cells as Tool to Study the Effects of Shiga Toxin on the Vascular Endothelium: The BO(ST)EC-Study

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Background: Hemolytic Uremic Syndrome (HUS) is a form of thrombotic microangiopathy (TMA), which is characterized by hemolytic anemia, thrombocytopenia and acute renal failure. HUS is caused by infections with Shiga toxin (Stx) producing Escherichia coli with subsequent damage of the vascular endothelium (STEC-HUS or eHUS). We have established an *in vitro*system to screen for endothelial susceptibility factors: using Blood Outgrowth Endothelial Cells (BOECs) we can study the function of the endothelium of individual eHUS patients. We hypothesize that endothelial characteristics determine the response to Stx and thus the manifestation of eHUS.

Methods: BOECs from a healthy donor were used (male, 50 years old). Experiments were done in threefold (N=3) or as indicated in the figure. Previous literature has shown that Stx preferentially binds to the endothelial Gb3 receptor. In our study, Vero cells (positive control) and BOECs were cultured. Immunofluorescence imaging of live cells was used to confirm presence or absence of the Gb3 receptor on the cell surface. Using confocal immunofluorescence microscopy, binding of Stx to the cell surface was determined. A lactate dehydrogenase (LDH) cytotoxicity assay was used to assess for cytotoxicity of Stx and to standardize Stx concentrations for future experiments aiming at a level of cell damage of 50%. With flow cytometry, using antibodies for Annexin V and PI, necrotic vs. apoptotic cell death in response to Stx incubation was quantified. Finally, the effect of Stx on endothelial cell motility was determined in a scratch wound assay.

Results: We found that: 1) the Gb3 receptor is present on the cell surface of BOECs; 2) there is an expected positive dose-response relationship, wherein a higher concentration of Stx resulted in increased cell damage. Pre-treatment with TNF-alpha 10 ng/ml for 24 hours and treatment with Stx type 2 10^{-5} ug/ml resulted in 50% cell death; 3) incubation of BOECs with Stx resulted in more apoptotic than necrotic cell death; and 4) endothelial wound healing was impaired when cells were incubated with Stx.

Conclusions: BOECs are a promising tool with high translational potential to study effects of Stx on the vascular endothelium.

Funding: Government Support - Non-U.S.

FR-PO1067

Glomerular Endothelial Cells Lacking Neonatal Fc Receptor Have Decreased Major Histocompatibility Complex Type II Expression Due to Decreased Transcriptional Signaling

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Background: Glomerulonephritis (GN) requires intrinsic renal cells that express Major Histocompatibility complex type II (MHCII) to propagate the disease. Glomerular endothelial cells (GEnC) can express MHCII but it is unclear if they can present antigen. Neonatal Fc receptor (FcRn) is a trafficking protein that is required for antigen processing and presentation and is also expressed in GEnC. It has been demonstrated that when FcRn is globally knocked out, GN is prevented. The exact mechanism by which knock out of FcRn offers protection from GN is incompletely understood. An understanding of how FcRn is involved in MHCII expression by GEnC could lead to novel therapeutic options.

Methods: We isolated and purified GEnC from wild type (WT) & FcRn knockout (KO) mice by isolating glomeruli. We then used von Willebrand factor (vWF) coated dynabeads to isolate the endothelial cells. The cells were characterized using IF for vWF and a podocyte specific marker (WT1). Once characterized & purified, we used a temperature sensitive SV40 virus to conditionally immortalize both the cell lines. The cells were grown under permissive conditions at 33°C and differentiated at 37°C. Quantitative PCR (qPCR) was used to demonstrate appropriate expression of endothelial cell markers and verify the expression of FcRn in WT and absence in KO. We then treated our GEnCs with INFγ and TNFα and used flow cytometry to evaluate for the expression of CD146 (an endothelial cell marker) and MHCII. We also used qPCR to evaluate mRNA expression of MHCII, MHCII chaperone protein (CD74 also known as invariant chain), and transcript regulator protein (CIITA) to evaluate for differences in level of expression of MHCII and its key transcriptional components.

Results: We demonstrated by flow cytometry that while IFNγ significantly upregulated expression of MHCII in both WT and KO, KO GEnC had significantly less expression of MHCII compared to WT. We also found significantly less MHCII, CD74, and CIITA mRNA in KO compared to WT GEnC.

Conclusions: These findings suggest that the absence of FcRn alters the signaling needed for MHCII transcription. This finding may provide new insight and offer potential new targets for therapies GN.

Funding: NIDDK Support

FR-PO1068

Concerted Role of Kruppel-Like Factor 4 and Endothelial Nitric Oxide Synthase in the Renal Endothelium

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Background: Both the transcription factor, Kruppel-like Factor 4 (KLF4), and endothelial nitric oxide synthase (NOS3), play critical roles in the maintenance of a healthy endothelium. A cooperative relationship between the two genes is likely, as endothelial *KLF4* positively regulates *NOS3* expression. In the kidney, at baseline, endothelial deletion of either *Klf4* or *Nos3* does not result in overt changes. Upon stress however, endothelial *Klf4* knockout mice had exacerbated renal failure after ischemic reperfusion injury. Similarly, *Nos3* deletion resulted in increased glomerular injury and albuminuria in models of chronic kidney disease. Based on these data, we hypothesize that endothelial-specific double-knockout of *Klf4* and *Nos3* will disrupt maintenance of the renal endothelium in the healthy kidney.

Methods: Endothelial-specific *Klf4* knockdown mice ($Klf4^{\Delta EC}$) were generated (C57BL/6) by crossing $Klf4^{fl/fl}$ with *Cdh5-Cre* mice. $Klf4^{\Delta EC}$ and $Nos3^{-/-}$ mice were crossed to generate double knockout mice (DKO), and $Klf4^{fl/fl}$ mice used as control. Periodic acid-Schiff (PAS), electron microscopy (EM), immunofluorescence (IF), ELISA and RT-PCR were performed to investigate the effects of DKO on the renal endothelium. 12 week male mice we used in all studies.

Results: In the renal cortex, $Klf4^{\Delta EC}$ mice had decreased *Nos3* expression as compared with control, while $Nos^{-/-}$ mice exhibited increased *Klf4* expression. DKO mice had decreased expression of both *Klf4* and *Nos3*. DKO mice had increased albuminuria and serum creatinine as compared with $Klf4^{fl/fl}$, $Klf4^{\Delta EC}$, and $Nos^{-/-}$ mice. PAS of DKO mice revealed glomeruli with capillary congestion and endothelial cell (EC) swelling, and some glomeruli with widespread loss of ECs and tuft collapse, as well as increased glomerular volume, as compared to all other groups. On EM, DKO mice exhibited ECs with loss of fenestrae and focal areas of subendothelial widening, mesangiolysis and glomerular basement membrane duplication. IF revealed increased glomerular Isolectin B4 and complement membrane attack complex (C5b-9) in DKO mice as compared with all other groups, suggesting disruption of the endothelium and complement activation.

Conclusions: Our results suggest a synergistic interaction between endothelial *Klf4* and *Nos3* signaling in the maintenance of glomerular endothelial function and structure.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO1069

Anti-Angiogenic Factors Increase Thrombomodulin Expression in the Kidney in Pre-eclampsia: A Role for Endothelin?

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Background: Pre-eclampsia (PE) is a pregnancy related syndrome characterized by angiogenic imbalance, which results in symptoms such as hypertension. Furthermore, the kidney is frequently affected in PE. Similar symptoms are observed during treatment of patients with angiogenesis inhibitors like Sunitinib. Thrombomodulin is an essential endothelial regulator of inflammation and coagulation. Serum levels of the breakdown product of thrombomodulin are increased in PE. Here, we investigated thrombomodulin expression in kidneys of women with PE and hypertensive rats exposed to Sunitinib.

Methods: Renal tissue was collected from 34 pregnant women (23 controls, 11 PE) and 14 hypertensive non-pregnant women. Furthermore, kidneys were collected from male WKY rats treated with vehicle, Sunitinib (14 mg/kg/day) alone or in combination with endothelin receptor type A (ET_A) antagonist Sitaxentan (30 or 100 mg/kg/day) or non-selective $ET_{A/B}$ antagonist Macitentan (30 mg/kg/day) for 8 days. Blood pressure in rats was measured by telemetry. Thrombomodulin expression was investigated with immunohistochemistry and qPCR.

Results: Glomerular thrombomodulin protein expression is increased in kidneys of women with PE compared to pregnant women and hypertensive non-pregnant women ($P<0.01$). Renal thrombomodulin expression originated from the glomerular vascular pole, and is not associated with other histopathologic lesions. Exposure to Sunitinib results in 1.5-times higher renal thrombomodulin mRNA expression in WKY rats ($P<0.05$), and Sitaxentan at both doses ($P<0.001$), but not macitentan, normalized this increase. Both antagonists fully prevent the Sunitinib-induced rise in blood pressure.

Conclusions: Renal thrombomodulin expression is increased both in PE and during Sunitinib mediated angiogenic inhibition. Thrombomodulin upregulation appears to be ET_A receptor-mediated, and ET_B receptors counterbalance this effect in a blood pressure-independent manner. Our data suggest that selective ET_A receptor blockade may have long-term renoprotective effects. This may also be true in patients treated with angiogenesis inhibitors.

FR-PO1070

Functional Consequences of Complement Activation on Vascular Endothelial Cells - Results of a Pilot RNA Seq Study

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Background: Complement dysregulation on vascular endothelial cells (ECs) causes EC injury and leads to thrombotic microangiopathy (TMA), such as atypical hemolytic uremic syndrome (aHUS). As 50% of aHUS causing mutations are unknown, there is clinical need to find additional pathways and genes involved in the TMA phenotype. Here, we report the results of an unbiased RNA seq approach to investigate complement-induced responses of ECs on a molecular level.

Methods: Complement activation on ECs was induced via sensitization, activating the classical complement pathway, on blood outgrowth endothelial cells (BOECs) from healthy controls. RNA was isolated 1 hour after treatment. A stranded paired end RNA seq library was used, quality assessed with FASTQC software, and adapters trimmed using Trim Galore. Manual analysis of regulated genes was carried out with a cutoff of fold change > |1.5|. Gene function was determined based on literature analysis (pubmed; genecards). Functional assays included neutrophil adhesion in a microfluidic chamber (Bioflux), wound closure assay, measurement of transendothelial resistance with a voltohmmeter and IF staining for VE-Cadherin.

Results: RNA seq revealed three major findings, (i) upregulation of genes involved in leukocyte adhesion (e.g. ICAM, E-selectin); (ii) regulation of genes collectively resulting in loss of cytoskeletal re-arrangement (e.g. downregulation of RhoA activators and upregulation of ROCK 1 inhibitors); and (iii) downregulation of genes involved in cell adhesion (e.g. VE-Cadherin). Functional relevance of these findings was confirmed by complement-induced (i) EC neutrophil adhesion (Bioflux); (ii) defective EC migration (wound closure assay); and (iii) decreased transendothelial resistance and VE-Cadherin staining (voltohmmeter and IF). Importantly, all these effects were reversible when complement activation was blocked, using complement inactivated serum.

Conclusions: Complement activation on ECs results in an array of molecular responses functionally resulting in (i) neutrophil adhesion, (ii) defective cell migration, and (iii) loss of cell-cell adhesion. Detailed mechanism and their link to the clinical phenotype of TMA remains to be elucidated in future research.

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FR-PO1071

Erythropoietin Prevents TH17 Induction and Sodium Chloride-Driven Kidney Inflammation by Inhibiting SGK1-Dependent IL-17 Production

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Background: High sodium chloride (NaCl) intake worsens kidney pathology by promoting T_H17 differentiation. Since erythropoietin (EPO) is predominantly produced in the kidney where NaCl concentrations are high, and because EPO has newly recognized immunoregulatory functions, we tested the hypothesis that kidney-derived EPO prevents T_H17 differentiation and thereby modulates T_H17-dependent kidney pathology.

Methods: To study the role of endogenous and recombinant EPO on T_H17 cells *in vivo*, we used murine models of kidney disease associated with T_H17 induction, including aristolochic acid (ArA) nephropathy (+/- high NaCl diet), MRL-*lpr* and pristane lupus nephritis models. *In vitro* studies supplemented by adoptive transfer of naïve or T_H17 cells into $rag1^{-/-}$ mice were used to determine the direct role of EPO on T_H17 induction (**Figure 1A**).

Results: Recombinant EPO and transgenic EPO overexpression limited pathology, while *in vivo* shRNA-induced EPO downregulation augmented ArA-induced T_H17 formation and the clinical expression of disease. Recombinant EPO administration also prevented development of glomerular disease in lupus models, clinical results that were associated with reduced frequencies of T_H17 cells. In $rag1^{-/-}$ adoptive transfer experiments, EPO directly inhibited *in vivo* T_H17 development (**Figure 1B-C**) and promoted trans-differentiation of T_H17 into regulatory T cells. Using murine and human T cells, we then showed that EPO ligation of its T cell-expressed receptor abrogated NaCl-induced upregulation of *Sgk1* gene expression and blocked p38 activity to prevent SGK1 phosphorylation, thereby limiting RORC induction and T_H17 differentiation.

Conclusions: EPO physiologically and therapeutically inhibits T_H17 cell differentiation and T_H17-associated autoimmune kidney pathology by antagonizing intracellular signaling pathways required for NaCl-driven T_H17 differentiation.

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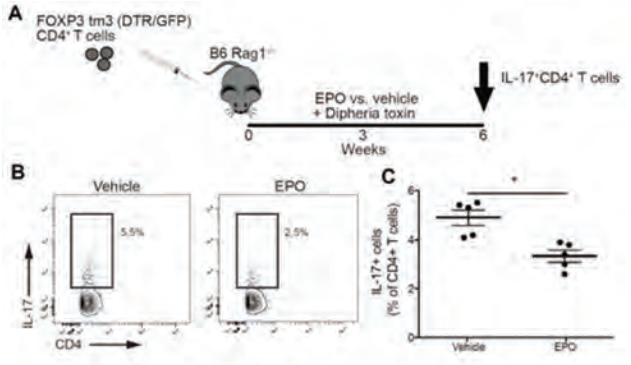

Figure 1. EPO inhibits T_H17 induction in vivo in a Treg-independent system. We transferred Foxp3-DTR naive CD4+ T cells into Rag1-/- mice and treated them with diphteria toxin +/- EPO (**A**). After 6 days, we measured IL17+CD4+ T cells (T_H17) (representative flow plots, **B** and data quantification, **C**). *P<0.05.

FR-PO1072

Role of the ICOS/ICOS-L Costimulatory Pathway and of Circulating Extracellular Vesicles as Potential Biomarkers and New Therapeutic Targets in Lupus Nephritis

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Background: The costimulatory pathway ICOS/ICOS-L and extracellular vesicles (EV), microparticles known to have a role in cell-to-cell communication, both appear to be involved in tissue injury associated with SLE. The aim of this study was to evaluate the association between ICOS, ICOS-L or EV plasma levels and clinical expression of lupus nephritis (LN).

Methods: Main clinical and laboratory parameters were compared among 67 SLE patients (52 with LN and 15 with only rheumatological SLE) and 50 healthy controls. Plasma levels of ICOS/ICOS-L were assessed by ELISA and EV were evaluated by Nanotrack and FACS analysis.

Results: Serum levels of ICOS and ICOS-L were significantly increased in SLE as compared with healthy controls ($p<0.001$) and associated with disease duration ($p=0.036$ for ICOS and $p<0.001$ for ICOS-L), presence and severity of LN at diagnosis ($p=0.017$ and $p=0.001$), proteinuria ($p=0.014$ and $p<0.001$) and nephritic sediment ($p=0.005$ and $p=0.010$). ICOS levels also correlated with established scores such as SLICC ($p=0.027$) and SLEDAI-2K ($p=0.001$) at diagnosis. At univariate logistic regression analysis, disease onset at younger age ($p=0.007$), ICOS ($p=0.044$) and ICOS-L levels ($p=0.009$) were associated with LN; however, at multivariate analysis only disease onset at younger age ($p=0.018$) and ICOS-L ($p=0,047$) were indipendently associated with renal involvement. Plasma EV levels were higher in SLE patients with LN ($p<0.001$) without discrimination between prolipherative and non-prolipherative classes: however, EV levels correlated with proteinuria ($p=0.032$) and ICOS levels ($p=0.026$). Of interest, FACS analysis revealed the presence of both ICOS and ICOS-L on EV surface.

Conclusions: ICOS and ICOS-L plasma levels are increased in SLE and appear to identify a subset of SLE patients with long-lasting disease and severe LN at presentation. In addition, plasma EV levels were also higher in SLE patients with LN and correlated with ICOS: circulating EV carried ICOS and ICOS-L proteins. ICOS/ICOS-L pathway and circulating EV may be potential biomarkers and new therapeutic targets in LN.

FR-PO1073

Targeting TH17 Plasticity in Immune Mediated Inflammatory Diseases

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Background: During T cell development, naive T cells can differentiate into effector T cells (e.g T_H1 and T_H17) or into regulatory T cells (e.g. $Foxp3^{Neg}T_R1$ and $Foxp3^{Pos}$ Treg cells). Originally every single CD4 T cell lineage was thought to be stable after differentiation and to represent a functional homogenous population of cells. Recent data suggest that CD4 T cells and T_H17 cells in particular, have higher plasticity in the brain and in the intestine, where T_H17 cells are able to convert into T_H1 cells and into T_R1 cells respectively.

Methods: To prove the conversion from TH17 cells towards TR1exTH17 and the role of TR1exTH17 cells in the kidneys of nephritic, we used Fate+ (Foxp3RFP IL-10eGFP IL-17AKata IL-17ACRE R26YFP mice) and IL17ACre IL10fl/fl mice. Mice were immunized with nephrotoxic sheep serum. Additionally we treated them with PBS or 15 µg of αCD3 monoclonal antibody (mAB) intraperitoneally (i.p.). Injections were done at day 8 and day 10 post immunization. The mice were analyzed 4 hours after the last injection. Multiparametric flow cytometric analysis was performed and clinical parameters were measured in urine and plasma. Moreover histological analysis was done using Periodic acid–Schiff (PAS) staining that detects polysaccharides and mucosubstances.

Results: We could show that spontaneous and induced conversion of TH17 cells into TR1exTH17 over the course of NTN induction take place. Furthermore induction of NTN in IL17ACre IL10fl/fl mice showed aggravated glomerulonephritis.

Conclusions: Our first aim was to demonstrate the existence of TR1exTH17 in the kidneys of nephritic mice. Moreover we showed that the regulatory fate of TH17 cells (IL-10 producing TH17 and TR1exTH17 cells) can play an important role. Furthermore preliminary data show that deletion of IL-10 production by TH17 and exTH17cells can result in aggravated outcome of GN. However whether kidney IL-10 producing Foxp3Neg CD4 T cells are a functional homogenous population of regulatory cells remains unknown and the molecular mechanism underlying the conversion of TH17 into TR1 cells remain to be discovered

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FR-PO1074

Elucidating the Role of Neutrophil Extracellular Traps in Atypical Hemolytic Uremic Syndrome

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Background: About 10% of patients manifest hemolytic uremic syndrome (HUS) without toxins or diarrhea. These cases are referred to as atypical HUS (aHUS) and occur due to a dysregulated complement system leading to unchecked complement activation on the vascular endothelium. Genetic mutations account for only 50-60% of aHUS cases only with a large variation in the age and severity of the disease phenotype. For the past decade, neutrophils have been shown to produce neutrophil extracellular traps (NETs), which are associated with proinflammatory and prothrombotic properties. We propose that NETs are involved in aHUS pathogenesis.

Methods: Resting neutrophils freshly isolated from healthy donors were used (male, ages 18-24 years old). Experiments were done at least threefold (N=3). We have previously shown that neutrophils contain complement components, which they deposit on NETs, and that NETs contribute to complement activation. In this study, we aim to determine if NETosis can be induced by complement activation. In order to activate complement, neutrophils were sensitized via a monoclonal anti-human CD59 (x30 min) followed by incubation with 50% human serum as source of complement (x4 h). Immunofluorescence (IF) imaging was used to quantify the kinetics of NETs formation.

Results: We found that: 1) the use of our complement sensitization protocol resulted in C3b deposition and C5b-9 complex formation on neutrophils; 2) NETosis could be induced in a complement-dependent manner; 3) both citrullinated Histone 3 (cit-H3) and myeloperoxidase (MPO) are both present in the NETs of complement-stimulated neutrophils.

Conclusions: Complement activation taking place on the surface of neutrophils induces NETosis, a new finding pointing towards a crucial role for neutrophils in the pathogenesis of complement-mediated TMA.

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FR-PO1075

Rituximab Associated Hypogammaglobulinaemia in Autoimmune Disease: Long Term Outcomes

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Background: Despite a low incidence of hypogammaglobulinemia (HG) in clinical trials using rituximab (RTX), HG occurs in follow-up of patients with autoimmune disease. Immunoglobulin replacement therapy (IRT) has been used to reduce infection rates but there is a paucity of data on its efficacy and impact on longer-term outcomes. We examined the characteristics of patients with RTX associated HG in autoimmune disease, and their long-term outcomes with and without IRT.

Methods: Patients attending a Vasculitis and Lupus clinic, who received RTX for autoimmune disease between 2004 and 2012, with an immunoglobulin G (IgG) <7 g/L on at least 2 occasions were included in this retrospective case note review. Patients were categorized into nadir IgG subgroups of <3 g/L, 3 to <5 g/L and 5 to <7 g/L. Categorical variables are summarised as proportions, and continuous variables as mean ± standard deviation or median [interquartile range (IQR)]. Differences between nadir IgG subgroups were assessed by Chi squared tests and trends across subgroups confirmed by Somer's D tests. Continuous variables were compared using analysis of variance (ANOVA), Kruskall-Wallis and Wilcoxon sign ranked tests as appropriate. Analyses were performed in SPSS.

Results: Of 142 patients, 101 (71.1%) had ANCA associated vasculitis, 18 (12.7%) systemic lupus erythematosus and 23 (16.2%) other diagnoses. Most received RTX for relapsing (69.3%) or refractory (25.0%) disease. Mean follow-up was 97.2 months. Progressive HG was observed. Median time to IgG <5 g/L was 22.5 months [IQR 3.0 to 61.5] and to IgG <3 g/L was 24.5 months [IQR 4.0 to 80.75]. Mycophenolate use prior to RTX ($p=0.05$) and prednisolone use following RTX ($p=0.04$) were associated with a lower nadir of IgG. IRT was commenced in 29 patients, the majority (65.5%) with IgG <3 g/L. It was well tolerated, with 2 discontinuing due to adverse effects. IRT was withdrawn without excess recurrent infections in 5 patients. IRT was associated with a reduction in annual infection rates ($p<0.001$). Severe infections (requiring intravenous antibiotics or hospital admission) were uncommon, with no change with the use of IRT.

Conclusions: RTX associated HG is progressively identified with longer term follow-up. Although annual infection rates were low, in patients with recurrent infection, IRT was associated with a reduction in infection burden.

FR-PO1076

Persistent B-Cell Depletion After Rituximab

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Background: Rituximab (RTX), an anti-CD20 monoclonal antibody, is an effective therapy for many glomerular diseases. Following RTX, B cell reconstitution occurs at a median of 8 months, and the vast majority of patients have B cell return by 18 months. We report 7 patients with autoimmune kidney disease who developed persistent B cell depletion following RTX.

Methods: We performed a retrospective analysis of patients with glomerular disease treated with rituximab between 2006-2017. Patients who had persistent B cell depletion, defined as undetectable CD20+ B cells determined by flow cytometry for > 2 years after their last rituximab dose, were included in the study. Patient characteristics, serological markers of disease, adverse events, and survival were examined.

Results: We identified 7 patients with persistent B cell depletion. Six patients were treated for ANCA vasculitis and one for lupus nephritis. Patients received a median of 13 RTX doses (range, 5 to 22). Following the final RTX, B cells in these patients have remained undetectable for a median of 5.2 years (range, 3.9 to 6.9). Four patients developed significant hypogammaglobulinemia (IgG < 400 mg/dL) and two received IVIG. RTX-induced late-onset neutropenia occurred in 3 patients. Five patients developed serious infections and one patient died in the setting of infection associated with recurrent late onset neutropenia. No patient had recurrence of their underlying autoimmune disease.

Conclusions: Persistent B cell depletion after rituximab is a rare but important complication of therapy that appears to be associated with late-onset neutropenia and serious infections. The mechanism of this phenomenon is unclear. Additional investigation into the risk factors and pathogenesis of this complication are needed.

Patient and Outcome Characteristics

Age	Gender	Disease	Years of B cell depletion	# rituximab doses	Significant hypogammaglobulinemia	IVIG given	LON episodes	Major infections
61	M	MPO ANCA	3.9	22	No	No	0	Recurrent sinusitis
67	M	MPO ANCA	4.2	13	No	Yes	22	Neutropenic sepsis
50	M	PR3 ANCA	6.2	21	Yes	No	0	None
43	F	SLE	6.9	7	Yes	Yes	3	Recurrent gastroenteritis, colitis
62	M	MPO ANCA	6.9	13	No	No	0	Recurrent pneumonia
34	F	MPO ANCA	5.2	5	Yes	No	4	Recurrent sinusitis
60	F	MPO ANCA	3.9	9	Yes	No	0	None

LON: late onset neutropenia

Major infections: infection leading to hospitalization or requiring intravenous antibiotics

FR-PO1077

The Oxidized Linoleic Acid Metabolite 12,13-Dihydroxy-9Z-Octadecanoid Acid (12,13-DiHOME) Mediates Recovery from Nephrotoxic Nephritis

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Background: The number of anti-inflammatory lipid molecules is increasing and their role in nephritis is not well investigated. In particular, the enzymatic activity of soluble Epoxide Hydrolyze (sHE) and its products such as 9,10-DiHOME and 12,13-DiHOME were shown to be critical for resolution of inflammation. Biosynthesis of these products starts from linoleic acid by cytochrome P450 (CYP) oxidases, followed by hydrolysis catalyzed by soluble epoxide hydrolases. We hypothesized that synthesis, metabolism or signaling of oxidized linoleic acid metabolites may be affected at the site of inflammation and that 12,13-DiHOME has an important role in resolution of nephritis.

Methods: To investigate changes in lipid profiles in differentially treated mice, lipidomic analysis was carried out by LC/MC in Lipidomics Core Facility (Wayne State University, Detroit, MI). Panel of 144 lipid molecules were measured in plasma of mice at day 7 after induction of nephrotoxic nephritis (NTN), induced by injection of nephrotoxic serum (13,5µl/g bw). Kidney endothelial cells were treated with 12,13-DiHOME (250nM) and TNF-α (10ng/ml) was added after 1h. TNF-α induced upregulation of VCAM-1 was investigated by flow cytometry after 24 h.

Results: Lipidomic plasma profiles of polyunsaturated fatty acid metabolites in nephrotic mice showed marked decrease of two molecules: 9,10-DiHOME and 12,13-DiHOME. The role of 12,13-DiHOME was further evaluated in NTN: after induction of nephritis mice were treated with 12,13-DiHOME (20ng/g bw) or vehicle, starting on day 2, than every 48h, and mice were sacrificed on day 7. 12,13-DiHOME treatment completely normalized both BUN levels and histology (NTN mice: BUN = 117.72 ± 3.2, NTN 12,13-DiHOME injected mice BUN = 15.50 ± 0.43, $p<0.0002$). In glomerular endothelial cells, 12,13-DiHOME treatment reduced TNF-α induced upregulation of VCAM-1 by 49%.

Conclusions: The results of the study suggest that administration of 12,13-DiHOME during NTN protects kidneys from severe inflammation, in part, by limiting upregulation of adhesion molecules on kidney endothelial cells and therefore, may have therapeutic potential for the treatment of nephritis.

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FR-PO1078

Urine Podocin to Nephrin mRNA Ratio Is Associated with Activity of Crescentic Necrotizing Glomerulonephritis

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Background: Crescentic necrotizing glomerulonephritis (CNGN) rapidly leads to progressive glomerulonephritis syndrome, which then leads to irreversible renal failure without appropriate therapy. To estimate the severity of CNGN, renal biopsy is required. However, renal biopsy is sometimes not applied because of a severe general condition. If urine podocyte-specific mRNA predicts the severity of CNGN, it may be a useful tool.

Methods: A total of 28 patients with biopsy-proven CNGN (males: 16, mean age: 64.6±12.8 years) were enrolled during the past 7 years, with pathological data available for 27 patients. Kidney biopsy samples were used for immunostaining of podocytes and urine samples for podocyte mRNA with the patient's consent by document.

Results: A blood test showed an estimated glomerular filtration rate of 24.9±18.7 mL/min and C-reactive protein level of 3.33±3.68 mg/dL. Histological analysis showed 3 patients with crescent class, 3 with sclerotic class, 9 with focal class and 12 with mixed class according to EUVAS classification. Immunostaining showed a podocyte number of 297.2±133/glom and podocyte density of 75.8±32/10^6µm^3. A urinary mRNA study showed a urine podocin:nephrin mRNA ratio (PNR) of 1.46±0.80 and urine podocin mRNA:urine creatinine ratio (U-pod/CR) of 476.8±525.3. The podocyte number and density were lower, and the PNR and U-pod/CR were higher compared with those of healthy controls in our previous report (419±81/glom, 129±49/10^6µm^3, 0.36±0.29, 4.3±4.6, respectively). Using EUVAS criteria, the podocyte number in the sclerotic class and podocyte density in the crescent and sclerotic classes tended to be lower compared with the other classes. The PNR and U-pod/CR in these classes, except for the sclerotic class, tended to be increased, which suggested a "podocyte-depleted" stage of sclerotic class. Remarkably, the PNR was significantly correlated with the percentage of glomeruli with acute crescents per unsolidified glomeruli ($p<0.01$, $R^2=0.28$). Log10 of the U-pod/CR was also correlated with it, except for 6 severe crescentic cases ($p<0.01$, $R^2=0.40$).

Conclusions: Urine podocyte mRNA, especially the PNR, might be a useful tool for evaluating activity of CNGN.

FR-PO1079

miR-150 Inhibitor Ameliorates Three Immune-Involved Kidney Diseases by Reducing Inflammation and Fibrosis

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Background: Renal fibrosis from immune-involved kidney diseases remains refractory. We previously reported that miR-150 increased in the repeated renal biopsies from patients with lupus nephritis (LN) and found that miR-150 mimic promoted fibrosis in three human kidney resident cells in vitro. We aimed to clarify whether miR-150 inhibitor can ameliorate renal fibrosis in three kidney disease mouse models and to identify the corresponding mechanisms.

Methods: We first examined miR-150 in renal biopsies from patients with new onset LN or focal segmental glomerulosclerosis (FSGS). Then we observed the time course of renal miR-150 in mouse models including spontaneously developed *Fcgr2b*$^{-/-}$ LN, adriamycin-induced FSGS, and folic acid-induced tubulointerstitial fibrosis (TIF). Lastly, the efficacy and safety of locked nucleic acid (LNA)-anti-miR-150 (2mg/kg, twice a week) were studied when it was subcutaneously injected to LN mice for 8 weeks, to FSGS mice for 6 weeks, and to TIF mice for 4 weeks. The kidney injury (proteinuria, serological indices, and histology damage on PAS and Masson staining), renal levels of pro-inflammatory cytokines (IFN-γ, IL-6, and TNF-α), profibrotic genes (TGF-β, α-SMA, fibronectin, and collagen1), antifibrotic gene suppressor of cytokine signaling 1 (SOCS1), and the infiltration of lymphocytes and macrophages were investigated in mice with LNA-anti-miR-150 treatment comparisons to the scrambled LNA.

Results: miR-150 was increased in renal biopsies of LN and FSGS patients compared to normal kidneys. miR-150 showed higher expression in the kidneys of mice than in other studied organs. LNA-anti-miR-150 downregulated renal miR-150 levels and ameliorated kidney injury in LN, FSGS, and TIF mice without any organ toxicity. The above observed pro-inflammatory cytokines, profibrotic genes, and the infiltration of lymphocytes and macrophages increased while antifibrotic gene SOCS1 decreased in the kidneys of disease mice. LNA-anti-miR-150 decreased the inflammation, fibrosis, and inflammatory cells while increased SOCS1 compared to the scrambled LNA.

Conclusions: miR-150 inhibitor played important renal protective roles in three immune-involved kidney diseases with final renal fibrosis. This suggests that miR-150 inhibitor might be a promising therapeutic agent for renal fibrosis.

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FR-PO1080

The Histopathological Spectrum of Monoclonal Gammopathies of Renal Significance: A Single Centre Experience

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Background: Monoclonal Gammopathy of Renal Significance (MGRS) encompasses renal histopathological entities caused by Monoclonal Immunoglobulins (MIg) in patients who do not meet criteria of symptomatic lymphoma or myeloma (MM). We describe the spectrum of MGRS histopathological diagnoses in the context of the underlying haematological disease in our centre.

Methods: Native renal biopsies performed during 2006-2017 were reviewed. Those with evidence of MIg or light chain in glomeruli, tubules, vessels and/or interstitium were included. C3GN and TMA were excluded.

Results: Out of 4,374 kidney biopsies, MIg-associated lesions were identified in 163 cases (3.7%). After exclusion of symptomatic MM and lymphomas 68 biopsies (1.5%) were consistent with MGRS. Renal histological diagnoses included: AIg amyloidosis (n=28, 41%), Proliferative GN with MIg Deposits(PGNMID) (n=13, 19%), MIg Deposition Disease(MIDD) (n=12, 18%), Light Chain Tubulopathy (n=5, 7%), Type-1 Cryoglobulinaemic GN (n=6, 9%), Intracapillary Monoclonocal IgM without Cryoglobulin (n=2, 3%), Crystal Cryoglobulinaemia (n=1, 1.5%) and Fibrillary Light Chain restricted GN (n=1, 1.5%). Only 24 out of 42 patients in whom Serum Free Light Chain assay was performed had an abnormal ratio. Overall, haematological diagnosis was possible in bone marrow histology (BMAT) or lymph node biopsy in 53 patients. These included: MGRS with less than 10% plasma cells in BMAT (n=30, 56.6%), Smouldering Myeloma (n=17, 32%), lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinaemia (n=2, 3.7%), chronic lymphocytic leukaemia (n=3, 5.6%) and marginal zone lymphoma (n=1, 1.8%). In 8/13 PGNMID and 3/12 MIDD cases a clonal B cell or plasma cell clone was undetectable in BMAT.

Conclusions: MGRS are increasingly recognised since the term introduction in 2012 and this type of renal histopathology is also frequent in Smouldering Myeloma. Renal histopathology must be interpreted in conjunction with the haematological diagnosis to guide treatment decisions. However, current diagnostic methods underperform and consensus diagnostic approaches incorporating renal and haematological histopathology are lacking.

FR-PO1081

Diagnosis and Outcomes of Monoclonal Gammopathy of Renal Significance: A Single Centre Study

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Background: Monoclonal Gammopathies of Renal Significance (MGRS) are caused by monoclonal immunoglobulins (MIg) produced by B cell or plasma cell clonal disorders, which do not meet criteria of symptomatic lymphoma or myeloma (MM). Treatment objective in MGRS is the preservation of kidney function.

Methods: Records of patients with native kidney biopsy during 2006 – 2017 were reviewed. Amyloidosis, C3GN and TMA were excluded.

Results: 41 biopsies out of 4.374 (1%) were consistent with MGRS. Mean age at diagnosis was 63±12 years. Renal histological diagnoses included: proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) (n=16, 39%), monoclonal immunoglobulin deposition disease (MIDD) (n=13, 32%), light chain tubulopathy (LCT) (n=5, 12%), type-1 cryoglobulinaemic glomerulonephritis (n=6, 15%), fibrillary glomerulopathy (FibGN) (n=1, 2%). 22/41 patients had abnormal protein electrophoresis and/or free light chain ratio. 32/41 had bone marrow biopsy and haematological diagnoses included: MGRS with <10% plasma cells (n=22, 69%), smouldering myeloma (n=5, 15%), Waldenstrom's Macroglobulinaemia (n=1, 3%), chronic lymphocytic leukaemia (n=3, 10%) and marginal zone lymphoma (n=1, 3%). 16 patients were treated with myeloma-based protocols (bortezomib ± autologous stem cell transplantation). In cases with very low or unidentifiable clone, treatment was heterogenous, including glomerulonephritis protocols (cyclophosphamide, steroids ±Rituximab) (n=16) or conservative management (n=9). During median follow-up of 26 months (4-123) in 38 patients, 26 had stable/improved renal function, 1 worsening renal function (>30% eGFR decrease) and 11 progressed to ESRD. 9 patients died (table 1).

Conclusions: Haematological assessment of MGRS must exclude symptomatic myeloma or lymphoma and identify the pathogenic clone to direct specific therapy. Case studies in our series indicate that early detection and treatment improves renal outcomes, however consensus diagnostic and treatment approaches are missing.

Table 1:

Characteristic		All	PGNMID	MIDD	LCT	Type 1 Cryo
Number of patients		38 **	15	12	4	6
Median follow-up(months)		26(4-121)	24(6-106)	40(4-121)	29(19-53)	20(14-48)
Treatment N(%)	None	8 (21%)	5	2	1	0
	Chemotherapy without SCT	11 (29%)	1	8	1	1
	Chemotherapy and SCT	5 (13%)	0	2	2	1
	CyC and pred +/- rituximab	14 (37%)	9	0	0	4
Renal Outcome N (%)	Stable/improved	26 (68%)	13	7	4	2
	Worsening*	1 (3%)	0	0	0	1
	ESRD	11 (29%)	2	5	0	3
Deaths N (%)		9 (24%)	2	2	0	3

*>30% decrease in eGFR from renal Biopsy eGFR. **1 patient with FibGN included

FR-PO1082

Multiple Deposition Phenotypes of Monoclonal Immunoglobulin Deposition Disease on Renal Biopsy: Significance of Treatment

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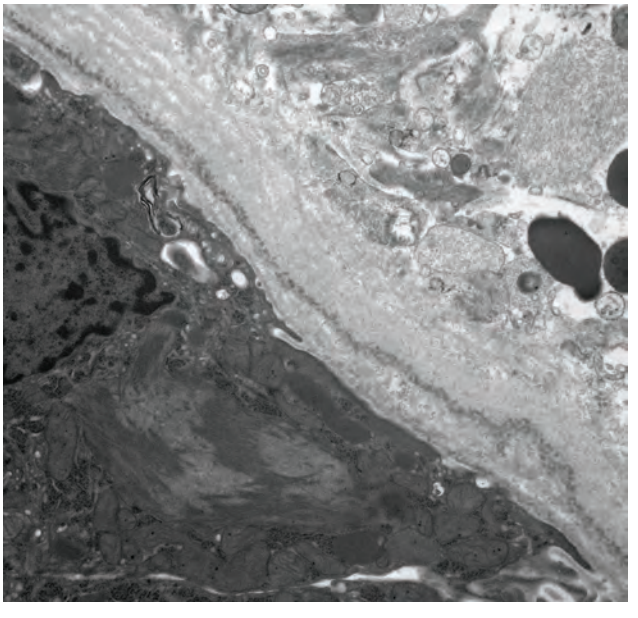
Introduction: Plasma cell dyscrasias frequently involve the kidney causing renal dysfunction. Various morphologies occur in kidneys, infrequently with several manifestations in one biopsy. We present a case, which revealed multiple pathological features on same biopsy, which responded to treatment.

Case Description: A 61 year old female presented with fatigue and dyspnea for 3 months. She had new onset renal failure with creatinine 3.0 mg/dL and proteinuria. Serological work up revealed monoclonal gammopathy with elevated K:L ratio of 1394. Renal biopsy revealed several paraprotein manifestations including kappa light chain deposition disease, monoclonal fibrillary glomerulonephritis, cryocrystalglobulenemia and fibrillary/tubular cast nephropathy. There was also incidental LECT 2 amyloidosis, negative for kappa light chain and confirmed by mass spectrometry. Bone marrow biopsy revealed 10-20% kappa restricted plasma cells. She received 8 cycles of CyBorD (Cyclophosphamide, Bortizomib and Dexamethasone) chemotherapy. Renal function improved with the recent creatinine 1.1 mg/dL and decreased proteinuria. K:L ratio improved to 1.7. Repeat bone marrow biopsy showed no evidence of abnormal plasma cells by immunohistochemistry. The patient is currently being evaluated for an autologous stem cell transplant.

Discussion: The finding of several concurrent morphologic manifestations of light chain deposition in one biopsy suggests local microenvironment effects in addition to structural properties of the light chain. The renal recovery demonstrates responsiveness to chemotherapy irrespective of the form of light chain deposition noted on biopsy. In this setting, amyloid may not always be light chain related, and other amyloid types should be considered when light chain staining is discrepant.



FR-PO1083

A Clone-Directed Treatment Approach for the Monoclonal Gammopathies of Renal Significance

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Background: Monoclonal gammopathy of renal significance (MGRS) is a non-malignant hematologic condition causing paraprotein-mediated kidney disease. We recently published our experience using a clone-directed approach to patients with PGNMID. Here, we present our experience using the same approach to 22 patients with non-PGNMID paraprotein-mediated nephropathies.

Methods: We retrospectively reviewed 22 patients with MGRS to describe their renal and hematologic presentations and outcomes. For patients with initial proteinuria <0.5 g, complete renal response (CR) was defined as proteinuria <0.01 g (24h urine) or g/g (Uprot/Cr ratio) and partial renal response (PR) as proteinuria reduction by 50%. For patients starting with nephrotic range proteinuria, CR and PR were defined as proteinuria <0.5 g and <3.5 g, respectively. For patients with initial proteinuria between 0.5 and 3.5 g, CR and PR were defined as proteinuria <0.49 g and 50% reduction of proteinuria, respectively. Renal response required stable/improved eGFR. Hematologic studies and responses are presented descriptively.

Results: Histologic diagnoses included LCDD (n= 9), immunotactoid glomerulopathy (n= 3), paraprotein-associated C3 GN (n= 2), monoclonal membranous nephropathy (n= 3), and 1 case each of monoclonal fibrillary GN, heavy chain deposition disease, light and heavy chain deposition disease, type 1 cryoglobulinemic GN, and light chain proximal tubulopathy. Median eGFR (interquartile range) was 30 mL/min (18 to 48 mL/min). Median baseline proteinuria (IQR) was 2.11 g (1.1 to 3.9 g). 4 patients presented on RRT. An underlying clone was detected in 18 patients (82%), of whom 13 had plasma cell clones and 5 had B cell clones. 17 (77%) patients had detectable paraprotein on serum or urine immunofixation. 4 patients were not treated due to stable renal disease. Of 18 patients who underwent treatment, 3 achieved renal CR and 6 achieved renal PR (50% overall response rate). No patient on HD came off RRT, and 1 patient progressed to ESRD during follow-up. Of patients who received clone-directed therapy and were not on RRT at diagnosis, the overall renal response rate was 64%. 71% of patients had an improvement in paraprotein levels.

Conclusions: Clone-directed therapy led to a high overall response rate in patients with MGRS.

FR-PO1084

Chemotherapy Response and 2 Years Follow-Up of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID)

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Background: The term monoclonal gammopathy of renal significance (MGRS) represents all monoclonal gammopathies that are associated with the development of a kidney disease but do not meet the definition of hematological malignancies. PGNMID is an uncommon MGRS–related glomerular disorder characterized by monoclonal Ig deposits resulting in an endocapillary proliferative or membranoproliferative histological pattern of injury. It usually manifests with proteinuria, microscopic hematuria and renal impairment. Treatment for PGNMID has included RAS blockage, rituximab, chemotherapy and immunosuppressive therapy with variable results. Nonetheless, reports with treatment outcomes are scarce, heterogeneous and retrospective, so the benefits of specific treatment remain unclear. Here we report for first time, the prospective results of 3 cases of PGNMID treated with a cyclophosphamide, thalidomide and dexamethasone (CTD regimen) based oral chemotherapy.

Methods: Prospective analysis. Three cases of PGNMID were identified during 2015 at Hospital del Salvador (Santiago, Chile). The biopsies were analyzed using standard techniques for light microscopy, IF, and EM. The presence of plasma cell dyscrasia and other conditions were evaluated. All patients received CTD regimen and RAS blockage.

Results: Two patients made their debut with impure nephrotic syndrome and rapidly progressive renal failure. Patient 2 had subnephrotic proteinuria and hematuria. In all cases M-protein could not be detected by serum or urine PEP/IF and only κ/λ relation was elevated. All patients had no bone marrow involvement, and autoimmunity study was negative. The IF revealed mesangial deposits restricted to IgG3-kappa in patients 1 and 3, and IgA kappa in patient 2. After CTD regimen, two patients achieved complete remission with no adverse effects and no relapses after 2 years of follow-up. The third patient had a serious pneumonia with severe AKI and dialysis requirement after 8 months of initiating chemotherapy. Thereafter had a serious *Clostridium difficile* infection, chemotherapy was stopped and the patient continued on dialysis.

Conclusions: The CTD chemotherapy regimen was successful in the treatment of PGNMID attaining long-term complete remission. CTD regimen seems to be an effective treatment, but we must put attention on chemotherapy related adverse effects

FR-PO1085

Comparison of Two Renal Staging Systems and Response Criteria of AL Amyloidosis

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Background: Light chain (AL) amyloidosis affects the kidney in 70% of the patients. Renal survival and response are critical for the treatment decision. We carried out this study to evaluate the two sets of baseline staging system and renal response and progression criteria (Palladini et al. and Kastritis et al.) recently proposed in our own population.

Methods: AL cases with renal involvement at Mayo Clinic between 01/2003 and 01/2015 were screened. Patients were excluded if: dialysis dependence at the time of diagnosis or <3 months of treatment initiation, incomplete data set and treatment initiation more than 1 month before AL diagnosis. Our cohort was evaluated at baseline and at 3, 6 and 12 months. The study's endpoint was renal survival, defined as the time from treatment initiation to dialysis initiation or of last follow up. We used competing risks statistical analysis and the C (Concordance) index to compare the two models.

Results: Out of 836 patients with AL and renal involvement, 495 were selected. The median age was 61(54-68) years and 62% were male. Median serum creatinine was 1.1(0.9-1.4) mg/dl, median eGFR was 66(47-82) ml/min/1.73 m^2 and median proteinuria was 5.1(2.5-8.2) g/d. Table 1 shows the distribution of our cohort in stages. For ESRD onset, hazard ratio (HR) for stage II vs I was 21[NL1] (p= 0.003) and for stage III vs II was 3.02(p<0.001) for the Palladini staging system (C= 0.74). HR for stage II vs I was 4.3 (p=0.161) and for stage III vs II was 4.76 (p< 0.001) for the Kastritis staging (C =0.73). At 3 months, neither criteria met statistically significant predictive value. The Palladini progression criteria were superior both at 6 months [HR: 9.68 (p<0.001, C =0.79) vs HR: 3.03 (p=0.002, C= 0.65)] and at 12months [HR: 7.24 (p<0.001, C =0.75) vs HR: 5.47(p<0.001, C=0.72)]. Both response criteria showed comparable results at 6 and 12 months after treatment initiation.

Conclusions: Both Palladini and Kastritis renal staging systems predict renal survival well. Renal progression and response assessed using serum creatinine and 24 hour urine protein appear to have little prognostic value earlier than 6 months.

Distribution of Patients by Different Staging Systems

	Palladini Stage System	Kastritis Staging System
Stage I	171 (34.5%)	89 (18%)
Stage II	257 (52%)	221 (45%)
Stage III	67 (13.5%)	185 (37%)

FR-PO1086

Renal Outcome and Prognosis Analysis of Light Chain Amyloidosis and Renal Involvement

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Background: Light-chain (AL) amyloidosis is the most common and serious type of systemic amyloidosis. Most studies only focused on the overall survival of AL amyloidosis. Renal involvement is one of the most common complications of the disease which can lead to end-stage renal disease (ESRD). Our study compared clinical features of the amyloidosis cohort in multiple aspects, and emphasized on renal outcomes. And we also aimed to validate two staging system for renal involvement in Asian populations firstly.

Methods: Patients with newly diagnosed AL amyloidosis and kidney involvement which was proved by renal biopsy in Beijing Union Medical College Hospital from January 1, 2002 to December 31, 2017 were included. Demographic characteristics and clinical features were summarized. Cases diagnosed after 2011 were followed up. A comparative analysis of the baseline condition and prognosis was made between primary and secondary amyloidosis, κ and λtype. Two renal staging system were proposed in 2014 and 2017, based on proteinuria (24hUP>5g/d) and eGFR (<50ml/min/1.73m²) or 24hUP/eGFR at diagnosis. Patients were divided into renal stage I-III and renal stage 1-3 respectively by two criteria. The baseline conditions and renal outcomes were analyzed and compared to evaluate the prognostic value of the two systems.

Results: A total of 76 cases were included. All cases had renal involvement. 44 cases were followed up. 49 cases (64.5%) showed nephrotic syndrome, and 28 cases (36.8%) showed renal insufficiency at the time of diagnosis. There was no significant difference in clinical features, organ involvement renal outcome and survival between κ and λ cases, primary AL amyloidosis and AL amyloidosis secondary to multiple myeloma(MM). The renal staging system based on 24hUP and eGFR were validated. There was a significant difference in renal outcome among renal stage I-III (p=0.003). Based on the 24hUP/eGFR system, there was no ESRD in both stage 1 and stage 2. A significant difference was seen between phase 3 and two other stages (p=0.008).

Conclusions: The clinical manifestations, renal outcome, and survival of AL amyloidosis are not affected by primary or secondary to MM, and different type of light chain. For the first time, the prognostic value of renal staging system based on 24hUP and eGFR was validated in Asian populations, which is of great significance in guiding clinical treatment.

FR-PO1087

Significant Reduction in Proteinuria After Treatment with Tafamidis

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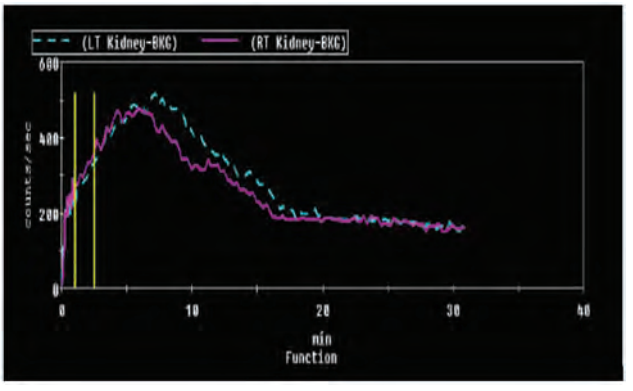
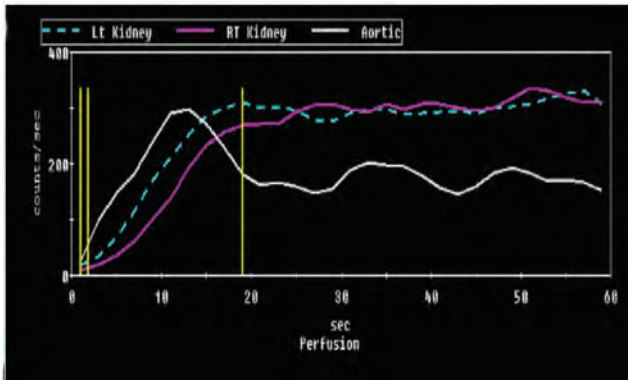
Introduction: Hereditary Transthyretin Amyloidosis (hATTR) in Mallorca represents the fifth world focus. Tafamidis (Vyndaqel, Pfizer) has been used since 2011 with promising expectations. It promotes stabilization of the TTR tetramer and slow tissue deposition. Consequently, it contributes to change the course of disease, slowing the presentation of clinical manifestations. The Portuguese group presented few cases with small reduction in proteinuria last year. We present now an interesting case of a significant decrease in heavy proteinuria.

Case Description: We display the first case presented (to our knowledge) with great proteinuria reduction from nephrotic range to mild range. This is a well documented female case of late onset Val30Met. Amyloid deposits were confirmed by positive congo red stain in a skin biopsy. Patient came into the outpatient consultation due to cardiology manifestations. Patient was studied in depth, and then neurologic, intestinal and nephrologic impairment was also found. Nephrotic range proteinuria of 4,2 g in 24h with kidney dysfunction were present. We also found an unusual dissociation among glomerular filtration rate formulas (urine and blood results). Therefore, we performed a 51Cr-EDTA renal function, and also conducted a dynamic study with 99mTc-MAG3 scintigraphy. 6 months after taking tafamidis, proteinuria was reduced to 1,6 g in 24h.

Discussion: This finding may be very promising for the future to slow the natural course of proteinuric kidney TTR amyloidosis disease. It will permit to avoid or slow progression to end-stage renal disease and renal replacement therapy.





FR-PO1088

Masked Hypertensive Disorders Are Prevalent in Active Lupus Nephritis Patients

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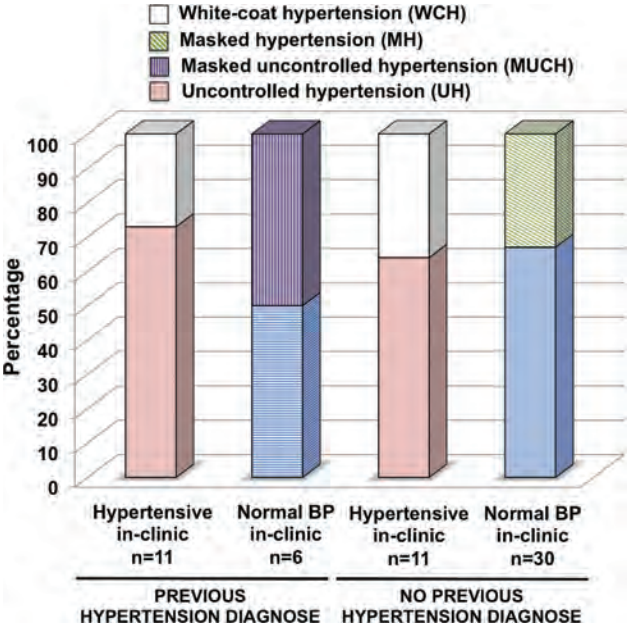
Background: SLE patients have an increased cardiovascular mortality. In CKD, 24h-ABPM studies demonstrate a high-prevalence of masked hypertensive disorders.

Methods: From March 2016 to April 2018, 58 active lupus nephritis patients were evaluated by 24h-BP monitoring the day of the renal biopsy procedure. Two validated oscillometric-based devices were used (Spacelabs 91207 and Welch Allyn 6100). A registry was considered appropriate if >20 daytime and >7 nighttime measurements were available. For analysis, patients were divided into those with or without previous hypertension.

Results: Out of 58 LN patients, 17 (29%) had a previous hypertension dx. These patients were older, had higher in-clinic BP and their renal biopsy showed higher interstitial fibrosis/tubular atrophy. In the 24h-BPM, patients with previous HT had higher overall, daytime and nocturnal BP. However, the nocturnal decrease of BP was diminished and not different between groups. Only 11 (19%) patients had normal dipping, in 30 (52%) it was decreased, and in 17 (29%) was absent. White-coat hypertension (WCH) was found in 3/11 (27%) in-clinic HT and masked uncontrolled hypertension in 3/6 (50%) of in-clinic controlled patients. In the non-previous HT group, WCH was found in 4/11 (36%) of in-office HT patients and masked hypertension in 12/30 (40%) of in-office controlled patients. The nighttime systolic and diastolic BP were more frequently abnormal compared to daytime measurements.

Conclusions: Masked hypertensive disorders are frequent in lupus nephritis patients. As BP thresholds are part of an appropriate management of proteinuric diseases, 24h blood pressure measurements should be considered in clinical practice. These studies were made as inpatients and should be corroborated with ambulatory measurements.



FR-PO1089

Urinary Soluble CD163 as a Biomarker for Lupus Nephritis

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Background: Recently, it has been reported that urinary soluble CD163 (UsCD163) reflects glomerular inflammation of ANCA-associated nephritis and lupus nephritis (LN). We examined the significance of UsCD163 as a biomarker for histological activity and treatment response of LN.

Methods: We investigated the levels of UsCD163 before and after treatment in 52 LN patients (49 females, median age 37 years old) who were diagnosed as ISN/RPS Class III, IV or V and treated for LN since 2010 to 2015 in Gunma University and Saitama Medical University hospitals by ELISA. We also examined whether UsCD163 could be a predictor of remission of LN.

Results: RESULTS: Levels of UsCD163/creatine (Cr) were higher in Cass IV and Class V compared to Class III: III, 2.55 (1.40-5.55); IV, 8.84 (3.05-19.1); V, 8.10 (7.14-10.3) ng/mgCr;, median, (IQR). Significant correlations were observed between levels of UsCD163/Cr and urinary protein/Cr or systemic lupus erythematosus disease activity index (SLEDAI) score, but not eGFR (r=0.421, p=0.0026; r=0.465, p<0.001; r=-0.212, p=0.143). Associations between UsCD163/Cr and histological parameters were shown in Table 1. Significant positive correlations were found between levels of UsCD163/Cr and activity index, leukocyte infiltration or cellular crescents. UsCD163/Cr levels rapidly decreased after treatments. Receiver operating characteristic analysis showed UsCD 163/Cr >17.3 ng/mgCr before treatment was predictor of the presence of cellular crescent (sensitivity 85%, specificity 44%). UsCD163/Cr <3.0 ng/mgCr before treatment was a predictive marker for early proteinuria remission defined as urine protein/Cr <0.3 g/gCr at 3 months after treatment (sensitivity 42%, specificity 92%, positive predictive value 92%, negative predictive value 69%).

Conclusions: UsCD163 could be a potential biomarker for histological activity and treatment response of LN.

Funding: Government Support - Non-U.S.

Variables	r	P Value
Activity index		
Endocapillary/ hypercellularity	0.39 (0.082 to 0.63)	0.015
Leukocyte Infiltration	0.52 (0.24 to 0.72)	<0.001
Subendothelial hyaline deposits	0.14 (-0.19 to 0.44)	0.40
Fibrinoid necrosis karyorrhexis	0.21 (-0.12 to 0.50)	0.21
Cellular crescents	0.68 (0.46 to 0.82)	<0.001
Interstitial inflammation	0.31 (-0.016 to 0.57)	0.062
Total	0.61 (0.35 to 0.78)	<0.001
Chronicity index		
Glomerular sclerosis	-0.26 (-0.54 to 0.062)	0.11
Fibrous crescents	-0.17 (-0.46 to 0.16)	0.32
Tubular atrophy	-0.033 (-0.35 to 0.29)	0.85
Interstitial fibrosis	0.25 (-0.077 to 0.53)	0.13
Total	-0.071 (-0.38 to 0.26)	0.67

Table 1. Correlation between UsCD163/Cr and histological parameters

FR-PO1090

A Composite Urinary Biomarkers to Predict Pathological Tubulointerstitial Lesions in Lupus Nephritis

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Background: This study aims to evaluate the clinical value of urinary biomarkers including kidney injury molecule-1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL) and monocyte chemoattractant protein 1 (MCP-1) in lupus nephritis.

Methods: A total of 109 biopsy-proven lupus nephritis patients were included, and 50 healthy individuals were collected as the normal controls. The urinary KIM-1, NGAL and MCP-1 levels were measured by ELISA, and the correlations of clinical and histological features with them were further assessed. Receiver operating characteristic curves were performed and cox regression model was applied to identify prognostic factors associated with renal outcomes.

Results: Active lupus nephritis patients exhibited elevated urinary levels of KIM-1, NGAL and MCP-1 in comparison with lupus nephritis patients in remission (P<0.001) and healthy controls (P<0.001). The urinary KIM-1 level was correlated with pathological tubular atrophy (r=0.208, P<0.05) and increased significantly in the presence of interstitial inflammatory lesions (P=0.031). The urinary KIM-1, NGAL and MCP-1 levels were higher in patients with active tubulo-interstitial lesions than those with only chronic lesions (P=0.015, P=0.230 and P=0.086, respectively). A combination of KIM-1, NGAL and MCP-1 was a good indicator for diagnosing active tubulo-interstitial lesions (AUC: 0.796). The combination of KIM-1 and NGAL was identified as an independent risk factor for renal outcomes (HR 7.572, P<0.05).

Conclusions: The urinary KIM-1, NGAL, MCP-1 levels were associated with kidney injury indices in lupus nephritis. The combination of the three biomarkers increased its power in predicting tubulo-interstitial lesions and renal outcomes.

Funding: Government Support - Non-U.S.

FR-PO1091

Urine Epidermal Growth Factor Is a Biomarker of Tubulointerstitial Damage in Lupus Nephritis (LN)

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Background: An agnostic proteomic survey of urine from patients with LN showed significantly decreased levels of pro-epidermal growth factor (EGF) in patients who had developed chronic kidney disease (CKD). Urine (u)EGF has previously been shown to predict progressive CKD in several glomerular diseases. Therefore, we examined the association of uEGF with kidney biopsy findings and kidney function in patients with LN.

Methods: EGF was measured by specific ELISA in urine collected at the time of kidney biopsy in 23 Mexican and 29 Midwestern (45% African American, 45% Caucasian) LN patients, and was characterized by immunoblotting. uEGF was also measured in serial urine samples from patients with 1-5 years of longitudinal follow-up.

Results: Results: uEGF in 29 Midwestern LN patients at kidney biopsy was 11.7±10.1 ng/mg Cr compared to 26.5±13.7 ng/mg Cr in 8 lupus patients with no history of LN (p<0.05). Immunoblotting demonstrated uEGF was mainly high molecular weight (pro-EGF forms). uEGF correlated inversely with serum creatinine (SCr), biopsy chronicity index (CI), tubular atrophy and interstitial fibrosis (Table). There was no correlation with proteinuria, biopsy activity index (AI) or the histologic components of the AI (Table). Patients (n=7) with stable CKD showed low but steady levels of uEGF over 1-4 years of follow-up. Patients with progressive CKD (n=6) showed a decline in uEGF over 1-5 years. uEGF fell in patients with acute kidney injury (AKI, n=7), rebounded in 4 (57%) patients when AKI resolved but remained below baseline in 3 (43%) patients, who either did not recover AKI or recovered but later developed CKD.

Conclusions: uEGF is a biomarker of chronic tubulointerstitial damage in LN. Low and falling uEGF suggests progressive CKD. uEGF also decreases in AKI and may signal future CKD if levels do not improve.

Funding: NIDDK Support, Private Foundation Support

	Mexican Cohort (n=23)		Ohio Cohort (n=29)	
Clinical or Pathologic Variable	r	p	r	p
SCr	-0.70	0.0002	-0.82	<0.0001
Proteinuria	-0.16	0.46	0.15	0.48
AI	-0.09	0.66	0.11	0.48
CI	-0.65	0.0009	-0.59	0.0009
Interstitial Fibrosis	-0.79	<0.0001	-0.66	0.0001
Tubular Atrophy	-0.61	0.002	-0.57	0.001

FR-PO1092

Polyomavirus BK, BKV MicroRNA, and Urinary Neutrophil Gelatinase-Associated Lipocalin Can Be Used as Potential Biomarkers of Lupus Nephritis

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Background: Lupus nephritis (LN) frequently progresses to end-stage renal disease. Finding a biomarker for LN and a predictor for the development of chronic kidney disease (CKD) is important for patients with systemic lupus erythematosus (SLE).

Methods: Ninety patients with SLE were divided into biopsy-proven LN (n = 54) and no kidney involvement (non-LN) (n = 36) groups and followed up for 54 months.

Results: Of 36 patients with LN, 3 (5.6%) had class II disease, 3 (5.6%) had class III, 35 (64.8%) had class IV, 10 (18.5%) had class V, and 3 (5.6 %) had class VI (advanced sclerosis). Compared to the non-LN group, patients in the LN group had higher autoimmunity evidenced by a higher proportion of low C3 and C4 levels, positive anti-double-stranded DNA antibody levels, and lower estimated glomerular filtration rates (eGFR). Urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels were significantly higher in the LN group (LN vs non-LN, 670 vs 33 ng/mL, respectively). The patients with LN had a higher urinary polyomavirus BK (BKV) load (3.6 vs 3.0 log copies/mL) and a lower urinary BKV miRNA (miR-B1) 5p level (0.29 vs 0.55 log copies/mL, p = 0.025), while there was no significant difference in the level of miR-B1-3p. Urinary miR-B1-5p level but not urinary BKV load was negatively correlated with uNGAL level (r = -0.22, p = 0.004). At the cutoff value of 80 ng/mL, the receiver operating characteristic curve analysis showed that uNGAL level as a predictor of the presence of LN had a high sensitivity (98%) and specificity (100%) (area under the curve [AUC], 0.997; p < 0.001). During the 54-month follow-up period, 14 (7%) patients with LN and none of the non-LN patients developed CKD. Multivariate Cox regression analysis revealed that baseline uNGAL level was the only predictive factor for CKD development, while baseline serum creatinine level and eGFR were not.

Conclusions: An elevated urinary BKV viral load with a decreased level of miR-B1 implies the presence of LN. In addition, an increased uNGAL level is a good biomarker not only in predicting the presence of LN but also for prediction of CKD development in patients with SLE.

FR-PO1093

Glomerular Phospholipase A2 Receptor Antigen in Lupus Membranous Nephritis

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Background: Phospholipase A2 receptor (PLA2R) is the major pathogenetic antigen in idiopathic membranous nephropathy (iMN). Anti-PLA2R antibody is detected in approximately 70% with iMN and glomerular PLA2R expression by immunofluorescence and serum PLA2R antibody are often observed. Its prevalence and characteristics in lupus membranous nephritis remains to be undetermined.

Methods: We conducted a cross-sectional study at two-centers in Japan, including patients whose renal biopsies show ISN/RPS Class V lupus nephritis, between May 25, 2012 to March 31, 2018. We performed immunofluorescence analysis of frozen section for PLA2R expression using anti-PLA2R antibody. We evaluated the clinical and pathological features between positive-PLA2R group (PLA2R-P) and negative group (PLA2R-N) and checked the serum anti-PLA2R antibody only in PLA2R-P.

Results: We analyzed the glomerular expression of PLA2R Ag in 23 patients, as many as 5 patients had positive glomerular PLA2R antigen expression. As shown in the Table, we compared the characteristics between PLA2R-P and PLA2R-N. The age and the duration from the diagnosis of SLE to biopsy were higher in PLA2R-P, but not significantly. Although the difference in the levels of proteinuria was not significant, the level of serum total protein was significantly lower in PLA2R-P. The levels of C3 and C4, and the intensity of glomerular IgG1 deposition were significantly higher in PLA2R-P. On the other hand, serum anti-PLA2R antibody level are all normal in the PLA2R-P.

Conclusions: Significant proportion of class V lupus nephritis showed positive PLA2R in kidney specimen in spite of absence of circulating anti-PLA2R antibody. Cases with positive PLA2R had significantly lower serum total protein and higher complement levels. Higher complement and proteinuria level may indicate poor activity of lupus nephritis and more phenotypical similarity to iMN.

		Lupus class V (N = 23)		
		PLA2R-P	PLA2R-N	P value
N of patients		5 (21.7%)	18 (78.3%)	
Age (yrs)		48.0 (46.1-73.6)	45.7 (34.0-52.8)	0.174
Duration from the diagnosis of SLE to biopsy (yrs)		17.3 (2.0-22.0)	6.3 (3.3-12.8)	0.581
Serum total protein (g/dL)		5.3 (4.2-6.2)	6.5 (5.7-6.9)	0.03
Urine protein (g/gCr)		5.0 (1.2-7.3)	1.5 (0.4-3.8)	0.446
C3 (mg/dL)		86.0 (74.0-98.5)	58.5 (49.0-73.3)	0.024
C4 (mg/dL)		25.0 (13.5-37.0)	10.0 (4.0-18.0)	0.044
Glomerular IgG subclass deposition	IgG1	1.0 (1.0-2.0)	1.0 (0.5-1.0)	0.039
	IgG4	0.5 (0.25-1.25)	0 (0-0.5)	0.111

Characteristics of lupus nephritis ClassV.

FR-PO1094

APOL1 Risk Variants in Brazilians with Lupus Nephritis

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Background: APOL1 2 risk variants have been associated to collapsing glomerulopathy and end stage renal disease (ESRD) in lupus nephritis (LN) patients. The prevalence of APOL1 G1 and G2 variants in Brazilians is unknown. The present study aimed to analyze the frequency of APOL1 risk variants in a cohort of LN patients in 3 GN clinics in Brazil.

Methods: APOL1 G1 and G2 variants were genotyped in 173 patients who fulfilled SLEDAI criteria for lupus and LN class III, IV or V, randomly chosen in three outpatient clinics. DNA extraction from whole blood was performed using the PureGene system. Two single- nucleotide polymorphisms (SNPs) in the APOL1 G1 nephropathy risk variant (rs73885319; rs60910145) and an indel for the G2 risk variant (rs71785313) were genotyped using Taqman assays on the ViiA 7 platfom (Applied Biosystems for Life Tech). Clinical and lab data were analyzed using R studio.

Results: Patients data are summarized in table1. G1/G1 genotype was found in 3 non-white women (1.7%). They were 21, 29 and 51 years and had LN for 12, 120 and 47 months, respectively. All of them had LN class IV and received treatment with CF, MMF and steroids. Their outcomes in the last follow-up were ESRD in the youngest and CKD stage 4 in the others.

Conclusions: APOL1 risk variants are rare in Brazilians LN patients, however all patients who expressed 2 risk variants had worse outcomes (ESRD or CKD stage 4).

Table 1: Clinical characteristics and outcomes of 173 patients.

Mean age (SD), years	34.5(±11)
Female sex	90%
Non-White	77%
Mean BMI (SD)	25(±5)
Positive ANA	97%
Mean SLICC (SD)	6.8(±2)
Median LN age(25th-75th), mo	48(18-89)
LN Class III(+/-V)	26%
LN Class IV(+/-V)	54.3%
LN Class V	19.7%
Induction treatment: CF	69.5%
Maintenance treatment: MMF	86%
Partial or Complete response (last F/U)	66%
CKD, eGFR<60mL/min (last F/U)	22%
ESRD (last F/U)	8%

CF: Cyclophosphamide; MMF: Micophenolate Mophetil; F/U: follow-up.

FR-PO1095

What Is the Value of a Repeat Kidney Biopsy in Children and Young Adults with Lupus Nephritis?

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Background: Adult lupus nephritis (LN) studies have shown a lack of correlation between follow-up kidney biopsy results and clinical parameters. This study investigated whether kidney biopsy findings in children and young adults with LN performed after induction and maintenance therapy would better determine the response to medical therapy than clinical parameters.

Methods: 64 subjects, 11-18 yrs of age, met 1997 revised ACR classification criteria for systemic lupus erythematosus (SLE) with biopsy proven LN at Rady Children's Hospital in San Diego between 1/1/2005 - 1/1/15. 12 subjects had a repeat biopsy 1 yr after diagnosis and 14 additional subjects had a repeat biopsy within 5 yrs of diagnosis. ACR criteria for complete remission (CR), partial remission (PR) and no remission (NR) were assessed at the time of repeat biopsy. Correlation between clinical remission status and biopsy findings was investigated. The study had IRB approval (#161748X, 6/30/17).

Results: At the time of repeat biopsy, 6 of 26 subjects achieved CR, 3 subjects achieved PR and 17 subjects had NR. Changes in IgG deposition, activity, and chronicity were statistically significant between the CR and NR groups. However, within CR and NR groups there were unexpected results: Among the 6 subjects achieving CR, 4 had the same or worse WHO class, 1 had higher activity and 3 had higher chronicity scores at the time of repeat biopsy. Among the 17 NR subjects, 5 had better or stable WHO classification. Furthermore, repeat kidney biopsies led to significant changes in therapy in both CR and NR groups.

Conclusions: In general, there was poor concordance between ACR remission criteria and repeat biopsy findings in children who achieved CR and NR, with notable exceptions. The discrepancy between clinical findings and kidney biopsy results in such cases should be further investigated. The large number of NR patients likely reflects bias toward repeat biopsy in clinical non-responders.

Comparison of Complete and No ACR Remission Groups

	WHO Class	Autibody Deposition	Biopsy Activity	Biopsy Chronicity	Laboratory Results
Complete remission (n=6; all females)	Better 3 → 2 4 → 2 Same 2 → 2 3 → 3 4 → 4 Worse 4 → 4 +5	IgG: 2.0 ± 0.6 → 0.8 ± 0.9 IgM: 1.9 ± 0.8 → 0.8 ± 0.3 IgA: 1.8 ± 0.9 → 0.5 ± 0.8 C3: 2.2 ± 0.4 → 0.9 ± 0.9 C1q: 1.8 ± 0.7 → 0.7 ± 0.8	5.8 ± 4.1 → 2.2 ± 1.5	1.3 ± 2.0 → 1.7 ± 0.5	eGFR: 131.6 ± 72.5 → 144.9 ± 26.9 C3: 50.3 ± 16.9 → 94.0 ± 16.8 DSDNA: 5864.4 ± 8737.2 → 42.6 ± 33.6 Albumin: 5.5 ± 0.6 → 4.3 ± 0.3 UProt/Ucreat: 4.4 ± 6.5 → 0.1 ± 0.1 uRBC: 1.8 ± 1.3a → 0.4 ± 0.0
No remission (n = 17; 2 males, 15 females)	Better 4+5 → 5 Same 4 → 4 (n=6) 5 → 5 3+5 → 3+5 4+5 → 4+5 Worse 2 → 5 3 → 4 4 → 3 +5 4 → 4 +5 (n=2) 5 → 3 + 5 5 → 4+5	IgG: 1.9 ± 0.8 → 1.9 ± 0.7* IgM: 0.8 ± 0.6* → 0.8 ± 0.6 IgA: 1.5 ± 0.7 → 1.0 ± 0.8 C3: 2.3 ± 0.6 → 1.4 ± 0.8 C1q: 1.5 ± 0.8 → 1.2 ± 0.9	5.6 ± 4.1 → 4.4 ± 2.5*	2.1 ± 1.8 → 3.7 ± 2.6*	eGFR: 120.2 ± 30.7 → 135.9 ± 44.0 C3: 50.9 ± 25.5 → 85.0 ± 25.2 DSDNA: 2947.0 ± 6547.8 → 85.0 ± 25.2 Albumin: 2.9 ± 0.7* → 3.4 ± 0.9* UProt/Ucreat: 5.5 ± 7.2 → 6.5 ± 9.2* uRBC: 22.0 ± 76.9 → 5.3 ± 8.9

All columns show results at the time of the initial and repeat kidney biopsy. * statistical difference ($p<0.05$) between CR and NR groups.

FR-PO1096

Lupus Nephritis IV-S versus IV-G: Different Characteristics and Renal Outcomes

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Background: The ISN/RPS classification of lupus nephritis (LN) divided class IV into segmental and global (IV-S and IV-G), based on evidence suggesting different characteristics and renal outcomes. However, others subsequent studies failed to detect these differences. The aim of this study was to compare characteristics and renal outcomes of classes IV-S and IV-G.

Methods: Retrospective cohort of adult patients with lupus and biopsy proven class IV according to ISN/RPS classification. Clinicopathological characteristics and long-term follow-up were analyzed. Primary end point was ESRD.

Results: Clinicopathological data and renal outcomes of 89 patients with LN class IV are shown in Table 1. There was no difference in tubular atrophy and interstitial fibrosis between classes. Compared to patients with class IV-S, patients with class IV-G had a risk 2.8 times greater of doubling sCr (95%CI 1.4-6.7; p=0.001) and 3.9 times greater of ESRD (95%CI 1.4-5.6; p=0.006).

Conclusions: Patients with class IV-G had more severe clinicopathological presentation and worse renal outcomes compared to patients with class IV-S.

Baseline clinicopathological characteristics and renal outcomes of 89 patients with lupus nephritis class IV

Characteristics	IV-S N=34	IV-G N=55	p-value
Age, median (min-max) (years)	27.5 (18-51)	33.0 (18-57)	0.114*
Female, %	97.1	94.5	1.000¥
Race (non-white), %	55.9	70.9	0.148‡
Hypertension (BP≥140x90mmHg), %	64.7	88.9	0.006‡
Rapidly progressive glomerulonephritis, %	29.4	60.0	<.001‡
Serum creatinine (mg/dl)	1.2 (0.9-2.5)	2.0 (0.9-3.4)	0.085§
Creatinine Clearance, ml/min/1.73m2	56.0 (25.6-79.3)	30.9 (15.8-79.2)	0.085§
Proteinuria, g/24h	3.5 (2.2-4.8)	3.9 (2.2-7.0)	0.346§
Induction Treatment, % Cyclophosphamide Mycophenolate Mofetil	76.5 23.5	83.6 16.4	0.403‡
Pathological characteristics Number of glomeruli, median (min-max) Fibrinoid necrosis, % Wire-loops, % % glomeruli with crescent 50% of glomeruli with crescents, %	16.5 (10-29) 2.9 23.5 0 (0-19) 5.8	14.0 (10-38) 5.5 34.5 26 (0-50) 34.5	0.215§ 1.000¥ 0.272‡ 0.001§ 0.002‡
Follow-up (months) Complete remission, % Partial remission, % Renal flare, % Final serum creatinine (mg/dl) Final creatinine clearance, ml/min/1.73m2 Doubling serum creatinine, % End stage renal disease, %	62,5 ± 34,2 20 (58.8) 10 (29.4) 8 (23.5) 0.9 (0.7-1.3) 79,7 ± 37,5 7 (20.6) 3 (8.8)	54.0 ± 39.5 18 (32.7) 17 (30.9) 15 (27.3) 1.6 (0.8-4.1) 56,0 ± 41,9 32 (58.2) 19 (34.5)	0.299* 0.016‡ 0.887‡ 0.695‡ 0.010§ 0.009* 0.001‡ 0.006‡

Values expressed as median with range (25th – 75th percentile); Creatinine Clearance was calculated by CKD-EPI equation; * T-test; ¥ Fisher's exact test; ‡ Chi-squared test; § Mann-Whitney test.

FR-PO1097

Activation of the Alternative Complement Pathway Predicts Renal Outcome in Patients with Lupus Nephritis

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Background: The aim of this study was to clarify the glomerular activation of complement pathways in patients with lupus nephritis, and to elucidate the association between these complement activation types and clinical outcomes.

Methods: We enrolled 100 patients with biopsy-proven lupus nephritis from 2003 to 2016 from the lupus cohort at the Busan Paik Hospital and the Jeju National University Hospital in Korea. The patients were divided into two groups based on the patterns of glomerular complements deposits: The presence of C4 and C1q deposits with C3 deposits in the glomerulus was considered to be the evidence for the activation of the classical pathway (group I, n=83) and glomerular C3 deposition without C4 and C1q deposits was considered as a marker for the activation of the alternative pathway (group II, n=17). The study endpoint was progression of kidney dysfunction defined as the decline rate of estimated glomerular filtration rate (GFR) of more than 1 ml/min/1.73 m^2 per year.

Results: The mean age of the patients was 32.9 ± 10.7 years. Ten patients were male, 34 patients were hypertensive, 24 patients had a GFR < 60 ml/min/1.73 m^2, and 38 patients had nephrotic range of proteinuria at the time of kidney biopsy. Compared to the group I patients, those in group II were older (31.1 ± 10.1 vs. 41.5 ± 9.5 years, p <0.001), more hypertensive (29% vs. 59%, p=0.020), and more male dominant (6% vs. 29%, p=0.003). Considering histopathologic features, group I patients had higher glomerular deposition of IgG and IgA than those in group II. Endocapillary hypercellularity and fibrinoid necrosis were also more frequently found in group I patients compared with those in group II. The median follow-up time was 4.3 years (interquartile range: 2.6–7.6 years). The rate of decline in estimated GFR was greater in group II patients than in group I patients (-5.7 ml/min/1.73 m^2 per year vs. 1.4 ml/min/1.73 m^2 per year; p=0.034).

Conclusions: This study showed that the patients with the alternative complement activation had poor renal outcome compared to the patients with the classical complement pathway, suggesting that the alternative complement activation may play a pathogenic role in the progression of lupus nephritis.

FR-PO1098

The Clinical Indicators to Predict Active Lesion in Kidney Biopsy Specimen in Patients with Lupus Nephritis

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Background: The histological activity of International Society of Nephrology/Renal Pathology Society (ISN/RPS) class IIIa or IVa lupus nephritis affect physician's decision making in treatment. Because renal biopsy has inevitable risk for bleeding, it is preferable that we can make decision only with clinical parameters. However, few studies have addressed this important issue so far.

Methods: We reviewed the renal biopsy specimen of 120 patients with SLE retrospectively. We analyzed whether and which laboratory findings are correlated with histological activity.

Results: The histologically active lesion of lupus nephritis was found in 73.3% of all the patients, in 50% of the patients with the group of no hematuria, and in 70.8% of the patients with intermittent hematuria. Hematuria significantly correlated with histological activity with a sensitivity of 86.4% and a specificity of 37.5%, and significant proteinuria [≧0.5 g/gram creatinine (gCr)] significantly correlated with histological activity with a sensitivity of 84.1% and a specificity of 34.4%. If combining hematuria and proteinuria, the sensitivity for histological active lesion increased to 96.6%. Low serum C3 (< 65 mg/dl) significantly correlated with renal disease activity with a sensitivity of 79.1%, and high serum anti-DNA antibody (≧10 IU/ml) significantly correlated with histological activity with a sensitivity of 91.4%. Existence of at least one of these clinical indicators (hematuria, proteinuria, high anti-DNA antibody and low C3) showed 100% sensitivity for histological activity. Those with high specificity were persistent hematuria (specificity 71.5%), anti-DNA antibody≧40 IU / ml (specificity 73.1%), and existence of all 4 of the clinical indicators (specificity 81.3%).

Conclusions: Isolated or intermittent hematuria did not predict histological activity so well. In order to avoid overlooking active lupus nephritis without kidney biopsy, we should count not only hematuria but also significant proteinuria, low C3 and high anti-DNA antibody. If the renal biopsy is not possible, but we still suspect activity such as in cases with progressive decline in kidney function, persistent hematuria, anti-DNA antibody≧40 IU/ml and presence of all 4 of clinical indicators strongly suggest disease activity and may help us make decision for active treatment.

FR-PO1099

Lupus Nephritis (LN) Patients with Crescentic Proliferative Lesions Show Lower IgG Glomerular Staining

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Background: Literature is scarce in describing outcomes and histological associations of LN patients with crescents. The immunofluorescence findings may suggest the pathophysiology of lesions and therefore have implications in the clinical behavior of LN. Our objective was to evaluate renal outcome and histological associations of patients with proliferative LN with and without crescents.

Methods: In this single-center, retrospective cohort study, 138 eligible LN patients were evaluated. The clinical features at baseline and at the end of follow-up were evaluated. eGFR was calculated using CKD-EPI equation. Kidney biopsies were classified according to the ISN/RPS Classification and immunofluorescence patterns. We performed comparative analyses between groups with different proportions and without crescentic lesions in kidney biopsy. Univariate analysis utilized Chi Squared test (n,%) for count and one-way analysis of variance, followed by Student- Newman Keuls tests for continuous variables.

Results: As shown in the image below.

Conclusions: Patients with crescentic (≥50% crescents) form showed at baseline, lower CKD-EPI (p<0.05), higher activity index (p<0.05) and lower intensity of IgG staining (p<0.05) than patients with no crescents on biopsy. The groups presented no difference in clinical outcomes, however, at the end of follow-up, the crescentic group presented a trend towards a higher proportion of individuals with CKD-EPI under 60ml/min/1.73m2.

	No Crescents	1-25% Crescents	26-49% of Crescents	≥50% of Crescents
N	38 (27.5%)	57 (41.3%)	31 (22.5%)	12 (8.7%)
Age (years)	31 ± 10.0	28.9 ± 9.8	26.6 ± 8.9	30.3 ±13.8
CKD-EPI - baseline	64.0 ± 34.3	57.4 ± 37.2	46.8±26.3	33.1 ± 26.9*
Proteinuria (g/day or g/g) - baseline	3.7 ±2.6	4.8 ±2.8	5.2 ±3.3	5.8±3.9
Serum Albumin (g/dL) - baseline	2.9 ±0.9	2.6 ± 0.8	2.8 ±0.7	2.4 ±0.4
Hemoglobin (g/dL)– baseline	10.0 ±2.1	10.6 ± 2.1	10.0 ±2.0	10.0±1.012
C3 (mg/dL)– baseline	48 (37.3-63.5)	54.9 (±25.2)	65.7 ± 31.7	54 ± 37.3
ANCA positive (n/%)	4 (14.3%)	5 (12.2%)	5 (23.8%)	1 (16%)
Kidney Biopsy				
Class III or III +V (n/%)	11 (29%)	7 (12%)	7 (22%)	0 (0%)
Class IV or IV + V (n/%)	27 (71%)	50 (88%)	24 (78%)	12 (100%)
Activity index	3.8 ±1.4	5,7 ± 2.0	5,6 ±2.1	7,7±4.2*
Chronicity index	2.5 ± 2.1	2.6 ±1.9	3.7 ±2.5	4.0 ±1.5
IgG staining ++ or +++	20 (58.8%)	34 (65.4%)	14 (46.6%)	3 (25%)*
C1q staining ++ or +++	7 (20.6%)	10 (19.2%)	9 (30%)	1 (9%)
Follow-up (months)	137 ±67.5	102.8 ±52.6	92,7 ±56.4	109.0±71.8
Doubling of serum creatinine or ESRD	9 (23.7)	15 (26.3%)	10 (32.6%)	3 (25%)
(CKD-EPI) - final	67 ± 37.5	67.8 ± 41.1	59.7 ±41.1	52.8 ±30.7
CKD-EPI < 60 at end of follow-up	18 (47.4%)	24 (42.1%)	14 (45%)	8 (66.7%)
Data are mean ± SEM or n (%) *p<0.05 vs No crescents				

FR-PO1100

Evaluation of the Full-House Immunofluorescence Pattern (FH) in Patients Without Systemic Lupus Erythematosus (SLE): A Single Centre Observation Study

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Background: Strong interest is shown recently for FH pattern in patients without SLE nephritis. The purpose of the study is to identify patients with the above-mentioned entity and to evaluate clinical-laboratory findings and outcomes.

Methods: It consists of 8 patients with a FH pattern, defined as concomitant deposition of immunoglobulins (IgA, IgM, IgG) and two complement factors (C3, C1), non-diagnosed SLE who have undergone kidney biopsy over 4 years. Existing biopsies were reassessed by a nephropathologist and categorized according to the international histological classification of SLE. Anthropometry, eGFR, proteinuria, clinical course and histological findings were recorded.

Results: Two groups, idiopathic FH-non-lupus-nephropathy (iFHN) (n = 4) were identified based on the absence of histological findings defining specific glomerulonephritis(GN) (e.g. absence of PLA2R-antigen expression etc.) and secondary FH-non-lupus-nephropathy (sFHN) (n = 4) (e.g., expression of PLA2R-antigen, IgA +++, etc.). Patients with iFHN exhibit higher proteinuria (mean 9.45g / 24h), low eGFR (mean 28.8 ml / min / 1.73m2), significant consumption of C1q, C3, significant glomerulosclerosis and interstitial inflammation. The most common light microscopy pattern was membranoproliferative GN and response to personalized treatment was unsatisfactory. Patients with sFHN exhibit lower proteinuria (mean 7.32 g / 24 h), high eGFR (mean 81.1 ml / min / 1.73 m 2), mild deposition of C1q, C3, mild glomerulosclerosis and interstitial inflammation. The prominent light microscopy pattern was membranous nephropathy and response to treatment was satisfactory.

Conclusions: IFHN may reflect a clinicopathological entity with aggravating features and an unfavorable prognosis. Further studies are needed in order to corroborate that conclusion and to establish better approach to the treatment.

FR-PO1101

Chronic Changes in Lupus Nephritis Biopsies – When to Treat? Could Complement C3c Be an Indicator for Missed Activity?

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Background: Management of biopsies showing chronic disease only is a common clinical conundrum in lupus nephritis (LN), especially when the biopsy is performed due to clinical features indicating activity. We have recently demonstrated that complement C3c staining is an indicator of current activity of the complement pathway in LN. We analysed characteristics that prompted treatment of patients with biopsies showing LN class III/IV(C) only from our LN cohort & reviewed whether positive C3c staining is a surrogate for disease activity.

Methods: Demographic, clinical, histopathological & outcome data were reviewed for renal biopsies showing III/IV(C) LN between 1/1/1996 & 1/1/2016. Treated patients were compared with untreated patients. C3c positive & C3c negative biopsies were then compared.

Results: 129 biopsies were performed over the 20 years which showed III/IV(C) disease only. 53% of these patients had escalation of their treatment post biopsy. 31 of the patients with a "chronic" biopsy had a subsequent biopsy available for review.

Conclusions: Deciding to treat patients with only chronic changes on biopsy was significantly associated with indication for biopsy, positive C3c staining, presence of subendothelial deposits & eGFR at the time of biopsy. However, our analysis thus far does not show a benefit of treating these patients as uPCR is actually higher in treated patients at 1 year although improved from baseline & eGFR, better at baseline in the treated group, actually falls. The repeat biopsies may suggest that not treating those with C3 positivity may lead to progressive scarring.

Baseline Variables	Treated	Untreated	p value
Indication for biopsy:			
1st presentation LN (16% biopsies)	23%	5%	0.009
Presumed renal flare (42%)	56%	26%	0.001
Persistent proteinuria (22%)	18%	28%	ns
Staging (20%)	3%	41%	<0.0001
C3c positive staining	91%	56%	0.002
Subendothelial or subepithelial deposits on Electron Microscopy	90%	66%	0.015
Proteinuria uPCR (median, mg/mmol)	305	143	0.0002
eGFR (median)	77	58	0.008

Table 1. Clinical & histopathological variables at baseline

Outcome Variables	Treated	Untreated	p value
Median eGFR at one year	69	57	ns
Median uPCR at one year	177	130	ns
1-31 year survival with eGFR >60mls/min/1.73m2 (min 1yr follow-up)	44%	34%	ns

Table 2. Clinical variables at one year post biopsy

Histopathological variable	C3c positive	C3c negative	p value
Change in % of glomeruli in the biopsy showing chronic changes	Increase 8%	Decrease 8%	ns
Change in % interstitial fibrosis & tubular atrophy (IFTA)	Increase 7.5%	0%	ns

Table 3. Histopathological features indicating chronic changes in C3c positive & negative patients.

Histopathological variable	C3c positive treated	C3c positive untreated	p value
Change in % of glomeruli in the biopsy showing chronic changes	Increase 5%	Increase 21%	ns
Change in % IFTA	Increase 7.5%	Increase 5%	ns

Table 4. Histopathological features indicating chronic changes in C3c positive patients with treatment escalated & with no escalation in treatment (untreated).

FR-PO1102

Comparison of Treatment Eras in a Large Cohort of Lupus Nephritis: Maintenance of Long Term Outcomes with Significantly Lower Burden of Immunosuppression and Corticosteroid Use

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Background: Lupus Nephritis (LN) is a common & severe manifestation of systemic lupus erythematosus (SLE) requiring long courses of immunosuppression. Our lupus centre was established when 2 renal units merged in late 2005 & new protocols were developed focused on reducing the use of corticosteroids & increasing the use CD20+ B cell depletion therapy. We reviewed our large multi-ethnic cohort to assess the impact of these changes.

Methods: Demographic, clinical, histopathological & outcome data were reviewed for all patients with renal biopsies showing LN from 1/1/1996 to 1/1/2016. Patients treated 1996-2005 & 2006 onwards were compared. Data analysed per patient or per biopsy as appropriate.

Results: 819 biopsies (151 pre 2006, 668 post 2006) were performed on 476 patients over the 20 years. 172 patients were diagnosed with LN pre 2006 & 302 post. Whilst there was no significant difference in patient gender or ethnicity between the eras, age at diagnosis was significantly different with a mean of 32 pre 2006 & 37 post 2006 ($p<0.001$). The baseline eGFR, urine protein creatinine ratio & dsDNA titres were not significantly different between the eras.

Conclusions: Treatment regimens have altered significantly post 2006 with a much greater use of anti CD20 therapy & a significant reduction in (high dose) CyP & prednisolone exposure for patients. Despite the significant reduction in the burden of immunosuppression, rates of response to treatment, flare & 10 year survival with preserved renal function have been maintained.

Baseline variables	1996-2005	Post 2006	p value
• Antiphospholipid positive	37%	22%	0.002
• Antinuclear antibody positive	89%	91%	ns
• Anti-Sm antibody positive	14%	38%	<0.001
• dsDNA positive	78%	77%	ns
• Complement low	85%	81%	ns
• Proportion of biopsies class III or IV +/- V	68%	62%	ns
• Proportion of biopsies pure class V	21%	27%	ns
Treatment			<0.001
• Anti CD20 therapy (+ MMF/Aza/Tac +/- Pred)	8%	68%	
• Cyclophosphamide ((Cy)Pge/orally NIH protocol)	37%	11%	
• Anti CD20 therapy + CyP (Euenlupus doses)	2%	11%	
• Oral (MMF/Aza/Tac +/- Pred)	53%	11%	
• Hydroxychloroquine use	51%	77%	<0.001
• Oral prednisolone use	86%	51%	<0.001
Outcomes			
• Complete response to treatment	41%	48%	ns
• Flare	32%	39%	ns
• Extra-renal features SLE	64%	76%	0.015
• 10 year survival with eGFR >60ml/min/1.73m²	76%	69%	ns

FR-PO1103

Characteristics Associated with Repeat Native Renal Biopsy in Lupus Nephritis

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Background: There is great interest in using repeat kidney biopsies to determine the response to treatment and outcomes of patients with lupus nephritis (LN). Although some patients with lupus nephritis undergo a repeat kidney biopsy, the factors that lead to the decision to repeat a biopsy and how the repeat biopsy alters treatment are not well understood. We evaluated the timing and explored factors associated with repeat kidney biopsy.

Methods: We identified 42 patients ≥ 18 years old with biopsy proven LN who underwent a repeat native renal biopsy from 2010 to 2018. A retrospective review was performed focusing on the clinical and histopathologic characteristics associated with a repeat biopsy. Both the reference and repeat biopsies were evaluated via the ISN/RPS classification.

Results: Of the patients included, 37 (88%) were women, 30 (71%) were black. The median age at reference biopsy was 28.74 years (IQR: 22.41, 37.77) and 34.33 years (26.70, 43.58) at repeat biopsy. The median interval time to repeat biopsy 2.96 (2.21, 7.83). The interval time between biopsies increased over the selected time period. The serum creatinine increased between reference and repeat biopsies (median 1.12 (0.1, 1.70) vs. median 1.38 (0.90, 2.54)). The results of the clinical and histological factors are addressed in the figure below.

Conclusions: Several factors were associated with the decision to repeat a native kidney biopsy in patients with lupus nephritis including time from reference biopsy, elevated serum creatinine, active urine sediment, hypoalbuminemia, and anti dsDNA positivity. The decision to repeat a biopsy was associated with a change in immunosuppression for the majority of our cohort. Looking ahead, we hope to use these clinical and histopathologic factors to establish and clarify how a repeat biopsy can lead to changes in management in our patients with lupus nephritis.

	Repeat biopsy
Albumin (g/dL)	N=36, median 2.9 (IQR 2.4, 3.3)
UPCR (g/g)	N=41, median 2.5 (1.5,6.5)
Low C3	20/38 (52)
Low C4	19/38 (50)
Positive Anti dsDNA	22/33 (67)
Active urine sediment	24/35 (69)
Indication	
Worsening kidney function	21 (50)
Worsening proteinuria	25 (60)
Active urine sediment	28 (67)
Prognosis	3 (7)
Protocol	0
Persistent activity post induction	0
Histologic class change from first biopsy	18/32 (56)
Change from proliferative to non-proliferative class	0/34
Change from non-proliferative to proliferative class	5/7 (71)
Change in immunosuppression following repeat biopsy	32/41 (78)

*N=42 unless otherwise specified with (percentage)

FR-PO1104

A Nationwide Analysis of Outcomes of Adult Lupus Nephritis in Japan

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Background: Although the prognosis of lupus nephritis (LN) has been improved, some patients reached end-stage renal disease (ESRD). We aimed to examine recent prognosis of LN in Japan using nation-wide registry.

Methods: This study is a retrospective cohort study. Adult patients (18 years old or older) who were registered as LN in Japan Renal Biopsy Registry (J-RBR) between 2007 and 2012 were examined. Primary endpoint was defined as doubling serum creatinine (S-Cr) or ESRD requiring renal replacement therapy. Data were expressed as median (IQR).

Results: 498 patients (88 male), age 39 (30-52) years-old, from 27 institutions were evaluated. New-onset of LN, 348 patients; relapse, 106 patients; refractory, 35 patients; others, 9 patients. Clinical data at the renal biopsy were as follows: eGFR 78.3 (56.3-100.8) ml/min/1.73m^2, urinary protein 2.04 (0.87-4.30) g/gCr. 40.0% of patients had nephrotic syndrome and 12.2% of patients showed rapidly progressive glomerulonephritis clinically. The frequency of each ISN/RPS Class was as follows: I, 1.6%; II, 5.8%; III, 26.9%; IV, 46.6%; V, 18.5%; VI, 0.6%. During the observation period of 63 (49-82) months, 36 patients (7.2%) reached primary endpoints, 75 patients (15.1%) reached 1.5 times increase in S-Cr or ESRD, and 27 patients (5.4%) died. Renal survival (not doubling S-Cr or ESRD) curve in each Class was calculated by Kaplan-Meier analysis and shown in Figure 1. The 5-year renal survival and 5-year patient survival was 94.0% and 94.8% in total patients, and 92.1% and 93.1% even in Class IV, respectively. Among patients with new-onset LN (n=348), the 5-year renal survival and 5-year patient survival was 94.8% and 94.2% in total patients, and 93.1% and 92.4% in Class IV, respectively.

Conclusions: Recent prognosis of LN are relatively good at least 5 years after renal biopsy in real-world clinical practice in Japan.

Funding: Government Support - Non-U.S.

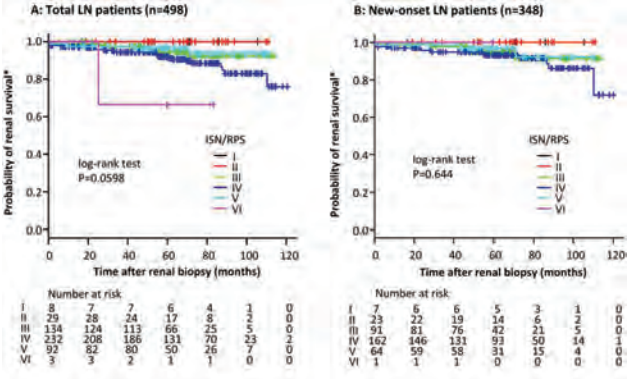

Figure 1. Kaplan-Meier Curve for renal survival by ISN/RPS classification.

* Renal survival was defined as not reaching doubling S-Cr or ESRD requiring renal replacement therapy.

FR-PO1105

A Proposal for Outcome Prediction in Lupus Nephritis Based on Bayesian Statistics

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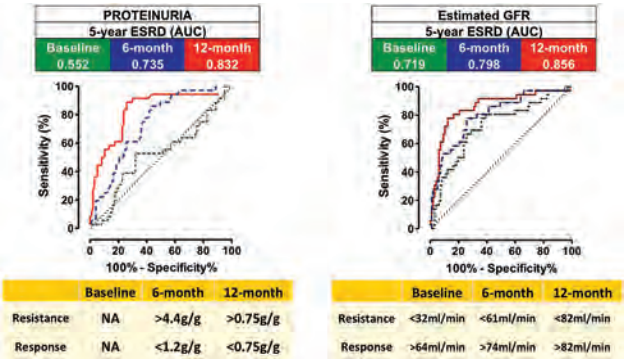
Background: A focus in lupus nephritis (LN) is to define the best criteria for response to therapy based on hard renal outcomes. The definition of resistant disease remains heterogeneous.

Methods: The aim of the study was to determine the prognostic value of clinical parameters to predict renal survival and progression to ESRD. Clinical predictors were evaluated at 6/12 months after treatment as absolute values, absolute or percentage changes and predictor's value normalization. The best cutoff was defined as the value where positive likelihood ratios (+LR) were persistently >3.0 for renal survival (response) or ESRD development (resistance).

Results: Of 248 patients with proteinuria >2.0g/g and complete induction treatment, we included 133 patients with >5 years follow-up. 36 (27.1%) progressed to ESRD. The best predictors for response were creatinine or eGFR at 6/12 months (AUC 0.798/0.856), proteinuria at 6/12 months (0.735/0.832) and hemoglobin at 6/12 months (AUC 0.689/ AUC 0.786). Predictors for resistance after 6 months of treatment included creatinine or eGFR (AUC 0.815), proteinuria percentage change (0.735), and albumin percentage change (AUC 0.599). Hematuria and serological parameters (dsDNA-antibodies, C3, C4) were not appropriate prognostic predictors. After censoring at different times of follow-up, it was observed that the longer the follow-up, the cutoff for each parameter had a lower valule. The best prognosis for renal survival was given by 12-month proteinuria <0.75g/g (+LR=3.08),

eGFR>82ml/min (+LR=3.00) and hemoglobin>12g/dl (+LR=3.04). The best predictors for resistance were 6-month eGFR<61ml/min (+LR=3.13), proteinuria decrease <10% (+LR=3.29) and increase of serum albumin <0.3g/dl (+LR=3.39).

Conclusions: Likelihood ratios may be used to define the best values for response and resistance to therapy in LN. Proteinuria, renal function and hemoglobin at 12-months predict renal survival while proteinuria, eGFR and change in serum albumin may define resistant disease.



	Baseline	6-month	12-month
Resistance	NA	>4.4g/g	>0.75g/g
Response	NA	<1.2g/g	<0.75g/g

	Baseline	6-month	12-month
Resistance	<32ml/min	<61ml/min	<82ml/min
Response	>64ml/min	>74ml/min	>82ml/min

FR-PO1106

The Risk of ESRD in Systemic Lupus Erythematosus: A Nationwide Population-Based Study in Korea

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Background: SLE is known to be one of the leading cause of end-stage renal disease (ESRD). The aim of this study was to estimate the incidence rate of ESRD and the risk factors for progression to ESRD in SLE patients compared to general population.

Methods: 21,253 SLE patients (mean age, 41.91±13.22 years; female, 90.4%) were extracted from the Korean National Health Insurance Service database between 2008 and 2014. Age-and sex-matched controls (n=106,265) were randomly sampled in a 5:1 ratio from non-SLE individuals. Both cohorts were followed up for incident ESRD until 2015.

Results: During the total 8 years of follow-up, 145 (0.14%) cases of ESRD was newly developed in SLE patients and 533 (2.51%) cases in matched controls (incidence: 4.075 and 0.219 per 1000 person-year, respectively). SLE patients were at higher risk for ESRD development compared to matched controls (odd ratio (OR), 10.134; 95% confidence interval (CI) 8.368-12.343) after multivariate adjustment. In subgroup analysis, the risk for ESRD was higher in male with SLE (OR, 7.952; 95% CI 5.26-12.272), in female with SLE (OR, 10.82; 95% CI 8.719-13.526), in 20-39 year-old patients with SLE (OR, 22.57; 95% CI 14.588-36.449), in 40-64 year-old patients with SLE (OR, 22.57; 95% CI 14.588-36.449), in elder than 65 year-old patients with SLE (OR, 5.122; 95% CI 3.431-7.649) than matched control, respectively.

Conclusions: SLE was associated with an increasing incidence of ESRD

FR-PO1107

Outcomes of Pure Membranous Lupus Nephritis in an Urban Predominantly African-American Patient Population

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Background: Treatment options for pure membranous (class V) lupus nephritis (LN) include prednisone, cyclophosphamide (CYC), calcineurin inhibitors (CNI), and mycophenolate mofetil (MMF). There is a paucity of data on the use of MMF; a pooled analysis from studies for the treatment of proliferative LN have compared MMF to CYC for the treatment of pure membranous LN. We are comparing the outcomes of pure membranous LN patients treated with MMF in comparison to other therapies in our urban predominantly African-American patient population.

Methods: Kidney biopsy log from 2010 – 2017, and a retrospective chart review was completed. We excluded any patients with proliferative disease (active or chronic). We analyzed data (t-test comparison) comparing LN class V patients treated with MMF in comparison to other therapies.

Results: There was 101 patients with pure membranous LN and 54 patients with sufficient follow-up data were included. Induction regimens: MMF (n=29) and (n=25) other therapies (6=CYC, 3=CNI, 12=prednisone alone, 3=azathioprine, 1=ARB alone). Racial demographics: 51=black race (94%), 1=Hispanic, 1=white, 1=native Hawaiian. 52 female patients. Average follow-up 3.5 years. MMF treated group: initial serum creatinine (Scr) - 0.85 mg/dL, initial serum albumin (Salb) 2.67 g/dL, and initial urine protein/creatinine ratio (UPC) of 4.14 mg/g. Other therapies group: initial Scr – 1.58 g/dL, initial Salb 2.53 g/dL, and initial UPC of 4.32 mg/g. MMF treated: final Scr – 0.89 mg/dL, final Salb 3.30 g/dL, and final UPC 1.39 mg/g. Other therapies: final Scr – 1.53 mg/dL, final Salb 3.55 g/dL, and final UPC of 0.70 mg/g. There was no difference in percent with abnormal C3, C4, or dsDNA. At baseline Scr was 1.58 mg/dL (other group) vs. 0.85 mg/dL (MMF group) p <.05, and at final Scr 1.53 mg/dL (other group) vs. 0.89 mg/dL (MMF) p =.08.

Conclusions: In our predominantly African-American patient population MMF is effective as other therapies for Class V LN. There was a significant difference in initial Scr between the MMF and other therapies group, and the difference remained throughout. There was a greater than 50% reduction in UPC in both groups. The study displayed a good prognosis in both groups at the end of treatment.

FR-PO1108

Progressive Improvement of Renal Survival over the Last Five Decades in 499 Italian Patients with Lupus Nephritis

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Background: To examine the changes in lupus nephritis (LN) prognosis during the course of the last fifty years and to search for the prognostic factors associated with patient and renal outcomes.

Methods: Four hundred and ninety-nine patients (pts) (85.6% women) were included in the study; they were followed for a median period of 10.6 years (IQR 4-18). They were diagnosed from 1970 to 2016 and were subdivided into three periods (P) based on the year of LN diagnosis: P1 1970-1985: 106 pts; P2 1986-2001: 158 pts; P3 2002-2016: 235 pts.

Results: As Induction therapy, in each period, more than 2/3 of pts received methylprednisolone pulses, and more than 50% received cyclophosphamide. Azathioprine was given to 16% of pts in P1, 12% in P2, and 4% in P3, mycophenolate mofetil (MMF) in 3% of pts in P2 and in 34% in P3. For maintenance therapy, azathioprine and MMF were used respectively in P1 in 28% and in 1% of patients, in P2 in 39% and in 15%, and in P3 in 30 and in 54%. The CKD free survival at 10 and at 20 years was 75% and 66% in P1, 85.5% and 80.2% in P2 and 91.5% in P3 (p=0.0069). The ESRD free survival at 10 and at 20 years were respectively 87% and 80% in P1, 94% and 90% in P2 and 99% in P3 (p=0.0019). Patient survival at 10 and at 20 years were respectively: in P1 94% and 87%, in P2 98% and 94% and in P3 95%. At multivariate analysis, carried out in the entire cohort, among the characteristics at presentation, Log serum creatinine (RR 2.39 for any increase in Log serum creatinine), high activity (RR 1.06 for any unit increase in activity index) and chronicity index (RR 1.13 for any unit increase in chronicity index), arterial hypertension (RR4.16) and the absence of maintenance immunosuppressive therapy (RR 2.08) predicted CKD. The same features predicted ESRD with the addition of male gender (RR 3.34). Male gender (RR 2.88), older age (1.07 for any increase in one year of age) and Log serum creatinine (RR1.8) were independent predictors of death.

Conclusions: The progressive improvement in renal survival in our cohort is the result of a comprehensive approach, which includes a prompt diagnosis of renal involvement, treatment based on renal biopsy, and increased clinical experience in the management of LN complications.

FR-PO1109

The Short and Long Term Effect of Methylprednisolone Pulse Therapy for Lupus Nephritis Treated with Multi-target Therapy

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Background: Muti-target therapy was applied to the severe lupus nephritis, especially the patients with severe proteinuria. Methylprednisolon pulse therapy was used in the initial phase of induction therapy in some patients. We conducted this study to assess the short and long term effect of methylprednisolon pulse therapy on the lupus nephritis patients treated with muti-target therapy.

Methods: It's a retrospective study from 2007-2016, 43 patients diagnosed as lupus nephritis received muti-target therapy in our center, including prednisone combined with MMF and tacrolimus. 19 patients received methylprednisolon pulse therapy in the initial phase of induction therapy, 24 patients only received prednisone combined with MMF and tacrolimus. The dose of methylprednisolon pulse therapy was intravenous injection 500mg*3 days, following prednisone dose was 0.8-1.0mg/kg. The dose of MMF was 1.0-1.5g/d, the initial dose of tacrolimus was 0.05 mg/kg/d, the target trough levels was 3 to 8 ng/mL for 24 weeks, and then reduced to 3 to 6 ng/mL. In the patients combined with acute renal injury (AKI), we accessed the short term outcome by the decrease of serum creatinine in 1 and 3 month. Long term outcome variables included mean remission rate, average remission time.

Results: There was a significant difference in the decrease of creatinine between the two groups in 1 month (P=0.04). However, there was no significant difference in 3 month. In the 12 months follow up, 16 of 19 patients in the methylprednisolon pulse therapy group (84.2%) experienced remission (either complete or partial), and 12 of 19 patients (63.1%) experienced complete remission. In the group only receive muti-target therapy, 20 of 24 (83.3%) patients experienced remission, and 13 of 24 patients (54.2%) experienced complete remission. There were no significant difference in remission rate and remission time between the two groups (p=0.93 p=0.87). We also did not found significant difference in the serum creatinine and UP/Cr in 3, 6, 12month.

Conclusions: Methylprednisolon pulse therapy seemed had no significant effect on the long-term prognosis of lupus nephritis treated with muti-target therapy, but maybe it had better effect on the recovery of AKI patients.

FR-PO1110

Mycophenolate Mofetil in Lupus Nephritis: Long Term Efficacy and Safety Outcomes

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Background: There is a lack of long-term (LT) efficacy and safety data for Mycophenolate mofetil (MMF) in the treatment of lupus nephritis (LN) [1]. We have used MMF since 1999 and undertook a retrospective case-note review of all patients whose treatment included MMF and at least 10 years follow-up (FU).

Methods: 96 patients with biopsy-proven LN who started MMF ≥10 years ago were identified for the study.

Results: 75 (78%) were female; 20 (21%) Black and 8 (8%) Asian. At diagnostic renal biopsy, median age was 35 years (IQR 26-45), serum creatinine (SCr) 90umol/l (IQR 73-140) and UPCR 318 mg/mmol (IQR 153-569). The median length of FU was 11.6 years (IQR 10.7-13.6). Median cumulative MMF exposure was 8.4 years (IQR 5.5-11.5). 17/96 (18%) reached ESRD (median 67 months, range 3-188) and 5/96 (5%) died during FU (median 124 months, IQR 86-129). The rates at 7 years FU (12/96 and 1/96) were not statistically different to those reported in the LT FU of the MAINTAIN trial (p= 0.55, p=0.08) [2]. Median duration of MMF was 5.4 years (IQR 2.0-7.2) in the patients who died. At our unit, treatment regimens changed during the time period reviewed, moving to induction with MMF +/- Rituximab, mostly without oral steroids. We found no difference in adverse events between the Cyclophosphamide and MMF regimens, and patients did equally well on either regimen (Table 1). Importantly, no significant difference in adverse events was seen with MMF exposure ≥10 years vs <10 years (p=0.91) (IQR 11.2-13.6 vs 3.8-7.6).

Conclusions: This is the largest study to report LT outcomes in patients receiving MMF and the first to report data over ten years. LT treatment with MMF appears to be safe and our data supports the use of non-CyP based regimens. The increase in number of patients with ESRD or who died after 7 years FU emphasises the importance of LT follow up data in these cohorts. **References** [1] Bertsias GK *et al. Ann Rheum Dis* 2012;**71:**1771-1782 [2] Tamirou F *et al. Ann Rheum Dis* 2016;**75**:526–531

Table 1: Cyclophosphamide (CyP) vs MMF induction regimens

	CyP induction (n=40)	MMF induction (n=56)	P Value *=sig
LN Class II/III/IV/V	1/4/23/7	5/10/20/15	ns/ns/0.04*/ns
Baseline SCr (umol/l) (IQR)	88 (74-172)	99 (71-122)	0.802
Baseline uPCR (mg/mmol) (IQR)	231 (106-488)	367 (178-801)	0.071
Length of FU (mths) (IQR)	145 (137-168)	135 (125-160)	0.020*
Cumulative MMF exposure (yrs) (IQR)	8.26 (5.66-12.08)	8.77 (5.48-11.28)	0.850
Double SCr	11 (27.5%)	11 (19.6%)	0.226
ESRF	8 (20%)	9 (16.1%)	0.787
Death	2 (5%)	3 (5.36%)	1.000
CKD class - negative change	21 (52.5%)	24 (42.9%)	0.409
CKD class – positive change	5 (12.5%)	10 (17.9%)	0.575
Infectious episodes	25 (62.5%)	30 (53.6%)	0.410
Cancer	4 (10%)	3 (5.36%)	0.446
Patients with pregnancies	7 (17.5%)	8 (14.3%)	0.778

FR-PO1111

Mycophenolate Mofetil in the Treatment of Chinese Patients with Active Lupus Nephritis: A Systematic Review and Meta-Analysis

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Background: Mycophenolate mofetil (MMF) has been recommended as induction and maintenance therapy for lupus nephritis (LN). MMF has shown superiority over cyclophosphamide (CYC) in LN patients of Hispanic or mixed race. So far, there has been no comprehensive review of the efficacy and safety of MMF in the treatment of LN that focused on Chinese patients. Thus, the present study aims to investigate the efficacy and safety of MMF in the treatment of Chinese patients with LN.

Methods: The following databases were searched: PubMed and EMBASE (from January 1979–January 2018); and the Cochrane Collaboration, China National Knowledge Infrastructure, Wanfang, and SinoMed (in January 2018). The search strategies comprised: (mycophenolate mofetil AND (cyclophosphamide OR azathioprine)) AND (lupus nephritis OR lupus glomerulonephritis OR proliferative glomerulonephritis OR membranous glomerulonephritis OR systemic lupus erythematosus) in English and in Chinese. Two reviewers independently assessed each identified clinical trial. Meta-analysis was conducted by using RevMan5.3 software.

Results: A total of 12 eligible randomized controlled trials (RCTs; 5 English and 7 Chinese articles; total 557 patients) were included. Nine RCTs reported complete remission (CR). The complete remission rate was significantly higher in the MMF group (48.9%) than in the CYC group (37.4%) (relative risk [RR] 1.28; 95% confidence interval [CI]: 1.05, 1.55; p=0.01). There was no significant difference in the total remission rate between the two groups of induction therapy (TR [CR + partial remission]; RR 1.11; 95% CI: 0.97, 1.26; p=0.12). MMF versus CYC during induction therapy was associated with significantly lower risks of infection (RR 0.58; 95% CI: 0.41, 0.84; p=0.004), leukopenia (RR 0.26; 95% CI: 0.11, 0.66; p=0.004), alopecia (RR 0.12; 95% CI: 0.03, 0.43; p=0.001), and amenorrhea (RR 0.15; 95% CI: 0.04, 0.56; p=0.004). No significant difference in relapse rate was evident between the MMF and AZA groups (RR 1.15; 95% CI: 0.59, 2.26; p=0.68).

Conclusions: MMF for induction treatment of lupus nephritis in China is superior to CYC in complete remission and is safer.

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FR-PO1112

Insights from Machine Learning Analysis of Collated Lupus Nephritis Trials

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Background: Machine learning (ML) analyses are being increasingly used in diverse fields of medical research to identify parameters associated with disease progression and/or outcome. We tested this method for identifying variables associated with complete renal response (CRR) in lupus nephritis (LN).

Methods: Data collated from two clinical trials, LUNAR (NCT00282347)[1] and BELONG (NCT00626197)[2], compared the addition of rituximab[1] or ocrelizumab[2] vs. placebo in addition to background therapy for the treatment of LN. We deployed supervised ML method of symbolic regression using Eureqa® software to analyze variables for CRR in these studies. For patients with baseline creatinine >1, CRR was defined as urine protein/creatinine ratio (UPCR) <0.5 and creatinine <1 at 1 year. CRR for patients with baseline creatinine <1 was UPCR <0.5 and creatinine <125% of baseline at 1 year. Logistic regression was used to validate the association between identified variables and CRR found via ML analyses.

Results: We found that unbiased ML analysis identified variables known to be associated with CRR, such as baseline UPCR and eGFR. Furthermore, ML analysis identified other variables to be associated with CRR, including systolic blood pressure (BP) at baseline and Week 16, and positive anti-RNP antibody at baseline. Logistic regression determined that every 10 mmHg increment in systolic BP had an odds ratio (OR) of 0.84 (95% CI: 0.73, 0.96) for CRR at 1 year. At Week 16, every 10 mmHg increment in systolic BP had an OR of 0.82 (95% CI: 0.7, 0.95) for CRR at 1 year. Logistic regression showed an OR of 2.1 (95% CI: 1.3, 3.5) for CRR at 1 year with anti-RNP antibody positivity at baseline (n=182), adjusting for treatment received, baseline proteinuria, and eGFR.

Conclusions: In conclusion, ML algorithms can be successfully used in identifying variables associated with clinical response, especially in a complex and heterogeneous disease such as LN. These analyses highlighted systolic BP at baseline and Week 16, as well as baseline anti-RNP antibody positivity, to be associated with CRR. The association between anti-RNP antibody at baseline and CRR at 1 year warrants further investigation. 1. Rovin et al., *Arthritis Rheum* 2012; **64**, 1215-26. 2. Mysler et al., *Arthritis Rheum* 2013; **65**, 2368-79.

Funding: Commercial Support - Genentech, Inc., South San Francisco, CA, USA

FR-PO1113

Clinical Outcomes and Response to Anti-Thrombotic Treatment Among Patients with Concomitant Lupus Nephritis and Thrombotic Microangiopathy: A Multicentre Cohort Study

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Background: The renal vascular involvement is an important prognostic marker of lupus nephritis (LN). The thrombotic microangiopathy (TMA) presents with severe clinical manifestations and have a high mortality. However, the management of patients (pts) with TMA and LN needs further investigation. AIM: We sought to assess renal outcomes to anti-thrombotic treatments in addition to conventional immunosuppression (IS) in pts with biopsy proven LN and TMA

Methods: 97 pts with biopsy-proven LN and TMA were retrospectively analysed. A complete response (CR) was defined as proteinuria <0.5 g/24h and normal or near-normal (within 10% of normal GFR if previously abnormal) GFR. Partial Response (PR) was defined as a ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR. Renal outcomes were assessed at 1 year post biopsy.

Results: The mean age of the pts was 38.9±15.2 years. The clinical presentations were nephrotic syndrome, nephritic syndrome, and asymptomatic urinary abnormalities. 9 pts were classified Class III (including 2 as ClassIII + V), 82 as Class IV (10 as Class IV-segmental(IV-S) and 72 as Class IV-global (IV-G), including 4 as Class IV-G +V) and 6 as Class V. 42 (43%) pts presented with acute and 55 (57%) with features of chronic TMA. All pts had received treatment with standard IS and steroids. At 12 months, CR was observed in

37 pts (38.1%), PR in 22 (22.6%) and no response in 38 (39.1%). 61 patients (62.9%) were antiphospholipid positive (aPL) and 37 (38.1%) received anticoagulation with vitamin-K antagonist (VKA) and/or heparins. Presence of aPLs (OR, 2.4; p=0.03), anti-DNA positivity (OR, 12.8; p=0.002), and chronic features of TMA (OR, 3.0; p=0.04) were all found to be associated with no response. In aPL positive pts, variables that were significantly associated with CR+PR were features of acute TMA rather than chronic (OR, 8.62; 95% CI 1.4–97.1; p=0.03) and the use of VKA/heparins (OR, 2.1; 95% CI 1.02–16.2; P=0.046).

Conclusions: In pts with concomitant LN and TMA, the presence of aPL and chronic features of TMA were associated with poorer renal outcomes. In pts with aPL, the use of anticoagulation appeared protective and warrants further investigation as a therapeutic tool, especially in the setting of acute TMA.

FR-PO1114

Herpes Zoster and Disseminated Zoster in Lupus Nephritis: Incidence Rates in Real-World Claims Data

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Background: Herpes zoster is a highly morbid condition. Overall rates of herpes zoster in immunocompetent individuals in a claims database were 0.45 per 100 PY, with risk increasing with age [1]. Rates of herpes zoster and disseminated herpes zoster among patients with lupus nephritis (LN) have not previously been described. This study characterized rates of herpes zoster and disseminated zoster infections in patients with LN using population-based claims data.

Methods: We conducted a retrospective cohort study using the Truven Healthcare MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database between 2000 and 2014. Patients with LN were identified using modifications to a validated claims data algorithm [2]. Herpes zoster cases were identified using ICD9 codes 053.xx. All patients received medical care in the U.S. and had 6 months of continuous medical and drug coverage ± first LN diagnosis (i.e. index). End of study was the first of end of enrollment or end of database.

Results: 11,068 patients with LN were identified and followed for a mean of 6.8 years (Table). Among patients with LN there were 955 incident cases of herpes zoster events reported, of which 157 (16%) were considered disseminated. Incidence rates of herpes zoster and disseminated zoster were 2.6 (95% CI 2.4 to 2.7) and 0.4 (95% CI 0.3 to 0.5) per 100 PY, respectively.

Conclusions: Patients with LN appear to be at increased risk for herpes zoster relative to the general population. A substantial minority of LN patients with herpes zoster develop dissemination. Further characterization of the relative contributions of age, immunosuppressive therapies, and disease factors is warranted. 1. Johnson BH et al. BMC Infectious Diseases, 2015;15:502. 2. Chibnik LB et al. Lupus, 2010;19:741-3.

Funding: Commercial Support - Genentech, Inc.

	LN Cohort N=11,068	
	No. of patients	Percent
Gender		
Female	9,323	84.2%
Age at Index		
0-17	435	3.9%
18-34	1,905	17.2%
35-44	1,933	17.5%
45-54	2,488	22.5%
55-64	2,532	22.9%
65+	1,775	16.0%
Insurance Plan		
Comprehensive	1,374	12.4%
Health Maintenance Organization	1,944	17.6%
Preferred Provider Organization	5,789	52.3%
Others	1,961	17.7%
Region		
Northeast	1,399	12.6%
North Central	2,705	24.4%
South	4,569	41.3%
West	2,269	20.5%
	Mean	Median (IQR)
Age at Index (years)	49	50 (37 - 60)
Enrollment Duration (years)	6.8	6.0 (3.5 - 9.6)

FR-PO1115

Clinical Implications on Simple Attachment and Endothelial Damage in the Glomeruli of Adult Nephrotic Focal Segmental Glomerulosclerosis (FSGS): A Retrospective Cohort Study

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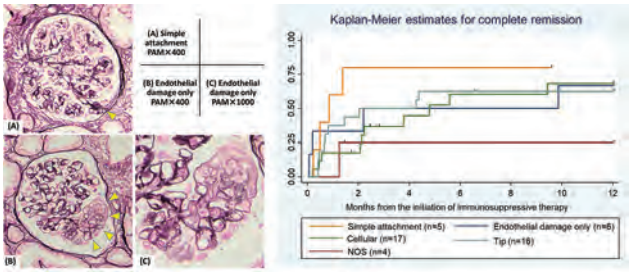
Background: Although Columbia classification are widely used, clinical importance of specific pathological findings in FSGS is unclear. We focused on simple attachment and findings of endothelial damage in the glomeruli on light microscopy and evaluated the association between these findings and therapeutic reactivity of adult nephrotic FSGS.

Methods: Forty-eight out of 183 biopsy-proven FSGS during 2005-2015 were included: ≥20 years old, nephrotic syndrome, received immunosuppressive therapy and whose pathological slides or paraffin blocks were available. Pathological review was done by 3 nephrologists and 1 renal pathologist. Among 11 patients who did not fit the definition of any variants in Columbia classification, cases who only have small synechia to Bowman capsule were categorized to "simple attachment" and who only have findings indicating endothelial damage i.e., mesangiolysis and/or double contour of GBM without matrix accumulation were categorized into "endothelial damage only". Response to immunosuppressive treatment of these patients were compared with that of typical FSGS variants.

Results: There were 16 TIP (33.3%), 17 CEL (35.4%) and 4 NOS (8.3%). None showed collapsing or perihilar variant. There were 5 "simple attachment" cases and 6 "endothelial damage only" cases. No difference was observed in the details of immunosuppressive treatment among the subgroups. Kaplan-Meier method revealed that "simple attachment" cases showed the best therapeutic response and NOS showed the worst response. And "endothelial damage only" cases showed similar response to CEL or TIP.

Conclusions: Synechia or findings of endothelial damage are commonly observed in FSGS on light microscopy, although they do not play key roles in diagnosis and classification of FSGS. In adult nephrotic FSGS, simple attachment indicated good therapeutic response. On the other hand, even if patients only have the findings of endothelial damage, it might be clinically equivalent to other variants of FSGS.



FR-PO1116

Renal Disease in Pregnancy - Doing Biopsy Matters to Lives

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Background: Renal disease is extemely rare in pregnancy but presents a therapeutic dilemma when diagnosed. It is a poor prognostic marker for fetal and maternal health. There is limited data and recommendations to guide therapy in this subset of population are lacking. We report our experience with 19 pregnant patients undergoing renal biopsies over a period of 5 years.

Methods: All pregnant patients undergoing renal biopsy at our facility were included in this retrospective analysis. Electronic medical records of nephrology, obstetrician services and histo-pathological reports were accessed. Patient confidentiality was preserved. Data was collected from january 1, 2013 to april 30, 2018.

Results: Nephrotic syndrome was the most common indication for a renal biopsy during pregnancy accounting for 16/19 patients (84%). Lupus nephritis was diagnosed in 4/18 patients necessitating an immunosuppressive regimen. The median gestation was 32 weeks (range 20–40) with loss of two fetuses. Non diabetic patients with nephrotic syndrome were at a higher risk for pre ecclampsia than diabetic patients with nephrotic syndrome ($p<0.05$). Three patients progressed to end stage renal failure needing dialysis, there were no maternal deaths during the follow up period. Table 1 shows characteristic features of this group.

Conclusions: Our series of selected pregnant patients undergoing renal biopsy demonstrates the variety of pathology in this group. Ante partum renal biopsy is safe in early pregnancy but should be considered only if there is a high likelihood to alter conventional therapy, and aid progression of pregnancy to fetal viability. Close monitoring and early intervention is key to improving feto-maternal outcomes particularly in non diabetic patients with nephrotic syndrome.

	Age	Gravida	Gestational age (weeks)	Indication for renal biopsy	Histological diagnosis	Pregnancy outcome
1	20	1	22	Nephrotic syndrome	Focal segmental glomerulo sclerosis	Pre ecclampsia
2	36	2	14	Nephrotic syndrome with positive lupus serology	Lupus nephritic Class V	Pre ecclampsia
3	25	4	16	Nephrotic syndrome with no history of DM	Diabetic glomerulosclerosis	Uneventful
4	27	3	23	Nephrotic syndrome with no history of DM	Diabetic glomerulosclerosis	Uneventful
5	27	1	12	Nephrotic syndrome	Focal segmental glomerulo sclerosis	Pre ecclampsia
6	26	1	12	Nephrotic syndrome with positive lupus serology	Lupus nephritic Class IV and V	Pre ecclampsia
7	19	1	23	Nephrotic syndrome	Minimal change disease	Pre ecclampsia
8	29	1	12	Nephrotic syndrome	Diabetic glomerulosclerosis	Uneventful
9	30	3	20	Nephrotic syndrome	Ig A nephropathy	Pre ecclampsia
10	23	4	22	Nephrotic syndrome with hematuria	Lupus nephritic Class IV	Pre ecclampsia
11	31	3	24	Positive lupus serology	Pre ecclampsia changes	Pre ecclampsia
12	22	3	24	Nephrotic syndrome	Membranous glomerulonephropathy	Pre ecclampsia
13	29	3	20	Nephrotic syndrome with positive lupus serology	Lupus nephritic Class V	Pre ecclampsia
14	30	5	14	Proteinuria and elevated creatinine	Ig M nephropathy	Uneventful
15	28	3	22	Nephrotic syndrome with elevated creatinine	Focal segmental glomerulo sclerosis	Pre ecclampsia
16	25	3	14	Nephrotic syndrome	Minimal change disease	Uneventful
17	26	2	18	Nephrotic syndrome with history of gestational DM	Diabetic glomerulosclerosis	Uneventful
18	32	3	24	Nephrotic syndome with elevated creatinine	Diabetic glomerulosclerosis	Pre ecclampsia with fetal demise
19	24	1	20	Hematuria, elevated creatinine	Thrombotic microangiopathy	Pre ecclampsia with fetal death

Table 1

FR-PO1117

Histopathological Findings in Mixed Connective Tissue Disease with Renal Involvement

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Background: Renal involvement in mixed connective tissue disease (MCTD) is uncommon and present in up to 20% of patients, most commonly, an immune-complex nephropathy. The aim of the study was to identify the prevalence of renal involvement and describe renal histophatological findings in MCTD.

Methods: Single center retrospective cohort of MCTD (2003-2017) according to the Alarcón-Segovia criteria, assessed to identify cases with renal involvement. Histological findings of biopsied patients are described.

Results: 131 MCTD patients were identified, of which 14 (10.7%) had renal involvement, 7 underwent a renal biopsy, 6/7 were women; mean age at onset of renal involvement 47.1 ± 7.5 years. Most frequent extra-renal clinical manifestations were: Raynaud's phenomenon and arthritis, both in 7 (100%), puffy hands in 6 (85.7%), sclerodactily in 5 (71.4%), myositis in 5 (71.4%), and interstitial lung disease in 3 (42.8%). Median time elapsed from MCTD diagnosis to renal involvement was 82 (2-208) months. Four (57.1%) presented with sub-nephrotic proteinuria, 3 (42.8%) with nephrotic range proteinuria and 3 (42.8%) with CKD-EPI eGFR <60ml/min/1.73m^2. Histological diagnoses: pauci-immune focal necrotizing and crescentic glomerulonephritis (GN) (2 pts; one developed positive ANCA antibodies), lupus nephritis (LN) class III + V ISN/RPS 2003 (1), LN class IV ISN/RPS 2003 with thrombotic microangiopathy (1), non-LN membranous GN (2) and minimal mesangioproliferative GN (1). Six (85.7%) achieved either total or partial remission at a median follow up of 61 (1-363) months with combination of steroids and other immunosuppressant. No patient required renal replacement treatment.

Conclusions: In our cohort of MCTD, prevalence of renal involvement was low. Renal biopsy demonstrated a diversity of histological patterns: glomerulonephritis, vasculopathy, and overlap with ANCA associated vasculitis; these options should be considered in the differential diagnoses of MCTD patients with renal involvement.

FR-PO1118

Clinical Outcomes of Renal Biopsy-Proven Thrombotic Microangiopathy

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Background: The kidney is the most commonly affected organ by thrombotic microangiopathy (TMA)-associated pathologic changes, however, there is lack of studies regarding the clinical outcomes of renal-biopsy proven TMA.

Methods: The patients diagnosed as TMA from 2005 to 2018 in 2 tertiary hospitals were enrolled. Of these 186 patients, children and those who not diagnosed with renal biopsy were excluded. These patients divided into 3 groups according to causes of TMA; typical hemolytic uremic syndrome (HUS), atypical HUS, and secondary TMA. Only 1 patient who classified typical HUS was excluded in the statistical analysis. Renal outcome was defined in 2 ways; renal function deterioration to end-stage renal disease (ESRD) who were depended on dialysis or kidney transplantation (KTPL) and the last measured estimated glomerular filtration rate (eGFR) <45mL/min/1.73m^2. Age, sex, eGFR rate at diagnosis, systolic blood pressure (SBP), hemoglobin, platelet, albumin, diabetes, hypertension, and classification of TMA were included as covariates in the multivariable analysis.

Results: Among 67 patients, patients who diagnosed with TMA after KTPL were 15(22.3%). Mean age was 54.0±15.5 years and 44(62.0%) were male. During 48.6 months of follow-up, 12 (17.9%) patients died, and 18(26.9%) patients (11 [26.8%] of secondary TMA vs. 7 [26.9%] in aHUS) had maintenance dialysis or KTPL. The patients who had last eGFR <45mL/min/1.73m^2 was 35(49.3%). There was no significant difference in all-cause mortality (log-rank *P*=0.293) and ESRD (log rank *P*=0.378) between atypical HUS and secondary TMA. SBP (hazard ratio [HR] 1.030, 95% confidential interval [CI] 1.006-1.055, *P*=0.015) and eGFR at diagnosis (HR 0.966, 95% CI 0.939-0.993, *P*=0.014) were associated with ESRD progression in univariate analysis, however, these associations did not observed in multivariable analysis. eGFR at diagnosis was the only risk factor for the final measured eGFR <45mL/min/1.73m^2 in multivariate logistic regression (OR 0.952, 95% CI 0.920-0.985, *P*=0.004). Only age was associated with all-cause mortality (HR 1.079, 95% CI 1.010-1.152, *P*=0.024) in multivariable analysis.

Conclusions: SBP and eGFR at diagnosis were significantly associated with ESRD progression in renal biopsy-proven TMA. There was no significant difference in all-cause mortality and ESRD progression between atypical HUS and secondary TMA.

FR-PO1119

A Combined Unenhanced Computed Tomography and Biopsy-Based Method for Estimating the Total Nephron Number in Humans

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Background: Methods for estimating the individual total nephron number in the clinical setting may be useful for predicting the progression of renal diseases. Rcently, simple methods have been proposed for estimating the total nephron number by the combined use of enhanced computed tomography (CT) and a renal biopsy in living kidney donors. However, renal disease patients are often not suitable candidates for intravenous contrast media administration. Thus, these methods are limited in daily clinical use for such patients, with further improvements in the methodology required. This study aimed to establish a method of estimating the total nephron number by the combined use of unenhanced CT and biopsy-based stereology.

Methods: We made a model for estimating the renal cortex volume measured by enhanced CT imaging as a true renal cortex volume. Using pre-donation contrast CT angiograms, transplantation donor kidneys were three-dimensionally reconstructed, and the total renal cortical volume was measured. The cortical volume estimates in unenhanced CT were determined by multiplying the semi-automatically measured parenchymal volume and the cortex coefficient. The total nephron number was determined by the combined use of the CT-based cortical volume and the glomerular density per volume in an implantation biopsy. The relative errors were calculated to assess the agreement between the methods.

Results: The values for the parenchymal volume and those for the cortical volume measured in enhanced CT showed a tight correlation (r = 0.949). The cortical to parenchymal volume ratio (0.715) was unaffected by any clinical factors, including age, body size and hypertension, and was defined as the cortex coefficient. The cortical volume and total nephron number estimated by unenhanced CT were consistent with those estimated by enhanced CT, with minimal relative errors (**Table**).

Conclusions: These results support the feasibility of estimating the total number of nephrons by the combined use of unenhanced CT and biopsy-based stereology, with a possible application for renal disease patients.

	Enhanced CT	Unenhanced CT	Relative error
Parenchymal volume per kidney	125 ± 27 cm^3	128 ± 29 cm^3	-0.7 ± 4.5 %
Cortical volume per kidney	92 ± 21 cm^3	92 ± 21 cm^3	0.0 ± 10.3 %
Total nephron number per kidney	653,000 ± 225,000	651,000 ± 215,000	0.1 ± 9.2 %

FR-PO1120

The Total Nephron Number and Responses to Corticosteroid Therapy in Patients with Minimal Change Nephrotic Syndrome

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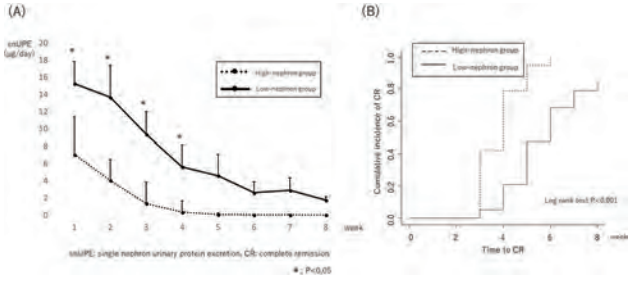
Background: The etiologies of minimal change nephrotic syndrome (MCNS) remain largely unknown; however, indirect evidence suggests that the weight at birth, which is related to the total nephron number, may affect the response to corticosteroid therapy. This study investigated the involvement of the total nephron number in the clinical course of MCNS.

Methods: Patients who exhibited acute-onset nephrotic syndrome, with a histological diagnosis of MCNS, were retrospectively analyzed. The total nephron number was estimated using a simplified method based on the combined use of unenhanced computed tomography and the non-sclerotic glomerular density of renal biopsy specimens. The single nephron glomerular filtration rate (snGFR) and single nephron urinary protein excretion

(snUPE) values were calculated by dividing the eGFR or UPE by the total nephron number. The glomerular volume (GV) was estimated by the measured mean glomerular area.

Results: A total of 38 MCNS patients were analyzed. The estimated total nephron number ranged from 140,000 to 1,800,000 per kidney among the patients and was inversely correlated with GV (r=-0.433, p=0.007). At the time of the diagnosis, the snGFR and snUPE values of the low-nephron group were significantly higher than those of the high-nephron group (139 vs 58 nl/min/1.73m^2 and 15.3 vs 7.1 µg/day, respectively). There was no significant difference in the total amount of UPE (7.4 vs 8.7 g/day) or the selectivity index (0.05 vs 0.05) of the groups. The reduction in snUPE (**Figure A**) and the time to complete remission (**Figure B**) during corticosteroid therapy were significantly slower in the low-nephron group, with no difference in the dose of corticosteroids. The total nephron number was found to be associated with the UPE at four weeks after the initiation of corticosteroid therapy, independent of age and the renal function.

Conclusions: Individual differences in the total nephron number in MCNS patients may influence the responses to corticosteroid therapy, possibly through the alteration of the single nephron dynamics.



FR-PO1121

The Impact of Birth Weight in Children with Biopsy Confirmed Nephrotic Syndrome

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Background: Nephrotic syndrome is a growing cause of chronic kidney disease (CKD) in children and can lead to end-stage kidney disease (ESKD). This study evaluates the impact of low birth weight (LBW) in children with nephrotic syndrome. Additional risk factors such as gestational age and kidney size were also assessed.

Methods: This retrospective cohort study reviewed the medical records of 75 children included in the UNC Glomerular Disease Collaborative Network ages 0-18 years with biopsy proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN) for both modifiable and non-modifiable risk factors to determine potential associations between birth history and disease and its impact on disease progression to ESKD.

Results: Thirteen (17%) were born with LBW. FSGS was more frequent in LBW children (92%) compared to normal birth weight (NBW) (55%), while NBW children were more likely to develop MCD (37%) compared to LBW children (8%). LBW children had higher body mass index (BMI) compared to NBW children. The proportion of LBW and NBW children progressing to ESKD was similar (23% vs 27% respectively).

Conclusions: Our findings suggest that LBW is associated with disease type, specifically FSGS, and higher weight. Although numbers are small, progression to eGFR≤30 appeared similar by birth weight. A larger sample size and longer follow-up is needed to further investigate the potential impact of low nephron number from LBW, especially in the setting of these glomerular diseases, and the relationship with overweight/obesity status.

Cohort Characteristics	Low Birth Weight N=13	Normal Birth Weight N=62	P Value*
Disease Type n(%)			0.0413
FSGS	12(92)	34(55)	
MCD	1(8)	23(37)	
Membranous	0(0)	5(8)	
Race n(%)			0.6964
Black	8(62)	29(48)	
White	4(31)	23(38)	
Other	1(8)	9(15)	
Sex n(%)			1.000
Male	7(54)	31(50)	
Gestational Age* n(%)			<0.0001
Full term	0(0)	53(91)	
Late Preterm	6(50)	5(9)	
Very Premature	6(50)	0(0)	
Hypertension n(%)			1.000
Yes	8(62)	40(65)	
Overweight[1] (BMI >85th%) n(%)			0.0556
Yes	9(75)	25(42)	
BMI % (Mean)			0.0307
Median(IQR)	0.91(0.85, 0.98)	0.79(0.65, 0.92)	
Age at onset (Years)			0.2207
Median(IQR)	9.93(6.09,11.79)	6.20(3.52, 12.12)	
Kidney Size at First Measure n(%)	N=13	N=58	0.112
Not WNL	7(54)	17(29)	
WNL	6(46)	41(71)	
Kidney Size at Last Measure n(%)	N=6	N=23	1.000
Not WNL	1(17)	5(22)	
WNL	5(83)	18(78)	
eGFR≤30 or ESRD n(%) Yes	3(23)	17(27)	1.0000
Time to eGFR≤30(Years)	N=3	N=17	0.8209
Median(IQR)	4.69(2.75,12.45)	5.00(2.23,9.69)	
Follow UP (Years)			0.2155
Median(IQR)	7.59(4.60,10.14)	4.32(2.11,7.53)	

* P values were calculated by Fisher Exact test and Wilcoxon two sample test.
[1]Overweight is defined as a BMI at or above the 85th percentile for children and teens of the same age and sex

FR-PO1122

Variability in Treatment of Childhood Nephrotic Syndrome in Africa

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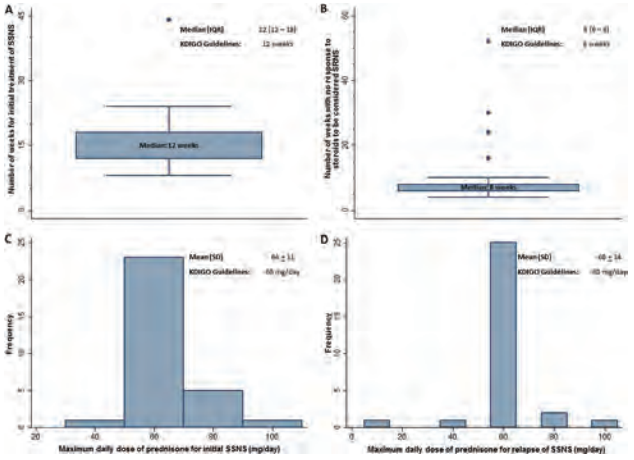
Background: Idiopathic nephrotic syndrome (NS) is the most common glomerular disease in African children. Clinical practice is guided based on limited resources for diagnosis and management of NS in most of the African continent. We aimed to determine variability in treatment of NS in Africa to develop a consensus guideline for the treatment of NS in middle and low-income countries.

Methods: Using the KDIGO guidelines as the basis for the management of NS, we developed a survey to assess current practices in 6 Sub-Saharan African countries. Approximately 50 adult and pediatric nephrologists from West, East and South Africa, in the H3 Africa Kidney Disease Research Network, were invited to complete the survey. Responses on treatment choices, duration of therapy, management of relapses and management of steroid resistant NS (SRNS) were collected.

Results: 30 nephrologists (20 pediatric, 4 adult and 6 both) from 19 hospital centers located in Nigeria, Ghana, Cameroon, Uganda, Tanzania and South Africa, completed the survey. Variability in treatment choices and practice were observed when compared with international guidelines. The definition of child varies by country, ranging from ages 12-18 (median 17), thus adult nephrologists also manage idiopathic NS. The initial treatment of steroid sensitive NS, and the definition and management of relapses varied widely across the respondents (Figure). Remission was defined by negative urinary protein ranging from 3-7 days (median 3). Only about 50% prescribed calcineurin inhibitors for children with SRNS.

Conclusions: Management of NS varied widely across and within countries in Africa, thus the importance of a consensus guideline tailored to an African context. Adult nephrologists often manage adolescents and youth, thus need to be aware of the pediatric management. Standardizing practice across the continent will provide an opportunity to understand the burden and long-term outcomes of NS.

Funding: NIDDK Support, Government Support - Non-U.S.



Variability in treatment of NS

FR-PO1123

Effects of LDL-Apheresis in Adult Refractory Nephrotic Syndrome and Its Reproducibility

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Background: In 2018, Humanitarian device exemption allowed to utilize LDL-apheresis (LDL-A) for the treatment in adult patients with nephrotic-range focal segmental glomerulosclerosis (FSGS), but the efficacy is still uncertain. We performed case series of LDL-A in patients with refractory nephrotic syndrome, including FSGS, in a tertiary care center in Japan.

Methods: The efficacy of LDL-A was evaluated in 15 cases of refractory nephrotic syndrome (FSGS, n=4; minimal change disease (MCD), n=7; membranous nephropathy (MN), n=4) enrolled from April 2008 to April 2018. Demographic and clinical parameters were compared before and after performing LDL-A. Additionally, the efficacy of the second trial of LDL-A was evaluated in relapsed cases after the first trial of LDL-A.

Results: In 15 patients, all patients, except one, received immunosuppressive agents (prednisolone, 14; cyclosporine, 6; cyclophosphamide, 2), and there was no statistically significant reduction in proteinuria before initiating LDL-A (p=0.051; t-test). However, there were statistically significant reduction in proteinuria after performing the first trial of LDL-A in all groups (FSGS, 9.1 ± 1.9 g/day to 2.6 ± 1.0; MCD, 5.4 ± 1.4 to 0.4 ± 0.1; MN, 6.4 ± 0.5 to 2.3 ± 0.5; p <0.005; MANOVA). Multivariate analysis revealed the rate of remission was higher in MCD compared to other groups (R^2=0.49, p<0.005). In relapsed cases after the first trial of LDL-A (n=7), the second trial of LDL-A was effective to reduce proteinuria, and there was no statistically difference in between the first trial and the second trial of LDL-A (First trial, 5.6 ± 1.1 to 0.7 ± 0.3; Second trial, 7.2 ± 1.5 to 0.8 ± 0.5, p=0.382; MANOVA).

Conclusions: This study suggested that LDL-A was effective for reducing proteinuria in patients with refractory nephrotic syndrome, and its effectiveness was reproducible. This may contributed to planning treatment strategies in these patients.

FR-PO1124

Lower Doses of Prednisolone Are Sufficient for Initial Treatment in Adult-Onset Minimal Change Nephrotic Syndrome

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Background: KDIGO Guideline suggests that prednisolone (PSL) should be given at a single daily dose of 1 mg/kg, as initial treatment in adult-onset minimal change nephrotic syndrome (MCNS). However, there is no convincing evidence to support the guideline's suggestion. It remains unclear how much the initial dose of PSL for MCNS should be given. On the other hand, from the viewpoint of side effects, the lower dose of PSL is fairly advantageous.

Methods: This retrospective cohort trial was performed in a single center between 1987 and 2017. Inclusion criteria were adult-onset MCNS diagnosed by kidney biopsy. These participants were classified into Low PSL group (L group, < 0.6 mg/kg), Moderate PSL group (M group, ≧ 0.6 mg/kg and < 0.8 mg/kg) and High PSL group (H group, ≧ 0.8mg/kg). The primary outcomes of interest were time to first remission and first relapse of proteinuria. They were analyzed with ANOVA, log-rank test, and multivariate Cox proportional hazards models.

Results: A total of 58 patients were enrolled in this clinical trial. All of these patients at any dose of prednisolone achieved remission within a median of 16 (8-45) days in L group, 14 (6-166) days in M group, and 20 (8-37) days in H group. Long-rank test showed that there were no significant differences in the primary outcomes among three groups. Multivariate Cox proportional hazards revealed that although age (per 10 yr) and serum creatinine (per log 1mg/dl) were prognosis factors for the time to the first remission, PSL dose was not a significant factor (HR, 1.07; 95%CI, 0.43 to 2.79 (L group vs H group), 0.99 ; 95%CI, 0.41 to 2.44 (M group vs H group)). Additionally, multivariate Cox regression analysis for the incidence of relapse did not significantly indicate any prognostic factor.

Conclusions: Low or moderate doses of PSL are sufficient for initial treatment in adult-onset MCNS regarding the time to remission and incidence of relapse.

FR-PO1125

Adult Outcome of Childhood-Onset Steroid-Dependent Idiopathic Nephrotic Syndrome in the Rituximab Era

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Background: Idiopathic nephrotic syndrome (INS) represents the most frequent glomerular disease in childhood, with up to 60% of patients experiencing frequent relapses and steroid dependency requiring long-lasting steroid therapy and immunosuppressive (IS) drugs. Outcome and optimal therapy at adulthood, as well as long-term complications of childhood IS exposure is poorly documented.

Methods: We retrospectively analyzed a monocentric cohort of 43 patients with childhood-onset steroid-dependent INS. Relapses in adulthood were treated with steroids or a combinaison of steroids and rituximab (RTX), with the exclusion of all other IS.

Results: Median age at the INS diagnosis and at the last follow-up was 4 years (1-17) and 24 (19-40) years, respectively, with a median duration of follow-up at adulthood of 7 (1-21) years. At pediatric age, 42 (98%) patients received at least one nonsteroidal IS drug, including calcineurin inhibitors in 29 (67%), mycophenolate mofetil in 26 (60%), RTX in 17 (39%), an alkylating agent in 15 (35%), and levamisole in 13 (30%). At entry in the adult care, 16 (37%) of the patients still received an IS drug other than RTX. Relapse occurred in 32 (74%) of patients at adult age with 5 patients presenting at least 2 episodes. In 9 patients, relapse occurred more than 3 years after steroids and IS discontinuation. Relapses were treated with steroids alone in two patients, while the other 29 received a combination of steroids and RTX, followed, for 20/29 patients, by a reinfusion of RTX either at B-cell recovery or at fixed intervals (6 to 12 months), up to 24 months. At last follow-up, 36 (84%) patients were in complete remission, with a treatment-free duration of more than 24 months in 12 (28%), of 12 to 24 months in 8 (19%) and of less than 12 months in 16 (37%). All but one patients were free of steroids and IS drugs. No patient experienced infection or cytopenia and one patient developed neoplasia most likely unrelated to IS.

Conclusions: Childhood-onset steroid-dependent INS remains a concern at adulthood with a high rate of relapse occurring after a variable delay. RTX is a safe and efficient steroid-sparing agent allowing maintenance of remission and discontinuation other IS. No late-onset severe complication related to childhood therapies was recorded.

FR-PO1126

Identifying Functional Subclasses of Nephrotic Syndrome by Consensus Non-Negative Matrix Factorization Clustering of Glomerular Transcriptome

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Background: Defining nephrotic syndrome in mechanistic terms is a prerequisite to develop targeted therapies. Consensus non-negative matrix factorization (NMF) is a clustering approach used with tumor specimen transcriptomics to identify functionally relevant subtypes.

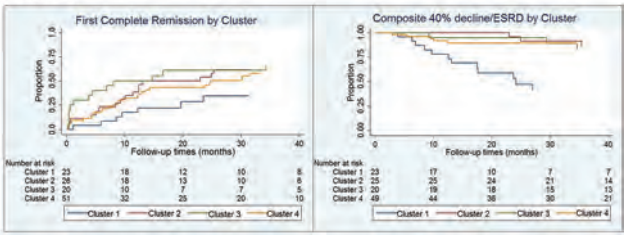
Methods: NMF clustering was applied to glomerular mRNA expression from nephrotic syndrome patient biopsies (NEPTUNE cohort). Individual gene expression levels from the glomerular compartment were normalized to mean expression to maximize individual patient differences over shared disease & tissue expression. Cox proportional hazards models were fit for complete proteinuria remission (CR, UPCR <0.3 mg/mg) and ESRD/40% eGFR decline. Significance analysis of microarray identified cluster specific differentially expressed genes that were used in pathway enrichment analysis to determine functional relevance.

Results: NMF separated 138 patients into 4 clusters which did not differ by diagnosis (MCD, FSGS, MN and IgAN, p 0.25), age (p 0.72), sex (p 0.25) or UPCR (p 0.28). Cluster 1 had lower mean eGFR (63 mL/min vs 81, 77 and 85; p 0.04) and greater black race (54% vs 10%, 24%, 19%, p <0.01). In unadjusted models, cluster 1 had least CR (HR 0.51, 95%CI 0.3–1.0, p-value 0.06) and greatest loss of eGFR (HR 5.4 95%CI 2.5–12.0, p-value <0.01). The eGFR association persisted after adjustment for baseline eGFR and race. Pathway enrichment of cluster-specific genes demonstrated unique processes: cluster 1-targetable signaling pathways (e.g. integrin, EGF-R, TLR), cluster 2-pentose phosphate metabolism, cluster 3-metabolic pathways (e.g.Vit D, pyruvate, galactose), cluster 4-cadherin signaling.

Conclusions: NMF clustering of glomerular kidney tissue mRNA expression levels revealed 4 clusters which were distinct from conventional classification. Pathway enrichment of gene signatures for each cluster revealed distinct molecular processes which may help to inform future treatment strategies.

Funding: NIDDK Support, Other NIH Support - NCATS, Private Foundation Support

Figure: Kaplan-Meier survival curve for time to (A) first complete remission and (B) composite of ESRD/40% decline in eGFR from baseline.



FR-PO1127

APOL1 Risk Alleles Are Critical for the Development of Collapsing Glomerulopathy in Brazilian Children

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Background: Collapsing glomerulopathy (CG) is associated with worse renal outcome than any FSGS histologic variant, while *APOL1* risk alleles are associated with FSGS and increased susceptibility to CG. In pediatric population, such alleles are related to later FSGS presentation, worse eGFR and faster progression to ESKD.

Methods: A retrospective analysis of 41 children with steroid-resistant nephrotic syndrome (SRNS) or congenital NS (CNS) with onset at 2 months-16 years was performed. All had biopsies analyzed by renal pathologists. Mutational analysis in 42 genes related to glomerular diseases was performed using a capture-based, customized panel followed by NGS using an Illumina MiSeq V2.

Results: CG was diagnosed in 10/41 patients, all negative for HIV, hepatitis B and C and CMV. Of these 10, 5 were Caucasian (C) and 5 mixed race (MR); all self-reported. Five CG children were treated with prednisone plus FK506/CyA/MMF and 2 with methylprednisolone boluses (renal failure at presentation). Two with CNS were given no immunosuppression. 8/10 CG patients reached ESKD within 0.0-3.8 years after initial manifestation. The other 2 have eGFR of 88 and 60 mL/min/1.73m^2, after 4 and 5 years of follow-up, respectively. A high-risk (HR) *APOL1* genotype was detected in 5/10 CG patients, 2 C and 3 MR. 2/5 were extreme preterm; the other 3 had birth weight <3 kg. Of the remaining 5 with CG, 2/5 had 1 *APOL1* risk allele (1 C and 1 MR), 1 was homozygous for a novel likely pathogenic variant in *PLCE1* (p.L1233P), and 1 was heterozygous for a rare, frameshift variant in *LAMB2*. Of the 31 without CG, 4 had a single *APOL1* risk allele and 27 none. Overall, Brazilian children with CG had significantly higher odds of harboring a HR *APOL1* genotype (OR=∞, CI:6.6,∞: p=0.0003).

Conclusions: For Brazilian children with SRNS/CNS, as compared to other histologic diagnoses, those with CG have greatly increased odds of having a HR *APOL1* genotype. Furthermore, the burden of *APOL1*-associated SRNS/CNS spanned self-described races. Finally, all with CG and HR *APOL1* genotype had an abnormal birth history. The discovered racial, histologic, and birth history correlates of a HR *APOL1* genotype have important implications for future *APOL1* genotyping efforts in research and clinical settings in Brazil.

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FR-PO1128

Predictors of Remission in Collapsing Glomerulopathy

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Background: Collapsing Glomerulopathy (CG) has usually been associated with poor renal outcomes. The goal of this study was to identify predictors of remission in the CG.

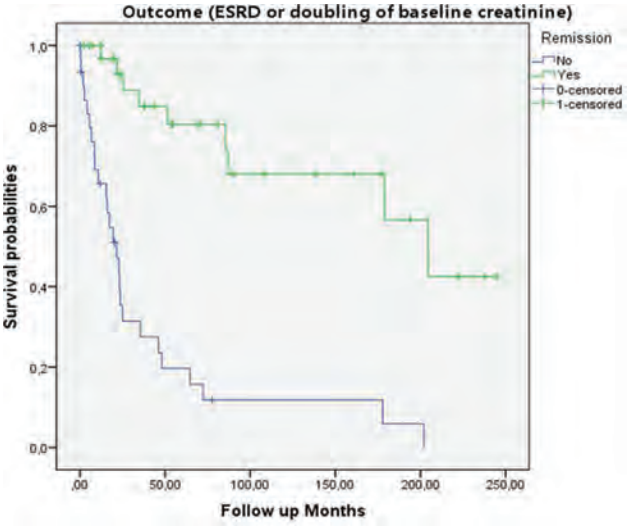
Methods: A retrospective analysis was performed on all CG diagnosed by kidney biopsy between 1996 and 2016. Clinical and laboratory data were collected at baseline and at the end of follow up. Remission has been defined as 50% reduction in baseline proteinuria and <3.5 g/day. Outcome was defined as ESRD or doubling of baseline creatinine.

Results: Logistic regression analysis showed that remission was significantly associated with a better renal outcome (OR 0.08, 95%CI 0.02-0.3, p<0.001), even after adjustments for baseline CKD-EPI and proteinuria. Clinical features of the groups with and without remission are summarized in Figure 1. A second logistic regression analysis showed that female and interstitial fibrosis are the only independent predictors associated with remission in CG (OR 0.28, 95%CI 0.09-0.84, p 0.02 and OR 10.9,95%CI 1.2-98 p 0.034)

Conclusions: Predicting remission with baseline features is difficult, but female and patients without interstitial fibrosis are more likely to achieve remission. Moreover, patients with CG who showed remission had a better outcome and this should be (a goal of therapy) attempted.

n	Remission (n=34)	No Remisson (n=33)
Age (Y)	34.6±15.4	30.2±15.2
Male (n,%)*	14 (41%)	22 (66%)
CKD-EPI baseline	53.4±35.8	52.9±34.4
Proteinuria g/day	6.7±6.1	9.1±6.1
No Interstitial Fibrosis (n, %)*	8 (24%)	1 (3%)
Immunosuppression (n,%)	26 (76%)	24 (73%)
CKD-EPI at the end*	64.3±39.9	19.6±29.2
Proteinuria end (g/day)*	1.3±1.6	6.9±4.7
Follow up (months)*	82.6±75.6	30.9±46.7
Outcome*	9(27%)	28(85%)

Data showed as mean (+/-SD). * p<0.05.



FR-PO1129

Collapsing Glomerulopathy in Hepatitis C Virus Positive Patients: A Retrospective Autopsy Study of 95 Cases

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Background: Patients (pts) with hepatitis C virus (HCV) infection may present with a variety of glomerular diseases, however Collapsing glomerulopathy (CG) is an uncommon presentation. In most pts, this lesion is associated with human immunodeficiency virus (HIV) infection while in a small number of cases, CG is considered to be idiopathic. The aim of this study was to determine the prevalence of CG in HCV-positive, HIV-negative (HCV+ HIV-) pts, using autopsy material to explore the significance of this association through clinical, pathological and laboratory correlation.

Methods: We performed a retrospective autopsy study, examining the renal parenchyma of 95 HCV+ pts. Pts with positive or unknown HIV status or those who had exposure to interferon (IFN) therapy were excluded. Thereafter, the presence of CG (test group) or absence of CG (control group) was recorded using hematoxylin and eosin, periodic acid-Schiff and Jones stains. Clinical and laboratory correlation included evaluation of demographics, terminal serum creatinine, HCV serology, viral load (VL), dipstick proteinuria, serum albumin (Alb), and cause of death. A t-test (pooled variances) was used for comparison of continuous variables such as age, BMI, HCV VL and Alb. Comparison of categorical variables such as gender, race, and HCV genotype was based on contingency analysis.

Results: Forty cases were excluded based on HIV status and IFN exposure. CG was identified in 19/55 pts (34.5 %). There was no significant difference in age, race, BMI, Alb, creatinine, proteinuria or cause of death among the two groups. HCV VL was higher in the test group but the difference was not statistically significant.

Conclusions: To our knowledge, this is the largest autopsy study describing the occurrence of CG in HCV+ HIV- pts. Our results demonstrate an association and prevalence of CG in HCV infection that have not been previously established. Therefore, CG should be considered in HCV+ HIV- pts who present with renal failure and proteinuria. Further studies are needed to elucidate prevalence and pathogenesis of CG in these pts.

FR-PO1130

Quantitative Mass Spectrometry Aided Urine Biomarker Analysis in Nephrotic Syndrome

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Background: Accurate and precise diagnosis of chronic renal diseases can be aided using biomarkers. Methodological advancements in mass spectrometry and bioinformatics have improved the ability to identify and quantitate protein biomarkers induced in disease. Proteins and peptides that are present in patient urine are indicative of changes in homeostasis of the kidney and other organs. Identification and quantitation of these components of the urine proteome will be useful in determining effective new biomarkers of kidney disease. Loss of kidney function corresponds with increased leakage of protein and peptide components into the urine. Profiling and quantitation of urinary markers of renal disease progression is important towards a better understanding and characterization of distinct glomerular diseases.

Methods: In this work we present a mass spectrometry workflow utilizing multiplex tandem mass tag (TMT) quantitation of whole urine proteins from patients with nephrotic syndrome and in remission.

Results: Combined 2D-LC-MS/MS-TMT analysis yielded ~800 protein identifications, ~480 were quantitated. Over 200 proteins were upregulated in disease and 50 were downregulated.

Conclusions: Our current study includes urine TMT analysis from 3 patients with nephrotic syndrome and post-treatment follow-up upon remission. The sample set, though small, is ideal for looking at effects of normalization on intra and inter-patient protein quantitation as we were also able to see a difference in the effects of race and sex in one sample that clearly clusters differently from the other two patients. Clinical data, specifically urinary creatinine, was used to normalize TMT values. Employing these methods on larger patient cohorts will help in uncovering novel biomarkers of nephrotic syndrom.

Funding: NIDDK Support, Private Foundation Support

FR-PO1131

Clinical and Histological Risk Factors Predicting Progression to ESRD in Patients with Secondary FSGS

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Background: Secondary FSGS is a proteinuric renal disease that develops as a result of increased hemodynamic stress on the glomeruli. The aim of study was to identify clinical characteristics and histological factors in patients with secondary FSGS that predicted progression to ESRD.

Methods: Adult patients (>18 y) with a native kidney biopsy and diagnosis of FSGS between 1993-2015 were identified. Those with additional glomerular lesions (e.g. diabetes or vasculitis) or missing clinical or biopsy data were excluded. Comprehensive chart review was performed on the remaining FSGS patients to identify candidate clinical and histological predictors (n=149). Cox proportional hazards regression models were used to identify predictors for incident ESRD (eGFR <15 or need for transplantation or dialysis).

Results: Out of 149 patients, 60 had primary FSGS (S. albumin <3.5 g/dL & urinary protein (UP) ≥ 3.5g/24h), 89 had secondary FSGS (S. albumin ≥3.5 g/dL & any degree of proteinuria). In patients with secondary FSGS mean (SD) age was 52 (17) years, 41% female, & 73% white. Median [IQR] BMI was 30 [26-34] kg/m^2, S. creatinine was 1.7 [1.3-2.4] mg/dL, $eGFR_{creatinine}$ was 40 [28-57] ml/min, 24h UP was 2.6[1.3-4.4] g, and median follow-up was 34 [12-60] months. ESRD occurred in 33% of these patients. Clinical predictors of ESRD were older age, lower eGFR, use of immunosuppression, and absence of renin-angiotensin blockade (Table 1). The only renal biopsy histological predictor of ESRD was severe arteriosclerosis, though IFTA was borderline significant. The degree of global sclerosis, foot process effacement and glomerulomegaly was not predictive. Severe arteriosclerosis was predictive after adjusting for age (p=0.04).

Conclusions: Arteriosclerosis appears to be an important and under-recognized predictor of progression to ESRD in patients with secondary FSGS independent of age.

Univariate analysis

Variable	Hazard Ratio(CI) (P value)
Female	0.5 (0.08-1.77) (0.36)
Age @ Biopsy / 10 years	1.66 (1.22-2.37) (0.002)
eGFR per 10 ml/min	0.96 (0.53-0.94) (0.03)
Urine Protein per g/day	1.08(0.93-1.23) (0.21)
Global glomerulosclerosis per %	1.00(0.98-1.02) (0.38)
IFTA >50%	2.4 (0.97 – 6.8) (0.07)
Arteriosclerosis > 50%	7.26 (1.87-24.43) (0.004)
Use of immunosuppression	1.38(0.39-3.88) (0.04)
Use of ACE-I/ARB	0.3 (0.12-0.72) (0.008)

FR-PO1132

Clinicopathological Discrimination of Primary and Genetic Focal Segmental Glomerulosclerosis in Children

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Background: (Background) FSGS is classified as primary FSGS caused by unidentified humoral factor(s) and secondary FSGS including genetic abnormalities, and the cause of the disease of each patient has crucial implication on treatment strategies and renal transplant success. Sethi S, et al. described that >80% foot process effacement covering glomerular surface area is suggestive of primary form in adult FSGS by comparing nephrotic patients with non-nephrotic ones (Nephrol Dial Transplant, 2015). However, it is known that nephrotic syndrome can be observed not only in primary form but genetic one in children. Therefore, we conducted a clinicopathological study comparing clinically proven primary FSGS with genetic FSGS.

Methods: Pediatric FSGS patients (10 primary and 8 genetic) who progressed to ESRD and underwent renal transplantation were included in this study. All the primary FSGS patients had posttransplant recurrence, and all the patients with genetic FSGS carried pathogenic mutations and did not have posttransplant recurrence. We retrospectively analyzed their clinical course and histology of the native kidneys before transplantation. The degree of foot process effacement (FE) of podocytes was calculated as the ratio of the FE area on capillary loops to glomerular surface area.

Results: There were no differences between primary and genetic FSGS on age at onset (5.5 ± 3.0 years, 4.6 ± 3.0 years) and the period from onset to ESRD (5.5 ± 4 years, 4.5 ± 3.5 years). The period from onset to kidney biopsy was significantly shorter in genetic than primary FSGS (0.7 ± 1.4 years vs 3.4 ± 3.4 years) (p = 0.02). The rate of nephrosis at onset, and of edema observed during the course, and of the initial responsiveness to steroid treatment were all significantly higher in primary FSGS (p <0.01). Serum total protein (TP) at the time of kidney biopsy was significantly lower in primary FSGS (3.7 ± 0.6 g / dl vs 5.3 ± 1.1 g / dl) (p <0.01) with TP above 3.9 g/dl predicting genetic (sensitivity 100%; specificity 75%; AUC 0.927). The percentage of FE at 80% completely discriminated primary from genetic cases (98 ± 6% vs 61 ± 12%).

Conclusions: Discrimination between primary and genetic FSGS could be possible by integrating the pathological findings with clinical information.

FR-PO1133

Idiopathic FSGS: Outcome in Adult Patients with Initial Steroid-Resistance

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Background: Idiopathic focal segmental glomerulosclerosis (iFSGS) is a common cause of nephrotic syndrome (NS) in adults. Guidelines advise initial therapy with corticosteroids (CS). The clinical outcome of patients with initial steroid-resistance is ill-defined.

Methods: Retrospective cohort study of adult patients with biopsy-proven FSGS, nephrotic syndrome, and steroid-resistance (no complete remission (CR) after 8 weeks of treatment with high dose CS). We evaluated late response (CR or partial remission (PR); use of second line immunosuppressive treatment; predictors for kidney function deterioration; and long-term outcome.

Results: We included 51 patients (31 males), mean age 46 years, referred to our academic clinic between 1995 and 2014. Only 6 patients were in PR at 8 weeks. High dose CS monotherapy was continued for a median of 17 weeks (IQR 11-21), with a total duration of 56 weeks (IQR 28-83). The cumulative incidence of CR and PR were 0 and 16 patients at 16 weeks and 1 and 23 patients at 24 weeks of treatment. In total, 9 patients (18%) attained a CR and 16 patients (31%) attained a PR during initial (continued) treatment with CS. Seven patients in PR were subsequently treated with other immunosuppressive therapy (IS), resulting in CR in three. 22 patients received additional immunosuppressive therapy because of persistent nephrotic range proteinuria, seven attained a CR and 10 attained a PR. Additionally, one patient attained a spontaneous CR 2.5 years after IS therapy was discontinued. At end of FU 12 patients were in CR, 22 in PR, 17 had a (persistent or relapsed) NS. 6 patients had developed ESRD. In 29 patients eGFR was below p5 of age-matched controls.19 patients had kidney function deterioration ≥ 3ml/min/1.73m^2 per year. Older age, FSGS-tip, and CR were associated with stable kidney function. Remarkably, PR was not a predictor for a stable kidney function. The definition of PR as recently proposed by Troost et al. (a 40% reduction in proteinuria (<1.5 g/g)) was also not associated with a stable kidney function.

Conclusions: Long-term outcome in patients with steroid resistance is not uniformly dismal. Still, kidney function deterioration ≥ 3ml/min/1.73m^2 per year occurs in 37%. Better biomarkers are needed to predict long term outcome in patients with iFSGS.

FR-PO1134

Kidney Outcome with Primary Focal Segmental Glomerulosclerosis (FSGS) by Using a Predictive Model

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Background: To develop a model of prediction of chronic kidney disease (CKD)/ end-stage kidney disease (ESKD) (dialysis or kidney transplantation) in patients with primary FSGS by baseline clinical, laboratory and pathological findings as predictors.

Methods: 201 patients with primary FSGS (59% male, mean age: 38±15 years, baseline serum creatinine (bSCr): 1.89±1.64 mg/dl, eGFR 65±38 ml/min/1.73 m² (MDRD) and mean proteinuria: 4.6±3.6 g/24 hours were followed. Time-dependent Cox model and C statistics for discrimination were used to develop a predictive model. The patients were classified into 3 risk groups of low (bSCr<1.5 mg/dl and interstitial fibrosis/ tubular atrophy (IF/TA) and segmental glomerulosclerosis (SGS)< 25%, medium (bSCr: 1.5- 2 mg/dl, and IF/TA and SGS: 25-50%) and high (bSCr>2 mg/dl and IF/TA and SGS> 50%). Kaplan–Meier and the log-rank tests were used to estimate kidney survival in each group. Interaction between independent variables was estimated.

Results: During the mean follow-up of 55±27 months, 46 patients (23%) developed CKD and 36 (18%) ESKD. Ninety patients (44%) did not respond to treatment and among them, 76 patients (84%) developed CKD/ESKD. In multivariate model 1 mg/dl higher bSCr (HR: 1.63, 95% CI: 1.12-2.37), 1% increase in SGS (HR: 1.04, 95% CI: 1.01-1.08) and 1% increase in IF/TA (HR: 1.06, 95% CI: 1.03-1.09)in kidney biopsy, were associated with increased risk. In adjusted model, higher baseline proteinuria and collapsing variant (NOS variant as reference) were not significantly associated with risk of CKD/ESKD (P=0.671 and P=0.136, respectively). The median kidney survival was 8.1 years (95% CI, 7.7-8.6 years) in low risk and 3.1 years (95%, 2.2- 4.1 years) in high-risk patients. In prediction model the accuracy of the applied score for prediction of CKD with discrimination by C statistics was C= 0.84 (95% CI: 0.78-0.91) for 5 years.

Conclusions: In patients with primary FSGS, higher bSCr, SGS and IF/TA scores were the strongest predictors for CKD/ESKD. In adjusted model higher proteinuria at baseline was not associated with increased risk of CKD/ESKD. Interestingly collapsing variant did not increase the risk of CKD/ESKD after adjustment for IF/TA score. These findings indicated the importance of baseline GFR and the degree of chronicity at biopsy rather than histologic variants as predictors of kidney outcome.

FR-PO1135

Utility of Columbia Classification in Focal Segmental Glomerulosclerosis: Renal Prognosis and Treatment-Response Among the Pathological Variants

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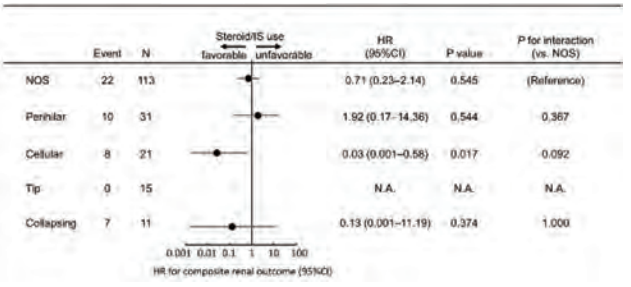
Background: The utility of the Columbia classification (Col-class) for focal segmental glomerulosclerosis (FSGS) has not yet been fully proven.

Methods: We extracted 201 FSGS patients from 10 nephrology centers in Japan and investigated the differences of a composite renal endpoint, defined as doubling of serum creatinine and/or development of end-stage renal disease, in pathological variants. Sensitivity analysis was used to prove the utility of the Col-class to predict renal outcomes. Additionally, the renal protective effects of steroids and/or immunosuppression (steroid/IS) were investigated in patients stratified according to Col-class.

Results: The patients were classified into the variants as follows: not otherwise specified (NOS) (n=120, 60%), perihilar (n=31, 15%), cellular (n=24, 12%), tip (n=15, 7%), and collapsing variant (n=11, 5%). No tip variant patients reached the renal endpoint. The renal outcome in the collapsing variant was significantly poorer than those in the NOS (hazard ratio [HR] 3.65, *P*=0.010), while the outcome in perihilar and cellular variant were similar to those in NOS. In the sensitivity analysis, the area under the receiver operating characteristics curve for the renal endpoint was increased by adding Col-class to a model including common risk factors (*P*=0.041). Steroid/IS use was associated with good renal outcome in the cellular variant (HR 0.03, *P*=0.017).

Conclusions: The Col-class is useful to predict renal prognosis in Japanese patients with FSGS. In addition to good prognosis in the tip and poor in the collapsing variant, renal protective effect of steroid/IS in the cellular variant was newly revealed.



Effect of steroid/immunosuppressant use on composite renal survival in each pathological variant of focal segmental glomerulosclerosis.

FR-PO1136

Systolic Blood Pressure Z-Score Accurately Predicts Development of Posterior Reversible Encephalopathy Syndrome in Children

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Background: While posterior reversible encephalopathy syndrome (PRES) is often reversible, it increases morbidity and mortality in children and adults. High blood pressure (BP) is a major risk factor for PRES and is thought to alter cerebral vascular autoregulation leading to vasogenic edema. However, little is known about what severity of high BP predicts PRES, especially in children, as most patients with high BP do not develop PRES. The purpose of this study is to determine a clinically meaningful BP threshold above which the risk of developing PRES is increased.

Methods: We recorded the maximum systolic BP and diastolic BP and BP z-scores in the 14 days preceding development of PRES in a case-control study of 35 children with PRES compared to 14 controls matched on similar risk factors (underlying disease, renal function, and medications) and who had clinical concern for PRES but had normal brain magnetic resonance imaging. We used logistic regression models to determine the effect of maximum BP on the risk of developing PRES, reported as odds ratios with 95% CI. We then constructed receiver operator characteristic (ROC) curves for different maximum-BP cut points to determine their prognostic ability to predict PRES and calculated sensitivity, specificity, and positive and negative predictive values.

Results: Cases had a higher rate of baseline hypertension (97.1% vs 64.3%, *p*=0.005) but were otherwise well matched. 14-day maximum SBP z-score was strongly associated with PRES (OR 4.0, 95% CI 1.6 to 9.6). ROC analysis revealed that 14-day maximum SBP z-score ≥3.0 accurately predicted PRES (AUC 0.95, 95% CI 0.88 to 1.0) with 91.2% sensitivity (95% CI 81.4 to 100%) and 84.6% specificity (65.2 to 100%), indicating a positive predictive value of 93.9% (84.3 to 100%) and a negative predictive value of 78.6% (56.9 to 100%).

Conclusions: Our study demonstrated that a maximum SBP z-score of 3.0 or higher in the preceding 14 days accurately predicted PRES development in pediatric cases as compared to controls with similar risk factors. This indicates that the SBP 99th percentile for age, sex, and height (equivalent to a z-score of 3.0) may be a clinically relevant threshold indicating that aggressive BP reduction is warranted in children at high risk for PRES in order to prevent target organ damage in the brain.

FR-PO1137

Standardizing and Optimizing Blood Pressure Measurement Across 16 Pediatric Transplant Centers: The Improving Renal Outcomes Collaborative

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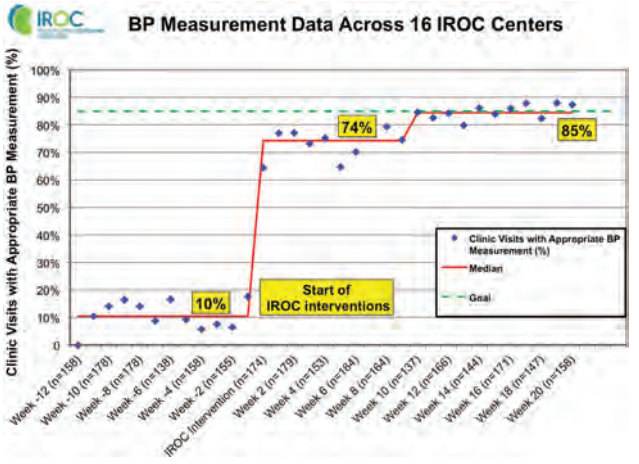
Background: Hypertension is prevalent in 60-90% of pediatric renal transplant recipients. Uncontrolled hypertension contributes to cardiovascular (CV) death and graft loss. Non-standardized blood measure (BP) measurement limits the ability to control hypertension in this population. Here, we report efforts from the Improving Renal

Outcomes Collaborative (IROC) to standardize appropriate BP measurement across 16 pediatric kidney transplant centers.

Methods: In total, 16 centers participated in structured quality improvement (QI) activities as facilitated by the IROC QI fundamentals course. We prospectively collected clinic BP data from August 2016 to May 2018 and calculated the proportion of visits with appropriate BP measurement according to 5 criteria from published guidelines. For each center, data were analyzed over 2 time periods: a 12-week baseline pre-intervention period and a 20-week post-intervention period. We used run charts to quantify improvements in BP measurement.

Results: We analyzed BP measurement data from 5,242 transplant clinic visits. Prior to IROC interventions, BP was measured appropriately at 10% of visits. Less than 15% of centers were measuring arm circumference, allowing 5 minutes of rest, or averaging 2 manual readings if the initial BP was elevated. Within 10 weeks post-intervention, BP was measured appropriately at 85% of visits. This improvement was sustained for at least 10 weeks (Figure).

Conclusions: Using the infrastructure of the IROC learning health system, we standardized BP measurement across 16 pediatric transplant centers, allowing for more accurate assessment of BP and further interventions to reduce CV risk in pediatric kidney transplant recipients.



FR-PO1138

Effect of Elevated Systolic Blood Pressure and Pulse Pressure on the Progression of CKD in Children

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Background: Increased systolic blood pressure (SBP) and pulse pressure (PP) are associated with the progression of chronic kidney disease (CKD) and there is a good correlation between increased left ventricular mass index (LVMI) and decline in glomerular filtration rate (GFR). However, the exact nature of the relationship between PP, SBP, and LVMI has not been established in children with CKD, which this study aims to investigate.

Methods: This is a retrospective study of pediatric patients with CKD utilizing Chronic Kidney Disease in Children (CKiD) database from the National Institute of Diabetes and Digestive Kidney Disease (NIDDK) registry. Only children with iohexol-based GFR (iGFR) < 60 ml/min/1.73 m^2(n=620) were included for analysis. Analysis of relationships between SBP vs iGFR, diastolic blood pressure (DBP) vs iGFR, PP vs iGFR and LVMI vs iGFR were done using a two-tailed significance test and Pearson's correlation coefficient. Statistical analysis was done using SPSS software.

Results: The clinical characteristics at baseline were age 9.8 ± 4.4 years (mean ± SD), iGFR 37.9 ± 12.1 ml/min/1.73 m^2, SBP 107.9 ± 13.5 mm Hg, DBP 66.3 ± 11.4 mm Hg, PP 41.7 ± 10.8 mm Hg, and LVMI 30.9 ± 9.3. Increasing SBP and PP strongly correlated with decreasing iGFR (r=-0.16, p<0.001 and r=-0.08, p<0.003) (Figures 1 & 2). Increasing DBP also correlated well with decreasing iGFR (r=-0.11, p<0.01). This inverse relationship was also maintained between LVMI and iGFR (r=-0.09, p<0.05). No significant association found between PP and LVMI (r = 0.037; p = 0.334).

Conclusions: A strong inverse relationship exists between iGFR and LVMI, SBP, DBP, PP. These findings suggest that effective blood pressure control is of paramount importance in CKD children to decrease the rate of decline in renal function.

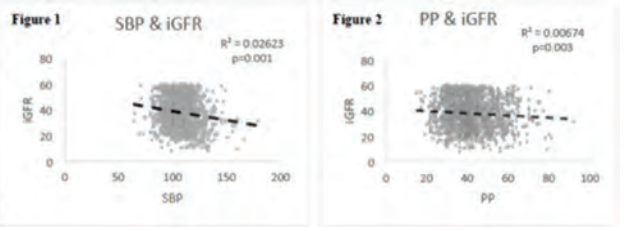

Figure 1 & 2. Relationship between iohexol-based GFR (iGFR)with systolic blood pressure and pulse pressure in children with chronic kidney disease

FR-PO1139

Hypertension in Children with Acute Lymphoblastic Leukemia in the Modern Era

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Background: In recent decades, the prognosis of acute lymphoblastic leukemia (ALL) has improved with innovations in chemotherapy, bone marrow transplantation (BMT), & better supportive therapy. Given these better outcomes, understanding & managing complications associated with ALL have become more important. Hypertension (HTN) is a known complication of ALL & has been attributed to multiple factors, including renal leukemic infiltration, AKI, & high dose steroids. There is a paucity of data on the incidence of HTN in children diagnosed with ALL in the recent decades. Prior studies have shown wide variation in incidence of HTN ranging from 6.3-52.9% in children with ALL. The aim of this study is to define the incidence of acute & chronic HTN in pediatric patients diagnosed with ALL in more recent years.

Methods: This study is a retrospective chart review of pediatric patients diagnosed with ALL at Nationwide Children's Hospital between 1/1/2008 & 12/31/2016. BP data was collected from diagnosis to 9 yrs post-diagnosis or until a following end point: lost to follow-up, received BMT, or deceased. BP values obtained in the lower extremity or while the patient was agitated were excluded. Acute HTN was defined as systolic blood pressure (SBP) %/or diastolic blood pressure (DBP) ≥ 95th %tile for age/height at diagnosis & 1 month post diagnosis. Chronic HTN was defined as 2 consecutive SBP %/or DBP readings ≥ 95th %tile for age/height 6 months or more after ALL diagnosis.

Results: 222 patients were reviewed. The incidence of acute HTN was 35% & chronic HTN 34%. 52% of pts who had acute HTN developed chronic HTN, whereas 24% of pts who were normotensive in 1st month of diagnosis developed chronic HTN. There was an overall trend in increased HTN indices (subject's BP/subject-specific 95th %tile) from diagnosis to 1 month post diagnosis. Median HTN indices for SBP increased from 0.98 to 1.04 & for DBP increased from 0.91 to 1.00. A large percentage of hypertensive patients did not receive anti-HTN therapy - 55% with acute HTN & 76% with chronic HTN were untreated.

Conclusions: Among children with ALL, there is a high incidence of HTN at time of diagnosis & in long-term follow-up. There is an overall trend for higher blood pressures after initiation of induction chemotherapy. In children with ALL, HTN often goes undiagnosed & untreated & yet is likely to convey long term sequelae.

FR-PO1140

Left Ventricular Mass Index (LVMI) Improves with Resolution of Hypertension in Incident Pediatric Hemodialysis Patients

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Background: Left ventricular hypertrophy (LVH), determined by increased left ventricular mass indexed for allometric height^ 2.7 (LVMI), is highly prevalent in children receiving chronic dialysis (CD). Natural history of LVH in pediatric (ped) CD patients (pts) is not well known; one study showed no change in LVMI after 6 months of starting CD. We have shown LVMI improves with control of HTN in CD patients. For this study, the aim was to investigate the relationship of fluid overload (FO) and HTN with LVMI in incident HD patients.

Methods: Retrospective chart review from a single center to identify pts starting HD from 2012-2017. Pts with echocardiogram (ECHO) within 3 months of starting HD and repeat ECHO in 6-12 months while continuing HD were included. Pts were excluded if follow up ECHO was not available or pts initiated CD at another center and initial ECHO not available. Charts reviewed for demographics, relevant labs, hypertension (HTN) defined by treatment with antihypertensive meds; FO as identified by % above dry wt; LVMI was converted to percentiles based on published normative values for age and gender.

Results: 43 pts (22 male), mean age 13.1 (range 3-17.41 years); 38/43 pts who had HTN at HD initiation also had increased LVMI (96.6 ± 8.09%tile vs. 81.25 ± 12.5%tile). Mean LVMI from initiation decreased significantly on follow up ECHO (initiation 94.7 ± 9.94 %tile vs. 81.13 ± 24.8%tile, p= 0.0006), independent of age or gender. Those who had resolution of HTN had improved LVMI, while those with continued HTN did not improve LVMI (Table). Pts in our study had only minimal FO over the 6-12 month period: (3.6 ± 1.2 %, range 1.25% -6.54%). FO was not associated with LVMI change (mixed effects model p=0.2). Hgb, phosphorus, calcium or PTH were also not associated with LVMI change.

Conclusions: Ped HD pts with HTN at initiation had elevated LVMI. LVMI improved significantly within 6-12 months of HD initiation. Hypertension resolution was associated

with improvement of LVMI. In our population of pts with tight fluid control, FO was not associated with change in LVMI.

43 patients total	HTN resolved*(26)	HTN persisted** (17)
LVMI%tile at start	95 ± 9.4	96±10.7
LVMI%tile after 6-12 months	79 ± 26.6	90 ± 17.2

*p=0.003, ** NS; paired t test

FR-PO1141

Left-Ventricular Hypertrophy and Diastolic Dysfunction in Korean Children with CKD: Data from the KNOW-Ped CKD Study

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Background: Left-ventricular (LV) hypertrophy (LVH) and LV diastolic dysfunction are early marker of cardiovascular disease in pediatric chronic kidney disease (CKD), and the early detection of LVH is important to prevent morbidity and mortality in children with CKD. However, there is no consensus on the ideal method of defining LVH in pediatric CKD patients. The aim of this study was to evaluate the LVH measurement methods and the association the presence of LVH and LV diastolic dysfunction in Korean children with CKD.

Methods: We used the baseline data of the KoreaN cohort study for Outcome in patients With Pediatric Chronic Kidney Disease (KNOW-Ped CKD), a nationwide, 10-year, prospective, observational cohort study of pediatric CKD. A total 310 patients were included in the final analysis.

Results: The mean age of the patients was 10.3±5.2 years, and male to female ratio was 2.2:1. The mean value of LV mass index (LVMI) was 38.3g/m$^{2.7}$. The mean ejection fraction and fractional shortening was 66.8 and 36.6%, respectively. According to an LVH diagnosis by LVMI ≥ 38.6 g/m$^{2.7}$, 128 patients (41.3 %) were diagnosed with LVH. Using the z-score > 1.64 reference values, 19 patients (6.1 %) were diagnosed with LVH. According to the ratio of early/late diastolic myocardial velocity (E/A ratio < 0.9 or > 2.0), 101 patients (32.5 %) had diastolic dysfunction. Sixteen patients (6.4 %) were diagnosed as having diastolic dysfunction by mitral peak velocity of early filling to early diastolic mitral annular velocity (E/E' ratio > 15). Kappa coefficient showed a significant value of 0.076 between LVH by LVMI >38.6g/m$^{2.7}$ and diastolic dysfunction by E/E' ratio > 15. LVMI calculation for predicting E / E '> 15 by Youden's index method is 32.1g/m$^{2.7}$

Conclusions: The study suggests that the definition of LVH by LVMI ≥ 38.6 g/m$^{2.7}$ could be more associated with diastolic dysfunction according to E/E' > 15. Further investigation to find a better method of defining LVH to predict cardiac dysfunction in the children with CKD is necessary.

Funding: Government Support - Non-U.S.

FR-PO1142

Secular Trends in Prevalence of Hypertension and Elevated Blood Pressure Among Korean Children and Adolescents: The Korea National Health and Nutrition Examination Survey 2007-2015

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Background: Hypertension is an important health problem and the prevalence of hypertension in children and adolescents has been gradually increasing. We aimed to analysis the recent trends in blood pressure (BP) levels and the prevalence of hypertension among Korean children and adolescents. We also analyzed the potential contributing factors.

Methods: This study examines data obtained from the Korea National Health and Nutrition Examination Survey (KNHANES) 2007-2015 which were combined into 3 time periods (2007-2009, 2010-2012, and 2013-2015). The KNHANES is a nationally representative surveillance system, which has been conducted cross-sectionally since 1998 by the Korea Centers for Disease Control and Prevention and the Ministry of Health and Welfare. In the present study, a total of 7,889 Korean children and adolescents aged 10-18 years were included.

Results: The distributions of sex and age were not significantly different across 3 periods (2007-2009, 2010-2012, and 2013-2015). There were no significant changes in proportion of obesity and overweight from 2007-2009 to 2013-2015, while body mass index z-score significantly increased in total population from 2007-2009 to 2013-2015. Additionally, weight circumference and abdominal obesity were significantly increased from 2007-2009 to 2013-2015. For dietary factors, daily intake of calories, total fat, carbohydrate, protein and fiber increased, while daily intake of sodium decreased significantly. Mean systolic BP levels significantly increased from 2007-2009 to 2013-2015 in total population, while diastolic BP values did not increase in total population. In 2013-2015, the prevalence of elevated BP and hypertension were 8.8% and 9.0%, respectively. Compared to those in 2007-2009, the prevalence of elevated BP in 2013-2015 increased in total population, especially, boys, and obese subgroup. The prevalence of hypertension in obese group in 2013-2015 was 27.7%, which was significantly increased from 2007-2009 to 2013-2015. Regression analysis revealed the association between central obesity and diastolic BP. Girls were less likely to have hypertension than boys.

Conclusions: Mean systolic BP and the prevalence of elevated BP increased from 2007-2009 to 2013-2015. The possible influencing factor is obesity, and further analysis is necessary.

Funding: Government Support - Non-U.S.

FR-PO1143

Association of Body Mass Index with CKD and Hypertension 4 Years After Pediatric Cardiac Surgery

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Background: We previously found that children undergoing cardiac surgery (CS) are at high risk of developing chronic kidney disease (CKD) and hypertension (HTN); however, CKD was not associated with post-operative (postop) acute kidney injury. Hypothesis: Body mass index (BMI) and peri-operative factors are associated with long-term CKD and HTN development after pediatric CS (PedCS).

Methods: Prospective cohort study (Montreal, Canada; Cincinnati, USA). Subjects: <18 years(y) old having CS, recruited pre-operatively (preop) followed postop and serially for 4y. At 4y, clinical data, height/weight, blood pressure (BP), blood and urine were collected. **4y outcomes**: *CKD* (eGFR<90ml/min/1.73m^2) *or* albumin-to-creatinine ratio≥3 mg/mmol; *HTN*: BP≥95th percentile. Age at surgery <1y, RACHS-1 (surgical complexity score)≥3, preop eGFR, and 4y BMI z-score and overweight (OW, BMI≥85th percentile), were compared between outcome groups. 4y BMI association with CKD (adjusted for perioperative factors) was evaluated using multiple logistic regression (LR).

Results: 96/124 children had 4y data available: 24% had CKD; 13% had HTN; 22% were OW. Age<1y at surgery, RACHS-1≥3, smoking and OW were more common in CKD *vs.* no CKD patients(Table). No study variables were significantly associated with 4y HTN(Table). In multiple LR including age, RACHS-1 and preop eGFR, age<1y at surgery and each 10-unit decrease in preop eGFR were associated with a 5.9 (95% CI 1.8-18.6)-fold and 1.2 (95% CI 1.0-1.4)-fold adjusted risk for 4y CKD, respectively. When adjusted for age, RACHS-1 and preop eGFR, each 1 unit BMI z-score increase (at 4y) was associated with 1.5 (95% CI 1.0-2.2)-fold adjusted risk for 4y CKD. Sample size did not allow for LR analysis on HTN risk.

Conclusions: Young age at surgery and OW at follow-up are associated with CKD 4y after PedCS. Research is needed to understand the relation between young age and other risk factors for CKD development after PedCS. Post-PedCS interventions should aim to reduce long-term cardiovascular risk.

Funding: NIDDK Support

Table. Comparison of peri-operative characteristics and BMI between CKD *vs.* non-CKD and HTN *vs.* non-HTN groups

	No CKD n=67	CKD n=29	No HTN n=80	HTN n=12
Age at surgery<1	51%	79%*	58%	42%
RACHS-1 ≥3	49%	52%	44%	58%
Pre-operative eGFR (ml/min/1.73m^2)	125±40	115±39	127±40	110±34
Smoking reported	0	17%*	2.5%	8.3%
BMI z-score	0±1.2	0.8±2.0	0.1±1.2	-0.1±1.1
BMI ≥85th percentile (OW)	17%	38%*	23%	17%

* = p<0.05 for difference between outcome groups.

FR-PO1144

Diacylglycerol Kinase Epsilon (DGKE) Deficiency in Endothelial Cell Results in Marked Abnormalities in Phosphoinositides

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Background: Loss-of-function mutations in DGKE cause a rare form of atypical hemolytic-uremic syndrome (aHUS) that does not implicate complement hyperactivation. Patients are typically diagnosed before age 1, have disease relapses until age 5 and develop end-stage kidney disease before adulthood. There is currently no treatment, but renal transplantation is safe. Diacylglycerol (DAG) is produced when phosphatidylinositol

4,5-bisphosphate (PIP_2) is cleaved by phospholipase C. DGKE is a lipid kinase that phosphorylates DAG to phosphatidic acid (PA). When produced, PA is shuttled to the endoplasmic reticulum where it is used to reconstitute the pool of PIP_2 (as part of the PI cycle). The consequences of DGKE deficiency in human endothelial cells are unknown. A better understanding of DGKE disease pathophysiology is critical to developing new therapies for these patients. Our objective is to quantify the impact of DGKE deficiency in endothelia on membrane lipids that play key roles in DGKE biology, including diacylglycerol, phosphatidic acid and phosphoinositides.

Methods: We used orthogonal methods to compare the lipid levels in wild-type and DGKE-deficient endothelial cells derived from human vein endothelial cells (HUVEC) with a CRISPR/Cas9-engineered deletion in the DGKE gene. These methods included mass spectrometry lipidomics, cellular labelling with ^{3}H-inositol followed by high-performance liquid chromatography (HPLC), and live-tracking of transfected fluorescent-labelled PIP_2 biosensor. The novel mass spectrometry lipidomics approach that we developed was also applied to an endothelial cell line derived from a patient with novel pathogenic DGKE mutations (c.A494G; p.D165G) and glomeruli extracted from the kidneys of a new Dgke-null mouse model (generated with CRISPR/Cas9).

Results: Mass spectrometry lipidomics revealed significant PIP_2 reduction in DGKE-null HUVEC. These results were corroborated using the same protocol applied to a patient-derived endothelial cell line and glomeruli from Dgke-null mice. ^{3}H-inositol labelling and fluorescent lipid biosensor experiments confirmed a significant reduction in PIP_2 in DGKE-deficient HUVEC.

Conclusions: Low endothelial PIP_2 levels is likely to play a central role in the triggering the pro-thrombotic phenotype observed in patients with DGKE aHUS.

Funding: Other NIH Support - Kidney Foundation of Canada

FR-PO1145

Child and Parental Perspectives on Communication and Decision-Making in Pediatric CKD: A Focus Group Study

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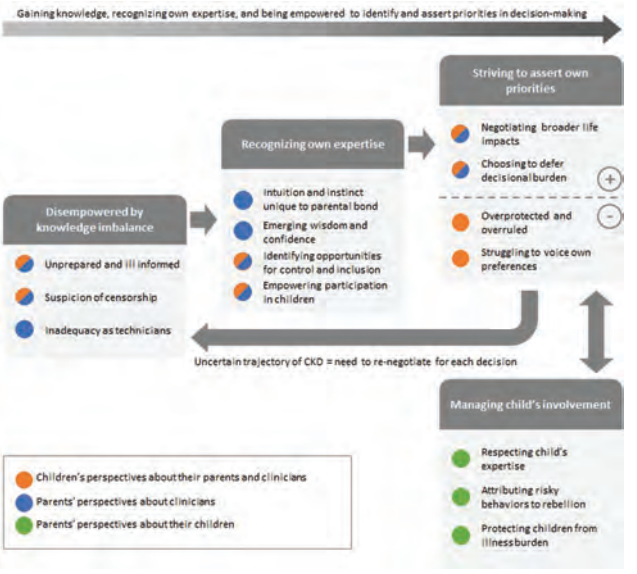
Background: Effective communication and shared decision-making improves quality of care and patient outcomes, but can be particularly challenging in pediatric chronic disease as children depend on their parents and clinicians to manage complex healthcare and developmental needs. This study aims to describe the perspectives of children with chronic kidney disease (CKD) and their parents with regard to communication and decision-making.

Methods: Children with CKD (n=34) and parents (n=62) from six centers across six cities in Australia, Canada and the United States participated in 16 focus groups. Transcripts were analyzed thematically.

Results: We identified four themes: (1) disempowered by knowledge imbalance (unprepared and ill-informed, suspicion of censorship, inadequacy as technicians); (2) recognizing own expertise (intuition and instinct unique to parental bond, emerging wisdom and confidence, identifying opportunities for control and inclusion, empowering participation in children); (3) striving to assert own priorities (negotiating broader life impacts, choosing to defer decisional burden, overprotected and overruled, struggling to voice own preferences); and (4) managing child's involvement (respecting child's expertise, attributing 'risky' behaviors to rebellion, protecting children from illness burden).

Conclusions: Parents value partnership with clinicians and consider long-term and quality of life implications of their child's illness. Children with CKD want more involvement in treatment decision-making but are limited by vulnerability, fear, and uncertainty. There is a need to support the child to better enable them to become partners in decision-making and prepare them for adulthood. Collaborative and informed decision-making that addresses the priorities and concerns of both children and parents is needed.

Funding: Government Support - Non-U.S.



FR-PO1146

Timing of Dialysis Education and Patients' and Families' Preferences in Children with CKD

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Background: There is no strong evidence favoring PD or HD in children; it is recommended that patients actively participate in the choice of dialysis modality. The first step for including patients in the decision-making process is to provide them with information on dialysis modalities. However, there is currently limited data on the timing of RRT education in children with CKD and on families' and patients' preferences.

Methods: The CKiD study is a prospective cohort study that enrolled patients 1–16 yrs with an eGFR of 30–90 mL/minute/1.73 m^2. Clinical data and laboratory data are collected annually. Patients and families are asked at baseline and annually about the information received on dialysis modalities and their preferred dialysis modality. Logistic regression was used to study factors associated with education status.

Results: 240/370 patients reported not having received any information on RRT prior to inclusion in the cohort. Patients informed at baseline were more likely to have advanced CKD; there was a trend toward a lower probability of information in African American patients or if no family history of CKD. There was no association between CKD duration and the probability of information on RRT. Among the 94 patients who discussed dialysis with their provider during follow-up, 69 (73%) had no preference between PD and HD. Among them, 22 had repeated assessment of their preference; 5 decided on HD, 3 on PD. CKD progression was the only factor associated with change in modality preference. 118 patients discussed transplantation with their provider during follow-up; 23 discussed only deceased donor transplantation, 3 only living donor, 22 both options and 70 reported not being informed of donor sources.

Conclusions: Patient and family self-reported prevalence of education on RRT is low. Starting education on RRT at earlier CKD stages and focusing on populations reporting a low level of information such as African American patients and patients with no familial history of kidney disease may improve education rates. Moreover, the extremely low rate of selecting a dialysis modality is very concerning and could lead to less thoughtful decision-making when patients approach ESRD. Further studies are needed to develop educational interventions and assess their ability to help the patients and families choose their dialysis modality.

FR-PO1147

Sex and Glomerular Filtration Rate Trajectories: Insights from the CKiD Cohort Study

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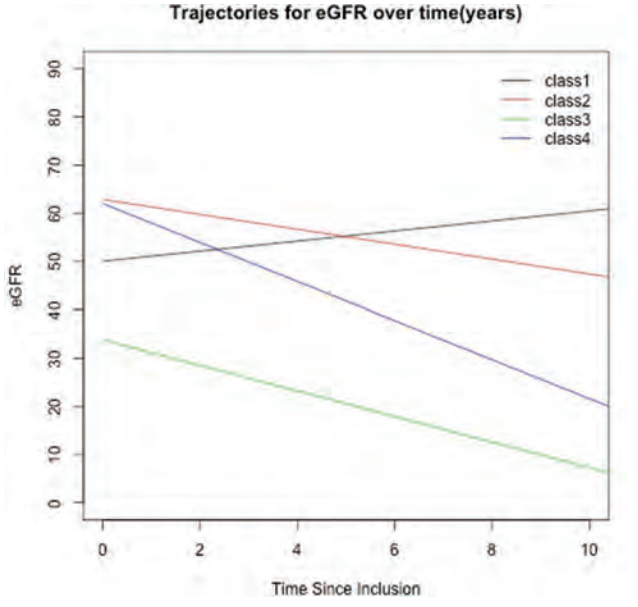
Background: The effect of gender on CKD progression has not been specifically studied in children. Moreover, differences in CKD progression have been hypothesized to partially explain gender disparities in access to transplantation. This study aims to identify distinct trajectories of GFR decline and to investigate the effect of gender on GFR decline.

Methods: The CKiD study is a prospective cohort study that enrolled patients 1–16 yrs with an eGFR of 30–90 mL/minute/1.73 m^2. Clinical and laboratory data, including GFR, are collected annually. Latent class mixed model was used to identify GFR trajectories. Multinomial logistic regression was used to study patient characteristics associated with each trajectory.

Results: 888 patients were included. Among nonglomerular patients (613), we observed 4 GFR trajectories: 35 with median baseline GFR/no decline; 327 with high baseline GFR/slow decline; 231 with low baseline GFR/slow decline and 20 with high baseline GFR/rapid decline (Figure 1, class 1 to 4 respectively). Known risk factors of progression differed between trajectories. The proportion of girls was higher in the group with stable GFR (57%) than in other groups (32-35%). Patients with stable GFR had lower prevalence of acidosis, anemia and proteinuria. Female gender remained associated with the absence of progression (OR 2.7 [1.3-5.5]) after adjusting for other risk factors. This effect remained after stratification on pubertal status. Among glomerular patients (275), progression was mostly related to the underlying glomerulopathy.

Conclusions: The slower progression in girls is driven by a subgroup with nonglomerular diseases and stable GFR. The effect of gender seems independent of pubertal status, arguing against a direct effect of sex hormone to explain gender disparity in CKD progression.



FR-PO1148

Impact of Chronic Illness in Children on Families: Kidney Disease (KD) versus Diabetes Mellitus (DM)

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Background: Chronic illness in children has adverse effects on family members besides the patient and can impact the integrity and function of the family unit. Most previous studies have examined a single disease entity. However, there has been limited assessment comparing the effect of different illnesses on family function.

Methods: Established patients treated in the pediatric ambulatory Nephrology or DM clinics were included in the study. Their parents were asked to complete the 2-page Pediatric Quality-of-Life Family Impact Module (PedsQL-FIM), version 2.0, a validated survey instrument. Clinical and laboratory data were retrieved from the electronic health record. Data were summarized as mean±SD. Disease group and child age were entered as predictors in linear regression analyses with FIM total and subscale scores as outcome variables. Comparisons between groups were assessed using paired t-tests.

Results: 96 patients (43 F: 53 M) were evaluated in the Nephrology Clinic and 55 (30 F: 25 M) in the DM Clinic. The mean age of the patients was 13.0±3.9 and 10.4± 6.3 yr, respectively. Within the KD sample, older age was significantly associated with lower scores on all FIM subscale scores. Gender was not a significant predicator for FIM scores in either disease group. Controlling for age, chronic illness group was a significant predictor of the FIM total and subscale scores. Parents of D patients endorsed significantly lower total FIM scores compared to the KD patients (D 58±16; KD 79±17 p <0.001) as well as on subscales of physical, emotional, social, and cognitive functioning, communication, worry, daily activities, family relationships, and reports of health-related quality of life (P<0.01).

Conclusions: Our findings confirm that chronic illness in childhood adversely affects a wide range of aspects of family function. The impact is greater in older children with KD and varies depending on the disease context. Families with children who have DM manifested greater disturbances than those with children who have isolated KD. Further study is warranted to assess the effects of the underlying renal disease and intensity of medical care and whether there are specific features can be used to identify vulnerable families.

Funding: NIDDK Support, Clinical Revenue Support

FR-PO1149

Serum Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) Levels During Pregnancy

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Background: suPAR is an inflammatory mediator that has been linked to the pathogenesis of FSGS and progression of chronic kidney disease in children and adults. Overexpression of suPAR leads to reduced nephron development in preclinical models. This study was designed to measure suPAR in pregnant women to determine the range of fetal exposure to this molecule and its potential influence on antenatal human kidney growth.

Methods: Pregnant women enrolled in the Children's Health and Environment Study (CHES) provided serum samples obtaining during 1-3 trimesters. Clinical information was obtained from the electronic health record. suPAR levels were determined by ELISA (Virogates, Copenhagen, Denmark). Data are presented as mean±SD. Results were analyzed by Pearson correlation and ANOVA.

Results: 515 mothers were studied, age 31±6 yr, and racial distribution 44% Caucasian, 7% African American, 9 % Asian, and 41% other/unspecified. 46% of the women were Hispanic. 29% had completed a high school education or less and 28% had an annual income <$50,000. There were 464 livebirths, 50.4% girls. The serum suPAR levels (mean, SD, minimum, maximum) are summarized in the Table. The suPAR levels in the subgroup of women who provided more than one sample during pregnancy were closely correlated (r=0.79-0.94, P<0.0001)). The decline in serum suPAR levels from trimester 1 to 3 was highly significant (P<0.001).

Conclusions: Maternal suPAR levels are detectable throughout pregnancy but decline from trimester 1 to 3. The levels are highly correlated and steady during the course of pregnancy in an individual woman. There is more than a 10-fold range in suPAR concentration which may contribute to the biological variation in nephron number at birth. Follow-up assessment in the infants will be performed in the prospective Environmental Influences on Child Health Outcomes (ECHO) cohort study.

Funding: NIDDK Support

Serum suPAR :Levels During Pregnancy

Trimester (T)	N	Mean	SD	Minimum	Maximum
T1	426	2.86	0.92	1.08	14.47
T2	133	2.68	1.33	1.15	13.65
T3	171	2.34	1.00	0.65	11.00

FR-PO1150

Establishing an Organisational Entity to Support Development of Therapeutics in Children with CKD: A KHI Initiative

Michelle N. Rheault,[1] H. William Schnaper,[8] Pam Duquette,[7] Debbie S. Gipson,[2] Teresa Lewis,[9] Alicia Neu,[10] Franz S. Schaefer,[3] Melissa West,[4] Johan Vande walle,[5] Stuart Goldstein,[6] Katrin Uhlig.[11] *[1]University of Minnesota, Minneapolis, MN; [2]University of Michigan Mott Children's Hospital, Ann Arbor, MI; [3]University of Heidelberg, Heidelberg, Germany; [4]American Society of Nephrology, Washington, DC; [5]UZGent, Gent, Belgium; [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [7]Nephcure Kidney International, Baltimore, MD; [8]Feinberg School of Medicine, Chicago, IL; [9]The University of Oklahoma Health Sciences, Oklahoma City, OK; [10]Johns Hopkins University School of Medicine, Baltimore, MD; [11]Keryx Biopharmaceuticals, Brookline, MA.*

Background: A Kidney Health Initiative (KHI) workgroup on 'Overcoming Barriers to Drug Development in Children with CKD' identified the need for more concerted and rational planning and conduct of clinical trials in children with CKD to address EMA and FDA regulatory requirement.

Methods: An Implementation Committee was charged to establish an organizational entity that will help optimize planning of therapeutic trials in children with CKD. Its charter addresses aims, guiding principles, composition of a standing Leadership Committee, committee operations, and funding.

Results: The aims of the new entity are to a) Enable feasibility assessment of available patient populations through data sharing and access to CKD pediatric registries b) Facilitate assessment of the capacity of various pediatric kidney clinical trial organizations c) Assist with identification of expertise that can provide consultation on study planning. To manage potential conflicts of interest, this entity needs to adhere to guiding principles regarding transparency, information sharing, international participation and collaboration, and financial independence, while respecting the rights and intellectual property of principal investigators, sponsors, and trial networks, and ensuring the confidentiality of proprietary information and protected patient information. The Leadership Committee will be comprised of representatives from pediatric collaborative trial networks, patient/family support groups and subject matter experts without industry sponsors. Operationally, industry sponsors will be able to submit queries and requests that will be reviewed, triaged, and addressed by the Leadership Committee. The Implementation Committee will draft a finance model, sustainability plan, and identify a permanent administrative home with a commitment to transparency, equity, and economy. In the interim, KHI will continue to support this entity.

Conclusions: This new entity will seek collaboration with other stakeholders to better support therapeutic development in children with CKD.

FR-PO1151

Risk Factors for Progression of CKD in Children: Results from the Korean Cohort Study for Outcome in Patients with Pediatric CKD (KNOW-Ped CKD)

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Background: The prevalence of chronic kidney disease (CKD) has increased over the last decades. Several large studies of Western countries have reported risk factors of CKD progression in pediatric patients, while comprehensive studies on pediatric CKD are rare in Asian countries. We aimed to evaluate risk factors for the progression of CKD of Korea using KNOW-Ped CKD data.

Methods: In KNOW-PedCKD, 437 children with stage 1 to 5 of CKD were enrolled and 432 patients were followed more than 6 months between July 2011 and May 2017. The progression of CKD was defined as a composite renal event of renal replacement therapy or a ≥50% decline in estimated glomerular filtration rate. The baseline clinical and laboratory variables were analyzed.

Results: The progression of CKD occurred in 136 (31.4%) patients after median follow ups of 1.9 (IQR 0.7-3.2) years. In Kaplan-Meier analysis, the median renal survival of all analyzed CKD patients was estimated as 5.2 years. In multivariate analysis, after adjustment with Cox regression model, 6 variables remained as independent risk factors of CKD progression: male sex, CKD stage 4 and 5, hypertension, urine protein/creatinine ratio ≥0.5 mg/mg, serum albumin <3.8 mg/dL, and anemia. Among them, proteinuria, hypoalbuminemia, hypertension and anemia could be modifiable and treatable, in accordance to previous findings in the Western studies.

Conclusions: In KNOW-pedCKD cohort, risk factors for CKD progression in Korean pediatric patients were found, including modifiable factors. Applying these findings to the clinic might improve the outcome of pediatric CKD.

Funding: Government Support - Non-U.S.

FR-PO1152

Observational Descriptive Analysis from the Korean Pediatric CKD Registry

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Background: The prevalence of chronic kidney disease (CKD) has increased over the last decades. Nevertheless, there still are limited data on epidemiology of childhood CKD in Korea. To improve the understanding and management of Korean pediatric patients with CKD, we established the Korean Pediatric CKD Registry in 2004. We aimed to assess the incidence and prevalence of end stage renal disease (ESRD), etiology, renal replacement therapy (RRT) modalities in children with CKD.

Methods: From January 2004 to December 2016, 713 patients <20 years of age with CKD have been registered in the Korean Pediatric CKD Registry. Demographic and clinical data were collected from 16 centers. Updating of the data was done at least once a year. We analyzed patients who started RRT before the age of 20 years.

Results: Among 713 enrolled patients, 442 patents developed end stage renal disease at mean age of 9.8±5.4 years. The age distribution was as follows: <5 years 21.0%, 5-9 years 27.1%, 10-14 years 33.0%, and 18.8% were >15 years. The main causes of ESRD were glomerulopathy (40.7%) and congenital anomalies of kidney and urinary tract (CAKUT, 24.8%). Glomerulopathy predominated in females, while CAKUT was the majority among males. The annual incidence of ESRD had increased from 1.75 per million age-related populations (pmarp) in 2004 to 2.58 pmarp in 2016. The point prevalence of ESRD was 2.38 pmarp in 2004, and 4.67 pmarp in 2016. The first modality of RRT was peritoneal dialysis in 240 (54.3%), hemodialysis in 118 (26.7%), and preemptive kidney transplantation in 84 (19.0%) patients. Pre-emptive kidney transplantation was more common in older age group (5.1% in age of 0 to <5 years and 28.9% in age of 15 to <20 years).

Conclusions: This study provided the epidemiologic profile of Korean pediatric patients with ESRD. The number of pediatric patients with ESRD had steadily increased. Peritoneal dialysis was the preferred method of RRT for children in Korea.

FR-PO1153

Longitudinal Measures of Serum Bicarbonate and Kidney Disease Progression: Results from the CKiD Cohort

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Background: Acidosis is a frequent complication of pediatric CKD; however, the longitudinal changes of serum bicarbonate over time in glomerular and non-glomerular kidney disease has not been examined.

Methods: This study consisted of 787 children with at least two serum bicarbonate measurements in the CKiD cohort. To describe baseline bicarbonate levels and changes over time, linear mixed models with random intercepts were fit with bicarbonate in the log scale. The relationship between bicarbonate and eGFR was described using a repeated measures linear regression with generalized estimating equations. All analyses were stratified by underlying non-glomerular and glomerular diagnoses.

Results: 558 children with non-glomerular CKD contributed 3325 visits, and 229 with a glomerular diagnosis contributed 1050 visits. The prevalence of acidosis (serum bicarbonate <22 mmol/L) at baseline was 38% and 28% for those with a non-glomerular and glomerular diagnosis, respectively (p= 0.01). The prevalence of alkali therapy at baseline was 30% and 8%, respectively. For those with non-glomerular disease, the mean baseline bicarbonate level was 23.1 mmol/L (95%CI: 22.9, 23.3) and the mean change per year was +0.1% (95%CI: -0.1%, +0.3%). Among those with glomerular disease, the mean baseline bicarbonate level was 24.0 mmol/L (95%CI: 23.6, 24.4) and the mean change per year was -0.4% (95%CI: -0.7%, -0.003%), indicating a significant reduction over time. Per 20% decrease in eGFR, those with non-glomerular CKD had a decrease of -2.39% (-2.79% to -1.99%) while children with glomerular disease had a -3.23% decrease (-3.72% to -2.74%) in their bicarbonate levels (p=0.01 for the comparison). Baseline acidosis was associated with a faster decline in eGFR (-6.0% [-12.8% to -1.0%] vs. -2.9% [-6.8% to -0.4%], p<0.001) in non-glomerular CKD but not in glomerular CKD (-4.8% [-14.9% to 0.3%] vs. -6.0% [-14.0% to -1.4%]).

Conclusions: In non-glomerular CKD, bicarbonate levels start lower but do not decrease as rapidly as in children with glomerular CKD. However, low baseline bicarbonate levels are associated with a faster decline in eGFR only in those children with non-glomerular CKD. Future data will assess whether these relationships may be attenuated by effective alkali therapy.

FR-PO1154

Primary Care Prescriptions of Nephrotoxic Medications to Children with CKD

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Background: Nephrotoxic medication (NTM) prescription practices for children with chronic kidney disease (CKD) are unknown. Our objective was to determine if primary care prescriptions of NTMs differ for children with and without CKD.

Methods: We conducted a retrospective, population-based, matched cohort study of patients aged <18 years registered at a general practice participating in the UK Clinical Practice Research Datalink (CPRD) from 1997 to 2017, with linkage to Hospital Episode Statistics data. Patients with incident CKD were matched 4:1 to non-CKD patients on CKD diagnosis date, sex, age, CPRD practice, and number of pre-cohort entry physician visits.

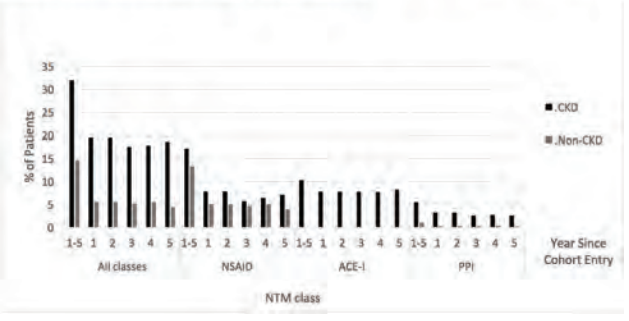
Prevalence of prescription of NTM was compared between CKD and non-CKD patients, with adjusted prescription rates calculated using multivariable binomial regression.

Results: From our base cohort of 1,535,816 patients, we identified 1018 with incident CKD and 4072 non-CKD matches; mean age: 9.8 years [range: 1.1-17.9]; 52% male; mean follow-up time 3.2 vs. 3.3 years in CKD *vs.* non-CKD patients. CKD patients had higher prevalences of diabetes, hypertension, heart failure/surgery, and past hospitalizations (p<0.01 for all). A total of 32% CKD patients and 14.6% non-CKD patients were prescribed ≥1 NTM during follow-up (p<0.01). Excluding ACE-inhibitors and salicylates, 25.8% and 14.5% were prescribed ≥1 NTM, respectively. From cohort entry to end of follow-up, the proportion of CKD patients receiving ≥1 NTM remained similar (17.6%-19.5%/year). Adjusted NTM prescription rates in CKD *vs.* non-CKD patients were 37.0 (95% CI 19.4-70.6) *vs.* 3.7 (95% CI 2.1-6.6) prescriptions/100 person-years, respectively (rate ratio [RR]: 9.9 (95% CI 7.3-13.4). Excluding ACE inhibitors and salicylates, the adjusted RR was 4.1 (95% CI 2.1-6.6).

Conclusions: NTMs are prescribed at elevated rates to children with CKD. There may be a need for awareness/education interventions aimed at primary care practitioners on potential harm from NTMs on pediatric CKD progression.

Funding: Government Support - Non-U.S.

Figure 1: Proportion of Patients who Received ≥1 Nephrotoxic Medications (NTM) During Entire 5-Year Follow-up and by Each Year of Follow-Up



FR-PO1155

Long-Term Safety of Cinacalcet in Pediatric CKD Subjects on Dialysis

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Background: The calcimimetic cinacalcet is indicated for treatment (tx) of secondary hyperparathyroidism in adults with CKD on dialysis. Its use was evaluated in pediatric CKD subjects (subj) on dialysis in 2 parent trials: NCT01439867 (single arm; age 28d-<6y) and NCT02138838 (open-label; cinacalcet vs standard of care [SOC]; age 6-<18y). This phase 3, single-arm, open-label extension evaluated cinacalcet use in subj who completed the parent trials or were still on study at early parent trial termination.

Methods: This 32-week (W) (28 tx+4 follow-up) study assessed the safety of cinacalcet based on incidence of tx-emergent adverse events (TEAE) of interest (primary endpoint [EP]). Secondary EP included ≥30% mean iPTH reduction during W11+15 and 23+28, % mean iPTH change during W23+28 (each assessed only in SOC subj in NCT02138838), and ≥30% mean iPTH reduction and change in serum Ca and P during W23+28 (all subj). Cinacalcet subj in the parent study continued the same dose; SOC subj had iPTH ≥300pg/mL and Ca ≥8.8mg/dL, and received initial doses of 0.2mg/kg/d. Cinacalcet was titrated (up to 2.5mg/kg/d; ≤60mg/d [age <6y] or ≤180mg/d [age ≥6y]) to PTH ≥150-<300pg/mL and to maintain corrected Ca ≥8.4mg/dL or ionized Ca ≥1.05mmol/L for subj 6-<18y, and ≥9.0mg/dL or ionized Ca ≥1.13mmol/L for subj <2y.

Results: Of 28 enrolled subj, 5 discontinued tx due to renal transplant (n=2), parathyroidectomy, death unrelated to tx, and subj request (n=1 each). Mean (SD) age and cinacalcet exposure were 12.6 (3.9) y and 170 (52) d. 10 (40%) (W11-15) and 4 (18%) (W23-28) subj had ≥20% of doses withheld. 20 (71.4%) subj had ≥1 TEAE, most commonly hypocalcemia and pyrexia (n=3 each). Incidence of TEAE of interest were: hypocalcemia (n=5,17.9%), nervous system disorders excluding seizures (n=4,14.3%), hypersensitivity (n=2,7.1%), drug-related hepatic disorders, and fracture (n=1,3.6% each); none deemed serious. The proportion achieving ≥30% iPTH decrease is below. Median (Q1,Q3) iPTH change (prior SOC only) at W23+28 was 11.4% (-20.6, 27.3). Overall W23+28 median (Q1,Q3) serum Ca and P (mg/dL) change was -0.25 (-0.66, 0.10) and 0.06 (-0.94, 0.69).

Conclusions: There were no new/unexpected safety concerns in these pediatric CKD subj on dialysis.

Funding: Commercial Support - This study was funded by Amgen, Inc.

	Prior SOC only (NCT0213883) Weeks 11 and 15 N=13	Prior SOC only (NCT0213883) Weeks 23 and 28 N=13	Total (NCT01439867 + NCT02138838) Weeks 23 and 28 N=26
n (%) achieving ≥30% reduction in mean iPTH	4 (31%)	3 (23%)	4 (14%)

FR-PO1156

Response to Erythropoietin in Pediatric Patients with CKD: Insights from an In Vitro Bioassay

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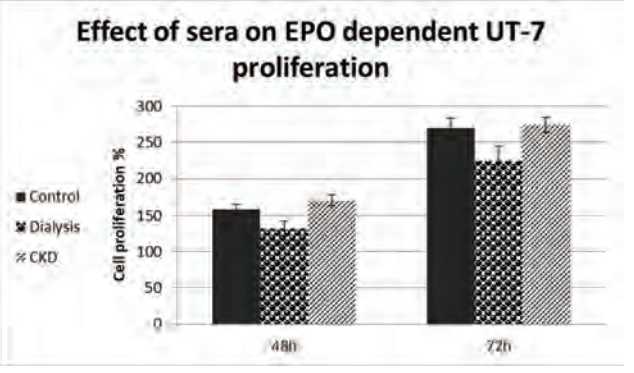
Background: Decreased production of erythropoietin (EPO) is a major cause of anemia associated with chronic kidney disease (CKD). Treatment with recombinant human EPO (rHuEPO) improves patients' quality of life and survival, yet, there is a marked variability in response to rHuEPO. At present, there is no available laboratory test which can evaluate responsiveness to EPO treatment. The aim of the present study was to exploit an in vitro bioassay for estimating the inhibitory effect of uremic environment on EPO-dependent erythroid cell proliferation

Methods: EPO-dependent human erythroleukemia cells (UT-7) were incubated with exogenous EPO (2u/ml) and sera obtained from 60 pediatric patients (age 1-23 years). Three groups were studied: 1) 12 children on dialysis (4 peritoneal, 8 hemodialysis), 2) 28 patients with CKD1-5 (not on dialysis) and 3) 20 healthy children.

Results: Sera from dialysis patients inhibited UT-7 cell growth in comparison to the CKD group and healthy controls at 48 hours (p=0.003 and p=0.04, respectively) and at 72h (p=0.02 and p=0.07, respectively). In 18 patients treated with rHuEPO, a significant inverse correlation was found between the EPO resistance index and cell proliferation at 48 (p=0.007, r=-0.63) and 72 hours (p=0.03, r=-0.52).

Conclusions: Our findings support the presence of erythropoiesis inhibitory substances in uremic sera. EPO/EPO-R dependent mechanisms may play a role in inhibiting erythropoiesis. The in vitro bioassay described herein may serve as an indicator of rHuEPO responsiveness and enable further investigation of underlying mechanisms of EPO resistance



FR-PO1157

Ultrafiltration Rates Observed in a Large Pediatric Hemodialysis Cohort Routinely Exceed Weight Based Adult Limit: Call for Action

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Background: Ultrafiltration rates (UFR) in adult hemodialysis (HD) patients of >10 and especially >13 ml/kg/hr were found to be associated with greater risk of cardiovascular (CV) morbidity and mortality, leading to limiting UFR in adults to 13 ml/kg/hr. CV disease is the main cause of death in children on HD. Children have higher need for UF than adults to allow adequate nutrition and growth, but there is no data of UFR routinely provided to children. This is the first study to report UFR from a large pediatric HD cohort.

Methods: We retrospectively analyzed data from 17844 HD sessions in 1592 children and adolescents 1-18 years and weight (wt) 8.3-163 kg, receiving standard outpatient HD in DaVita centers between 2004 and 2016. There were total of 2535 patient-years with median 16 (interquartile range (IQR): 5-42) HD sessions per patient. Median UFR [ml/kg/hr; (preWt-postWt)/postWt/hr)] was calculated for each patient and year of age. HD was provided 3x/week for a duration of 1.75-5 (median 3.25, IQR: 3.0-3.6) hrs. UFR of >10 and >13 were analyzed in relation to age, weight and HD duration (Chi-squared/Fisher-exact test).

Results: UFR was significantly different between patients of different age and wt, and among patients receiving different HD duration (Table). UFR >10 and >13 ranged between 35-57% and 17-46% respectively based on age (P<0.05) while it was 14-62% and 1-43% respectively based on wt (P<0.001). Patients with highest UFR were 6-11 years old and weighed 25-50 kg. UFR >13 mL/kg/min remained similar (30-34%) for HD durations 93-210 min, but decreased to 27% and 18% for longer sessions of 211-240 and >240 min, respectively.

Conclusions: Pediatric UFR frequently exceed upper limit recommended for adults if HD lasts <4 hrs especially in children weighing 25-50 kg. Additional studies are needed to define pediatric-specific upper UFR limits that could decrease CV mortality. If lower UFR is found to be beneficial in children, a global change in chronic pediatric HD prescription will be required allowing longer and/or more frequent HD treatments.

Funding: Private Foundation Support

Summary by age	1-2 y	3-5 y	6-11 y	12-18 y		P
Number of patient-years	34	68	190	2243		
UFR_mLkgh (median [IQR])	6.03 [3.1, 11.0]	7.41 [2.2, 13.5]	11.98 [5.9, 17.2]	9.84 [6.0, 13.8]		<0.001
UFR ≥ 10 mL/kg/h [n (%)]	12 (35.3)	29 (42.6)	109 (57.4)	1101 (49.1)		0.031
UFR ≥ 13 mL/kg/h [n (%)]	6 (17.6)	19 (27.9)	87 (45.8)	656 (29.2)		<0.001
Summary by weight	**<25 kg**	**25-50 kg**	**50-75 kg**	**75-100 kg**	**>100 kg**	**P**
Number of patient-years	222	857	1059	282	115	
UFR_mLkgh (median [IQR])	10.70 [4.0, 17.5]	12.02 [7.1, 16.3]	9.77 [6.0, 13.3]	7.25 [4.8, 9.9]	6.57 [4.6, 8.9]	<0.001
UFR ≥ 10 mL/kg/h [n (%)]	115 (51.8)	533 (62.2)	518 (48.9)	69 (24.5)	16 (13.9)	<0.001
UFR ≥ 13 mL/kg/h [n (%)]	92 (41.4)	370 (43.2)	283 (26.7)	22 (7.8)	1 (0.9)	<0.001
Summary by session duration	**93-150 min**	**151-180 min**	**181-210 min**	**211-240 min**	**241-323 min**	**P**
Number of patient-years	43	559	1036	612	285	
UFR_mLkgh (median [IQR])	6.60 [2.3, 13.8]	9.63 [5.2, 14.6]	10.34 [6.0, 14.5]	9.97 [6.2, 13.5]	8.98 [6.0, 12.0]	0.008
UFR ≥ 10 mL/kg/h [n (%)]	16 (37.2)	272 (48.7)	538 (51.9)	305 (49.8)	120 (42.1)	0.022
UFR ≥ 13 mL/kg/h [n (%)]	13 (30.2)	178 (31.8)	356 (34.4)	169 (27.6)	52 (18.2)	<0.001

FR-PO1158

Acquired Cystic Kidney Disease in Children and Young Adults Undergoing Dialysis

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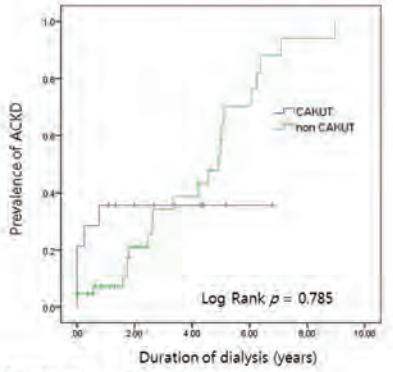
Background: Acquired cystic kidney disease (ACKD) describes bilateral cystic degeneration of the kidneys in patients who do not have cystic diseases. It is known as a common complication of end-stage renal disease (ESRD) in adults, however pediatric studies were scarce. We aimed to determine the prevalence, time of occurrence, and complications of ACKD in children and young adults undergoing dialysis.

Methods: We retrospectively reviewed the medical records of ESRD patients who were followed at Seoul National University Children's Hospital between January 2015 and April 2018. We enrolled a patient if he/she had taken kidney imaging of ultrasonography or computer tomography after initiating maintenance dialysis. Patients with hereditary cystic disease were excluded.

Results: A total of 64 patients (male : female = 40 : 24) were enrolled. Maintenance renal replacement therapy was required at their mean age of 9.3 ± 6.0 years old. Causes of ESRD were non-cystic congenital anomalies of the kidney and the urinary tract (CAKUT) in 14 (21.9%), non CAKUT (glomerulonephritis in 34, nephrotoxin induced nephropathy in 4, hyperoxaluria in 2, and so on) in 44 (68.8%), and unknown in 6 (9.4%). Forty seven (73.4%) patients were on peritoneal dialysis, 12 (18.8%) on hemodialysis, and 5 (7.8%) on both. ACKD was found in 32 (50.0%). ACKD was detected 3.0 ± 2.5 years after the start of dialysis. In non CAKUT, the prevalence of ACKD increased with duration of dialysis, however it was not significant in non-cystic CAKUT (Fig. 1). Four (non CAKUT in 3 and unknown etiology in 1) had serious complications of ACKD; two had renal cell carcinomas, and 2 experienced massive hemorrhage. Complications occurred 3.9 to 12.2 years after the start of dialysis.

Conclusions: ACKD complicates ESRD of children and young adults as well. Since ACKD may accompany serious complications such as malignancy and hemorrhage, routine surveillance is necessary in high risk patients on maintenance dialysis.

Kaplan-Meier curve comparing the prevalence of ACKD by ESRD etiolgy



FR-PO1159

Distribution of the Pediatric Refugee Population with Renal Replacement Therapy in Germany

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Background: In 2016, about 2 million people immigrated to the EU. With 1 million people Germany reported the largest number of immigrants, of which an estimated 300,000 were children. Data on prevalence and management of refugee patients with end-stage renal disease are rare. Numbers focusing on the pediatric cohort are not available. Our goal was to obtain information on the size and distribution of the pediatric refugee population with renal replacement therapy (RRT). In addition, we wanted to gain insights into the problems and challenges in the care of these patients.

Methods: We interviewed all pediatric dialysis centers in Germany about the number of pediatric refugee patients on RRT at the time of the survey. We also asked the number of patients from the most common countries of origin (Syria, Afghanistan and Iraq). Subjective problems and challenges in the care of this cohort should be listed.

Results: 86% of the centers indicated that they provide care to refugee children on RRT. A total of 69 refugee children were treated with RRT in the centers surveyed. 52/69 (75%) received dialysis therapy, 43 of which were on HD and 9 on PD. 17/69 children (25%) underwent RTx. 34/69 (46%) came from either Syria, Afghanistan or Iraq. In 2017 a total of 232 children were on dialysis in Germany, which makes the group of dialyzed refugee children account for approximately 22% of the total German pediatric dialysis population. With regard to the challenges in the care of these patients, difficulties in communication, non-compliance, administrative as well as psychosocial problems were most frequently mentioned. In summary, most centers indicated that the care of this group of patients presents their institution with great financial and logistical challenges.

Conclusions: Our survey shows that the majority of pediatric dialysis centers care for refugee children. The refugee population represents a large proportion of the total pediatric dialysis population in Germany. The challenges in treating these patients are complex and consume many personnel and logistical resources. To ensure holistic care for these children close cooperation between medical staff, dieticians, social workers, interpreters and psychologists is required. Interdisciplinary training should be established in the treating centers. The additional burden should be registered and compensated for by public authorities.

FR-PO1160

Serum Albumin and Hospitalization Among Pediatric Patients Who Started Dialysis Therapy

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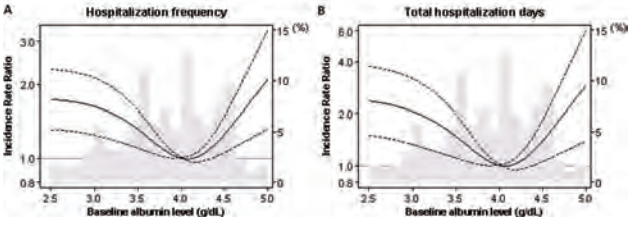
Background: Hypoalbuminemia is a strong predictor of hospitalization in adult dialysis patients. However, there are scarce data on the association between serum albumin levels and hospitalization among pediatric patients new to dialysis therapy.

Methods: In a cohort of children (1–17 years) who received dialysis therapy at a large US dialysis organization during 2007–2011 and who had available data on serum albumin within 1 year following initiation of dialysis, we examined the association of serum albumin levels with hospitalization frequency and total hospitalization days using negative binomial regression models. Hospitalizations for transplantation were excluded.

Results: Among eligible patients, median (IQR) age was 14 (10–16) years and mean±SD baseline serum albumin level was 3.7±0.8 g/dL. There appeared to be a U-shaped association between serum albumin and hospitalization frequency; hospitalization rates (95% CI) were 2.7 (2.2–3.2), 1.9 (1.5–2.4), 1.6 (1.3–1.9), 2.7 (1.7–3.6) per patient-year among patients with serum albumin levels <3.5, 3.5 to <4.0, 4.0 to <4.5 and ≥4.5 g/dL, respectively. The case mix-adjusted incidence rate ratios (IRRs) (95% CI) were 1.63 (1.24–2.13), 1.32 (1.10–1.58), and 1.25 (1.06–1.49) at serum albumin level of 3.0, 3.5, and 4.5 g/dL, respectively (ref: 4.0 g/dL). Consistent trends were observed in hospitalization days [Figure].

Conclusions: Both high and low serum albumin levels were associated with hospitalization in children with ESRD on dialysis. Hospitalization for high serum albumin may be due to favorable or unfavorable status, such as access placement or dehydration, respectively.

Funding: NIDDK Support



FR-PO1161

Analysis of Survival of Low Weight Children (<15 kg) Undergoing Chronic Hemodialysis: Mortality and Risk Factors

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Background: With the technological advances in hemodialysis, it is currently possible to offer this type of therapy to young and low weight children. Our objective is to analyze the survival of children undergoing hemodialysis and risk factors impacting mortality

Methods: Retrospective analysis of patients undergoing chronic hemodialysis between January 2015 and January 2018 was performed. The sample included 65 patients (14F and 51M) with median age at start of hemodialysis of 1.3 years (13 days - 9.6 years) and median follow-up of 536 days (54 days - 5.2 years). The most frequent etiology was CAKUT (63%) followed by Renal Dysplasia (8%). At study baseline, median weight was 8.1Kg (2.3kg-13.7kg), median Z-score for weight/age -3.94 and median Z-score for height/age -3.16. Enteral feeding was required in 32 patients via gastrostomy. In this sample, 30 patients had anuria and 43 patients had undergone peritoneal dialysis prior to hemodialysis. 61 patients were on daily hemodialysis (8 patients had 7 sessions/week) with 90-180 minute sessions according to individual needs. Vasoactive drugs to maintain adequate blood pressure for the procedure were required in 26 patients.

Results: Of the 65 patients, 30 (46%) were transplanted, 27 (42%) remained on HD and 8 (12%) died. The cumulative survival rate was 96% for 1-year, 86% for 2-year, 80% for 3-year and 70% for 5-year survival. Considering transplant as a concurrent event, the following factors had the greatest impact: a) Cardiopathy – presence associated with a 23 times greater probability of death (95%CI= 5 - 103; p<0.001) b) Anuria – presence associated with an 8 times greater probability of death (95%CI = 1 - 67; p=0.050) c) Z-score for height/age - every 1 SD increase in Z-score reduced chance of death by 46% (95%CI = 16% - 66%; p=0.006) d) Z-score for weight/age - every 1 SD increase in Z-score reduced chance of death by 56% (95%CI = 33% - 71%; p<0.001)

Conclusions: Hemodialysis is a viable therapy in low weight children awaiting kidney transplant. Survival rates found were similar to those reported in the literature. The presence of cardiopathy risk factor had the greatest impact on probability of death in the sample. The patients with highest survival rates were those with better nutritional status and residual renal function.

FR-PO1162

End-of-Life Care in Young Dialysis Patients

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Background: Although end-stage kidney disease in the young is often a progressive disorder with high mortality, end-of-life care in this population has not been well characterized. In particular, it is unknown whether end-of-life care has changed over time and whether racial and ethnic disparities are present.

Methods: We used United States Renal Data System files to examine these issues among patients dying on maintenance dialysis in the US at age 0-20 years, between 2000 and 2014 (N=1647).

Results: While the proportions that discontinued dialysis were similar in 2000-2006 and 2007-2014 (14.8% Vs. 17.9, *P*-Value 0.09), the proportions receiving hospice care (3.6% Vs. 12.8%, *P*-Value <0.001) and dying outside of hospital (25.1% Vs. 33.8%, *P*-Value <0.001) both rose. Dialysis discontinuation (20.6% in white Vs. 10.4% in African American, *P*-Value <0.001), hospice care (11.1% in white Vs. 3.9% in African American, *P*-Value <0.001) and non-hospital death (35.6% in white Vs. 23.7% in African American, *P*-Value <0.001) were less likely in decadents from minority populations than in those of non-Hispanic white race-ethnicity. Findings regarding temporal trends and racial disparities were similar when adjustment was made for age, sex, and race/ethnicity.

Conclusions: While end of life care has changed substantially over time, discontinuation of dialysis, hospice care and death outside of hospital remain exceptional in young patients dying on maintenance dialysis. In addition, substantial racial and ethnic disparities are present.

FR-PO1163

A Nephrology Transition Clinic in the Adult Care Setting: A Pilot Program

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Background: Young adults (YA) with chronic illnesses transitioning care from pediatric to adult medical facilities face many obstacles. Pediatric care providers are mindful of barriers to a smooth transition and the importance of a formal transition process, while adult care providers are often unaware, leading to an inconsistent transition process in the adult care setting. Three years ago, Northwestern Medicine (NM) Nephrology implemented a pilot transition of care program for YA with renal disease transitioning from Lurie Children's Hospital to NM. We report here on our experiences.

Methods: Pediatric nephrology providers identified patients who they deemed ready to transition to adult providers. Prior to transition clinic, the adult multidisciplinary team, consisting of the nephrologist, physician assistant (PA), and social worker, reviewed patients with the pediatric team. The first appointment occurred at Lurie Children's Hospital, which is located across the street from NM. Subsequent visits were then held at NM. At the initial visit, the patient was seen by the PA, nephrologist and if deemed appropriate, the social worker. The transition team reviewed each patient bimonthly to determine if proper follow up including testing and appointments had occurred, and if not, the patient was contacted to arrange for these.

Results: A total of 69 patients were seen in a three year period. Of these, 6 patients have been lost to follow up. 5 patients were no longer able to be followed due to insurance changes. 2 patients were deemed not to require further nephrology follow up. 42 patients have followed up as instructed at NM. There are 9 patients who have pending follow ups. 4 patients started peritoneal dialysis and are thus are no longer cared for in the transition clinic. Finally, 1 patient started hemodialysis right away, was subsequently transplanted, and is now seen back in the transition clinic.

Conclusions: Based on our three year pilot experience, transition of care from pediatric to adult nephrology providers can be successfully facilitated with engagement of an adult nephrology team, close communication with a pediatric team, and a formal transition clinic protocol. In the future, we plan to continue this as a formal program in nephrology as well as extending it to other medical specialties within the NM system.

FR-PO1164

Evaluating Renal Outcomes in Adolescents Born Extremely Premature of the ELGAN (Extremely Low Gestational Age Newborn) Cohort

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Background: Premature birth is associated with decreased nephron number and an increased lifetime risk for chronic kidney disease (CKD). Yet there is lack of recommendation for renal follow up of children born prematurely. The aim of the study is to characterize the prevalence of macroalbuminuria, elevated blood pressure, and/or abnormal renal mass (predictors of CKD) in adolescents with a history of extremely premature birth.

Methods: We obtained 2 manual blood pressures, a random urinalysis, and sonographic measurements of kidney length and volume on 17 consecutively enrolled 15-year old children born at <28 weeks gestation of the UNC Extremely Low Gestational Age Newborns (ELGAN) cohort.

Results: Of the 17 currently enrolled participants, 65% were male, 53% were Caucasian (33%identified as Hispanic) and 47% were African-American. Their mean age was 15 years. Median blood pressure was 115/69 mmHg with 35% of the cohort demonstrating elevated mean blood pressures. Median urine albumin/creatinine ratio was 7.75µg/mg with 24% of the cohort demonstrating significant random macroalbuminuria (>30µg/mg). Sonographic measurements are listed in Table 1. Twenty-nine percent of participants demonstrated abnormal renal mass (18% right renal hypoplasia, 6% right renal hypertrophy, 6% left renal hypoplasia, 6% left renal hypertrophy). No gross renal anatomical abnormalities were seen via ultrasound.

Conclusions: Nearly half (47%) of adolescents in this extremely low gestational age cohort were found to have abnormal renal mass, macroalbuminuria, or elevated blood pressures. Enrollment is ongoing. This data suggests that renal follow up of children with a history of extremely premature birth should be considered.

Funding: Other NIH Support - KL2TR001109, National Institutes of Health, John Buse, MD, PhD (PI), North Carolina Translational & Clinical Sciences Institute, Scholar Project: Renal outcomes in children with a history of extreme prematurity. Role of first author: Post-Doctoral KL2 Scholar

Table 1: Sonographic Renal Measurements of Adolescents of the ELGAN cohort

	ELGAN Cohort	Normative Data
Mean Right Kidney Length(cm)	9.09 (+/-0.85)	9.2(+/-0.7)
Mean Right Body Surface Area related Kidney Volume (ml/m2)	61.82(+/-17.3)	45-85
Mean Left Kidney Length(cm)	9.47(+/-1.1)	9.9(+/-0.6)
Mean Left Body Surface Area related Kidney Volume (ml/m2)	67.77(+/-17.6)	45-85
Mean Total Kidney Volume (cm3)	219 (+/-78.5)	256.43(+/-14.58)

FR-PO1165

Incidence and Long-Term Outcomes of Neonatal Renal Vein Thrombosis in Ontario: A Population-Based Cohort Study

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Background: There is limited data at a population level on the burden and long-term outcomes of neonatal renal vein thrombosis (nRVT). We conducted a cohort study to determine the incidence and long-term outcomes including hypertension (HTN), chronic kidney disease (CKD), end-stage renal disease (ESRD) and mortality associated with nRVT during a period of 24 years.

Methods: Health administrative databases, housed at the Institute for Clinical Evaluative Sciences, were used to identify all neonates ≤28 days of age born in Ontario, Canada from 1992-2016 and compared all neonates with nRVT vs. the total neonatal population without nRVT. The primary outcome was the composite risk of long-term outcomes including CKD, ESRD (chronic dialysis or kidney transplant) and all-cause mortality. The secondary outcome was the long-term risk of HTN. Incidence rates (IR) were calculated and Cox proportional hazard models were fitted for all outcomes.

Results: The annual IR of nRVT in Ontario from 1992-2016 was 2.6 per 100,000 live births (total 85 cases from 3,001,637 live births). The median follow-up was 11 years in both cohorts. There was a male preponderance (64%) of nRVT. A greater proportion of nRVT vs. comparator cohort was premature (45% vs. 8%, Standardized Difference 0.92). After adjusting for confounders, patients with nRVT were at a 17-fold increased risk of CKD

or death (Hazard Ratio (HR) 16.9, 95% CI 12.3-23.2, p<.0001) and an 18-fold increased risk of HTN (HR 17.7, 95% CI 12.6-25.0, p<.0001) vs. the comparator cohort. None of the nRVT cohort developed ESRD.

Conclusions: Patients with nRVT remain at higher risk than the general neonatal population of long-tern morbidity and mortality, indicating the need for long-term follow-up.

Table 1: Incident rates and hazard ratios of adverse outcomes among patients with nRVT in Ontario from 1992-2016

Outcomes		Proportion of live births with outcome		Risk of adverse outcomes			
		nRVT Cohort n=85	Comparator Cohort n=3,001,552	Unadjusted HR	95% CI†	Adjusted HR*	95% CI†
Primary Outcome	CKD or Death	43%	0.7%	67.6	49.4 - 92.5	16.9	12.3 - 23.2
Secondary Outcome	HTN	39%	2%	30.0	21.3 - 42.2	17.7	12.6 - 25.0

† All outcomes were significant with p<0.0001

*Adjusted for sex, congenital heart disease, respiratory distress syndrome, sepsis, maternal preeclampsia or eclampsia, and maternal diabetes.

CKD, chronic kidney disease; HTN, hypertension; HR, hazard ratio; CI, confidence interval.

FR-PO1166

Common Clinical Markers Predict ESRD in Children with Obstructive Uropathy

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Background: Obstructive uropathy (OU) is the leading cause of pediatric chronic kidney disease (CKD) and end stage renal disease (ESRD). Children who escape the newborn period with mild to moderate CKD continue to be at increased risk for progression, especially as they undergo pubertal changes. The predictive ability of clinical markers throughout childhood is poorly defined in OU.

Methods: Patients with OU were identified in the Chronic Kidney Disease in Children Study (CKiD), a prospective observational cohort of children with mild to moderate CKD. The primary outcome of interest was ESRD (Cases). OU patients who did not progress to ESRD during follow-up (Controls) were age matched to Cases. Glomerular Filtration Rate (GFR), urine (protein/Cr and microalbumin/Cr), and serum (CO_2, phosphate, albumin, and hemoglobin), were evaluated as predictor variables both at baseline and over time.

Results: Median age at baseline and outcome was 10 vs.16 years(y) respectively. Cases (n=27) and Controls (n=41) had significant differences in baseline GFR (36.9 vs. 53.5 ml/min/1.73m^2), urine protein/Cr (0.40 vs. 0.22) and microalbumin/Cr (0.58 vs. 0.03), and serum $C0_2$ (20 vs. 22 mmol/L) and hemoglobin (12.4 vs. 13.2 g/dL) respectively. GFR declined 3.07 ml/min/1.73m^2/y faster in Cases (p<.0001) (Figure). Urine protein/Cr and microalbumin/Cr declined 0.16/y and 0.11/y faster in Cases respectively (p≤0.001 for both). Serum phosphate increased 0.11 mg/dL/y and albumin and hemoglobin decreased 0.04 g/dL/y and 0.14 g/dL/y faster for Cases respectively (p<0.05 for all).

Conclusions: Baseline and longitudinal evaluation of clinical measures predicts ESRD in children with mild to moderate CKD from OU. Optimal cutoff values require further evaluation so that children identified at high risk can undergo closer surveillance that may allow changes in management to slow or halt progression.

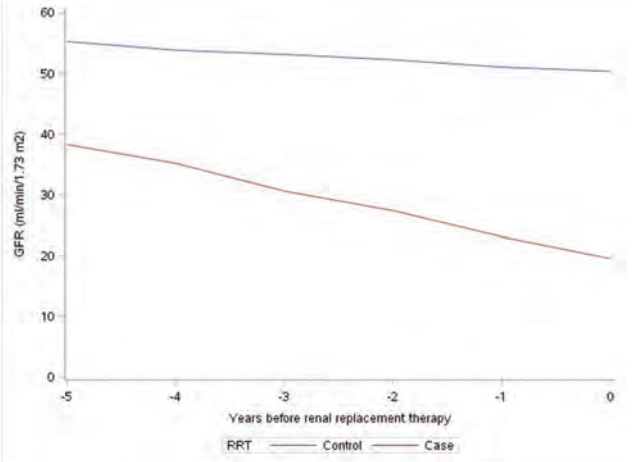

Figure. Estimated change in GFR over time in the CKiD OU cohort

FR-PO1167

Antibiotic Prophylaxis for Prevention of Urinary Tract Infections in the First Year of Life in Children with Vesicoureteral Reflux Diagnosed Following Antenatal Hydronephrosis: A Systematic Review

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Background: Children with antenatal hydronephrosis (ANH) and vesicoureteral reflux (VUR) are presumed to be at higher risk of urinary tract infection (UTI) after birth. As such, continuous antibiotic prophylaxis (CAP) has been empirically recommended for newborns who have ANH and VUR to reduce the rate of UTI during the first year of life, however, there is limited data to support this practice. The objective of this systematic review was to determine whether CAP prevents UTI within the 1st year of life in children with VUR diagnosed in the workup of ANH.

Methods: A systematic search of all relevant studies was conducted using 4 electronic (Medline, Embase, CINAHL, and CENTRAL) databases using appropriate key words without language restriction by an expert librarian. A time limit of January 1985 to May 2017 was applied. Eligible studies included children with VUR diagnosed in the workup of ANH with or without antibiotic prophylaxis, and reported development of UTI. Two independent reviewers performed title and abstract screening and full-text review. Primary outcome was to compare rate of UTI among those on CAP to those not on CAP.

Results: Of 6903 citations screened, 17 were selected, giving a total population of 845 (69.1 % male, median age 6 days (IQR= 29) who met the inclusion criteria. Most studies were retrospective, and of low quality evidence. Overall, 14.7% of patients developed at least one breakthrough UTI despite being on CAP. A common theme throughout studies was that higher grade VUR (IV-V) was associated with higher incidence of breakthrough UTI. Only two studies included in our review compared UTI rates in children on CAP (combined UTI risk 13.2%) compared to those not on CAP (UTI risk 42.7%), and thus meta-analysis could not be performed.

Conclusions: Despite the use of CAP, 14.7% of children with VUR diagnosed in the setting of ANH continue to develop UTI. However, there is limited published literature comparing UTI rates in this patient population to those not on CAP, thereby making any meaningful inference impossible. The effect of CAP on UTI rates in patients with ANH and postnatal VUR thus remains unclear and requires further investigation.

FR-PO1168

Congenital Nephrogenic Diabetes Insipidus: A Review of 50 Pediatric Patients from MWPNC Centers

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Background: Congenital Nephrogenic Diabetes Insipidus (NDI) is a rare genetic disorder that causes massive polyuria. To better understand NDI in children, we present, to our knowledge, the largest retrospective case series to date. Our objective for this study was to describe clinical presentation, genetic etiology, treatment and outcomes in patients < 21 years with NDI.

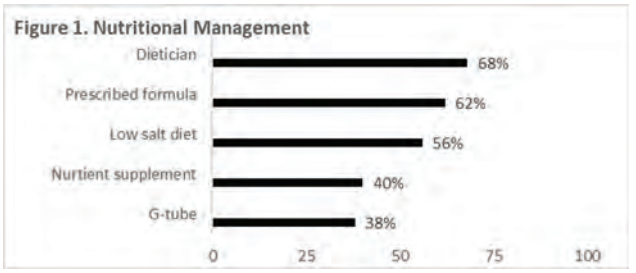
Methods: Midwest Pediatric Nephrology Consortium centers (MWPNC) conducted a retrospective chart review.

Results: We report 50 subjects from 12 centers. Median age at diagnosis was 125 days (interquartile range (IQR), 37, 296) with 86% male. 66% were white, 14% black, 8% Asian and 12% other race. 18% had a water deprivation test and 50% had a DDAVP loading test (median age at DDAVP 155 days (IQR, 101, 392)). At diagnosis, 74% had an elevated serum osmolality (> 300 MOsm/L). 54% had genetic testing with mutations in *AVPR2* (65%), *AQP2* (14%), and unavailable (21%). 28% had a diagnosis of CKD; 55% Stage 1, 36% Stage 2 and 9% Stage 5. Median age at time of CKD diagnosis was 4.1 years (IQR, 3.1, 9.4). 18% had abnormal renal ultrasound findings; the majority were hydronephrosis and pelvicaliectasis. Table 1 lists pharmacologic interventions. Other medications included chlorothiazide (2%), chlorthiadone (4%), other NSAIDS (8%) and spironolactone (6%). Figure 1 lists nutritional management. At last follow-up, 52% reported to have enuresis.

Conclusions: Our results suggest a multi-centered approach to this rare disease yields robust information that can inform future novel treatment studies and creation of a clinical consensus for management of children with NDI.

Pharmacologic Interventions

Intervention	Used % (n=50)	Start age in days Median (IQR)	Length of treatment in days Median (IQR)
Hydrochlorothiazide	96	136 (57, 334)	446 (233, 1823)
Amiloride	64	369 (64, 949)	175 (13, 1721)
Indomethacin	44	580 (89, 863)	162 (9, 1685)



FR-PO1169

Albuminuria Sparing Effects of Hydroxyurea in Children with Sickle Cell Anemia

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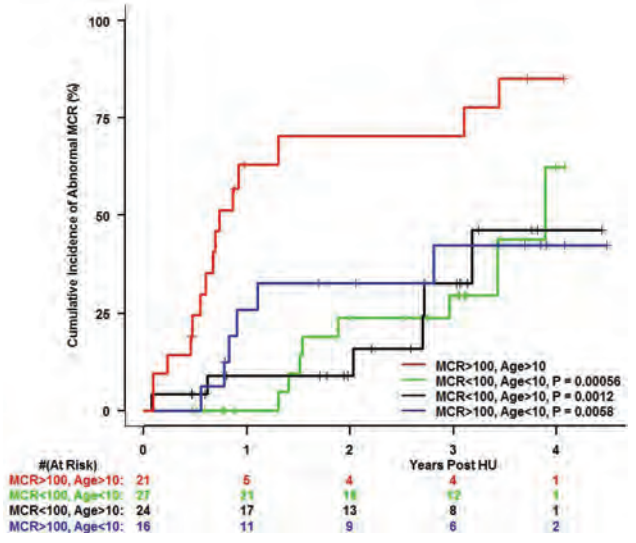
Background: Renal complications in sickle cell anemia (SCA) begin early in childhood as hyposthenuria, glomerular hyperfiltration and albuminuria. Hydroxyurea (HU) use in SCA improves anemia, induces fetal hemoglobin and reduces sickle cell complications. We evaluated the long term effects of initiating hydroxyurea in patients with albuminuria and without albuminuria. We tested the hypothesis that initiation of HU in SCD children and young adults with albuminuria would improve urine measurements.

Methods: Participants were children < 18 yrs of age with SCA who were enrolled in two prospective cohorts and had longitudinal assessment of urine albumin to creatinine ratios (ACR) available. ACR values were captured at baseline, during the first 12 months of HU therapy and every year thereafter. The main outcome of the analysis, the development of albuminuria, was evaluated by two methodologies: a comparison of proportion between baseline and on hydroxyurea therapy and a time-to-development of albuminuria during hydroxyurea therapy.

Results: Albuminuria was present at baseline in 49% of our cohort. At one year of HU treatment, 38% with albuminuria normalized. Participants older than 10 at HU initiation had a 1.35x increase in the hazard ratio for developing ACR compared to younger than 10 years. We found that an ACR level of ≥ 100 mg/g to be a significant cut-point for recurrence.

Conclusions: The impact of HU on normalizing albuminuria may be dependent on baseline age at initiation of treatment and level of albuminuria. Our study provides the novel finding that hydroxyurea, initiated in younger age with lower levels of albuminuria can strongly benefit from the addition of HU therapy and titration to the maximal tolerated dose. Clinicians should not defer initiating HU for renoprotection until patients are older and experiencing moderate to severe albuminuria.



FR-PO1170

Morbidity of Childhood Nephrotic Syndrome: The Childhood Nephrotic Syndrome Observational Study, a Midwest Pediatric Nephrology Consortium Study

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Background: Childhood nephrotic syndrome (NS) is one of the most common pediatric chronic kidney diseases. Systematic studies of the complexity of treatment and disease complications are rare.

Methods: The Childhood Nephrotic Syndrome Study (CNOS) is an international, prospective, observational study of children 1-18 yrs with idiopathic NS enrolled within 2 mos of NS diagnosis. Demographic and clinical data are collected at presentation, 3 mos, and yearly. We describe healthcare utilization, treatment, treatment response, and disease complications among CNOS participants followed for at least 1 yr. Changes in corticosteroid (CST) treatment response from initial episode were noted.

Results: As of April 1, 2018, 127 had completed 12 mos follow-up. All patients were hospitalized at least once, with a total of 265 hospitalizations (2.1 hospitalizations/patient-year). The most common primary reason for hospitalization (82/265, 31% hospitalizations) was edema. Hospitalizations were complicated by blood clots in 3 patients (2.4%) and infections in 13 (10.2%). The majority of patients (77.2%) responded to the initial course of CST; however, an additional 5/98 (5.1%) were CST-resistant at 1 yr (i.e., late steroid-resistance). Frequently relapsing or CST-dependent NS was seen in 38/127 (29.9%). Second-line therapies were used in 69/127 (54.3%, Table). One patient (0.8%) reached end-stage renal disease.

Conclusions: Healthcare utilization and disease morbidity are high in childhood NS. Treatment is complex, with a large proportion of patients exposed to immunosuppressive agents in addition to CST, even among those initially responsive to CST. Further research and quality improvement efforts are needed to decrease hospitalizations and morbidity in children with NS.

Funding: Private Foundation Support

Immunosuppressive therapies in first year of NS diagnosis

Treatment, n (%)	Steroid-responsive NS (N=98; 77.2%)	Steroid-resistant NS (N=29; 22.8%)	Total* (N=127; 100%)
Intravenous corticosteroids	6 (6.1%)	2 (6.9%)	8 (6.3%)
Cyclophosphamide	3 (3.1%)	0	3 (2.4%)
Cyclosporin	1 (1.0%)	4 (13.8%)	5 (3.9%)
Tacrolimus	12 (12.2%)	15 (51.7%)	27 (21.3%)
Mycophenolate mofetil	17 (17.3%)	8 (27.6%)	25 (19.7%)
Rituximab	2 (2.0%)	0	2 (1.6%)

*Disease classification based on response to initial course of CST

FR-PO1171

Risk Stratification for Disease Recurrence in Children with Steroid Resistant Nephrotic Syndrome (SRNS) Following Kidney Transplantation (Midwest Pediatric Nephrology Consortium [MWPNC] Study)

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Background: Steroid resistant nephrotic syndrome (SRNS) due to FSGS and MCD is a leading cause of end stage kidney disease (ESKD) in children. Recurrence of primary disease following transplantation is a major cause of allograft loss. The clinical determinants of disease recurrence are not completely known. Our objective was to determine risk factors for recurrence of FSGS/MCD following kidney transplantation.

Methods: Multicenter study of pediatric patients with kidney transplants performed for ESKD due to SRNS between 1/2006-12/2015. Patients with primary-SRNS (PSRNS) were defined as those initially resistant to corticosteroid therapy at diagnosis, and patients with late-SRNS (LSRNS) as those initially responsive to steroids who subsequently developed steroid resistance. We performed logistic regression to determine risk factors associated with nephrotic syndrome (NS) recurrence.

Results: We included 158 eligible participants in our analysis; 64 (41%) had recurrence of NS in their renal allograft. Disease recurrence occurred in 78% of patients with LSRNS

compared to 39% of those with PSRNS. Patients with MCD on initial native kidney biopsy had a 76% recurrence rate compared with a 40% recurrence rate in those with FSGS. The recurrence rate in patients with monogenic SRNS was 0%. Multivariable analysis showed that MCD histology (OR; 95% CI: 5.6; 1.3-23.7) compared to FSGS predicted disease recurrence.

Conclusions: Pediatric patients with MCD and LSRNS are at higher risk of disease recurrence following kidney transplantation. Based on our findings, it is possible to use genetic findings, native kidney biopsy findings and pattern of therapy response prior to kidney transplant to stratify patients with SRNS undergoing renal transplant into a low-risk group (monogenic NS), a medium-risk group (FSGS on native kidney biopsy and PSRNS), and a high-risk group (MCD on native kidney biopsy and/or LSRNS).

Funding: NIDDK Support

FR-PO1172

Renal Recovery and Prognostic Factors in Children Following Liver Transplantation: A Single Center Experience

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Background: Progression to chronic renal disease (CKD) is highly prevalent in adults following liver transplantation (LT) with a profound impact on patient survival, assuming that the prevalence of renal dysfunction is also considerably high in children. We report our experiences in a large paediatric transplant center and try to identify risk factors leading to a decline of renal function.

Methods: We retrospectively analyzed all 161 LT patients at our hospital from 2010 to 2017 (84 female). Medical records were reviewed for demographic, laboratory and clinical data. Patients were stratified into groups < 5 kg, 5-10 kg and > 10 kg. Change of renal function (slopes) was defined as loss/increase of GFR using the Schwartz formula and progress to renal failure within the first 4 weeks after LT was stratified according to the pRIFLE criteria. Mean observation time was 31 months (6 to 93 months).

Results: Out of 161 patients, 134 were younger than 6 years at time of LT (74%). Average survival time in 5 years was 86%. CKD preexisted in 16 children (10%), nine undergoing dialysis before LT (5.5%). 7/145 proceeded to ESRD over 5 years (4.8%). Other patients developed pRIFLE I (21%), II (23%), III (11%) within the first 4 weeks after LT. Average GFR within 4 weeks after LT was lower in group <5kg (66 ml/min/1.73m^2) compared to 81 (5-10 kg) and 114 (>10kg) ml/min/1.73m^2. All GFR-slopes remained stable and were not significantly different from each other (<5kg: 0.01 vs. >5-10kg: 0,01 vs. >10kg: -0,35 ml/min/1,73m^2/28 days). Within the entire observation time, all GFR-slopes showed a significant increase (<5kg: 14 vs. 5-10kg: 4 vs. >10kg: 3 ml/min/1.73m^2/year). Regarding potential risk factors, 16 patients (10%) exceeded ABPM mean blood pressure values higher the 95th percentile, and 8 patients (5%) higher the 75th percentile. All other patients remained lower the 50th percentile. Albuminuria was rare (4%) and did not occur significantly more often in any subgroup. No independent risk factors for a decline of GFR to ESRD could be detected in all patients.

Conclusions: In contrast to adults, progress to ESRD in children following LT was rare (<5%) and most patients developed a normal GFR. Independent risk factors could not be defined. However, renal function, hypertension and proteinuria should be monitored regularly.

FR-PO1173

Trends in Living Donation by Race/Ethnicity in Pediatric ESRD

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Background: Living donation is the best treatment option for children with ESRD, yet living donation rates have declined. With increased knowledge about living donor (LD) risk, racial/ethnic disparities in LD rates for children may have increased.

Methods: We performed a retrospective cohort study of children <18 yrs with incident ESRD 1995-2015 in the US Renal Data System. Using Cox models, we examined associations between race/ethnicity, LD transplant rates and changes over time, adjusting for recipient and donor factors. We also examined donor-recipient relationships by race/ethnicity.

Results: Among 14,926 children, 46.8% received LD transplants. Overall, LD rates declined by 3%/yr since 1995, however the LD rates for Asian children remained stable. Notably, differences in LD rates by race/ethnicity persisted (Fig. 1). Compared with non-Hispanic whites (NHW), Hispanic children were 50% less likely (HR 0.50 (0.45-0.55)), Asians 57% less likely (HR 0.43(0.35-0.52)) and Blacks 70% less likely (HR 0.30 (0.27-0.34)) to receive LD transplant within 2 yrs. of ESRD onset. While 96% of NHW recipients had white donors, only 59% of Asian recipients had Asian donors (p<0.001). Asian recipients were more likely to have non-related donors and Black recipients were less likely to have parents as donors (p< 0.001, Table 1).

Conclusions: Stark racial/ethnic disparities in pediatric access to LD transplant persist. Differences in donor-recipient relationships as contributors to these disparities should be further explored.

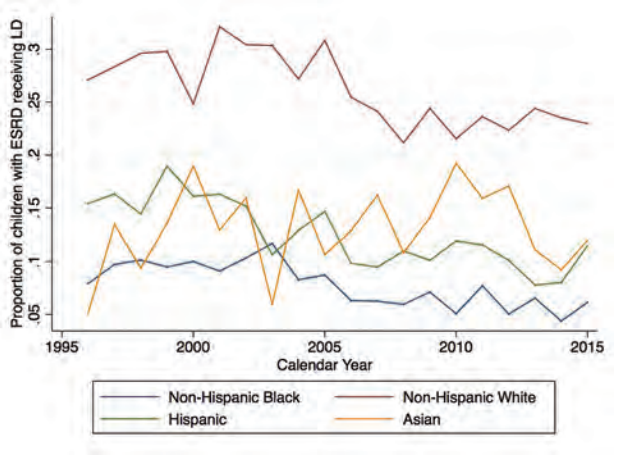

Fig.1. Time trends in LD transplant by race/ethnicity, 1995-2015.

Table 1: Characteristics of donor-recipient pairs

%	NHW recipient N=4710 (67.4%)	Black recipient N=876 (12.5%)	Hispanic recipient N=1197 (17.1%)	Asian recipient N=205 (2.9%)	P-value for difference
Median living donor age [IQR]	39 [32, 44]	35 [28, 42]	36 [30, 42]	39 [32, 44]	<0.001
Living donor race (%)					
White (70)	**96**	11	17	27	<0.001
Black (11.5)	0.8	**86**	0.8	2	
Hispanic (15.8)	2	3	**81**	6	
Asian (2.3)	0.6	0.3	0.7	**59**	
Other (0.5)	0.3	0.5	0.2	5	
Male donor Living	44	41	40	45	0.047
Living donor relationship to recipient					<0.001
Parent	69	**63**	69	65	
Sibling	7	13	14	8	
Other related	11	11	9	8	
Non-related	13	13	8	**19**	

Table 1. Donor-recipient characteristics by race/ethncity.

FR-PO1174

Risk Factors for Early Readmission Post Pediatric Kidney Transplantation

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Background: Early hospital readmissions are associated with morbidity, mortality and significant health care costs. To date, no published studies have evaluated risk factors for early readmission following pediatric kidney transplantation.

Methods: Retrospective chart review was performed for all pediatric kidney transplant recipients from 2012 – 2017 at the University of California, San Francisco. Early hospital readmissions were defined as any unplanned admission within 30 days of being discharged from the hospital following a kidney transplant; admissions for elective procedures were excluded. Baseline characteristics evaluated included age, insurance, race, education, prior dialysis, donor type, cold ischemia time, prior transplantation, peritoneal placement of transplant, immunosuppressive regimen, length of hospital stay, weekend/holiday discharge, discharge medications, tacrolimus level, hemoglobin, albumin, and creatinine at discharge. Analysis was done using Student t-test and Pearson chi square test.

Results: There were 90 pediatric kidney transplant recipients. The rate of early readmission was 25%. Causes for readmission were: elevated creatinine (26%), vomiting/diarrhea with dehydration (26%) and hypertension associated complications (9%). Pre-transplant dialysis significantly predicted readmission (Hemodialysis 43.7%, peritoneal dialysis 21.4% and pre-emptive transplants 10.3%, p<0.05). Racial distribution among readmissions was also found to be statistically significant (Blacks 62%, Whites 21%, Hispanic 23%, Asian 0%, other 42%, p=0.05). Other non-significant predictors for readmission included: public versus private insurance (30% vs 16%, p=0.8) and number of anti-hypertensives at time of discharge (36% on 2 or more medications vs 18% on none, p=0.3). No difference was seen in readmission rates based on age, education, donor type or immunosuppressive regimen.

Conclusions: The rate of early readmissions for our pediatric population was less than for adult patients (25% vs 30-36%). The most common causes for readmission were elevated creatinine and vomiting/diarrhea. Prior dialysis and race significantly predicted readmission. Targeted interventions for patients identified as being at risk based on these results may help reduce the rate of readmissions for pediatric patients after kidney transplantation.

FR-PO1175

Change in Kidney Function for Three Years in Pediatric Kidney Transplant Recipients

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Background: Few data show the changes in graft function after kidney transplantation (KTx) in children. We retrospectively investigated the change in kidney function for three years in pediatric kidney transplant recipients based on estimated glomerular filtration rate (eGFR).

Methods: We enrolled the recipients aged 2–15 years who underwent living-donor KTx at our institution between 2009 and 2017. We excluded the recipients with primary non-function (n=2), low muscle bulk due to being bedridden (n=2). In 56 recipients, changes in eGFR were evaluated for three years after KTx. eGFR was calculated by the creatinine-based equation for Japanese children and adolescents aged 2–18 years.

Results: During follow-up, patient and graft survival rates were 100%. Twenty-five recipients (44.6%) experienced acute rejection with treatment. The mean age of recipients and donors were 8.1±4.0, and 41.1±7.8 years old. Congenital anomalies of the kidney and urinary tract (n=34) was the most common disease for end stage kidney disease. The mean eGFR (ml/min./1.73m^2) at 1, 4, 12, 24, and 36 months (M) after KTx were 85.1±18.6, 73.4±16.6, 67.0±15.7, 65.3±15.0, 66.4±18.9, respectively. eGFR at 1 and 12 M post-transplant showed significant difference ($p<0.0001$, paired t-test). eGFR became stable at 12 M post-transplant and thereafter. In 17 recipients (30.4%), eGFR at 36 M was below 60. On multivariable logistic regression analyses, eGFR <60 at 1 M after KTx was the impact factor related to eGFR <60 at 36 M.

Conclusions: Approximately 70% of the recipients showed kidney function equivalent to over CKD stage 3 at three years after KTx, though eGFR declined within the first year post-transplant. To preserve long-term kidney graft function, the recipients with low eGFR at one month post-transplant need careful management.

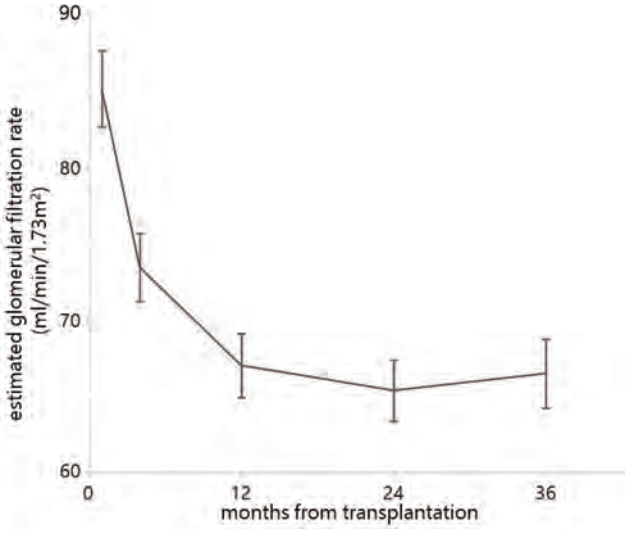

Fig. Change of the mean eGFR of 56 pediatric recipients after living-donor KTx.

FR-PO1176

Co-Produced Videos to Improve Knowledge Among Patients and Caregivers with a Kidney Transplant

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Background: The Improving Renal Outcomes Collaborative (IROC) is a networked learning health system of 23 pediatric centers committed to improving the health, longevity, and quality of life of children with kidney disease. IROC's Community Engagement Workgroup (CEW) was established to engage patients and caregivers in co-production to achieve health care goals. In line with IROC's first aim to improve blood pressure (BP) control in children with kidney transplants, the CEW implemented a project to raise awareness of BP management amongst its members using video content.

Methods: CEW members created a list of questions regarding the relevance of BP control to health, accurate BP measurement, and treatment of high BP. They then co-produced 10 short videos of pediatric nephrologists teaching these topics on camera. Videos were distributed to patients and caregivers and multiple-choice questions were used to assess knowledge of topic areas before and after viewing the content. Open-ended questions prompted viewers to describe future behaviors influenced by watching each video. Paired responses were analyzed to determine knowledge of topic areas most improved by the video content. Thematic analysis of free-text responses was used to identify future behaviors.

Results: A total of 23 participants (3 patients, 14 caregivers, 4 healthcare professionals and 2 caregiver/healthcare), viewed a median of 5 (IQR 3-9) videos. Videos had on average 11.4 ± 1.1 viewers who submitted paired pre- and post-video responses. Participants demonstrated the largest improvements in knowledge about the prevalence of high BP after kidney transplant (correct response 7% pre- vs 92% post-video), ideal BP levels (45% vs 100%), and the nutrient focus of the DASH diet (25% vs 100%). Future behaviors stimulated by the content viewing included BP self-monitoring, implementation of lifestyle modification, and desire to have more in-depth conversation with healthcare providers about BP management.

Conclusions: Co-produced videos improved BP knowledge among participants who also appear motivated to engage in self-care and conversations with healthcare providers about lifestyle modifications for BP control. We intend to use the feedback from this pilot to create a patient education program at IROC centers using the Knowledge-Attitude-Behavior (KAB) model.

FR-PO1177

Ethnography: A Novel Approach to Improving Care for Pediatric Kidney Transplant Recipients

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Background: Current models of care for pediatric kidney transplant recipients (pKTRs) may be ill-suited to meet their needs, leading to suboptimal utilization, barriers to adherence, and psychosocial stressors that adversely affect both patients and families. Optimizing care delivery for these complex patients requires insight into their social and emotional needs, perceptions of care, and future goals. Aiming to inform design of an improved system of care, we assessed convergent and divergent perceptions of pKTRs and their families.

Methods: We conducted a qualitative analysis of semi-structured interviews and ethnographies with pKTRs (n=12; ages 11-22) and caregivers (n=15) identified in the Improving Renal Outcomes Collaborative (IROC). Participants were selected and stratified according to medical and psychosocial complexity, and level of engagement with their transplant team. Audio recorded interviews were transcribed and assessed for themes using a grounded theory approach.

Results: *Considerations around Kidney Care* was the major theme that emerged from both pKTRs and caregivers, particularly experience on dialysis and learning about kidney disease care. Other cross-cutting themes included maintaining a sense of normalcy; inability to recognize signs of kidney disease prior to transplant; and reluctance to meet other pKTRs. Major themes more common among caregivers were *Family Dynamics* (e.g. caregiver stress/strain and consideration of family members as organ donors; $p<0.001$) and *Life Stressors* (e.g. moving or traveling for a child's transplant care; $p<0.001$). More common among patients were *Education/Social Development* (e.g. impact of disease on school and extracurricular activities; $p<0.001$), and *Transition of Care* (e.g. transition to an adult provider; $p<0.001$). Co-produced with patients and families, ethnographies were used to generate thematic personas to aid in the development of IROC, our learning health system designed to improve health and quality of life for pKTRs.

Conclusions: Understanding patient and family motivations and needs are fundamental to designing new, more effective systems of care. Such systems should address both common motifs as well as those specific to patients and caregivers in order to foster engagement and shared decision making between patients and the medical team.

FR-PO1178

Proteinuria in Children and Adolescents Following Renal Transplantation: Results from the Cooperative European Pediatric Renal Transplant Initiative (CERTAIN)

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Background: Proteinuria is a major risk factor for the progression of chronic kidney disease and - in patients after renal transplantation (RTx) - associated with higher mortality and an increased risk of graft failure. Pediatric studies are rare, often limited due to small patient numbers and present heterogenous results regarding prevalence and outcome.

Methods: Data of 195 children (mean age at RTx 10.6±5.2 years, 60% male) from the CERTAIN registry was analyzed 3 months, 1 and 3 ys post RTx. Prevalence, quantity and quality of proteinuria was correlated with GFR and potential influencing factors were evaluated (underlying disease, BMI, dialysis, HLA-mismatch, cold ischemia time, immunosuppression (IS), BKV infection).

Results: 77% of patients developed proteinuria >200mg/g creatinine (crea) within 3 months post RTx, 9% of these > 1000mg/g crea; Proteinuria was of glomerular origin in 71% and decreased by 40% within 3 ys. Increasing proteinuria was negatively correlated with GFR especially in the long-term follow-up ($p=0.004$, 3ys post RTx). Patients with glomerulopathies had significantly higher proteinuria ($p<0.001$) after 3ys post RTx. BMI SDS was positively correlated with proteinuria ($p<0.03$) at time of RTx, but this effect did not persist over time. Cold ischemia time was correlated with the extent of proteinuria ($p=0.01$) as well as the number of HLA mismatches. Patients with BKV infection developed proteinuria in 52% (with higher urinary protein excretion compared to BKV negative patients ($p<0.001$). The mode of dialysis and the type of IS did not influence proteinuria

significantly, but we detected slightly higher levels of urinary protein in patients with a history of peritoneal dialysis and in mTOR inhibitor-based IS, respectively. Proteinuria did not correlate with hypertension, duration of dialysis, CMV/EBV or urinary tract infections.

Conclusions: The majority of pediatric patients developed proteinuria following RTx, Although proteinuria was of only mild to moderate extent in most patients and decreased over time, it was significantly correlated with a reduction of GFR. Proteinuria was associated with several risk factors with the highest impact for a prolonged cold ischemia time, high number of HLA mismatches and BKV infection.

Funding: Clinical Revenue Support

FR-PO1179

Differential Cytokine Profiles for Non-Human Leukocyte Antigen (Non-HLA) and HLA Antibodies in Pediatric Kidney Transplantation

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Background: The inflammatory profiles associated with human leukocyte antigen (HLA) and non-HLA antibodies to G-protein coupled receptors in kidney transplant recipients (KTRs) are unknown. We have recently shown that angiotensin II type 1 receptor antibody (AT1R-Ab) and Endothelin-1 Type A receptor antibody (ETAR-Ab) are prevalent and associated with poor outcomes in pediatric KTRs. We aimed to compare inflammatory profiles of AT1R-Ab, ETAR-Ab, and HLA donor specific antibodies (DSA) in pediatric KTRs.

Methods: 233 blood samples from 65 pediatric KTRs were analyzed. ETAR-Ab (ELISA), AT_1R-Ab (ELISA), HLA DSA (Luminex), and TNF-α, IL-1β, IL-8, IFN-γ, IL-17, IL-6 (Luminex) were measured in blood samples taken at 6 months (m), 12m, and 24m post-transplant and during episodes of rejection. Based on a receiver operating curve analysis, > 10 and >17 units/ml was considered positive for ETAR-Ab and AT_1R-Ab and ≥1000 MFI was considered positive for HLA DSA.

Results: HLA DSA, AT1R-Ab, and ETAR-Ab were positive in 25 (11%), 92 (40%), and 50 (22%) of samples respectively. 96% of samples positive for ETAR-Ab also had AT1R-Ab. All three antibodies were associated with elevations in IL-8 while AT1R-Ab was associated with elevations in all 6 cytokines (Table 1).

Conclusions: AT1R-Ab is associated with a distinct inflammatory profile compared to HLA DSA or ETAR-Ab in the first 2 years post-transplant. Further studies are needed to understand the distinct mechanisms of HLA vs. non-HLA antibody mediated allograft injury.

Funding: Private Foundation Support

Cytokine	**HLA DSA** OR (95% CI)	p-value	**AT1R-Ab** OR (95% CI)	p-value	**ETAR-Ab** OR (95% CI)	p-value
TNF-α	1.6 (0.66 - 3.85)	0.297	2.29 (1.27 - 4.13)	0.006	1.66 (0.81 - 3.42)	0.166
IL-1β	1.45 (0.78 - 2.7)	0.236	1.87 (1.25 - 2.79)	0.002	1.48 (0.92 - 2.39)	0.106
IFN-γ	1.4 (0.86 - 2.28)	0.176	1.6 (1.14 - 2.23)	0.006	1.67 (1 - 2.78)	0.052
IL-17	1.44 (0.78 - 2.65)	0.241	1.67 (1.1 - 2.55)	0.017	1.47 (0.87 - 2.48)	0.150
IL-8	1.74 (1.74 - 1.75)	<0.001	2.16 (1.47 - 3.17)	<0.001	2.03 (1.22 - 3.39)	0.007
IL-6	1.93 (0.92 - 4.03)	0.081	2.04 (1.26 - 3.31)	0.004	1.71 (0.95 - 3.05)	0.072

Table 1: The Association of HLA DSA, AT1R-Ab, and ETAR-Ab and Serum Cytokines. Logistic Regression Models controlled for patient level random effects are shown. Cytokines were log transformed prior to analysis. OR, odds ratio; CI, confidence interval

FR-PO1180

Weight Changes on Dialysis and During Transplant Associate with Mortality Risk in Children

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Background: Few studies have explored how weight change during ESRD may associate with survival in children. Our objective was to examine the association between weight changes during RRT and risk of death in a prevalent cohort of children with ESRD. Secondarily, we sought to determine whether the association between weight changes and mortality would differ based on ESRD treatment modality (dialysis vs. transplant).

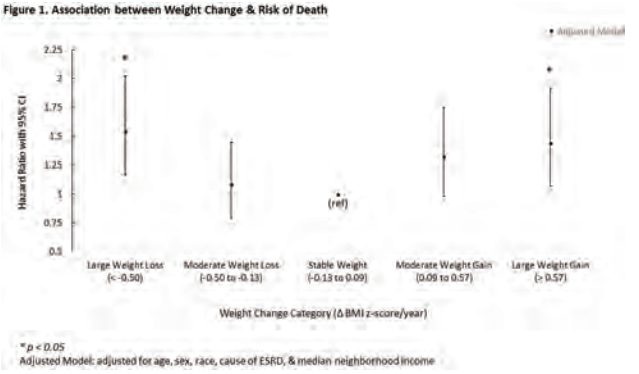
Methods: We performed a retrospective cohort study using data from the Pediatric Growth and Development Special Study, a longitudinal study within the United States Renal Data System that followed children with ESRD over a 3-year period. The primary predictor was annualized BMI z-score changes divided into quintiles. Cutoff values for these BMI z-score changes were -0.50, -0.13, 0.09, and 0.57, and the middle quintile served as the reference category. Outcome was all-cause mortality. We used Cox models (adjusted for age, sex, race, cause of ESRD and median neighborhood income) to examine the association between the predictor and outcome and to test for an interaction with treatment modality.

Results: We included 1,182 children followed for a median duration of 19 years, of whom 35% died during follow-up. Mean age was 15 years, 40% were female, and 21% had CAKUT as the cause of their ESRD. We found a U-shaped association between weight change and mortality (Figure 1): both large declines in BMI z-score (>-0.50 per year) and large gains in BMI z-score (>0.57 per year) were associated with an increased risk of death. No interaction was noted between annualized BMI z-score change and treatment modality (p=0.15). Results were similar when follow-up was limited to 5 and 10 years after the last weight and height measurements were obtained.

Conclusions: Weight gain and weight loss after dialysis initiation or during transplant are strong predictors of long-term survival for children with ESRD. Maintenance of a stable weight may be associated with better survival in children receiving RRT, regardless of RRT modality.

Funding: Private Foundation Support

Figure 1. Association between Weight Change & Risk of Death



*$p < 0.05$
Adjusted Model: adjusted for age, sex, race, cause of ESRD, & median neighborhood income

FR-PO1181

Executive and Intellectual Functions of Young Hungarian Kidney Transplant Recipients

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Background: CKD is frequently associated with impaired executive functions, intellectual problems and atypical development in children and adolescent. Results of the last decade indicate that neuropsychological outcomes with kidney transplant (Tx) recipients are more favorable than was detected in earlier reports. However, data on factors associated with neurocognitive dysfunctions in Tx recipients are limited.

Methods: We conducted a cross-sectional analysis comparing digital measuring of executive functions (using Wisconsin Card Sorting Test /WCST/, Corsi Test /Corsi/, Stroop Effect Test /STROOP/) of 26 kidney transplant recipients by matching them in pairs on gender, age, maternal education and IQ with healthy controls. Socio-demographic characteristics, laboratory data and comorbidities have been collected.

Results: The average age was 17±2 years, 73% was male, the average estimated GFR was 60±14 ml/min. Kidney transplant adolescent had a below average overall IQ (WISC-IV/WAIS-IV IQ=85±17). The first preliminary data on executive functions suggest no significant differences between the achievement of transplant and IQ matched healthy pairs in visuo-spacial short term memory (Corsi) (F=2.37, p=0.41), cognitive flexibility (WCST) (F=0.31, p=0.95) and selective attention and inhibition (STROOP) (F=2.97, p=0.32). All IQ domain of Tx recipients had significant negative correlation with transplant vintage (Full IQ scores: R=-0.52, p<0.01). The intellectual function had also inverse correlation with cumulative lifetime length of hospitalization (R=-0.47, p=0.01). Hospitalization time and maternal education had strong negative correlation (R=-0.57, p<0.01) while IQ and maternal education had no relation in our sample of Tx group (R=0.31, p=0.13). Cognitive flexibility (perseverative (R=-0.42 p=0.03) and conceptual level responses (R=-0.59 p=0.001) indicated a strong inverse correlation with lifetime cumulative dialysis vintage in Tx recipients.

Conclusions: Young kidney transplant recipients have impairments of intellectual function that are associated with transplant vintage and lifetime hospitalization. IQ matched transplant and healthy groups had no differences in executive functions. Higher dialysis vintage of Tx adolescents indicated lower cognitive flexibility.

Funding: Government Support - Non-U.S.

SA-PO001

Outcomes of Belatacept Regimen with the Use of Precision Medicine in Kidney Transplantation

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Background: Belatacept is a costimulation blocker that has been increasingly used as maintenance immunosuppression to improve long term outcomes in kidney transplant recipients. Since acute rejection in patients on belatacept have been noted to be more frequent and histologically more severe, identifying the select population of patients with Precision Medicine who will benefit from belatacept is important. We investigated pretransplant recipient immune profiles to determine which lymphocyte populations would be the best predictor in identifying patients who will be at lowest risk for costimulation blockade-resistant rejection.

Methods: We prospectively enrolled 64 kidney transplant recipients (44 deceased; 20 living donors) at our center to receive denovo belatacept from August 2012 to March 2017. PMBCs were collected prior to transplantation and at the time of cause and protocol biopsies. All patients received thymoglobulin for induction with belatacept 10mg/kg administered on POD 1, 4, 14, 28, 56, and 84. Monthly maintenance dose of 5mg/kg was given starting week 16. Patients were initially on MMF but were converted to everolimus after 1 month. Prednisone was maintained on 56 patients and withdrawn on 8 patients. Protocol biopsies were performed at 6 months.

Results: On cause biopsies, 3 patients were noted to have ACR 1a (at 4 weeks, 6 weeks, 4 months), 1 with ACR 1b (at 2 months), 3 with ACR 2b (at 2 months, 3 months, 9 months), 1 with AMR (at 4 months), and 1 with simultaneous ACR 1a and AMR (at 7 months). In addition, 16 patients were found to have borderline rejection on protocol biopsies. 28 patients did not have any inflammation on biopsies. 56 patients remained on belatacept and 8 patients were converted to tacrolimus (1 patient was switched to tacrolimus due to poor intravenous access and not due to rejection). 6 of the 9 rejections occurred in those who were on MMF and not on mTORi. 2 of 9 patients who were noted to have rejection were patients on steroid withdraw.

Conclusions: CD28-CD8 T cells are associated with belatacept-resistant rejection since these are memory cells unaffected by CD28 blockade. Pretransplant immunotyping and functional assessment of circulating lymphocytes may provide a useful tool for selection of patients suitable for belatacept therapy.

At 12 months (median):

	Total (N=64)	Acute rejection (N=9)
Serum creatinine (mg/dL)	1.13	1.2
eGFR (mL/min)	65	46
Urine protein/creatinine (g/g)	0.195	0.29

SA-PO002

One Year Kidney Transplant Outcomes Using Belatacept and Sirolimus Maintenance Immunosuppression

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Background: Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppression fafter kidney transplantation, but are associated with adverse events when used long term. Belatacept, a CTLA4-Ig fusion protein, is a costimulation blocker that prevents T-lymphocyte activation. It provides effective immunosuppression post kidney transplant and allows CNI free immunosuppression. Typical regimens include belatacept with mycophenolate mofetil and steroids, and have been associated with higher acute rejection rates than CNI based regimens. We describe our experience using a belatacept and sirolimus based maintenance immunosuppression regimen.

Methods: This is a retrospective analysis of patients treated with belatacept maintenance therapy at a single center. Patients were eligible for belatacept if: age<70, BMI<35, EBV IgG positive, no donor specific antibody. They received alemtuzumab induction (30 mg, intravenously), infusion of belatacept (10mg/Kg Day 0,4 and end of week 2,4,8, and 12; then 5 mg/kg every month, and oral sirolimus 2mg daily, dose adjusted for 24-hour trough 8-10ng/ml.

Results: Baseline demographics are outlined in table 1. There was 100% patient and graft survival at one year. There was no delayed graft function. Acute rejection occurred in 13.6%. Median GFR at one year was 55ml/minute. Median protein/creatinine ratio was 262 mg/g Creatinine. There were 25 infections in 13 patients. There were 9 viral infections. CMV and BK virus occurred at a rate of 13.6% and 13.6%, respectively. There were 10 bacterial infections-the majority (80%) were urinary tract infections. There were 6 fungal infections-all were mucocutaneous infections. There were no cases of post transplant lymphoproliferative disease.

Conclusions: A combination of costimulation blockade with belatacept, alemtuzumab induction and daily sirolimus enables use of a CNI and steroid free maintenance immunosuppression regimen in select patients. There were excellent one-year graft outcomes, and it was well tolerated with an acceptable side effect profile. Longer follow up is needed.

Baseline Demographics

Demographic	
Age (mean)	51 years
Gender (Male)	68.2%
Race African american Other	 18.2% 82.8%
Donor Type Living Related Living Unrelated Deceased	 50% 45.5% 4.5%
Panel Reactive Antibody at time of transplant (mean) Class I Class II	 4.4% 7.2%

SA-PO003

The Epidemiologic Burden of Tacrolimus Variability Among US Kidney Transplant Recipients

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Background: Within-patient tacrolimus level variability has been shown to be a risk factor for *de novo* donor specific antibody (DSA) formation and increased death censored graft failure (DCGF) among kidney transplant recipients in single-center reports. We evaluated the correlation between subtherapeutic tacrolimus levels and tacrolimus variability in a large national data set.

Methods: We evaluated all tacrolimus levels drawn at any LabCorp® facility in the United States, between November 2011 and September 2017, with a diagnosis code for kidney transplant. Levels drawn within the six months after the earliest value were excluded, to exclude patients with new allografts. Patients were included if there were at least three tacrolimus levels thereafter. Tacrolimus variability was calculated as the coefficient of variability of the tacrolimus levels as: 100 x (standard deviation/mean) and compared to a risk threshold of 30% (Rodrigo et al., 2016). The percentage of subtherapeutic (< 4.0 ng/dL) tacrolimus levels (%subT) was calculated for each subject. The associations of tacrolimus variability with %subT were assessed with correlation analysis and linear regression.

Results: There were 410,257 tacrolimus levels among 27,375 patients, of whom 43.1% were women. Mean age was 52.5±14.4 years. Median follow-up was 26.5 (IQR=12.8-46.1) months. The median number of tacrolimus levels per patient was 11 (IQR=6-20). Median tacrolimus variability was 30.6%, with 51.6% of patients exceeding 30% variability. Median %subT was 11.1% (IQR=0-30.8%), and 34.3% of patients had no subtherapeutic levels. The correlation coefficient between tacrolimus variability and %subT was 0.253 (P<0.001). In linear regression, tacrolimus variability increased 1.86% for each 10% increase in %subT (P<0.001), but R-squared for this model was only 0.06.

Conclusions: More than half of established kidney transplant patients from a large national sample exhibited a level of tacrolimus variability that has been previously associated with 2 to 3- fold increased hazards of DSA and DCGF. Tacrolimus variability has an association with subtherapeutic levels, but likely reflects a complicated constellation of clinical factors and scenarios that merit further study.

SA-PO004

Calcineurin Inhibitors, Macrolides, and the Risk of Adverse Drug Events in Kidney Transplant Recipients

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Background: Calcineurin inhibitors (CNI; cyclosporine, tacrolimus) are critical for kidney transplant immunosuppression, but have multiple potential drug interactions, such as with macrolide antibiotics. Clarithromycin and erythromycin inhibit CNI metabolism and increase the risk of CNI nephrotoxicity, while azithromycin does not.

Methods: We conducted a retrospective cohort study using linked healthcare databases in Alberta, Canada to study kidney transplant recipients from 2008-2015. We identified CNI-macrolide co-prescriptions and compared outcomes in those who received clarithromycin/erythromycin vs. azithromycin. The primary outcome was a composite of all-cause hospitalization, acute kidney injury (creatinine increase ≥0.3 mg/dL or 1.5-times baseline), or death within 30 days of the macrolide prescription.

Results: Of the 293 recipients who were co-prescribed a CNI and a macrolide, 38% (n=112) were prescribed clarithromycin/erythromycin while 62% (n=181) were prescribed azithromycin. Over half of the clarithromycin/erythromycin prescriptions were from general practitioners. There was no significant difference in the primary outcome between the two groups (17% vs. 11%, p=0.11); however, the risk of all-cause hospitalization was 3-times higher in the clarithromycin/erythromycin group than in the azithromycin group (10% vs. 3%; odds ratio [OR] 3.18, 95% CI 1.14 to 8.84, p=0.02). The odds of having an outpatient serum creatinine measurement within 30-days of the macrolide prescription were 41% less likely for clarithromycin/erythromycin users compared to azithromycin users (56% vs. 69%; OR 0.59, 95% CI 0.36 to 0.96, p=0.03). Although there was no difference in acute kidney injury between the two groups, there was a significantly greater decrease in eGFR in the clarithromycin/erythromycin group compared to the azithromycin group (-5.4 vs. -1.9 mL/min/1.73 m^2, p<0.05).

Conclusions: In conclusion, clarithromycin and erythromycin were frequently co-prescribed in kidney transplant recipients on CNIs despite known drug interactions. Clarithromycin/erythromycin users were at higher risk of hospitalization compared to azithromycin users. Safer prescribing practices in kidney transplant recipients are warranted.

SA-PO005

Trough Tacrolimus Levels in Kidney Transplant Recipients and Non-Melanoma Skin Cancer Risk over Follow Up

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Background: Whether Tacrolimus exposure is independently associated with non melanoma skin cancer (NMSC) incidence has not been fully characterised.

Methods: Retrospective analysis of the Irish National Kidney Transplant database linked with laboratory data from clinical practice. Generalised estimating equations with random effects were used to investigate repeated measures of trough Tacrolimus levels tested in clinical practice in recipients (as a time-varying covariate) and NMSC development. Exposure to Tacrolimus was also calcuated using the trapezoid rule to calcuate area under the curve (AUC), and time-averaged trough values. SAS v9.4 was used for data analysis.

Results: N=1540 kidney transplant recpieints were included, 95% of whom were deceased donor transplants and 41% female. 38% of donors were female. NMSC development (N=188), was independently associated with serum trough Tacrolimus levels over follow up (see table 1). However this association was not significant after adjusting for era of transplantation. This was true both of serum tacrolimus as a time-varying parameter and AUC Tacrolimus. Factors such as mean, median, min, max, and variability in Tacrolimus were not associated with NMSC overall. Limiations include possible confounding by overall imunnosupressive burden, survivor bias as well as the fact that follow up length and frequency of testing varied for each participant.

Conclusions: From repeated measures analysis of clinical practice laboratory data, while Tacrolimus exposure as measured by trough values and AUC associate with NMSC development over follow up, this association is attenuated after accounting for transplant vintage.

Results of generalized estimating equation analysis with trough Tacrolimus levels as a time-varying covariate

Parameter	Estimate	Standard error	P value
Intercept	4.05	0.58	<.001
Tacrolimus trough	0.006	0.003	0.005
Recipient age	0.06	0.008	<.001
Recipient sex (female)	0.69	0.24	0.004
Number of kidney transplants	0.73	0.2	0.0003
Biopsy proven rejection within year 1 (clinical need)	0.06	0.27	0.83
PRA	0.007	0.004	0.09
Updated estimates after adjusting for era of transplantation and an interaction between era and Tacrolimus trough levels			
Tacrolimus trough	0.007	0.004	0.08
Era (for Era 1)	2.19	0.49	<.001
Era by Tacrolimus trough interaction	0.009	0.005	0.08

SA-PO006

Outcomes in Simultaneous Pancreas Kidney Transplant in the US Stratified by Induction and Use of Corticosteroids

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Background: Simultaneous Pancreas Kidney (SPK) transplantation is an excellent option for patients with significant renal impairment and diabetes. Outcomes for SPK have improved over the past decade. However, the ideal immunosuppression and induction remains unclear. We sought to analyze outcomes of graft loss and death as stratified by induction and use of low dose corticosteroid.

Methods: Between 2000-2016, 14676 SPK transplants were analyzed in the Scientific Registry of Transplant Recipients (SRTR) database. Groups were made by no induction, IL-2 antagonism, anti-thymocyte globulin (ATG), and alemtuzumab induction with (CCS) and without steroids (CSW). We adjusted for multiple variables including donor age, recipient age, PRA, length of time on dialysis, sex, race, history of heart disease, and HLA mismatches. We analyzed HR for death, kidney and pancreas allograft loss. Adjustment factors included: era; donor and recipient age, sex, race, weight and number of HLA mismatches; recipient time on dialysis, comorbidity, and panel reactive antibodies.

Results: Mean follow up for the cohort was 7.4 years. Regarding induction and steroid strategies, the likelihood of kidney allograft loss was lowest with CCS/ATG (13.2%, adjusted hazards ratio [AHR] 0.63 [0.53-0.76], P-Value <0.01, Table 1); pancreas allograft loss was least likely with CSW/ATG (15.9%, AHR 0.61 [0.51-0.73], P-Value <0.01, Table 2); death likelihood was lowest with CCS/ATG (12.7%, 0.8 [0.66-0.96], P-Value 0.02, Table 3).

Conclusions: In 14676 SPK transplants from the US, different induction and maintenance steroid strategies were associated with substantial variationin allograft survival and death. Kidney and pancreas allograft survival were longer with corticosteroids and overall survival was longer with CCS/ATG.

Table 1, Kidney Allograft Loss.

	Percent	AHR (95% CI)	P-Value
CSW/No induction	18	1	Ref.
CSW/ATG	14.8	0.78 (0.64-0.95)	0.02
CSW/IL2Ra	19.8	0.92 (0.63-1.35)	0.67
CSW/Alemtuzumab	16.4	0.9 (0.71-1.14)	0.38
CCS/No induction	20.4	0.68 (0.56-0.83)	<0.01
CCS/ATG	13.2	0.63 (0.53-0.76)	<0.01
CCS/IL2Ra	19.4	0.59 (0.49-0.72)	<0.01
CCS/Alemtuzumab	15.9	0.88 (0.68-1.13)	0.32

Table 2, Pancreas Allograft Loss.

	Percent	AHR (95% CI)	P-Value
CSW/No induction	22	1	Ref.
CSW/ATG	15.9	0.61 (0.51-0.73)	<0.01
CSW/IL2Ra	23.5	0.83 (0.59-1.19)	0.31
CSW/Alemtuzumab	16.2	0.65 (0.52-0.81)	<0.01
CCS/No induction	24.9	0.8 (0.67-0.95)	<0.01
CCS/ATG	17.1	0.67 (0.57-0.79)	<0.01
CCS/IL2Ra	23.8	0.69 (0.58-0.82)	0.01
CCS/Alemtuzumab	18.3	0.74 (0.58-0.93)	0.01

Table 3, Death.

	Percent	AHR (95% CI)	P-Value
CSW/No induction	16.4	1	Ref.
CSW/ATG	13.5	0.87 (0.7-1.08)	0.2
CSW/IL2Ra	22.8	1.14 (0.79-1.66)	0.48
CSW/Alemtuzumab	13.5	0.85 (0.66-1.1)	0.21
CCS/No induction	21.4	0.88 (0.72-1.07)	0.2
CCS/ATG	12.7	0.8 (0.66-0.96)	0.02
CCS/IL2Ra	22.4	0.84 (0.69-1.02)	0.08
CCS/Alemtuzumab	12.3	0.92 (0.7-1.22)	0.58

SA-PO007

Utility of Induction Agents in Simultaneous Liver-Kidney Transplantation

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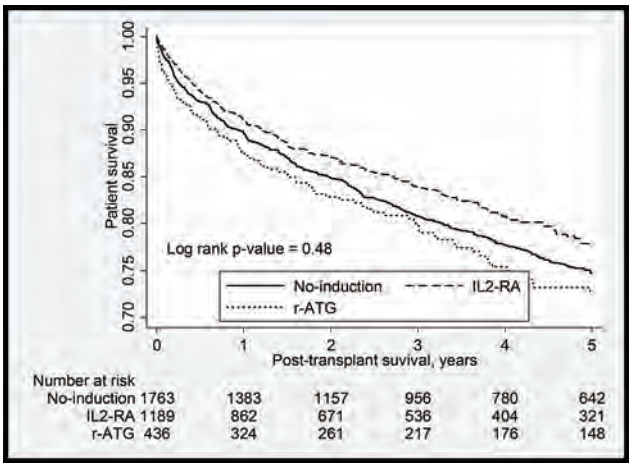
Background: The number of simultaneous liver-kidney transplants (SLKT) and utilization of induction therapy in SLKT is on the rise. There is little published evidence of utility of induction agents when contemporary maintenance immunosuppression regimen with tacrolimus, mycophenolic acid, and prednisone (TAC/MPA/PRED) is used.

Methods: We queried the OPTN registry for adult SLKT recipients in the US between 2002-2016. We divided the cohort into three groups based on induction agent: rabbit anti-thymocyte globulin (r-ATG, N=436), interleukin 2 receptor antagonists (IL2-RA, N=1,189) and no-induction (N=1,763) being the reference group. All patients were maintained on TAC/MPA/PRED at the time of discharge. The primary outcomes were post-transplant all-cause mortality and acute rejection rates at 6 months. Survival rates were analyzed using Kaplan-Meier (KM) method and compared between groups using the log rank test. We estimated hazard and odd ratios for our primary outcomes using a propensity score analysis (inverse probability weighting -IPW) adjusted Cox proportional hazard and logistic regression models.

Results: Compared with no-induction, the multivariable IPW adjusted Cox proportional hazard analyses showed an increased mortality with r-ATG (HR=1.31, 95% CI 1.04-1.65, p-value=0.02). At six-months post-transplant, acute rejection rates (both liver and kidney) were less than 10% and were not statistically significant between three induction categories

based on multivariable IPW adjusted logistic regression analysis. Mortality secondary to infection was statistically higher in r-ATG group.

Conclusions: In SLKT recipients maintained on TAC/MPA/PRED, induction categories were associated with similar rejection rates at six-months. Compared to no induction, r-ATG appears to increase mortality risk, probably secondary to infections. Benefit of IL2-RA induction in SLKT remains controversial.



SA-PO008

Steroid Maintenance and Outcomes in Kidney Transplant Recipients with Native Kidney Glomerulonephritis: An Analysis of OPTN/UNOS Database

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Background: Kidney transplant recipients with history of native kidney glomerulonephritis (GN) are at increased risk of graft loss from recurrent GN. It is unclear if steroid maintenance could help in preventing recurrent disease and improve outcomes in these patients.

Methods: Using the United Network for Organ Sharing database, we identified adult kidney-only transplant recipients from 2001-2015, who had GN as cause of ESRD, who received induction therapy and were discharged on calcineurin inhibitor/mycophenolic acid with steroid maintenance (SM), n=14,610 or steroid withdrawal(SW), n=6, 406. Using a multivariate Cox-model adjusting for donor, transplant and recipient related factors, overall and death censored graft failure rates and patient death rates were compared between the SM and SW groups in patients with GN.

Results: There was significant difference between SM and SW groups in overall graft failure and patient death with a Hazard ratio (95% CI) of 1.10 (1.03-1.19) p-value of 0.009 and 1.21 (1.09-1.34) p-<0.001, respectively. However, there was no significant difference between the groups for death censored graft failure, hazard ratio 1.04 (0.95-1.14).

Conclusions: Despite a presumed potential benefit of steroid maintenance in reducing the risk for recurrent post-transplant GN, our study found increased risk for death with functioning graft associated with steroid use in KTRs with history of native kidney GN who received peri-operative induction followed by CNI/MMF maintenance. This could be a consequence of enhanced cumulative immunosuppression since these patients were likely exposed to prior immunosuppressive therapy for native kidney GN. Limitations are retrospective study design and possibility of residual confounding.

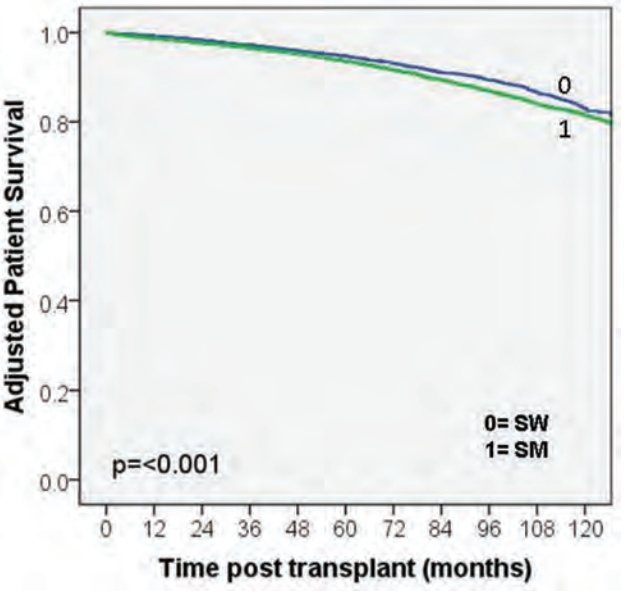

Figure: Patient Survival comparing Steroid Maintenance(SM) vs Steroid Withdrawl(SW) in Transplant Recipients with Glomerulonephritis

SA-PO009

Corticosteroid Avoidance Among Low Immunologic Risk Adult Renal Transplant Recipients of a Living Donor: A Meta-Analysis

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Background: Chronic kidney disease is a devastating condition causing global public health burden with high economic cost to health care systems. Renal Transplantation is the standard of care among other forms of renal replacement therapy. Corticosteroids have a critical role, yet its long-term use is associated with a multitude of adverse effects leading to a greater deal of morbidity and mortality post-transplantation. Most researches include heterogenous group of populations: adult and pediatric, low and high immunologic risk recipient of a living or deceased donor. Studies including deceased organ donor population may not be applicable in our local setting since deceased organ donation in some countries are low, mainly due to scarcity of potential donor. Outcome studies on rejection rates may be varied by the immunological-risk status of the donor-recipient pair. Despite the increasing research, corticosteroid sparing following renal transplantation remains a controversial issue, hence the first meta-analysis to focus on a corticosteroid avoidace among low immunologic risk adult renal transplant recipients of a living donor.

Methods: Systematic literature review of the electronic database Cochrane Library, MEDLINE Ovid SP and Clinical Trials.gov were searched for randomized-controlled trials from September-November 2017. Statistical analyses used was random-effects model.

Results: Included 5 studies met the eligibility criteria (N=788). There is no increased risk in the steroid avoidance group having biopsy proven acute rejection at 12 months (RR:0.72[0.51,1.01]) I^2 10% p=0.05). A significant reduction towards the risk of New Onset of Diabetes Mellitus After Transplantation (RR:0.41[0.25,0.67]; I^2=0% p=0.0003). Likewise, hypertension (RR:0.35[0.12,1.02] I^2=82%p=.05) and Infection (RR:0.69[0.46,1.04]; I^2=71%p=0.07) was reduced post-transplantation.

Conclusions: Steroid avoidance is non-inferior to maintenance group in terms of biopsy proven acute rejection at 12-months. Metabolic complications and risk of infection were reduced post-transplantation as well.

SA-PO010

Clinical Outcomes and Factors Related with Mycophenolate Mofetil Withdrawal in Kidney Transplant Recipients

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Background: Although the most effective initial maintenance immunosuppressants in kidney transplantation (KT) have been known as a combination of calcineurin inhibitor (CNI), steroid, and mycophenolate mofetil (MMF), immunosuppressive regimen has been changed due to several reasons within 1-year after KT. The most common changing pattern was MMF withdrawal, but the clinical course of the kidney transplant recipients (KTRs) after MMF withdrawal was not known clearly. The purpose of this study is to investigate the causes of MMF withdrawal, and the clinical outcomes and factors related with MMF withdrawal in KTRs.

Methods: We retrospectively analyzed the medical records of 626 KTRs performed KT at Dongsan Medical Center between 2000 and 2016. We evaluated the incidence of acute rejection, allograft and patient survival rates, and factors related with MMF withdrawal.

Results: Mean age of KTRs was 44.1 ± 11.6 years. Median time between KT and MMF withdrawal was 6.4 (range, 3.2 – 32.1) months. The most common cause of MMF withdrawal was infection (70.7%), followed by hematologic abnormalities (9.1%), and gastrointestinal trouble (7.7%). The proportion of cytomegalovirus infection was the highest (60.5%) among all infections, followed by BK virus infection (18.4%). The proportion of female KTRs and the incidence of BPAR were significantly higher in the MMF withdrawal arm compared with the non-MMF withdrawal arm (57.7% vs. 34.4%, P < 0.001; 27.4% vs. 8.9%, P < 0.001). Death-censored graft survival and patient survival rates were significantly lower in the MMF withdrawal arm compared with the non-MMF withdrawal arm (P < 0.001; P < 0.001). In multivariate analysis, MMF withdrawal was an independent risk factor for graft failure after adjustment for recipient age, gender, infection, and deceased donor KT (HR 6.058, 95% C.I., 3.172-11.569, P < 0.001).

Conclusions: The incidence of acute rejection, graft failure, and patient mortality rates in KT were high after MMF withdrawal. Therefore, MMF withdrawal should be considered carefully and resumed as soon as possible.

SA-PO011

A Promising Novel Approach with Everolimus-Based Quadruple Maintenance Therapy in Kidney Transplant Recipients with Difficult-to-Treat Rejections

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Background: Chronic rejections and treatment-resistant acute rejections are difficult to treat and lead to progressive loss of graft function in kidney transplant recipients (KTR). Here we review our experience with a novel approach to treat such rejections by adding everolimus, an inhibitor of mammalian target of rapamycin (mTOR) as a "rescue therapy" to the conventional triple maintenance therapy (prednisolone + mycophenolate mofetil + calcineurin inhibitor).

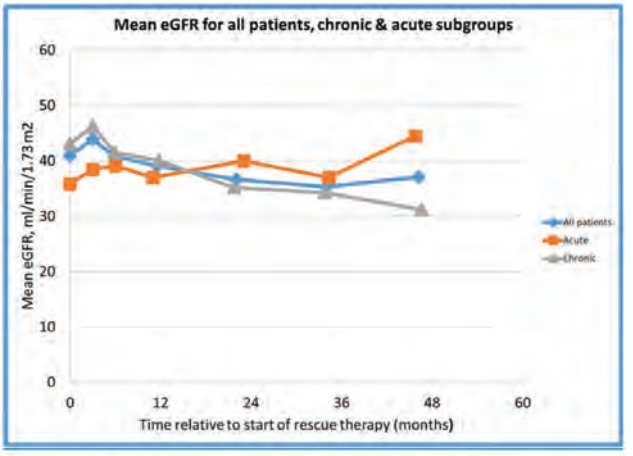
Methods: We analysed in detail electronic medical charts of 34 KTR who received everolimus-based quadruple therapy for biopsy-proven chronic rejections or treatment-resistant acute rejections between 2011-2017. A response to treatment was defined as an improvement/stabilization in the graft function (eGFR slope/year ≥1 ml/min/1.73m2/year).

Results: The results are summarized in the table below. Stabilization in graft function (eGFR) was seen at 48 months after treatment (table + figure), more so in acute as compared to chronic rejection subgroup. Treatment was stopped in 10 patients due to adverse events.

Conclusions: Everolimus-based maintenance quadruple therapy appears to be apromising novel approach for chronic rejections and treatment-resistant acute rejections, both of which are difficult to treat. Further randomized controlled studies are needed to confirm our findings.

Patients receiving quadruple therapy (N=34)

10 with acute rejection (2 acute cellular, 2 mixed cellular and antibody-mediated) 24 with chronic rejection (7 chronic cellular, 6 chronic antibody-mediated, 11 mixed)	
Age in years (mean ± SD)	44.5 ± 18.5
Gender (% males)	53%
Time from transplant to quadruple therapy in months (mean ± SD)	28.4 ± 31
Duration of treatment (mean ± SD)	29.7 ± 18.9
Response to treatment	14/34 (41%)
eGFR in ml/min/1.73m2, at baseline vs 48 months in all patients, acute and chronic subgroups, respectively (mean ± SD)	37.1 ± 19.2 vs 40.9 ± 16.8, 35.9 ± 8.8 vs 44.5 ± 23.1, 47.0 ± 19.0 vs 31.2 ± 15.3 (P=NS for all)
Patient and graft survival at 6 years after start of treatment (Kaplan-Meier)	77% and 51%, respectively. Not significantly different between the acute and chronic subgroups



Patients still on treatment at each point on the curve, n.							
Month:	0	3	6	12	24	36	48
A) All patients	34	33	32	31	27	18	9
B) Acute	10	10	10	10	8	7	4
C) Chronic	24	23	22	21	19	11	5

SA-PO012

Immunosuppression in the Failing Allograft: To Wean or Not to Wean?

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Background: Sensitization is frequent after failed allograft yet there are no clear management strategies for tapering of immunosuppression.

Methods: We performed cross-sectional chart review of patients who were re-listed for repeat kidney transplant after either failed/failing allograft and subdivided them based upon their most recent calculated panel reactive antibody (cPRA) into two groups, LOW PRA, cPRA of <10% (n=18) or HIGH PRA, cPRA 100% (n=20).

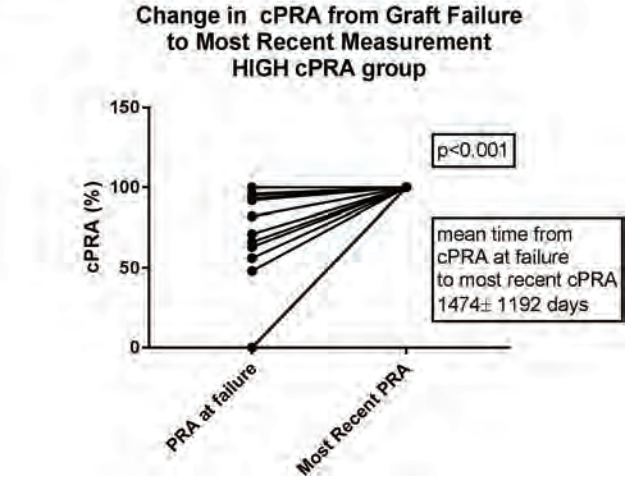
Results: Table 1 describes the baseline characteristics. More patients in the 100% cPRA group had >1 prior transplant (35% versus 5.5%, p=0.05), but there was no difference in other sensitizing events or acute rejection episodes between the groups. All patients in the HIGH cPRA had failed allografts, while 8 patients in the LOW PRA group were pre-emptive and had functioning grafts (p<0.001). In the HIGH CPRA group, 30% had 0 CPRA at time of graft failure and the CPRA significantly increased in this cohort at follow up (Figure1; p<0.001), most of which (75%) were taken off immunosuppression during that time.

Conclusions: Graft failure leading to subsequent tapering of immunosuppression may be a risk factor for increase in CPRA while awaiting re-transplant. There is a need for a more standardized approach to weaning immunosuppression to avoid sensitization.

Table 1

Characteristic	Low cPRA n=18	High cPRA n=20	P value
Age (years)	58.61±11.94	53.35±14.42	0.23
Sex (Female)	6/18 (33.3%)	7/20 (35%)	1.00
Type of Transplant (%Living donor)	8/18 (44.4%)	9/20 (45%)	1.00
Race	9/18 (50%)	3/20 (15%)	0.0354
Sensitization events			
Pregnancy	5/6 (83.3%)	3/8 (37.5%)	0.14
>1 prior transplant	1/18 (5.5%)	7/20 (35%)	0.05
Transfusion	15/18 (83.3%)	18/20 (90%)	0.65
Acute Rejection	5/18 (27.8%)	10/20 (50)%	0.53
AMR	6/7 (85.7%)	9/10(90%)	1.0
Viral Complications	5/18 (27.8%)	3/20 (15%)	0.44
Mean Time to Failure (Days)	2101.0±1383	1796.2±1479.7	0.59
Graft Failure	10/18 (55.5%)	20/20 (100%)	<0.001
cPRA at graft failure (mean±SD)	8.1±16.1	50.26±41.85	0.01
cPRA at last measurement (mean±SD)	1.33±3.04	100±0	<0.001
Mean time from graft failure cPRA to most recent	790±472.2	1474±1192	
Immunosupression at PRA sample			
Prednisone	8/18 (44.4%)	5/19 (26.3%)	0.31
Tacrolimus	12/18 (66.6%)	1/19 (5.3%)	<0.001
MMF	8/18 (44.4%)	1/19 (5.3%)	<0.001
Immunosupression at Graft Failure			
Prednisone	11/18 (61.1%)	14/18 (77.7%)	0.47
Tacrolimus	16/18 (88.8%)	15/16 (93.8%)	1.0
MMF	15/18 (83.3%)	16/16 (100%)	0.23
Any Immunosupression at time of PRA measurement	12/18 (66.6%)	5/20 (25%)	0.02

Panel A



SA-PO013

Trends in Transplant Nephrectomy After Kidney Allograft Failure in the United States

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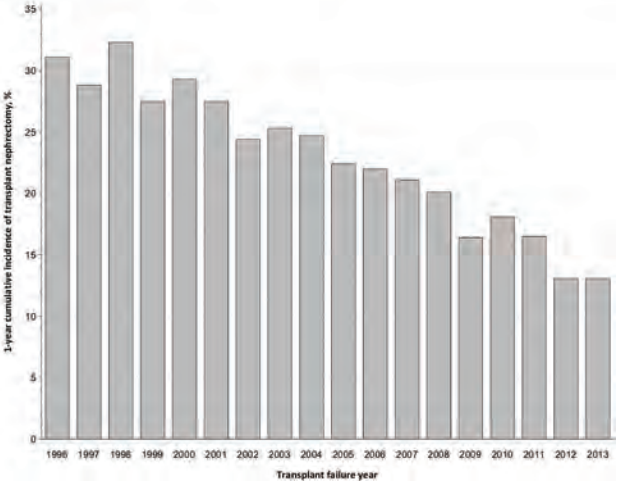
Background: Patients with end-stage kidney disease whose transplants have failed experience worse outcomes compared to those on dialysis not previously transplanted. Following allograft failure, transplant nephrectomy is commonly considered in patients with symptomatic rejection, infections, malignancy, or resistant anemia. Over the years, early allograft nephrectomies have declined due to improved short-term transplant outcomes, but information on the trends regarding nephrectomy among patients with later allograft failure is lacking. This study examined the trends over two decades in transplant nephrectomy following kidney allograft failure.

Methods: We used the US Renal Data System to identify all patients whose first kidney allograft failed >90 days after transplant and who had Medicare fee-for-service at the time. Patients were followed for any allograft nephrectomy within 1-year post-allograft failure. We used Cox proportional hazards models with year of allograft failure as the exposure of interest while adjusting for sociodemographic and health-related patient characteristics. Follow-up was censored at 1 year, loss of Medicare fee-for-service, re-transplantation, or death

Results: We included 29,496 patients whose first kidney transplant failed between 1996 and 2013. Multivariable-adjusted Cox models indicated non-significant hazard ratios (HR) for transplant nephrectomy between 1996 (referent) and 2006; thereafter, the rates of transplant nephrectomy declined considerably with HR of 0.85 (0.73, 1.00) for 2007 and 0.58 (0.49-0.69) for 2013

Conclusions: While adjusted rates of transplant nephrectomy were essentially static between 1996 and 2006, they have decreased considerably thereafter. The reasons for this trend are unclear but may reflect greater recognition of transplant nephrectomy-associated allosensitization.

Figure 1: Trends in 1-year Cumulative Incidence of Transplant Nephrectomy after Failure of a First Kidney Transplant



SA-PO014

Successful Kidney Transplantation in Adults with Antibody Deficiencies

Melanie Schoutteten, Maarten H. Christiaans. *Maastricht University Medical Centre, Eersel, Netherlands.*

Introduction: Antibody deficiencies (common variable immunodeficiency (CVID) and hypogammaglobulinemia (HGG)) associate with a high prevalence of infections, autoimmunity, granulomas and malignancies. Immune suppression in transplantation may amplify this risk. Therefore, in many centers these patients are not considered as suitable candidates for renal transplantation. In literature, only 2 cases of kidney transplantation in CVID patients are reported, both with bad short-term outcome. Because our center has a long track record in kidney transplantation with reduced immune suppression we decided to develop a set of preconditioning criteria and pioneered a transplantation program. We present 1 patient with CVID and 1 with HGG, both transplanted with good clinical and renal outcome.

Case Description: A 43-year old female known with ESRD due to reflux nephropathy and CVID, received a 43-year old DBD-renal transplant. Immunosuppression consisted of tacrolimus and low dose steroids. IVIG was continued. Protocol biopsy at month 3 was normal and steroids were withdrawn. Posttransplant, she had a few recurrent urinary and respiratory infections for which prophylactic azithromycin was given. 3 years posttransplantation patient is still in good clinical condition without malignancies and with a persistent good renal function (eGFR 40ml/min). A 61-year old male with ESRD due to polycystic kidney disease, known with HGG, was transplanted with a 64-year old DCD donor kidney with IGF. Immunosuppression consisted of tacrolimus, low dose steroids for 10 days and mycophenolate mofetil for 3 months. IVIG was continued. He had no acute rejection nor infection besides twice an asymptomatic cystitis. Until now, 2 years after transplantation, he has a persistent renal function of 28.3ml/min.

Discussion: Uniqueness of the cases We present 2 pioneer cases of successful renal transplantation in patients with antibody deficiency. Take away lesson Our data provide a framework for a pre-transplant risk reduction strategy combined with a specific immune suppressive regimen under an umbrella of IVIG supplementation allowing safe kidney transplantation of immune deficient patients.

SA-PO015

Induction Therapy in Elderly Kidney Transplant Recipients with Low Immunological Risk

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Background: Thymoglobulin (ATG) and Basiliximab (BSX) lead to similar rejection rates in low immunological risk patients. ATG could be benefit on Delayed Graft Function (DGF) and allow corticosteroid avoidance, supporting its use in elderly recipients. In contrast, it seems to be associated with infectious and malignancy risk, supporting the use of BSX, especially in recipients with low immunological risk. The benefit-risk balance remains unclear. We thus compared post-transplantation outcomes in elderly recipients with low immunological risk according to their induction therapy.

Methods: We conducted a French multicentric study on non-immunized ≥ 65 years patients receiving a first kidney transplant between 2010 and 2017 and an induction therapy by ATG or BSX. The principal outcome was patient and graft survival. We also studied the cumulative probabilities of infection, first acute rejection episode, malignancy; de novo DSA and eGFR at 1-year post transplantation; and occurrence of DGF. Cox, logistic or linear models were used depending on the studied outcome. To consider possible confounding variables, we weighted the models on the propensity scores.

Results: 204 (53.3%) patients were included in the BSX group, 179 (46.7%) in the ATG group. Average age was respectively 71.0 and 70.5 years. Patient and graft survival at 3 years post-transplantation were 74% (95%CI from 65% to 84%) in the ATG group, and 68% (95%CI from 60% to 78%) in the BSX group. The corresponding HR (Hazard Ratio) equalled 0.96 between the BSX group compared to the ATG group (95%CI from 0.58 to 1.60). The probability of infection at 1-year post-transplantation were 52% (95%CI from 59% to 44%) in the BSX group versus 51% (95%CI from 59% to 42%) in the ATG group, without significant difference. There was no difference in all the others evaluated outcomes as indicated in **Figure 1**.

Conclusions: In elderly recipients, induction therapy by ATG does not seem to lead to poorer outcomes compared to BSX.

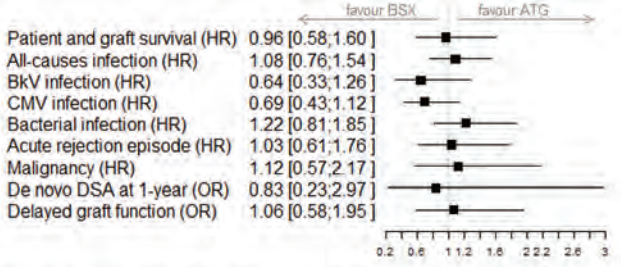

Figure 1: Summary of the relative risks of using Basiliximab instead of Thymoglobulin for the studied outcomes (BSX: Basiliximab; ATG: Thymoglobulin; OR: Odds-Ratio; HR: Hazard-Ratio).

SA-PO016

Is More Intensive Induction Immunosuppression Therapy for Highly Sensitized Kidney Transplant Recipients Better?

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Background: Induction immunosuppression for highly sensitized kidney recipients varies, in particular the use of plasma exchanges (PE) and rituximab following transplantation to prevent antibody-mediated rejection (ABMR) and increase graft survival. We compared two induction strategies for patients undergoing kidney transplantation with a high level (MFI>3000) of pre-formed donor-specific antibody (DSA).

Methods: Our retrospective study included 45 kidney transplant recipients in two French centers, transplanted between 2012 and 2017. All patients had at least one pre-formed DSA (MFI > 3000) within 6 months before transplantation. All patients received anti-thymocyte globulin, a calcineurin inhibitor, mycophenolate mofetil and steroids on the day of transplantation. 22 of these 45 patients also received 5 PE and one rituximab dose (group A), whereas the remaining 23 patients did not (group B). Patients were followed for 1 to 6 years after transplantation.

Results: Comparing group A to group B, recipients' age (48±14 vs. 47±12 years), donors' age (54±16 vs. 57±12 years), cold ischemia time (16±6 vs. 19±7 hours) and MFI of the immunodominant DSA (8735±4192 vs. 10106± 6015) were similar (p=ns for all). There was no overall difference in the rate of biopsy-proven acute rejection at 1 year post-transplantation (n=9, 41% in group A vs. n=7, 30% in group B). ABMR occurred in n=6 vs. n=7 patients, and T-cell mediated rejection was observed in n=3 vs. n=0 patients, respectively in groups A and B. There was no difference in graft survival rate at 1 year post-transplant (91% in group A vs. 83% in group B, p=ns). Finally, the incidence of infectious, anaphylactic, thrombotic or hemorrhagic events was similar between the two groups.

Conclusions: Our study suggests that an intensive induction immunosuppressive therapy using PE and rituximab during early post-transplantation period does not decrease ABMR incidence or improve 1-year graft survival in highly sensitized recipients. An effect of PE on anti-thymocyte globulin pharmacokinetics could not be excluded.

SA-PO017

Risk Factors for Delayed Graft Function in Deceased Donor Kidney Transplantation: Is Intra-Operative Thymoglobulin Preventive?

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Background: Delayed graft function (DGF) is associated with significant adverse outcomes in deceased donor kidney transplantation including lower graft survival. However, risk factors and potential preventive strategies like intraoperative thymoglobulin (ATG) have not yet been fully evaluated.

Methods: We retrospectively examined medical records of 182 first time cadaveric kidney transplant recipients from two major kidney transplant centers from 2014-2016. Risk factors for DGF in recipients were evaluated using multivariate logistic regression analysis.

Results: The mean age was 43±13 years and the majority of participants were male (64%). The rate of intra-operative blood transfusion was 16%. The overall rate of DGF was 24.2%. Mean serum creatinine at discharge and length of hospital stay were significantly higher in patients with DGF compared with those without DGF (2.5 vs. 1.4 mg/dl and 25 vs. 14 days, respectively). Intra-operative ATG was significantly associated with a lower rate of DGF (adjusted odds ratio [AOR], 0.33, 95% CI, 0.11-0.95). Intra-operative transfusion (AOR, 3.7, 95% CI, 1.4-9.9) and diabetes mellitus (AOR, 3.7, 95% CI, 1.5-8.9) were significantly associated with higher risk of DGF. There was no statistically significant association between DGF and recipients' age, sex, body mass index or duration of pre-transplant dialysis.

Conclusions: This study showed that intra-operative blood transfusion and diabetes mellitus were independent risk factors for the development of DGF. Meanwhile, administration of intra-operative ATG was associated with a reduced odds ratio of DGF. Future studies are needed to evaluate the potential role of ATG in DGF-related renal outcomes.

SA-PO018

Role of Liver Transplantation in the Treatment of Fibrinogen Aa-Chain Amyloidosis

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Background: Variants of fibrinogen Aα-chain (AFib) cause the commonest type of hereditary amyloid nephropathy in Europe and probably the US. Fibrinogen production is exclusively hepatic and kidney transplants often fail within 1-5 years with recurrent amyloidosis. The addition of liver transplantation (LT) offers curative potential. We present the long-term experience of the first 15 AFib patients who received liver grafts in our Institutions in the UK and US, and discuss the merits and scope for optimal utilisation of this valuable resource.

Methods: Ten British and 5 US patients with AFib E526V and amyloid nephropathy were listed for transplantation between 1995-2017. Dominant features were proteinuria (66%) median 7.37 (2.5-9.8) g/D and kidney impairment, median GFR 25 (0-104) ml/min. Extra-renal amyloid manifestations included cardiac (40%) and gastrointestinal (66.6%) autonomic neuropathy and clinically significant splenic amyloidosis (27%). Thirteen patients, median age 59 (49-63), 9 male, received liver-kidney transplant (LKT); two females aged 54 and 58, kidney disease stage 1 and 3 respectively, received isolated liver grafts (LT).

Results: At median posttransplant fol-up 133 months (12-277), there is no amyloid progression and cumulative patient survival in the entire cohort is 80%. LKT patient survival is 76.9%, kidney/ liver graft 92.3%, posttransplant GFR 46 (41-78) ml/min. Three adverse outcomes due to biliary or vascular complications occurred early postoperatively in the subgroup of 9 patients who received LKT after long-term haemodialysis (survival only 66.7%). In contrast, in those receiving pre-emptive LKT or LT alone patient survival was 100%. Both recipients of isolated LT maintain normal liver and stable renal function with diminishing proteinuria at 12 and 95 months.

Conclusions: The therapeutic potential of liver transplantation in fibrinogen amyloidosis is truly curative. Best transplant benefit from the addition of liver to kidney grafts was achieved in low risk pre-dialysis patients. Timely intervention in the pre-dialysis

setting utilising liver transplantation alone is rational, feasible and effective. We support consideration of this approach to halt disease progression and prevent haemodialysis.

SA-PO019

Impact of CYP3A5 Polymorphism on Clinical Outcome After Renal Transplantation

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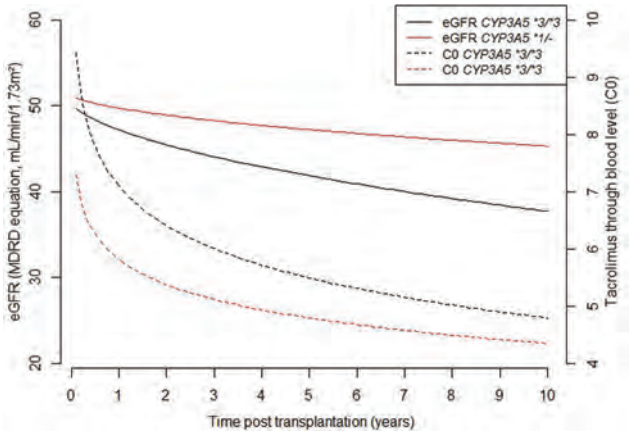
Background: Tacrolimus exhibits pharmacokinetics variability partly explained by CYP3A5 activity. In contrast to *3/*3 genotype, those carrying at least one *CYP3A5*1* allele exhibit higher enzyme activity leading to lower Tac through blood level despite higher daily dose. In this study, we aimed to evaluate the impact of CYP3A5 polymorphism on renal graft outcome

Methods: This monocentric cohort includes 1252 renal transplant recipients with a mean follow up (FU) of 4 years (up to 12.1y). Genotyping of the 6986A>G allelic variant corresponding to *CYP3A5*3* was systematically performed. After 3-months post-transplant, Tac through blood level target range was 5-7ng/ml. However in order to avoid Tac-induced nephrotoxicity, Tac daily dose was limited to a maximum of 0.1 mg/kg/day irrespective of CYP3A5 genotype

Results: Our sample includes 224 *CYP3A5*1/-* patients (13.9%) including 35 *1/*1 genotype recipients. During the FU, we observed 221 graft losses or deaths (17.65%). At baseline, there was no significant difference in characteristics between *3/*3 and *1/- groups. Despite higher daily dose, *1/- recipients exhibit systematically significant lower Tac through blood level during the FU (p<0.01). Multivariate analysis doesn't show any significant influence of *1/- genotype (HR=0.73, CI95% 0.48–1.09, p=0.12) on patient-graft survival. However, GFR decline was significantly lower for the *1/- group (p=0.004). At five years, eGFR was significantly better for *1/- recipients (47 vs 42 mL/min/1.73m2, p<0.001). *CYP3A5* genotype doesn't impact the risk of rejection (HR for *1/- group=0.96, CI95% 0.66-1.42, p=0.87)

Conclusions: In this long-term study, *CYP3A5*1/-* recipients exhibited lower Tac through blood level with no impact on the rejection rate. Renal survival was independent of CYP3A5 genotype. However, the kidney graft function was significantly better in this subgroup showing a lower Tac-induced nephrotoxicity



SA-PO020

HLA Desensitization Using Rituximab/Immunoadsorption Before Kidney Transplantation

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Background: Many kidney-transplant (KT) candidates are sensitized against HLA-antigens, making it difficult to find a suitable HLA-compatible donor. Pretransplant HLA-desensitization strategies have shown improved patient survival after transplantation. This single-centre study included 14 KT candidates (of which seven had a potential living-donor) that underwent kidney transplantation after desensitization comprising two rituximab injections (375 mg/m2) with concomitant immunosuppression [tacrolimus + mycophenolic acid + steroids, and semi-specific immunoadsorption (IA) (GlobaffinÒ columns)].

Methods: IA sessions were performed until anti-HLA alloantibodies become ≤3,000 mean fluorescent intensity (MFI). At transplantation, all patients were induced with ATG. On average, recipients of a living-kidney had 12 (12-15) pretransplant IA sessions; at transplant their donor-specific alloantibodies (DSA) had MFI of ≤3,000 except for 2 with no rebound at posttransplant. Recipients of deceased donors had 15 (8-83) pretransplant IA sessions; all of them had a DSA at transplantation; however, MFI was ≤4,000 in all cases but one (anti-DPA1 at 7,000). After transplantation, there was no prophylactic IA therapy in both groups.

Results: No living-kidney recipients and one deceased-donor recipient had antibody-mediated rejections (ABMR), which was successfully treated with eculizumab. Follow-up kidney biopsies (at a median of 12 months posttransplantation) were normal except for two cases in which there were signs of subclinical ABMR. There was no significant infectious complications.

Conclusions: Semi-specific immunoadsorption was very effective at achieving HLA desensitization.

SA-PO021

De Novo Complement-Activating Donor Specific Antibodies Are Highly Responsive to Therapy

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Background: After recognizing that graft failure was more common in our patients with positive *de Novo* DSAs (*dn*DSAs) by C1q we started using the C1q assay as a guide to therapy of rejection. The aim of this study was to investigate response to treatment as well as characteristics and allograft function of pediatric renal transplant patients with positive *dn*DSA by C1q.

Methods: Retrospective cohort of 35 pediatric renal transplant patients, age 1-20 years, who formed C1q *dn*DSAs identified by screening or investigation of allograft dysfunction with at least 6 month follow up. C1q *dn*DSAs were identified by single-antigen flow bead assay. Outcomes were evolution of C1q *dn*DSAs and graft function in patients with C1q. GFR was estimated using Schwartz method. The same pathologists reviewed all biopsies.

Results: Followup was 36 months (11-96) (Median (range).) Figure 1 shows evolution of C1q. Therapy consisted of Solumedrol (n=19), Thymoglobulin (n=15), IVIG (n=23), Rituximab (n=20) and 1 received Bortezomib / plasmapheresis. Steroid free immunosuppression was converted to steroid based in 9 patients. Maintenance immunosuppression was adjusted/increased when appropriate, adherence anticipatory guidance was provided as needed. During the follow up period, 5 patients, had allograft failure. Figure 2 shows Kaplan–Meier curves for renal survival.

Conclusions: Interventions directed against complement-binding DSA at our center, reduced or eliminated the C1q biomarker significantly. Persistence of C1q antibodies was associated with worse allograft outcome

Patient characteristics		
DSA evolution	C1q eliminated N=28	C1q persisted N=7
Identified risk of rejection (n)		
BK/EBV/CMV (decreased immunosuppression)	6	0
Non-adherence	3	6
Lymphocytopenia (off MMF)	1	0
PTLD (decreased immunosuppression)	0	1
Banff scores prior to treatment (n)		
No rejection	2	0
Borderline rejection.	6	1
Banff IA	0	2
Banff IB	6	1
Banff IIA	2	1
Banff IIB	2	0
CD4+	11	2
No biopsy	10	2

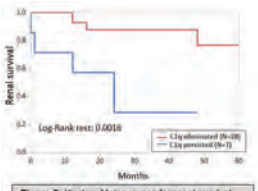

Figure 2: Kaplan–Meier curves for renal survival, defined as decline of at least 50% of GFR or ESKD

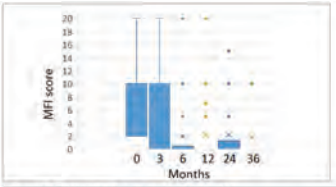

Figure 1: De Novo DSA titer trend by C1q I and II.
Time 0 represents when dnDSA were detected. DSA is plotted using relative intensity score (RIS.) Ranges from 0 points = No DSA; 2 points = <5000MFI (weak intensity); 5 points = 5000-10,000 MFI (moderate intensity); 10 points = >10,000MFI (strong intensity).

SA-PO022

Predictors of Graft Survival at Diagnosis of Antibody-Mediated Renal Allograft Rejection

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Background: Treatment of antibody-mediated rejection (ABMR) after renal transplantation is unsatisfactory. In order to improve treatment efficacy, it is necessary to identify parameters, which independently predict graft survival at diagnosis.

Methods: We investigated 54 consecutive renal allograft recipients with a diagnosis of ABMR between 2005 and 2015. Patients were treated with five different consecutive treatment groups of 10-12 patients. Patient characteristics, renal function and HLA antibody status at diagnosis, baseline renal biopsy results and immunosuppressive treatment were thoroughly recorded. The identification of diverse risk factors of graft loss at 24 months after diagnosis was investigated uni- and multivariate by a Cox proportional hazard model.

Results: Concerning the underlying patient characteristics including baseline parameters at diagnosis, we found no major differences between treatment groups. Multivariable analysis showed that transplant glomerulopathy, microvascular inflammation, and eGFR were predictive for graft loss at 24 months after diagnosis (table 1). In our analysis proteinuria (per 500mg/day) was statistically not a risk factor in the univariate analysis (HR 1.12; 95% CI 0.99-1.27; p=0.072). Notably, a significant (>10%) decrease of DSAmax (HR 0.62; 95% CI 0.25-1.52; p=0.294) following treatment was not associated with an improved graft survival compared to patients with no significant DSA decrease. Treatment with cyclophosphamide (6x15mg/m^2) plus high-dose intravenous immunoglobulins (IVIG) (1.5g/kg) was superior compared to treatment with rituximab (1x500mg) (HR 0.10; 95% CI 0.02-0.54; p=0.008) or bortezomib (4x1.3mg/m^2) plus low-dose IVIG (30g) (HR 0.16; 95% CI 0.02-0.99; p=0.049).

Conclusions: Histopathological signs of acute and chronic ABMR as well as renal function at diagnosis are independent risk factors for graft survival. Treatment with cyclophosphamide plus high-dose IVIG seems to be advantageous. Prospective studies including patients with defined risk factors are needed in order to further improve treatment efficacy.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

Table 1- Risk factors for graft loss at 24 months after transplantation – multivariate analysis

	HR	95% CI	p value	c-statistics
Glomerular double contours (cg) (grade 0-3)	1.57	1.01 ; 2.58	0.045	0.61
Interval between transplantation and diagnosis (per year)	1.11	0.99 ; 1.24	0.065	0.60
eGFR (CKD-EPI, per mL/min) at diagnosis	0.94	0.89 ; 0.98	0.018	0.65
Microvascular inflammation (mvi) (g+ptc, per grade, 0-6)	1.37	1.01 ; 1.88	0.048	0.53

c-statistics = Harrel's C (range 0.5 to 1), measure for the predictive power of a risk factor of graft loss at 24 months

SA-PO023

Outcomes Following Living Donor Kidney Transplantation in Patients with Donor-Specific HLA Antibodies After Desensitization with Immunoadsorption

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Background: Due to the current organ shortage, living donor kidney transplantation is increasingly performed over human leukocyte antigen (HLA) or ABO antibody barriers. Uncertainty still exists concerning the risk for antibody-mediated rejection episodes, possibly limiting long-term graft survival. The present study aimed to evaluate the outcomes of kidney transplantations performed after desensitization in patients with donor-specific HLA antibodies compared to standard risk recipients.

Methods: Thirty-eight sensitized patients were included in the study. Sixteen patients had a positive CDC and/or ELISA crossmatch result with their prospective living donor and 32 patients had Luminex-detected donor-specific HLA antibodies (DSA). Patients were successfully desensitized by immunoadsorption treatment (median of 8 treatments) and anti-CD20 antibody rituximab (N=36) combined with antithymocyte globulin (N=20) or anti-IL2 receptor antibody therapy (N=18). Twelve patients were additionally treated by plasmapheresis. All patients received a kidney transplant from a living donor. Postoperative apheresis was performed in 28 patients. The outcomes of the 38 patients were retrospectively compared to outcomes of 76 standard risk recipients (2:1 matching).

Results: During a median of 8 pretransplant immunoadsorption treatments, IgG was reduced by 98% and IgM by 78% in sensitized patients. After transplantation, sensitized patients showed comparable death-censored graft survival and patient survival compared to standard risk recipients. Infectious complications, surgical complications and rejection rates (18% in both groups) were not significantly different between groups. Median 1-year serum creatinine was with 1.31 mg/dL in sensitized recipients not significantly different to the 1.38 mg/dL in standard risk recipients. One-year urinary protein excretion was also not significantly different with a low 10.8 and 10.5 g/mol creatinine, respectively.

Conclusions: Our desensitization protocol for sensitized living donor kidney transplant recipients results in good graft outcomes with comparable side effects and rejections rates to standard risk recipients.

SA-PO024

Outcomes in Sensitized Kidney Transplant Recipients Treated with Rituximab

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Background: Donor specific antibodies (DSAs) are associated with increased risk of rejection & graft loss following kidney transplantation (KT). Patients with DSA & positive flow cytometry crossmatch (XM) were treated with rituximab at transplant while those with negative XM and DSA were not. We evaluated clinical outcomes of patients with DSA at time of transplant stratified by rituximab therapy.

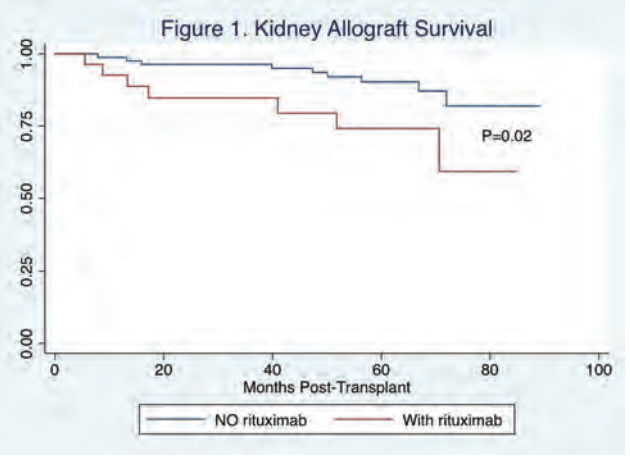
Methods: Retrospective review of sensitized KT recipients with DSA were studied excluding ABO-incompatible transplants. Graft survival was compared using log-rank test & multivariable analysis was performed using logistic regression.

Results: Individuals treated with rituximab were more likely to receive steroid maintenance & had higher DSA MFI-Sum (Table 1). One-year acute rejection rates were not different between those treated with & without rituximab. The survival of rituximab treated group was significantly lower (Fig. 1, P=0.02). In a logistic regression model, none of the variables were independent predictors of graft survival, rituximab therapy (P=0.24), steroid therapy (P=0.83), MFI-Sum category (P=0.44).

Conclusions: Among sensitized patients, those treated with rituximab had higher levels of DSA and had decreased overall graft survival. Treatment with rituximab was not independently associated with increased risk of graft loss. Additional studies are need to truly evaluate the risks & benefits of rituximab therapy in the highly sensitized patient population.

Table 1: Baseline Characteristics and Outcomes in Sensitized Patients with and without Anti-CD20 Therapy

	Rituximab (N=27)	No Rituximab (N=83)	p-value
Age (years, mean ± sd)	58 ± 11	55 ± 15	0.41
Sex: Female - no. (%)	16 (59)	43 (52)	0.50
Race: African American - no. (%)	9 (33)	21 (25)	0.40
Cause of ESRD - no. (%)			0.26
DM - no. (%)	3 (15)	17 (85)	
HTN - no. (%)	3 (16)	16 (84)	
SLE - no. (%)	4 (33)	8 (67)	
GN - no. (%)	2 (33)	4 (67)	
PKD - no. (%)	3 (23)	10 (77)	
Other - no. (%)	12 (30)	28 (70)	
DDRT - no. (%)	13 (48)	34 (41)	0.65
DSA Characteristics:			
DSA Class I Sum (mean ± sd)	6411 ± 8177	3094 ± 3541	**0.038**
DSA Class II Sum (mean ± sd)	9755 ± 11329	3795 ± 3805	**0.013**
DSA Class I+II Sum (mean ± sd)	16167 ± 11124	6890 ± 4131	**<0.0001**
MFI-Sum Group:			**<0.0001**
MFI-Sum 3-6K (N=50) – no. (%)	4 (8)	46 (92)	
MFI-Sum 6-10K (N=29) - no. (%)	7 (24)	22 (76)	
MFI-Sum >10K (N=31) - no. (%)	16 (52)	15 (48)	
Anti-thymoglobulin Induction - no. (%)	26 (96)	74 (89)	0.26
Steroid Maintenance - no. (%)	27 (100)	51 (61)	**<0.0001**
Acute Rejection at One Year - no. (%)	7 (26)	11 (13)	0.12
Antibody Mediated Rejection - no. (%)	6 (86)	6 (55)	
Acute Cellular Rejection - no. (%)	1 (14)	5 (45)	



SA-PO025

The Risk of Renal Re-Transplantation

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Background: Renal transplant programs comprise around 15% of re-transplantations. We aimed to know if renal re-transplantation (Tx2) has a higher risk than first transplantation (Tx1), and if so, to analyze the reasons for it.

Methods: This is a retrospective monocenter study by comparing graft and patient survival of all 162 Tx2 patients transplanted 2000 to 2009 (study group) with 162 Tx1 patients matched for age (± 10 years), gender, date of transplantation (± 18 months), and the kind of kidney donation (control group). We looked for differences in clinical parameters with a possible influence on graft and patient survival (observation time 8 to 17 years).

Results: Graft and patient survival of TX2 was inferior to that of TX1 patients (p=0.0011 resp p=0.0477, test for paired data). Group TX2 had a longer dialysis treatment than TX1 (113.0±52.5 vs 65.6±33.9 months; p<0.0001); more often HLA mismatches (MM) (2.54±1.75 vs 2.08±1.65, p=0.0129) and preformed panel reactive HLA-antibodies (PRA) >30% (15.4% vs 1.9%, p=0.0001); and more often induction therapy by thymoglobulin instead of IL-2R antibody (59.9% vs 1.9%, p<0.0001). The number of patients with rejection (39.57% vs 36.4%) and of rejections per patient (0.58±0.92 vs 0.56±0.87) were not different; however, graft failure by acute and chronic rejection was more frequent in the Tx2 group (32.22% vs 21.21%, p=0.0137). The number of patients with severe infections threatening life and/or graft function was not different (41.36% vs 39.5%); however, death by severe infection was more frequent in group Tx2 (0.0411). Testing several variables by Kaplan-Meier curves, Tx2 show an inferior graft survival than Tx1 patients with a higher number of HLA-MM (logrank p=0.0137), with humoral rejection (logrank p=0.0037), and have a higher mortality with several concomitant diseases, (logrank p<0.0001), especially cardiovascular disease (logrank p<0.0001), and severe infection (logrank p=0.0001).

Conclusions: Tx2 patients have several reasons for an inferior graft and patient survival compared to Tx1 patients: a) Immunologic reasons (more often HLA MM and high PRA, more often graft failure by rejection); b) higher mortality by concomitant diseases, especially cardiovascular disease and infection; c) less capacity to adapt to immunologic and infectious problems and failure to cope with them.

SA-PO026

Kidney Transplantation Outcomes in Patients with Idiopathic Membranous Nephropathy as Primary Disease

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Background: Kidney transplantation (KTx) is the treatment of choice for patients with glomerular diseases. However, in some occasions relapse of the primary disease in the graft may impact graft survival. We aimed to explore the outcome of KTx in patients who ended in ESRD due to idiopathic membranous nephropathy (IMN), the frequency of disease relapse in the graft along with the response to the current treatment options.

Methods: We retrospectively studied all patients with IMN as primary disease, transplanted in our hospital between 1990-2016. All patients had biopsy proven IMN in their native kidneys. Demographics and characteristics related to the donors and the recipients at KTx were recorded, including, dialysis time, immunosuppressive schemes, histocompatibility data, acute rejection episodes, patient and graft survival, and eGFR at the end of the follow up time. Relapses of IMN were recorded in conjunction with the given treatment and the related response. All patients with IMN relapse were initially treated with an ACE inhibitor (fosinopril) and depending on the response or not, received either the Ponticelli protocol, as 2ndline therapy, or more recently rituximab.

Results: We identified 18 patients with ESRD due to IMN who received a graft between 1990-2016 in our hospital. The mean age at the time of KTx was 47±11.5 years and 13(72.2%) of them were males. The mean time in dialysis was 63.2(±51.5) months, the graft was from deceased donors in 13 cases (72.2%), with a mean donor age of 46(±15.46) years. During a follow up time of 84.97(±57.6) months after KTx, 7 patients (38.8%) experienced at least one episode of IMN relapse. Time to relapse was 45.6(±42.7) months from KTx and 24-hour proteinuria was 4.12(±2.88) gr. Two patients experienced acute rejection, one of them during the relapse of IMN. At the end of the follow up time, patients' survival was 100%, graft survival was 88.9%, with a mean serum creatinine of 1.8(±0.23) mg/dl, eGFR of 60.84 (±27.3) ml/min/1.73m^2 and mean 24-hour proteinuria of 0.75(±0.58) gr.

Conclusions: Relapse of IMN in the graft is not rare, but in most occasions is responsive to therapy, either with inhibition of the renin angiotensin system, either with enhancement of immunosuppressive treatment, and generally it does not affect long term graft survival.

SA-PO027

Outcomes of Kidney Transplant Recipients with Pre-Transplant, Recurrence, and Post-Transplant Malignant Melanoma

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Background: Kidney transplant recipients (KTRs) have an increased risk of malignancy, especially skin cancer. Patients with pre-transplant melanoma usually wait a longer period before transplantation than their counterparts with non-melanoma skin cancers as there is limited data on risk of recurrence and outcomes of pre, recurrent and post-transplant melanoma.

Methods: We analyzed the outcomes of KTRs transplanted at our center between 01/01/1994 and 12/31/2014 who reported pre-transplant melanoma, recurrence of melanoma after transplant and post-transplant melanoma.

Results: Of 4941 KTRs within the abovementioned time-period, thirty-four had a history of melanoma prior to renal transplant, of which 6 (18%) had recurrence of melanoma post-transplant. Mean wait time from melanoma diagnosis to transplant was 389 ± 311 days for non-recurrent patients and 422 ± 411 days (p=0.32). The mean interval to recurrence of melanoma was 6.2 ± 3.7 years after transplant. Five of the 6 patients with recurrence had end stage renal disease due to diabetes. All KTRs with or without recurrence were Caucasian. The cumulative incidence of biopsy-confirmed rejection was 50% (n=3) in those with recurrence, compared to 4% (n=1) in those without recurrence (p=<0.001). The mean interval from transplant to rejection was 2.9 ± 1.6 and 1.4 years respectively. The cumulative incidence of death censored graft loss was 17% (n=1) among recurrent melanoma patients with an interval from transplant to graft loss of 6.0 years while the incidence among only pre-transplant melanoma was 14% (n=4) with an interval of 5.0 ± 3.1 years. Similarly, there were a total of forty-five Caucasian KTRs with post-transplant melanoma. The mean interval from transplant to melanoma was 4.4 ± 3.1 years. The incidence of death censored graft loss was 11% (n=5) at last follow-up.

Conclusions: Recurrence of melanoma is common among KTRs with pre-transplant melanoma, especially among KTRs with diabetes. Incidence of biopsy proven rejection and graft failure among recurrent melanoma is high. Proper risk stratification and early diagnosis may improve patient and graft survival.

SA-PO028

History of Posttraumatic Stress Disorder, and Mortality After Kidney Transplantation

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Background: History of posttraumatic stress disorder (PTSD), if uncontrolled, represents a relative contraindication for kidney transplantation. However, no previous large study assessed the association between pre-transplant history of PTSD and post-transplantation outcomes.

Methods: We examined 4,479 US veterans who underwent kidney transplantation. The diagnosis of history of PTSD was based on a validated algorithm. Associations between pre-transplantation PTSD and all-cause mortality was examined in unadjusted and multivariable adjusted Cox proportional regression models.

Results: From among 4,479 veterans, 282 (6.3%) had a history of PTSD. The mean±SD age of the cohort at baseline was 61±11 years, 91% were male, 66% and 28% of patients were white and African-American, respectively and 31% received living transplantation. Compared to patients without history of PTSD, patients with a history of PTSD had similar risk of all-cause death [Hazard Ratio (HR) (95% Confidence Interval (CI)): 1.12 (0.82-1.51)] in our unadjusted model as shown in Figure 1. After adjustment for socio-demographic, comorbidity, medication, dialysis and transplant related variables there was no association between history of PTSD and all-cause mortality [HR (95%CI): 1.17 (0.83-1.65)].

Conclusions: After careful selection, pre-transplantation PTSD does not appear to be associated with higher mortality in kidney transplant recipients.

Funding: NIDDK Support

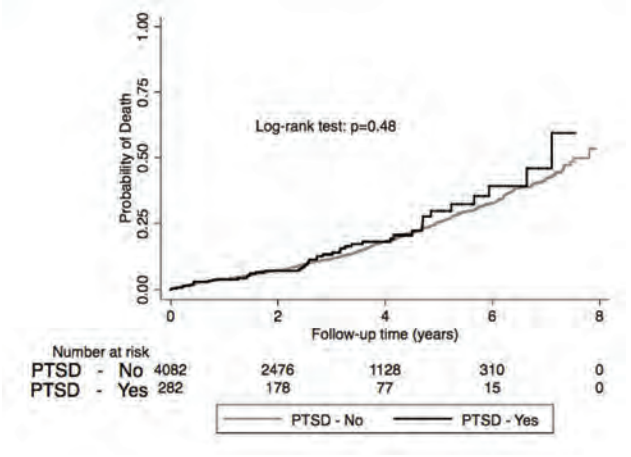

Figure 1: Probability of Death in Recipients with and without PTSD

SA-PO029

Establishing a Core Outcome Measure for Life Participation: A Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) Consensus Workshop Report

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Background: Kidney transplantation confers substantial survival and quality of life benefits for many patients with end-stage kidney disease compared with dialysis but complications and side effects of immunosuppression can impair participation in daily life activities. Life participation is a critically important patient-reported outcome for kidney transplant recipients but it is inconsistently and infrequently measured in trials. We convened a consensus workshop on establishing a core outcome measure for life participation for use in all trials in kidney transplantation.

Methods: Twenty-five (43%) kidney transplant recipients/caregivers and 33 (57%) health professionals from eight countries participated in six facilitated breakout group discussions. Transcripts were analyzed thematically

Results: Four themes were identified. *Returning to normality* conveyed the patients' goals to fulfil their given roles (i.e. in their family, work, and community) and re-establish a normal lifestyle. *Recognizing the diverse meaning and activities of 'life'* explicitly acknowledged life participation as a subjective concept that could refer to different activities (e.g. employment, recreation, family duties) for each individual patient. *Capturing vulnerability and fluctuations post-transplant* (e.g. due to complications and side-effects) distinguished between experiences in the first year post-transplant and the long-term impact of transplantation. *Having a scientifically rigorous, feasible and meaningful measure* was expected to enable consistent and frequent assessment of life participation in trials in kidney transplantation.

Conclusions: A feasible and validated core outcome measure for life participation is needed so this high-priority patient-reported outcome can be consistently and meaningfully assessed in trials in kidney transplantation to inform decision-making and care of patients.

SA-PO030

Fatigue Predicts Graft and Patient Survival After Kidney Transplant

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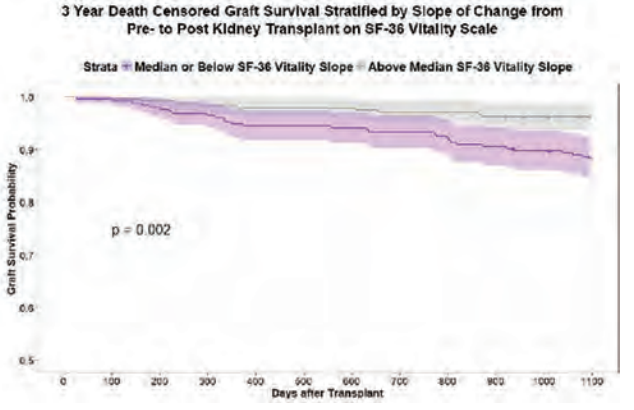
Background: Fatigue is a prevalent post- kidney transplant (KT) symptom, and it is associated with reduced overall health-related quality of life and decreased kidney function. Yet, its association with graft and patient survival is unclear.

Methods: Using the SF-36 Vitality (Vit) scale and a single question from the Functional Assessment of Cancer Therapy – Kidney Symptom Index, "I have a lack of energy" (GP1), we examined change in fatigue from pre- and post-KT (3 months and 1 year) among **528** KT patients between 10/29/2007 and 08/18/2016 at a large academic transplant center. The Vit scale ranges from 0-100, and GP1 ranges from 0-4. On both measures, higher scores indicate less fatigue. We examined whether pre-KT fatigue and slope of change in fatigue from pre- to post-KT were associated with 1- and 3-year death censored graft survival (DCGS) and patient survival.

Results: Respectively, mean Vit and GP5 scores increased from pre-KT to 3 mo and 1 year post-KT: Vit - 45.4, 63.5, 67.3 (p<0.001); GP1 – 1.8, 2.7, 2.9 (p<0.001). There was a significant association with change in creatinine from pre- to post-KT with fatigue measured by both the Vit and GP1 (p<0.001 for each). Patients with median or below Vit scores pre-KT had significantly lower 1 year DCGS rates (93.2% vs. 96.9%, p=0.045) and patient survival rates (96.2% vs. 99.6%, p=0.006). Patients with median or below slope in Vit score change from pre- to post-KT had lower 3 year DCGS rates (88.5% vs. 96.2%, p=0.002) (Figure). Similar to these results, patients with median or below slope in GP1 score change from pre- to post-KT had lower 3 year DCGS rates (88.8% vs. 94.6%, p=0.04).

Conclusions: Fatigue is associated with reduced kidney function, graft failure, and mortality after KT. Patients with high risk for graft loss and mortality also suffer from higher fatigue after KT than those with well working kidneys. Future research should explore how monitoring fatigue might improve post-KT follow-up.



SA-PO031

Long-Term Outcome of Kidney Transplant Recipients Admitted to the Intensive Care Unit

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Background: The goal of this study was to evaluate the course and outcome of kidney transplant (KT) recipients admitted to ICU.

Methods: We reviewed the data of all adult renal transplant recipients who are admitted to the ICU at our center, between 1997 and 2017 that included the demographic features, causes of end-stage renal disease (ESRD), causes of admission, time between transplantation and admission and ICU courses and outcome. Among 379 KT followed up in our center, 60 patients were admitted to ICU and were categorized to early (during first 3 months; n=28); intermediate (3–12 months; n=7); and late (12 months and afterwards, n=25).

Results: The rate of ICU admission was 15.9% and the mean age was 48.3 ± 12.6 years. The main cause of admissions was surgical complication (71%) in early group and infection (57% and 80%) in later groups, respectively. Mortality on discharge was significantly higher in late admission (52%) (p=0.0001) and the leading cause of death in all groups was sepsis (89%). Twenty patients required ventilator that was an independent risk factor for mortality (P < 0.05). There was statistically significant decrease in the overall 5-year and 10-year patient survival (P = 0.031) in KT patients admitted to the ICU.

Conclusions: Our study shows that the main reason for ICU admissions was infections especially in late admission. Mortality rate were relatively high and was linked to need for ventilators. Admission to the ICU is usually associated with decrease in the graft and patient survival.

SA-PO032

Anemia at One Year After Kidney Transplantation Is a Risk Factor of Graft and Patient Survival

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Background: Post-transplant anemia is multifactorial and highly prevalent. The purpose of this study was to assess whether the presence of anemia at 12 months year is an independent risk factor of mortality and graft survival.

Methods: All patients followed-up at a single center who survived at least 1 year after transplantation and with serum creatinine ≤140 μmol/l (n = 297) were included. Demographic and clinical data were collected at baseline and at 1 year. Patients were divided into two groups (anemic and nonanemic) based on the presence of anemia (hemoglobin; 13 g/dl in men and 12 g/dl in women) at 12 months.

Results: Baseline characteristics such as age, gender, type of donor, etiology of end-stage kidney disease, pre-emptive transplant, duration of pre-transplant dialysis, type of primary immunosuppression and mismatches were similar in both groups. There was statistically higher use of induction therapy (p=0.021), rate of acute rejection after the first year (p=0.020), CMV infection (p=0.015) and chronic allograft damage (p=0.004) in anemic group compared to nonanemic group. Creatinine clearance at last follow-up was significantly lower in anemic (59.3 ± 10.8 ml/min) and nonanemic groups (45.3 ± 12.5 ml/mim)

(P = 0.039). A Kaplan–Meier survival analysis at 10-year post-transplant showed significantly poorer death-censored graft survival in the anemic group, P = 0.04 and patient survival (p=0.03). There was more statistically rate of death with function graft in anemic group (p=0.043).

Conclusions: In this study, anemia at 1 year was independently associated with death-censored graft and patient survival. Anemic patients have higher rate of acute rejection, and chronic allograft damage.

SA-PO033

The Combination of Area Under Curve of Estimated Glomerular Filtration Rate for 2 Years and Annual Rate Change of Estimated Glomerular Filtration Rate Predicts Long-Term Outcome in Kidney Transplants

Eun jeong Lee, Song in Baeg, Hyo jin Boo, Minjung Kim, Hye Ryoun Jang, Jung eun Lee, Dae Joong Kim, Yoon-Goo Kim, Ha Young Oh, Wooseong Huh. *Samsung Medical Center, Seoul, Republic of Korea*.

Background: Improvement of short-term outcomes in kidney transplant (KT) has required clinical trials to evaluate long-term hard outcomes for validation of new therapies. However, because of time and cost, it is very difficult to conduct a clinical trial using hard outcomes in KT. To solve the problem, the use of surrogate marker should be considered. We examined the possibility of the combination of area under curve of estimated glomerular filtration rate for 2 years ($AUCeGFR_{2yrs}$) and % change in estimated glomerular filtration rate (eGFR) between years 1 and 2 after KT as a surrogate marker for long-term graft failure.

Methods: We studied 1423 kidney transplants performed from 1996 to 2013 at Samsung Medical Center, Seoul, Korea, including 202 graft losses (time to graft failure, median 8.4 years [5.4 - 12.4]) and 54 deaths (time to death, median 9.1 years [5.7 - 13.2]). Combination of $AUCeGFR_{2yrs}$ (>1300 ml/min·month vs ≤ 1300 ml/min·month) and % change in eGFR (> 2% vs ≤ 2%) was assessed to determine risk of graft failure using Cox proportional hazard analysis.

Results: The combination was significantly associated with graft failure ($p < 0.0001$). Patients with $AUCeGFR_{2yrs}$ ≤ 1300 ml/min·month and % change in eGFR ≤ 2% formed 16.7% of all patients and showed higher graft failure risk (hazard ratio [HR], 3.36; 95% confidence interval [95% CI], 2.52 to 4.48). The Harrell C-index of the combination was 0.65 (95% CI, 0.60 to 0.69), and was internally validated via 5-fold cross-validation (average Harrell C-index, 0.64; 95% CI, 0.60 to 0.68). We also evaluated a known surrogate marker, ≥ 30% decline in eGFR between years 1 and 3 after KT. The incidence of ≥ 30% decline in eGFR was 6.9% of patients. HR of graft failure was 7.18 (95% CI, 5.22 to 9.89) and Harrell C-index was 0.65 (95% CI, 0.63 to 0.66).

Conclusions: We conclude the proposed combination might be useful as a surrogate outcome in KT trials in that it requires shorter surveillance period (2 years) than the known surrogate marker (3 years) while having comparable predictability. External validations should be conducted.

SA-PO034

Impact of Donor Age on Outcome of Kidney Transplantation from Deceased Donor with Histologic AKI

Myung-Gyu Kim, Junyong Lee, Jihyun Yang, Sewon Oh, Sang-Kyung Jo. *Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea*.

Background: The shortage of donors has expanded donor criteria and kidneys from elderly donors with AKI have been used for transplant recently, but safety and prognosis are not well known. Here, we examined the effect of donor age on outcomes of kidney transplant (KT) from donor with histologic AKI.

Methods: We analyzed retrospectively the medical records of 59 deceased-donor KT with acute tubular necrosis (ATN) on pre-implantation donor kidney biopsy between March 2012 and October 2017. Histologic quantifications of ATN and inflammation, glomerular sclerosis (GS), interstitial fibrosis, tubular atrophy, and arterial sclerosis were performed.

Results: Twenty and thirty nine recipients were received kidney from old (>60, 68.9±5.0) and young donors (≤60, 45.9±9.6) with ATN, respectively. In the old donors, a significant increase in donor Cr was observed only in 44%, diabetic patients were higher, women were dominant, and the percent of GS(%) was significantly higher than in young donors. After KT, six months eGFR was significantly lower in recipients who received kidney from old donors than form young donors. Donor creatinine level and AKI severity according to AKIN criteria did not significantly affect the recipient outcome in both groups during 6mo post-transplant. However, only in KT from old donors, the presence of ATN and GS(%) were found to be significant factors exacerbating renal outcome at 6mo, but not in KT from young donor. In particular, in multivariate analysis, the sum of ATN scoring and GS percent was the strongest independent factor for predicting elderly recipient renal function, suggesting that aged kidney is an important factor in modifying the outcomes of AKI.

Conclusions: Taken together, the assessment of AKI based on creatinine is not useful for predicting prognosis, but in KT from old donors, acute tissue injury as well as GS could predict renal outcome. Therefore, a donor allocation protocol with evaluating histologic acute and chronic lesions through pre-implantation donor kidney biopsy need to be developed when KT from old donors.

SA-PO035

Incidence, Outcomes, and Predictors of Pregnancy in Kidney Transplant Recipients

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Background: Although kidney transplant improves reproductive function in women with end stage renal disease (ESRD), pregnancy in kidney transplant recipients remains challenging due to risk of adverse outcomes. Temporal trends in pregnancy rate, fetal outcomes and its predictors in women with kidney transplants are not well studied.

Methods: We evaluated women aged 15-49 years who received a kidney transplant between 1/1/2005 and 12/31/2011 from the United States Renal Data System and who had Medicare as the primary payer for the entire 3 years after the date of transplantation or until graft failure or death. Temporal trends in pregnancy rates and fetal outcomes were studied. Case mix adjusted multivariate Poisson regression analysis was used to determine predictors of pregnancy.

Results: Overall, 308 pregnancies were identified in 9939 women. Mean maternal age was 30±7 year. Pregnancy rate was 11.4 per 1000 person-year (95% CI, 10.1-12.7). Pregnancy rates were roughly constant in the years 2005-2011. Of the known pregnancy outcomes, rate of live-birth was 42.6%, and stillbirth was 3.7%. Another 14.4% were reported as either live birth or stillbirth. Rate of spontaneous abortion was 32.4%, therapeutic abortion was 6.5% and ectopic pregnancy was 1.4%. Compared to women aged 25–29 years at time of conception, the pregnancy rate was lower in women aged 30–34 years (Incidence risk ratio [IRR], 0.56; CI, 0.41-0.77), 35-39 years (IRR, 0.16; CI 0.10-0.25), 40-44 years (IRR, 0.08; CI, 0.04-0.13), and 45-49 years (IRR, 0.06; CI, 0.03-0.10). Hispanic women had higher rates of pregnancy as compared to White women (IRR, 1.6; CI, 1.2-2.1). In transplant recipients, as compared to women with ESRD due to diabetes, pregnancy rate was higher in women with ESRD due to hypertension (IRR, 1.3; CI, 1.0-1.7), glomerulonephritis (IRR, 2.4; CI, 1.1-5.3), and cystic/hereditary diseases (IRR, 3.3; CI, 1.4-7.8). Women had higher rate of pregnancy in the second (IRR, 1.7; CI, 1.3-2.3) and third post transplant year (IRR, 1.7; CI, 1.3-2.3) as compared to first post transplant year.

Conclusions: Pregnancy in kidney transplant recipients is not uncommon and rates were relatively constant in in the last decade. Younger and Hispanic patients; and those with conception after the first post transplant had the highest rates of becoming pregnant.

SA-PO036

Pregnancy Outcomes in Women with Kidney Transplant: Meta-Analysis and Systematic Review

Silvi Shah,[1] Renganathan Lalgudi venkatesan,[1] Ayank Gupta,[3] Emily B. Kean,[1] Maitrik K. Sanghavi,[1] Tiffany J. Grant,[1] Anu Gupta.[2] *[1]University of Cincinnati, Cincinnati, OH; [2]Buffalo Medical Group, Buffalo, NY; [3]The University of Cincinnati, Cincinnati, OH.*

Background: Reproductive function in women with end stage renal disease generally improves after kidney transplant. However, pregnancy remains challenging due to the risk of adverse clinical outcomes. This systematic review aimed to determine the pregnancy outcomes in patients with kidney transplant, including live birth rate, nature and rates of maternal and fetal adverse events, and risk of graft failure.

Methods: We searched PubMed/MEDLINE, Elsevier EMBASE, Scopus, BIOSIS Previews, ISI Science Citation Index Expanded, and the Cochrane Central Register of Controlled Trials from their date of inception through August 2017 according to PRISMA guidelines for studies reporting incidence and outcomes of pregnancy in women with kidney transplant.

Results: Of 1343 unique studies, 87 met inclusion criteria, representing 6712 pregnancies in 4174 kidney transplant recipients. Mean maternal age was 29±2 years. The live-birth rate was 72.9% (95% CI 70.0-75.6). Other pregnancy outcomes included induced abortions (12.4%; 95% CI, 10.4-14.7), miscarriages (15.4%; 95% CI, 13.8-17.2), stillbirths (5.1%; 95% CI, 4.0-6.5), and ectopic pregnancies (2.4%; 95% CI, 1.5-3.7). Maternal complications that were determined included preeclampsia (21.5%; 95% CI, 18.5-24.9), gestational diabetes (5.7%, 95% CI 3.7-8.9), pregnancy induced hypertension (24.1%; 95% CI, 18.1-31.5), and cesarean section (62.6%, 95% CI 57.6-67.3). Fetal complications of preterm delivery was 43.1% (95% CI 38.7-47.6). Mean gestational age was 34.9 weeks, and mean birth weight was 2470 grams. With regards to graft outcomes, rate of acute rejection during pregnancy was 9.4% (95% CI, 6.4%-13.7%). Adverse pregnancy outcomes of cesarean section and neonatal deaths were highest, and live birth rate were less favorable in the 2-3 year interval as compared to 1-2 year and > 3 year interval following kidney transplant. Rates of spontaneous abortion were highest in women with mean maternal age < 25 years and > 35 years as compared to women aged 25-35 years.

Conclusions: Majority of pregnancies following kidney transplant are successful and do not have an adverse impact on fetal survival. However the risks of maternal and fetal complications are high in women with kidney transplant and should be considered in patient counseling and clinical decision making.

SA-PO037

Timing of Native Nephrectomy and Kidney Transplant Outcomes in Children

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Background: Native nephrectomies are indicated for various reasons in pediatric kidney transplant (pKtx) candidates. Nephrectomies may be performed prior to (2-stage) or at the time of transplant (1-stage). The optimal timing of nephrectomies remains controversial and there are no data comparing the outcomes associated with two approaches.

Methods: We retrospectively examined 32 consecutive pKtx recipients who underwent native nephrectomies at the University of Minnesota between 01/01/2011 and 12/31/2016. We investigated the effect of the timing of nephrectomy on patient and graft survival using Kaplan-Meir and log-rank test. We compared categorical variables using Fisher exact and continuous variables using Wilcoxon rank sum tests.

Results: Our cohort included 21 patients with 1-stage and 11 patients with 2-stage nephrectomies. Clinical characteristics are presented in table 1. Although statistically insignificant, patients with 2-stage tended to be older. Indications for nephrectomy included vesicoureteral reflux/urinary infections (40.6%), nephrotic syndrome (31.3%) and cystic kidney diseases (15.6%). There were no differences in the indications for nephrectomy between 1-stage versus (vs.) 2-stage patients. There was no difference in the rate of peri-operative complications between two groups. For 2-stage, median length of hospital stay (LOS) after nephrectomy was 7.5 days (range: 6-10), and median time to transplant was 4.3 months (range: 3-73) for living and 15 months (range: 3 -180) for deceased donor recipients. Posttransplant LOS was significantly shorter for 2-stage patients (median days: 12 vs. 8, p 0.03). There were no differences in 1-year patient (100% vs. 100%, p 1.0) or graft survival (95% vs. 90.9%, p 0.68) between 1-stage vs. 2-stage patients.

Conclusions: There were no differences in 1-year patient and graft survival between pKtx recipients with 1-stage vs. 2-stage native nephrectomies. Posttransplant LOS was shorter for patients undergoing 2-stage nephrectomies; however, they required two hospitalizations.

Variables	1-stage procedure N= 21	2-stage procedure N = 11	p value
Age at transplant in years Median (range)	2 (1-17)	7 (1-16)	0.09
Male % (n)	52.4 (11)	54.6 (6)	0.9
Caucasian % (n) African American % (n) Other % (n)	76.2 (16) 4.8 (1) 19.1 (4)	63.6 (7) 9.1 (1) 27.3 (3)	0.74
Donor source % (n) Deceased	57.1 (12)	45.5 (5)	0.71
Pre-nephrectomy Dialysis % (n)	71.4 (15)	54.6 (6)	0.44

SA-PO038

Solid Organ Transplantation and Mortality Following Diffuse Large B Cell Lymphoma

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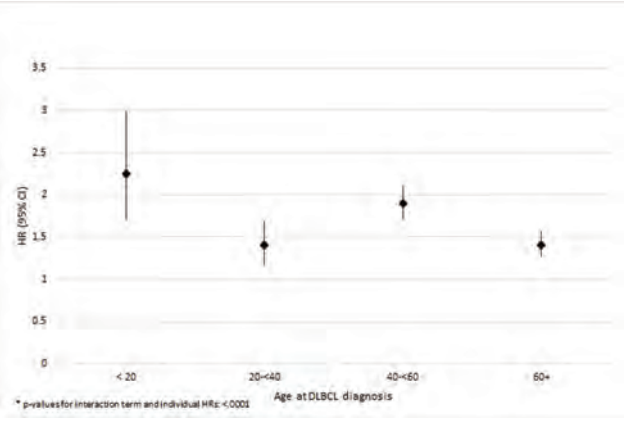
Background: Diffuse large B cell lymphoma (DLBCL) is a common malignancy in all age groups after solid organ transplant. The effects of prior transplant on mortality following DLBCL and the effect modification by age at diagnosis have not been described.

Methods: We used 11 state cancer registries to identify all DLBCL cases in those states and ascertained history of organ transplant through a linkage to the Scientific Registry of Transplant Recipients. We used a Cox proportional hazard model to examine the effect of transplant on mortality after adjusting for age at DLBCL diagnosis, sex, race, year of diagnosis, site of DLBCL, stage of cancer at diagnosis and treatment. We also investigated an interaction between age at diagnosis and transplant status.

Results: Our cohort included 1,338 DLBCL cases with prior organ transplant and 132,713 without. Compared with non-transplant patients, transplant recipients had lower mean age at diagnosis (48.5 vs. 62.4 years, p <0.0001), male preponderance (67.5 vs. 53.3%, p <0.0001), higher incidence of extranodal disease (49.7 vs. 37.5%, p <0.0001), and higher prevalence of distant stage at diagnosis (47.5 vs. 43%, p <0.0001). After multivariate adjustment, overall (adjusted hazard ratio (aHR): 1.83, 95% CI: 1.71-1.96) and cancer-specific mortality (aHR: 1.21, 95% CI: 1.1-1.33) were higher in transplant recipients than in non-transplant patients. The effect of transplant on mortality following DLBCL was highest in patients aged younger than 20 years at diagnosis (Figure).

Conclusions: Prior organ transplant is associated with an increased risk of overall and cancer-specific mortality following DLBCL. The effect of transplant on mortality is highest in DLBCL patients aged younger than 20 years at diagnosis.



Overall mortality of patients with DLBCL with prior organ transplant compared to those without

SA-PO039

Adult Educational and Vocational Outcomes of Pediatric Solid Organ Transplant Recipients in Canada

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Background: There are a paucity of data on educational attainment and vocational outcomes in young adults who received solid organ transplants in childhood.

Methods: Young adults (18-25 years) who had received a solid organ transplant at <18y old completed questionnaires in outpatient transplant clinics at seven centres across Canada. The transplant cohort was compared with the age-matched general Canadian population over the same time period (2016-2017) using Statistics Canada survey data (over 3.5 million people 18-25 years).

Results: There were 161 transplant recipient participants with a mean age of 22 ±2.3 years; 55% were male. The median age at diagnosis of organ failure was 9.5 years [IQR 2, 15]. There were 112 (70%) who had received a kidney, 37 (23%) a liver, and 12 (7%) a heart. Compared with the age-matched general population, transplant recipients were less likely to have a university degree (9.3% vs. 14.9%; risk difference -5.5% [95%CI -10.0% to -1.1%]; P=0.048) or to be employed (68.4% vs. 83.0%; risk difference -14.6% [95%CI –22.0% to -7.2%]; P<0.0001). Among those employed, a higher percentage of transplant recipients (81.6%) earned less than the Low Income Cut-Offs (LICO) compared to the general population (64.6%); risk difference 17.1%[95%CI 8.9% to 25.2%]; p<0.001). LICO is defined as an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter, and clothing than the average family.

Conclusions: Young adult survivors of pediatric solid organ transplantation in Canada have lower educational achievement and are less likely to be employed than the age-matched general population. Similar findings were recently reported in Europe. In order to improve the educational and vocational outcomes, greater advocacy and support are needed for pediatric recipients of solid organ transplant as they transition to adulthood.

Funding: Government Support - Non-U.S.

SA-PO040

MR Urogram Without Contrast in Transplant Obstructive Uropathy

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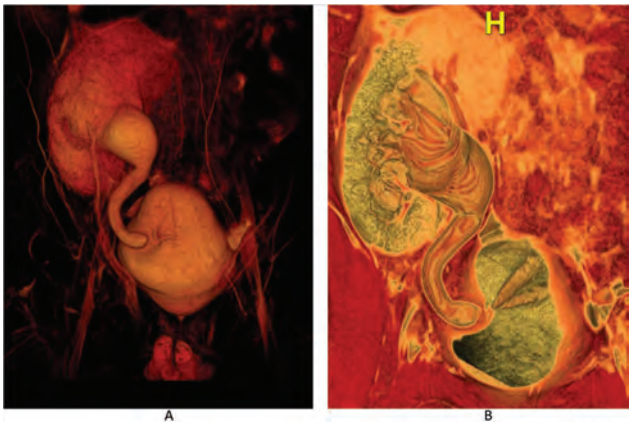
Introduction: After kidney transplantation, hydronephrosis is a common problem that may result from obstruction or reflux. A voiding cystourethrogram entails urethral catheterization, radiation exposure, and patient discomfort. Alternatively, an MR urogram (MRU) can be performed without any potentially toxic intravenous (IV) contrast agent. We present a case that shows the feasibility MRU with an IV saline bolus and furosemide only.

Case Description: A 17 year-old boy with a kidney transplant presented with rising creatinine and recurrent hydronephrosis 9 months after the transplant. The immediate post-transplant course was notable for hydronephrosis and stricture in the ureterovesical junction (UVJ) treated with balloon ureteroplasty one month after surgery. The hydronephrosis improved after balloon ureteroplasty, but over the next 5 months there was a gradual decline in kidney function and the patient experienced recurrent episodes of acute kidney injury (AKI). Renal ultrasound showed recurrence of the hydronephrosis; the differential included recurrence of the UVJ stricture versus reflux. An MRU without contrast revealed "moderate hydroureteronephrosis with tight narrowing at the UVJ." Intraoperatively, stone fragments were discovered along the wall of the distal ureter causing obstruction of the UVJ, but no stricture was present. The ureteral re-implantation was revised to allow passage of possible

future stones. There were no further episodes of AKI or hydronephrosis up to 4 months after the revision.

Discussion: MRU using IV saline and furosemide can yield high-quality 3D images that identify targets for intervention in the setting of renal dysfunction while also avoiding nephrogenic systemic fibrosis.



3D MR urogram without contrast showing (A) moderate hydroureteronephrosis and tight narrowing near the UVJ. (B) Hollow view shows the narrowing near the UVJ followed by the urine jets in the bladder, consistent with partial obstruction.

SA-PO041

Outcomes of Dialysis and Transplantation in Cystinosis from NAPRTCS Database

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Background: Cystinosis (Cys) is a rare genetic disease. There are no sufficient published data on outcomes of dialysis and kidney transplantation in Cys patients (pts). North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) was established in 1987 with the goal to study transplant pts. The database was expanded in 1992 to include dialysis pts. As of 2015, the NAPRTCS has data on over 7039 dialysis and 18225 transplant pts.

Methods: Retrospective analysis of NAPRTCS database of registered dialysis and renal transplant cystinosis pts. Data on Cys pts are compared to other registry pts with non-recurrent, i.e. non-immunologic causes (NIC) of potential graft loss. Specific aims were to investigate potential differences among studied dialysis and transplant pts.

Results: Dialysis data from 95 Cys pts were compared to 1472 NIC dialysis pts. There was statistical significance in blood pressure (BP), height and weight Z-Score, growth deficit, the use of rGH, calcium and PTH levels. Dialysis survival was better in Cys pts (p-value 0.046). There is no statistical difference in gender, dialysis modality, anemia, erythropoietin use, albumin, phosphorus level and time to transplant while on dialysis. Transplant data from 231 transplant Cys pts were compared to 2844 transplant NIC pts. Data was collected in 6 months (mo) interval from baseline at 30 days post transplant (p/Tx) to 60 mo p/Tx. Baseline height Z-Score was low in both groups: with mean Z-Score in NIC -2 and in Cys – 3.39 (p-value<0.005). Though improved height Z-Score at 60 mo p/TX to mean -1.84 in NIC, vs.-2.92 in Cys, the difference remains statistically significant. Weight Z-Score between 2 groups remains statistically significant with baseline mean at -1.22 for NCI vs. -2.59 for Cys. Although weight Z-score is gradually improving over time in both groups, at 60mo p/Tx mean Z-Score for NIC is -0.33 vs Cys -1.68 (p-value <0.005). There was no statistical difference in gender, creatinine levels, systolic and diastolic blood pressure Z-Scores, graft survival, donor source (LRD vs. DD), preemptive transplant, time to first rejection, number of transplants.

Conclusions: Height and weight Z-Scores in Cys dialysis and transplant pts were poorer when compared NIC pts. Cys pts have improved dialysis survival. Cys transplant pts did not differ from NIC pts in BP Z-Scores, donor source, preemptive transplant, graft survival, time to first rejection.

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SA-PO042

Mortality and Morbidity in Kidney Transplant Recipients with a Failing Graft

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Background: There is little information on mortality and morbidity in kidney transplant recipients with a failing graft. Due to their history of renal disease and exposure to immunosuppression, recipients may be at higher risk of adverse outcomes compared to non-transplant controls with similar degree of chronic kidney disease.

Methods: We performed a retrospective study of kidney transplant recipients with a failing graft in Alberta, Canada (2002-2013), defined as ≥2 eGFR measurements between 15-30 mL/min/1.73 m^2 that were 90-365 days apart. We propensity-score matched (1:1) recipients with a failing graft to non-transplant patients on several demographic characteristics, clinical, and laboratory data. We used Cox regression to compare the hazard for death between the two groups and negative binomial regression to compare hospital admission rates.

Results: We identified 521 kidney transplant recipients with a failing graft and matched 487 (93%) of them to a non-transplant control. The median age of the cohort was 56 years (IQR 45-65) and 41% were women. Compared to matched non-transplant controls, kidney transplant recipients with a failing graft had a higher rate of death (hazard ratio 1.25, 95% CI 1.01-1.55; p=0.039) and hospitalization (rate ratio 1.72, 95% CI 1.44-2.06; p<0.001). Kidney transplant recipients also had significantly higher rates of hospitalization for cardiovascular events and infections, but not cancer.

Conclusions: A failing kidney transplant adds further mortality and morbidity burden to chronic kidney disease. This information may assist the discussion of prognosis in kidney transplant recipients with a failing graft and the design of strategies to minimize risks.

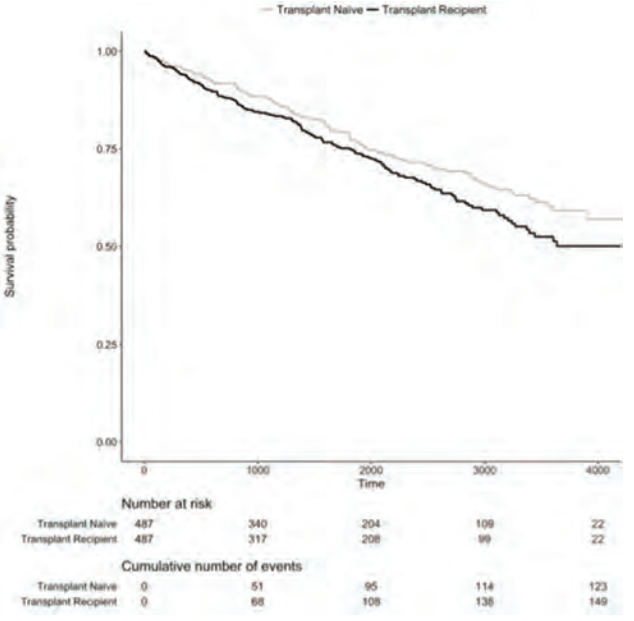

Figure. Kaplan-Meier estimated survival probabilities stratified by transplant status

SA-PO043

Benzodiazepines and Opioid Co-Prescriptions: Outcome Implications in Kidney Transplant Recipients

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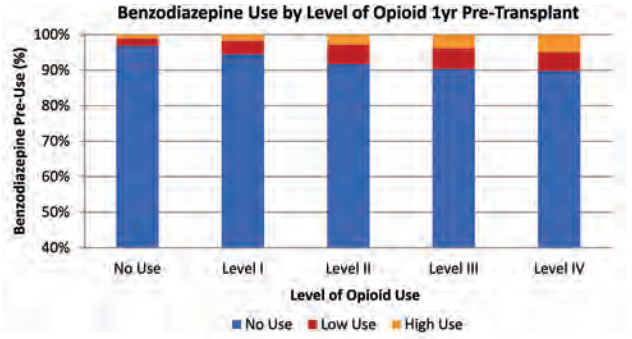
Background: Recent studies identify coprescription of benzodiazepines and opioids as a risk factor for adverse outcomes in the general population. We previously described associations of opioid use before kidney transplantation (KTx) with mortality after KTx, but the implications of benzodiazepine use in the KTx population have not been described.

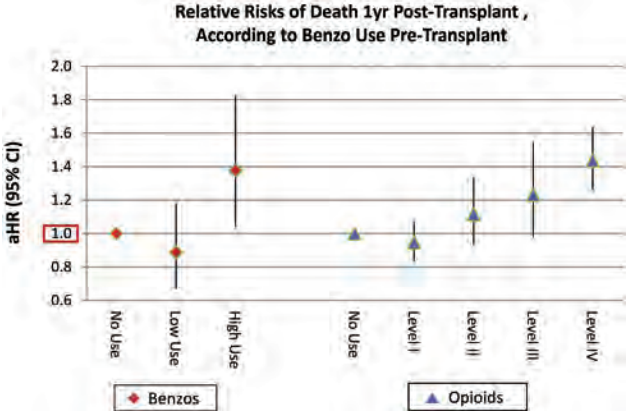
Methods: We examined a novel linkages of SRTR registry data with records from a pharmaceutical claims warehouse (2008-2015) to characterize benzodiazepine and opioid use in the year before KTx and associations (adjusted hazard ratio, $_{95\%\ LCL}$aHR$_{95\%\ UCL}$) with death over 1yr post-KTx.

Results: Among 75,430 KTx recipients with available medication data in the year prior to KTx, 7.3% & 43.1% filled a prescription for a benzodiazepine or opioid in the pre-KTx year. Use of both medications was more common among recipients who were white, unemployed, and received prior KTx. Benzodiazepine use rose with higher opioid use, from 3.2% among opioid non-uses to 10.2% among those with highest level opioid use (**Fig 1**). Compared to non-users, high-level pre-KTx benzodiazepine use was associated with a 51% (aHR $_{1.14}1.51_{1.99}$) increased risk of death in the year after transplant. Opioid use bore a strong graded relationship with post-KTx survival, and prognostic impact high pre-KTx benzodiazepines was preserved after adjustment for opioids, although an interaction was not present (aHR $_{1.04}1.37_{1.83}$) (**Fig 2**).

Conclusions: Benzodiazepines use is correlated with opioid fills before KTx, and these agents have additive associations with post-KTx mortality. Future research is needed

to examine mechanisms of these associations and impact of reducing coprescription on improving outcomes after KTx.





SA-PO044

Transplantation for Veterans Receiving Dialysis in VA and Non-VA Settings

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Background: Veterans with end-stage renal disease can receive dialysis under a range of different settings and payment structures including Medicare community dialysis, VA, and VA-purchased community-based dialysis (VA-PC). An earlier study reported similar rates of renal transplant among VA and Medicare users but little is known about rates of transplantation among Veterans receiving dialysis in different settings. This study compares receipt of renal transplantation among Veterans across dialysis settings.

Methods: We merged VA and Medicare data to construct a national cohort of VA-enrolled Veterans who initiated chronic dialysis in 2008-2011. Cohort members were classified based on dialysis setting during the 2-year period immediately following dialysis initiation: VA, VA-PC in community, Medicare-financed dialysis in community, or more than one of these arrangements ("Dual settings"). We used a Cox proportional hazards model (censoring at death) to examine associations between 2-year dialysis setting and transplantation, adjusting for patient characteristics.

Results: Of the 27,301 cohort members, 67% received dialysis under Medicare only, 11% received dialysis through VA-PC only, 4% were treated in VA only, and 18% were treated in Dual settings. Roughly 2.5% of Veterans received a kidney transplant within 2 years, in an average 375 days after dialysis start (median=366, IQR=358). In adjusted analyses, Veterans receiving dialysis in VA, VA-PC, and Dual settings had similar transplantation rates that were lower than those under Medicare (HR=0.45, 95% CI= 0.29, 0.72; HR=0.49, 95% CI=0.35, 0.68; and HR=0.57, 95% CI=0.43, 0.76, respectively). Estimated 2-year transplant rates are shown in Fig 1.

Conclusions: Rates of renal transplant are lower among Veterans who receive any VA-financed dialysis than for those receiving Medicare-financed dialysis. More work is needed to identify barriers to kidney transplant among Veterans whose dialysis is financed by the VA.

Funding: Veterans Affairs Support

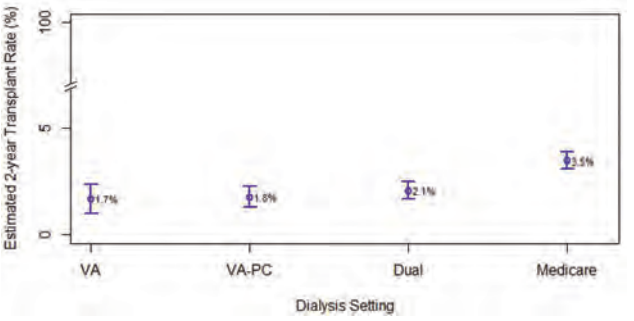

Fig 1. Estimated 2-year transplantation rates, by dialysis setting

SA-PO045

Is It Time to Switch? Comparing Transplant Outcomes Among Dialysis Modalities: Analysis from the United States Renal Data System (USRDS)

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Background: The effect of pre-transplant dialysis modality (DM) on transplant (Tx) outcomes has been a topic of study for many years. However, studies have largely compared patients (pts) on a single modality, either hemodialysis (HD) or peritoneal dialysis (PD). Though still controversial, pts on PD have been shown to have a higher likelihood of Tx, shorter time to Tx, and higher recipient survival rates than pts on HD. It is unknown whether pts who switch from HD to PD benefit similarly. This question has become particularly important given the incentive provided by the prospective payment system dialysis bundle for transitioning pts to PD. The aim of our study was to compare the effect of DM, including pts who switch from HD to PD, on the likelihood of Tx, time to Tx and recipient survival.

Methods: Our study is a retrospective analysis of data obtained from the USRDS from May 2012 to December 2015. Pts were divided into 3 groups: HD only (n=637778), PD only (n=43733) and pts who switched from HD to PD (n=23816); pts who switched from PD to HD were excluded. Groups were then compared to determine the likelihood of Tx among each group. Groups were further divided into pts who had received a single kidney Tx to determine the effect of DM on time to Tx and recipient survival rate. Statistical analysis included Contingency Analysis for likelihood of Tx, Oneway ANOVA for time to Tx, Kaplan-Meier survival curves, and Cox Proportional Hazards for the effects of predictor variables on pts survival.

Results: Pts in the HD to PD group had a higher likelihood of Tx (5% absolute, $p<0.01$), shorter time to Tx (1.54 years, $p<0.01$), and higher recipient survival compared to the HD only group ($p<0.01$). Besides higher age upon dialysis initiation, the only baseline characteristic negatively affecting survival in the HD to PD group was the presence of diabetes. This group also had similar advantages over the PD only group except for likelihood of Tx.

Conclusions: Our study showed that pts who switched from HD to PD had a higher likelihood of Tx, shorter time to Tx and improved recipient survival compared to other DM. Given the potential benefit gained by pts on PD, switching to PD regardless of initial modality may lead to improved Tx outcomes.

SA-PO046

Cost of Follow-Up Care within the First Year of Kidney Transplantation at the National Kidney and Transplant Institute

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Background: The high cost of kidney transplantation (KT) and follow-up care contribute to the low rate of transplantation among Filipino End Stage Renal Disease (ESRD) patients. The cost of transplant procedures is better understood and provided basis for a transplant benefit package in the National Health Insurance Program. However, no studies on the cost of follow-up care, particularly on which subgroups of patients incur higher costs have been done in the Philippines. **Objectives.** This study aims to estimate the direct medical cost of follow-up care within the first year of kidney transplantation.

Methods: We analyzed records of 129 adult Filipino patients who underwent primary kidney transplant from June 2014 to May 2016 at the National Kidney and Transplant Institute (NKTI). A subgroup analysis based on immunologic risks as well as comorbidities using the Charlson comorbidity index (CCI) was also done. Direct costs of medical care were estimated by computing for the average cost of medical care consisting of professional fees, medicines and supplies, and diagnostics for both outpatient consults and hospital admissions.

Results: The estimated average direct cost of medical care within the first year of transplantation was PHP 655,616 (USD 13,312 based on USD1=PhP50) per patient. Those with high CCI incurred 46% higher average direct cost than those with low CCI (USD 17,899 vs USD 11259). Diabetics incurred 56% higher costs compared to non-diabetics (USD 20,237 vs USD 11,399). The difference in average cost between those with high immunologic risk and low immunologic risk was negligible. The cost of care showed a downward trend in the first year post KT, regardless of immunologic risk or CCI score. For

outpatient care, medications (85%) was the main cost driver while for admitted cases it was diagnostic work-up (37%).

Conclusions: The high cost of outpatient medications, especially for immunosuppressive drugs and insulin therapy, indicate the need for financing of follow-up care after kidney transplantation. A prospective study with a span of more than a year is needed to better understand the cost of follow up care after transplantation.

SA-PO047

Economic Impacts of Alternative Kidney Transplant Immunosuppression: A National Cohort Study

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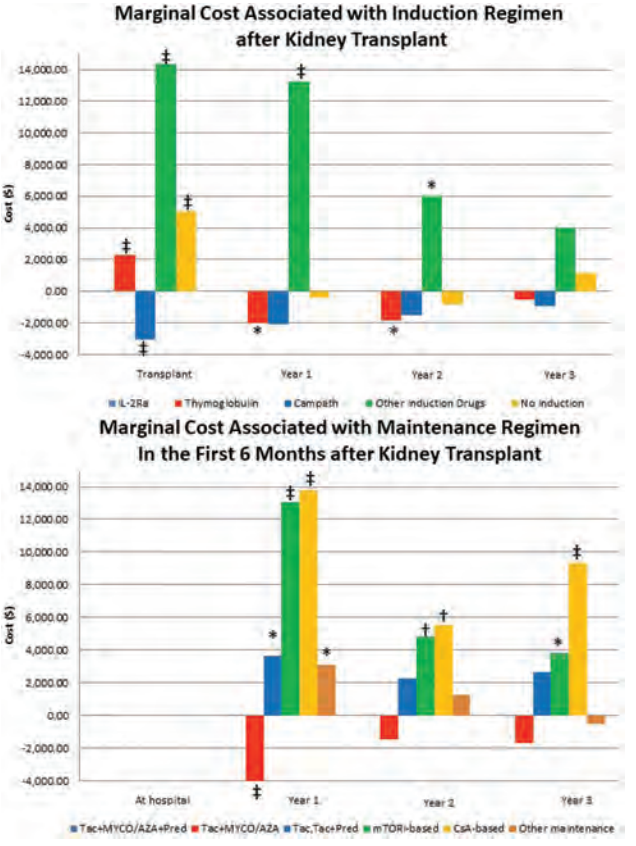
Background: Economic outcomes are increasingly considered along with clinical efficacy to guide choice of alternative therapies. We examined the cost impact of kidney transplant (KTx) induction and maintenance suppression (ISx) in a large national US cohort.

Methods: Cost data for the transplant hospitalization were drawn from linkage of the SRTR registry with financial records from the University HealthSystem Consortium of US academic hospitals (2002 –2013, N= 62,002 KTx). Cost of post-transplant care were estimated from Medicare Part A %B payments (N= 62,698). Marginal costs of induction (all periods) and maintenance (Yr 1, Yr 2, Yr 3) ISx were estimated from multivariate regression, including adjustment for baseline recipient, donor, and transplant factors.

Results: Compared to IL2rAb, Thymoglobulin (TMG, $10,066) and other induction ($21,627) was associated with increased costs of the transplant hospitalization, while Campath was initially cost saving ($4,208. Subsequently, patients induced with TMG had significantly lower costs in Yr1 ($2,108) and Yr 2 ($1,834) post-KTx. Compared to triple maintenance ISx, steroid-free recipients incurred lower costs in Yr 1 ($4,011), while all other maintenance regimens were associated with higher costs in Yr 1. Patients who received mTORi-based and CsA-based ISx continued to incur higher costs in Yrs 2 and 3 post-KTx. (**Figure**)

Conclusions: Induction and maintenance ISx are associated with differential costs of care during the transplant hospitalization and post-transplant periods, which may be mediated by different complication rates. Initial higher costs of TMG induction appear to be followed by later cost savings

Funding: NIDDK Support



SA-PO048

RISE to Transition: A Structured Transition Protocol for Renal Transplant Recipient Children

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Background: The transition from pediatric to adult medical services is an important time in the life of an adolescent or young adult with a renal transplant. Failure to properly transition can lead to medical non-adherence and subsequent loss of graft and/or return to dialysis.

Methods: To establish a locally-adapted, patient-focused, kidney transplant transition program, we implemented the RISE protocol. This was defined by four competency areas: Rise, Insight, Self-Reliance, and Establish; identified through literature review and experience. Seventeen patients (6 female and 11 males, mean age 14.5 yrs), who received a renal transplant in the preceding 2-9 years (mean 5.6 years, median 7), went through transition protocols. The transition process spanned two years to overlap medical care between pediatric nephrologists and key adult physicians and related services. The final transition was completed at 21 years of age.

Results: Adolescents and parents did not differ significantly in their general views and stated that they would appreciate the support provided by a transition program. However, the parents appreciated the support during transfer significantly more than did the adolescents. Eighty five percent of patients and family felt generally well informed of the RISE transition. However, 70% preferred to receive more information about their disease and overall health during their transfer period. When asked for the key person during the transfer, 62% of respondents mentioned the pediatrician, 6% said "others," and 30% stated that it was the nurses. The relevant issues during transfer were cited as medication (35%), education and employment (27%), disease knowledge (13%), and environment in the adult service (25%).

Conclusions: RISE protocol and its four competency areas are the key to an effective transition to the adult services. Self-reliance and the establishment of healthy choices aim to improve patient autonomy and emotional burden, and to minimize disruptions in their daily lives. Recognition and insight aim to educate the patient in all aspects of their disease. Education about medical, social, vocational/educational, and interpersonal effects of their disease and treatment will help to improve adherence as well as alter patient perspectives of their disease.

SA-PO049

Kidney Cancer After Renal Transplant: 14 Year Review

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Background: Renal transplant patients are 7 times more likely than the general population to have renal cell carcinoma (RCC). Possible explanations include immunosuppression leading to increased oncogenic viral infections and acquired cystic kidney disease from hemodialysis. Due to the rapid growth and metastasis of RCC, renal ultrasounds (US) have been used as a screening tool; however, there is no uniform guideline on US frequency after renal transplantation.

Methods: Retrospective chart review of 962 renal transplant recipients at Sentara Norfolk General Hospital from 7/1/04-9/30/17 was performed. All patients received similar immunosuppression regimens and serial US by protocol at year 1,3,5,7,9,11 and 13 after transplant. Data involving gender, race, age at transplant, underlying cause of ESRD, and US results were collected. Tumor characteristics including timing of development, mass location, pathology, staging, and outcome were assessed.

Results: 27 RCC cases were diagnosed in 19 patients. RCC incidence was 2.8%. Multifocal RCC was seen in 4 patients (3 at the same interval, 1 four years after previous nephrectomy) and all had bilateral nephrectomies. RCC was significantly higher in males than females (89% males, 11% females, $p<0.05$). Median time of RCC diagnosis was 3.55 years. Tumor staging was 78% T1aNxMx, 18% T1bNxMx, 4% T3aNxMx. All patients had nephrectomies.

Conclusions: Renal US at 2 year intervals after transplant captured all RCC cases. 5 patients were diagnosed in between the standard interval due to symptoms (e.g. hematuria). Men are at increased risk of RCC. Polycystic kidney disease is not associated with developing RCC. All RCC involved native kidneys and were cured with nephrectomy. Biannual US should be continued indefinitely after transplant and on any remaining kidneys after nephrectomy due to multi-centric occurrence.

US post-transplant (years)	RCC cases/total RCC	Age of transplant (years)	RCC cases/total RCC	Etiology of ESRD	RCC cases/total RCC	Tumor characteristics	RCC cases/total RCC
0-1	3.7%	30-40	15%	Hypertension	44%	Clear cell	33%
1-3	22%	40-50	22%	Diabetes mellitus type 2	37%	Papillary	41%
3-5	48%	50-60	30%	Polycystic kidney disease	4%	Oncocytoma	7%
5-7	19%	60-70	33%	Unspecified glomerulonephritis	11%	Chromophobe	4%
7-9	0%			Calcineurin inhibitor nephrotoxicity of previous transplant	4%	Tubulocystic	4%
9-11	3.7%					Unclassified	11%
>11	3.7%						

SA-PO050

Exposure to a Functioning Kidney Transplant and Cancer Risks

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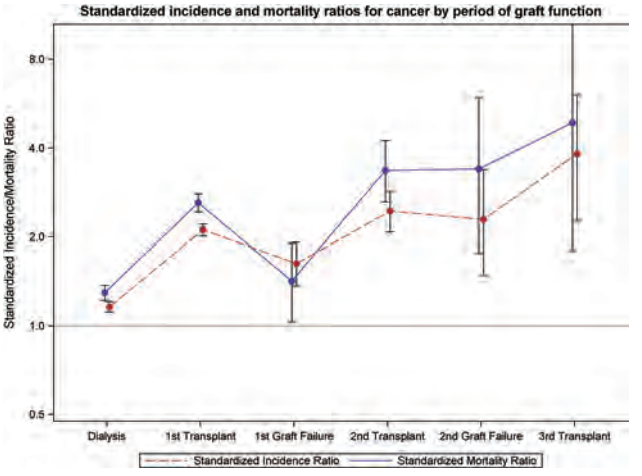
Background: Kidney transplant recipients experience higher cancer incidence and mortality compared to the general population. It is uncertain whether this increased risk varies with graft function. This study aims to compare the cancer incidence and mortality rates in transplant recipients during periods of graft function and graft failure with the age- and gender-matched general population.

Methods: All Australian patients who commenced renal replacement therapy between 1982 and 2014 were included from the Australia and New Zealand Dialysis and Transplant Registry. Cancer incidence and mortality for dialysis patients and transplant recipients during periods of graft function and graft failure were compared with the Australian general population using standardized incidence (SIR) and mortality (SMR) ratios.

Results: A total of 47,127 dialysis patients without transplants, 15,413 with 1st transplants, 3873 after 1st graft failure, 1596 and 545 with 2nd transplants and 2nd graft failure were identified and followed for 297,626 patient-years. The standardized incidence and mortality rates (per 100,000 patient-years) were 727 and 336 in dialysis patients; 1322 and 675 in recipients with 1st transplants; 1017 and 367 after 1st graft failure; 1531 and 870 for 2nd transplants and 1434 and 880 after 2nd graft failure. Cancer SIRs (95% CI) and SMRs (95% CI) were 1.2 (1.1-1.2) and 1.3 (1.2-1.4) for dialysis patients; 2.1 (2.0-2.2) and 2.6 (2.4-2.8) for recipients with 1st transplant; 1.6 (1.4-1.9) and 1.4 (1.0-1.9) after 1st graft failure; 2.4 (2.1-2.9) and 3.4 (2.6-4.2) for 2nd transplants; 2.3 (1.5-3.4) and 3.4 (1.8-5.9) after 2nd graft failure.

Conclusions: An increased cancer incidence and mortality risk is observed during periods with a functioning kidney transplant. Among patients with failed allografts, cancer incidence and mortality remained higher than the general population, but the increased risk appears lower than recipients with functioning grafts.

Funding: Government Support - Non-U.S.



SA-PO051

Post-Transplant Survival Among Patients with Pretransplant Treatment for Prostate Cancer

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Background: Optimal pre-kidney transplant treatment and waiting time for transplant among patients with prostate cancer is unclear.

Methods: We studied male patients, 40 years or older, with ESRD who had Medicare claims for prostate cancer and two main types of treatment (radiation and prostatectomy) utilizing USRDS (United States Renal Data System). We stratified patients into three categories based on waiting time to transplant from the time the prostate cancer was treated (0-2, 2-5, >5 years). We used Kaplan-Meier method to compare post-transplant survival among the strata. We used Cox proportional hazards model to assess relative risks of death between the groups.

Results: There were a total of 920 patients who had kidney transplants with prior history of treatment for prostate cancer. Figure 1a shows KM curves, stratified by waiting time (p-values = <0.01). Compared to 0-2 years of waiting time, 2-5 years had 13% higher likelihood of death (HR: 1.13, 95% CI:0.88-1.44) and >5 years had 73% higher likelihood of death (HR: 1.73, 95% CI:1.30-2.3). Prostatectomy was associated with a better post-transplant survival than radiation (Figure 1b).

Conclusions: Prostatectomy and kidney transplant without significant delay may be optimal choices for patients with prostate cancer and eligible for kidney transplant.

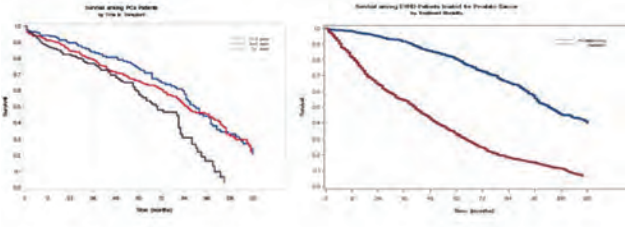

Figure 1a Figure 1b

Kaplan Meier survival curves for patients, stratified by waiting time (1a) and type of treatment (1b)

SA-PO052

Long-Term Outcomes of Sequential Hematopoietic Stem Cell Transplantation and Kidney Transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) patients are known to be at risk for both acute and chronic kidney disease. Experience on sequential HSCT and kidney transplant (KT) is limited.

Methods: We conducted a retrospective cohort study of adult patients who underwent both HSCT and KT at Mayo Clinic, Rochester, between 1988 and 2018.

Results: In our cohort of 54 patients, male represented 57% (n=31) and the median age was 64.2 (56.8, 70.1) years-old. Thirty-six patients (66.7%) received HSCT first followed by KT, while 18 (33.3%) received KT prior to HSCT. In both groups, immunoglobulin related amyloidosis represented 50% of hematologic diagnosis. Living kidney donor was equally distributed in both groups, representing 83% (n=45) of the donors, with 60% (n=27) from a relative. T-cell depleting induction was significantly more frequent in

the KT first group (94% vs 19%, p<0.001). Primary kidney disease recurrence was not significantly different in HSCT first vs KT first (19% vs 39%, p=0.19), and both groups displayed excellent kidney allograft survival at 1y (94% vs 89%) and 5y (94% vs 89%), p=0.51. KT first did not affect allograft outcome (HR 1.7, 95% CI 0.4-7.9, p=0.51) nor did maintenance immunosuppression (HR 2.8, 95% CI 0.6-11.9, p=0.16). Acute cell mediated rejection (ACMR) seemed to worsen KT prognosis (HR 10.7, 95% CI 1.6-71.7, p=0.01). However, in multivariate analysis, ACMR revealed only a trend towards significant worse allograft prognosis (HR 22.8, 95% CI 1.0-520.8, p=0.05). Overall patient survival was better in patients submitted to HSCT first, both at 5y (97% vs 76%) and 10y (90% vs 63%), p=0.0001. EBV seronegative status at KT (HR 2.9, 95% CI 1.1-7.8, p=0.039), KT first (HR 6.0, 95% CI 2.2-16.5, p=0.0001), use of T-cell depleting agent (HR 3.2, 95% CI 1.2-8.7, p=0.02), severe infection (HR 19.6, 95% CI 2.6-148.1, p=0.004) and renal allograft failure (HR 3.2, 95% CI 1.2-8.8, p=0.02) were significantly associated with poor patient outcome. In multivariate analysis, only history of severe infection was significantly associated with poor survival (HR 14.0, 95% CI 1.6-125.8, p=0.02).

Conclusions: Our study supports KT safety in patients with history of HSCT, with better allograft function and overall patient survival observed when HSCT is performed first.

SA-PO053

Post Transplantation Anemia: Causes, Severity and Their Association with Graft and Patient Survival

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Background: Post transplantation anemia (PTA) is common among kidney transplant patients. PTA is associated with increased graft loss and in most studies with increased mortality. We aimed to evaluate association of PTA its severity and specific causes with late outcomes.

Methods: Patients who underwent kidney transplantation in Rabin Medical Center (RMC). Data were collected from the kidney transplant registry during the years 2002-2016. Anemia was defined in accordance with World Health Organization (WHO) criteria, severe anemia was defined as hemoglobin lower than 11 g/dL. We evaluated all separate anemia events during the follow-up period, for each event a full laboratory workup was collected. Specific causes for each anemia episode were documented (acute rejection, acute kidney injury [AKI], infection and nutritional deficiencies). Primary outcome was a composite of patient and graft survival. We used univariate and multivariate time varying Cox models to evaluate association between severity and specific causes of anemia to the outcomes.

Results: Our cohort included 1139 patients, out of which 412 (36.2%) had PTA during the follow-up period. Distribution of causes of anemia were acute rejection and/or AKI (11.9%), infections (16.7%), hematological disorders, bleeding or hemolysis (9%) and nutritional deficiencies (29.1%). No obvious reason was found in 137 patients (33.3%). On multivariable analyses, the anemia group was significantly associated with a composite of graft loss and mortality, (HR 2.063, 95% CI 1.542-2.761, p<0.001), and with each outcome separately. Severe anemia was significantly associated with graft loss and mortality combined (HR 4.362, 95% CI 3.035-6.270, p<0.001) and separately. A weaker association was found between mild anemia and graft loss, but not with mortality. Causes of anemia: AKI & acute rejection (HR 5.570, 95% CI 3.784-8.198, p<0.001), infectious (HR 2.483, 95% CI 1.536-4.016, p<0.001) and nutritional deficiencies (HR 1.882, 95% CI 1.203-2.942, p=0.006) were all associated with graft loss or mortality.

Conclusions: PTA is associated with graft loss and mortality. Anemia severity and etiology affects this association. An anemia workup is recommended for PTA.

SA-PO054

Predicting CKD in Lung Transplant Recipients

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Background: There is a high incidence of chronic kidney disease (CKD) following lung transplantation. We examined baseline risk factors for CKD in a cohort of patients who had undergone lung transplantation.

Methods: Retrospective cohort study of 333 patients who underwent lung transplantation between January 2005 and September 2016. The follow-up period ended April 2018. Of 333 patients, we excluded: 22 underwent transplantation elsewhere; 26 had prior CKD; 8 had fewer than two outpatient serum creatinine values available; 10 died within 6 months; 2 were excluded for missing BMI data; and 17 lacked data on pre-transplant pulmonary arterial systolic pressure. The primary outcome was CKD III at up to 2 years following lung transplantation, defined by two eGFR values < 60 ml/min/1.73 m^2 at least three months apart on outpatient labs.

Results: Of the 248 eligible patients, 185 developed CKD III or worse. In a multivariate logistic regression model, age (OR 1.06, per year, 95% CI 1.02-1.11) and female sex (OR 4.42, 95% CI 1.92-10.18) were associated with a higher risk of CKD III. The following pre-transplant variables were not significantly associated with increased risk of CKD: body mass index (BMI), pulmonary arterial systolic pressure (PASP), diabetes, hypertension, or etiology of lung disease. Higher pre-transplant eGFR showed a trend towards a lower risk. New onset hypertension post-transplant was not associated with CKD III.

Conclusions: Older and female patients are at higher risk for developing CKD III after lung transplantation. Future research should evaluate risk factors for additional renal outcomes, including acute kidney injury, dialysis and renal transplantation.

Funding: NIDDK Support

Multivariate adjusted odds ratios for CKD III in lung transplant patients

Effect	Odds Ratio	95% CI	
Age, y	1.06	1.02	1.11
Female	4.42	1.92	10.18
BMI, kg/m2	1.02	0.94	1.12
Estimated GFR (eGFR), per 10 ml/min/1.73m2	0.84	0.64	1.00
Pulmonary Artery Systolic Pressure, mmHg	1.02	1.00	1.04
Cystic Fibrosis vs other	2.00	0.55	7.24
Chronic Obstructive Pulmonary Disease vs other	2.94	0.61	14.22
Idiopatic Pulmonary Fibrosis vs other	2.19	0.83	5.78
Pre-transplant Diabetes Mellitus	0.81	0.33	1.96
Pre-transplant Hypertension	0.95	0.37	2.45
New Onset Hypertension	1.25	0.54	2.88

SA-PO055

Outcomes of CRRT in Patients with End Stage Liver Disease (ESLD)

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Background: Patients with ESLD have high mortality when dialysis is required. In 2015, a hepato-renal service was started in order to improve outcomes of patients with combined kidney-liver failure. We compared outcomes of all ESLD patients that underwent CRRT (venous-venous hemofiltration) before and after the implementation of the novel inpatient rounding service.

Methods: Patients undergoing CRRT with a concomitant diagnosis of ESLD (based on ICD-9/10 codes) were identified in the pre year (all of 2013 n = 46) and the post hepatorenal service year (all of 2016, n = 39). Charts were then manually reviewed to confirm diagnoses, and compare the cohorts by t-test/Mann/Whitney for continuous variables, and chi-square/Fisher's exact for categorical variables.

Results: There were no differences in the two cohorts (2013 and 2016) for age, gender, BMI, cause of ESLD, ascites, etoh intake, smoking and baseline co-morbidities on admission. More patients had a history of CKD in 2013 than in 2016 (p<0.002). CRRT was started after 4 and 7 days from admission (median, 2013 and 2016 respectively). At the time of initiation of CRRT, there was no difference between the two cohorts in laboratory data (albumin, sodium, INR, creatinine, bilirubin), or MELD score. The outcomes of patients in both cohorts are shown in Table 1.

Conclusions: Patients with ESLD requiring CRRT have very high mortality within 90 days unless transplanted, higher than predicted by MELD scores. The implemtation of a hepato-renal inpatient rouding service staffed by both Nephrology and Hepatology facilitated collaborative and consistent decisions about goals of care in these critically ill patients, increasing the proportion of patients transplanted.

Outcomes of ESLD patients receiving CRRT

	Admit MELD Score (mean/SD)	Transplanted p = 0.04	Alive at 30 days from admission	Alive at 90 days from admission (p = 0.35)	Discharged home/LTAC at 90 days (p = 1.0)
2013	33 ± 7.0	0 out of 46	6 out of 46	4 (8%)	3
2016	31 ± 7.2	5 out of 39 (three livers, one liver-kidney, one multi-visceral)	7 out of 39 (3 on dialysis, 4 transplant) Multi visceral tx died	7 (18%)	6

SA-PO056

Systematic Review of Risk Indices Used in Pancreas Transplantation

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Background: Risk indices (RI) using donor and recipient characteristics assist in organ allocation and acceptance decisions by predicting post-transplant outcomes such as graft and patient survival. While RI have been derived for use in pancreas transplantation (PTx), they are not widely utilised. We intend to review the ability of available RI to predict PTx outcomes.

Methods: Medline Plus, Embase via OVID and the Cochrane Library were searched for studies describing derivation or use of RI in PTx up to 1st November 2017. Primary outcomes of interest were pancreas graft and patient survival, with secondary outcomes of organ acceptance. Data extraction was performed using the Checklist for Critical Appraisal and data extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) and risk of bias assessment was done via the Quality in Prognostic Studies (QUIPS) tool.

Results: 2418 abstracts were screened with 32 studies entering full-text analysis. Of these 32 studies, 8 were abstracts with no full-text retrievable despite contacting authors. 10/32 studies derived 23 models predicting outcomes of interest. 2/23 models were RI that were externally validated in 24/32 studies. 21/23 models were derived without external validation. RI were the pancreas donor risk index (PDRI) and the pancreas pre-procurement score (P-PASS). Apart from their covariates, common covariates in other models included recipient age and body mass index (BMI), dialysis duration pre-transplant, history of diabetes, transplant type, and immunosuppression regimen. Risk of bias was generally low in the studies with model derivation. Conversely, abstracts tended to have high risk of bias. Deficiencies in reporting included handling of missing data, covariates and follow-up duration. Discrimination and calibration was only described in 10 and 2 studies respectively.

Heterogeneity was present in model derivation method, outcome definitions and study results. PDRI was significantly associated with pancreas graft survival in 9 studies and P-PASS was significantly associated with pancreas donor acceptance in 3 studies.

Conclusions: RI in PTx have not been widely validated apart from P-PASS and PDRI. Within a validated cohort, PDRI (as a categorical variable) and P-PASS have value in predicting pancreas graft survival and in predicting donor pancreas acceptance respectively.

SA-PO057

One-Year Outcome Experience of Deceased Donor Kidney Transplantation Post-KAS Implementation

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Background: The new kidney allocation system (KAS) implemented on December 4, 2014, has a goal to improve access to transplant for under represented groups, such as the highly sensitized patients (calculated panel reactive antibodies, cPRA ≥90%).

Methods: We performed a single-center retrospective review of transplants performed on highly sensitized recipients and compared outcomes, in relation to the implementation of KAS.

Results: 164 DDKT were performed in 22 months prior to KAS implementation whereas 187 were performed 22 months post-KAS implementation. Out of 351 transplants during this period, 33 had a PRA of ≥ 90% (11 pre-KAS, 22 Post) and 14 had a PRA of 100% (2 Pre, 12 Post) consistent with the bolus effects seen in the previous reports. We also compared the one-year outcomes of patients with '0' cPRA with ≥ 90% CPRA. Out of 148 patients selected between periods of December 2014 to October 2016, 126 had cPRA of 0% and 22 had a cPRA of ≥ 90. All patients had at least one-year post-transplant follow up. We didn't find any significant differences in primary outcomes of graft survival, all-cause mortality, delayed graft function and return to dialysis (table 1). Cold ischemia time was significantly higher post KAS possibly owing to a greater regional sharing (table 2). Although biopsy-proven rejection was more prevalent in highly sensitized patients compared to non-sensitized it was not statistically significant. Unlike previously published reports, we didn't find any difference in outcomes among the two groups based on waitlist time and time on dialysis. Additionally, duration of hospital stay, readmissions and serum creatinine was similar in both groups.

Conclusions: Results are reassuring as we found no differences in outcomes between both groups but it still warrants long-term follow up.

Table 1 – Odds ratio of outcomes of zero cPRA when compared to high cPRA

	Odds ratio	Confidence interval	P-value
Delayed graft function	3.26	0.72-14	0.18
All-cause mortality	0.47	0.089-2.5	0.71
Graft survival	3.1	0.52-17.7	0.51
Any type Rejection	0.425	0.13-1.3	0.25
Dialysis at 1 year	0.867	0.09-7.8	0.89

Table 2 – Medians of baseline characteristics of zero CPRA compared to high cPRA

	Median 0 cPRA	Median 90-100% cPRA	Mann-Whitney U stats	P-value
Cold ischemia time (hours)	12.42	17.54	734	0.0004
Dialysis days before transplant	1556	1736	1191	0.29
Waitlist time (days)	1599	1736	1160	0.22
Hospital days during transplant admission	6	7	1284	0.57
Creatinine	1.62	1.43	1213	0.35
Number of readmissions	1	2	1267	0.51

SA-PO058

The Impact of New Kidney Allocation System on Health Care Utilization

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Background: The kidney allocation system (KAS) in the United States was dramatically changed in December 2014 with the goal of increasing access, decreasing inequities and improving longevity matching. Studies have shown that duration of pre-transplant dialysis, cold ischemia times and delayed graft function rates significantly increased as a result. We hypothesize that these downstream effects of KAS would impact health care resource utilization- namely readmission rates and length of hospital stay.

Methods: The Organ Procurement and Transplantation Network's Standard Transplant Analysis and Research (STAR) file containing only adult deceased-donor kidney only transplants from 6/3/14- 6/5/2015 was analyzed. The cohort of recipients transplanted in the 6 months prior to KAS was compared to a cohort of those transplanted during the first 6 months after the allocation change.

Results: A total of 11,964 kidney-only transplants with six months of post-transplant follow-up data were included in the analysis. Demographics were comparable between the two groups. Median length of hospital stay post-transplant was not different between groups (median 5 days, IQR 4-8 for both). Hospital readmissions within 6 months of transplant discharge, however, were significantly higher post-KAS (37.4% vs. 40.1%, p=0.004). Reasons for readmission were not included as part of the dataset, but due to increased rates of delayed graft function and its consequences in the post-KAS cohort 23.7% pre vs. 29.9% (p<0.001), it is hypothesized that known related complications such as hyperkalemia, acid-base disturbances and fluid imbalance may have contributed to readmissions.

Conclusions: Although the new kidney allocation system seems to be achieving many of the goals it set out to accomplish, it appears that more health care resources are being utilized post-transplant as measured by readmission and delayed graft function rates. Insurers and hospital administrators should be aware of the potential constraints and make accommodations in contract language and reimbursement rates as a result of the observations from this study. A formal cost-effectiveness analysis should be the subject of future investigations.

SA-PO059

Use of Virtual Crossmatch Exclusively to Allocate Deceased Donor Kidney Transplant

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Background: Virtual crossmatch (VXM) using Luminex single antigen bead has significantly improved prediction of a negative crossmatch due to its high sensitivity. An actual pretransplant lymphocyte crossmatch such as complement dependent cytotoxicity crossmatch (CDCXM) or flow cytometry crossmatch (FCXM) is typically required; however, it may delay deceased donor renal transplantation (DDRT) and possibly affect allograft outcomes. We evaluated the safety of only using VXM pretransplant without waiting for actual crossmatch to allocate DDRT.

Methods: In our center, we have initiated a protocol to allocate kidneys from brain-dead deceased donors based on VXM since 2015. 46 DDRT were performed at our center between 2010 to 2017. 21 (45%) recipients only underwent pretransplant VXM, and all were found to have a negative FCXM retrospectively. We evaluated the effect of this protocol on cold ischemia time (CIT), delayed graft function (DGF), acute rejection (AR) within first year post transplant, and graft survival.

Results: There was a significant reduction of CIT by more than 6 hours (P=0.001) when FCXM was not done prospectively prior to transplant. 3 out of 25 (12%) patients with prospective FCXM had DGF, while no DGF was observed in retrospective FCXM (P=0.2). AR within first year occurred in 4% of prospective vs. 5% retrospective FCXM. 1-year and 3-year graft survival rates were 96% vs. 100% and 92% vs. 88%, in prospective vs. retrospective FCXM, respectively.

Conclusions: Use of pretransplant VXM exclusively for final DDRT allocation decision reduces duration of CIT and may reduce incidence of DGF without increasing risk of AR or affecting graft survival

SA-PO060

Disproportionate Allocation of High Quality Kidneys to Highly Sensitized Recipients in the New Kidney Allocation System Despite a Limited "Bolus Effect"

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Background: The 2014 Kidney Allocation System (KAS) aims to minimize death with functioning grafts, and increase transplantation rates among highly sensitized patients (PRA≥98%). We examined if preferential allocation to high PRA patients results in disproportionate allocation of high quality kidneys (Kidney Donor Performance Index < 0.2) to these patients, and if a "bolus effect" dissipates the allocation over time.

Methods: Using the UNOS data, kidney transplantations from the start of the new system 12/4/2014-12/31/17 (study group) were compared with those for two preceding years - 12/4/2012-12/3/2014 (control group) for pre- and post-transplant characteristics, and overall graft and patient survival.

Results: Excluding living donors (n=28,785) and multi-organ transplants (n=8,896), there were 37,933 recipients in study group, and 21,412 in control group. One year patient and graft survival in the study versus the control group were 96.8% vs 96.9% (p<0.0001) and 94.4% vs 94.2% (p<0.0001) respectively. In the study group, 4,564(12%) high PRA patients were transplanted, compared to 704(3.3%) in the control group. 1,384/8,180 (16.9%) of high quality kidneys in the study group were received by high PRA patients, compared to 181/4,542 (4%) in the control; four-monthly analysis of the study group shows that high PRA recipients of these kidneys decreased from 116/532 (21.8%) in December 2014–March 2015 to 122/936 (13.03%) in September–December 2017. Among these high PRA recipients of high quality kidneys, there was no difference in one year patient (98% vs 96.1%, p=0.8) and graft survival (96.6% vs 92.2%, p=0.5) between the study and control group respectively.

Conclusions: Despite a decreased trend in high quality kidney allocation to high PRA patients in the new system over time, it is still significantly higher than in the old system. Thus, any bolus effect is only partial. While there is no difference in patient and graft survival in this cohort, follow-up may be too short to show a difference. As such, a national policy may be needed to optimize this allocation in the new KAS.

SA-PO061

Association Between Kidney Donor Risk of ESRD (KDRE) and Donor Selection/Deferral

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Background: The Kidney Donor Risk of ESRD equation (KDRE) provides transplant centers a tool to assess the patient-specific risk of developing ESRD in living kidney donors based on age, sex, race, body mass index (BMI), and relationship to the recipient (http://www.transplantmodels.com/donesrd/). The goal of this study was to determine whether medical decisions surrounding donor eligibility align with the empirical KDRE predicted risk. We hypothesized that higher KDRE scores would be associated with a higher likelihood of donor deferral due to medical unsuitability.

Methods: The KDRE was determined by chart review of donor evaluations performed at a single center from 2009 - 2017 for a convenience sample of potential donors. The association between the 5-year predicted risk of ESRD and odds of deferral/acceptance was examined using unadjusted logistic models. Due to a lack of association between the KDRE score and donor deferral, we adjusted for factors within and outside of the KDRE (systolic BP, smoking) to determine which factors were most strongly associated with deferral from donation.

Results: 313 donors had sufficient data to calculate the KDRE score. Mean age was 31±10 years and median BMI was 33. Evaluated donors were 49% White, 31% Hispanic, 6% Black; 44% male, and 52% of donors were related to the recipient. 34% of evaluated donors were deferred. There was no association between the KDRE predicted ESRD risk and donor deferral (Table), even after accounting for factors not in the KDRE score (systolic BP and smoking). When we adjusted for factors already in the KDRE score, older age was the only factor that was strongly associated with odds of deferral (OR 2.14 per 10-year increase in age [95% CI 1.48-3.10]).

Conclusions: We did not find the KDRE predicted ESRD risk to be associated with donor deferral or acceptance. Of the factors considered, older age was the strongest factor that was associated with donor deferral.

Funding: NIDDK Support

Table 1. Models comparing different predictors of the likelihood of deferral from donation.

Model Predictors All OR for KDRE are per 1 point increase in risk	Odds Ratio (95% CI)
KDRE estimated risk (per 1 point increase)	1.08 (0.88-1.31)
KDRE estimated risk + SBP (per 1 mm Hg increase)	1.09 (0.86-1.38) 1.01 (0.99-1.03)
KDRE estimated risk + current smoker (vs. never)	1.09 (0.86-1.38) 1.07 (0.25-1.04)
KDRE estimated risk + SBP + smoking	1.07 (0.81-1.39) NS
KDRE estimated risk + Age (per 1 year increase)	1.01 (0.82-1.24) 1.04 (1.02-1.07)
KDRE estimated risk + age, race, sex, donor relationship to recipient, and BMI	0.80 (0.50-1.29) NS*

NS = not statistically significantly associated; p>0.05
*No factors were associated with outcome except age as reported in abstract

SA-PO062

State-Wide Coordination of the Follow-Up of Living Kidney Donors Only Marginally Improves the Follow-Up Rate

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Background: Post-donation follow-up care is recommended by KDIGO for Living kidney donors (LKD). There is little long-term data on living kidney donors in Australia due to incomplete follow-up. In 2012 we centralised the follow-up of all LKD within the state. Our aim was to audit the effectiveness of this intervention and the effect on the rate of LKD follow-up.

Methods: In 2012 we reported follow-up of LKD at 1 year of 70%, but less than 10% at 5 years. Statewide follow-up was changed to be coordinated out of a single follow-up centre, with tests and appointments organized by standard mail and follow-up phone calls. We reviewed the effectiveness of this intervention.

Results: We identified 183 LKD, of which 126 (63% female, mean age 62 years, mean time since donation 9 years) were recorded in the both the statewide database and the Living Kidney Donor Registry (LKDR) at ANZDATA. Changing to a single, statewide follow-up centre achieved 50-70% of follow-up every year from 2014-17. This ranged from 75% at one year post-donation, 61% at 5 and 48% > 5 years post-donation as recorded locally in 2017. Reporting to the LKDR was lower at 25%, 33% & 22% respectively. From the ANZDATA follow up, 63 patients had a recorded systolic blood pressure measurement at their last follow up. 31% of these patients had hypertension requiring anti-hypertensive medication with 1.3 the average number of agents required.

Conclusions: The results show that clinical follow up decreases as time post donation increases. Statewide coordination of donor follow-up improved baseline results but there is still further improvement to be made. There is discrepancy between local data collection and submission to the Living Kidney Donor Registry at ANZDATA. Improved coordination and data submission would allow for more accurate follow up data of LKD.

SA-PO063

Differences in Transplant Rates Across Race/Ethnicities Post-KAS Implementation

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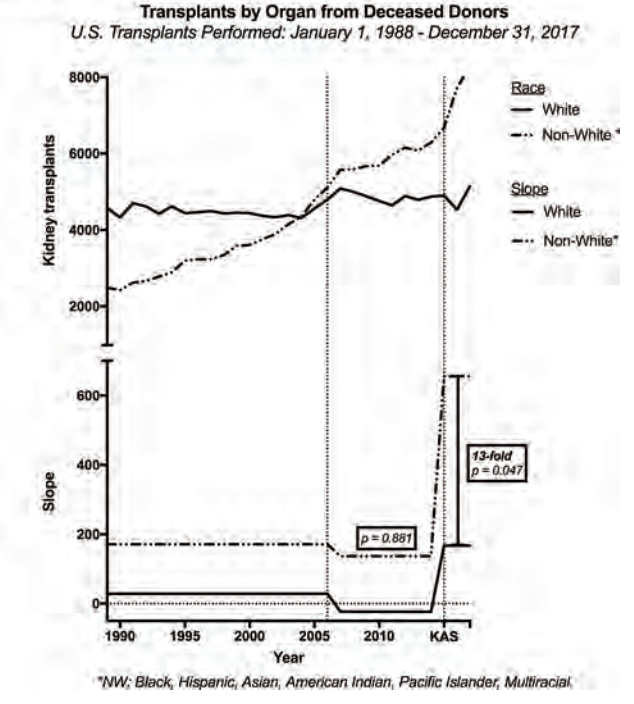
Background: The Kidney Allocation System (KAS) aimed to decrease racial allocation disparity, indirectly improving transplant rates (TR) for non-Whites. 3 years after implementation, we lack evidence of this specific efficacy. We here assess whether the waitlisting and transplant rates across races/ethnicities have improved after KAS implementation.

Methods: To assess any systematic difference in US TR (1989-2017) and the effect pre-(1989-2014) and post-KAS (2015-2017), we calculated the slope per year basis. We then, using linear regression, estimated the effect of race/ethnicity on kidney waitlist addition and TR across periods, also addressing donor type for TR. To eliminate improved deceased donation effect, we compared kidney and liver TR. A difference indicates a positive impact of KAS. Finally, we similarly evaluated the rate of change for kidney waitlist additions. We used data from OPTN database and for linear models R.

Results: We show three distinct periods wherein the kidney TR varied. Between 1989–2006 and 2015–2017, there was a significant positive slope, higher in the later. However, between 2006–2014 there was no change in TR. Furthermore, compared to deceased liver TR after KAS implementation (2015-2017), kidney TR increased up to 76% (p=0.02). Before 2015, there were no differences between the two groups (p>0.2). Moreover, kidney TR has steadily risen for non-Whites compared to Whites (p=0.03). KAS implementation increased the rate for non-Whites 13-fold compared to Whites (p=0.04). Lastly, this improvement was not mirrored in the waitlist additions, and KAS did not change the slope.

Conclusions: We have preliminary evidence that KAS allocation has improved TR especially benefiting non-Whites (Blacks, Hispanics, Asians). Waitlist addition did not equally change, arguing for the need to alter referral and listing practice.

Figure. Number of kidney transplants performed between 1998 – 2017 and TR as a function of three time periods.



Figure

SA-PO064

Should Kidneys at High Risk for Discard Be Allocated to Preemptive Deceased Donor Kidney Transplant Candidates?

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Background: Over 19% of recovered kidneys are discarded annually in the US. Identifying patients with favourable outcomes after transplantation with kidneys at high

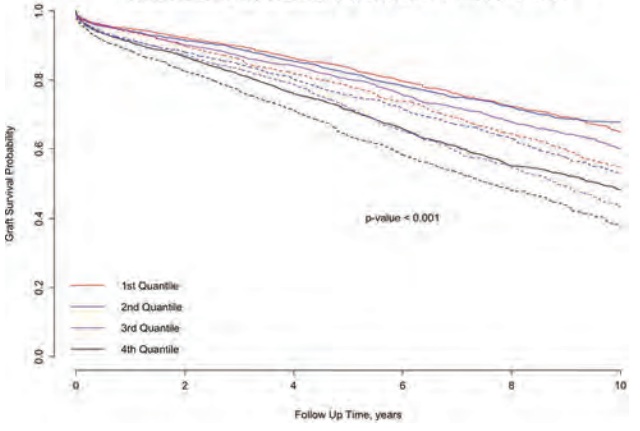
risk of discard may inform strategies to increase organ utilization. Preemptive deceased donor kidney transplant recipients have superior post-transplant outcomes compared to recipients on dialysis, partly due to the presence of native kidney function. We hypothesize that allocation of kidneys at high risk of discard to selected preemptive candidates could offer acceptable outcomes.

Methods: We ranked and grouped into quartiles all deceased donors in SRTR between 2000-15 based on their probability of kidney discard using a validated score that predicts discard based on donor characteristics. We conducted a paired kidney analysis, where 1 kidney was transplanted in a preemptive recipient and the mate kidney from the same donor was transplanted into a nonpreemptive recipient, to compare the risk of DGF and all cause graft loss (ACGL) in non-preemptive and preemptive recipients, stratified by donors' risk of kidney discard using Cox and logistic regression models.

Results: The figure shows unadjusted graft survival in preemptive and non-preemptive recipients, stratified by donors' probability of kidney discard. The risk of discard was associated with inferior graft survival, as recipients of kidneys at the greatest risk of discard (Q4) demonstrated the worst graft survival. However, outcomes among preemptive recipients were significantly better. After adjusting for recipient and transplant factors, preemptive recipients who received kidneys at the greatest risk of discard (Q4) had a significantly lower risk of DGF (OR; 95%CI 0.22; 0.18-0.26) and of ACGL (HR; 95%CI 0.81; 0.72-0.90).

Conclusions: Allocation of kidneys at high risk of discard to selected preemptive candidates (eg. patients with prolonged wait-times) may increase organ utilization while optimizing outcomes.

Figure: Kaplan-Meier curves of all cause graft loss in mate kidney cohort stratified by quartiles of predicted donor risk of discard.



SA-PO065

APOL1 Genotyping in Potential Kidney Donors of African Descent

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Background: Inheritance of two *APOL1* risk variants accounts for the excess risk of non-diabetic ESRD in African Americans when compared to Caucasian, Hispanic and Asian Americans. African American living donors have a higher risk of ESRD than matched non-black donors. *APOL1* genotyping in potential kidney donors of African descent may identify individuals at risk for progressive CKD following donation.

Methods: We report the retrospective analysis of *APOL1* genotyping in a cohort of African American potential kidney donors. In July 2016, we initiated targeted genotyping of all African American kidney donor candidates. African American candidates with two *APOL1* risk variants were excluded from kidney donation.

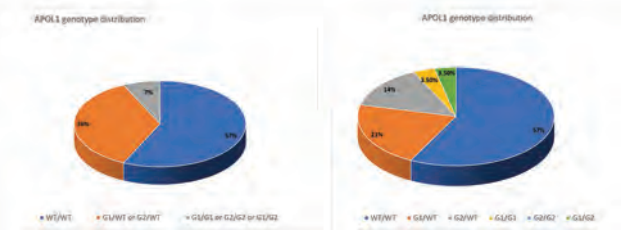
Results: A total of 28 African American kidney donor candidates were evaluated between July 2016 and April 2018. 2 (7%) were found to have two *APOL1* risk variants (high risk genotype). Low risk genotype was identified in 10 (36%) candidates who had one risk variant and 16 (57%) candidates who had none. To date, 15 candidates have completed their donor work-up. Of these, 7 (47%) have already undergone donor nephrectomy, and 4 (27%) were cleared for surgery and are awaiting operation. 4 (27%) of the candidates did not meet our center specific criteria for donation. 2 out these 4 candidates who were excluded from donation were ruled out expressly for having been found to have two *APOL1* risk variants.

Conclusions: *APOL1* genotyping led to the exclusion of two donors who might have previously been allowed to donate, possibly mitigating their risk of CKD/ESRD and suboptimal graft outcomes in recipients.

Baseline characteristics of potential kidney donors

	APOL1 High risk genotype Mean ± SD	APOL1 Low risk Genotype Mean ± SD	p-value
Age (years)	40.5 ± 6.3	36 ± 10.2	0.52
Gender – Male: n (%)	13 (50%)	0 (0%)	not calculated
BMI (kg/m2)	32.4 ± 2.5	27.2 ± 4.2	0.23
Creatinine (mg/dL)	0.8 ± 0.002	0.9 ± 0.026	0.09
Systolic BP mm Hg	118 ± 11.3	115 ± 7.9	0.78
Diastolic BP mm Hg	75 ± 7.1	70.9 ± 9.3	0.76
MDRD eGFR (ml/min/1.733m2)	101.5 ± 10.6	106.9 ± 19.8	0.76

Figures



SA-PO066

Community Deliberations on APOL1 Testing in African Americans

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Background: African Americans (AA) are 2-4 times more likely to develop ESRD, compared to whites. Apolipoprotein L1 (*APOL1*) variants have been associated with greater risk of developing non-diabetic ESRD among African Americans (AAs), and greater risk of developing incident CKD, proteinuria, and transplant failure. Mechanisms of risk and penetrance, and effective preventive measures for kidney disease remain unclear. We engaged AAs to discuss potential pros and cons of *APOL1* risk testing in routine patient and kidney transplant care.

Methods: As part of a larger assessment of stakeholder views, we conducted community deliberations with self-identified AAs in Seattle WA (n=14), Nashville TN (n=14), and Jackson MS (n=11). Information on *APOL1* genetic risk was provided prior to, and during each meeting. Plenary and small group discussions were held followed by 2 rounds of polling on *APOL1* testing options. Deliberations occurred over 2 days for 10 hours per site. Participants at each site reviewed results and provided feedback.

Results: Participants were diverse in gender, age, education, and kidney disease experience. With regard to routine patient care, responses varied on who should be tested: all AAs(64%); AAs with CKD risk factors(21%); AAs with signs of CKD(10%); no AAs(5%). Increased knowledge, improved self-care, and aid to clinical management and research were reasons to support testing. Lack of clinical utility and increased psychological burdens, potential discrimination and cost, were reasons to oppose testing. Participants agreed unanimously that deceased donor kidneys be tested. Views on *APOL1* testing in other kidney transplant scenarios varied: offer testing to potential living donors(95%); require testing in potential living donors(73%), and prevent living donors with *APOL1* risk from donating(10%). Participants felt that *APOL1* testing was 'actionable' in the transplant setting, but expressed concern that it might reduce kidney supply.

Conclusions: Well-informed AAs have valuable input on best practices in *APOL1* testing in routine patient and kidney transplant care. There was consensus that deceased donor kidneys should be tested for *APOL1* risk; however, views on *APOL1* risk testing in other scenarios were divergent. Continued stakeholder deliberation is imperative as the science evolves to inform best practices.

Funding: Other NIH Support - NIH / National Human Genome Research Institute (NHGRI)

SA-PO067

Prevalence of G1 and G2 APOL1 Gene Variants in Afrodescendant Patients from the Unit of Kidney Transplant in a High Complexity Medical Center in Cali, Colombia

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Background: In recent years, the presence of APOL1 genetic variants has been recognized as a risk factor of chronic kidney disease in afrodescendant patients, especially variants related to the risk alleles G1 and G2 (1)(2). Patients with two allelic variants are at higher risk, and tend to require dialysis up to 9 years earlier than patients with no risk alleles (2). In addition, receptors of kidney transplant from donors with APOL1 variants seem to have a worse posttransplant prognosis and higher risk of graft dysfunction (3)(4) (5). The aim of this study is to determine the prevalence of these allelic variants among the afrodescendant patients from the kidney transplant unit at Fundacion Valle del Lili (FVL).

Methods: Observational, cross-sectional study including afrodescendant patients with chronic kidney disease from the kidney transplant unit at FVL, who were on the waitlist or were already recipients of kidney transplant. The study period was defined from January to November 2017

Results: A total of 103 patients were included, 56% (n=57) were female. The mean age was 48 years old (SD 13 years), the mean time of dialysis before kidney transplant was 4 years, 89% had clinical history of arterial hypertension. APOL1 gene variants were found in 62% (n=64) of patients, of them 32.8% (n=21) were G1 heterozygotes, 39% (n=25) were G1 homozygotes, 4.6% (n=3) were G2 homozygotes, and 23.4% (n=15) were mixed G1/G2. There were none G2 heterozygotes.

Conclusions: This study describes that in the afrodescendant population with chronic kidney disease at FVL the frequency of APOL1 variants is high, nevertheless these results cannot be extrapolated to the general population, and larger population studies are required to accurately assess the frequency of APOL1 variants in our country. This study represents

a cornerstone for new lines of research on this field in our institution, a national referral center for kidney transplants.

SA-PO068

Racial Disparities in Long-Term Outcomes in Kidney Transplantation from Elderly Donors in United States

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Background: Kidney transplantation offers survival benefit and improved quality of life in end stage renal disease (ESRD) patients. Because the waiting list continues to grow, there has been an increase in the utilization of kidneys from older donors. We examined the racial disparities in graft and patient outcomes of patients after transplantation with old kidneys.

Methods: We identified 19,820 kidney transplant recipients based on donor age ≥ 60 year between January 2000 and December 2016 from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research data. Using case-mix adjusted logistic regression models; we examined the effects of race on 3-year death censored graft loss (DCGL) and 3-year recipient survival in kidney transplant recipients (KTR) of elderly donors.

Results: Elderly donors accounted for 7.9% of all donors. Of the 19,820 recipients of old kidneys, 57.9% were Whites, 22.8% were Blacks, 6.4% were Asians, 11.1% were Hispanics and 1.9% were others. 45.6% were males. Mean donor age was 64±3 years and mean recipient age was 59±11 years. Overall, 3-year DCGL was 12% and 3-year recipient survival was 86.2%. In adjusted analyses, Blacks were more likely than Whites (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.08-1.36, p<0.001) to experience DCGL at 3 years. Additionally, both Hispanics (OR, 0.77; CI, 0.66-0.91, p=0.002) and Asians (OR, 0.72; CI, 0.58-0.90, p=0.003) were less likely than Whites to experience DCGL at 3 years. In adjusted analyses, Blacks (OR, 0.83; CI, 0.74-0.92, p<0.001), Hispanics (OR, 0.71; CI, 0.61-0.82, p<0.001) and Asians (OR, 0.75; CI, 0.62-0.90, p<0.001) were less likely than Whites to die at 3 years after receiving a kidney from an elderly donor.

Conclusions: Among KTR of elderly donors, Blacks are at 21% higher risk of graft failure than Whites at 3 years but survive longer after transplantation. As compared to Whites, both Hispanics and Asians are less likely to experience DCGR at 3 years and are less likely to die within 3 years of getting a kidney transplant from older donor. Further studies are needed to assess additional factors contributing to disparities in graft and recipient survival in KTR of old kidneys.

SA-PO069

Genetic Ancestry as a Predictor of Kidney Transplant Outcomes

Y. Dana Neugut, Lili Liu, Junying Zhang, David Fasel, Karla Mehl, Jaclyn L. Wold, Fatih Ozay, Olivia Balderes, Sumit Mohan, Jai Radhakrishnan, Lloyd E. Ratner, David J. Cohen, Ali G. Gharavi, Krzysztof Kiryluk. *Columbia University Medical Center, New York, NY.*

Background: African-American (AA) kidney recipients have higher rates of allograft rejection and failure. However, it is unknown to what extent the inferior outcomes in self-reported AA's are due to genetic effects or confounding by socioeconomic status (SES). In this study, we test the effects of recipient African admixture, a quantitative measure of genetic ancestry derived from genome-wide SNP data, in multivariable models adjusted for SES factors.

Methods: Our study used a multiethnic retrospective single center cohort of 1,083 kidney allograft recipients, including 206 self-reported AA's. Subjects were genotyped with high resolution SNP arrays (MEGA chip, Illumina); African admixture proportions were derived using ADMIXTURE software. All subjects were geo-coded and U.S. census tract variables were used as proxies of SES. Multivariable Cox models were constructed to predict time to biopsy-proven rejection and time to death-censored allograft failure, and race-related variables of interest were tested in each model.

Results: The cohort median follow-up time was 78.3 months, and included 432 patients with rejection (median 5.9 months) and 193 with failure (median 72.3 months). We confirmed significant impact of recipient's self-reported AA race (HR 1.47 (95% CI: 1.18-1.83)) and African admixture proportion (HR 1.64 (95% CI: 1.22-2.19)) on acute rejection. Both race-related metrics also had similar effects in the adjusted models of allograft failure (self-report: HR 1.42 (95% CI: 1.02-1.97); admixture: HR 1.48 (95% CI: 0.96-2.29)). Recipient *APOL1* risk genotype status, associated with African ancestry and several kidney diseases, did not explain these associations. U.S. census-derived median income and education level did not confound the association between race and either rejection or failure.

Conclusions: Our study is the first to test a genetic measure of recipient African ancestry for inclusion in clinical models of kidney transplant outcomes. Based on our results, self-reported AA race and a genetically-derived continuous measure of African ancestry performed similarly in predicting the risk of allograft rejection and failure, and both predictors were independent after multivariable adjustment for U.S. census-based metrics of SES.

Funding: NIDDK Support

SA-PO070

The Multiple Faces of a Hepatitis C Donor

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Background: Public Health Service (PHS) increased risk donors are on the rise in the US and provide an underutilized pool of organs. With the advent of a myriad of Hepatitis C treatment options, use of these organs has become an attractive option for select recipients. An updated list of characteristics of all PHS increased risk donors is presented here.

Methods: UNOS database was queried for all deceased donor kidneys retrieved between 4/1/2015 and 9/30/17. The study population was divided into four categories based on their hepatitis C antibody (Ab) and nucleic acid testing (NAT): Ab-/NAT-, Ab-/NAT+, Ab+/NAT-; Ab+/NAT+. Characteristics of age, gender, race, donation after cardiac death (DCD), PHS increased risk, BMI, diabetes, macrovesicular fat, and KDPI are investigated across the four donor categories.

Results: Mean age of Ab-/NAT- donors is slightly higher than Ab-/NAT+, Ab+/NAT+, and Ab+/NAT- donors; Ab-/NAT-, Ab+/NAT-, and Ab+/NAT+ donors are predominantly male. Region 2 has the highest number of donors with NAT and/or Ab + carrier status. Ab+/NAT- donors have the highest, mean KDPI of 54.1. Less than 10% of all deceased donors are diabetics. While 21% of Ab-NAT- donors were characterized as PHS increased risk, nearly 15% of NAT and/or Ab + carrier donors did not meet PHS criteria by definition.

Conclusions: Our data sheds light into characteristics of all deceased donors over a 2.5 year period. It questions the accuracy of screening criteria for PHS increased risk donors. Delineation of these features allows for identification of an underutilized organ pool for an appropriate kidney transplant recipient group.

Donor Characteristics

	Ab-/NAT-	Ab-/NAT+	Ab+/NAT-	Ab+/NAT+	p-value
N	28740	33	372	739	
Age (mean years +/- standard deviation)	37.9 ± 15.8	27.4 ± 8.4	35.2 ± 10.1	32.6 ± 8.2	< 0.001
Sex N (% male)	17618 (61.3%)	11 (33.3%)	192 (51.6%)	497 (67.3%)	< 0.001
Black (%) Hispanic (%) Other (%) White (%)	4054 (14.1) 3931 (13.7) 1312 (4.6) 19443 (67.7)	1 (3.0) 3 (9.1) 0 (0) 29 (87.9)	8 (2.2) 24 (64.5) 7 (1.9) 333 (89.5)	24 (3.2) 74 (10.0) 15 (2.0) 626 (84.7)	< 0.001
DCD N (%)	6118 (21.3)	2 (6.1)	42 (11.3)	59 (8.0)	< 0.001
BMI (mean +/- standard deviation)	27.95 ± 7.2	26.09 ± 6.6	27.45 ± 5.7	25.9 ± 4.9	< 0.001
Diabetes N (%)	1977 (6.9)	0 (0)	7 (1.9)	8 (1.1)	< 0.001
Macrovesicular Fat of <= 40% N (%)	7425 (25.8)	18 (54.5)	181 (48.7)	431 (58.3)	< 0.001
KDPI (mean)	47.1 ± 26.5	20.8 ± 16.9	54.1 ± 17.8	48.6 ± 16.3	< 0.001
PHS N (%)	6139 (21.4)	28 (84.8)	276 (74.2)	616 (83.4)	< 0.001

SA-PO071

Ten-Year Analysis of Transplant Recipients of High KDPI Kidneys

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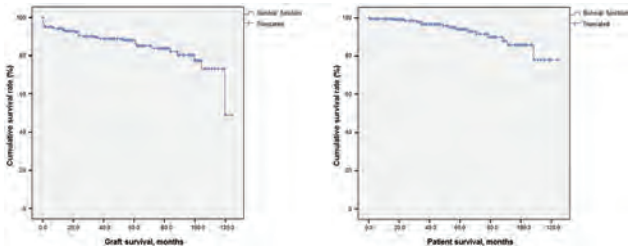
Background: The growing shortage of transplantable kidneys have pointed a great attention on the use of expanded criteria donors (ECDs). About 15% of deceased donor kidneys come from marginal donors, but there is some evidence to indicate that ECD recipients have poorer prognosis, higher incidence of DGF (31% vs 23%) and elevated risk of graft loss, up to 70%. However, the use of ECDs is an effort to increase the pool of organs available for transplant, reduce waiting times on transplant list and ensure optimal allocation of marginal kidneys in the elderly. Kidney Donor Profile Index (KDPI) is a score, ranging from 0% to 100%, based on the quality of all kidneys recovered in the previous year, and estimates the potential function of a donated kidney. A donor KDPI>85% is assumed to be equivalent to an ECD kidney. UNOS data show that only 11% of kidneys from donors with KDPI>85% are used for transplant, and their 5-year survival approximates only 50%.

Methods: This is a retrospective analysis of KDPI in 246 adult kidney transplants (192 single, 54 double) from ECD donors between 2007 and 2016. The mean recipient age was 60.2 years, donor age 67.4 years, KDPI 90.5%, cold ischemia time 14 h, total Karpinski score 3.9, glomerulosclerosis 0.4, interstitial fibrosis 0.9. tubular atrophy 0.6, IFTA 1.5, vascular score 1.1.

Results: Ten-year graft and patient survival were 76% and 80%, respectively (Fig. 1). The incidence of DGF was 44.7%, that of acute rejection 14.6%. GFR at discharge, at 1 year, at 5 years, and at 10 years were 41.5±21.8, 44.9±18.4, 49.5±20, and 53.4±27 mL/min, respectively. Considering total Karpinski score or single histological lesions, no correlation was found with graft and patient survival, DGF and rejection rates. KDPI, donor age and recipient age were predictive of 1-year eGFR decline.

Conclusions: The high survival rates and the satisfying functional performance suggest a good medium-long term prognosis for renal transplant recipients of high KDPI kidneys considered as marginal according to the ECD classification.



SA-PO072

Usefulness of the Assessment of CT-Based Donor Kidney Function Compared with Radionuclide Scintigraphy

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Background: Pretransplant graft volume and function has been demonstrated to be an important factor in subsequent allograft outcomes. Most transplant centers underwent renal split function test to assess functional asymmetry with technetium dimercaptosuccinic acid (^{99m}Tc-DMSA) renography and/or computed tomography (CT). We evaluated which of the two methods better reflected posttransplant renal function.

Methods: We analyzed 159 living donors who underwent pretransplant kidney evaluation with both ^{99m}Tc-DMSA renography and CT, and their matching recipients. We measured glomerular filtration rate (GFR) in donor with ^{51}Chromium (Cr) plasma clearance and in recipients using the chronic kidney disease epidemiology collaboration formula (CKD-EPI) equation at 1, 6, and 12 months after transplantation. Kidney volumes were calculated using semi-automatic, three-dimensional (3D) CT volumetry methods. Absolute transplanted graft GFR was calculated by donor GFR (ml/min) x the proportion of donated kidney to total kidney (transplanted kidney volume/total kidney volume in CT, and transplanted kidney isotope uptake/total uptake in renography).

Results: The mean absolute transplanted graft GFR were 53.3±10.6 ml/min by renography and 53.5±10.7 ml/min by CT (p=0.872). Posttransplant graft functions were 84.5±18.6, 72.3±14.1, and 74.9±16.7 ml/min/1.73m^2, at 1, 6, and 12 months after transplantation, respectively. Pearson correlation coefficients between absolute transplanted graft GFR and posttransplant GFR were 0.289, 0.362, and 0.256 in renography (all p<0.001), and 0.318, 0.378, and 0.269 (all p<0.001) in CT at 1, 6, and 12 months, respectively. Multiple linear regression analysis adjusted by age and gender demonstrated that a 1 ml/min increase in absolute transplanted graft GFR calculated by 3D CT volume was associated with 0.56±0.13 ml/min/1.73m^2 increase in posttransplant GFR, and one year increase in recipient age was associated with a 0.46±0.12 ml/min/1.73m^2 reduction of GFR.

Conclusions: 3D CT volumetry method is more useful to predict renal graft outcome than isotope renography before transplantation.

SA-PO073

Patients with a Failed Transplant Derive a Greater Survival Benefit from Transplantation Than Primary Transplant Recipients

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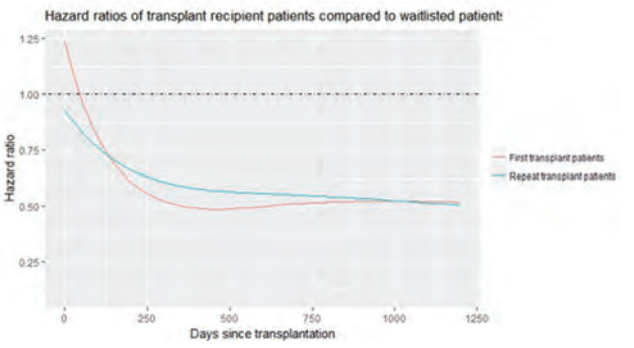
Background: The organ shortage demands evidence to support the use of deceased donor kidneys in higher risk groups. Repeat transplant recipients have a higher risk of allograft failure than first transplant recipients.

Methods: Using data from the United States Renal Data System between 2000-2016 we determined the relative risk of death in adult patients wait-listed for a first (n=334,162) or repeat (n= 26,815) deceased donor kidney transplant using multivariate non-proportional hazards analyses in which transplantation was treated as a time dependent co-variate. The models adjusted for differences in patient age, sex, race, cause of ESRD, comorbid conditions and year of wait-listing.

Results: The figure shows the relative risk of death in patients who received a first or repeat transplant at different time points after transplantation compared to similar patients (i.e. either first or repeat wait-list candidates) who remained on dialysis. Early after transplantation, first transplant recipients had a higher risk of death compared to first transplant candidates who remained on dialysis; this risk declined with time after transplantation. In contrast repeat transplant recipients had an immediate decreased risk of death compared to failed transplant recipients who remained on dialysis and this risk continued to decrease over time. Accordingly the time to equal risk of death compared to continued treatment with dialysis was 105 days in first transplant recipients versus 0 days in repeat transplant recipients; and the time to equal survival compared to treatment with dialysis was greater in first transplant recipients than in repeat transplant recipients.

Conclusions: Transplantation is associated with a *greater* survival benefit in repeat transplant candidates. Further studies are needed to determine whether current wait-listing practices of patients with a failed transplant are overly restrictive.

Funding: Government Support - Non-U.S.



SA-PO074

Applying Computer Vision to Evaluate Percent Global Glomerulosclerosis in Donor Kidney Biopsies

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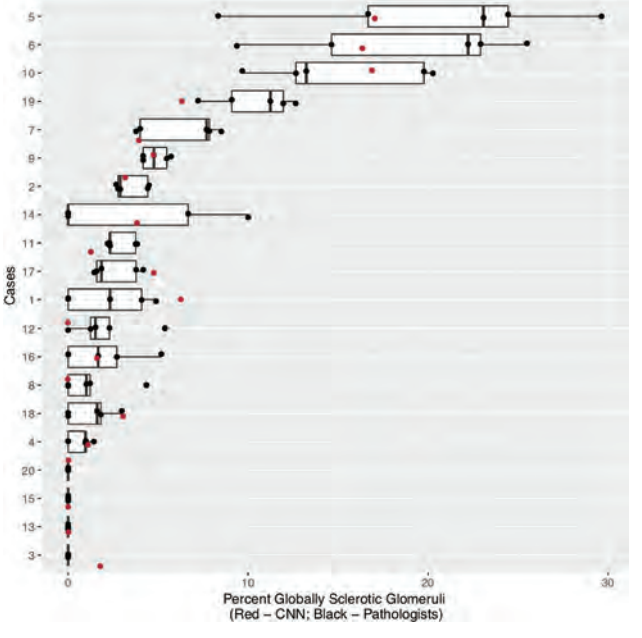
Background: Determining percent global glomerulosclerosis (GS) in donor kidney frozen wedge biopsies is used to determine organ viability. However, pathologic examination is labor-intensive and error prone. Previously, we developed a convolutional neural network (CNN) to quantify percent GS in scanned kidney biopsy whole slide images (WSI). The aim of this study is to compare CNN with pathologist evaluation of percent GS in scanned WSI.

Methods: Twenty consecutive donor kidney frozen wedge biopsies taken from April to August 2016 were scanned at 20x using an Aperio Scanscope CS scanner as part of routine clinical workflow. Four pathologists and one trainee manually enumerated globally sclerosed and non-sclerosed glomeruli using Aperio ImageScope, blinded to clinical data, in a setting mimicking routine clinical practice. The CNN evaluated the same WSI. Pathologist agreement was assessed using intraclass correlation coefficient (ICC).

Results: ICCs for pathologist evaluation of percent GS showed excellent agreement (0.8). Variability increased among cases with >10% GS. Percent GS determined by the CNN was within the pathologist range in 15/20 (75%) cases (Figure 1). CNN determined mean absolute difference of percent GS from pathologist median was 2% (range 0 – 6.1%).

Conclusions: The CNN quantifies percent GS in frozen section donor kidney wedge biopsies with performance comparable to pathologists and has potential to be incorporated in clinical practice.

Funding: Private Foundation Support



SA-PO075

Estimation of the Total Nephron Number in Japanese Living Kidney Donors Using Combined CT Angiography and Biopsy Approach

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Background: Increasing evidence suggests that individuals with low nephron number have an increased lifetime risk of renal insufficiency, thereby emphasizing the importance of evaluating total nephron number in each individual. In recent years, new methods have been described for estimating human total nephron number using a combination of image analysis and renal biopsy, though the reproducibility and accuracy of these methods remain uncertain. This study estimated total nephron number in healthy Japanese subjects using such a method.

Methods: Implantation biopsies from forty-four living kidney donors were analyzed. Using pre-donation contrast CT angiograms, transplantation donor kidneys were three-dimensionally reconstructed, and total renal cortical volume was estimated. Total nephron number was estimated based on glomerular density in biopsy specimens and total renal cortical volume. The obtained results were analyzed in relation to clinical variables and compared with those of a previously reported Japanese autopsy study.

Results: The estimated total nephron number in this cohort was 650,000±220,000 (mean±SD) per kidney. Total nephron number ranged from 280,000 to 1,220,000 per kidney (4.4-fold) and correlated directly with eGFR (r=0.328, p=0.030) and inversely with age (r=-0.355, p=0.018). The estimated total nephron number obtained in the present study was 25% less than that reported in American living kidney donors using the same procedure, and similar to that obtained in a previous Japanese autopsy study using the dissector/fractionator method (**Table**).

Conclusions: These results confirm the feasibility of a combined CT angiography and biopsy-based method to estimate total nephron number in humans.

Comparison of estimated total nephron number by different methods

Study population	Methods	Sample size	Age (year) (mean±SD or mean)	Estimated nephron number per kidney (mean±SD or mean)	Reference
Caucasian autopsy series (normotensive)	Dissector/fractionator	55	41	901,011 ± 298,334	Am J Kidney Dis 2008
Japanese autopsy series (normotensive)	Dissector/fractionator	9	64.1 ± 6.3	640,399 ± 160,016	JCI insight 2017
American kidney donors (92.7% Caucasian)	CT angiogram and biopsy	1638	43.2 ± 11.7	873696	J Am Soc Nephrol 2017
Japanese kidney donors	CT angiogram and biopsy	44	56.7 ± 9.5	650,000 ± 220,000	This study

SA-PO076

Outcomes of Declined Kidneys Subsequently Transplanted Elsewhere: A National Registry Analysis

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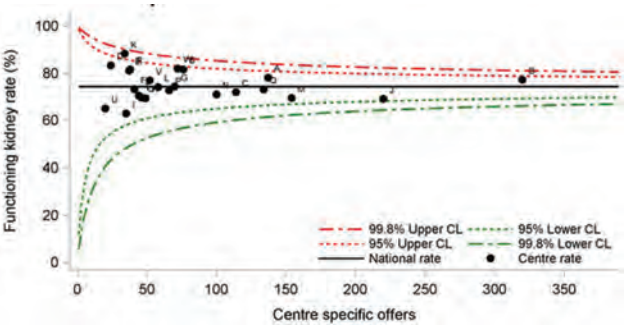
Background: A recent trend in donor demographics has led to transplantation of organs from donors with increasing age and comorbidities in the UK. In view of this changing climate, individual assessment of kidneys offers is increasingly important.

Methods: Data from the UK Transplant Registry held by National Health Service Blood and Transplant (NHSBT) were analysed. Offers made to adult patients through the National Kidney Allocation Scheme (NKAS) from donation after brain-death (DBD) donors between 1 January 2010 and 31 December 2014 were included. A cohort of 5,973 offers was identified, excluding offers made via the UK fast track scheme and those leading to dual or en bloc transplants. Only kidneys declined for donor-specific reasons were examined.

Results: There was a large variation in offer decline rates between centres across the UK, ranging from 17% to 54%. 'Donor unsuitable - past medical history' was the most common reason for decline. Comparisons were made for kidneys that were declined, subsequently transplanted elsewhere, and remained 'functioning ' (as defined as patients with an eGFR > 20 at 12months) and stratified by centre (Figure 1). There was some disparity between centres however no significant outliers were identified. Centre specific outcomes of patients on the waiting list for whom kidney offers were declined, where the kidney was subsequently transplanted (n=976) in another patient and remained functioning, were also analysed. In this cohort, up to 9% of patients were removed from the transplant waiting list due to clinical deterioration and mortality was up to 15% for each centre.

Conclusions: There is variation in donor-specific decline rates across centres in the UK which could reflect a disparity in 'risk-appetite' amongst clinicians. Approximately 75% of declined DBD kidney offers that are transplanted elsewhere have >20 at 12 months. Mortality and morbidity of patients who remain on the waiting list is high. Better means of assessing donor risk are needed due to a high decline rate of these organs.



SA-PO077

Appropriateness and Outcomes of Premature Pre-emptive Renal Transplants (PPRT), i.e. Renal Transplants at GFR>/= 19mL/min

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Background: A pre-emptive kidney transplant is the best renal replacement therapy for ESRD patients. There are no guidelines for the GFR at which pre-emptive transplantation should occur. Pre-emptive renal transplants at GFR >15 ml/min represent about nine percent of total recipient population per year. The goal of this study is to evaluate the outcomes of PPRTs. Another objective of this study is to outline the donor, recipient, and transplant characteristics of pre-emptive renal transplants.

Methods: Retrospective analysis of the UNOS database was performed on19,207 preemptive renal transplants, including deceased donors (n=12,951) and living donors (n=6,256), between years 2010-2016. Patient survival or death-censored graft survival were compared across predetermined eGFR groups at the time of transplantation, using Kaplan-Meier curves. Relevant donor, transplant & recipient characteristics were compared using t-/Wilcoxon-Mann-Whitney & Chi-sq/Fishers exact tests. Logistic regression was used to identify factors associated with pre-emptive renal transplants. Cox regression analysis was used to identify risk factors for adverse outcomes.

Results: In PPRT with all types of donors, the rate of graft survival is lower at higher GFRs (>/=19). History of diabetes in the recipient (OR=1.176, p=0.000), high number of previous transplants (OR=1.332, p=0.000) & older age (OR=1.004, p=0.012) increase the odds of receiving pre-emptive renal transplants. High BMI (OR=0.988, p=0.000) and high levels of HLA mismatch (OR=0.965, p=0.001) are less likely to receive a preemptive transplant. Increased risk of graft failure is seen in recipients with an increased number of previous transplants (HR=1.155, p=0.029), higher KDRI (HR=1.567, p=0.009) and diabetes (HR=1.218, p=0.021).

Conclusions: PPRT is associated with worse graft outcomes across all donor and recipient characteristics studied. Installation of guidelines for GFR at which pre-emptive renal transplants should occur is warranted through further research. This is especially important as PPRTs, (transplants occurring at GFR >/=19) may represent wastage of existing renal function in recipients, earlier exposure to surgical risks for live donors and recipients, and potential early requirement of next renal transplant.

SA-PO078

Clinical Significance of Kidney Donor Profile Index on the Post-Transplant Clinical Outcomes Between Elderly and Young Kidney Transplant Recipients: A Multicenter Cohort Study

Woo Yeong Park,[1,2] Jong hoon Lee,[3] Jeong Ho Kim,[4] Kyubok Jin,[1,2] Seungyeup Han,[1,2] Bumsoon Choi,[3] Chul Woo Yang,[3] Byung ha Chung.[3] *[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea; [3]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [4]Daejeon St. Mary's Hospital, Daejeon, Republic of Korea.*

Background: We investigated the clinical significance of Kidney Donor Profile Index (KDPI) system for the prediction of the clinical outcomes of elderly- or young kidney transplant recipients (KTRs) in deceased donor kidney transplantation (DDKT).

Methods: Six hundred fifty-seven KTRs receiving kidneys from 526 deceased donors (DDs) were included from four transplant centers. We divided high KDPI and low KDPI by 65%, the median value of KDPI score, and divided elderly KTRs and young KTRs at 55 years old. We investigated the incidence of delayed graft function (DGF), biopsy-proven acute rejection (BPAR), allograft and patient survival rates between elderly and young KTRs donated from DDs with high KDPI- or low KDPI score.

Results: We analyzed 224 (34.1%) elderly KTRs and 433 (65.9%) young KTRs. There were no significant differences in the incidence of DGF and BPAR between elderly KTRs and young KTRs donated from DDs with high KDPI- or low KDPI score. In elderly KTRs, there was no significant difference of death-censored graft survival and patient survival rates between high KDPI-KT and low KDPI-KT groups. However, in young KTRs, high KDPI-KT group was significantly lower in death-censored graft survival rate compared with low KDPI-KT group (P=0.006), and there was no significant difference of patient survival rate between the two groups. In multivariate analysis, high KDPI score was an independent risk factor for allograft failure in young KTRs after adjustment for recipient

and donor age, gender, acute rejection, and induction immunosuppresant (HR 2.376, 95% C.I., 1.251-4.511, P = 0.008), but not in the elderly KTRs. Among 4 groups, high KDPI-young KT group showed the highest risk for allograft failure compared with other three groups and a significant interaction between high KDPI donors and young KTRs on the allograft outcome (P=0.002).

Conclusions: High KDPI in DDs showed significant adverse impact on the allograft survival in young KTRs, but it was not prognostic factor in elderly KTRs.

SA-PO079

Follow-Up Care of Living Kidney Donors

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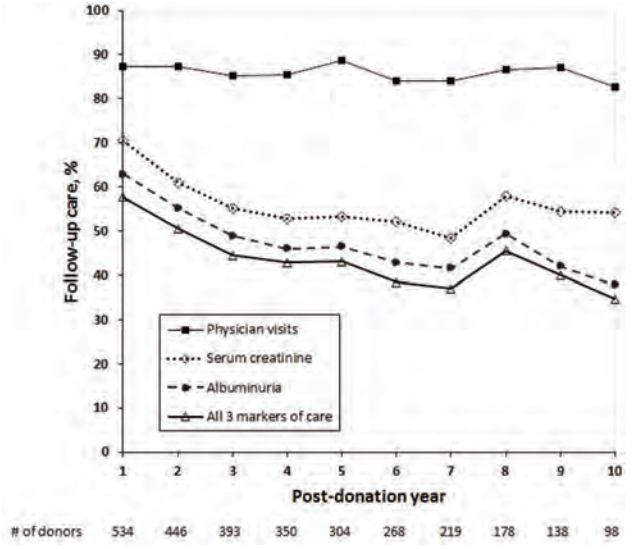
Background: Previous guidelines recommend that living kidney donors receive lifelong annual follow-up care to assess renal health. Whether these best practice recommendations are currently being followed is unclear.

Methods: We conducted a retrospective study using linked databases in Alberta, Canada to follow living kidney donors from 2002 to 2014. We determined the proportion of donors who had an annual outpatient physician visit and laboratory measurements for serum creatinine and albuminuria.

Results: There were 534 living kidney donors with a median follow-up of 7 years (maximum 13 years). The median age at the time of donation was 41 years and 62% were female. Overall, 25% of donors had all three markers of care (physician visit, serum creatinine, albuminuria measurement) in each year of follow-up. Adherence to physician visits was higher than serum creatinine or albuminuria measurements (67% vs. 31% vs. 28% of donors, respectively). Donors with guideline-concordant care were more likely to be older, reside closer to the transplant center, and receive their nephrectomy in more recent years.

Conclusions: These findings suggest significant evidence-practice gaps, in that the majority of donors saw a physician, but the minority had measurements of kidney function or albuminuria. Future interventions should target improving follow-up care for all donors.



Proportion of donors who have evidence of follow-up care during each post-donation year.

SA-PO080

Trends in the Timing of Preemptive Kidney Transplantation in Children

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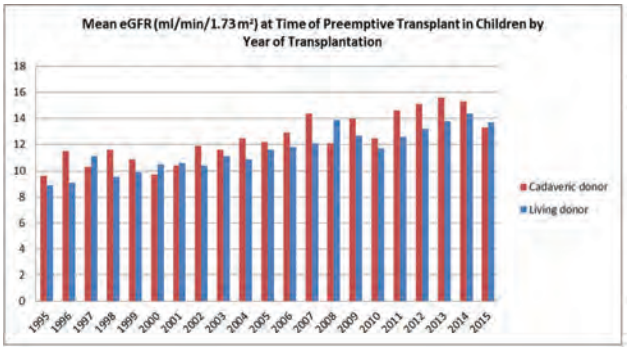
Background: There has been a recent trend toward starting dialysis at higher levels of kidney function in children. Whether there has been a similar trend for preemptive kidney transplantation (PKT) in children is unknown.

Methods: We identified 3,278 children (age 1-17 years) in the US Renal Data System who underwent PKT between 1995 and 2015 and had data available to estimate glomerular filtration rate (eGFR) using the bedside Schwartz equation. We evaluated the trend in eGFR at time of PKT over time and differences in recipient characteristics between those who received PKT early (eGFR >10 ml/min/1.73m^2) vs. late (eGFR ≤10 ml/min/1.73m^2).

Results: Mean eGFR at the time of PKT increased significantly over time (Figure), from 9.1 ml/min/1.73m^2 in 1995 to 13.5 ml/min/1.73m^2 in 2015 (p<0.001). The trend toward earlier transplantation was similar among recipients of living and deceased donor organs (p for interaction=0.67). The proportion of children undergoing PKT early increased from 31% in 1995 to 71% in 2015. Overall, 57% of children underwent PKT early (mean eGFR 15.5 ml/min/1.73 m^2). Compared to children who underwent PKT late (mean eGFR 7.5 ml/min/1.73 m^2), those who were transplanted early were older, more often of white race, and less likely to have a living donor (Table).

Conclusions: PKT is occurring at higher levels of eGFR over time in children. Further studies should examine possible reasons for this trend and whether timing of PKT is associated with allograft survival or mortality.

Funding: NIDDK Support



	Early PKT (N=1,880)	Late PKT (N=1,398)	P-value
eGFR (ml/min/1.73m^2), mean (SD)	15.5 (6.1)	7.5 (1.8)	<0.001
Age (years), median (IQR)	12 (8,15)	11 (6,15)	<0.001
Female, N (%)	686 (36.4)	483 (34.6)	0.28
White, N (%)	1560 (82.8)	1,109 (79.3)	0.01
Glomerulonephritis as cause of CKD, N (%)	223 (11.8)	165 (11.8)	0.98
Body Mass Index, median (IQR)	18.8 (16.6, 22.2)	19.0 (16.8, 23.0)	0.15
Serum albumin, median (IQR)	4.1 (3.7, 4.4)	4.1 (3.7, 4.4)	0.76
Living donor PKT, N (%)	1,143 (60.8)	980 (70.1)	<0.001

SA-PO081

Mapping Compensatory Renal Hypertrophy and Hyperfiltration in Living Kidney Donors Using Multiparametric Magnetic Resonance Imaging

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Background: Despite sustained glomerular hypertrophy and hyperfiltration, the vast majority of living donors do not develop hyperfiltration injury with fibrosis and progressive GFR decline. Our study uses serial multiparametric MRI to assess volume and blood flow of the remaining kidney in the first month post-donor nephrectomy. Relationships between changes in kidney volume, renal blood flow (RBF) and single kidney GFR (SKGFR) may reflect functional reserve of the remaining kidney and provide insight into the early stages of nephron loss in the development of CKD.

Methods: 6 living kidney donors underwent 3 sessions of MRI and creatinine-based eGFR measurements prior to, 4 days after, and 4 weeks after nephrectomy. The non-contrast multiparametric MR protocol includes: whole kidney volumetric assessment by manual delineation using a multi-slice T1-weighted (inversion-recovery) turbo-spin echo; assessment of RBF using a FAIR arterial spin labelling (FAIR-ASL) technique; and quantitative T1-mapping using a MOLLI technique.

Results: Median age of the donors was 57 (35 to 67); baseline kidney volume was 141±21mL, increasing to 183±38mL at day 4 and 179±32mL at week 4. SKGFR was 46±5mL/min at baseline, increasing to 61±12mL/min at day 4 and 60±9mL/min at week 4. RBF per unit weight did not change significantly at either day 4 (5.7±0.8 mL/g/min) or week 4 (6.4±0.4mL/g/min) from baseline (5.8±1.6mL/g/min). T1 value of the renal cortex saw a small increase at day 4 (1.64s) compared to baseline (1.53s), which is maintained at week 4 (1.62s).

Conclusions: The results show that compensatory hypertrophy and hyperfiltration started rapidly following renal tissue loss, became established within a few days, and sustained over the next 3-4 weeks. Given adult glomerular number does not increase in compensatory hypertrophy, our preliminary findings indicate that average single glomerular volume and GFR rose post-donation. As RBF per unit weight did not change post-nephrectomy in our cohort, with glomerular hypertrophy, this suggests that overall single glomerular blood flow would also increase. Further study into this growth of normal tissue is required to identify imaging biomarkers for nephron reserve and capacity for compensation before the onset of hyperfiltration injury.

Funding: Commercial Support - Shire Pharmaceuticals

SA-PO082

Clinical Significance of the Kidney Donor Profile Index in Deceased Donors for Prediction of Post-Transplant Clinical Outcomes: A Multicenter Cohort Study

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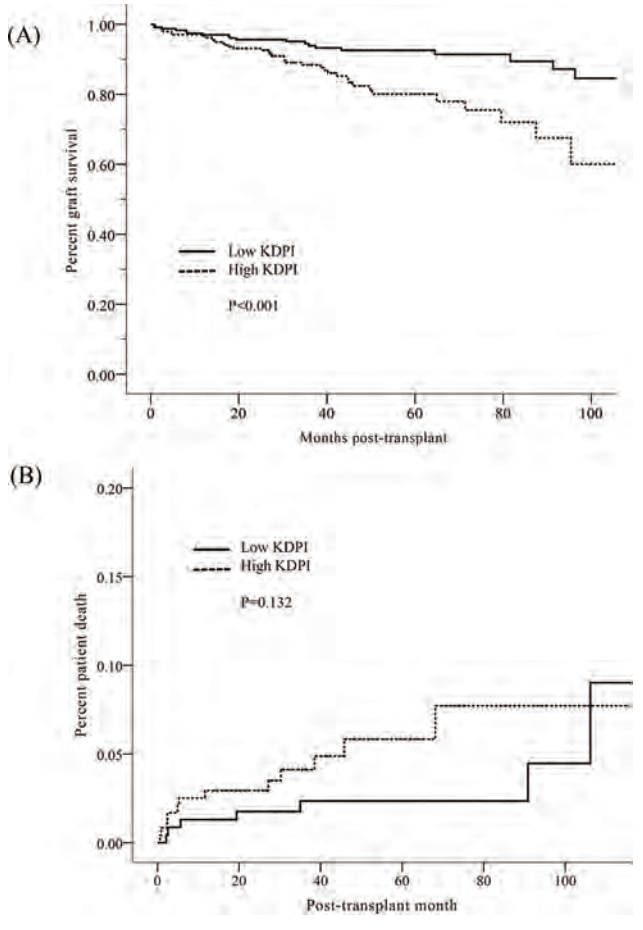
Background: We investigated whether the Kidney Donor Profile Index (KDPI) system is useful in predicting clinical outcomes in deceased donor kidney transplantation (DDKT).

Methods: Four hundred sixty-nine kidney transplant recipients (KTRs) receiving kidneys from 359 deceased donors were included in this study, which involved three transplant centers. KTRs were divided into high and low KDPI KTR groups based on the median KDPI score of 67%. We compared clinical outcomes between the high KDPI and low KDPI groups.

Results: There were no significant differences in the incidence of delayed graft function and acute rejection between high and low KDPI KTR groups. In comparison with histologic findings in allograft tissues obtained within three months from KT, the proportion of glomerulosclerosis was significantly higher in the high KDPI KTR group than in the low KDPI KTR group. With Kaplan-Meier analysis, the graft survival rate was significantly lower in the high KDPI KTR group than in the low KDPI KTR group (Log rank, P=0.017), and multivariate analysis also demonstrated that a high KDPI score was a significant risk factor for death censored allograft failure (HR 2.62, 95% CI, 1.29–5.33, P=0.008).

Conclusions: The KDPI scoring system is useful in predicting allograft outcomes in a Korean DDKT cohort.



Analysis of long-term outcome. (A) Comparison of death-censored graft survival rates between high and low KDPI KTR groups (P<0.001, Log-rank test) (B) Comparison of patient survival rates between high and low KDPI KTR groups (P=0.132, Log-rank test)

SA-PO083

Interdisciplinary Care Improves Transplant Evaluation Rates Prior to ESRD Among High-Risk Patients with Advanced CKD

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Background: Despite the established benefits of kidney transplantation for patients with advanced CKD, data suggest that referral to transplant nephrology is often delayed, even among patients with established nephrology care. Healthcare delivery interventions to foster transplant evaluation prior to developing ESRD are greatly needed. Interdisciplinary care (IDC), which includes nurse practitioner care coordination, is a promising intervention that may increase transplantation evaluation among patients with CKD.

Methods: We compared incident ESRD patients who received nurse practitioner care coordination as part of our IDC clinic (n= 100) to a contemporaneous cohort of incident ESRD (n= 1872) patients who received usual nephrology care alone at Montefiore Medical Center from 10/1/2013 - 10/31/2017. Montefiore Medical Center is a large tertiary institution that serves a predominately urban and poor African American and Hispanic population. All patients studied had established care with a general nephrologist and were eligible for IDC but receipt of IDC was limited by resource availability.

Results: Of the 1,972 patients included in our study, the mean age was 58 (SD 14.8), 43% were female, and 69% self-identified as African American or Hispanic. The baseline characteristics were similar between the two groups. Patients who received IDC were more likely to be evaluated by transplant nephrology prior to developing ESRD, 44% versus 24% ($p < 0.001$). The odds of transplant evaluation prior to developing ESRD was 3 times higher (OR 3.0 [CI 1.9- 4.6) for patients who received IDC versus usual care alone after adjusting for age, race, ethnicity, sex, and baseline comorbidities including diabetes, hypertension and cardiovascular disease. African Americans or Hispanics were less likely and younger patients were more likely to be evaluated by transplant nephrology prior to ESRD.

Conclusions: Interdisciplinary care (also known as multidisciplinary care) is associated with greater likelihood of transplant evaluation prior to ESRD compared to usual nephrology care alone in a racially and ethnically diverse population of lower SES. Larger multicenter studies are needed to determine the impact of IDC on transplant evaluation rates among patients with advanced CKD.

SA-PO084

Use and Outcomes of Kidneys from Donors with Angiomyolipoma: A Systematic Review

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Background: Renal angiomyolipoma (AML) is the most frequent mesenchymal tumor of the kidney. Although there is a rare possibility of malignant transformation of AML, this risk has not been studied in immunosuppressed patients. The safety of donors with AML and their kidney transplant recipients has not been well established.

Methods: A literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through May 15th, 2018. We included studies that reported outcomes of kidney donors with AML or recipients of donor with AML. The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018095157).

Results: 15 studies with a total of 17 donors with AML were identified. None of the donors had a diagnosis of tuberous sclerosis (TSC), pulmonary lymphangioleiomyomatosis (LAM), or epithelioid variant of AML. Donor age ranged from 35 to 77 years, and recipient age ranged from 27 to 62 years. 92% of the donors were female. Only 8% were deceased donor renal transplant. The majority of donors underwent ex-vivo resection (65%) prior to transplantation, followed by no resection (18%), and the remaining had in-vivo resection. Tumor size varied from 0.4 cm to 7 cm, and the majority (87%) were localized in the right kidney. Follow up time ranged from 1 to 107 months. Donor creatinine pre-nephrectomy ranged 0.89-1.1 mg/dL and post-nephrectomy creatinine 1.0 to 1.17 mg/dL. In those who did not have resection of the AML, tumor size remained stable. None of the donors with AML had end-stage renal disease or died at last follow-up. None of the recipients had malignant transformation of AML.

Conclusions: These findings are reassuring for the safety of donors with AML (without TSC or LAM) as well as their recipients without evidence of malignant transformation of AML. As such, this can also positively impact the donor pool by increasing the number of available kidneys.

SA-PO085

Racial Disparities in Access to Kidney Transplant: Medically (In) Appropriate?

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Background: Racial and ethnic disparities are known to be present in kidney transplant access. Our objective was to understand whether differences in recipient medical eligibility contribute to these known disparities.

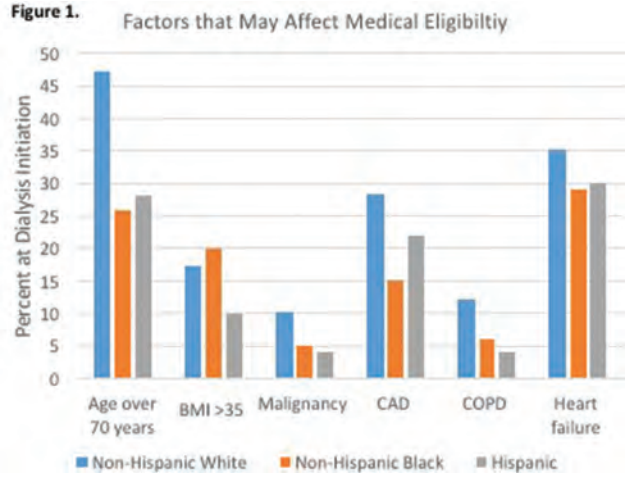
Methods: We included 1,573,786 adults who started dialysis between 1995-2015 according to the US Renal Data System. The exposure was race/ethnicity (non-Hispanic white [NHW], non-Hispanic black [NHB], or Hispanic). Outcomes were differences in medical eligibility for and time to kidney transplant after dialysis initiation. We used multivariable Cox models to examine the association between predictor and outcome. We then repeated our Cox models, excluding individuals who may be medically ineligible for transplant (e.g. age>70, malignancy, heart disease, and body mass index>35 kg/m^2).

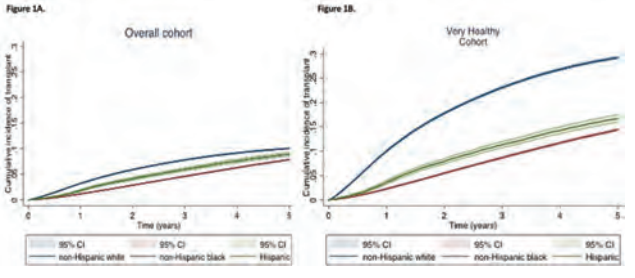
Results: During 4.1 years of mean follow-up, 129,820 patients received a transplant. NHBs and Hispanics had a lower prevalence of potential medical barriers [Figure 1] to transplant at time of dialysis initiation than NHWs. Overall, access to transplant was 56% lower in NHBs and 43% lower in Hispanics compared to NHWs [Figure 2A]. When we repeated our Cox models after excluding patients who may be medically ineligible for transplantation (70% of the population), these disparities widened in the remaining "very healthy" subcohort [Figure 2B].

Conclusions: NHBs and Hispanics had fewer medical contraindications but lower access to transplantation than NHWs. Differences in medical eligibility do not appear to explain racial/ethnic disparities in access to transplant, and in fact, may mask the magnitude of the inequities that are present. These findings are concerning, as the healthiest candidates appear to have the lowest access to transplant.

Funding: NIDDK Support

Figure 1.





SA-PO086

Effects of Age and Body Mass Index on Enlargement of the Remaining Kidney in Living Kidney Transplant Donors

Makoto Tsujita. *Nagoya Daini Red Cross Hospital, Nagoya, Japan.*

Background: In living kidney transplant donors, recent studies have reported some problems related to long term safety of living kidney donations. After nephrectomy, compensatory hypertrophy of the remaining kidney occurs to recover kidney function. To know how large it would be is very informative. However, factors that affect compensatory hypertrophy remain unknown.

Methods: Kidney volumes were measured using computed tomography volumetry before donation and one year after kidney donation in continuous 83 living kidney transplant donors from 2014 to 2015 at Nagoya Daini Red Cross Hospital, Japan. Ratio of kidney volume before donation and one year after donation was measured. Factors such as age, body mass index (BMI), estimated glomerular filtration rate (eGFR), blood pressure (BP) and so on which could affect the ratio were evaluated. Selection of kidney transplant donors was done according to the guideline set by the Japanese Society of Transplantation.

Results: Thirty-seven donors among all kidney donors evaluated in the study were men. Mean age before donation was 57.0 ± 10.7 years. eGFR before donation was associated with kidney volume (r=0.24 p=0.04). Age had a negative correlation with the ratio (r=0.40, p<0.001), but BMI and eGFR had a positive correlation respectively (r=0.21 p=0.05, r=0.24 p=0.04, respectively). However, the difference in eGFR before donation and one year after donation was not associate with the ratio. Multivariate analysis showed that age and BMI had strong association with the ratio.

Conclusions: Age and BMI were associated with compensatory renal hypertrophy. These factors would be taken more into consideration in the selection of living kidney transplant donors.

SA-PO087

Renal Transplantation: Does Race Play a Role?

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Background: Multiple studies have revealed discrepancy in healthcare access and outcomes in certain racial populations. We present a retrospective cohort study of end stage renal disease (ESRD) patients from our institution scrutinizing whether or not race is a factor in the referral process for renal transplantation.

Methods: The study population included all of the adult 200 ESRD patients who are currently receiving hemodialysis at the outpatient dialysis unit at the University of Florida (UF) Health in Jacksonville from January 2016 to February 2018. We divided race into 3 categories: Blacks, Whites, and Others, which consisted mostly of Hispanic patients together with other races/ethnicities. Outcomes were categorized as the patients who refused referral, who were not referred for transplant, and who were referred for transplant. We also collected established factors in the transplant evaluation process such as age, Hemoglobin A1c ≥ 7, Body mass index ≥ 40, left ventricular ejection fraction ≤ 40, presence of coronary or peripheral arterial disease (PAD/CAD), albumin level < 3.5, and cancer, cirrhosis and smoking history. All data were collected using chart review and analyzed using univariate analyses and multinomial logistic regression. Associations between the race and outcome categories are presented as adjusted Odds Ratios (OR) with 95% confidence interval (CI) using the not-referred group as the reference category. The study was approved by the UF IRB committee.

Results: In the univariate analysis, age, PAD/CAD, and albumin level were found to be potential confounders and were included in the final model. Blacks (OR=16.0, 95%CI 3.3-77.2, p=0.018) and Whites (OR=22.5, 95%CI 3.4-149.8, p=0.013) were more likely to be referred for transplant than not compared to Others. The odds of transplant refusal versus a non-referral in Blacks and Whites were not different from Others (p=0.270, and p=0.171, respectively).

Conclusions: In our nephrology practice, Blacks and Whites were more frequently referred for renal transplant than other ethnicities/races. There was no difference between the races in transplant refusal, which might point to satisfactory education and communication across the race groups. At this point we speculate the lack of funding and immigration status might play a role in the observed differences. Future studies are needed to address these possibilities.

SA-PO088

Does Financial Assistance for Travel and Subsistence Costs Alleviate Racial/Ethnic Disparities in Living Kidney Donation? An Analysis of NLDAC and SRTR Data

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Background: The National Living Donor Assistance Center (NLDAC) enables living donor kidney transplants (LKDT) through means-tested financial assistance of living kidney donors (LKD). Since LKDT occurs at lower rates in minority populations, we aimed to determine whether NLDAC utilization is associated with minority donor and recipient characteristics.

Methods: We retrospectively matched LKD data from NLDAC to Scientific Registry of Transplant Recipients (SRTR) data (2012-2015). We compared sociodemographic factors between NLDAC-using and non-NLDAC-using donors. Generalized linear mixed models with center-level random effects were used to estimate the impact of demographics on donor NLDAC use.

Results: There were 16,822 LKDT from 2012-2015. Matching to SRTR was successful for 86% of 1,419 NLDAC LKDT. Compared to non-NLDAC LKD, NLDAC LKD had a higher proportion of females (67% vs 62%), black race (15% vs 11%), Latino ethnicity (20% vs 14%), and were less educated (less than bachelors vs bachelors or more, 48% vs 45%).. NLDAC LKDT recipients were more often black (17% vs 13%), Latino (20% vs 14%), and less educated (all p<0.05). On multivariable analysis, NLDAC utilization was associated with LKD characteristics included LKD black race (OR 1.46, p=0.008), Latino ethnicity (OR 1.32, p=0.029), and female sex (OR 1.23, p=0.001); and LKDT recipient characteristics of black race (OR 1.38, p=0.017), Latino ethnicity (OR 1.29, p=0.047), and lower education (OR 1.17, p=0.012).

Conclusions: Living donor and recipient racial and ethnic minority status, as well as recipient educational status, were associated with higher NLDAC utilization among LKDT in the US. These data suggest that financial assistance programs for living donors alleviate disparities in access to LKDT.

Funding: Other U.S. Government Support

SA-PO089

Impact of Machine Perfusion on Delayed Graft Function and Graft Survival from High-Risk Donors

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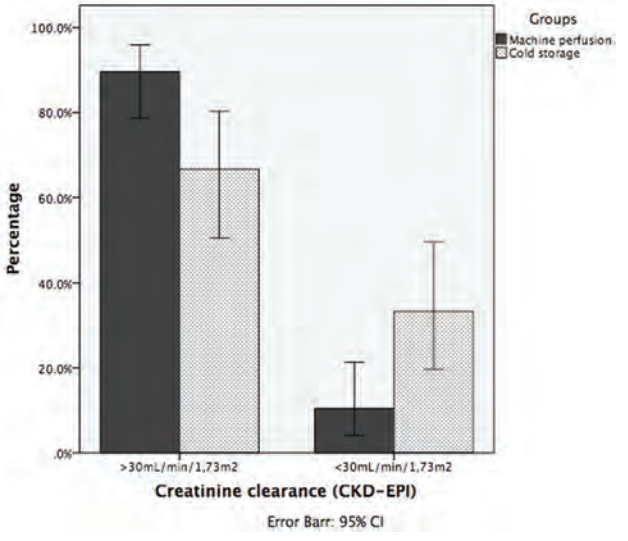
Background: After kidney transplantation(KT), graft may not function immediately and patient needs to undergo dialysis, characterizing delayed graft function (DGF). DGF increases length of hospital stay (LHS), costs and reduces graft survival (GS). DGF incidence is higher in expanded criteria donor (ECD), prolonged cold ischemia time (CIT) and donors with renal dysfunction. Machine perfusion (MP) is a method of preservation that can reduce DGF incidence. We analyzed DGF incidence, its duration, CIT, LHS, 1-year graft and patient survival and renal function estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) at 1, 3, 6, 9 and 12 months in KT with CS compared to MP after CS.

Methods: Retrospective cohort, in a single center. We included KT from DCE or standard deceased donors if CIT ≥ 24 hours, cardiorespiratory arrest before donation or creatinine ≥1.8mg/dL prior to retrieval from January 2015 to December 2016, 1-year follow up.

Results: Sample was 92 patients, 52 in MP group. Differences between groups were: age of recipient higher in MP group and donor creatinine prior to retrieval 0.7mg/dL higher in CS group. DGF incidence was 86.5% in MP group and 95% in CS group, p=0.29. There were no differences in DGF duration or LHS. CIT was 8.19 hours higher in the MP group, p<0.01. GS was 90.4% in the MP group and 87.5% in CS group. Patient survival was 94.2% in MP group and 95% in CS group. There were no differences in CKD-EPI at 1, 3, 6, 9 and 12 months. After 1-year KT, 89.6% of MP group and 66.7% of CS group had CKD-EPI higher than 30mL/min/1.73m2, p=0.01. In multivariate analysis, risk factors for worse 1-year graft function were: donor age (OR 1.11 CI95% 1.01-1.22; p=0,03) and CS preservation (OR 6.52 CI 95% 1.46-29.08; p=0.01).

Conclusions: The higher CIT in MP group did not increase incidence of DGF. 1-year graft function were better in MP preservation.



SA-PO090

Selecting and Educating Hepatitis C Virus (HCV) Un-infected Kidney Transplant (KT) Waiting List Recipients for a Clinical Trial to Receive an HCV-Infected KT

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Background: Using HCV-infected (HCV+) donors for KT into HCV-uninfected (HCV-) recipients is a novel strategy to increase access to KT and decrease high rates of organ discard. Patient (pt) selection and education is key to ensure ability to comply with protocol requirements and fully understand risks/benefits.

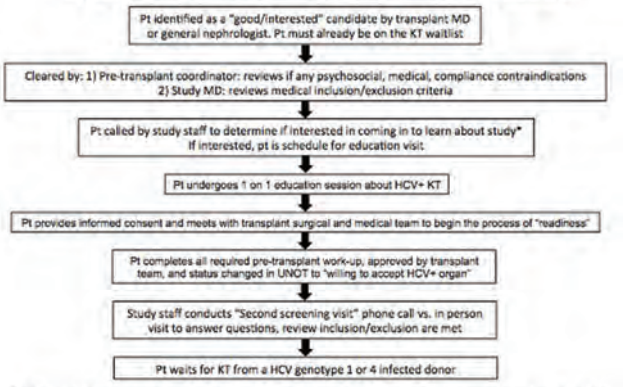
Methods: NCT02945150 is an investigator-initiated clinical trial to transplant 11 HCV- KT pts with a HCV+ KT. Pre-emptive use of elbasvir/grazoprevir to cure HCV in the recipient. We describe the criteria used to select pts, education process, characteristics of the consented pts, and study outcomes of HCV+ KT.

Results: We present enrollment criteria and rationale, which focus on ensuring that high quality HCV+ kidneys are accepted for transplantation and recipients have been selected to maximize safety and benefit. The process of enrolling pts is shown in **Figure 1**. Pt education focuses on 5 themes: 1) HCV in general 2) Effect of HCV on kidney availability 3) Genotypes of HCV and treatment 4) Logistics of study visits 5) Side effects of elbasvir/grazoprevir. The full "education session" is provided. 23 pts have provided consent, mean age 57 (SD 8), 61% Male, 78% White, 13% Black, 9% Hispanic. Two were excluded due to psychosocial or medical comorbidities. Twelve are undergoing medical clearance for KT. Nine were approved and their UNOS status changed to "willing to accept HCV+ organ." Five underwent KT and four are waiting. All donors had genotype 1A infection. None had resistance-associated variants. (Numbers, transplant, and viral outcomes to be updated at time of presentation).

Conclusions: It is important to have a multidisciplinary team to identify the appropriate pts for HCV+ to HCV- KT and a thorough process of education, consent, and evaluation so that pts understand the risks of the protocol and the KT itself.

Funding: Commercial Support - Merck

Figure 1. Identification, Education, Readiness for HCV+ KT



* All pts have already signed consent to be contacted for research purposes. Abbreviations: PT = patient, KT = kidney transplant, HCV = hepatitis C virus

SA-PO091

Access to the Kidney Transplant Waitlist for Patients with HIV and ESRD

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Background: Patients with HIV and end-stage renal disease (ESRD) experience higher mortality on dialysis than those without HIV. These HIV+ dialysis patients may face barriers to kidney transplantation (KT) that result from delayed referrals or factors identified at the time of evaluation.

Methods: We used a prospective, longitudinal multi-center cohort to study 98 HIV+ and 3,105 HIV- patients with ESRD who were evaluated for KT between 2008 and 2017. We compared patient characteristics and estimated the likelihood of listing by HIV-status using adjusted Cox regression. The presence of comorbidities was defined as a Charlson comorbidity index (CCI) score ≥1; cognitive impairment was defined as a mini-mental state exam score ≤80.

Results: Patients with HIV were more often young (median 54 vs. 56 years old), African American (91 vs. 43%), men (72 vs. 59%), with cognitive impairment (15 vs. 6%), and longer time on dialysis prior to KT evaluation (median 2.4 vs. 1.3 years) than those without HIV. Within 1 year of KT evaluation, 52 HIV+ and 2,010 HIV- patients were listed for KT; median time from evaluation to listing was 133 days for HIV- patients and 315 days for HIV+ patients (Figure 1). Adjusting for age, gender, African American race, comorbidities, and cognitive impairment, patients with HIV were less likely to be listed (aHR: 0.70, 95%CI: 0.52-0.93; p<0.05). However, additionally adjusting for time on dialysis attenuated this difference (aHR: 0.90, 95%CI: 0.67-1.20; p=0.5).

Conclusions: HIV+ patients have a lower likelihood of KT listing that is not explained by differences in patients' characteristics other than time on dialysis prior to evaluation. Decreasing time from dialysis initiation to referral for evaluation may improve access to KT for HIV+ patients with ESRD.

Funding: NIDDK Support, Other NIH Support - F30DK116658 (Shaffer), T32AG000247 (Chu), F32AG053025 (Haugen), K24DK101828 (Segev), K01AG043501 & R01AG055781 (McAdams-DeMarco)

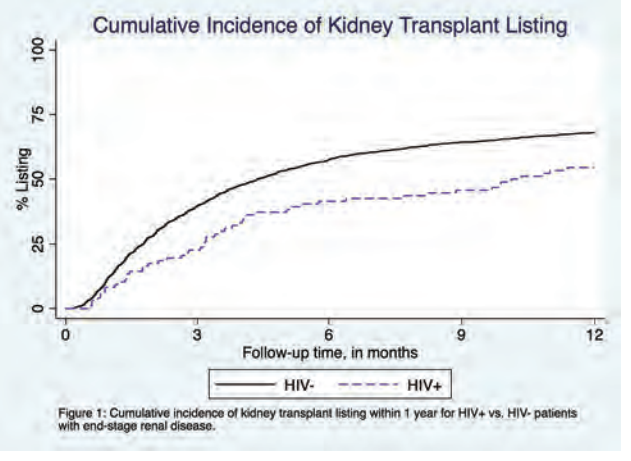

Figure 1: Cumulative incidence of kidney transplant listing within 1 year for HIV+ vs. HIV- patients with end-stage renal disease.

SA-PO092

Kidney Transplant Evaluation with Blood Oxygen Level Dependent (BOLD) and Diffusion-Weighted MRI: A Pilot Study

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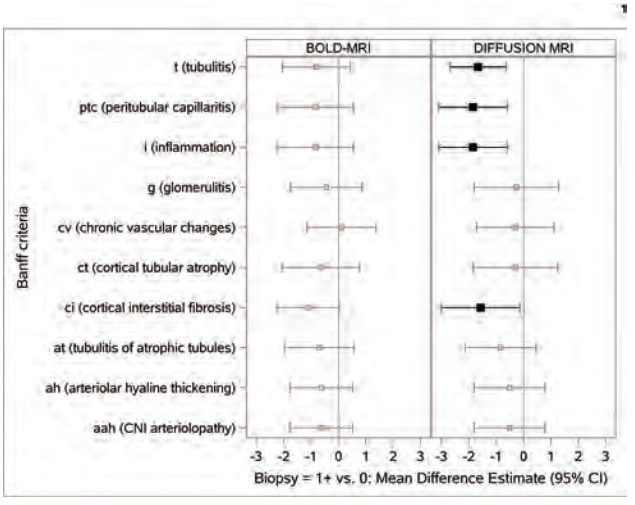
Background: Methods to identify etiologies of kidney allograft dysfunction in kidney transplant recipients (KTR) are generally limited to biopsy (bx). Blood oxygen level-dependent (BOLD) MRI can provide surrogate markers of tissue oxygen bioavailability. Diffusion-weighted (DW) intravoxel incoherent motion (IVIM) method can assess capillary perfusion and molecular diffusion, which may indicate tissue fibrosis. We explored these MRI methods as a non-invasive strategy to evaluate KTR undergoing bx.

Methods: We enrolled 14 KTR who underwent bx (12 protocol, 2 cause) at our center. Participants underwent research MRI scanning using BOLD and IVIM-DW protocols. Allograft bx were scored using Banff criteria by a single trained renal pathologist per clinical protocol. Individual Banff criteria were categorized as ordinal variables and corresponding MRI values were compared by the Kruskal-Wallis test. The mean difference estimate of the standardized MRI values between dichotomized abnormal and normal categories of Banff scores was calculated. Receiver operating characteristics (ROC) analysis was performed.

Results: Mean age was 50 (+/- 16); 9 (64%) were women. More severe grades of total inflammation (ti) were associated with lower BOLD R2* values (12.6 v. 13.8 v. 15, p=0.05); this may reflect lower oxygen consumption. Higher Banff scores for t, ptc, and i were associated with reduced capillary perfusion measured by IVIM-DW MRI (Fig). Area under curve (std error) for cortical interstitial fibrosis 0.8 (0.15) by BOLD and 0.95 (0.07) by DW.

Conclusions: BOLD and IVIM-DW MRI measures correlate with tissue pathology. IVIM-DW MRI may have more precision than BOLD to distinguish certain pathologic features on allograft bx. Functional MRI measures may be a useful screening tool to minimize kidney allograft bx.

Funding: NIDDK Support, Private Foundation Support



SA-PO093

Ferumoxytol-Enhanced MR Angiography (FeMRA) vs CT Angiography (CTA) for the Assessment of Potential Kidney Transplant Recipients

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Background: Conventional vascular imaging techniques are problematic in chronic kidney disease (CKD) patients due to associated risks, invasiveness and imprecision. CT angiography (CTA) is routinely used to assess the vasculature of CKD patients before transplant listing. Ferumoxytol, licensed for iron-deficiency anaemia, was originally developed as an MRI contrast agent and reduces T1 properties of tissue on MRI.

Methods: Prospective comparative study of ferumoxytol-enhanced MRA (FeMRA) vs CTA for aortoiliac imaging in kidney transplant (KT) candidates. MRA using ferumoxytol 3mg/kg as intravenous contrast agent was performed in addition to CTA. We also used a specific MRI sequence called StarVIBE to detect vascular calcifications in similar way to CT using contrast-free techniques. Two independent readers assessed the FeMRA/StarVIBE and a third reader the CTA (gold standard). Interclass correlation coefficient (ICC) was performed to assess interobserver agreement. Comparisons of lumen diameter, calcification, and signal intensity at predefined vascular sections were performed. For continuous variables, mean differences (and CI) were estimated and Bland-Altman plots of interobserver variability were created. Steady-state images were analyzed using the Horos image viewer (vs3, LGPL-3.0).

Results: 28 patients (mean age 68 [SD 15] yr; 58% men; 42% diabetics) undergoing CTA for pre-operative KT candidacy assessment were enrolled. There was excellent intraobserver agreement in assessment of the arterial diameter, vein diameter and calcification (ICC 0.91 [95% CI 079-0.96], 0.89 [0.79-0.94] and 0.95 [0.89-0.98], respectively). There were no significant differences in assessment of the arterial diameter and calcification between FeMRA/StarVIBE and CTA (arterial diameter 1.34 [0.42] vs 1.30 [0.44]cm; p=0.63, area of calcification 0.43 [0.35] vs 0.39 [0.29]mm^2; p=0.53, respectively). However, signal intensity and qualitative lumen depiction in the venous vasculature was superior with FeMRA (p<0.001).

Conclusions: FeMRA combined with StarVIBE is comparable to CTA for assessment of lumen diameter, calcification and signal intensity in the abdominopelvic arterial vasculature of CKD patients due for KT listing with the significant advantage of improved venous depiction with no nephrotoxicity.

Funding: Commercial Support - AMAG Pharmaceuticals

SA-PO094

Contrasting Relationships Between Deprivation, Kidney Transplantation, and Live Donation

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Background: Socioeconomic deprivation (SED) is associated with reduced access to pre-emptive and live kidney donation for end stage kidney disease (ESKD). We investigated the association between SED and access to, and progression through, potential live donor (PLD) assessment.

Methods: Retrospective analyses of routinely collected healthcare data were performed. A postcode of residence-based tool, the Scottish Index of Multiple Deprivation (SIMD), was used as a marker of SED; the cohort was grouped numerically into those with greater deprivation (SIMD≤3) and those without. A survival analysis was performed to test for interaction between SIMD and time to either drop-out or live donor nephrectomy.

Results: Of 7765 patients attending clinic, 1298 reached ESKD; 113 received a pre-emptive transplant. Patients receiving pre-emptive transplant had higher SIMD (5±7 vs 4±5; p=0.003); SIMD, cardiovascular disease, referral age and proteinuria were independently associated with pre-emptive transplant on logistic regression. 1208 PLDs were evaluated between 2009 and 2018 with an age of 45.8±21.4 years, follow-up 3.4±8.5 months and SIMD of 4±5. The PLDs from deprived areas were assessed at younger age (42.9±21.6 vs 48.4±21.1 years; p<0.001). SED was not asssociated with likelihood of successful donation (8 vs 11%; p=0.13) but was associated with more frequent referral for psychological assessment (13 vs 9%; p=0.03); there was no difference in discussion of the National Kidney Sharing Scheme (7 vs 9%; p=0.22). The cumulative incidence of successful donation was no different between groups (log rank p=0.27). In an analysis of the recipients of the PLDs, there was no association between SED and renal replacement therapy status (pre-emptive recipients 55 vs 62%; p=0.21), nor recipient eGFR (13.0±8.4 vs 13.1±7.6 ml/min/1.73m^2, p=0.56) at time of PLD approach. In an evaluation by postal code sector, there was no association between lower SIMD and the number of PLDs per 100,000 population (r = -0.024, p=0.75).

Conclusions: Although SED is associated with reduced incidence of live and pre-emptive transplantation, in recipients in whom PLDs are assessed, deprivation does not affect outcome of the evaluation process. Resources should be focused on encouraging an approach of PLDs for all suitable patients nearing ESKD.

SA-PO095

Multiparametric MRI Characteristics of the Renal Allograft in the Early Post-Transplant Period

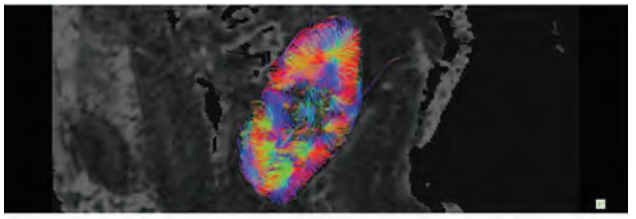
Keith Gillis,[1] Sarah Allwood-Spiers,[2] Alastair J. Rankin,[1] Giles Roditi,[2] Aleksandra Radjenovic,[1] Rajan Patel,[1] Patrick B. Mark.[1] Glasgow Renal Research Group *[1]University of Glasgow, Glasgow, United Kingdom; [2]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.*

Background: Renal allograft function is currently measured using estimated glomerular filtration rate (eGFR) and proteinuria, however these do not provide comprehensive information regarding prognosis or presence of important pathological features such as fibrosis. Use of multi-parametric magnetic resonance imaging (MRI) may yield novel biomarkers for prediction of outcome and response to therapy in renal transplantation.

Methods: Patients undergoing renal transplantation underwent multi-parametric MRI at 6 weeks post operatively. Routine clinical and biochemical measures were made. MRI protocol entailed arterial spin labelling (ASL) perfusion, T1 relaxation time and R2*. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were measured, and tractography maps produced, by diffusion weighted imaging.

Results: 20 patients were recruited with median age 55.5±12.8 years, eGFR of 51.8±27.4 ml/min/1.73m^2, and trough tacrolimus of 8.7±2.5 ng/mL. Cortical ASL was 283.0±116.2 ml/min/100g, ADC 1.69±0.11 x10^{-3} mm^2/s, FA 0.22±0.04, T1 was 1715±114 ms. ADC had a significant correlation with eGFR (r=0.48, p=0.03), and a negative association with cold ischaemia time (r=-0.55, p=0.01) and recipient age (r=-0.45, p=0.04). There was also a negative correlation between recipient age and cortical ASL (r=-0.60, p=0.04), Differences in transplant function were visible on diffusion tensor imaging (figure 1).

Conclusions: Diffusion weighted imaging may provide a novel method of evaluating renal transplant structure and function. Further research is required to determine if this provides increased prognostic information additional to existing biochemical measures.



Tractography map of kidney allograft derived from diffusion tensor imaging

SA-PO096

Social Determinants of Quality of Life in Patients Evaluated for Kidney Transplant

Hannah Wesselman,[2] Shu Wang,[2] Chung-Chou H. Chang,[2] John R. Pleis,[5] Kellee Kendall,[2] Emilee J. Croswell,[2] Mary amanda Dew,[2] Mark L. Unruh,[3] Ron Shapiro,[4] Larissa Myaskovsky.[1] *[1]University of New Mexico, Albuquerque, NM; [2]University of Pittsburgh, Pittsburgh, PA; [3]University of New Mexico, Los Ranchos, NM; [4]Recanati/Miller Transplantation Institute, New York, NY; [5]VA Pittsburgh, Pittsburgh, PA.*

Background: Non-Hispanic African Americans (AA) have a higher incidence of ESRD but lower rates of kidney transplant (KT), and poorer quality of life (QOL) compared to non-Hispanic whites (WH). Disparities persist after adjusting for medical factors (e.g., comorbidity, dialysis). We assessed whether race disparities in QOL would persist in patients evaluated for KT after adjusting for medical and social determinants, including demographic (e.g., age, income), cultural (e.g., perceived discrimination, medical mistrust), psychosocial (e.g., social support, emotional distress), and knowledge (e.g., knowledge, learning activities) factors.

Methods: We conducted a longitudinal cohort study with 1035 (AA=260; WH=775) patients undergoing KT evaluation at the UPMC Starzl Transplant Institute. Patients completed an interview after initiating KT evaluation to assess social determinants; and another interview after being accepted, rejected, or withdrawing from evaluation, to assess kidney-specific (symptoms/problems, sleep, lifestyle effects, burden, cognitive function, work, sexual function) and general QOL (mental and physical composite scores) using the Kidney Disease QOL scale. We built multivariable regression models to test the hypothesized relationships.

Results: Our sample was 38% female, mean age=57, 73% had family income < $50,000, 52% married, 35% public insurance, 27% private, and 38% public/private. Race differences in kidney-specific QOL outcomes were no longer significant when social determinants were included in the model. Instead, psychosocial (e.g., mastery, social support, emotional distress), transplant knowledge (e.g., concerns, learning activities, knowledge), and demographic (e.g., age, sex, income, insurance) factors were significant predictors. For general QOL outcomes, race continued to be a significant predictor even after we identified several significant psychosocial, transplant knowledge, and demographic predictors (all predictors significant at $p<.05$).

Conclusions: A combination of social determinants predicted QOL outcomes for KT patients, which mediated race differences, especially for kidney-specific QOL. Transplant centers may help ensure better QOL in their patients as they await KT by promoting psychosocial support, and ensuring candidates' understanding of KT.

Funding: NIDDK Support, Private Foundation Support

SA-PO097

The Impact of Systematic Review of Status 7 Patients on the Kidney Transplant Waitlist

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Background: Patients (pts) listed status 7 on the kidney transplant (Tx) waitlist are more likely to die rather than be transplanted. They need to overcome one or more barriers in order to move to status 1. These barriers could either be medical or psycho-social (PS) but are significant enough to exclude them from recieving organ offers. We speculated that by systematically re-evaluating status 7 pts, we might overcome the barriers and expedite their Tx.

Methods: Biweekly status 7 re-evaluation meetings were started in April 2016 and continued through April 2018. The attendees were a transplant physician champion and members of all components of the transplant team. These were held in parallel to the recipient selection meetings. For each status 7 patient, the attendees performed an intense scrutiny of the individual barriers against activation and developed a specific action plan. A descriptive analysis of the status 7 pts at the start and end of study was performed and patient demographic and listing outcomes were studied.

Results: A total of 266 status 7 pts were evaluated(Table1). 18.4% of them overcame remaining barriers preventing activation and majority (85.7%) in this group recieved a Tx after being inactive on the waitlist for average 805 days. 39% of inactive patients were deemed ineligible and were removed from the waitlist. These pts were older than those who recieved a Tx (mean age 60.6 versus 52.7 years) and were inactive for average 1593 days. 17.6% status 7 pts died while only 73 (27.4%) pts still remain inactive on the waitlist. Common barriers against activation were CP and PS issues in all categories.

Conclusions: Re-evaluation of status 7 pts has the potential to expedite their transplantation or removal of those pts from the waitlist who are unlikely to get activated for a kidney Tx. We have incorporated this process on a continuing basis.

Current waitlist status	Status 7	Activated and/or transplanted	Died	Removed from the waitlist
Number of patients(%)	73(27.4%)	49(18.4%) activated; 42 of these transplanted	47(17.6%)	104(39%)
Mean age (years)	51.3	53.4	59.3	60
Common barriers against activation(%)	CP(52) PS(30)	CP(41) PS(33) Onc(17)	CP(54) PS(21) Onc(15) I(13)	CP(46) PS(26) Onc(10)
Average inactive duration (days)	1685	805	1198	1593

CP-Cardio-pulmonary, PS-Psycho-social, Onc-Oncologic, I-Infection

SA-PO098

Aged Kidney Grafts: Another Potential Long-Term Risk in Living Kidney Transplantation

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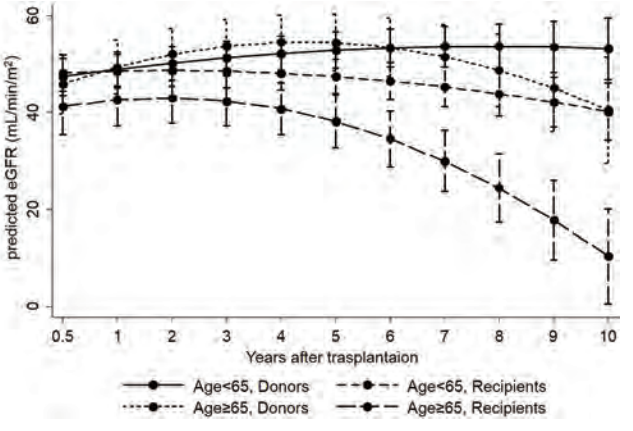
Background: As marital kidney transplantaion increases, the living kidney donor's age, or the age of the kidney graft at transplantaion, becomes older in Japan; however, its effect on graft survival has not been well-studied. We evaluated the long-term kidney function of both donors and recipients in transplantaion with aged or non-aged kidney grafts.

Methods: In this prospective observational study, we enrolled 130 consecutive living kidney donors and recipients (65 pairs) in a single transplant unit in Japan from November 1, 2008 to May 31, 2013. We divided them into two groups by donor's age (D-Age<65 and D-Age≥65), and longitudinally followed estimated glomerular filtration rate (eGFR) every year until May 31, 2018. The temporal changes in eGFR of donors and recipients were analyzed by mixed effects models with random intercepts and random slopes, allowing a quadratic term for time-interaction and a 2-by-2 factorial interaction (D-Age and donor-recipient).

Results: The median donors' and recipients' ages were 60 and 46 years old, respectively. We had 19 donors (29.2%) who were over 65 years old. We had 39 females (60%) in donors and 25 females (38.5%) in recipients. There was no significant difference in eGFR before donation between D-Age<65 and D-Age≥65 group. In the D-Age≥65 group, eGFR declines started in donors and recipients four years and two years after transplantation, respectively, while in the D-Age<65 group eGFR was sustained in donors and slightly decline in recipients (p for interaction<0.01). No significant difference in trajectory of eGFR was observed between recipients and their donors in D-Age≥65 group (p=0.50).

Conclusions: In this study, eGFRs in both donors and recipients were declined after living kidney transplantation with aged grafts. We should be careful when we use aging kidney in transplantaion.



SA-PO099

Postdonation Renal Function Predicts New Onset Antihypertensive Medication Use After Living Kidney Donation

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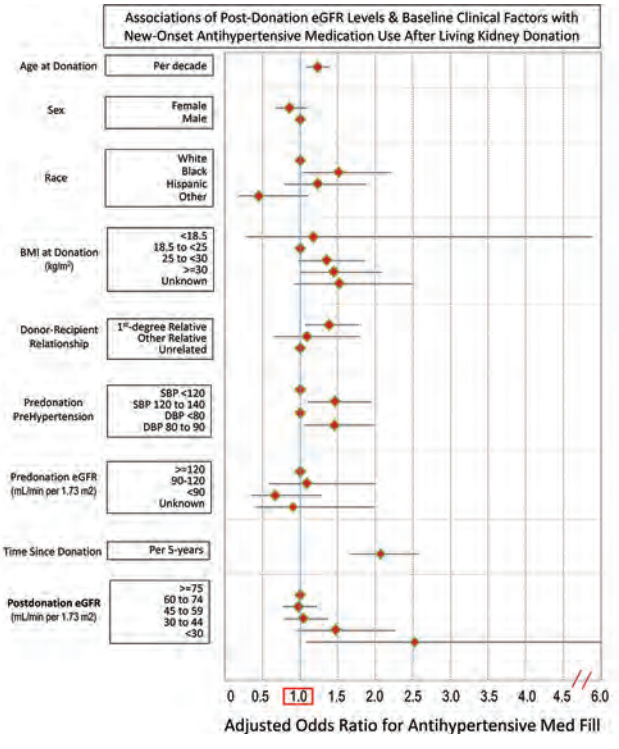
Background: Limited data are available on the outcome implications of renal function after living kidney donation.

Methods: We constructed a novel database linking SRTR registry identifiers, serum creatinine (SCr) values from an electronic medical records warehouse, and pharmacy fill records for 3,593 living kidney donors (1989–2016) without predonation hypertension per the registry. Estimated glomerular filtration rate (eGFR, ml/min/1.73 m2) was computed from SCr by the CKD-EPI equation. Pharmacy enrollment was assessed within ±90 days of each postdonation SCr, followed by identification of antihypertensive medication (AHM) fills in those with pharmacy records eligibility. A mixed effects model was constructed to assess associations of postdonation eGFR (adjusted odds ratio, $_{95\%LCL}$ aOR $_{95\%\ UCL}$) and other baseline factors with AHM treatment requirements after donation.

Results: The linked database captured an average of 3 post-donation SCr values per donor (range: 1 to 38). Lower postdonation eGFR bore a graded association with increased AHM use (eGFR 30–44: aOR $_{0.95}1.47_{2.26}$; <30: aOR $_{1.08}$ $5.90_{2.52}$). Other significant (P<0.05) correlates of postdonation AHM fills included black race (aOR 2.22), BMI >30 kg/m^2 (aOR 2.09), first-degree donor-recipient relationship (aOR 1.79), "pre-hypertension" at donation (SBP 120-139: aOR 1.94; DBP 80-89: aOR 1.99), and longer time since donation. Predonation eGFR was not significantly associated with AHM use in the multi-level model. [**Fig**.]

Conclusions: Lower eGFR levels after living kidney donation are associated with need for AHM treatment. Further work should define relationships of postdonation renal function with renal and cardiovascular morbidity.

Funding: NIDDK Support



SA-PO100

Which US-Listed Candidates Travel Abroad for Kidney Transplant?

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Background: Kidney transplant (KT) candidates listed in the United States (US) wait several years to receive a transplant. Some candidates opt to withdraw from the US waitlist and receive a KT abroad.

Methods: Using the SRTR 2010-2016, we compared 364 adult KT candidates who received KT abroad to 76,133 candidates removed for deceased donor KT. We assessed factors associated with receiving KT abroad using adjusted logistic regression accounting for possible race/citizenship interactions.

Results: KT candidates who received a KT abroad were more often male (p<0.001), younger (p<0.01), college educated (p<0.001), and had private insurance (p<0.001). These candidates spent less time on dialysis (1.6 vs. 3.8 years, p<0.001), and were often first-time KT candidates (p<0.001). The likelihood of KT abroad differed by race and citizenship (interaction p<0.001). White US citizens/residents (C/R) were the reference group. White non-US citizens/non-US residents (NC/NR) had the highest odds of KT abroad (aOR: $_{63.27}113.59_{203.92}$, p<0.001). Hispanic C/R residents had a 2.6-fold (aOR: $_{1.75}2.60_{3.84}$, p<0.001) higher odds and Hispanic NC/NR had a 13.9 fold (aOR: $_{6.04}13.87_{31.87}$, p<0.001) higher odds of KT abroad. Asian C/R had a 15.7-fold (aOR: $_{11.69}15.67_{20.99}$, p<0.001) higher odds and Asian NC/NR had a 34.2-fold (aOR: $_{14.11}34.16_{82.70}$, p<0.001) higher odds of KT abroad. The countries most frequently traveled to were the Philippines (n=93) and India (n=52) (Figure 1).

Conclusions: Although travel for transplant remains a rare practice for US-listed candidates, those with the means to travel, lower access to transplant, and possible connections outside the US might opt to travel abroad for transplant. Since follow-up care will primarily take place in the US, the nephrology community needs better data on these candidates and their post-transplant outcomes.

Funding: NIDDK Support, Other NIH Support - T32 HL007055 (Thomas), K01AG043501 (McAdams-DeMarco), R01AG055781 (McAdams-DeMarco), K24 DK101828 (Segev), K01 DK114388 (Henderson), Private Foundation Support

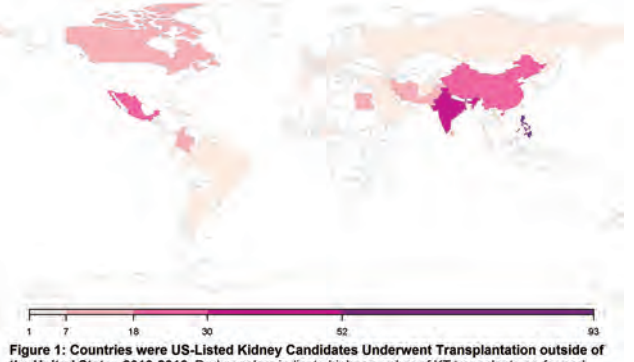

Figure 1: Countries were US-Listed Kidney Candidates Underwent Transplantation outside of the United States 2010-2016. Darker colors indicate higher number of KT transplants performed. The countries with the high number of kidney transplants of US listed candidates were the Philippines (n=93), India (n=52), China (n=30), Mexico (n=30), Iran (n=18), Pakistan (n=17), Canada (n=12), and Egypt (n=12).

SA-PO101

Nephron Dose Does Not Predict Renal Function After Live Donor Renal Transplantation

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Background: In our live donor transplant programme we consider isotopic determinations of donor glomerular filtration rate (GFR) as an indicator of the donor kidney quality. We also measure isotopic split renal function and thus by multiplying the two together we can calculate the potential "nephron dose" of the transplant. This has been used anecdotally as a guide to the quality of the graft and to inform the likely outcome in terms of function. This consideration has recently become more pertinent with the expansion of the national live donor sharing scheme since multiple potential donors may be considered for any particular recipient.

Methods: We recorded 147 patients from August 2008 to August 2017 excluding: those without follow up data; paediatric patients; and those with early graft loss (< year). Data set included estimated and measured GFR, split function of kidneys, Recipient body surface area (BSA), and recipient eGFR (MDRD equation) at 3, 6 and 12 months post transplant. We determined Nephron Dose using the formula: Measured isotopic GFR x percentage function of donated kidney = Nephron dose. We also measured the recipient's eGFR post transplant at t=3, 6 and 12 months, and corrected these measurements to recipients BSA. We measured the strength of the association using correlation coefficients.

Results: We report that the was no clear correlation with nephron dose to renal function at 3, 6 or 12 months whether eGFR was corrected for recipient body surface area or not, (table).

Conclusions: Nephron dose was not found to be strongly correlated with recipient transplant function at 3, 6 or 12 months following live donor renal transplants. This may

represent inaccuracy of either isotopic studies in donors to determine renal function or the MDRD formula to estimate true GFR post renal transplant. However we propose that postoperative transplant function is determined by a complex interplay between several factors, many of which are either recipient derived or external (e.g. viral infections and drug toxicity). The weak correlation demonstrated does not support overzealous interpretation of donor functional data even when derived from isotopic studies.

Correlation Coefficients for Nephron Dose and eGFR

	3 Months	6 Months	12 Months
eGFR	0.355	0.320	0.342
eGFR Adjusted for BSA	0.359	0.321	0.340

SA-PO102

Characterization and Establishment of Non-Human Primate Models of Diabetic CKD

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Background: The lack of translatable diabetic nephropathy animal models has greatly dampened the development of novel CKD therapies. This study aims to characterize a large cohort of high-fat diet (HFD)-induced type 2 diabetic nephropathy (T2DN) NHPs with substantial translational value to CKD drug development.

Methods: Animals with FBG ≥150 mg/dL and HbA1c ≥6% were screened from >1,500 male cynomolgus monkeys on HFD for ≥1.5 years. The following parameters were monitored: 24-h albumin-creatinine ratio (ACR); BP measurements; and, GFR by FITC-inulin. Animals were classified based on GFR severity grades and renal histology was scored based on the *International Pathologic Classification of Glomerular Changes in Diabetic Kidney Disease*.

Results: A 25% prevalence of T2DN-CKD was observed. Similar to human DN, albuminuria was confirmed as the earliest marker of glomerular disease. Serum creatinine was normal except in animals with kidney failure. DN-CKD monkeys had significantly elevated ACR levels compared to age-matched lean and obese monkeys, and to insulin-treated T2D monkeys. Systolic, diastolic and mean arterial pressure levels were significantly higher in DN-CKD. Over 75% had overt albuminuria with moderate to severe GFR reduction (GFR Stages 3-4) while 2% had kidney failure (GFR Stage 5). GFR reduction occurred even without substantive shifts from normo- or micro- to macroalbuminuria. No marked correlation between GFR and ACR was observed. These findings suggested that, as seen in human patients, macroalbuminuria did not represent an obligatory phase for renal function reduction in T2DN-CKD. Albuminuria with GFR Stages 3-4 were associated with mesangial expansion and thickening and/or fibrosis of the basement membranes (Class 1 to 2a/b). Kimmelstiel–Wilson lesions (Class 3) were seen with kidney failure.

Conclusions: A large cohort of DN-CKD monkeys was characterized using quantitative clinical laboratory and histopathologic indicators of DKD development and progression. The cynomolgus monkey CKD model resembles the disease characteristics in man and can be regarded as one of the most clinically relevant models for the efficacy evaluation of new therapeutic modalities for DN-CKD.

SA-PO103

A Novel Surgery-Induced Rat Model of Diabetic Nephropathy Displaying Progressive Albuminuria, Glomerular Hypertrophy, and Glomerulosclerosis

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Background: Diabetic nephropathy (DN) is a long-term complication of diabetes characterized by albuminuria and loss of kidney function. No new therapies targeting DN have been introduced for decades, partly due to the lack of preclinical animal models recapitulating key features of human DN. Here, we characterized a novel preclinical model of DN in pancreatectomized (Px) uni-nephrectomized (UNx) rats.

Methods: Px-UNx (n=11) and sham (n=12) operations were performed at 8 wks of age in male SPD rats. Blood glucose was >18 mmol/L in Px-UNx rats from 2 wks post-surgery. Urinary renal injury markers were measured 2, 6 and 9 wks after surgery and glomerular filtration rate (GFR) 9 wks after surgery. At termination 11 wks post-surgery, kidneys were processed for histology, stereology and next generation sequencing (NGS).

Results: Urinary albumin and NGAL excretion was increased from 2 wks post-surgery in Px-UNx vs Sham and highest after 9 wks for both albumin (13473±7619 vs 370±170 µg/mg creatinine, p<0.001) and NGAL (13.28±1.76 vs 2.68±0.43 µg/mg creatinine, p<0.001). Urinary podocalyxin excretion was increased from 6 wks and peaked 9 wks post-surgery in Px-UNx (195.2±41.9 vs 11.8±2.0 ng/mg creatinine, p<0.001). GFR was higher in Px-UNx vs Sham (8.2±0.3 vs 6.6±0.3 mL/min/kg, p<0.01). At termination, plasma urea was increased in Px-UNx (9.4±0.7 vs 5.5±0.2 mmol/L, p<0.001). Right kidney weight and volume was nearly doubled in Px-UNx vs Sham (both p<0.001), as were renal cortex (69.1% increase, p<0.001) and glomerulus volumes (57.7% increase, p<0.001). Kidney fibrosis (398±24 vs 210±9.8 mg collagen III, p<0.001) and glomerulosclerosis (11.1±0.8 vs 6.3±0.3 mm^3 collagen IV, p<0.001) was increased in Px-UNx vs Sham rats. Px-UNx increased gene expression of tubular injury markers (KIM-1, NGAL), collagens and fibronectin in renal cortex and reduced nephrin expression.

Conclusions: The Px-UNx model of DN develops extensive renal hypertrophy, hyperfiltration and fibrosis concomitant with early excretion of both glomerular and tubular injury markers. In rats, Px in combination with UNx represents a novel time-saving and robust alternative to STZ-induced diabetes and genetic models for preclinical drug development targeting DN.

SA-PO104

Dysregulation of the Ubiquitin Ligase Component Kelch-Like 3 Causes Na-Cl Cotransporter Activation and Salt Retention in Type 2 Diabetes Mellitus

Kenichi Ishizawa,[1,2] Qin Wang,[1] Jinping Li,[1] Yoshikazu Nemoto,[1] Chikayuki Morimoto,[1] Toshiro Fujita,[3] Shunya Uchida,[1] Shigeru Shibata.[1] *[1]Teikyo University School of Medicine, Tokyo, Japan; [2]Shinsen Ikebukuro Clinic, Tokyo, Japan; [3]The University of Tokyo, Tokyo, Japan.*

Background: Salt-sensitive hypertension is frequently associated with type 2 DM. However, the pathogenesis remains unclear. Kelch-like 3 (KLHL3) is a component of an E3 ubiquitin ligase complex that targets With-No-Lysine kinases for degradation, thereby regulating downstream Na-Cl cotransporter (NCC). Mutations and inactivation of KLHL3 increase NCC activity, resulting in hypertension and hyperkalemia. Previously, we have reported that angiotensin II (Shibata et al. PNAS 2014) and K^+ depletion (Ishizawa et al. BBRC 2016) inactivate KLHL3 by protein kinase C (PKC)-mediated phosphorylation at S433 in the Kelch-domain. In this study, we examined the possible involvement of KLHL3 in the diabetic kidney, using a model of type 2 diabetes.

Methods: KLHL3 phosphorylated at S433 ($KLHL3^{S433\text{-}P}$), total KLHL3, and NCC levels were evaluated in the kidney of db/db mice by Western blotting. In some experiments, db/db mice received a PKC inhibitor bisindolylmaleimide I (BIMI), SGLT2 inhibitor ipragliflozin, and a thiazolidinedione pioglitazone.

Results: $KLHL3^{S433\text{-}P}$, NCC and active PKC levels were all increased in the kidney of db/db mice. Administration of BIM to db/db mice significantly reduced $KLHL3^{S433\text{-}P}$ and NCC levels ($P < 0.05$). Consistently, urinary Na^+ levels were increased in db/db mice receiving BIM (76 ± 8.7 µEq/6h in db/db mice receiving BIM vs. 48 ± 4.5 µEq/6h in db/db mice receiving vehicle; $P < 0.05$). To evaluate the effects of SGLT2 inhibition on this pathway, db/db mice received ipragliflozin or pioglitazone (as a control). Of note, KLHL3 phosphorylation and NCC induction were reduced by ipragliflozin but not by pioglitazone, although blood glucose levels were similarly reduced by the two hypoglycemic agents. PKC activity was reduced by ipragliflozin but not by pioglitazone, explaining the distinct effects of the two hypoglycemic agents on KLHL3 and NCC.

Conclusions: These data demonstrate the involvement of KLHL3 in the increased salt reabsorption in obese diabetes mellitus, and provide insights into the mechanisms for the protective effect of SGLT2 inhibitors.

Funding: Government Support - Non-U.S.

SA-PO105

A Mouse Model of Moderate Diabetic Nephropathy on a Metabolic Syndrome Background

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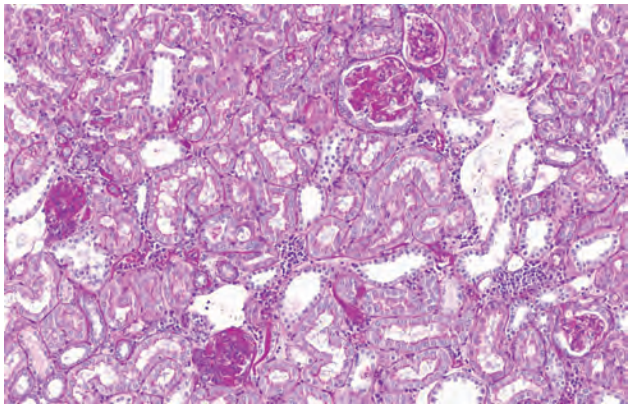
Background: Mouse models of diabetic nephropathy (DN) which not only recapitulate the early phases of the disease but also progress to a more advanced phase are urgently needed. We aim to develop a translational DN mouse model on metabolic syndrome background by incorporating the three main features of DN viz hyperglycemia, hyperlipidemia and hypertension.

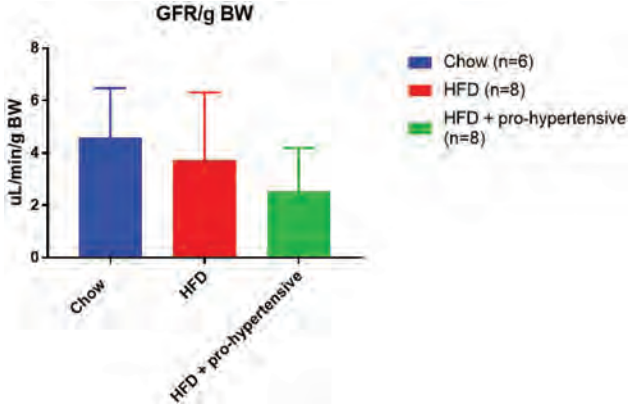
Methods: Male KKAy mice were uninefrectomized and received high fat (45%) diet alone (HFD) or with prohypertensive (HFD+hyp) for 14 wk. At regular intervals, systolic blood pressure (SBP), 24h diuresis and plasma was collected. At sacrifice, GFR (inulin clearance) was determined, and renal injury was scored using histology. Age-matched chow-fed animals were controls.

Results: Mice fed with HFD developed hyperglycemia and hyperlipidemia. The prohypertensive group developed hypertension. GFR was significantly reduced in the HFD+hyp group compared to controls (2.5µl/min/g BW vs 4.6µl/min/g BW). Renal injury score showed glomerular hypertrophy, mesangium expansion, glomerulosclerosis, hyalinosis, micro-aneurisms and tubulo-interstitial fibrosis.

Conclusions: Combining three key features of DN in one mouse model induces moderate DN with a decline in GFR and morphological features resembling the human situation. We are currently forming a consortium to identify the temporal dynamics of key processes involved in disease development and progression.

Funding: Government Support - Non-U.S.





SA-PO106

Glomerular Injury and Progressive Cardiac Dysfunction in the Obese ZSF1 Rat, a New Model of Diabetic Nephropathy and Heart Failure with Preserved Ejection Fraction

Elyse Di marco,[1] Erik Michaëlsson,[1] Charlotte Ericson,[1] Margareta Behrendt,[2] Maria Stromstedt,[1] Magnus Soderberg,[1] Johannes Wikstrom,[1] Anna Granqvist.[1] *[1]AstraZeneca, MOLNDAl, Sweden; [2]CVRM IMED Biotech, Gothenburg, Sweden.*

Background: Efforts to develop effective therapies against interlinked cardiac and renal diseases are hampered by the lack of preclinical models. We have investigated whether the hypertensive, diabetic, obese ZSF1 rat represents a valid experimental disease model for diabetic nephropathy (DN) and heart failure with preserved ejection fraction (HFpEF).

Methods: The renal (glomerular filtration rate- GFR, albuminuria, histology) and the cardiac (functional non-invasive imaging/invasive haemodynamics, histology) phenotypes were investigated in obese and lean male ZSF1 rats. Uninephrectomy (UNX) was performed in obese rats at 12-weeks of age followed by administration of high-salt diet (HSD) and treatment with ACE inhibitor Lisinopril for 10 weeks.

Results: Obese UNX ZSF1 rats displayed progressive albuminuria, reduced GFR and glomerular injury evidenced by increased desmin and reduced WT1 immunostaining, reduced podocyte-specific gene expression (podocin, nephrin, WT1) compared to lean ZSF1 rats. The renal histological phenotype was severely aggravated by HSD, consistent with marked increases in urinary biomarkers KIM-1, NGAL and Cystatin C. UNX rats fed HSD showed an increase in NTproBNP, a marker of cardiac stress, in line with progressive cardiac hypertrophy and impaired ventricular relaxation. Lisinopril treatment of UNX+HSD-rats had no effect on the renal phenotype or cardiac relaxation, but markedly improved systolic function.

Conclusions: The obese ZSF1 rat with UNX is a suitable model of renal dysfunction with progressive glomerular injury and the addition of HSD elicits a HFpEF phenotype. This model now allows us to investigate potential therapies targeting these interlinked diseases.

Funding: Commercial Support - AstraZeneca

SA-PO107

Loss of Podocyte Glucocorticoid Receptor Worsens Fibrosis in a Mouse Model of Diabetes

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Background: Glomerular fibrosis, which is a key component of diabetic nephropathy, is characterized by deposition of extracellular matrix, alteration of the glomerular structure and dysfunction of the glomerular filtration barrier. The role of the podocyte glucocorticoid receptor (pGR) in the pathogenesis of diabetic nephropathy has not been explored yet. Based on previous studies which showed that pGR was critical in the response to renal injury, we hypothesized that loss of pGR would result in worsened fibrosis.

Methods: Streptozotocin (STZ) 200 mg/kg was used to induce diabetes in 10-week old pGR KO mice (($GR^{fl/fl}$; podocin Cre+) and control litter mates ($GR^{fl/fl}$; podocin Cre-). After STZ injection, mice were maintained for 4 months prior to sacrifice. Body weight, kidney weight, blood glucose and urine microalbumin/creatinine ratio were assessed in normal and diabetic mice of both genotypes. Glomerular fibrosis and segmental glomerulosclerosis were analyzed by staining kidney sections in diabetic mice of both genotypes. Western blot and immunofluorescent staining were also used to examine key pro-fibrotic targets. One way ANOVA with Tukey's post-test was used to determine statistical significance.

Results: Non-diabetic control and pGR KO mice did not have any differences in body weight, kidney weight, blood glucose, urinary microalbumin excretion, or kidney histology. Diabetic control and pGR KO mice showed similar body weight, and blood glucose levels, but kidney weight was significantly higher in diabetic pGR KO mice (15.8 vs. 14.7 mg/g body weight, n= 5/group, p=0.04). Glomerular collagen deposition, glomerular surface area and mesangial expansion were all significantly increased in pGR KO mice. We did not observe any significant differences in the level of interstitial fibrosis. Western blotting and immunofluorescent staining of kidney sections revealed induction of mesenchymal activation which was associated with glomerular deposition of fibronectin and collagen I in diabetic pGR KO mice.

Conclusions: From these results we conclude that: 1. loss of pGR worsens the severity of fibrosis in our mouse model of diabetes 2. pGR is tonically suppressing mesenchymal activation pathways 3. modulation of pGR may represent a novel therapeutic pathway for diabetic nephropathy

Funding: NIDDK Support

SA-PO108

Regulation of Renal Gluconeogenesis in Acidotic Proximal Tubule-(PT) Targeted Dual Insulin/Insulin-Like-Growth Factor (IGF) Receptor Knockout Mice

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Background: Acidosis is associated with an increase in renal gluconeogenesis due to upregulation of ammoniagenesis, which liberates α-ketoglutarate, a substrate for gluconeogenesis. Insulin and IGF1 have been postulated to upregulate transport of glutamine into PT (precursor of ammoniagenesis), but may also be associated with decreased gluconeogenic capacity by phosphorylating forkhead box protein 01 (FOX01). Thus, net regulation of renal gluconeogenesis by insulin in the context of acidosis is uncertain.

Methods: We bred PT-select dual Insr/Igf1r knockout mice with Cre-recombinase driven by the γ-glutamyltransferase promoter. Male and female KO and WT littermates were made acidotic by consuming 280 mM NH4Cl in the drinking water for 7 days.

Results: Male KO mice demonstrated a 23% increase in fasting glucose (18-hr) with acid loading, while this increase was 2% in the WT males. In contrast, female WT mice had a mean 8% decrease and KO a 5% increase, indicating less sensitivity of females. Acid-treated male KO mice had lower blood pH and bicarbonate as compared to same sex WT (significant interaction). Female mice did not show this genotype dichotomy. Ex vivo capacity to synthesize glucose (with unlimited substrate) was measured in proximal tubule suspensions harvested from acid- and control- treated WT and KO mice. PT harvested from control KO males produced 56% more glucose then WT males. In agreement, the ratio of phosphorylated (Serine 256) FOX01 to total FOX01 was 37% lower in PT from the KO versus WT male mice. Acid loading increased glucose producing capacity of PT only in the WT males, while reducing the pFOX01/FOX01 ratio in all groups. In agreement, in males, acidosis significantly increased renal protein abundances of two rate-limiting enzymes in gluconeogenesis, i.e., fructose bisphosphatase-1 (FBP1) and phosphoenolpyruvate carboxykinase (PEPCK). The increase in FBP1 was 2-fold higher in the KO mice; however, KO mice also had significantly lower cortical expression of glucose-6-phosphatase (terminal gluconeogenic enzyme).

Conclusions: Chronic acidosis increases the capacity of the PT to produce glucose. Insulin and/or IGF1 appear to be involved in homeostatic regulation of this production via FOX01.

Funding: Clinical Revenue Support

SA-PO109

Anti-Proteinuric Actions of Angiotensin II Receptor Blockade in a Mouse Model of Diabetic Nephropathy

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Background: The progress in the research field of Diabetic nephropathy (DN) has been disturbed by the lack of reliable animal models. We have developed a mouse model exhibiting cardinal characteristics of human DN including high-grade albuminuria, glomerulosclerosis and genetic susceptibility to kidney damage. Because responsiveness to blockade of the renin-angiotensin system (RAS) is a key feature of human DN, we examined the impact of an angiotensin II receptor blocker (ARB) in our mouse model.

Methods: We generated mice with heterozygous for the *Ins2*^{C96Y} (*Akita*) allele combined with a single-copy renin transgene (*ReninTg)*, with renin expression under control of the albumin promoter. *Akita-ReninTg* mice on a 129/SvEv inbred background, which tends to exhibit exaggerated susceptibility to kidney disease, were generated through back-crossing. In the *Acute* protocol, losartan (10mg/kg/day) was given to 16-week old 129 *Akita-ReninTg* for 10 days, whereas in the *Chronic* protocol, losartan was administered daily from 12-24 weeks of age. Urine samples were collected over a 24-hour period using metabolic cages and albumin levels were measured with immunoassay.

Results: By 24 weeks of age, 129 *Akita-ReninTg* mice develop substantial albuminuria with severe renal pathological changes including mesangial expansion, nodular glomerulosclerosis and renal interstitial inflammatory cells accumulation. In 16-week old 129 *Akita-ReninTg* mice, *Acute* ARB administration caused an abrupt and significant reduction of albuminuria from 1049±325 to 308±156 μg/day (p=0.004). In the *Chronic* protocol, baseline levels of albumin excretion were similar between treated and untreated groups (767±154 vs 905±169 μg/day). ARB treatment prevented the progressive increase of albuminuria compared to untreated controls at 18 (721±136 vs 142±27 μg/day; p=0.001) and 24 (1480±562 vs 193±42 μg/day; p=0.045) weeks of age.

Conclusions: 129 *Akita-ReninTg* mice replicate key features of human DN, including responsiveness to RAS blockade. As in humans, the anti-proteinuric actions of ARB can be seen early after initiating treatment, likely representing acute reversal of abnormal glomerular hemodynamics and/or permeability. Chronic ARB administration causes a significant reduction in albuminuria that is sustained during the entire treatment period, likely due to protection against Ang II-dependent kidney injury.

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SA-PO110

Protein O-GlcNAcylation Regulates Renal Lipolysis During Fasting and Diabetes

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Background: Energy metabolism in kidney proximal tubular cells (PTCs) is unique because their ATP production largely depends on lipolysis rather than glycolysis, regardless of feeding or fasting. Furthermore, disrupted renal lipolysis is involved in the pathogenesis of tubular damage in various kidney diseases including diabetic kidney disease. Thus, elucidating detailed mechanisms of renal fatty acid metabolism should contribute to a novel therapy for kidney diseases. O-GlcNAcylation is a post-translational modification and acts an intracellular nutrient sensor. This study was designed to examine the role of O-GlcNAcylation in renal fatty acid metabolism under fasting and diabetes.

Methods: O-GlcNAc transferase (Ogt) is the sole enzyme for O-GlcNAcylation. We generated inducible PTC-specific Ogt-knockout mice (PTC-Ogt$^{y/-}$mice) by crossbreeding female Ogt$^{f/f}$mice with male tamoxifen-inducible PTC-specific Cre transgenic mice (NDRG1-CreER^{T2}mice), and analyzed their renal phenotype under fasting and high fat diet (HFD)-induced obese diabetes.

Results: PTC-Ogt$^{y/-}$mice showed no significant renal phenotype under *ad-libitum* feeding condition, but showed significant increases in urinary excretions of albumin, glucose and various ions after 48 hours fasting. Cellular apoptosis, significant intracellular lipid droplet accumulation, mitochondrial fragmentation and decreased ATP contents in renal cortex were observed in PTCs of fasted PTC-Ogt$^{y/-}$mice. Furthermore, PTC-Ogt$^{y/-}$mice developed severe tubular cell damage under HFD-induced obesity diabetic condition. Proteomic analysis revealed that PTC-Ogt$^{y/-}$mice showed significant change in lipid metabolism pathway and dramatic decrease in protein expression level of a neutral lipid esterase, Carboxilesterase-1 (CES-1), which was associated with decreased activity in Farnesoid X receptor (FXR).

Conclusions: Protein O-GlcNAcylation is essential for maintaining renal lipolysis under fasting and obesity diabetic condition through regulating FXR-CES1 axis.

SA-PO111

Elevation of NMN in the TG Mice Overexpressing Nampt in the Proximal Tubules Suppresses Albuminuria and Diabetic Tubulopathy by Maintaining Megalin Expression

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Background: Nicotinamide phosphoribosyltransferase (Nampt) synthesizes **nicotinamide mononculeotide (NMN)**, which is the precursor of **nicotinamide adenosine diphosphate (NAD)**. Nampt is expressed more abundantly in proximal tubules (PTs) than in other tissues. NMN injections have been shown to suppress acute kidney injury; however, the effects of renal NMN or Nampt in diabetic nephropathy remain unclear. We created kidney-specific Nampt-overexpressing transgenic (TG) mice using the promoter **sodium-phosphate cotransporter IIa (Npt2)** driven specifically in PTs for investigating them.

Methods: Wild-type littermate (WT) or TG 8-week old male mice were subjected to intraperitoneal injections of 50 mg/kg/day streptozotocin (STZ) or saline (Sal) for 5 days (WT+Sal, WT+STZ, TG+Sal, TG+STZ).

Results: After 16 weeks, **Nampt, NMN**, and **NAD** levels in WT+STZ were decreased, but were rescued in TG+STZ. Tubular Basement membrane (**TBM) thickening**, **type IV collagen deposition**, and **PT apoptosis** were significantly higher in WT+STZ, and were attenuated in TG+STZ. Our DNA microarray analyses showed the profibrotic and proapoptotic gene, **tissue inhibitor of metalloproteinases 1 (TIMP-1)**, was highly increased in WT+STZ, but suppressed in TG+STZ. Glomerular changes such as glomerular basement membrane (GBM) thickening and podocyte foot-process effacement occurred in both WT+STZ and TG+STZ. However, the albuinuria present in WT+STZ was significantly suppressed in TG+STZ. Thus, we hypothesized that TG elevates albumin reabsorption despite not affecting podocytes. Consistent with this, **albumin endocytosis** and **megalin** expression were reduced in WT+STZ, but retained in TG+STZ, whereas cubilin was not altered. In promoter assays, the decrease in Nampt/NMN/NAD repressed **Sirt6** activity, which acetylated and activated **RelA** binding to TIMP-1 promoter regions. The transfection of TIMP-1 vector in cultured PTs causes excessive collagen IV production and **Erk** phosphorylation, which reportedly reduces megalin expression and elevates PT apoptosis. These changes were totally blocked in TG mice.

Conclusions: Nampt TG/NMN/NAD potentiates Sirt6 activity, deacetylating RelA and silencing TIMP-1 transcription. This protects against TBM thickening, type IV collagen deposition, and Erk activation. Thus, Nampt appears to maintain megalin and albumin reabsorption.

SA-PO112

Dapagliflozin Reduces Glomerular Hyperfiltration and Improves Urine Parameters in db/db Mice on High Protein Diet: A 4-week Model of Diabetic Nephropathy

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Background: Preclinical animal models of glomerular hyperfiltration and diabetic nephropathy (DN) are needed for rapidly evaluating novel drugs targeting these complications. In this goal, obese and diabetic db/db mice are routinely used, but require several weeks to only show mild-albuminuria and early kidney disorders seen in human DN. Since high protein diet (HPD) are known to accelerate DN in human and animal models, we therefore developed a 4-week HPD fed db/db mouse model, in which the sodium glucose cotransporter 2 inhibitor dapagliflozin (DAPA) was evaluated.

Methods: 12-week old db/db male mice were placed on a HPD (60%kcal from protein) and treated with vehicle or DAPA 10mg/kg orally once daily for 4 weeks. Non-diabetic db/+ males on HPD treated with vehicle were included as negative control. Oral glucose tolerance test (OGTT), biochemical assays and glomerular filtration rate (GFR), assessed with FITC-sinistrin i.v. injection and transdermal monitors, were performed.

Results: Compared to db/+, db/db mice on HPD were strongly hyperglycemic, showed increased urine glucose excretion (UGE), higher albuminuria (+127%), and evident hyperfiltration, with a 40% higher GFR vs. db/+ ($p<0.05$ for all parameters). Compared to db/db treated with vehicle, DAPA blunted hyperglycemia in fasting state and during the OGTT (73% reduction in glucose area under the curve) and strongly increased fasting plasma ketone levels by 300% (all $p<0.001$). As expected, DAPA increased UGE by 116% ($p<0.01$ vs. vehicle) and reduced albumin/creatinine ratio by 40%, although not significantly. Compared with vehicle, DAPA reduced proteinuria and creatinine clearance by 36% ($p<0.001$) and 45% ($p<0.05$). Additionally, DAPA significantly reduced hyperfiltration with a 12% and 21% reduction in GFR at 2 and 4 weeks of treatment, respectively.

Conclusions: The present data indicate that DAPA shows significant benefits on kidney dysfunction in the 4-week HPD fed db/db mouse model. This fast model should be useful to rapidly evaluate drugs targeting diabetic nephropathy and glomerular hyperfiltration.

Funding: Commercial Support - PHYSIOGENEX SAS

SA-PO113

Unilateral Nephrectomy and Salt Loading Differentially Alter Glomerular Filtration Rate in the Hypertensive, Obese, Type 2 Diabetic SDT Fatty Rat Model of Diabetic Nephropathy

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Background: Evaluation of drugs targeting diabetic nephropathy (DN) requires diabetic animal models developing renal complications and alteration of glomerular filtration rate (GFR) in a short period of time. These models should exhibit hyperfiltration followed by a >50% GFR decline. The hypertensive, obese, Spontaneously Diabetic Torii (SDT) fatty rat develops kidney lesions and may serve as a relevant model for DN. To promote alteration of GFR, we here evaluated the effects of unilateral nephrectomy (Unx) and salt loading in SDT fatty rats.

Methods: 10-week old, male SDT fatty rats were included into 4 treatment groups (n=7/group): 1) normal water without Unx, 2) 0.3% salt water with Unx, 3) 0.6% salt water without Unx or 4) 0.8% salt water without Unx. Biochemical parameters and GFR were then followed for 13 weeks.

Results: Compared to SDT fatty rats under normal water without Unx, salt supplementation and Unx slightly attenuated the diabetic phenotype, with lower hyperglycemia (~400mg/dL vs. ~600mg/dL). However, it also resulted in a progressive induction of dyslipidemia, leading to a strong hypertriglyceridemia (~2000mg/dL vs. ~500mg/dL in rats under normal water without Unx) and hypercholesterolemia (~450mg/dL vs. ~150mg/dL) at 13 weeks. Under normal water without Unx, SDT fatty rats showed a gradual increase in hyperfiltration over 13 weeks with GFR raising from 13 +/- 2 to 22 +/- 5 mL/min/kg. This gradual increase was abolished by 0.6% salt without Unx, with stable GFR values over 13 weeks. However, 0.8% salt without Unx induced a progressive decline in GFR (36% lower at 13 weeks vs. baseline). In sharp contrast, 0.3% salt with Unx resulted in a rapid GFR decline from 2 weeks to 13 weeks (63% lower than baseline).

Conclusions: In the SDT fatty rat, Unx and salt loading have limited effect on diabetic state while they favor induction of dyslipidemia and differentially alter GFR. Depending on the experimental setting, this rat model should be helpful to evaluate the effects of drugs on hyperfiltration and GFR decline for the treatment of DN.

Funding: Commercial Support - SCOHIA PHARMA Inc.

SA-PO114

Effect of Dual Inhibition of Dipeptidyl Peptidase IV (DPP4) and Sodium/Glucose Cotransporter (SGLT2) on Tacrolimus-Induced Diabetic Rats

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Background: Sodium/glucose co-transporter-2 inhibitor (SGLT2i) and depeptidyl peptidase IV inhibitor (DPP4i) are promising antidiabetic drug but their combined use in tacrolimus (TAC)-induced diabetes mellitus (DM) is still undetermined. We evaluated the effect of dual inhibition of dipeptidyl deptidase IV (DPP4) and sodium/glucose cotransporter (SGLT2) on TAC-induced diabetes mellitus (DM) and renal injury in an experimental rat model. DM.

Methods: DM was induced by injection of injection of TAC (1.5mg/kg, subcutaneously) for 3 weeks, then DPP4i gemigliptin (20mg/kg/day, oral gavage) and/or SGLT2i empagliflozin (10mg/kg/day, oral gavage) were given for 4 more weeks. The effect of gemigliptin and/or empagliflozin was evaluated by assessing intraperitoneal glucose tolerance test (IPGTT) and by measuring markers of oxidative stress, apoptosis. Also, Morphologic change of kidney was observed.

Results: IPGTT showed that dual inhibition of DPP4 and SGLT2 showed synergistic effect on glucose lowering compared to DPP4i alone or SGLT2i alone group. In Kidney, combination treatment group of gemigliptin and empagliflozin alleviated TAC-induced renal dysfunction and decreased albumin excretion and histopathogic injury compared with TAC group or gemigliptin or empagliflozin alone group. Increased oxidative stress and apoptotic cell death by TAC was remarkably decreased with gemigliptin or empagliflozin treatment in serum and renal tissues, and this improvement was significantly prominent in combination group compared to gemigliptin or empagliflozin alone group. TAC induced a two-fold increase in SGLT-2 expression, while combination of gemigliptin and empagliflozin decreased SGLT-2 expression and further increased urinary glucose excretion compared to the TAC group.

Conclusions: In conclusion, dual inhibition of DPP4 and SGLT2 is effective in controlling TAC-induced hyperglycemia and has protective effect on TAC-induced renal injury, this finding provides basis clinical use of dual inhibition of DPP4 and SGLT2 in renal transplant patients with TAC-induced DM.

SA-PO115

NADPH-Oxidase NOX5 Aggravates Renal Injury in Akita Mouse Model of Diabetic Nephropathy

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Background: Renal reactive oxygen species (ROS) play an important role in mediating kidney injury in diabetes. Increasing evidence suggests that the pro-oxidant enzyme, Nox5 plays a significant role in human diabetic nephropathy (DN). Nox5 is present in humans and rabbits but not in mice or rats. Thus, there is a paucity of information about Nox5 in conventional animal models of DN. We examined the role of Nox5 in the insulin deficient diabetic Akita mice model using human inducible transgenic mice that express Nox5 selectively in endothelial cells (VEcad+Nox5+) or in mesangial cells (SM22+Nox5+). We also examined the endogenous expression of Nox5 in a high fat fed rabbit model of kidney disease.

Methods: At week 10 mice were culled and kidneys were removed for the assessment of structural damage as well as gene and protein expression of markers of inflammation, fibrosis and oxidative stress. Protein expression of Nox5 and its localization in glomerular cells (endothelial and mesangial cells) were examined in transgenic mice by immunostaining. We also examined expression of pro-fibrotic gene in high fat fed rabbits by next generation sequencing (NGS) and RT-PCR and renal injury by histochemistry

Results: Expression of Nox5 was confirmed in glomerular endothelial and mesangial cells of transgenic mice. Diabetes induced increase in glomerulosclerosis, gene and protein expression of fibronectin and MCP-1 as well as nitrotyrosine were further increase in both diabetic Nox5 transgenic mice. Moreover, increased expression of Nox5 in high fat fed rabbits versus normal diet fed rabbits was associated with increased expression of fibronectin, CTGF, collagen IV and VCAM-1 as well as increased mesangial expansion in the kidney.

Conclusions: These findings in both transgenic mice model (endothelial and mesangial cells) suggest that Nox5 plays a significant role in mediating renal injury in diabetes.

SA-PO116

Suramin Inhibits Activation of Inflammasome and Protects Against Progression of Diabetic Kidney Disease in KK-Ay Mice

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Background: Inflammasome is a protein complex that leads to production of IL-1β and IL-18 through activation of caspase-1, and danger-associated molecular patterns (DAMPs) trigger inflammasome activation via P2 receptors (P2Rs). We have shown that both serum and urinary IL-18 levels are elevated in patients with diabetic kidney disease (DKD). Mass spectrometry imaging has revealed that ATP, one of the major DAMPs, is increased in the glomeruli of diabetic mice. The aim of this study was to determine if suramin, a non-selective P2Rs antagonist, protects against DKD in KK-Ay mice.

Methods: Four weeks-aged male C57BL/6 (B) mice and diabetic KK-Ay (K) mice (KK-A^y/TaJcl strain) were randomly assigned to four groups: B+vehicle (BV), B+suramin, K+vehicle (KV) and K+suramin (KS), n=6-12/group. Vehicle or suramin (1 mg/kgBW) were injected intraperitoneally once every two weeks over an 8-week period. Glomerular size and mesangial matrix area were assessed by morphometric analysis. Expression of inflammasome-related genes and proteins were quantified by quantitative PCR and western blot. The localization of P2Rs were examined by double staining.

Results: Urinary albumin/creatinine ratio was elevated in KV (280.0 ± 29.3 mg/gCr, p<0.001) vs. BV (1.7 ± 0.3 mg/gCr), and significantly reduced in KS (160.6 ± 27.3 mg/gCr, p<0.01), whereas there were no significant differences in body weight or HbA1c between both diabetic groups. Glomerular size and glomerular mesangial matrix area were significantly increased in KV and reduced to 78% (p<0.001) and 66% (p<0.001) of KV levels by suramin treatment, respectively. Importantly, mRNA expression of P2X4R and P2X7R in both renal cortex and isolated glomeruli were significantly suppressed in KS compared with KV (p<0.05). P2X4R and P2X7R were mainly distributed in mesangial cells in the glomerulus of KK-Ay mice. Protein expression of NLRP3, a key component of inflammasome, was increased in KV vs. BV, and significantly suppressed in KS (p<0.05). The increase in IL-18 mRNA expression in KV was significantly suppressed in KS (p<0.01), and a similar trend was observed in IL-18 protein level in renal cortex.

Conclusions: We found that suramin can improve features of DKD with type 2 diabetes and may be renoprotective via suppression of inflammasome activation. Suramin may be beneficial for the treatment of DKD.

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SA-PO117

Marked Improvement of Renal Lesions by Treatment with Mimetic Peptide of SOCS1 in the Diabetic Model BTBR ob/ob

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Background: Type 2 Diabetes (T2D) is a global public health problem, with Diabetic Nephropathy (DN) being the main cause of chronic renal disease worldwide. Although current treatments delay the evolution of the disease, it is necessary to establish new therapeutic strategies in early stages of DN, in order to promote renoprotection. The JAK/STAT signaling pathway participates in the diabetic renal disease, through the induction of genes involved in inflammation and oxidative stress. Among the different mechanisms for JAK/STAT control, the family of SOCS proteins has been proposed as new molecular targets for the treatment of DN. Our aim was to evaluate the effect of SOCS1 mimetic peptide (MiS1) on the development of early renal damage associated with T2D.

Methods: Four groups of BTBR ob/ob mice (6 weeks old) were treated 3 days/week for 7 weeks with active peptide (2 and 4 μg), mutant peptide (4 μg) or vehicle. At the end of the study, animals were sacrificed to obtain blood, urine and kidney tissue samples for further analysis.

Results: The treatment of diabetic mice with active MiS1 significantly reduced the ACR ratio and renal weight, improves the glomerular and tubulointerstitial damage and increased podocyte numbers. Treated mice exhibited a decrease in the renal inflammatory infiltrate (F4/80 and CD3), lower gene expression of proinflammatory cytokines (Tnfα and Il-12) and chemokines (Ccl2 and Ccl5) and reduced phosphorylation of STAT1 and STAT3. No changes were observed in glycemia and body weight. Concomitantly, peptide administration diminished the renal levels of superoxide anion and 8-hydroxy-2'-deoxyguanosine (marker of DNA oxidative damage) and altered the expression of the Nrf2/-heme oxygenase-1 pathway and redox balance enzymes (Nox4, Sod1 and Catalase). Finally, we observed a reduction of lipid peroxidation (4-hydroxy-2-hexenal) and gene expression of scavenger receptors (SR-B/CD36 and SR-A/CD204).

Conclusions: In conclusion, the MiS1 peptide improves the renal damage and is efective in modulating the inflammatory milieu and oxidative stress in an early renal damage in the BTBR ob/ob model. *Fondecyt Project N° 1160465. PhD. Grant N° 21150768, CONICYT, CHILE. MINECO Project SAF2015-63696R and FIS Proyect PI17/01495, SPAIN.*

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SA-PO118

Overexpression of Sirtuin 3 in Obesity-Induced CKD Mice Model

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Background: Obesity and metabolic syndrome are independent risk factors for chronic kidney disease (CKD). Obesity-induced CKD is characterized by a progressive decline of the renal function and the development of tubulointerstitial fibrosis. Recently, studies showing ectopic lipid depositions in proximal tubular cells have emerged along with mitochondria dysfunction, suggesting a lipotoxicity in these cells. However, molecular mechanisms underlying these processes are still unclear. Our study will focus on the involvement of sirtuin 3 (SIRT3), a NAD^+-dependent deacetylase, in the ectopic lipid accumulation in kidney cells leading to CKD. SIRT3, mainly expressed in mitochondria, is known to play a critical role in metabolic responses and mitochondria functions.

Methods: Male C57BL/6 WT and SIRT3 transgenic mice were assigned either to a low fat diet (LFD) or a high fat diet (HFD) for 20 weeks. At the end of the protocol, urine, blood and kidney samples were collected. Kidney function was investigated and morphological analyses were performed.

Results: Wild-Type HFD mice presented renal hypertrophy and impaired renal function as attested by an increased albuminuria and proteinuria. Evidence of proximal tubule injury was observed in these mice with the presence of enlarged lipid vacuoles. In addition, these alterations were associated with the reduction of AMPK activity and the decrease in the relative mRNA and protein expression of SIRT3. Interestingly, renal hypertrophy and impaired renal function were significantly improved in SIRT3 transgenic mice fed a HFD. This was also associated with a reduced number and size of ectopic lipid vacuoles in proximal tubular cells.

Conclusions: These findings reveal that SIRT3 plays a critical role in ectopic lipid accumulation in proximal tubular cells and impairment of renal function. Systemic overexpression of SIRT3 normalizes the renal alterations observed in HFD WT mice and may thus be a potential strategy to improve altered lipid metabolism in HFD-induced CKD.

Funding: Government Support - Non-U.S.

SA-PO119

VHL Deletion in Renal Proximal Tubules of Mice Ameliorates Hallmarks of Diabetic Nephropathy

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Background: Diabetic nephropathy is the leading cause of end-stage renal disease and frequently affects patients with type 2 diabetes mellitus. Glomerular hyperfiltration and phenotypic changes in proximal tubule epithelial cells (PTECs) are the initial signs of diabetic nephropathy. Systemic activation of hypoxia-inducible factors (HIFs) was shown to prevent diabetes-induced alterations in kidney oxygen metabolism.

Methods: To analyze in detail whether renal tubular HIF activation is sufficient to prevent functional and morphological alteration of diabetic nephropathy, $SGLT2^{Cre}/VHL^{flox}$ mice were generated and diabetes mellitus was induced by streptozotocin application.

Results: FITC-inulin clearance analysis revealed a strong increase in diabetic VHL^{flox} control mice which was abrogated in diabetic $SGLT2^{Cre}/VHL^{flox}$ mice showing similar values as the non-diabetic control mice. Blood glucose concentration and urinary volume excretion were significantly increased in diabetic mice without significant differences between genotypes. However, osmotically-induced hyponatremia was only observed in diabetic VHL^{flox} mice whereas diabetic $SGLT2^{Cre}/VHL^{flox}$ had values similar to non-diabetic controls. Urinary electrolyte, glucose and phosphate excretion was increased in diabetic mice and more pronounced in diabetic $SGLT2^{Cre}/VHL^{flox}$ compared to diabetic VHL^{flox} mice.

Conclusions: In summary, our study reveals that induction of proximal tubular HIF are able to prevent diabetes induced glomerular hyperfiltration. Additionally, osmotically-induced hyponatremia was also prevented upon HIF activation most probably through reduced proximal tubular glucose reabsorption and thereby leading to its increased urinary excretion.

Funding: Private Foundation Support

SA-PO120

The Iron-Klotho-VDR Axis Is a Major Determinant of Proximal Convoluted Tubule Injury in Haptoglobin 2-2 Genotype Diabetic Nephropathy Patients and mice

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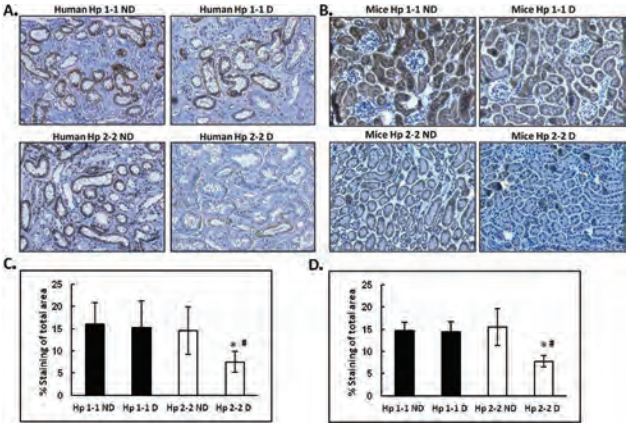
Background: The haptoglobin (Hp) genotype (1-1, 2-2) is a major determinant of DN progression in DM patients. Hp 2-2 DM patients & mice have increased iron deposits in the PCT, leading to renal injury. The mechanism of the PCT injury in DN remains elusive. In the kidney, 1,25(OH)2D3 suppresses the inflammatory response to renal tubular injury and requires normal renal expression of the α-klotho protein. Increased renal iron deposits in the PCT of Hp 2-2 DN may affects α-klotho-Vitamin D receptor axis and exacerbates PCT injury

Methods: Seven-week-old male mice were made diabetic by IP injection of 50 mg/kg of STZ per day for 5 consecutive days. Mice were sacrificed after a DM duration of 2 months. DM **mice with Hp 2-2 and Hp1-1, DM and non-DM CKD patients were included. Kidney biopsies from mice and patients were subject to immunohistochemistry (IHC) and PAS staining. Mice kidney lysates were subjected to western blot analysis.**

Results: A marked accumulation of iron deposits in the renal PCT of Hp 2-2 DM mice compared to Hp 1-1 DM or with Hp 2-2 non-DM mice. The expression of renal α-klotho was reduced significantly in the PCT of DN mice and patients with the Hp 2-2 genotype in mice and humans compared to DM Hp 1-1 genotype in mice and CKD humans Western blot analysis of the mice renal lysates show that VDR renal expression was decreased significantly in the PCT of DN Hp 2-2 sections compared to DM Hp 1-1 genotype. The renal expression of 1-α-hydroxylase was increased significantly in DN mice with Hp 2-2 genotype compared with DM Hp 1-1 genotype

Conclusions: The Iron-Klotho-VDR axis is a key player in themechanism of iron-mediated PCT injury in DN mice and patients with Hp 2-2 genotype Increased iron deposits in the PCT of Hp 2-2 genotype can lead to reduced renal expression of α-klotho and VDR protein level and PCT injury. Targeting the iron-klotho-Vit. D axis in DM Hp 2-2 patients may explore new ideas on pathog. and TX of early DN



SA-PO121

Overexpression of Hedgehog Interacting Protein in Renal Proximal Tubule Promotes Renal Tubulointerstitial Fibrosis in a Type I Diabetes Model

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Background: We previously reported (*Sci. Report 2018*) that renal hedgehog interacting protein (*Hhip*) gene expression is highly elevated in the kidneys of diabetic animal models and promotes the development of diabetic nephropathy. Since the molecular mechanism(s) of action in renal proximal tubular cells (RPTCs) is incompletely known, we examined the action of Hhip and its underlying mechanisms under diabetic conditions in RPTCs.

Methods: At 11 weeks of age male wild type (WT, C57BL6) and Hhip-transgenic (Tg) mice that specifically overexpressed Hhip in their RPTCs had diabetes induced with streptozotocin (STZ) (i.p., 50 mg/kg/day) for five consecutive days. Mice were euthanized 4 weeks after the STZ injection. Physiological parameters, kidney function (urinary albumin/creatinine ratio (ACR) and glomerular filtration rate (GFR)), renal morphology and molecular analysis of genes expression in renal proximal tubules were carried out. For *in vitro* studies, a rat *immortalized RPTCs cell line (IRPTCs) was used.*

Results: Non-diabetic Hhip-Tg mice were phenotypically indistinguishable from WT animals but had higher mRNA levels of fibrotic genes (*TGFβ1, α-SMA*) in their RPTCs. As compared to diabetic WT animals, diabetic Hhip-Tg mice exhibited pronounced tubulointerstitial fibrosis -- 'tubulopathy' features-- and increased renal heparanase (HPSE) [HPSE is a key player in renal fibrosis by mediating TGFβ1- related epithelial-mesenchymal transition (EMT) in tubular epithelial cells]. *In vitro*, recombinant Hhip (rHhip) dose-dependently stimulated HPSE expression and increased rat *TGFβ1* promoter activity (pGL4.20/TGFβ1 (N-1016/+143)) in IRPTCs. Transient transfection of Hhip cDNA enhanced the expression of HPSE vs. control plasmid in IRPTCs. Finally, Hhip siRNA attenuated high glucose-stimulation of HPSE expression and/or TGFβ1- EMT signaling and ameliorated tubular fibrosis and apoptosis.

Conclusions: Overexpression of Hhip in RPTCs, which aggravates diabetes-related renal tubulointerstitial fibrosis, is mediated, at least in part, via elevated HPSE-TGFβ1-EMT signaling.

Funding: Government Support - Non-U.S.

SA-PO122

Angiotensin-Neprilysin Inhibition Protects Glomerular Function and Structure and Lowers TRPC6 in Diabetic Hypertensive Rats

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Background: Dual blockade with Angiotensin Receptor/Neprilysin Inhibition (ARNI) reduces glomerulosclerosis better than single AR blockade (ARB) in diabetic, hypertensive rats, but the renoprotective mechanisms remain unknown. Here, we hypothesized that this is mediated by superior blood pressure regulation, improved renal hemodynamics, protection of podocyte integrity and/or suppression of renal inflammation.

Methods: To address this, TGR(mREN2)27 rats (a model of angiotensin II-dependent hypertension) were made diabetic for 12 weeks and treated with vehicle (n=10), valsartan (n=7) or sacubitril/valsartan (ARNI; n=8) for the final 3 weeks. Mean arterial pressure (MAP) was measured via radiotelemetry.

Results: Sacubitril/valsartan lowered MAP by 50±4 mmHg and valsartan by 43±4 mmHg (P=0.3). Sacubitril/valsartan resulted in better glycemic control and lower heart weight compared to vehicle and higher urinary atrial natriuretic peptide vs. valsartan (P<0.05 for all). Histologically, sacubitril/valsartan resulted in markedly lower glomerulosclerosis scores than both valsartan and vehicle (P<0.05). Despite higher effective renal plasma flow and glomerular filtration rates, sacubitril/valsartan did not improve filtration fraction. Analysis of the renal cortex for protein abundance of the transient receptor potential cation channel C6 (TRPC6) showed ~50% reduction after sacubitril/valsartan (P=0.06 vs. vehicle). Kidney immune cell infiltration did not differ between groups.

Conclusions: In conclusion, ARNI offers drug-class specific renoprotection in a pre-clinical model of diabetes and hypertension. Renoprotection is unrelated to renal hemodynamics or inflammation but may be related to the protective effects of natriuretic peptides and/or improved glycaemia on podocyte integrity, possibly via attenuation of Ca^{2+} influx through TRPC6 channels.

SA-PO123

Angiopoietin-Like Protein 2 Promotes the Progression of Diabetic Kidney Disease

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Background: Angiopoietin-like protein 2 (ANGPTL2) is a circulating, pro-inflammatory protein. To examine the role of ANGPTL2 in the pathogenesis of diabetic kidney disease (DKD), we studied the epigenetic regulation of *angptl2* expression in diabetes patients.

Methods: We determined the relationship between serum ANGPTL2 levels and the progression of DKD in cross-sectional (220 patients) and cohort (145 patients, 7-year follow-up) studies. In addition, we investigated the effect of DNA methylation on *angptl2* expression and also studied the direct effect of ANGPTL2 on the podocyte function.The main outcome is the progression of DKD.

Results: Multivariate logistic regression analyses revealed that the baseline level of serum ANGPTL2 was an independent risk factor for the progression of DKD during follow-up periods. We found that DNA methylation levels of ANGPTL2 promoter in circulating monocytes were correlated with the serum ANGPTL2 levels in diabetes patients. Furthermore, *in vitro*, ANGPTL2 directly increased albumin permeability of the cultured podocyte through the translocation of zona occludens-1 from the membrane to the cytosol via the activation of focal adhesion kinase.

Conclusions: ANGPTL2 could be a strong mediator of DKD and serves as a good predictive biomarker for its progression.

SA-PO124

A1AR Alleviates Tubulo-Interstitial Fibrosis by Inhibiting Peritubular Capillary Loss in Diabetic Nephropathy

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Background: We previously observed A1 adenosine receptor (A1AR) had a protective role in the progression of diabetic nephropathy. But the mechanism was not clear. The disintegration of interstitial pericytes may cause peritubular capillary(PTC) loss and interstitial fibrosis. In this study, we used A1AR deficient diabetic mice to prove whether A1AR plays a role in the pericyte detachment mediated PTC loss and in the progress of renal interstitial fibrosis.

Methods: Eight week-old male C57BL/6J $A1AR^{-/-}$ and WT mice were given two consecutive days' intraperitoneal injection streptozotocin to establish type 1 diabetic nephropathy mice. At 4w and 16w for modeling, mice were sacrificed to collect blood, urine and kidney samples for intensive detection.

Results: We successfully established streptozotocin induced type 1 diabetic nephropathy model in WT and A1AR deficient mice. At 4 weeks, albuminuria and mild renal pathological leisure were observed in WT diabetic mice, with up-regulation of A1AR protein expression *(1.3times, P=0.042)*. At 16weeks, more serious albuminuria and renal pathological leisure were observed in WT diabetic mice than at 4weeks, along with pericyte detachment induced platelet-derived growth factor receptor (PDGFR) activation(*1.3times, P=0.023*) and peritubular capillary injury(CD34 staining). While in $A1AR^{-/-}$ diabetic mice, severer renal tubular interstitial fibrosis and increased pre-clollagen I expression(*1.8times, P<0.001*) were observed than in WT diabetic mice, along with activation of inflammation, including increased inflammasome nod -like receptor protein 3 (NLRP3, 2.0 times, P=0.006), and it's downstream proinflammatory cytokine IL-1β. Meanwhile more increased protein expression of PDGFR (*1.4times, P=0.008*) and PTC lost (*1.3times, P=0.016*) were detected by immunohistochemistry and western-blot.

Conclusions: A1AR plays a protective role in the PDGFR-mediated peritubular capillary loss to alleviate renal tubular interstitial fibrosis in type 1 diabetic nephropathy.

SA-PO125

High Protein Diet and Potassium Depletion Exacerbate Ammonia Synthesis and Renal Hypertrophy in Rats with Type I Diabetes

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Background: We have previously reported that the early onset of hyperglycemia stimulates ammoniagenesis, which contributes to the development of early renal hypertrophy in both type 1 (T1) and type 2 diabetes mellitus (DM) (ASN abstarct, 2017). In these studies, we examined whether other ammoniagenic conditions such as K^+ depletion and high protein (HP) diet worsen renal hypertrophy in rat with T1 DM.

Methods: Male rats were housed in metabolic cages with free access to paired control diet and water and subjected to vehicle or streptozotocin (STZ)-induced DM. After 1 week, diabetic rats were divided into 3 groups: one group was switched to a K^+-free (KD) diet (DM+KD), another group was switched to a HP diet (DM+HP) and the 3rd group remained on normal diet for another week (DM). Vehicle-treated rats were fed control diet (control), K^+-free or HP diets for 1 week. On the last day, 24 hour urine was collected and assayed for NH_4^+ excretion. The animals were sacrificed, kidneys were removed, weighed and cortex was isolated. The protein abundance of ammoniagenic enzymes (glutaminase or GA and glutamate dehydrogenase or GDH) and glutamine transporter SN1 in the cortex was examined by immunoblotting.

Results: The results showed that NH_4^+ excretion and kidney mass (kidney weight/BW) were significantly increased in DM, KD and HP diet vs. control with a further increase in DM+KD and DM+HP diet vs. DM alone. Immunoblotting studies showed a significant increase in the protein abundance of GA, GDH and SN1 in KD and in HP diet, respectively, vs. control. Interestingly, the protein abundance of GA, GDH and SN1 was unchanged in DM vs. control. The results further showed a significant upregulation of GA (4-fold), GDH (2.5-fold) and SN1 (8-fold) in DM+KD vs. DM alone. In DM+HP group, GA (138%) and GDH (158%) were upregulated, but SN1 remained unchanged vs. DM alone.

Conclusions: 1- In all three conditions (DM, KD and HP diet), the stimulation of ammoniagenesis correlates with the development of renal hypertrophy. 2- Diabetic animals exhibited a further increase (additive effect) in ammonia production and renal mass when subjected to potassium depletion or high protein diet, indicating that these conditions activate different and synergistic signaling mechanism(s). 3- KD and HP diet are risk factors for rapid progression of kidney disease in diabetes mellitus.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO126

The β2-Adrenergic Receptor Agonist Formoterol Improves Renal Function and Decreases Fibrotic and Mitochondrial Fusion/Fission Proteins in a Mouse Model of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a significant cause of chronic kidney disease and accounts for 50% of all end-stage renal disease. Current therapies for DN, such as glycemic and blood pressure control and renin-angiotensin system blockade, only slow the progression of DN. Therefore, we examined the effect of formoterol, a β_2-adrenergic receptor agonist previously shown to induce mitochondrial biogenesis and promote recovery from acute kidney injury, on renal function and fibrotic and mitochondrial proteins in db/db mice, a validated mouse model of DN.

Methods: Female diabetic db/db and non-diabetic db/m (control) mice 9 weeks of age were treated with formoterol (0.3 mg/kg, i.p.) or saline daily for three weeks. Mice were placed in metabolic cages weekly for 18 hr and urine collected. Body weight and serum glucose were measured weekly and renal function was measured by serum creatinine levels. Kidneys were harvested after three weeks and changes in expression of mitochondrial and fibrotic proteins were measured using immunoblot analysis.

Results: At 12 weeks of age, formoterol decreased serum glucose and creatinine in diabetic mice compared to vehicle treated mice without altering body weight. Mitochondrial fission protein phospho-Drp1, and fibrotic proteins TGF-β1, phospho-SMAD3 and α-SMA were increased in diabetic mouse kidneys and were restored to control levels with formoterol treatment. Additionally, mitochondrial fusion proteins Mfn1 and Mfn2 were decreased in diabetic mouse kidneys and increased to control levels with formoterol treatment. Complete DN phenotyping is ongoing.

Conclusions: Formoterol treatment in a DN model resulted in improved serum creatinine, decreased kidney profibrotic protein levels and restored mitochondrial fusion/fission protein levels in a DN model. These results suggest that formoterol could be a potential therapy for DN.

SA-PO127

RIP1 and RIP3 Inhibition Ameliorate Albuminuria and Renal Tubular Injury in Diabetic Nephropathy

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Background: Hyperglycemia is a key factor in the development of diabetic nephropathy, which is characterized by renal tubular inflammation, apoptosis and interstitial fibrosis. Receptor interaction protein 1 (RIP1) and 3 (RIP3) plays important role in necroptosis, apoptosis, autophage and inflammation. The present study was aimed to confirm the hypothesis that RIP3 mediated high glucose-mediated renal tubular cells and that inhibition of RIP3 confer protection against this injury in type 2 diabetes.

Methods: 10-week diabetic db/db mice were administrated with selective RIP1 inhibitor, necrostatin-1 (1.65 mg/kg.d, ip), or RIP3 inhibitor, GSK2399872A (1.9mmol/kg.d, ip), or an equal volume of PBS, or ramipril (3 mg/kg.d, po) for a total of 8 weeks. Non-diabetic db/m mice were used as control.

Results: In db/db mice, renal tubular RIP1 and RIP3 expression was significantly stonger than db/m mice. Treatment of necrostatin-1 or GSK2399872A ameliorate albuminuria, reducing the expression of TGF-β, collagen I, fibronectin, α-SMA, and caspase 3 in diabetic kidney. The albuminuria lowering effects of GSK2399872A (820.08±98.52 mg/g) is better than that of necrostatin-1 (1058.7704±102.35 mg/g) and ramipril (1800.66±15.68 mg/g).

Conclusions: Our findings suggest a pathogenic role of overexpressed RIP1 and RIP3 in diabetic nephropathy. Inhibition of Rip1 and Rip3 ameliorates albuminuria, renal tubular apoptosis and fibrosis in type 2 diabetes.

SA-PO128

Empagliflozin Ameliorates Diabetic Nephropathy in BTBR ob/ob Mice

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Background: The SGLT2 inhibitor empagliflozin has demonstrated success in regulating elevated blood sugars in diabetic patients via enhanced glucose excretion in the urine, and has been successful in ameliorating complications of type II diabetes including cardiovascular disease and nephropathy. We sought to test whether treatment with empagliflozin (EMPA) with and without concurrent losartan (LOS) treatment would ameliorate pathology, proteinuria and restore podocyte number in the BTBR *ob/ob* model of diabetic nephropathy. The latter may be a relevant mechanism that contributes to the observed benefits seen in type II diabetic patients treated with this drug.

Methods: At 18 weeks of age BTBR *ob/ob* and BTBR WT female mice (n=12 each group), proven to be diabetic by elevated blood glucose levels, were fed chow formulated with 300 mg/kg EMPA with and without concurrent LOS treatment (EMPA/LOS), normal chow or were given leptin (LEP) vis osmotic minipump. They were treated for 6 weeks. At the end of the experiment, at 24 weeks of age, the mice were placed into a metabolic chamber for 6 hours to obtain a timed urine and a fasting blood glucose level was recorded. The mice were then euthanized, blood collected via cardiac puncture and organs harvested for study.

Results: Treatment with LEP, EMPA and EMPA/LOS all resulted in a significant reduction of blood glucose. Only treatment with LEP resulted in weight loss. EMPA and EMPA/LOS treatment did not affect proteinuria in individual BTBR *ob/ob* mice while LEP replacement resulted in a significant drop in proteinuria in individual BTBR *ob/ob* mice. Group averages of albumin creatinine ratios (ACR) and albumin excretion extrapolated to 24 hour urines did drop significantly in all treatment groups. Additionally, all treatment arms resulted in a significant reduction of mesangial matrix accumulation and prevented glomerular hypertrophy. Analysis of podocyte number is pending.

Conclusions: From these studies, we conclude that EMPA and EMPA/LOS is nearly as effective as LEP replacement in ameliorating some of the pathology and clinical manifestations of diabetic nephropathy in the leptin deficient BTBR *ob/ob* mouse. Further analysis will be done to determine whether podocyte number is restored by these treatments, which may be a contributing factor to the improvement seen in human diabetic patients being treated with SGLT2 inhibitors.

Funding: Commercial Support - Boehringer Ingelheim and Lilly IIS Grant Program for Diabetes

SA-PO129

Low Doses of GDT-01 Improve Diabetic Nephropathy and Preserve GFR in ZSF1 Rats over 7 Months by Improving In Vivo Sialylation

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Background: Studies on rat diabetic nephropathy using the previously published sialic acid precursor ManNAc (Clement LC et al Nature Medicine Jan 2011) worsen hyperglycaemia in ZDF rats, which is harmful in the long term. We conducted a 7 month study to improve in vivo sialylation in the glomerulus using the compound GDT-01 with the goal of studying its effect on CKD and hyperglycaemia in rat diabetic nephropathy.

Methods: We treated 5 month old male ZSF1 rats (n = 6 rats / group) with taps water or GDT-01 in tap water over a period of 7 months, and measured proteinuria, BUN, creatinine, blood glucose, other blood parameters, and assessed renal histological changes on the termination of the study.

Results: A declining dose regimen for GDT-01 was used, and the actual dose delivered (mg / Kg; mean ± SE) over 3 separate periods was as follows: Period A, Days 0 to 95, 136.8 ± 11.8; Period B, Days 96 to 122, 21.5 ± 5; Period 3, Days 123 to 222, 3.7 ± 0.2. Proteinuria was consistently lower in the treated group in Period C (10/14 readings, P<0.05), occasionally in Period B (1/4 readings) and rarely lower in Period A (2/14 readings). Blood glucose levels were similar between the GDT-01 and water groups. BUN and creatinine were consistently lower in the treatment group in Period C (BUN, 7/14, P < 0.05 to 0.01; creatinine, 5/14, P<0.05), and only occasionally in Periods A and B. Detailed renal histology and sialylation analysis are ongoing.

Conclusions: Low oral doses of the sialylation inducing compound GDT-01 improve GFR and proteinuria over prolonged periods of time without worsening hyperglycaemia in ZSF1 diabetic rats.

Funding: NIDDK Support

SA-PO130

H+-ATPase Blockade Reduced Renal Gluconeogenesis and Mitochondria Metabolism and Lowered Plasma Glucose in a Type 2 Diabetic Rat Model

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Background: Vacuolar H^+-adenosine triphosphatase (ATPase) plays important roles in urinary acid excretion, vesicular acidification to activate enzymes, endocytosis, and the membrane recycling of transporters in the kidney. We have recently reported blockade of H^+-ATPase reduced plasma glucose in type 1 diabetic rat by reducing renal gluconeogenesis. Using proteome analysis of the kidney of type 2 diabetic rats, we investigated effect of bafilomycin B1, a specific blocker of H^+-ATPase, on renal glucose metabolism.

Methods: Male Spontaneously Diabetic Torii (SDT) rats were treated with Bafilomycin B1(BFM)100nmol/kg BW for 7 days. After 24-hour starvation in the metabolic cage, the kidneys were analyzed using iTRAQ protein expression and relative quantification analysis.

Results: Renal expression and activity of H^+-ATPase were increased with elevated urinary ammonium excretion. In the diabetic kidney, the enzymes in gluconeogenesis, TCA cycle, mitochondria respiratory chain, and ammoniagenesis were relatively increased compared with those in the kidney of control rat. The BFM reduced urinary ammonium excretion and decreased the plasma glucose level in diabetic rats (298±38 vs. 171±27 mg/dL, p<0.02, n=6). The protein expression of enzymes in mitochondria respiratory chain, TCA cycle, and gluconeogenesis were decreased by BFM treatment.

Conclusions: H^+-ATPase inhibitor, bafilomycin, lowered plasma glucose after 24-hour starvation by suppression of renal gluconeogenesis and mitochondria metabolism. H^+-ATPase could be a new therapeutic target for diabetes mellitus.

Funding: Government Support - Non-U.S.

SA-PO131

Renal Phospholipid Accumulation in High-Fat Diet Fed Streptozotocin Induced Diabetic Mice Depends on Ketohexokinase

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Background: Excessive fat intake contributes to the development of obesity and metabolic syndrome, which is associated with renal dysfunction in CKD patients including diabetic kidney disease (DKD). It has been reported that renal lipid metabolism may play a direct role in DKD progression. However, the detailed mechanisms of lipid metabolism in renal tubular cells of DKD remain unclear. Recently, we have reported that western diet induced steatohepatitis was dependent on ketohexokinase, a primary enzyme of fructose. Fructose is produced endogenously in DKD through the activation of polyol pathway. In this study, we investigated that the effects of fructose metabolism on lipid accumulation in DKD.

Methods: In male, C57BL6/J background wild type (WT) mice and ketohexokinase-knockout (KHK-KO) mice, which lack both KHK isoforms; KHK-A and C, diabetes was induced by streptozotocin (50mg/kg 5 consecutive days, intraperitoneal injection). They were fed 45% high fat diet (HFD) for 24 weeks, and then analyzed for renal lipid and fructose metabolism, and renal injury.

Results: Biochemical analysis demonstrated lipid parameters and blood glucose was not different between HFD fed diabetic WT and KHK-KO mice. We found remarkable vacuolization in renal proximal tubule in diabetic WT fed HFD. However, this vacuolization was prevented in diabetic KHK-KO fed HFD. This vacuolization was considered as phospholipid droplets by results of oil red o staining, toluidine blue staining and electron microscope images. The lipidomics showed renal phosphatidylglycerol (PG) was significantly increased in diabetic WT fed HFD compared to diabetic KHK-KO fed HFD. These increased renal PG was significantly correlated with phospholipid droplets, however renal triglyceride was not correlated significantly. The renal gene expressions of fatty oxidation (ACOX1, CPT1a) and cholesterol efflux (ABCA1, ABCG1, ApoE) were significantly decreased in diabetic WT fed HFD compared to diabetic KHK-KO fed HFD. These decreased gene expressions were significantly correlated with the number of phospholipid droplets.

Conclusions: These findings suggested that the inhibition of fructose metabolism in high fat fed diabetic mice ameliorated the renal phospholipid accumulation by improving the impaired fat oxidation and cholesterol efflux in kidney.

SA-PO132

The Role of PCSK9 on the Glomerular Lipid Accumulation and Renal Injury in the Diabetic Kidney Disease

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Background: Glomerular lipid accumulation is one of the pathologic characteristics of diabetic kidney disease (DKD). Recent evidences suggested that proprotein convertase subtilisin kexin type 9 (PCSK9) has a particular effect on the cellular lipid homeostasis. We aimed to evaluate the role of PCSK9 on the lipid accumulation in glomeruli and podocyte under the diabetic conditions.

Methods: C57BL/6 and PCSK9 knockout (KO) mice were maintained with high fat diet for 12 weeks with low dose streptozocin intraperitoneal injection. Urinary albumin-to-creatinine ratio (ACR), total cholesterol and triglyceride in kidney tissues were measured. BODIPY 493/503 staining was performed for evaluating lipid accumulation in the kidney. Foot process effacement in glomeruli was evaluated by standard transmission electron microscopy. In vitro study, mouse podocytes were stimulated with TNF-α and palmitic acid, and PCSK9 was up- or down-regulated by overexpressing lenti virus or siRNA. Apoptosis, mitochondrial morphology and energy metabolic key enzymes were evaluated both in vivo and vitro.

Results: Blood glucose and serum cholesterol were significantly increased, and urinary ACR and foot process effacement were increased in diabetic mice and these changes were exaggerated in the PCSK9 KO mouse with diabetes. Cholesterol and triglyceride levels in the kidney tissues were higher in PCSK KO mice with diabetes than those in control and diabetic mice. Mitochondrial morphology and the expression of energy metabolic enzymes were disturbed in the kidneys of diabetic PCSK KO mice. In vitro, the intracellular lipid contents was increased and apoptosis combined with mitochondrial swelling and crista disruption were also increased in podotyes with TNF-α and palmitic acid stimuli. All of these changes were ameliorated through mPCSK9 overexpression and aggravated by PCSK9 siRNA treatment.

Conclusions: These findings suggest that PCSK9 down-regulation in the podocytes is involved in lipid accumulation and consequent mitochondrial dysfunction and apoptosis in the DKD.

SA-PO133

Whole-Kidney 3D Imaging for Assessment of Glomerular Number and Size in a Mouse Model of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a major long-term complication of diabetes characterized by kidney hypertrophy and hyperfunction. To facilitate a rapid and unbiased evaluation of drug efficacy on glomerular size and number in preclinical studies, we investigated the use of light sheet microscopy as a new high-end 3D methodology to study whole-kidney glomerular changes in a mouse model of DN.

Methods: Unilateral nephrectomy (UNx) was performed in diabetic *db/db* mice to accelerate the development of nephropathy. UNx was performed in 18 weeks-old male *db/db* mice and terminated 6 weeks later. Mice were stratified and randomly assigned into UNx (n=8) or sham (n=8) based on baseline blood glucose levels. To determine the effect of UNx on whole-kidney glomerular morphology, mice were injected with lectin-594 prior to termination. Intact kidneys were scanned using light sheet microscopy (LSM). Using 3D image analysis, the total number of glomeruli were quantified and segmented according to individual size.

Results: Progression of diabetes remained similar in *db/db* control and *db/db* UNx mice. In contrast, terminal kidney weight was increased in *db/db* UNx mice, indicative of renal insufficiency leading to kidney hypertrophy. In agreement with stereology-based quantitative analyses on tissue sections, 3D-LSM confirmed an increase in kidney glomerular size in *db/db* UNx mice compared to *db/db* sham controls, while glomerular numbers were similar in both groups (≈14.000 glomeruli/kidney). Lectin-594 labelled kidneys were subsequently processed for Wilms' tumor-1 (Wt1), collagen IV and podocin expression using conventional immunohistochemistry. All antigens were readily detected, confirming that whole-kidney imaging was compatible for subsequent conventional immunohistochemistry.

Conclusions: In conclusion, LSM was successfully applied to evaluate renal and glomerular hypertrophy at the whole-organ level in a *db/db* UNx mice model of DN. Whole-kidney 3D imaging offers a novel approach for evaluating changes in key glomerular markers of DN, while maintaining the ability to perform conventional immunohistochemistry on the same tissue. The detailed analysis of all glomeruli enables for high-resolution evaluation of glomerular effects of novel treatment modalities in DN.

SA-PO134

Morphological Changes in the Kidney, Liver, and Pancreas of Type 2 Diabetic Rats Treated with H+-ATPase Inhibitor

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Background: We reported that H^+-ATPase specific inhibitor, bafilomycin (BFM), lowered fasting plasma glucose via suppression of renal gluconeogenesis in type 1 diabetic rat. To elucidate the plasma glucose lowering effect of BFM, we investigated morphological changes in the kidney, liver, and pancreas in the type 2 diabetic rats.

Methods: Male Spontaneously Diabetic Torii (SDT) rats were treated with BFM B1 100 nmol/kg for 7 days., After collecting urine, insulin glucose test was performed and then, the organs were fixed and observed with light microscope and electron microscope.

Results: H^+-ATPase was expressed in the proximal tubule, collecting duct, hepatocytes, and pancreatic islet cells. The endocytosis vesicles on the luminal side of the proximal tubules were increased in diabetics. BFM treatment decreased apical endocytotic vesicles, whereas vesicles were accumulated in the basal area of proximal tubule. Enlarged mitochondria in diabetic rats became smaller by BFM treatment. The liver of diabetic rat showed fatty changes, which was suppressed by BFM treatment. The islets of pancreas and insulin vesicles were decreased in diabetic rat. BFM treatment restored islet atrophy and increased insulin vesicles. Insulin sensitivity evaluated by KITT values was significantly decreased in diabetic rat compared with that in control (1.4±0.8 in diabetes vs. 8.8±1.1 in control, $p<0.001$), which was ameliorated by BFM treatment (3.4±0.1, $P<0.05$). BFM significantly reduced fasting blood glucose in diabetes.

Conclusions: In type 2 diabetes, H^+-ATPase inhibitor bafilomycin suppressed proximal tubular endocytic vesicles and mitochondrial enlargement, reduced hepatic fat accumulation, and restored pancreatic insulin vesicles in diabetic rat. Thus, bafilomycin lowered fasting plasma glucose and ameliorated insulin sensitivity.

Funding: Government Support - Non-U.S.

SA-PO135

Urinary Serum Amyloid A and Clinical Outcomes in Advanced Diabetic Kidney Disease

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Background: Serum amyloid A (SAA) is elevated in the kidneys from humans and mice with diabetic kidney disease (DKD). SAA promotes a broad inflammatory response and overexpression of SAA exacerbates albuminuria and glomerulosclerosis in diabetic mice. The study aim was to determine the relationship of urinary SAA to clinical outcomes in patients with advanced DKD.

Methods: Urinary SAA was measured (enzyme-linked immunosorbent assay) in a cohort with type 2 diabetes and advanced DKD defined by urine protein-to-creatinine ratio >500 mg/g. Associations of urinary SAA with ESRD and death were tested using Cox-proportional hazard models. The models were adjusted for DKD risk factors: age, sex, race, hemoglobin A1c, and systolic blood pressure.

Results: Baseline characteristics included: age 57±8 (mean±SD) years, women (65/115; 57%), Mexican-American (82/115; 71%), hemoglobin A1c 8.6±2.3%, systolic blood pressure 153±28 mm Hg, urine albumin-to-creatinine ratio 1874, 756-3950 mg/g (median, interquartile range), estimated glomerular filtration rate (eGFR; CKD-EPI-creatinine) 56±22 mL/min/1.73m^2, diabetes duration 15±6 years, body mass index 32±9 kg/m^2, renin angiotensin system inhibitor use (92/115; 80%). Participants with SAA-positive urine (58/115; 50%) had lower eGFR (SAA-positive 51±19 mL/min/1.73m^2 versus SAA-negative 60±24 mL/min/1.73m^2, p=0.025), and higher albuminuria (SAA-positive 3094 [1180–4677] versus SAA-negative 1089 [55 –1955], p=0.030). SAA positivity in urine was associated with ESRD (hazards ratio [HR] 2.50, 95% confidence interval [CI] 1.23–5.08, p=0.011), but not death (HR 0.92, 95% CI 0.44–1.94, p=0.83) over a median of 3.5 years. After DKD risk factor adjustment, risk of ESRD imparted by SAA positivity in urine remained similar (HR 2.42, 95% CI 1.15 – 5.12, p=0.020).

Conclusions: In patients with advanced DKD, those with SAA-positive urine had lower eGFR and higher albuminuria compared to those with SAA-negative urine. Urinary SAA forecasted ESRD after adjustment for DKD risk factors. These relationships point to SAA as a candidate mechanism for DKD progression in diabetic patients with advanced DKD.

SA-PO136

Urine Metabolites Report on Dysregulated Kidney Metabolism in Diabetes and Hypertension

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Background: Interrogating the molecular pathophysiology of kidney disease is challenged by limited clinical biopsy specimens. We evaluated concordance of kidney and urine metabolites in mouse models of diabetes mellitus (DM) and hypertension (HTN) to explore urine metabolomics as a tool to investigate kidney diseases in patients.

Methods: We profiled kidney and urine metabolites in the Akita model of type 1 DM (Akita$^{+/-}$), the Akita Renin transgene model of DKD (Akita$^{+/-}$Rtg$^{+/-}$), the Rtg$^{+/-}$ model of HTN, and wild type mice (WT; n=14 each). 24h urines were collected by metabolic cage and organs harvested at 12 wks. Kidneys were frozen and homogenized in acetonitrile:formic acid and urines concentrations were standardized. Nontargeted GC/MS was performed and annotated with spectral libraries. Unidentifiable metabolites or those missing >50% were removed, with other values imputed. Comparisons utilized principal components (PC),

partial least squares discriminant analysis (PLS-DA), and sparse generalized canonical correlation.

Results: Using PLS-DA, higher levels of multiple metabolites discriminated DM ($Akita^{+/-}$ and $Akita^{+/-}Rtg^{+/-}$) from non-DM ($Rtg^{+/-}$ or WT) including: branched chain amino acids, simple sugars, and ketones (β-hydroxybutyrate; BHB) in kidneys; and lactate, pyruvate, and ketones (BHB and acetoacetate) and related compounds (2-hydroxybutyrate) in urine. After data reduction by PC, similar kidney and urine PCs were correlated within phenotypes. In DM, kidney PC1 contained valine, pyruvate and simple sugars. This correlated with urine PC1 (r=0.65) characterized by branched fatty acids, keto acids and acyl glycines. Within non-DM, urine PC1 composed primarily of tricarboxylic acid (TCA) cycle-related organic anions (OAs) correlated directly with a similar TCA-cycle related PC in kidney lysates (r=0.71) with levels higher in $Rtg^{+/-}$.

Conclusions: Similar kidney and urine metabolite PCs correlate in models with and without DM. The predominance of sugars and ketones in profiles from uncontrolled DM models may obscure discovery relevant to treated DM in patients. Studies in non-DM highlight urine TCA cycle-related OAs as potential biomarkers of kidney metabolism. Whether TCA cycle-related OAs may be useful in human studies involving treated DM requires confirmation.

Funding: NIDDK Support

SA-PO137

Effects of the SGLT-2 Inhibitor Dapagliflozin on Volume Status in Patients with Type 2 Diabetes and Elevated Albuminuria

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Background: SGLT-2 inhibitors reduce the risk for heart failure events in patients with type 2 diabetes at high cardiovascular risk. These beneficial effects are thought to be attributed to diuretic effects. The aim of this study was to assess whether these diuretic effects can be attributed to osmotic or natriuretic diuresis in patients with type 2 diabetes and elevated albuminuria.

Methods: A post-hoc analysis was performed of a randomized placebo controlled cross-over trial that assessed the effects of dapagliflozin (DAPA) 10 mg/day therapy in 31 patients with type 2 diabetes and elevated albuminuria (median UAE 521 mg/24h). Blood samples and 24-hour urine were collected at start and end of each 6-weeks treatment period. Markers of volume status including sodium, urea, copeptin, renin, NT-proBNP and osmolality were measured. Free water clearance (FWC) was calculated as urine flow minus osmolar clearance.

Results: Compared to placebo, DAPA therapy increased fractional lithium excretion (reflecting reduced sodium reabsorption), urinary glucose excretion, urine osmolality, copeptin and renin, and it decreased FWC (table). DAPA therapy did not change plasma osmolality, sodium, and NT-proBNP.

Conclusions: The observed increases in fractional lithium excretion, glucose excretion and urine osmolality, and the combined increase in copeptin and renin during DAPA therapy suggests that both osmotic and natriuretic diuresis are involved. These findings are based on 6-weeks changes in fluid markers, when patients already have reached a new steady state. Further research is needed to characterize acute volume and diuretic effects of DAPA.

Volume biomarkers	DAPA Mean (95% CI)	PLACEBO Mean (95% CI)	Effect of DAPA vs PLACEBO Mean (95% CI)	P-value
Urea (mmol/l)	1.2 (0.6 to 1.8)	0.1 (-0.5 to 0.7)	1.1 (0.3 to 1.9)	<.01
Sodium (mmol/l)	0.3 (-0.4 to 1.1)	-0.1 (-0.8 to 0.7)	0.4 (-0.4 to 1.2)	0.35
Plasma osmolality (mosmol/kg)	-0.2 (-2.0 to 1.5)	-1.0 (-2.7 to 0.7)	0.8 (-1.1 to 2.7)	0.40
Copeptin (pmol/l)	3.4 (2.1 to 4.8)	-0.3 (-1.7 to 1.0)	3.8 (2.1 to 5.5)	<.01
Renin (%)	71.6 (33.0 to 121.4)	14.2 (-10.7 to 45.9)	50.3 (7.0 to 111.2)	0.02
NT-proBNP (%)	-3.6 (-19.6 to 15.5)	-10.6 (-24.9 to 6.4)	7.8 (-16.2 to 38.7)	0.55
Urine osmolality (mOsmol/kg)	34.3 (-8.5 to 77.2)	-27.5 (-67.5 to 12.4)	61.8 (12.2 to 111.5)	0.02
Fractional lithium excretion (%)	24.3 (10.1 to 40.3)	2.7 (-8.6 to 15.5)	21.0 (4.9 to 39.6)	0.01
Urinary glucose excretion (mmol/24h)	217.5 (176.0 to 259.0)	7.9 (-30.7 to 46.5)	209.5 (148.7 to 270.4)	<.01
FWC (ml/24h)	-503.7 (-794.3 to -216.2)	88.4 (-229.8 to 306.6)	-542.1 (-880.2 to -204.1)	<.01

SA-PO138

Effects of Dapagliflozin on Albuminuria, Renal Function, and Renin-Angiotensin-Aldosterone Hormones in Type 2 Diabetes

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2i) have shown a cardio- and renoprotective effect. The mechanism for this effect and the interaction with the renin-angiotensin-aldosterone system (RAAS) is only partially understood. Therefore, we aim to evaluate the effect of dapagliflozin treatment on albuminuria, measured GFR, 24h blood pressure (BP) and hormone levels of the RAAS when added to standard care including RAAS blocking treatment in patients with type 2 diabetes (T2D).

Methods: Double-masked randomized placebo-controlled crossover trial of 12 weeks treatment with dapagliflozin 10 mg or matching placebo. All patients were treated with RAAS blocking treatment. Included patients (n=40) had T2D and albuminuria at baseline. At the end of the treatment periods 3 consecutive morning spot urines were collected as well as 24h BP measurement and ^{51}Cr-EDTA clearance performed. Values at the end of treatment periods (placebo vs. dapagliflozin) were compared using mixed model analysis.

Results: Baseline age was 65 (SD±8), 90% were male, HbA_{1c} was 73 mmol/mol (SD±15), 24h BP 148/82 mmHg (SD±12.5/7.7), geometric mean urinary albumin creatinine ratio (UACR) 147 (IQR 75-289) mg/g and mean eGFR 85 ml/min/1.72 m^2 (SD±19.7). After 12 weeks treatment UACR was reduced 36% (95% CI 16-56%) during treatment with dapagliflozin vs. placebo (p<0.01), GFR decreased 10.9 (5-16) ml/min/1.72 m^2 (p<0.01), HbA1c was reduced 7.4 (5-10) mmol/mol (p<0.01) and 24h BP 4.8/2.7 mmHg (p=0.023/0.031). Plasma renin concentration increased 37% (9-66%, p = 0.012), plasma renin activity increased 41% (7—74%, p = 0.019), angiotensin II increased 37% (1-73%, p = 0.046) whereas plasma aldosterone was unchanged.

Conclusions: When added to standard RAAS blocking treatment dapagliflozin 10 mg vs. placebo once daily was associated with a significant reduction in albuminuria, 24h BP and GFR in patients with T2D and albuminuria. A concomitant increase in RAAS hormones was observed, possibly caused by increased diuresis as an effect of natriuresis.

Funding: Commercial Support - AstraZeneca

SA-PO139

Effect of Dapagliflozin on Cardiac Function and Biomarkers in Patients with Type 2 Diabetes and Albuminuria – A Randomized Study

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2i) have shown cardio- and reno-protective properties. The aim here is to evaluate the effect of dapagliflozin (dapa) treatment on myocardial function assessed with advanced echocardiography (TTE), and cardiac biomarkers when added to standard care in patients with type 2 diabetes (T2D).

Methods: This is a sub-study of a double-masked randomized placebo-controlled crossover trial of 12 weeks treatment with dapa 10 mg once daily or placebo. All patients (n=40) were on RAS blocking treatment, had T2D and albuminuria at baseline. At the end of the treatment period TTE was performed, ^{51}Cr-EDTA, albuminuria and 24h blood pressure were measured, as well as cardiac markers in plasma; NTproBNP, troponin I, MRproANP, MRproADM, TNF-α, IL-6 and copeptin. Global longitudinal strain (GLS) was the primary systolic echocardiographic endpoint. To assess diastolic function a combined diastolic endpoint was used including mean early diastolic myocardial velocity (e'), ratio between early transmitral inflow velocity (E) and e' (E/e'), atrial volume and pulmonary pressure (TRmaxPG).

Results: Baseline geometric mean urinary albumin creatinine ratio (UACR) was 147 (IQR 75-289) mg/g, mean eGFR 85 (SD±19.7) ml/min/1.72 m^2. Baseline HbA_{1c} was 73 (SD±15) mmol/mol, 24h blood pressure 148/82 (SD±12.5/7.7) mmHg, diabetes duration 16.5 (SD±4,8) years, age 65 (SD±8) years and 90% were male. After 12 weeks treatment with dapa vs. placebo, HbA_{1c} was reduced by 7.4 (5-10) mmol/mol (p<0.01) and 24h blood pressure decreased 4.8/2.7 mmHg (p=0.023/0.031). Left ventricular ejection fraction after placebo was 55.5 (SD±6.7) % and 53.7 (SD±6.7) % after active treatment – a non-significant change. GLS did not change whereas diastolic function improved significantly with 19.8% (3.3-36.3%, p = 0.021). Plasma concentration of NTproBNP, troponin I, MRproANP, MRproADM, TNF-α and IL-6 did not change. Plasma concentration of copeptin increased with 32.3% (p<0.0001).

Conclusions: Treatment of dapa 10 mg vs. placebo in patients with albuminuria was associated with an improvement in diastolic function but not in GLS in people with T2D and albuminuria. Also an increase in copeptin was observed possibly reflecting increased diuresis due to natriuresis.

Funding: Commercial Support - AstraZeneca

SA-PO140

Dapagliflozin Added to Verinurad plus Febuxostat Reduces Serum Uric Acid Without Increasing Urinary Uric Acid Excretion in Subjects with Hyperuricemia

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Background: Hyperuricemia is associated with gout, kidney stones and CV events. An intensive urate lowering strategy combines a xanthine oxidase inhibitor (febuxostat [FEB]) and a URAT-1 inhibitor (verinurad [VER]) to maximize serum uric acid (sUA) reduction. Dapagliflozin (DAPA, SGLT2 inhibitor) reduces sUA by an unknown mechanism(s). Excessive UA excretion may damage renal tubules due to crystallization at high levels, so any DAPA-mediated effect on urinary UA (uUA) should be explored. We examined effects of DAPA on sUA and uUA excretion on top of VER+FEB in hyperuricemia.

Methods: A randomized, placebo-controlled, 2-way crossover study was conducted in adults with asymptomatic hyperuricemia over 7-d periods after washout. Groups (1:1) received oral VER 9mg+FEB 80mg+DAPA 10mg (Gp1), or VER+FEB+placebo (Gp2). Urine was collected hourly and for 24h on D–1 (baseline [BL]) and D7 of each period. Primary endpoint was difference from D7 to D–1 in peak uUA excretion between groups (ΔGp1–ΔGp2). Secondary measures were change in serum levels and 24-h urinary excretion of UA, Cr, and Na. AEs were monitored. Data are shown as mean (SD) and LSM (95% CI).

Results: Enrolled subjects (n=24) were male, mean age 43y. At BL (D–2), median BMI and eGFR were 29 kg/m^2 and 85 mL/min/1.73m^2 with mean (SD) sUA 445.3 (60.8) µmol/L. BL levels of sCr and sNa were (Gp1/Gp2) 93.8/95.8 µmol/L and 138/139 mmol/L, respectively. Peak uUA was available for 13 subjects and 24h urine for all. After DAPA, subjects showed no increase in peak UA excretion on D7 (mg/h); Grp1 –5.33 (–15.04, 4.37), Gp2 –7.20 (–16.91, 2.51); mean difference 1.87 (–7.63, 11.36). No difference was seen in total 24h UA excretion. After DAPA, subjects showed significantly reduced sUA levels; mean difference (Gp1 vs Gp2) on D7 was –76.35 (–104.02, –48.68) µmol/L (p<0.01). No between-group differences were seen in sCr or sNa. 8 subjects had 9 AE (Gp1 n=5; Gp2, n=4), all mild, no inter-group differences. DAPA did not affect VER or FEB PK.

Conclusions: Addition of DAPA to an intensive UA lowering strategy with VER+FEB provides additional sUA lowering without increase in urinary UA excretion, or changes in sCr; suggesting a DAPA+VER+FEB combination will not adversely affect kidney function (NCT03316131).

Funding: Commercial Support - AstraZeneca

SA-PO141

Can Improvements in Cardiac and Vascular Hemodynamic Markers Explain the Kidney Benefit with Empagliflozin in the EMPA-REG OUTCOME® Trial?

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Background: In the EMPA-REG OUTCOME trial (NCT01131676) empagliflozin (EMPA) added to standard of care significantly reduced clinically relevant kidney outcomes by 39% in patients with type 2 diabetes (T2D) and established cardiovascular disease (CVD). As EMPA can reduce arterial stiffness and improve vascular compliance, these effects could be potential mediators of the kidney protective effects observed. We assessed whether the effect of EMPA on indices of arterial stiffness and vascular compliance could be related to kidney outcomes.

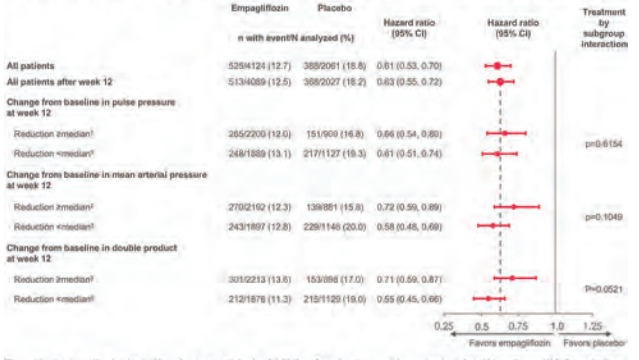
Methods: Patients were randomized (1:1:1) to EMPA 10 mg, EMPA 25 mg, or placebo (PBO); this post-hoc analysis compared the pooled EMPA group vs PBO. We calculated change from baseline to week 12 in indices of arterial stiffness (pulse pressure), vascular resistance (mean arterial pressure), and cardiac workload (double product). Subgroups for these indices (depicted as changes above or below the median) were used to assess potential effects on incident or worsening nephropathy (composite of progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or renal death) and all outcome events occurring after week 12 were included in this analysis.

Results: A total of 7020 patients were randomized and treated with ≥1 study drug dose. As previously reported, EMPA significantly reduced cardiac and vascular hemodynamic markers vs PBO at week 12. However, the reduction in risk of incident or worsening nephropathy with EMPA was consistent between the three subgroups for indices, regardless of magnitude of their respective changes (Figure).

Conclusions: In patients with T2D and established CVD, empagliflozin produced a consistent benefit on kidney outcomes between subgroups for indices of arterial stiffness, vascular resistance, and cardiac workload.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure: Incident or worsening nephropathy* following week 12 by changes from baseline in cardiac and vascular hemodynamic markers at week 12



*Progression to macroalbuminuria, doubling of serum creatinine level, initiation of renal-replacement therapy, or death from kidney disease. †Median reduction at week 12 = 1.5 mmHg; 896 patients excluded due to missing subgroup variable. ‡Median reduction at week 12 = 2.0 mmHg; 896 patients excluded due to missing subgroup variable. §Median reduction at week 12 = 156.33 mmHg x bpm; 896 patients excluded due to missing subgroup variable. Cox regression analysis in patients treated with ≥1 dose of study drug. Pulse pressure = SBP−DBP, mmHg; mean arterial pressure = ([2 x DBP] + SBP)/3), mmHg; double product = SBP x heart rate, mmHg x bpm. DBP, diastolic blood pressure; SBP, systolic blood pressure.

SA-PO142

Reduction in Weight and Adiposity Indices and Kidney Outcomes with Empagliflozin in Patients with Type 2 Diabetes (T2D): Results from the EMPA-REG OUTCOME® Trial

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Background: Empagliflozin (EMPA), a sodium-glucose co-transporter-2 inhibitor, significantly reduced the risk of prespecified kidney outcomes by 39% when added to standard of care in patients with T2D and established cardiovascular disease (CVD) in the EMPA-REG OUTCOME® trial. As obesity increases the risk for chronic kidney disease (CKD) and its progression to end-stage kidney disease, we explored the potential interaction between changes in weight/adiposity and the kidney-protective effects of EMPA.

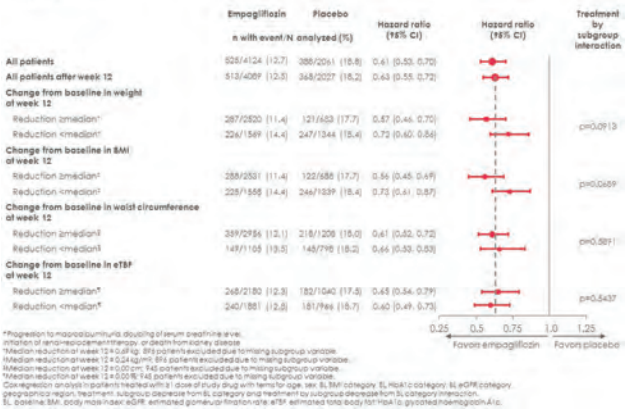
Methods: In EMPA-REG OUTCOME®, 7020 patients were randomized (1:1:1) to daily EMPA 10 or 25 mg or placebo (PBO). Background glucose-lowering therapy was unchanged for the first 12 weeks. We analyzed kidney outcomes in subgroups based on change in weight and adiposity markers from baseline to week 12. Differences in risk for pooled EMPA vs PBO were assessed using a Cox proportional hazards model adjusting for clinical covariates.

Results: Median observation time was 3.1 years. At baseline, the EMPA and PBO groups had similar mean weight (86.6 vs 86.2 kg, respectively), body mass index (30.7 vs 30.6 kg/m^2), waist circumference (105.0 vs 104.7 cm), and estimated total body fat (33.4% vs 33.5%). Changes in these parameters from baseline to week 12 did not significantly affect the reduced risk of incident or worsening nephropathy observed after week 12 with EMPA vs PBO (Figure; treatment by subgroup interaction p-value >0.05 for all).

Conclusions: The beneficial effect of EMPA on kidney outcomes was consistent irrespective of changes in weight or body fat in T2D patients with established CVD. The EMPA-KIDNEY trial will provide further insight into the effects of EMPA on adiposity and kidney outcomes in CKD patients with or without diabetes.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure. Incident or worsening nephropathy* after week 12 by change from baseline in weight and adiposity indices



*Progression to macroalbuminuria, doubling of serum creatinine level, initiation of renal-replacement therapy, or death from kidney disease. †Median reduction at week 12 = 0.69 kg; 895 patients excluded due to missing subgroup variable. ‡Median reduction at week 12 = 0.24 kg/m^2; 895 patients excluded due to missing subgroup variable. §Median reduction at week 12 = 0.00 cm; 945 patients excluded due to missing subgroup variable. ¶Median reduction at week 12 = 0.00 %; 948 patients excluded due to missing subgroup variable. Cox regression analysis in patients treated with ≥1 dose of study drug with terms for age, sex, BL BMI category, BL HbA1c category, BL eGFR category, geographical region, treatment, subgroup, decrease from BL category and treatment by subgroup decrease from BL category interaction. BL, baseline; BMI, body mass index; eGFR, estimated glomerular filtration rate; eTBF, estimated total body fat; HbA1c, glycated haemoglobin A1c.

SA-PO143

Effects of Canagliflozin on Serum Potassium in the CANVAS Program

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Background: Canagliflozin (CANA) is a sodium glucose co-transporter 2 (SGLT2) inhibitor used for the treatment of type 2 diabetes mellitus (T2DM). The US label Warnings and Precautions section notes a risk of hyperkalemia with CANA in patients with moderate renal impairment who are taking medications that interfere with potassium excretion. Serum potassium levels were assessed in patients at high cardiovascular (CV) risk in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program, comprised of the CANVAS and CANVAS-R trials.

Methods: The CANVAS Program randomized 10,142 participants with T2DM and high CV risk to CANA or placebo (PBO); 80% were on renin-angiotensin aldosterone system (RAAS) inhibitors at baseline. Serum potassium measurements were performed in a central laboratory; values meeting predefined limit of change criteria (PDLC) were prespecified and assessed using results obtained up to 2 days after the last dose of study drug.

Results: In the CANVAS Program, the risk of decreased serum potassium (PDLC <3.4 mEq/L and >15% decrease from baseline) was similar between the CANA and PBO arms (**Table**; hazard ratio [HR] 0.96 [95% confidence interval (CI) 0.72, 1.28]). The HR (95% CI) for increased serum potassium (PDLC >5.4 mEq/L and >15% increase from baseline) was 1.03 (0.89, 1.20) and for serum potassium ≥6.5 mEq/L was 0.84 (0.50, 1.41). Generally similar results were seen in subgroups by baseline eGFR (<45, 45-<60, & ≥60 mL/min/1.73 m^2; **Table**).

Conclusions: In the CANVAS Program, no significant differences in the risk of hypo- or hyperkalemia were observed with CANA versus PBO overall or in participants with renal impairment.

Funding: Commercial Support - Janssen Research & Development, LLC

Table. Patients with Serum Potassium Values Outside Predefined Limits in the CANVAS Program

PDLC	Baseline eGFR	Events	CANA Rate per 1000 PY	PBO Rate per 1000 PY	HR (95% CI)
Potassium <3.4 mEq/L (LLN) and >15% decrease from baseline	Total	197	6.39	7.15	0.96 (0.72, 1.28)
	≥60 mL/min/1.73 m^2	153	5.89	6.98	0.93 (0.67, 1.28)
	45 to <60 mL/min/1.73 m^2	28	7.02	7.29	0.95 (0.45, 2.04)
	<45 mL/min/1.73 m^2	16	14.59	9.77	1.50 (0.50, 4.55)
Potassium >5.4 mEq/L (ULN) and >15% increase from baseline	Total	723	26.36	24.80	1.03 (0.89, 1.20)
	≥60 mL/min/1.73 m^2	549	24.10	23.09	1.00 (0.84, 1.20)
	45 to <60 mL/min/1.73 m^2	122	35.38	28.92	1.21 (0.84, 1.75)
	<45 mL/min/1.73 m^2	52	45.07	42.26	0.87 (0.48, 1.56)
Potassium ≥6.5 mEq/L	Total	62	2.06	2.13	0.84 (0.50, 1.41)
	≥60 mL/min/1.73 m^2	39	1.49	1.76	0.73 (0.38, 1.38)
	45 to <60 mL/min/1.73 m^2	11	3.05	2.41	1.14 (0.33, 3.93)
	<45 mL/min/1.73 m^2	12	10.62	7.87	0.94 (0.27, 3.30)

PDLC, predefined limit of change criteria; eGFR, estimated glomerular filtration rate; CANA, canagliflozin; PBO, placebo; PY, patient-years; HR, hazard ratio; CI, confidence interval; LLN, lower limit of normal; ULN, upper limit of normal.

SA-PO144

Comparison Between Clinical Trial and Real-World Use of Sodium-Glucose Co-Transporter-2 Inhibitors According to CKD Status

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Background: Clinical trials typically enroll highly selective patient populations and often include few participants with chronic kidney disease (CKD). Our objective was to compare participants characteristics and outcomes in trials of sodium-glucose co-transporter-2 inhibitors (SGLT-2i) with SGLT-2i users in real-world settings according to CKD status.

Methods: We compared characteristics, mortality, and HbA1c change at 12 weeks among SGLT-2i users in the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) with patients in the Geisinger Health System from June 2013 to January 2017 according to CKD status. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 according to Modification of Diet in Renal Disease equation or macroalbuminuria.

Results: From 2013 to 2016, prescription of SGLT-2i increased in each category of eGFR (G1-2 [0.3% to 5.3%] and G3-5 [0.2% to 2%], all *P*<0.001). Compared to trial participants, real-world users of SGLT-2i were younger, more obese, with a much lower prevalence of coronary artery disease (Table). Real-world users had lower mortality than their counterparts in the trial, and these differences were present in patients with and without CKD. The magnitude of HbA1c reduction from baseline to 12 weeks was similar between trial participants and real-world users.

Conclusions: Despite the difference in baseline characteristics between trial and real-world users, SGLT-2i appeared to have similar glucose-lowering effect in individuals with diabetes regardless of CKD status. Further research is warranted to investigate the effects of SGLT-2i on cardiovascular and kidney outcomes in patients with CKD.

Funding: Other NIH Support - T32HL007024

Baseline characteristics	Patients with CKD		Patients without CKD	
	EMPA-REG OUTCOME trial (N=1,498)	Geisinger (N=288)	EMPA-REG OUTCOME trial (N=3,149)	Geisinger (N=1,603)
Age, years	66.2 (8.0)	62.5 (10.4)*	61.6 (8.4)	56.5 (10.9)*
Male	69.0	50.0*	72.1	54.3*
Body mass index, kg/m^2	30.8 (5.4)	37.1 (7.8)*	30.5 (5.2)	36.3 (7.4)*
eGFR, mL/min/1.73 m^2	54.5 (16.2)	60.3 (22.8)*	83.4 (17.2)	96.2 (23.6)*
HbA1c, %	8.11 (0.87)	8.54 (1.50)*	8.04 (0.84)	8.70 (1.44)*
Coronary artery disease	75.9	37.5*	75.5	21.3*
Outcomes				
All-cause mortality, per 1000 person-years	32.5	15.4 §	13.4	4.1*
Mean HbA1c change (SE) from baseline at week 12, %	-0.46 (0.03)	-0.45 (0.14) †	-0.79 (0.02)	-0.80 (0.05) ‡

Values are mean (SD) or %, unless indicated otherwise. * p<0.001; § p=0.07; † p=0.93; ‡ p =0.84

SA-PO145

Intensive Insulin Therapy Reduces Urinary Angiotensinogen in Type 1 Diabetes: A Possible Mechanism of Renoprotection via Renin Angiotensin System (RAS) Downregulation

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Background: Optimal glycemic control is well known to protect people with diabetes from developing kidney disease but the mechanism is unknown. Kidney angiotensinogen (AOG) gene expression has been shown to be regulated by glucose that stimulates AOG mRNA and also by insulin that inhibits glucose induced stimulation of AOG transcription in proximal tubule cells via an insulin responsive element that binds two transcription factors, hnRNP F & hnRNP K. We examined if in patients with type1 diabetes and microalbuminuria, urinary angiotensinogen (uAOG) is reduced by intensive insulin therapy. For this, we evaluated uAOG in biosamples from the Diabetes Control and Complications Trial (DCCT) participants with type1 diabetes and microalbuminuria allocated to either intensive or standard insulin therapy

Methods: Urine samples from DCCT participants provided by the NIDDK repository consisted of participants who had been allocated to intensive (n=58) or standard insulin (n=41) and had microalbuminuria at study entry. uAOG was measured after a median of 5years of therapy (range 3-6) in both groups. Patients were not taking any medications such as RAS blockers that could have influenced uAOG results. Mann-Whitney test was used to measure the differences in levels of uAOG between the two groups

Results: At the study entry, there were no significant differences in age, gender, disease duration, blood pressure, GFR, albumin excretion rate and HbA1C between the two groups. At the study visit there were again no significant differences in age, gender, disease duration, blood pressure or GFR. Albumin excretion rate was also not significantly different. HbA1c was higher in the group on standard when compared to intensive therapy (median 8.9, range 5.7-9.2 vs 7.0, 6.8-12% P<0.001). uAOG was significantly decreased in participants on intensive compared to standard therapy (median 3.98, range 0.4-96 vs 7.4, range 1.3-295ng/mg, P=0.005)

Conclusions: In type1 diabetes with microalbuminuria, intensive insulin decreases uAOG when compared to standard insulin. This suggests that optimization of glycemic control with intensive insulin, by suppressing uAOG downregulates kidney RAS overactivity and unravels an important mechanism for the well-known renoprotective effect of insulin in humans.

Funding: NIDDK Support

SA-PO146

Primary Efficacy Analyses from a Phase 2 Trial of the Safety and Efficacy of Bardoxolone Methyl in Patients with Type 1 Diabetes

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Background: Bardoxolone methyl (BARD) has been shown to significantly increase eGFR in patients with CKD and type 2 diabetes or Alport syndrome suggesting that the anti-inflammatory and anti-fibrotic effects of BARD may target the common pathways contributing to GFR loss in multiple forms of CKD. As a result, a Phase 2 trial (PHOENIX, NCT03366337) was initiated to test the hypothesis that BARD will improve kidney function in patients with CKD due to type 1 diabetes mellitus (T1DM) as well as other forms of CKD.

Methods: The Phase 2 open-label, multicenter study enrolled a cohort of patients T1DM confirmed by fasting C-peptide levels. Eligible patients were 18 to 65 years of age with eGFR values between 30 to 90 mL/min/1.73 m^2 and urine albumin to creatinine ratio (UACR) ≤ 2500 mg/g. Patients received BARD at an initial dose of 5 mg, dose-escalated to 20 mg (for patients with baseline UACR ≤ 300 mg/g) or to 30 mg (for patients with baseline UACR > 300 mg/g) and were treated for 12 weeks. The primary efficacy endpoint was the change from baseline eGFR after 12 weeks of treatment. Interim results for the cohort enrolling patients with T1DM are described herein.

Results: At data cutoff on May 15th, 2018, 3/19 (16%) of the enrolled patients with T1DM had completed the study. From a mean (± SE) baseline eGFR of 68.2 ± 3.8 mL/min/1.73 m^2, BARD treatment resulted in a significant increase from baseline in eGFR of 7.9 ± 2.9 mL/min/1.73 m^2 (p=0.008) at Week 12. No patients have discontinued from the study and no serious AEs considered related to BARD have been reported in this ongoing trial.

Conclusions: BARD was generally well tolerated and significantly increased eGFR in patients with T1DM. In patients with other forms of CKD, short term eGFR increases with BARD are predictive of durable eGFR improvements and additional studies are needed to study the longer-term effects of BARD on eGFR in T1DM.

Funding: Commercial Support - Reata Pharmaceuticals

	Mean Change from Baseline in eGFR (mL/min/1.73 m^2)			
	Week 1	Week 4	Week 8	Week 12
N	18	13	5	3
Mean ± SE	1.4 ± 1.3	6.2 ± 1.5	6.6 ± 1.9	7.5 ± 2.7

SA-PO147

Disease Characteristics and Outcomes in Patients with CKD and Type 2 Diabetes: A Matched Cohort Study of Spironolactone Users and Non-Users

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Background: This study aimed to assess disease characteristics and outcomes in cohorts of spironolactone users and non-users with chronic kidney disease (CKD) and type

2 diabetes (T2D) who were matched on demographic and clinical characteristics, including CKD stage.

Methods: Patients with CKD and T2D were identified in the US claims database PharMetrics Plus using ICD-9 and ICD-10 codes. Outcomes of interest including CKD progression, clinical events, healthcare use and costs were described in the matched cohorts using summary statistics; mortality analyses were conducted in a sub-cohort with linkable data in Experian. The impact of persistent or non-persistent spironolactone use (≥6 vs. <6 months treatment duration) was also evaluated.

Results: The matched cohorts (n=5,465 each) both had a median age of 62 years and 61% of patients were male. Despite matching, spironolactone users had more comorbidities at baseline than non-users (Charlson comorbidity index score 4+, 89% vs. 78%). During one-year of follow-up, progression to a more severe CKD stage occurred in 30% of spironolactone users and 18% of non-users. Annual median healthcare costs per person were $33,013 for spironolactone users and $22,598 for non-users; 62% and 50% of patients had at least one inpatient visit, respectively. The mortality rate per person-year was 4% for spironolactone users and 7% for non-users; however, the mortality rate assessment was conducted in a younger sub-cohort with lower rates of heart failure (n=1,431 each). Persistent spironolactone users had fewer clinical events, lower healthcare use and costs and a reduced likelihood of CKD progression than non-persistent users.

Conclusions: In this study, spironolactone users were more severely ill, had worse clinical outcomes and higher healthcare use and costs than non-users. These findings highlight the unmet medical need in this patient population and the need for better treatment options.

Funding: Commercial Support - Bayer AG

SA-PO148

Low Dose Anti-Thromboxane Reduces Urinary Albumin in Patients with Diabetic Kidney Disease

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Background: Thromboxane facilitates coagulation but is also a pro-inflammatory endogenous agent. SER150 is an oral, small molecule with a novel dual mode of action that inhibits thromboxane synthase and simultaneously blocks the thromboxane receptor. SER150 inhibited thrombocytes agglutination both in healthy and diabetic patients. Studies in healthy volunteers and in patients with Type 2 diabetes doses from 0,375 to 2,5 mg/kg body weight, SER150 dose-dependently increased bleeding time from insignificant values and up to 294 seconds after the highest dose investigated. However, a dose of 0,16 mg/kg insignificantly attenuated bleeding time compared to placebo and insignificantly reduced agglutination of ex-vivo stimulated (U16466) thrombocytes for few minutes.

Methods: A double-blind, placebo-controlled, clinical study included 49 diabetic patients with HbA1c of 7,08 mmol/mol, blood pressure of 132/75 mmHg and urine albumin > 30 mg/g creatinine (ACR). The patients were treated with SER150 at doses of either 15 mg BID or 30 mg BID (0,16mg/kg or 0,32mg/kg BID) for 4 weeks.

Results: SER150 treatment caused ACR gradually to decrease during the 4 weeks and was statistically significant reduced from baseline ($p<0,02$ and $p<0.04$ respectively). 25% of patients with micro-albuminuria at baseline (ACR >30 £300) became normo-albuminuric during the 4 weeks on SER150 treatment. All patients with macro-albuminuria (ACR >300) experienced a decrease in urinary albumin and 45% shifted from macro-albuminuria to micro-albuminuria.

Conclusions: These findings suggest two different sites of action with different dose-efficacy relation of the anti-thromboxane agent SER150. One at the thrombocytes and one at different, still unknown, site of action in the kidney at sites essential for the damage of renal filtration barrier in patients with diabetic kidney disease. The aim of the next clinical study is to confirm SER150 induced decrease in ACR in patients with diabetes and macro-albuminuria (ACR >500). Furthermore, to demonstrate that decrease in ACR is maintained over time (6 month) with a dose of 15 mg BID. The primary endpoint will be a composite of ACR and a group of relevant renal surrogate markers.

Funding: Commercial Support - Serodus ASA, Norway

SA-PO149

Randomized Placebo-Controlled Trials of Tangshen Formula in Diabetic Kidney Disease

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Background: Patients with diabetic mellitus are at high risk of progressing into diabetic kidney disease (DKD), which is associated with high morbidity and mortality. Current drug therapies for DKD are not entirely satisfactory. Tangshen Formula (TSF) is a Chinese herbal medicine remedy for DKD based on empirical evidence gleaned from Chinese medicine practitioners.The multinational, randomized, double-blind, placebo controlled trials of TSF Treatment on DKD (TTD)-1 and TTD-2 evaluated the effects of TSF on DKD when added to standard therapy.

Methods: In TTD-1 trial, we randomly assigned 180 DKD patients with mild to moderate disease (urinary albumin excretion rate (UAER) >20 μg/min, and/or 24-hour urinary protein (24h UP) between 0.5 and 2.0 g/d, and estimated glomerular filtration rate(eGFR) between 60 ml/min and 130 ml/min) to receive either placebo or TSF. In TTD-2 trial, 146 DKD patients with moderate to severe disease (24h UP between 0.5 and 3.5 g/d, and serum creatinine < 265 μmol/L (3 mg/dl)) to receive either placebo or TSF. Each trial continued intervention for 24 weeks. Primary outcome was urinary protein level, measured by UAER for participants with microalbuminuria, 24h UP for participants with macroalbuminuria. Secondary outcomes included renal function, serum lipids, quality of life, symptoms, and adverse events.

Results: For participants with macroalbuminuria, TSF displayed a statistically significant decrease in 24h UP in TTD-1(TSF –0.21 compared with placebo 0.36g, with a mean difference of –0.57g; 95% CI, –1.05 to –0.09, P=0.024), while no statistically significant difference was found in TTD-2(TSF 0.74 compared with placebo 0.21 g, with a mean difference of 0.55g; 95% CI, -0.03 to 1.13, P=0.111). The eGFR was improved in both trials (TTD-1: TSF 1.96 compared with placebo –7.05 ml/min/1.73m^2, with a mean difference of 9.01 ml/min/1.73m^2, 95% CI, –0.10 to 18.13, P=0.031) (TTD2: TSF 4.22 compared with placebo -4.8 ml/min/1.73m^2, with a mean difference of 7.8 ml/min/1.73m^2, 95% CI, 2.10 to 12.68, P=0.016). Other secondary outcomes showed no statistically significant difference between groups or in the incidence of adverse events in both trials.

Conclusions: TSF appears to provide additional benefits in improving eGFR in DKD patients, based on conventional treatments. Trial Registration TTD-1:Chinese Clinical Trial Registry ChiCTR-TRC-10000843 TTD-2: ChiCTR-TRC-13003566

SA-PO150

Tie2 Activation via VE-PTP Inhibition for Treatment of Diabetic Kidney Disease

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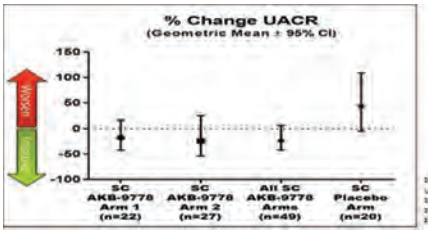
Background: Considering the current epidemic of diabetes, new treatments for diabetic vascular complications, including diabetic kidney disease (DKD) are urgently needed. VE-PTP is a vascular endothelial receptor tyrosine phosphatase that negatively regulates Tie2 activation, a critical axis for maintaining endothelial function and vascular stability. Importantly, VE-PTP is upregulated by hyperglycemia and hypoxia, conditions associated with decreased Tie2 activation and progression of diabetic complications. Thus, targeting VE-PTP inhibition to restore Tie2 activation is a promising approach to treat diabetic vascular complications, including DKD. Here we report results from a post-hoc analysis demonstrating improvement in UACR in patients with diabetic eye disease treated for three months with AKB-9778, a potent and selective small molecule VE-PTP inhibitor.

Methods: The TIME-2 study was a Phase 2a, double-masked, parallel-group trial in which 144 patients with diabetic retinopathy complicated by diabetic macular edema were randomized to one of three treatment groups: AKB-9778 (15 mg) subcutaneous (SC) BID monotherapy plus sham intravitreal injection; AKB-9778 SC BID plus monthly Lucentis (0.3mg) intravitreal injection; and placebo SC BID plus monthly Lucentis intravitreal injection monotherapy. Although the study was designed to assess the effect of AKB-9778 on diabetic eye disease, UACR was measured at baseline and at end of the 3-month treatment period. Patients with increased UACR at baseline (UACR ≥30 mg/g) were included in the analysis.

Results: About 50% of patients in the study had UACR ≥30 mg/g at baseline, approximately equally distributed among the three treatment groups. There was an ~ 20% reduction in geometric mean UACR from baseline in both AKB-9778 active treatment arms, while there was an increase in UACR in the placebo arm (Figure 1).

Conclusions: These findings represent the first clinical evidence of potential beneficial effects of a VE-PTP inhibitor in patients with DKD and underscore the therapeutic potential of Tie2 activation in DKD and other diabetic vascular complications.

Funding: Commercial Support - Aerpio Pharmaceuticals, Inc.



SA-PO151

Effects of Senolytic Agents on Blood- and Urine-Borne Extracellular Vesicles from Senescent Cells in Diabetic Kidney Disease: A Pilot Study

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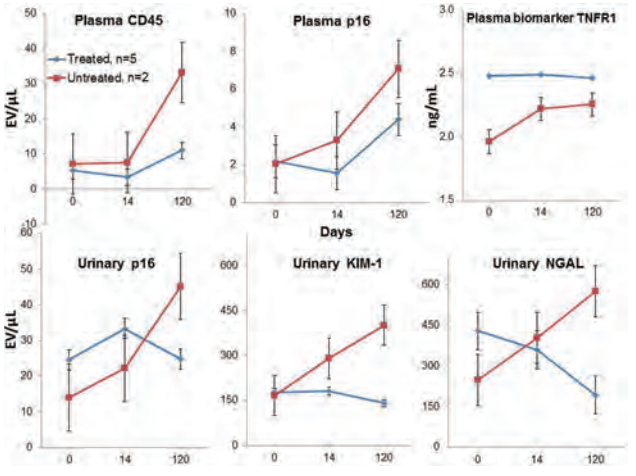
Background: Cellular senescence, from DNA damages leading to cell cycle arrest and increased expression of p16, contributes to the pathogenesis of diabetic kidney disease (DKD). Affected blood and kidney cells generate pro-inflammatory cytokines causing kidney injury. Extracellular vesicles (EV) shed by cells represent novel biomarkers of disease and disease activity. We tested the hypothesis that clearance of senescent cell abundance via senolytic agents would decrease markers of senescence, inflammation and kidney injury which could be identified through EV examination.

Methods: DKD subjects were randomized to senolytic drugs (**n=5**; a single 3-days oral regimen) vs "no treatment" (**n=2**). EVs were characterized and quantified in platelet-free plasma and cell-free urine sampled at Days 0, 14, and 120 by standardized digital flow cytometer methods using fluorophore conjugated preselected markers specific antibodies: senescence (p16), inflammation (CD45), kidney injury (KIM-1, NGAL). A non-EV (soluble) plasma biomarker of DKD progression, tumor necrosis factor receptor-1 (TNFR-1), was also measured.

Results: Of 7 male subjects, mean age was 71±6 years and eGFR 29±10 mL/min/1.73m^2. Over 120 days, treated subjects had decreased levels of inflammatory and senescent cell-derived EVs in plasma while untreated subjects showed progressive increases (**Figure**). Plasma TNFR1 biomarker levels did not differ. Similarly, senescent cell-derived urinary EVs and kidney injury marker (KIM-1 and NGAL) positive urine EVs tended to fall over time in treated while EVs rose in untreated subjects.

Conclusions: These early pilot study findings suggest that senolytic agents may attenuate progression of senescent cell abundance, inflammation, and kidney injury in patients with DKD.

Funding: NIDDK Support, Private Foundation Support



Inflammatory and senescent-cell derived EVs in DKD subjects by senolytic-treated and untreated groups

SA-PO152

Patient Motivation Scoring and Outcomes in the Diabetes CKD Clinic

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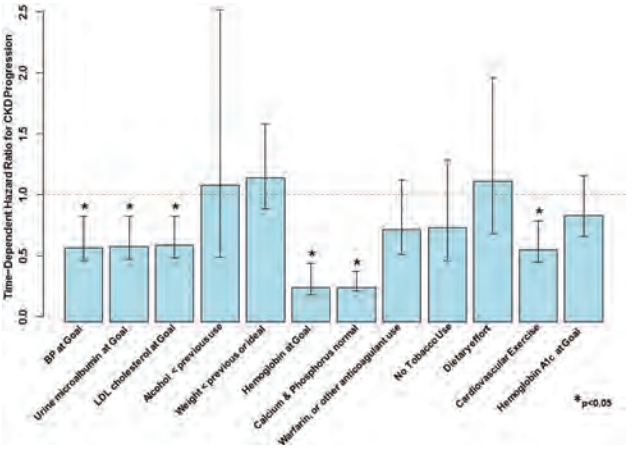
Background: Given the global CKD burden, innovative methods to improve patient's perception of autonomy and self-care are needed. We examined the association of variables in a patient motivation "Kidney and Heart Health" (KHH) Scoring system on CKD progression.

Methods: Diabetic-CKD (DM-CKD) patients were treated in a single-center, specialized clinic combining consultation from 1) hypertension-trained nurses and 2) physician/advanced practitioners. At each visit, patients were assigned points for meeting **lifestyle** (tobacco use, weight loss, alcohol use, exercise, and healthy diet) **and objective** (blood pressure, hemoglobin, LDL cholesterol, bone mineral metabolism, proteinuria, hemoglobin A1c, aspirin use) **goals**. CKD progression composite endpoint was defined as eGFR<10, dialysis, kidney transplant, or 40% reduction baseline eGFR. Time dependent cox hazards regression models examined the association between each KHH goal and CKD progression.

Results: From 2010-2016, 422 DM-CKD (eGFR 10-60mL/min/1.73m^2 inclusion) patients were treated; 61% male, 91% white, mean Charlson index 8.7±3.5, mean eGFR 31.8 ±12.1. Mean KHH score was 8.8±3.5 (out of 12). KHH categories with <75% patients reaching goal were: LDL (68%), weight (68%), bone metabolism (63%), exercise (51%), hemoglobin A1c (47%), and proteinuria (43%). Over 2.6 years (median), 177 met CKD progression composite endpoint (86 dialysis, 26 transplant, 53 eGFR <10, and 127 had 40% reduction eGFR). 82 died. Univariate hazard ratios for each category are shown, **Figure**. Multivariable models revealed older age, achieving BP, LDL, hemoglobin, bone metabolism, and exercise goals significantly associated with lower risk of CKD progression while weight and lower eGFR associated with higher risk compared to those not meeting lifestyle or objective goals.

Conclusions: Patient motivation scores used in a specialty CKD clinic relate to observed DM-CKD progression outcomes.

Funding: NIDDK Support, Private Foundation Support



SA-PO153

Effect of Oral Sodium Bicarbonate on Urine TGF-β1 in Non-Acidotic Diabetic Kidney Disease (DKD)

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Background: Oral $NaHCO_3$ may preserve GFR in CKD patients with normal serum (s) HCO_3^- by attenuating physiological responses that enhance H^+ excretion to maintain normal s-HCO_3^-, but cause kidney fibrosis. Along these lines, urine (u) NH_4^+ is directly associated with uTGF-β1 in CKD. $NaHCO_3$ reduces uNH_4^+ and, in hypertensive CKD, uTGF-β1. Whether $NaHCO_3$ reduces uTGF-β1 in DKD is unknown.

Methods: We conducted a single-center, randomized, double-blinded, placebo-controlled study in 74 US veterans with stage 2-4 DKD, ACR ≥30 mg/g, and s-HCO_3^- 22-28 meq/L. Participants received $NaHCO_3$ (0.5 meq/kg-LBW/d, n=35) or placebo (n=39) for 6 months. The primary analysis applied a mixed effect model to compare mean Δ from baseline in uTGF-β1/Cr over 3- and 6-months after controlling for baseline uTGF-β1/Cr.

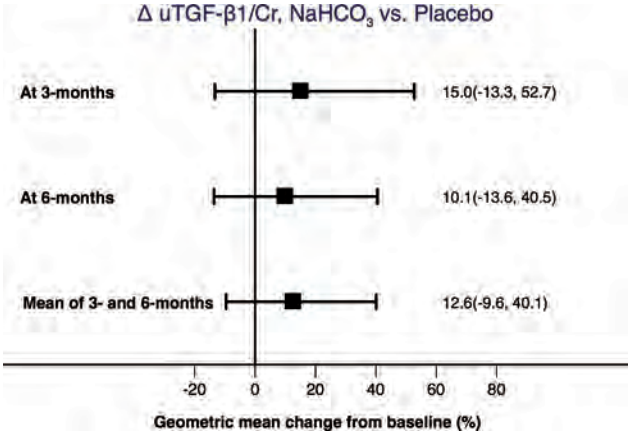
Results: Mean baseline values were age 71 years, eGFR 51 ml/min/1.73m^2, SBP 127 mm Hg, ACR (median) 121 mg/g, s-HCO_3^- 24 meq/L, u-pH 5.5, uNH_4^+ 1.4 meq/hr, and u-titratable acids (uTA) 1.3 meq/hr. Baseline characteristics were similar between groups. $NaHCO_3$ had expected effects on u-pH, u-TA, and s-HCO_3^- but did not lower uNH_4^+ (Table) or uTGF-β1/Cr (Figure). $NaHCO_3$ had no effect on ACR, however eGFR was higher with $NaHCO_3$ (5.7 ml/min/1.73m^2, 95% CI 1.2-10.2). There were no significant differences in BP, weight, or s-K^+ between groups during follow-up.

Conclusions: Oral $NaHCO_3$ did not reduce uTGF-β1 or uNH_4^+ in persons with non-acidotic DKD. The effect of $NaHCO_3$ on kidney NH_3 production may be attenuated in DKD, perhaps because kidney gluconeogenesis also produces NH_3. $NaHCO_3$ increased eGFR, however long-term effects of $NaHCO_3$ on eGFR in DKD should be determined.

Funding: Veterans Affairs Support

Mean values of acid-base indices over 3- and 6-months by treatment group.

Acid-base variable	Placebo	$NaHCO_3$	p
s-HCO_3^- (meq/L)	24.3 (1.8)	25.4 (2.6)	0.07
u-pH	5.5 (0.4)	6.2 (0.5)	<.01
u-TA (meq/hr)	1.3 (0.7)	0.9 (0.6)	0.02
u-NH_4^+ (meq/hr)	1.3 (0.7)	1.2 (0.7)	0.47



SA-PO154

Design of Pentoxifylline in Diabetic Kidney Disease (VA PTXRx)

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Background: Diabetic kidney disease (DKD) is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the U.S. Despite control of blood pressure and blockade of the renin-angiotensin-aldosterone system (RAAS), many patients continue to progress to ESRD, requiring costly dialysis or transplantation and resulting in high mortality. The non-specific phosphodiesterase inhibitor pentoxifylline (PTX) was approved by the FDA in 1984 for the treatment of peripheral vascular disease. Recent experimental and clinical data suggest that PTX, when added to usual care, leads to a reduction in albuminuria and inflammation and may decrease progression of DKD. However, a large scale multicenter randomized clinical trial is needed to determine whether this agent can reduce hard endpoints such as ESRD and death in patients with DKD.

Methods: VA PTXRx is a randomized, controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the incidence of ESRD and death in type 2 diabetic patients with DKD when compared to usual care plus placebo. Secondary endpoints will be: (1) quality of life (2) time until doubling of serum creatinine, (3) hospitalization for congestive heart failure (CHF), (4) a three-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) peripheral vascular disease (PVD), (6) percentage of participants with ≥ 50% reduction in urinary albumin-to-creatinine ratio (UACR) from baseline, (7) Rate of change in estimated glomerular filtration rate (eGFR) per year during the study period. Drug safety will also be analyzed as a secondary outcome. The key statistical assumption is that the primary endpoint will occur in 26.6% of the placebo group at six years with a risk reduction of 19% for PTX compared with the placebo group. The study aims to randomize 2510 participants to either PTX or placebo. The expected event rates were estimated using retrospective data from a cohort of veterans meeting study inclusion criteria obtained from a nationwide VA database.

Results: N/A

Conclusions: If PTX is found to reduce the incidence of ESRD and/or death with an acceptable safety profile, this will reduce the personal and financial burden of renal replacement therapy for patients with DKD.

Funding: Veterans Affairs Support

SA-PO155

Pharmacokinetic-Pharmacodynamic Relationships for the Effect of Selonsertib on eGFR in a Phase 2 Study in Subjects with Diabetic Kidney Disease

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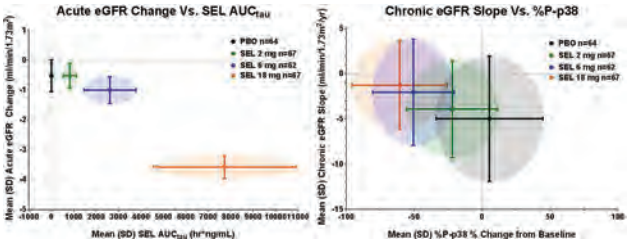
Background: Selonsertib (SEL) is a first-in-class, small molecule apoptosis signal-regulating kinase 1 (ASK1) inhibitor in clinical development for the treatment of diabetic kidney disease (DKD) and nonalcoholic steatohepatitis. In a Phase 2 dose ranging study in subjects with Stage 3a to 4 DKD, SEL was safe and well tolerated, showed a dose-dependent acute reduction in eGFR (baseline to WK4, as a result of inhibition of renal creatinine secretion), and at the 18 mg dose resulted in 75% reduction in the slope of chronic eGFR decline (WK4 to WK48) compared to placebo. This analysis characterizes the pharmacokinetic-pharmacodynamic (PK/PD) relationships observed in this study.

Methods: Subjects were administered 2, 6, or 18 mg SEL, or placebo once daily for 48 WKs. Serum creatinine based eGFR was assessed at baseline and throughout treatment. Samples were collected for plasma exposure of SEL (AUC_{tau} by population PK) and phosphorylation status of p38 (%P-p38: downstream marker of ASK1 inhibition) in blood. PK/PD relationships for SEL exposure, %P-p38 and eGFR were characterized.

Results: 260 subjects with measureable SEL AUC_{tau},%P-p38, and eGFR estimates were included in this analysis. SEL PK/PD relationships (figure) depict the acute and chronic changes in eGFR versus SEL exposure or dose (A) and %P-p38 (B), respectively. Mean exposure from SEL 18 mg provided near maximal %P-p38 inhibition (74% of E_{max}), and resided on the flat portion of the exposure-response curve for effect on chronic eGFR slope.

Conclusions: These PK/PD analyses provide further understanding of the relationships between SEL, ASK1 pathway inhibition, acute change and chronic slope of eGFR, supporting further clinical evaluation of the safety and efficacy of SEL 18 mg in subjects with DKD.

Funding: Commercial Support - Gilead Sciences Inc.



SA-PO156

Toxic Renal Effects from Intravitreal Bevacizumab for Proliferative Diabetic Retinopathy in the Patients with Chronic Diabetic Kidney Disease

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Background: Intravitreal injection of Bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), has revolutionized the management of proliferative diabetic retinopathy and diabetic macular edema. Here we evaluate the effects of intravitreal bevacizumab on renal parameters.

Methods: This study is a consecutive case-control retrospective study performed from January 01, 2016 to January 01, 2017 at the Olive View-UCLA Medical Center. An initial screening of all 2763 encounters in the outpatient adult renal clinic during the study period was performed to identify patients with proliferative Diabetic retinopathy (**PDR)** recieving bevacizumab intravitreal injections and were age matched controls with dilated fundoscopic exams demonstrating sin diabetic retinopathy (**sDR**), non-proliferative diabetic retinopathy (**NPDR**), or **PDR** without bevacizumab. T0 is defined as the first injection of bevacizumab. The average follow-up prior to T0 was empirically determined to be 13.15 months. Data collected from EMR and statistical tests were performed on Microsoft Excel.

Results: Patients treated with bevacizumab had significantly higher incidence of dialysis with 50% requiring dialysis as compared to 7.1% in NPDR and PDR groups. After injection the eGFR decline over 12 months in the bevacizumab group was twice as rapid as PDR without bevacizumab (p=0.02) and four times as rapid as NPDR (p = 2.67E-0.5). There was an increase in the amount of anti-hypertensive medications used to manage HTN from 1.9 ± 1.2 to 3.2 ± 1.3 (p=0.01)

Conclusions: Diabetic patients with diabetic CKD receiving intraocular anti-VEGF therapy have more rapid rate of progression of their CKD, have higher incidence of dialysis initiation and require more antihypertensive medications. We also noted both progression and higher level of proteinuria but could not capture this effect statistically based on our study scale.

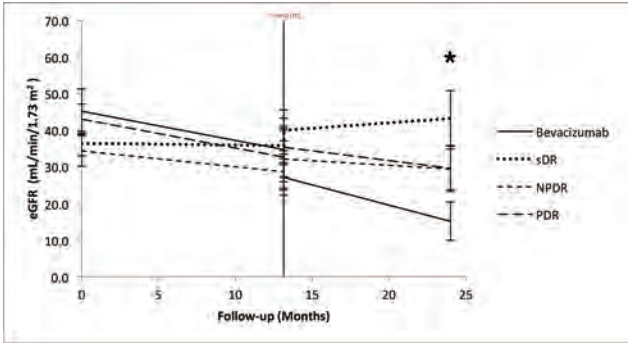

Figure 1. Rate comparison for e-GFR change between groups

SA-PO157

Effect of Bariatric Surgery on Renal Function in Morbidly Obese Patients

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Background: Morbid obesity is associated with glomerular hyperfiltration, which favours the occurrence of proteinuria. We studied the effect of bariatric surgery on renal function in morbidly obese patients at 6 months post surgery.

Methods: This was a prospective observational study of 75 patients who underwent laparoscopic sleeve gastrectomy for weight reduction. Baseline pre-surgery BMI was calculated and serum creatinine, HbA1C level, 24 hour urinary protein excretion and creatinine clearance(CrCl) was estimated. Investigations were repeated 6 months post surgery to assess change in the renal parameters.

Results: Mean age was 38.8 years (60% females, 40% males). 51.5% patients were hypertensive & 17.6% had diabetes mellitus. Mean weight before bariatric surgery was

119.93kg with a reduction of 25.60kg (21.34%) at 6 months post surgery (p<0.0001). Mean BMI before surgery was 45.13 kg/m2 with a reduction of 9.79 kg/m2 (21.69%) at 6 months post surgery(p<0.001). Mean serum creatinine before surgery was 0.82 mg/dl with a reduction of 0.08 mg/dl (9.75%) 6 month post surgery (p<0.001). Mean pre-op HbA1c was 6.3% with a reduction of 0.74% (11.7%) at 6 months post surgery (p<0.001). Mean CrCl before surgery was 140.69 ml/min with a reduction of 22.89 ml/min (16.2%) 6 month post surgery (p<0.0001). Mean proteinuria before surgery was 224.82 mg/d with a reduction of 57.98 mg/dl (25.77%) 6 month post surgery (p<0.0001). Mean albuminuria before bariatric surgery was 62.53 mg/day with a reduction of 17.35 mg/day (27.74%) 6 months post surgery (p<0.0001). Sub-group analysis showed that pre-operative CrCl was higher in diabetics (144.50 ml/min vs 139.88 ml/min), but the reduction in creatinine clearance was similar between the two groups (p-0.092). Mean baseline proteinuria was higher in diabetics (331.25 mg/day vs 202.02 mg/day) and reduction in proteinuria at 6 month post op was more in diabetics (128.92 mg/day (38.91%) vs 42.79 mg/day (21.18%), p-0.001).

Conclusions: This study shows that obesity related glomerular hyperfiltration improves significantly after bariatric surgery with significant decline in proteinuria. The improvement in hyperfiltration may prevent the development of overt obesity related glomerulopathy.

SA-PO158

Acute Hyperoxia and Slow Deep Breathing Improve Baroreflex Sensitivity in Long-Duration Type 1 Diabetes Irrespective of Macroalbuminuria

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Background: In previous studies, hyperoxia and slow deep breathing (SDB) acutely improved measures of autonomic dysfunction in young patients with type 1 diabetes (T1D) and in patients with type 2 diabetes (T2D). Such effects have not been addressed in patients with T1D and concomitant macroalbuminuria and/or existing autonomic dysfunction. The aim of this study is to examine the effect of acute oxygen inhalation and SDB on measures of autonomic dysfunction and whether these could be modified by albuminuria or existing autonomic dysfunction.

Methods: Fifty-four patients with T1D (57% male) were enrolled in a cross-sectional study where 29 patients had normoalbuminuria and 25 had presence of/or historical macroalbuminuria. Mean age (SD) and diabetes duration were 59.8 years (9.5) and 37.5 years (14.4) respectively. Patients were exposed to acute oxygen inhalation and SDB, while obtaining measures of autonomic function and blood oxygen saturation. Autonomic function was assessed by baroreflex sensitivity (BRS) and the standard deviation of the normal-normal intervals (SDNN).

Results: Acute oxygen inhalation was associated with an increase of 21.3% (95%CI 9.8;34) and 8.3% (95%CI 0.1;17) in BRS (ms/mmHg) and SDNN (ms) respectively. SDB was associated with an increase of 31.6% (95%CI 13.2;5) and 32.8% (95%CI 18.2;49.1) in BRS (ms/mmHg) and SDNN (ms) respectively. Combined oxygen inhalation and SDB was associated with an increase of 29.8% (9.8;53.4) and 44.2% (95%CI 27.1;63.5 in BRS (ms/mmHg) and SDNN (ms) respectively. Patients with existing autonomic dysfunction had an improved effect of combined interventions on BRS. Albuminuria or existing autonomic dysfunction did not modify any other associations.

Conclusions: Hyperoxia and SDB improve BRS and SDNN in T1D even in the presence of macroalbuminuria and existing autonomic dysfunction. This suggests that hypoxia might be involved in the pathogenic mechanisms of autonomic dysfunction in T1D. Further studies exploring the pathological pathways causing tissue hypoxia may improve the understanding of diabetic neuropathy.

SA-PO159

Both High Levels of Hb1Ac and HbA1c Variability Are Associated with Increased Risk of All-Cause Mortality in Patients with Diabetes and Maintenance Dialysis

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Background: Little is known of the association between variability of glycemic control and the risk of all-cause mortality in patients with diabetes and maintenance dialysis. **Aim:** We assessed the relationship between long-term glycemic control, as estimated using mean values and variability of blood HbA1c, and the risk of all-cause mortality in diabetic patients on chronic dialysis.

Methods: We included 3930 patients (age 65±14 years, 63% men) with diabetes (type 1 or 2) and regular dialysis treatment [hemodialysis (HD), n = 2487 (63%); peritoneal dialysis (PD), n = 796 (20%); and both HD and PD, n = 647 (17%)]. Data were available from the Swedish Renal Register (SNR); the follow-up period was 2008 - 2017 (mean follow-up: 2.3± 2.2 years). HbA1c was defined as the mean of the reported values. HbA1c variability was determined by the coefficient of variation (CV), calculated as the ratio between the standard deviation (SD) and the mean HbA1c, HbA1c(SD)/HbA1c(mean). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using time-dependent Cox models, which included adjustments for demographics, laboratory findings and comorbidity.

Results: During follow-up, 2027 (52%) deaths occurred. We used HbA1c 31-42 mmol/mol (5- 6%) as reference group. The multivariate Cox analyses showed increased mortality risk for HbA1c 62-72 mmol/mol (7.8-8.7%; HR 1.40, 95% CI 1.17 - 1.65) and HbA1c 73-82 mmol/mol (8.8-9.7%; HR 1.70, 95% CI 1.34 - 2.13) (both P<0.001). In a subanalysis of 2061 patients, we estimated the association between HbA1c variability and the risk of death. HbA1c CV< 0.5 was used as reference group. In the multivariate Cox analyses, HbA1c CVs of 2.84-4.60 and > 4.6 were associated with increased risk of mortality (HR 1.98, 95% CI 1.54- 2.47 and HR 1.99, 95% CI 1.54- 2.57, respectively) (both P<0.001).

Conclusions: We did not find a J-shaped relation between HbA1c level and risk of mortality in dialysis patients with diabetes. Instead, low mean HbA1c was associated with improved survival, and HbA1c variability was strongly associated with increased risk of all-cause mortality. These findings suggest that glycemic control as well as the stability of glycaemia level are important in patients with diabetes and maintenance dialysis treatment.

SA-PO160

Glycated Hemoglobin and Serum Fructosamine as Indicators of Glycemic Status in Patients with Type 2 Diabetes and CKD

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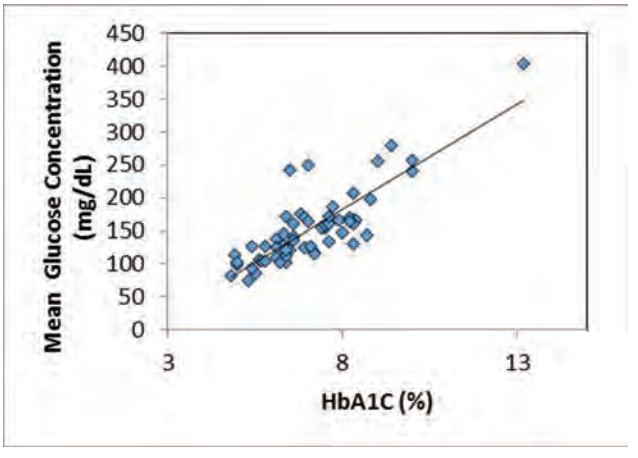
Background: Among patients with type 2 diabetes mellitus (T2DM) and nondialysis chronic kidney disease (n-CKD) it is unclear whether measures of chronic glycemia, HbA1C and serum fructosamine (SF), are accurate. Previous studies have been of very small sample size or failed to use continuous glucose monitoring (CGM), relying instead on a few random glucose levels. The purpose of this study was to determine the accuracy of HbA1C and SF in T2DM and n-CKD by relating to CGM data.

Methods: We studied 60 patients with T2Dm and n-CKD defined as eGFR 0-45 ml/min. Patients wore the CGM (Abbott FreeStyle Libre Pro) for 14 days, with glucose recorded every 15 minutes (maximum of 1,344 glucose measurements). Blood tests were drawn in the fasting state after the 14 day CGM. HbA1C and SF were compared by linear regression to patients' average glucose concentration (AGC) calculated as all of a patient's CGM glucose results divided by the total number of measurements.

Results: 60 patients wore the CGM for a mean of 12.7±2.9 days. Mean age was 72.4±10.4 years, 75% of patients were men, 15% were black, and mean eGFR 25.6±10.5. The mean glucose concentration was 152.2±56.6 mg/dL, mean HbA1C 7.1±1.5% and SF 301.9±57.7 μmol/L. HbA1C was significantly correlated with AGC, r=0.83, p<0.0001. The relationship was characterized by the formula, AGC=31.8 x HbA1C - 73.3. A sensitivity analysis among the 39 patients with eGFR < 30 ml/min. HbA1C remained significantly correlated with AGC, r=0.80, p=0.01 in these patients. There was no significant correlation between serum fructosamine and AGC, r=0.54, p=0.8.

Conclusions: HbA1C, but not serum fructosamine, was an excellent measure of chronic glycemic control among patients with type 2 diabetes and CKD. Further studies with larger sample sizes would be helpful to confirm these findings.

Funding: Clinical Revenue Support



SA-PO161

BP and Hemoglobin A1c Threshold Associated with Higher Prevalence of CKD in Elderly People with Diabetes

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Background: Chronic kidney disease (CKD) is a major health problem in elderly with diabetes. The study examined the clinical parameters associated with CKD in elderly diabetes, stratified by age groups.

Methods: Total 3068 patients with diabetes ≥ 65 years old (YO) were identified. CKD was defined as albuminuria or eGFR < 60mL/min/1.73m². CKD prevalence was analyzed according to age (65-69, 70-74, ≥75 YO), HbA1c (<6.5%, intermediate, ≥7.5%) and blood pressure (BP) (<130/80, intermediate, ≥140/90mmHg).

Results: CKD prevalence increased with age (65-69 YO group: 40%, 70-74 YO group: 51%, ≥75 YO group: 67%, P < 0.001). CKD prevalence increased with HbA1c in

65-69, 70-74 YO group, but not in ≥75 YO group (P<0.001, P<0.001 and P=0.081 for trend, respectively). With higher BP levels, CKD prevalence also increased in 65-69, 70-74 YO group, but not in ≥75 YO group (P=0.002, P<0.001 and P=0.281 for trend, respectively). Multivariate analysis showed that age, sex, body mass index, HbA1c ≥7.5%, BP ≥140/90mmHg, diabetes duration were associated with CKD. However, when stratified by age, higher HbA1c and BP were not associated with risk of CKD in subjects ≥75 YO (Table 1).

Conclusions: Overall, the thresholds associated with increased prevalence of CKD were 7.5% for HbA1c level and 140/90 mmHg for BP in elderly diabetes. However, the association of CKD with BP and HbA1c levels were not evident in subjects ≥75 YO.

Table 1. Multivariate logistic regression analysis to examine the associations between covariates and chronic kidney disease

	All		65-69 YO		70-74 YO		≥75 YO	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age (x 1 year)	1.1 (1.083-1.118)	<.001	1.038 (0.957-1.125)	0.371	1.119 (1.016-1.231)	0.022	1.122 (1.062-1.185)	<.001
Male sex	1.293 (1.103-1.517)	0.002	1.31 (1.04-1.65)	0.022	1.679 (1.278-2.207)	<.001	1.06 (0.76-1.479)	0.732
Body mass index (x 1kg/m2)	1.061 (1.034-1.089)	<.001	1.087 (1.045-1.131)	<.001	1.077 (1.031-1.125)	0.001	1.082 (1.026-1.14)	0.003
BP category (ref. <130/80 mmHg) intermediate ≥140/90mmHg	1.012 (0.848-1.208) 1.502 (1.183-1.907)	0.002 0.893 0.001	1.007 (0.778-1.304) 1.474 (1.026-2.117)	0.09 0.957 0.036	1.157 (0.847-1.58) 1.862 (1.22-2.841)	0.016 0.358 0.004	0.78 (0.531-1.147) 1.066 (0.658-1.728)	0.31 0.207 0.794
Diabetes duration (x 1 year)	1.038 (1.028-1.048)	<.001	1.052 (1.036-1.069)	<.001	1.028 (1.012-1.045)	0.001	1.025 (1.007-1.044)	0.007
HbA1c category (ref. ≤ 6.5%) intermediate ≥7.5%	0.934 (0.772-1.132) 1.423 (1.149-1.762)	<.001 0.487 0.001	1.175 (0.875-1.578) 1.427 (1.032-1.973)	0.091 0.283 0.031	0.82 (0.595-1.132) 1.806 (1.254-2.603)	<.001 0.228 0.002	0.791 (0.523-1.197) 1.229 (0.767-1.968)	0.085 0.268 0.391
Hypertension	1.249 (0.972-1.605)	0.082	1.491 (1.005-2.21)	0.047	1.047 (0.67-1.636)	0.842	1.257 (0.787-2.005)	0.338
Myocardial infarct	1.311 (0.967-1.779)	0.081	1.741 (1.071-2.831)	0.025	0.864 (0.53-1.408)	0.557	1.907 (0.945-3.846)	0.071

OR, Odds ratio; CI, Confidential interval; BP, Blood pressure; ref., reference

SA-PO162

Anemia Modifies the Associations Between Hemoglobin A1c and Outcomes in CKD

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Background: CKD and diabetes commonly co-occur. However, glycemic control and glycemic targets in these patients remain undefined.

Methods: In 1,833 participants of the Chronic Renal Insufficiency Cohort with diabetes, we assessed the association between baseline hemoglobin A1c (A1c) and death, first cardiovascular disease (CVD) event, and CKD progression using multivariable-adjusted Cox models. We also investigated: a) effect modification by anemia, eGFR, or albuminuria; and b) linearity of the association using spline models.

Results: At baseline, mean age was 59 years, mean eGFR was 41 mL/min/1.73 m2, mean A1c was 7.6%, and mean hemoglobin was 12 g/dL. During a median 6 years of follow-up, higher A1c was associated with worse outcomes (Figure 1); risk per 1% higher A1c was 10% for death, 10% for CVD events, and 5% for CKD progression. Anemia (hemoglobin<11 g/dL) was associated with non-linear associations for all three outcomes (Figure 2). A1c was associated with CKD progression in patients with eGFR≥30 ml/min/1.73m2 but not below that level. There was no effect modification by albuminuria.

Conclusions: In patients with CKD and diabetes, poor glycemic control contributes to a higher risk of death and CVD events. Individualized A1c targets and/or alternative markers of glycemia may be useful in diabetic CKD patients with anemia.

Funding: Other NIH Support - U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060902, UL1TR000003, UL1TR000439 , UL1RR029879, P20 GM109036, UL1 RR-024131, T32 HL007024

Figure 1. Association of A1c (per 1% increase) with Outcomes in 1,833 CRIC Participants with Diabetes
CKD Progression: 50% reduction in eGFR or ESRD

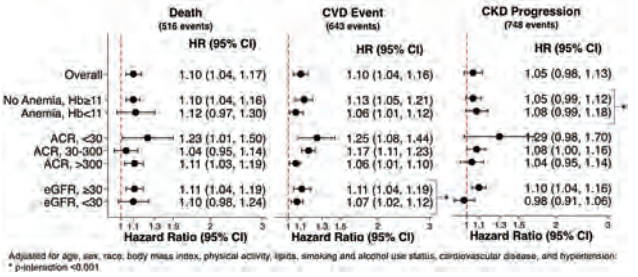
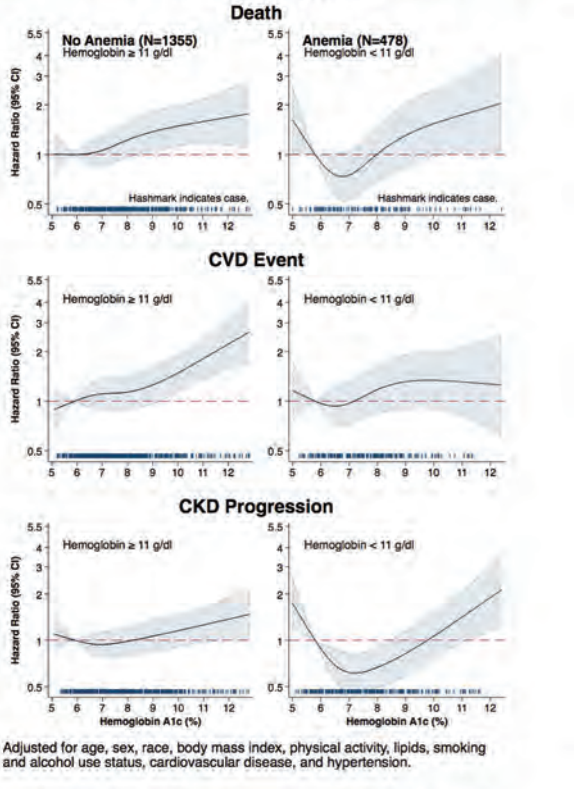


Figure 2. Association between A1c with Outcomes in 1,833 CRIC Participants with Diabetes, Stratified by Anemia



SA-PO163

Poor Glycemic Control Increases Mortality in Elderly Dialysis Patients with Diabetes - A Nationwide Prospective Cohort in Korea

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Background: Glycemic control, defined as glycated hemoglobin (HbA1c), was known to be an important factor for mortality in diabetic end-stage renal disease (ESRD) patients. However, the clinical impacts of glycemic control had not been fully elucidated in the elderly diabetic ESRD patients. We investigated whether glycemic control had clinical impact on all-cause mortality of elderly dialysis patients with diabetes.

Methods: A total of 755 diabetic patients (≥ 65 years) who had a value of HbA1c at the time of cohort enrollment were extracted from a nationwide prospective ESRD cohort in Korea between August 2008 and February 2015. The patients were divided into three groups according to the degree of glycemic control (< 6.5%, 6.5-7.9%, and ≥ 8.0%).

Results: The patients in the highest group of HbA1c (≥ 8.0%) were 132 (17.5%), which were younger, had higher vintages of dialysis, and higher percentage of peritoneal dialysis than the other two groups. Mortality rate was 57.2% during the median follow-up of 56.3 months. Patients with poor glycemic control (≥ 8.0%) had a higher risk of mortality compared with those in the HbA1c < 6.5% (hazard ratio [HR] 1.37; 95% confidence interval [CI] 1.06-1.77; P = 0.016). In subgroup analysis by dialysis modality, HbA1c ≥ 8.0% was a risk factor for mortality in the patients on peritoneal dialysis (HR 1.66; 95% CI 1.02-2.70; P = 0.041). Multivariate analysis adjusting for age, sex, comorbidity, dialysis vintage, and dialysis modality verified a significant association between poor glycemic control (≥

8.0%) and mortality rate in the elderly diabetic ESRD patients (HR 1.53; 95% CI 1.17-2.00; P = 0.002).

Conclusions: Poor glycemic control was significantly associated with mortality in the elderly dialysis patients, which suggests that lowering HbA1c to at least less than 8.0% might decrease mortality rate.

SA-PO164

Nutritional Status Is the Strongest Factor for Hemodialysis (HD)-Mediated Improvements in Insulin Resistance in Patients with Type 2 Diabetes

Satoshi Funakoshi,[1] Jyunichiro Hashiguchi,[2] Kenji Sawase,[1] Tayo Kawazu,[1] Yuko Maruyama,[3] Takashi Harada,[3] Yoko Obata,[4] Tomoya Nishino.[5] *[1]Nagasaki Kidney Center, Nagasaki, Japan; [2]Nagasaki Kidney Center, Nagasaki, Japan; [3]Nagasaki Kidney Center, Nagasaki, Japan; [4]Nagasaki University Hospital, Nagasaki, Japan; [5]Nagasaki University School of Medicine, Nagasaki, Japan.*

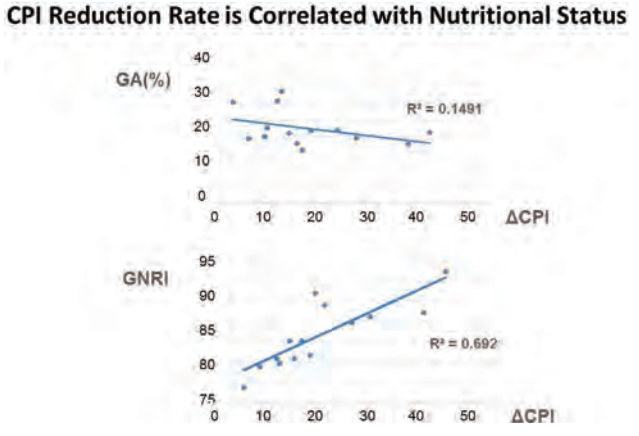
Background: Changes in C-peptide index (CPI) and HOMA-R before and after hemodialysis (HD) were compared to explore factors associated with insulin resistance in diabetic patients receiving HD.

Methods: Fasting blood samples were drawn from type 2 diabetic patients receiving maintenance HD but not insulin therapy at our clinic before HD on the first day of the week they went on HD (pre-HD) as well as on the next day (post-HD). Then CPI and HOMA-R were calculated from serum glucose, C-peptide and Immunoreactive Insulin (IRI) values to examine correlations between changes in CPI, HOMA-R, serum parameters and patient characteristics.

Results: The mean post-HD CPI and HOMA-R were significantly lower than the mean pre-HD values (CPI; 6.7 ± 2.7 vs. 8.1 ± 3.3 ng/mL, HOMA-R; 0.7 ± 0.3 vs. 1.1 ± 0.3 μU/mL, respectively) in the 19 type 2 diabetic patients (men/women, 12/7) included in the study. The rate of decrease in CPI and HOMA-R was strongly positively correlated with geriatric nutritional risk index (GNRI) (R^2 = 0.6423) in these patients, while it was not correlated with their glycoalbumin (GA) or fasting glucose values.

Conclusions: Despite reports that HD leads to resolution of uremia and excessive fluid overload resulting in improvements in insulin resistance, to date, very few reports compared insulin resistance before and after HD. This study showed that the rate of decrease in CPI was not increased in patients with favorable glycemic control but significantly increased in those with favorable nutritional status, suggesting that the patient's overall status may have a role to play in HD-mediated improvements in insulin resistance in the short term.

Funding: Private Foundation Support



SA-PO165

Free Vitamin D Is Independently Associated with Mean Arterial Blood Pressure in Diabetic Patients with Impaired Kidney Function

Daniela S. Bachert,[6] Mira Pavkovic,[3] Peter Sandner,[3] Shufei Zeng,[1] Carl-Friedrich Hocher,[5,3] Oleg Tsuprykov,[2,7] Saban Elitok,[4] Berthold Hocher.[2] Charité University Berlin *[1]Charité University Berlin, Berlin, Germany; [2]University of Potsdam, Potsdam, Germany; [3]Bayer AG, Pharmaceuticals, Wuppertal, Germany; [4]Department of Nepherology and Endocrinology/Diabetology, Klinikum Ernst von Bergmann, Potsdam, Germany; [5]Charles University, Prague, Prague, Czechia; [6]Dialysiscenter Potsdam /Institute for Nutritional Science, University of Potsdam, Potsdam, Germany, Potsdam, Germany; [7]IFLB, Institute for Laboratory Medicine Berlin, Berlin, Germany.*

Background: Blood pressure control is key for the prevention of complications of diabetes such as CKD progression. Vitamin D is thought to play a role in blood pressure regulation in diabetic patients. Total 25-hydroxyvitamin D are currently routinely used in clinical practice to assess vitamin D status. In the circulation, vitamin D – like other steroid hormones – is bound to a special carrier – vitamin D-binding protein (DBP). Only very tiny amounts of the total vitamin D are free and potentially biologically active, because only free vitamin D interact with the vitamin D receptor. The aim of the study was to compare the association of free and total vitamin D with blood pressure in diabetic patients with impaired kidney function.

Methods: Free and total vitamin D concentration were measured in 225 diabetic patients with impaired kidney function. Mean arterial blood pressure (MAP) was calculated based on 3 independent ambulatory blood pressure measurements and was 93.1 +/- 11.0 mmHg. Patients received cholecalciferol if needed. The cholecalciferol dose was adjusted after total vitamin D measurements every 3 months to meet vitamin D serum targets as defined by the German Society of Nutritional Medicine. Multiple linear regression analysis considering age, sex, BMI, eGFR, family history of hypertension, treatment with antihypertensive drugs and diuretics as confounding factors.

Results: This study revealed that free vitamin D was independently associated with MAP (p=0.026, CI: -1.285 – -0.049) whereas total vitamin D was not associated with MAP (p=0.308; CI: - 0.285 – 0.091).

Conclusions: Free – but not total - vitamin D serum concentrations in patients with diabetes and impaired kidney function are interdependently invers correlated with blood pressure, a key disease progression factor. This study suggests that free vitamin D measurements might be a better clinical tool – as compared to measurements of total vitamin D - to adjust vitamin D therapy in diabetic patients with impaired kidney function. However, reference values and treatment targets for free vitamin D in diabetic patients with impaired kidney disease have to be established.

SA-PO166

Trends of Non-Traumatic Lower Extremity Amputation in People with ESRD, by Diabetes Status, United States, 2000-2015

Jessica L. Harding, Meda E. Pavkov, Nilka Rios Burrows, Edward Gregg. *Centers for Disease Control and Prevention, Atlanta, GA.*

Background: Non-traumatic lower extremity amputation (NLEA) is a complication of end-stage renal disease (ESRD) and diabetes mellitus (DM). Contemporary trend data on NLEA among people with ESRD are lacking.

Methods: We estimated incident NLEA hospitalizations during 2000-2015 in adults with ESRD from the U.S. Renal Data System. Rates of first NLEA were estimated for any NLEA, minor NLEA (below ankle) and major NLEA (through or above ankle) using ICD-9 procedure codes from January 2000 to September 2015 and ICD-10 from October to December 2015. Hospitalization rates were stratified by primary cause of ESRD (DM or no-DM). Time trends were assessed using Joinpoint regression and annual percent changes (APC) reported.

Results: Among ESRD-DM, age-standardised rates for any NLEA declined 32% (from 36.4 to 24.9 per 1,000 persons) from 2000-2010 (APC= -3.87, p<0.05), and then did not change from 2010-2015 (APC=0.21, p=0.8) (Figure). Major NLEA rates declined 49% throughout the period (APC=-4.98, p<0.05), and minor NLEA rates declined 22% from 2000-2009 (APC=-2.63, p<0.05) and then did not change from 2009-2015 (APC=1.42, p=0.08). Among ESRD-noDM, rates for any NLEA declined 25% (from 5.3 to 4.0 per 1,000 persons) from 2000-2008 (APC=-3.66, p<0.05), and then did not change from 2008-2015 (APC=0.52, p=0.4). Major NLEA rates declined 39% from 2000-2011 (APC=-4.95, p<0.05) and then did not change from 2000-2015 (APC=1.02, p=0.6), and minor NLEA rates did not change from 2000-2008 (APC=-1.31, p=0.08) and then increased 19% from 2008-2015 (APC=2.47, p<0.05).

Conclusions: Despite an initial period of decline, the later stagnation in rates of any NLEA in adults with ESRD seem to be driven by a lack of further declines in minor NLEAs. Increased attention to preventive foot care in the ESRD population might be considered, particularly for those with ESRD-DM where NLEA rates remain almost six times higher than ESRD-noDM.

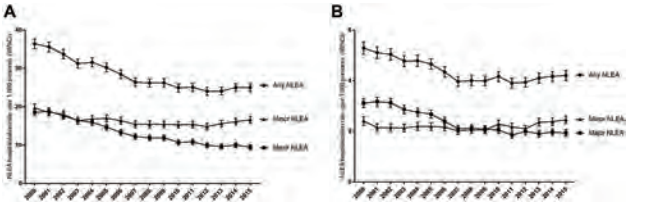


Figure Age-standardized hospitalization rates for non-traumatic lower extremity amputations (NLEA) among people with ESRD with diabetes (DM) (A) and without diabetes (noDM) (B), United States, 2000-2015

SA-PO167

A European Hemodialysis Multicenter Implementation of a Standardized Diabetic Foot Examination Protocol

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Background: Diabetics on hemodialysis (HD) have an increased risk for foot ulcers (FU), infections, and limb amputation. Pain and other symptoms are often reduced due to

neuropathy resulting in late diagnosis. We assessed the frequency of foot complications following implementation of a standardized foot examination in a cohort of prevalent diabetic HD patients in 26 DaVita centers in Germany, Poland and Portugal. We analyzed differences and associations with demographic data, practices and laboratory data.

Methods: A standardized foot examination was performed in 1025 diabetic HD patients in Germany (n=674), Poland (n=179) and Portugal (n=172). The examination includes: previous FU, amputation etc; inspection of feet (skin, nails); examination of pedal pulses (a dorsalis pedis and tibialis posterior) and foot sensory level. Foot complications were classified according to Wagner (grade 0-5); PAD was classified by clinical pulse measurement (normal=0, weak=1, missing=2).

Results: Mean (SD) patient age was 70.4 (14) years (NS between countries). 8.7% had a prior amputation; this was less common in Germany ($p<0.001$). A normal pulse in left and right a dorsalis pedis was present in 45% and 44% of patients, respectively, pulses were absent in 33% and 34% ($p<0.001$ between countries). For left and right a tibialis posterior, normal pulse was present in 37% and 37% of patients, respectively, pulses were absent in in 43% and 42% ($p<0.001$ between countries). Wagner classification score was 0 or 1 in 95.5% of patients and 4-5 in 1.8% (NS between countries). In a subgroup of 351 patients from Poland and Portugal there were no significant correlations between Wagner score and age, sex, BMI, Kt/V, vascular access, Charlson comorbidity index, Hb, albumin, phosphorus, and PTH. Patients with skin edema were older ($p<0.05$), had higher Charlson comorbidity index ($p<0.05$), lower Hb ($p<0.05$), lower albumin ($p=0.01$) and higher phosphorus ($p=0.004$).

Conclusions: Implementation of a standardized foot examination protocol in a large cohort of European diabetic patients on HD revealed a high prevalence of clinically significant complications that warrant close attention. This simple clinical tool is suitable to identify patients at high risk and could be the basis of a program to improve health outcomes.

Funding: Commercial Support - DaVita, Inc

SA-PO168

Prevalence of Increased Rate of Reduced Estimated Glomerular Filtration despite Advances in Diabetes Mellitus Treatment

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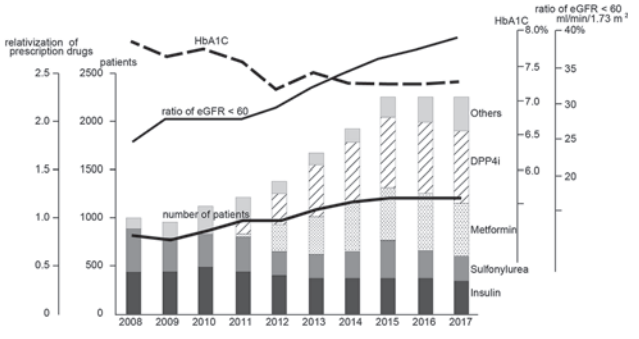
Background: Unlike in other countries, diabetes treatment in Japan follows a unique approach, such as the rare use of metformin before 2010 and the frequent use of dipeptidyl peptidase-4 inhibitor (DPP4i) after 2009. We investigated the pharmacological effects of antidiabetic drugs on glycemic control and renal function in Japan.

Methods: We conducted a retrospective, serial, cross-sectional analysis of individuals aged ≥18 years who used more than one antidiabetic drug at a single center in Japan between 2008 and 2017. The exclusion criteria were individuals who had continuously sustained an estimated glomerular filtration rate (eGFR) of <10 ml/min/1.73 m^2 (including those who received chronic dialysis). All data were extracted from patient's medical records.

Results: Between 2008 and 2017, the number of patients with diabetes mellitus has increased from 805 to 1190, and the average age of diabetic patients has increased from 65.6 to 68.8 years. Meanwhile, the number of prescription drugs has increased by 2.3 times. The use of antidiabetic drugs has remarkably increased the DPP4I and metformin levels (0% to 34% and 24%, respectively), whereas the insulin (46% to 15%) and sulfonylurea (42% to 11%) levels have decreased. The hemoglobin A1c levels have improved (7.8% to 7.3%); however, eGFR has decreased (from 73 to 65 ml/min/1.73 m^2), and the ratio of eGFR <60 ml/min/1.73 m^2 group has increased (from 25% to 39%). This tendency remained unchanged even when analyzed for background-matched cases between 2008 and 2017.

Conclusions: Pharmacological advances in the treatment of diabetes mellitus can improve glycemic control but not renal function.



SA-PO169

Declining CKD Prevalence Among Patients with Diabetes in the United States

Jennifer L. Bragg-Gresham, Xiaosong Zhang, William H. Herman, Rajiv Saran. *University of Michigan, Ann Arbor, MI.*

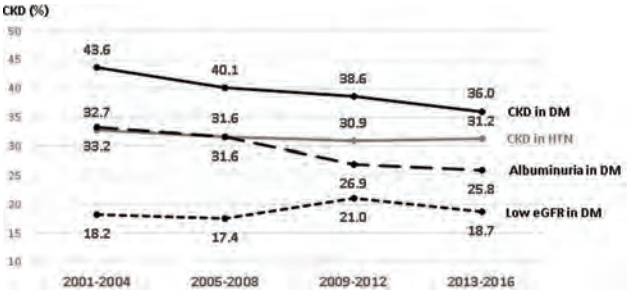
Background: Diabetes mellitus (DM) is a major risk factor for the development of chronic kidney disease (CKD) and is the assigned primary cause for almost half of all new end stage renal disease cases in the US. Diabetics with high blood pressure, poor glucose control, inherited tendency, and poor diet are at an increased risk of developing CKD. In this work, we sought to examine the prevalence of CKD among diabetics over time in the US.

Methods: Data from 5,278 patients with DM (diagnosed, taking medication, or HbA1c > 7%) from the National Health and Nutrition Examination Survey (NHANES, 2001-2016) was examined to estimate prevalence of CKD in 4-year cohorts, using population survey weights. CKD was defined either as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 or urine albumin-to-creatinine ratio (UACR) > 30 mg/g. Weighted logistic regression was used to assess significance of this decline.

Results: The prevalence of CKD among patients with DM declined steadily from 2001 to 2016. In contrast, the prevalence of CKD among patients with hypertension (HTN; diagnosed, receiving antihypertensive medication, or blood pressure >140/90) did not show a similar trend. The decline in CKD prevalence for DM is primarily driven by a lower prevalence of albuminuria (UACR > 30 mg/g) rather than low eGFR, which appeared stable over these years. This trend was significant with an OR=0.90 (95% CI: 0.85-0.96) per each 4-year more recent time period and increased in magnitude when adjusted for patient demographics (OR=0.88, 95% CI: 0.82-0.94).

Conclusions: The prevalence of CKD, in particular albuminuria, among patients with DM has decreased steadily in the US over the past 16 years, while its prevalence among patients with HTN has been stable. Future work will investigate potential reasons for this steady decline, such as greater awareness of diabetes and its complications, improvements in blood pressure control, glycemic control, adherence to healthier diet, weight control, and physical exercise.

Funding: NIDDK Support



SA-PO170

Younger Age, Afro-Caribbean Ethnicity, and Residual Albuminuria Predict Renal Function Decline in Patients with Diabetic Kidney Disease on Renin Angiotensin System Blockade

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Background: There is heterogeneity in the progression of renal function decline in diabetic kidney disease (DKD). The clinical markers and patient features that predict loss of renal function in DKD despite renin angiotensin system (RAS) treament remain unclear.

Methods: In a single centre study we studied 266 (n=50 Type 1 and n=216 Type 2) patients with DKD on RAS blockade. All patients had baseline estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease Study equation >45 ml/min. Patients were followed up for a median 10 years with standardised clinical care measures. Primary endpoint was progression of DKD defined as eGFR fall >5ml/min/year or end stage renal disease (ESRD-dialysis or transplantation). In a cause specific Cox proportional hazards model predictors of ESRD were also evaluated with death from any cause as competing event.

Results: In the T1DM cohort patients with progression (n=13) as compared to those without (n=37), In multivariate analyses [odds ratio (OR) and 95% confidence intervals (CI)] duration of diabetes OR 0.74 (0.56 - 0.99), baseline eGFR 1.09 (1.01 to 1.17) and ACR 9.5 (1.35- 66.7) were independent predictors of progression, $p<0.05$ for all. Similarly for T2DM cohort (n=216, 62% male, 40% Afro-Caribbean), 20% (n=50) had progression. Baseline eGFR, OR (95%CI), 1.04 (1.02 to 1.06) and ACR 1.4 (1.05-1.9) were independent predictors of progression, $p<0.05$ for all. In T2DM 44 patients developed ESRD, these patients as compared to those without ESRD (n=172) were younger (57.3 ± 10.5 vs. 62 ± 10.4 years), more likely to be Afro-Caribbean (87% vs. 34%) with higher ACR [30.0 (12.7 - 30.0) vs. 9.1 (2.0 - 30.0) mg/mmol], $p<0.05$ for all. In cause specific competing risk analyses, hazard ratio (95% CI), age 0.94 (0.91 - 0.98), Afro-Caribbean ethnicity 2.30 (1.07 - 4.90), and ACR 1.53 (1.08 - 2.16) were independent predictors of ESRD, $p<0.05$ for all.

Conclusions: In DKD residual albuminuria despite RAS blockade increased risk of significant renal function decline. In T2DM younger age, residual albuminuria and Afro-Caribbean ethnicity increase risk of ESRD. Treatments that reduce residual albuminuria despite RAS may help reduce progression of DKD.

SA-PO171

Comparison of Risk Prediction Using the CKD-EPI Equations or the MDRD Study Equation for Estimated Glomerular Filtration Rate in Chinese Patients with Diabetic Nephropathy

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Background: To evaluate risk implications of estimated glomerular filtration calculated by CKD-EPI equations ($eGFR_{CKD\text{-}EPI\text{-}CysC}$, $eGFR_{CKD\text{-}EPI\text{-}Cr\text{-}CysC}$) compared to eGFR by $eGFR_{CKD\text{-}EPI\text{-}Cr}$ and $eGFR_{MDRD}$ in Chinese patients with diabetic nephropathy (DN).

Methods: A retrospective study was conducted 363 patients with renal-biopsy DN, 227 patients of them were followed up at least one year. The stages of chronic kidney disease (CKD) were classified by different equations. The eGFR concordance between each two equations was assessed by Bland–Altman plots. The correlation between eGFR and pathological findings was using Spearman analysis. The end point was defined by receiving renal replacement therapy (RRT). Log Rank and Cox regression were employed to evaluate risk implications of $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$.

Results: Overall, the proportion of CKD 3-5 stages (eGFR, 60mL/min/1.73 m^2) was 57.2%, 56.1%, 72.1%, and 64.1% by the $eGFR_{MDRD}$, $eGFR_{CKD\text{-}EPI\text{-}Cr}$, $eGFR_{CKD\text{-}EPI\text{-}CysC}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr\text{-}CysC}$ respectively. The concordance between $eGFR_{CKD\text{-}EPI\text{-}CysC}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr\text{-}CysC}$ (mean bias: 1.20), and between $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr}$ (mean bias: 4.21) were superior to others. However, the bias of $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr}$ enlarged when eGFR was great than 60mL/min/1.73 m^2. Compared to $eGFR_{CKD\text{-}EPI\text{-}Cr}$, 40% and 18% of patients were reclassified from CKD 1-2 stages to CKD 3-5 by CKD-EPI-CysC and CKD-EPI-Cr-CysC, respectively, and reached the end point quicker than not reclassified patients (P<0.01); 67.6% and 55.3% of patients with $eGFR_{CKD\text{-}EPI\text{-}Cr}$ 45-60 were reclassified to CKD 3b-5 stages by CKD-EPI-CysC and CKD-EPI-Cr-CysC, respectively, however, no significant difference of renal survival time was observed compared to not reclassified patients. The results were similar when compared to $eGFR_{MDRD}$. The hazard ratio was 0.960 (95% CI 0.949-0.971), 0.961 (95% CI 0.950-0.971), 0.940 (95% CI 0.925-0.955) and 0.947 (95% CI 0.934-0.960) for $eGFR_{MDRD}$, $eGFR_{CKD\text{-}EPI\text{-}Cr}$, $eGFR_{CKD\text{-}EPI\text{-}CysC}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr\text{-}CysC}$ respectively, when eGFR was regarded as continuous variables.

Conclusions: $eGFR_{CKD\text{-}EPI\text{-}CysC}$ and $eGFR_{CKD\text{-}EPI\text{-}Cr\text{-}CysC}$ classified more patients to CKD 3-5 stages and more accurately categorized the risk of RRT than did $eGFR_{CKD\text{-}EPI\text{-}Cr}$ in Chinese DN patients.

Funding: Government Support - Non-U.S.

SA-PO172

Socioeconomic, Demographic, and Clinical Associations of CKD in Diabetes in a Population-Based Australian Cohort: Results from the EXTEND45 Study

Louisa Sukkar,[1,2] Amy Kang,[1] Min Jun,[3] Celine Foote,[1] Roberto Pecoits-Filho,[4] Brendon L. Neuen,[1] Kris Rogers,[1] Alan Cass,[7] Carol A. Pollock,[5] Germaine Wong,[5] John Knight,[1] David Peiris,[1] Martin P. Gallagher,[1] Meg J. Jardine.[6] EXTEND45 Steering Committee *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]School of Public Health, The University of Sydney, Sydney, NSW, Australia; [3]The George Institute for Global Health, UNSW Sydney, Newtown, NSW, Australia; [4]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [5]The University of Sydney, St. Leonards, NSW, Australia; [6]The George Institute for Global Health, UNSW, Newtown, NSW, Australia; [7]Menzies School of Health Research, Darwin, NT, Australia.*

Background: Type 2 diabetes is the leading cause of Chronic Kidney Disease (CKD) in the developed world. Identifying people with diabetes at increased risk of developing CKD is the first step to developing preventative strategies to reduce this burden. We aimed to estimate the incidence rate and associations of CKD in people with diabetes.

Methods: Based on data from the EXTEND45 study (the 45 and Up Study linked to [1] hospital and community pathology datasets by the Centre for Health Record Linkage [CHeReL] and [2] the Medicare Benefits Schedule [MBS] and Pharmaceutical Benefits Scheme [PBS] datasets provided by the Department of Human Services), we identified a population-based Australian cohort (2006-2014) of 24,400 people aged ≥45 years with diabetes. We used Poisson regression to estimate CKD (eGFR<60 ml/min/1.73m^2) incidence and prevalence. Multivariable Cox regression was used to examine associations between baseline sociodemographic factors, comorbidities and incident CKD

Results: Of 24,400 participants with diabetes, 2,789 (11.4%) had prevalent CKD and 1,771 (7.2%) developed incident CKD over a mean follow-up of 4.3 years. CKD incidence rate was 4.93 (95% confidence interval [CI]: 4.70-5.16) per 100 person-years. Compared to those who had no CKD, those with CKD were older (mean age: 64.7, 75.2, 70.2 years, for no CKD, prevalent CKD, incident CKD respectively), had a lower proportion of current smokers (7.9%, 3.1% 4.7% respectively) and a lower proportion with an annual household income of >$70,000 (17.1%, 6.2%, 10.5%). Incident CKD was predicted by age (hazard ratio [HR]: 1.07 [1.07-1.08] per year increase), geography (Outer regional vs major city: 1.41 [1.17-1.69]), BMI (obese vs normal: 1.43 [1.23-1.68]), presence of hypertension (1.48 [1.27-1.73]), coronary heart disease (1.24 [1.11-1.40]) and depression (1.26 [1.09-1.45]).

Conclusions: In a contemporary cohort of Australians with diabetes, the incidence of CKD is high and independently predicted by age as well as geography, obesity, a baseline history of cardiovascular disease and depression. These associations provide potential targets for early intervention in these at risk groups.

Funding: Commercial Support - The EXTEND45 Study is funded through peer-reviewed (NSW Cardiovascular Research Network Collaborative Project Grant), and unrestricted industry (from MSD, Amgen and Eli Lilly) research grants.

SA-PO173

Large Cross-Sectional Study Revealed the Conditions, Pathogenesis, and Progression of Diabetic Kidney Disease and Early Decliner in Japan

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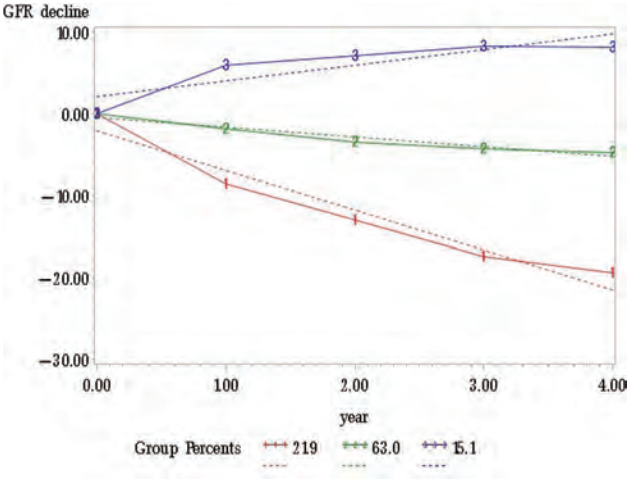
Background: Estimated glomerular filtration rate (eGFR) decline precedes albuminuria in a certain portion of diabetic patients. Thus, albuminuria and/or low eGFR in diabetic patients were defined as 'Diabetic Kidney Disease (DKD)'. In addition, the existence of 'early decliner' attracts a lot of attention, whose eGFR declines rapidly from early stage in DKD patients. To understand the prevalence of DKD and the risk factor of early decliner, we integrated several cohorts and cross-sectional data.

Methods: We continue adding up the 14,000 patients data with 9 hospitals, who were diagnosed as diabetes mellitus and did not receive dialysis. Prevalence was calculated based on cross-sectional data in the baseline of each cohort. We defined DKD as albuminuria ≥ 30 mg/gCr and/or eGFR < 60 ml/min/1.73m^2. We did 2 types of analysis to look for the risk factors of early decliner, firstly by defined eGFR declined by more than 5 ml/min/1.73m^2/year with normal eGFR in the baseline and secondly by trajectory analysis to compare with the provisional standard.

Results: The proportion of DKD was 52% in total with available data. 8.3% patients were categorized as early decliner with the definition of eGFR decline by more than 5 ml/min/1.73m^2/year. By trajectory analysis, 21% patients were classified as early decliner whose eGFR decline rate was 4.84 ml/min/1.73m^2/year (Image). Two kinds of analyses revealed that the common risk factors with early decliner group were high level of albuminuria and eGFR in the baseline.

Conclusions: The proportion of DKD were over 50% in all diabetic patients in Japan. The mean eGFR decline rate of early decliner by trajectory analysis was 4.84 ml/min/1.73m^2/year, similar to provisional standard. The common risk factors of early decliner were high level of albuminuria and eGFR in the baseline status by two types of analyses.



Classification of eGFR trajectories.

SA-PO174

Inflammation and Kidney Injury in Diabetic African American Men

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Background: African Americans (AA) are disproportionately burdened by diabetes and diabetic kidney disease (DKD). However, little is known about the cellular and molecular mechanisms underlying the onset and progression of DKD in this population. AA men are especially underrepresented in biomedical research. We recently reported undiagnosed kidney injury in a significant proportion of diabetic AA men served by a community clinic in Greensboro, NC. The goal of the current study was to determine the association between specific inflammation markers and kidney injury in diabetic AA men.

Methods: We recruited three groups of AA men aged 18-65 years: 1) diabetics without diagnosed kidney disease (n=87); 2) diabetics with diagnosed DKD (n=20); and 3) age-matched non-diabetic controls (n=81). Assays for urinary albumin and creatinine as well as plasma kidney injury molecule 1 (KIM-1) and urinary neutrophil gelatinase associated lipocalin (NGAL) were used for biochemical assessment of kidney function. Enzyme-linked immunosorbent assays were used to measure the plasma and urinary levels of seven inflammatory markers: adiponectin, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), TNF receptor 1 (TNFR1), TNF receptor 2 (TNFR2), interleukin-6 (IL-6), and intercellular cell adhesion molecule-1 (ICAM-1). A heat map was generated for the "inflammation profile" for each individual in the study.

Results: Plasma levels of TNF-α, TNFR1 and TNFR2 increased with severity of DKD and were significantly higher in diabetic patients with macroalbuminuria compared to non-diabetic controls and diabetics with normoalbuminuria or microalbuminuria. Likewise, urinary levels of ICAM-1 were higher in diabetic patients with macroalbuminuria compared

to the other groups. Indeed urinary ICAM-1, plasma TNF-α, and plasma adiponectin had moderate positive correlations with UACR while the levels of TNFR1 and TNFR2 in the plasma were strongly correlated with kidney injury. In contrast, though plasma CRP was elevated in diabetics relative to non-diabetic controls, its levels did not correlate with kidney injury. The number of individuals with elevated levels of multiple inflammation markers increased with the severity of kidney injury.

Conclusions: These data suggest that inflammation, particularly that mediated by the TNF-α/NF-κB signaling axis, may play a role in the pathogenesis of DKD in AA men.

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SA-PO175

Sex Disparity to Kidney Transplant Varies by Cause of ESRD

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Background: Women are significantly less likely to undergo transplantation than men. The possibility that transplant access differs by underlying cause of ESRD among men and women has not been thoroughly evaluated.

Methods: Using data from the US Renal Data System (USRDS), we performed a retrospective cohort study of adults who required their first renal replacement therapy between January 1, 1995 and June 30, 2016. In two approaches, considering either all patients with ESRD or only those with a waitlist date, we examined the association between sex and likelihood of transplant by cause of ESRD (including diabetes mellitus type 2 (DM2), hypertension, cystic/obstructive disease, and diabetes mellitus type 1) using adjusted Cox models.

Results: There were 266,616 kidney transplants among 2,228,769 adults with ESRD. In fully adjusted analyses, the likelihood of transplant for women was 0.82 (95% CI 0.82-0.83) times that of men in the full cohort and 0.91 (95% CI 0.90-0.92) times that of men considering only those registered on the waitlist. In both analyses, cause of ESRD modified the association between sex and access to transplantation ($p<0.001$), such that likelihood of transplant was markedly lower in women (vs. men) with ESRD due to DM2. In contrast, the sex disparity in transplant access was less profound in women with other causes of ESRD (figure).

Conclusions: Sex disparity in kidney transplant access varies substantially by cause of ESRD. Regardless of whether analyses included all patients with ESRD or only those registered on the waitlist, women (vs. men) with DM2 had the lowest access to kidney transplant compared to women (vs. men) with other attributed causes of kidney disease. This disparity is concerning, given that DM2 is the leading cause of ESRD in the US, and these patterns were observed even among those waitlisted for transplant.

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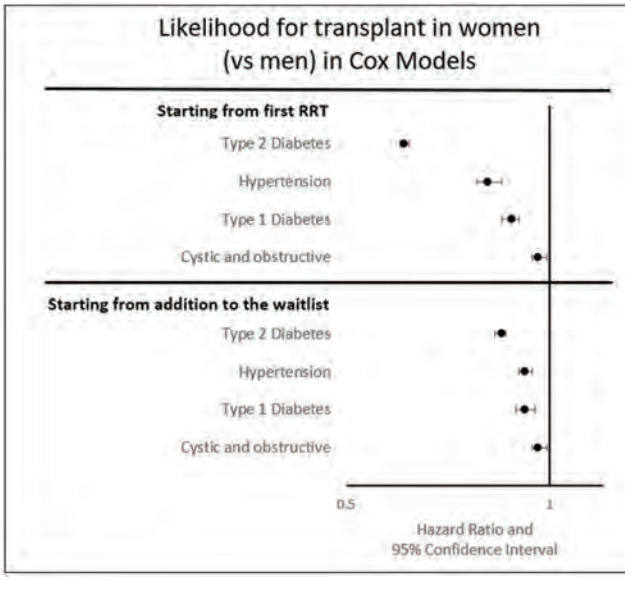

SA-PO176

Establishing a Hazard Predictive Model of Renal Outcomes for Diabetic Nephropathy

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Background: The present study aims to find out the independent risk factors associated with loss of renal functions in diabetic nephropathy (DN) and to further establish a hazard predictive model to evaluate prognosis of DN patients.

Methods: We enrolled patients with biopsy-proven DN in our hospital between January 2004 to June 2014. They were followed up until reaching the renal end-points including renal replacement therapy and doubling of serum creatinine before 31 December 2014. Univariate and multivariate Cox regression models were used to determine the independent variables associated with prognosis. A hazard predictive model was established based on the prognostic index (PI) determined by the regression coefficients in the multivariate Cox model.

Results: The mean follow-up duration was 25.9 months. Of the 57 people enrolled in this study, 25 reached the renal outcomes. The clinical and pathological parameters associated with renal outcomes in the univariate Cox regression models were introduced into the multivariate Cox models which showed that estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), hemoglobin and scoring of interstitial fibrosis and tubular atrophy (IFTA) were independent risk factors for reaching renal end-points. The independent risk factors were included in the PI calculations to establish the hazard predictive model of renal outcomes. Participants were randomly divided into the training set ($n = 38$) and the validation set ($n = 19$). Patients with PI≤0.807 were assigned to the low-risk group while patients with PI>0.807 were assigned to the high-risk group based on the cut-off point of the ROC curve (AUC 0.901, 95%CI 0.800-1.000, $P = 0.000$) with the renal endpoints as the state variable and PIs as the test variable in the training set. The survival analysis showed that there was significant difference in the renal survival curves between the low-risk group and the high-risk group in both sets. The AUCs of ROCs in both sets were greater than the AUCs of ROCs of any single risk factors.

Conclusions: The hazard predictive model combining clinical and pathologic independent variables were able to predict prognosis of DN with more accuracy so as to help clinicians act early to patients with high risk of developing ESRD.

SA-PO177

The Relationship of Pathologic Classification and Prognosis in Diabetic Nephropathy

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Background: The present study is aimed to explore the relationship between clinical manifestations and pathological changes in diabetic nephropathy (DN) and to assess the predictive power of the pathologic classification for DN established by the Renal Pathology Society in 2010.

Methods: Patients with type 1 or type 2 diabetes and biopsy-proven DN in the Third Affiliated Hospital of Sun Yat-sen University between January 2004 to June 2014 were enrolled in the present study and were followed up until 31 December 2014. The outcome was defined as renal end-points including renal replacement therapy and doubling of serum creatinine as well as all-cause mortality. The laboratory and histologic data were analyzed and outcomes were assessed using survival analysis.

Results: The Fifty-seven people enrolled in this study were categorized into Class IIa ($n = 9$), Class IIb ($n = 9$), Class III ($n = 25$) and Class IV ($n = 14$) while no participants belonged to Class I. The changes of Class IIa were slight and those of Class IV were severe both in the clinical data (diabetic duration, blood pressure, eGFR, urine protein excretion rate, albumin and hemoglobin) and the pathological data (percentage of global glomerulosclerosis, percentage and scoring of interstitial fibrosis and tubular atrophy, scoring of interstitial inflammation and incidence of large vessel lesions). There were no significant differences between Class IIb and III in the above variables except for the scoring of arteriosclerosis. The mean follow-up duration was 25.9 months. Twenty-five patients reached the renal outcomes and six people reached all-cause mortality. The survival analysis showed that there were significant differences among the renal survival curves of different glomerular classes and of different interstitial and vascular scorings, but not in the survival curves related to all-cause mortality.

Conclusions: The glomerular classes were not completely associated with renal prognosis in that the clinical manifestations and renal outcomes were benign in Class IIa, moderate but similar in Class IIb and III and severe in Class IV. The glomerular classification and interstitial and vascular scorings were associated to renal prognosis but not to mortality.

SA-PO178

Similarity and Difference of Clinicopathological Features Between Diabetic Nephropathy and Hypertensive Nephrosclerosis: A Nationwide Kidney Biopsy Study in Japan

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Background: Diabetic kidney disease is the major cause of end-stage kidney disease in developed countries. Moreover, hypertensive nephrosclerosis is increasing cause of end-stage kidney disease in Japan. In this study, we evaluated clinicopathological features between diabetic nephropathy and hypertensive nephrosclerosis using nationwide biopsy samples in Japan.

Methods: The clinical data of 600 biopsy-confirmed diabetic nephropathy patients and 184 biopsy-confirmed hypertensive nephrosclerosispatients were collected retrospectively from 13 centres throughout Japan under the support from the Japan Agency for Medical Research and Development. Pathological features and decreasing rate ofestimated GFR (eGFR) were evaluated between the two biopsy cohorts under the CKD heat map classification.

Results: The median observation period was 70.4 (IQR; 20.9-101.0) months in diabetic nephropathy and 73.2 (IQR; 31.2-116.4) months in hypertensive nephrosclerosis. In the CKD heat map categories, Green and Yellow (G&Y), Orange and Red category contained 103, 149, and 348 cases in diabetic nephropathy and 36, 57, and 91 cases in

hypertensive nephrosclerosis, respectively. In clinical factors, body mass index, systolic and diastolic blood pressure were higher in patients with hypertensive nephrosclerosis than diabetic nephropathy in G&Y category. Declining speed of eGFR was no difference between two cohorts (diabetic nephropathy, hypertensive nephrosclerosis; 1.7, 2.4 mL/min/1.73 m^2/year, respectively). However, there was no difference in pathological findings between two groups in the category. In contrast to G&Y category, declining speed of eGFR was higher in patients with diabetic nephropathy than hypertensive nephrosclerosis in Red category (diabetic nephropathy, hypertensive nephrosclerosis; 5.8, 1.3 mL/min/1.73 m^2/year, respectively). In accordance with the clinical findings, pathological findings of interstitial fibrosis and cell infiltration and arteriolar hyalinosis were progressed in diabetic nephropathy in Red category.

Conclusions: Although, it is so difficult to clearly distinguish pure kidney lesions caused by diabetes and hypertension, it would be important that these overlapped pathological findings be confirmed on kidney biopsy in diabetic cases with hypertension.

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SA-PO179

The Safety and Feasibility of Obtaining Research Kidney Tissue from Patients with Diabetes: Transformative Research in Diabetic Nephropathy (TRIDENT Study)

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Background: There is a paucity of novel or specific therapeutics for diabetic kidney disease (DKD) due, in part, to its pathogenetic heterogeneity and lack of human kidney tissue for direct interrogation. TRIDENT (NCT02986984) is a multicenter consortium aimed at generating a longitudinal observational cohort study of 300 adults with diabetes and kidney tissue available for multi omics characterization of DKD. As part of the study initiation, we determined the safety and feasibility of obtaining research kidney tissue from patients undergoing clinical biopsy.

Methods: Individuals with diabetes, scheduled for clinical kidney biopsy, provided written consent to allow for an extra core of kidney tissue for research purposes. Inclusion criteria included confirmation of diabetic glomerulosclerosis, including superimposed non-DKD. A clinically significant complication was defined as a perinephric hematoma >5cm, drop in hemoglobin >2g/dl, need for transfusion or procedure to halt bleeding or anesthesia related complications leading to prolonged hospital stay.

Results: Recruitment began in JAN 2017. To date, 69 individuals (>70% of those approached) have provided written consent, 56 biopsies performed, 49 research cores obtained; 6 patients excluded due to a lack of diabetic glomerulosclerosis on biopsy. 40 participants met inclusion criteria with 18 instances of superimposed nondiabetic pathology: 12 diagnoses of GN, 2 of AIN, 2 of acute tubular injury, 1 CTIN, and 1 pyelonephritis. The mean age was 54 years (±13) and 15 (38%) were female and 13 (33%) African American. Of the 49 biopsies in which an extra core was obtained, there were 2 clinically significant complications; 1 was a hematoma >5cm and the other was respiratory distress from anesthesia-related aspiration.

Conclusions: These preliminary results indicate that it is safe and feasible to obtain research kidney tissue from patients with diabetes undergoing clinical kidney biopsy. The TRIDENT Study is positioned to generate the molecular profiles necessary to unravel the heterogenous pathways involved in DKD.

Funding: Commercial Support - Boehringer-Ingelheim, GSK, Regeneron

SA-PO180

Hyperkalemia in CKD: Can Virtual Patient Simulation Improve Management?

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Background: We sought to determine if an online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists and primary care physicians (PCPs) in the evidence-based management of chronic kidney disease (CKD)-associated hyperkalemia.

Methods: The intervention comprised two patients presenting in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments mirroring the scope and depth of actual practice. Eevidence-based clinical guidance (CG) was provided following each decision, followed by the opportunity to modify their clinical decisions. Each user's baseline (pre-CG) decisions were compared to their post-CG decisions using a 2-tailed paired t-test to determine *P* values. The CME launched online February 13, 2018, and data were collected through May 7, 2018.

Results: Case 1 (n=51 Nephrologists; n=367 PCPs): Diagnose hyperkalemia: 16% improvement among nephrologists (51% pre-CG vs 67% post-CG; P=.051), 51% improvement among PCPs (50% pre-CG vs 71% post-CG; P<.001) Continue/modify spironolactone therapy: 12% improvement among nephrologists (14% pre-CG vs 26% post-CG; P=.085), 15% improvement among PCPs (11% pre-CG vs 26% post-CG; P<.001) Order follow-up potassium test: 12% improvement among nephrologists (59% pre-CG vs 71% post-CG; P=.105), 17% improvement among PCPs (50% pre-CG vs 67% post-CG; P<.001) Prescribe a potassium binder: 22% improvement among nephrologists (16% pre-CG vs 18% post-CG; P=.395), 0% improvement among PCPs (4% pre-CG vs 4% post-CG; P=.5) Case 2 (n=34 Nephrologists; n=307 PCPs): Diagnose CKD Stage 3b: 41% improvement among nephrologists (9% pre-CG vs 50% post-CG; P<.001), 26% improvement among PCPs (17% pre-CG vs 43% post-CG; P<.001) Appropriately initiate hyperkalemia therapy: 47% improvement among nephrologists (18% pre-CG vs 67% post-CG; P<.001), 48% improvement among PCPs (7% pre-CG vs 54% post-CG; P<.001) Appropriately discontinue spironolactone: 29% improvement among nephrologists (9% pre-CG vs 38% post-CG; P=.001), 24% improvement among PCPs (30% pre-CG vs 54% post-CG; P<.001)

Conclusions: VPS that immerses and engages physicians in an authentic and practical learning experience improved evidence-based clinical decisions of both nephrologists and PCPs related to hyperkalemia management.

SA-PO181

The Electrolyte Club: A Flipped Hyponatremia Curriculum for Internal Medicine Residents to Promote Integration of Sodium and Water Physiology into Clinical Care

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Background: Decreased interest in nephrology has been linked to perceptions that nephrology encompasses complicated and poorly taught subjects. The flipped classroom has emerged as an innovative teaching approach by encouraging higher-order thinking and active participation. We examined the effectiveness and acceptability of a flipped hyponatremia curriculum for Internal Medicine Residents with the goals of improving hyponatremia knowledge and confidence in applying basic sodium and water physiology into clinical care.

Methods: Residents rotating in the renal service at UPMC Presbyterian hospital from June 2017 to May 2018 were eligible to participate. Residents were excluded if they declined to participate or were unable to either attend all sessions or undergo assessment. Residents rotated in 4-wk blocks. Residents in a given block were assigned to either a standard curriculum (SC) or a flipped curriculum (FC). Each curriculum was applied 6 times during the year. Residents in FC were required to watch 2-3 video lectures before each session. For this purpose, 10 video lectures on hyponatremia were developed using Camtasia software. FC in-class activities consisted of four 45-min sessions with a facilitator that included a clicker quiz, time for questions, and case discussions. SC consisted of two 1-h chalk talks. Residents completed a pretest, a posttest, and a 5-point Likert scale survey at the end of each curriculum. Paired sample t-test was used to compare pretest and posttest scores within each curriculum and two-sample t-test was used to compare knowledge improvement (posttest-pretest) between the two curricula.

Results: Twenty-nine residents were included in the study. There was a significant knowledge improvement after both curricula. There was no difference in knowledge improvement between FC and SC (33±15.6% vs. 31.7±14.9% respectively, P=0.79). Residents in FC rated 4.5±0.6 their confidence in applying basic sodium and water physiology into patient care, 3.9±1.1 their preference for the flipped classroom model over the traditional lecture, and 4.4±0.6 their overall satisfaction with FC.

Conclusions: FC improved residents' hyponatremia knowledge but was not superior to SC. FC improved resident confidence in applying basic sodium and water physiology into patient care. FC had a great acceptability among residents.

SA-PO182

Self-Guided Video-Based Modules to Teach Hyponatremia to Trainees: A Pilot Study

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Background: Hyponatremia is the most commonly encountered electrolyte disturbance in the hospital with an estimated prevalence up to 42%. Despite its prevalence, medical students and residents do not feel comfortable managing this condition. Hyponatremia encompasses many complex concepts in renal physiology making it a difficult topic to learn and teach. We conducted a pilot study to evaluate the impact of an online video module on learners' ability to diagnosis and manage hyponatremia.

Methods: UCSF nephrologists created a module consisting of short online videos reviewing the pathophysiology of hyponatremia coupled with self-directed high-yield cases. This module is available on the UCSF collaborative learning environment website. We asked medical students and residents rotating through the nephrology elective to complete the module over the course of an assigned two-week block. We used ten board-style multiple-choice questions as a surrogate marker of comprehension. Learners were instructed to complete the same questions before and after completion of the module. Participants also completed a short Likert-scale survey to evaluate their experience with the module.

Results: Over nine months, six medical students and one resident completed the module. Paired sample T-test was conducted to compare mean scores pre and post module.

There was a statistically significant difference between scores before (mean = 4.38, SD 1.30) and after the module (mean = 5.25, SD 1.58, t(7) = -2.81, p = 0.026). Learners reported spending between 2-8 hours on the material. Of the seven learners who completed the survey, all felt more comfortable diagnosing and proposing a treatment plan for hyponatremia after completion of the module.

Conclusions: The results suggest learners' comprehension and comfort with hyponatremia concepts and treatment plans improves after completing our online module. Survey feedback regarding the mixed video and case format was positive. Our module is an effective method to teach hyponatremia and can serve as a guide for future online educational curricula on complex renal topics.

SA-PO183

On-line vs Face-to-Face Education to Improve Dietitians' Clinical Competence in Early CKD

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Background: Adequate clinical competence (CC) of dietitians for prevention and management of early chronic kidney disease (CKD) would have an important impact to reduce the burden of ESRD. Unfortunately, this is not frequently observed, particularly in primary health-care. Online education offers advantages for continuing education; however, its effect on CC remains unclear. Aim: To compare the impact of an online *vs* face-to-face education program on dietitians' CC regarding nutritional care of early CKD

Methods: Eighty-one dietitians were included; renal dietitians or those who were currently taking any CKD training were excluded. Dietitians were included in an *online* group (N 56) or *face-to-face* group (N 25). Educative interventions were developed by a multidisciplinary team (clinical and education experts), based on constructivism paradigm and focused on nutritional aspects of prevention and management of early CKD. Education content and duration (8 weeks) of both interventions were similar; online education was asynchronic, face-to-face was performed 1 session (4h)/week. To evaluate CC, a validated questionnaire (0-120 points) measuring dietitians' capability to identify risk factors, integrate diagnosis, correctly use of nutritional therapeutic resources and identify iatrogenic behaviors, was applied at the beginning and the end of study

Results: Age, gender, work experience (yrs), and previous attendance to online courses were similar between groups. Baseline CC score was low in both groups: face-to-face 47 (41-56) *vs* online 48 (39-58), p=0.60, but increased in both of them at the end of study: face-to-face 74% (29-97, p<0.0001) and online 63% (26-91,p<0.0001); no difference in intergroup comparison was observed (p=0.57). In general, 58% of dietitians increased from low to high CC (p<0.0001). Terminal efficiency was >90% in both groups, and >90% of participants rated the interventions as good or very good

Conclusions: Online and face-to-face educative interventions were successfully developed. CC of dietitians increased similarly after both educative interventions. Online education could be useful and effective to train dietitians in prevention and management of early CKD, overcoming limitations of time, distance and costs of face-to-face education

SA-PO184

WhatsApp in Nephrology Training

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Background: We are living in an era of technology where smart phones and hence social media have entered into many aspects of our life. Novel educational means are necessary to transfer knowledge in the current era of digital learners. WhatsApp is one such application that is used by several individuals to communicate internationally. The role of this app is unknown in medical education and specifically in nephrology education.

Methods: To explore the potential of WhatsApp as an instructional strategy for nephrology fellows via asynchronous question/answer methodology. To evaluate the WhatsApp fellows educational venture, focus groups are planned with experienced qualitative researchers.

Results: All fellows in our training program-8, participated for a 6 month pilot period. 5 faculty were assigned to run the app. The faculty would ask 1-2 questions per week that were board style multiple style questions and responses were received from all 8 fellows for 90% of the questions, with explanations provided. The faculty would then provide the correct answer along with the detailed discussion and references. Dialogues and discussions would be sparked as a result of questions. There was 100% satisfaction of fellows participating in the project. The questions ranged from various topics from ESRD, acid base, AKI, glomerular diseases and transplantation. Two focus groups are being planned to better evaluate the use of the app as a pedagogical tool integrated into fellowship training. First focus group will involve the fellows and a second one will involve the faculty. Results are pending for the focus group component of the project.

Conclusions: WhatsApp is an effective social media tool to motivate, augment and perhaps improve the learning of nephrology fellows in training. Similar strategies should be evaluated in resident and medical student education of nephrology.

SA-PO185

Handheld Ultrasound Devices May Lead to a Transformation of Physical Diagnosis Practices in Much the Same Way as Laënnec's 1816 Invention of the Stethoscope

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Background: Ultrasonography is a fundamental tool for assessing kidney dysfunction and volume status in multiple settings. As new handheld devices connected to small US probes have become available, it is now more practical for students to accurately and rapidly perform kidney and volume assessments themselves at the bedside. The lack of formal kidney US training during medical school and frequent clinical difficulties in determining volume status in settings of acute kidney injury (AKI) lead to trainee incompetence with regard to kidney imaging and AKI evaluation and management. Thus, our aim was to determine whether handheld US technology helps trainees learn significant and practical nephrology content.

Methods: *For this IRB-approved project, we measured the usefulness of handheld US among medical students.* We taught basic skills for focused US examination in hospitalized settings of AKI to exclude hydronephrosis, determine kidney size and echogenicity, and assess volume status by visualizing the inferior vena cava. These interactive, educational sessions were incorporated into the University of Utah "*Transition to Internship*" clerkship for 4th-year medical students. Introductory and interactive modules described basic US physics and additional concepts to acquire and interpret kidney sonograms. Teaching sessions were then followed by an 8-hour hands-on workshop. After participating, students were given surveys consisting of questions with five-point Likert scales.

Results: Out of the 64 students that filled out survey responses, 98% indicated that the curriculum enhanced their medical education, made them feel competent to perform handheld US, and that the handheld US technique was helpful for volume assessment. All responding students indicated that handheld US improved their understanding of 3D renal anatomy. Ninety-six percent of students wanted more US incorporated into the medical curriculum.

Conclusions: Handheld US was very well-received as a valuable teaching tool among 4th-year medical students. Students were able to demonstrate proper US technique and focused interpretation with regard to kidney and volume status assessment, and nearly all indicated that the experience enhanced their education.

SA-PO186

Hemodialysis Central Venous Catheter Placement by Nephrology Fellows

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Background: There is no evidence about the number of central venous catheter (CVC) procedures required for a nephrology fellow to acquire competency, besides, these procedures are now being perform by other specialties, moving those away from the basic training of a nephrology program. Nevertheless, in low and middle-income countries, the nephrologist has a key role in CVC placement. Our main objective is to present the experience in CVC placement in a nephrology fellowship program.

Methods: During March 2017 to February 2018, six first-year nephrology fellows performed 362 procedures. We collected information about number of catheter placed by every fellow, technique (anatomic landmarks or ultrasound guidance [USG]), if it was urgent, vascular region, number, and type of complications. Then we analyzed factors related to occurrence of complications in a multivariate model adjusted for vascular region, urgency of the procedure, use of USG and the time since the beginning of the study year.

Results: The median number of procedures was 60 (range 31-90) per fellow. The overall success rate was 95.3%, with 98 (27.1%) minor and no major complications. The more prevalent complications were bleeding (40, 11%), hematoma formation (15, 4.1%), >3 punctures (25, 6.9%), and arterial punctures (17, 4.7%). In the logistic regression model, the use of USG had a trend toward to a significant association for complications (OR 0.62, CI 95% 0.38-1.00, P =0.05), while in a Cox regression the use of USG reached significance with a 48% risk reduction for complications (HR 0.52 CI 95% 0.33-0.80, P <0.01). USG use increased after 90 days of training; therefore, we analyzed the association of USG to complications considering time as a covariate. Before 90 days the presence of complications was independent to USG usage (HR 0.81 CI 95% 0.47-1.41, P=0.47), and after 90 days there were a higher risk reduction (HR 0.23 CI 95% 0.11-0.5, P <0.01).

Conclusions: The CVC placement by nephrology fellows is safe and successful; it should be part of nephrologist formation and include training on USG to reduce the risk for complications.

SA-PO187

Dialysis Catheter Placement Experience of US Adult Nephrology Fellows: A National Survey

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Background: Nephrology fellows in the United States (US) are required to acquire skills and demonstrate competency in the placement of temporary/non-tunneled hemodialysis catheter (NT-HDC) during fellowship. To gain a greater insight in the dialysis catheter placement experience of US adult nephrology fellows, we carried out a national survey of nephrology fellows.

Methods: An anonymous on-line survey was created and sent to US adult nephrology fellows via fellowship program coordinators in May 2018.

Results: So far, 113 fellows have responded to our survey. 48% were graduating in 2018. Most NT-HDCs were placed in the hospital. While 26% had not placed any femoral NT-HDC during fellowship, 28% had placed >10. 36% had placed >10 internal jugular NT-HDC during fellowship, while 28% had placed none. 34% received simulation based training, 12% received bedside training, 23% received both simulation and bedside training, while 31% did not receive any formal training in NT-HDC placement. 53% had most of their NT-HDC placements supervised by a nephrology attending. However, 49% had no nephrology attending placing NT-HDC in their institutions. 43% needed to place at least 5 NT-HDCs before independently performing this procedure during fellowship, while 16% required ≥10. While 70% reported having received adequate training in NT-HDC placement during their fellowship, only 32% planned to place NT-HDC after graduation. While 67% felt that fellowship programs should be required to train fellows in NT-HDC placement, majority (57%) felt that nephrologist should not place NT-HDC in clinical practice. Reasons cited for those who had inadequate or no training in NT-HDC included: lack of formal training (23%), lack of opportunities to place NT-HDC (23%), lack of nephrology faculty interest (20%) and lack of faculty expertise (16%). 16% had placed at least 1 tunneled HD catheter and only 1 fellow had placed 1 PD catheter during fellowship.

Conclusions: While majority of fellows report adequate training in NT-HDC placement, a significant percentage of fellow had not placed a femoral or internal jugular NT-HDC during fellowship. Majority received simulation based training, however a significant percentage did not receive any formal training in NT-HDC placement during fellowship. Fellowship programs should take measures to ensure that all fellows receive adequate training in NT-HDC placement.

SA-PO188

Journal Publications of U.S. Adult Nephrology Fellowship Training Program Directors

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Background: Publication in peer-reviewed journals can be considered as one measure of scholarly activity among academicians. Peer-reviewed journal publications (PR-JPs) of current US adult nephrology fellowship training program directors (N-TPDs) are not known.

Methods: A PubMed search for PR-JPs was conducted for a period of 3 years (2015-2018) for N-TPDs serving in academic year 2017-18. Data was abstracted in May 2018. Publications were categorized as follows: basic science research (BSR), prospective clinical study (PCS), retrospective clinical study (RCS), clinical outcomes research (COR), randomized clinical trial (RCT), meta-analysis (MA), educational research (ER), quality improvement study (QIS), case report/series (CR/S), review article (RA), editorial (E) and letter to editor (LT-E). Data was analyzed for 150 N-TPDs.

Results: 35 (23%) N-TPDs had no PR-JP in the last 3 academic years. While 33% had ≤3 publications, 31% had 4-9 publications and 12% had ≥10 publications. We identified 656 PR-JPs by N-TPDs over the past 3years, out of which 125 (19%) publications had an N-TPD as the primary author (PA), 176 (27%) had an N-TPD as a corresponding author (CA) and 96 (15%) had an N-TPD as both the primary and CA. 37% were clinical research (PCS, RCS, COR, RCT, MA) related publications. The remaining publications were as follows: RA-22%, CR/S-16%, BSR-7%, ER-6%, E-6%, LT-E-3%, and QIS-2%. While 35% of N-TPDs had at least one PR-JP as a PA over the past 3 years, 41% had at least one publication as CA and 31% had at least one as primary and CA. In the last 3 years, 83 (55%) N-TPDs had authored at least one clinical research related publication, 25 (17%) had an ER related publication, while 18 (12%) had a BSR publication. When analyzed by gender, 51 female N-TPDs had total of 247 PR-JPs with a mean of 4.8 ±5.09 in past 3 years as compared to 99 male N-TPDs who had total of 409 PR-JPs with a mean of 4.1 ±5.05. There was no statistically significant difference between both groups ($p = 0.42$).

Conclusions: Nearly one in 4 N-TPDs had no PR-JP over the last 3 years. Nearly one-third N-TPDs were primary and CA on at least one PR-JP over the last 3 years. While half of the PR-JPs were either clinical research, BSR or ER related publications, the remaining were CR/S, RA, E, LT-E, or QIS. The top 2 categories with the most publications were RA and CR/S. Female N-TPDs had more PR-JPs than male N-TPDs.

SA-PO189

Enhancing Interest and Learning in Nephrology Among US Medical Students

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Background: Interest in nephrology careers remains low among United States (US) medical graduates. The type of nephrology elective that US medical students experience may play an important role in creating and enhancing interest in nephrology career.

Methods: A redesigned 4-week nephrology elective was created at our institution for US medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of kidney donor evaluation clinic, 2 half-days of PD clinic and 3 half-days of outpatient HD rounding. Our redesigned elective also included educational conferences. To evaluate the elective experience, all medical students were asked to complete an on-line survey following the completion of their rotation.

Results: From July 2012 to February 2018, twenty-five 4th year medical students (from 15 different US medical schools) completed our redesigned elective. All students responded to our survey. All reported adequate OP nephrology experience during their elective. 80% of the students had worked with 1 or 2 faculty members during the IP setting. In comparison, 88% were exposed to at least 4 different faculty members during the OP experiences. 92% had interacted with at least 4 different fellows during the elective. All reported that the elective experience enhanced their exposure and knowledge in nephrology. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 88% of the students reported that this elective experience created an interest in nephrology career. Majority (64%) of the students responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: Measures to enhance interest and learning in nephrology among medical students are needed. We believe that the restructured elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend all nephrology training programs to consider this elective structure for medical students.

SA-PO190

Development and Preliminary Validation of a Formative Peritoneal Dialysis Objective Structured Clinical Examination

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Background: Only about 10% of incident end-stage renal disease patients beginning renal replacement therapy select peritoneal dialysis (PD) in the US. One reason may be limited PD experience during Nephrology fellowship training. Training programs often use simulation to boost experience in the absence of clinical opportunities. Structured test questions can provide this simulation, help to assess fellow knowledge in this area, and aid in determining program level practice patterns.

Methods: We devised a formative objective structured clinical examination (OSCE) focusing on the management of a PD patient with peritonitis and ultrafiltration dysfunction. After blueprint development and identification of key objectives (based on the International Society for Peritoneal Dialysis Peritonitis practice guideline), the case and the scoring rubric were constructed based on a real-life example. After review by 2 subject experts, it was evaluated by a 9-member test committee consisting of 8 board-certified nephrologists (4 academic, 4 clinical) and one experienced PD nurse. The final case consisted of 10 free response questions (total 22 points) and required written orders for PD exchanges and antibiotic management.

Results: The final OSCE was sent to two groups (test and validation committees) to determine the passing threshold. The test committee set the passing threshold using Ebel's method. The passing score was set at 16 of 22. Median relevance was essential or important for all questions with a content validity index of 91%. The validation committee (16 board-certified practicing nephrologist a median of 5 years (IQR 9) post-graduation) took the test. Mean score was 19 (SD 2). 94% of the validators passed the test and scored 85% on evidence based questions. Median time to take the test was 33 minutes (IQR 19).

Conclusions: Preliminary validation is now complete, and the next phase will involve testing of nephrology fellows who have just completed their first year of fellowship training. *Disclaimer: The views expressed are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States Government.*

Funding: Other U.S. Government Support

SA-PO191

Safety of Kidney Biopsy Performed by Nephrology Trainees vs Interventional Radiology

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Background: Kidney biopsy is the gold standard in the diagnosis and management of kidney diseases, yet most nephrology fellows are not getting adequate training in kidney biopsies. Our aim was to review kidney biopsies performed by nephrology trainees under the supervision of nephrologist with outcomes compared to interventional radiology (IR).

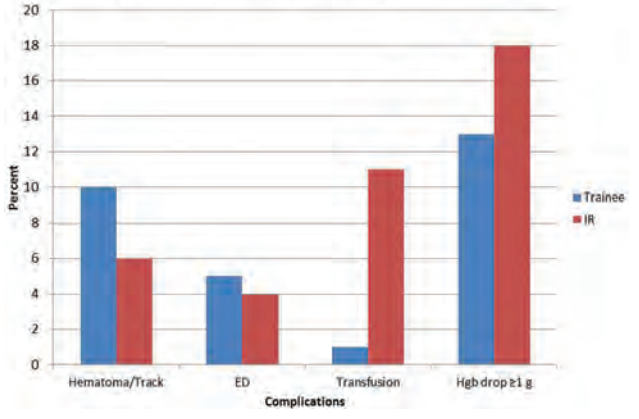
Methods: This is a retrospective cohort study of 251 patients who underwent a native kidney biopsy at Mount Sinai Hospital (MSH) and Albany Medical Center (AMC) from 2016 - 2017. Biopsies done at MSH were performed by nephrology fellows under nephrology supervision while those done at AMC were done by IR.

Results: There were 251 patients who underwent kidney biopsy; mean age was 51 ± 16 years, 52% were male, and 60% were done by nephrology fellows. The most frequent indication for biopsy was non-nephrotic range proteinuria, 83 (33.2%). ddAVP was given in15 of biopsies performed by nephrology trainees and 1 of biopsies performed by IR; there was no difference in BUN between the MSH or AMC cohorts (40±24 mg/dL vs 37±27 mg/dL respectively, P=0.24). Diagnostic yield (≥11 glomeruli) did not differ by operator, trainee 89% vs. IR 94%, p=0.14. There was no difference in hematoma or track formation by proceduralist (IR 6% vs. trainee 10%, p=0.1) or for ED visits for outpatient biopsies (IR 4% vs trainee 4%). Transfusions were higher in those performed by IR (11% vs. 1%, P<0.001). Mean change in hemoglobin while not statistically different was clinically meaningful (trainee 0.2±0.7 g/dL vs. IR 1.6±10.7, P=0.1) After adjustment for patient and biopsy characteristics, prebiopsy hemoglobin but not proceduralist type was a significantly associated with higher odds of 1gm drop in hemoglobin, (adjusted odds ratio 1.4, 95% CI 1.1 – 1.7).

Conclusions: Nephrology trainees can safely perform kidney biopsies with similar diagnostic yield and complication rates.

Funding: NIDDK Support

Figure 1: Complication rates of kidney biopsy by proceduralist



SA-PO192

Viability and Fidelity of Low-Cost Gelatin Percutaneous Renal Biopsy Phantom in Simulation Training

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Background: Percutaneous renal biopsies are crucial for the accurate diagnosis and prognosis of many renal diseases. Most trainees learn this procedure directly on patients, despite its risks. Commercially available phantoms are available for simulation training, but they are expensive and have a limited number of needling attempts. We developed and evaluated an inexpensive kidney biopsy phantom created using ingredients available in most grocery stores.

Methods: The renal biopsy phantom was constructed by inserting a weighted porcine kidney into a gelatinous solution consisting of a mixture of unflavored gelatin, sugar-free psyllium hydrophilic mucilloid fiber (Metamucil), and boiling water. The phantom was refrigerated to allow the gelatin to solidify before use. We evaluated this phantom during three separate 1-hour workshops attended by a combination of nephrologists, nephrology fellows, and radiology and internal medicine residents. Each workshop consisted of a 10-minute didactic demonstration on how to perform ultrasound-guided renal biopsies. The participants then had the opportunity to perform simulated ultrasound-guided biopsies on 1) the gelatin-phantom, and 2) a commercially available phantom (cost ~ $4000 USD). Participants evaluated the workshop and the phantoms using anonymous surveys. Data were analyzed using descriptive statistics and two sample t-tests.

Results: A reproducible gelatin phantom was engineered with a material cost under $20 USD. 39 individuals participated in the 3 workshops and completed the surveys. Most participants agreed that kidney biopsy simulations are helpful in training residents, and found the workshop effective. The gelatin and commercial phantoms were rated similarly over a number of characteristics, including size, consistency and sonographic changes with multiple needling. Overall, the gelatin phantom was considered superior by 80% of participants. Participants commented: "Great session!", and "Gelatin phantom is a brilliant simulation tool. It is cheap and you can make new models as needed for tracks".

Conclusions: We were able to construct an inexpensive and easily reproducible gelatin-based renal biopsy phantom. Our phantom was non-inferior to a more expensive commercial counterpart.

SA-PO193

Identifying and Integrating Patient and Caregiver Perspectives in Clinical Practice Guidelines for Percutaneous Renal Biopsy

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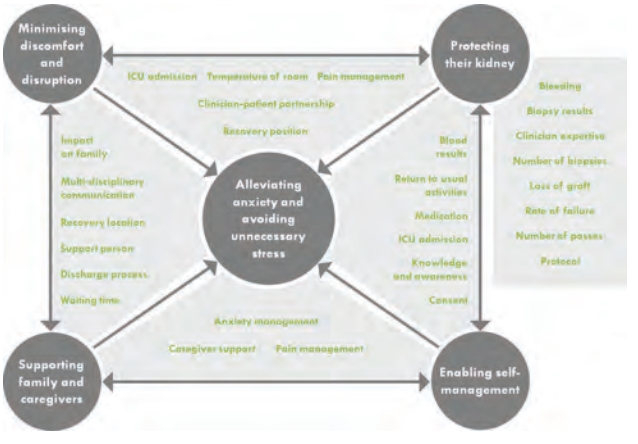
Background: Percutaneous renal biopsy is often essential for providing reliable diagnostic and prognostic information for people with suspected kidney disease, however the procedure can lead to complications and concerns among patients. This study aims to identify and integrate patient priorities and perspectives into the Kidney Health Australia – Caring for Australasians with Renal Impairment clinical practice guidelines for renal biopsy, to ensure patient-relevance.

Methods: We convened a workshop, consisting of three simultaneous focus groups and a plenary session, with ten patients who had undergone a renal biopsy and seven caregivers. Topics and outcomes prioritized by patients and their caregivers were compared to those identified by the guideline working group, which was comprised of seven nephrologists. Transcripts and flipcharts were analyzed thematically to identify the reasons for participants' choices.

Results: In total, 34 topics/outcomes were identified, 14 of which were common to the list of 28 previously identified by the guideline working group. Most of the new topics identified by patients/caregivers were related to communication and education, psychosocial support, and self-management. We identified five themes underpinning the reasons for topic and outcome selection: alleviating anxiety and unnecessary distress, minimizing discomfort and disruption, supporting family and caregivers, enabling self-management, and protecting their kidney. A new topic on patient care and education was added to the guideline as a result.

Conclusions: Patient and caregiver involvement in developing guidelines on renal biopsy ensured that their concerns and needs for education, psychosocial support, and self-management were explicitly addressed; enabling a patient-centred approach to renal biopsies.

Funding: Government Support - Non-U.S.



SA-PO194

Breaking Bad News: A 2 Year, Multi-Center Simulation Exercise Assessing Renal Replacement Therapy and Kidney Biopsy Communication Skills

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Background: There are few quantitative, simulation-based assessments for nephrology-specific interpersonal communication skills (ICS) and professionalism (PROF) milestones. We developed a "Breaking Bad News" simulation to assess fellow counseling competence in 3 scenarios: a surrogate decision maker for acute renal replacement therapy (RRT), a patient with end stage kidney disease for RRT, and a patient with glomerulonephritis for kidney biopsy.

Methods: After reviewing a clinical summary, fellows counsel each of the 3 simulated patients (SPs) who have received a summary of their character's medical and social situation. Faculty were instructed on the scenarios, use of the Mini-CEx, and the information provided to fellows and SPs. Fellow performance was assessed using 2 previously validated tools: the Mini-Clinical Examination Exercise (Mini-CEx) and the Essential Elements of Communication-Global Rating Scale 2005 (EEC-GRS). Both have a 1-5 rating scale with scores of 3 or greater being satisfactory. SPs rate fellow ICS and PROF using the EEC-GRS, and nephrology faculty, observing from outside of the room, use the Mini-CEx to evaluate medical knowledge and ICS. Fellows receive 5 minutes on-the-spot performance feedback at the end of each 15 minute scenario from both SP and faculty.

Results: 56 fellows completed the OSCE. The 2017 administration included 26 fellows (5 training programs), and the ongoing 2018 administration included 30 fellows (6 of a total 8 programs). EEC-GRS scores were not significantly different between first and second year fellows (p=0.27). No significant difference was found between training years when comparing any EEC-GRS score <3 or any Mini-CEx score <3. Only 13% of fellows scored <3 on any item in the chronic dialysis counseling Mini-CEx, while 45% and 43% respectively scored <3 on at least one item on the acute RRT counseling and kidney biopsy scenarios.

Conclusions: Overall, fellows communicate well and professionally with high ratings on EEC-GRS. Fellows counsel patients well on chronic RRT but had deficiencies in counseling on risks of acute RRT and kidney biopsy. The results allow program directors to adjust curriculum and provide quantitative assessment of ACGME milestones progress.

Funding: Other U.S. Government Support

SA-PO195

Differing Expectations of Transitions of Care Within a Nephrology Practice: Should We Transition to Train More?

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Background: Ineffective transitions of care (TOC) communication is a major contributing factor to medical errors.

Methods: As part of an endeavor to standardize TOC practice in our division, we conducted a two-step survey-based study of TOC perceptions among faculty and fellows over the last one year. Data was collected anonymously via two different electronic surveys. The first (Survey1) focused on providers' perceptions of the TOC practice in the division. The second (Survey2) asked for a self-assessment about providers' own TOC procedure. Fisher's exact test was used for statistical analysis of the survey results.

Results: Attendings were significantly less satisfied with the current division TOC practice as compared to fellows (table). Both attendings and fellows appeared equally satisfied with their own TOC methods. APP response fell between physician and fellow responses for most questions. Most faculty (71%) and fellow (66.7%) responses indicated they would prefer changes in current TOC practice.

Conclusions: Our results reveal a gap between TOC expectations and self-reflection amongst faculty and fellows in one division. This may reflect a lack of formal training to align expectations in TOC practice. The general acceptance of the division TOC environment by fellows likely stems from the fact that the majority of TOC documentation is done by this group. Overall, most providers were interested in changes to improve TOC practices. We plan on step-wise changes including instituting a standardized division TOC policy, EMR support, formal training in TOC, and continuing assessment of TOC practice and environment in the division.

	Physician (%)	Advanced Practice Provider (APP; %)	Fellow (%)	P-value
Survey1 respondents	75% (12/16)	75% (6/8)	83.3% (5/6)	
Always satisfied with weekend call sign-out received ?	0% (0/9)	NA	100% (5/5)	<.001
Mostly satisfied with weekend call sign-out received ?	55.6% (5/9)	NA	NA	NA
Felt patient safety compromised due to lack of appropriate TOC ?	41.75% (5/12)	33.3% (2/6)	0% (0/5)	0.298
I have adequate time to provide sign-out ?	83.3 % [10/12]	100% (5/5)	80% (4/5)	1.000
TOC is always valued in our Division ?	16.7% (2/12)	0% (0/6)	100% (5/5)	<.001
Survey2 respondents	81.3% (13/16)	77.8% (7/9)	67% (4/6)	
I am always satisfied with the sign-outs that I provide	23% (3/13)	0% (0/7)	50% (2/4)	0.376
I am mostly satisfied with the sign-outs that I provide	61.5% (8/13)	85% (6/7)	25% (1/4)	0.142
The details in the sign-outs I provide are the right amount	76.9% (10/13)	71.4% (5/7)	75% (3/4)	1.000
The sign-out I provide is always up to date	61.5% (8/13)	57% (4/7)	25% (1/4)	0.468

SA-PO196

Leveraging the Internet to Showcase Abstracts and ePosters: Online Engagement at a National Meeting

Vijay Lapsia, Joseph A. Vassalotti. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Scientific posters are traditionally printed and presented on site to interactively share research findings. However, this format is limiting, particularly with digital media and archival that allows for review of posters by attendees virtually after the meeting is over. It is unknown if hosting abstracts and posters online can improve access and enhance engagement.

Methods: Authors of accepted abstracts for National Kidney Foundation's 2018 Spring Clinical Meetings were invited to upload posters in an online gallery displaying abstracts, posters and supplementary media. As a part of the submission, authors completed a brief survey. Web analytics software tools were embedded to measure audience engagement and usage during and after the meeting. Categorical data from the survey and audience data from web analytics were analyzed for frequency & descriptive statistics and usage trends.

Results: A total of 458 abstracts with 254 supplementary media files were submitted for consideration, 365 of which were accepted for publication and currently displayed at https://nkf2018scm.site online. Almost all authors gave permission to publish the poster online (96.7%) and a little over half (58.6%) uploaded posters to the online gallery. The survey response rate was 35.2%. Top features that users recommended included the ability to connect with other authors (73.2%), comment and save gallery items (68%), ability to view the gallery as well as media files including video and images on smartphones (64.6%) and integration with social media to share submissions (52.7%). Audience analytics revealed 2,114 users from 59 countries accessed the gallery within 30 days of the meeting, 1,190 of which came online during the 4 day meeting. Users were predmoninatly from the USA (78.04%), more than half (55.95%) used a mobile device, with 78.5% on iOS devices and 30.2% using the chrome browser. Peak gallery usage coincided with the first two days of the meeting with late morning and early evening being the busiest hours. Notable referral sources included stocktwits.com a social media platform for investors (98 referrals), medical news sites and pharma company intranets.

Conclusions: Hosting abstracts, posters and supplementary media in an online gallery can extend and enhance engagement during and after the meeting. Access to the gallery on mobile devices may be key to improving usage.

SA-PO197

Use of a Standardized Curriculum to Increase Resident Interest in Nephrology

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Background: Interest in nephrology fellowship continues to be low among current internal medicine residents. While there are many reasons for this decline, several studies have suggested that residents develop negative perceptions of the field during their training. Given that most residents only spend a little time during their training working with the nephrology service, it is possible that they have minimal exposure to areas such as transplant, nephropathology, critical care nephrology, and interventional nephrology. This quality improvement project aims to increase resident interest in nephrology by implementing a curriculum for residents rotating on the nephrology consult service, increasing exposure to different aspects of the field, and facilitating mentorship. At our institution, residents have an opportunity to rotate through with the nephrology inpatient consult service during elective time. Currently, there are no guidelines for the residents while on the nephrology elective; they generally see 1-2 consults per day with guidance from a fellow or attending. Without any recommended guidelines, many residents finish their elective with no exposure to the breadth of the field.

Methods: A preliminary ten question survey was sent to the internal medicine residents. This survey was simple, with yes or no questions, determining what residents had exposure to during their elective. The final question assessed their interest in nephrology. Based on these findings, a curriculum was given to residents at the beginning of their rotation. Every six months, the survey will be resent and the curriculum revised based on the findings.

Results: A majority of residents received basic didactic lectures for topics such as acute kidney injury and fluids/electrolytes. But, most did not have exposure to dialysis catheter placement or renal biopsies, had no bedside teaching regarding how dialysis or CRRT machines work, and did not review renal pathology with the in-house renal pathologists. These are among the regular activities performed at our institution.

Conclusions: Without any guidelines, the survey confirmed that many residents were missing out on unique opportunities in nephrology. While the project is ongoing with changes to come, the preliminary findings suggest that a standardized curriculum with focus on mentorship can potentially improve resident experiences in our field.

SA-PO198

Keeping It Renal: Grassroots Effort to Increase Local Interest in Nephrology

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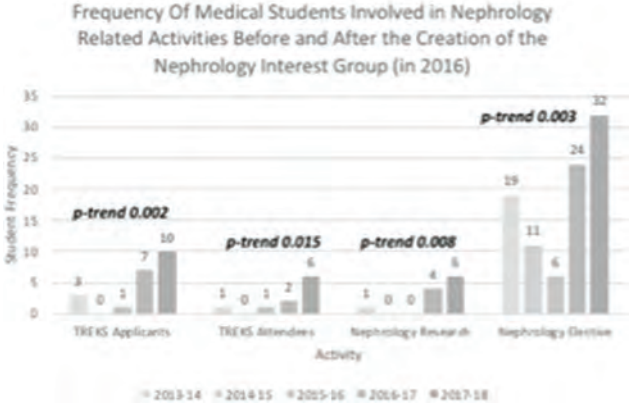
Background: National efforts have been made to increase medical student interest in nephrology through ASN sponsored programs like TREKS and STARS. Our goal was to create a local effort at University of Wisconsin (UW) to publicize nephrology as a career option for medical students to improve recruitment to nephrology.

Methods: As a result of curricular tranformation at UW in 2016, renal pathophysiology was taught during the first months of medical school with students learning about complex renal diseases early in their career with a more hands-on, case-based approach. This early exposure provided the opportunity to create a forum where students with an interest in nephrology could come together with nephrology faculty and explore the options of the field. As a result, the students created the nephrology interest group (N-IG). We describe the early experience of this, and analyze trends in involvement in nephrology-related activities.

Results: The N-IG hosts three events during the year: 1. Discussing different career trajectories in nephrology by faculty in various roles, 2. "Night with Nephrology", which was a jeopardy style game with a combination of trivia and nephrology questions and 3. Discussing interesting cases in nephrology with faculty to apply pathophysiology to patient care. By highlighting the cognitively stimulating and diverse nature of nephrology, we were able to increase the number of students spending dedicated time in nephrology related activities, most of them showing a statistically signifcant trend by year (Figure 1)

Conclusions: At our institution, a student led nephrology interest group was effective in increasing recruitment to nephrology related experiences. Similar interest groups can be created at other institutions by early nephrology involvement in the medical school curriculum, harnessing the energy of enthusiastic students, and utilizing support of nephrology faculty. Long-term follow up will determine if this involvement is fruitful for recruitment into the field.



SA-PO199

Targeted Primary Prevention Pilot for High School Students Living in High-Risk Areas for ESRD

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Background: Development of chronic kidney disease (CKD) risk factors depends heavily on behaviors learned early in life. There is a paucity of research examining ways to improve youth health behavior and education to prevent later development of CKD.

Methods: A Health and Wellness community-based program partnered with clinicians and educators at one academic medical center to develop a kidney education module. This module was delivered by two kidney doctors to 11th grade students at an urban high school in Detroit, Michigan. The 1.5 hour kidney education module included didactic and hands-on exercises that were literacy-sensitive and introduced students to kidney anatomy, physiology, and function as well as risk factors for CKD and health behaviors needed to prevent it. Pilot aims were to; 1. Examine feasibility of delivering the kidney education module to high-school science classes, and 2. Determine student perceptions about the usefulness of the kidney education module.

Results: Thirty-seven students and one science teacher received the kidney education module in March 2016. Thirty-six students filled out voluntary surveys consisting of six questions asking about their perceptions of the kidney education module. All students (n=36, 100%) were of African American race and in the 11th grade. One-hundred percent (n=36) said the kidney education was personally helpful and that they learned "a good amount / a lot". Forty-four percent (16 students) reported knowing someone afflicted by kidney disease. The majority said the kidney education module would be helpful for future students (n=34, 94%), and that they would share what they learned with family (n=24, 67%) and friends (n=22, 61%). The program was repeated in Spring of 2017, and is now incorporated into the standard curriculum -- taught annually by the high school science teacher.

Conclusions: This pilot offers a promising model for educating and empowering youth to learn about chronic kidney disease and its prevention. Feasibility was supported in rapid uptake and adoption at the school. Student perceptions were overwhelmingly positive. There may be secondary gains when students share what they learned with family / friends. Next steps include adapting the program for other schools and examining its impact on behaviors, knowledge and clinical indices over time.

Funding: NIDDK Support

SA-PO200

Improving Health Behavior and Supporting Kidney Health Literacy in Kids to Prevent Kidney Disease

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Background: The majority of chronic kidney disease (CKD) is preventable and largely depends on health knowledge and behaviors acquired early in life. There is a paucity of research examining ways to improve youth health behavior and education to prevent CKD.

Methods: The objective of this study was to pilot test a literacy-sensitive kidney education module to support healthy behavior and reduce long-term modifiable risk factors for kidney disease in youth located in two middle schools; one within the city of Detroit, Michigan. The other, in a suburb outside of Detroit. The kidney education module included 3 kidney health lesson plans delivered to 6th and 7th-grade students by their science teachers during science class. Content was didactic and hands-on, and included education on kidney structure, function and behaviors needed to reduce risk for CKD. We assessed feasibility of and fidelity to the kidney education module by direct observation, and elicited student and teacher perspectives about the program using standardized surveys.

Results: One-hundred and ninety-one (n=191) students received the kidney education module; 53% were located in the Detroit-based middle school and 47% in the outlying suburb. Collective demographics were: 28% African American, 50% female, 33% Hispanic or Latino, 12% Asian, and < 10% other / combined races. Science teachers (n=3) exhibited high fidelity with 100% completion of all 3 lesson plans at both middle schools. Eighty-five percent of students said they learned "a good amount / a lot"; 76% thought the kidney education would be helpful for other students; 51% shared what they learned with family or friends; and 65% said they were interested in receiving more science lessons about other body systems. Teachers and students reported an increase in knowledge about the kidneys and kidney disease. Next steps will include assessment of long-term knowledge gains and intent for behavior change in students over time.

Conclusions: Our kidney education module was feasible to implement seamlessly into two diverse middle school science curriculums. Both teachers and students reported immediate knowledge gains. Students rated the program very favorably. Future work will examine associations between the kidney education module and additional psychosocial, behavioral and clinical indices in students over time.

Funding: NIDDK Support

SA-PO201

Raising Awareness on AKI: A Latin American Experience

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Background: Raising awareness on acute kidney injury (AKI) is an essential strategy for minimizing the burden of this lethal syndrome, and so the AKI Commission of the Latin American Society of Nephrology and Hypertension carried out an educational program based on network learning.

Methods: Two online courses with similar methodology were done, one for nephrologists and the other for primary care physicians (PCP). The courses were developed as a distance education, asynchronous online modality with multiple educational strategies: readings, videos, e-rounds and clinical simulation. Knowledge gain was explored through a 10-question test before and after completing the course.

Results: Course for Nephrologist: 779 participants from 21 countries; 52% male; 46% under 35 yrs. Mean qualification increased from 5.87 to 8.01 (36% gain of knowledge). Course for PCP: 2011 participants, 81% of whom physicians. Time from graduation <5 years in 52%. In both courses, clinical simulation was considered the best part and lack of time the main limitation for learning. Because 48% of attendees of the nephrologists' course stated their will to participate in AKI activities, a Latin American AKI Network site (RedIRA) composed by a brief review, a clinical forum, a self-assessment and a

bibliography on AKI was launched on a monthly basis on November 2016. To date there are 335 users from 18 countries.

Conclusions: Distance education techniques were effective for learning about AKI, and are a potential tool for the development of a sustainable structure for communication, exchange and integration of physicians involved in the care of patients with AKI.

Funding: Private Foundation Support

Comparative table of course's feaures

	Nephrologists	Primary care physicians
Study workload/duration	30 hours/2 months	14 hours/1 month
Participants	779	2011
Countries	24	27
Access	For a fee	Free
Number of entries to texts	19289	7162
Number of entries to videos	21384	13197
Gain of knowledge	36.5%	N/A
Evaluation good/very good	94%	97%
The best	Clinical simulation	Educational design
The worse	Nothing in particular 65%	Nothing in particular 64%
Main limitation for learning	Lack of time	Lack of time

SA-PO202

Will the Nephrologist See You Now? Results from the ASN/ERA-EDTA/ISN Global Nephrology Workforce Survey

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Background: In low- and middle-income countries, concerns exist about nephrology workforce adequacy to meet population needs; and in high-income regions, concerns exist about declining interest in nephrology among trainees. ASN, ERA-EDTA, and ISN initiated a joint project to determine how kidney care delivery trends may affect future workforce demands by quantifying variation in nephrology scope of practice at the country- and region-specific level.

Methods: A survey was designed to capture national kidney health delivery measures, including nephrology training/certification and scope of practice; number of nephrologists/country; and range of kidney care provided by nephrologists, other physicians, and extenders. Given the global audience, the tool was translated and adapted to several formats before being distributed to leaders of national nephrology or medical societies in 167 countries.

Results: Sixty-eight countries (41%) have responded. There was little variation between regions in the scope of nephrology practice, with nephrologists the primary physicians for most key kidney health services/therapeutic areas (Fig 1 left). Yet ~50% noted nephrologists were not the primary physician for CKD stages 1–3 and hypertension. Nephrologists commonly prescribe biopsies (98%) yet are less likely to perform them (71%) (Fig 1 right). Stratified by region, Europe demonstrated the most intra- and interregional variability in scope of practice (e.g., 42% of European respondents reported nephrologists were primarily responsible for CRRT vs. 64% globally). A majority (60%) required nephrologists to be present in the dialysis facility, and many nephrologists rounded each dialysis session (hospitals, 50%; other facilities, 41%).

Conclusions: The *Global Nephrology Workforce Survey* found less interregional, but substantial intraregional, variation in the scope of kidney health services provided by nephrologists. A complete analysis of kidney health delivery trends will be translated to help assess nephrology workforce demands and inform regional efforts to ensure patients receive consistent, high-quality care.

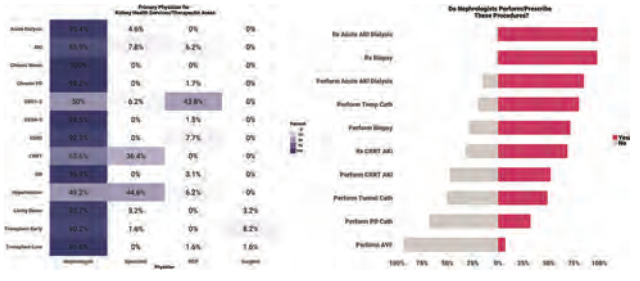

Fig 1

SA-PO203

The 2018 NKF Survey of Nephrology Advanced Practitioners

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Background: For the last 10 years, NKF has administered a biannual online survey open to all nephrology APs asking about demographics, scope of practice, working experience and benefits. We describe the survey process and key findings from the most recent survey administered in early 2018.

Methods: A *Survey Monkey* link was sent to all nephrology APs (PAs, NPs, CNS) belonging to NKF's Council of APs. Respondents were encouraged to share the survey link with any nephrology AP, NKF member or not. The survey was open from 1/18-4/18 with monthly reminders & a push for responses at Spring Clinical Meetings. Response rate was 64%.

Results: Survey responses included 47 states and DC, with the most results from TX, OH, NC, GA and IL (18,16,14,13,13 respectively). The 2018 survey indicated an increase in minority representation among APs & a shift towards a younger workforce. HD management has been, and continues to be, a major activity of nephrology APs with 86% involved. Among APs reporting HD management, 82% conducted MCP visits. The average number of HD patients/wk is 50-100, a decrease from previous surveys. The average number of HD units/wk is 2-3 & 1-2 hours/wk driving. Office/Clinic duties were reported by 71% of the respondents with CKD clinic & emergent appointments (hospital discharge/ESRD/AKI work-ins) common. Teaching (patients, APs, RNs, staff) was reported by 54% of respondents, while 23% of respondents saw PD patients; mainly in PD clinic. 47% of respondents see patients in the hospital, with the majority seeing consults and inpatient rounds. More APs report taking call (HD/PD, hospital and office) although the majority report no after-hours call. Average salaries increased to $106,000/yr with PAs earning more than NPs. This was the 10th year in a row of salary increases, although the rate of increase has decreased. Most common benefits include CME, malpractice, retirement and health insurance.

Conclusions: The NKF survey includes a detailed overview of the nephrology AP workforce in the United States. While the nephrology AP job description has changed slightly over time, with more time spent on call, outpatient dialysis remains an important area of AP involvement and APs continue to work in hospitals, office/clinic and are involved in education. It will be important to continue monitoring the evolution of the role of APs in nephrology, as they continue to complement the needs of the nephrologist and increase income to the practice.

Funding: Private Foundation Support

SA-PO204

A Biopsy of the Nephrology Workforce in a Low-Middle Income Country: The Guatemalan Example

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Background: Chronic kidney disease (CKD) is an increasing global health concern, with increasing prevalence in low to middle income countries. The availability of nephrologists is integral to providing care to a large population of CKD patients. In this study, we describe and characterize the nephrology workforce in Guatemala.

Methods: Using the National Registry of Nephrologists, we divided practices by private settings, academic settings, or those in both settings. We reported the number of nephrologists per million inhabitants using data from the Guatemalan Institute of Statistics. We also determined the area of practice (urban or rural), and characterized practitioners based on the country of training. Lastly, we determined the number of fellowship positions available in Guatemala.

Results: We note a total of 72 nephrologists in Guatemala, of which 64 were adult nephrologists and 8 were pediatric nephrologists. This represents 4.9 nephrologists per million inhabitants. 68% of nephrologists practice in Guatemala City (urban area), while 32% practice in rural areas. Overall, 64% work in private settings, 6.25% in academics, and 30% in both settings. 74% trained in Guatemala, while 26% trained abroad. The workforce is 73% male. There are two adult and one pediatric nephrology fellowship training programs in Guatemala and all are located in Guatemala City (urban area). Currently, there are a total of 14 fellows in training of which 13 are adult nephrology fellows and 1 is pediatric nephrology fellow.

Conclusions: In Guatemala, there are only 4.9 nephrologists per million people. The majority of nephrologists are male and were trained in Guatemala. Most nephrologists work in private settings, and only one-third practice in a rural area. There are three nephrology programs in Guatemala. We still have room for improvement. Based on these results, we should focus in increasing educational opportunities, create incentives to increase the number of nephrologist practicing in rural areas, open more opportunities for female physicians, increase the number of nephrology fellowship training programs in rural areas and create incentives for physicians interested in academic medicine to increase the number of nephrologist practicing in academic settings.

SA-PO205

Teaching Communications Skills in Nephrology Utilizing Sociodrama

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Background: Although conversations between patients and nephrologists regarding chronic kidney disease (CKD) prognosis are associated with improved patient care and decreased surrogate burden, they reportedly occur infrequently. Most Nephrology training programs lack dedicated communication skills training (CST), and graduating fellows feel unprepared for these difficult conversations. Simulated conversations using standardized patients are effective in CST but are costly, and it is difficult to find and train committed actors. Alternatively, incorporating sociodrama techniques have been successful in Oncology CST. Sociodrama involves group members enacting social situations guided by a facilitator using techniques (primarily role-play, role reversal, and doubling--revealing unspoken thoughts and feelings) to enhance learning.

Methods: We developed a one-day, sociodramatic, facilitator-led nephrology CST workshop. Workshops began with warm-up exercises to reduce anxiety and promote participation. Learners are then guided in enacting the clinical scenarios they find most challenging. Key communication skills are taught during these role-plays. Topics included giving bad news, discussing prognosis, eliciting goals of care, and addressing family concerns. Strategies included were giving information and assessing understanding as well as responding to emotion with empathic statements (e.g. 'tell me more", and 'I wish' statements). Participants were asked to complete surveys anonymously after the workshop.

Results: 24 surveys (18 trainees and 6 faculty) were collected in 2017 and 2018. Although 42% of participants were apprehensive of sociodramatic enactments, only 17% had some difficulty. 100% of responses indicated that sociodrama enhanced learning and 92% indicated plans to incorporate learned skills into practice with 75% interested in further CST. Participants also indicated the day-long session to be lengthy.

Conclusions: Teaching communication skills in nephrology utilizing sociodrama is feasible, effective, and economical. Most participants found the workshop effective and intended to incorporate learned skills into practice. Follow-up surveys are needed to determine whether participants have used learned skills. Incorporating CST in an abridged format intermittently in the context of fellowship training may further increase the impact of this training.

SA-PO206

Using Social Media to Augment Traditional Medical Education Delivery During Inpatient Rotations

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Background: Social media in medicine has the potential to encourage lifelong learning. Medical students and residents frequently use social media for a variety of purposes. We devised a pilot project to assess to utility of using social media to deliver medical education to trainees during inpatient rotations.

Methods: Two online tools (Twitter question polls and YouTube videos) created by an internal medicine resident were utilized to deliver educational content during a month-long inpatient rotation, including nephrology ward rotation. Medical students and internal medicine residents were notified about these teaching tools via website and by direct email. Twitter was used to post a one question poll for 5 days on important topics in nephrology relevant to inpatient nephrology. Trainees answered questions online and received a 5-10 minutes lecture about the topic on the following day. Short animation videos (2-3 minutes) were made on clinical trials about contrast induced acute kidney injury by the internal medicine resident, and posted on YouTube (https://youtu.be/DoOQ5-xFcvc). An anonymous electronic survey was conducted regarding trainees' educational experience after two months.

Results: From the total of 73 responses, 81% completed the survey: 26% interns, 55% residents and 19% medical students. 37% were women. Over a month, two videos received 290 combined views. Overall, 90% reported watching the online videos less than 3 times, 7% 3-5 times and the remaining more than 5 times. On their educational experience; 73% rated it as "very educational", 23%"somewhat educational" and only 4% as "minimal educational value". In addition, 63% of respondents believed the videos were extremely helpful to remember the clinical trial results and 97% of respondents said they would watch any upcoming videos, and would be keen to participate again in the online questions on Twitter.

Conclusions: Social media tools such as Twitter and YouTube can augment traditional content delivery to enhance the learners experience. These tools can be effectively deployed on inpatient rotations. Implementing innovative tools such as social media, can improve the educational experience for trainees.

SA-PO207

Landmark Nephrology: A Multi-faceted Interactive Tool Showcasing the Classic Trials in Nephrology

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Background: Nephrology has a long history of truly landmark clinical studies that have helped guide our clinical practice and make it evidence-based. To recognize the genesis of our current guidelines, it is critical to be familiar with the clinical studies that inform our current practice. Highlighting these studies also demonstrate the advances this field has made and motivates developing nephrologists to participate in clinical research. We took on the challenge of showcasing these landmark studies in nephrology in a way that is interactive, fun and useful.

Methods: We formed a committee of nephrology fellows and faculty from multiple major academic centers across US. A list of topics in clinical nephrology was developed and landmark clinical studies within each topic were selected, based on the relevance of these studies to current nephrology practice. Using these topic areas and leveraging concepts in adult learning, we created narrated short videos, visual abstracts, question banks, quizzes and games.

Results: We have developed a portal **landmarknephrology.com** which has free and easily accessible content on landmark clinical trials. Eight content areas are currently represented, ranging from peritoneal dialysis adequacy to steroids in IgA nephropathy. Another 12 topics are in production. The distribution of this content is via the website, and social media including YouTube and Twitter. The website also provides options for nephrology educators to easily identify the landmark studies and download material to create stimulating classroom lectures.

Conclusions: Landmark Nephrology provides a portal for trainees and practicing nephrologists to learn about evidence based practice in nephrology and challenge their knowledge about clinical trials in the field. It is a passionate effort to find new, exciting ways to showcase nephrology's track record of producing truly landmark clinical studies and motivate the next generation of renal clinicians and scientists.

Website Homepage

SA-PO208

Renal-Limited TMA (Thrombotic Microangiopathy) in Patients with HSCT (Hematopoietic Stem Cell Transplant): An Endothelial Variant of Graft vs Host Disease (GVHD)

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Introduction: Thrombotic microangiopathy (TMA) and graft versus host disease (GVHD) are well-recognized complications of hematopoietic stem cell transplantation (HSCT). TMA in HSCT (TA-TMA) is characterized by endothelial injury triggered by chemo-radiotherapy, infections or immunosuppressive drugs. Recent data suggests that GVHD itself may be a trigger of TA-TMA. We report 2 cases where GVHD in HSCT was associated with renal-limited TMA.

Case Description: A 58-year-old female with history of HSCT one year ago, was admitted with sub-acute acute kidney injury (AKI), worsening hypertension (HTN), nephrotic range proteinuria and anemia. Patient was on cyclosporine treatment for gastrointestinal GVHD at the time of admission. During the hospitalization, cyclosporine was discontinued. However, kidney function continued to worsen and she eventually required dialysis. A kidney biopsy confirmed acute on chronic TMA with minimal fibrosis. She received 2 doses of rituximab which led to the resolution of her AKI over 6 weeks. The patient eventually died due to sepsis. Our other patient, a 58-year-old-female with a second HSCT on tacrolimus therapy for skin GVHD, developed AKI 1 year after transplant along with worsening HTN, new onset proteinuria, and anemia. Her SCr worsened from 1.1mg/dl to 3.8mg/dl despite discontinuation of tacrolimus. A kidney biopsy revealed chronic TMA, with tubular reticular inclusion bodies (TRIs) without any viral etiology demonstrable by serology or immunohistochemistry.

Discussion: A relationship between GVHD and TA-TMA has been previously described but was confounded by calcineurin inhibitor use, infections, heterogeneous study populations, and retrospective study designs. Our findings suggest a possible link between GVHD and TA-TMA since both our patients presented with active GVHD in another organ concomitant with renal HSCT-TMA. Our first patient's gastrointestinal GVHD and TA-TMA improved following anti-B cell therapy (rituximab). Our second patient showed evidence of a high interferon state (TRIs) in the kidney which is also seen in GVHD. Our findings suggest that TA-TMA represents a form of "renal GVHD" or "endothelial GVHD". However, more research is needed to understand the exact mechanism of development of GVHD associated TA-TMA.

SA-PO209

Influenza Triggered Thrombotic Microangiopathy

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Introduction: Thrombotic microangiopathy(TMA) is a clinical entity characterized by intravascular microangiopathic hemolytic anemia, thrombocytopenia and acute kidney

injury. Influenza virus triggered TMA(iTMA) has been rarely reported. Paucity in literature of this clinical entity prompted this report of iTMA. With this report we would like to highlight the importance of understanding other potential causes of TMA in a patient on proteasome inhibitor, also known to cause TMA.

Case Description: A 69 year old lady with diabetes mellitus, hypertension, chronic kidney disease and multiple myeloma on chemotherapy, presented with fever, weakness, shortness of breath and cough for past one day. She received her 14th cycle of carfilzomib and dexamethasone, two days prior to presentation. Her blood pressure was 188/98 mm Hg. Laboratory testing showed creatinine at baseline of 2.2 mg/dl but revealed positive Influenza A. She was admitted for hypertensive urgency and sepsis due to influenza. She was started on Osteltamivir and cancer chemotherapy was held. On day 4 of admission, nephrology was consulted for elevated creatinine of 3.18 mg/dl. Despite volume resuscitation her creatinine continued to rise to 6.88 mg/dl. Further evaluation showed that her hemoglobin drop to 7.7gm/dl, platelets 34,000/uL, lactate dehydrogenase elevated at 849U/l, undetectable haptoglobin. This in addition to hypertensive urgency prompted the diagnosis of TMA. ADAMSTS 13 activity was normal. Hemodialysis was started for worsening renal function and oliguria. Renal biopsy suggested presence of TMA. She received a course of ostelamivir and needed dialysis for a week. After the therapy she stayed off dialysis and returned to baseline creatinine in 2 weeks. Our patient was on carfilzomib for the last 11 months, known to cause TMA, however she developed it only after the influenza infection. She couldn't restart carfilzomib due to financial issues.

Discussion: Influenza associated TMA is a rare entity. It has been reported to occur around 4 days after the onset of infection, like in our patient. The outcome of iTMA is generally favorable with supportive care.. Our patient was on carfilzomib for 11months and the only apparent trigger for the TMA was influenza. Identification of the etiology and differentiation between drug induced complement dysregulation and influenza associated HUS without identifiable complement abnormalities are crucial for treatment.

SA-PO210

Renal Thrombotic Microangiopathy with Multiple Myeloma: Resolution with Chemotherapy

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Introduction: Thrombotic microangiopathy (TMA) is a clinical entity described by systemic microvascular occlusion, causing hemolytic anemia and thrombocytopenia resulting in end-organ ischemia. Numerous mechanisms may cause the condition including direct immunoglobulin deposition or chemotherapy. TMA is a pathological diagnosis characterized by fibrin thrombi within arterial vessels including the capillaries. Recent literature shows up to 13.7% of patients with thrombotic microangiopathy have monoclonal immunoglobulin. We present a case in which renal TMA-associated acute kidney injury responded to multiple myeloma treatment.

Case Description: A 43-year-old male with history of recent Bell's palsy and peripheral neuropathy presented with abdominal distension, dyspnea and unintended weight loss. Initial evaluation was significant for anemia (Hgb 8.9g/dL), normal platelet count (265,000/mm^3), normal LDH (139 U/L) and acute kidney injury (Creatinine 2.2mg/dL). CT of abdomen and pelvis demonstrated large-volume ascites and nonspecific sclerotic density in left iliac bone. Subsequent workup included a bone marrow biopsy significant for 30% plasma cells with 90% cellularity, and serum protein electrophoresis of positive IgA lambda monoclonal gammopathy (IgA 928mg/dL, M spike 0.5g/dL). Diagnosis of plasma cell myeloma was made. Renal biopsy was consistent with chronic thrombotic microangiopathy without immunoglobulin deposits by IFM or EM. The patient was treated with cyclophosphamide and prednisone (50mg). Renal function improved within the first three weeks of treatment to 1.3mg/dL.

Discussion: Very few cases have reported renal TMA with multiple myeloma to date. Distinct from the typical light-chain associated renal tubular injury of multiple myeloma, AKI due to TMA is also described. Our patient is one of few reported cases in which myeloma treatment resulted in improvement in renal TMA-induced renal insufficiency. Further investigation is needed to establish management guidelines for renal failure in this setting.

SA-PO211

A Case of Diffuse and Nodular Glomerulosclerosis in Waldenstrom's Macroglobulinemia

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Introduction: Diffuse and nodular glomerulosclerosis (DNGS) is commonly associated with diabetic nephropathy and occasionally with tobacco users. However, it has also been associated with amyloidosis, cryoglobulinemia, and light-chain deposition disease. To the best of our knowledge, there is no published data on DNGS without light chain deposition in Waldenstrom's Macroglobulinemia (WM). We present a case of DNGS in a non-diabetic, non-smoker with WM.

Case Description: A 72-year-old male with past medical history of Waldenstrom's Macroglobulinemia develops worsening renal function after CP-R (cyclophosphamide/prednisone plus rituximab) treatment with partial remission. He does not have diabetes, hypertension or other comorbidities; he is a non-smoker. He uses minimal NSAIDs and denies recent or prior intravenous contrast use. Two months after completion of CP-R regimen, creatinine started rising from baseline 1.0mg/dL to 2.2mg/dL over two years. Serum IgM decreased from 3414 to 2360 after treatment. Blood glucose, liver function panel, and albumin levels were normal. Renal ultrasound showed normal echogenicity without hydronephrosis. Kidney biopsy showed moderate diffuse and nodular glomerulosclerosis with focal cortical atrophy, hypoperfusion and focal global and segmental glomerulosclerosis and moderate vascular sclerosis. Biopsy showed stronger background staining for kappa light chains compared to lambda light chains, without Randall-type electron dense deposits. There was no evidence of monoclonal immunoglobulin deposition, amyloidosis, light chain tubulopathy or light chain cast nephropathy.

Discussion: Waldenstrom's Macroglobulinemia is a hematologic malignancy characterized by clonal proliferation of B-lymphocytes producing IgM monoclonal gammopathy secretion. It could involve the kidney through large intracapillary IgM deposition, cryoglobulin or amyloidosis related injury. Per literature review, there are no documented cases of DNGS in a patient with WM without history of diabetes or tobacco use. Further research is required to evaluate the prevalence and mechanism behind the association of DNGS and WM.

SA-PO212

Anti-C5 Antibody for Thrombotic Microangiopathy in Scleroderma Renal Crisis

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Introduction: Scleroderma renal crisis(SRC), presenting as malignant hypertension, acute kidney injury(AKI), thrombocytopenia and microangiopathic hemolytic anemia, is a major complication of systemic sclerosis. Seen more common in patients treated with glucocorticoids. Prognosis remains severe despite treatment with angiotensin converting enzyme inhibitor(ACEI). Studies suggest that complement activation trigger thrombotic microangiopathy(TMA) in SRC. We report a case of SRC with TMA treated with anti-C5 antibody

Case Description: 51 yr-old female with hypertension, hypothyroidism, dyspnea due to interstitial lung disease(ILD), without kidney disease, presented with worsening vision and severe headache. She was on myfortic and prednisone for the past 8 months for ILD. Her computed tomography scan revealed frontal cortical subarachnoid hemorrhage and bilateral posterior parietal subcortical hypo densities. For her high blood pressures she was started on Cardene drip. Hemodialysis was started for uremic symptoms with creatinine of 4.06 mg/dl and blood urea nitrogen 92 mg/dl. Laboratory evaluation with platelets 161,000/cmm, LDH 800U/L, hemoglobin10.5g/dl and haptoglobin undetectable, few schistiocytes, normal ADAMTS13activity, AKI and hypertensive emergency indicated possibility of TMA, likely atypical hemolytic uremic syndrome. Rheumatological evaluation of ILD revealed nucleolar pattern ANA and high PMSL antibody indicating NSIP with PM-Scl overlap without skin involvement. There was high suspicion of SRC, possibly precipitated with the use of glucocorticoids. Despite captopril she did not show any signs of renal recovery. Renal biopsy done revealed presence of acute TMA with arterial, arteriolar and glomerular C5b-9 staining. These findings were suggestive of the presence of complement dyregulation and therefore decision to start anti-C5 antibody(ecluzimab) was made. The patient's platelets count recovered with 3 doses of ecluzimab. The patient is currently on the maintenance dose of ecluzimab. She has improved renal functions, requiring dialysis once a week. Her genetic testing is awaited

Discussion: Scleroderma renal crisis have high incidence of end stage renal disease despite use of ACEI. Since, complement activation has been described in autoimmune disorders including SRC, we considered the use of anti-C5 antibody in the treatment of TMA in our patient to achieve decreased dialysis dependence.

SA-PO213

Eculizumab Responsive Atypical Hemolytic Uremic Syndrome Triggered by a Multisystem Lupus Flare

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Introduction: Uninhibited alternative complement pathway activation leads to complement mediated hemolytic uremic syndrome. Infections, pregnancy, drugs or ongoing lupus activity can trigger this cascade. Concurrent occurrence of aHUS with lupus is rare. We present a case of aHUS with hematological and renal responsiveness to eculizumab

Case Description: A 25-year-old Caucasian female with HTN, IgA deficiency and class III A + V lupus nephritis on maintenance prednisone, mycophenolate and hydroxychloroquine, presented with abdominal pain and encephalopathy. Workup showed Hb of 7.9g/dl, thrombocytopenia, schistocytes, low haptoglobin and elevated LDH. TTP and autoimmune hemolysis were ruled out. Hypocomplementemia and positive dsDNA and ANA were noted. Soluble membrane attack complex level was elevated and membrane cofactor protein was low. Factors H, I, B were within normal limits. Factor H autoantibody, antiphospholipid antibody panel and scleroderma antibodies were negative. Creatinine peaked at 5 mg/dl (baseline1.2mg/dl)and she had nephrotic range proteinuria -6g. Hemorrhagic pancreatitis and cerebritis seen on imaging. Infectious etiologies were ruled out. Renal biopsy showed Class III and V Lupus with moderate activity, thrombotic microangiopathy and diffuse ATN. Despite initiation of pulse dose steroids, cyclophosphamide she developed multisystem organ failure requiring mechanical ventilation, renal replacement therapy and multiple transfusions. Plasma exchange was deferred due to IgA deficiency. Subsequently initiated on eculizumab with improvement

in hematological parameters after 2 doses. Renal recovery with discontniuation of dialysis occurred after 4 doses. She remains in remission on prednisone, MMF, hydroxychloroquine and eculizumab at 9 month follow up with a Cr of 0.7 and proteinuria of 0.5g.

Discussion: Active Lupus serves as a driver for aHUS. Thrombotic microangiopathy is an independent risk factor for poor outcome in lupus nephritis with mortality rates of over 30% despite the use of multimodal treatment strategies. Terminal complement inhibitors can effectively induce hematological and renal response and there should be a low clinical threshold to initiate eculizumab in the setting of refractory disease. Data regarding the optimal dosing schedule, monitoring and treatment end points is lacking and needs additional studies.

SA-PO214

Eculizumab Treatment in Recurrent Dense Deposit Disease

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Introduction: Dense deposit disease (DDD) is a rare complement-mediated glomerular disease typically affecting children and young adults. About 50% of affected patients develop end stage renal disease by 10 years. Treatment decisions are primarily based on case reports, expert opinion, etc. Terminal complement proteins are thought to be involved in the pathogenesis of DDD. Eculizumab, an anti-C5 antibody, prevents the formation of the terminal complement complex, however the efficacy with this drug has been mixed.

Case Description: We present a 23 years old female with DDD diagnosed at age 10. She underwent cadaveric renal transplant at age 19. A year later, she developed biopsy proven recurrent DDD in her renal allograft. She also had elevation in the C5-9 complex (328 ng/mL), creatinine (1.65 mg/dL), and protein/creatinine ratio (6.1 grams). She was started on Eculizumab 900 mg weekly injection for 4 weeks and then 1200 mg every two weeks for 16 months. Biochemical markers normalized after 1 dose without adverse events. She was in clinical remission from DDD for 18 months when her creatinine (baseline 1-1.2 mg/dL) rose and peaked at 2.59 mg/dL with nephrotic range proteinuria (pro/cr ratio was 12 grams). Biopsy of her renal allograft again revealed recurrent DDD. She had elevated plasma Ba fragment and soluble C5b-9 and low C3, C4, and C5 which are consistent with abnormal activation of the alternative pathway. The alternative pathway functional assay was low and is consistent with the consumption of the above complements. The complement Bb level was borderline elevated. The C3Nef, C4Nef, C5Nef, and Nef activity assay were all negative. Complement factor I, factor H, and properdin levels were normal. In summary, these results support the recurrence of DDD. Subsequently, the patient was given Eculizumab 1200 mg every two weeks with rapid improvement in peripheral edema, creatinine, and proteinuria.

Discussion: Our patient suffered from DDD, a rare and incurable kidney disease, but demonstrated quick and effective response to eculizumab. Eculizumab induced remission in our patient. The natural history of this disease has a high recurrence rate which was evident in our patient. However, it is promising that she demonstrated clinical response despite relapse. This case suggests eculizumab may be effective in treating recurrent DDD and preserving the renal allograft.

SA-PO215

Eculizumab for the Treatment of Recurrent C3 Glomerulonephritis Caused by a C3 Gain of Function Mutation

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Introduction: C3 glomerulonephritis (C3GN) is a glomerular disease caused by excessive activation of the alternative complement pathway and often leads to end-stage renal disease. Following kidney transplantation, the recurrence risk is high and may cause premature allograft failure. Eculizumab prevents the membrane attack complex (MAC) formation and provides terminal complement inhibition. Here we present a case of early recurrent post-transplant C3GN in a patient with a C3 gene mutation that was successfully treated with eculizumab.

Case Description: A 38 year old female with a history of chronic kidney disease received a living unrelated kidney transplant. Prior to her transplant, she was diagnosed with C3GN which was refractory to corticosteroids, mycophenolate, and rituximab. Evaluation revealed a C3 gain of function mutation. Complement inhibitory factors were normal and she did not have a C3 nephritic factor. An elevated level of soluble MAC (sMAC) was noted prior to transplantation. She had immediate graft function following her transplant and she was maintained on tacrolimus, mycophenolate, and prednisone following basiliximab induction. Her creatinine reached a nadir of 1.1 mg/dl, but she developed early acute allograft dysfunction and proteinuria within the first few weeks of transplant and biopsy revealed early recurrence of C3GN. She was treated with high dose corticosteroids and plasmapheresis, but continued progression of renal dysfunction with rising sMAC levels, proteinuria, and activity of C3GN on a repeat biopsy. After initiation of eculizumab, her sMAC levels normalized, proteinuria resolved, and the allograft function improved. She is now >1 year out from transplantation with stable allograft function and no evidence of complications related to the eculizumab.

Discussion: Eculizumab appears to have a role in select patients with recurrent C3GN. Since not all patients with C3GN improve with eculizumab, more research is needed to define patients expected to benefit from this therapy. Patients with recurrent C3GN due to a gain of function mutation in the C3 gene should be considered for early eculizumab therapy to preserve allograft function and decrease excessive complement activity.

SA-PO216

C3 Glomerulonephritis, a Rare Etiology of the Pulmonary Renal Syndrome

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Introduction: C3 Glomerulopathy (C3GN) is a rare disease due to complement factor deposition in the glomerulus as a result of dysregulation of the alternative complement pathway. We present a rare case of C3GN presenting with diffuse alveolar hemorrhage (DAH) as a pulmonary-renal syndrome.

Case Description: A 20 year old female presented to the emergency department with flank pain and hematuria. Approximately 8 weeks prior, she had polyarthralgia, purpuric rash over the abdomen, buttocks and lower extremities with associated edema. She was treated for post-streptoccocal infection in the setting of high ASO titer (1490 IU/mL). On examination, she demonstrated persistent petechial rash and new right sided CVA tenderness. Blood pressure was 126/70 mmHg. On investigation, she was anemic with hemoglobin 8.1, had an acute kidney injury with creatinine 1.6 mg/dL and urinalysis showed 3.5 grams predicted 24 hour proteinuria, dysmorphic hematuria, >100 RBCs per high power field. Serology tests were notable for negative ANA, PR3-ANCA, MPO-ANCA, anti-GBM, Cryoglobulin, Hepatitis, HIV serology and paraproteinemia studies. Kidney biopsy showed focal endocapillary proliferative, crescentic, and necrotizing glomerulonephritis with bright glomerular C3 staining. On electron microscopy there was mesangial, intramembranous and sub-endothelial deposits with absence of sub-epithelial humps. She was initiated on pulse dose steroids and subsequently developed spontaneous hemoptysis requiring emergent intubation. Bronchoscopy confirmed DAH with cytopathology showing 0% hemosiderin-laden macrophages. Further work up revealed low complement (C3 40, C4 6 mg/dL) with decreased function of the alternate complement pathway at 55% (75-170% normal range). A diagnosis of C3GN with associated pulmonary hemorrhage was made. She required plasmapheresis and transitioned to prednisone and mycophenolate mofetil. As an outpatient, genetic testing showed 3 copies of C3GN risk alleles, but with negative mutations for complement factor H and factor I, negative factor H autoantibody or C3 nephritic factor. Renal function deteriorated despite aggressive immunosuppression and eculizumab therapy and she required hemodialysis.

Discussion: C3GN should also be considered part of the differential diagnosis in the setting of ANCA negative pulmonary renal syndrome.

SA-PO217

C3 Glomerulonephritis in Children

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Introduction: C3 glomerulonephritis (C3GN) is marked by subendothelial and/or mesangial electron dense deposits, which displays isolated glomerular C3 deposition without concomitant staining for Ig. Since clinical manifestations and long-term outcome of C3GN have not been clarified yet, especially those in children, we reviewed our cases of pediatric C3GN. Among more than two thousand biopsy cases performed in our center since Jan 2004 (for 15 years), ten cases (M:F 5:5) were compatible to C3GN. Their medical records were retrospectively reviewed.

Case Description: Pediatric C3GN patients at our center presented at their median age of 9.2 years with asymptomatic urinary abnormality (n=6), acute glomerulonephritis (n=3) or nephrotic syndrome (n=1). Hematuria was noted in nine (6 microscopic and 3 gross hematuria). Initial renal function was normal range in all. Initial serum C3 levels were low in all the cases but one. Pathologic diagnoses were C3GN for three, but those who were presented before 2015 had been initially diagnosed as PIGN (n=3) or MPGN (n=4); One patient with pathologic diagnosis of PIGN had follow-up biopsy in 20.2 months and finally diagnosed C3GN. All the patients were managed with ACE inhibitor or ARB, and eight were treated with additional steroid and other immunosuppressants of CNI or MMF. One patient with poor compliance progressed to ESRD in 5 years, despite therapeutic trial of eculizumab. The other 9 patients had normal renal function at last visit; Last serum C3 levels were normal in 4 and persistently low in the rest.

Discussion: Pediatric cases of C3GN showed diverse presentation, and some of the were initially mis-diagnosed as PIGN. Interestingly their outcome was fair, although our number of subjects was too small to draw any conclusion. For better understanding of this entity, further study on regulatory system of ACP is required, as well as other markers which can predict clinical course of C3GN.

Patient characteristics

Male to female ratio	5:5
Age at the onset	9.2 [4.5-14.0]
Clinical manifestation during the disease period Microscopic HU Gross HU Over nephrotic range PU	6 (60%) 3 (30%) 6 (60%, 3 of 6 got remissioned after tx)
C3 Consistently low Normalized after Tx Persistently normal	6 (60%) 3 (30%) 1 (10%)
Hypertension Yes : No	3 : 7
Treatment Steroid Other IS (CNI, MMF etc.) ACE inhibitor or ARB Eculizumab	7 (70%) 8 (80%) 10 (100%) 1 (10%)
Outcome (over 5yr) Normal renal function ESRD	9 (90%) 1 (10%)

SA-PO218

LCAT Deficiency with C3 Glomerulopathy: Case Report

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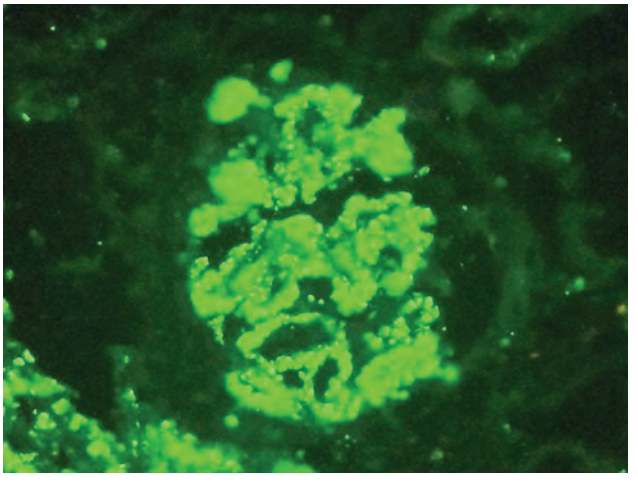
Introduction: Lecithin cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disorder of lipoprotein metabolism that produces deposit of unesterified cholesterol in the cornea, kidneys, and erythrocytes. Kidney biopsy typically shows vacuolation of glomerular capillary walls, foam cells and spiculation as well as duplication of the glomerular basal membrane (GBM). The immunofluorescense (IF) studies are typically negative although C3 non specific depositions are described. Here we present a case of LCAT deficiency that showed some C3 glomerulopathy aspects.

Case Description: We report a case of a 19-year-old woman with a brother diagnosed with LCAT deficiency who presented with low limb edema, foamy urine and corneal fish-eye-like alterations. Laboratory tests showed extremely low HDL levels (3 mg/dl), normal renal function (CKD-EPI 137 ml/min/1,73m2), subnefrotic proteinuria (1,8 gr/24 hours), anemia (hemoglobin 10,0g/dl) and normal complement (C3 108 mg/dL; C4 27,4 mg/dL). Kidney biopsy evidenced podocyte and mesangium vacuolation, double-contour basal membrane and subendothelial as well as intramembranous hyaline deposits. On IF we found only C3 granular depositions with medium intensity (2+) on the glomerular capillary wall and tubular basal membrane with diffuse distribution.

Discussion: In literature, we found two cases reported of LCAT deficiency associated with dense deposit disease (DDD). Our patient had mixed lesions of LCAT deficiency and medium (2+) intensity C3 deposition pointing more to a C3 glomerulopathy than to a non specific deposition. Electronic microscopy in process should define the diagnosis. It has been affirmed that structural changes in renal GBM could occur due to alterations in galactosyl fraction provoked by extraneous material deposition. Therefore, we can speculate that deposition of abnormal non esterified cholesterol in LCAT deficiency could be related to activation of complement cascade.



SA-PO219

What Lies in-Between: A Case of C3 Glomerulopathy with Non-Hemolytic Renal Microangiopathy and a Unique C3 Variant

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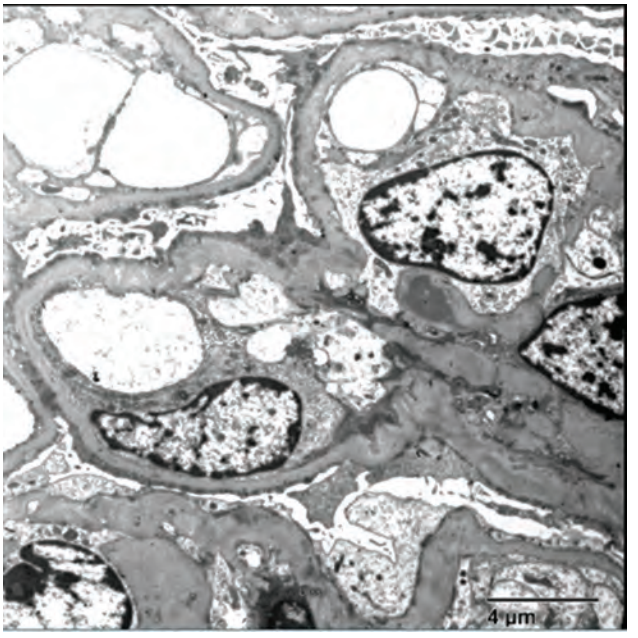
Introduction: A difference in location of alternate pathway dysregulation is thought to be the cause of the distinct clinical disorders of C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS).

Case Description: A 36 year-old female with history of prior alcohol abuse presented with abdomen pain, nausea, and vomiting for one day prior to admission. Serum creatinine (S.Cr) was 2.6 mg/dL (unclear baseline) and serum lipase was 445 U/L. Urinalysis showed hematuria and urine protein-creatinine ratio (UPC) was 6.35 g/g. Her pancreatitis was managed conservatively. Pain improved but S.Cr reached 7.5 mg/dL by hospital day (HD) #5 - a kidney biopsy was performed and pulse dose steroids were initiated. [Fig1] A membranoproliferative glomerulonephritis with focal crescents and positive C3 was found. Severe diffuse endothelial swelling and small amounts of electron dense deposits were seen on electron microscopy. No hemolysis was detected but plasmapheresis (PP) was started due to worsening S.Cr. Renal function improved; patient was discharged on steroids and cyclophosphamide as eculizumab was not approved by insurance. Complement genetic testing revealed a unique variant in 1 allele of C3 gene and a heterozygous deletion of CFHR3-CFHR1. Now, two months later, patient is readmitted with recurrence of her renal syndrome and pancreatitis.

Discussion: Endothelial damage, recurrent pancreatitis and response to PP are features of aHUS. These, together with a C3 positive crescentic glomerulonephritis, sparse deposits and a unique C3 genetic variant strongly suggest the possibility of a syndrome with overlap between C3G and aHUS.



SA-PO220

Postpartum Associated Atypical Hemolytic Uremic Syndrome

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Introduction: Pregnancy associated atypical hemolytic uremic syndrome is a rare, life threatening, progressive systemic disease of uncontrolled activity of the alternate complement pathway resulting in systemic thrombotic microangiopathy during pregnancy or postpartum period. The diagnosis of this condition is challenging and can mimic various diseases found during pregnancy and the postpartum.

Case Description: 35 year old woman without significant past medical history who presented to our hospital for elective delivery at 37th weeks gestation. During the induction period the labor arrested, the patient became hypertensive to 170/100 mmHg with subsequent fetal bradycardia necessitating a C-section. Immediately postpartum uterine atony with severe hemorrhage was observed. The patient was intubated and was placed on pressor support. Severe anemia was registered with hemoglobin drop to 6.8 from 12.0 g/dl. The hemoglobin level was 6.9 g/dl after transfusion 4 units of PRBC. There were no overt signs of bleeding. Additional studies showed: LDH 1324 u/l, haptolgobin <10 mg/dl, and platelets – 62 from 212 K/uL; schistocytes were noticed on peripheral smear. Deterioration of the renal function was observed over the next 48 hours with anuria, creatinine peaked to 7.02 mg/dl. Hemodialysis was initiated for oliguria, hyperkalemia and fluid overload. Subsequent studies showed decreased level of C3 at 73 mg/dl with normal C4. Differential diagnosis included TTP, severe pre-eclampsia, aHUS, malignant hypertension and ischemic ATN. Plasma exchange was started with iv prednisone 100 mg/daily, ADAMTS13 was 42% excluding TTP. Eculizumab 900 mg/weekly was started 5 days POD. Gradually the hemoglobin level and platelets stabilized. The patient was extubated and the hemolysis resolved. HD treatment was discontinued on POD 19 after significant improvement of the renal function and good control of blood pressure. During the hospital stay she received total of three doses of eculizumab. The patient was discharged with continuation with eculizumab biweekly

Discussion: Diagnosis of pregnancy associated aHUS must be considered early in postpartum period in patient with hemolysis, rapid deterioration of renal function despite the possibility of superimposed acute tubular injury, abnormal complement function and normal ADAMTS13 activity. Early initiation of treatment with plasma exchange and eculizumab has proven its efficacy in postpartum aHUS.

SA-PO221

A Rare Case of Clostridium Difficile Causing Atypical Hemolytic Uremic Syndrome

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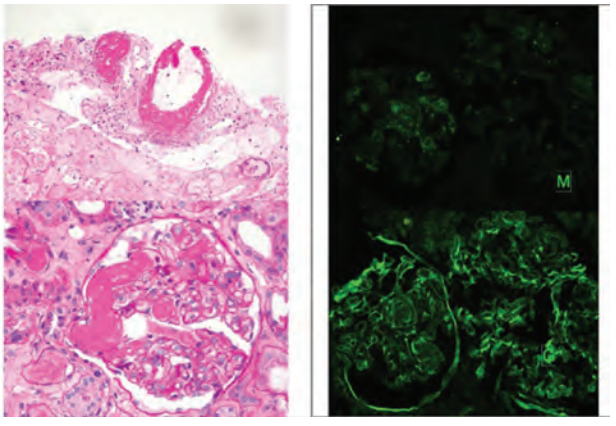
Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy mediated by excess activation or dysregulation of the alternate complement pathway. The incidence is 2 per 1 million people in the United States. We present a case of aHUS caused by *C. difficile* with persistent renal failure.

Case Description: 52-year-old morbidly obese man with hypertension, sleep apnea, and recurrent deep vein thrombosis admitted for worsening fatigue and bloody diarrhea since treatment with clindamycin then trimethoprim-sulfamethoxazole 2 weeks prior. He had acute renal failure with creatinine 4.9 and oliguria, hemolytic anemia, thrombocytopenia, leukocytosis, and active urine sediment with RBCs, WBCs and protein. CT abdomen and

renal ultrasound were unremarkable. Left renal biopsy showed severe acute glomerular microangiopathic injury. He began intermittent hemodialysis (HD) and plasma exchange. ADAMTS13, total complement, C3/C4, ANA and ANCA and tests for *E.coli* 0157:H7, Shiga toxin, HIV, and hepatitis were normal. aHUS genotype panel was equivocal. Stool was positive for *C. difficile*. After plasma exchange and steroids, he remained oliguric on HD. Eculizumab was started for aHUS. Despite treatment, he remains HD dependent awaiting transplant.

Discussion: 90% of HUS is secondary, usually to *E.coli* 0157:H7 or Shiga toxin (typical diarrhea+ HUS), *S. pneumoniae* infection, pregnancy, or drugs. There is no known causation by clindamycin or trimethoprim-sulfamethoxazole. Normal complement and equivocal aHUS genotype results do not rule out aHUS. A few case reports suggest *C. difficile* infection may cause HUS, though prior cases had full renal recovery. Our patient's clinical, lab, and histopathologic findings support diagnosis of aHUS from *C. difficile* infection. Though rare, *C. difficile* must be considered as a cause of aHUS. Our patient presents further difficulty as renal function remains poor despite antibiotic therapy and eculizumab.



Biopsy with cortical necrosis, severe acute glomerular microangiopathy

SA-PO222

Myeloma Kidney with C3 Deposition

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Introduction: Renal complications of multiple myeloma (MM) include monoclonal immunoglobulin deposition disease and myeloma cast nephropathy. Up to 50% of MM patients present with renal impairment at diagnosis, 20% may present with acute kidney injury (AKI) and 10% require dialysis. In C3 glomerulopathy, which is one of the complement-mediated types of Membranoproliferative Glomerulonephritis (MPGN), defects in complement regulatory proteins promotes the excessive activation of the alternative pathway.

Case Description: A 59-year-old man with a two-year history of hypertension presented with generalized weakness for the past 3 months. Physical examination reveals a well-appearing male with a bp 137/77 mmHg, pulse 103 bpm, with fairly normal physical findings. On admission: Hb 9.1 g/dl; RBC 1.45 mil/mm^3; WBC 3.2 th/mm^3; plt 94 th/mm^3; BUN 94 mg/dl; Cr 10.47 mg/dL (baseline Cr 1.5 mg/dL); BUN/Cr 8.77; FeNa 8.7%; Na 130 mEq/L; K 6.2 mEq/L; HCO3 14 mEq/L; Urine analysis showed 2+ protein with bland urine sediment and microscopic hematuria. 24-hour urine protein was 2g/day. Renal ultrasound showed 0.6 cm right renal cyst. The patient was admitted to ICU for hyperkalemia with AKI and was consequently hemodialyzed. Serologies were notable for low levels of C3 (46 mg/dL) with normal C4 were observed. Immunofixation by Electrophoresis of both serum and urine showed free Lambda band present. Serum plasma electrophoresis showed two M-spikes: Lambda light chains and IgG Lambda. Free kappa/lambda ratio <0.01. Urine electrophoresis showed three monoclonal bands. Serum levels of IgG 2500 mg/dl. A renal biopsy was performed and cast nephropathy was identified with mesangial staining for C3. Bone marrow biopsy showed CD 56 positive Plasma Cell Myeloma. MM was diagnosed with IgG lambda cast nephropathy and ESRD on dialysis with pancytopenia. He was treated with Velcade, Cytoxan, and dexamethasone. SPEP status post chemotherapy showed two M-spikes with improvement of renal function and normal C3 levels. At 4 months post-biopsy, the patient remained dependent on hemodialysis therapy and required multiple blood transfusions.

Discussion: We hypothesize in monoclonal gammopathy induced C3 glomerulopathy, paraprotein itself is acting as a trigger that activates and dysregulates the AC pathway systemically. Thus, it is highly feasible to tailor the treatment to reduce the amount of paraproteins in C3 glomerulopathy associated with Myeloma kidney.

SA-PO223

Myeloma-Like Cast Nephropathy in a Patient with Pancreatic Mixed Acinar-Neuroendocrine Cancer

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Introduction: Myeloma cast nephropathy is a very serious diagnosis, which triggers immediate work-up for multiple myeloma and aggressive chemotherapy. However, there are rare renal conditions with morphological features similar to myeloma cast nephropathy but without evidence of plasma cell dyscrasia or monoclonal gammopathy. "Myeloma"-like casts result from precipitation of abnormal proteins along with Tamm Horsfall glycoprotein in distal tubules and collecting ducts leading to an inflammatory response with giant cells and acute kidney injury. Myeloma-like casts have been reported occasionally in patients with pancreatic adenocarcinoma, thyroid cancer, HIV, antibiotic and cisplatin use. We present here a case of myeloma-like cast nephropathy in a patient with pancreatic mixed acinar-neuroendocrine cancer (MANEC).

Case Description: The patient was a 60-year old male undergoing chemotherapy for biopsy-confirmed pancreatic MANEC with metastasis to liver. He presented with acute kidney injury (AKI) and mild proteinuria without hematuria or pyuria. Ultrasound showed normal renal size and echogenicity with no signs of obstruction. The kidney biopsy was obtained due to AKI with no clear etiology. The biopsy showed diffuse acute tubular epithelial injury with focal tubular obstruction by casts that varied in size. Some casts appear crumbled or moth-eaten. Focal casts were also associated with an inflammatory reaction that included neutrophils and/or syncytial multinucleated giant cells. No monoconal paraprotein detected in the biopsy, serum or urine. HIV screening test was negative and patient had no history of cisplatin use.

Discussion: Pancreatic MANEC is very rare. Myeloma-like cast nephropathy associated with pancreatic neoplasia is even rarer and has been seen only with adenocarcinomas. Thus, in this case, the myeloma-like cast are more likely associated with the exocrine component (acinar carcinoma), which produces excessive proteins obstructing the distal tubules, and cause tubular epithelial injury and inflammation with multinucleated giant cells. To our knowledge, this is the first report of myeloma-like cast nephropathy associated with neuroendocrine neoplasms. Because of the significant clinical associations and treatment differences, it is critical not to misdiagnosis this entity as myeloma cast nephropathy.

SA-PO224

A Case of Monoclonal Gammopathy Presenting with an Unexpectedly High Level of Serum Creatinine Due to Positive Interference in an Enzymatic Assay

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Introduction: In Japan, serum creatinine level is routinely measured by enzymatic method and a variety of enzyme assay kits are available. Monoclonal gammopathy can interfere with enzymatic assay for creatinine.

Case Description: A 78-year-old man was referred to the department of thoracic surgery in our hospital for the evaluation of lung tumor. At the initial visit to our hospital, the level of serum creatinine increased sharply from 1.03 mg/dl to 4.68 mg/dl during 5 days before the referral. He was generally well, and did not complain of anorexia, fever or oliguria. (No causative drug or infection was detected.) Other laboratory tests revealed a BUN level of 21 mg/dL, almost normal urinalysis (with microscopic hematuria), and an IgM level of 1366 mg/dL. We performed kidney biopsy, but could not identify the cause of AKI. In the meantime, we diagnosed lymphoplasmacytic lymphoma based on bone marrow biopsy. Despite high creatinine level measured in our hospital, that measured in the other hospital soon after the biopsy was nearly normal. To elucidate the cause of the discrepancy in the measured values, we analyzed the measurement methods. We observed the formation of white precipitation after addition of the reagent of the creatinine assay kit using in our hospital to the serum of this patient. This turbidity was not found when measuring by Jaffe method or by enzymatic method after protein removal from his sera, leading to the diagnosis of pseudohypercreatininemia secondary to paraproteinemia. GFR estimated from serum cystatin C was 33.3 ml/min/1.73m^2, consistent with that from "true" serum creatinine.

Discussion: Pseudohypercreatininemia should be considered in the search for the cause of isolated creatinine elevation in patients with paraproteinemia. In such patients, we should measure serum creatinine by multiple methods to evaluate renal function accurately. Comprehensive evaluation of creatinine measured by multiple methods and cystatin C may provide accurate renal function of patients with monoclonal gammopathy.

SA-PO225

Where's the Clone? Successful Treatment of Monoclonal Gammopathy of Renal Significance with Type 1 Cryoglobulinemia with Plasma-Cell Directed Therapy

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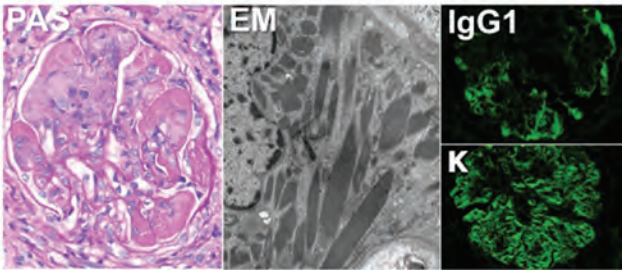
Introduction: Type 1 cryoglobulins are monoclonal immunoglobulins produced by clonal expansion of B cells. They are often associated with an overt hematologic malignancy, but sometimes occur without identification of a monoclonal cell population. We describe a case of type 1 cryoglobulinemia with a rare crystalline morphology on renal pathology and without an evident monoclonal population, that had excellent response to plasmapheresis and plasma-cell directed therapy.

Case Description: A healthy 61 year old woman initially presented with one year of intermittent knuckle swelling in cold weather and bilateral calf pain. She later developed generalized weakness and was admitted with hypertensive emergency, AKI [serum creatinine (SCr) 2.0 mg/dL], edema, livedo reticularis, and blurry vision. Workup was notable for dysmorphic red cells on urine sediment, 2 grams of proteinuria, low complements, normal serum calcium, serum Kappa/Lambda ratio 5.73, IgG kappa M spike, and 2% type I cryoprecipitate. Renal biopsy showed crescentic and necrotizing cryoglobulinemic glomerulonephritis with crystalline morphology of monoclonal IgG1 kappa (see Figure). Bone marrow biopsy showed no clonal cell population. The patient was treated with pulse steroids, plasmapheresis, and maintained on cyclophosphamide, bortezomib and dexamethasone, resulting in rapid improvement of symptoms and SCr to 0.96 mg/dL after 7 weeks.

Discussion: This case illustrates a classical presentation of monoclonal gammopathy of renal significance, where renal damage ensues from cryoglobulin deposition, likely produced by a monoclonal population not detectable by standard testing. Treatment of this hidden population by clonal cell-directed therapy resulted in excellent renal and symptomatic recovery. Additionally, pathology images reveal the assembly of monoclonal immunoglobulins into crystals, a rare variant of cryoglobulinemia.



SA-PO226

The Clone Wars: Evolving Treatment of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Deposits

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID) is a recently described entity and as we become more aware of this in our patients, its treatment poses the next challenge. Here we present a patient we cared for and the dynamic changes in his response to therapy that helped us guide his treatment regimen.

Case Description: A 63 year old male was found to have 8 g/d proteinuria and chronic kidney disease at the time of a cardiac evaluation 14 years ago. Kidney biopsy was reported elsewhere as membranous nephropathy and was treated initially with cyclophosphamide (C) and prednisone(P) with improvement in his proteinuria down to 3 g/d. Rituximab (R) was added with improvement in proteinuria to 1 g/d but was not continued due to coverage issues, and was eventually maintained on cyclosporine. He came to us for a second opinion and the diagnosis of PGNMID was made with no evidence of systemic disease. His kidneys eventually failed and he underwent a deceased donor kidney transplant. After 4 years he developed proteinuria of 800mg/d. Kidney allograft biopsy showed recurrence of PGNMID with same IgG kappa. Serology and bone marrow was negative but flow cytometry showed rare polyclonal plasma cells. He was treated with Rituximab initially with improvement in proteinuria down to 267mg/d but slowly increased to 1.1g/d after 3 months despite negative CD20. RCP was given with a more sustained response and his treatment was changed to be directed at CD38 cells with Rituximab and bortezomib (V) for a likely LPL clone with continued improvement in proteinuria.

Discussion: PGNMID in native kidney can be indolent but post-transplant it is usually aggressive and hence need prompt clone-directed therapy. The clones capable of producing PGNMID are plasma cell, lymphoplasmacytic (LPL) clone, and CLL clone. Our patient had no confirmed clone. Initial response to Rituximab suggests that it was a CD20 clone but he progressed and the regimen of RCP was given to knock out cells affecting both CD20 and CD38. His initial response to rituximab and quick recurrence is suggestive that he may have an LPL clone with CD38 cells that are more difficult to eradicate and considering his prior cytoxan exposure was switched to a bortezomib based regimen. The choice of therapy can be difficult, requiring a deeper understanding of PGNMID disease process.

SA-PO227

Plasmablastic Lymphoma Associated with IgD Lambda Light Chain Monoclonal Gammopathy and Severe AKI

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Introduction: Light chain cast nephropathy is the most common pattern of acute kidney injury in patients with multiple myeloma, seen in up to 47.5% of cases. Free light chains (FLC) are freely filtered and undergo endocytosis by proximal tubular cells via apical receptors. When these receptors become saturated, the resultant load of urinary free FLC co-aggregate with uromodulin causing precipitation and obstruction of the distal tubules, and inducing an inflammatory response. Most cases result from a single plasma clone of multiple myeloma. 2% of myeloma cases are of the IgD variant; only 5 cases have been reported to cause light chain cast nephropathy, and none as a result of lymphoma. This report describes the first case of presumed IgD lambda light chain cast nephropathy due to plasmablastic lymphoma.

Case Description: 74 year-old man status-post nephrectomy at age 2, history of diffuse large B cell lymphoma status post R-CHOP in 2016 attaining complete remission, recent biopsy of new perisplenic lymph node revealing plasmablastic lymphoma, who presented with anorexia and decreased urine output. Nephrology was consulted for acute kidney injury (AKI) with creatinine of 9.7mg/dL (baseline of 1.2mg/dL). He was found to have an IgD monoclonal gammopathy (1.4 g/dL), increasing serum lambda light chains (from 91mg/dL 3 weeks prior to 624mg/dL), and a kappa:lambda ratio of <0.01. 24-hour urine protein was 2.39g with M-spike of 1.65g and urinary immune-fixation positive for IgD lambda light chains. There was no obstruction on renal ultrasound. Bone marrow biopsy showed 0.2% lambda restricted clone, but no plasmacytosis. Although kidney biopsy was not obtained, the presumed diagnosis was IgD lambda light chain cast nephropathy. He was given intravenous hydration followed by cyclophosphamide, bortezomib, and dexamethasone. Serum creatinine improved rapidly to 3.1 mg/dL, serum lambda FLC improved to 40 mg/dL over the following week and patient was discharged home.

Discussion: Our patient developed severe AKI in the setting of IgD lambda FLC gammopathy likely leading to the development of cast nephropathy. Multiple myeloma literature reports up to 80% chance of renal recovery in patients with 60% reduction of serum FLC by 21 days. This patient had a similar remarkable response to standard myeloma therapy although his underlying pathology was plasmablastic lymphoma.

SA-PO228

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin M Deposits

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID) was first described as a distinct entity in 2004. Only few case reports of PGNMID with IgM or IgA dominant deposition have been described. Here we report our case with clinical and histopathological features of PGNMID with Ig M dominant deposit.

Case Description: A 37 year old gentleman with diabetes mellitus-type 2, hypertension and obesity, presented with leg swelling and foamy urine for two weeks. Clinical exam was significant for BP 155/97mmHg and 2+ pedal edema. Labs revealed elevated serum creatinine(1.28mg/dl, baseline 0.9mg/dl, peak over the course of follow up 6.26mg/dl) and albumin of 2.5gm/dl. Urinalysis showed specific gravity of 1.015, pH of 6.4, 4+ protein and 2+ blood, 11-30 RBCs per hpf. Urine microalbumin to creatinine ratio was 5680 and urine protein creatinine ratio was 8gm per gm. Hemoglobin A1c was 6.8. There was no M spike. Serum free light chains were mildly elevated with normal ratio. Bone marrow biopsy did not show monoclonal plasmacytosis. Cryoglobulin levels were repeatedly normal. Kidney biopsy showed moderately advanced diabetic nephropathy and nodular diabetic glomerulosclerosis, class III superimposed by IgM kappa proliferative glomerulonephritis. There was significant endocapillary and mesangial cellularity on light microscopy. Immunofluoroscence revealed granular 3+ IgM,3+ kappa light chain, 1-2+ C3 and 1-2+ C1q along the glomerular capillary walls and focally in the mesangium; and nonspecific 1+IgG, 1+ lambda and kappa light chains along the glomerular capillary walls, mesangial areas and tubular basement membrane. Electron microscopy showed scattered finely granular subendothelial electron dense deposits. He was treated with statin, diuretics and ARB was added when creatinine stabilized. He was given pulse dose of iv steroids, plasmapheresis (to remove IgM) and iv rituximab. Since he did not respond, he was further treated with cyclophosphamide and mycophenolate mofetil with regression of proteinuria and creatinine improvement.

Discussion: PGNMID is characterized by immunofluorescence findings of monoclonal IgG deposits and electron-dense deposits (EDDs) localized to glomeruli. Our case with histopathological features of PGNMID but with Ig M deposits adds to handful of similar case reports. We propose expansion of Nasr et al's classification to include IgM and IgA dominant variant.

SA-PO229

Proliferative Glomerulonephritis with Monoclonal IgG Deposits

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Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a form of monoclonal gammopathy of renal significance (MGRS). We

present a case of rapidly progressive glomerulonephritis in a patient with smoldering multiple myeloma (SMM) who responded to steroid pulse in addition to bortezomib and cyclophosphamide.

Case Description: This was a 74-year-old female with SMM who presented with serum creatinine of 3.06mg/dl from 0.9mg/dL one week prior, normal C3/C4, negative cryoglobulin, κ/ λ ratio of 82.6/11.3 (7.29), serum albumin of 2.4g/dl, and no monoclonal spike on serum or urine protein electrophoresis. However, free κ light chains were present on urine immunofixation. The urinalysis revealed 5RBC/HPF and 24-hour urine protein was 3.93g. Bone marrow biopsy done at an outside facility showed κ light chain myeloma with 10-15% marrow involvement. Kidney biopsy (Figure 1.) showed a membranoproliferative pattern of glomerulonephritis with monoclonal IgG-kappa deposits by immunofluorescence and there were 8 glomeruli (of 31) with cellular crescents. No other monoclonal paraprotein related diseases were present. Electron microscopy showed occasional electron dense deposits in the subendothelial space and fine focal mesangial electron dense deposits. The patient was treated with methylprednisolone 500mg daily followed by a prednisone taper and bortezomib twice weekly 1.3mg/m^{2}alternating with cyclophosphamide along with dexamethasone. The serum creatinine had peaked at 6.8mg/dl and improved with treatment to 1.8mg/dl by day 25 of initial presentation

Discussion: First described in 2004, PGNMID is a renal-limited glomerular disease, characterized by paucity of circulating paraproteins with presence of monoclonal IgG (usually IgG3-kappa) deposits in the glomeruli. The optimal treatment for this disease is not known. This case is unique due to rapid renal progression and prompt response to treatment. Considering PGNMID as a differential diagnosis of AKI in a patient with SMM and RPGN "picture" is important since early treatment may alter the renal prognosis in such patients.

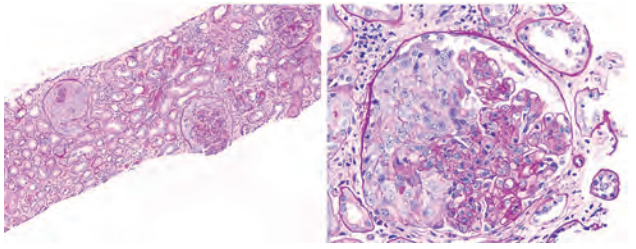

Figure-1

SA-PO230

Proliferative Glomerulonephritis with Monoclonal IgG Deposits Leading to the Diagnosis of B Cell Lymphoma

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare glomerular disease within the MGRS spectrum, first described in 2004. Membranoproliferative GN is the most common histologic pattern.

Case Description: A 70-year-old female with a history of mild hypertension (HTN) was referred for renal insufficiency and uncontrolled HTN. On examination, BP was 180/84 with otherwise normal cardiopulmonary exam and no edema. Lab data showed elevated S Cr of 1.9 mg/dL. Urinalysis displayed proteinuria and microhematuria with dysmorphic RBCs. The urine protein:Cr ratio was 1.9 g/g with serum albumin of 3.8 g/dL. CBC showed Hb of 11.6 g/dL with normal WBC count and differential. Serology for hepatitis, cryoglobulin, C3, C4, ANCA and anti-GBM antibody were negative. Serum immunofixation revealed IgM- kappa and IgM-lambda M-spikes with FLC kappa/lambda ratio of 2.2. Renal biopsy showed diffuse endocapillary proliferative GN with membranoproliferative features. Immunofluorescence revealed mesangial and glomerular capillary wall staining for IgG, C3, C1q and kappa light chain, with restricted positivity for IgG subtype 3. EM displayed granular mesangial and subendothelial electron dense deposits. The findings were diagnostic of PGNMID with monoclonal IgG3-kappa deposits. Bone marrow biopsy showed (1%) kappa-restricted B cell lymphoma. She received four weekly doses of rituximab infusion after which she achieved clinical renal remission. Ten weeks after initiating rituximab, S Cr and UPCR had fallen to 1.3 mg/dL and 0.2 g/g respectively.

Discussion: PGNMID presents typically with nephrotic range proteinuria, renal insufficiency, hematuria and HTN and 20% of patients progress to ESRD. Only 20-30% of patients have a detectable M-protein in the serum or urine. The MIg detected in the serum may not be identical to the MIg in the kidney deposits, as shown in this case. Our case illustrates that an onconephrologic approach to detect and target the underlying B-cell clone can lead to clinical remission of PGNMID.

SA-PO231

Outcome of Patients with Multiple Myeloma Who Undergo Autologous Stem Cell Transplantation Followed by Renal Transplantation: A Case Series Report

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Introduction: Autologous stem cell transplantation (ASCT) and novel therapies have improved the prognosis of patients with multiple myeloma (MM). For those who undergo ASCT whilst on dialysis, a similar survival compared with the overall MM population has been reported. For patients achieving remission following ASCT, kidney transplantation is an attractive option, offering an improved quality of life and significant economic advantage.

Case Description: This case series investigates the outcome of 5 subjects who underwent an ASCT for MM with subsequent kidney transplantation. Subjects were identified from our regional hospitals between 2006 and 2012. 2 females and 3 males were identified. All patients were Caucasian with a median age of 54years (range 37- 64). 4 patients presented with end stage renal disease (ESRD) and 1 progressed to ESRD shortly after diagnosis. Induction chemotherapy regimens with novel agents including thalidomide and bortezomib were utilised. Following attainment of very good partial remission (VGPR) or complete remission (CR), high dose melphalan ASCTs were performed after a median of 11 months (range 8-22months). Kidney transplantation (living donor, n=3, deceased donor, n=2) with tacrolimus based immunosuppression regimens were completed at a median of 27 months after ASCT (range 16-43months). Patients 1 and 3 experienced relapse of myeloma at 40 months and 13 months after kidney transplantation. Patient 1 received bortezomib based treatment to achieve CR, but later relapsed again. He developed sepsis related AKI and commenced dialysis. He died 1 month later. Patient 3 was treated with thalidomide and achieved VGPR. He developed a second relapse 5 months later and died with a functioning allograft (eGFR 21). Patients 2, 4 and 5 remained alive at the end of the follow up period (median time 67months) with eGFRs of 62, 11 and 50 respectively. Median kidney graft survival time was 66 months (range 47–95months).

Discussion: 5 patients with MM undergoing ASCT followed by renal transplantation achieved dialysis independence for a median of 66 months. Our study adds to the literature supporting kidney transplantation as the preferred treatment for ESRD following successful ASCT for MM and is useful when counselling patients reagrding renal and haematological outcomes.

SA-PO232

IgA Heavy Chain Monoclonal Immunoglobulin Deposition Disease in a Kidney Transplant Recipient

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Introduction: IgA heavy chain deposition disease should be differentiated from disease with polytypic IgA deposits given distinct clinical, histological and pathophysiologic features. Here, we present a case of IgA heavy chain monoclonal immunoglobulin deposition disease in a transplant recipient with a reported primary disease of IgA nephropathy.

Case Description: A 49-year-old man with a reported history of IgA nephropathy who failed medical therapy including cyclophosphamide, prednisone and mycophenolate resulting in ESRD. He received a renal allograft 3 years prior which was reportedly lost due to recurrent disease. He underwent a second living unrelated transplant with alemtuzumab/steroid induction and tacrolimus/mycophenolate/steroid maintenance immunosuppression. Two years posttransplant, he developed worsening kidney function with a SCr of 2 mg/dL (baseline 1.6 mg/dL) and new proteinuria of 3.7g/g. Kidney biopsy was performed and light microscopy revealed mild to moderate mesangial expansion with apparent eosinophilic deposits and segmental double contours of the glomerular basement membrane (GBM). Immunofluorescence, showed 3+ pseudolinear staining along GBM and tubular basement membranes (TBM), smudgy mesangial staining and vascular staining for IgA without corresponding light chain staining. By electron microscopy, punctate amorphous deposits were present along the inner aspect of GBM and outer aspect of TBM and around vascular smooth muscle cells with mesangial deposits showing focal short fibrillary substructure. He was referred to hematology and a bone marrow biopsy which showed a plasma cell neoplasm. He was started on bortezomib and dexamethasone but after 1 cycle developed severe AKI requiring HD. He did not recover function and was ultimately declared ESRD.

Discussion: IgA heavy chain monoclonal immunoglobulin deposition disease is a distinct clinico-pathologic entity which if left unrecognized or untreated can cause kidney allograft loss. This disease warrants a careful hematologic work-up to evaluate for a plasma cell dyscrasia and progression towards symptomatic IgA multiple myeloma. Although unsuccessful in this case, anti-myeloma agents appear to favorably influence renal prognosis. A hematological response may ultimately permit successful kidney transplantation with improved graft viability and decreased risk of recurrence.

SA-PO233

A Rare Case of Crystalglobulin-Induced Nephropathy

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Introduction: The term monoclonal gammopathy of renal significance (MGRS) describes paraprotein-dependent kidney diseases that do not meet criteria for overt multiple myeloma, including cast nephropathy, Ig deposition disease and amyloidosis. Crystalglobulin-induced nephropathy (CGN), a rare paraprotein-related disease, is most commonly associated with multiple myeloma. We herein report an extremely rare case of CGN associated with MGRS.

Case Description: A 75 year-old man with metastatic prostate cancer and normal renal function presented with anuric AKI requiring dialysis. Serum protein electrophoresis showed 0.3 g/dl IgG kappa monoclonal protein. Serum free κ/λ ratio was 2.3 (ref. 0.5-2.43). ANCA, anti-GBM, hepatitis serologies, rheumatoid factor, C3, C4, and cryoglobulins were normal. Hydronephrosis was not seen on renal ultrasound. Renal biopsy revealed overt coagulative necrosis (infarction) of 40% of sampled cortical tissue on light microscopy. Abundant PAS-positive crystalline thrombi were present in interlobular arteries, glomerular arterioles and capillaries, and focally extending into proximal tubules. (Fig. 1) Congo red staining was negative. Immunofluorescence showed dim IgG kappa staining in crystalline thrombi. By electron microscopy, crystalline thrombi displayed polygonal and angulated forms with distinctive fine parallel linear organization. Findings confirmed crystalglobulin-induced nephropathy. Bone marrow biopsy was then performed, revealing metastatic prostate cancer without demonstrable multiple myeloma. His hospital course was complicated by GI bleed and thromboembolic cerebral infarcts. He died 6 weeks after initial presentation upon discontinuing dialysis.

Discussion: CGN is a rare entity usually associated with multiple myeloma, whereas our patient had MGRS. Given a potentially devastating outcome, CGN should be considered in patients presenting with AKI and monoclonal gammopathy.

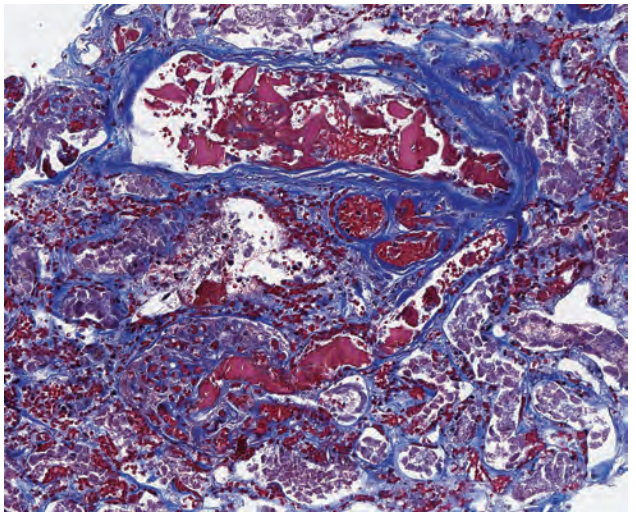

Fig. 1

SA-PO234

Crystalglobulinemia: A Rare and Complex Clinical Entity

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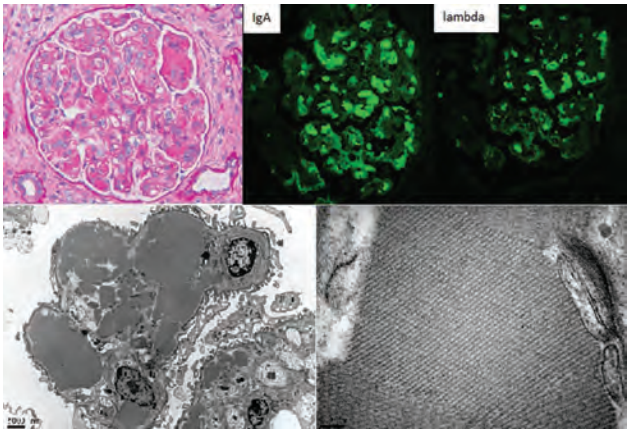
Introduction: Crystalglobulinemia (CryG) is a rare Monoclonal Gammopathy of Renal Significance (MGRS) that results in a crystalline appearing precipitation of paraproteins in the glomeruli. These paraproteins are unique in that they are not cryoprecipitable, but form immune aggregates that appear crystalline on Electron Microscopy (EM). Clinical manifestations include purpura, arthropathy and AKI. We present a case of crystalglobulin-induced AKI in a pt with a monoclonal IgA lambda paraproteinemia. Early recognition and treatment led to resolution of her AKI.

Case Description: A 44-y/o F p/w arthralgias, HTN and edema. Labs: Cr of 1.4 mg/dL and Alb 3.7 g/dL. UA: +RBCs with a urine alb/Cr ratio of 6.3 g/g. Workup: ANA, ANCA, C3, C4, and hepatitis all neg or nml. Monoclonal IgA lambda was seen on serum and urine immunofixation. Serum k/l ratio was 0.76. A renal biopsy demonstrated on Light Microscopy: Lobular glomeruli with the majority showing intracapillary eosinophilic thrombi that stained 3+ for IgA and lambda (kappa-). EM: the thrombi were composed of crystalline structures with an organized substructure of parallel linear arrays (Fig 1). No evidence of cast nephropathy. Serum cryoglobulins were repeatedly negative. She developed AKI (Cr of 4.2) and was started on plasmapheresis (TPE) and steroids. A bone marrow biopsy showed a plasma cell neoplasm in 7% of cells with lambda predominance by flow cytometry. Therapy with bortezomib and cyclophosphamide was administered. A bone survey showed no lytic lesions. Three weeks following initiation of therapy, her Cr improved to 1.0.

Discussion: CryG is rare and illustrates the complexity of the MGRS spectrum. Diagnosis requires histologic evidence of characteristic crystalglobulin deposition within the vasculature in the absence of circulating cryoglobulins. This case emphasizes the importance of specific histologic diagnosis to guide treatment for pts with MGRS. In this case, TPE and steroids served as a bridge until directed chemotherapy was started.



Renal Biopsy

SA-PO235

A Case of Waldenström Macroglobulinemia Recovering from Dialysis-Requiring AKI by Steroid Monotherapy

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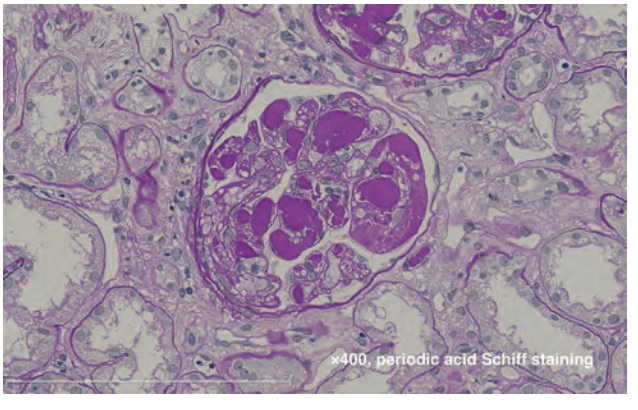
Introduction: Lymphoplasmacytic lymphoma (LPL) is an uncommon mature B cell lymphoma, whereas Waldenström macroglobulinemia (WM) is a subset of LPL involving the bone marrow with an IgM monoclonal gammopathy in blood. WM mainly presents with symptoms associated with anemia and hyperviscosity syndrome. WM-associated nephropathy is rare and its prognosis is unknown. Here, we report a case of LPL/WM recovering from dialysis-requiring acute kidney injury by steroid monotherapy.

Case Description: A 76-year-old Japanese woman who had been previously healthy admitted to the hospital with complaint of abdominal pain. She became anuric soon after admission, followed by progressive dyspnea due to pulmonary edema. She was referred to our hospital and hemodialysis was started for volume control. She presented with no neurological symptoms but funduscopy showed dilated and tortuous retinal veins with hemorrhagic exudates, which suggested hyperviscosity syndrome. She had severe anemia with rouleaux formation, high level of serum IgM (3776 mg/dl) and monoclonal IgM with lambda light chain on serum immunoelectrophoresis. Bone marrow biopsy demonstrated infiltration by small lymphocytes that exhibit plasma cell differentiation and she was given a diagnosis of LPL/WM. Renal biopsy demonstrated acute tubular necrosis with cast nephropathy and neoplastic lymphocytic infiltration in the interstitium. There were IgM deposits in the glomerular basement membrane and widespread thrombi in the capillaries. She underwent the treatment with high-dose dexamethasone, which steadily made her renal insufficiency ameliorated. Finally, hemodialysis therapy was discontinued at the 31st hospital day.

Discussion: Prognosis of WM-associated nephropathy depends on the type of renal pathology. This case suggested that acute kidney injury mainly caused by neoplastic lymphocytic infiltration might be reversible by chemotherapy.



SA-PO236

IgA Nephropathy Associated with Cystic Fibrosis: Role of Recurrent Infections as Etiology

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Introduction: Cystic fibrosis (CF), is the most common autosomal recessive condition in the caucasian population, and is due to mutations in cystic fibrosis transmembrane regulator (CFTR) gene that codes for a regulated chloride channel. CF is multisystem disorder primarily affecting the lungs, digestive system, sweat glands and reproductive tract; renal involvement is relatively uncommon in CF despite the high expression of CFTR in the kidney. Reported glomerular diseases associated with CF include AA amyloidosis, membranoproliferative and post-infectious glomerulonephritis. We present a 28 year old Caucasian male with CF who presented with worsening renal function, and nephrotic range proteinuria diagnosed with IgA Nephropathy

Case Description: A 28 year old Caucasian male with CF for over 10 years presented progressive worsening proteinuria from 700 mg/day two years ago to more recently 8 grams/day. His prior renal history included recurrent episodes of respiratory infections and acute kidney injury and the progressive loss of renal function. Evaluation of proteinuria noted negative ANA, ANCA, anti-dsDNA, but a low serum C3. Serum creatinine levels ranged from 2-3 mg/dL. Urine microscopy revealed many dysmorphic RBC's. A renal biopsy was performed and light microscopy revealed mild to moderate mesangial widening with mesangial hypercellularity but no endocapillary hypercellularity. IF staining was positive for IgA and C3. The tubulointerstitium demonstrated widespread interstitial fibrosis and tubular atrophy. Congo red stain was negative for amyloid. The MEST indices were noted as M1, E0, S0, and T2. The patient was treated conservatively with losartan and without immunosuppression. Renal function remained stable and proteinuria decreased from 8 grams to 5 grams/day over a four month period.

Discussion: Frequent mucosal infections and inflammation, as seen in CF, may be associated with a chronic production of IgA. This patient had an extensive 10 year history of recurrent mucosal infections which were poorly treated. This may have led to aberrant IgA production due to abnormal glycoforms leading to mesangial immune complex deposition and complement activation (low C3) as observed in our case. Therefore recurrent infections associated with CF may have an important role in the pathogenesis of IgA nephropathy.

SA-PO237

IgA Dominant Membranoproliferative Glomerulonephritis

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Introduction: IgA Nephropathy is widely accepted as the most common cause of glomerulonephritis worldwide. Far less common and somewhat controversial is IgA Dominant Membranoproliferative Glomerulonephritis. Most mentions of this unique pathology are described in case studies with suggested etiologies including: cirrhosis, burn victims, and children.

Case Description: We present a case of a 74 year old woman who presented with acute encephalopathy after one month of cough and URI like symptoms. She had recently returned from a family gathering where she was exposed to several sick contacts. The patient had prior history of CKD-3b, hypertension, and carcinoid tumor, for which she was on active treatment with octreotide for several years. Initial labs were significant for acute kidney injury with serum creatinine of 2.67mg/dL and urine protein to creatinine ratio of 18,134mg/g. She was initially treated with IV fluids and antibiotics with no improvement to her renal function. She underwent renal biopsy which demonstrated the characteristic features of MPGN on light and electron microscopy along with a notable predominance of IgA on immunofluorescence microscopy. She eventually required hemodialysis and pulse dose IV steroids followed by tapering course of oral steroids. Given the paucity of reported cases, along with the lack of proven treatment strategies and the issue of her active carcinoid tumor, our treatment options were limited to steroids. She was referred for re-evaluation and was cleared of carcinoid. She then began a trial of oral cyclophosphamide (CPA). After two weeks of treatment, she developed issues of recurrent *E.coli* UTI and later development of community acquired pneumonia, forcing us to stop CPA. She continued on hemodialysis for a total of three months before renal recovery allowed her to stop dialysis. At last follow up, the patient had returned to her baseline serum creatinine of 1.2 mg/dL and had improvement of her proteinuria with urine protein/creatinine ratio of 5121mg/g. She continued to have intermittent episodes of frank hematuria. The patient had not undergone repeat biopsy. She was pending infectious clearance to resume her course of CPA.

Discussion: Given the lack of proven treatment modalities, we felt that this case presented an opportunity to share a reasonable and effective treatment option for future patients.

SA-PO238

Membranoproliferative Glomerulonephritis Due to Monoclonal Gammopathy of Renal Significance: The Value of Pronase-Digestion

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Introduction: Membranoproliferative glomerulonephritis (MPGN), a characteristic light microscopic (LM) finding seen on renal biopsy, is further classified based on immunofluorescence (IF) findings. Immune-complex deposition is one cause of MPGN and may be secondary to monoclonal immunoglobulin deposits. IF on pronase digested tissue can aid in revealing masked monoclonal deposits. A wide spectrum of hematologic diseases are associated with kidney deposition of monoclonal immunoglobulin deposits; however in many patients, there is no identifiable hematologic condition and the term monoclonal gammopathy of renal significance (MGRS) has been applied.

Case Description: A 65-year-old male presents with hypertension, weight gain with bilateral lower extremity edema, and subacute kidney injury with creatinine of 1.81 mg/dl (baseline: 0.9 mg/dl). Urinalysis demonstrated 3+ protein, 2+ blood, with protein creatinine ratio of 10.3 g/g and a serum albumin of 2.8 g/dL. Serum immunofixation was positive for IgG-kappa; remainder of paraprotein workup and glomerular serologies, including complement levels, were either normal or negative. Renal biopsy findings on light microscopy were consistent with an MPGN pattern of injury, subacute, with nodular mesangial sclerosing features; initial IF demonstrated trace to 1+ granular to semi-linear glomerular capillary wall staining for C3 only; repeat IF performed on pronase-digested tissue revealed trace to 1+ granular to semi-linear glomerular capillary wall staining for IgG with trace C3 and trace kappa, and no significant staining for lambda. Electron microscopy did not reveal any evidence of dense deposit disease. These findings support the diagnosis of MPGN with IgG-kappa monoclonal deposits. Subsequently patient underwent bone marrow biopsy and full body PET scan, neither of which demonstrated any evidence of B-cell clonal expansion/population. Given these findings, the patient's MPGN appears to be secondary to MGRS. Therapy was initiated with oral corticosteroids and Rituxamab.

Discussion: An MPGN pattern of injury represents a diagnostic and therapeutic challenge. Findings on IF are critical to help determine the underlying cause. This case demonstrates MGRS as underlying etiology of MPGN, and the value of IF analysis via pronase-digestion to aid in "unmasking" hidden monoclonal deposits.

SA-PO239

Idiopathic Membranoproliferative Glomerulonephritis: A Grey Zone

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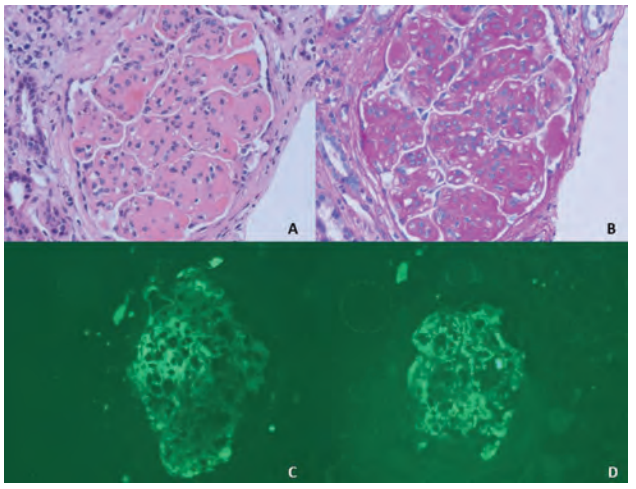
Introduction: 'Idiopathic' membranoproliferative glomerulonephritis (MPGN) is rare compared to secondary forms and usually a progressive disease. Studies evaluating the role of steroids were primarily done in children and the data is sparse in adults. Mycophenolate mofetil is effective and can be used as a steroid-sparing agent in the treatment of idiopathic-MPGN.

Case Description: A 22-year-old White man a recent diagnosis of hypertension was referred to Nephrology department for elevated serum creatinine and proteinuria. He was asymptomatic at presentation except for swelling in the legs for few months. Laboratory data was significant for a creatinine of 2mg/dL, serum albumin 2.5g/dL, low serum complements and urine protein-creatinine ratio ~17g/g (Ref: <150 mg/g). Renal biopsy demonstrated MPGN [Figure] with moderate interstitial fibrosis. Secondary causes of MPGN including hepatitis C, lupus, and monoclonal gammopathies were excluded by appropriate tests. He was started on prednisone 80mg/day and proteinuria reduced to ~3.7g/g in 8 weeks. However, he did not tolerate steroid taper and proteinuria worsened. He was then started on Mycophenolate mofetil (MMF) 1000mg twice-a-day with reduction in proteinuria to 1.8g/g in ~6 weeks and serum albumin improved to 3.3g/dL. We plan to continue MMF monotherapy for 2-3 years similar to lupus nephritis treatment.

Discussion: Idiopathic MPGN is very uncommon in developed countries and the evidence base underlying the treatment recommendations is weak. MMF is a potent immunosuppressive agent which is being increasingly used in primary glomerulonephritides, along with lupus nephritis. Current data from small studies including our case supports the use of this agent in idiopathic MPGN.



SA-PO240

MPGN and Sarcoidosis: A Rare Presentation

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Introduction: Sarcoidosis is a chronic multi-system disease characterized by non-caseating granulomas. It can affect kidneys, but glomerular involvement is rare. There are few case reports of sarcoidosis with membranoproliferative glomerulonephritis (MPGN) where the causality was not proven clearly. Last case described in literature was in 1986. To best of our knowledge, our case is the first in which MPGN is causally related to Sarcoidosis, presented with rapidly progressive glomerulonephritis and severe AKI and first one to be reported since the new classification for MPGN has been proposed.

Case Description: A 32 years old African American male with past medical history of bilateral knee arthritis presented to the hospital with bilateral ankle edema and rash in lower extremities. He was in acute kidney injury (AKI) with creatinine of 3.5 mg/dL. Creatinine 2 years ago was 1.3 mg/dL. Urinalysis showed proteinuria, hematuria, no red blood cell cast. Proteinuia was 6.2 gm/day. Hepatitis B and C, and HIV tests were negative. Cryoglobulin and paraprotein studies were negative. ANA was positive at 1:40, other autoimmune serologies and complements were negative. Angiotensin converting enzyme was elevated at 92 U/L. Renal ultrasound was unremarkable. CT chest showed bilateral hilar lymphadenopathy. Renal biopsy showed MPGN of uncertain etiology. Immunofluorescence (IF) was positive for IgG, IgA, IgM, C3, C1q deposits. Creatinine improved from a peak of 7.4 mg/dL to 3.4 mg/dL with pulse steroids and was discharged on prednisone. A week later he presented back with worsening renal function and was started on dialysis. Lymph node biopsy revealed non caseating granulomas and no infection. Bone marrow biopsy was negative. Cellcept was added to his regimen. His interdylactic rise of creatinine is decreasing. Renal recovery is anticipated.

Discussion: Patient's presentation with arthritis and rash raised suspicion of sarcoidosis related vasculitis supported by a "full house" on IF in renal biopsy and non caseating granulomas on lymph node biopsy. Work up for lymphoma, paraproteinemia, infection and other autoimmune diseases were negative. In Summary, MPGN with Sarcoidosis is very rare. However when no other etiology is identified, Sarcoidosis should be considered in the differential. There is no consensus on treatment. Steroid is treatment of choice. Aggressive therapy, namely Rituximab, cellcept, plasmapheresis should be considered in severe AKI.

SA-PO241

Type 1 Cryoglobulinemia with Skin, Nerve, Pulmonary, and Renal Involvement Preceding a Diagnosis of Multiple Myeloma

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Introduction: Type 1 cryoglobulinemia is a rare cause of glomerulonephritis(GN). Here we present a case of a patient with type 1 cryoglobulinemic vasculitis with multiorgan involvement who met criteria for multiple myeloma 1.5 years after initial presentation.

Case Description: A 56-year-old Caucasian male presented with progressively worsening bilateral lower extremity pain and numbness followed by a lacey purple rash and small volume hemoptysis. Serologic workup was negative for ANA, anti-cardiolipin-ab, ANCA, anti-GBM ab, hepatitis B/C, RF, CCP, and cryoglobulin. He had low C3(73mg/dL), normal C4, elevated M protein(0.3gm/dL), elevated serum kappa(175mg/dL) and normal lambda light chains. Bone marrow (BM) biopsy showed 5% monoclonal plasma cells. BM and fat pad biopsies were negative for amyloid. Bronchoscopy was unrevealing. Skin biopsy was inconclusive, but was notable for leucocytoclastic vasculitis vs thrombotic process. He was initiated on high dose prednisone and rituximab therapy. His symptoms waxed and waned and ultimately he developed hematuria, nephrotic-range proteinuria, and acute kidney injury (creatinine 2.3mg/dL) a year later. Kidney biopsy revealed segmental endocapillary hypercellularity, sub endothelial and mesangial eosinophilic immune deposits with 20% crescents. IF was positive for IgG(3+), kappa light chain(2-3+), and C3(1+). EM showed organized immune deposits with straight to slightly curved rods 10-17 nm in diameter very characteristic of cryoglobulinemic GN. A repeat BM biopsy showed expansion of the monoclonal plasma clone to 20%.He was initiated on plasmapheresis, steroids, cyclophosphamide, and carfilzomib with improvement in his symptoms and renal function. Repeat serum cryoglobulin and cryofibrinogen remained undetectable.

Discussion: This case highlights the challenges with diagnosing cryoglobulinemia based on serologic tests alone, and the differential diagnosis and treatment of cryoglobulinemia due to multiple myeloma. We emphasize therapy should be directed toward the causative plasma cell clone, which in this case was rituximab resistant. We present good outcomes after an induction therapy with steroids and plasmapheresis for a rapidly progressive GN due to cryoglobulinemia. Finally, we present a regimen of steroids, cyclophosphamide and carfilzomib in place of bortezomib for patients with significant nerve involvement.

SA-PO242

Persistent HCV-Related Cryoglobulinemic Glomerulonephritis Following Sustained Virologic Remission and Rituximab Monotherapy

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Introduction: Hepatitis C virus (HCV)-related cryoglobulinemia is treated with direct-acting antiviral therapy and immunosuppression if severe end-organ damage is present. We present a patient with persistent HCV-related cryoglobulinemic glomerulonephritis (GN) years after sustained virologic remission (SVR) refractory to rituximab monotherapy. With the help of our oncology colleagues we are targeting therapy to a low grade lymphoproliferative disorder producing cryoglobulins.

Case Description: A 62 year-old Caucasian man presented with palpable purpura on his lower extremities, nephrotic syndrome, and acute kidney injury in 2010. Serologic workup was notable for HCV (peak viral load 1.3 million iU/mL), depressed C4 level, markedly elevated rheumatoid factor (>650 iU/mL, nl 0 – 14) and type II cryoglobulinemia (monoclonal IgM kappa and polyclonal IgG); SPEP, UPEP, and serum free light chains were unremarkable. Kidney biopsy showed membranoproliferative GN with IgM kappa deposits, suggestive of cryoglobulinemic GN. A bone marrow biopsy did not show a clonal cell population. He achieved SVR at three months following treatment with simeprevir and sofosbuvir, but his nephrotic range proteinuria and purpura persisted. In 2015, the patient was treated with two courses of rituximab, however he continued to have nephrotic range proteinuria and cryoglobulinemia. A kidney biopsy was repeated and showed membranoproliferative GN with hyaline thrombi as well as subendothelial and mesangial deposits without a clear substructure, and a low-grade CD-20+ B cell lymphoma. He is currently being treated with rituximab and bendamustine for low grade B cell lymphoma. At last follow-up proteinuria improved from 8.1 to 4.2 grams/day; eGFR declined from 30 to 18ml/min/1.73m2.

Discussion: HCV-related cryoglobulinemic GN following SVR is increasingly recognized. This case of cryoglobulinemia highlights the intersection between HCV (typically types II-III) and lymphoproliferative disorders (typically type I), and draws attention to the need for appropriately targeted therapies. Given the growing use of direct-acting antiviral agents for HCV, novel therapeutic strategies are needed to effectively treat refractory cases of HCV-related cryoglobulinemic GN.

SA-PO243

Cry, Cry Again: A Case of Idiopathic Cryoglobulinemia

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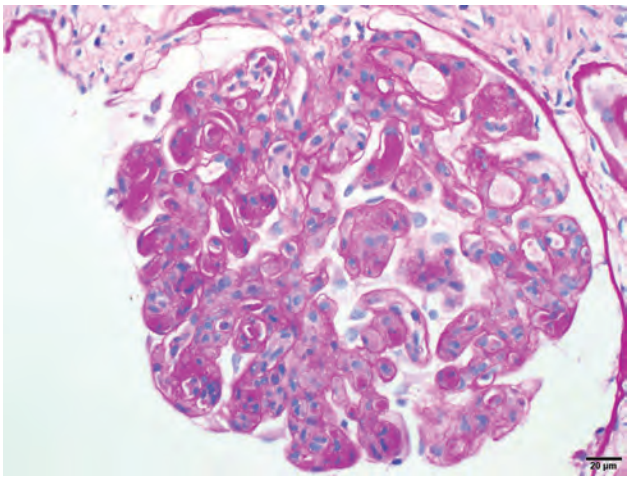
Introduction: Cryoglobulinemia is characterized by the presence of cryoglobulins in the serum, and it is commonly associated with persistent viral infections, autoimmune diseases, and lymphoproliferative disorders. Although there are standardized treatments for viral or malignancy associated cryoglobulinemia, a protocol for idiopathic non-viral cryoglobulinemia has yet to be described. Literature supports using a combination of high dose glucocorticoid therapy and plasmapheresis. In true idiopathic cryoglobulinemia, Rituximab has improved outcomes in published cases. Here, we present a patient with newly diagnosed idiopathic cryoglobulinemia in whom Rituximab was added to high dose steroids resulting in improvement of renal function

Case Description: A 66-year old male with a history of leukocytoclastic vasculitis diagnosed by biopsy of a right leg rash 7 years prior, presented with 2.5 weeks of new onset lower extremity edema and scrotal swelling. He had new onset hypertension, acute kidney injury, hyperkalemia, and non-anion gap metabolic acidosis. A 24-hour urine collection was consistent with nephrotic range proteinuria. A laboratory work-up showed an undetectable C4, low-normal C3, positive rheumatoid factor, and positive ANA with titer >640. Kidney biopsy revealed immune deposits consistent with cryoglobulinemia and immunofluorescence was negative for other pathology (Figure 1). The remaining viral and autoimmune laboratory work up was negative, including both Hepatitis panel and HCV RNA. The patient received three days of pulse dose steroids followed by a single dose of rituximab at 375 mg/m2. His creatinine, proteinuria, and overall clinical picture improved and has persisted.

Discussion: Guidelines to treat idiopathic non-viral cryoglobulinemia do not exist. Rituximab may be an effective and intuitive adjunct treatment, per literature review and in our patient.



SA-PO244

Novel Approach to Treatment of Mixed Cryoglobulinemia with Kidney Involvement: Case Report

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Introduction: Mixed cryoglobulinemia (CG) is rarely associated with hepatitis B virus (HBV) infection. Monoclonal CG can result from an underlying lymphoproliferative disorder. We report a case of mixed CG with treated HBV and a low-grade lymphoproliferative disorder. Adverse reactions to standard therapies motivated a novel proteasome-inhibitor based approach

Case Description: A 67-year-old woman with a 5-year history of mixed CG and membranoproliferative glomerulonephritis experienced cerebrovascular and gastrointestinal ischemia with deteriorating kidney function, persistent hematuria, and proteinuria, while receiving maintenance tacrolimus and prednisone. Prior therapies included mycophenolate (persistent disease activity), rituximab (serum sickness), cyclophosphamide (leukopenia), and azathioprine (persistent disease activity). Labs included: +RhF, +HBV sAg with negative sAb (treated with entecavir with undetectable viral load), negative HCV, +IgM monoclonal gammopathy, and hypogammaglobulinemia. Before further immunosuppressive therapy, she received subcutaneous immunoglobulin for hypogammaglobulinemia. She developed palpable purpura, increasing creatinine (2.1 to 4.3 mg/dL), and increasing cryocrit, consistent with an immunoglobulin-triggered CG vasculitis flare. Given underlying monoclonal gammopathy, we initiated bortezomib and dexamethasone. Her creatinine initially declined to 2.8 mg/dL; however, she then developed severe diarrhea (attributed to bortezomib toxicity). Repeat kidney biopsy revealed 5 of 19 glomeruli with global sclerosis, 6 of 19 with cellular crescents, and large IgM Kappa positive subendothelial cryoglobulin deposits. She received 5 days of plasma exchange and intravenous corticosteroids followed by carfilzomib as an alternate proteasome inhibitor: response pending at time of abstract submission.

Discussion: Unlike prior cases of HBV-associated CG, our patient had persistent disease activity despite viremia clearance. Cryoglobulinemic vasculitis flares following intravenous or subcutaneous immunoglobulin have not been widely reported. A proteasome inhibitor-based approach might represent a novel treatment option when standard therapies fail.

SA-PO245

Gall Bladder Arteritis in a 35-Year-Old Lady with Mixed Cryoglobulinemia Syndrome

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Introduction: Mixed Cryoglobulinemia Syndrome is a systemic disease caused by the deposition of circulating immune complexes (cryoglobulins) in small and medium –sized arteries. Type II cryoglobulinemia is most often due to Chronic Hepatitis C infection and it is also seen in autoimmune disorders such as SLE and Sjogren's syndrome. Whilst skin and renal involvement are common clinical features, gall bladder involvement is very rare and we report a case of cholecystitis due to cryoglobulinemic vasculitis.

Case Description: A 35-year-old lady with Sjogren's syndrome presented in August 2016 with systemic symptoms, acute kidney injury(AKI), hypertension, significant hemoproteinuria, low C3 and C4 and positive cryoglobulins (type II). ANCA and anti GBM antibodies were negative. PET CT scan and a bone marrow trephine were done to exclude lymphoma. She underwent a kidney biopsy which confirmed cryoglobulinaemic glomerulonephritis and was managed with plasmapheresis, Rituximab and Methylprednisolone followed by oral prednisolone. Her systemic symptoms, kidney function and proteinuria improved. In December 2016 her condition relapsed with systemic symptoms, skin rash, worsening renal function and positive cryoglobulins (cryocrit 8%). She responded to another course of plasmapheresis, Rituximab and prednisolone. In May 2017 she was admitted under Gastroenterology for right upper quadrant pain, raised CRP and deranged liver function tests. She was diagnosed with acute cholecystitis. At this time she developed another cryoglobulinemic relapse with oliguric AKI. She was managed again with plasmapheresis, Rituximab and prednisolone. She also needed hemodialysis briefly. She had an interval cholecystectomy. The gall bladder histology was reported to show florid arteritis in the medium sized arteries related to cryoglobulinemia (images will be provided in the poster). Her kidney biopsy was repeated and it also showed arteritis with severe chronic damage. Cyclophosphamide was added to the treatment regimen to prevent further relapses and because of the extra-renal disease.

Discussion: To our knowledge this is the first case report of cryoglobulinemic vasculitis that manifested in the gall bladder and mimicked acute cholecystitis during a relapse. The diagnosis can be missed or delayed and therefore careful examination and correlation with the clinical picture is essential.

SA-PO246

Fungal Endocarditis and ANCA-Vasculitis: More Than a Mere Coincidence?

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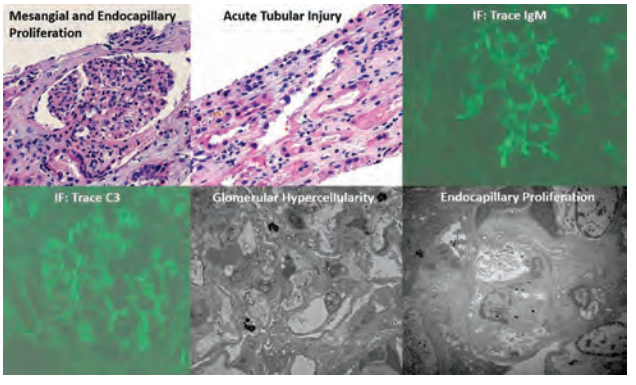
Introduction: Glomerulonephritis (GN) due to infective (bacterial) endocarditis is well documented, with the most common lesions being necrotizing and crescentic GN, followed by endocapillary proliferative GN. Prominent C3 staining and subepithelial immune deposits on EM are commonly associated with infection-related GN than Pauci-immune picture of ANCA vasculitis. Herein, we present a case of Pauci-immune proliferative GN in a patient with fungal endocarditis.

Case Description: A 52-year-old White man with a history of intravenous drug abuse, chronic hepatitis C and diabetes mellitus initially presented to our institution with fever and bilateral lower extremity rash/palpable purpura. Biopsy of the rash demonstrated small and medium vessel vasculitis. He was also found to have native aortic valve endocarditis with ~1.5 cm vegetation and *Candida parapsilosis* fungemia which failed treatment with Micafungin and therefore switched to amphotericin B and flucytosine. Later, he developed worsening renal function with sub-nephrotic proteinuria and work up revealed dysmorphic RBCs in the urine, hypocomplementemia, positive C-ANCA, PR3 and cryoglobulins. In the presence of multiple confounding factors and varied differentials (e.g. hepatitis C-MPGN, post-infectious GN, ANCA vasculitis), a renal biopsy was obtained which showed proliferative Pauci-immune glomerulonephritis with ATN [Figure]. His renal function worsened requiring dialysis. Immunosuppressive therapy was not attempted because of active fungemia.

Discussion: Interestingly, ANCA antibody is found in up to 28% of the tested patients with infective endocarditis. However, Post-infectious Pauci-immune GN in association with *Candida parapsilosis* has never been reported in the literature to the best of our knowledge. It is likely that the fungal capsular polysaccharide activates complement cascade and triggers inflammation. Whether ANCA-antibody was a coexistent distinct entity or induced by fungal infection or underlying hepatitis C in our patient remains elusive.



SA-PO247

Relapsing Hepatitis B (HBV)-Associated Vasculitis with Features of Polyarteritis Nodosa (PAN) and cANCA-Associated Vasculitis

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Introduction: HBV-associated vasculitis typically manifests as the medium vessel vasculitis, PAN. HBV-associated PAN (HBV-PAN) is ANCA(-), without glomerulonephritis (GN) or pulmonary involvement; relapse does not occur after successful HBV seroconversion. We describe a unique case of HBV-associated vasculitis with features of a small and medium sized overlap vasculitis and atypical long term course.

Case Description: The patient is a 60-year-old male with hypertension and HBV who initially presented with abdominal pain and scrotal swelling. Abdominal angiogram revealed beaded morphology and aneurysms involving mesenteric, hepatic, and

intraparenchymal renal arteries. Hepatitis B core antibody, cANCA, PR3, and rheumatoid factor were (+). He received pulse steroids and Cytoxan for treatment of PAN and Entecavir for HBV, resulting in resolution of symptoms. Serum Cr rose from 0.8 mg/dL to 2.0 mg/dL during the first 2 months of treatment, and then remained stable. Multiple urinalysis (UA) measurements were negative. Two years later, the patient developed abdominal pain, orchitis, hemoptysis, and acute kidney injury (serum Cr of 11 mg/dL). HBV viral load was negative. UA showed 3+ blood and 3+ protein. Renal biopsy displayed pauci-immune crescentic GN with active crescents involving ~ 50% of the glomeruli (Figure A, Jones stain). Two arteries had evidence of past arteritis with elastic lamina disruption (Figure B, EVG stain); acute necrotizing arteritis was not present. The patient recovered renal function (most recent serum Cr=3.2 mg/dL) after therapy with pulse steroids, plasma exchange, Rituxan, and Cytoxan.

Discussion: Our patient with HBV-associated vasculitis initially presented with manifestations of medium vessel involvement, but with an unusual feature of cANCA/PR3 seropositivity. Relapse occurred 2 years later with PAN symptoms (orchitis, severe abdominal pain) and evidence of ANCA-associated small vessel vasculitis (GN, hemoptysis). While the initial trigger may have been HBV, the vasculitis later became self-perpetuating as it recurred during a time when there was no HBV viremia. Patients with HBV-PAN who are ANCA+, should be closely followed because they could be at higher risk of vasculitis relapse.

SA-PO248

ANCA Negative Pauci-Immune Crescentic Glomerulonephritis Associated with Cervical Carcinoma

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Introduction: Glomerulonephritis (GN) associated with solid tumors is a rare but well-known entity. Various forms of paraneoplastic GN have been described in the literature, most common being membranous and minimal change disease. Here we present a case of cervical cancer and rapidly progressive crescentic GN involving near 100% of the glomeruli sampled.

Case Description: A 58-year-old woman admitted for rising creatinine found on routine labs prior to initiation of chemotherapy. Medical history was significant for recently diagnosed poorly differentiated cervical carcinoma, AJCC stage IIB., for which she had been actively receiving radiation therapy. She denied prior kidney disease, use of non-steroidals nor recent antibiotics. On presentation, Cr was 2.4 mg/dL from baseline of 0.9 mg/dL a month prior to presentation. Urinalysis revealed active sediments. 24-hour urine quantified proteinuria in nephrotic range (8 gms/24-hr). Extensive GN work-up was negative. Serum protein electrophoresis and urine immunofixation showed no monoclonal gammopathy. A renal ultrasound showed normal size kidneys. A kidney biopsy divulged severe, active necrotizing and crescentic glomerulonephritis involving nearly 100% of 22 sampled glomeruli. There were cellular crescents and amyloidosis, type AA, with extensive glomerular and focal vascular involvement. Acute tubular injury and extensive tubulointerstitial inflammation were also noted. Patient's renal function continued to deteriorate in parallel to progression of her malignancy and was eventually started on hemodialysis five months after her initial diagnosis of GN. Unfortunately, patient was never deemed a candidate for chemotherapy due to poor performance status. She continued to decline and transitioned to comfort care passing less than 7 months from her initial renal diagnosis.

Discussion: We present a unique case of rapidly progressive crescentic GN associated with cervical cancer. There have been cases of membranous glomerulonephritis associated with cervical cancer but crescentic GN has not been reported in the literature to the best of our knowledge. As in other cases of paraneoplastic GN, treatment targeted towards the cancer results in resolution of the GN in most cases but our patient was not a chemotherapy candidate and her disease ultimately progressed to end stage renal disease.

SA-PO249

Necrotizing ANCA Positive Glomerulonephritis Associated in Culture Negative Endocarditis

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Introduction: Renal involvement is a common extra cardiac manifestation of infective endocarditis (IE) affecting up to 50% of all patient. Kidney manifestations in IE are variable, including direct consequence of infection such septic emboli, immune complex glomerulonephritis and more interestingly ANCA associated glomerulonephritis have been described. Making challenging the differentiation between infectious endocarditis related glomerulonephritis and small vessel vasculitis. Even more a subgroup of patient with culture negative infectious endocarditis has been associated with glomerular disease and seropositive ANCA titers caused by *Bartonella species*, been the most common cause of culture negative endocarditi. Diagnosis relies on clinical suspicion and serologic titers diagnostic tools.

Case Description: Case of a 73 year old with no past medical history who presented with progressive shortness of breath for 3 weeks associated with fever and chills. Complaining of bloodey sputum for the past 3 days. Physical Exam showed bilateral ronchies and crackles. Pitting edema +2. Labs serum cr 5.90mg/dL, eGFR 9mL/min/1.73m^2. WBC 7.7, Hgb 6.5g/dl. UA RBC > 182, WBC 27, Upr > 100mg/dL. UPCR 4.4, C3 73, C4 14.8, ANCA PR3 positive. CT chest showing bilateral calcified granulomas. Echocardiogram showed 1.5 x 1.4cm calcified irregular mass noted in the tricuspid valve. Received broad spectrum antibiotics. Blood cultures negative. Renal biopsy showed crescetic focal necrotizing glomerulonephritis, with moderate fibrosis. Immunofluorescence(IF) showed mensagial IgG(1+), IgA(1+), IgM(2+), C3(2+),C1q(2+), kappa(2+) and lambda(2+). Ultrastructurally showed mesangial matrix immune complex type dense deposits. Bartonella henselae titers IgG 1:1024. Treated antimicrobial and pulse steroid followed by tapered.

Discussion: This case highlights the unique complexity in differentiating between primary small vessel vasculitis vs infectious endocarditis related glomerulonephritis, where initial serology can be misinterpreted. Ultimately with the clinical and renal biopsy findings along with bartonella titers lead to the diagnosis of culture negative endocarditis related glomerulonephritis

SA-PO250

Eosinophilic Granulomatosis with Polyangiitis - Renal Biopsy Can Aid in Guiding Therapy

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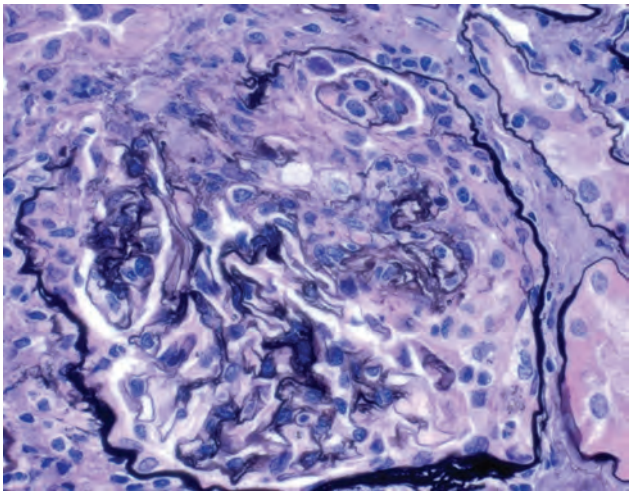
Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA), a rare systemic vasculitis; can cause end organ damage with eosinophilic infiltration of the extravascular tissue and necrotizing vasculitis. Patients with renal involvement usually develop rapidly progressive glomerulonephritis (GN).

Case Description: 61-year-old female with 1.5-year history of asthma, recurrent sinusitis with nasal polyposis presented with fever. Lab work showed leukocytosis (WBC 23,400/mm^3 with 29% eosinophils), serum creatinine (SCr) 0.7 mg/dL, microscopic hematuria, proteinuria and positive antineutrophil cytoplasmic antibody (ANCA) 1:320 with myeloperoxidase specificity. Therapy with glucocorticoids was initiated. She developed acute kidney injury, initially atrribited to volume depletion; when SCr worsened to 1.9 mg/dL and improved to 1.3 mg/dL with IV fluids. Renal biopsy showed segmental necrotizing pauci-immune GN with crescent formation. Treatment with cyclophosphamide (CYC) (10mg/kg) was initiated. On 3 week follow up, SCr worsened to 2.7 mg/dL when CYC was escalated to 15mg/kg/dose for the next 3 doses. Her SCr improved and stabilized at 2 mg/dL over the next 2 months.

Discussion: Renal function as measured by SCr can be relatively preserved in crescentic ANCA vasculitis. Biopsy showing renal involvement affected the decision to initiate therapy with CYC in this patient. The rapidity of decline in renal function despite treatment foretells that the patient could have had a worse renal outcome with delay in appropriate immunosuppressive (IS) therapy. Our case emphasizes the importance of doing a renal biopsy in patients with systemic features of EGPA and active urine sediment even with normal relatively preserved SCr, not only for definitive diagnosis but also guide clinicians to pursue aggressive early IS therapy and improve renal prognosis.



Glomerulus showing a cellular crescent (methanamine silver staining)

SA-PO251

PSGN – When Kidneys Take a Hit

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Introduction: Complication of Streptococcal pharyngitis leading to post-streptococcal glomerulonephritis.

Case Description: 12 year old boy presented with hematuria, oliguria, arthralgia, periorbital and peripheral edema in the setting of acute kidney injury. 10 days prior to admission, patient was diagnosed with recurrent strep throat infection which was treated with Amoxicillin-Clavulanic acid. Examination findings were positive for diffuse maculopapular rash and presence of cola colored urine. On admission, lab work was significant for Cr 1.10 (baseline Cr 0.50), elevated ASO titer 983, DNase B Ab 1390 and UA

positive for blood and protein. What was surprising, that the patient had normal complement (C3 and C4) levels at presentation. Appropriate fluid resuscitation was initiated, resulting in an improvement in urine output and renal function, but a fall in C3 and total complement levels was noted. Given this atypical presentation, along with possible concerns for other forms of vasculitis especially Henoch Schonlein Purpura, a short burst of steroid treatment was initiated. Patient showed significant clinical improvement with complete resolution of hematuria, oliguria, proteinuria, edema and rash. Follow up with PCP and nephrology in 6 weeks revealed a normal complement level and given this scenario, a diagnosis of post-streptococcal glomerulonephritis (PSGN) was made.

Discussion: The hallmark of GN is inflammation within the glomeruli that typically manifests as hematuria and proteinuria. Renal function may be reduced, depending on the severity of the acute condition or the presence of chronic glomerular injury. Post-streptococcal glomerulonephritis is the leading cause of acute nephritic syndrome. Most cases are sporadic, although the disease has been known to occur in epidemic form. The overall incidence of PSGN in the United States has significantly decreased with good long term prognosis. More than 95% of patients recover spontaneously and return to baseline renal function within three to four weeks with no long term sequelae. Acute PSGN usually is diagnosed on clinical and serologic grounds without the need for biopsy, especially in children with a typical history.

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A Challenging Diagnosis and a Missed Treatment Opportunity: A Case of Bartonella Endocarditis Complicated with Rapidly Progressive Glomerulonephritis

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Introduction: Bartonella is the most common cause of culture negative endocarditis in the USA which is complicated by kidney failure in 45% of patients. Diagnosing Bartonella endocarditis is very challenging but crucial. Treating bartonella associated glomerulonephritis (GN) with immunosuppressants is fatal.

Case Description: This is a 52-year-old male with a history of bioprosthetic aortic valve replacement (AVR) who presents to the ED with 6 days of bilateral flank pain and hematuria. Physical exam was largely unremarkable including no rashes. Creatinine was 7 mg/dl. Urinalysis was remarkable for gross blood, 100 RBCs, proteinuria and RBCs casts. Imaging of abdomen and pelvis were unremarkable. Autoimmune workup was negative. Urgent hemodialysis (HD) and corticosteroids were started. Kidney biopsy was inconclusive due to inadequate tissue. He was discharged on outpatient HD and a steroid taper. One month later, repeat kidney biopsy showed crescentic segmental necrotizing GN and focal deposits of IgM, C19 and C3. He was readmitted for plasmapheresis and a steroid course and then discharged with maintenance HD. Over the next 2 months, the patient had multiple episodes of fever, but blood cultures were persistently negative. After four months from initial presentation, he presented to the ED with chest pain and fever. He was diagnosed with NSTEMI. Trans-esophageal echocardiogram showed a small mildly calcified echodensity on the bioprosthetic AVR indicating endocarditis and a small echolucent area in the perivalvular region suggestive of an aortic root abscess. The patient subsequently underwent a sternotomy and aortic valve replacement. PCR performed on the vegetation was positive for Bartonella, as well as Bartonella henselae serology was positive for IgG (1/1024) and IgM (> 1/20).

Discussion: The interval development of endocarditis on echocardiogram, positive Bartonella antibodies and PCR suggest the patient developed GN associated with Bartonella endocarditis. Bartonella is a frequent cause of culture negative endocarditis. Immune deposits showing C3 dominance with IgM staining are consistent with chronic infection related GN. This case highlights the importance of ruling out infectious etiologies of GN before starting immunosuppressants. As treating an active infection with immunosuppressive agents can be life threatening.

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Bartonella Endocarditis Causing Immune Complex Mediated Glomerulonephritis

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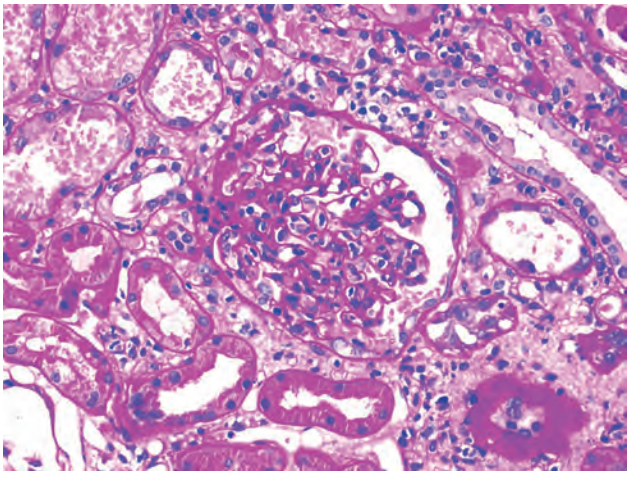
Introduction: Bartonella is associated with subacute bacterial endocarditis. While vegetations are commonly seen, rarely there are cases of subacute endocarditis showing only valvular thickening. We describe one such case of bartonella endocarditis with immune complex mediated glomerulonephritis.

Case Description: A 63-year-old male with history of aortic bioprosthetic valve presented with fevers, chills and myalgias. On presentation, labs showed pancyctopenia- Hb 6.6 g/dL, ANC 1500 per mm^3 and platelet 39 k/mm^3. Creatinine was 3.8 mg/dL, urinalysis showed proteinuria 2+ along with hematuria. LDH was 293 U/L, haptoglobin 25 mg/dL, peripheral smear did not show any schistocytes. Serological work-up showed low C3 at 71 mg/dL, normal C4, negative ANA, positive c-ANCA (1:256) and positive PR-3 Ab. Bone marrow biopsy showed myeloid hyperplasia, reactive-appearing along with polyclonal expansion of plasma cells 10-20%. Renal biopsy showed endocapillary proliferation with no fibrinoid necrosis or cellular crescents. IF showed near full house immune complex deposition with granular, mesangial staining for IgG (2+), IgM (1+), C3 (2+), C1q (trace), kappa (2-3+) and lambda (1+). Infectious work-up showed positive titers for Bartonella Henselae, both IgG (>1:1024) and IgM (1:512), serum PCR was negative. TEE showed severe stenosis of the prosthetic aortic valve and patient was started on doxycycline for Bartonella endocarditis. Four weeks later, he was noted to have partial recovery in renal function but continued to be dialysis dependent given high fluid gains.

Discussion: Bartonella endocarditis can lead to immune complex mediated glomerulonephritis. Even with absence of characteristic vegetations, presence of positive antibody titers along with hypocomplementemia and immune -complex mediated GN, support the diagnosis of endocarditis. Bartonella PCR even though has high specificity, its sensitivity is only about 40-70%. Timely initiation of appropriate antibiotic therapy may improve renal outcome.



SA-PO254

Triple Hit – Case of IgA nephropathy with Thin Glomerular Basement Disease and Nutcracker Syndrome

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Introduction: Included in the differential of hematuria are IgA nephropathy (IgAN) and thin glomerular basement membrane disease (TGBM). IgAN is the most common cause of idiopathic glomerulonephritis with slow progression to End Stage Renal Disease in up to 50% of patients. IgAN has been reported to be associated with TGBM. Recurrent gross hematuria could also be seen in nutcracker syndrome, the incidence of which is increasing with the use of CT/MR-angiography. We report a patient diagnosed concomitantly with nutcracker syndrome, IgAN, and TGBM

Case Description: We present a case of 33-year-old Caucasian female with hematuria. She reported microscopic hematuria since the age of 7 and strong family history of microscopic hematuria. Five years prior to presentation she started developing intermittent gross hematuria with periods of stress and URTIs. Her past medical history is significant for long-standing abdominal and pelvic pain. She also reported episodes of orthostatic hypotension. She was diagnosed with median arcuate ligament syndrome and underwent MAL release in 2015 without resolution of symptoms. Physical exam was unremarkable. Laboratory and other work up was unremarkable except for 3+ blood with numerous RBC/hpf without evidence of infection on urinalysis. Urine protein:creatinine ratio ranged from 0.62-2.04. She had orthostatic proteinuria. Her renal function was stable. Her prior MRA from 2015 revealed a focal narrowing of left renal vein (LRV) between aorta and SMA. Given this constellation of symptoms, not completely explained by one pathology, possibility of nutcracker syndrome was entertained and CTA was repeated which confirmed the LRV narrowing. However, due to her family history of hematuria, intermittent episodes of gross hematuria and proteinuria, a renal biopsy was performed with findings suggestive of IgAN and TGBM.

Discussion: There are published case reports about the association between IgAN and TGBM as well as IgAN and nutcracker syndrome. However, coexistence of all three diseases has not been reported. There are no distinguishing clinical or laboratory features. The causal relationship and prognosis remains unclear. The presence of multiple glomerular pathology poses a unique diagnostic and management challenge. This, combined with anatomic vascular abnormality, further complicates management.

SA-PO255

A Terrible Triad: A Case of Anti-GBM, Membranous, and Waldenstrom's

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Introduction: Anti-GBM disease is a rare disease with a very rapid and destructive course. Much of the knowledge gained has been through case reports and case series. Here, we describe a case of anti-GBM complicated by many factors and the treatment regimen used.

Case Description: A 52y/o man with cryoglobulinemia manifested only by pruritus presented with 12 days of fever, malaise, night sweats and anorexia. Admission creatinine was 1.7, from a baseline 3 days prior of 0.9. Creatinine rapidly worsened and he became oliguric by the 3rd hospital day. Renal biopsy was done on day 4. A dialysis catheter was placed on day 5, anti-GBM resulted at 7.6 and light and IF of renal biopsy showed membranous nephropathy, anti-GBM with necrotizing crescentic GN and severe tubulointerstitial disease. He was pulsed with steroids, started on plasmapheresis,

dialysis, and IV cyclophosphamide. Because of the membranous nephropathy, history of paraproteinemia, increased IgM lambda and lymphadenopathy, bone marrow biopsy was done, showing Waldenstrom's macroglobulinemia. However, due to prior reports that Waldenstrom's is linked to a number of autoimmune diseases including cases of RPGN, he was switched to rituximab, with increasing urine volume up to 2L/day, and decreasing pre-dialysis BUN and creatinine. However, after 6 of 8 cycles of ritumab, anti-GBM titer rebounded to 144. He was re-pulsed with steroids, restarted on cyclophosphamide and underwent daily plasmapheresis for 3 weeks until the GBM titer was zero. Despite preserved urine volume, he remains on hemodialysis.

Discussion: Although there are reports of simultaneous membranous and anti-GBM, or Waldenstrom's and membranous, we could find only one case report of anti-GBM disese and Waldenstrom's, and none with all three. Rituximab, an accepted treatment for Waldenstrom's and membranous nephropathy has been used in a few patients with anti-GBM, mostly those who failed cyclophosphamide. Despite an initial response to therapy, he relapsed after completion of plasmapheresis, while still receiving rituximab. We suspect membranous nephropathy secondary to Waldenstrom's. PLA2R was negative but obtained after plasmapheresis/dialysis. We speculate uncovering of the Goodpasture's epitope, secondary to another underlying process.

SA-PO256

A Case of Concurrent IgA Nephropathy and Microscopic Polyangiitis

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Introduction: IgA nephropathy is the most common cause of glomerulonephritis worldwide. It is rarely seen to concur with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. This is a case of a elderly female patient with an overlap of microscopic polyangiitis and IgA nephropathy responsible for acute kidney injury which responded to immunotherapy.

Case Description: An 82 year old lady with a history of hypertension and diabetes mellitus presented to the hospital for evaluation of AKI detected on routine blood work. Her creatinine was 5.3 mg/dL from a baseline of 1.2 mg/dL and she had hematuria for over 1 year. She has a past medical history of multiple autoimmune diseases, including thyroid disease, vitiligo, keratoconjunctivitis sicca, arthritis, and myopathy, and remote pancreatic adenocarcinoma status-post Whipple procedure. Review of systems was positive for fatigue, chills, arthralgias, myalgias, back pain, and dysuria. Physical exam was unremarkable. UA was significant for glycosuria (50 mg/dL), hemoglobinuria (3+), hematuria (34 RBC/hpf), and proteinuria (3.0 grams). Serology shown a positive ANA, positive ANCA with anti-MPO specificity, and hypocomplementemia (C3 48 mg/dL, C4 9 mg/dL). A renal biopsy revealed crescentic glomerulonephritis, glomerular IgA-dominant immune complex deposition, and peritubular capillaritis in the setting of advanced arterio-nephrosclerosis. A severe, active glomerulonephritis with fibrous and fibrocellular crescents was present, concurrent with low grade immune complex deposition, which was IgA-dominant and was restricted to the mesangium. This suggested that the ANCA-associated process was predominant, with concurrent IgA nephropathy. The patient was treated with Cytoxan and pulse steroid therapy. The patient had an acute drop in hemoglobin to 6.5 mg/dL with respiratory distress with increased oxygen requirements, and was found to have an alveolar hemorrhage. The patient was given oxygen, red cell transfusions, and plasmapheresis. There were no additional complications and the patient had improved respiratory and renal function at follow up.

Discussion: Although IgA nephropathy and ANCA-associated vasculitis do not frequently overlap clinically, recognition of concurrence is critical, as these cases are associated with aggressive disease with rapidly progressive glomerulonephritis, yet have good outcomes with immunosuppressive therapy.

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Concomitant Atypical Hemolytic Uremic Syndrome and Lupus Nephritis in a Pregnant Woman

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare but devastating condition. It involves uncontrolled activation of alternative complement pathway either due to genetic mutation or autoantibodies leading to dysfunction of regulatory proteins. Various triggering factors have been associated with aHUS including infections, pregnancy, drugs, and systemic lupus erythematosus (SLE). In pregnancy with known SLE, diagnosing aHUS can be delayed as the presentation may mimic a flare of lupus nephritis.

Case Description: A 20-year female diagnosed with lupus nephritis (Class III) diagnosed at the age of 13 was on maintenance therapy with prednisone and mycophenolate mofetil with preserved renal function for 6 years, creatinine 0.6 mg/ml. She stopped taking immunosuppressive medications on her own initiative. Two months later she became pregnant. At 10 weeks gestation, creatinine had increased to 3.3 mg/dl accompanied by severe anemia, thrombocytopenia, high anti-ds DNA titers, and severe hypocomplementemia. Her pregnancy was terminated, and she was placed on hemodialysis and was discharged after being treated as a lupus nephritis flare with prednisone and cyclophosphamide. She was readmitted 2 weeks later with shortness of breath worsening anemia and thrombocytopenia with numerous schistocytes. ADAMTS13 activity level was 100% prompting initiation of plasmapheresis, but without improvement. aHUS panel showed low complement factor H levels with normal complement factors I and B. Renal biopsy showed class V lupus nephritis and thrombotic microangiopathy with focal interstitial fibrosis consistent with aHUS. She was initiated on eculizumab as well as prednisone and mycophenolate mofetil and continues on hemodialysis and this pharmacologic regimen.

Discussion: Diagnosis of aHUS can be difficult and is often delayed in patients as the clinical presentation may mimic lupus nephritis particularly in pregnancy or may be present together with lupus nephritis. Assessment of the alternative complement pathway, early diagnosis and treatment with eculizumab is important in these setting.

SA-PO258

Vancomycin Associated AKI: Think of Thrombotic Microangiopathy

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Introduction: Vancomycin-induced renal toxicity is common and thought to be due to interstitial nephritis or direct tubular toxicity. Vancomycin can also induce an immunological response, leading to production of drug-dependent anti-platelet antibodies and cause immune-mediated thrombocytopenia. A similar antibody mediated process can be associated with drug-induced thrombotic microangiopathy (TMA) and AKI.

Case Description: A 51 year old woman, who recently completed a 2 week course of Levofloxacin for pneumonia, was diagnosed with a lung abscess and empyema and initiated on Vancomycin, Cefepime and Metronidazole along with a chest tube placement. She remained hemodynamically stable with kidney function at baseline. On hospital day 5, she developed oliguric AKI with supratherapeutic vancomycin levels. She was also noted to be thrombocytopenic. Hemolysis labs were abnormal with LDH 730 and haptoglobin <10. Peripheral smear showed 10-12 schistocytes/hpf. Liver function tests, disseminated intravascular coagulation workup, complement levels, auto-immune and vasculitis serologies were within normal limits. ADAMTS13 activity was markedly low (<5%) and ADAMTS13 inhibitor presence was confirmed with Bethesda assay. Vancomycin-dependent anti-platelet antibody (tested at Blood Center of Wisconsin) was positive. Diagnosis of acquired TTP was made and managed with discontinuation of vancomycin and initiation of plasma exchange for a total of 4 exchanges and prednisone with improvement in platelet count, hemolysis parameters and kidney function. (Table 1).

Discussion: We report a case of acquired TTP with ADAMTS13 inhibitor and vancomycin-dependent antiplatelet antibody. A previous study reported one patient with suspected vancomycin-induced TMA with presence of anti-platelet antibodies but ADAMTS13 activity was not tested. In our case, timing of TMA and AKI after 5 days of vancomycin exposure along with presence of the antibody point towards a vancomycin associated immune mediated process. It is difficult to ascertain if the antiplatelet antibody was detected as the ADAMTS13 inhibitor or if both antibodies co-existed. TMA should be identified as a cause of vancomycin associated AKI.

TABLE 1. LABORATORY PARAMETERS

	Day 1	Day 4	Day 5	Day 6	Day 10 (After PLEX started)	Discharge
Serum Creatinine (mg/dL)	0.6	0.6	3.1	5.2	2.2	0.9
Hemoglobin (g/dL)	10.6	9.8	9.4	7.2	7.9	8.5
Platelet Count X10^3/μL	273	132	23	27	55	286
Vancomycin level μg/mL	15	22.5	60.9	47.2	10.2	2.3

SA-PO259

Eculizumab in the Setting of Gemcitabine Induced Thrombotic Microangiopathy

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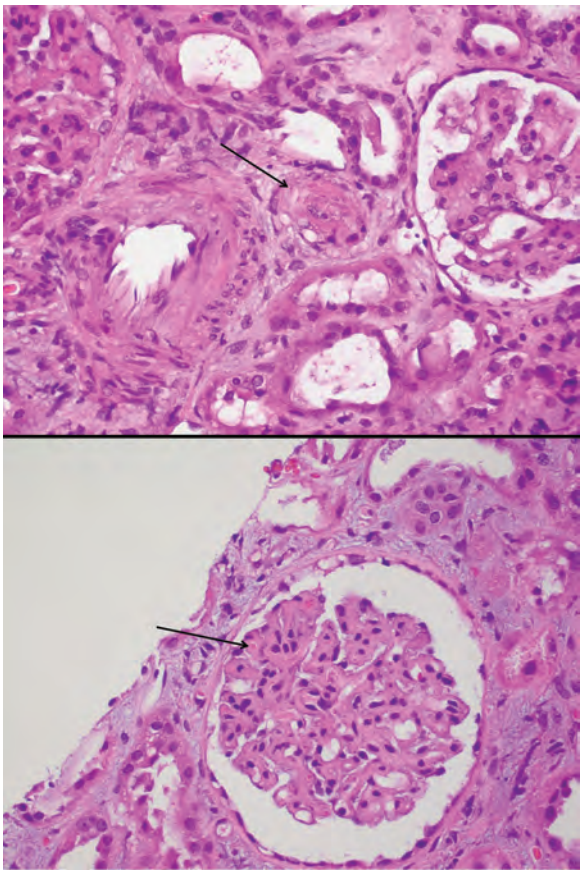
Introduction: Thrombotic Microangiopathy (TMA) is a rarely encountered side effect in gemcitabine use. Previous studies have suggested that eculizumab might be an effective treatment in gemcitabine induced TMA. We present a case of gemcitabine induced TMA in a patient who did not improve with supportive care and withdrawal of the offending agent, who was successfully treated with eculizumab.

Case Description: A 68-year-old female with history of hypertension and metastatic breast cancer, previously treated with carboplatin and gemcitabine presented with anemia and fever. The patient was noted to have hemoglobin 4.6g/dL, reticulocyte percentage 4.79, elevated total bilirubin 2.5 mg/dL, evidence of hemolysis (haptoglobin < 20 mg/dL, elevated LDH 2810.0 U/L, and schistocytes on the peripheral smear), and thrombocytopenia (platelet count 83 x 10^3/uL). The patient had initiated treatment with gemcitabine two days before presenting to the Emergency Department. The patient's creatinine on admission was 2.7 mg/dL, previously 0.80 mg/dL. Despite discontinuation of gemcitabine and institution of supportive care, the patient's creatinine continued to rise throughout her hospitalization and she became anuric requiring dialysis. Needle core kidney biopsy demonstrated thrombotic microangiopathy. The patient underwent treatment with eculizumab and had recovery of her kidney function with improvement in her creatinine and urine output.

Discussion: Treatment with eculizumab in gemcitabine induced TMA has shown good results in previous case studies as well as an observational, retrospective, multicentric study previously performed in four French centers. In this report, the use of eculizumab supports the benefit of C5 inhibition for the treatment of gemcitabine induced TMA refractory to supportive care.



SA-PO260

Successful Treatment of Refractory Gemcitabine-Associated Thrombotic Microangiopathy with Eculizumab

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Introduction: Gemcitabine can lead to thrombotic microangiopathy (TMA) which is characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia and AKI. We report a novel treatment approach for a man with pancreatic carcinoma with refractory gemcitabine associated TMA successfully treated with eculizumab, a monoclonal antibody against C5 complement.

Case Description: A 69-year-old man with a history of pancreatic adenocarcinoma treated with gemcitabine and normal baseline renal function (Cr 1.0mg/dl) presented with thrombocytopenia (platelets 31 K/uL), MAHA (schistocytes and LDH 582 IU/L), and AKI (Cr 2.1mg/dl) concerning for Gemcitabine-associated Thrombotic Microangiopathy (GA-TMA), subsequently diagnosed by renal biopsy. Initially, chemotherapy was held and patient was started on high dose glucocorticoids and 20 PLEX treatments, with rituximab added the next month due to ongoing TMA. There was mild improvement in renal function, but hemolysis and thrombocytopenia persisted, prompting implementation of eculizumab a month later. Patient's hematologic parameters improved and kidney function stabilized. In the meantime, chemotherapy was delayed for 5 months, his cancer progressed, and he passed away 7 months after presentation.

Discussion: This case report demonstrated that eculizumab could successfully treat refractory GA-TMA. GA-TMA is a rare condition that carries mortality rates from 50-70%. Discontinuing gemcitabine, initiating steroids, PLEX, dialysis, and rituximab have been standard therapy. Eculizumab has been shown in a few case reports to normalize some or all the parameters of the disorder, indicating that dysregulation of the complement pathway may play a significant role. Our patient did not respond well to steroids, PLEX and rituximab prompting a novel approach with eculizumab, with subsequent significant improvement in the hemolytic parameters and stabilization of renal function. Further research should focus on randomized controlled trials comparing eculizumab with standard therapy for GA-TMA, and potentially as first line therapy to possibly allow for earlier initiation of non-Gemcitabine chemotherapeutic agents. We need an improved understanding of the mechanisms by which certain chemotherapeutic agents induce TMA, and be able to better identify patients that would be most likely to benefit from eculizumab.

SA-PO261

Ideal Clinical Outcome and Potential Cost Savings with Individualized Eculizumab Dosing using Bayesian Modeling in Atypical Hemolytic Uremic Syndrome

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Introduction: Ecullizumab (Ecu) acquisition cost is approximately $7,000 per 300mg vial. There is limited literature regarding individualized Ecu dosing in atypical hemolytic uremic syndrome (aHUS), particularly in pediatric patients and as disease activity varies.

Case Description: A previously healthy 4 year old male presented with acute onset muscle weakness, elevated creatine kinase, and elevated liver enzymes. He subsequently developed anemia, thrombocytopenia, hypertension, and anuric acute kidney injury requiring dialysis. A muscle biopsy revealed microthrombi in skeletal muscle vessels, and a renal biopsy confirmed thrombotic microangiopathy. He showed clinical improvement with Ecu, although he required an increase in dose amount and frequency to maintain clinical stability and Ecu level >100mcg/mL. With increased dosing, he achieved remission with eventually normalized kidney function. Dosing was adjusted based on Ecu levels to maintenance on standard Ecu dosing. Pharmacokinetic (PK) analysis using Bayesian fitting with population PK parameters (Fig.1) now indicates a sufficient Ecu level could be maintained with every 3 week dosing. The cost of the Ecu doses required to suppress his early, severe disease was $84,000. Standard dosing costs $14,000 every 2 weeks; $364,000 per year. Spacing to every 3 weeks would cost $242,200, a savings of $121,800 per year.

Discussion: This report describes an unusual presentation of aHUS with severe multisystem involvement and highlights the potential for improved clinical outcomes and cost savings by individualizing Ecu dosing in aHUS patients.

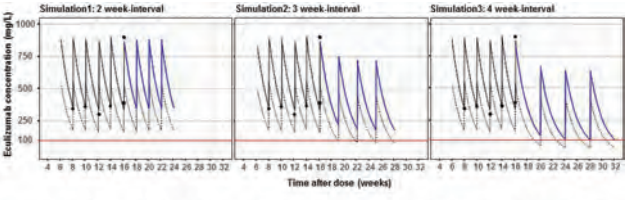

Figure 1: Bayesian Modeling of Ecu Dosing in an aHUS Patient. Dashed lines show the population PK curve in aHUS patients based on mean PK parameters in FDA approval document. Solid lines show this patient's PK profile based on 5 Ecu levels (black circles). Red lines show the recommended concentration of Ecu to control aHUS. Blue lines are simulated PK profiles of this patient with 2, 3 and 4 week-interval dosing.

SA-PO262

Therapeutic Plasma Exchange in Carfilzomib Associated Thrombotic Microangiopathy

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Introduction: Thrombotic microangiopathy (TMA) was reported to be associated with second generation proteasome inhibitors. The role of therapeutic plasma exchange(TPE) in management of carfilzomib induced TMA is not clear. Here we present our experience on TPE use in management of carfilzomib induced TMA.

Case Description: 61 year old man with past medical history of congestive heart failure, type 2 diabetes mellitus, hypertension, chronic kidney disease, diagnosed with kappa light chain multiple myeloma in February 2016. He was started on Cybor-D chemotherapy in March 2016. His chemotherapy was interrupted several times due to acute kidney injury (AKI). Subsequently, he progressed and he was transitioned to carfilzomib, revlimid, and dexamethasone combination of chemotherapy in May 2017. Two months after initiation of carfilzomib therapy patient developed markedly elevated BUN and serum creatinine. Patient underwent kidney biopsy, which revealed abundant glomerulosclerosis (8/10 globally sclerotic) and ~ 70% of interstitial fibrosis and tubular atrophy. Some non-sclerotic glomeruli showed global capillary thrombosis and necrosis. Patient underwent eight sessions of TPE. Lactate dehydrogenase improved after termination of carfilzomib and continued to improve after TPE. Haptoglobin improved after TPE. Platelet count did improve despite termination of chemotherapy and TPE. Unfortunately, because of severity of AKI patient never regained kidney function and required chronic hemodialysis.

Discussion: We presented case of TMA after initiation of carfilzomib for the treatment of multiple myeloma. Patient did not have ADAMTS 31 deficiency. TPE was held to assess for platelet response, which remained stable then increased and therefore TPE was not resumed. In our patient platelete transfusion given prior to renal biopsy confounded interpretation of total TPE. Given the pattern of minimal hematological and clinical response in our patient to TPE compared to the response in patients with idiopathic TTP, we speculate the optimum role of TPE is minimal or not established in Carfilzomib associated TMA. Discontinuation of the drug remains an important management strategy and the role of TPE is still not categorized by ASFA. Clinicians should be aware of rare association between carfilzomib underlying TMA. Discontinuation of the drug, future drug avoidance and supportive care is the corner stone of management.

SA-PO263

Reversible Dialysis Dependent AKI Due to Carfilzomib Induced Thrombotic Microangiopathy (TMA)

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Introduction: Renal complications of carfilzomib, a second-generation proteasome inhibitor used in treatment of relapsed or refractory multiple myeloma, are typically mild and reversible. However, severe acute kidney injury (AKI) related to TMA and tumor lysis have also been reported. We report an additional patient with kidney biopsy confirmed TMA leading to dialysis dependent AKI that fully resolved after discontinuing caflizomib without the use of immunosuppressive medications or plasmapheresis.

Case Description: 56 year old male with stage 1 IgG kappa light chain restricted multiple myeloma with 50-60% of bone marrow replacement with CD138+ plasma cells with t(11;14) translocation received intial treatment with bortezomib, lenalidomide and dexamethasone with minimal response. He was then treated with one cycle of carfilzomib (20 mg/m^2 on 2 consecutive days), lenalidomide, and dexamethasone. He subsequently presented two weeks later with non-oliguric AKI with a serum creatinine of 10.3 mg/dL (pre-treatment creatinine, 0.9 mg/dl). He was euvolemic by clinical examination and no kidney abnormalities were noted on kidney ultrasound. Additional laboratory included: uric acid 11.7mg/dL, serum calcium 7.5mg/dL, phosphorus 4.8mg/dL and potassium 3.6mg/dL. Hemoglobin had decreased from 13.8 to 9.8 g/dl, platelet count decreased from 384 to 72 K/ul, and schistocytes were noted on the peripheral blood smear. AKI worsened despite discontinuing carfilzomib and the administration of intravenous fluids and rasburicase. Temporary hemodialysis support was required for one week. Renal biopsy revealed thrombotic microangiopathy, acute tubular injury, moderate arteriosclerosis and arteriolar hyalinosis. AKI rapidly resolved with follow up serum creatinine of 1.1 mg/dL. Similarly, hemoglobin and plateltet count gradually returned to pre- treatment values. He is currently being evaluated for autologous stem cell transplantation and has not been rechallenged with carfilzomib..

Discussion: Our patient had renal biopsy proven TMA following a single cycle of carfilzomib treatment that resulted in dialysis dependent non-oliguric AKI with associated microangiopathic anemia and thrombocytopenia. AKI was reversible after discontinuing carflizomab without concomitant use of plasmapheresis or immunosuppressive medications, consistent with direct drug induced toxicity.

SA-PO264

A Rare Case of Methamphetamine Induced Thrombotic Microangiopathy and End Stage Renal Failure

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Introduction: Recreational drug abuse is not only a major public health problem with significant morbidity and mortality, but also one of the frequently neglected risk factors for End Stage Renal Disease (ESRD). Amongst these inconsiderate risk factors, methamphetamine induced Thrombotic Microangiopathy (TMA) and ESRD is indeed a rare entity. We report a rare case of ESRD from methamphetamine induced TMA and stress the importance of recognizing methamphetamine as a cause of ESRD.

Case Description: A 26 year-old-man with history of drug abuse presented with fatigue, dyspnea and epistaxis for two weeks. Exam revealed a pale young man with tachycardia, pedal edema and a BP of 210/124 mm of Hg. Labs showed hemoglobin of 5gm/dl with mild thrombocytopenia and renal failure with BUN of 171mg/dl and creatinine of 20mg/dl. Peripheral smear revealed schistocytes, consistent with microangiopathic hemolysis, yet did not favor hemolytic uremic syndrome-thrombotic thrombocytopenic purpura due to minimally elevated LDH, normal haptoglobin, bilirubin and ADAMTS13 activity. Serological work up for vasculitis was unrevealing and a renal biopsy was done which showed thrombotic microangiopathic injury and advanced glomerulosclerosis. He was declared ESRD based on biopsy and remained dialysis-dependent. TMA induced ESRD is doubtlessly from methamphetamine abuse, as the patient admitted to using crystal methamphetamine on a weekly basis for many years with several episodes of hypertensive surges as evident by severe left ventricular hypertrophy on echocardiogram.

Discussion: Methamphetamine is a psycho-stimulant, sympathomimetic drug, well known to cause systemic hypertension and cardiomyopathy. A recent study from South Africa showed malignant hypertension in 44.7% and chronic kidney disease in 95.7% of methamphetamine users. Our case report illustrates the need for detailed drug history and considering methamphetamine as a potential cause of TMA and ESRD, as early identification and cessation of drug abuse could prevent irreversible renal damage.

SA-PO265

A Curious Case of Methamphetamine Induced Renal Pseudo-Vasculitis

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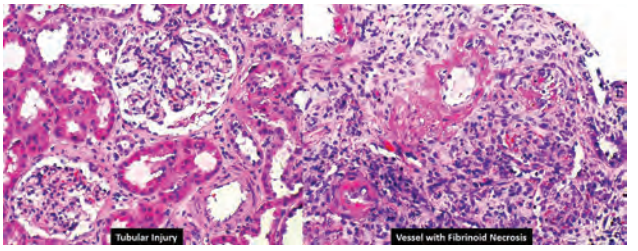
Introduction: Methamphetamine is a synthetic-drug that is widely abused by young adults and can have deleterious effects on many organ systems including the kidney. Hyponatremia and AKI from non-traumatic rhabdomyolysis are the most common manifestations pertinent to renal system. Herein, we present a case of methamphetamine ingestion mimicking systemic vasculitis in a patient with multiorgan failure.

Case Description: A 38-year-old man who was otherwise healthy except for chronic back pain presented to the local hospital with weakness and epigastric pain. Examination revealed several skin pustules on his legs, which he attributed to insect bites. His urine toxicology screen was positive for amphetamines and serum creatinine (Scr) was 1.4mg/dL. He soon developed sepsis with respiratory failure requiring mechanical ventilation and AKI requiring dialysis and transferred to our facility for further management. On exam, petechial and purpuric lesions were noted on legs and laboratory data including serum CPK, liver enzymes, IgG4 were within normal limits. Viral Hepatitis and HIV testing, vasculitic work up including ANA, ANCA, cryoglobulin was negative. Skin biopsy was not suggestive of vasculitis but could not yield specific etiology. Renal biopsy was consistent with ATN but also showed medium vessel vasculitis (Figure) which can be associated with illicit drug use such as cocaine and methamphetamine. Patient had renal recovery and was dialysis independent at discharge.

Discussion: Amphetamine derivatives are widely abused drugs for their euphoric, stimulant and hallucinogen properties. Hyponatremia and AKI are frequent complications of their use. AKI typically results from rhabdomyolysis. Other rare manifestations such as isolated proximal tubular dysfunction, obstructive nephropathy from bladder neck dysfunction and seronegative necrotizing vasculitis as in our patient have been reported and Nephrologists have to be familiar with these for appropriate management.



SA-PO266

Resistant Hypertension in Dialysis Patients: Pitfalls of Biochemical Testing

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Introduction: Hypertension is common in patents with End Stage Renal Disease (ESRD). Fluid retention and excess sympathetic activity are thought to be responsible for high blood pressures in majority of these patients. Rarely, pheochromocytomas have been reported in patients with ESRD. Non-specific elevation of catecholamine levels in renal failure, inability to check urinary catecholamine levels and interference from medications can make diagnosis challenging. We present a patient with ESRD with severely elevated catecholamine levels.

Case Description: 68-year-old female with ESRD on hemodialysis presented with a BP of 260/80 mm Hg and pulmonary edema. She was started on a Nicardipine infusion and underwent dialysis with aggressive ultrafiltration. She was restarted on her usual antihypertensive medications (Amlodipine 10 mg daily, Clonidine 0.3mg TID, Hydralazine 100mg TID, Labetalol 300mg TID, Losartan 100 mg daily and Prazosin 2mg bid). A work up for secondary causes of hypertension revealed markedly elevated norepinephrine levels of 7332 pg/ml (ref range 80- 520) and plasma normetanephrine at 3.26 nmol/L (ref range 0-0.89). Epinephrine and metanephrine levels were within normal limits. Patient underwent an extensive imaging for occult pheochromocytoma including CT scan of abdomen and pelvis, 123 MIBG scan, Octreotide scan and whole body PET scan, all of which failed to reveal any evidence of a catecholamine secreting tumor.

Discussion: Catecholamine levels are often elevated in patients with ESRD and normal levels in chronic kidney disease or ESRD have not been established. Our patient had levels of norepinephrine that were 14 fold higher than upper limit of the reference range. She was on Mirtazapine, Prazosin and Labetalol, all of which can specifically increase norepinephrine levels. Normal metanephrine levels, absence of tumors on imaging, improvement in blood pressures with ultrafiltration and a downward trend in norepinephrine levels suggested the elevated norepinephrine levels were due to a combination of medications and ESRD. We conclude that one should be cautious in interpreting biochemical tests for pheochromocytoma in patients with kidney disease, particularly those on dialysis. Elevations in metanephrines might be more specific for pheochromocytoma. More studies are necessary to establish cut offs for catecholamine levels in dialysis patients.

SA-PO267

Holy "Molly!" An Intriguing Case of AKI

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Introduction: Molly is the slang for 'molecular', which refers to the powder or crystal form of the synthetic psychoactive drug MDMA (3,4-methylenedioxymethamphetamine). Molly is often mixed with other drugs and substances such as bath salts (e.g. 4-methyl-apyrrolidinohexanophenone) and is not safe. While urine toxicology can detect amphetamines, current drug screens do not typically detect bath salts and other contaminants. MDMA can lead to severe hyperthermia, hyponatremia, liver, kidney and cardiovascular failure. Herein, we present a case of severe AKI in a Molly abuser.

Case Description: A 41-year-old man with a history of polysubstance abuse including alcohol, cocaine and molly presented to our institution with abdominal pain and vomiting. He has been taking molly prior to presentation and urine drug screen was positive for amphetamine. Labs showed AKI with a serum creatinine of 9 mg/dL (baseline 0.9), hyperkalemia (K 7 mmol/L) and hyperphosphatemia (P 18 mg/dL). Serum sodium

was relatively normal (134 mmol/L). Serum creatine kinase (CPK) was elevated at 6814 U/L (Ref: 5-180). UA showed large blood on dipstick with 5 RBC/hpf consistent with myoglobinuria. Imaging excluded obstructive nephropathy and he was treated with intravenous hydration and supportive care. His renal function improved gradually over next several days.

Discussion: AKI associated with MDMA is primarily attributable to rhabdomyolysis, which could result from direct myocyte toxicity or seizures from symptomatic hyponatremia. Excessive physical exertion in the setting of inadequate water intake and impaired thermoregulation often complicates the picture. Direct tubulotoxicity, necrotizing vasculitis and malignant hypertension are other mechanisms of AKI. Rarely, it can cause bladder neck dysfunction leading to obstructive nephropathy. In addition, bath salts that contaminate molly can cause ATN and rhabdomyolysis. In addition to tubular toxicity, our patient could have had more severe rhabdomyolysis prior to presentation leading to pigment-induced AKI though the presentation CPK was not very high. It is also not certain whether his kidney injury is a result of MDMA alone or related to bath salts/other contaminants as well. Clinicians need to consider all these possibilities while evaluating patients with AKI and suspected drug abuse. History may not be always clear, especially in obtunded patients.

SA-PO268

Spontaneous Renal Artery Dissection: A Diagnostic and Therapeutic Challenge

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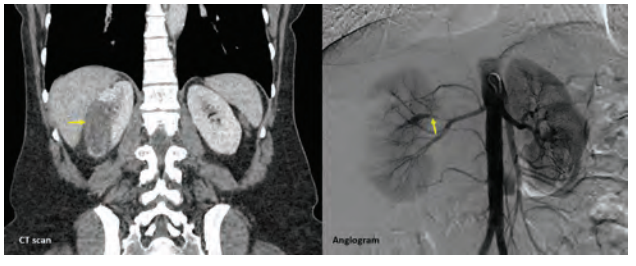
Introduction: Spontaneous renal artery dissection (SRD) is a rare and under-recognized entity and is distinct from traumatic or iatrogenic causes of renal artery dissection. Herein, we present a case of SRD that mimicked a urinary tract infection (UTI).

Case Description: A 44-year-old woman presented to our institution for worsening right flank pain associated with fever and chills. 5 days prior to presentation, she was empirically treated at a local facility for UTI with an oral antibiotic, which failed to relieve her symptoms. Laboratory data was significant for neutrophil-predominant leukocytosis and elevated lactate dehydrogenase. Because of the persistent flank pain, a CTA of the abdomen was obtained which showed right renal infarct and irregularity of the lumen of the renal artery, concerning for focal dissection. Vasculitis work up was negative. Angiogram demonstrated proximal dissection with distal aneurysmal dilatation affecting the superior segmental branch of the right renal artery. Several branches arising from the abnormal vessel appeared to perfuse viable renal parenchyma, mostly within the superior pole and embolization was not performed due to the risk of infarcting such a large volume of tissue, possibly leading to abscess formation. The patient was treated conservatively with medical management for pain and hypertension and was discharged in a stable condition.

Discussion: SRD is most commonly encountered in middle aged men and has been associated with malignant hypertension, fibromuscular dysplasia, collagen vascular diseases, cocaine use and extracorporeal shock wave lithotripsy in the literature. The symptoms can be nonspecific and often mimic other conditions such as pyelonephritis and nephrolithiasis. Conservative management includes hypertension and pain control with or without systemic anticoagulation. Endovascular interventions and surgical revascularization are reserved for patients with hemodynamically significant occlusions of the arteries, uncontrolled renovascular hypertension and worsening renal function or progression of dissection.



SA-PO269

Methimazole-Induced Severe Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis with Rapidly Progressing Glomerulonephritis

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Introduction: Vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) is a rare complication of treatment with antithyroid medications. It has been mainly described in patients treated with Propylthiouracil(PTU), and rarely with use of Methimazole(MMI). While most reported cases of MMI induced ANCA associated vasculitis(AAV) were diagnosed on skin or lung pathology, we report a unique case of severe, systemic, kidney biopsy proven drug induced AAV with MMI.

Case Description: A 64-year-old Guyanese woman with primary hyperthyroidism presented with abdominal pain and diarrhea. On admission, herserum creatinine(Scr) was 2.8mg/dl (baseline 1.2mg/dl). She denied use of NSAIDs, PPIs or herbal medications however reported to have completed course of clarithromycin for a respiratory infection 2 weeks ago. Her only home medication at the time of presentation was methimazole. During the course of her hospitalization, she developed gross hematuria with worsening AKI. UA showed 173 RBCs, 13 WBCs and spot urine protein to creatinine ratio of 1.2. Serological work up was positive for Anti-Nuclear Antibody (ANA 1;640), p(perinuclar)-ANCA (1:320) and Myeloperoxidase antibody (MPO 109.4). C(cytoplasmic)-ANCA, proteinase 3(PR3) and double stranded DNA antibodies were negative. She was initiated on pulse dose corticosteroids and underwent kidney biopsy which showed 25 glomeruli, of which 2 were globally sclerosed, 4 had cellular crescents with all arteries revealing extensive necrosis and signs of small vessel vasculitis with minimal chronic changes and no tubular changes; Pathology findings were consistent with pauci immune vasculitis/ AAV, thought to be drug induced. Methimazole was held. Few days later, she developed hemoptysis and was initiated on plasmapheresis for concern of pulmonary alveolar hemorrhage. She eventually became oliguric requiring hemodialysis. Worsening of her vasculitis lead to her demise despite aggressive medical management.

Discussion: The reported incidence of MPO ANCA Vasculitis for PTU is 39.2 times higher compared to that with MMI. Although uncommon, MMI can lead to AAV. Nephrologists, rheumatologists and endocrinologists should all be aware of this rare, life threatening complication of MMI.

SA-PO270

A Case of Golimumab-Associated Pauci-Immune Glomerulonephritis

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Introduction: Golimumab is a monoclonal TNF-alpha inhibitor approved for rheumatoid arthritis (RA), ulcerative colitis (UC), psoriatic arthritis, and ankylosing spondylitis. It may be preferred in some patients due to easier dosing (monthly subQ injections) and ability to control symptoms in UC. Clinical trials studying golimumab have not reported glomerulonephritis as an adverse event, though there is at least one report of golimumab accelerating preexisting lupus nephritis. To our knowledge, there have been no reports of golimumab-associated, new-onset glomerulonephritis. Here, we present a patient with RA on golimumab who developed a pauci-immune crescentic glomerulonephritis with no signs of systemic vasculitis.

Case Description: 87-year-old male with hypertension and rheumatoid arthritis referred by his rheumatologist with a creatinine of 2.6 mg/dL. He had a baseline creatinine of 1.29 mg/dL and 0.9 mg/dL, four months and nine months prior to his presentation, respectively. His RA was previously managed by steroids but was switched four years ago to monthly golimumab, last dose was 2 months ago. Urinalysis showed 3+ protein, negative leukocytes, 80-100 RBC/hpf, and 5-7 acanthocytes/hpf. Labs including C3, C4, ANA, ANCA, dsDNA, anti-histone antibody, cryoglobulin, Hepatitis B and C serologies, SPEP, UPEP were ordered; all eventually came back negative. Renal biopsy showed 18 of the 36 glomeruli had extracapillary proliferation, 14 of which had evidence of fibrinoid necrosis or cellular crescents. Findings were consistent with a diagnosis of pauci-immune crescentic glomerulonephritis. Over the course of the patient's 5-day hospital stay, his creatinine was stable with a range of 2.5-2.8 mg/dL. He was discharged on 60 mg prednisone daily, golimumab was not restarted.

Discussion: This case represents the first report of crescentic pauci-immune glomerulonephritis associated with golimumab. With increasing use of TNF-alpha inhibitors, there lies a risk of increased episodes of glomerulonephritis associated with these medications. As with this patient, renal limited vasculitis may not appear until years into treatment, and could present with aggressive features. Patients should be monitored for glomerulonephritis and screening protocols with serial urinalysis and serum creatinine may be necessary. Long term data may help define relative risk with individual medications.

SA-PO271

PR3 Positive Crescentic Glomerulonephritis in Pembrolizumab Treated Metastatic Melanoma

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Introduction: Immune checkpoint blockade has demonstrated to be effective for treating various cancers including melanomas. Pembrolizumab, a monoclonal antibody that targets the programmed cell death (PD-1) receptor of lymphocytes, enhances immunologic destruction of cancer cells. The PD-1 pathway plays an important role in immunologic homeostasis, enabling the body to defend against pathogens while protecting against self-reactivity. Use of these medications may lead to dysregulation of T cell activation, causing a pathologic immune response, including inciting autoimmunity.

Case Description: A 73 year old woman with metastatic melanoma with normal renal function was treated with 4 doses of Pembrolizumab. Creatinine rose to 1.7 mg/dL. Biopsy revealed acute and chronic interstitial nephritis. After the drug was held, Prednisone 60 mg daily was started. Creatinine remained at 1.6 - 1.9 mg/dL. Twelve months later, she developed arthralgias and targetoid lesions on her fingers. A skin punch biopsy showed vasculitis. Creatinine was 5.2 mg/dL. UPC was 2.9 g/g. Complements were normal. Cryoglobulin, MPO, HIV, hepatitis panel and renal ultrasound were negative. She tested positive for PR3-ANCA at 1675 U/mL (normal 0-19 U/mL). Biopsy revealed pauci-immune crescentic glomerulonephritis (GN). She received 6 sessions of plasmapheresis, weekly Rituximab with Methylprednisolone, and later switched to Prednisone 60 mg daily. Creatinine improved with a decrease in PR3 titers. Rituximab maintenance infusions were terminated due to progression of melanoma.

Discussion: There are a few cases of Minimal Change Disease and IgA Nephropathy reported with PD-1 inhibitor, and a case of Granulomatous Polyangiitis after a single dose of Pembrolizumab. Immune-related adverse events have been cited to start within a few weeks to months after treatment, but can occur anytime after treatment discontinuation, with skin events usually the first to appear. Our patient presented with skin findings and

had severe renal injury from PR3-positive GN. T-cell activation has been implicated in the development of crescentic GN. We postulate that Pembrolizumab set the scene for a dysregulation of T cell function, with development of a pathogenic autoantibody such as PR3-ANCA, as well as possibly unmasking an underlying autoimmunity. This report highlights an important potential renal effect from this drug.

SA-PO272

Immune Checkpoint Inhibitor (ICI) Induced Necrotizing Granulomatous Arteritis, Interstitial Nephritis, and Dermatitis

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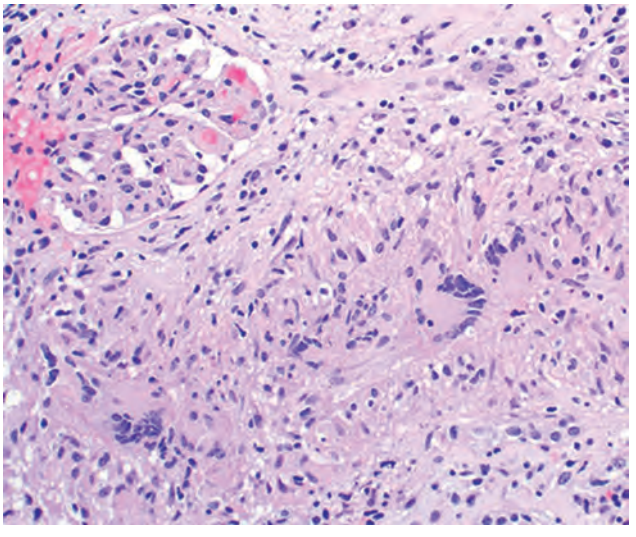
Introduction: With emergence of ICIs as potent agents against melanoma, there has been a rapid surge in use of drugs like ipilimumab, targeted against cytotoxic T lymphocyte associated antigen 4(CTLA-4), and nivolumab, targeted against programmed death 1(PD-1) protein. Immune related adverse events (IRAE), including skin lesions and AKI, have been reported with use of ICIs. Nivolumab has been associated with sarcoidal pattern of granulomatous dermatitis while both drugs have been associated with acute interstitial nephritis (AIN). We present a case of skin and renal complications following concomitant nivolumab and ipilimumab therapy.

Case Description: A 67 yo man diagnosed with melanoma 9mos ago, on 3rd cycle of ipilimumab and nivolumab presented with fever, skin rash and AKI. Serum creatinine (Cr) was 2.65 mg/dL (baseline 0.8 mg/dL). Skin biopsy (B_x) showed granulomatous dermatitis compatible with granuloma annulare. Renal B_x showed necrotizing granulomatous arteritis with interstitial fibrosis and tubular atrophy (Fig). ANA and ANCA were negative. Mycobacterial and fungal causes were excluded. Given the suspicion of ICIs related cutaneous and renal side effects, both drugs were stopped and 80mg daily oral prednisone was initiated for 1mo followed by slow taper. Rash improved rapidly and Cr returned to baseline.

Discussion: These findings describe another pathological manifestation of ICIs. We suspect that synergistic effects of anti-CTLA-4 and anti-PD1 therapy triggered the granulomatous arteritis. With increasing use of ICIs for melanoma and other cancers, it is important to be vigilant of their side effects. Steroid therapy, initiated early, appears to have utility in reversing IRAEs.



Renal B_x showing obliteration of an intralobular artery by granulomatous inflammation with multinucleated giant cells, accompanied by interstitial hemorrhage and AIN. H&E, 200x

SA-PO273

Lupus Nephritis Due to Anti-TNF Alpha Therapy

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Introduction: Drug induced lupus erythematosus is a lupus-like syndrome temporally related to continuous drug exposure which resolves upon drug discontinuation. Findings include skin manifestations, arthritis, serositis, and ANA/anti-DS DNA seropositivity. It can be divided into systemic, subacute cutaneous, and chronic cutaneous forms. Drugs most frequently associated are hydralazine, procainamide, and quinidine. In rare cases, anti-TNF alpha therapies have also been implicated. It is estimated that up to 10% of SLE cases are drug-induced. Such autoimmunity is idiosyncratic and unpredictable.

Case Description: An 80 year old male with a past medical history significant for DM II, hypertension, resolved hepatitis B infection, seropositive Rheumatoid Arthritis (RA), and CKD stage III with a baseline creatinine of 1.5 mg/dl was started on Etanercept (anti-TNF alpha therapy) due to severe erosive RA. After 6 months of treatment he presented with joint pains and swelling of the extremities, was noted to have acute renal failure with a creatinine of 2.0 mg/dl, proteinuria of 1.2 gm, new onset microscopic hematuria, hypocomplementemia, and anti -DsDNA/ANA seropositivity. Renal biopsy revealed diffuse endocapillary glomerulonephritis with immunofluorescence staining for IgG, IgA, C3, c1q, kappa and lambda; electron microscopy was devoid of tubuloreticular inclusion bodies. Given the lack of extra-renal SLE findings and the timing of etanercept, the biopsy findings were attributed to TNF-alpha inhibitor therapy, which was subsequently discontinued. The patient was treated with corticosteroids, with stabilization of renal parameters and resolution of anti-DsDNA and ANA positivity. Of note, the patient exhibited no other SLE type symptoms prior to or since TNF-alpha inhibitor therapy. Therapy for RA was switched to Rituximab.

Discussion: Anti-TNF alpha induced lupus represents a major therapeutic challenge. Most cases are caused by infliximab, followed by etanercept and adalimumab. Symptoms range from mild cutaneous lesions, to more systemic involvement including pericardial effusions, deep venous thrombosis, pneumonitis, and lupus nephritis. Most of the reported clinical features of anti-TNF-alpha -induced SLE present as cutaneous lesions, which are similar to those present in idiopathic SLE. This case exhibits the silent menace of the exceedingly rare anti-TNF-alpha induced lupus nephritis.

SA-PO274

An Unusual Case of Hydronephrosis Caused by Iliac Artery Aneurysm

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Introduction: Isolated internal iliac artery aneurysm is a rare but serious condition of which nephrologist should be aware. The natural history is one of continued expansion and rupture with high mortality rate. These can result in hydronephrosis and hydroureter with displacement of the ureter by a mass lesion. With proper treatment survival can be improved. Here we discuss a case of patient with acute renal failure in the setting of a pelvic kidney and symptomatic iliac artery aneurysm.

Case Description: A 66 year old male with a history of hypertension, hyperlipidemia, and smoking was admitted with angina. Serum creatinine was 1.7 mg/dl, and urinalysis showed trace proteinuria with no blood. Cardiac catheterization revealed 2 vessel disease. Within 12 hours of admission the patient developed vomiting, diarrhea, hypotension and new onset paresis of the left upper extremity. Creatinine rose in a saw-tooth pattern to 4.0 mg/dl over 5 days. MRI of the brain without contrast revealed a small right posterior frontal cortical infarct as well as multiple lacunes in the right basal ganglia, and 60% stenosis of the origin of the right internal carotid with an ulcerated plaque. During the angiogram, films of the aorta revealed mild right renal artery stenosis and an ectopic left pelvic kidney with hydronephrosis due to a 3.3 cm left common iliac artery aneurysm impinging on the ureter. Surgery was performed to repair the common iliac artery aneurysm and relieve the obstructed ureter of the pelvic kidney. Hydronephrosis of the left pelvic kidney was partially relieved, and subsequent renal scans showed no significant hydronephrosis.

Discussion: This patient demonstrates an obstructed pelvic kidney by an asymptomatic common iliac artery aneurysm. Isolated iliac artery aneurysms are exceedingly rare, account for <7% of all intra-abdominal aneurysms and are found in only 0.03% of the population in autopsy studies. They are most often due to atherosclerotic vascular disease occurring in males in the 7th or 8th decade. Symptoms vary and are related to pressure by the aneurysm on the ureter, the internal iliac vein, the lumbosacral nerve trunk, the external iliac vein, obturator nerve, and the colon. The risk of hydronephrosis may be increased in the pelvic kidney due to malrotation of the kidney and an anteriorly placed renal pelvis. This case exhibits the silent menace of an iliac artery aneurysm.

SA-PO275

Drug Induced Lupus Nephritis in Psoriasis Secondary to Adalimumab Use

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Introduction: Adalimumab, an anti-Tumor necrotic factor α agent (anti-TNF α), is approved by the FDA for treatment of moderate to severe chronic plaque psoriasis. The drug is generally well-tolerated, however auto immunity with the development of systemic lupus erythematosus (SLE) is a rarely reported. We describe a case of Adalimumab being used for chronic plaque psoriasis in which the patient developed lupus nephritis.

Case Description: A 32 year-old-lady with refractory chronic plaque psoriasis had been on Adalimumab for 3 months and presented with a 3-day history of bilateral lower extremity swelling. On evaluation, she was found to have a malar rash and alopecia, hemoglobin 6.7g/dL, creatinine 0.6 mg/dL, albumin 1.5g/dL, UA 3+ protein and 50 RBCs. A spot urinary protein: creatinine ratio was 4.8g/g with microalbumin of >1g. Further work up for proteinuria revealed a positive ANA, SSA, Anti Ro, Anti La, RNP, Anti Smith (519 AU/mL), ds DNA (1257 IU/mL), anti-histone (>999 AU/mL) while other serological work up was negative. A renal biopsy was performed on day 3: focal proliferative glomerulonephritis with 1 focally sclerosed glomerulus and full house staining on immunofluorescence consistent with class III lupus nephritis was found. The adalimumab was stopped and she was started on Prednisone and Hydroxychloroquine. On follow up, she was started on cyclophosphamide. Subsequently, her proteinuria and other symptoms improved.

Discussion: "Anti-TNF α-induced lupus (ATIL)" is characterized by high prevalence of anti-dsDNA antibodies (>90%) and low prevalence of ant histone (57%) with respect to the classic form of SLE. The presence of SLE meeting the American college of rheumatology guidelines and concomitant exposure to lupus-inducing drug are widely accepted criteria for ATIL. There have been no cases reported in the literature of adalimumab induced lupus nephritis. In our case, the lupus nephritis improved after discontinuation of the drug, supporting the diagnosis of ATIL. Symptoms resolve within 3 weeks to 6 months after

stopping the drug. Additional immunosuppressant medications may be required to achieve full remission.

SA-PO276

Glomerular Injury Related to Immune Related Adverse Events: IgA Nephropathy After Nivolumab Therapy for Postoperative Recurrence of Lung Cancer

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Introduction: Immune checkpoint inhibitors (ICIs; anti-PD-1 or anti-CTLA-4) are becoming a common and an important therapeutic option for cancer patients. ICIs are associated with a unique category of side effects calld immune-related adverse events (irAE) and physicians should be aware of its clinical importance. According to previous reports, renal irAEs are less frequent than other organ involvement and glomerulonephritis is not typical. In this report, we present a case of nivolumab associated mesangial proliferative glomerulonephritis (IgA nephropathy), previously not reported.

Case Description: A 72-year-old man with postoperative recurrence of lung squamous cell carcinoma treated with nivolumab (anti-PD-1 antibody) who developed proteinuria and worsening kidney function was referred to our department. Ten months previously, he had been started on intravenous nivolumab therapy because of the postoperative recurrence of lung squamous cell carcinoma (cT3N2M0 stage IIIA). Six months after the first nivolumab treatment, the patient's creatinine began to increase and proteinuria was noted. Kidney biopsy showed mesangial proliferative glomerulonephritis with C3 and IgA deposition. Electron-microscopy demonstrated a small amount of high electron-dense deposits in the subepithelial and mesangial regions. After drug withdrawal, the proteinuria improved and the deterioration of the renal function was halted.

Discussion: To our knowledge, this is the very rare case of biopsy-proven immune complex glomerulonephritis following treatment with ICI. Although it may be difficult to prove a causal relationship of ICI and IgA nephropathy, we suspect nivolumab played a role in the pathogenetis of IgA nephropathy. The patient did not have disease-precipitating events such as upper respiratoty infection prior to the disease onset and we observed the decrease in proteinuria and improvement in serum creatinine after drug withdrawal. The previous study showed PD-1 knockout mice develop immune complex glomerulonephritis. These findings suggested that PD-1 signaling pathway is important to minimize T-cell-mediated renal inflammation. Glomerular lesions have been exacerbated from subacute to chronic course in our case, which suggests the possibility of another type of disease progression.

SA-PO277

IgM Nephropathy, M-Spike, and Chronic EBV Infection with Certolizumab Use

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Introduction: IgM Nephropathy is a rare cause of nephrotic syndrome seen in children and young adults. We describe IgM nephropathy causing nephrotic syndrome in an elderly male with normal serum IgM levels and having Rheumatoid Arthritis (RA); who also had tubuloreticular inclusions in his kidney likely caused by chronic EBV infection.

Case Description: A 60 year old male with known RA and ulcerative colitis, on Certolizumab and prednisone therapy, presented with nephrotic range proteinuria. Erosive hand joints and pedal edema were seen. He has known high-titer Rheumatoid factor positive RA with negative anti-CCP antibodies. Labs revealed a normal electrolyte panel, total protein, albumin and renal function. UA showed 3(+) protein. 24-hour-urine specimen revealed 3360 mg of protein. ANA titers were 1:160 (homogenous pattern). Anti-dsDNA, anti-MPO and Proteinase-3 antibodies; and ANCA panel were negative. Complements were low (C3 – 67, C4 – 14). Hepatitis B, C, HIV and CMV serologies were negative. EBV IgM titers were negative, but EBV IgG (728 U/ml) titers were markedly elevated. Serum IgM was normal (178 mg/dl), with a mild increase in IgA (657 mg/dl) and IgG (1858 mg/dl) levels. No monoclonal proteins were seen on UPEP. SPEP revealed an IgG Kappa monoclonal band. Renal biopsy was performed and LM showed mild mesangial hypercellularity, mild to moderate interstitial fibrosis with tubular atrophy. IF showed mesangial regions staining for IgM (3+), IgG (1+), IgA (1+), C3 (1+), and trace kappa and lambda light chains. EM demonstrated patchy podocyte foot processes effacement, several electron dense deposits in an expanded mesangial matrix. Few subepithelial and subendothelial deposits were noted, and many tubuloreticular inclusions were seen. Oncology opined that the IgG Kappa monoclonal band in the SPEP was likely secondary to Certolizumab use, and his Certolizumab was held and a repeat SPEP is pending. Oral diuretics and Lisinopril were started given his edema and proteinuria.

Discussion: Renal IgM deposits can be seen in RA. RA patients' have impaired control of EBV infection and have high antibody titers against EBV antigens. Our patient had IgM nephropathy with a normal serum IgM level, and our case highlights the need to test for EBV in the setting of RA and IgM nephropathy.

SA-PO278

Membranoproliferative Glomerulonephritis (MPGN) Associated with Nivolumab Therapy

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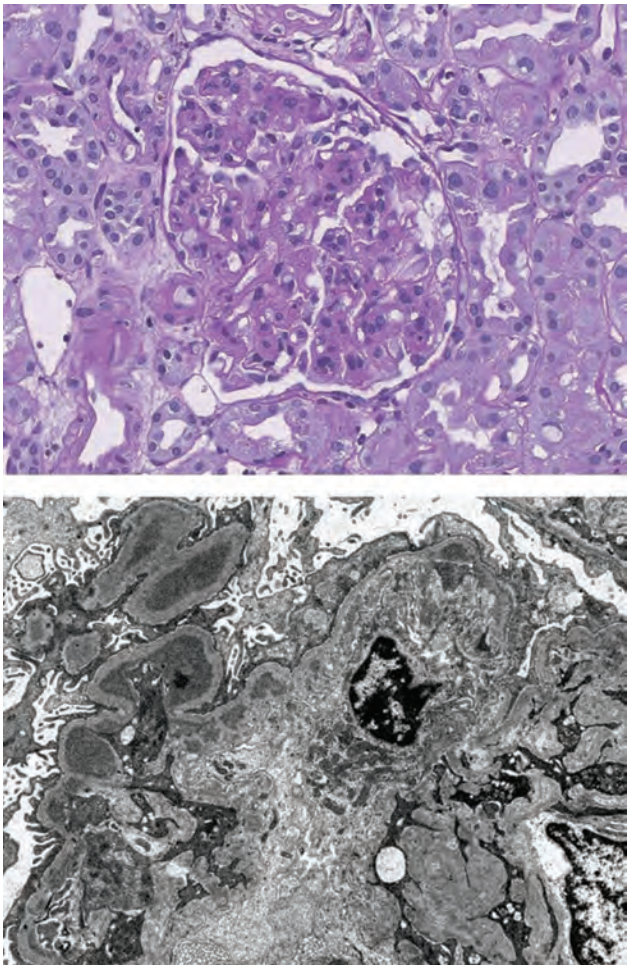
Introduction: Nivolumab is a chemotherapeutic checkpoint inhibitor targeting PD-1 receptors on T cells. Nivolumab has classically been associated with acute interstitial nephritis (AIN). We present a case of Nivolumab associated nephrotic syndrome due to MPGN.

Case Description: 75-year-old female with a history of non-Hodgkin's lymphoma s/p allogenic bone marrow transplant 10 years prior was diagnosed with metastatic anal cancer. She was unresponsive to surgery and chemoradiation, and thus Nivolumab was initiated. Two months into Nivolumab therapy, her creatinine rose from 1.07 to 1.63mg/dl. Nivolumab was held and she was started on prednisone for presumed AIN. Atypically, she had edema and new onset proteinuria with 12.5 g/g on spot UPCR. Urinalysis was otherwise negative. Workup showed C3 and C4 were low at 76 and 10. Paraproteins, ANA, ASO, HBsAg, HCV ab, ANCA, and cryoglobulin were negative. After four weeks of prednisone, her proteinuria persisted. Kidney biopsy showed subendothelial deposits of C3 and IgM consistent with MPGN and mild interstitial inflammation. No features of TMA were found. Findings were felt due to persistent Nivolumab injury. Nivolumab was held for 3 months while prednisone continued. Her creatinine and proteinuria improved but unfortunately her cancer progressed, and she chose to pass away on hospice. Spot UPCR at that time was 1.1 g/g.

Discussion: This case demonstrates an atypical association of Nivolumab with MPGN. Nephrotic syndrome has been rarely reported with checkpoint inhibitors, though prior cases were minimal change disease and membranous nephropathy. We believe this to be the first case of checkpoint inhibitor associated MPGN, suggesting these agents can lead to a broad spectrum of immune-related kidney disorders



PAS / EM with MPGN and subendothelial deposits of C3 and IgM

SA-PO279

Secondary (AA) Amyloidosis Associated with Checkpoint Inhibition

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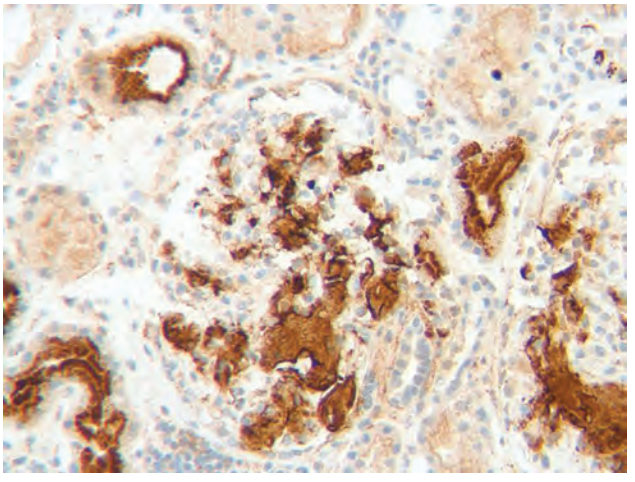
Introduction: Nivolumab (Nb) is an immune checkpoint inhibitor (CPI) which targets solid tumors but can cause nephrotoxicity by accelerating systemic inflammation. We report a case of a patient who achieved partial remission of squamous cell lung cancer (SCLC) with Nb but later developed nephrotic syndrome from secondary (AA) amyloidosis.

Case Description: A 75 y.o. white man presented with anasarca. He was diagnosed with metastatic SCLC 2 years ago and received 4 cycles of Nb. His last dose was 10 months ago. It was stopped due to failure to thrive as he had acheived partial remission. Exam notable for diffuse anasarca. Alb 1.1 g/dL, Cr 0.76 mg/dL. ANA (-). C3 77, C4 25 mg/dL, RF 67 IU, CRP 86.8 mg/L, ESR >140 mm/hr. SIEP and UIEP (-) for monoclonal protein. A year ago, Alb 2.6 g/dL, UA trace protein. Renal biopsy demonstrated apple green birefringent deposits in the glomeruli and arterioles on Congo red (Figure 1). Amyloid A immunostain was (+). IF was (+) for full house mesangial staining of IgG (3+), IgA (3+), IgM (2+), C3 (3+), C1q (3+) and C4 (1+) and equal for κ & λ stain (3+). EM with randomly arranged fibrils 8-12 nm in the GBM & mesangium. He was started on prednisone, bactrim, and colchicine and his U P/C improved to 5.1 g/g in 3 months. His inflammatory markers improved and his SCLC remained in partial remission.

Discussion: We present a patient with secondary (AA) amyloidosis with diffusely positive mesangial IF 10 months after receiving Nb. Although progressive cancers can be associated with AA amyloidosis, his SCLC was in partial remission, making it an unlikely etiology. In addition, his elevated ESR, CRP, RF, and full house IF are signs of active inflammation. CPIs exert their antineoplastic action by accelerating inflammation, causing interstitial nephritis. In contrast, our case illustrates the possibility that the immune checkpoint inhibitor created an uncontrolled inflammatory response leading to secondary (AA) amyloidosis.



SA-PO280

Dasatinib-Associated FSGS: A Case Report

Valentina Loi,[1] Nicola Lepori,[1] Matteo Floris,[1] Anna Maria Asunis,[2] Andrea Angioi,[1] Riccardo Cao,[1] Alice Atzeni,[1] Doloretta Piras,[1] Gianfranca Cabiddu,[1] Antonello Pani.[1] [1]*Nephrology, Ospedale Brotzu, Cagliari, Italy;* [2]*Anatomic Pathology, Ospedale Brotzu, Cagliari, Italy.*

Introduction: Renal adverse effects associated with the use of TKI include arterial hypertension, proteinuria, acute kidney injury (AKI), and thrombotic microangiopathy (TMA); however there are only a few reports of TKI-associated nephrotic syndrome

Case Description: A 69 y/o woman was diagnosed in June 2016 with Philadelphia chromosome-positive chronic myeloid leukaemia for which she was initially treated with hydroxyurea 1.5 g/day for 2 weeks and then with Dasatinib100 mg/day achieving complete remission. Her past medical history included arterial hypertension, type 2 diabetes mellitus and dyslipidaemia. Her previous kidney function was normal and she had no proteinuria. After 8 months on Dasatinib, the patient developed a progressive and rapid worsening of her kidney function (sCr from 0.76 to 2.2mg/dL) associated with the onset of a nephrotic syndrome with proteinuria up to 6g/24h, hypoalbuminemia (serum albumin 2.4g/dL), lower extremity pitting oedema and mild pleural and pericardial effusion. Blood cell count showed a mild anaemia; ANA, ANCA, HBV and HCV markers, complement were normal. In consideration of this clinical picture, the drug dose was reduced to 100mg every other day. Over the next few months her kidney function remained stable with sCr of 1.7mg/dL, proteinuria of 3.5g/24h, serum albumin of 2.9g/dL, total cholesterol level of 297mg/dL. In October 2017 the patient underwent a kidney biopsy. Light microscopy showed glomeruli with segmental collapse of the tuft with concomitant pseudo-crescents. A mild mesangial expansion with a limited cellular proliferation was diffusely observed. Of interest, endothelial cells showed swollen cytoplasm with evident nuclei, suggestive of a diffuse endothelial injury. Tubuli, interstitium and vessels were unremarkable. IF was unremarkable. The patient was started on prednisone (0,5 mg/Kg/die) and Dasatinib was discontinued. After 6 months of treatment, proteinuria improved to 2,2g/24 hours, albuminemia raised to 3.5 g/dl and sCr improved to 1.5 mg/dl

Discussion: The improvement in proteinuria and albuminemia after cessation of Dasatinib and steroid treatment strongly imply this association between the nephritic syndrome and the treatment. This is, to our knowledge, the first case of focal segmental glomerulosclerosis secondary to Dasatinib treatment in an adult patient

SA-PO281

A Case of Lenalidomide-Induced Tubulointerstitial Nephritis

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Introduction: Lenalidomide is a thalidomide-derivate immunomodulatory drug that has shown efficacy in multiple myeloma and relapsed Hodgkin Lymphoma (HL). Renal insufficiency with lenalinomide is commonly-observed but poorly characterized. We describe a patient with relapsed HL who developed AKI and lower extremity rash while taking lenalidomide, with kidney biopsy showing tubulointerstitial nephritis.

Case Description: A 24-year-old male had refractory HL previously treated with autologous stem cell transplant four years prior to presentation, and nivolumab, pembrolizumab, and chimeric antigen receptor T cell therapy two years prior to presentation. During this time his SCr increased from 0.5-0.8 mg/dL to 1.1-1.6 mg/dL. Lenalidomide was started and over four months his SCr elevated to 2.3 mg/dL. Urinalysis was negative for protein, blood and leukocyte esterase, and microscopy showed no red blood cells or white blood cells. Peripheral blood eosinophils were elevated with a peak of 14%. Imaging revealed no evidence of obstruction. Lenalidomide was discontinued without improvement of his SCr. During the same month of discontinuing lenalidomide, he developed a rash on his lower extremity, and skin biopsy showed psoriasiform epidermal hyperplasia and chronic inflammation. A kidney biopsy showed patchy tubulointerstitial inflammation accompanied by tubulitis with mild chronicity, and approximately 10% interstitial fibrosis consistent with a diagnosis of tubulointerstitial nephritis. Mononuclear infiltrative cells were negative for lymphoma. He received three days of intravenous methylprednisolone 125 mg and oral prednisone with a subsequent steroid taper. His SCr returned to his prior baseline of 1.1 to 1.6 mg/dL at one month follow-up and his lower extremity rash resolved. Peripheral blood eosinophils returned to normal.

Discussion: Renal insufficiency associated with lenalidomide is commonly reported in plasma cell dyscrasias, but very few patients undergo kidney biopsies to establish the mechanism of kidney injury. The patient's treatment exposures prior to receiving lenalidomide included multiple T cell modulating therapies. Three case reports to date have been published describing lenalidominde-associated interstitial nephritis in patients with multiple myeloma. This is the first case to describe lenalidomide-induced interstitial nephritis in a patient undergoing treatment for HL.

SA-PO282

Varenicline Associated Acute Interstitial Nephritis

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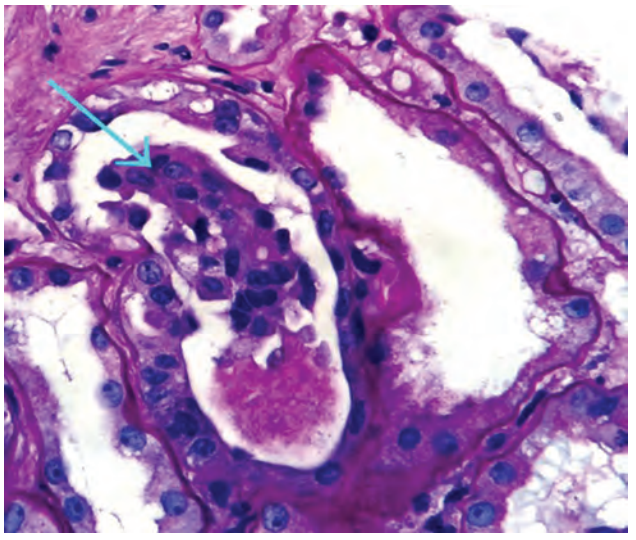
Introduction: Varenicline is a nicotinic receptor partial agonist with proven benefits in smoking cessation. It is not known to cause renal toxicity. 2 case reports describe acute insterstitial nephritis (AIN) due to varenciline with pre-existing renal impairment. We describe a case with normal renal function who presented with acute renal failure soon after starting varenicline.

Case Description: 59-year-old male with history of HIV, hepatitis C, hyperthyroidism, hypertension and diabetes mellitus. Patient presented with worsening lower extremity edema. He was on HAART therapy with darunavir, etravirine and raltegravir. Other medications included amlodipine, lisinopril, metformin, glipizide, terazosin and varenicline. Varenicline was started 1 month prior to presentation and was the only new medication. Patient had normal kidney function at baseline serum creatinine (sCr) 1.1 as per labs drawn 2 months prior. Physical exam showed a middle-aged man with normal vitals, bilateral pitting edema up to the ankles, mild abdominal distension. Initial labs showed sCr 6.5, BUN 60, albumin 3, normal CBC, LFTs, lipase and CPK. On Urinalysis, blood 2+, protein 300, WBC 20-50, WBC esterase 1+,. Spot urine protein to creatinine ratio was 6.5. Ultrasound showed subtle hypoechoic bilateral renal pyramids with increased echogenicity in the renal parenchyma possibly related to underlying renal disease or inflammation. Patient was started on intermittent hemodialysis due to declining urine output and uremia. A renal biopsy was performed during admission that confirmed acute interstitial nephritis. Varenciline was held, patient was started on steroids. Renal function began improving and dialysis was stopped. sCr returned to baseline at clinic follow up.

Discussion: This is only the third case describing Varenciline associated AIN. A careful medication history with biopsy was essential in diagnosing cause for kidney injury in this patient with multiple comorbidities.



SA-PO283

Novel Oral Anticoagulant and AKI: Apixaban Induced Acute Interstitial Nephritis

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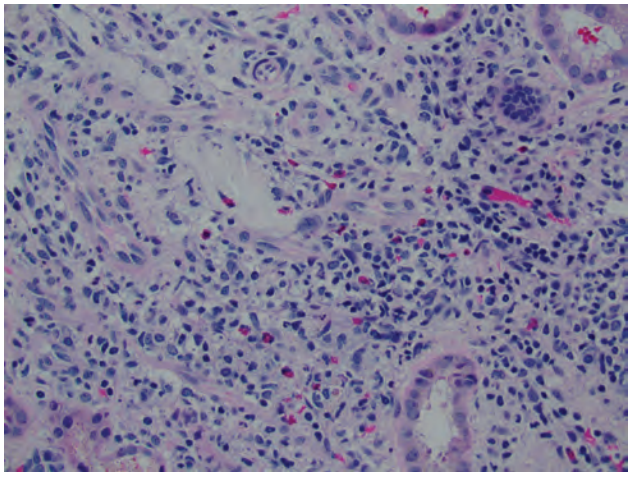
Introduction: Novel Oral AntiCoagulants (NOACs) are changing the landscape of clinical practice for patients requiring short and long term anticoagulation. This case presentation of Apixaban-induced acute interstitial nephritis (AIN) shows a side effect of an increasingly common medication.

Case Description: A 70 year-old male with PMH of HTN, CHF, Atrial Fibrillation presented with a 2-month history of fatigue and intermittent hematuria. Home medications were Apixaban, Amlodipine, Epleronone, Cholecaliferol, Dofetilide, Metoprolol, and Rosuvastatin. He denied NSAID or PPI use. Physical exam showed normal vitals with trace edema and no rash. Laboratory studies showed S Cr of 2.6 mg/dL (baseline 0.90 mg/dL). Renal US showed no hydronephrosis or stones. Urinalysis showed 11-20 WBC, 100 RBC/hpf with urine protein:creatinine ratio of 0.57 g/g. ANA, ANCA, C3, C4 and SPEP were negative. While holding Apixaban for a renal biopsy, S Cr trended down to 2.2 mg/dL. Renal biopsy showed acute tubulointerstitial nephritis with eosinophilic component. The immunofluorescence microscopy displayed weak mesangial granular staining with IgA and glomerular tuft staining with C3 suggestive of IgA nephropathy. He received Prednisone 60 mg daily for two weeks with a taper. Apixaban was restarted and the patient's S Cr increased to 3.8 mg/dL. Apixaban was discontinued and Warfarin was started. S Cr improved slowly to 1.3 mg/dL and his hematuria improved to microscopic hematuria over a 4-month period.

Discussion: Oral anticoagulant can cause AKI by inducing glomerular hematuria or rarely AIN. Our patient had IgA nephropathy which can explain his persistent microhematuria while on the anticoagulants. The biopsy results and the patient's clinical improvement substantiate the diagnosis. Given the increasing use of Apixaban, it is worth recognizing that it can cause AIN at any time. To the best of our knowledge, there are only two reported biopsy proven cases of Apixaban induced AIN.



SA-PO284

A Case of Rivaroxaban Associated Nephropathy

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Introduction: The adverse effects of oral anticoagulants (ACs) are commonly related to bleeding, however, a less common complication described with warfarin is the development of AC nephropathy. Novel ACs are quickly replacing warfarin, as they do not require monitoring of INR. Because they have not been used as long, the scope of their adverse effects are still coming to light.

Case Description: A 55-year-old Caucasian man was referred to the Nephrology clinic for worsening renal function. His PMHx includes a nerve sheath sarcoma in his right arm treated with surgery, radiation, and ifosfamide 15 years prior, stable CKD-II, and a large unprovoked pulmonary embolism 3 years prior. There was no history of hypertension or diabetes. He was placed on rivaroxaban with the intention of lifelong anticoagulation. He had otherwise been active and well. He denied hematuria, cloudy/frothy urine, nephrolithiasis, dysuria, edema, or dyspnea. Medications were rivaroxaban 20 mg daily, famotidine, and tramadol PRN. Social and family history was unremarkable. Physical exam revealed clear breath sounds and absent lower extremity edema. On presentation, creatinine (Cr) was 1.6 mg/dL and GFR was 45 mL/min. Other lab testing was unremarkable. His previous baseline serum Cr was stable at 1.2-1.4 mg/dL until two months before referral. UA revealed 1+ blood, 1+ protein, 3-5 RBCs/HPF, and no casts. Spot protein/Cr ratio revealed a value of 0.18, compared to a single measurement of 1.2 a year prior. Renal US was normal. Renal biopsy revealed eosinophilic granular intratubular casts with occasional RBCs, and mild acute tubular injury. Glomeruli showed congestion with RBCs and focal duplication of the glomerular basement membrane. Electron microscopy revealed multilayering of the peritubular capillary basement membranes but no other abnormalities. No immune complex-mediated disease was identified. Two months after biopsy serum creatinine is unchanged.

Discussion: There have been few published reports of nephropathy associated with novel ACs. As these drugs become more popular, it is possible that the incidence of associated nephropathy will increase. Extrapolating his decline in GFR suggests the patient could need renal replacement therapy in the next 10 years. Therefore, it is important to raise awareness that novel oral ACs such as rivaroxaban may be a cause of worsening kidney function.

SA-PO285

Aminocaproic Acid Induced Anuria

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Introduction: 59 year old woman with leukemia and severe thrombocytopenia developed acute kidney injury following treatment with Aminocaproic acid.

Case Description: A 59 year old female with leukemia and severe thrombocytopenia developed the acute onset of bilateral lower back pain. Prior to this, she had been receiving Aminocaproic acid (Amicar) for epistaxis and easy bruising related to her thrombocytopenia (platelets < 2000 repeatedly). Subsequently, she became anuric and serum creatinine increased from 0.55 mg/dl to 1.98 mg/dl. Potassium was 6 mEq/L. A renal sonogram showed bilateral hydronephrosis. A foley catheter was placed with minimal output. Contrast tomography was performed with IV contrast and showed no masses or hematoma. Urology was consulted and was initially hesitant to perform invasive testing due to her thrombocytopenia and immune suppressed state. She was started on dialysis for management of hyperkalemia. She ultimately underwent cystourethroscopy and was found to have clots bilaterally obstructing the ureteral openings in the bladder without any other filling defects. In the following 2-3 days, urine output began to increase with improved clearance and intermittent dialysis was stopped. Patient had full renal recovery.

Discussion: We believe this case has important clinical relevance due to the use of aminocaproic acid leading to obstruction and need for short term dialysis. Recognizing the clinical presentation of Amicar related renal failure can help direct the care and provide resolution such as in our case. It is known that in patients with upper urinary tract bleeding, the use of Amicar has resulted in intrarenal obstruction in the form of glomerular capillary thrombosis or clots within the renal pelvis and ureters. Keeping this in mind, benefits should outweigh the risks if Amicar is to be used. A question to be asked is the adverse effect of renal failure dose related or is it merely due to exposure of the drug. An important point to remember is that Amicar is renally excreted which would change dosing in a patient with pre-existing renal dysfunction or would need dynamic dose regulation in someone who suffers new kidney injury while on the drug. Contrast Induced injury was less likely in our patient due to acute kidney injury occurring earlier than expected in CIN. Also, renal recovery occurring after obstruction was corrected is more of a reason that renal injury was due to Amicar related obstructive uropathy.

SA-PO286

Osmotic Nephrosis: SGLT2 Inhibitor (SGLT2-i) Leaves a Footprint Behind

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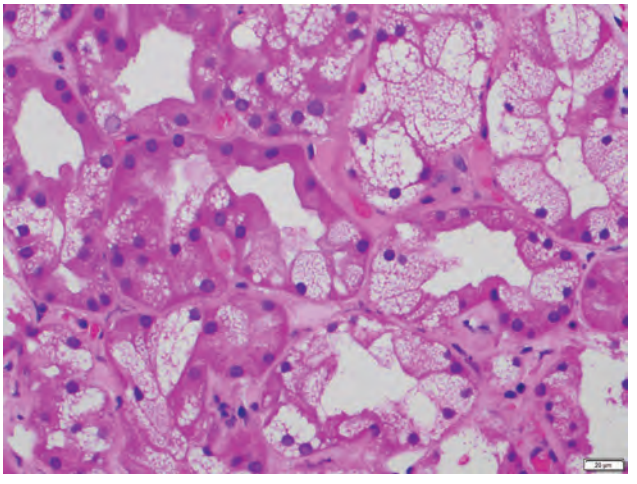
Introduction: SGLT2-i causing acute kidney injury has been reported. Our case, defines the pathogenesis of severe AKI due to SGLT2-i. This class of medications cause functional reduction in GFR by activating tubuloglomerular feedback from enhanced distal sodium delivery. Osmotic nephropathy due to use of Canagliflozin has not been reported.

Case Description: A sixty eight year old diabetic, hypertensive Caucasian male, recovering from left septic knee due to group B streptococcus infection at a swing bed, got admitted with oliguric renal failure. His baseline creatinine was 1.2 mg/dL, with eGFR 62 ml.min and no baseline proteinuria, last A1c of 7.2% one month prior. One week prior to admission, he was started on Canagliflozin 300 mg daily. No history of volume depletion, and no evidence of hypotension, contrast exposure, or NSAID use noted. He was on furosemide 80 mg daily, Enalapril 5 mg daily. Complements were normal, urine revealed active sediment and 2.3 grams proteinuria. Hemodialysis was initiated due to oliguric AKI. Canagliflozin was stopped. Week after admission, creatinine improved to 1.7 mg/dL and the patient is off dialysis. Biopsy revealed features of osmotic nephrosis (Fig. 1).

Discussion: Enhanced **glucose** delivery to S3 segment of proximal tubule (PT) due to it's blocked uptake at S1 segment of PT by SGLT2-i, activates osmosensitive aldose reductase. Glucose is converted to sorbitol and to fructose. Fructose-uric acid axis is postulated in pathogenesis of **chronic kidney injury** related to diabetic nephropathy. In our case, although the exact etiology of osmotic nephrosis is not known, we hypothesize that higher concentrations of intracellular fructose may have caused local toxicity leading to the described pathological changes and severe **acute renal failure.**



Osmotic Nephrosis : Proximal tubule cell with severe vacuolization, loss of brush border, and cell death

SA-PO287

Euglycemic Diabetic Ketoacidosis Caused by a Sodium Glucose Cotransporter-2 Inhibitor

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Introduction: The use of Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitors in the treatment of diabetes mellitus has continued to grow in the last several years, owing to their ability to reduce cardiovascular morbidity and mortality, and prevent incident or progressive diabetic nephropathy. With their increasing use, providers must understand the side effect profile of this new drug class. Here, we present a case of euglycemic diabetic ketoacidosis secondary to empaglliflozin, which is a rare, but potentially life threatening complication of SGLT-2 inhibitors.

Case Description: A 53-year-old man with type 2 diabetes mellitus managed with metformin and empagliflozin, presented with progressive nausea and vomiting, and was found to have a severe anion gap metabolic acidosis. On presentation, his pH was 7.11, serum bicarbonate 5 mmol/L, and anion gap was severely elevated. His blood glucose was 184 mg/dl. Beta-hydroxybutryate was markedly elevated, serum lactate was normal at 0.8 mmol/L, and serum creatinine was 1.0 mg/dl. He was diagnosed with non-hyperglycemic diabetic ketoacidosis based on strong clinical suspicion. Although glucose was < 200 mg/dl, he was treated with IV insulin and withdrawal of his empagliflozin. Within two days his acidemia had resolved with serum pH improving to 7.37, serum bicarbonate increasing to 24 mmol/L, and resolution of his anion gap.

Discussion: Ketoacidosis is a rare complication of SGLT-2 inhibitors. Unlike diabetic ketoacidosis in patients with type 1 diabetes mellitus, patients taking SGLT-2 inhibitors do not present with overt hyperglycemia. Due to this, ketoacidosis may go unrecognized leading to a delay in diagnosis and therapy. The cause of this complication is assumed to be due to decreased insulin production and loss of regulation of glucagon leading to increased glucagon secretion. As many nephrologists are now using SGLT-2 inhibitors regularly in patients with type 2 diabetes mellitus, providers need to be aware of this rare, but potentially serious complication in order to make a prompt diagnosis and institute timely treatment.

SA-PO288

ARF Caused by Tacrolimus Nephrotoxicity Due to Enhanced Absorption Mediated by Ledipasvir Inhibition of Gut Permeability-Glycoprotein

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Introduction: Recently discovered Novel Direct-acting antivirals (DAA's) have completely changed the spectrum of Hep.C treatment with multiple studies showing sustained virological response of over 90% in many genotypes. Treatment of hepatitis C with DAA's in renal transplant has been associated with nephrotoxicity at the pharmacodynamic level due to indirect interaction with immunosuppressive medications especially tacrolimus. We report a case of acute renal failure from increased tacrolimus plasma levels secondary to Harvoni mediated inhibition of gut permeability- glycoprotein.

Case Description: 65-yo M with a h/o renal transplant for ESRD due to DM and HTN and hep.C being treated with Harvoni (ledipasvir/sofosbuvir) was admitted for incidental ARF when presented initially for lesions on his AVF.His immunosuppression was tacrolimus 5 mg q 12 h and MMF 1 g bid. Physical exam was within normal limits. Lab was remarkable for an acute bump in Cr from his baseline of 1.5 to 2.1 mg%, along with blood tacrolimus level of 14 ng/ml. There were no identifiable nephrotoxic insults or medications. The clinical diagnosis of tacrolimus nephrotoxicty was made and was attributed to excessive gut tacrolimus absorption because ledipasvir is known to inhibit the gut p-Glycoprotein which normally limits the absorption of tacrolimus. His dose was gradually reduced from the home regimen of 5 mg bid to 2 mg bid, with a subsequent drop in his tacrolimus levels and recovery of serum creatinine to baseline of 1.5 mg% at a tacrolimus level of 7.8 ng/ml. After resolution of his ARF, he was discharged on 2 mg bid with the target tacrolimus level 6-8 ng/ml while he was still getting Harvoni. After the completion of his 12-week course of Harvoni, he was put back on a higher dose of tacrolimus, to avoid allograft rejection due to inadequate tacrolimus level secondary to the sudden drop in gut absorption without ledipasvir.

Discussion: Emerging DAAs seem to have a reduced potential for drug interactions, which will facilitate their use in the treatment of HCV in renal transplant patient. Close monitoring and dose titration of immunosuppressive medication especially Tacrolimus in renal transplant HCV infected patients being treated with DAA's is important to prevent Nephrotoxicity from higher plasma levels and renal rejection from lower plasma levels of tacrolimus.

SA-PO289

Severe Drug-Induced Bilateral Obstructive Nephropathy in a Lung Transplant Recipient: A Case Report and Literature Review

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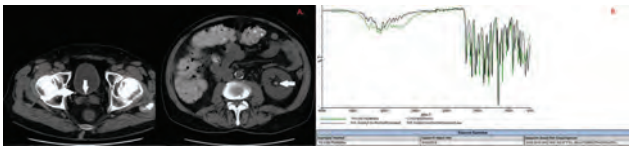
Introduction: Drug induced nephrolithiasis is rare and accounts for 1-2 % of all renal stone disease. Sulfamethoxazole mediated renal injury is mostly from interstitial nephritis and crystalluria with occasional renal stone formation. We present a rare case of Sulfamethoxazole induced acute bilateral ureteral stones causing hydronephrosis and severe AKI in a lung transplant recipient.

Case Description: A 59-year-old lung transplant recipient presented with a 3-day history of bilateral flank pain, weakness, anorexia, and decreased urine output after 4 weeks of high dose sulfamethoxazole-trimethoprim (Bactrim DS 2 TID) for cavitating Nocardia pneumonia. Examination was significant for moderate volume depletion, bilateral flank tenderness and oligo-anuria. Serum chemistry was significant for creatinine of 5.08 mg/dL (baseline 0.9), hyponatremia (130meq/L), and hyperkalemia (5.2meq/L) with a normal uric acid level. UA showed aciduria (pH=5.0). US and CT showed bilateral ureteral stones, hydronephrosis and bladder sediment layering (Fig.1a). Patient underwent bilateral ureteral stent placement and the urine (frank hematuria, unable to appreciate crystals) was strained and subjected for stone analysis. The infrared spectroscopy (IS) showed > 95% of absorbance pattern consistent with N4-acetylsulfamethoxazole, confirming the diagnosis of sulfamethoxazole stone (Fig.1b). Cessation of Bactrim therapy, urine alkalization, and volume replacement resulted in resolution of hydronephrosis and complete recovery of renal function.

Discussion: Bactrim induced interstitial nephritis, hyperkalemia and crystalluria is frequently seen. However, acute bilateral ureteral stone causing obstructive nephropathy is rare and to our knowledge not reported. The major risk factors include higher dose of medication, low urinary pH (poor solubility), and volume depletion. Our case exemplifies the importance of monitoring patient's urine pH, crystalluria, renal function, and volume status when using high doses of Bactrim.



A. CT showing Distal Rt & Proximal Lt ureteral calculus with stone layering in bladder. B. IS showing stone composition matching metabolite of sulfamethoxazole.

SA-PO290

Stones and Woes: A Case of Tiopronin Associated Proteinuria

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Introduction: Cystinuria is a rare genetic disorder characterized by impaired renal cystine transport causing increased cystine excretion and cystine nephrolithiasis. Treatment aims at maintaining urine cystine concentration below solubility level by hydration and alkalization. Patients resistant to conservative measures or who have a high cystine excretion rates are treated with Tiopronin or D-penicillamine. Tiopronin is usually well tolerated. Here we report a rare side effect of Tiopronin induced nephrotic range proteinuria.

Case Description: A 41 year-old woman with kidney stones for six years, presented to our stone clinic with complaints of recurrent stone passage. Her past medical history is significant for multiple urological procedures for stone removal. Her stone analysis showed 100% cystine calculi. She was managed with increased hydration and potassium citrate (60meq/daily) for stone prevention and she reported good compliance to treatment. However, CT of abdomen showed recurrent bilateral staghorn renal calculi. She underwent bilateral complicated procedures, and eventually the stone burden was cleared. Given the resistance to conservative treatment, she was started on Tiopronin at 800mg per day, which was gradually increased to 1000mg per day. At six months followup, 24 hour urine test showed decreased supersaturation and increased capacity of cystine. Repeat imaging of kidneys showed no new stone formation. However, she developed proteinuria from a baseline of 0.11mg/dL to 3.8mg/dL. Initially, a lower dose of Tiopronin was attempted with no improvement in the proteinuria. Subsequently, Tiopronin was withdrawn, and a resolution of the proteinuria was noted after that.

Discussion: Tiopronin is effective in reducing cystine stones in up to 70% of patients. With a better side effect profile compared to D-penicillamine, Tiopronin is first line for patients resistant to conservative therapy. Proteinuria due to Tiopronin is a rare, dose dependent side effect that resolves with cessation of therapy. Optimal monitoring for adverse effects is still not well defined; nonetheless, clinicians remain vigilant by monitoring urine protein to creatinine ratios every three to six months while patients are on Tiopronin.

SA-PO291

Sulfadiazine Induced Crystalluria

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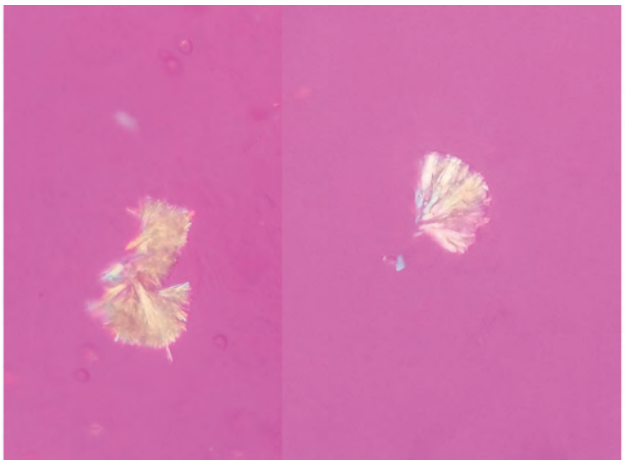
Introduction: Crystal-induced acute kidney injury (AKI) is caused by the intratubular precipitation of crystals, which results in obstruction. Crystal-induced AKI mostly occurs as a result of acute uric acid nephropathy and following the administration of drugs or toxins that are poorly soluble.

Case Description: A 23 year-old man with history of untreated HIV presented with 1 week history of right sided weakness. HIV viral load was 274,000 copies/mL and absolute CD4 count was 2 /cu mm. Brain MRI showed bilateral ring enhancing lesions. Patient was started empirically on pyrimethamine 75 mg daily, sulfadiazine 1.5 g q6 hours and leucovorin 25 mg daily. Brain biopsy confirmed the diagnosis of toxoplasmosis. Hospital course was complicated by AKI 8 days after starting this regimen. Labs revealed BUN 12 mg/dL and serum creatinine 2.0 mg/dL (baseline 0.8 mg/dL). Urinalysis showed no hematuria or pyuria; pH was 6. Urine protein/creatinine ratio was 0.42 g/g. Kidney ultrasound showed non-obstructing bilateral ureteral stones. Examination of urine sediment under polarized light revealed multiple yellow brown asymmetric rosette shaped crystals (sulfonamide crystals) (figure 1). Sulfadiazine was discontinued and patient was switched to clindamycin. Patient was treated with IV fluids (sodium bicarbonate) to alkalinize the urine (urine pH goal was > 7 with urine output goal was 2 L/day). The patient's serum creatinine returned to baseline within 8 days.

Discussion: Sulfadiazine induced crystalluria is a serious complication in patients with AIDS who are treated for toxoplasmosis. Predisposing factors include high dose of sulfadiazine and volume depletion. It usually presents with AKI within 3 weeks of starting the medication. Treatment requires stopping the offending agent, aggressive IV hydration (UOP at least 1.5 L/day) and bicarbonate infusion to alkaline the urine (goal pH > 7).



SA-PO292

Two Cases of Lurasidone-Associated AKI

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Introduction: Lurasidone (Latuda) is a novel atypical antipsychotic used for schizophrenia and bipolar disorder. AKI has rarely been reported with lurasidone in trials. We report the first two clinical cases of AKI with lurasidone, including the first case of biopsy proven chronic interstitial nephritis (CIN).

Case Description: Case 1: 70-year old bipolar female was sent to ER for serum creatinine (Scr) of 8.4mg/dL. Scr was 1mg/dL six months prior. Medications included lurasidone, escitalopram, lamotrigine, lithium (Li), alprazolam, amphetamine, anastrazole, propranolol, and metformin. Lurasidone was the only new medication, started 6 months prior. Vitals and physical exam were unremarkable. Serum potassium was 6mmol/L, CO2 13mmol/L and Li 0.6mmol/L. 24-hr urine protein was 0.7g. Serologic work-up was negative. Metformin and Li stopped and patient discharged with Scr of 6.2mg/dL. Patient re-hospitalized one month later for Scr 9.8mg/dL requiring 3 sessions of hemodialysis for uremia. Kidney biopsy showed ATN and severe chronic interstitial nephritis (CIN). The lack of micro-cysts or granulomatous CIN was inconsistent with Li or lamotrigine induced AKI respectively. Oral corticosteroids initiated and lurasidone was held. Scr decreased to 2.6mg/dL four weeks later. Case 2: 50-year old male with schizophrenia was seen in clinic for elevated Scr of 1.6mg/dL. Scr was 1.3, 6 months prior to presentation. Medications included lurasidone, clozapine, clozaril, klonopin, lamictal, tamsulosin and metoprolol. Physical exam was unremarkable. Spot urine total protein-to-creatinine was 0.1. Serological work-up was negative. Lurasidone dose was reduced from 160mg to 80mg daily and Scr subsequently decreased to 1.3mg/dL.

Discussion: A review of FDA Adverse Event Reporting System (FAERS) revealed AKI in 18/3076 users of lurasidone. All cases were female ≥60years with AKI seen within 1yr of drug initiation. CrCl <50mL/min raises serum levels of lurasidone thereby increasing risk of AKI, as does adjunctive therapy with Lithium. AKI improved in our cases after discontinuation and steroids, or reduction of lurasidone therapy alone. It is important for clinicians to be aware of the potential AKI and CIN risk associated with lurasidone so renal function can be closely monitored in these patients.

SA-PO293

Rapid Loss of Kidney Function Associated with the Use of Capreomycin

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Introduction: Capreomycin (CPM) is used in the treatment of resistant forms of tuberculosis (TB), resulting in the adverse effect of nephrotoxicity. In the acute forms, tubular necrosis or glomerular alteration occurs, which is reversible if the use of the drug is suspended. Chronic impairment is characterized by interstitial nephritis. We report the case of a patient who developed severe renal dysfunction associated with the use of CPM.

Case Description: Male (aged 65), diabetes mellitus (DM) for 4 years, diagnosed with pulmonary TB (positive smear microscopy), initiated treatment with Rifampicin (RFP), Isoniazid, Pyrazinamide (PZA) and Etambutol (ETB). After 9 months, he remained symptomatic and GeneXpert detected resistance to RFP. In June 2017, he initiated treatment with CPM, ETB, Levofloxacin, Terizidone and PZA. At this time, he presented with creatinine (Cr mg/dL) 0.58 and hemoglobin (Hb g/dL) 13. After 6 months on the new treatment, he presented with Cr 2.5. In the ninth month, with negative sputum culture and undetectable GeneXpert, CPM and PZA were suspended, as recommended by the Brazilian Ministry of Health. In the tenth month, Cr was 2.64 and Hb 8.2, and the dosage of the other medications was adjusted according to the glomerular filtration rate (GFR). Although CPM was suspended, the patient evolved with no improvement in the GFR, with Cr 2.46, an

absence of proteinuria, hematuria or leukocyturia and proteinuria/24h 162mg. He presented a normal kidney ultrasound and a fundoscopy with non-proliferative diabetic retinopathy. Renal biopsy: normal glomeruli, no mesangial, endo or extracapillary proliferation, necrosis, sclerosis or thickening of the basement membrane; mild atrophy and interstitial fibrosis, with interstitial mononuclear infiltrate and arterial segment with mild fibro-intimal hyperplasia. Immunofluorescence did not demonstrate immunocomplexes.

Discussion: This case demonstrates a rapid, severe alteration of the GFR in a diabetic, normotensive patient with no evident proteinuria. The biopsy did not reveal kidney impairment from the DM. The literature reports few cases on nephrotoxicity from CPM. This study emphasizes the importance of strict controlling the GFR in patients on CPM, especially the elderly and those with comorbidities.

SA-PO294

Effectiveness of Hemodialysis and L-Carnitine in Severe Valproate Overdose

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Introduction: Valproic acid (VPA) is used to treat seizure disorders and psychiatric illnesses. Acute VPA intoxication usually results in mild, self-limited CNS depression. VPA and its metabolites are low molecular weight, osmotically active acids and anions that may cause elevated osmolar and anion gap metabolic acidosis, hypocalcemia, hypernatremia, hyperammonemia with or without hepatic failure, cerebral edema leading to death if ingested in large doses. Prospective studies are lacking with regard to the management of VPA overdose, and the available data is mainly from case reports or retrospective studies. We present a case of sodium valproate overdose where hemodialysis was used due to rapid clinical deterioration

Case Description: A 24 year old female with seizure disorder on VPA and prior suicide attempts was brought to the ED with incoherent speech and encephalopathy after ingesting 100 tabs (100mg each) of VPA Shortly after arrival, she became agitated and required mechanical ventilation and pressor support. VPA level was >1200μg/ml along with AGMA, osmolar gap, hypernatremia, hypocalcemia and hyperammonemia (see table). CT head was negative for cerebral edema. She was admitted for acute VPA Toxicity. Charcoal suspension via NGT and L-carnitine infusion were initiated. Due to rapid clinical deterioration, she required a single 6 hour session of emergent hemodialysis with an Optiflux F160 dialyzer, Qb 400cc/min. Following dialysis, she clinically improved and VPA level was 439μg/ml at 24hrs

Discussion: Our patient presented with classic symptoms and lab abnormalities seen in acute VPA toxicity. Due to its low molecular weight and high free serum levels at supratherapeutic doses, hemodialysis seems an effective treatment. Mitochondial dysfunction and carnitine depletion occurs with VPA toxicity which leads to hyperammonemia. Retrospective studies suggest the use of L-carnitine to reverse these defects and hemodialysis can also be used for further ammonia clearance

Labs	Initial Labs	Subsequent Labs (24 hours)	Subsequent Labs(48 hours)
Sodium (134-145 MEQ/L)	154	136	136
Potassium (3.5 - 5.2 MEQ/L)	4.2	3.6	3.8
Chloride (96 - 108 MEQ/L)	109	101	107
Bicarbonate (22.0 - 30.0 MEQ/L)	19	21	21
Calcium (8.5 - 10.5 mg/dL)	7.8	7.9	8.2
Blood Urea Nitrogen(6-23 mg/dL)	15	3	4
Creatinine (0.50 - 1.10 mg/dL)	0.69	0.41	0.47
pH (7.35 - 7.45)	7.24	7.33	7.46
Osmolality (280 - 296 mOsm/kg)	339	–	–
Osmolar Gap (0 - 10)	21	–	–
Serum Glucose (mg/dL)	89	–	–
Anion Gap (10-12)	26	17	12
Valproate Level (ug/ml)	>1200	439	85
Ammonia (9-30 umol/L)	144	42	28

SA-PO295

A Case of Phenobarbital Overdose - Managed by High Flux Hemodialysis

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Introduction: Intentional and accidental drug overdose result in approximately 10, 000 death per year. While some overdose can be managed with antidote, others might require more invasive care. Although techniques such as charcoal hemoperfusion have gone obsolete, hemodialysis (HD) has become the new standard to remove drugs that are moderately protein bound but small in size. We present a case of phenobarbital (PB) overdose corrected by HD.

Case Description: A 52 year old female with a history of seizure on PB who was brought to the hospital because of unresponsiveness secondary to an apparent suicide attempt via medication overdose. Ingestions occurred more than 24 hours prior to arrival. Vitals:T 36.8C, BP 106/82, HR 113, RR 40, Sat: 96% on non-rebreather. GCS< 8 She was breathing spontaneously and pupils were small but reactive to light. She was intubated for airway protection. Serum chemistry was within normal limits. Urine drug screening was positive for PB, benzodiazepine, and opioids. The rest of the toxicology workup was negative. Urine PB level was 147.9 ug/ml and therapeutic range is between 30 to 40 ug/ml. CT brain did not show cerebral pathology. EEG was consistent with cortical irritability and potential for seizure. Given that there was a national shortage of bicarbonate solution, serum and urine alkalization were not performed. One session of four-hour hemodialysis (HD) was initiated. Initial post-HD PB level was 54.2 ug/ml. Two hour post-HD PB level was 35.6 ug/ml. Patient was able to open her eyes the following day with drug level 43 ug/ml. No further dialysis was required.

Discussion: The therapeutic level of PB for seizure disorder is 30-40 ug/ml. A concentration above 60 ug/ml is considered toxic. The half life of PB in adults is between 50 to 140 hours depends on patients' age. Although PB is 20-45 percent protein bound, its plasma volume of distribution is large, between 0.6-1.0 L/kg, and the molecular size is only 232 daltons, making elimination of the drug easily with HD. The calculated time for this patient to reach non-toxic level of drug concentration with native renal clearance would be at least 100 hours. However, it took less than 24 hours to reach similar level with the help of HD. Take home message: While PB overdose can be treated with supportive care, in patients who are intubated, implementation of HD can effectively reduce the serum drug level and potentially reduce ventilator time.

SA-PO296

Outpatient Drug Dosing for Patients with CKD: Is It Time to Include Pharmacists?

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Introduction: Neurotoxicity due to inappropriate valacyclovir dosing in patients with chronic kidney disease (CKD) is a recognized adverse effect. Electronic databases such as Lexicomp provide pharmacists and physicians with standard dose reductions for renal clearance. Our cases demonstrate the inadequacy of our current systems, which unfortunately failed to avert these preventable outcomes.

Case Description: Case 1 51-year-old male with end-stage renal disease (ESRD) on hemodialysis (HD) was seen in primary care clinic for shingles. Due to ongoing renal transplant workup, he was given valacyclovir 1g three times daily (immunocompromised dosing). Two days later, he presented to the emergency department (ED) with confusion and visual hallucinations. A pharmacist reviewed the dose and recommended switching to acyclovir 800mg five times daily based on clinical indication rather than renal dosing. He later returned to the ED with worsening symptoms. His pre-dialysis acyclovir level was 12mg/L, improved to 3.5mg/L after 3 hours of HD. He had daily HD for 3 days and discharged on valacyclovir 500mg daily for 7 days. **Case 2** 53-year-old male with HIV and ESRD on HD developed shingles treated with valacyclovir 1g three times daily (HIV dosing). He became somnolent, agitated and confused. He was admitted for neurotoxicity due to inappropriate valacyclovir dosing, treated with urgent HD for 3 hours. Symptoms improved over 24 hours and he discharged on valacyclovir 500mg daily for 7 days.

Discussion: Our cases demonstrate the limitations of our current electronic medical record, which does not alert prescribers to data present in the chart at the time of medication order entry, namely glomerular filtration rate (GFR) and diagnosis of CKD. Such alerts can reduce the risk of inappropriate renal dosing. We also propose that community pharmacists be granted access to the medical record to properly verify dosing in the outpatient context as it occurs on inpatient wards. This would provide added safety to a currently disjointed prescriber-pharmacist interface in the outpatient setting. Another solution would be an identifying bracelet for patients with GFR<30 mL/min per 1.73m^2, similar to community Do Not Resuscitate (DNR) bracelets, which would also foster greater public and provider awareness regarding the vulnerability of this patient population to such medical errors.

SA-PO297

Fibromuscular Dysplasia in a Patient with Vascular Type Ehlers-Danlos Syndrome Who Presented with Spontaneous Renal Artery Perforation

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Introduction: Fibromuscular Dysplasia (FMD) is a rare segmental disease of small and medium sized arterial wall musculature. FMD is noninflammtory and nonatherosclerotic in nature and affects renal and internal carotid arteries in 75% of cases. Renovascular hypertension in young females is the most common presentation, while spontaneous dissection, bleeding and renal infarction is rare; however these are seen more often in males affected by FMD. We present a rare case of coexistent FMD and Ehers-Danlos Syndrome presenting as spontaneous renal artery dissection.

Case Description: A 44-year-old male presented to the ED with severe left flank pain. Patient was hypotensive (S.B.P 80 mmHg), in hemorrhagic shock and had AKI, Hb 9.8 gm/dL, Cr 1.69 mg/dL). CT angiogram abdomen revealed massive retroperitoneal bleed from left renal artery. Emergent laparotomy confirmed pseudoaneurysm from dissected left renal artery extending to sub-segmental arteries. Revascularization attempt was futile due to friability of the vessels and left nephrectomy was performed. Histologic evaluation of the kidney demonstrated marked fibrointimal thickening with hypocellular intimal sclerosis and focal cellular fibroplasia, medial hypertrophy, and abrupt broad regions deficient in internal elastic lamina. The severe fibro-obliterative renovascular disease findings were consistent with fibromuscular dysplasia, with features of both the medial fibroplasia and intimal type. Genetic testing was performed confirming pathogenic mutation in COL3A1 gene (c.1106G>T) diagnostic of Vascular Ehlers-Danlos Syndrome (vEDS).

Discussion: Spontaneous renal artery dissection is rare, and has been associated with FMD (especially in males), malignant hypertension, severe atherosclerosis, severe trauma, Marfan syndrome, or Ehlers-Danlos syndrome. vEDS has an Autosomal Dominant

inheritance, and is the most severe form of EDS, increasing the risk of arterial aneurysm rupture. Co-existing FMD and vEDS of renal artery has not been described before. This case highlights the need for genetic testing of patients diagnosed with FMD, to rule out additional connective tissue disorders, as co-existence of both conditions can potentially increase the risk of life threatening complications.

SA-PO298

Takayasu's Arteritis Induced Bilateral Renal Artery Stenosis Refractory to Medical Therapy

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Introduction: Takayasu's arteritis (TAK) is a granulomatous large-vessel vasculitis. It primarily affects women of age 10 to 40 years. In patients with TAK, the prevalence of hypertension varies from 23% to 76% across the world and about half of the case are secondary to renal artery involvement. In this study, we present a patient with difficult to control hypertension and worsening renal function secondary to TAK induced renal artery stenosis in spite of adequate medical management.

Case Description: A 39-year-old Caucasian female presented with sudden onset chest pain, left arm pain, muscle ache, and 50-pound weight loss over the past one year. Patient has a past medical history of multiple sclerosis, ulcerative colitis, and cigarette smoking. On exam, blood pressure was 110/72 mmHg in the right arm and 88/70 mmHg in the left arm. A left subclavian bruit was present with a feeble left radial pulse. EKG showed an anterior STEMI. A coronary angiogram revealed 99% LAD ostial stenosis and incidentally showed high-grade stenosis of the proximal left subclavian and bilateral renal arteries. The patient underwent an urgent coronary artery bypass graft. On further workup, a CT angiogram showed severe stenosis of the proximal left subclavian artery, superior and inferior mesenteric artery, celiac artery and bilateral renal artery (80% RRA and 90% LRA stenosis). A clinical diagnosis of Takayasu's arteritis was made and the patient was started on prednisone and methotrexate. At a six-month follow-up, the patient was found to have BP of 160/90 mmHg in spite of being on four antihypertensives including an ACE-I and a decreased eGFR of 40 ml/min/1.73m^2. MRA abdomen showed a completely occluded right renal artery with an atrophied right kidney. Renal Duplex US showed LRA proximal stenosis with a significantly increased PSV of 760 cm/sec and RRI of 60%. An aortogram confirmed the RRA occlusion. The patient underwent left aorto-renal bypass grafting of her solitary kidney. A six-month follow-up showed improved eGFR to 76 ml/min/1.73m^2 and a decrease in antihypertensive medicines to carvedilol and enalapril.

Discussion: In TAK with advanced renal artery stenosis refractory to medical therapy, endovascular or surgical revascularization is the treatment of choice. The patient was prevented from becoming dialysis dependent by the timely recognition, close monitoring, and intervention.

SA-PO299

Baroreceptor Failure – A Rare Form of Secondary Hypertension

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Introduction: Baroreceptors in the neck play a large role in blood pressure (BP) regulation. They sense distension of the vessel wall and help stabilize blood pressures during changes in volume and/or posture. Injury to the baroreceptors can cause extremely labile blood pressure with BP surges. We present a case of baroreceptor failure, a rare form of secondary hypertension.

Case Description: A 65-year-old male with hypertension (HTN), anxiety and soft palate cancer s/p radiation therapy was admitted for planned carotid endarterectomy. Patient's BP rose to 290/102mmHg when he was placed supine in the operating room. Surgery was aborted and nephrology was consulted to assist with BP therapy and secondary workup. Patient stated these BP surges had been occurring for years. However, they only began after he received radiation therapy to his neck at age 55. His current medications were Felodipine 10mg daily and Carvedilol 12.5mg twice daily. Patient kept detailed BP logs 6 times a day with average BP 210s/100s mmHg, with surges to 260 mmHg systolic. Patient stated he used to be on many BP medications to treat his surges, but it would cause severe hypotension if he didn't have surges. Patient had a secondary HTN workup which was negative for pheochromocytoma, hyperaldosteronism, and renal artery stenosis. He also had Positron Emission Tomography and Computerized Tomography scans done for surveillance of his cancer, which were negative for new masses. As a result, we concluded the patient likely had baroreceptor failure caused by radiation therapy to his neck. Review of the literature showed that Clonidine and benzodiazepines are beneficial in limiting BP surges. He was started on Clonidine 0.1mg/24hr patch and discharged with follow-up to titrate his Clonidine and wean his other BP medications. His Alprazolam for anxiety was switched to Diazepam as well. After 3 months, patient was on Clonidine 0.4mg/24hr patch, Valium 10mg BID and no longer on Felodipine or Carvedilol. His peak surge BPs are now 180 mmHg systolic, and average BP is now 160-180/70-90 mmHg.

Discussion: Baroreceptor failure is a rare form of secondary hypertension, but it can be suspected if a patient presents with very labile blood pressure and high BP surges. Very commonly, there is a history of neck trauma (i.e. radiation therapy, neck surgery). Clonidine (central alpha-2 agonists) and benzodiazepines are effective in reducing blood pressure surges.

SA-PO300

Hypertension Associated with Herbal Supplements: "Diosmin Complex," "Raphacholin C," and "Herbatka Fix Na Cholesterol": A Case Report

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Introduction: We report a case of hypertension associated with the ingestion of several Herbal Supplements (Diosmin Complex, Raphacholin C, and Herbatka Fix Na Cholestrol).

Case Description: A 60-year-old female patient, who had been ingesting these supplements sporadically for years, had increased her intake to twice a day for a month. Over the course of that month the patient developed palpitations, weight gain, trace edema, and mild jugular venous distention. Laboratory findings were notable for hypokalemia, hypocalcemia and hypomagnesemia with normal renal function. Urine chemistries confirmed mineralocorticoid excess with the presence of renal potassium wasting. The nutritional substance was subsequently ceased and supportive treatment was begun with low-dose carvedilol 6.25mg BID, and oral and IV potassium supplement. Further investigation was done of the renin aldosterone axis which confirmed the absence of primary hyperaldosteronism or high plasma renin activity. The patient's condition improved rapidly with supportive treatment and ceasing of the supplements.

Discussion: Current information regarding the adverse effects of these herbal supplements is very scarce, therefore potential damage should be kept in mind before ingesting these nutritional supplements or anything similar. This report serves as an important reminder to the public, as well as healthcare providers, of the potential of hypertensive urgency related to such nutritional supplements.

SA-PO301

Application of a Central Iliac Arteriovenous Coupler Device in Severe Resistant Hypertension: A 3.5-Year Follow-Up

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Introduction: In patients with resistant hypertension (RH), iliac arteriovenous (AV) coupler implantation leads to blood pressure (BP) reduction via decreased total vascular resistance and improved arterial compliance. However, long-term efficacy and safety need to be further explored. We report on the first case of 3.5-year follow-up (FU) in a patient treated by coupler implantation, who underwent repeated right heart catheterization (RHC).

Case Description: A patient with RH was admitted to hospital. Despite treatment with 6 anti-hypertensives his BP was poorly controlled. Previously, he had undergone renal denervation, not leading to significant BP decrease. Therefore an AV coupler was implanted in our catheterization laboratory, causing a periinterventional BP decrease from 198/90 to 163/69mmHg. The patient was discharged with a BP of 122/71mmHg. After 3 months there was a sustained BP decrease, whereas later it was fluctuant (office BP: 147-173/85-95mmHg, ABPM: 153-166/81-94mmHg) probably due to medication non-adherence, confirmed by a urinary screening test. One year later the patient was hospitalized with iliac venous stenosis, which was treated by venoplasty and stenting. After 3.5 years he complained about progressive dyspnea and weight gain. FU RHC showed an increased pulmonary artery-, right atrial- and wedge-pressure as well as cardiac index and a decreased pulmonary vascular resistance. Central aortic pressure had decreased indicating device effectiveness. An invasive closure maneuver led to an immediate BP increase (+30mmHg) and a similar decrease after re-opening of the coupler, verifying its functionality. To unload the right ventricle, an intensive diuretic therapy was introduced leading to clinical improvement.

Discussion: This is the first case of 3.5-year FU after arteriovenous coupler implantation, leading to significant BP decrease. We verified a proper long-term function of the device and demonstrated changes in hemodynamic parameters related to volume congestion, which were resolved by an intensified diuretic therapy.

Hemodynamic changes obtained by RHC

Date of RHC	Right atrial pressure [mmHg] (s/d/m)	Pulmonary artery pressure [mmHg] (s/d/m)	Cardiac index (Fick) [l/min/m^2]	Pulmonary vascular resistance [dyn x sec/cm^5]	Central aortic BP [mmHg] (s/d/m)
Baseline	11/10/7	36/13/21	2.6	160	214/105/141
0.5-year follow-up	13/9/7	39/13/23	3.0	129	214/92/133
3.5-year follow-up	14/13/12	56/20/35	4.1	114	165/70/105

S-systolic/d-diastolic/m-mean

SA-PO302

Post-Implantation Syndrome Following Abdominal Aortic Aneurysm Repair Causing Podocytopathy

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Introduction: A systemic inflammatory response of fever, leukocytosis, and pleural effusion following various vascular interventions including endovascular aortic repair (EVAR) is well recognized phenomena known as post-implantation syndrome. We describe a case of podocytopathy following EVAR.

Case Description: A 69-year-old man with no significant previous medical history presented with fevers progressive generalized edema and shortness of air after undergoing EVAR for ruptured abdominal aortic aneurysm (AAA) one month prior. He underwent repeat CT of the chest abdomen and pelvis, revealing bilateral pleural effusions that were proven exudative, with intact endovascular repair. His serum albumin fell to 2.0g/dl from a previous baseline of 3.8g/dl, with 2+ proteinuria on urinalysis. Urine microscopy was notable for Maltese crosses reflecting lipid droplets. The serum creatinine (SCr) remained at baseline of 1.4 mg/dl. A renal biopsy showed 4 glomeruli, 1 with global sclerosis, focal interstitial infiltrate of lymphocytes and plasma cells, global foot process effacement on electron microscopy without immune complex deposition. Immunofluorescence was not completed. A final diagnosis of MCD or unsampled primary focal segmental glomerulosclerosis (FSGS) was given by the renal pathologist and given scarring with interstitial infiltrate a clinical diagnosis of FSGS was more likely. A unifying diagnosis of post-implantation syndrome was made after an extensive infectious, vasculitis, and rheumatologic work up were negative. Prednisone 60mg daily with loop diuretics was started. Upon follow up his serum albumin rose to 3.6g/dl, his edema and pleural effusions had resolved.

Discussion: Post-implantation syndrome describes the clinical entity of systemic inflammatory response after repair of AAA. The incidence of the syndrome has been reported to vary widely between 3% and 60% for AAAs. We describe the first case of podocytopathy following EVAR in a patient with post-implantation syndrome, that responded to corticosteroids.

SA-PO303

A Tough Nut to Crack

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Introduction: "Nutcracker Kidney" is a puzzling diagnosis which conventional imaging can miss. We present a case with a high degree of clinical suspicion wherein positional Doppler imaging was required to confirm the diagnosis.

Case Description: A 37 year old African American male with no past medical history presented with several months of intermittent gross hematuria associated with left sided flank pain radiating to his bladder, which was exacerbated with vigorous physical activity and would resolve completely with rest. He had been self-medicating for the pain with NSAIDs on a daily basis (200-400 mg/d). Physical exam revealed a male of thin, tall stature, with a mild tenderness over the suprapubic region and left CVA. Labs: serum creatinine of 1.21 mg/dl (GFR MDRD 82 ml/min/1.73 m2), and urine microscopy with non-dysmorphic red blood cells (>250 on UA, no WBC), 24 hour urine protein of 338 mg/day. Negative urine culture and urine fungal culture. C3 was 91 mg/dl, C4 was 10 mg/dl and ANA was negative. He had a normal hemoglobin electrophoresis, 24 h urine calcium 128 mg/d. CT scan of abdomen/pelvis was significant for absence of renal calculi, cysts, or hydroureteronephrosis. CT also noted an unremarkable bladder, no papillary necrosis, no AVM, and widely patent bilateral renal veins. A cystoscopy revealed negative cytology without bladder masses. A renal doppler study in the supine and standing position was obtained due to a high suspicion for dynamic renal vein compression. The study revealed a normal right renal vein in the supine, seated, and standing positions. Two left renal veins were noted. While one left renal vein was non-pathologic, the second left renal vein doppler showed intact flow in the supine and seated positions, but continuous flow suggestive of compression in the standing position. The patient was offered intravascular intervention, but elected conservative therapy by limiting provocative physical activity.

Discussion: "Nutcracker kidney" is a challenging clinical diagnosis. The mechanism of "nutcracker kidney" is venous hypertension from compression of the left renal vein between the aorta and superior mesenteric artery. Clinicians must maintain a high index of suspicion to diagnose it with targeted dynamic imaging. In this case, all standard imaging failed to reveal the etiology and only the use of positional (standing) Doppler interrogation confirmed the diagnosis.

SA-PO304

A Diagnostic Challenge: Acute Nutcracker Abdomen

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Introduction: Nutcracker syndrome or left renal vein entrapment syndrome is a rare condition caused by the compression of left renal vein between the abdominal aorta and superior mesenteric artery (SMA). We describe the case of a young female presenting with intractable pain.

Case Description: 26-year old woman with history of recently diagnosed untreated H. pylori gastritis presented with sudden onset severe abdominal pain which lasted three weeks. The pain was sharp and worsened with food intake. She denied fever, nausea, vomiting, blood in urine, or recent NSAID use. She was tender to palpation over right and left upper quadrants of abdomen. Labs were normal. CT scan with IV contrast revealed left renal vein compressed between the aorta and the SMA, congested left kidney, medullary edema, and numerous retroperitoneal venous collaterals. This was thought to be incidental. She was diagnosed as gastritis and discharged on H. pylori treatment. However, she returned one month later with persistent abdominal pain. Renal doppler ultrasound showed significant narrowing of left renal vein with significant velocity gradient, consistent with Nutcracker syndrome. Contrast venography revealed proximal left renal vein narrowing, with elevated distal left renal vein pressure, which resolved with stent placement. She became pain-free after the procedure.

Discussion: Nutcracker syndrome was first described in 1937. It occurs due to an idiopathic decrease in the angle between the aorta and the SMA (to less than 35 degrees), with consequent compression of the left renal vein. It is most often asymptomatic, painless, and requires a high index of suspicion to diagnose. Serum biochemistry and urinalysis are often unremarkable. Our patient presented atypically with only acute abdominal pain, which can have a broad differential, making this diagnosis easy to miss. In some cases of nutcracker syndrome, severely increased pressure can lead to abnormal thin-walled collaterals which rupture leading to gross or microscopic hematuria, which was not seen in our patient. The diagnosis is usually made based on degree of stenosis and increased flow velocity as seen on doppler ultrasound. Venography is confirmatory. Treatment can be conservative or surgical. Given the rarity of the condition and limited evidence, the long-term prognosis remains to be elucidated.

SA-PO305

Deletion of Matrix Metalloproteinase-10 Ameliorates Aldosterone-Induced Glomerular Injury in Guanylyl Cyclase-A Knockout Mice

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Background: Recently, we and others have unveiled the novel renal function of natriuretic peptide receptor/guanylyl cyclase-A (GC-A) system on antagonizing aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. We previously investigated uninephrectomized, aldosterone-infused, and high salt diet-fed (ALDO) systemic GC-A knockout (KO) mice, resulting in hypertension, massive albuminuria, mesangial expansion and podocyte injury. However, genes involved in glomerular injury are elusive.

Methods: To identify responsible genes for podocyte injury, we compared glomerular mRNAs from ALDO control mice with ALDO systemic GC-A KO mice using microarray. Furthermore, we examined the role of the identified gene using its KO mice. We performed immunofluorescence study for an identified protein.

Results: Microarray analysis revealed that matrix metalloproteinase-10 (MMP-10) was upregulated more than 40 times in glomeruli of ALDO GC-A KO mice. To investigate the role of MMP-10, we generated double KO (DKO) mice for systemic GC-A and systemic MMP-10. ALDO systemic GC-A and MMP-10 DKO mice showed 80% reduction of albuminuria (4657μg/mgCr vs 24516μg/mgCr, $p<0.05$), and amelioration of podocyte injury demonstrated by improvement of foot process effacement and preservation of podocyte number, compared with ALDO systemic GC-A KO mice. Glomerular mRNA expression of extracellular matrix-related genes such as Tgfb1, Ctgf, and Col4a3 was upregulated in ALDO GC-A KO mice, and the upregulation was canceled by deletion of MMP-10. Immunofluorescence study revealed that MMP-10 expression was pronounced mainly in glomerular cells in ALDO GC-A KO mice. MMP-10 expression was also increased in proliferative lesions of human glomerular diseases such as Lupus nephritis, ANCA related nephritis, and IgA nephritis. *In vitro*, mRNA expression of MMP-10 was increased in human podocytes with TNF-α or TGF-β stimulation.

Conclusions: These results suggest that MMP-10 plays a crucial role in aldosterone-induced podocyte injury in GC-A KO mice, and can be a potential new target for treating kidney diseases.

SA-PO306

Par3A and Par3B Orchestrate Podocyte Polarity

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Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the function of the glomerular filtration barrier of the kidney. Despite its well-established role in aPKC-mediated signaling, Par3A appears to be dispensable for the function of the glomerular filtration barrier. Interestingly, loss of Par3B also did not result in albuminuria and glomerulosclerosis.

Methods: To study potential compensatory mechanisms between Par3A and Par3B, we employed conditional *in vivo* targeting strategies specifically in podocytes and generated podocyte-specific Par3A/B double knockout mice.

Results: Within 8 weeks Par3A/B DKO mice developed severe proteinuria and renal failure. We utilized *Drosophila* nephrocytes to further study the interplay between the

different Par3 proteins. Here, we show co-localization of the Par3A/B homolog bazooka and the nephrocyte diaphragm proteins Sns (nephrin) and Duf (NEPH1) at different developmental stages. Silencing bazooka expression resulted in disturbed nephrocyte diaphragm morphology, severe filtration defects and delayed larval development. To investigate the functional role of Par3A and Par3B, we re-expressed different murine Par3 variants in a *bazooka* knockdown background using the UAS-GAL4 system. Here, we performed several morphological and functional studies and observed different degrees of rescue potential. We utilized high resolution microscopy to resolve the nephrocyte diaphragm pattern and observed a decreased coverage and severely changed localization of Duf (dNeph) and Pyd (dZO-1) after nephrocyte-specific depletion of bazooka. This phenotype can be partially rescued by re-expression of aPKCiota-binding Par3 variants, while the 100kDa Par3A variant and Par3B present with almost no rescue. As none of the Par3 variants is able to provide a full rescue and to study the potential compensatory phenotype between Par3A and Par3B we generated Par3A/B double rescue flies and could show an almost complete rescue in Duf (dNeph) and Pyd (dZO-1) localization, confirming the compensatory potential of the two Par3 variants.

Conclusions: Taken together, these findings support the hypothesis of a potential compensatory mechanism between Par3A and Par3B to maintain polarity signaling at the slit diaphragm which are - at least partially – independent of aPKC.

SA-PO307

Complete Lack of Synaptopodin Causes No Overt Podocyte Defects

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Background: Synaptopodin (Synpo) is an actin-associated protein found in podocyte foot processes and in dendritic spines. Many functions in regulating the actin cytoskeleton via RhoA and other pathways have been ascribed to Synpo, yet no pathogenic mutations in *SYNPO* have been discovered in patients. Several naturally occurring Synpo isoforms have been described (e.g., Synpo-short and -long), and a novel truncated protein (Synpo-T) was detected in the podocytes of *Synpo*mutant mice. Synpo-T was reported to maintain some Synpo functions, thus preventing a major podocyte phenotype from emerging. To further investigate the functions of Synpo in podocytes, we attempted to knockout the majority of the *Synpo*gene and prevent production of a protein.

Methods: We used CRISPR/Cas9 in embryos with two guide RNAs targeting near the 5' and 3' ends of the Synpo gene to attempt to either delete most of the gene or mutate each end to prevent protein production. DNA sequencing was used to identify specific mutations. Immunofluorescence and western blotting using antibodies to amino-terminal, internal, and carboxyl-terminal epitopes were used to assay for Synpo protein. Mutant mice were observed for up to 12 months. Urine, blood, and tissue were taken at select time points to evaluate albuminuria, BUN, histopathology, and glomerular capillary wall ultrastructure. Super-resolution imaging was used to characterize the cytoskeleton. Adriamycin injections were performed.

Results: Many mutations were discovered in 80 founder mice: small deletions and insertions that shifted the reading frame; two deletions of 8 kb between the gRNA target sites; a 6 kb inversion; and a 3' deletion of 7 bp that produced a truncated protein. Several of these were made homozygous or compound heterozygous. There were no significant differences in body weight between the mutants and controls. Urinary protein levels were normal up to 12 months regardless of the Synpo mutation(s) present. There were no obvious histological or ultrastructural abnormalities in 36-week-old mutant mice, and the actin cytoskeleton showed no obvious defects other than the absence of Synpo. However, Synpo mutant podocytes had worse injury from ADR.

Conclusions: Synaptopodin is dispensable for the development and maintenance of podocytes and for function of the glomerular filtration barrier. This is consistent with the lack of *SYNPO* mutations found in proteinuric patients.

Funding: NIDDK Support

SA-PO308

Protecting Glomerular Disease Progression in Mice Lacking Podocyte Associated Talin1 by Tangshen Formula

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Background: Loss of podocyte associated talin1 in mice results in severe proteinuria and kidney failure. Tangshen Formula (TSF), a traditional Chinese Medicine, has been confirmed to play a renal protective effect in rats with diabetic kidney disease and in patients with type 2 diabetic kidney disease. In this study, we further investigate the effect of TSF in genetic mouse model of disease where robust proteinuria is evident.

Methods: Twelve 8 weeks old *Tln1*$^{fl/fl}$ Pod-rtTA TetO-Cre mice (i*Tln1* KO) were induced with doxycycline for three weeks to specifically delete talin1 expression in the podocytes. After 2 weeks of doxycycline induction, the mice were separated into two groups +/- TSF treatment (6 *vs* 6). TSF were delivered by oral gavage at a dosage of 2.4g/Kg body weight/day for total of 5 weeks.

Results: Two weeks of doxycycline induction in the i*Tln1* KO mice, resulted in robust albuminuria prior to treatment (TSF treatment group: 817.35 ± 69.99 vs 53.02 ±10.34 μg/mg creatinine; Placebo treatment group: 781.97 ±72.70 vs 63.49 ±15.52 μg/mg creatinine) measured by ELISA. Following TSF or Placebo treatment for 5 weeks, TSF treatment in the i*Tln1* KO mice significantly reduced albuminuria compared to the placebo group (2136.88 ±270.32 vs 4028.4±516.67 μg/mg creatinine, P<0.05). TSF treatment in the i*Tln1* KO mice improved renal function measured by plasma creatinine (0.46±004 mg/dl to 0.33±0.03 mg/dl. P<0.05). TSF treatment in i*Tln1* KO mice ameliorated glomerulosclerosis and inhibited tubulointerstitial injury including interstitial fibrosis, tubular dilatation, and proteinaceous casts. Ultrastructural examination by transmission electron micrographs also showed improvement in foot process effacement and thickness of the basement membrane in i*Tln1* KO mice treated with TSF.

Conclusions: These results suggest a potential therapeutic role of TSF mice with proteinuric kidney disease and may have a protective role in human glomerulonephropathies.

Funding: Government Support - Non-U.S.

SA-PO309

Deletion of NuRD Component MTA2 in Nephron Progenitors Results in Renal Hypoplasia and Focal Segmental Glomerulosclerosis

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Background: The Nucleosome Remodeling and Deacetylase Complex (NuRD) is a large multi-protein, evolutionarily conserved chromatin remodeling complex that harnesses the power of ATP via the ATPase Chd4 (Mi2β) to mediate nucleosome sliding and remodeling. It also has histone deacetylase activity via Hdac 1/2. We showed that the NuRD component Mi2β and the association between Sall1-NuRD is required for the regulation of nephron progenitor cells (NPCs).

Methods: In this study we deleted the NuRD specific component *Mta2* in Six2+ NPCs.

Results: Mutant mice were viable, although mild renal hypoplasia was evident at embryonic day (E)14-16 (kidney area/body weight 41.2±2.6 vs 53.6±1.7 mm^2/gm). Immunostaining for nephron segment specific markers showed that the nephrogenic zone was not reduced and all differentiating nephron structures appeared normal in the mutant. RNA-seq analysis at E17 showed a number of downregulated genes important for metabolic pathways (23 genes, $p=9.78X10^{-4}$), indicating reduced metabolic fitness of NPCs may account for renal hypoplasia. By 2 months of age *Mta2* mutant mice developed proteinuria (1614±469 vs 53±15 ug albumin/mg creatinine, n= 20 mut, 13 control). Analysis of mutant kidneys revealed findings consistent with focal segmental glomerulosclerosis (FSGS), including mesangial hypercellularity, segmental glomerular scarring, and tip lesions. At 6 months of age albuminuria progressed in the mutant (7110±3739 vs 25±4, n=8 mut 8 control); histopathology showed an increase in globally sclerotic glomeruli, proliferation of parietal epithelial cells with formation of pseudo-crescents, and trichrome staining revealed tubulo-interstitial fibrosis. Mitochondrial dysfunction in podocytes has been shown to contribute to development of FSGS. Transcriptional profiling at 2 months of age revealed significant enrichment in the oxidative phosphorylation pathway for downregulated genes in the mutant (35 genes, $p=1.18 \times 10^{-18}$). Mutant mice frequently die after 6 months of age, however survivors at 1 year of age have significantly elevated sCr (0.16±0.013 vs 0.122±0.009 mg/dL, p=0.035, n= 5 mut, 10 control).

Conclusions: Our results suggest that regulation of metabolic homeostasis by NuRD is required for proper kidney development and for maintenance of normal glomerular function after birth.

Funding: NIDDK Support

SA-PO310

Intervention with the Novel Fibrokinase Inhibitor ANG3070 Mitigates Glomerular Scarring and Attenuates Proteinuria in a Model of Focal Segmental Glomerulosclerosis

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Background: Steroid-resistant (SR) primary Focal Segmental Glomerulosclerosis (FSGS) is accompanied by nephrotic-range proteinuria and necessitates renal replacement therapy. We investigated the effects of a novel small molecule platelet-derived growth factor (PDGF) receptor + vascular endothelial growth factor (VEGF) receptor inhibitor, ANG3070, in a clinically relevant model of FSGS.

Methods: Adult male rats were administered puromycin ((puro), 100 mg/kg, intraperitoneal) or saline (sham). On day 3, after onset of proteinuria, the puro cohort was randomized to vehicle or ANG3070. Twenty-four hour urine was collected on days 7 and 14 at which kidneys were retrieved for analysis.

Results: Puro administration was associated with accumulation of PDGF in the glomerulus, increased glomerular dimension and scarring, and proteinuria. Intervention with ANG3070 attenuated proteinuria on days 7 and 14. Puro-induced glomerular hypertrophy and scarring were both reduced with ANG3070 intervention. Proteinuria-induced tubular toxicity was also reduced with drug.

Conclusions: In a clinically relevant model of FSGS, intervention with ANG3070 is beneficial. These data, form, in part, the basis for using a Precision Medicine approach to evaluate safety and efficacy of this drug in SR primary FSGS.

SA-PO311

Differences in Podocyte Regeneration Between Cortical and Juxtamedullary Nephrons Defined by 3D Analysis and STED Imaging

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Background: Podocyte injury is a central pathomechanism of glomerulosclerosis. Regeneration of lost podocytes from podocyte progenitors along Bowman's capsule can occur but the number of new podocytes seemed to be rather low. We hypothesized that traditional 2D tissue analysis underestimates podocyte regeneration and that injury and regeneration are not equally distributed between cortical and juxtamedullary nephrons.

Methods: To test this concept we employed *Nphs2.rtTA;TetO.Cre;mT/mG* and *Pax2.rtTA;TetO.Cre;mT/mG* mice to quantify adriamycin (ADR)-related podocyte loss and de novo podocyte formation from Pax2+ podocyte progenitors by lineage tracing, using Z-stack confocal microscopy for 3D quantitative analysis and STED microscopy to assure integration of new podocytes into the glomerular filtration barrier. CXCL12 inhibition was used to assess drug-related enhancement of podocyte regeneration.

Results: 2D analysis underestimated the percentage of glomeruli showing podocyte regeneration in comparison to 3D (8.05% *vs* 25.23% $p<0.05$). Doxycyclin-induced podocyte labeling in *Nphs2.iCreER;mT/mG* mice revealed a higher number of podocytes in juxtamedullary glomeruli vs. cortical glomeruli (52.56±1.5 *vs* 81.96±2.85, $p<0.001$). In contrast, doxycyclin-induced Pax2+ progenitor labeling in *Pax2.rtTA;TetO.Cre;mT/mG* mice revealed that less juxtamedullary glomeruli had progenitors along Bowman's capsule vs. cortical glomeruli (79.03±0.15% *vs* 46.15±2.2%, $p<0.05$). Upon ADR exposure, *Nphs2.iCreER;mT/mG* mice juxtamedullary glomeruli lost a higher percentage of podocytes as compared to cortical glomeruli (13.79±3.18% vs 34.11±1.65%, $p<0.05$). *Pax2.rtTA;TetO.Cre;mT/mG* mice revealed that podocyte regeneration was limited in juxtamedullary glomeruli, while cortical glomeruli revealed new progenitor-derived podocytes, a difference that increased with CXCL12 inhibition (24.03±4.8 *vs* 75.96±4.8, $p<0.05$). STED microscopy revealed the ultrastructure of new podocytes, including secondary and tertiary foot processes. CXCL12 blockade also resulted in proteinuria improvement ($p<0.05$ at 28 days).

Conclusions: These results show that juxtamedullary and cortical nephrons differ in their capacity to regenerate podocytes upon injury and explain the clinical observation that FSGS starts and is more severe in juxtamedullary nephrons.

Funding: Government Support - Non-U.S.

SA-PO312

Mechano-Growth Factor (MGF) Mediation of Glomerulosclerosis (GS) Involves Activation of PKC

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Background: We previously reported PKC ß1 and PKC a activation in our non-diabetic GS mouse model Fvb Os/+, with reduced glomerular numbers, glomerular hypertension, and increased SNGFR. GS develops rapidly after birth leading to renal failure and premature demise. MGF is expressed in the glomeruli and is responsive to stretch in other tissues. Here we investigate MGF expression in Fvb Os/+ glomeruli, in cultured Fvb Os/+ mesangial cells(MC), and potential MGF-regulation of PKC activation. We hypothesize that MGF activation of PKC may explain the GS in Fvb Os/+ mice and excess extracellular matrix (ECM) in cultured Fvb Os/+ mesangial cells (MC).

Methods: 1. Fvb Os/+ and Fvb +/+ mouse kidneys were harvested and fixed at age 4 weeks for PAS staining and immunolabelling (0 - 4+) for MGF, active PKC ß1 and active PKC a; Total glomerular or MC proteins were also isolated for Western analyses of selected proteins then semiquantitated. 2. Primary culture MC's from mice of both genotypes were grown to 80-100 % confluence in DMEM medium 8mM glucose,10% FBS at 37 C and 5% CO_2. 3. Normal mouse MC's transduced (pWZLneo MoMuLV expression vector) to overexpress (MGF-S), or suppress (MGF-AS) MGF were examined with Western analyses to investigate potential PKC regulation by MGF. 4. Mean ± SEM was determined and statistical analyses performed with one way ANOVA, & Students T-test where indicated.

Results: 1. Fvb Os/+ glomeruli exhibited > 2-fold ($P < .005$) increase in glomerular MGF vs. control. 2. Fvb Os/+ MC's had 1.6-fold elevated MGF ($P < 0.05$), with increased active PKC ß1 (3.5-fold, $P < 0.005$) and active PKC a (2.9-fold, $P < 0.005$). This correlated with increased fibronectin (FN) and Type IV collagen (Col-IV) in the cells. 3. MGF-S had 4.5-fold overexpression of MGF protein, ($P < 0.02$), with increased active PKC ß1 (4-fold, $P < 0.05$) and PKC a (4-fold $P < 0.05$). MGF-AS had 50% suppression of basal PKCß1.

Conclusions: 1. Increased MGF was observed in FvbOs/+ glomeruli and cultured Fvb Os/+ MC, correlating with PKC B1 and PKC a activation in both. High MGF and PKC activation were maintained with passage of Fvb Os/+ MC in vitro, associated with high FN and Col-IV. 2. MGF-S also exhibited activation of PKC ß1 and PKC a, which may mediate the increased ECM in these cells as well.

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SA-PO313

The Molecular Mechanism of Action of AT2R Agonist Compound 21 (C21) on Ameliorating Murine FSGS

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Background: We previously reported (*J Pathology 2017*) that angiotensin II type 2 receptor (AT_2R) deficiency is associated with podocyte loss and podocyte transition from normal morphology to apoptotic and/or fibrotic-like phenotype via hedgehog interacting protein (Hhip) gene expression. Here, we examined whether the administration of AT_2R agonist Compound 21 (C21) would ameliorate murine FSGS and investigated the underlying mechanisms both *in vivo* and *in vitro*.

Methods: FSGS was induced by a single intravenous injection of doxorubicin (18 mg/kg, body weight, in saline) in both male wild type (WT) and AT_2R knockout (KO) mice at 8 weeks of age. Mice were euthanized 4 weeks after doxorubicin injection. Five subgroups of mice including WT [Control (WT-Con), WT-FSGS, FSGS treated with C21 (0.3 mg/kg/day, intraperitoneal (i.p.) (WT-FSGS-C21] and AT_2R KO mice [Control (KO-Con) and KO-FSGS] were studied. Physiological parameters, renal morphology/function analysis and molecular analysis in glomeruli were carried out; *in vitro* studies were done in a mouse podocyte cell line (mPODs).

Results: FSGS was far more severe in AT_2RKO mice as compared to WT-FSGS mice, evidences by profound glomerulosclerosis on Periodic Acid Schiff and Masson trichrome staining, increased podocyte loss (synaptopodin- and p57-immunofluorescence (IF) staining) and more proteinuria (urinary albumin/creatinine ratio measurement and urinary Coomassie blue staining), together underscoring the key role of AT_2R in FSGS-related podocyte-glomerulopathy. As compared with WT-Con, WT animals with FSGS had high numbers of parietal epithelial cells (PECs), which are paired homeobox 2 (Pax2) positive cells, but fewer podocytes (IF-p57 positive and IF-Pax2 negative cells). Intriguingly, C21 administration (WT-FSGS-C21) ameliorated the features of FSGS (proteinuria, renal morphology/function) via inhibition of glomerular Hhip expression. *In vitro*, increased Hhip and Pax2 gene expression with transient transfection of respective cDNAs promoted apoptotic and/or fibrotic-like phenotype shift in podocytes.

Conclusions: The glomerular AT_2R-Pax2-Hhip axis appears to be involved in the transition of podocytes to PECs; we speculate such transition occurs through AT_2R-Pax2-Hhip modulation of PEC-related profibrotic effects and subsequent podocyte loss/sclerosis in FSGS

Funding: Government Support - Non-U.S.

SA-PO314

Klotho Ameliorates Diabetic Glomerulonephritis by Suppressing TRPC6 in Podocytes

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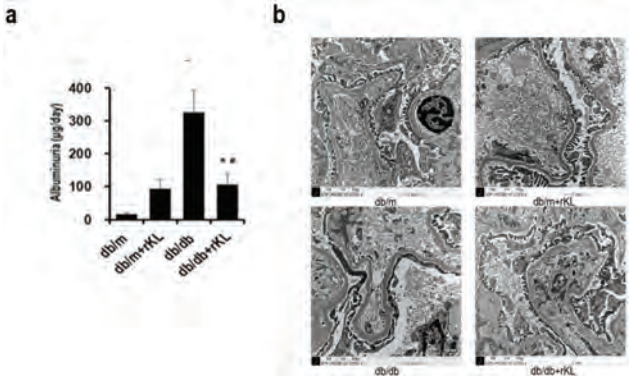
Background: Glomerular podocyte injury is the hallmark of diabetic nephropathy (DN). This damage is related with increase of transient receptor potential channel 6 (TRPC6) calcium channel in podocytes, mediating calcium influx, thus causing foot process effacement. Since klotho is reported as a TRPC6-suppressing factor in nephrectomized mice, we hypothesized that klotho may also inhibit diabetes-induced TRPC6 up-regulation in podocytes, thereby reduce albuminuria.

Methods: We injected recombinant klotho protein (rKL) into db/db and db/m mice for 8 weeks, and collected the urine and the kidney. We treated rKL to cultured podocytes, with or without high glucose (HG, 30mM) exposed.

Results: rKL treated db/db mice showed dramatic glomerular recovery, including amelioration of basement membrane thickening and foot process effacement, as well as remarkably reduced albuminuria. We also confirmed increased renal expression of TRPC6 and its downstream molecules, PI3K and calcineurin in diabetic mice, were normalized by rKL. Next, we analyzed TRPC6, PI3K and calcineurin in podocytes. HG-mediated increase of TRPC6 in podocytes is normalized by rKL treatment, showing improved cell survival and reduced intracellular calcium in HG environment.

Conclusions: Our data reveals that klotho protects the podocytes in diabetic condition by suppression of TRPC6.



rKL treat to db/db mice induced: a) reduced albuminuria, and b) glomerular recovery.

SA-PO315

A TRPC5 Inhibitor Protects Podocytes from Injury in a Minimal Change Disease Rat Model

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Background: Inhibition of the Rac1-TRPC5 disease pathway in podocytes using specific TRPC5 ion channel inhibitors has been shown to protect from podocyte injury and loss in two pre-clinical animal models: a transgenic rat model of FSGS and a spontaneous hypertensive rat model of FSGS. Since the Rac1-TRPC5 disease pathway has been implicated in the earliest cytoskeletal podocyte changes leading to the development of nephrotic range proteinuria, we asked whether TRPC5 inhibition can confer benefit in a rat model of minimal change disease (MCD).

Methods: We investigated the effect of the specific TRPC5 inhibitor AC1903 in a puromycin aminonucleoside (PAN)-induced rat model. PAN treatment has been shown to induced podocyte injury, foot process effacement and proteinuria with no glomerular histological changes in rats, which most closely resembles human MCD.

Results: We found that a single injection of 50 mg/kg PAN caused podocyte injury and led to a significant increase in proteinuria 7 days after a single injection of PAN. Treatment with AC1903 administered intraperitoneally (i.p.) twice daily significantly reduced the amount of proteinuria induced by PAN injection as measured in 24 hour urine collected in metabolic cages on day 7 post-PAN injection. In histologic analysis of rat kidney tissue, no glomuerular lesions or other obvious changes were found, whereas electron microscopy revealed severe foot process effacement (FPE) induced by single PAN injection. This was significantly ameliorated after treatment with AC1903. Western blotting from rat kidney lysates showed that treatment with AC1903 preserved synaptopodin and podocin abundance in PAN rats.

Conclusions: Taken together, these results show that inhibition of TRPC5 ion channels by AC1903 protects podocytes from injury in a rat model of MCD. Our data thus highlight the potential of this therapeutic strategy for the full spectrum of nephrotic syndrome from MCD to FSGS.

Funding: NIDDK Support

SA-PO316

Differential Effects of TRPC5 and TRPC6 Channels in Angiotensin II Induced Glomerular Hyperpermeability

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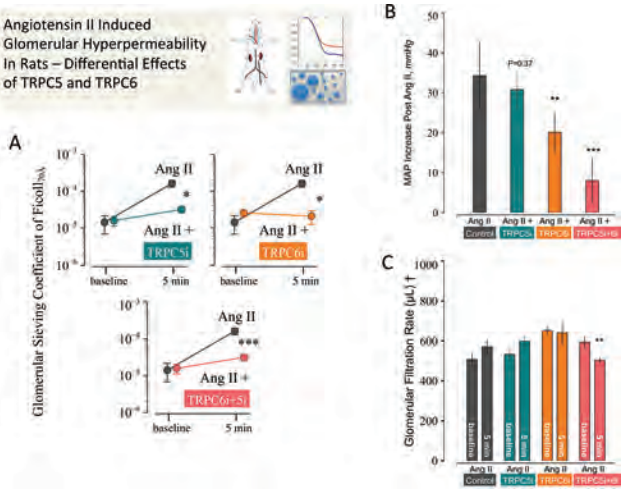
Background: Angiotensin II (Ang II) rapidly induces marked, dynamic increases in the permeability of the glomerular filtration barrier (GFB) in rats. After binding to its receptor(s), Ang II elicits Ca^{2+} influx into cells mediated by TRPC5 and TRPC6 (transient receptor potential canonical type 5 and 6). We here identifed TRPC5 and TRPC6 as regulators of Ang II induced glomerular hyperpermeability while the latter also appears to be involved in the hemodynamic effects induced by Ang II.

Methods: In anesthetized Sprague-Dawley rats, the left ureter was cannulated for urine collection and blood access was achieved. Rats were infused with Ang II (80 ng kg^{-1} min^{-1}) alone, or together with the TRPC5 blocker clemizole or low dose La^{3+} (activates TRPC5, blocks TRPC6) or high dose La^{3+} (blocks both TRPC5 and TRPC6). Plasma and urine samples were taken during baseline and at 5 min after the start of the infusions and analyzed by high-performance size-exclusion chromatography for determination of glomerular sieving coefficients (θ) for Ficoll 10-80Å (1-8 nm).

Results: Ang II infusion into rats caused marked increases in glomerular permeability to large Ficoll molecules (Ficoll 50–80Å), which were abrogated by the TRPC5 blocker clemizole, having no effect on glomerular filtration rate (GFR) or Ang II mediated increase in MAP (ΔMAP). In contrast, agents blocking TRPC6 (high and low dose La^{3+}) significantly lowered ΔMAP and nearly completely abrogated Ang II induced hyperpermeability effects. The higher dose of La^{3+}, blocking both TRPC5 and TRPC6, significantly lowered left-kidney GFR.

Conclusions: Our data unveil differential effects of Ca^{2+} signaling via TRPC5 and TRPC6 following Ang II stimulation. Especially, it appears that inhibition of TRPC5 in rats can abrogate AngII-induced glomerular hyperpermeability without affecting GFR or Ang II induced increases in MAP. Inhibition of TRPC5 may thus be a potential target for a novel antiproteinuric agent.

Funding: Government Support - Non-U.S.



SA-PO317

Small Molecule Inhibition of TRPC5 Protects Against Podocyte Injury and Proteinuria in FSGS

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Background: FSGS is a rare kidney disorder of the podocyte with a high likelihood of progression to kidney failure. The activation of the TRPC5-RAC1 pathway in podocytes is a critical driver of proteinuria in many forms of familial and sporadic FSGS. The Ca^{2+}permeable TRPC5 channel is a critical mediator of proteinuria in FSGS. Inhibition of TRPC5 channel activity protects against proteinuria and podocyte loss in AT1R transgenic and Dahl salt sensitive rats (Zhou et al. Science, 2017).

Methods: We performed high throughput screening of a structurally diverse compound collection followed by lead optimization for the development of several potent TRPC5 inhibitors. We then analyzed the TRPC5 inhibitors in several in vitro models of podocyte injury (protamine sulfate induced cytoskeletal disruption, restoration of stress fibers in synaptopodin-depleted podocytes, inhibition of pathogenic podocyte migration) and in the DOCA-salt rat model of FSGS in vivo.

Results: Here we report the identification of potent and selective small molecule inhibitors of TRPC5. activity against TRPC5 and selectivity across other TRP channels were determined using FLIPR based assays and electrophysiology. We show that TRPC5 inhibition protects against protamine sulfate induced loss of stress fibers. TRPC5 inhibition also restores stress fibers in podocytes after knockdown of synaptopodin. We further show that inhibition of TRPC5 suppresses pathogenic podocyte motility in a scratch assay. Finally, we demonstrate that inhibition of TRPC5 suppresses proteinuria in hypertension-induced FSGS in uninephrectomized DOCA salt rats without altering blood pressure.

Conclusions: In summary, we have identified new selective small molecule inhibitors of TRPC5 for the treatment of proteinuria in FSGS.

Funding: Commercial Support - Goldfinch Bio, Inc.

SA-PO318

Aldosterone Causes Albuminuria by Inducing MMP-Mediated Glomerular Endothelial Glycocalyx Dysfunction

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Background: Aldosterone contributes to renal disease. Mineralocorticoid receptor (MR) inhibitors slow disease progression but side effects limit their use. Damage to the endothelial glycocalyx (glx), a luminal biopolymer layer, has been implicated in pathogenesis of endothelial dysfunction and albuminuria. We investigated if glx damage contributes to aldosterone-induced renal disease.

Methods: *In vitro human* glomerular endothelial cells (GEnC) *were exposed to 0.1nM aldosterone for 5 days* +/- 1µm spironolactone. *In vivo* mice received aldosterone (0.6µg/g/day via osmotic minipump) and 1.0% NaCl drinking water +/- 5mg/kg MMP2/9 inhibitor I.P. daily. Tail cuff blood pressure (BP) measurements were conducted after 5 days training. MMP2 activity was studied using a specific activity assay. Multiphoton microscopy was used to measure the glomerular sieving coefficient for albumin (GSC_{alb}) and a novel peak-to-peak method was developed to assess changes in GEnC glx thickness

over time. ELISAs were used to measure syndecan-4 ectodomain concentrations and urine albumin levels.

Results: *In vitro* aldosterone reduced GEnC syndecan-4 ectodomain expression 0.76 fold (p=0.02) and increased MMP2 mRNA 4.5 fold (p=0.0003). Spironolactone blocked these effects. *In vivo* aldosterone resulted in significant albuminuria by day 10. Aldosterone increased glomerular MMP2 mRNA expression 5.3 fold (p=0.003) and plasma active MMP2 (22 vs 27ng/ml, p=0.045) without altering the systolic BP. The GSC_{alb} increased 7.6 fold by day 10 (p=0.0079) and the GEnC glx thickness fell from 1.1μm to 0.59μm (p=0.0013). No significant changes were detected in controls. Daily IP MMP2/9 inhibitor prevented glx loss, maintained the GSC_{alb} and prevented albuminuria without affecting the BP. Changes in glx depth predicted changes GSC_{alb} within the same glomeruli (R^2=0.8185, p=0.0028), highlighting the importance of the glx in limiting albumin filtration.

Conclusions: Syndecan-4 (a key glx component and known substrate for MMP2) is shed in response to aldosterone via an MR-MMP dependent pathway. *In vivo* aldosterone results in significant thinning of the GEnC glx and albuminuria. MMP inhibition preserved the glx and prevented albuminuria and could represent a novel potential therapeutic strategy.

Funding: Government Support - Non-U.S.

SA-PO319

Ezetimibe Protects from Renal Dysfunction in a Mouse Model of Alport Syndrome

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Background: Alport Syndrome (AS) is characterized by renal disease inevitably progressing to end-stage kidney disease (ESKD), and no treatment strategies are currently available. We have recently discovered an important contribution of renal parenchyma lipid accumulation to ESKD in mice affected by AS. We hypothesized that treatment with the lipid-lowering compound ezetimibe (EZ), which targets the cholesterol transport protein Nieman Pick C1-like 1 protein and has been shown to modulate fatty acid uptake in other organs, can prevent renal lipid accumulation and podocyte injury in an experimental mouse model of AS thus improving renal function.

Methods: EZ was administered for 4 weeks by oral gavage at 5 mg/kg to 4-week-old knockout (KO) and wildtype (WT) mice. All mice were sacrificed at 8 weeks of age. The following four groups of mice were analyzed: WT, WT + EZ, KO and KO + EZ.

Results: We detected a significant decrease in the albumin-to-creatinine ratio (ACR) in KO mice treated with EZ when compared to untreated KO mice (p<0.01). Additionally, a decrease of BUN and serum creatinine levels was observed (p<0.05). EZ treatment of KO mice also resulted in a significant reduction in the body weight loss observed during disease progression (p<0.05). Furthermore, EZ normalized renal lipid metabolism as indicated by decreased total kidney cortex triglyceride content in EZ treated KO mice compared to untreated mice (p<0.05).

Conclusions: Based on these results, we conclude that EZ improves renal function in experimental AS and could represent a new repurposing strategy for the treatment of affected patients.

Funding: Private Foundation Support

SA-PO320

Differential Pathogenic Roles of Notch4 and Notch3 in the Progression of HIV Associated Nephropathy

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Background: Notch pathway activation plays a central role in pathogenesis of many glomerular diseases. We have previously shown that Notch 4 and Notch 3 were up-regulated in various renal cells in HIV associated Nephropathy (HIVAN) patients and rodent models of HIVAN. Notch inhibition by gamma secretase inhibitors ameliorated disease progression in the Tg26 mouse model of HIVAN. Since gamma secretase inhibitors are associated with toxicity in clinics, here we explore individual effects of genetic inhibition of Notch4 and Notch3 on HIVAN pathogenesis.

Methods: Tg26 mice were bred with mice deleted for the intracellular domain of Notch 4 and Notch 3 separately to generate Tg26 mice with homozygous Notch4 deletion and homozygous Notch3 deletion, respectively. The effect of Notch4 and Notch3 deletion in Tg26 mice was determined by analyzing renal function, histology, cell proliferation/ podocyte differentiation and inflammatory markers.

Results: Deletion of either Notch 4 or Notch 3 in Tg26 mice significantly decreased the mortality rate and reduced kidney injury in Tg26 mice. While, Notch 4 deletion in male Tg26 mice reduced kidney injury, controlled cell proliferation, cell differentiation and inflammatory response of NF kappa B positive cells in Tg26 mice, it was not enough to significantly reduce proteinuria and blood urea nitrogen (BUN) levels. In contrast, genetic depletion of Notch3 appeared to be effective in a broader way, controlling proteinuria and BUN in Tg26 mice. In addition, histological studies indicated a significant improvement in kidney injury as evident by the reduction in glomerulosclerosis, tubule-interstitial fibrosis and interstitial inflammation in Notch3 deleted Tg26 mice. More studies are underway to reveal subtle roles of Notch4 and Notch3 activation in HIVAN.

Conclusions: Our study supports a non-redundant role of Notch 4 and Notch 3 in HIVAN pathogenesis and suggests therapeutic implications of Notch3 and Notch 4 inhibition in HIV associated nephropathy.

Funding: NIDDK Support

SA-PO321

Targeted Inhibition of Calpain-1 and -2 Activities Improves the Progression of Proteinuric Kidney Disease in Mice Following Podocyte Injury

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Background: We have previously shown that calpain activation occurs in mice glomerular injury models and in urine samples of proteinuric patients with FSGS. However, calpain's function in podocyte biology has not been fully elucidated. This study examines whether the decrease in calpain-1/-2 activities, by calpain inhibitor or deletion of podocyte-associated *CAPN4* improves the progression of mice podocyte injury.

Methods: Using the proteinuric models *Tln1$^{fl/fl}$* Podcin-Cre mice (Germline Talin1 podocyte knockout mice, *Tln1* KO) and Doxycycline inducible *Tln1$^{fl/fl}$* Pod-rtTA TetO-Cre mice (i*Tln1* KO), inhibiting calpain-1/-2 activities with calpain inhibitor III (CI) was examined for albuminuria, histological changes, and kidney function. Furthermore, a mouse model with podocyte-specific deletion of *CAPN4* was generated abrogating both calpain-1/-2 activities. We investigated the above changes on the *Tln1$^{fl/fl}$ CAPN4$^{fl/fl}$* Podcin-Cre mice (*Tln1+CAPN4* DKO) and *Tln1$^{fl/fl}$* Pod-rtTA TetO-Cre mice (i*Tln1+CAPN4* DKO).

Results: Treatment of *Tln1* KO mice with CI (30mg/kg B.W/day, i.p) was started at 2 weeks of age when robust albuminuria was already present. At 8 weeks, significantly reduced albuminuria was observed in the CI treated mice (18229.61±1537.80 vs 12963.55 ±1182.49 μg/mg creatinine). Furthermore, treatment with CI prolonged the survival of the *Tln1* KO mice (median survival: 9 weeks vs 4 weeks). Treatment with CI for 4 weeks in the i*Tln1* KO mice also reduced the degree of albuminuria (4949.55±320.46 vs 3327.87 ±217.28 μg/mg creatinine), improved renal histological lesions, and kidney function. Mice with genetic ablation of *CAPN4* in podocytes on the background of *Tln1* KO or *iTln1* KO reduced the degree of albuminuria (18574.82±1703.31 vs 13398.37 ±1457.07 μg/mg creatinine in *Tln1* KO vs *Tln1+ CAPN4* DKO at 8 weeks of age; 4335.27±438.42 vs 2445.92 ±367.28 μg/mg creatinine in i*Tln1* KO vs i*Tln1+CAPN4* DKO), while also improving the renal histological lesions and kidney function, and leading to the prolonged survival (median survival: 9 weeks vs 4.5 weeks in *Tln1+CAPN4* DKO vs *Tln1 KO*).

Conclusions: Proteinuric kidney disease in both germline *Tln1* KO or i*Tln1* KO mice are attenuated by reduction of calpain-1/-2 activities, thus representing a potential novel therapeutic strategy for the progression of proteinuric kidney disease.

Funding: NIDDK Support

SA-PO322

Elucidating the Pathogenesis of Focal Segmental Glomerulosclerosis Using CRISPR/Cas9 Mediated Genome Engineering

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Background: *NPHS2* encodes for the PHB-domain protein podocin and is one of the most frequently mutated genes in patients with Focal Segmental Glomerulosclerosis (FSGS). Currently, loss of podocytes is regarded as the hallmark of the pathogenesis of FSGS. Investigating the initial molecular events causing podocyte injury and depletion is of utmost importance for future preventive and therapeutic strategies.

Methods: Here, we present a mouse model for a late-onset FSGS phenotype. Using CRISPR/Cas9 mediated genome engineering, we separately integrated two point mutations in the *Nphs2* gene which, in compound-heterozygosity, represent a commonly found genotype in patients with a late-onset.

Results: *In vivo* data of compound-heterozygous animals reveal an early onset of mild proteinuria long before the manifestation of FSGS lesions. The proteinuria increases gradually and reaches nephrotic range in young adult mice (> 8 weeks). Histologically, FSGS lesions are found between 8 and 20 weeks. By using STED microscopy at different time points (P0, 2, 4, 8, 20 weeks) we show a shortening and widening of the foot processes and a decreasing containment of the capillary surface by the secondary processes in compound-heterozygous in comparison to control mice. Quantification of podocyte numbers in kidney sections revealed a progressive decline in mutant mice. The glomerular proteome at 3 weeks shows a general decrease in podocyte specific proteins, in particular of polarity related proteins.

Conclusions: In this study, we have generated a late-onset FSGS disease model resembling human genetic disease by using CRISPR/Cas9 mediated genome engineering. Mutant mice develop progressive proteinuria accompanied by a full blown morphological manifestation of FSGS. Delineation of the foot process microarchitecture by STED microscopy shows a loss of the distinct microarchitecture of the podocyte and a decreased containment of the capillary surface as an early pathological sign that precedes the onset of massive proteinuria. Interestingly, the containment is relatively steady throughout the first phase of podocyte depletion, possibly by expansion of individual foot processes. The shift in the glomerular proteome is consistent with a podocyte dedifferentitation and/or loss of polarity.

SA-PO323

Podocyte-Specific Deletion of Hypoxia-Inducible Factor 1α (Hif-1α) Identifies Downstream Mediators That Are Targets to Prevent Proteinuria and Subsequent Glomerulosclerosis

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Background: While augmentation of signals mediated by HIFs preserves organs in ischemia, the role of HIFs in more chronic glomerulopathies following podocyte injury is rather controversial. We recently reported that mice in which systemic knockout of HIF-1α is induced at the age of 6 weeks demonstrate significantly less fibrosis in Adriamycin (ADR)-induced glomerulopathy. Others previously reported that podocyte-specific deletion of von Hippel Lindau protein, that targets HIFs for degradation, resulted in increased expression of HIFs and severe glomerulopathy in mice. These results suggest that HIFs aggravate glomerular injury. Here, we further evaluated the roles of HIF specifically in podocytes, using mice that lack podocyte HIF-1α.

Methods: HIF-1$\alpha^{f/f}$ mice were crossed with NPHS2-Cre mice. Adriamycin (ADR, 10mg/kgBW) was administered intravenously to the HIF-1$\alpha^{-/-Podo}$ or their wild-type (WT) littermates to induce glomerulopathy, and urine and kidneys were obtained on day14. RNA was isolated from cryosectioned glomerular samples using laser-capture microdissection, and HIF-1α-target gene were evaluated by qPCR. HIF-1α knockdown podocytes were generated using lenti-viral shRNAs.

Results: HIF-1$\alpha^{-/-Podo}$ mice were viable and no proteinuria was detected basally. ADR caused severe proteinuria, glomerular fibrosis and podocyte effacement in WT mice, whereas in HIF-1$\alpha^{-/-Podo}$ mice, proteinuria and glomerular sclerosis were minimally observed and podocyte structures were preserved. Among known HIF-1α-target genes tested, *Irg2* and *Mif* were increased in glomeruli of WT mice treated with ADR but not in HIF-1$\alpha^{-/-Podo}$ mice, whereas *ApoE* expression was elevated in both WT and HIF-1$\alpha^{-/-Podo}$ glomeruli. *PGK* expression was not changed in either group of mice. In cultured mouse podocytes, *Mix1, Eef1a1* and *ApoE* were differentially expressed in the presence or absence of HIF-1α after TGF-β1 treatment, whereas *Irf7, Mt2* and *Plod2* were regulated independent of HIF-1α.

Conclusions: We have identified several HIF-1α target genes that could play a role in in proteinuria and glomerulosclerosis. These could be novel therapeutic targets for glomerulopathy.

Funding: NIDDK Support

SA-PO324

Inhibiting Podocyte Endoplasmic Reticulum Stress-Mediated Apoptosis to Treat Genetic Nephrotic Syndrome

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Background: Pierson syndrome (OMIM 609049) characterized by congenital nephrotic syndrome (NS) and diffuse mesangial sclerosis, is caused by mutations in *LAMB2* encoding laminin β2. The major laminin heterotrimer in the mature glomerular basement membrane is laminin α5β2γ1, and laminin trimerization occurs in the endoplasmic reticulum (ER). There is no effective treatment for Pierson syndrome and most cases of genetic forms of NS. Here for the first time, we have shown that targeting podocyte ER stress-specific apoptosis may provide a new therapeutic approach to treat Pierson syndrome and other genetic nephrotic syndromes.

Methods: To recapitulate human Pierson syndrome, *Lamb2* null mice were generated. We isolated mouse glomeruli and cultured primary podocytes before the onset of significant proteinuria to investigate ER stress signaling cascades. Western blot was utilized to determine ER stress-induced pro-apoptotic pathway. Furthermore, *Lamb2*$^{-/-}$ mice were crossed with *Chop*$^{-/-}$ mice to investigate the functional consequence of CHOP (C/EBP homologous protein) deletion in the disease development.

Results: At the early stage of NS, LAMB2 deficiency induced podocyte ER stress and selectively activated ATF6 (activating transcription factor 6) pathway without involvement of IRE1α and PERK pathways. Moreover, LAMB2 depletion differentially triggered ER stress-specific CHOP pro-apoptotic pathway, but not caspase 12 and JNK pathways, in mutant podocytes. Most importantly, CHOP ablation in *Lamb2*$^{-/-}$ mice significantly prolonged the lifespan of *Lamb2* null mice.

Conclusions: Despite the importance of podocyte ER dysfunction in the pathogenesis of NS, there is no treatment that targets the podocyte ER. Our promising results indicate that antagonizing the pro-apoptotic CHOP pathway in ER-stressed podocytes may lead to paradigm-shifting innovative therapeutic strategies to combat genetic or acquired NS.

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SA-PO325

GLEPP1 Deficiency Alters GBM Composition and Extracellular Matrix (ECM) Deposition in Aging Mice

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Background: Proteinuria results from a defect in the glomerular filter which is composed of the fenestrated endothelium, the glomerular basement membrane (GBM) and the podocytes. Major components of the GBM are collagen IV (col IV), agrin, nidogen and laminin. Col IV of the mature GBM is composed of alpha 3, 4, 5 chains while the immature GBM is built of col IV alpha 1, 2, 1 chains. Mutations in the GLEPP1 gene lead to nephrotic syndrome in humans. GLEPP1 is a receptor tyrosine phosphatase within podocytes and its deficiency leads to morphologic GBM alterations and proteinuria in aging mice. Its molecular function is still unknown.

Methods: GLEPP1 WT and KO mice were analyzed at 4, 6 and 10 months of age. Glomeruli were isolated. For col IV analysis, glomeruli were digested with collagenase to release col IV NC1 domains. Immunofluorescence of mouse kidneys was performed for col IV chains. Primary podocytes were isolated and analyzed for purity by WT1 immunofluorescence staining. Podocytes were lysed, ECM digested with collagenase and subjected to western blot analysis. Col IV chain specific antibodies against NC1 domains of col IV alpha 1, 2, 3 and 5 were used. In addition, antibodies against laminin alpha 1, agrin and nidogen 1 were used.

Results: Glomerular col IV alpha 1 and 2 protein chain expression is significantly enhanced in 6 and 10 month old GLEPP1 KO mice, while col IV alpha 1 and 2 protein expression levels are reduced in GLEPP1 KO mice at 4 months of age. Glomerular laminin alpha 1 protein expression is significantly elevated in GLEPP1 KO mice compared to controls at 10 months of age. Immunofluorescence of col IV chains in kidney sections of GLEPP1 WT and KO mice localized enhanced expression of immature col IV chains within the GBM. Purity of primary podocytes of GLEPP1 WT and KO mice was confirmed by WT1 staining. Col IV deposition by GLEPP1 KO primary podocytes in cell culture resembles the col IV expression pattern with increased expression of col IV alpha 1 and 2 and decreased expression of col IV alpha 5 in GLEPP1 KO mice. These data confirm our previous results from rt-PCR and immunofluorescence.

Conclusions: GLEPP1 deficiency leads to an immature GBM composition which is responsible for less mechanical stability of the GBM and proteinuria in aging mice and humans.

SA-PO326

Development of a Glomerular Specific Targeting System with Perfluorocarbon Nanoparticles

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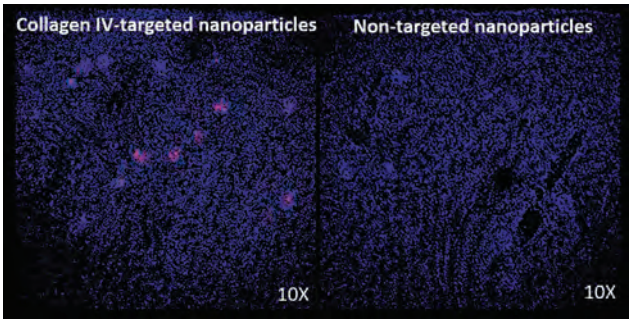
Background: Perfluorocarbon (PFC) nanoparticles (NPs) are primarily limited to intravascular space. Glomerular basement membrane (GBM) is the only site where collagen IV (Col4) has direct contact with blood via fenestrated capillary endothelium. Our goal is to develop a novel Col4-targeted PFC NP that selectively targets kidney glomeruli as a local therapeutic vehicle.

Methods: Col4 -targeted PFC NPs were formulated by coupling PFC NPs to a Col4-targeting ligand. The binding specificity and efficiency of the Col4 -targeted NPs were evaluated on Col4 coated plate surfaces, *in vitro* with primary glomerular endothelial cells and mesangial cells, and *in vivo* in C57BL/6 mice.

Results: Rhodamine labeled Col4 targeted or non-targeted PFC NPs were applied in Col4 pre-coated 96 wells plate at stepwise doses (1, 2, 5, 10 and 20 ul/ml). The binding affinity was determined by fluorescence intensity with IVIS. The wells incubated with Col4 targeted PFC NPs showed a dose dependent increase in fluorescence as radiant efficiency e^{10} (0.37 ± 0.03, 0.51 ± 0.05, 1.33 ± 0.07, 2.38 ± 0.19, 2.71 ± 0.28). Minimal non-specific binding appeared. To evaluate the targeting properties *in vitro*, 1ul/ml rhodamine labeled Col4 targeted or non-targeted PFC NPs were applied on glomerular endothelial cells and mesangial cells. Significant cellular uptake of the Col4 targeted PFC NPs was observed, while it was not detectable in the cells incubated with non-targeted NPs. To evaluate the targeting properties in vivo, C57BL/6 mice were treated i.v. with 100ul rhodamine labeled Col4 targeted or non-targeted PFC NPs. Col4 targeted PFC NPs localized to glomeruli in the kidney sections, whereas non-targeted PFC NPs were undetectable, as shown in Figure.

Conclusions: We have designed PFC nanoparticles that selectively target glomeruli by binding to Col4 of GBM.

Funding: NIDDK Support



SA-PO327

The Hippo Effector Tead1 Interacts with Wt1 on a Gene-Regulatory Level by Co-Binding at Podocyte Enhancers

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Background: In a genome-wide analysis of gene-regulatory functions of the transcription factor (TF) Wt1 in podocytes we identified an interaction of Wt1 with hippo signaling, which has since emerged as a key pathway relevant to podocyte health and disease. However, gene regulatory effects of hippo signaling in podocytes have not been examined in detail. Here we investigate Wt1 and Tead1 co-regulation in wildtype podocytes in vivo by ChIPseq.

Methods: ChIP-seq for Tead1 and Wt1 was carried out on wildtype mouse glomeruli. Bioinformatic analyses were conducted using standard software and algorithms.

Results: ChIP-seq for Tead1 on mouse glomeruli identified more than 19,000 high confidence and reproducible Tead1 peaks. Tead1 binding occurred at both, promoters and enhancers as indicated by histone modification signatures obtained from ENCODE ChIPseq data. Functional analysis of Tead1 binding events by GO enrichment algorithms revealed differential functions of enhancer vs promoter binding. Promoter binding sites were predominantly located at genes involved in pathways canonically linked to hippo signaling such as regulation of apoptosis and cell cycle. In contrast, enhancer binding occurred at genes of signaling pathways highly relevant to podocytes, such as integrin signaling, the actin cytoskeleton, and Tgf-beta/Smad signaling. Tead1 also bound enhancers relevant to Vegf-, and PDGF-signaling genes suggesting novel links between hippo signaling and further signaling pathways in podocytes as well as novel contexts of hippo signaling in general. Integrative analysis of Wt1 and Tead1 ChIPseq data showed co-binding of the two TFs in ~7,000 instances with predominance of enhancer binding events. Enhancer co-binding of Wt1 and Tead1 showed speicifc overrepresentation of genes relevant to adherens junctions and focal adhesions when compared to datasets obtained from one TF only. Furthermore, many of the cis-regulatory regions co-bound by Wt1 and Tead1 were associated with genes relevant to glomerular disease and FSGS in particular.

Conclusions: In summary, integrative analysis of Tead1 and Wt1 ChIPseq data in podocytes in vivo reveals novel candidate pathways interacting with hippo signaling. We identify a functional interaction of the TFs to control cell-adhesion signaling bearing high relevance to glomerular disease.

SA-PO328

APOL1 G1 Risk Variant Contributes to Podocyte Injury in a Mouse Model of FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing chronic kidney disease. Susceptibility to FSGS in African Americans is associated with the presence of genetic variants of the Apolipoprotein L 1 gene (APOL1) named G1 and G2. We recently published that mice with podocyte-specific, doxycycline (Dox)-inducible expression of constitutively active NFATc1nuc (NFAT) represent a valuable new model for FSGS.

Methods: Human BAC transgenic mice that express the different APOL1 genetic variants (G0, G1, G2) under the endogenous promoter were used in this study. Podocyte specific Dox-inducible constitutively active NFATc1 mice (NFAT;Podocin-rtTA, DT) were expanded for consecutive breeding to G0, G1 or G2 BAC transgenic mice to generate triple transgenic mice (APOL1;NFAT;Podocin-rtTA, TT). NFATc1nuc transgene expression was induced by feeding of doxycycline chow (200 ppm) for 4 months. Urinary albumin-to-creatinine ratios were determined using mouse specific albumin ELISA and creatinine companion kits. Blood samples collected from mice at sacrifice were analyzed for BUN. Perfused kidneys were fixed and paraffin embedded for H&E, PAS staining.

Results: We tested the relative contribution of APOL1 risk variant expression to podocyte injury in mice expressing each of the APOL1 genetic variants under the control of the endogenous promoter region at baseline as well as in a mouse model of FSGS-like injury. Glomerular expression of APOL1 mRNA was similar among BAC transgenic mice carrying APOL1 G0 and G1, but significantly lower in G2 carrying mice ($p<0.01$) and these mice did not develop proteinuria for at least up to 7 months of age. Histological analysis among APOL1 transgenic mice carrying each of the APOL1 genetic variants and wildtype mice revealed no differences. However, Dox-induced TT mice carrying the G1 allele showed increased proteinuria, higher serum BUN levels and a more severe form of glomerulosclerosis when compared with induced TT mice carrying G0 or G2. Induced G1 TT mice were also characterized by an earlier onset of proteinuria which remained sustained over time.

Conclusions: Our data reveal that transgenic APOL1 risk variant expression in mice does not impair kidney function at baseline whereas APOL1 G1 expression may contribute to APOL1 mediated susceptibility in NFAT-mediated FSGS.

Funding: NIDDK Support

SA-PO329

ApoL1 G0, G1, and G2 Are Expressed on the Podocyte Cell Membrane with Similar Overall Topologies

Nidhi Gupta, Suzie J. Scales. *Genentech, South San Francisco, CA.*

Background: Human Apolipoprotein L1 (ApoL1) is responsible for innate immunity against trypanosome infections. Two variants of ApoL1, G1 and G2, are responsible for the high rate of kidney disease in African diaspora and cause kidney podocyte damage by unclear mechanisms. ApoL1 can form pH-gated cation (K^+ and Na^+) channels in lipid bilayers, as well as pH-independent chloride channels in liposomes. Two papers showed overexpressed ApoL1 in HEK-293 cells forms potassium efflux channels at the cell surface, which leads to stress-activated protein kinase stimulation and cell death. However, contradictory results were obtained regarding ApoL1 G0 toxicity thereby questioning if G1 and G2 toxicity is variant specific or expression level dependent. Total expression levels (by Western Blot) may not be indicative of cell surface ApoL1 levels. It is actually unclear if endogenous ApoL1 and its variants are found at the cell surface and whether differences in trafficking, expression level or topology could account for the differential toxicity. Also, not much is known regarding toxicity in podocytes.

Methods: Using a panel of in house generated ApoL1-specific monoclonal antibodies to various domains, we performed flow cytometry on wild type podocytes. We also generated several clones of ApoL1 knockout podocytes stably re-expressing doxycycline-inducible ApoL1 G0, G1 or G2 to avoid any interactions (potential heterozygosity) with endogenous ApoL1. Cells were also tested for variant specific cell toxicity at comparable surface expression levels.

Results: By flow cytometry, endogenous ApoL1 was found at the cell surface of wild type podocytes, with most of the pore forming domain and end of the SRA-interacting domain exposed, but not the membrane-addressing domain. Surface ApoL1 was increased up to 500x in the inducible podocytes in a dose-dependent manner, but G0/G1/G2 maintained similar topology to endogenous ApoL1. We aim to clarify if cytotoxicity correlates with cell surface expression or variant genotype.

Conclusions: Endogenous ApoL1 and stably transfected G0/G1/G2 are all expressed on the podocyte plasma membrane with similar gross topology and are therefore correctly located to form potential surface ion channels. Thus, any differential ionic conductance is likely not due to gross topology differences at the plasma membrane.

Funding: Commercial Support - Genentech

SA-PO330

ApoL1 Is Not Normally Internalized by Podocytes

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Background: Human Apolipoprotein L1 (ApoL1) is secreted by the liver and circulates on HDL particles, where it protects from human African trypanosomiasis (sleeping sickness). This innate immunity is achieved by internalization of HDL particles to the trypanosome lysosomes, where ApoL1 forms pores leading to trypanolysis. ApoL1 G1 and G2 variants evolved in Africans to kill additional species of trypanosome, but greatly increase the risk of chronic kidney disease (ApoL1-nephropathies) by unclear mechanisms involving loss of kidney podocytes. The "internalization model" posits that circulating ApoL1 is internalized into podocytes to cause damage akin to trypanolysis, while the "intrinsic model" supposes that endogenous ApoL1 variants in podocytes are cytotoxic. Recombinant ApoL1 was reportedly internalized into podocytes, potentially supporting the internalization model, but the destination compartment was unclear. Most other studies support the intrinsic model, but have yet to agree on a cellular mechanism, ranging from ER stress, mitochondrial or lysosomal permeability, endocytic or autophagy disruption to cell surface cation channel activity. Clarification on whether intrinsic ApoL1 or ApoL1 in HDL particles is really internalized in podocytes might help to pinpoint the correct mechanism.

Methods: We evaluated internalization of recombinant ApoL1, ApoL1 in HDL particles, endogenous ApoL1 and stably expressed ApoL1 variants in cultured podocytes by immunofluorescence microscopy with ApoL1-specific monoclonal antibodies.

Results: Recombinant ApoL1 was internalized by podocytes, but only by virtue of being sticky, as it bound to other proteins in the media. Non-sticky ApoL1 in native HDL particles up to 1mg/ml or in amphipol was not visibly internalized by podocytes. Monoclonal antibodies detected endogenous ApoL1 in podocytes at the cell surface, but were not endocytosed. Overexpressed ApoL1 in podocytes likewise remained at the cell surface, unless the antibodies were aggregated.

Conclusions: Neither intrinsic ApoL1 nor HDL-bound ApoL1 is detectably internalized by podocytes *in vitro*, suggesting ApoL1 is not actively trafficked to endosomes or lysosomes. These data do not support the circulating model of ApoL1 activity and further suggest that intrinsic secreted ApoL1 might exert its effect at the plasma membrane rather than in the endolysosomal system.

Funding: Commercial Support - Genentech

SA-PO331

Semaphorin3A-Inhibitor Ameliorates Podocytopathy and Tubular Fibrosis in Adriamycin-Induced Renal Injury

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Background: Semaphorin3A (SEMA3A) is a guidance protein that regulates angiogenesis, cell motility, immune cell regulation and cancer progression. In the

mammalian adult kidneys, SEMA3A and its receptor, neuropilin-1 (NRP1) are expressed in podocytes, tubular cells and collecting ducts. However, the pathophysiological roles of the SEMA3A in renal diseases are still unclear. Here we analyzed the role of the SEMA3A-NRP1 signaling using the adriamycin (ADR)-induced podocytopathy mouse model and examined the therapeutic effect of SEMA3A-inhibitor.

Methods: Wild-type male Balb/c mice (10-week old) were assigned into three groups (n=5): ADR group (single injection of 10 mg/kg ADR by tail vein), ADR+SEMA3A-I group (ADR injection + daily intraperitoneal injection of 20 μg SEMA3A-inhibitor) and control group (saline injection by tail vein). All the mice were sacrificed 2 weeks after the ADR injection, and the expression of SEMA3A and NRP1, proteinuria, tubular injury and renal fibrosis were analyzed. We also examined the effect of recombinant SEMA3A and SEMA3A-inhibitor on immortalized mouse podocytes and proximal tubular cells (mProx24 cells) in vitro.

Results: The expression of SEMA3A in podocyte and NRP1 in proximal tubular cells were dramatically increased in ADR group compared to control group. SEMA3A-inhibitor significantly attenuated ADR-induced albuminuria (urinary albumin / creatinine ratio (mg/gCr): ADR group vs. ADR+SEMA3A-I group; 626.5±102.9 vs. 66.0±7.4, $p<0.05$), tubular injury and tubular fibrosis as well as the cell apoptosis in both podocytes and tubular cells. In vitro, SEMA3A caused the cell apoptosis in cultured podocytes and proximal tubular cells as well as the increase of TGF-β1 expression. In addition, the treatment with TGF-β1 increased NRP1 mRNA expression in the podocytes (5.2-fold) and proximal tubular cells (1.7-fold) compared to the control, implying SEMA3A-NRP1 signaling is associated with tubular fibrosis. Taken together, increased SEMA3A expression in podocytes induced by ADR might cause podocytopathy and proximal tubular injury by accelerating cell apoptosis and renal fibrosis.

Conclusions: SEMA3A-inhibitor ameliorates podocytopathy and tubular fibrosis in ADR-induced renal injury. It would be the therapeutic target for preventing the progression of the renal injury.

Funding: Government Support - Non-U.S.

SA-PO332

ARHGEF7 Promotes Stress Fiber Loss in Podocytes by Activation of Rac1

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Background: Today it's known that most kidney diseases are caused by damages to the glomerular filtration barrier, partially by disruption of the actin cytoskeleton in the podocyte. Mutations in several actin regulatory proteins have been identified in patients with renal disease with several of them found to be present in proteins regulating actin cytoskeleton formation. The small RhoGTPase proteins are central in actin cytoskeleton regulation and lately several studies support the detrimental role of activation of the small RhoGTPase Rac1 and its role in stress fiber loss in podocytes.

Methods: In this study we aimed at identifying RhoGTPase regulatory proteins important in actin cytoskeleton loss in podocytes by using phosphoproteomics, lentiviral shRNA knockdown and stressfiber analysis on cultured podocytes, in combination with RNA sequencing of glomeruli from diabetic nephropathy animal models.

Results: By using protamine sulfate, known to cause actin cytoskeleton injury, on cultured podocytes followed by phosphoproteomics and pathway analysis we identified actin cytoskeleton to be the top ranked activated pathway. The guanine nucleotide exchange factor ARHGEF7 was identified to be phosphorylated at Ser 340, a site when phosphorylated known to cause Rac1 activation. Podocytes depleted of ARHGEF7 was protected from stress fiber loss when exposed to protamine sulfate, further confirming the involvement of ARHGEF7 in actin cytoskeleton rearrangement. In combination, RNA sequencing data from two diabetic nephropathy models, BTBR ob/ob and eNOS db/db mice, showed increased levels of ARHGEF7 in isolated glomeruli, indicating increased ARHGEF7 activity in nephrotic syndrome.

Conclusions: These data reviles upregulation of ARHGEF7 in diabetic nephropathy mice models and that ARHGEF7 plays a central role in podocyte actin cytoskeleton regulation, promoting loss of actin cytoskeleton in podocytes by the activation of Rac1.

Funding: Commercial Support - AstraZeneca, Private Foundation Support, Government Support - Non-U.S.

SA-PO333

Extracellular Vesicles as Local Messengers in Glomerular Cross-Talk

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Background: The crosstalk between the podocyte and glomerular endothelial cells (GEC) is vital for the maintenance of glomerular function. Any slight alteration of their communication propagates injury and disruption of glomerular function, commonly observed during CKD. Extracellular vesicles (EV) have key paracrine functions in physiological and pathological processes. Thus, we hypothesize that EVs play important role in glomerular crosstalk through horizontal transfer of their cargo to the target cells, especially during CKD when the glomerular filtration barrier is damaged. In particular, this study focuses on the transfer and paracrine signaling of GEC-EV to podocytes.

Methods: We isolated EV from GEC and characterized them by Nanosight analyzer, PCR, WB and flow cytometry for size distribution, RNA and protein content, and for surface marker expression. We used a no-cell-contact co-culture model to establish the transfer and intake of GEC-EV by podocytes, which was further confirmed in isolated glomeruli by the Cre-lox method. Podocytes exposed to GEC-EV were analyzed by PCR. To study EV transfer *in vivo* we used a transgenic model of CKD, Alport syndrome - characterized by a deficiency in the type IVα5 collagen and expression of *td*Tomato in endothelial cells, including GEC. TEM studies using immunogold co-labeling for *td*Tomato and CD63 were used to identify EV origin and uptake.

Results: GEC-EVs expressed exosomal CD9, C63, cell-adhesion and angiogenic markers, especially the VEGF receptors type I and II. In vitro, transfer of normal GEC-EV to podocytes was confirmed by the Cre-lox activation of the *td*Tomato in podocytes by the Cre protein delivered via the GEC-EV. Transfer of GEC-EVs maintained podocyte morphology, WT1, podocin, nephrin and VEGF expression, while podocytes exposed to EVs isolated from Alport GEC showed alteration of these markers, thus possibly indicating that Alport GEC-EVs present a different cargo than normal GEC-EVs. *In vivo*, TEM data showed a presence of GEC-EV in podocytes, confirming EV transfer across the glomerular filtration barrier.

Conclusions: Our data suggest that EV transfer across the glomerular filtration barrier is an essential physiological event that regulates cellular function in podocytes. Identification of novel mediators of endothelial-podocyte crosstalk may lead to the development of more effective treatments for glomerular kidney disease.

Funding: Private Foundation Support

SA-PO334

Association of uTWEAK Levels with Histological Findings, Endothelial and Tubulointerstitial Markers (VEGF/VCAM-1, TGFβ) in Patients with Lupus Nephritis (LN)

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Background: Urinary TWEAK levels (uTWEAK) are a sensitive and specific biomarker in the evaluation of LN in patients with SLE, however, its association with histological findings and expression of endothelial and tubulointerstitial lesion marker is unknown.

Methods: Cross-sectional study. We determinate the degree of association between uTWEAK with histological findings and markers of endothelial lesion (VEFG and VCAM-1) and tubulointerstitial (TFGβ) in patients with LN that have not been received immunosuppressive treatment. Non parametric statistics, logistic regression model, 95%CI, and $p<0.05$ were performed as statistically significant.

Results: Thirty-six patients were evaluated, 83.3% (30) were female. With predominance of histological class IV+V (41.6%). In the histological findings, 63.8% had a low chronicity index (<6 points), the activity index (AI) was 50% >12 points. The uTWEAK according to the histological class did not show statistically significant differences. In 72.2% of the patients, VEGF at glomerular was ≥50% and at the arteriolar level, 77.8% of the patients presented deposits of ≥50%. In Figure 1, the correlation between the histological findings and the endothelial and tubolointerstitial biomarkers is observed. Although, uTWEAK was not associated significantly with AI and arteriolar VEGF deposits (OR 4.18, p= 0.223 and 11.298, p= 0.120), effect size (d-Cohen) was of 0.78 and 1.33 respectively.

Conclusions: The uTWEAK represents a sensitive and specific biomarker in the evaluation of LN in patients with SLE, however, his expression does not seem to distinguish between the different classes of LN; an association was found with AI and VEGF. It is relevant to evaluate the outcome of the patients and to establish if the markers evaluated have an impact on the prognosis of the patients.

Activity Index		
Marker	**r value**	***p* value**
VCAM-A	0.009	0.959
VCAM-G	0.076	0.669
VEGF-A	0.139	0.386
VEGF-G	0.425	0.012
Chronicity Index		
VCAM-A	0.209	0.236
VCAM-G	0.659	0.000
TGF-β	.104	0.560
IFTA		
VCAM-A	0.413	0.012
VCAM-G	0.826	0.000
TGF-β	.238	0.162

SA-PO335

Antigen-Specific IgG Subclasses in Primary and Malignancy-Associated Membranous Nephropathy

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Background: The immunologic mechanisms leading to initiation of primary MN are assumed to be different from those in cancer-associated MN, however, the evidence for this proposal has not been systematically evaluated. For decades primary MN was considered to have an IgG4-driven autoimmune genesis, while secondary MN associated with other diseases, most notably cancer, was not linked to IgG4. The identification of the phospholipase A_2 receptor 1 (PLA_2R1) and thrombospondin type-1 domain-containing 7A (THSD7A) as target antigens of autoimmunity in MN now allows a pathogenesis-driven differential diagnosis and may help to better understand the differences between the pathomechanisms of primary and secondary MN. Recent data showing a molecular link between THSD7A expression in tumors and THSD7A-antibody positive MN suggest a similar pathogenesis of malignancy-associated and primary MN.

Methods: In this study we systematically analyzed circulating antigen-specific IgG subclasses in the serum of 76 patients with PLA_2R1-associated MN and 41 patients with THSD7A-associated MN in relationship to concurrent malignancy and disease outcome. All IgG subclasses were analyzed by Western blot. Twenty-three patients in the study had a malignancy-associated MN. Human lung and glomerular protein extracts were analyzed under non-reducing conditions for expression of both PLA_2R1 and THSD7A.

Results: At baseline all 117 patients were positive for IgG4-antibodies against either PLA_2R1 or THSD7A, while IgG3, IgG1 and IgG2-antibodies were found in 87%, 72% and 26% of patients, respectively. There were no differences in the IgG subclass distribution between patients with primary versus cancer-associated MN and no association with disease outcome. Both podocytes and lung bronchioles showed expression of both PLA_2R1 and THSD7A when analyzed by immunofluorescence and Western blot. Every antigen-specific IgG subclass showed identical antigen-binding in both organs and autoantibodies bound the respective antigen only under non-reducing conditions.

Conclusions: We conclude that antigen-specific IgG subclasses do not differentiate between primary and malignancy-associated MN or predict disease prognosis. The data support the view that one common pathway may lead to primary and cancer-associated MN induced by PLA_2R1- or THSD7A-antibodies.

Funding: Government Support - Non-U.S.

SA-PO336

The Conformational Anti-Phospholipase A2 Receptor Autoantibodies in Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (PMN) is a leading cause of nephrotic syndrome in adults. The dominant antigen, phospholipase A2 receptor (PLA2R) is detected in the subepithelial immune deposits in over 80% of the PMN patients. Anti-PLA2R autoantibodies (PLA2R-Ab) bind to PLA2Rs on the basal surface of the podocytes triggering immune complex formation *in situ* that impairs the glomerular filtration barrier function causing massive leakage of the plasma proteins into the urine. We and others determined that the dominant epitope for autoantibody binding is located at the N-terminus of PLA2R. Additional studies also reported that 3 independent epitopes are present in PLA2R and that epitope spreading occurs in the patients and is associated with disease progression. Here we further characterized the autoantibody-PLA2R epitope interaction using 48 patient samples.

Methods: 48 PLA2R-Ab positive sera from patients with biopsy-proven MN were collected and assessed for their reactivities to PLA2R using Western-blot, immunoprecipitation under the native condition and immunodiffusion assays.

Results: 6 serum samples were identified to react strongly to the region of CysR-FnII-CTLD1-3, but weakly to the region of CysR-FnII-CTLD1 when diluted at 1:5000 on the Western-blot. 42 samples collected from patients who had relapsed disease all reacted strongly to the CysR-FnII-CTLD1 region at the same dilution. Follow-up studies in 3 patients who did not receive immunosuppressive treatment demonstrated that the autoantibodies initially reacted to the large CysR-FnII-CTLD1-3 region but later switched to the small CysR-FnII-CTLD1 region, coinciding with the worsening of proteinuria. Further analysis of autoantibody interaction with the purified PLA2R extracellular region in the immunodiffusion assay indicated that no insoluble lattice could be formed with any of the collected sera, suggesting that PLA2R is unlikely to have independent, separated epitopes in the extracellular region.

Conclusions: Our results indicated that two overlapping PLA2R epitope regions are present in the PMN patients with the autoantibody reaction to CysR-FnII-CTLD1-3 is likely to occur before the reaction to CysR-FnII-CTLD1. This data suggest that the overall conformation of PLA2R plays an important role in autoantibody formation and that autoantibody maturation is associated with PMN progression.

SA-PO337

Proteomic Analysis of Complement Factors in PLA2R-Positive Membranous Nephropathy

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Background: Membranous nephropathy (MN) is characterized by deposition of immune-complexes and complement factors along the glomerular basement membrane. Phospholipase A2 receptor (PLA2R) is the target antigen in approximately 70% of MN. Although complement deposition is seen PLA2R-associated MN, a comprehensive and detailed analysis of complement factors in PLA2R-associated MN has not been done.

Methods: We used laser microdissection and mass spectrometry (MS) to dissect glomeruli and identify the glomerular and complement proteins in 7 cases of PLA2R-associated MN. For control cases, we used 6 cases of time 0 transplant protocol biopsies.

Results: MS identified very high total spectral counts (TSC) for PLA2R in all cases of PLA2R-associated MN with average TSC of 87 (range 45-135). In comparison, the avarage TSC in control cases was only 5 (range 0-7) which is similar to many house-keeping proteins. With regards to complement factors, C3 was the most abundant complement protein with average TSC of 413 (range 324-708), followed by C4 (C4-B avg 176, C4-A avg 174). Moderately high TSC of C9 (avg 79,) and C5 (avg 54) were also detected. Lesser amounts of C6 (avg 31), C7 (avg 20) and C8 (avg 21) were also present. C1 was absent or present in very low spectral counts. In addition, complement regulating facors- complement factor H (avg 57), complement factor H-related protein 5 (avg 65.5) and complement factor H-related protein 1 (avg 30) were also detected. The average TSC of complement factors in control cases for C3, C4-B, C4-A and C5 was 107, 40, 39, and 5, respectively. With regards to immunoglobulins (Ig) in PLA2R-associated MN, IgG4 was the most abundant Ig (avg 91), followed by IgG1 (avg 68), IgG3 (avg 64) and IgG2 (avg 49). The avgerage Ig total TSC in control cases for IgG4, IgG1, IgG3 and IgG2 was 22, 56, 45 and 45, respectively.

Conclusions: Using MS analysis, we show accumulation of large amounts of C3 and C4, followed by C9 and C5, and lesser amounts of C6, C7 and C8 indicating a role of complement in the pathogenesis of PLA2R-associated MN. The TSC of C3 and C4 was much higher than the TSC of PLA2R or Ig indicating amplification and accumulation of complement factors in greater amounts than the PLA2R antigen or Ig. The large amounts of C3 and C4 and absence of C1 suggests involvement of the lectin pathway.

SA-PO338

Exostosin 1/Exostosin 2-Associated Membranous Nephropathy

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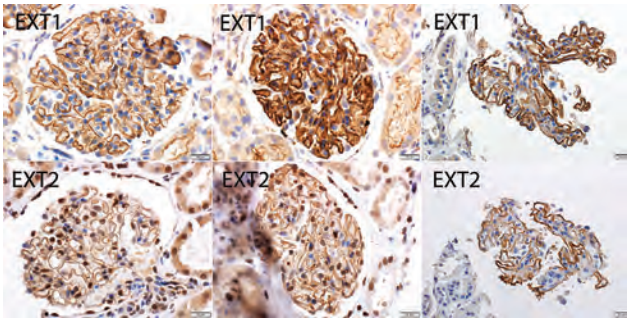
Background: Membranous nephropathy (MN) is is characterized by deposition of immune-complexes and complement along the glomerular basement membrane (GBM). Phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain containing 7A are target antigens in ~70% and 5% cases, respectively. In the remaining cases, the target antigen is unknown.

Methods: We studied 22 cases of MN: 7 PLA2R-positive and 15 PLA2R-negative; and 6 control time 0 transplant protocol biopsies. Glomeruli were laser microdissected and mass spectrometry (MS) was performed to detect the proteomic profile. This was followed by immunohistochemical studies (IHC) to identify and localize the overexpressed proteins.

Results: MS identified high total spectral counts (TSC) for PLA2R in cases of PLA2R-positive MN. In 5 of the 15 PLA2R-negative MN, high TSC for both exostosin 1 (EXT1) and exostosin 2 (EXT2) were present. The TSC of EXT1 and EXT2 were comparable to the TSC of PLA2R in PLA2R-positive cases. EXT I and II are glycosyltransferases that exist as heterodimers and are responsible for the synthesis of the heparin sulfate backbone in the GBM. Of the remaining 10 PLA2R-negative cases, 2 cases of negative PLA2R by IF were positive for PLA2R, 3 cases had suboptimal tissue, and in 5 cases comparable high TSC of a single protein was not present. EXT1 and EXT2 were absent in PLA2R-positive and control cases. None of the PLA2R negative cases showed THS7DA. In all MN cases, high TSC for complement factors and Ig were also present. To confirm the findings we performed IHC that showed bright granular EXT1 and EXT2 GBM staining in EXT1/EXT2-positive MN cases, in a distribution similar to Ig (Figure 1). Furthermore, EXT1/EXT2 staining was specfic as staining for Exostosin-like 2 (EXTL2) was negative in the EXT1/EXT2-positive cases. All control and PLA2R-positive cases were negative for EXT1/EXT2/EXTL2.

Conclusions: A subset of PLA2R-negative MN is associated with accumulation of EXT1 and EXT2 in GBM, representing a distinct subtype of MN.



EXT1 and EXT2 staining in 3 cases of PLA2R-negative MN. Each column is 1 case.

SA-PO339

Generating a Mouse Model of Membranous Nephropathy (MN)

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Background: 75% of patients with MN develop autoantibodies against PLA2R, which is expressed on podocytes. Autoantibody binding causes immune complex deposition in the glomerular basement membrane (GBM), podocyte effacement and the clinical phenotypes of proteinuria and nephrotic syndrome. The lack of an *in vivo* model for MN, due to rodents expressing minimal PLA2R on podocytes, has impeded the investigation of disease mechanisms and novel therapeutics. The aims of this study were to 1) develop a podocyte-specific PLA2R knock-in mouse and 2) induce MN through passive transfer of anti-PLA2R antibodies.

Methods: A transgene was created for insertion of a flag-tagged PLA2R fragment (NC3) containing the transmembrane and the first 5 extracellular domains, including the immunodominant epitope of PLA2R. Podocyte restricted expression of NC3 is driven by the *NPHS2* promoter. Transgene positive pups were bred with BL6/J mice to spawn heterozygous knock-in mice. Kidneys, glomeruli and podocytes were isolated from subsequent offspring for analysis by reverse transcription PCR (RT-PCR), targeted locus amplification (TLA) sequencing, western blotting (WB), and immunohistochemistry (IHC). Induction of MN in PLA2R knock-in mice will be achieved by intravenous injection of human anti-PLA2R and analysed for glomerular deposition, proteinuria and complement activation.

Results: TLA sequencing confirmed successful in-frame insertion of the transgene in PLA2R knock-in mice. RT-PCR and WB analysis of kidneys and glomeruli demonstrated the expression of NC3 mRNA and protein in PLA2R knock-in mice. IHC of kidney sections using human anti-PLA2R antibodies indicated strong podocyte staining of NC3 in the glomerulus of PLA2R knock-in mice. PLA2R knock-in mice demonstrated no differences to wild type mice in regards to proteinuria, weight and histology under basal conditions. We anticipate that injection of MN patient IgG will induce the MN phenotype in PLA2R knock-in mice.

Conclusions: We have successfully developed a PLA2R knock-in mouse. Expression of NC3 did not induce a phenotype under basal conditions. Current work focusses on the induction of MN using patient IgG. This mouse model gives exciting prospects for validating the pathogenicity of anti-PLA2R antibodies and the role of immune complex formation, complement activation and GBM thickening in causing proteinuria.

SA-PO340

T-Regulatory and B-Regulatory Cells in Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (PMN) is an antibody-mediated disease. Both T-regulatory (TREGs) and B-regulatory (BREGs) cells are decreased in patients with autoimmune disease. The data on TREGs and BREGs in PMN is very scanty. We evaluated the TREG and BREG population in patients of PMN treated with cyclical cyclophosphamide and steroid therapy (cCTX/GC).

Methods: Twenty-four patients of PMN and 10 healthy controls were enrolled in the study at Nehru Hospital, PGIMER, Chandigarh. All the patients were resistant to restrictive strategy and were treated with cCTX/GC therapy. The proteinuria, serum creatinine and serum albumin were tested at monthly intervals and blood samples were collected prior to starting cCTX/GC and at 6 and 8 (2 months wash out) months of therapy. The peripheral blood mononuclear cells (PBMCs) were isolated from the collected blood samples using density gradient centrifugation. PBMCs after staining with fluorochrome-conjugated antibodies were then subjected to flow cytometric analysis for detection of TREGs ($CD3^+CD4^+CD25^{hi}CD127^{lo}FoxP3^+$) and BREGs ($CD19^+CD5^+CD1d^{hi}IL10^+$) at all time-points. TREGs and BREGs are presented as the percentage of CD3+CD4+ and CD19+ cells, respectively.

Results: The mean proteinuria, serum albumin and creatinine at baseline was 8.74±4.85 g, 2.33±0.80 g/dL and 1.06± 0.53 mg/dL, respectively. Patients with PMN had a lower percentage of TREGs and BREGs compared to healthy controls ($p<0.05$). There was a significant increase in both BREGs and TREGs with the treatment at 6 and 8 months (Table). The rise in both BREGs and TREGs were apparent after stopping (8 months) immunosuppressive therapy (Table).

Conclusions: As compared to the healthy controls, patients with PMN displayed a lower percentage of TREGs and BREGs. Both TREGs and BREGs significantly improved with disease-specific therapy. The increase in both the regulatory cells is apparent after two months of stopping cCTX/GC.

Funding: Government Support - Non-U.S.

BREGs and TREGs in Primary Membranous Nephropathy

	Control (n=10)	Baseline (n=24)	6 mon (n=24)	8 mon (n=24)	Baseline vs. control	Baseline vs.6 vs.8 mon (ANOVA)	Baseline vs. 6 mon	Baseline vs. 8 mon	6 vs. 8 mon
TREGs (CD3+ CD4+25Hi Fox3+ 127Lo)	7.55 ± 4.64	4.37±2.69	4.77±4.01	6.06±2.53	0.01	0.18	0.54	0.03	0.18
BREGs (CD19 +, CD5+CD1dhiIL10)	3.19±2.75	1.25±1.72	1.29±1.80	4.52±4.76	0.0007	0.0003	0.83	0.0001	0.001

Values are expressed as frequencies. TREGs- Regulatory T cells, BREGs- Regulatory B cells

SA-PO341

Pre-Diagnostic Evaluation of Anti-Phospholipase A2 Receptor Antibodies in Primary Membranous Nephropathy

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Background: M-type phospholipase A_2 receptor antibodies (PLA_2R –Ab) are present in 60-80% of primary membranous nephropathy (pMN) cases at diagnosis. PLA_2R-Ab is assumed to directly contribute to pMN pathophysiology, but there has not been confirmatory animal models or evaluation of PLA_2R –Ab before pMN diagnosis. We sought to describe PLA_2R-Ab levels before both biopsy diagnosis and documented proteinuria before biopsy diagnosis to better understand pMN pathophysiology.

Methods: We performed a retrospective case-control Department of Defense Serum Repository (DoDSR) study comparing PLA_2R-Ab in patients with pMN, presumed secondary MN, and healthy controls. MN cases were first identified and confirmed by review of the military electronic medical record. Background data was collected to include the earliest date of abnormal proteinuria and the most recent date of negative proteinuria before biopsy diagnosis. Based on background and biopsy data, MN patients were divided into pMN and secondary MN cases. The DoDSR then provided up to 4 prediagnostic specimens for each MN case and age, race, sex and age of serum matched healthy controls. PLA_2R-Ab was measured at the NIH using a luciferase assay.

Results: More pMN cases had elevated PLA_2R-Ab than secondary membranous disease controls before biopsy diagnosis [44% (59/134) vs. 2.8% (1/35), $p<0.001$]. No matching healthy controls had detectable PLA_2R-Ab at any time point. PLA_2R-Ab became elevated a median of 274 days prior to biopsy diagnosis (IQR: 63days, 811 days). 15 cases demonstrated significantly elevated prediagnostic PLA_2R-Ab at or up to 5 years prior to the earliest documentation of non-nephrotic range proteinuria before biopsy diagnosis. Two unique cases demonstrated elevated PLA_2R-Ab with confirmed negative proteinuria over a year before biopsy diagnosis.

Conclusions: PLA_2R-Ab is detectable not only before biopsy proven pMN, but also prior to the earliest subclinical presence of non-nephrotic range proteinuria which supports a direct contribution to the pathogenesis of pMN. Early serum testing of PLA_2R-Ab in patients with unexplained non-nephrotic range proteinuria may allow for early diagnosis and monitoring of pMN.

Funding: Other NIH Support - Dr. Peter Burbelo ran the samples at the NIH, Other U.S. Government Support

SA-PO342

PLA2R1 Epitope Recognition Patterns and Clinical Outcome in Patients with Membranous Nephropathy

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Background: Phospholipase A_2 receptor 1 antibodies (PLA_2R1-ab) are found in 80% of patients with membranous nephropathy (MN). While PLA_2R1-ab levels are closely associated with treatment response and disease prognosis, the clinical role of epitope regions targeted by autoantibodies is less clear.

Methods: The epitope recognition patterns of PLA_2R1-ab from 150 patients with newly diagnosed PLA_2R1-associated MN were analyzed by Western blot and correlated with disease activity, clinical characteristics and outcome.

Results: In addition to the three known epitope regions in the CysR, CTLD1 and CTLD7 domains, we identified a fourth epitope region in the CTLD8 domain of PLA_2R1. While PLA_2R1-ab from all patients recognized an epitope in the N-terminal region (defined as CysR – CTLD1 domains), 82.7% of patients also recognized a C-terminal epitope in PLA_2R1, namely in the CTLD7 and/or CTLD8 domain. Patients with C-terminal epitope recognition had almost 10-fold higher PLA_2R1-ab levels, higher proteinuria and needed immunosuppressive treatment twice as often as patients with epitope recognition confined at the N-terminal region of PLA_2R1. After adjusting for these factors in multivariate analyses, C-terminal epitope recognition was not predictive for any of the clinical study endpoints, defined as depletion of PLA_2R1-ab, remission of proteinuria, and doubling of serum creatinine during follow-up. Additional dilution of sera recognizing C-terminal epitopes of PLA_2R1 led to abolishment of C-terminal epitope recognition, while N-terminal epitopes remained detectable. Therefore, one can speculate, that some of the 17.3% of patients in our cohort, who only showed reactivity to the N-terminal region of PLA_2R1, may also have had autoantibodies targeting the C-terminal region, however, the sensitivity of the method was not sufficient to detect them.

Conclusions: There are at least four target epitope regions in the PLA_2R1 and a clear association between epitope recognition patterns and PLA_2R1-ab levels. C-terminal epitope recognition is not associated with disease outcome if all other clinical variables are adjusted for, therefore considering PLA_2R1-ab levels is fundamental for the interpretation of the clinical relevance of PLA_2R1 epitope recognition patterns.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO343

Relation Between Anti-PLA2R Titer and the Likelihood of Spontaneous Remission in Membranous Nephropathy

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Background: In idiopathic membranous nephropathy (iMN), the antibody titer of anti-PLA2R correlates with the activity of the disease and the likelihood of spontaneous remission (SR). Based on measurements of the basal anti-PLA2R titer, some authors have proposed algorithms, for guiding the decision making process regarding the timing for initiation of immunosuppresive treatment in patients with iMN. Objectives: 1.- To analyze the probability of SR based on the initial titer of anti-PLA2R antibodies. 2.- Analyze if the dynamic of the antibody titer during the observation period, allows for a better estimation of the likelihood of SR.

Methods: 94 patients with iMN with anti-PLA2R antibody titers> 20 U / mL at the time of diagnosis. The patients were followed for at least 6 months before initiation immunosuppressive therapy. Blood samples were obtained prospectively at the time of diagnosis, at 8 weeks, at 12, and at 24 weeks after diagnosis. The measurement of the anti-PLA2R titer, and the predictive capacity of these titers on the likelihood of SR was analyzed with ROC curves, univariate and multivariate analysis.

Results: 28 of 94 patients (29.8%) entered immunological remission followed by clinical remission, which was total in 5 patients (5.31%) and partial in 23 (24.4%). The mean interval between diagnosis and immunological and clinical remission was 5.9 ± 1.6 months and 6.5 ± 2.3 months, respectively. Patients with SR presented lower proteinuria, lower anti-PLA2R titers at diagnosis, and a significant decrease thereof over time. The probability of SR was associated linearly with ranges of values, but not with a single value. The logistic model with greater predictive capacity included the basal titers and the change at 12 weeks.

Conclusions: In patients with iMN, the probability of SR can be estimated with adequate predictive power from the baseline anti-PLA2R antibodies, but a best estimation model is obtained when adding the antibody titer at 12 weeks.

SA-PO344

PLA2R Expression in Pediatric Membranous Nephropathy: A Multi-Institution Retrospective Study

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Background: Membranous nephropathy (MN) is a rare cause of nephrotic syndrome in children and can be idiopathic (IMN) or secondary to systemic diseases (i.e. SLE, chronic infections and malignancy). In adults with IMN, antibodies against phospholipase A2 receptor (PLA2R) are present in 57-82% of patients and expression of PLA2R is increased in glomeruli by histochemical staining. The latter is a useful diagnostic tool allowing the pathologist to suggest an idiopathic versus secondary process. However, PLA2R expression in children with MN has not been studied in large cohorts, and small case series have shown lower sensitivity (6-45%) compared to adults.

Methods: We retrospectively collected 82 cases of IMN and secondary MN (lupus-related (SLEMN) and non-SLEMN) from 4 Institutions. Formalin fixed paraffin embedded sections were stained for PLA2R and scored blindly as positive or negative and results were correlated with clinical, histomorphologic, IF and electron microscopy (EM) findings.

Results: Of 37 IMN, PLA2R-positivity was observed in 62% of cases, was variable in non-SLEMN (54%) and mostly negative in SLEMN (91%). Thus, PLA2R staining alone was not sufficient to parse IMN from non-SLEMN (p=0.61). SLEMN were more likely to show mesangial expansion compared to IMN and non-SLEMN (p<0.0001 and p=0.0016 respectively), subendothelial deposits (p<0.0001) and more mesangial deposits compared to IMN (p=0.0004) but not non-SLEMN (p=0.1228). Tubuloreticular inclusions were more frequent in SLEMN and non-SLEMN compared to IMN (p<0.0001 and 0.0004 respectively) with no difference between SLEMN and non-SLEMN. IF patterns were similar in IMN and non-SLEMN with more "full-house" patterns in SLEMN. PLA2R-negative cases were more likely to have mesangial expansion, full house staining, subendothelial and mesangial deposits (p=0.0381, 0.0341, 0.0008 and 0.0351 respectively). Glomerular basement membrane alterations, global/segmental glomerulosclerosis (%) and tubulointerstitial scarring (%) did not differ significantly between groups.

Conclusions: We show a higher prevalence (62%) of PLA2R positive IMN compared to previous reports. However, PLA2R positivity was observed in a 54% of secondary MN (non-SLEMN). PLA2R-positivity did not correlate with any specific histological characteristics but was uncommon in SLEMN.

SA-PO345

Hypocomplementemia and Membranous Nephropathy Among the Patients with Anti-U1 Ribonucleoprotein (RNP) Antibody

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Background: The significance of anti-ribonucleoprotein (RNP) antibody and anti-Sm antibody remains still unclear on patients with systemic lupus erythematosus (SLE) or mix connective tissue disease (MCTD).

Methods: Thirty patients showing the positivity for antinuclear antibodies (ANA) and anti-RNP antibody, who were diagnosed with SLE or MCTD and received renal biopsy in our hospital between January 1980 and December 2014, were retrospectively enrolled into this study. These 30 patients were classified into 4 groups based upon anti-dsDNA (+)/(-) and anti-Sm (+)/(-); group A (n = 10): anti-dsDNA(-) plus anti-Sm(-), group B (n = 7): anti-dsDNA(-) plus anti-Sm (+), group C (n = 6): anti-dsDNA(+) plus anti-Sm(-), and group D (n = 7): anti-dsDNA(+) plus anti-Sm(+). Among these 4 groups, clinical marker and renal histology were compared. Renal histology showed 3 types including pure subepithelial membranous nephropathy(MN), mesangial proliferative nephropathy(MES), and MN plus MES.

Results: Thirty patients with anti-RNP antibody included SLE (n = 25) and MCTD (n = 5). The mean age (SE) was 38.6 (2.5) years, and 26 out of 30 patients (87%) were women. Fourteen patients (47%) showed the positivity for anti-Sm antibody and thirteen patients (43%) showed the positivity for anti-dsDNA antibody. Anti-Sm (-) groups showed normocomplementemia, and anti-Sm (+) groups showed hypocomplementemia. Pure MN was noted in anti-dsDNA (-) group or anti-Sm (-) group. The comparison between group A and group B showed that anti-Sm (-) has a close relation with normo-complementemia and MN lesion, and anti-Sm (+) has close relation with hypo-complementemia and MES lesion on patients with RNP(+) and ds-DNA(-). The comparison between group C and group D showed that anti-Sm (+) has close relation with hypo-complementemia, but does not have any relation with renal histology on patients with RNP(+) and ds-DNA(+).

Conclusions: Our study indicates that the single positivity of anti-RNP antibody contributes to MN formation with normocomplementemia, while additional positivity of anti-Sm antibody results in hypocomplementemia-related MES formation.

SA-PO346

Patients with Membranous Nephropathy Display Unexpectedly Decreased Circulating T Follicular Helper (TFH) and TH17 Cells and Increased Regulatory B Cells (Breg)

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Background: Primary membranous nephropathy (PMN) is characterized by the presence of antibodies to the podocyte, but little is known on circulating T and B cell populations, especially the percentages of T_{FH} and Breg.

Methods: We performed a comprehensive follow-cytometric analysis of 38 T and B lymphocyte subpopulations, including intracellular staining for IFN-g, IL-4, and IL-17 production in 16 patients with severe PMN and compared them with 12 age-matched healthy individuals.

Results: Within the T cell compartment, we found that patients with PMN had significantly fewer $CD4^+CD25^+CD127^{lo}$ Tregs (Treg; p=0.04), IL-17^+CD4^+ T_H17 cells (p=0.01), and $CD4^+CXCR5^+PD1^+$ T_{FH} cells (p=0.02) than healthy controls (**Figure 1A**). While $CD4^+CD45RO^+CD27^-$ effector T cells were not differentially increased in PMN patients compared to healthy controls, they positively correlated with proteinuria in the PMN patients at baseline (r^2=0.33; p=0.02). Within the B cell compartment, PMN patients had significantly fewer $CD19^+CD27^+IgD^+$ unswitched B cells (p=0.01) and $CD19^+IgD^+CD27^-CD24^{lo}CD38^{lo}$ naïve transitional B cells (p<0.0001) and significantly more $CD19^+CD25^+CD71^+$ Bregs (p=0.046) than healthy controls (**Figure 1B**). Within PMN patients, we did not find a relationship between anti-PLA_2R antibodies and any of the T or B cell subsets investigated.

Conclusions: Consistent with previous reports, patients with PMN display a unique immune phenotype characterized by reduced Treg and naïve B cell percentages. Unexpectedly, we newly found that PMN patients also display increased Breg, fewer T_{FH}, and a positive correlation between $CD4^+$ effector T cells and proteinuria, suggesting a pathogenic link.

Funding: NIDDK Support

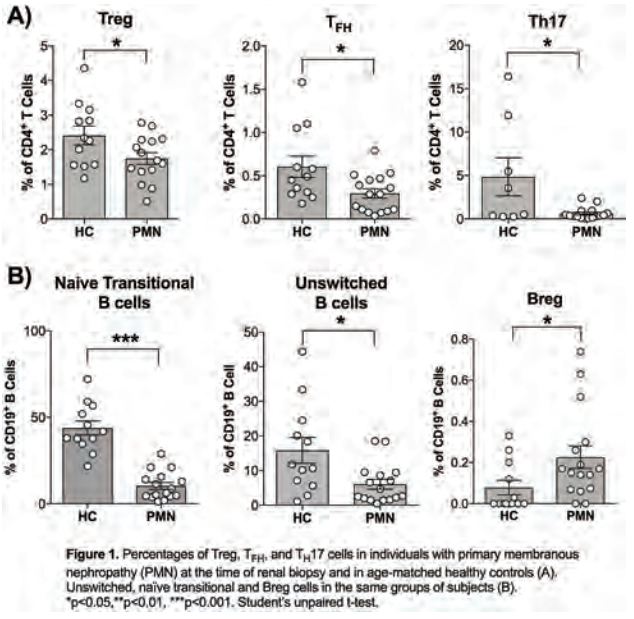

Figure 1. Percentages of Treg, T_{FH}, and T_H17 cells in individuals with primary membranous nephropathy (PMN) at the time of renal biopsy and in age-matched healthy controls (A). Unswitched, naïve transitional and Breg cells in the same groups of subjects (B). *p<0.05,**p<0.01, ***p<0.001. Student's unpaired t-test.

SA-PO347

Clinical Characteristics and Renal Outcomes in Patients Developing Membranous Nephropathy After Allogeneic Stem Cell Transplantation

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Introduction: The overall probability of developing nephrotic syndrome (NS) in allogeneic stem cell transplant (allo-SCT) patients with graft-versus-host disease (GVHD) is estimated to be 8%. Membranous nephropathy (MN) accounts for the majority of these cases and has been ascribed to renal-specific manifestation of GVHD based on MN association with GVHD in other organs, immunosuppression (IS) reduction at the time of MN diagnosis and negative tissue PLA2R staining. Treatment regimens range from corticosteroids (CS) to rituximab with variable clinical response.

Case Description: Chart review identified 8 cases of clinically diagnosed NS at our institution that developed after allo-SCT from 2010 through 2017 and was evaluated with kidney biopsy. No transplants had antigen mismatch. All had a history of, but no concurrent GVHD in the settings of IS reduction. Minimal change disease was responsible for 3 and MN for 5 cases. Stain for PLA2R was present in the glomerular capillary loops in 4 of 5 MN cases. Plasma PLA2R titers were negative when checked. Partial or complete remission of proteinuria (PTN) was achieved in 4 MN cases with the utilization of single agent Tacrolimus or its combination with CS, without complications arising from the treatment (Table).

Discussion: We report a series of MN cases diagnosed after allo-SCT and characterized by PLA2R-positive tissue staining. Although the presence of PLA2R in the glomerular tissue is thought to be specific for idiopathic MN, our findings raise the possibility of PLA2R being an epi-phenomenon occurring in both idiopathic and GVHD-related MN. Tacrolimus alone appears to be effective in inducing at least partial remission of PTN. Additional CS may confer a faster and more durable response; however, this benefit must be weighed against the side effects associated with their long-term use.

Patient	Age	Hematological Diagnosis	Post-transplant time (d)	GVHD status	PLA2R tissue	PLA2R Plasma	Initial Treatment	Treatment duration (d)	Treatment response (UPC)	Subsequent treatment
1	55	AML	839	prior	+	-	Tacrolimus + CS	160	partial (1.0)	none
2	66	MDS	864	prior	+	Indeterminate	Tacrolimus + CS	294	complete (0.1)	none
3	35	TCL	937	prior	+	not checked	Tacrolimus	394	complete (0.1)	Tacrolimus
4	73	AML	1248	prior	+	-	Tacrolimus	90	none (17)	Tacrolimus + CS
5	56	AML	1065	prior	-	not checked	Tacrolimus	747	partial (1.5)	Mycophenolate Mofetil

AML, acute myeloid leukemia; CS, corticosteroids; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; TCL, T-Cell lymphoma

SA-PO348

Complement Activation Products in the Circulation and Urine of Primary Membranous Nephropathy

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Background: Complement activation plays a substantial role in the pathogenesis of primary membranous nephropathy (pMN). C5b-9, C3c, MBL, and factor B have been documented in the subepithelial immune deposits. However, the changing of complement activation products in circulation and urine is not clear.

Methods: We measured the circulating and urinary levels of C1q, MBL, C4d, Bb, properdin, C3a, C5a, and sC5b-9, in 134 patients with biopsy-proven pMN, by enzyme-linked immunosorbent assay. All the plasma values were corrected by eGFR and all the urinary values were corrected by urinary creatinine and urinary protein excretion. Anti-PLA2R antibodies were measured in all patients.

Results: The plasma complement activation products were elevated both in the patients with and without anti-PLA2R antibodies. C3a levels were remarkably increased in the circulation and urine, much higher than the elevated levels of C5a. C5b-9 was in normal range in plasma, but significantly higher in urine. The urinary C5a had a positive correlation with anti-PLA2R antibody levels and urinary protein. The plasma level of C4d was elevated, but C1q and MBL were comparable to healthy controls. Positive correlations were observed between plasma C4d/MBL and urinary protein, only in the patients with positive anti-PLA2R antibodies but not in those without. The plasma level of Bb was elevated and had positive correlation with urinary protein only in the patients without anti-PLA2R antibodies.

Conclusions: Complement activation products were remarkable increased in pMN and may serve as sensitive biomarkers of disease activity. The complement may be activated through lectin pathway with the existence of anti-PLA2R antibodies, while through alternative pathway in the absence of antibody.

Funding: Government Support - Non-U.S.

SA-PO349

Identification of Novel Target Antigens in Sera of Membranous Nephropathy Patients Using Whole Proteome Peptide Array Technology

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Background: Membranous nephropathy (MN) autoantigens have been discovered using the established laboratory technique of Western blotting, in which human sera from patients with MN were utilized to screen for specific reactivity with proteins extracted from human glomerular fractions. The objective of the present study was to investigate a highly characterized group of patients using a technology routinely adopted in antibody epitope mapping.

Methods: Sera from patients with membranous nephropathy, selected to have good (n=5) or bad prognosis (n=5) at hospitalization (T0) or twelve months after (T12) were hybridized with a whole proteome peptide array chip. The intensity of the signal retrieved by whole proteome peptide array chip was used to feed a weight gene co-expression network analysis (WGCNA) algorithm to identify a network of relationships between the signals and renal outcome in search of established and novel antigens of MN.

Results: Whole proteome peptide array technology allowed retrieving known antigens (*e.g.*, PLA2R1 or THSPD7A) and identified specific peptide sequences on those proteins recognized by autoantibodies predictive of renal outcome. Peptides belonging to previously unknown target antigens in MN were also retrieved.

Conclusions: Whole proteome peptide array and extracellular protein microarray technologies can be profitably applied to the study of autoimmune diseases. The technologies identify known antigens of MN and novel unknown ones. Those preliminary findings need extensive validation in a large patient set.

SA-PO350

Deletion of the Mitochondrial Complex-IV Co-Factor Heme A: Farnesyltransferase Causes FSGS and Interferon Response

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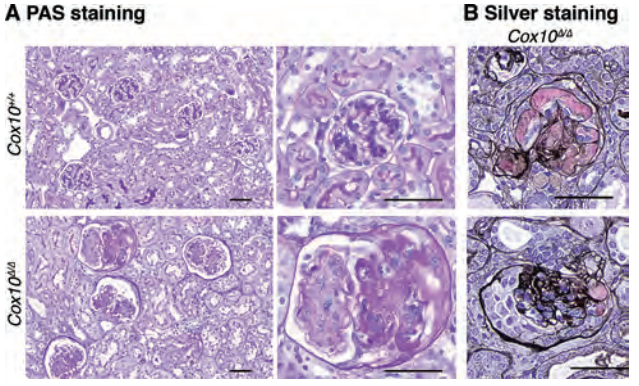
Background: Mutations in mitochondrial DNA as well as in nuclear-encoded mitochondrial proteins have been reported to cause tubulointerstitial kidney diseases and focal segmental glomerulosclerosis (FSGS). More recently, genes and pathways affecting mitochondrial turnover and permeability have been implicated in adult onset FSGS. Furthermore, dysfunctioning mitochondria may be capable of engaging intracellular innate immune sensing pathways.

Methods: To determine the impact of mitochondrial dysfunction in FSGS and secondary innate immune responses, we generated Cre/*loxP* transgenic mice to create loss-of-function deletion mutation of the Complex IV assembly co-factor heme A:farnesyltransferase (COX10) restricted to cells of the developing nephrons.

Results: These mice develop severe, early onset FSGS with innate immune activation, and die prematurely with kidney failure. Mutant kidneys showed loss of glomerular and tubular epithelial function, epithelial apoptosis and in addition a marked interferon response. *In vitro* modeling of *Cox10* deletion in primary kidney epithelium compromises oxygen consumption, ATP generation, and induces oxidative stress. In addition, loss of *Cox10* triggers a selective interferon response, which may be caused by the leak of mitochondrial DNA into the cytosol activating the intracellular DNA sensor, STING.

Conclusions: This new animal model provides a mechanism to study mitochondrial dysfunction *in vivo* and demonstrates a direct link between mitochondrial dysfunction and intracellular innate immune response.

Funding: Other NIH Support - DK093493 and DK094768, Commercial Support - Biogen



SA-PO351

B-Cell Profiles in FSGS Rituximab Responders with T-Cell Hyporesponsiveness

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Background: We recently reported a subgroup of focal segmental glomerulosclerosis (FSGS) patients bearing an immunological signature of T-cell hyporesponsiveness who responded to rituximab treatment, suggesting a possible role of B-T cell interactions in modulating podocyte injury. This study aimed to investigate the B-cell profiles in this subgroup of immune-mediated FSGS.

Methods: At baseline before rituximab treatment, FSGS patients were stratified into the hyporesponsive T-cell activation (HT) and non-HT groups. HT group is defined by activated IFN-γ+CD3+ expression <2.5% following PMA and ionomycin stimulation. Blood samples were washed thrice before staining of B-cell subsets using lysed whole blood method. B-cells were isolated using CD19 microbeads and stimulated with lipopolysaccharide (LPS) for 4 hours. Cytokine levels in culture supernatants were quantified using multiplex suspension bead array system.

Results: 19 FSGS patients receiving rituximab were recruited of which 11 patients were in the HT group. At baseline, the FSGS HT group showed significantly higher percentage of double negative (DN) memory B cells (CD19+CD27-IgD-) (7.8±1.1%) compared to FSGS non-HT patients (3.8±0.6%) (P=0.009), although this did not reach statistical significance compared to 14 controls (4.8±0.6%) (P=0.08) and 12 patients with minimal change disease (MCD) (5.8±0.9%) (P=0.2). Following stimulation, of the 27 cytokines analysed, B-cell production of IL-4, IL-9 and IL-10 levels were also significantly higher in FSGS HT group compared to non-HT group (Table 1). Among these cytokines, only IL-4 and IL-10 levels in FSGS HT group were significantly higher than MCD.

Conclusions: FSGS rituximab responders with HT phenotype demonstrated elevated DN memory B cells, IL-4 producing Be-2 cells and IL-10 producing regulatory B-cells, possibly explaining the T-cell hyporesponsiveness.

Funding: Government Support - Non-U.S.

Cytokines (pg/ml)	HT FSGS (n=13)	Non-HT FSGS (n=9)	Healthy controls (n=14)	MCD (n=6)
IL-4	4.9±0.6[a,b,d]	2.8±0.4	3.1±0.4[f]	1.7±0.3
IL-9	31.0±2.6[a,b]	22.5±3.3	22.6±2.1	25.5±5.1
IP-10	132.6±31.6[a,d]	60.7±12.9[b,e]	104.6±14.6[f]	13.2±10.6
IL-10	6.2±1.7[a,b,d]	2.2±0.3[e]	4.0±1.3[f]	0.5±0.4
MCP-1	51.5±33.9[a,b]	4.2±0.8	3.6±1.0	5.3±1.9

Mann-Whitney U test with P<0.05 comparison between: a) HT vs non-HT FSGS; b) HT vs healthy controls; c) non-HT FSGS vs healthy controls; d) HT FSGS vs MCD; e) non-HT FSGS vs MCD; and F) healthy controls vs MCD

SA-PO352

Complement Components Activation in Subjects with Primary FSGS Associates with Reduced Glomerular Expression of Decay Accelerating Factor (DAF)

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Background: Split products of complement system activation (Ba, Bb, C4a and C5b9) have been identified in plasma and urine of subjects with primary FSGS at the time of diagnosis. We hypothesized that complement system activation in FSGS results from a downregulation of DAF (CD55), a cell surface expressed complement regulator.

Methods: We measured urine C3a and C5a in 23 subjects with primary FSGS at the time of diagnosis and serially thereafter and in 10 healthy controls by ELISA. We stained for C3d and DAF in renal sections of 10 subjects with primary FSGS and of 10 healthy controls (healthy sections obtained from nephrectomies for neoplasm).

Results: At the time of diagnosis, patients with primary FSGS have detectable urinary C3a and C5a, whose values are positively correlated with proteinuria (**Figure 1A-B**). Urine of healthy subjects was undetectable for both C3a and C5a. After therapy, proteinuria decline was paralleled by a reduction in both C3a and C5a in the urine (**Figure 1C**). In patients with primary FSGS, glomerular C3 deposits were associated with reduced expression of CD55 (**Figure 1D**).

Conclusions: Reduced glomerular expression of DAF is associated with glomerular C3 deposits and higher levels of complement components in the urine, suggesting a possible effect of DAF in complement activation during FSGS, and, possibly, in mediating renal injury.

Funding: NIDDK Support

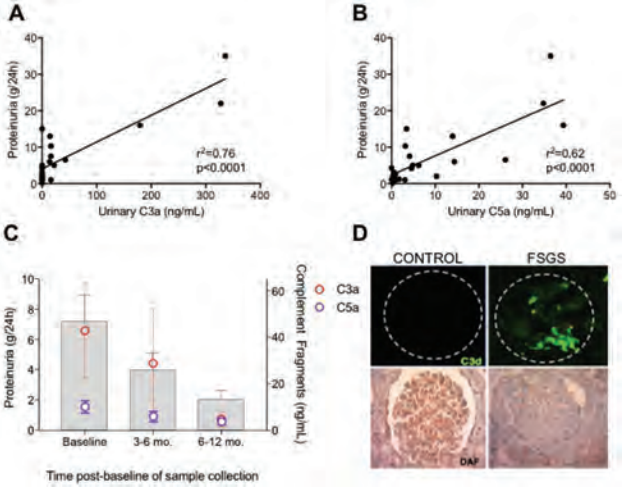

Figure 1. C3a (**A**) and C5a (**B**) in the urine from FSGS patients at the time of biopsy. Levels of proteinuria, urinary C3a, and C5a at the time of biopsy and serially thereafter (**C**). Representative C3d deposit (IF) and DAF expression (IHC) in the glomeruli from FSGS patients and control kidneys (**D**).

SA-PO353

Complement Activation Mediates Accelerated Tubular and Glomerular Inflammaging in Adriamycin (Adr)-Induced FSGS

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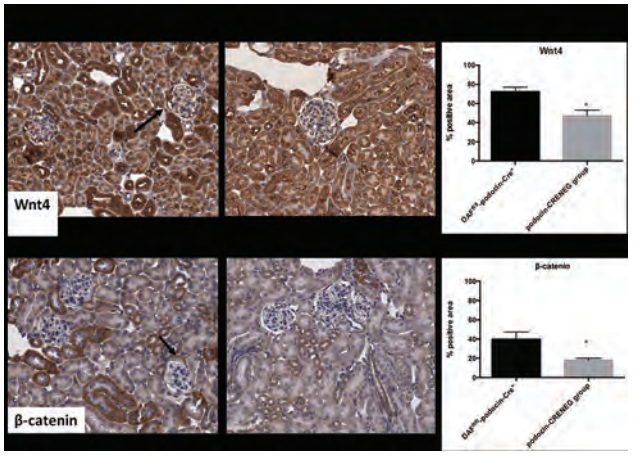
Background: Complement activation and chronic low-grade inflammation (inflammaging) have been implicated in renal disease progression. Whether complement activation on podocytes promotes inflammaging and mediates progression of FSGS is unknown.

Methods: We stimulated human primary podocytes with C5a (10-7M) and H_2O_2 (300μM; positive control) for 24h and then we measured *p21* gene expression by qPCR to assess senescence. Then, we injected newly developed DAF$^{fl/fl}$ podocin-Cre^{POS} and DAF$^{fl/fl}$ podocin-Cre^{NEG} controls (on a B6 background) with Adr (20mg/kg, i.v.). We serially measured urine albumin/creatinine (A/C) and at 6 weeks we quantified histological injury and stained sections for complement activation products and for senescence markers (WNT4, β-catenin, and p16^{INK4a}).

Results: C5a stimulation induced cellular senescence in podocytes as demonstrated by an increase in p21 marker *in vitro* ($p<0.05$). While podocin-CRE^{NEG} mice were resistant to Adr, $DAF^{fl/fl}$-podocin-Cre^{POS} had glomerular deposition of C3b and severe proteinuria (albumin/creatinine: 788.9±342.7 vs. 52.8±59.1mg/g; $P<0.05$). Immunohistochemistry analyses showed that $DAF^{fl/fl}$-podocin-Cre^{POS} had a significant increase in tubular WNT4, β-catenin and $p16^{INK4a}$ expression in the nuclei compared to podocin-CRE^{NEG} mice ($p<0.05$). Podocytes and epithelial cells of Bowman's capsule also showed significantly increased WNT4 and β-catenin expression in $DAF^{fl/fl}$-podocin-Cre^{POS} compared to podocin-CRE^{NEG} animals ($p<0.05$) (**Figure**).

Conclusions: We demonstrated that DAF deficiency and complement activation induce accelerated senescence in podocytes and tubular epithelium. These data provide a rationale for testing inhibition of cell senesce as a strategy to retard complement-mediated renal disease progression.



SA-PO354

A Composite Diagnostic Assay for FSGS

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Background: Proteolytic cleavage of the membrane bound urokinase-type plasminogen activator receptor (uPAR) leads to the release of its soluble form suPAR, which has been identified in body fluids. The full-length suPAR undergoes further cleavage and exists in two additional forms: $suPAR_{II-III}$ (fragment consists of domain 2 and 3) and $suPAR_I$ (fragment consists of domain 1). Elevated levels of plasma suPAR and suPAR mediated β3 integrin activation on podocytes have been associated with renal dysfunction and the onset of chronic kidney disease (CKD). However, an increase in suPAR level has also been reported in other disease conditions such as cancer. Therefore, only suPAR level may not be sufficient as a diagnostic parameter for CKD. Here, we sought to develop a composite scoring system, which considers multiple biomarkers, to generate an efficient diagnostic platform for focal segmental glomerulosclerosis (FSGS), a type of CKD.

Methods: Serum samples obtained from healthy individuals and patients with FSGS were analyzed. The levels of full-length suPAR, $\alpha_v\beta_3$ integrin activation and the presence of $suPAR_{II-III}$ fragment were determined. The data were statistically analyzed to develop a biomarker based predictive assay for FSGS.

Results: The majority of FSGS patients exhibited high levels of suPAR and $\alpha_v\beta_3$ integrin activation on human podocytes in culture. A subset of patients' serum was positive for the presence of $suPAR_{II-III}$ fragment.

Conclusions: The composite diagnostic assay suggests suPAR fragment driven $\alpha_v\beta_3$ integrin activation in FSGS.

Funding: NIDDK Support

SA-PO355

Complement Deposits Are Not Just Non-Specifically Entrapped in FSGS: C4d Can Precede the Development of Recurrent FSGS in Allograft Biopsies

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Background: Complement deposition in focal segmental glomerulosclerosis (FSGS) is often considered aspecific entrapment in sclerotic lesions. However, recent studies showed that complement activation may be involved in the development of FSGS. We previously found that C4d deposition precedes the development of segmental glomerulosclerosis in an animal model of FSGS, and that C4d is present in non-sclerotic glomeruli of patients with FSGS. Here, we investigated if complement activation can precede the development of recurrent FSGS after transplantation. To this end, we studied C4d deposition in transplantation biopsies prior to the development of recurrent FSGS lesions.

Methods: We stained allograft biopsies without FSGS lesions from 34 patients with native primary FSGS for C4d: 18 patients developed recurrent proteinuria or recurrent FSGS in follow-up biopsies and 16 patients did not. As controls, we included allograft biopsies from 34 patients with a native kidney disease other than FSGS. Patients with confounding factors for C4d deposition were excluded.

Results: In allograft biopsies of patients with recurrent proteinuria or recurrent FSGS, glomerular C4d preceded the recurrence of FSGS lesions in 72% of patients (n=18). This was significantly more prevalent than in transplantation controls (27%; p=0.001). In 16 patients who did not develop recurrent proteinuria or FSGS, the prevalence of glomerular C4d was similar compared to transplantation controls (50% and 27%, respectively; $p<0.10$).

Conclusions: Our data show that C4d deposition precedes the recurrence of segmental lesions in patients with native FSGS, specifically at the onset of proteinuria. As the FSGS lesions had not yet developed, our data refute the hypothesis of non-specific entrapment as sole etiology for observed complement deposition. As C4d is a stable biomarker of complement activation, our data provide further evidence for complement activation in the development of FSGS. We suggest that a subgroup of patients with FSGS may have increased susceptibility to complement-mediated injury. Complement-inhibiting therapies could be promising in these cases.

SA-PO356

Apolipoprotein L1 Dynamics in Human Parietal Epithelial Cell (PEC) Molecular Phenotype Kinetics

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Background: PECs do not express APOL1. We hypothesize that APOL1 expression emerges in PECs for podocytes' (PDs) renewal (PECs' transition) in adverse milieus. We further hypothesize that the absence of APOL1 favors the PEC phenotype and that the induction of APOL1 transitions to PD renewal.

Methods: Immortalized human PECs, which proliferate at 33°C and differentiate (transition) after 14 days after incubation in special media were characterized and used. PECs' expression of APOL1 was evaluated at different time intervals (0, 4, 8, 14 days) during their transition (Tr). Effects of a miR193a inhibitor/ overexpression of miR193a as well as APOL1-silencing/APOL1-overexpression was evaluated on PECs' expression APOL1 and miR193a. Effects of vitamin D receptor agonist (VDA), IFN-γ, and HIV were examined on the induction of APOL1 and associated expression of PD markers in HEKs and PECs. Luciferase assay was used to establish a putative interaction between miR193a and APOL1 in PECs. To confirm the PEC induction of APOL1 *in vivo*, renal biopsy specimens of HIVAN patients were co-labeled for APOL1 and synaptopodin.

Results: PECs at 33°C did not exhibit APOL1 expression. During PECs' transition, APOL1 expression coincided with the expression of PD markers (PEC transition) along with down-regulation of miR193a. The induction of APOL1 down-regulated miR193a and induced PD markers in PECs; whereas, the APOL1-silencing in Tr-PECs up- regulated miR193a expression suggesting a reciprocally linked feedback loop relationship between APOL1 and miR193a. HIV, IFN-γ, and VDA down-regulated miR193a expression as well as induced the expression of APOL1 and PD markers both in PECs. Since silencing of APOL1 attenuated HIV-, VDA-, and IFN-γ-induced expression of PD makers, it appears that APOL1 is an important functional constituent of miR193a-APOL1 axis. This notion was further confirmed by enhanced expression of PEC markers in APOL1 silenced Tr-PECs despite down-regulation of miR193a. Luciferase assay suggested a putative interaction between miR-193a and APOL1. Renal biopsy specimens from HIVAN patients revealed PECs' expression of APOL1 and synaptopodin.

Conclusions: APOL1 absence favors PECs' phenotype but its expression facilitates PECs transition

Funding: NIDDK Support

SA-PO357

Modulation of APOL1-miR193a Axis Protects Against Apoptosis in Adverse Milieus

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Background: Both Puromycin aminonucleoside (PAN) and adriamycin are known to promote podocyte (PD) apoptosis in both *in vitro* and *in vivo* studies. We have recently reported that APOL1 wild-type (G0) has a potential to preserve podocyte molecular

phenotype in high glucose milieu. APOL1 inversely regulates PD expression of miR193a and forms reciprocally linked feedback relationship. We now hypothesize that upregulation of APOL1-miR193a axis has a potential to prevent PD apoptosis in PAN and adriamycin milieus.

Methods: To aim differentiation, immortalized human podocytes (PDs) stably expressing vector (PDV) or APOL1G0 (wild- type, PDG0) were incubated in media for 10 days. Differentiated (D) PDVs and PDG0 were treated with different concentrations of Adriamycin (0,5, 15, 30, 50, and 100 nM) or PAN (0, 5, 10, 25, 50, and 100 nM) for 48 hours (n=4); in other sets, DPDVs were incubated in media containing Adriamycin (30 mM), PAN (50 nM), with/without miR193a inhibitor (25 nM) for 48 hours (n=4). Cells were evaluated for reactive oxygen species (ROS) generation (DCF detection assay), caspase-3 cleavage, and apoptosis (TUNEL assay). Proteins and RNAs were extracted from cells treated under similar conditions (n=4). Protein blots were probed for APOL1 and caspase-3; RNAs were assayed for miR193a. DPDs were transduced with either empty vector and miR193a plasmid and evaluated for APOL1 and caspase-3 expressions.

Results: PDVs displayed higher (P<0.01 vs. respective controls) generation of ROS and a greater (P<0.01 vs. respective controls) percentage of apoptosis when compared to PDG0, both in adriamycin and PAN milieus. PDG0 displayed enhanced (two-fold) expression of APOL1, but decreased (2.8-fold) miR193a levels when compared to PDVs. Both Adriamycin and PAN exhibited enhanced PD expression of miR193a and caspase-3. MicroRNA193a inhibitor decreased (3-fold) miR193a levels, increased APOL1 (1.8-fold) expression, and attenuated (P<0.5 vs. adriamycin and PAN) apoptosis in both adriamycin and PAN milieus. DPDs overexpressing miR193a displayed decreased expression of APOL1 and enhanced cleavage of caspase-3.

Conclusions: APOL1Go provides protection against apoptosis in adverse milieus through down-regulation of miR193a and attenuated generation of ROS.

Funding: NIDDK Support

SA-PO358

A Cross-Talk Between HIV-Injured Podocytes and Parietal Epithelial Cells (PECs) Results in Proliferation of PECs

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Background: HIV-associated nephropathy is characterized by an abundance of proliferating PECs in Bowman's space. The involved mechanism of PECs proliferation in HIV milieu is not clear. Interleukin (IL)-1 β has been reported to stimulate PECs proliferation. We have recently reported that HIV infection stimulates generation of IL-1β by PDs. We now hypothesize that a cross-talk between HIV-infected PDs and PECs would promote PECs proliferation.

Methods: Immortalized differentiated human PDs (DPDs) were transduced with either vector (DPDV) or HIV (NL4-3, DPDHIV) and assayed for pyroptosis (morphologic assay). Control DPDs and DPDHIV were incubated in serum-free media for 24 hours. Incubation (conditioned, C) media was collected and stored at -80°C. PECs were incubated in serum-free media containing 10% of control (DPDV) and experimental (DPDHIV) conditioned media for 48 hours. In another set of experiments, PECs were incubated in serum-free media containing 10% control and experimental media with or without IL-1β (neutralizing) antibodies for 48 hours. Cells were evaluated for proliferation by MTT cellular growth assay. To confirm the role of cross-talk, PECs were grown in outer wells and DPDV/DPDHIVs were seeded into inner wells (Trans-well plates). After 48 hours, cells in outer wells were assayed for proliferation. Cellular lysates/incubation media of DPDVs and DPDHIVs were assayed for IL-1β by ELISA. Additionally, PECs grown on coverslips were treated with 10% control and experimental media for 48 hours followed by immunolabeling for either PCNA or Ki67.

Results: DPDHIV displayed a higher percentage of cells with pyroptosis (P<0.01 vs respective controls). Cellular lysates and incubation media of DPDHIV showed increased (P<0.05 vs. DPDV) content of IL-1β. Conditioned media of DPDHIV promoted PECs proliferation; however, anti-IL-1β antibody partially inhibited DPDHIV-conditioned media-mediated proliferation. PECs growing in outer wells of trans-well plates containing DPDHIV also displayed enhanced proliferation. PECs treated with DPDHIV conditioned media exhibited a higher percentage (P<0.01 vs. DPDV) of PCNA/Ki67 +ve cells.

Conclusions: A cross-talk between PDs to PECs promotes PECs proliferation in HIV milieu.

Funding: NIDDK Support

SA-PO359

HIV-Induced Parietal Epithelial Cell Proliferation: Role of miR193a

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Background: miR193a has been reported to play an important role in the determination of glomerular epithelial cells' phenotype. miR193a is a tumor suppressor gene and its downregulation has been associated with enhanced cellular proliferation. HIV-associated nephropathy (HIVAN) is characterized by an accumulation of proliferating parietal epithelial cells (PECs) in the Bowman's space; however, the involved mechanism is not clear. Since HIV down-regulates the expression of miR193a, we asked whether HIV is stimulating PECs proliferation through down-regulation of miR193a.

Methods: Immortalized PECs were transduced with vector (PECV) or different concentrations of HIV (10^4, 10^3, 10^2, and 10^1 GEU/ml; PECHIV) followed by growth arrest (24 hours), followed by incubation in media containing 1% serum for 48 hours (n=4). Cell growth was assayed by cell count and MTT assay. To determine the role of miR193a, PECVs and PECHIV were transduced with empty vector (25 nM), miR193a (25 nM), an inhibitor of miR193a (25 nM) plasmids (n=4). After 48 hours, proteins and RNAs were extracted. Protein blots were probed for molecular markers of mTOR (p-mTOR, p-70S6K, p-4EBP, and p-eEF) and epithelial-mesenchymal transition (α-SMA, SNAIL, and fibronectin; EMT) pathways and reprobed for β-actin. RNAs were assayed for miR193a. *In vivo* studies, renal tissues of 4-week old control and HIV transgenic (Tg26) mice (n=6) were evaluated for the activation of mTOR and EMT pathways (Western blotting analysis and immuno-labeling of renal cortical sections). Renal tissues from control and Tg26 mice were also examined for miR193a expression (Fluorescent in situ hybridization, FISH).

Results: PECHIV stimulated PEC proliferation at lower concentrations (10^3 and 10^2 GEU/ml). PECHIVs-overexpressing miR193a exhibited a decrease in proliferation when compared to PECHIVs. PECHIVs and renal tissues from Tg26 mice showed the activation of the mTOR as well as EMT pathways. Renal cortical sections of Tg26 mice showed a decrease in miR193a expression when compared to control mice; additionally, renal cortical sections of Tg26 mice displayed enhanced proliferation of PECs as indicated by an increased number PCNA +ve cells in Bowman's space.

Conclusions: HIV induces PEC proliferation through down-regulation of miR193a.

Funding: NIDDK Support

SA-PO360

Disrupted APOL1-miRNA Axis Induces an Imbalance Between Autophagic Load and Handling in Podocytes Expressing APOL1 Risk Alleles

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Background: MicroRNA193a has been reported to enhance autophagy in several cell types. A recent report suggests that human podocytes (PDs) expressing APOL1 risk alleles (G1 and G2) have an altered autophagic reflux. We hypothesize that disruption of APOL1-miR193a axis would contribute to an imbalance between autophagic load and handling in PDs expressing APOL1 risk alleles.

Methods: Immortalized human podocytes (PDs) stably expressing vector, APOL1G0/G1/G2 were differentiated and evaluated for APOL1 (protein and mRNA) and miR193a expressions. To determine the effect of miR193a on autophagy, PDs were transfected with empty vector or different concentrations of miR193a plasmid (0, 50, 100 nM), or an inhibitor of miR193a (0, 25, 50, and 100 nM), followed by an evaluation for autophagy markers (P62, LC3II, and beclin 1). To determine the role of the mTOR pathway, PDs were transfected with either empty vector, miR193a, or a miR193a inhibitor (plasmids) followed by analysis for phos-mTOR and GAPDH by Western blotting. To examine the role of miR193a-APOL1 axis, PDs were transfected with either scrambled or APOL1 siRNA and then evaluated for miR193a expression and autophagy markers. To examine autophagic flux, PDs expressing vector (PDV), APOL1G0/G1/G2 were transfected with GFP-tagged LC3II plasmid and treated with Bafilomycin (100 nm) and examined at 0, 2, and 4 hours under a confocal microscope.

Results: APOL1G0 down-regulated but APOL1G1 and APOL1G2 upregulated miR193a expression in PDs. Overexpression of miR193a down-regulated but a miR193a inhibitor enhanced the expression of phos-mTOR. APOL1-silenced PDs showed enhanced expression of miR193a as well as of autophagy markers. PDs expressing APOL1G1 and G2 displayed a higher expression of LC3II in a time course manner in Bafilomycin blockade experiments, suggesting an increased load or sluggish autophagic flux. Since APOL1 risk alleles displayed 2.5- fold higher expression of miR193a when compared to PDs expressing

APOL1G0, it appears that they carried an enhanced autophagic load, in addition to sluggish autophagic flux.

Conclusions: Disrupted APOL1-miR193a axis induces an imbalance between autophagic load and handing in podocytes expressing APOL1 risk alleles.

Funding: NIDDK Support

SA-PO361

What's the RUSH? The Role of Calcium in APOL1 Toxicity

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Background: APOL1 is an innate immunity protein that forms toxic ion channels in trypanosomes. Variants of APOL1, G1 and G2 but not G0, are linked to kidney disease, however the mechanism responsible remains controversial. Here we propose that the key upstream event is APOL1 localization to the plasma membrane (PM), where it forms channels that lead to the passage of ions across the membrane, with Ca^{2+} influx being a driver of cell death.

Methods: APOL1 was expressed in FlpIn TREX 293 cells or HEK and CHO cells via the Retention Using Selective Hooks (RUSH) system. RUSH is a streptavidin-binding method that retains tagged APOL1 in the ER until biotin addition. Toxicity was measured via LDH release. rAPOL1 was purified from *E. coli* and reconstituted in planar lipid bilayers to measure channel selectivity. High throughput widefield microscopy was performed to quantify cytosolic and ER Ca^{2+} in cells expressing indicators GCaMP6f and ER-LAR-GECO, along with viability dye DRAQ7. IF with confocal microscopy was performed to quantify APOL1 localization.

Results: When retained in the ER, G1 and G2 are not toxic, and only release from the ER leads to cell death. The toxicity of G1 is delayed relative to G2, and G0 is not toxic. A previous study in *Xenopus* oocytes reported that APOL1 leads to Ca^{2+} influx. We tested rAPOL1 selectivity and found that all variants form channels that are permeable to Ca^{2+}. Furthermore, G1 and G2 toxicity is dependent on extracellular Ca^{2+}, as increasing [Ca^{2+}] led to more cell death, while chelation with EGTA rescued. Measurement of cytosolic Ca^{2+} revealed that G1 and G2, only after ER release, led to a significant Ca^{2+} influx over 2-4h that preceded cell swelling and death. IF indicated that APOL1 localizes to the PM prior to Ca^{2+} influx, and that G1 traffics slower than G2. Simultaneous measurement of cytosolic and ER Ca^{2+} demonstrated that there is no ER Ca^{2+} release.

Conclusions: These data demonstrate that the toxicity of G1 and G2 requires PM localization and an influx of Ca^{2+}. We also report a novel difference between the trafficking and toxicity kinetics of G1 and G2. The ion channel at the plasma membrane is likely the key event that leads to cell death, and the sustained influx of Ca^{2+} may unify the disparate theories of APOL1 toxicity, from mitochondrial damage to inflammatory pathways, which can all be triggered by Ca^{2+}.

Funding: Other NIH Support - BREAD: Basic Mechanisms Underlying Species-Specific Trypanosome Resistance #0965413, Private Foundation Support

SA-PO362

Characterization of Novel APOL1 G0, G1S342G and APOL1-/- Podocyte Cell Lines and Their Response to HIV Infection

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Background: Persons with APOL1 high risk genotypes are at increased risk of several forms of progressive CKD and remarkably, have a 29 to 89-fold increased risk of HIV-associated nephropathy (HIVAN). HIV gene expression in renal epithelial cells, including podocytes, is a critical mediator of HIVAN pathogenesis but previous studies have failed to detect an increase in APOL1 expression in HIVAN biopsy specimens, suggesting that changes in APOL1 function, and not expression levels, may drive pathogenesis. The APOL1 G1 risk allele consists of 2 nonsynonymous SNPs (S342G and I384M) and S342G is likely sufficient to drive the risk attributed to G1. Since overexpression models may not accurately model APOL1 function, we used CRISPR-Cas9 to generate isogenic human podocyte lines with APOL1 G0, $G1^{S342G}$, and $APOL1^{-/-}$ and determine the effects of APOL1 genotype upon response to HIV infection.

Methods: We used CRISPR-Cas9 to modify conditionally immortalized $APOL1^{G0/G0}$ podocytes. Guide RNAs and single stranded oligonucleotides were designed to target the APOL1 locus to generate the $G1^{S342G}$ allele or delete exons 4 and 5 ($APOL1^{-/-}$). In lentiviral transduction studies, podocytes were transduced with VSV-pseudotyped NL4-3DG/P-EGFP (HIV), or HR-IRES-EGFP (control). Endogenous APOL1 was immunprecipitated after HIV or control infection and APOL1-binding proteins were identified by mass spectrometry.

Results: Clonal homozygous $G1^{S342G}$ and $APOL1^{-/-}$ podocytes lines were generated. All podocyte lines expressed normal podocyte markers, including podocin. APOL1 expression was lower in $G1^{S342G}$ than G0 podocytes and APOL1 expression increased as podocytes were differentiated at 37C. Proteasome inhibition increased APOL1 protein abundance, suggesting that it is degraded by the ubiquitin-proteasome system. HIV infection did not increase APOL1 expression in any podocyte cell lines. Immunoprecipitation of endogenous APOL1 after HIV or control infection and identification of APOL1 binding proteins by mass spectrometry identified numerous cellular proteins that differentially bind $G1^{S342G}$ in the presence of HIV infection with known roles in kidney injury.

Conclusions: We developed novel podocyte cell lines with alterations in the APOL1 coding sequence that will allow for studies to determine changes in function of the APOL1 alleles when expressed at physiologic levels.

Funding: NIDDK Support

SA-PO363

APOL1 RNA Is Differentially Spliced in Nephrotic Syndrome and in Response to Therapy

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Background: *APOL1* has been a subject of intense research since the discovery of the association of its risk alleles with heightened risk for end stage kidney disease in African Americans. However, the potential role of alternate splicing of *APOL1* in podocyte biology and in the regulation of kidney disease is unknown. Recent evidence suggests that the presence and/or absence of exons 2 and 4 distinguish known splice variants of *APOL1*, and that exon 4 contributes to cytotoxicity. We hypothesized that *APOL1 RNA is differentially spliced in nephrotic syndrome (NS) and in response to glucocorticoid (GC) therapy, thus playing a potential pathophysiological role in both disease and health, regardless of APOL1 haplotype.*

Methods: *APOL1* RNA and splice variant expression was analyzed in podocytes injured with puromycin aminonucleoside (PAN), and treated with dexamethasone (Dex) by RT-PCR using splice variant specific primers. Splice variant analyses were also performed in circulating leukocytes of children with steroid sensitive (SSNS) and steroid resistant NS (SRNS), before and following initial GC therapy (N =8 SSNS and 8 SRNS paired samples). T-test and 2 way ANOVA statistical analyses were performed to measure relative variant expression.

Results: Podocytes expressed all 5 known splice variants of *APOL1* [v.A, variant3 v.A, v.B1,v.B3 and v.C]. Higher relative expressions of exon 4 (+) [v.A, v.B1] and exon 2 (-) [v.A, v.C] forms were observed, with variant 1 [v.A] the most predominantly expressed form. Dex increased the relative expression of splice variants exon 4 (+) and exon2 (-), which in contrast was decreased with PAN-induced injury. Although RNASeq data analysis was unable to detect these variants, in-depth RT-PCR analyses revealed that both exon 4 (+) and (-) variants were expressed in the circulating leukocytes of SSNS and SRNS patients, while exon 2 (+) forms were only minimally expressed. SRNS patients had increased levels of almost all *APOL1* variants [except exon 2 (+)] compared to SSNS patient prior to GC treatment. GC treatment induced expression of most of the recognized splice variants increased in SSNS, but decreased them to varying degrees in SRNS.

Conclusions: Cultured podocytes and circulating human leukocytes express distinct *APOL1* splice variant patterns and differential splicing of *APOL1* is associated with NS and in response to GC therapy.

SA-PO364

CD80 and CD163 as Biomarkers of Nephrotic Syndrome

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Background: Cellular expression of CD80 and CD163 may play a role in the pathogenesis of certain glomerulopathies. Urinary or blood concentrations may predict and/or track response to specific immunosuppressive therapies and long term renal function.

Methods: Urine was obtained from Mayo Clinic patients (286) and NEPTUNE cohort participants (104) with biopsy-proven minimal change disease (MCD, 103), focal segmental glomerulosclerosis (FSGS, 97), lupus nephritis (LN, 31), IgA nephropathy (IgAN, 28), and membranous nephropathy (MN, 54), as well as non glomerular disease patients with autosomal dominant polycystic kidney disease (ADPKD, 9), pyuria (19), and controls (34). Data expressed as (mean, median (IQR)) was analyzed by Kruskal-Wallis test, generalized estimating equation models (GEE) or receiver operating characteristic (AUC) curve analysis.

Results: CD80/Creatinine and CD163/Creatinine were higher in relapse vs remission in paired urine samples of MCD and FSGS cases (GEE: Active vs. remission $p<0.0001$); MCD vs. FSGS $p<0.0001$). Urinary CD80/Creatinine ratios were higher in active MCD, LN, DN and CD163/Creatinine was higher in active LN compared to active cases of other glomerular diseases or controls (**Table 1**). Differences remained significant after adjusting for proteinuria ($p \leq 0.01$; GEE).

Conclusions: Urinary CD80 and CD163 excretions varied between disease groups and by disease activity. These results suggest a pathogenic role for these molecules in certain glomerular diseases, including diabetic nephropathy.

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Urinary CD80/creat and CD163/Creat discriminate by proteinuric kidney disease type.

	# samples	CD80 (ng/g Creat) Median (IQR)	p vs. Control	p vs. MCD	CD163 (µg/g Creat Median (IGR)	p vs. Control
Control	32	46 (21, 76)	REF	<.01	0.3 (0.2, 0.9)	REF
MCD	47	139 (79, 221)	<.01	REF	5.3 (2.2, 18.3)	<.01
FSGS	58	82 (40, 114)	0.03	<.01	5.6 (3.1, 8.6)	<.01
IgAN	9	19 (7, 52)	0.09	<.01	3.9 (2.9, 6.7)	<.01
Lupus	10	165 (76, 395)	0.02	0.86	51.1 (13.4, 156.1)	<.01
MN	27	64 (28, 96)	0.18	<.01	7.3 (4.7, 11.4)	<.01
DN	8	160 (124, 300)	0.05	0.51	14.1 (13.2, 30.3)	<.01
Pyuria	19	31 (14, 44)	0.20	<.01	0.4 (0.2, 0.8)	0.89
ADPKD	9	45 (34, 61)	0.07	0.02	0.8 (0.3, 2.4)	0.02

GEE analysis of Log-CD80/Creat and CD163/Creat across controls, pyuria, ADPKD and samples with proteinuria ≥2 for DN, FSGS, IgAN, Lupus, MCD, and MN.

SA-PO365

Identifying the Role of Soluble Circulating Permeability Factors in Proteinuria in a Zebrafish Parabiosis Model

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Background: Proteinuria may be induced by an impairment in any component of the glomerular filtration barrier. To determine the role of circulating permeability factors to cause proteinuria through glomerular damage as a result from reduced specific podocyte protein expression, we developed a parabiosis-based zebrafish model to generate a common circulation between two zebrafish larvae.

Methods: Zebrafish eggs were dechorionated at the 128-cell blastula stage and moved to the desired orientation for fusion that was achieved by a micro cell transfer from one embryo to the other with a glass micropipette. We injected npnt-morpholino (MO) into the yolk of a 1-4 cell embryo of *Tg(flk1-mCherry)* zebrafish and performed the fusion at a 256-cell stage with control *Tg(l-fabp:eGFP-DBP)* zebrafish embryos. By using a FITC-labelled MO, we ruled out a MO-transfer between both parabionts. Common circulation and loss of plasma proteins were investigated and the glomeruli of both zebrafish pairs were analyzed using electron microscopy.

Results: We fused blastulae from *Tg(l-fabp:eGFP-DBP)* zebrafish that express a green fluorescent vitamin D binding protein in their blood plasma with blastulae of *Tg(flk1-mCherry)* zebrafish that express a red fluorescent endothelium. Confocal imaging of parabiotic zebrafish with these backgrounds showed a detectable green fluorescent plasma protein from the *Tg(l-fabp:eGFP-DBP)* zebrafish in the red fluorescent blood vessels of the *Tg(flk1-mCherry)* parabiotic partner at 72 hpf, indicative of a common circulation system. Fluorescence analysis of the parabiotic zebrafish larvae after npnt knockdown revealed a reduction of the eGFP-labelled protein from the common circulatory system suggestive of proteinuria. Knockdown of npnt in the injected parabiont showed podocyte effacement and altered glomerular basement membrane. Remarkably, also the control parabiotic partner developed podocyte effacement and glomerular endothelial swelling as well but had a regular glomerular basement membrane. We could not only detect proteinuria and glomerular damage caused by the knockdown of the podocyte gene npnt in injected fish, but also in the fused partner.

Conclusions: These data suggest that circulating permeability factors may be induced by proteinuria even when an induced dysregulation of a podocyte gene is the initiating cause.

SA-PO366

Podocyte-Specific Crb2 Knockout Mice Cause Proteinuria

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Background: Crumbs 2, Crb2 is known to be expressed in the podocytes. Knockdown of crb2 caused cardiac edema in zebrafish and full knockout of Crb2 resulted in embryonic lethality. Moreover, there have been reports of steroid-resistant nephrotic syndrome by CRB2 mutations. However, its precise mechanism is still elusive.

Methods: We generated conditional Crb2 floxed mice that possessed loxP sites flanking exon 7 and 8. Podocyte-specific Crb2 knockout mice were generated by breeding Crb2 conditional knockout mice with NPHS2-Cre mice. Urine, blood, and renal histology were examined in NPHS2-Cre or Crb2 flox/flox or NPHS2-Cre & Crb2 flox/flox mice.

Results: NPHS2-Cre & Crb2 flox/flox mice showed massive proteinuria at two or six months of age compared to NPHS2-Cre mice or Crb2 flox/flox mice. Blood urea nitrogen or serum creatinine at two months of age was comparable among the three groups. Although renal histology at two months of age was also comparable among the three groups, glomerular sclerotic indices of NPHS2-Cre & Crb2 flox/flox mice at six months of age were significantly higher than those of NPHS2-Cre mice or Crb2 flox/flox mice.

Conclusions: Knockout of Crb2 in the podocytes might play an important role in developing proteinuria.

SA-PO367

Podocyte-Expressed STAT5 Confers Protection During Experimental Glomerulonephritis and Adriamycin Nephropathy in Mice

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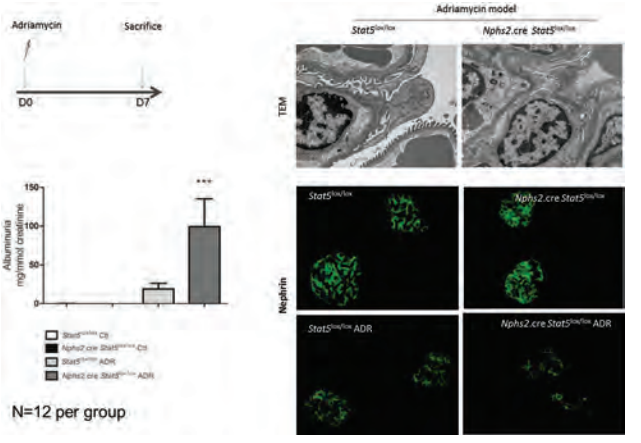
Background: Glomerular diseases are a leading cause of chronic kidney failure and the podocyte is one of the main target of these diseases. We previously evidenced a protective role for a podocyte-expressed immune receptor such as the common gamma chain (γC) during glomerulonephritis. We also found that STAT5, a transcriptional factor classically described and activated downstream γC in T cells is upregulated in podocytes during glomerulonephritis. Hitherto, STAT5 role in podocyte remains to be determined.

Methods: Using mice with a podocyte-specific deletion of *Stat5*, we analyzed the role of STAT5 in two experimental models of glomerular diseases.

Results: First, during crescentic glomerulonephritis, podocytic-STAT5 deficient mice developed increased proteinuria compared to their wild-type littermates. Second, during adriamycin induced-nephropathy, the absence of podocyte STAT5 led to increased albuminuria and severe podocytic injuries in comparison to controls (**Figure 1**). Moreover podocytic lesions were associated with loss of podocyte differentiation markers such as WT1 especially in podocytic-STAT5 deficient animals. Renal T-cells and macrophages infiltration were not affected by the deletion of podocytic Stat5.

Conclusions: Taken together, our results suggest an yet unsuspected protective role of podocytic γC /STAT5 signaling during glomerular diseases.



SA-PO368

Expression of Chemokine Receptor 2 (CCR2) on Renal Podocyte Progenitor Stem Cells

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Background: Several lines of evidence support a role for chemokine receptor 2 (CCR2) through interaction with its ligand CCL2 in the pathogenesis of kidney diseases. We have shown recently that inhibition of CCR2 by small molecule inhibitors markedly reduce proteinuria, improve renal function and preserve or restore podocyte density in murine models of Focal Segmental Glomerulosclerosis (FSGS). To understand the mechanism of this protection, we have examined the expression of CCR2 on human and murine kidneys.

Methods: CCR2 expression on the kidneys was assessed by immunohitochemistry (IHC) on formalin fixed, paraffin-embedded human and mouse kidney sections, and by flow cytometry with freshly isolated murine renal cells.

Results: IHC with a human CCR2 antibody revealed CCR2 expression on glomerular cells in human CCR2 knock-in, but not CCR2 knockout mouse kidneys. Flow cytometry of freshly isolated murine kidney cells confirmed CCR2 expression on CD45 negative-cells, indicating that the positive IHC signal was not due to mature blood cells. CD133 and CD24 are cell surface markers of a heterogeneous population of renal progenitor cells, and approximately 5% of these cells also express the podocyte marker podocalyxin (PDX), marking them as podocyte precursors. By flow cytometry we found that ~8% of the murine renal CD133+CD24+ PDX+ cells, were also positive for CCR2, indicating that CCR2 was present on a subset of cells destined to become mature podocytes. Finally we used IHC to examine CCR2 expression on human renal biopsies of FSGS patients and non FSGS patients and found out that increased staining for CCR2 in the FSGS kidneys in the glomerulus and Bowman's capsule areas. These data provide clear evidence that CCR2, the target of the small molecule that we have shown reduces proteinuria and improves renal function in murine models of FSGS is present on non-hematopoietic cells in the kidney.

Conclusions: This is the first demonstration of the presence of CCR2 on renal progenitor cells that are destined to become podocytes, and reveals a potential new role for this chemokine receptor whose function as been heretofore mainly connected to monocyte/macrophage biology. Taken together, these data provide the foundation for a mechanistic understanding of the therapeutic benefit of CCR2 antagonists in FSGS, and possibly other renal diseases.

Funding: Clinical Revenue Support

SA-PO369

Anti-Proteinuria Effect of Antibody Against ANGPTL3 Coiled-Coil Domain on Adriamycin-Induced Nephropathy in Mice

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Background: We firstly found that Angiopoietin-like-3 (Angptl3) expression is increased in glomerular podocytes of nephrotic syndrome. Our previous research showed Angptl3 plays an important role in podocyte injury and proteinuria. This study aims to confirm whether proteinuria in Adriamycin-induced nephropathy mice can be alleviated though neutralizing Angptl3 by antibody.

Methods: The polyantibody against Angptl3-CCD was prepared (namely Anti-angptl3-antibody). Nephropathy was established by Adriamycin injection in 8-12 wk-old female mice. The blockade of Angptl3 by Anti-angptl3-antibody (20mg/kg) was performed every three days for nine times after Adriamycin injection. All mice were sacrificed on day 28. Proteinuria was measured weekly. Albumin, TG and T-CHO in serum were measured on day 28, Histological changes were observed by light microscopy and transmission electron microscope. The distribution of antibody was confirmed by IF analysis.

Results: The Anti-angptl3-antibody can recognize angptl3 specifically. On the 14th day after modeling, proteinuria in the ADR group was significantly increased, but not in ADR plus Anti-angptl3-antibody group until 28th day. The proteinuria of the ADR plus Anti-angptl3-antibody group was significantly lower than that of the ADR group both on the 21th day and 28th(4.46±0.88 vs 11.36±1.00,P=0.010, 21th day; 6.11±1.33 vs 18.97±4.33,P=0.008, 28th day). Compared to the ADR group, serum ALB was higher (p=0.05, n=5), serum CHO (p<0.01, n=5) and TG (p=0.026, n=5) were lower in the ADR plus Anti-angptl3-antibody group. The levels of serum creatinine did not show significantly difference in each group. Focal sclerotic glomeruli were found in the renal tissue of the ADR group, but not found in the ADR plus Anti-angptl3-antibody group. Podocyte injury in the ADR plus Anti-angptl3-antibody group was markedly relieved compared with the ADR group, in which Podocyte foot processes were widely fused. The Anti-angptl3-antibody was detected in the liver and kidney where Angptl3 is expressed in higher amount.

Conclusions: This study demonstrated that Anti-angptl3-antibody can delayed the appearance of proteinuria and decreased the level of proteinuria in Adriamycin-induced nephropathy in mice.

SA-PO370

A Novel Mouse Model Embodying Minimal-Change Nephrotic Syndrome Through Crumbs 2-Mediated Signaling to the Cytoskeleton in Podocytes

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Background: The cellular events in podocyte injury causing minimal-change nephrotic syndrome (MCNS) remain largely obscure. Recent reports implicated genetic mutation of crumbs homolog 2 (CRB2), a type-1 transmembrane protein, as a cause of congenital nephrotic syndrome. However, an involvement of CRB2 dysfunction in the selective permeability barrier of mature glomerulus has not been demonstrated. The aim of the present study is to determine whether MCNS is caused by alteration of CRB2-mediated signaling in podocytes.

Methods: A partial recombinant protein including the extracellular part of mouse CRB2 was produced in an *Escherichia coli* system. An Enzyme-Linked Immunosorbent Assay was established to measure anti-CRB2 antibody in the serum. C3H/HeNmice and A/Jmice (complement C5 deficient mice) were injected with CRB2 recombinant protein. Urinary protein was analyzed, and kidney tissue was subjected to immunofluorescence microscopy, light microscopy, electron microscopy and immuno-electron microscopy of actin. Isolated glomeruli were subjected to Western blot analysis of phosphorylated moesin.

Results: Both C3H/HeNmice and A/J mice developed massive proteinuria at 4-6 weeks after immunization with CRB recombinant protein, which was associated with elevation of anti-CRB2 antibody. Light microscopy revealed minimal glomerular lesions even at a heavily proteinuric stage. Electron microscopy revealed prominent foot process effacement where broad dense areas were seen. Immuno-electron microscopy showed that these areas were positively immunostained for actin. Immunofluorescence microscopy revealed positive IgG staining in podocyte foot processes, but not complement C3. Finally, Western blot analysis showed phosphorylation of moesin in glomerular samples at the proteinuric stage.

Conclusions: The present study reveals a novel pathway involved in the pathophysiology of MCNS through an interaction between CRB2-mediated signaling and the actin cytoskeleton network. CRB2 may be an important scaffold molecule that mediates outside-in signaling in podocytes, thereby leading to actin cytoskeleton reorganization and resulting in MCNS.

SA-PO371

Knockout of the Neonatal Fc Receptor (FcRn) Abrogates IL6 Mediated Signaling in Podocytes

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Background: FcRn has been shown to be required for antigen presentation in dendritic cells and global knockout of FcRn attenuates immune mediated kidney disease. FcRn is expressed in podocytes but the role of podocyte FcRn in immune mediated renal disease is unknown. Previous work has shown that podocytes express the IL6 receptor and produce IL6 under proinflammatory conditions. Here we examine the role of FcRn in the IL6-mediated inflammatory response in podocytes.

Methods: We examined IL6 production by ELISA and expression by qPCR in WT and FcRn knockout (KO) podocytes after treatment with proinflammatory stimuli including albumin, IgG, interferon gamma (IFNγ) and immune complexes. We performed western blot analysis of the IL6-mediated Jak/STAT signaling pathway after treatment of WT and FcRn KO podocytes with IFNγ and immune complexes. We also examined podocyte motility in WT and FcRn KO podocytes in vitro after a proinflammatory challenge. In vivo, we examined synaptopodin expression in WT and podocyte-specific FcRn KO mice as inhibition of IL6 has been shown to decrease synaptopodin expression.

Results: We found that FcRn KO podocytes produced minimal amounts of IL6 after treatment with albumin, IgG or immune complexes whereas WT podocytes had a robust response. FcRn KO podocytes also had minimal expression of IL6 as measured by qPCR compared to WT after an immune challenge. By western blot analysis, FcRn KO podocytes expressed significantly less phosphorylated STAT3, a key component in the IL6 signaling pathway, than WT after treatment with IFNγ or immune complexes. In a scratch assay to assess mobility, FcRn KO podocytes showed increased mobility compared to WT, suggesting defects in actin dynamics. Expression of synaptopodin in the glomerulus was also significantly reduced in podocyte-specific FcRn KO mice compared to controls at 6 and 12 months of age, suggesting FcRn mediated defects in synaptopodin regulation.

Conclusions: This study shows that in podocytes, FcRn modulates the IL6-mediated response to proinflammatory stimuli and regulates podocyte motility and synaptopodin expression.

Funding: NIDDK Support

SA-PO372

Impact of Toxic Loss of Function of Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) on Podocyte Integrity

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Background: The deubiquitinating enzyme ubiquitin C-terminal hydrolase L1 (UCH-L1) is highly *de novo* expressed in affected podocytes in human membranous nephropathy (MN), its role in podocyte injury remains elusive. We could previously demonstrate that UCH-L1 induces podocyte hypertrophy in MN. Furthermore, chemical inhibition of UCH-L1 hydrolysis function was shown to ameliorate experimental MN, suggesting a disease-perpetuating effect of UCH-L1 activity in podocytes. It is known that oxidative modification of UCH-L1 in the brain secondary to oxidative stress could lead to a dysfunctional mutant protein, which could affect neuronal proteostasis by aberrant protein interactions. We therefore investigated the differential contribution of intact and oxidative modified UCH-L1 for the development of podocyte injury in MN. Furthermore, we searched for the existence and binding affinity of reported UCH-L1 autoantibodies to intact and modified UCH-L1 in sera of patients with MN.

Methods: To assess the effects of altered enzymatic and biochemical properties of UCH-L1, mice with a podocyte-specific overexpression of UCH-L1 wildtype or with an enzymatic-deficient UCH-L1 I93M protein were generated and investigated by Western blot, enzyme activity assays and immunohistochemistry. Sera from patients with MN were investigated for the occurrence of UCH-L1 autoantibodies by Western blot. For this purpose flag-tagged human wildtype UCH-L1 or human mutant I93M protein were cloned and transiently overexpressed in HEK-293T cells.

Results: UCH-L1 I93M induced a significant accumulation of polyubiquitinated proteins in isolated glomeruli of transgenic mice resulting from proteasomal impairment. Expression of intact UCH-L1 on the other hand eventuated in increased proteasomal capacity accompanied by a dedifferentiated podocyte phenotype and mild proteinuria. A subset of sera (30 %) from MN patients contained anti-UCH-L1 autoantibodies. The quantification of UCH-L1 autoantibody reactivity showed a higher binding capacity to the defect I93M UCH-L1 protein than to the wildtype UCH-L1 protein.

Conclusions: Expression of UCH-L1 I93M results in a protein accumulative phenotype in podocytes similar to the one observed in human MN. Anti-UCH-L1 antibodies with an enhanced binding capacity to the defect I93M UCH-L1 protein are present in a subset of MN patients.

SA-PO373

Malignant Hypertension Induced Vicious Circle Culminating in Podocyte Detachment

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Background: . Renal injuries induced by increased intra-glomerular pressure coincide with podocyte damage and proteinuria. In a previous study we have demonstrated that in a direct response to pressure, podocytes increase Angiotensin-II levels and via AT1 receptors to structural changes in adhesion proteins, culminating in viable podocyte detachment. The aim of this study was to further investigate the pathophysiologic effect of malignant hypertension on podocyte mitochondrial functions, NOX4, SOD2 and inflammatory mediators.

Methods: Human Podocyte cells were exposed to high hydrostatic pressure for 1h, to mimic the incidence of malignant hypertension. Podocytes were placed in mesangial cell media pre-exposed to pressure to simulate the paracrine effect. Mitochondrial function, NOX4, SOD2, Angiotensin-II, inflammatory mediators, integrinβ1 expression and Podocyte detachment were evaluated.

Results: Pressure enforcement decreased mitochondrial membrane potential accompanied by a reduction of SOD2. Moreover, augmented detachment of viable/apoptotic podocytes with decrease expression of integrins β1, mediated via AT1/AT2, was induced by the high pressure. Mesangial pre-exposed to pressure release exaggerated amounts of Angiotensin-II and TGFβ1. Podocytes placed in this mesangial media induced an inflammatory flare-up increase via TGFβ1 and Il-6. In addition, an increase of NOX4

and decline of SOD2 resulted in mitochondrial membrane potential decrease mediated via AT1/AT2 leading to apoptosis.

Conclusions: Malignant hypertension, induced mitochondrial dysfunction combined with structural changes and detachment of Podocyte mediated by increase Angiotensin-II. The paracrine effect, mediated by increasing production of Angiotensin-II by the mesangial cells, increase apoptosis and enhance mitochondrial dysfunction via decrease SOD2, activation of NOX4 and flare-up of inflammatory mediators.

SA-PO374

Sorting Nexin 9 Facilitates Podocin Endocytosis in the Injured Podocyte

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Background: The irreversibility of glomerulosclerotic changes depends on the degree of podocyte injury. We have previously demonstrated the endocytic translocation of podocin to the subcellular area in severely injured podocytes and found that this process is the primary disease trigger. We identified the protein sorting nexin 9 (SNX9) as a novel facilitator of podocin endocytosis in a yeast two-hybrid analysis. SNX9 is involved in clathrin-mediated endocytosis, actin rearrangement and vesicle transport regulation.

Methods: We conducted co-immunoprecipitation assays to confirm the interaction between podocin and SNX9 using lysates of FLAG-podocinand GFP-SNX9-overexpressing cells. To map the podocin binding site(s) in SNX9, we tested the abilities of various truncated GFP-SNX9 constructs to co-precipitate with FLAG-podocin. To further demonstrate that podocin can directly bind to SNX9, we performed GST pull-down assays with purified recombinant proteins. To detect SNX9 expression in kidney samples, we subjected normal and adriamycin (ADR)-injected mice to immunofluorescence staining. To evaluate SNX9 expression *in vitro*, we performed immunofluorescence staining on non-treated and ADR-treated cultured human podocytes. To assess SNX9 expression in human kidney glomeruli, we subjected human kidney biopsy specimens to immunofluorescence staining.

Results: Our results revealed and confirmed that SNX9 interacts with podocin exclusively through the Bin–Amphiphysin–Rvs (BAR) domain of SNX9. Immunofluorescence staining revealed the expression of SNX9 in response to podocyte adriamycin-induced injury both *in vitro* and *in vivo*. Finally, an analysis of human glomerular disease biopsy samples demonstrated strong SNX9 expression and co-localization with podocin in samples representative of severe podocyte injury, such as IgA nephropathy with poor prognosis, membranous nephropathy and focal segmental glomerulosclerosis.

Conclusions: We identified SNX9 as a facilitator of podocin endocytosis in severe podocyte injury and demonstrated the expression of SNX9 in the podocytes of both nephropathy model mice and human patients with irreversible glomerular disease.

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SA-PO375

Novel Role for Albumin and Its Modifications in Podocyte and Glomerular Injury

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Background: Albuminuria is both a characteristic hallmark and a known risk factor for progressive glomerular disease. We previously identified that both albumin deficiency and albumin overload resulted in enhanced glomerular injury. We thus hypothesized that glomerular and podocyte injury can be regulated by modifications of albumin levels, binding to free fatty acid (FFA) and associated factors, and molecular charge.

Methods: *In vitro* podocyte injury was studied following exposure to native albumin (anionic), delipidated albumin, FFA, and cationic albumin. The ability of plasmapheresis effluents (PE) from nephrotic patients to induce podocyte injury *in vivo* and *in vitro* was also analyzed. Additional analyses included testing the ability of various clinically applicable matrices to ameliorate albumin- and PE-induced podocyte injury.

Results: While exposure of podocytes to albumin or FFA (lauric acid, oleic acid and arachidonic acid) alone reduced podocyte viability, supplementation of FFA with delipidated albumin restored podocyte viability. Albumin exposure also activated the kinases p38 MAPK, JNK/SAPK and AKT. While arachidonic acid and delipidated albumin alone did not activate these kinases, activation was moderately increased when podocytes were exposed to their combination. Additionally, cationic albumin induced greater podocyte toxicity vs. albumin, even at 1000x lower concentration. Translational studies in nephrotic PE revealed diverse signs of direct podocyte injury, including reduced viability, actin cytoskeletal disruption, lipid accumulation, activation of Erk1/2 and JNK/SAPK, and induction of COX-2. Importantly, some of these responses were attenuated by pretreatment of PE with selected matrices (charcoal, blue sepharose, liposorber gel and dextran sulfate). Finally, compared to the albumin alone-treated rats, we found significantly greater albuminuria at 48 hr in rats also injected with nephrotic PE.

Conclusions: Albumin modifications, including altered levels, binding to FFA and associated factors, and altered ionic charge can regulate albumin-induced podocyte and glomerular injury. Moreover, treatment with clinically applicable matrices appears to be able reduce this injury, thus representing a potential novel mechanistic approach to reduce glomerular injury and disease progression.

SA-PO376

Predicting and Defining Steroid Resistance in Pediatric Nephrotic Syndrome by Cytokine Profiling

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Background: Steroids (glucocorticoids, GC) are the cornerstone of therapy for nephrotic syndrome (NS). However, they only induce remission of NS in ~50% of adults and ~80% of children. Unfortunately, there are no validated biomarkers able to predict steroid response in NS. Several clinical and experimental observations suggest that reversible immune dysregulation is a key feature of idiopathic NS. This study aims to identify early prognostic immunological biomarkers and molecular pathways associated with steroid resistance in NS pediatric patients.

Methods: Paired plasma samples were collected from 26 steroid-sensitive NS (SSNS) and 13 steroid-resistant NS (SRNS) patients, obtained both at initial disease presentation and after ~7 weeks of GC therapy, when SSNS *vs* SRNS was clinically determined. The cytokine profiling was performed using a 27 cytokine panel on a Luminex® Technology platform using a bead-based fluorescence assay. Data were compared using the nonparametric Wilcoxon signed-rank test and the Mann Whitney U test (statistically significant differences at $p<0.05$).

Results: In comparison to SSNS, SRNS patients at presentation showed higher plasma levels of IL-1β, IL-6, IL-8, TNF-α, IFN-γ, IL-7, and MIP-1α, and reduced levels of IL-1Ra, IL-2, IL-9, MIP-1β. GC treatment of SSNS patients induced significant reductions in all of the elevated cytokine levels above (IL-6 undetectable at presentation in most SSNS patients). Of note, circulating cytokine levels appear not be influenced by differences in proteinuria, as we found reduced levels in SSNS patients in remission. In contrast, GC therapy in SRNS patients failed to induce remission or to significantly reduce the above plasma cytokine levels (except for TNF-α).

Conclusions: These studies suggest that an increase in a panel of plasma pro-inflammatory cytokines, produced primarily by monocytes/macrophages and Th1 cells, may be able to predict steroid resistance in NS prior to GC treatment. In addition, steroid-resistance is also associated with persistence elevated levels of pro-inflammatory cytokines, suggesting a potential pathogenic role for these circulating factors in SRNS.

SA-PO377

The Proteasomal Degradation System Plays a Prominent Role in Podocyte Protein Homeostasis

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Background: Protein degradation plays a major role in protein quality control and therefore in cell homeostasis. Two different degradation systems are responsible for clearance of disused or defective proteins, the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system (ALS). During membranous nephropathy the UPS is upregulated. The aim of the project is to understand the significance and interplay of the proteasomal and lysosomal degradation system for podocyte proteostasis under naïve conditions and during THSD7A-associated membranous nephropathy.

Methods: For proteasomal inhibition, Balb/C mice were treated with epoxomicin over 4 days. As models of lysosomal impairment Balb/C mice were treated with the lysosomal inhibitor leupeptin A over 4 days or mice with general lysosomal dysfunction (Mucolipidosis (ML) type II) were analyzed. To investigate the effect of the degradation systems on disease progression, THSD7A-associated MN was induced and mice were treated in a preventive and a therapeutic regimen with proteasomal inhibitors and leupeptin A. Renal function was assessed by BUN and creatinine measurements, podocyte injury by proteinuria. The glomerular and tubulointerstitial integrity was assessed by PAS, confocal and electron microscopy. The effects of proteasomal or lysosomal inhibition on glomerular cell proteostasis were analyzed by Western blotting and enzyme activity assays.

Results: Mice treated with epoxomicin developed proteinuria with abnormal glomerular protein accumulations in the subepithelial space and in podocytes. Leupeptin A treatment did not affect proteasomal activity in glomeruli and the tubulointerstitium. Morphological analyses were significant for abnormal accumulations in tubular cells and the glomerular mesangium. MLII mice showed severe lysosomal dysfunction in glomeruli and tubulointerstitial cells without the development of proteinuria. Morphologically, MLII mice exhibited accumulations of large lysosomes in all resident glomerular cells. Therapeutic and preventive inhibition of both degradation systems during THSD7A-associated MN led to increased proteinuria compared to the controls.

Conclusions: Failure of the proteasomal degradation system has a great impact on podocyte cell proteostasis. Inhibition of either the proteasomal or the lysosomal degradation system enhances the progression of THSD7A-associated MN.

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SA-PO378

P2X7-ATP May Mediate Propagation of Podocyte Damage

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Background: We previously generated a mosaic mouse model in which a fraction of podocytes express hCD25 and can be injured by hCD25-directed immunotoxin, LMB2. After injection with LMB2, not only hCD25(+) podocytes but also hCD25(-) podocytes were injured. A possible mechanism is that damage-associated molecular patterns (DAMPs) released from the damaged podocytes may secondarily injure the hCD25(-) podocytes. In the present study, we aim to find a candidate molecule that mediates spreading of podocyte damage.

Methods: Mosaic mice (n=4, each time point) were injected with 25 ng/g BW of LMB2, hCD25(+) and (-) podocytes were harvested by FACS sorting, and RNAs were analyzed with Agilent's 8X66K microarray. Functional assay was performed in primary cultured mouse podocytes by transiently transfecting expression plasmid.

Results: Among DAMPs and their receptors, we found that P2X7 mRNA was markedly increased both in hCD25(+) podocytes (>3000 folds) and in hCD25(-) cells (59 folds) 4 days after LMB2, which were confirmed by qRT-PCR analysis (>40,000 folds, 53 folds). P2X7 is a receptor for extracellular ATP and triggers signaling pathways leading to inflammation and cell death in immune cells. To test the role of P2X7-ATP in podocytes, we transfected primary cultured podocytes with P2X7 expressing plasmid. By 2 hours after administration of ATP (1 mM), cell number decreased by 53.4%, with 18.6% of cells incorporating propidium iodide. This is contrasting to P2X7 expressing cells without ATP, or mock-transfected cells with or without ATP, in which cell number decrease was <5% and propidium iodide incorporation was <2%. 6.7% of P2X7 expressing podocytes were stained with Annexin V one hour after ATP, whereas 2.6% of mock + ATP cells and 0% of P2X7 without ATP were Annexin V +.

Conclusions: These suggest that podocytes in damaged glomeruli express P2X7, respond to ATP released from adjacent dying podocytes, and are secondarily damaged. Thus, P2X7-ATP may mediate propagation of podocyte damage.

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SA-PO379

Angiotensin II-Induced Podocyte Apoptosis Is Ameliorated by AMPK Activation and the Improvement of CD2AP

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Background: Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. CD2-associated protein (CD2AP) in podocytes, anchoring slit diaphragm proteins to actin filaments of podocyte cytoskeleton, facilitates the nephrin-induced PI3-K/AKT signaling, which protects podocytes from apoptosis. AMP-activated protein kinase (AMPK), as a sensor of cellular energy status, has been known to play an important role in the pathophysiology of metabolic diseases, including diabetes, and its renal complications. We investigated the role of AMPK on the changes of CD2AP and podocyte apoptosis induced by Ang II.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and AMPK-related agents. The changes of CD2AP and podocyte apoptosis were observed by confocal imaging, western blotting, TUNEL assay and FACS assay according to the presence of Ang II.

Results: CD2AP and AMPKα were located diffusely but predominantly in peripheral cytoplasm and co-localized with nephrin. Ang II reduced AMPKa in time and dose-sensitive manners and also decreased CD2AP stainings diffusely and induced spatial separation from concentrated nephrin, similar to those of compound C-treated condition. AICAR and metformin, AMPK activators, ameliorated the abnormal distributional changes of AMPKα and CD2AP. Ang II also reduced (Thr172) phosphorylation of AMPKα and CD2AP in time- and concentration-dependent manners, which were significantly recovered by metformin and AICAR. Ang II type 1 receptor antagonist, losartan also recovered CD2AP suppressed by Ang II. LY294002, a PI3-K inhibitor, reduced CD2AP suppressed by Ang II. Ang II increased apoptosis in time- and concentration-dependent manners, which were ameliorated by AMPK activators, however, aggravated by siCD2AP.

Conclusions: Our findings suggest that Ang II induces the relocation and suppression of podocyte CD2AP and AMPKα via Ang II type 1 receptor and through the inhibition of PI3-K signaling, which trigger podocyte apoptosis induced by Ang II.

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SA-PO380

IL-9 Ameliorates Progressive Glomerulosclerosis

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Background: It has been established that IL-9 expression enhances tissue regeneration after lung injury, but data about the involvement of IL-9 in renal tissue protection are still very limited. Especially, the potential role of IL-9 in immune-mediated kidney disease is largely unknown. In this study, we focus on the role of IL-9 in Adriamycin-induced nephropathy (AN), a mouse model of focal and segmental glomerulosclerosis.

Methods: Progressive glomerulosclerosis in wild-type and *Il9*$^{-/-}$ mice was induced by injection of Adriamycin and analyses of histopathology, renal function parameters, albuminuria and renal immune cell infiltration were performed. The role of selective IL-9 deficiency of either the innate or the adaptive immune system for the outcome of AN was examined in *Il9*$^{-/-}$*Rag2*$^{-/-}$ mice and IL-9^{deltaT,B} mixed bone marrow chimeras, respectively. *Il9*^{Cre} x *R26r*^{eYFP} fate reporter mice were used to assess the cellular source of IL-9 in AN.

Results: *Il9*$^{-/-}$ mice with AN displayed accelerated development of proteinuria, aggravated glomerulosclerosis and deterioration of kidney function, as compared to wild type (WT) mice. In line, electron microscopy revealed early aggravation of podocyte damage in *Il9*$^{-/-}$ mice. First experiments with IL-9 fate reporter mice suggested that T cells might be a major source of IL-9 in the injured kidney. Accordingly, innate IL-9 deficiency in *Il9*$^{-/-}$ *Rag2*$^{-/-}$ mice did not alter the outcome of AN, whereas selective deficiency of adaptive IL-9 in IL-9^{deltaT,B} mixed bone marrow chimeras resulted in aggravation of glomerulosclerosis and kidney impairment, comparable to the phenotype observed in the completely IL-9-deficient mice. Possible mechanisms of the protective IL-9 effect, such as a direct pro-survival effect on glomerular epithelial or endothelial cells, are under active investigation.

Conclusions: In summary, we demonstrate here that IL-9 deficiency aggravates kidney failure in Adriamycin-induced nephropathy. As a cellular source of IL-9, T cells seem to play an important role in this model. The tissue-protective mechanisms of IL-9 need to be further elucidated and may offer a therapeutic approach in immune-mediated kidney diseases in the future.

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SA-PO381

Beneficial Effect of Low-Density Lipoprotein Apheresis via Modifying Immune System in Patients with Refractory Nephrotic Syndrome

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Background: In refractory nephrotic syndrome (rNS), in addition to direct injury of heavy proteinuria, longstanding hypercholesterolemia is known to provide poor renal outcome. The amelioration of dyslipidemia by low-density lipoprotein apheresis (LDL-A) in combination with conventional therapy was reported to induce rapid remission of NS primarily in focal segmental glomerulosclerosis (FSGS) and evidence of these beneficial effect has additionally accumulated in minimal change nephrotic syndrome (MCNS) and membranous nephropathy (MN). As the mechanism of action, in addition to the renal protection by rapid removal of low-density lipoprotein cholesterol (LDL-C), LDL-A has been proved to provide amelioration of macrophage dysfunction, restore steroid and cyclosporine susceptibility and adsorption of circulating permeability factors. To investigate immune-modulatory effect, we measured serum cytokines and chemokines level before and after LDL-A in a patient of FSGS and compared with familial hypercholesterolemia (FH) and reported significant and specific increase of Interleukin-10 (IL-10) after LDL-A in rNS, but not in FH. In the present study, in order to obtain more precise elucidation of immunological effect and disease specificity of LDL-A, the changes of not only serum but peripheral blood mononuclear cell (PBMC) cytoplasmic cytokines in patients with FSGS, MCNS and MN were evaluated.

Methods: Serum cytokines level before and after LDL-A sessions was assessed in three cases of rNS due to FSGS (6 sessions), MCNS (12) and MN (4), and compared with a non-NS, arteriosclerosis obliterans (ASO) patient treated by LDL-A (5 sessions). 27 types of cytokines were measured by Bio-Plex Pro human 27-plex kit (Bio-Rad). Cytoplasmic cytokines among PBMC were evaluated by flow cytometry.

Results: IL-10 was significantly elevated after LDL-A in all NS patients ($p=7.2x10^{-5}$). In ASO, IL-10 was not detected in sera before nor after LDL-A. Cytoplasmic IL-10 was positive in $CD19^{+}CD5^{+}$ cells, $CD19^{-}CD5^{-}$cells and $CD19^{-}CD5^{+}$cells. In addition, another anti-inflammatory cytokine, IL-1 receptor antagonist (IL-1Ra) was significantly elevated after LDL-A ($p<0.002$) in both NS and ASO.

Conclusions: LDL-A may induce rapid remission in rNS patients, via immunomodulation by session synchronized elevation of IL-1Ra and IL-10 regardless of causative disease.

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SA-PO382

Proteasome Inhibitors (PIs) Reduce PAN Induced Proteinuria by Enhancing FOXO3a/β-Catenin Complex in Minimal Change Disease (MCD)

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Background: Proteasomes play a major role in the pathophysiology of several disease processes in part through its action on a crucial transcription factor, nuclear factor-kappa B (NF-κB). NF-κB regulates the expression of a variety of inflammatory genes and plays a major role in MCD. The role of PIs in ongoing glomerular injury and the potential beneficial effects of PIs have not been previously examined. We show here that administration of PIs resulted in marked protection against puromycin aminonucleoside (PAN) -induced proteinuria by enhancing nuclear FOXO3a/β-Catenin complex, increasing expression of antioxidant enzymes and attenuates reactive oxygen species (ROS).

Methods: MCD was induced in rats by injecting PAN IV as a single dose and proteinuria measured as albumin to creatinine ratio (ACR) (μg/mg) until day 10. MG-132 was administered by osmotic pumps and Carfilzomib (CAR) was administered IV. Proteins were analyzed by Western Blot and immunocytochemistry. Immunohistochemical analysis was also performed on the kidney cortical sections.

Results: Administration of MG-132 and CAR prevented PAN induced proteinuria (PAN 147±29, MG132+PAN 98±32*, CAR+PAN 75+18*; P<0.05* compared to PAN

alone). This was accompanied by marked decrease in lipid peroxidation in PIs-treated rats compared to PAN alone. MG-132 significantly decreased the nuclear translocation of NF-KB, activation of IL-6, up regulation of CYP, significantly reduced H2O2 release and 8-Oxo-dG expression in cultured human podocytes. Electron Microscopy data showed that MG-132 and CAR treatment prevented foot process effacement of podocytes. Immunohistochemical analysis of cortical sections of PIs treated rats and immunocytochemical analysis of cultured human podocytes treated with PIs revealed increased β-Catenin and FOXO3a colocalization. Human podocytes treated with PIs showed upregulated PAN induced HO-1 and SOD with significant decrease in cell death.

Conclusions: These in vitro and in vivo data imply the crucial role of proteasome in progressive glomerular injury. CAR, which is currently used in humans should be considered as a potential therapeutic alternative in MCD.

SA-PO383

Nephrotic Range of Proteinuria with Cholesterol Crystal Embolization

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Introduction: Cholesterol crystal embolism(CCE) is often caused by transcatheter therapy, vascular surgery or anticoagulant therapy, clinically characterized by vessel obstruction from cholesterol crystals and the subsequently provoked immune response. Once it developed in kidney, renal function may gradually decline. Moreover, renal prognosis is poor with the majority of patients having progressive kidney failure. Generally, proteinuria is rare with CCE patients.

Case Description: Here, we report a case of nephrotic range of proteinuria caused by CCE. A 72-years-old man with atherosclerotic disease such as hypertension, diabetes mellitus and an abdominal aortic aneurysm, underwent percutaneous coronary intervention(PCI) on February 1, 2017. Acute kidney injury and nephrotic range of proteinuria occurred after four months of PCI. Kidney biopsy was performed to determine the etiology of renal dysfunction and massive proteinuria. Renal pathological diagnosis revealed CCE and focal segmental glomerulosclerosis(FSGS), severe endocapillary proliferation with foam cells. Steroid pulse therapy and oral prednisolone at a dose of 30 mg/day were administered. After those therapy serum-creatinine level and protein to creatinine ratio improved from 2.5 mg/dL to 1.3 mg/dL and 8 g/gCr to 0.5 g/gCr, respectively.

Discussion: Renal cholesterol crystal embolization with massive proteinuria is rare. In this case, endocapillary proliferation with foam cells thought to be caused by CCE. These suggests that steroid therapy might be effective treatment for CCE with FSGS lesions accompanied by proteinuria.

SA-PO384

(STEC-HUS) in Adults: An Underrecognized Cause of Thrombotic Microangiopathy

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Background: In children, most cases of hemolytic uremic syndrome (HUS) are caused by an infection with a Shiga toxin-producing *Escherichia coli* (STEC). In contrast, in adults most cases of HUS are considered to be atypical HUS (aHUS), attributed to dysregulation of the alternative complement system. However, during major outbreaks of STEC infection, hemolytic uremic syndrome in adults is not uncommon and morbidity and mortality, especially in elderly patients, may be considerable. Only few sporadic cases of STEC-HUS in adults have been described. Typically, STEC HUS is preceded by diarrhea, which is reported to be bloody in 60% of the patients. In the Netherlands routine screening for STEC is not recommended in adults with TMA, unless diarrhea is present.

Methods: Since 2015/2016, patients presenting with TMA in the Netherlands, in which aHUS is suspected, are discussed by the Dutch aHUS working group. Diagnostic options are carefully evaluated. This has increased awareness for STEC-HUS testing.

Results: Of 44 TMA patients who were discussed in the Dutch aHUS Working Group in the time period 2015/2016-2018, aHUS was diagnosed in 24 patients. STEC-HUS was found as the cause of TMA in 10 adult patients. Detailed clinical information could be obtained from seven STEC-HUS patients. The age of the patients ranged between 17 and 74 years. Of note, in three patients no diarrhea was reported. All presented with TMA (median thrombocytes 30 x 10^9/L (range 8-33), LDH 1409 g/L (range 946-3265) and an undetectable haptoglobin (<0.10 g/L)). Fecal or rectal swab PCR for Shiga toxin (Stx) was positive in all patients. In five patients PCR *Stx2* was positive; two of them also had a positive PCR for *STx1*. Serotype could be identified in four patients: O157, O27:H6, O-:H34 and O183:H18. Acute renal injury was seen in six patients, and four were treated with hemodialysis. Renal function recovered in five patients, however one patient remaining dependent on dialysis. Median eGFR was 83 ml/min/1.73 m^2 (range <5-133) after a follow-up of 1 to 15 months after presentation.

Conclusions: STEC HUS among adults is not uncommon and may not be preceded by diarrhea. We advocate routine screening for STEC infection in adults patients presenting with TMA.

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SA-PO385

Systemic Sclerosis Medications and the Prevention of Scleroderma Renal Crisis

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Background: Scleroderma Renal Crisis (SRC) develops abruptly in systemic sclerosis (SSc) and is associated with significant morbidity and mortality. High risk SSc subjects may benefit from treatment to prevent SRC. Though angiotensin converting enzyme inhibitors (ACEi) are the standard of care for SRC at diagnosis, previous case series found no benefit for initiation at SSc diagnosis to prevent SRC and a potential paradoxical association with development of SRC. There are no previous cohort studies of the potential prophylactic benefit for calcium channel blockers (CCB), angiotensin receptor blockers (ARB), endothelin receptor blockers (ERB), non-steroidal anti-inflammatory drugs (NSAID), or mycophenolate mofetil (MMF) to prevent SRC.

Methods: : In this retrospective cohort study of the entire military electronic medical record between 2005 and 2016, we compared the use of ACEi, ARB, CCB, NSAID, ERB and MMF after SSc diagnosis for 31 cases who subsequently developed SRC to 322 SSc without SRC disease controls. We conducted logistic regression analyses to evaluate for medications independently associated with SRC.

Results: Baseline ACEi use was more common in SSc patients that subsequently developed SRC [77% (24/31) vs. 33% (108/322), p<0.001]. ACEi was associated with an increased risk for SRC adjusted for age, race, gender, and prednisone use [odds ratio (OR) 4.0, 95% confidence interval (CI) 1.6-10.3, P=0.003]. On stratified analyses, there was no association between ACEi and SRC in the absence of proteinuria, while in the presence of proteinuria, ACEi was significantly associated with SRC [OR 5.28, 95% CI 1.1-29.2, p=0.03]. In addition, a doubling of ACEi dose [61% (19/31) vs. 12% (38/322), p<0.001) and achieving maximum ACEi dose [45% (14/31) vs. 4% (14/322), p<0.001] after SSc diagnosis was associated with future SRC. CCB, ARB, NSAIDs, ERB, and MMF use were not significantly associated with SRC.

Conclusions: Medications commonly used in SSC were not associated with a reduced risk of SRC. Paradoxically, ACEi use at SSC diagnosis was associated with an increased risk of SRC. This relationship was observed only in those with a heightened risk for SRC from proteinuria, suggesting that it may be a passive marker of evolving subclinical disease. SSC patients that require ACEi should be more closely monitored for SRC.

Funding: Other U.S. Government Support

SA-PO386

N-Acetylmannosamine (ManNAc) Therapy Mitigates Glomerular Hyposialylation and Proteinuria

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Background: Glomerular hyposialylation of glycoproteins and glycolipids has been implicated in human and experimental nephrotic syndromes. In this study we assessed the prevalence of glomerular hyposialylation in human nephrotic syndromes and explored therapeutic potential of the sialic acid precursor *N*-acetylmannosamine (ManNAc) in three different nephrotic mouse models.

Methods: We created neuraminidase-induced and adriamycin-induced nephrotic mice and a nephrotic knock-in mouse model deficient in *Gne*, a central enzyme in sialic acid biosynthesis. ManNAc was administered in drinking water (~1 g/kg/d) to all three mouse models and clinical/biochemical parameters were assessed at different timepoints. Human glomerular sialylation was assessed by lectin histochemistry and confocal imaging in kidney biopsies of 91 well-phenotyped subjects with minimal change disease (MCD; 29 subjects), focal segmental glomerulosclerosis (FSGS; 37 subjects) or membranous nephropathy (MN; 25 subjects) supplied by the Nephrotic Syndrome Study Network (NEPTUNE).

Results: In all three mouse models, ManNAc administration increased glomerular sialylation and markedly reduced proteinuria and podocyte injury within a week of treatment. Hyposialylation was detected in an unexpectedly high percentage (~72%) of human kidney biopsies across all three disease entities, indicating that this condition may occur frequently, remains greatly unexplored and, importantly, may be treatable. Correlating sialylation status to clinical, pathological or other documented subject data, showed a trend of correlation of severe glomerular hyposialylation with decreased eGFR, increased interstitial fibrosis and increased tubular atrophy, in particular in FSGS subjects.

Conclusions: These encouraging preclinical data, together with minimal toxicity of oral ManNAc therapy in humans (demonstrated in Phase 1 and 2 clinical trials for the rare hyposialylation disorder GNE myopathy) led to obtaining an Investigational New Drug approval to start a Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of ManNAc in subects with primary podocyte diseases (ClinicalTrials.gov NCT02639260). Preliminary results of this ongoing study are promising regarding safety and tolerability in subjects with glomerular disease.

Funding: NIDDK Support, Other NIH Support - NHGRI support, Commercial Support - Escala Therapeutics, Leadiant Biosciences

SA-PO387

Two Cases of Multicentric Castleman Disease with Nephrotic Syndrome Treated with Tocilizumab

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Introduction: Multicentric Castleman disease (CD) is a systemic lymphoproliferative disease with an incompletely understood etiology. Renal complications of this disease have been reported in a few cases. We herein report two cases of multicentric CD with nephrotic syndrome treated with tocilizumab.

Case Description: ***Case 1*** A 58-year-old man was diagnosed with multicentric CD by lymph node biopsy 7 years previously. He was followed closely without therapy because of his asymptomatic condition. He was admitted to our hospital with acute onset of nephrotic syndrome [albumin, 2.0 g/dl; urine protein:creatinine ratio (UP/UCr), 4 g/g creatinine). Light microscopic examination of kidney biopsy specimens revealed membranous nephropathy with cellular and fibrocellular crescents. Based on these findings, we diagnosed the patient with secondary membranous nephropathy due to CD. Steroid and tocilizumab therapy was started. After 3 months, the proteinuria had improved (UP/UCr < 1 g/g creatinine). ***Case 2*** A 49-year-old woman was diagnosed with multicentric CD by lymph node biopsy 9 years previously. She was followed closely without therapy because of her asymptomatic condition. She was admitted to our hospital with acute onset of nephrotic syndrome (albumin, 2.0 g/dl; UP/UCr, 5 g/g creatinine). Light microscopic examination of kidney biopsy specimens revealed Congo red stain-positive amyloid deposition. Based on these findings, we diagnosed the patient with secondary amyloidosis due to CD. Steroid and tocilizumab therapy was started.

Discussion: Few reports have described the various renal complications of CD, such as minimal change disease, mesangial proliferative glomerulonephritis, membranous glomerulonephritis, and amyloidosis. We have herein described two rare cases of multicentric CD with nephrotic syndrome and effective treatment with tocilizumab. Tocilizumab may be another therapeutic choice for multicentric CD with nephrotic syndrome.

SA-PO388

Serum Cystatin C Is a Significant Marker of Early Glomerular and Tubular Interstitial Lesions in Patients with Primary Glomerulonephritis: Results from Single Center Cross-Sectional Single-Blind Study

Elena Saganova, Olga Galkina, Vasiliy Sipovskii, Alexey Smirnov. *Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russian Federation.*

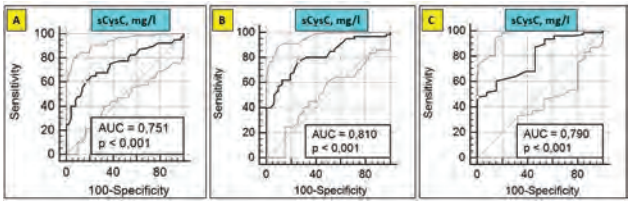
Background: Serum Cystatin C (sCysC) is well known endogenous alternative marker of GFR in research and clinical practice. sCysC can be used as a predictor of adverse outcomes in patients with CKD. However, the role of sCysC is not still obvious in patients with glomerulonephritis (GN) especially as a predictor of morphological lesions. Our aim was to assess sCysC as a predictor of various morphological lesions in patients with GN

Methods: 91 patients [50 male,41 female; age Me(min 18;max 83) – 42(28; 55) years] with biopsy proven GN and without AKI, infectious diseases, severe heart failure, respiratory insufficiency, cancer, abnormal thyroid status and treatment with prednisolone more than 10 mg/per day were enrolled in the study. Based on the results of kidney biopsy in 31% of cases a focal segmental glomerulosclerosis was diagnosed, in 28,5% – membranous nephropathy, in 40,5% – IgA-nephropathy. sCysC was measured in the morning on the day of biopsy by immunoturbidimetric method. The extent of glomerulosclerosis (GS) was assessed quantitatively. Tubulo-interstitial fibrosis (TIF) and tubular atrophy (TA) – semi-quantitatively. According to the degree of each morphological lesions all patients consistently were separated into 2 groups: *"light"* (GS less than 25% or TIF/TA grade 0 or 1) and *"severe"* (GS ≥ than 25% or TIF/TA grade 2-3). We evaluated specificity, sensitivity, diagnostic accuracy of sCysC regarding to the extent of each morphological lesion (GS/TIF/TA) by ROC-analysis

Results: sCysC was positively associated with GS (p<0,001;r=0,53), TIF (p<0,001;r=0,68) and TA (p<0,001;r=0,68). sCysC was significantly higher in patients with "light" GS (p<0,001), TIF (p<0,001) and TA (p<0,001). All patients were separated in 2 groups using sCysC according to the degree of morphological lesions ("light" or "severe") (Figure 1)

Conclusions: sCysC is a significant marker of various morphological lesions in patient with GN. sCysC can be used as a predictor of mild degree of glomerular and interstitial sclerosis, tubular atrophy with high diagnostic value

Funding: Government Support - Non-U.S.



SA-PO389

First-in-Man Cross-Sectional Single Center Study of Multimarker Panel Validation for Early Prediction of Morphological Lesions in Patients with Primary Glomerulonephritis

Elena Saganova, Olga Galkina, Vasiliy Sipovskii, Alexey Smirnov. *Pavlov First Saint-Petersburg State Medical University, Saint-Petersburg, Russian Federation.*

Background: Measurement of various biomarkers (BM) as a predictors of morphological lesions can improve detection and risk stratification for CKD progression. Our aim was to evaluate combination of serum und urinary BM as a predictor of various morphological lesions in patients with glomerulonephritis (GN)

Methods: 100 patients[52 male; age Me(min 18;max 83) – 39(27; 54) years] with biopsy proven GN, without AKI, infectious diseases, severe heart failure, respiratory insufficiency, cancer, abnormal thyroid status, prednisolone treatment more than 10 mg/per day were included in the study. Based on the results of kidney biopsy in 9% of cases minimal change disease was diagnosed, in 28% – focal segmental glomerulosclerosis, in 26% – membranous nephropathy and in 37% – IgA-nephropathy. Serum/urine (24-hour collection) creatinine (sCr/uCr), cystatin C (sCysC/uCysC), EFMg, urinary transferrin (uTr), IgG (uIgG), α1-microglobulin, β2-microglobulin were measured in the morning on the day of biopsy. The extent of glomerulosclerosis (GS) was assessed quantitatively, tubulo-interstitial fibrosis(TIF), tubular atrophy(TA) - semi-quantitatively. According to the degree of each morphological lesions (GS/TIF/TA) all patients consistently were separated into 2 groups: *"light"*(GS less than 25% or TIF/TA grade 0 or 1) and *"severe"*(GS ≥ than 25% or TIF/TA grade 2-3). We evaluated specificity, sensitivity diagnostic accuracy of BM panel regarding to the extent of GS/TIF/TA by multivariate and ROC-analysis

Results: Discriminant linear function analysis followed by ROC analysis showed that from included to the panel BM (Figure 1): GS (Biomarker Panel 1 (BP1); p<0.001; Fig1A), TIF (BP2; p<0.001; Fig1B), TA (BP3; p<0.001; Fig1C) were associated with sCr, sCysC, uTr, uIgG

Conclusions: Combination of sCr, sCysC, uTr, uIgG is a significant biomarker panel of various morphological lesions in patient with GN and can be used as a strong predictor of mild degree of GS, TIF and TA with high sensitivity, specificity and accuracy.

Funding: Government Support - Non-U.S.

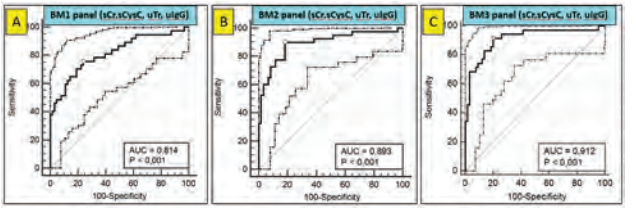


Figure 1. ROC curves with 95% CI of Biomarkers Panels for A – GS; B – TIF; C – TA

SA-PO390

Geospatial Clustering of Incident Glomerulonephritis Suggests Disease-Specific Risk Factors

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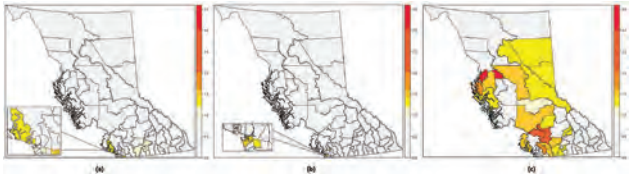
Background: Few studies have rigorously evaluated regional differences in the incidence of glomerulonephritis (GN) subtypes, thus limiting our understanding of potential sociodemographic or environmental risk factors. As such, we used population-level data from British Columbia (BC), Canada, to investigate geospatial differences in the incidence of biopsy-proven membranous nephropathy (MN), IgA nephropathy (IgAN) and ANCA-associated vasculitis (AAV).

Methods: All native kidney biopsies in BC from 1/1/2000 to 12/31/2012 were analyzed from a central registry to identify all cases of GN. Patient-level data were captured via linkage with provincial administrative databases. We used local health authorities (n=75) to define discrete geographical regions in BC (population 4.6 million) with region-level age, sex and race distributions from census data. For each GN we employed a hierarchial Bayesian model to estimate the incidence rate ratio (IRR) for each region accounting for adjacent spatial correlation. Contiguous regions with high probability of IRR>1.0 were combined into super-regions to estimate the IRR adjusted for age, sex and race.

Results: A total of 1624 patients were included: 401 MN (mean age 56, 57% male); 824 IgAN (mean age 44, 61% male); 399 AAV (mean age 61, 45% male). For each GN we identified several regions with high probability of being a cluster (Figure). The number of clusters and magnitude of increased risk were greatest for AAV (IRR 1.1-3.5), intermediate for IgAN (IRR 1.2-2.2) and lowest for MN (IRR 1.1-1.9). Results were similar for aggregated super-regions after multivariable adjustment.

Conclusions: Using a novel and robust approach, we describe geospatial clustering of biopsy-proven GN which varied by GN subtype and was not explained by inter-regional differences in age, sex and race. Our findings suggest that health services delivery for each type of GN needs to be tailored to individual regions at higher risk, and that there are likely disease-specific environmental and/or genetic risk factors that require further study.



Areas with high probability of being a cluster for MN (a), IgAN (b) and AAV (c). The color gradient represents the magnitude of IRR.

SA-PO391

The Impact of a Diagnostic Support System on Rare Disease Cases

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Background: Diagnostic support systems (DSS) can be used to enhance clinical diagnosis. We report about the use of Ada/DX, a DSS in development, in an outpatient clinic for rare inflammatory systemic diseases with kidney involvement. Presenting preliminary results, we evaluate the system's diagnostic accuracy and potential impact on the time to diagnosis.

Methods: This retrospective study is being conducted at the outpatient clinic for rare inflammatory systemic diseases with kidney involvement at the Hannover Medical School, Germany. To date, 67 (of a total 120) patient cases with confirmed diagnosis were included. The time of the visit of first documented symptoms and the time of diagnosis was identified. Time to diagnosis (TD) was calculated. Information from the medical record was transferred to the DSS and the disease suggestions in the DSS were evaluated. Primary endpoint was the correctness of top disease suggestions for the visit of diagnosis. In these cases, secondary endpoints were the time to first correct top rare disease suggestion (TR) and the time to first correct top 5 rare disease suggestion (T5R). The difference between TD and TR and the difference between TD and T5R was calculated. Wilcoxon signed-rank test was conducted.

Results: On preliminary evaluation, primary accuracy of top suggestions of the DSS at the time of diagnosis was 80.6% (71.1% to 90,3%, 95% CI). The table shows a comparison of time to diagnosis with and without the aid of the DSS. The Wilcoxon signed-rank test shows a significant difference for TD - TR (z-score -4.78, α=0.05, p<0.001) and TD - T5R (z-score -5.44, α=0.05, p<0.001).

Conclusions: The DSS suggested the correct diseases based on information from the medical record in most of the analysed rare disease cases. The DSS often suggested the correct diseases at times prior to the visit of diagnosis. DSS might help to reduce time to diagnosis and improve patient outcomes. Prospective research is needed to verify the results.

Comparison of the original time to diagnosis and the time to correct DDS disease suggestions

	Mean	Std Dev	PCTL 25	PCTL 50	PCTL 75
TD	56.53	87.2	3.0	17.0	55.5
TR	23.0	47.4	0.0	2.0	19.0
T5R	11.3	31.5	0.0	0.0	4.0
TD - TR	32.4	74.5	0.0	1.0	20.5
TD - T5R	44.2	82.7	0.8	8.0	39.4

Times expressed in months

SA-PO392

Studying Rare Disease Using an Electronic Health Record (EHR) and Machine Learning Based Approach: The Kaiser Permanente Southern California (KPSC) Membranous Nephropathy (MN) Cohort

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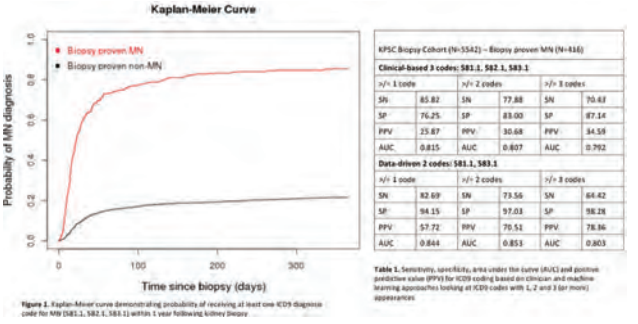
Background: Large scale epidemiology studies on glomerular disease such as MN are needed. Identifying MN patients using EHR is limited by the need to manually review kidney biopsy pathology reports (gold standard diagnostic test) to confirm cases. An ability to accurately identify patients with MN using only structured EHR data (e.g. diagnosis codes) would enhance the efficiency and scale of observational and comparative effectiveness studies within this population.

Methods: A retrospective cohort study was performed among KPSC patients who underwent a kidney biopsy 6/28/1999-6/25/2015 (n=5542). Biopsies were manually reviewed and designated as MN or non-MN. The sensitivity (SN), specificity (SP), and positive predictive value (PPV) of ICD9 diagnosis codes appearing w/in 1 yr after biopsy were determined using 2 approaches: 1) Clinical (581.1, 582.1, or 583.1, MN specific codes) AND 2) Machine learning (ICD9 codes, kidney-related or not, with highest predictive performance).

Results: Among biopsy proven MN cases, 59% and 86% received a MN diagnosis w/ in 30 days and 1 yr after biopsy, respectively. The SN and SP of this clinical approach were 86% and 76% respectively, but the PPV was 26%. If >2 codes were required, SP increased and PPV improved, but SN declined. Machine learning approach detected that using just 2 ICD9 codes (581.1 or 583.1) improved SP to 94% and PPV to 58% with a decrease in SN to 83%. SP was 98%, PPV 78%, and SN 64% if ≥3 codes was required.

Conclusions: Our study is the one of the first to leverage the EHR (ICD codes) to identify patients with biopsy-proven MN. Data-driven approaches showed better overall performance than a solely clinical-based approach. Expanding machine learning approaches to include demographics, additional clinical data, or free text from pathology reports might further increase diagnostic performance.



KPSC Biopsy Cohort (N=5542) – Biopsy proven MN (N=616)

Clinical-based 3 codes: 581.1, 582.1, 583.1					
>/= 1 code		>/= 2 codes		>/= 3 codes	
SN	85.82	SN	77.88	SN	70.63
SP	76.25	SP	83.00	SP	87.14
PPV	25.87	PPV	30.68	PPV	34.59
AUC	0.815	AUC	0.807	AUC	0.792
Data-driven 2 codes: 581.1, 583.1					
>/= 1 code		>/= 2 codes		>/= 3 codes	
SN	82.69	SN	73.56	SN	64.42
SP	94.15	SP	97.03	SP	98.28
PPV	57.72	PPV	70.51	PPV	78.86
AUC	0.844	AUC	0.853	AUC	0.803

Table 1. Sensitivity, specificity, area under the curve (AUC) and positive predictive value (PPV) for ICD9 coding based on clinician and machine learning approaches looking at ICD9 codes with 1, 2 and 3 (or more) appearances

Figure 1. Kaplan-Meier curve demonstrating probability of receiving at least one ICD9 diagnosis code for MN (581.1, 582.1, 583.1) within 1 year following kidney biopsy

SA-PO393

Conceptualizing the Future of Personalized Precision Medicine for Glomerular Disease

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Background: Glomerular disease therapy selection and outcomes have been hampered by imprecise disease characterization. Scientific advances have been generated in research contexts but few have crossed the research - patient care divide.

Methods: We hypothesized that comprehensive clinical, demographic and molecular phenotypes could be integrated into a personalized, comprehensive disease profile that could be used to understand the disease within nephrotic syndrome subjects. Physician- scientists and project managers from NEPTUNE were invited to participate in the model development. A multicenter, interdisciplinary NEPTUNE Kidney Review Board (KRB) model was created. Testing of this model used archived cases from the NEPTUNE study cohort. Return of results to caregivers or subjects was prohibited during this model testing phase.

Results: Data domains including, clinical phenotype, pathology, genetics, renal gene expression, and proteomics, were evaluated for each case. KRB participants were educated about data domain content, analytic methods, results display and supporting evidence from published literature. Multicenter web-enabled conferences were used to a) present case-specific information, b) review subject-specific data for each domain and c) integrate the multi-scalar data to develop theoretical management and treatment strategies for the subject. The multicenter, NEPTUNE KRB pilot was launched in February 2018. This pilot phase allowed the team to practice baseline evaluation of each case using a systems biology approach in a blinded manner, assemble the information into a case specific knowledge environment. Following discussion, the outcome of the case based on longitudinal observation was disclosed.

Conclusions: Integration of clinical, pathologic and molecular data will enable personalized disease profiling and will be essential in matching the right therapies for the right patients. In order to accomplish this, a prepared community of clinicians and scientists are needed to effectively interpret the strengths and limitations of the evidence. Furthermore, addition of patient advisors and ethicists will strengthen this initiative. KRBs provide a rational and effective strategy to bring precision health to the glomerular disease community.

Funding: NIDDK Support, Other NIH Support - NIDDK, NCATS, RDCRN

SA-PO394

Changes of Epidemiology, Renal and Patient Outcomes over Time in Glomerular Disease of Korea

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Background: Epidemiology of glomerular disease has been revealed temporal changes according to the population sanitation standard, socioeconomic status, and improvement of medical care. We aimed to explore changes of epidemiology, renal and patient outcome over time in glomerular disease (GD) in Korea, which is one of countries experienced rapid socioeconomic changes during short time.

Methods: After excluding 98 with more than the second times biopsy, 7,402 biopsy-proven primary and secondary GD patients from 1979 to 2018 are included from 2 tertiary hospitals. The outcome is CKD progression and all-cause mortality. CKD progression is defined as either incident ESRD or halving eGFR.

Results: During median 59 (18 - 138) months of follow-up period, patients who were taken kidney biopsy tended to be significantly older and more women over time. In overall, the most common primary GD was IgA nephropathy (IgAN), followed by membranous nephropathy (MN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS) with similar proportions. The most common secondary GD was lupus nephritis (LN), diabetic nephropathy (DN), and hepatitis-B-associated GN (HBGN). Proportion of IgAN had continuously increased over time, however it showed plateau since 2009, then it decreased to a certain degree. Proportion of MCD had decreased, whereas that of crescentic GD had increased as times go by. Diagnosis of MN or FSGS was not affected by the time change. Among secondary GDs, LN remained most common, however, it has decreased recently. DN has increased dramatically, whereas HBGN has decreased continuously. Patients presenting nephrotic syndrome has been decreased recently. 10-year renal survival was the lowest in DN (45.0%), followed by crescentic GD (62.0%), FSGS (78.4%), and IgAN (83.7%). Patient survival was the lowest in crescentic GD (76.6%), followed by DN (88.6%). Other GN showed similar patient survival with more than 90% of rate.

Conclusions: From our large cohort with long term follow-up, we identified significant changes in demographic or epidemiologic characteristics as well as outcomes of overall GDs. Improvement of socioeconomic and medical care may contribute to these changes.

SA-PO395

A Review of Therapies over 17 Years for Glomerular Disease in a Single Center

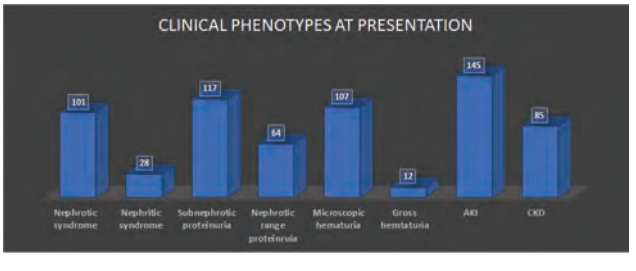
Sara Syeda, Sairah Sharif. *Brown University, Cranston, RI.*

Background: Glomerular disease is the third leading cause of end stage renal disease in adults in the United States. There is lack of consensus on treating glomerular disease due to general lack of randomized control trials in this field. There is a lot of variability in therapy both due to physician and patient factors.

Methods: We undertook this study to evaluate the trends in therapies of the most common glomerular diagnosis over the years in our center. This is a retrospective chart review of medical therapies of 322 patients who underwent a kidney biopsy between year august 2000 to october 2017. We also reviewed pregnancy outcomes of patients who were diagnosed with glomerular disease. Patients who did not have a renal biopsy at our center were excluded.

Results: Results: Our study population is ethnically diverse with 68% white, 16% black, 3% asian and 2% hispanic patients. The 3 most common clinical presentation that lead to renal biopsy were acute kidney injury, nephrotic syndrome and a combination of both. Amongst nephrotic syndrome FSGS was treated with steroids 80%, cyclosporine 20%, tacrolimus 14%, MCD was treated with steroids 99%, and membranous nephropathy was treated with steroids 90%, cyclophosphamide 30% of the cases. Patients with IgANP got renin angiotensin inhibitors 72%, steroids 22% of the time. Patients with ANCA vasculitis got steroids 95% of the time, cyclophosphamide 64% and rituximab 30% of the time. The therapy changed over time and rituximab use was more after 2012. Out of females between ages 18 to 50 years, 20 got pregnant any time after renal biopsy. Out of these pregnancies the live birth was 30%. The most common immunosuppressive drug to be used during pregnancy was mycophenolate and most common anti-hypertensive methyldopa. Pregnancy induced hypertension and preeclampsia was frequent 72%.

Conclusions: In our ethnically diverse population we found that LN, FSGS, MGN and IgANP were the most common glomerular disease. We found a great variability in treatment of glomerular disease including more rituximab after 2012.



SA-PO396

Changes in Patient-Reported Outcomes and Glomerular Disease Activity: CureGN

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Background: Prior cross sectional studies suggest that health-related quality of life (HRQOL) is worse in patients with active glomerular disease compared with inactive patients. This analysis was conducted to assess changes in longitudinal HRQOL with changing disease status.

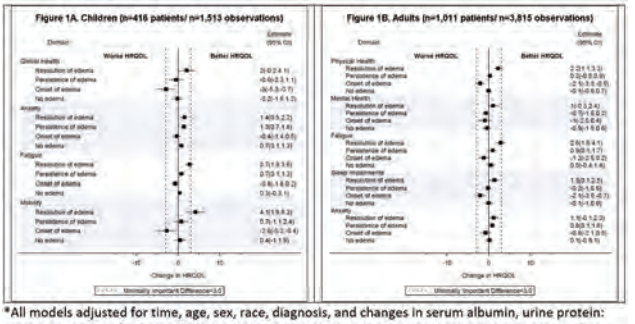
Methods: Longitudinal data were collected in CureGN, a cohort of patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, IgA vasculitis or IgA nephropathy. HRQOL was assessed at enrollment and at visits ranging from 1 - 3 times annually for up to 5 years with the Patient Reported Outcomes Measurement Information System (PROMIS). Global Health, Anxiety, and Fatigue domains were measured in all; Mobility was measured in children; and Sleep was measured in adults. Linear mixed effects models were used to evaluate HRQOL responsiveness to changes in disease activity.

Results: 416 Children and 1,011 Adults with PROMIS scores were included in the analysis. Edema was associated with all PROMIS domains other than Adult Mental Health (Figure). For example, children with edema resolution had improved Mobility (change +4.1; 95% CI +1.9 to +6.3), while those with edema onset had worse Mobility (change= -2.8 CI=-5.2 to -0.4). Serum albumin also associated with HRQOL for Child Global Health, Child Mobility, and all Adult Domains (effect sizes of +0.8 to +2.1 points per g/dL, $p<0.05$).

Conclusions: HRQOL, as measured by PROMIS, was responsive to changes in glomerular disease patient edema and serum albumin levels with score changes ranging from 0.3 - 1.3 times the PROMIS minimally important difference of 3. Future studies may reveal a glomerular disease specific PRO instrument to be more sensitive to within patient changes in disease status.

Funding: NIDDK Support

Figure. The impact of within-patient changes in edema status on changes in PROMIS domain scores: results of adjusted* mixed-effects models.



*All models adjusted for time, age, sex, race, diagnosis, and changes in serum albumin, urine protein: creatinine ratio, eGFR, hemoglobin and immunosuppressive therapy were tested as covariates. After backwards selection, final models for Child Global Health, Child Mobility, and all Adult Domains adjusted for changes in serum albumin. Adult Physical Health and Adult Fatigue final models also adjusted for changes in eGFR.

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Disease Activity in Longstanding Glomerular Diseases: The Columbia University-CureGN Experience

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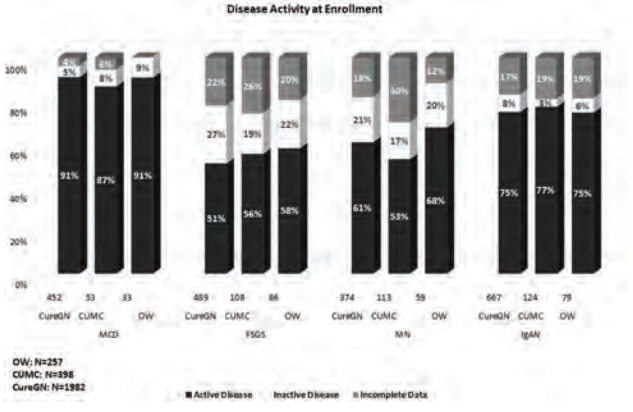
Background: Glomerular diseases are characterized by variable disease activity over many years. The CureGN study enrolls patients (pts) with minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA nephropathy (IgAN) whose 1st biopsy falls within 5 years of enrollment. We aimed to determine whether pts with more longstanding disease would show similar disease activity as CureGN pts.

Methods: Using CureGN's definitions of disease activity, we compared activity in pts followed at Columbia & excluded from CureGN due to their 1st biopsy done prior than 5 years from screening (Out of Window, OW) to both enrolled Columbia pts (CUMC) & to the entire CureGN cohort. For the OW, we assessed disease activity at the 1st clinical encounter from Nov 2014 (when CureGN enrollment opened). For the CureGN pts, we used disease activity at enrollment.

Results: OW and CUMC pts were similar in age, sex, and race; the CureGN cohort had a greater representation of African-Americans compared to the CUMC and OW. OW pts had, on average, lower eGFR than both CUMC and CureGN ones. For each disease subtype, disease activity in the OW cohort was equal or higher than disease activity in both the entire CureGN and the CUMC cohort (Fig1). When limiting our comparisons to disease activity in "incident" CUMC pts (1st diagnostic biopsy within 6 months of enrollment), OW pts demonstrated similar activity rates as incident pts (91% MCD, 60% FSGS, 73% MN, 80% IgA). Disease activity also did not differ by comparison for treatment thresholds.

Conclusions: Disease activity did not differ among pts with shorter vs longer duration of disease. Our OW cohort may include pts with more severe disease variants who still require a careful follow-up >5 years after initial diagnosis. Such pts are potentially highly informative for understanding the clinical course and pathogenesis of glomerulopathies and can help identify risk factors mediating more chronic subtypes of disease.

Funding: NIDDK Support



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Factors Associated with Incident Diabetes in Patients with Glomerular Disease: The CureGN Study

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Background: Glomerular disease is often complicated by incident diabetes which may raise the long-term risk:benefit ratio of immunosuppressive treatment. There is a paucity of information regarding descriptive characteristics of individuals with glomerular disease and incident diabetes.

Methods: We studied 2009 individuals from the CureGN Cohort Study, an observational cohort study of people with IgA Nephropathy/Vasculitis (IgAN/IgAV), Membranous Nephropathy (MN), Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD), followed prospectively starting less than 5 years after kidney biopsy. We compared sociodemographic and clinical characteristics of individuals with versus without incident diabetes diagnosed after kidney biopsy. Statistical significance was calculated using Chi-square or Fisher's exact test for categorical or Kruskal-Wallis test for continuous variables.

Results: There were 71 individuals with incident diabetes diagnosed a median of 4 (IQR 0-22) months after kidney biopsy. Diabetes was considered medication induced in 44 (62%) and 75% were treated with insulin. Characteristics of individuals with and without incident diabetes are shown in the table. Incident diabetes was more frequent in MN than in other glomerular diseases. Patients with versus without incident diabetes were older, more likely to have a family history of diabetes, and had a greater prevalence of obesity, smoking, hypertension and cardiovascular disease at enrollment. There was no difference in cumulative exposure to steroids between those with versus without incident diabetes.

Conclusions: Incident diabetes was more common in MN than other glomerular diseases, possibly due to older age at presentation of this disease. The absence of a difference in steroid exposure between those with versus without incident diabetes was unexpected and will be the focus of future analyses.

Funding: NIDDK Support

Table 1. Sociodemographic and clinical characteristics of CureGN participants with versus without incident diabetes from the time of kidney biopsy.

	Incident diabetes (N=71)	Without diabetes (N=1948)	P-value[a]
Age at biopsy (years), median (IQR)[1]	54 (40, 63)	25 (11, 46)	<0.001
Female	29 (41%)	839 (43%)	0.71
White Race[2]	45 (63%)	1313 (67%)	0.79
Hispanic/Latino Ethnicity[1]	13 (18%)	252 (13%)	0.16
Glomerular disease			
MCD	12 (17%)	454 (23%)	
FSGS	17 (24%)	482 (25%)	0.01
MN	24 (34%)	362 (19%)	
IgA	18 (25%)	650 (33%)	
BMI severity at enrollment[2]			
Overweight	12 (17%)	505 (26%)	0.002
Obese	42 (59%)	651 (33%)	
Triglyceride levels at enrollment (mg/dl), median (IQR)[3]	199 (109, 336)	139 (88, 208)	0.01
History of hypertension at enrollment[1]	53 (75%)	809 (42%)	<0.001
Systolic BP at enrollment (mmHg), median (IQR)[2]	133 (115, 145)	118 (107, 130)	<0.001
Diastolic BP at enrollment (mmHg), median (IQR)[2]	79 (70, 86)	73 (64, 80)	<0.001
Smoking status at enrollment[1]			
Current	19 (27%)	216 (11%)	<0.001
Ever	22 (31%)	232 (12%)	
Never	30 (42%)	1459 (75%)	
History of cardiovascular disease at enrollment[1]	13 (18%)	142 (7%)	<0.001
Family history of diabetes[1]	39 (55%)	436 (22%)	<0.001
Cumulative exposure to any steroids (months), median (IQR)[1]	5 (2, 14)	9 (5, 19)	0.26

N (%) unless otherwise noted, percentage reported among non-missing observations
[1] < 3% missing, [2] < 6% missing, [3] 70% missing, [4] 28% missing

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Predictors of Non-Linearity in eGFR Trajectories in the Nephrotic Syndrome Study Network (NEPTUNE)

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Background: Surrogate outcomes for end-stage kidney disease (e.g. eGFR slope or 40% decline) often assume linear changes, which may not always reflect true eGFR trajectories. The objective of this study was to identify patient characteristics associated with non-linear eGFR trajectories in a cohort of patients with nephrotic syndrome.

Methods: Data were obtained from the NEPTUNE study, a multicenter observational cohort study of adult and pediatric patients with >500mg/day of proteinuria enrolled at the time of clinically indicated biopsy or initial presentation of disease without biopsy (pediatric patients). eGFR was calculated using the CKD-Epi formula for patients ≥18 years old and modified CKiD-Schwartz formula for patients <18. Probability of non-linearity (PNL) was calculated using Bayesian smoothing of individual eGFR trajectories, and patient demographic and clinical variables and follow-up time were used to predict PNL in multivariable linear regression.

Results: 385 patients with ≥3 eGFR measurements and ≥1 year of follow-up were included (median follow up time 39 months). Median PNL was 0.047, with 15.6% and 6.5% having a PNL >50% and >75%, respectively. Higher baseline eGFR and UPCR, black race and steroid use at baseline were associated with higher PNL (9% increase per 10 unit increase in eGFR, p=0.001; 4% increase per unit increase in UPCR, p=0.011; 40% higher in black patients, p=0.038; 56% higher with steroid use at baseline, p=0.008, Table). Age and maximum follow-up time were associated with lower PNL (16% decrease per 10 year increase in age, p<0.001; 34% decrease per year increase in follow-up time, p<0.001).

Conclusions: While non-linear eGFR trajectories were common in this cohort, increasing follow-up time resulted in more linear trajectories. Higher baseline eGFR, younger age, black race, and steroid use were associated with higher probability of non-linear eGFR trajectories. Surrogate outcomes that assume linearity may be valid with sufficient follow-up.

Table: Factors associated with probability of non-linearity (PNL) of eGFR trajectories

	PNL Ratio (95% CI)	p-value
Baseline eGFR (per 10 mL/min/1.73m²)	1.09 (1.09,1.10)	0.001
UPCR (per 1 mg/mg)	1.04 (1.01,1.07)	0.011
Age (per 10 years)	0.84 (0.83,0.85)	<0.001
Male	1.10 (0.83,1.44)	0.508
Black race	1.40 (1.02,1.91)	0.038
Cohort		
MCD	1 (ref)	
FSGS	0.72 (0.49,1.05)	0.091
MN	0.82 (0.52,1.31)	0.405
Other	0.67 (0.44,1.02)	0.061
Follow-up time (per year)	0.66 (0.65,0.66)	<0.001
Steroids	1.56 (1.12,2.16)	0.008
CNI	1.33 (0.79,2.23)	0.289
RAAS Blockade	0.77 (0.58,1.03)	0.076
Diuretics	1.09 (0.79,1.49)	0.602

PNL was log-transformed. All factors were assessed at baseline.

SA-PO400

Infectious Complications in Patients with Glomerular Disease: An Analysis of the Cure Glomerulonephropathy (CureGN) Study

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Background: Infections are an important contributor to patient morbidity and mortality in glomerular disease (GD). We sought to understand the epidemiology of infections and infection-related healthcare utilization among patients with GD.

Methods: CureGN is a prospective multi-center cohort study of patients with minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA Nephropathy/Vasculitis (IgAN/IgAV). We describe the rate of infections requiring hospitalization or emergency department (ED) visit, primary infection sites, hospital lengths of stay, and ICU use within this cohort, stratified by age and GD type.

Results: Overall, 202 confirmed infections occurred in 158 (8%) of 1965 participants over a mean follow up time of 1.3 years (SD 0.9), a rate of 0.08 infections per person year. Ten percent of all hospitalizations or ED visits were due to infection. The rate of infection-related hospitalizations or ED visits was significantly higher in children (p<0.001), and in patients with MCD relative to MN (p=0.02) or IgAN/IgAV (p=0.004). Admission to the ICU was required in 9% of infection-related hospitalizations. The most frequent sites of infection were the lower (23%) and upper (23%) respiratory tract, and gastrointestinal system (13%).

Conclusions: Infection-related ED visits and hospitalizations are an important contributor to healthcare utilization among patients with GD. Further study is needed to analyze risk factors for infection and develop strategies to mitigate these events. Attention should focus on children and those with MCD, who have the highest rates of infection-related healthcare utilization.

Funding: NIDDK Support

Cohort Characteristics		Overall n=1965	MCD n=443	FSGS n=487	MN n=365	IgAN/IgAV n=670
Age Category n(%)	<18 yrs	770(39)	288(65)	180(37)	37(10)	265(40)
	≥18yrs	1195(61)	155(35)	307(63)	328(90)	405(60)
Age (y) mean (SD)		31(21)	21(20)	32(21)	49(19)	29(18)
Sex: male n(%)		1124(57)	248(56)	245(50)	226(62)	405(60)
Race	White	1316(71)	278(66)	269(59)	254(73)	515(82)
	Black	317(17)	84(20)	145(32)	60(17)	28(4)
	Asian	164(9)	40(10)	25(6)	30(9)	69(11)
	Other	60(3)	17(4)	19(4)	5(1)	19(3)
Ethnicity	Hispanic or Latino	256(13)	48(11)	71(15)	37(10)	100(15)
Follow up time (years)[1] mean(SD)		1.28(0.86)	1.19 (0.88)	1.15(0.87)	1.29 (0.88)	1.43(0.80)
ED Visits / Hospitalizations for Infection		**Overall**	**MCD**	**FSGS**	**MN**	**IgAN/IgAV**
Infectious Events[2]	Total (n)	202	58	48	33	63
	Hospitalizations n(%)	113(56)	35(60)	30(63)	20(61)	28(44)
	<18yrs	52(46)	23 (66)	16(53)	1(5)	12(43)
	≥18yrs	61(54)	12 (34)	14(47)	19(95)	16(57)
	ED visits n(%)	89(44)	23(40)	18(38)	13(39)	35(56)
	<18yrs	51(57)	19 (83)	11(61)	3(23)	18(51)
	≥18yrs	38(43)	4 (17)	7(39)	10(77)	17(49)
Infectious events / person year		0.08	0.11	0.09	0.07*	0.07*
	<18yrs	0.11	0.12	0.13	0.09	0.08
	≥18yrs	0.06	0.09	0.06	0.07	0.05
Infectious events per subject n(%)	1	125(79)	35(80)	34(85)	19(76)	37(76)
	2	24(15)	5(11)	5(13)	4(16)	10(20)
	≥3	9(5)	4(9)	1(3)	2(8)	2(4)
Length of stay (days)[3] median(IQR)		4(2, 6)	3(2, 6)	4(2, 8)	4(2, 7)	3(1, 5)
ICU stay due to Infection[4] n(%)		10(9)	2(6)	4(13)	0(0)	4(14)
Primary Site of Infection n(%)		**Total**	**MCD**	**FSGS**	**MN**	**IgAN/IgAV**
Pulmonary / Lower Resp Tract		47(23)	12(21)	10(21)	12(36)	13(21)
Upper Respiratory Tract / Throat		46(23)	14(24)	7(15)	9(27)	16(25)
Gastrointestinal		26(13)	10(17)	6(13)	4(12)	6(10)
Multisystem Infection		20(10)	7(12)	4(8)	2(6)	7(11)
Genitourinary		19(9)	3(5)	8(17)	0(0)	8(13)
Skin and Soft tissue		18(9)	7(12)	3(6)	4(12)	4(6)
Bacteremia and Septicemia		14(7)	2(3)	6(13)	0(0)	6(10)
Ear and Nose		7(4)	1(2)	3(6)	1(3)	2(3)
Bone and Joint		2(1)	1(2)	1(2.1)	0(0)	0(0)
Eye		2(1)	1(2)	0(0)	0(0)	1(2)
CNS		1(1)	0(0)	0(0)	1(3)	0(0)
Total		202(100)	58(100)	48(100)	33(100)	63(100)

1) Follow up time is determined from date of first study visit; 2) Infectious events (IE) occurring within 14 days of a previous IE of the same type are excluded. Only confirmed infections are included; 3) Length of stay for hospitalized infections only; 4) Expressed as number of infections requiring ICU admission and percent of all hospitalizations due to infection. *P-value<0.05 for each disease compared to MCD using binomial principles for incidence rates.

SA-PO401

Patient Experience in ANCA-Associated Vasculitis - Challenges from Diagnosis and Need for New Approaches

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Background: ANCA-associated vasculitis (AAV) brings challenges to patients in terms of acute illness and then a long term remitting relapsing condition. Therapy is complex and associated with significant acute toxicity as well as cumulative damage. Relatively little is known about the patient experience and how it evolves over time.

Methods: Qualitative research was performed using 1 on 1 interviews with 33 AAV patients (11 male) from 4 EU countries. 20 patients had granulomatosis with polyangiitis, 12 microscopic polyangiitis, and 1 had eosinophilic granulomatosis with polyangiitis. AAV duration (median 3.5 years, range 1-32) and patient age (3 < 40 years, 25 aged 40-80 years and 25 > 70 years) allowed rich insight from diagnosis through follow up.

Results: Thematic analysis of the interviews identified issues along the patient journey. Key findings were: (1) Suboptimal referral – long delays in diagnosis lead to long lasting psychological damage, worsened with treatment; (2) Recognition - sudden onset and misdiagnosis impairs patient experience. Patients are concerned over low empathy and understanding of their needs by healthcare professionals; (3) Knowledge gaps – patients want to know when they will return to normal and the duration of therapy and its impact; (4) Measuring response – patients have a low awareness of how their response is assessed clinically with scales/scores; instead they refer to the importance of "feeling better" and going home; (5) Decision making – patients report a low involvement in treatment decisions particularly over glucocorticoids (GCs) and immunosuppression; and (6) Unmet needs – patients have high regard for the efficiency of GCs in the acute phase but report major side effects which impair quality of life and functional status as GC dose changes. Findings were consistent across the 4 countries; differences reflected variations in healthcare system and organization.

Conclusions: Patients are challenged before and after diagnosis and once treatment begins with evolving experience over time. Physicians need to be aware of AAV patients concerns and needs from first interaction, when assessing response, and if treatment changes are needed. GCs pose a particular problem for patients and new therapies which reduce the significant treatment burden of AAV would be beneficial.

Funding: Commercial Support - Vifor Pharma

SA-PO402

Patients with Relapsing ANCA-Associated Vasculitis (AAV) Experience Unmet Needs around Remission Induction and Therapy Related Adverse Events

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Background: Relapse in AAV remains a clinical challenge, with 5-10% of patients experiencing relapses of varying severity each year. Such patients are at risk from both acute vasculitis damage but also drug toxicity and cumulative organ damage related to AAV and glucocorticoid (GC) adverse events. This study aimed to measure outcomes and adverse events in relapsing AAV patients in real clinical practice.

Methods: 268 relapsing AAV patients from 4 European countries received remission induction therapy between 2014-17 and data collected at baseline, 1, 3, 6 and 12 months following commencement of induction therapy was reviewed retrospectively.

Results: Patient mean age was 58.3 years with 60% male; 54% of patients had granulomatosis with polyangiitis, and 46% had microscopic polyangiitis. At the time of relapse, 7.1% of patients had experienced a past GC adverse event and only 16.0% were free from comorbidity. Birmingham vasculitis activity score (BVAS) was used in 17% at relapse diagnosis and 21% at time of relapse. Vasculitis was reported as mild/localized in 9.7 % of patients 64.6% as moderate systemic, and 25.7% as severe, life threatening. 44.0% of patients received rituximab and 35.1% received cyclophosphamide, whilst 76.5% received GCs. As BVAS was not used routinely, clinical response was assessed as full (no vasculitis activity and GC taper on track), partial (reduction in vasculitis activity), or no response (no improvement in vasculitis). Response to therapy varied, and adverse events and infections were common. Full response at 1 month was associated with good 12-month outcomes (81% full response), whereas a partial response at 1 month (53%) was associated with less favourable 12-month outcomes (49% full response).

Conclusions: Relapsing AAV patients frequently have comorbidities and their response to remission induction therapy is variable. An early positive response associates with a good response rate at 12 months. Many patients experience adverse events, and infections are common especially early in treatment. Relapsing patients still face unmet medical needs.

Funding: Commercial Support - Vifor Pharma

	1 month	3 months	6 months	12 months
Full Response %	14	40	57	54
At least one AE %	40.7	52.2	42.9	34.7
At least one infection %	28.4	30.2	26.5	23.1

SA-PO403

Real World Experience in ANCA-Associated Vasculitis (AAV) – A Complex Pathway of Patient Referral, Diagnosis, and Management

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Background: AAV is a severe systemic small vessel vasculitis with frequent renal involvement. Diagnosis can be difficult and referral pathways complicated with potentially several different specialists involved. Patient comorbidity is important but poorly reported. This retrospective study aimed to examine referral, diagnosis, and therapy outcomes in AAV patients managed in routine clinical practice.

Methods: A retrospective study was performed on 1197 patients receiving care from 399 physicians in 4 EU countries and 929 incident AAV patients are reported here. Patients were referred between 2014-17 and data collected at baseline and 1, 3, 6 and 12 months following commencement of therapy.

Results: Mean patient age was 56.8 years and 54% were male. 75% of patients were referred by other physicians, 25% direct acute presentations with only 16% referred with ANCA diagnosis. Referral symptoms were general in most cases – fatigue (58%), fever (54%), weight loss (53%), joint pain (47%) – 64% had renal disease. Physicians reported that 16% of patients had had symptoms for over 3 months. Comorbidities were common

(hypertension 45%, diabetes 18%, COPD/asthma 15%, coronary arterial disease 10%, arthritis 9%, osteoporosis 7% and cardiac failure 6%) with only 32% having none. At diagnosis, the median eGFR 35 ml/min, protein excretion median 595 mg/24 hours and 62% had microscopic haematuria; a renal biopsy was performed in 64%. Granulomatosis with polyangiitis was diagnosed in 54% of patients. In only 12% of patients was a formal scale (Birmingham Vasculitis Activity Scale, BVAS) used to assess activity. Clinically, 12% had mild disease, 54% had moderate/systemic disease and 34% had severe/rapidly progressive disease. Resource use at diagnosis and treatment was significant with a mean length of stay of 17 days including 3 intensive care unit days. 83% of patients were managed in collaboration with other specialties (Nephrologist 51%, Rheumatologist 27%, Internal Medicine 18%, Respiratory 16%, ENT 11%).

Conclusions: AAV patients have complex pathways to diagnosis and many have features of renal disease at presentation. Most patients have comorbidities which need to be considered during AAV therapy. BVAS is used rarely in clinical practice and resource utilization at presentation is significant.

Funding: Commercial Support - Vifor Pharma

SA-PO404

Response to Induction Therapy and Treatment Adverse Events in Incident ANCA-Associated Vasculitis (AAV) Patients

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Background: AAV is a severe systemic vasculitis with a variable clinical presentation and frequent renal involvement. Rapid induction of remission is desirable and therapy is typically a combination of high dose glucocorticoids (GC) with rituximab (RTX) or cyclophosphamide (CYC). Treatment-related adverse events (AEs) are common and contribute to long term organ damage as well as acute morbidity. This retrospective study aimed to document clinical outcomes and AEs in incident AAV patients managed in routine clinical practice.

Methods: 929 incident AAV patients from 4 European countries (399 physicians) were diagnosed between 2014-17 and data collected at baseline, 1, 3, 6 and 12 months following commencement of induction therapy was reviewed.

Results: 54% of patients had granulomatosis with polyangiitis, and 46% had microscopic polyangiitis; mean age was 56.82 years (SD 14.2) with 53.7% male. Birmingham vasculitis activity score (BVAS) was used in only 12% of cases. Physicians reported 12% patients as mild/localized, 54% as moderate systemic and 34% as severe life threatening AAV. Induction therapy varied with 59% receiving CYC, 24% RTX and 3% a combination of CYC+RTX+GC, whilst 83% received GCs. As BVAS was not used routinely, clinical response was assessed as full (no vasculitis activity and GC taper on track), partial (reduction in vasculitis activity), or no response (no improvement in vasculitis). Response rate varied and AEs were common. Full response at 1 month was associated with good 12-month outcomes (81% full response) whereas partial response at 1 month (56%) was associated with less favorable outcomes (58% full response at 12 months). 6% of incident patients relapsed within the first 12 months.

Conclusions: Response rate to remission induction therapy in AAV is still variable. Early response is associated with a better response rate at 12 months. Infections and treatment-related AEs are common, especially in the first 3 months. New targeted therapy options are needed to improve response rates and reduce burden of therapy.

Funding: Commercial Support - Vifor Pharma

	1 month	3 months	6 months	12 months
Full Response %	18	43	61	59
At least one AE %	45	42	35	30
Infection %	27	28	23	20
Still receiving GC %	82	79	67	53
Commenced dialysis %	16	3	1	1

SA-PO405

Adverse Events Due to Glucocorticoids in ANCA-Associated Vasculitis Are Frequent but Reporting Should Improve

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Background: High dose glucocorticoids (GCs) are an integral part of therapy in ANCA-associated vasculitis (AAV). The adverse event (AE) profile of GC is well known and can lead to acute and chronic toxicity, resulting in an unmet need in clinical practice to reduce GC exposure in AAV. This systematic literature review aimed to examine AEs related to GC use in AAV clinical studies.

Methods: A systematic literature review was performed of studies published between 1 Jan 2007 and 30 January 2018. Data on GC-related AEs (any untoward medical occurrence) and serious AEs (defined in European Medicines Agency CPMP/ICH/377/95) which threaten life or function were extracted from studies.

Results: Thirty-three studies were identified in which GC-related AEs were published. Of the 25,745 patients enrolled in the 33 studies, 24,566 were exposed to GCs. Seventeen studies reported AEs only, with 23 reporting serious AEs. Overall AE rate in AAV studies appears low possibly due to under-reporting, as GC effects are so well known. The most common serious AEs were infection and mortality. Infection was the leading cause of mortality, occurring more frequently in the first 6 months of treatment. Generally, infections are commonly reported but site and microbiological cause of infection were presented rarely. Metabolic and infection are the most common AEs, and 83% of metabolic events are due to diabetes mellitus. Musculoskeletal AEs and serious AEs are also relatively common.

Conclusions: GC related AE reporting in AAV studies can be improved and follow published guidelines (EULAR Ann Rheum Dis 2010; 69: 1913-19). Serious AEs such as mortality and infection remain a major clinical problem. Metabolic and musculoskeletal events are also a patient burden. New therapeutic options for AAV should aim to reduce this AE profile.

Funding: Commercial Support - Vifor Pharma

	Serious AE	AE
Patients exposed to GCs in studies reporting GC-related events (n)	3543	22278
Events (n)	1102	4284
Most common events reported	Mortality 33%	Metabolic 37%
	Infection 20%	Infection 15%
	Musculoskeletal 17%	Neuropsychiatric 8%
	Renal 15%	Musculoskeletal 8%

SA-PO406

Clinical and Therapy Related Risk Factors for Survival in ANCA-Associated Glomerulonephritis

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Background: Renal involvement and infectious complications have great impact on mortality in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Methods: We retrospectively investigated a multicenter ANCA-associated glomerulonephritis (GN) cohort for clinical and therapy related factors associated with relapse, end stage renal disease (ESRD) and survival in these patients.

Results: In 270 patients with a newly diagnosed, biopsy proven ANCA-associated necrotizing crescentic GN, the most sensitive markers for mortality were age and development of ESRD ($p<0.0001$, respectively). Gender, antibody and disease subtype did not influence patient survival. Patients with renal limited disease had the same renal and overall survival compared to patients with multi-organ involvement, e.g. patients with pulmorenal syndrome. Patients who were dialysis dependent at the time of diagnosis had a higher mortality during follow up ($p<0.05$). There was no difference in mortality between cyclophosphamide and rituximab treated patients. In the elderly population (age ≥ 70 years; n=84), a sub-cohort was given a reduced induction immunosuppression (4-6 cycles of 500mg; n=29). These patients had a higher rate of survival ($p<0.05$) compared to elderly patients with a regular cyclophosphamide induction while no differences in dialysis dependence or relapses were detected.

Conclusions: Our data suggest that a reduced induction immunosuppression in elderly patients may be appropriate, as this population seems not to benefit from a higher cyclophosphamide induction dosage.

Funding: Government Support - Non-U.S.

SA-PO407

The Cyclophosphamide-Sparing Role of an Intensified B-Cells Depletion Protocol in ANCA-Associated Vasculitis: A Case-Control Study

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Background: ANCA-associated vasculitis (AAV) are systemic diseases with relapsing chronic course. The management of AAV requires the use of immunosuppressive drugs whose use is associated with potential toxicity. This case-control study aims to evaluate the immunosuppressive-sparing effect of rituximab (RTX) used with cyclophosphamide (CYC), compared to a traditional regimen based on high-dose CYC.

Methods: 26 patients (pts) with AAV with a necrotising extracapillary glomerulonephritis were prospectively enrolled. 13 pts received the intensified protocol of B-lymphocyte depletion therapy (IBCDT) "4+2" with RTX and CYC (4 weekly infusions of RTX followed by 2 monthly followed by prednisone tapered to 5 mg/day in 3 months). 13 pts treated with the high-dose CYC treatment protocol followed by azathioprine as maintenance therapy were enrolled as controls.

Results: In the 13 cases treated with the IBCDT we observed a significant reduction in mean values of parameter of disease activity. After administration of RTX, a significant reduction of the mean s-creatinine values and BVAS was observed. All pts had full B-cell depletion on peripheral blood after the first IBCDT protocol after 1 year. No further maintenance therapy was given. In the cases, a response was observed in 8/13 cases. 4 pts did not respond and a death was observed for cardiovascular causes. No significant difference was observed in terms of response to therapy between the two groups. The IBCDT allows a significant reduction in the cumulative dose of CYC to which each patient was exposed during follow-up, reaching statistical significance levels ($p<0.001$). Calculated on a monthly basis, the "4+2" protocol allowed an average reduction in the CYC cumulative dose equivalent to 827 mg/month.

Conclusions: in a selected sample of patients with AAV with renal involvement, the IBCT regimen appeared to be non inferior in terms of the efficacy when compared to CYC-based standard regimens. Moreover, the IBCDT regimen allowed a net reduction in the cumulative average dose of CYC to which pts are exposed, quantifiable in approximately 1g/month.

SA-PO408

B Cell Suppression and Relapse of Vasculitis in Maintenance Therapy of Rituximab for Granulomatosis with Polyangiitis

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Background: The protocol of rituximab (RTX) use during the maintenance treatment for ANCA-associated vasculitis has not been established. Thus, we retrospectively investigated the efficacy of RTX between the regular and "on-demand" use in patients with granulomatosis with polyangiitis (GPA).

Methods: The subjects were 8 GPA patients in our hospital, and RTX was introduced by refractory active vasculitis with cyclophosphamide (CY) treatment difficulties or CY contraindications. The Japanese 8 patients with GPA refractory to or contraindicated for cyclophosphamide (CY) were investigated. The patients were 6 males and 2 females, with the median ages of 68 years old, and we compared B cell counts, relapse rates between 6 regular-use cases with every 6 months and 2 on-demand-use cases when RTX were administered after the reconstitution of B cells. We also examined glucocorticoid doses and safety profiles.

Results: The RTX were used as a single dose of 375 mg/m^2 in all patients. The periods from remission to the initial maintenance therapy were 7 to 12 months. The two "on-demand" patients showed eGFR less than 45 ml/min /1.73 m^2. In the regular-use group, no relapses of vasculitis or reappearance of B cells were observed. In the on-demand-use cases, the reappearance of B cells was seen after 8.5 months on average, and one of the two cases showed relapse of vasculitis with worsening renal function, proteinuria and CRP positivity after an interval of 20 months. Both groups showed comparable glucocorticoid doses and no serious infection was observed in both groups.

Conclusions: It is suggested that the regular use of RTX was well tolerated and may show persistent remission induction, rather than on-demand use, in the maintenance treatment for patients with GPA, although further study in the large cohort is required.

SA-PO409

10 Year, Age-Stratified Outcomes of ANCA Associated Vasculitis Treated with IV Cyclophosphamide

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Background: ANCA associated vasculitis (AAV) is a multisystem disease with morbidity and mortality associated with disease and treatment. The aim is to induce and maintain remission, and minimise side effects. Studies suggest high mortality among treated elderly patients and concerns have been raised about under-treatment in younger patients. We use IV cyclophosphamide (CyP) for induction (dose adjusted for age, weight and eGFR). We present mortality and renal outcomes in patients treated with IV CyP for AAV followed by maintenance therapy with Azathioprine or Mycophenolate.

Methods: Data was collected from medical records of patients treated with IV CyP from Jan 2007 to Jan 2017 with follow up until May 2018.

Results: 197 patients met the inclusion criteria: 54% men, 89% Caucasian, median age of 70(18-89) and 45% had PR3 antibodies. 41% were dialysis-dependent at diagnosis. IV steroids were used in 58% and Plasma Exchange in 32%. Induction with CyP was not completed in 4 patients due to intolerance/infection. Rituximab was given to 3 who failed to achieve remission. Median follow up was 60 months(10-133). 44(22%) patients died due to: infection(9), vasculitis(3), malignancy(6) and other(26). 5 died during induction: 2 of vasculitis and 3 of unknown causes. 42 had at least one relapse. Of the 80 who were dialysis-dependent at diagnosis, 52 recovered renal function. Age($p<0.01$) and end-stage renal failure(adjusted OR 8.1, $p<0.01$) were associated with mortality. 27 new cancers were detected during follow up.

Conclusions: We report on a single-centre cohort followed up for up to 10 years with a large number of elderly patients. The oldest age group had longest time to relapse, but also the highest unadjusted mortality and highest frequency of advanced CKD. There was a trend towards more relapses among younger patients. Although the dose of CyP is stratified according to age and renal function, this study highlights the possibility of under-treatment in younger patients.

Table 1 (Outcomes according to age)

Age Group	<50 years	50-65 years	65-80 years	>80 years
Number (% male)	22 (59% male)	51 (58% male)	97 (55% male)	27 (37% male)
Relapse (%)	9 (41%)	11 (22%)	17 (18%)	5 (19%)
Median time to relapse in months	21	31	30	33
Died during follow up (%), p<0.01	0	7 (14%)	28 (29%)	9 (33%)
Median time to death in months	NA	36	36	23
CKD stages 4-5 (%), p<0.01	3 (14%)	19 (37%)	47 (48%)	17 (63%)

SA-PO410

Pregnancy Outcomes in ANCA-Associated Vasculitis: A Retrospective Review

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Background: ANCA-Associated Vasculitis (AAV) is a small-vessel vasculitis that predominantly affects the kidneys and respiratory tract, among other organ systems. It has been traditionally associated with elderly males, but its occurrence in young, potentially childbearing, females is increasingly being recognized. In this study, we characterize the outcomes of pregnancy in ANCA-associated vasculitis.

Methods: We performed a retrospective chart review of all patients at the University of Iowa Hospitals and Clinics with a positive PR3 or MPO and a documented diagnosis of vasculitis between 2000 and 2017. Inclusion criteria included female sex and age younger than 45. Charts were reviewed to identify disease activity, clinical manifestations, medication regimens, and pregnancy outcomes.

Results: 24 patients met the inclusion criteria, of which 11 were pregnant at some point, accounting for 29 total pregnancies. Among these, 8 had at least one pregnancy after the diagnosis of AAV and 5 before the diagnosis. Those who were pregnant after diagnosis all had single pregnancies and accounted for 16 pregnancies in total. Seven pregnancies were viable, 2 are currently gravid, and 7 resulted in spontaneous abortions. Six (75%) were MPO positive while 2 (25%) were PR3 positive. Two patients were on moderate doses of prednisone (15mg – 20mg daily); the others were not on any immunosuppressive therapy. For induction therapy, 5 had cyclophosphamide, 1 had rituximab, and 2 had limited disease not requiring induction therapy. In vitro fertilization was documented in only 1 patient. Four were delivered by Caesarean section. All 6 who have completed pregnancy experienced complications, including premature birth (4), preeclampsia (2), preterm premature rupture of membranes (1), and cholestasis of pregnancy (1). One required tracheostomy for subglottic stenosis at 11 weeks.

Conclusions: Women with AAV should be considered at high risk for pregnancy complications due to the underlying disease and chronic immunosuppressive treatment regimens. With very close clinical monitoring, women with AAV may be able to conceive and give birth.

SA-PO411

The Endothelial Glycocalyx Is Damaged in Acute ANCA-Associated Vasculitis and Is Improved After Treatment

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Background: The endothelial glycocalyx (EG) lines and protects the luminal surface of the endothelium. Damage to this layer can be detected by increased serum levels of EG constituents as well as an increase in the perfused boundary region (PBR) of sublingual capillaries using the novel Glycocheck™ device. ANCA-associated vasculitis (AAV) is a widespread inflammatory process affecting blood vessels, causing endothelial dysfunction (ED). The effects of AAV on the EG are unknown.

Methods: We aimed to examine the effects of acute AAV and its treatment on the EG compared to healthy controls by collecting blood for EG markers (syndecan-1 and hyaluronan), markers of ED (vascular cell adhesion molecule: VCAM-1), urine for albumin:creatinine ratio (uACR), and performing a PBR measurement. Investigations for controls were performed once, whereas vasculitis patients were studied at the time of admission, after 2 weeks of plasma exchange (PEX) if indicated, and after 3 months of immunosuppressive therapy.

Results: Patients with acute AAV (n=8) and healthy controls (n=28) were recruited. Mean ages were 63 ± 13 years and 40 ± 13 years ($p<0.001$), respectively. AAV patients demonstrated EG damage at baseline compared to controls, with higher syndecan-1 and hyaluronan levels and a greater PBR. Three patients required dialysis, and one remained on dialysis at 3 months. After treatment, the median eGFR of AAV patients increased from 12 (3-40) mL/min at baseline to 19 (6-60) after plasma exchange ($p=0.031$, n=5), but not at 3 months. Median syndecan-1 levels decreased significantly from baseline to 3 months with a corresponding decrease in PBR values. However, no differences were detected in hyaluronan, VCAM-1 or uACR at any point.

Conclusions: Markers of EG damage were higher in the AAV patients at baseline compared to controls. The PBR and syndecan-1 levels of these patients improved at 3 months, reflecting an improvement in the EG layer due either to treatment or better renal function. The lack of change in hyaluronan and VCAM-1 levels warrants further investigation.

	Controls	Patients with acute AAV				
		Baseline	Post PEX	3 months	Paired t-test Controls vs. Baseline	Paired t-test Baseline vs. 3 months
PBR (μm)	2.04 ± 0.31	2.39 ± 0.23	2.43 ± 0.31	2.09 ± 0.16	0.0014	0.045
Syndecan (ng/mL)	26 (10-146)	100 (58-205)	76 (20-131)	44 (27-99)	<.0001	0.034
Hyaluronan (ng/mL)	32 ± 25	92 (16-134)	92 (24-175)	95 (24-240)	0.0002	0.562
VCAM-1 (ng/mL)	613 (379-1189)	1208 (27-1511)	465 (16-1372)	1091 (52-1597)	0.59	0.844
uACR (mg/mmol)	0.5 (0-2)	121 ± 87	431 ± 173	303 ± 270	<.001	0.625

SA-PO412

Urinary Cell mRNA Profiling Distinguishes Disease Activity in ANCA GN

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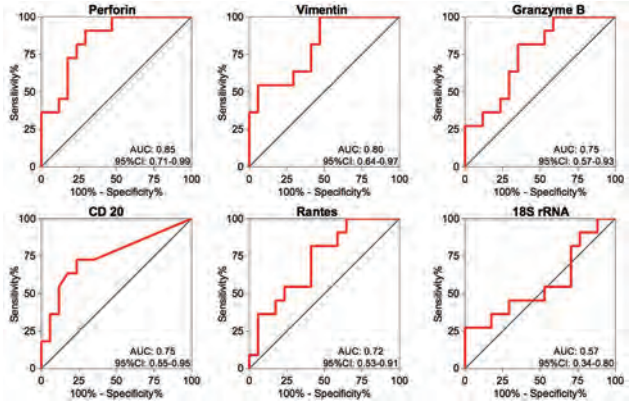
Background: Hematuria, proteinuria and increase in serum creatinine are noninvasive but inaccurate indicators of active GN. Renal biopsy is the gold standard for diagnosis of active GN but recurrent biopsies can be laden with risk. We aimed to ascertain if urinary cell mRNA profiling could be used to differentiate active versus remission phase in ANCA GN

Methods: Patients with biopsy proven ANCA GN were enrolled and activity was scored using BVAS. Patients in active phase had urine sample collected at the time of diagnostic biopsy and remission samples were collected during remission phase with a BVAS of zero. Total RNA was isolated from the urinary cells and mRNA expression of specific genes was examined by reverse transcription and PCR. We measured urinary cell levels of 19 mRNA's encoding proteins implicated in innate and adaptive autoimmunity. The levels of mRNA in the urinary cells for each sample were normalized by the levels of 18S rRNA in the same sample. Mann-Whitney U test and AUC were used to evaluate the ability of mRNA's to discriminate between groups

Results: Eleven patients with active disease and 17 in remission were enrolled. There were no significant differences between the groups with respect to age and ANCA subtype. Urinary expression of mRNA's for the cytotoxic attack molecules Perforin (p=0.001) and Granzyme B (p=0.02), B cell CD20 (p=0.012), Vimentin (p=0.0068), and RANTES (p=0.5) was significantly higher in active disease group compared to remission group. There were no significant differences between the groups for mRNA's encoding TGFβ1, FOX-3,CD25 ,Tbet,CD3GB,MCP1,MIG,C3,CXCR3,E-cad,NKCC2,VEGF,CD46 and IP10. ROC curve analysis demonstrates these markers can discriminate vasculitic activity (Image1)

Conclusions: This study demonstrates that urine mRNA profiling may be a non-invasive method of monitoring disease activity in ANCA GN. Elevated levels of perforin, granzyme B and CD20 are consistent with the role of cytotoxic T cells and B cells in ANCA GN



SA-PO413

Characterization of Lymphocytic Interstitial Infiltrate in ANCA GN

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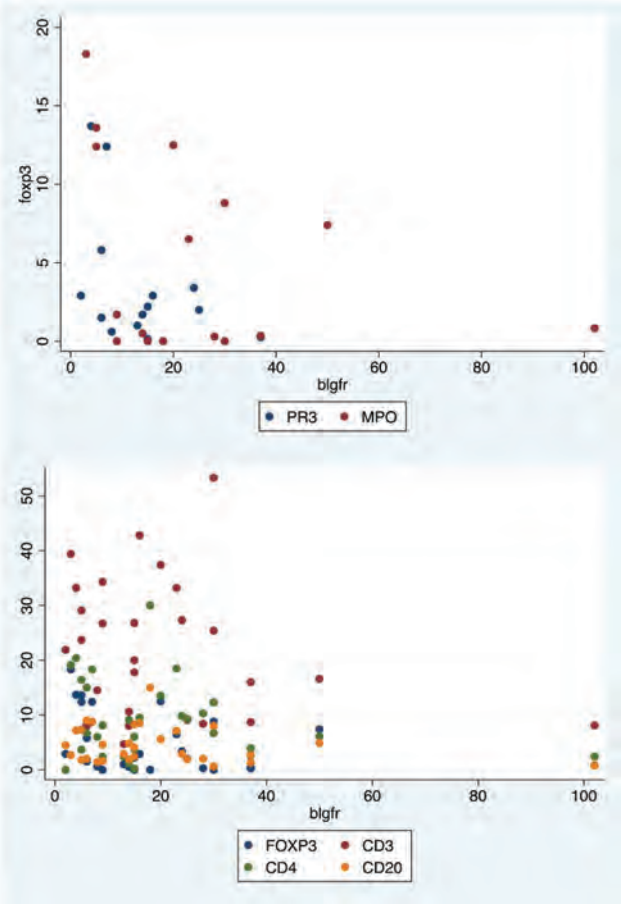
Background: B %T cells have a pathogenic role in ANCA associated vasculitis. There are differences in renal outcome based on ANCA type, therefore, we sought to characterize the interstitial lymphocytic infiltrate in ANCA GN to determine differences in relation to ANCA type and entry GFR.

Methods: Renal biopsies of patients with ANCA GN were stained for CD3, CD4, CD20, C4d and FOXP3. The percentage of cortical interstitium containing positive cells was determined by light microscopy. Demographics, ANCA type and entry eGFR were recorded. The level of staining was compared between ANCA type and entry eGFR using Wilcoxon rank sum test.

Results: Renal biopsies of 16 patients with MPO and 14 with PR3 ANCA GN were studied. CD3 cells were the predominant cells, with CD4 and FOXP3 staining positive in all biopsies. C4d staining was negative in all biopsies. There was no significant difference in staining between MPO and PR3 groups. However, regardless of ANCA type, FOXP3 staining was significantly higher in patients with baseline GFR<10 compared with GFR>10 (mean 7.54, SD 6.6 versus mean 2.67, SD 3.6; p=0.04). Image 1 demonstrates scatter plots of mean percentage of interstitial staining for markers and entry GFR(blgfr) in MPO and PR3 subsets.

Conclusions: These data confirm the role of CD4 cells in ANCA GN and demonstrate no differences in interstitial T and B cell infiltrates between PR3 and MPO ANCA GN. A higher FOXP3 signal suggests a role for regulatory T cells and merits further characterization of CD4 T cell subset.



SA-PO414

Urinary CD11b and CD163 Reflect Clinical and Histological Disease Activity in Renal Involvement of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitides

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Background: Glomerular leukocyte infiltration on histology reflects the renal inflammation in various forms of glomerulonephritis. Especially glomerular crescent formation, evidenced with robust extracapillary leukocyte and epithelial cell proliferation at the active stage, often present on glomerulonephritis complicated with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), has been proposed as a significant indicator of the disease activity and prognosis. Both cell surface molecules of CD11b, an α subunit of leukocyte integrin Mac-1 expressed on neutrophils and monocytes/macrophages, and of CD163, a scavenger receptor expressed on macrophages, have been demonstrated their cleavage from leukocyte upon inflammation-related cell activation. In the present study, we investigated the clinical significance of urinary CD11b (U-CD11b) and CD163 (U-CD163) as potential biomarkers for AAV.

Methods: We measured U-CD11b and U-CD163 by ELISA in AAV patient samples from the institutional (N-KDR; 61 patients at the diagnosis) and Japanese nation-wide (RemIT-JAV-RPGN; 138 at the diagnosis and 56 patients after 6 months treatment) cohorts, and evaluated those associations with clinical and histological parameters.

Results: Both U-CD11b and U-CD163 significantly correlated with renal score of Birmingham Vasculitis Activity Score (BVAS), and were particularly elevated in AAV patients classified in crescentic category by European Vasculitis Study Group (EUVAS) evaluation. Histological analysis for leukocyte profiles demonstrated significant association of U-CD11b levels with glomerular $CD11b^+$ cell numbers both in endo- and extra-capillary. On the other hand, U-CD163 reflected glomerular $CD163^+$ cells in extra-capillary. Significant reduction of U-CD163 (U-CD163; p<0.001, U-CD11b; p=0.26) was observed in identical AAV patients at 6 months following by the remission induction therapy.

Conclusions: U-CD11b and U-CD163 reflect clinical and histological disease activity of AAV renal manifestations, in particular glomerular crescentic formation. Moreover, these two biomarkers can respectively associate with the glomerular infiltrates of different leukocyte subsets in endo- and extra- capillary. U-CD163 may superior to U-CD11b for the evaluation of therapeutic efficacy in clinical settings.

SA-PO415

Molecular Risk Prediction in ANCA-Associated Crescentic Glomerulonephritis: Added Value over Clinical and Histologic Parameters

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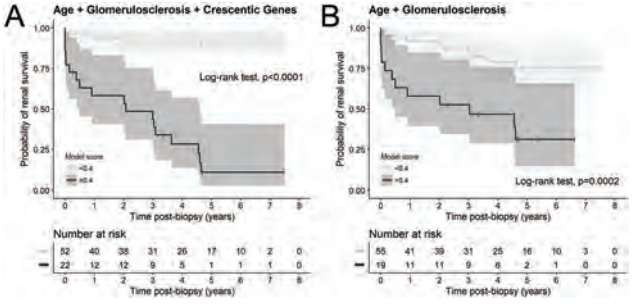
Background: Novel molecular tools have the potential to improve current clinical and histology-based risk classification systems for ANCA-associated crescentic glomerulonephritis (GN). We aimed to assess the utility of gene expression for improving biopsy-based risk prediction in these patients.

Methods: NanoString was used to measure the expression of 54 previously-described inflammation, nephron injury and crescent-related genes in 74 archival, formalin-fixed paraffin-embedded (FFPE) native kidney biopsies with ANCA-associated crescentic GN. Corresponding clinical and histologic data were retrieved. Multivariate Cox proportional hazards regression was used to identify the clinical, histologic and gene expression variables independently predictive of end-stage renal disease (ESRD). Receiver operating characteristic (ROC) curve, net reclassification index (NRI) and integrated discrimination improvement (IDI) analyses were used to compare full and reduced logistic regression models composed of the independently predictive variables. Kaplan-Meier renal survival curves were used to further assess differences in model performance. Data analysis was performed using nSolver and R.

Results: Multivariate Cox analysis demonstrated lower patient age (p=0.002), higher percentage global glomerulosclerosis (p=0.003) and higher expression of crescent-related genes (p<0.001) to be independently predictive of ESRD. Comparison of logistic regression models demonstrated that adding crescentic gene expression to age and global glomerulosclerosis significantly improved the prediction of ESRD versus age and global glomerulosclerosis alone (AUC 85.1 vs. 71.9, respectively, p=0.023; continuous NRI 94.1%, p<0.001; IDI 17.3%, p=0.001). Kaplan-Meier renal survival curves further demonstrated improved model performance with the addition of crescentic gene expression (Figure 1).

Conclusions: Adding FFPE-derived gene expression to existing clinical and histologic parameters improves the prediction of ESRD in ANCA-associated crescentic GN.



SA-PO416

Soluble CD163 Differentiates Active Vasculitis and Lupus Nephritis from Inactive Disease

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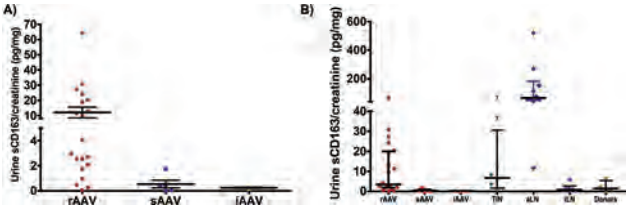
Background: Urine soluble CD163 (sCD163) is an enzymatically cleaved form of CD163 that has been described to discriminate active from inactive renal ANCA-associated vasculitis (rAAV) with 71-87% sensitivity and >97% specificity. sCD163 has also been reported to be elevated in active lupus nephritis (aLN).

Methods: The aim of the study was to evaluate urine sCD163 in patients with rAAV (n=20), systemically-active AAV without renal vasculitis (sAAV, n=5), inactive AAV (iAAV, n=4), aLN (n=10), clinically-inactive LN (iLN,n=5), and living-kidney donors (KD,n=5). To explore other diseases that may increase urine sCD163 we also evaluated patients with tubulointerstitial nephritis including tuberculous TIN (n=3) and IgG4 TIN (n=2).

Results: Median BVAS score was 19 (14-23), 7 (5-18) and 0(0-0) in rAAV, sAAV and iAAV respectively. Renal BVAS was 12 (10-12) in rAAV and 0 in both sAAV and iAAV. aLN patients had a median NIH activity score of 11 (10-12) and chronicity score of 4 (3-5). M edian urine sCD163 titers were 3.5ng/mg (1.8-20.0) in rAAV, 0.4ng/mg (0.03-1.1) in sAAV, and 0.2ng/mg (0.1-0.3) in iAAV (Figure 1A). The AUC was 0.919 to differentiate rAAV from non-renal AAV (p<0.001). With a cutoff>1.75ng/mg the sensitivity was 80% and specificity 100%. Median urine sCD163 was 66.3ng/mg (52.0-182.0) in aLN compared to 1.0ng/mg (0.3-3.8) in iLN with 100% sensitivity and specificity to differentiate between both groups (Figure 1B). Tuberculous TIN and IgG4 TIN had urine sCD163 values >3.0ng/mg.

Conclusions: Urine sCD163 is a good biomarker to differentiate both active renal AAV and active LN from inactive disease. Nevertheless, urine sCD163 titers were highest in aLN. This molecule can be also elevated in other diseases such as granulomatous and IgG4 TIN. Its use as biomarker should be further explored in longitudinal cohorts.



SA-PO417

The Association Between Lymphocyte Counts and Risk of Relapse and Risk of Serious Infection in Patients with ANCA-Associated Vasculitis

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Background: Patients with anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) commonly have relapses of their disease and/or infections. Lymphocyte counts may represent both a biomarker of adequate immunosuppressive treatment and an increased risk of infection. We assessed the association between lymphocytes counts and both infection and relapse in patients with AAV.

Methods: We conducted a single centre, retrospective review of patients with known AAV and abstracted patient characteristics at the time of relapse requiring immunosuppressive treatment up to 24 months after relapse. We assessed the relationship between lymphocyte counts and the outcomes of relapse and infection using multi-level logistic regression in which laboratory data including lymphocyte counts were treated as time-varying. All models were adjusted for age, neutropenia, need for dialysis and type of ANCA.

Results: We identified 158 patients of which 149 had useable data. During the follow-up period there were 87 relapses in 59 patients and 39 infections requiring antibiotics in 26 patients. Lymphocyte counts $<0.05 \times 10^9$ were not significantly associated with relapse (odds ratio 1.02, 95% confidence interval 0.26 to 3.98). Lymphocyte counts $<0.5 \times 10^9$ were independently associated with infection (odds ratio 7.00, 95% confidence interval 2.77 to 17.7).

Conclusions: Lymphopenia appeared more strongly associated with infection than it was protective of relapse. These data suggest inducing lymphopenia may cause more harm than benefit in patients with AAV.

SA-PO418

ANCA-Associated Vasculitis Through the Continuum of Age: A Retrospective Chart Review

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Background: ANCA-associated vasculitis (AAV) is a heterogenous group of small-vessel vasculitides that typically affects the kidneys, respiratory tract, and other organ systems. The onset of AAV may occur at any age, although literature suggests that this is more common in the elderly. We aim to characterize the clinical and laboratory manifestations of AAV based on age of onset in pediatric and adult patients younger than 35 years, compared to other age groups.

Methods: We performed a retrospective chart review of all patients with positive MPO or PR3 lab results by ELISA and a diagnosis of vasculitis from 2000 to 2017. Patients were classified into four groups according to age and divided into two groups each depending on MPO or PR3 serotypes. These features were compared to one another through descriptive statistics, as noted in table 1.

Results: 141 patients were identified based on the inclusion criteria, of which 31 were below the age of 35. The majority of patients were white females. Upper respiratory tract involvement and arthritis were much more common in the pediatric and adults younger than 35. PR3 was also more frequent in this group as well. Renal and lower respiratory involvement were comparable between the age groups.

Conclusions: Onset of AAV in young adulthood has distinct characteristics that more closely resemble pediatric AAV than compared to their older counterparts. Prior literature demonstrates a much higher percentage of extra-renal, extra-respiratory involvement in the pediatric population, which is consistent in our sample as well. Further analysis on clinical presentation, prognosis and treatment outcomes are forthcoming.

	Age < 18		18 < Age <35		35≤Age<65		Age≥65	
	MPO	PR3	MPO	PR3	MPO	PR3	MPO	PR3
Total Number	7	6	4	14	36	31	26	17
Female	6	4	3	6	20	14	18	7
White	7	6	3	12	34	30	25	16
Renal Involvement	6	5	3	11	26	25	24	10
Hematuria	6	5	2	8	25	21	22	9
Proteinuria	4	3	3	9	21	20	19	9
Glomerulonephritis by renal biopsy	2	1	3	3	14	5	12	2
ANA	2	2	3	2	12	8	14	5
Ear, Nose, and Throat	0	0	0	3	5	5	2	2
Respiratory	2	2	1	4	15	14	11	4
Arthritis	3	0	0	1	1	3	1	0

Table 1

SA-PO419

ANCA-Associated Vasculitis in a Predominantly Hispanic Population in the Western United States

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Background: ANCA-associated vasculitis (AAV) is a group of rare systemic autoimmune diseases with significant geographic and ethnic differences in disease prevalence and severity. Both environmental factors and genetic susceptibility are thought to contribute to such differences. Most published data thus far have been collected from Caucasian and Asian patients. The aim of this study is to characterize the features of AAV in a specific cohort of patients, predominately of Mexican descent, who reside in the Western United States.

Methods: A retrospective review of all native kidney biopsies for patients above age of 18 years old that were performed at the Los Angeles County University of Southern California Hospital from 2008-2018 was done. 43 patients with AAV were identified. Based on pathology results, we classified these patients into focal, crescentic, mixed and sclerotic subtypes.

Results: Among the 43 patients, 38 were Hispanic and 20 of which were from Mexico. The mean age at diagnosis was 49.8 years old. Patients' median serum creatinine on presentation was 2.4 mg/dl. 17 patients (39.5%) had kidney involvement alone, 5 patients (11.6%) with kidney and nasopharyngeal, 13 (30.2%) with kidney and lung, and 8 (18.6%) with kidney, lung and nasopharyngeal involvement. 30 patients (73.2%) were myeloperoxidase (MPO) positive and 10 (24.4%) were proteinase (PR3) positive. One patient was both MPO and PR3 positive. Pathological classification revealed 15 focal, 11 crescentic, 8 mixed, and 9 sclerotic subtypes. The majority (83%) of the patients received steroids with rituximab or steroids with cyclophosphamide. At 1 year of follow up, 7 (16.3%) patients relapsed, 12 (27.9%) patients had ESRD, and 4 (9.3%) patients died.

Conclusions: Our study showed that this predominately Mexican-American cohort residing in the Western United States from 2008-2018 presented with AAV at younger age and had worse 1-year renal survival as compared to data published on Asian and Caucasian populations. In addition, kidney involvement and MPO positivity dominated this cohort.

SA-PO420

Risk Factors for Progression to ESRD in Patients with ANCA Associated Vasculitis - Experiences from a Chinese Single Center

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Background: Although ANCA associated vasculitis (AAV) is not a common disease, AAV renal damage is the leading rapidly progressive glomerulonephritis leading to end-stage renal disease (ESRD). If we can screen out the risk factors for progression to ESRD, it will be valuable for the treatment.

Methods: 498 AAV patients diagnosed from October 23, 1999 to February 15, 2017 were enrolled, the latest follow up date was February 21, 2018. The general conditions, clinical manifestations, laboratory investigations, renal biopsy results, treatment regimens and prognosis (renal/patient survival) were analyzed.

Results: Among the 498 cases, there were 283 females and 215 males. The average onset age was 60.9±14.5 years old (10-90). MPO-AAV was more than PR3-AAV (91% vs 9%). 486 patients (97.6%) had renal impairment. 216 patients (44.4%) received renal biopsy. 54 patients (11.1%) received dialysis at the onset and 11 of them get rid of dialysis. Apart from 56 patients (11.2%) lost to follow up and 53 patients (10.6%) died, we divided patients to ESRD group (n=145) and Stable group (n=302). We compared the baseline data of the two groups (age, sex, onset to diagnosis time, clinical presentation, BVAS score and lab investigation) and treatment regimen (whether plasma replacement, whether or not glucocorticoid pulse therapy). The results showed that the parameters associated with the progression of the patients to ESRD included the type of vasculitis (P=0.016), the combination of hypertension (P<0.001), the combination of fever (P=0.048), hemoglobin level, platelet level, 24-hour proteinuria, serum creatinine level, eGFR level and the need for dialysis (P<0.001). Multiple factor Cox regression analysis showed that daily urine protein (3.21±2.46 vs 1.71±1.61g, 95% CI 0.67-0.99, P=0.041) and eGFR level (9.25±6.10 vs 44.37±40.76ml/min, 95% CI 1.018-1.159, P=0.013) were independent risk factors for the patient's progression to ESRD.

Conclusions: The prognosis of renal function was poor in patients with heavier proteinuria or lower eGFR level. Due to the low rate of renal biopsy, we found that the segmental crescentic ratio and fibrinous necrosis were associated with deterioration of renal function, but not independent risk factors.

SA-PO421

The Antineutrophil Cytoplasmic Antibody–Associated Vasculitides Concomitant with IgG4-Related Disease: A Case Series

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Background: Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) and IgG4-related disease (IgG4-RD) have similarities in clinical characteristics and histopathological features. Concomitance of these two diseases have been reported previously.

Methods: We compared the characteristics of AAV patients, IgG4-RD patients and concomitant AAV and IgG4-RD patients in our center. One hundred and sixty-nine AAV patients, 58 IgG4-related disease patients and 8 concomitant patients were included. The serum IgG subclasses of MPO-ANCA were measured.

Results: The patients in concomitant group had both elevated serum IgG4 level and positive ANCA. They had lower levels of hemoglobin, serum albumin, glomerular filtration rate and higher levels of platelet, serum creatinine, erythrocyte sedimentation rate and C-reactive protein compared with IgG4-RD group. Their involved organs were mainly kidney (100%), lung (62.5%) and lacrimal glands (62.5%). They had higher serum globulin level and even lower serum albumin level than patients with AAV. Six renal biopsies were performed in concomitant group. They achieved remission with improved renal function, one patient was on maintained dialysis and one patient died of acute gastric perforation. The IgG4 subclass of MPO-ANCA was higher in concomitant group than in AAV group (OD450 value 12.42±6.63 vs 3.03±3.67, P=0.017), whereas the other three subclasses (IgG1, IgG2 and IgG3) of MPO-ANCA were parallel between these groups.

Conclusions: We showed a new overlap syndrome of AAV and IgG4-RD, and the IgG4 subclass of ANCA may be a pathogenic factor in this concomitant disease. Besides, we suggested the concomitant patients be treated as AAV, as they were more likely to show the clinical features of AAV.

SA-PO422

A Cohort Study to Assess the Role of Sensitivity C-Reactive Protein Level in the Evaluation of Activity and Prognosis of Microscopic Polyangiitis

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Background: To investigate the role of high-sensitive C-reactive protein(hs-CRP) level for the evaluation of activity and prognosis of microscopic polyangiitis(MPA).

Methods: A total of 149 patients with MPA were enrolled from June 23rd, 2008 to January 20th, 2017. We collected demographic characteristics, biochemical parameters and pathological changes. These patients were divided into high hs-CRP group and low hs-CRP group at the cutpoint of 7.05 of the median of hs-CRP of these patients to compare the clinical features and prognosis between these two groups. A Kaplan–Meier survival analysis was performed to compare the survival rate using a log-rank test. Cox proportional hazards models were used to evaluate the association between hs-CRP levels and outcomes.

Results: The patients with crescentic type in the high hs-CRP group was significantly higher than that in the low hs-CRP group. The patients with sclerotic type was lower than that in the low hs-CRP group. The cases to reach the primary outcome (death, renal replacement therapy) in the hs-CRP group were significantly higher than that in the low hs-CRP group(Figure 1). A high level of hs-CRP(HR: 3.11, 95% CI: 1.10 to 8.80) and renal interstitial infiltrates(HR: 2.94, 95% CI: 1.14 to 7.58) were independent risk factors for the progression of microscopic polyangiitis by a multivariable COX regression analysis.

Conclusions: Baseline serum hs-CRP level was a risk factor for the progression of microscopic polyangiitis, indicating that serum hs-CRP could be adopted as a clinical parameter for the evaluation of microscopic polyangiitis.

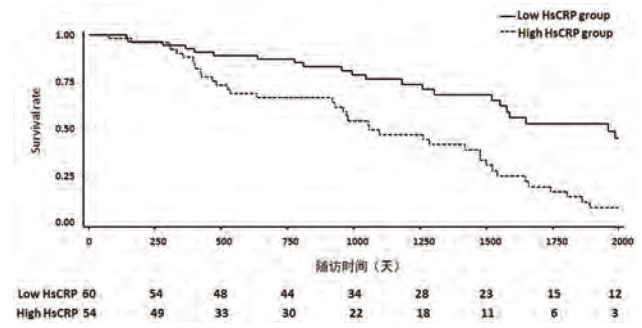

Figure 1. The patients survival rate in the high hs-CRP group was worse than that in the low hs-CRP group.

SA-PO423

Biomarkers of Complement Activity in C3 Glomerulopathy Patients

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Background: C3 glomerulopathies (C3G) are characterized by isolated or dominant glomerular C3 staining on immunofluorescence that implies an etiology rooted in dysregulation of the alternative complement pathway. To date, no biomarkers for disease activity have reliably predicted outcomes in C3G.

Methods: We measured circulating factor D, factor B, Ba, Bb, plasma and serum C3, and C3a as potential biomarkers of complement activity in a group of C3G patients with longitudinal outcome data. The primary outcome combined doubling of creatinine, progression to CKD stage 5, ESRD, transplantation, or death. The secondary outcome was remission, defined as stable creatinine with >50% reduction in proteinuria to subnephrotic range.

Results: We compiled a biomarker profile on 38 C3G patients (25 with C3 glomerulonephritis and 13 with dense deposit disease) with a mean follow-up of 62 months from diagnosis to last encounter. Factor D levels were low in 50% of patients, factor B levels were low in 21% of patients, plasma C3 levels were low in 53% of patients, and serum C3 levels were low in 42%. Factor B split products, Ba and Bb, were elevated in 66% and 55% of patients, respectively, while C3a was elevated in 61% of patients. Seven patients reached late or end stage kidney disease. In univariate analyses, Ba (p=0.002) and Bb (p=0.03) levels, but not C3a levels (p=0.2), emerged as predictors for the primary outcome. Plasma (p=0.04) but not serum (p=0.2) levels of C3 were also predictive of progression. Seventeen patients achieved disease remission, but no biomarker was predictive of this outcome.

Conclusions: Elevated levels of the factor B split products (Ba and Bb), which denote newly formed C3 convertase of the alternative pathway, are associated with progression of C3G to advanced and end stage kidney disease. These biomarkers may help risk-stratify newly diagnosed C3G patients and present a treatment target for disease.

Funding: Commercial Support - Achillion Pharmaceuticals

SA-PO424

Evaluation of Urine Complement Biomarker in C3G Following ΔΔComplement Alternative Pathway Inhibition with ACH-4471

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Background: C3 glomerulopathy (C3G) is a rare disease of complement alternative pathway (AP) dysregulation that is characterized by glomerular C3 fragment accumulation, progressive kidney damage, and proteinuria. Preliminary data from an ongoing 14-day proof-of mechanism clinical trial provided evidence that ACH-4471, an oral AP-specific inhibitor that blocks complement factor D (CFD) function, can reverse the systemic AP hyperactivation and reduce the proteinuria in C3G patients. Although complement biomarkers in blood are valuable for assessing systemic AP activation, their levels in urine may provide additional information about AP activation in the kidney. Here, we report a comparative evaluation of systemic and urinary AP biomarkers in C3G patients enrolled in the aforementioned clinical study of ACH-4471.

Methods: Urine and blood samples were collected from patients at protocol-specified timepoints prior to, during, and after dosing with ACH-4471. Complement biomarkers including the proximal and terminal complement activation products, Ba and sC5b-9, were measured in serum or plasma and in urine samples. Serum, plasma, and urine from non-study healthy volunteers served as control samples. Urinary levels of complement products were normalized to urinary creatinine levels and are denoted as "/Cr".

Results: Urinary Ba/Cr and/or sC5b-9/Cr levels at baseline were significantly higher in patients than in healthy controls, even though plasma Ba and sC5b-9 levels were not always above normal. Following dosing with ACH-4471, urinary Ba/Cr and/or sC5b-9/Cr levels were significantly decreased, often to a greater extent than the levels of plasma Ba and sC5b-9. Lastly, the reductions in urinary Ba/Cr and sC5b-9/Cr levels during treatment were independent of the accompanying reduction in proteinuria, as indicated by the comparable reductions observed when urinary Ba and sC5b-9 levels were normalized to urinary albumin.

Conclusions: Our findings suggest that complement proteins in urine may serve as additional biomarkers for understanding C3G pathology and predicting responsiveness to ACH-4471.

Funding: Commercial Support - Achillion Pharmaceuticals

SA-PO425

C3 Glomerulopathy: Clinical Determinants of Prognosis and Response to Immunosuppression

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Background: C3 glomerulopathy (C3G) is a clinicopathological entity secondary to a dysregulation of the alternative complement pathway. Despite significant advances in our understanding of the pathophysiology of this disease, less is known about its prognostic determinants.

Methods: Retrospective, observational study in 28 hospitals belonging to GLOSEN group. All patients fulfilling diagnostic criteria of C3G were included. Clinical, biochemical and histologic parameters of prognostic interest were recorded to analyze the main determinants of disease progression and response to different therapeutic regimens.

Results: The study group consisted of 104 patients: 90 C3 glomerulonephritis (C3GN) and 14 dense deposit disease (DDD). 17% were diagnosed during pediatric age, 49% between 18-50 years, and 34% above 50 years. A monoclonal gammopathy of unknown significance was observed in 16% of patients. The most common presentation in pediatric age was nephrotic syndrome, whereas acute kidney injury and isolated urinary abnormalities were the most frequent clinical findings in adults. Membranoproliferative glomerulonephritis was the most predominant pattern of injury, with C3 only deposition in 49% of cases. In a median follow-up of 48 months [IQR:18–100], 45 patients (43%) achieved remission (partial or complete). Treatment with steroids and mycophenolate mofetil was associated with significant improvement in renal survival compared to other treatments or conservative management. During the follow-up period, 45 patients (43%) developed end-stage renal disease (ESRD). By Cox regression analysis, the main determinants of ESRD were: age (HR: 1.026;C.I.95%: 1.008–1.044; p=0.004), serum creatinine at diagnosis (HR: 1.213;C.I.95%: 1.115–1.318;p<0.0001), and degree of interstitial fibrosis and tubular atrophy (HR: 1.891;C.I.95%: 1.384–2.582;p<0.0001). No differences were found between C3GN and DDD. Twenty-five patients (24%) underwent kidney transplantation, 14 of which (56%) had disease recurrence after a median follow-up of 12 months [3–107].

Conclusions: C3G is associated with poor renal outcome in a substantial percentage of patients. Steroids and mycophenolate were shown to be the most effective regimen to achieve remission. Older age, elevated serum creatinine and tubular atrophy/interstitial fibrosis were the main determinants of renal survival.

SA-PO426

Expression and Role of TET Proteins in Fetal Kidneys of Control and Nutrient-Restricted Rat Dams

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Background: The ten-eleven translocation (TET) proteins are enzymes that oxidize 5-methylcytosine to 5-hydroxymethylcytosine and regulate DNA methylation and hydroxymethylation, which are important epigenetic modifications in fetal programming. We previously reported that inhibition of DNA methylation reduces ureteric branching and kidney growth in organ culture (ASN 2015). We also showed that kidneys of offspring of nutrient-restricted rat dams were characterized by reduction in global DNA methylation, ureteric branching, and kidney size. In the present study, we examined global DNA hydroxymethylation and the expression of TET proteins in fetal kidneys of control (CON) and nutrient-restricted (NR) rat dams. The role of TET proteins was further examined in organ culture.

Methods: NR rats were subjected to 50% food restriction throughout pregnancy. Expression of TET1, 2, and 3 was analyzed by immunoblot in the kidney of embryonic day 18 (E18). Global DNA hydroxymethylation was quantified by ELISA. In organ culture, E13 to E14 metanephroi were cultured for 2 to 3 days in the presence or absence of ascorbic acid that facilitates TET enzyme activity, or dimethyloxallyl glycine (DMOG), a small-molecule inhibitor of TET.

Results: TET1, 2, and 3 were expressed in the E18 kidney and their expression was increased in NR compared with CON. Global DNA hydroxymethylation was also increased in NR compared with CON by 1.5-fold. Metanephroi cultured with ascorbic acid 0.1 mg/mL had significantly fewer ureteric bud tips (6.5±0.3 vs 9.0±0.3 per kidney) with no difference in kidney size (6.1±0.4 vs 6.1±0.5 arbitrary units) compared with those cultured with vehicle. DMOG 1 mM, on the other hand, significantly decreased both ureteric bud tip number (3.0±0.6 vs 9.7±1.7 per kidney) and kidney size (1.1±0.1 vs 1.9±0.2 arbitrary units). The effect of DMOG was similar in metanephroi cultured from nutrient-restricted dams. Thus ureteric tip number (2.7±0.3 vs 8.0±1.2 per kidney) and kidney size (1.2±0.1 vs 1.9±0.2 arbitrary units) were significantly decreased by DMOG.

Conclusions: TET proteins are expressed in fetal kidney with increased levels in NR, which is characterized by higher global DNA hydroxymethylation. Both stimulation and inhibition of TET disturb normal kidney development. Whether TET proteins regulate kidney development through DNA methylation and or hydroxymethylation needs to be investigated.

Funding: Government Support - Non-U.S.

SA-PO427

Spatiotemporal Patterning of Intrarenal Urothelium During Embryogenesis

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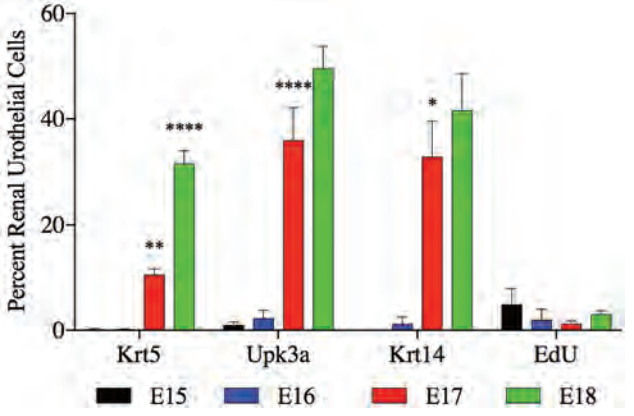
Background: Congenital urinary tract obstruction (UTO) is a leading cause of chronic kidney disease in children. Intrarenal urothelial remodeling occurs prior to parenchymal injury, and formation of a protective uroplakin (Upk) plaque is a key feature of UTO remodeling. Little is known about progenitor-progeny relationships within the renal urothelium during development, precluding efforts to promote adaptive urothelial remodeling during UTO.

Methods: Krt5$^+$, Krt7$^+$, Krt14$^+$, p63$^+$, and Upk$^+$ renal urothelial cells (RUCs) were localized at embryonic days (E)15-E18. EdU (thymidine analogue) was used to identify stage-specific proliferation indices. Krt7$^+$ was used to establish total RUC counts. Renal urothelial thickness was measured at each stage. *Krt5^{CreERT2}* and *Upk2^{CreERT2}* lines were used to indelibly label Krt5$^+$ or Upk2$^+$ cells and their daughters at E16.

Results: Renal urothelial thickness decreased from E15-E18, and demonstrated heterogeneous expression patterns in renal papilla, fornix and pelvis. Rare, discrete Upk$^+$ RUCs were first observed at E16 and formed a nearly contiguous apical lining by E18. Basal Krt5$^+$ RUCs were first identified at E17. Krt14$^+$ RUCs were robustly expressed at E17-E18. p63$^+$ RUCs were observed in basal renal urothelium beginning at E16, commonly localized to Krt5$^+$ RUCs at E17. Proliferation peaked at E15 and EdU co-localized more commonly to Krt5$^+$ rather than Upk$^+$ RUCs.

Conclusions: Renal urothelium thinned as RUC specification occurred. The identification of Upk$^+$ RUCs at E16 coincides with the initiation of urine production. The appearance of Upk$^+$ prior to Krt5$^+$ RUCs indicates an earlier need for terminally differentiated characteristics, while co-localization of EdU to Krt5$^+$ RUCs suggests a developmental progenitor role. Lineage assays will determine progenitor-progeny relationships and establish model systems to evaluate candidate pathways utilized during UTO remodeling.

Funding: NIDDK Support



Time course of renal urothelial differentiation. * p<0.05; ** p<0.005, ****p<0.0001

SA-PO428

Transient Hydronephrosis in the Developing Kidney Leads to Long-Term Epigenetic Changes and Increased Susceptibility to Acute Renal Failure in Adulthood

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Background: The criteria for surgical intervention in patients with congenital urinary obstruction are poorly defined and little is known about the long-term effects of hydronephrosis in the developing kidney. In this study, we evaluated the impact of developmental context on disease progression, the need for intervention, and long-term susceptibility to kidney disease.

Methods: Disease progression was compared in murine models of unilateral ureteral obstruction (UUO) at P1 during nephrogenesis, P14 during the proliferative growth phase, and P60 at maturity. A reversible UUO model (rUUO) was used in neonates to assess the impact of intervention and its timing on long-term outcomes at maturity including growth and maturation, kidney function, and susceptibility to acute renal failure after unilateral ischemic injury (IR/Nx). Disease progression was evaluated by histological methods, functional assessment (serum BUN/Cre), and whole transcriptome analysis (RNA-seq).

Results: While UUO at P60 leads to inflammation and fibrosis, disease progression in neonates is instead characterized by profound developmental deficits. UUO at P1 triggers a 43.8% decrease in nephrogenesis and 35.2% decrease in kidney growth. UUO at P14 results in a 61.6% decrease in proliferation and 26.3% decrease in kidney growth. Impaired renal maturation is prevented by early intervention following rUUO at P14 but not P1 (Recovery/ P1 – 27.1%, P14 – 67.1%). Although mice subjected to rUUO at P14 had only minimal differences in kidney weight and function after 12 weeks of recovery, whole transcriptome analysis showed significant changes in the expression of 30.4% of all genes. Furthermore, when these mice were challenged with an IR/Nx protocol that typically has only moderate effects, they strikingly exhibited acute renal failure (SrCre: CON – 1.8, rUUO – 3.1) and low rates of survival (CON – 100.0%, rUUO – 12.5%). [All results are $p<0.05$]

Conclusions: This study reveals that developmental context has a significant impact on disease mechanisms, long-term outcomes, and treatment strategies. While deficits in nephrogenesis are irreversible, early intervention restores proliferative growth and kidney function. Continued monitoring is required even after recovery as the epigenetic signature remains altered and there is an elevated risk for kidney disease.

Funding: NIDDK Support, Private Foundation Support

SA-PO429

Terminal Differentiation of the Intrarenal Urothelium Attenuates Kidney Injury During Congenital and Acquired Urinary Tract Obstruction

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Background: Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Despite timely detection and surgical correction of the primary obstructive lesion, outcomes vary widely with regard to CKD progression. We hypothesized that remodeling of the intrarenal urothelium confers a protective adaptation during congenital and acquired UTO, by terminal differentiation and elaboration of a highly compliant uroplakin (Upk) plaque.

Methods: The Upk plaque was destabilized in a congenital model of functional lower UTO by generating *Mgb$^{-/-}$;Upk1b$^{-/-}$* mice. As an acute UTO model, unilateral ureteral obstruction (UUO) was induced in young adult *Upk1b$^{-/-}$* and wild type (WT) mice. Alternatively, diphtheria toxin (DT)-mediated depletion of Upk(+) cells was induced following UUO. Urine UPK2 and UPK3A levels were measured by ELISA in children undergoing pyeloplasty for ureteropelvic junction obstruction (UPJO) versus nonobstructed controls.

Results: During congenital and acquired UTO, progressive hydronephrosis triggers reorganization of the intrarenal urothelium, which elaborates a continuous Upk plaque. *Upk1b$^{-/-}$;Mgb$^{-/-}$* mice experience accelerated onset of bilateral hydronephrosis with severe (>67%) parenchymal loss, leading to renal failure and mortality in adolescence. *Upk1b* deletion or depletion of Upk$^+$ cells accelerate renal parenchymal loss following ureteral ligation, attesting to a conserved, stabilizing role for Upk plaque deposition in the acutely obstructed kidney. Lineage analysis demonstrates that UUO triggers a sequence of Upk plaque loss, proliferation, and reacquisition of the Upk plaque by Upk+ cells. Children with UPJO manifest higher urinary UPK protein levels than unobstructed controls.

Conclusions: These complementary experiments provide the first evidence that the Upk plaque confers an essential, protective adaptation to preserve renal parenchymal integrity during congenital and acquired urinary tract obstruction.

Funding: NIDDK Support

SA-PO430

Urinary NGAL as a Risk Factor for Recurrence of Febrile Urinary Tract Infection in Children

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Background: Urinary neutrophil gelatinase-associated lipocalin (NGAL) has received attention recently as a sensitive biomarker of acute kidney injury. However, its ability to protect endogenously against urinary tract infection (UTI) is lesser known. That is, NGAL, which is expressed and secreted from activated neutrophils, acts as an iron chelator and antibacterial peptide that suppresses the growth of *Escherichia coli* and other bacteria. Purpose: To prove the hypothesis that reduced NGAL expression causes recurrence of febrile UTI (fUTI) in children.

Methods: The subjects were 45 children who were diagnosed as having fUTI and treated at our institution from 2012 to 2016 (median age, 1.5 years; 34 boys). We measured their urinary NGAL levels in the non-infected stage (at least 4 months since fUTI recovery). To examine risk factors for recurrence of fUTI, the subjects were divided into a non-recurrent group (24 cases) and a recurrent group (21 cases) according to the presence or absence of fUTI over 1 year. The following items were examined as risk factors: age, sex, presence or absence of grade III or higher vesicoureteral reflux (VUR; all cases received preventive antibiotics), presence or absence of renal scarring, and urinary biomarkers (NGAL and β2-microglobulin). The urinary biomarkers were corrected for creatinine (Cr) level.

Results: In a multiple logistic regression analysis, significant differences between the groups were not observed for age, sex, renal scarring, or β2-microglobulin/Cr level, while the recurrent group had significantly more cases with grade III or higher VUR ($p < 0.01$). Furthermore, the urinary NGAL/Cr in the recurrent group (median, 3.2 μg/gCr; interquartile range, 2.0–4.0 μg/gCr) was significantly lower than that in the non-recurrent

group (median, 16 μg/gCr; interquartile range, 11–20 μg/gCr; p = 0.016). We then created the ROC curve to examine the cut off value of NGAL for predicting recurrence of fUTI. In the area under the ROC curve, which was calculated for NAGL/Cr, was 0.86. Cut off value of 7.6 μg/gCr appeared to have the best predicting accuracy yielding a specificity of 81% and a sensitivity of 88%.

Conclusions: Reduced level of urinary NGAL, which functions to protect endogenously against UTI, is a risk factor of recurrence of fUTI and thus could serve as a biomarker.

SA-PO431

The Ribonuclease Inhibitor Regulates the Host Immune Response to Uropathogenic Escherichia coli

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Background: The Ribonuclease (RNase) A Superfamily encodes cationic antimicrobial peptides with bactericidal activity toward uropathogens. The endogenous RNase Inhibitor (RI) binds to RNases with femtomolar affinity and inhibits their antimicrobial activity. Here, we tested the hypothesis that RI serves a critical role in regulating the host innate immune response during experimental urinary tract infection (UTI).

Methods: We investigated RI expression in the urinary tract by immunofluorescence microscopy and evaluation of beta-galactosidase activity in RI^{LacZ} reporter mice. Using Cre/LoxP recombination, we deleted RI ubiquitously ($RI^{\Delta UBI}$) or selectively in urothelial cells ($RI^{\Delta URO}$) or leukocytes ($RI^{\Delta WBC}$) of adult mice. We transurethrally inoculated control and RI conditional knockout mice with uropathogenic *Escherichia coli* (UPEC) and enumerated bacterial burden in urinary tract tissues by homogenization and serial plating.

Results: We identified RI expression by bladder umbrella cells, renal collecting ducts, and phagocytes, all distinct sources of antimicrobial RNase secretion during UTI. Ubiquitous RI deletion led to rapid onset of erosive esophagitis and gastritis, resulting in profound weight loss and failure to thrive, precluding investigation of UTI susceptibility. $RI^{\Delta URO}$ mice were healthy and deletion of RI within umbrella cells did not lead to alterations in UPEC burden during experimental UTI. In contrast, $RI^{\Delta WBC}$ animals were protected from experimental UTI, with significantly reduced bladder UPEC burden, compared to controls.

Conclusions: RI is a negative regulator of the host leukocyte response to UPEC. Interfering with RI-RNase interactions represents a novel, rational approach to augment innate immunity during UTI.

Funding: NIDDK Support

SA-PO432

Ribonuclease 6 Protects the Kidney from Ascending Infection by Uropathogenic Escherichia coli

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Background: Ribonuclease 6 (RNase 6) is an evolutionarily-conserved antimicrobial peptide with potent bactericidal activity that is induced during urinary tract infection (UTI). Previously, we demonstrated that human and mouse RNase 6 kills uropathogenic *Escherichia coli* (UPEC) *in vitro* at low micromolar concentrations. Here, we investigated the hypothesis that RNase 6 serves an essential protective role in limiting ascending infection by UPEC *in vivo*.

Methods: We generated a $Rnase6^{EGFP}$ knock-in allele to (1) identify the cellular sources of RNase 6 in $Rnase6^{EGFP/+}$ mice; and (2) to determine the consequence of biallelic *Rnase6* deletion ($Rnase6^{EGFP/EGFP}$) on host susceptibility to experimental UTI. We evaluated EGFP fluorescence by flow cytometry and epifluorescence microscopy. We evaluated bactericidal activity and nitric oxide production by bone marrow-derived macrophages using gentamicin protection and fluorometric assays, respectively. We transurethrally inoculated $Rnase6^{EGFP/EGFP}$, $Rnase6^{EGFP/+}$, and control female mice with UPEC. We enumerated bacterial burden in urinary tract tissues by homogenization and serial plating.

Results: Flow cytometry in $Rnase6^{EGFP/+}$ mice reveals EGFP expression by circulating $Ly6C^{hi}$ monocytes which undergo maximal recruitment to the infected bladder by 6 hours post infection. In addition, we identified EGFP expression within resident macrophages of the bladder and kidney. In contrast, the *Rnase6* promoter is not active in renal or bladder epithelial cells. We confirmed *Rnase6* deletion in $Rnase6^{EGFP/EGFP}$ mice, which displayed normal urinary tract development, fertility, and hematopoiesis. *Rnase6* deficiency did not inhibit nitric oxide production or UPEC killing by bone marrow-derived macrophages. In contrast, *Rnase6* deficiency resulted in increased susceptibility to experimental UTI, with significantly higher UPEC burden throughout the urinary tract, compared to control mice.

Conclusions: Use of $Rnase6^{EGFP/+}$ mice offers a powerful approach to track cellular sources of RNase 6, as well as a means to screen compounds that regulate *Rnase6* promoter activity in the future. Use of $Rnase6^{EGFP/EGFP}$ mice confirms a critical role for RNase 6 in UPEC clearance *in vivo*.

Funding: NIDDK Support

SA-PO433

Dual Role for the Uroplakin Plaque in Establishment and Maintenance Phases of Urinary Tract Infection

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Background: Uropathogenic *Escherichia coli* (UPEC) account for up to 90% of human urinary tract infections (UTI). Specialized epithelial cells of the bladder produce glycosylated uroplakin (Upk) plaques, which bind to type I fimbriae of UPEC in a mannose-dependent manner. Here we evaluated the role and regulation of the Upk plaque during experimental UTI.

Methods: We established acute experimental UTI in 6-8 week old female $Upk1b^{-/-}$ and FVB/N mice by transurethral inoculation of UPEC or *Enterococcus faecalis*. Intracellular bacterial communities were detected based on β-galactosidase activity. Upk proteins were localized by immunohistochemistry, and plaque ultrastructure was visualized by transmission electron microscopy. Urothelial barrier function was evaluated on the basis of permeability to FITC-Dextran. We modeled chronic UTI by UPEC inoculation of 6-8 week old female C3H/HeOuJ mice.

Results: *Upk1b* deletion results in absent uroplakin plaque on the apical surface of bladder epithelial cells and increased permeability to FITC-Dextran. While intracellular bacterial communities were easily detectable in control urothelium, $Upk1b^{-/-}$ bladders lacked these intracellular reservoirs of UPEC entirely. Moreover, *Upk1b* loss led to reduced neutrophil infiltration of the bladder urothelium. Consistent with the failure of UPEC to invade the epithelium in the absence of the Upk plaque, $Upk1b^{-/-}$ mice exhibited reduced UPEC urinary tract colonization compared to controls ($p < 0.05$, Mann-Whitney U test). In contrast, Upk plaque loss did not impact the ability of *Enterococcus faecalis* to establish experimental UTI. When UTI were established in the chronic C3H/HeOuJ model, *Upk* mRNA and Upk protein levels decreased rapidly and remained suppressed for up to 4 weeks following infection.

Conclusions: Upk1b is critically required for Upk plaque assembly in superficial bladder epithelial cells. The Upk plaque initially facilitates UPEC invasion of the bladder, but this structure is dispensable for maintenance of infection, as chronic UTI results in downregulation of Upk plaque assembly at the mRNA and protein levels.

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SA-PO434

RNase 7 Shields the Kidney and Bladder from Uropathogens

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Background: In an era of multi-drug resistant pathogens, new therapies are needed to prevent urinary tract infections (UTI). Our laboratory identified Ribonuclease 7 (R7) as a human antimicrobial peptide that is secreted by the bladder urothelium and kidney's intercalated cells into the urine. Neutralization of R7's urinary antibacterial activity facilitates uropathogenic *Escherichia coli* (UPEC) replication. While R7 has potent bactericidal activity against UPEC, our understanding of its contributions to urothelial defenses is limited *in vivo* because its expression is absent in the laboratory mouse and restricted to humans/upper primates. Thus, we generated humanized transgenic R7 mice and assess R7's *in vivo* antimicrobial activity.

Methods: Using BAC-based recombineering, we integrated the human *RNASE7* gene into the mouse genome. BAC-R7 transcript and peptide expression was characterized in kidneys and bladders from R7 transgenic mice and littermate controls in states of health and after mice were transurethrally infected with UPEC. R7 cytotoxicity and its impact on murine immunity was evaluated with cytokine arrays, complete blood counts, serum chemistry, and histology. R7's antibacterial activity was evaluated by subjecting mice to experimental UTI. After infection, kidneys, bladders, and urine were collected and UPEC burden was quantitated.

Results: R7 transgenic mice had normal development, phenotypes, and urinary tract histology. R7 mRNA and peptide expression were detected in bladder and kidneys of transgenic mice. Immunostaining localized R7 production to the kidney's intercalated cells and the bladder urothelium, which mirrors human expression. R7 mice had normal renal function, cytokine profiles, and complete blood counts. After UTI, R7 transgenic mice had 2-3 fold lower urine, bladder, and kidney UPEC burden compared to littermate controls. Following UPEC inoculation, R7 mRNA and peptide expression increased in bladders and kidneys.

Conclusions: R7 expression in our transgenic humanized mice is similar to humans. R7 has limited cellular toxicity and does not impact basal murine immune function. Following experimental UTI, R7-expressing mice are significantly protected from UPEC. These studies provide the needed evidence that R7 has a key role in urothelial defense against UPEC and suggest that R7 may be an ideal candidate to develop as a new UTI therapy.

Funding: NIDDK Support

SA-PO435

Fibroblast Growth Factor 23 Is Associated with Impaired Cognition in Children with CKD

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Background: Plasma FGF23 concentrations increase early in the course of chronic kidney disease (CKD) in children and are a strong predictor of disease progression and left ventricular hypertrophy. High plasma FGF23 has been linked to cognitive dysfunction and cerebrovascular disease in adults with CKD. Whether FGF23 associates with impaired cognition in children is unknown.

Methods: In 538 children with CKD stages 2-4 enrolled in the Chronic Kidney Disease in Children (CKiD) study, we measured plasma C-terminal FGF23 and phosphorus and performed cognitive function tests of intelligence, academic achievement, and targeted executive functions. We used multivariate linear regression to analyze cross-sectional associations of baseline FGF23 and phosphorus concentrations with standardized cognitive test scores and cognitive risk (defined as a score ≥1 standard deviation (SD) below mean performance for age in healthy children), adjusting for age, sex, race, estimated GFR, proteinuria, blood pressure, and anemia.

Results: At baseline, median age was 12 [95% CI: 8.3, 15.2] years, eGFR was 54 [40.5, 67.8] ml/min/1.73 m^2, plasma FGF23 and phosphorus were 168 [78, 175] RU/ml and 4.2 [4, 4.9] mg/dl, respectively. In univariate analyses, higher tertiles of FGF23 were associated significantly with impaired test scores for errors of omission, a measure of attention regulation (p=0.002, 2-tailed Kruskal-Wallis rank test), and academic achievement (p=0.06). In fully adjusted analyses, we observed that each 50% increase in plasma FGF23 was associated with a 1 SD worsening of omission scores (β=2.07 [0.7-3.4], p=0.003). The percentage of children at risk for one or more cognitive deficits ranged from 18 to 32%. Furthermore, the cognitive risk for errors of omission was 14% higher in children in the highest compared to the lowest FGF23 tertile (p=0.01, 2-tailed chi-squared test). Plasma phosphorus, normalized for age, did not associate with cognitive test scores or cognitive risk.

Conclusions: In children with pre-dialysis CKD, higher baseline plasma FGF23 is associated with lower performance in targeted tests of executive function, specifically attention regulation, independent of GFR. These data suggest that high plasma FGF23 contributes to a greater risk for disorders of attention regulation as GFR declines.

SA-PO436

FGF23, Blood Pressure, and Urinary Sodium Handling in Young CKD Patients

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Background: FGF23 has been associated with hypertension, partly attributed, to experimental observations describing FGF23-mediated enhanced Na reabsorption in the distal tubule, ↓natriuresis, volume expansion and hypertension. We examined whether FGF23 levels and urinary Na excretion are associated with blood pressure (BP) measurements in patients with incipient chronic kidney disease (CKD).

Methods: Systolic (S) and Diastolic (D) Blood pressure (BP) height- and age-adjusted percentiles (%ti), and C-terminal FGF23, 24-hour natriuresis (UNa), and fractional excetion of Na (FENa) were analyzed in young patients with CKD stages 1,2 and 3. Estimated GFR (eGFR) were calculated by cystatin (cys) and creatinine (cr) equations.

Results: 57 patients (age± SD, 14.5 ±2.1 years; 41 males), 17 African Americans, 26 Whites and 14 of other ethnicities, were defined CKD stages 1,2 and 3 by eGFRcys (94±29; 37-188) and eGFRcr (97±33; 34-71) ml/min/1.73 m_2. Serum Na, P, 1,25$(OH)_2$D and plasma renin were normal. UNa (162±73 mEq/24 hours), FENa (0.6±0.46; 0.03-1.8 %) or FGF23 levels (113±83; 13-606 RU/ml, normal< 200 RU/ml) did not correlate with SBP %ti (69±32; >95 in 30%) or DBP %ti (66±24; >95 in 10%). Although FGF23 levels were higher in CKD stages 2 and 3 vs Stage1, natriuresis and FENa values did not differ among groups (Table). Patients with FENa < 1st quartile (0.24%) had FGF23 levels (103 ± 55 RU/ml) comparable to those in higher quartiles (119±94 RU/ml), and SBP %ti were similar in both groups (57±32 vs 71±31, respectively).

Conclusions: Despite higher levels of FGF23 in CKD stages 2-3 vs. Stage 1, FENa values were comparable, and neither FGF23 nor FENa correlated with BP. These observations do not support a role of FGF23-mediated increased tubular reabsorption of Na as a mediator of elevated BP in the earlier stages of CKD.

Funding: Clinical Revenue Support

Groups	N	eGFRcys (ml/min/1.73m2)	UNa (mEq/24 hours)	FENa (%)	FGF23 (RU/ml)
CKD Stage 1	33	106±24	155±81	0.56±0.36	95±47
CKD Stage 2-3	24	80±28**	172±61	0.58±0.50	137±110*
All Patients	57	94±29	165±73	0.57±0.46	114±83

**P=0.0001;*P<0.05, both vs. CKD Stage 1

SA-PO437

Persistent Asymptomatic Isolated Hematuria in Children in IgA Nephropathy: Histopathological Features and Prognosis

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Background: Patients with recurrent episodes of macroscopic hematuria and persistent isolated microscopic hematuria (proteinuria<0.03g/mmol creatinuria and EGFR> 90ml/min/1.73m2) in IgA nephropathy (IgAN) does not correlate with prognosis. Early studies suggest that gross hematuria was associated with better outcome and with normal or minor abnormalities tissue on biopsy. We studied clincial and histological findings and prognosis in children with biopsy-proven with persistent isolated microscopic hematuria.

Methods: Data on 82 consecutive children were reviewed. 14 children with persistent isolated microscopic hematuria (median 11.7 years old; median of clinical follow-up 4.3 years) were reviewed. Renal biopsies were scored for Oxford classification.

Results: 13 out 14 patients were male. Analysis of renal biopsies finds: Mesangial proliferation in 9 patients (64,3%), endocapillary proliferation in 7 (50%) patients and no patient have extracapillary proliferation. Focal glomerulosclerosis/adhesion was found in 8 (57.1%) patients, podocytopathic features in 1 (8.3%) patient and no patient have tubular atrophy/interstitial fibrosis. 2 (14.3%) patients received steroid therapy and 5 (35.7%) patients were treated with supportive care treatment alone (renin angiotensin system blockade (RASb)). At the last clinical follow up, no patients reach end-stage of renal disease, median eGFR was 100.9 ml/min/1.73m^2 and median proteinuria 0.15 g/g.

Conclusions: In western countries, recurrent isolated microscopic hematuria is not a common indication for kidney biopsy. In our study, we show that children with recurrent episodes of macroscopic hematuria and persistent isolated microscopic hematuria does not preclude normal or minor abnormalities tissue. Renal biopsy should be proposed in children with recurrent episodes of macroscopic hematuria and persistent isolated microscopic hematuria. Mesangial and endocapillary proliferation is significantly associated with a poor long-term renal outcome and should open discussion about treatment (steroid therapy and/or RASb) even in absence of proteinuria and renal dysfunction.

SA-PO438

Immunosuppressive Treatment in Children with IgA Nephropathy and Evidence to Support the Clinical Value of Podocytopathic Features

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Background: There is a need for treatment guidelines and prognostic factor identification in children with primary IgA nephropathy (IgAN). We analyzed the causative effect of steroids and the applicability of the Oxford classification

Methods: Data on 82 consecutive children (mean 10.6 years; median follow-up 3.3 years) were reviewed. 21 patients (25.6%) presented with acute kidney injury, and 6 (7.3%) with nephrotic syndrome. Renal biopsies were scored for Oxford classification, podocytopathic features, and extracapillary proliferation in two groups: a groupG1, treated with steroid therapy (later in association with cyclophosphamide) and supportive care (renin angiotensin system blockade) and a group treated by supportive care alone.

Results: The two groups were not comparable, since baseline clinical data were different. eGFR in immunosupressive group significantly improved between M0 and M6 from 89.9 (61.2–114.5) to 111.7 (101.7–120)ml/min/1.73m^2, p=0.001). Proteinuria also significantly decreased from (1.6 (1–4.3) to 0.3 (0.2–0.7)g/g creat, p<0.001). In the supportive care group group, eGFR and proteinuria remained stable. Podocytopathic features were predictive of renal function decline by univariable (-4.9±14.9ml/min/1.73m^2, p=0.0079) and multivariable analysis and of poor renal prognosis to a combined event (renal function impairment more than 10% of the eGFR baseline or chronic kidney disease stage 3 at 6 months) in univariable and multivariable analysis. MEST-C score failed to prove its prognostic value.

Conclusions: Immunosuppressive treatment, especially steroid therapy, seems beneficial in children with glomerular inflammation and proliferation. The Oxford classification does not appear to be entirely appropriate in predicting long-term renal prognosis for children, whereas the characteristics of podocytopathy are strongly predictive of renal prognosis.

SA-PO439

Clinical and Histological Differences Between Adults and Children in New Onset IgA Nephropathy

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Background: Recent studies showed that prognosis of children IgAN could be as severe as adults but would manifest differently. We addressed this question comparing clinical and histological characteristics at diagnostic of IgAN between children and adult.

Methods: Data on 211 consecutive patients, including 82 children and 129 adults were reviewed. Renal biopsies were scored for Oxford classification and podocytopathic features.

Results: Estimated glomerular filtration (eGFR) and serum albumin at diagnostic was lower in adults compared to children (64 vs 89.5 ml/min/1,73m^2; p=0.0001) and (3.4 vs 3.8g/dl, p=0.0001). Serum albumin was lower in children compared to adults (3.4 vs 3.8g/dl, p=0.0001) while proteinuria was not different. Histological analysis of kidney biopsy finds higher proportion of mesangial (M1) and endocapillary (E1) proliferation in children compared to adult (M1 (80.7% vs 27.9% p=0.0001); E1 (71.3% vs 30% p=0.0001). Focal glomerulosclerosis (S1), tubular atrophy/interstitial fibrosis ≥ 25% (T1) and podocytopathic features (P1) were higher in adult, (S1 (81.5% vs 61.3% p=0.0012), T1 (49.5% vs 1.35% p=0.0001), P1 (33.8% vs 16.4% p=0.007)). Proteinuria was associated with M1, E1 and C1 in children (M1, p=0.001; E1, p=0.0005; C1, p=0.0014) whereas proteinuria was associated with S1, P1 and T1 in adult (S1, p=0.0001; P1, p=0.0001; T1, p=0.001). After steroid treatment, proteinuria decreased in children (1.54 (0.9–3.6) to 0.03 (0.2–0.7)g/g, p<0.001) and in adult group (1.31 (0.77–2.2) to 0.4 (0.2–1)g/g, p<0.001). eGFR remain stable in adult (41.4 to 36.9 ml/min/1.73m2) and increase significantly in children (98.6 to 109,3 ml/min/1.73m2) between M0 and last follow-up.

Conclusions: In children IgAN, proteinuria is related to glomerular proliferative lesions whereas in adult proteinuria is related to chronic lesions. Steroid would be more effectiveness on eGFR and proteinuria in children due to the steroid sensitivity of glomerular lesion.

SA-PO440

Does MEST-C Score Predict Outcomes in Pediatric Henoch Schönlein Purpura Nephritis?

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Background: Children with Henoch-Schönlein purpura nephritis (HSPN) are at risk for long-term negative renal outcomes. HSPN renal biopsies have been graded using the International Study of Kidney Disease in Children criteria, which is limited by a lack of correlation with outcomes. The MEST-C scoring system by 2016 Oxford Classification has been shown to predict poor outcomes in IgA nephropathy (IgAN) but its utility in predicting outcomes in HSPN is incompletely described. Our hypothesis is that MEST-C score predicts outcomes in US children with HSPN.

Methods: Data of 32 children with HSPN referred to pediatric nephrology who underwent renal biopsy between April 1, 2004 and March 1, 2018 were reviewed. Logistic regression analysis was used to compare MEST-C scores to a composite outcome at the last known follow-up visit: hypertension (systolic or diastolic blood pressure ≥95% for age/sex/height), chronic kidney disease (glomerular filtration rate <90 mL/min/1.73 m^2), or proteinuria (urine protein-to-creatinine ratio >0.2 mg/mg).

Results: Their median baseline age was 7.9 years (IQR 5.9); 56% were male, 16% were Hispanic, 12.5% African-Americans, and 71.5% Caucasians. 31% of patients had a S1 score. After a median follow up of 2.7 years (IQR 4.3), 34% of patients reached the outcome. Of the MEST-C components, only S1 was significantly associated with the outcome (OR 10.5, 95% CI 1.9 to 59.4). ROC analysis revealed that an S1 score predicted the outcome (AUC 0.75, 95% CI 0.58 to 0.91) with 63.6% sensitivity (95% CI 30.8 to 89.1%) and 85.7% specificity (63.7 to 97.0%), indicating a positive predictive value of 70.0% (34.8 to 93.3%) and a negative predictive value of 81.8% (59.7 to 94.8%).

Conclusions: Our study demonstrated that MEST-C score, specifically S1, strongly predicted the development of hypertension, proteinuria, and chronic kidney disease in HSPN children in the US. Further investigation in larger, multi-center studies are warranted to validate our findings.

SA-PO441

Clinical Relevance of C4d Deposition in Pediatric IgA Nephropathy

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Background: Immunoglobulin A nephropathy (IgAN) is one of the most common causes of primary glomerulonephritis and is characterized by predominant IgA deposition in the glomerulus mesangium. Recently, it has been well-known that the activation of complement system plays an important role in the development and progression of IgAN. The aim of this study is to investigate the association between the evidence of C4d staining and clinical or histopathologic features of pediatric IgAN patients.

Methods: Fifty-six pediatric patients diagnosed with IgA nephropathy through renal biopsy from 2006 to 2017 were reviewed retrospectively. Immunohistochemical C4d staining was performed in all biopsy tissues. Clinical/histopathological features were statistically analyzed according to C4d staining positivity.

Results: A total of 56 patients (male 58.9%, female 41.1%) were included in the study and the mean age at diagnosis was 12.1 ± 4.7 years. Among the 56 patients, 31 (55.4%) showed positive glomerular C4d staining; a mesangial (n=16), a peripheral capillary (n=11), or a mixed (n=4) distribution pattern. Urine protein-to-creatinine ratio was significantly higher in C4d-positive patients (p = 0.001). The severity of mesangial proliferation according to the Haas and Oxford classification were significantly associated with positive C4d staining (p < 0.001). In the Haas classification, the positive rate of C4d in patients with subclass I was 12.9% (n=4), but in them with subclass III and IV were 45.2% (n=14) and 38.7% (n=12), respectively. In addition, as for the Oxford classification of IgAN, positive C4d staining turned out to be significantly associated with the evidence of mesangial proliferation (M1) (p<0.001). The positive rate of C4d in patients with M1 was 67.7% (n=21), but in them with M0, 32.3% (n=10). However, there was no significant association of the evidence of endocapillary hypercellularity, segmental sclerosis, and tubulointerstitial fibrosis/atrophy between the patients with positive C4d and them with negative C4d. Additionally, as for C4d staining patterns such as mesangial, peripheral capillary or mixed patterns, there was no significant correlation between these patterns and histologic severity of the Haas or Oxford classification.

Conclusions: Positive C4d staining was found to be significantly associated with clinical/histopathological progression of pediatric IgAN.

SA-PO442

Renal Involvement of Inflammatory Bowel Diseases in Children and Adolescents: From Korean Pediatric IBD Cohort

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Background: Recently, the incidence of inflammatory bowel disease (IBD) has been rising rapidly, and several reports have described renal complications of IBD. We evaluated the clinical manifestations of renal complications in children with IBD to enable early detection and prompt treatment of renal complications.

Methods: We retrospectively reviewed the medical records of 456 children and adolescents aged <20 years who had been diagnosed with IBD since 2000. We analyzed age, sex, medication use, IBD disease activity, and clinical manifestations of renal symptoms.

Results: Our study comprised 456 children with IBD including 299 boys (65.6%) and 157 girls (34.4%) with a mean age±SD of 14±3 years. The mean follow-up period was 4.61±2.93 years. The study included 346 children with Crohn's disease (CD, 75.9%) and 110 with ulcerative colitis (UC, 24.1%), and the incidence of CD was >UC. Among the 456 children studied, 67 (14.7%) showed confirmed renal manifestations, and 59 were identified as children with CD and 8 as children with UC. We observed 26 children (38.8%) with isolated hematuria, 30 (44.8%) with isolated proteinuria, and 11 (16.4%) with hematuria and concomitant proteinuria. A renal biopsy was performed in 7 children with CD. Of them, 5 children showed both microscopic hematuria and proteinuria. Persistent microscopic hematuria and recurrent gross hematuria was observed in 2 children. Histopathological examination revealed IgA nephropathy in 5 children (71.4%) and Henoch-Schönlein purpura (HSP) nephritis in 1 child (14.2%), whereas 1 child (14.2%) showed no histopathological abnormalities. IBD disease activity was evaluated in 102 children, of which 81 showed CD and 21 showed UC. No significant correlation was observed between the IBD disease activity and the presence of renal manifestations in 102 children in whom we were able to assess disease activity. In all 102 children, disease activity was mild, and the disease was well controlled.

Conclusions: Children with IBD are more likely to show kidney-related symptoms than healthy children and adolescents. Therefore, regular screening of urine and evaluation of renal function are necessary for early detection of renal complications.

SA-PO443

Long-Term Outcome of 62 Pediatric Henoch-Schönlein Nephritis Patients Treated with Methylprednisolone Pulses or Cyclosporine A

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Background: The optimal treatment of Henoch-Schönlein purpura nephritis (HSN) has remained unclear. We evaluated the outcome of pediatric HSN patients treated initially with methylprednisolone (MP) or cyclosporine A (CyA) in the five university hospitals in Finland between 1996 and 2011.

Methods: The medical charts were reviewed until the last follow-up visit and 47 (76 %) patients attended also additional urine and blood sample screening. MP-treated patients (n=42) received three 30 mg/kg pulses followed by oral prednisone for a median of 4.3 (IQR 3.8 – 5.9) months. Median treatment time for CyA-treated patients (n=20) was 1.2

(IQR 1.0 – 1.7) years with an initial target blood concentration of 150-200 μmol/l. Fifty-nine (95 %) patients had received ACE-Is and/or ARBs.

Results: Baseline characteristics at the time of renal biopsy and outcome after a mean follow-up of 10.8 years are shown in Table 1. Eighteen (90 %) CyA-treated and 26 (62 %) MP-treated patients achieved favorable treatment response with initial treatment and needed no additional immunosuppressive therapy (RR 1.45, 95 % CI 1.07 – 1.96, p=0.035; for favorable treatment response). One patient developed ESRD and another patient had decreased renal function (eGFR <60 ml/min/1.73m^2), both initially treated with MP. Six patients (5 MP, 1 CyA) had mildly decreased renal function (eGFR 60 – 89 ml/min/1.73m^2), one of them having non-nephrotic proteinuria.

Conclusions: Renal outcome was good in both treatment groups. However, CyA-treated patients needed less additional immunosuppressive treatment and none of the initially CyA-treated patients had decreased renal function (eGFR <60 ml/min/1.73m^2) after 10.8 years of follow-up. Urinary abnormalities may persist or develop and therefore long-term follow-up of HSN patients is mandatory.

Funding: Private Foundation Support

Table 1

Baseline characteristics at renal biopsy	Initial MP treatment (n=42)	Initial CyA Treatment (n=20)	p-value
Age (years)	9.5 ± 3.3	10.7 ± 3.4	0.16
Patients with nephrotic-range proteinuria (>40mg/m2/h)	36 (86 %)	14 (74 %)	0.29
ISKDC grade ≥ III (%)	29 (71 %)	18 (90 %)	0.12
Outcome at the end of follow-up			
Patients with proteinuria (%)	9 (22 %)	2 (11 %)	0.48
Patients with hematuria (%)	5 (13 %)	3 (17 %)	0.70
Patients with blood pressure medication (%)	8 (20 %)	7 (35 %)	0.22
eGFR (ml/min/1.73m2)	110 ± 21	109 ± 12	0.95

SA-PO444

Clinicopathological Significance in Juvenile-Onset Silent Lupus Nephritis

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Background: In patients with juvenile-onset systemic lupus erythematosus (SLE), there have been reports of silent lupus nephritis (SLN) patients without abnormal urinalysis and renal impairment. Currently, renal biopsies are the gold standard for diagnosis and monitoring of LN. The purpose of this study is to clarify the clinicopathological significance of juvenile-onset SLN.

Methods: Retrospective analysis of 57 patients who underwent renal biopsy among 59 patients diagnosed as juvenile-onset SLE who met the American College of Rheumatology criteria for the classification of SLE between December 2000 and March 2017 to compare clinical and pathological findings between SLN and others.

Results: There were 27 patients (47.4%) with SLN. Clinical findings showed significant differences (SLN vs. non-SLN) in eGFR (174.9 vs 147.5 ml/min/1.73m^2, p=.02) and serum C3 level (76.0 vs 46.5 mg/dl, p=.04). The distribution of ISN/RPS classes of LN was as follows: class I: II: III: IV: V (12: 11: 3: 1: 0 vs 2: 7: 6: 14: 1; p=.003). Though SLN group showed milder pathological presentation, 4 cases with SLN showed severe pathological findings such as class III or IV. The 4 patients with class III and IV had significantly higher dsDNA antibody titer (159.2 vs 42.1 IU/ml, p =.02) and lower serum C3 level (37 vs 77 mg/dl, p =.03) than the other SLN cases. As to immunofluorescence, all patients showed the deposition of immunoglobulins and the degree of deposition of IgG and C3 in SLN was significantly weaker than in non-SLN. In electron microscopy, the degree of subendothelial and subepithelial EDD was significantly weaker in SLN.

Conclusions: Most of the patients with SLN showed milder pathological presentation, but some cases showed severe pathological presentation regardless of minor clinical presentations. We confirmed an importance of renal biopsies for juvenile-onset SLE. Serum C3 level might be an important marker of the severity of SLN.

SA-PO445

Altered Expression of CD46 Mediated Tr1 Cytoplasmic Isoforms Associated with IL-10 Secretion Can Induce Remission of Active Lupus Nephritis

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Background: CD46-costimulated T cells in the presence of IL-2 acquire a Tr1 type Treg phenotype, secreting high amount IL-10 and granzyme B. There was two forms of CD46 cytoplasmic isoforms. Cyt1 inhibits and Cyt2 augments inflammation. To elucidate whether CD46 mediated Cr1 cells can induce remission in active lupus nephritis (LN) by intravenous methylprednisolone (IVMP) therapy, we evaluate IL-10 secreting Tr1 cells in peripheral blood mononuclear cells (PBMCs) and renal biopsy specimens, the capacity of CD46$^+$ Tr1 cells to induce IL-10 production, altered expression of CD46 cytoplasmic ioforms before and after IVMP therapy.

Methods: PBMCs were isolated from fourty pediatric class III or IV LN active LN patients and from ten healthy controls before and after three days of IVMP. Purified CD4$^+$ T cells from patients before and after IVMP as well as healthy controls were stimulated with anti-CD3 and CD46 mAbs in the presence of IL-2 to generated Tr1 cells.

Results: Decreased CD46 expression on CD4$^+$ T cell in PBMCs and renal biopsy specimens from active LN patients versus controls, correlating with higher anti-dsDNA Ab level and lower serum C3, C4 levels. IL-10, granzyme B, CCR4, CCR7 expression and CD4$^+$ T cell proliferation were diminished by CD3/CD46-activated Tr1 cells in active LN. CD4$^+$ T cell from active LN patients showed a statistically increase in IFN-r$^+$ T cells when compared to healthy control T cells following CD3 activation but failed to switch efficiently from IFN-r to IL-10 production following CD3$^+$/CD46 stimulation. After IVMP altered expression of CD46$^+$ Tr1 cell cytoplasmic isoform with increasing CD46-Cyt1/ -Cyt2 ratio. IVMP also increased AKT phosphorylation and enhanced adhesion, migration of CD3/CD46 activated Tr1 cells and IFN-r switch to IL-10 production in active LN patients.

Conclusions: Switching efficiency from IFN-r to IL-10 production of CD3$^+$/CD46 stimulated Tr1 cells was failed in active LN patients. IVMP rescue INF-r switching IL-10 production associated with induction of remission in active LN also increasing adhesion and migratory capacity to suppress inflammation by CD46-mediated Tr1 cells. Thus, pharmacologic intervention to alter pattern of CD46-Cyt1, -Cyt2 expression with inducing IL-10 secretion by CD46 medicated Tr1 cells are viable approach in active LN patients.

SA-PO446

Association of APOL1 Risk Variants with Subclinical Renal Disease in HIV Infected Children and Apparently Healthy Children from Central Africa (Democratic Republic of Congo)

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Background: Apolipoprotein-L1 (*APOL1*) risk variants G1 and G2 increase the risk of progressive chronic kidney disease (CKD), including HIV-related CKD, among sub-Saharan African descents. HIV infection, a substantial healthcare problem in sub-Saharan Africa, is an extremely potent trigger factor for *APOL1* kidney disease. However, data on *APOL1* risk genotypes from Central Africa still remain limited and the association with HIV-related CKD is not yet well documented. We aimed to describe the prevalence of *APOL1* risk variants in the Democratic Republic of Congo (DRC) and to assess the association between these variants and the subclinical renal disease in both HIV infected children and apparently healthy children.

Methods: A total of 813 participants, of whom 401 HIV infected children treated with antiretroviral therapy (ART) and 412 apparently healthy children, were enrolled from four large districts in Kinshasa, the capital of the DRC. *APOL1* high-risk genotype (HRG) was defined by the presence of 2 risk variants (G1/G1, G2/G2, and G1/G2) and low risk genotype (LRG) if 0 or 1 risk variants were present. As the main outcomes, reduced kidney function was defined as eGFR <60 ml/min per 1.73 m^2 and elevated urine albumin-to-creatinine ratio (ACR) ≥ 30mg/g.

Results: From 813 participants, *APOL1* sequence analysis revealed 52 (6.4%) carrying HRG. Regarding LRG, 168 (20.6%) participants carried G1/G0 while 116 (14%) carried G2/G0. Of 401 HIV infected children, 72 (18%) had elevated albuminuria versus 40 (9.7%) out of 412 apparently healthy children (p<0.001) and reduced kidney function was detected in 26 (6.5%) against 13 (3.1%) (p=0.019). Considering the association between *APOL1* HRG and renal disease, 18/23 (78.3%) HIV infected children carrying HRG had elevated albuminuria (0R 21.6, 95%CI 7.3-76.6; p<0.001) against 5/29 (17.2%) apparently healthy children (0R 2.1, 95%CI 0.6-6.0; p=0.137). No significant difference was found concerning the reduced renal function.

Conclusions: The *APOL1* risk variants are highly prevalent in the DRC. The HIV infection is strongly associated with the presence of subclinical renal disease, especially in those carrying the *APOL1* HRG.

SA-PO447

Novel Truncating Mutations in Autosomal Dominant FSGS Genes Cause Childhood Onset Steroid-Resistant Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a leading cause of end stage kidney disease in children. Most autosomal dominant genes are presumed to be due to gain-of-function mutations. Mutations in transient receptor potential canonical 6 (*TRPC6*) and inverted formin 2 (*INF2*) have been described in familial focal segmental glomerulosclerosis (FSGS). Most of the mutations described are missense mutations. Truncating (loss of function) mutations in these genes have not been well described.

Methods: We identified 181 families with SRNS in our worldwide cohort. Families were screened for variants in ten known autosomal dominant FSGS genes (*INF2, TRPC6, COL4A3, COL4A4, WT1, ACTN4, ANLN, CD2AP, ARHGAP24,* and *LMX1B*) using targeted sequencing of custom amplicons (TSCA). Causative mutations were defined as non-synonymous variants, obligatory splice site variants, or truncating variants that had a minor allele frequency <1% in the normal population. Non-synonymous variants were considered pathogenic if they were also reported to be deleterious by at least 2 *in silico* software models. Variants were confirmed using Sanger sequencing.

Results: We identified two novel truncating mutations in *TRPC6* and *INF2*, respectively, in two families with onset of disease at age <10 years. Family DUK34462 consists of three affected members with an autosomal dominant pattern of inheritance. We identified a novel stop codon change in *INF2* (p.E249X) in a child who presented with disease at the age of eight years. The second family is DUK40015 with one affected individual with onset of disease at the age of ten years. We identified a frameshift mutation in *TRPC6* (p.G39fsX41) in this child. Apart from early onset of disease, the phenotype in these two families was not different from individuals with missense mutations in the two genes, in that they both have therapy resistant disease.

Conclusions: In conclusion, truncating mutations in autosomal dominant SRNS/FSGS genes may cause early onset childhood SRNS, likely by haploinsufficiency effect on pathways that are critical for normal development of the glomerular filtration barrier.

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SA-PO448

Evidence Against Routine Genetic Testing for SRNS in an Outbred Population

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a leading cause of end stage kidney disease in children. Recent advances in genomic technology have led to the identification of more than 50 genetic causes of SRNS, most of which code for proteins located within the glomerular filtration barrier. Despite these advances, there are no clear clinical guidelines for genetic screening in patients with SRNS.

Methods: Our worldwide multi-ethnic cohort consisted of 492 individuals from 181 families with SRNS, of whom 86 families had familial disease and 95 individuals had sporadic disease. Initial genetic screening was performed by direct sequencing of candidate genes and whole exome sequencing. Analysis in recent years was performed using targeted high-throughput sequencing of 42 known SRNS genes and risk loci. Causative mutations were defined as missense variants, truncating variants, and obligatory splice site variants with a minor allele frequency <1% in the normal population. Non-synonymous variants were considered pathogenic if determined to be deleterious by at least two *in silico* software models. In order to provide clinical guidelines, we evaluated for differences in age at disease onset, sex, race, family history of SRNS or chronic kidney disease (CKD), extra-renal manifestations, and renal biopsy findings.

Results: We identified disease causing variants in 34/81 (39.5%) families with familial SRNS and 6/95 (6.3%) individuals with sporadic disease. Amongst families with hereditary disease, causative variants were identified in 44.6% of families with presumed autosomal dominant inheritance and 23.8% of families with presumed autosomal recessive inheritance. Variants in *INF2*, *COL4A3*, and *WT1* accounted for over half of all causative mutations. Family history of SRNS or CKD was the only significant clinical factor predictive of identifying a causative mutation (χ^2 p<0.00001).

Conclusions: In this worldwide cohort, we identified causative mutations in almost 40% of all families with hereditary SRNS, compared to only 6% of individuals with sporadic disease, making family history the single most important clinical predictor of monogenic causes of disease. These data support the use of genetic testing in patients with a positive family history of SRNS, and selective testing in those with sporadic disease.

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SA-PO449

Adrenal Suppression After Prednisolone Treatment in Children with Idiopathic Nephrotic Syndrome: A Multicenter Prospective Study

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Background: Severe iatrogenic adrenal insufficiency can occur after steroid treatment. However, there have been a limited number of studies in adrenal insufficiency after prednisolone (PSL) treatment in children with idiopathic nephrotic syndrome (NS), despite much repeated use of PSL.

Methods: We prospectively obtained data of patients with NS aged 2 to 19 years who underwent PSL treatment using International Study of Kidney Disease in Children (ISKDC) regimen from September 2016 to August 2017 at two children's hospitals in Tokyo. In the present study, adrenal insufficiency was defined as cortisol values less than 5 mcg/dL at 9 AM, based on our previous study in Kawasaki disease showing that single serum cortisol values less than 5 mcg/dL obtained at 9 AM from children treated with PSL were significantly correlated with peak serum cortisol value less than 15 mcg/dL in the corticotropin-releasing hormone stimulation test. Patients were divided into two groups and compared: an adrenal insufficient group (I) and a sufficient group (S) based on the serum cortisol values.

Results: Ninety-eight children (70 boys) were enrolled and analyzed in this study: 12 (12.2%, 10 boys) were in the I group and 86 children (87.8%, 60 boys) were in the S group. The median serum cortisol value was 7.7 mcg/dL [IQR 6.9-15.1]. There was no statistically significant difference in age, period from final PSL administration to the cortisol measurement, or number of relapses between the two groups. The median dosage of PSL over one year up to the cortisol measurement day in the I group was significantly higher than that in the S group (3000 mg [778-5359] vs 0 mg [0-1395], p=0.004), and the number of children who experienced relapses during PSL treatment in the I group was also more than those of the S group (4/12 (33.3%) vs 8/86 (9.3%), p=0.038).

Conclusions: Adrenal suppression can occur in a significant proportion of children with NS treated with PSL. Care must be taken to avoid adrenal insufficiency in these children. A measurement of serum cortisol values after PSL treatment is necessary, particularly in those receiving high-dose steroid within a year.

SA-PO450

Vitamin D Receptor Gene Polymorphisms in Childhood Idiopathic Nephrotic Syndrome

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Background: Idiopathic nephrotic syndrome (INS) is the most frequent type of nephrotic syndrome in children. The pathogenesis of remains controversial and may be mediated by the immune system and the imbalance between T-helper cell subtype 1 (Th1) and subtype 2 (Th2) cytokines, which are regulated by the vitamin D. Vitamin D exerts its effects through its receptor (VDR). Its response to steroids treatment are also varied. The aim of this study was to analyze the correlation between the VDR gene polymorphisms and the response to steroids treatment in INS children.

Methods: Thirty four patients with INS were enrolled and divided into 2 groups: 18 steroid-sensitive (SS) and 16 steroid-resistance (SR). To analyze the VDR gene polymorphisms, the SNP genotyping for Fok1, Apa1, Cdx2, Taq1, Bsm1 were performed using TaqMan Genotyping Assays. The genotypic and allele frequency were analyzed.

Results: The Apa1 C allele was associated with steroid resistance then A allele [OR 8.75, p=0.009]. The frequency of the C allele was significantly higher in SR than in SS subjects (0.84 vs. 0.47, respectively). The Bsm1 G allele was associated with steroid resistance then A allele [OR 7.00, p=0.017]. The frequency of the G allele was significantly higher in SR than in SS subjects (0.88 vs. 0.50, respectively). The Fok1 C allele was associated with steroid resistance then T allele [odds ratio (OR) 6.00, p=0.015]. The frequency of the C allele was significantly higher in SR than in SS subjects (0.66 vs. 0.33, respectively). There was no significant correlation in Cdx2 and Taq1 polymorphisms in VDR gene between treatment response.

Conclusions: Our results indicate that among our pediatric patients with INS, the VDR gene polymorphism: Fok1, Apa1, and Bsm1 were associated with steroid resistance; while the Cdx2 and Taq1 gene polymorphisms showed no statistical significance between these 2 groups.

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SA-PO451

Urine Biomarker Potential for Assessment of Disease Activity in Pediatric Nephrotic Syndrome

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Background: Biomarkers are considered to be a powerful tool of diagnosis and assessment of disease activity. Currently, proteinuria is the standard means of diagnosis of nephrotic syndrome (NS). Other non-invasive biomarkers are desired, especially those that may provide better understanding of NS activity than proteinuria.

Methods: We extracted urine RNA and using real-time PCR, examined the expression levels of various biomarkers. Expression levels were then compared between NS and other diseases. We also investigated the correlation between biomarkers and the conditions of disease across four stages; pre-treatment proteinuria (stage 1), proteinuria during treatment (stage 2), remission during treatment (stage 3) and post-treatment remission (stage 4). At our hospital, 117 RNA samples were taken from 104 consecutive patients with various kidney diseases (30 nephrotic syndrome, 27 IgAN, 15 isolated hematuria, 7 isolated proteinuria, 25 others). Across the four stages, the 30 NS patients provided 46 RNA samples (stage 1 = 7, stage 2 = 8, stage 3 = 12, stage 4 = 19).

Results: Using biomarkers, we could diagnose NS and observe its activity across the four stages. Pediatric NS samples showed significantly higher levels of liver fatty acid-binding protein (FABP-1) (p<0.01), megalin (p<0.01), cubilin (p<0.01) and lower level of podocin (p<0.01) compared to the other diseases. In NS samples only, FABP-1, cubilin and kidney injury molecule-1 (KIM-1) expression levels correlated positively with urine protein volume, whereas podocin correlated negatively. FABP-1 expression was around double and podocin expression was approximately 75% lower in relapse than in remission (Table 1). In stage 2, cubilin expression doubled. In stage 3, KIM-1 expression increased 170%.

Conclusions: Urine RNA expressions reveal clues to the pathophysiology of NS. Urine biomarkers other than proteinuria can be considered an effective non-invasive tool to understand disease activity in pediatric NS.

Funding: Government Support - Non-U.S.

Table 1. Urine RNA relative expression

	FABP-1	KIM-1	cubilin	IL-18	NGAL	megalin	podocin	Thy1	HSPG2
Pre-treatment proteinuria [stage 1, n=7]	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Proteinuria during treatment [stage 2, n=8]	1.3	0.9	1.8	1.5	1.6	1.7	1.0	1.5	3.5
Remission during treatment [stage 3, n=12]	0.4	1.7	0.9	2.3	2.0	1.4	3.7	1.8	3.6
Post-treatment remission [stage 4, n=19]	0.5	0.5	0.9	2.8	3.6	0.8	6.3	1.5	2.7

SA-PO452

Urinary CD80 as a Novel Biomarker of Podocyte Injury

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Background: CD80, which is expressed by antigen-presenting cells, was recently reported to also be expressed in podocytes in pathological conditions such as idiopathic nephrotic syndrome (INS); moreover, CD80 over-expression could be detected in urine (Reiser J, et al. 2004; Garin, EH, et al. 2009). However, as there are many skeptical reports, a conclusion has yet to be drawn. The purpose of this study was to clarify whether podocyte-derived CD80 appears in urine, where it may serve as a biomarker for podocyte disorder.

Methods: Patients with INS (median age 7.9 years, n=10) were grouped into initial attack and relapse (group A), and remission (group B), and compared with patients with other renal diseases (e.g., IgA vasculitis nephritis; median age 8.2 years, n=7; group C). Single voided urine and serum samples were collected at the same time. Urine and serum CD80 levels were measured by ELISA and compared among the three groups to examine potential correlations. The correlation between urine CD80 and urinary protein excretion was also investigated. In addition, puromycin was added to a human podocyte cell line to prepare an *in vitro* INS model, and expression of CD80 after 72 hours was confirmed using western blotting.

Results: (1) Urinary CD80 was significantly increased in group A compared with group B (group A:group B=465.94:0.00; ng/gCre, numerical value is median, p=0.0072). Group A was also higher than group C, however there was no significant difference (group A:group C=465.94:422.04, p=0.65). (2) Although there was no significant correlation between urinary CD80 and serum CD80 values, there was a correlation between urinary CD80 and urinary protein excretion (r=0.24, p=0.17; r=0.35, p=0.0031, respectively). (3) As a result of administration of puromycin to the human podocyte cell line, CD80 expression was increased almost two-fold compared with control (untreated podocytes: puromycin-treated poocytes=8201.26:16309.43, p=0.015).

Conclusions: A significant amount of CD80 was excreted in the urine of INS and other renal disease patients, and its concentration did not correlate with serum concentration. In addition, CD80 expression was also confirmed in an INS human cell line model. Furthermore, urinary CD80 was significantly correlated with amount of urinary protein reflecting podocyte injury, suggesting that it could be a biomarker of podocyte disorder.

SA-PO453

All-Trans Retinoic Acid Directly Acts on Podocytes by Regulating CD80 Expression

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Background: Pathogenesis of minimal change nephrotic syndrome (MCNS) remains unclear, though recent studies suggest a role for malfunction of regulatory T cells (Tregs) and abnormal expression of several podocyte-related molecules, such as CD80 (Garin E, et al. Pediatric Nephrology, 2016). All-trans retinoic acid (ATRA) has the potential to regulate the immune system, including induction and differentiation of Tregs, in addition to its vitamin function. Therefore, we aimed to investigate the potential of ATRA as a protective therapy for MCNS through suppression of CD80 *in vitro*.

Methods: Human-derived immortalized podocytes were treated with puromycin aminonucleoside (PAN) as an *in vitro* model of MCNS. Cells were treated with ATRA (10 μM) or DMSO in starvation medium on day 1 followed by PAN (50 μg/ml), or PBS on day 0. Samples were collected after 72 h for analysis. Protein expression levels of CD80 and retinoic acid receptor (RAR) were measured by western blotting.

Results: PAN induced increased protein expression of CD80 and RAR both of which were restored by ATRA treatment (Figure1). These results suggested that the overexpression of CD80 after PAN stimulation can be restored by ATRA through RAR.

Conclusions: ATRA suppresses CD80 overexpression caused by PAN stimulation through RAR in podocytes. ATRA might have an antiproteinuric effect on MCNS through its direct effect on podocytes.

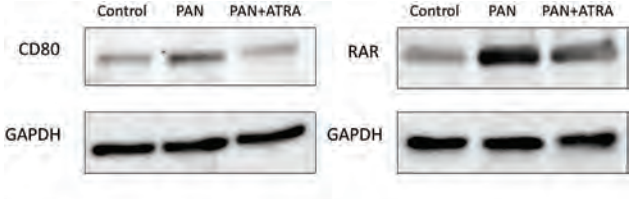

Figure1. Effect of ATRA on the expression of CD80 and RAR in podocytes

SA-PO454

Expression and Functional Activity of Multidrug Resistance-Associated Protein-1 and P-Glycoprotein on T-Cells Is Associated with Steroid Resistance Nephrotic Syndrome in Children

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Background: Steroid remains as mainstay of therapy for Idiopathic Nephrotic Syndrome (NS). Other than histological factors like changes from minimal change to FSGS, pharmacogenomic factors may affect steroid response, however not well studied. Overexpression of P-glycoprotein (P-gp) and Multidrug resistance associated protein 1 (MRP-1) modulate pharmacokinetics of steroid and contribute in steroid resistance.

Methods: P-gp, MRP-1 expression were evaluated on whole blood and functional activity on peripheral blood mononuclear cells (PBMCs) by Flow Cytometry in steroid sensitive NS (SSNS) (n=80,male 43, age=8.54±4.3 yrs);and steroid resistant NS (SRNS) (n=50, male 29, age=7.72±3.6yrs). Multi resistance activity factor (MAF) was calculated using formula (MAFMDR1=100× (FMDR1-F0)/FMDR1).

Results: Percentage of P-gp (10.35±2.15 vs 4.19±1.07, p<0.001);and MRP-1(17.03±3.45 vs 8.71±2.97, p<0.001) were significantly higher in SRNS than SSNS. Absolute P-gp (64.96±12.78 vs 32.63±12.07, p<0.001) and MRP-1 (64.72±10.27 vs 40.28±11.24, p<0.001) expression were also significantly high in SRNS. P-gp expression on CD4+ (6.08±1.06 vs 4.34±1.47, p<0.001); and CD8+cells (8.65±2.19 vs 3.99±1.72, p<0.001) was significantly higher in SRNS than SSNS. MRP-1 expression on CD4+ cells (12.06±2.91 vs 3.35±0.83, p=0.001); and CD8+cells (5.11±0.68 vs 1.59±0.39, p<0.001) was significantly high in SRNS.Functional activity of P-gp (66.12±12.71 v/s 28.22±7.35, p<0.001);and MRP-1 (72.30±8.38 v/s 32.38±8.89,p<0.001) was significantly increased in SRNS.

Conclusions: Overexpression of P-gp and MRP-1 on T cells contribute in steroid resistance and may be biomarker of steroid resistance. Use of P-gp and MRP-1 inhibitors may prevent SRNS status.

Funding: Government Support - Non-U.S.

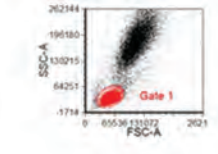

Figure 1

Figure 2

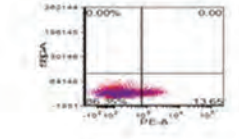

Figure 3

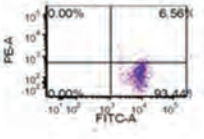

Figure 4

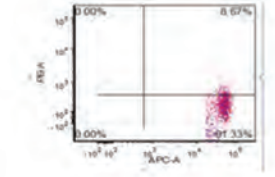

Figure 5

Lymphocytes were gated from whole blood on forward and side scatter plots (gate 1, Figure.1) and Quadrant was applied for P-gp positive cells for isotype control (Figure.2) and test sample (Figure.3), further Quadrant was applied for P-gp positive CD4 and CD8 cells(Figure.4 and Figure.5) respectively.

SA-PO455

Metabolite Predictors of CKD Progression in Children

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Background: We sought to perform the first large-scale discovery of novel metabolite biomarkers of CKD progression in children.

Methods: We evaluated an untargeted GC/MS2 and LC/MS2-based metabolomics quantification (Metabolon) of baseline plasma samples from 587 Chronic Kidney Disease in Children (CKiD) participants. Cox proportional hazards and lognormal regression were used to examine the association between standardized, log transformed metabolites and progression to end stage kidney disease (ESKD: dialysis/transplant), adjusting for age, sex, race, body mass index, hypertension, anemia, glomerular (G) vs. non-glomerular (NG) diagnosis, serum albumin, proteinuria, and estimated glomerular filtration rate (eGFR). Stratified analyses were performed within G and NG subgroups.

Results: Cohort characteristics were: 354 male (60%); median age 12.3 years; median eGFR 53.2 mL/min/1.73m^2; 409 (70%) NG diagnosis. 171 (29%) developed ESKD over a median observation time of 5.0 years (inter-quartile range 3.1-7.5). Of 949 known non-drug metabolites identified, 16 were associated with time to ESKD in both the fully adjusted Cox and lognormal models by the pathway specific false discovery rate threshold <0.05 (Figure). 13 were lipids and 6 were in the hexosylceramide pathway. 10 of the 16 metabolites remained associated in stratified analyses, mostly within the G subgroup, and the magnitude of the HR was generally greater than that for the full cohort. An additional 9 metabolites (4 in the lysoplasmalogen pathway) were identified in stratified analyses, predominantly within the G group.

Conclusions: Untargeted metabolomic profiling identified several novel metabolite biomarkers associated with CKD progression in children independent of established predictors, including hypertension, proteinuria and eGFR, and distinct from metabolites identified in adult studies. Further studies are needed to replicate these findings and delineate mechanism.

Funding: NIDDK Support

Compound	Sub Pathway	Full cohort HR	Full cohort P value	Stratified G and NG HR	Stratified G and NG P value	Stratified G and NG Group
glycosyl ceramide (d18:1/20:0, d16:1/22:0)*	Hexosylceramides	2.23	6.31E-05	3.78	1.77E-03	G
glycosyl-N-stearoyl-sphingosine (d18:1/18:0)	Hexosylceramides	2.37	8.06E-05	2.88	1.19E-02	G
glycosyl-N-behenoyl-sphingosine (d18:1/22:0)*	Hexosylceramides	2.56	1.49E-04	2.87	2.23E-02	G
glycocholenate sulfate*	Secondary bile acid metabolism	0.61	2.40E-04	0.47	4.76E-06	NG
lactosyl-N-behenoyl-sphingosine (d18:1/22:0)*	Lactosylceramides	1.77	4.10E-04	1.71	7.00E-03	NG
glycosyl-N-palmitoyl-sphingosine (d18:1/16:0)	Hexosylceramides	2.32	1.79E-03	3.70	9.01E-03	G
glycosyl ceramide (d18:2/24:1, d18:1/24:2)*	Hexosylceramides	1.99	2.83E-03	3.27	5.82E-03	G
phosphocholine	Phospholipid metabolism	1.90	3.61E-03	3.55	6.86E-04	G
glycosyl-N-nervonoyl-sphingosine (d18:1/24:1)*	Hexosylceramides	1.90	8.55E-03	2.75	1.36E-02	G
deoxycarnitine	Carnitine metabolism	0.69	3.81E-02	0.36	7.31E-03	G
N-palmitoyl-sphinganine (d18:0/16:0)	Dihydroceramides	2.01	2.12E-05			
imidazole lactate	Histidine metabolism	2.37	3.28E-04			
3b-hydroxy-5-cholenoic acid	Secondary bile acid metabolism	0.57	3.28E-04	NS in G and NG strata		
biliverdin	Hemoglobin & porphyrin metabolism	0.70	2.64E-03			
N-palmitoyltaurine	Endocannabinoid	0.73	3.94E-03			
pantothenate (Vitamin B5)	Pantothenate & CoA metabolism	1.35	4.06E-02			
tetrahydrocortisol sulfate (1)	Corticosteroids			0.57	1.22E-05	NG
sarcosine	Glycine, serine, threonine metabolism			3.84	1.81E-03	G
cortisol	Corticosteroids			0.64	3.97E-03	G
glycosyl-N-behenoyl-sphingadienine (d18:2/22:0)*	Hexosylceramides			3.08	6.53E-03	G
3-methylcytidine	Pyrimidine metabolism	NS in full cohort		1.98	9.46E-03	G
1-(1-enyl-oleoyl)-GPE (P-18:1)*	Lysoplasmalogen			1.97	2.48E-02	G
1-(1-enyl-palmitoyl)-GPC (P-16:0)*	Lysoplasmalogen			2.44	3.01E-02	G
1-(1-enyl-palmitoyl)-GPE (P-16:0)*	Lysoplasmalogen			2.11	3.04E-02	G
1-(1-enyl-stearoyl)-GPE (P-18:0)*	Lysoplasmalogen			2.08	3.99E-02	G

SA-PO456

Evaluation of Urinary C5b-9 as a Biomarker of Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy

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Background: Thrombotic microangiopathy (TMA) affects 39% of pediatric hematopoietic stem cell transplant (HSCT) patients. Renal involvement, characterized by hypertension, proteinuria, and kidney injury, may be confounded by the side effects of corticosteroids and calcineurin inhibitors, and highly sensitive and specific biomarkers for HSCT TMA are currently lacking. Urinary C5b-9 (uMAC) is associated with disease activity in other forms of TMA such as preeclampsia. However, complement activation has been demonstrated in vitro when plasma is acidified by mixing with urine. We hypothesized that uMAC would be associated with the diagnosis of HSCT TMA, but potentially confounded by BK cystitis.

Methods: uMAC was measured prospectively in 80 consecutive pediatric allogeneic HSCT patients weekly from Days 0 – 35, and Days 48, 60, and 100 using a commercial ELISA clinically validated for use with urine. Association of uMAC with patient, primary disease, and HSCT characteristics was assessed. We then analyzed the association between the clinical outcomes of measurable uMAC, hematuria, BK viremia, and BK cystitis with the diagnosis of TMA.

Results: 48 patients had at least one uMAC >0ng/mL. There were no patient, primary disease, and HSCT characteristics associated with having measurable uMAC. In univariate analysis, TMA was associated with uMAC (p=0.04), hematuria (p<0.001), BK viremia (p<0.01), and BK cystitis (p<0.01). In multivariate analysis, uMAC was no longer associated with TMA (p=0.94), whereas BK viremia (p<0.01) and hematuria (p<0.05) maintained their association with TMA.

Conclusions: uMAC is not associated with HSCT TMA. uMAC is confounded by hematuria, which may have implications for its use and interpretation in other disease processes. Unexpectedly, hematuria demonstrated a strong association with TMA diagnosis in HSCT patients, perhaps suggesting its utility as an additional diagnostic criterion in establishing the diagnosis of TMA.

SA-PO457

Coexisting Variations in Complement Regulatory Genes Increase Risk of Relapse in Anti-Factor H (FH) Antibodies Associated Atypical Hemolytic Uremic Syndrome (aHUS)

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Background: Patients with anti-FH antibodies, comprising one-half of children with aHUS in India, are managed by PEX and immunosuppression (IS). While deficiency of FH related protein-1 (*CFHR1*) is strongly associated, prevalence of additional variations and their impact on outcomes is unclear.

Methods: Of 435 children with anti-FH aHUS in the nationwide database, 93 (21%) were screened by targeted sequencing of 27 genes, comprising full length *CFH, CFI, CFB, C3, CD46, THBD, DGKE,* coding regions of *CFHR1-5, PLG, ADAMTS13* and lectin & terminal pathway. Genotype-phenotype correlation and risk-factors for relapse & adverse outcomes (eGFR <30 mL/min/1.73 m^2 or death) were evaluated.

Results: Patients aged 9±3 yr had high anti-FH titers (median 4684 AU/ml) that persisted >1000 AU/ml during remission in one-third. At 44-mo follow up, adverse outcome was seen in 20% and relapses in 30% (17% and 30% in database, respectively; P=0.02 and <0.001). Sequencing at mean depth of 123X (96% coverage) showed variants of unknown significance (VUS) in 6.5% (Table). MLPA showed homozygous deletion (90%) or duplication (N=1) of *CFHR1*. Severity of renal and extrarenal manifestations were independent of genetic variations. Prompt PEX (Hazard ratio, HR=1.03; P=0.009), lower anti-FH titers (HR=1.00; P=0.06) and lower peak creatinine (HR=1.2; P=0.008) were associated with improved outcomes. *MASP1* (c.*822C>T) polymorphism protected against relapses (allele frequency relapsers 0.015; non- relapsers 0.11; *P*=0.02). Maintenance IS (odds ratio, OR=10; *P*=0.02), no coexisting variations (OR=13; *P*=0.03); low C3 at onset (OR=5; *P*=0.03) and *MASP1* polymorphism (OR=8; *P*=0.06) independently reduced the risk of relapses.

Conclusions: Prompt PEX & IS improves long-term outcomes and prevents relapses in patients with anti-FH aHUS. Coexisting variations in regulatory genes might predispose to relapses.

Funding: Government Support - Non-U.S.

Variant (all heterozygous)	Pathogenicity	Age yr	C3 mg/dl	Anti-FH AU/ml	Relapse, at mo-	eGFR & outcome at follow-up
CFI: c.148C>G, p.P50A	Pathogenic^	4	74	8800	One, 24-mo	82 at 14 yr, ambulatory HPT
THBD: c.127G>A, p.A43T	Likely pathogenic^	6	42	16133	One, 6-mo	ESRD
DGKE: c.685G>A, p.G229R	VUS, rare	9	89	4260	None	89 at 21-mo; HPT, proteinuria
CFI: c.1931>C, p.Y65H	VUS, rare	9	40	7956	One, 6-mo	43 at 11-mo; HPT
THBD: c.596C>A, p.A199D	VUS, novel	4	40	26741	One, 9-mo	84 at 44-mo; HPT, proteinuria
C3: c.1402G>A,p.G468R	VUS, novel	7	43	3215	2,6 & 24 mo-	64 at 66-mo; HPT

^reported functional assay; HPT, hypertension

SA-PO458

CH50 Result Variability by Methodology in Eculizumab-Treated Patients with Atypical Hemolytic Uremic Syndrome

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Background: The advent of complement-targeted therapy for the treatment of atypical hemolytic uremic syndrome (aHUS) has led to an increasing use of pharmacodynamic monitoring in patients to ensure adequate complement blockade to suppress disease activity. Measurement of terminal pathway activity and functionality with plasma sC5b-9 and CH50, respectively, have gained wide acceptance as means to assess the adequacy of complement blockade in such patients. However, methodologies for the CH50 assay may vary widely among institutions, and some methodologies may be insufficiently sensitive to determine such adequacy of blockade.

Methods: In patients treated with eculizumab for aHUS and other forms of thrombotic microangiopathy, CH50 was clinically measured at regular intervals during the induction phase of treatment by a laboratory-developed standard hemolytic assay. We compared

these results to results obtained by two additional methods, the Wieslab CP assay and an instrument-based liposomal assay for CH50. Adequate complement blockade was defined as a CH50 value less than 10% of the lower limit of normal for each assay.

Results: We identified that in a number of patients treated with eculizumab, breakthrough of complement blockade prior to the next scheduled dose of eculizumab was noted by an upward trend of CH50 results obtained by hemolytic methodology, whereas values obtained by both Wieslab CP and instrument-based methodologies suggested ongoing suppression and did not detect this breakthrough in blockade. Breakthrough of complement blockade in several instances influenced therapeutic decision making, in which supplemental doses were administered to ensure sufficiency of suppression of disease activity.

Conclusions: These findings suggest that the sensitivity of CH50 to detect small but clinically meaningful changes in complement suppression may differ by assay methodology, and that care must be taken in the interpretation of the results of these assays for pharmacodynamic monitoring of patients on eculizumab.

SA-PO459

Pediatric CKD Is Associated with Lower Cortical and Cerebellar Brain Volumes

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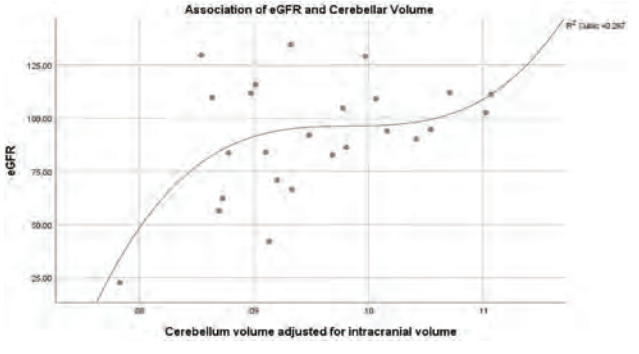
Background: Children with chronic kidney disease (CKD) are at risk for neurocognitive deficit. Neuroimaging studies provide the opportunity to accurately assess the brain and provide clues to the underlying mechanisms of observed neurocognitive abnormalities. To date, only a few published studies exist evaluating brain structure in pediatric CKD and often involve heterogenous samples with late CKD/end-stage populations of varying etiologies.

Methods: The purpose of this study is to quantitatively characterize brain structure in relationship to neurocognitive function in pediatric CKD patients with mild to moderate, non-glomerular CKD compared to age- and gender-matched, healthy controls using magnetic resonance imaging (MRI). Patients age 6-16 with congenital, non-glomerular causes of CKD (eGFR 30-90 ml/min/1.73m2) were invited to participate. Participants completed a neurocognitive evaluation, laboratory evaluation and MRI scan. The MRI scan included structural and functional sequences.

Results: Neurocognitive and structural MRI data were available for 26 participants (11 cases, 15 controls). Cases showed ***significantly lower cortical brain volume ($p = 0.046$) and notable volumetric decreases within the cerebellum*** ($p = 0.016$). There is specifically lower cerebellar gray matter in cases compared to controls ($p = 0.009$). Data suggest potential for a direct relationship between structural abnormality of the cerebellum and lower eGFR ($R^2 = 0.267$, see Figure 1).

Conclusions: Our data link volumetric differences noted most prominently in the cerebellums of CKD participants with lower eGFR. It is possible that the decline in renal function associated with CKD may perpetuate these findings. Understanding the influence of pediatric CKD progression and severity on the developing brain may allow enhanced awareness of the role of disease progression on neurodevelopmental outcomes in childhood and inform new approaches to treatment and patient education across the CKD lifespan.

Funding: NIDDK Support



SA-PO460

Genomic Disorders, CKD, and Neurocognitive Status in Youth

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Background: A subset of youth w/ chronic kidney disease (CKD) harbor genomic disorders that impair both kidney and neurobehavioral function. The resultant neurocognitive (NC) deficits may impact patient outcomes, e.g. suboptimal medication adherence or poor school/work performance.

Methods: We are conducting genomic and NC testing in youth aged 8-25y w/ CKD (CKD Stage 2-5, on dialysis, or transplanted). Analyses integrate assessment of microarray and exome sequence to identify pathogenic variants associated w/ CKD and neurodevelopmental disorders. Enrollment goal is 200 subjects.

Results: Thus far, 30 subjects have completed NC testing (**Table**) and 24 underwent genomic analysis. On NC testing (**Figure**), we noted impaired NC outcomes, including lower IQ, weaknesses in global executive functioning, worse attention, and higher anxiety. In 3 of 24 cases who completed exome sequencing, we detected putatively pathogenic variants for monogenic forms of CKD: 2 w/ COL4A5 variants, associated w/ X-linked Alport syndrome; 1 w/ a ROBO2 variant, associated w/ Vesicoureteral Reflux 2. None had known pathogenic variants associated w/ neurodevelopmental disorders.

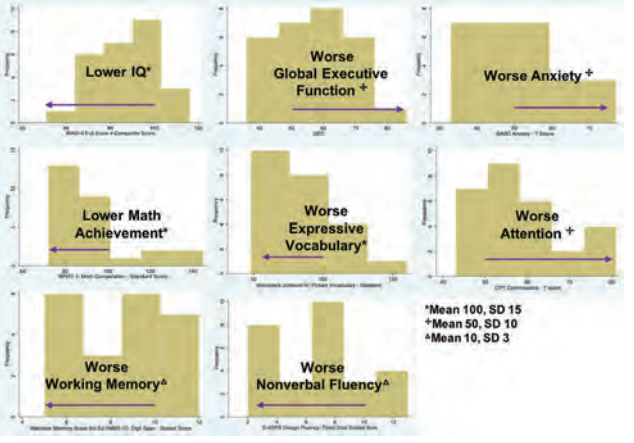
Conclusions: Our preliminary results support the need for genomic and NC assessment in youth w/ CKD to enable specific diagnosis and support early interventions. Further study incorporating genomic and NC performance data will help to elucidate genetic factors underlying CKD and NC deficits.

Funding: NIDDK Support

Participant Characteristics, N = 30

Age (years, Median [IQR])	18.7 [15.3-20.8]
Male	20 (67)
Race	
White	18 (60)
Black	9 (30)
Hispanic, Not Black	12 (40)
Bilingual, Spanish	10 (33)
Etiology of CKD	
Congenital Anomalies of the Kidney and Urinary Tract	18 (60)
Glomerulonephritis	8 (27)
CKD Stage 2 & 3	21 (70)
History of Kidney Transplant	13 (43)

Data as N (%)



Frequency tables of neurocognitive testing outcomes.

SA-PO461

Renal Complications in Congenital Anomaly Syndrome Patients with Genetic Variants

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Background: Early detection and early treatment of renal complications of patients with intellectual disabilities are critical for predicting their prognosis. However, phenotypes of kidney diseases are usually silent and, therefore, it is difficult to make early diagnosis. We assessed the renal complications among patients with intellectual disabilities.

Methods: 1211 patients who showed intellectual disabilities and congenital anomalies and their parents were recruited through the Japanese nation-wide undiagnosed disease program, Initiative on Rare and Undiagnosed Diseases (IRUD). Whole blood was collected from them after informed consent. Comprehensive genetic diagnosis was performed by medical exome sequencing (MES; Illumina TruSightOne, Illumina MiSeq) or whole exome sequencing (WES; Agilent SureSelect, Illumina HiSeq2000). Variants detected by the sequencer were filtered on quality, frequency, segregation pattern, previous reports, and genetic function and were confirmed by Sanger sequencing.

Results: Diagnoses were made in 417 patients (34.4 %) and renal complications were presented in 41(9.8 %) of these 417 patients. Among these 41 patients, kidney hypoplasia was present in seven patients, vesicoureteral reflux was present in one patients, hydronephrosis was present in seven patients, and multiple cystic kidney disease was present in one patient. Sequence analyses identified constitutional variants including *AUTS2*, *CHD7*, *CREBBP*, *EFTUD2*, *GNB1*, *KAT6A*, *KAT6B*, *KMT2A*, *KMT2D*, *MAGEL2*, *PBX1*, *PURA*, and *UBE3B*.

Conclusions: Renal phenotypes were not rare but critical complications of patients with congenital anomaly syndromes. Various types of kidney diseases were present in them and most of these diseases were able to be detected by urinary test or kidney echogram. However, it is difficult to make early diagnosis and early treatment of kidney complications if they were not taken into doctor's considerations. Furthermore, there were not only disease with high incidence of kidney phenotypes like CHARGE syndrome, or Rubinstein-Taybe syndrome, but also diseases with low incidence of kidney diseases, such as Kabuki

syndrome or Cornelia de Lange syndrome. Taken together, to perform both urinary test and kidney echogram at least once may be need for patients with congenital anomaly syndromes to be made early detection and treatment of kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO462

Primary Cause of Kidney Disease and Mortality in Children on Dialysis

Yusuke Okuda, Melissa Soohoo, Yoshitsugu Obi, Elani Streja, Ying Tang, Connie Rhee, Kamyar Kalantar-Zadeh. *Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA.*

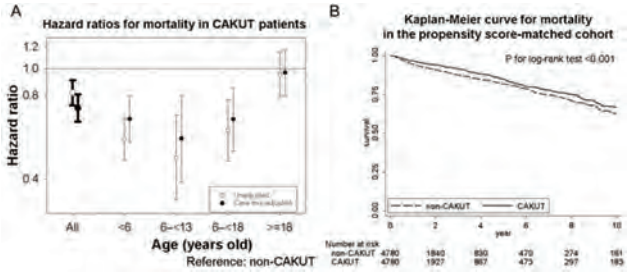
Background: Congenital anomalies of the kidney and urinary tract (CAKUT) has been associated with slower progression of chronic kidney disease in children. However, little is known about the association of CAKUT vs. other primary causes of kidney disease with mortality risk after dialysis initiation.

Methods: We used the United States Renal Data System to identify 25,761 incident dialysis patients who were ≤21 years old between 1995–2016. We examined the risk of the primary cause of kidney disease with mortality using adjusted Cox models. Sensitivity analyses included stratification on age and individual non-CAKUT causes, and propensity score (PS)-matched analyses. The PS was calculated based on case mix variables.

Results: The median (IQR) age was 17 (11–19) years and 4,780 (19%) had CAKUT. The case mix-adjusted hazard ratio (HR) for CAKUT patients was 0.72 (95%CI, 0.64–0.81) (ref: non-CAKUT). In age stratified analysis, the case mix-adjusted HRs (95%CIs) for CAKUT patients were 0.66 (0.54–0.80), 0.56 (0.39–0.80), 0.66 (0.50–0.86), 0.97 (0.80–1.18) in <6 years, 6–<13 years, 13–<18 years, and ≥18 years, respectively (ref: non-CAKUT) [Figure]. Among the non-CAKUT causes, mortality associated with primary glomerulonephritis (HR, 0.93; 95%CI, 0.80–1.10) and focal segmental glomerulosclerosis (HR, 0.89; 95%CI, 0.75–1.04) was comparable or slightly lower compared to CAKUT, whereas most other causes were associated with higher mortality risk. The lower mortality risk in CAKUT patients was consistent in the PS-matched cohort.

Conclusions: CAKUT was associated with lower mortality in children on dialysis, especially in those younger than 18 years old. Additional studies are needed to investigate the mortality risk for rare non-CAKUT causes.

Funding: NIDDK Support



SA-PO463

Estimated Glomerular Filtration Rate at Dialysis Initiation and Mortality in Children

Yusuke Okuda, Melissa Soohoo, Yoshitsugu Obi, Elani Streja, Ying Tang, Connie Rhee, Kamyar Kalantar-Zadeh. *Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California, Irvine, Orange, CA.*

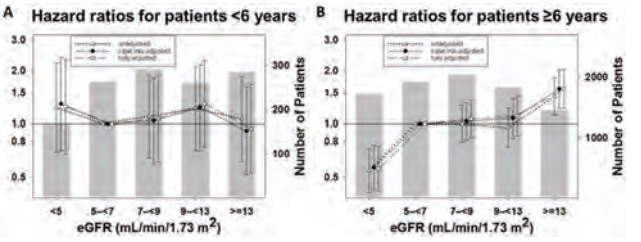
Background: The timing of dialysis initiation and estimated glomerular filtration rate (eGFR) has been hotly debated for adult dialysis patients. However, there are scarce data on the association between eGFR at dialysis initiation and mortality in children.

Methods: In a cohort of incident dialysis patients from 1995-2016 identified from the United States Renal Data System and aged 1–17 years old, we examined the association of eGFR at dialysis initiation with mortality. Mortality risk was estimated using Cox model with three levels of adjustment, i.e., unadjusted, case mix-adjusted, and fully adjusted model including height, body mass index, hemoglobin, and albumin. eGFR was calculated using the pediatric specific bedside Schwartz equation.

Results: Among 10,251 included patients, median age was 13 (IQR: 10–16) years and median eGFR was 7.8 (IQR: 5.7–10.5) mL/min/1.73 m^2. There appeared a trend toward higher mortality risk across higher eGFR. In particular, eGFR <5 mL/min/1.73 m^2 was associated with low mortality (fully adjusted hazard ratio [HR], 0.64; 95%CI, 0.50–0.84) (reference: eGFR 5 to <7 mL/min/1.73 m^2). This association was consistent in children ≥6 years old, whereas HR was 1.25 (95%CI: 0.67–2.31) for eGFR<5 mL/min/1.73 m^2 among those <6 years old (reference: eGFR 5 to <7 mL/min/1.73 m^2) [Figure].

Conclusions: Low eGFR at dialysis initiation was associated with lower mortality, especially for eGFR levels less than 5 mL/min/1.73 m^2 in incident dialysis children. The result does not suggest an independent indication of dialysis initiation based on eGFR. If the clinical status allows it, eGFR at dialysis initiation should be considered. Further considerations are needed in children younger than 6 years old.

Funding: NIDDK Support



SA-PO464

Cause of Death in Children and Young Adults Treated with Dialysis: 1990-2015

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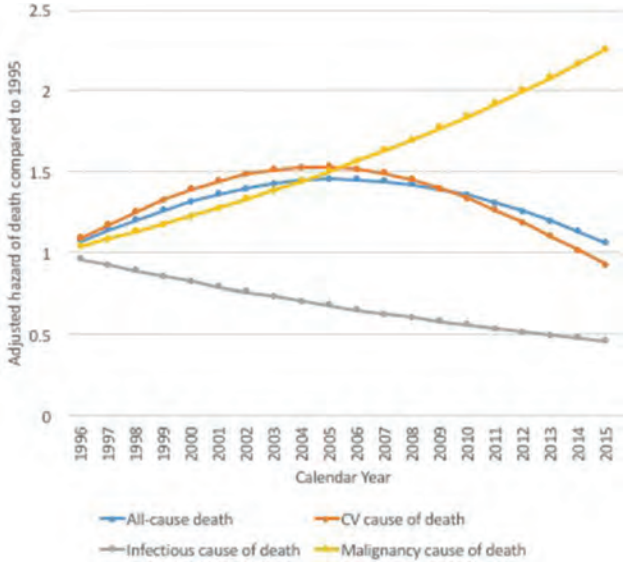
Background: Survival of children on dialysis has improved over the last two decades. However, few studies have examined whether there have been differences in attributed causes of death (cardiovascular, infectious, or malignancy-related) over time in children or young adults treated with dialysis.

Methods: We included patients ages 0-25 years who started dialysis between 1990-2010 followed through December 31, 2015 in the United States Renal Data System. We examined overall mortality and cause-specific mortality (categorized as cardiovascular (CV), infectious, or malignancy-related) by calendar year. We used Cox models to examine differences in the risk of all-cause and cause-specific mortality over time (using 1995 as a reference), accounting for age at dialysis initiation, sex, race, median neighborhood income, cause of ESRD, and insurance type. Follow-up was censored at receipt of a first kidney transplant.

Results: We included a total of 41,339 individuals who started dialysis between 1990-2010, of whom 6344 died during 3.5 years of follow-up. Mean age was 16 yrs, 56% were male. 54% of deaths were secondary to CV causes, 14% infectious causes, and 2% were secondary to malignancy. In adjusted analysis, risk of overall death appeared to increase initially up to 2006, then decreased thereafter (Figure, p<0.001 for non-linearity). Risk of CV-related death also increased initially, but then declined after 2006 (p<0.001 for non-linearity). Risk of infectious-related death steadily decreased over time by 4%/yr (p<0.001, Figure). In contrast, risk of malignancy-related death increased over time by 4%/yr, although this trend did not achieve statistical significance (p=0.08).

Conclusions: Survival in a prevalent cohort of children and young adults receiving dialysis appears to be relatively stable over the last two decades, but differed by cause of death. Risk of infectious-related death has steadily improved, whereas risk of malignancy-related death has steadily increased over time. Further studies are needed to understand the reasons for these findings.

Funding: Other NIH Support - NHLBI



SA-PO465

Impact of Fluid Overload on Growth of Low-Weight Children (<15 kg) Undergoing Chronic Hemodialysis

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Background: To assess whether fluid overload estimated by interdialytic weight gain (IWG) in low-weight children on hemodialysis (HD) impacts patient growth.

Methods: Prospective cohort study of 43 patients (11F and 32M) with weight <15 kg. 91% of patients underwent daily HD. IWG was defined as the difference between pre-HD weight and estimated dry weight of the patient, expressed as percentage of weight. IWG was estimated at each HD session and the median of all values during follow-up was then calculated for each individual. The following procedures were adopted to estimate possible effect of IWG on patient growth: a) Growth during the 6-month follow-up period was calculated, defined as the delta between the repeated measures of the Z-score of height for age parameter (first measure minus second measure).

Results: Median follow-up time was 151 days (IQR = 141 to 153 days). At study baseline, median patient age was 2.0 years (IQR = 0.8 to 2.9) and median Z-score for weight/age was -3.0 (IQR= -4.5 to -2.4). Median Z-score for height/age was -3.8 (IQR = -5.2 to -2.6) at study baseline and -3.5 (IQR=-4.8 to -2.8) at end of follow-up, a difference that was not statistically significant for the overall sample (p=0.365). The assessment of IWG of all patients at 6 months revealed a median of 2.8% (IQR 0.0% – 6.2%). Patients were classified according to IWG into: a) High IWG, where 20 patients had IWG exceeding the median (>2.8%); and b) Low IWG, where 23 patients had IWG lower than the median (<2.8%). Comparison of height delta revealed 0.22 (-0.02 to 0.53) in the Low IWG group versus -0.12 (-0.31 to 0.24) in the High IWG group, a statistically significant difference (p=0.030) indicating impaired growth in the children with High IWG. On the repeated measures model using the GEE, a significant difference (p=0.026) in slope of Z-score of height for age curves was evident between groups with Low IWG=0.3 (SE=0.1) and High IWG=-0.1 (SE=0.1).

Conclusions: Besides the specific factors of CKD that lead to growth deficit, High IWG can negatively impact growth, representing a further factor impairing height in these patients. Hypervolemia promotes greater energy expenditure and contributes to systemic inflammation, leading directly or indirectly to greater protein-calorie depletion.

SA-PO466

AKI Biomarkers Associate with Risk for Diabetic Nephropathy

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Background: Children with diabetes mellitus (DM) are at significant risk to develop diabetic nephropathy. While conventional therapies (glycemic control, treating microalbuminuria with ACE inhibition) can reduce this risk, other determinants of renal outcomes in children with DM are poorly understood. We measured urine biomarkers of acute renal tubular injury in children and young adults with DM to identify if these biomarkers correlate with traditional renal risk factors.

Methods: Subjects between the ages of 10-21 years were recruited from DM clinics. Inclusion criteria included Type 1 DM for 3 years or longer or Type 2 DM for any duration. Clinical data, blood samples, and urine samples were obtained. The urine biomarkers neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM1), and liver fatty-acid binding protein (L-FABP) were measured. Linear regression was used to analyze the relationship between each biomarker and clinical parameters (age, duration of diabetes, gender, hemoglobin A1c, presence of microalbuminuria > 30 mg/g).

Results: Of 155 subjects, 64 (41%) were female, 109 (70%) where white, and 129 (83%) had Type 1 DM. Mean (standard deviation, SD) age was 15.5 (2.7) years. Mean (SD) hemoglobin A1c was 9.1% (1.7) in those with Type 1 DM and 7.9% (2.6) among those with Type 2 DM. NGAL was associated with female gender (43 ng/mL higher in females), higher KIM-1 associated with microalbuminuria (6047 pg/mL higher in the presence of microalbuminuria), and L-FABP associated with hemoglobin A1c (0.23 pg/mL lower for each 1% increase of HgbA1c). These associations persisted when the analysis was restricted to subjects with Type 1 DM.

Conclusions: Amongst children and young adults with DM, acute kidney injury biomarkers have baseline associations with known risk factors for diabetic nephropathy. It will be important to determine if these biomarkers are associated with clinically relevant endpoints in the future.

Funding: Private Foundation Support

SA-PO467

Predictors of AKI in Pediatric Rhabdomyolysis

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Background: Rhabdomyolysis is an uncommon but serious disease in children. The most serious complication of rhabdomyolysis is acute kidney injury (AKI). Risk factors for AKI include greater hematuria, faster fluid administration, and higher initial creatine kinase (CK). Here, we describe the baseline characteristics of children with rhabdomyolysis and identify predictors of AKI in a large, urban tertiary care children's hospital.

Methods: This study was a retrospective cohort. Participants included children (aged less than 18 years) evaluated in the Children's Hospital at Montefiore (CHAM) 1/1/2006-12/31/2015 with CK >1000. The outcome is AKI defined as increase in sCr ≥0.3mg/dL. Potential covariates were identified from biologically plausible variables and include age, sex, race, and biochemical markers at presentation. Bivariate associations were explored using X^2 tests, *t* test or Mann-Whitney U test fas appropriate. All analysis was conducted using STATA v15.0. Protocols were approved by the AECOM IRB.

Results: A total of 447 participants were identified, of whom 124 had AKI. Participants with rhabdomyolysis and AKI were younger and more often female than those without; they did not differ by race. Participants with AKI had higher initial CK, were more acidotic, and had higher baseline phosphorus levels than participants without AKI but did not differ in baseline potassium or calcium (Table 1).

Conclusions: Demographic characteristics and baseline biochemistry are associated with increased risk of AKI in pediatric rhabdomyolysis. Strengths of this study include large sample size. Limitations include missing data and inability to confirm etiology; detailed chart review is ongoing. Next steps include regression analysis and validation of adult risk prediction equations.

Funding: Other NIH Support - 2 T32 DK 7110-43

Baseline Characteristics of Participants

n=447	No AKI (n=353)	AKI (124)	p
Age	11 (5, 15)	7 (2, 13)	0.001
Male	75%	65%	0.033
Race (n=414)			0.50
Black	45%	44%	
Other	43%	40%	
Baseline Labs			
CK (U/L)	2260 (1339, 5969)	3703 (1652, 9546)	0.008
Creatinine (mg/dL) (n=422)	0.7 (0.4, 0.9)	0.7 (0.4, 1)	0.26
Potassium (mEq/L) (n=363)	4.3 ± 0.67	4.3 ± 0.89	0.74
Bicarbonate (mEq/L) (n=386)	22.0 ± 4.47	19.6 ± 6.94	0.006
Calcium (mg/dL) (n=384)	9.3 ± 0.93	9.4 ± 1.49	0.76
Phosphorus (mg/dL) (n=252)	4.3 ± 1.57	5.9 ± 3.05	0.0002

SA-PO468

Novel Cardiac Biomarkers for AKI Risk Stratification After Pediatric Cardiac Surgery

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Background: Children undergoing cardiac surgery are at high risk for postoperative AKI. Novel biomarkers are needed to improve risk stratification of AKI with consideration given to changes in physiology and biomarker distribution throughout childhood.

Methods: We enrolled children from 1 month to 18 years old, undergoing cardiopulmonary bypass. Plasma ST2, galectin-3, and NTproBNP, three FDA approved biomarkers of cardiac stretch or fibrosis, were measured preoperatively and postoperatively on day 1, within 6 hours of cardiac surgery.

Results: Postoperatively, AKI, defined by a doubling of baseline serum creatinine or dialysis, was diagnosed in 79/395 (29%) children. NTproBNP was the only biomarker in the preoperative period that was significantly different between patients with *vs* without AKI (median 0.7 [0.3, 2.9] vs. median 0.4 [0.2, 1.1]). First post-operative ST2, galectin-3, and NTproBNP were significantly higher in patients with vs. without AKI (ST2: median 21.2 [9.7, 74.0] vs 7.7 [3.8, 24.2] ($p<0.001$), galectin-3: median 16.4 [10.6, 21.0] vs 13.3 [9.4, 17.9], NTproBNP: median 1.3 [0.7, 6.5] vs. 0.6 [0.2, 2.2). A significant interaction between biomarker and age was present for both galectin-3 and NTproBNP ($p<0.05$). In children ≥2 years old, after multivariable adjustment, the highest tertile of preoperative galectin-3 and NTproBNP as well as day 1 ST2, galectin-3, and NTproBNP were associated with AKI (Table 1).

Conclusions: Novel cardiac biomarkers, particularly ST2 measured within 6 hours of cardiac surgery, can be used for risk stratification of AKI. The performance of biomarkers after cardiac surgery is affected by age and additional research is required to develop novel cardiac biomarkers for children less than 2 years old.

Funding: NIDDK Support

Table 1. Association of cardiac biomarkers with acute kidney injury stratified by age

				Age<2 (n=194)	Age≥2 (n=201)
Variable Name	**Time Point**	**Value**	**# of Event (%)**	**Odds Ratio (95%CI)**	**Odds Ratio (95%CI)**
ST2	Pre-Operation	Log	63 (19.15%)	1.16 (0.76, 1.75)	1.27 (0.69, 2.36)
		0 vs 0	15 (13.76%)		
		1 vs 0	27 (24.55%)	1.51 (0.6, 3.79)	3.57 (1.09, 11.65)
		2 vs 0	21 (19.09%)	1.03 (0.42, 2.53)	2.33 (0.64, 8.49)
	Day 1 0-6 Hours	Log	71 (20.94%)	1.36 (1.03, 1.8)	2.02 (1.44, 2.84)
		0 vs 0	9 (7.96%)		
		1 vs 0	26 (23.01%)	2.44 (0.88, 6.81)	4.18 (1.05, 16.61)
		2 vs 0	36 (31.86%)	3.29 (1.2, 9.05)	8.47 (2.29, 31.34)
Gal3	Pre-Operation	Log	63 (19.15%)	0.97 (0.55, 1.72)	3.37 (1.42, 7.98)
		0 vs 0	13 (11.93%)		
		1 vs 0	25 (22.73%)	2.03 (0.81, 5.13)	3.33 (0.87, 12.78)
		2 vs 0	25 (22.73%)	1.34 (0.54, 3.34)	4.83 (1.27, 18.44)
	Day 1 0-6 Hours	Log	71 (20.94%)	1.69 (0.84, 3.39)	2.51 (1.07, 5.89)
		0 vs 0	18 (15.93%)		
		1 vs 0	18 (15.93%)	0.79 (0.32, 1.98)	1.17 (0.36, 3.86)
		2 vs 0	35 (30.97%)	1.56 (0.67, 3.61)	3.48 (1.22, 9.92)
NTproBNP	Pre-Operation	Log	63 (19.15%)	1.09 (0.87, 1.37)	1.55 (1.13, 2.14)
		0 vs 0	13 (11.93%)		
		1 vs 0	20 (18.18%)	0.85 (0.29, 2.46)	2.61 (0.84, 8.06)
		2 vs 0	30 (27.27%)	1.01 (0.39, 2.59)	6.57 (1.98, 21.81)
	Day 1 0-6 Hours	Log	71 (20.94%)	1.22 (0.98, 1.53)	1.48 (1.1, 1.98)
		0 vs 0	11 (9.73%)		
		1 vs 0	26 (23.01%)	3.24 (0.67, 15.63)	1.91 (0.71, 5.15)
		2 vs 0	34 (30.09%)	3.66 (0.79, 17.06)	3.34 (1.11, 10.06)

Pre-op values are adjusted for age, sex, race, RACHS category>=3, pre-op eGFR percentile, site
Day 1 0-6 hours values are adjusted for age, sex, race, CPB time > 120 mins, RACHS category>=3, pre-op eGFR percentile, site, delta creatinine (Day1 minus Pre-op)

SA-PO469

Open-Label, Single-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Etelcalcetide in Subjects Aged 2-<18 Years with sHPT Receiving Maintenance Dialysis

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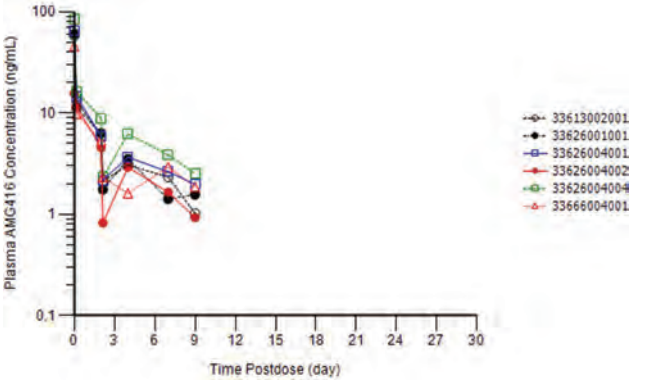
Background: Approximately 60% to 80% of the paediatric dialysis population receives treatment for secondary HPT with vitamin D. The burden of complications of secondary HPT in the paediatric dialysis population and limitations of current therapy underscore the need for better treatments for secondary HPT in these patients. Etelcalcetide is the only calcimimetic formulated for IV administration and is administered TIW (three times a week) as a bolus dose at the end of the haemodialysis treatment.

Methods: This phase 1 study was conducted to investigate the safety, tolerability, PK and PD characteristics of etelcalcetide after the administration of a single dose that may represent a safe starting dose for this titratable drug to paediatric hemodialysis patients. Subjects (2 to < 18 yrs old) received a single IV dose of 0.035 mg/kg etelcalcetide at the end of a hemodialysis session. Intensive PK and PD samples were collected on Day 1 at 10 min and 4 hours after etelcalcetide administration and for 10 days post dose with a safety follow-up period of up to 30 days post dose.

Results: Six subjects (3M, 3F, 6-15 yrs old) have completed the study. In general, the single dose of etelcalcetide was well tolerated. Adverse events reported during this study were consistent with the known safety profile of etelcalcetide. All corrected calcium levels reported were above 2.25 mmol/L. No clinical symptoms possibly related to hypocalcemia were observed. PK exposure was within the predicted range at this dose level (see Figure below- the dipping point on Day 3 was related to hemodialysis).

Conclusions: Single dose of 0.035 mg/kg etelcalcetide is well tolerated in paediatric patients on hemodialysis. The preliminary PK and safety data collected so far are within the predicted range at this dose level.

Funding: Commercial Support - This study was funded by Amgen, Inc.



See Figure - Plasma Etelcalcetide Concentration (Log) -Time

SA-PO470

Burosumab Improved Rickets and Clinical Outcomes Compared to Conventional Therapy in Children with XLH

Anthony A. Portale,[1] Erik Imel,[2] Craig Munns,[4] Leanne M. Ward,[3] Michael Whyte,[5] Jill Simmons,[6] Raja Padidela,[7] Meng Mao,[8] Alison Skrinar,[8] Javier San martin,[8] Francis H. Glorieux.[9] *[1]University of California San Francisco, San Francisco, CA; [2]Indiana University School of Medicine, Indianapolis, IN; [3]Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada; [4]The Children's Hospital at Westmead, Westmead, NSW, Australia; [5]Washington University School of Medicine, St. Louis, MO; [6]Vanderbilt University Medical Center, Nashville, TN; [7]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [8]Ultragenyx Pharmaceutical Inc., Novato, CA; [9]Shriners Hospital for Children-Canada, Montreal, QC, Canada.*

Background: In children with X-linked hypophosphatemia (XLH), high circulating levels of FGF23 cause hypophosphatemia with consequent rickets, skeletal deformities, and growth impairment. Burosumab is an FDA-approved fully human monoclonal antibody against FGF23 for patients ≥1 year of age with XLH. Conventional therapy consists of multiple daily doses of oral phosphate and active vitamin D (Pi/D).

Methods: In the study CL301 (NCT02915705), 61 children with XLH (1-12 years old) were randomized (1:1) to receive subcutaneous burosumab starting at 0.8 mg/kg every 2 weeks (wk) or Pi/D as prescribed by the investigator. Eligibility criteria included a Total Rickets Severity Score (RSS) ≥2.0.

Results: Burosumab showed significantly greater improvement than Pi/D in rickets as assessed by radiologists blinded to treatment using the radiographic global impression of change (RGI-C) at Wk 40 (primary endpoint). More subjects in the burosumab group had substantial healing (RGI-C ≥+2.0) at Wk 40, compared with the Pi/D group (21/29, 72% vs 2/32, 6%; odds ratio of healing 39.1, p<0.0001). Decreases in rickets severity assessed by RSS and alkaline phosphatase also were greater with burosumab. Increases in serum phosphorus were greater with burosumab than with Pi/D. Standing height Z-score increased from a baseline mean (SD) of -2.32 (1.17) to -2.12 (1.22) at Wk 40 for burosumab; and from -2.05 (0.87) to -1.97 (0.87) for Pi/D. Percent predicted distance walked increased with burosumab (Baseline to Wk 40: 62% to 72%) and was unchanged with Pi/D (76% to 75%). Adverse events of interest were higher in the burosumab group, but were mild to moderate in severity overall, with no discontinuations.

Conclusions: Burosumab resulted in significantly greater improvement in rickets and serum phosphorus than conventional therapy in 1-12 year-old children with XLH.

Funding: Commercial Support - Ultragenyx Pharmaceutical Inc.

Summary of Efficacy in UX023-CL301

Assessment	Pi/D (N = 32)	Burosumab (N = 29)	Difference, p-value
RGI-C Global Score at Week 40, LS Mean ± SE	+0.77 ± 0.11	+1.92 ± 0.11	1.14, p<0.0001
Total RSS, LS mean ± SE Change from Baseline to Week 40	-0.71 ± 0.138	-2.04 ± 0.145	-1.34, p<0.0001
Alkaline Phosphatase, U/L, LS Mean ± SE Change from Baseline to Week 40	-35 ± 19	-131 ± 13	-97, p<0.0001
Serum Phosphorus, mg/dL, LS Mean ± SE Change from Baseline to Week 40	+0.20 ± 0.06	+0.92 ± 0.08	0.71; p<0.0001
TmP/GFR, mg/dL, LS Mean ± SE Change from Baseline to Week 40	-0.17 ± 0.08	+1.16 ± 0.12	1.33, p<0.0001

Higher RGI-C and lower RSS = improvement; p-values from ANCOVA (Rickets) & GEE (ALP, TmP/GFR, and Pi).

SA-PO471

Bone and Circulating Sclerostin and Histomorphometry in Pediatric Patients with CKD

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Background: Serum sclerostin, a bone formation inhibitor, increases in CKD but little is known of its role in predicting turnover and mineralization states in pediatric renal osteodystrophy.

Methods: Serum sclerostin was measured in a group of 58 dialysis and 35 pre-dialysis CKD patients at the time of iliac crest bone biopsy. Sclerostin expression in bone biopsy specimens was quantified using immunohistochemistry (IHC). Spearman correlations and multivariable linear regression analyses were performed to determine the relationship between serum and bone sclerostin levels and parameters of the TMV bone classification system. Models were controlled for gender and PTH-two well-known confounders of serum sclerostin.

Results: Cohort characteristics are presented in Table 1. Median serum sclerostin levels were higher in the dialysis vs. CKD patients; although IHC expression was no different (Table 2). In dialysis patients, significant correlations ($p<0.05$) included sclerostin with osteoid thickness (OTH, r=-0.27), osteoid volume (OV/BV, r=-0.26) and osteoid surface (OS/BS, r=-0.26). These relationships were lost after adjustment for gender and PTH. In CKD patients, significant correlations included serum sclerostin with bone formation rate (BFR/BS, r=-0.37) and eroded surface (ES/BS, r=-0.48). Both relationships persisted after adjustment resulting in sclerostin predicting 3% lower BFR/BS and 2% lower ES/BS for every unit increase in sclerostin ($p=0.03$ and $p=0.01$, respectively). Bone expression of sclerostin predominated in cortical areas and likely for this reason failed to correlate with trabecular TMV parameters.

Conclusions: The association of serum sclerostin with bone histomorphometry varies across the spectrum of GFR. The association of sclerostin with bone turnover in CKD patients is consistent with descriptions of Wnt antagonism as an early determinant of bone turnover in CKD. Such findings may have potential therapeutic implications in CKD-MBD.

Funding: NIDDK Support

Table 1: Cohort Characteristics

N	93		**Dialysis, n (%)**	58 (62.4)
Age, median (IQR)	17 (14.6,19.1)		HD	29 (31.2)
Gender, n (%)			PD	29 (31.2)
Male	65 (69.9)		**CKD Stage, n (%)**	35 (37.6)
Female	28 (30.1)		2	11 (31.4)
Race, n (%)			3	17 (48.6)
Black	8 (8.6)		4	6 (17.1)
White	22 (22.6)		5	1 (2.9)
Hispanic	60 (64.5)		**Disease , n (%)**	
Asian	3 (3.2)		CAKUT	40 (43)
Unknown	1 (1.1)		GN	34 (36.6)
			Unknown	19 (20.4)

Table 2: Biochemical values of Dialysis and CKD patients

Variable, median (IQR)	Dialysis	CKD	P value
Sclerostin	65.8 (48.3, 84.2)	41.6 (34.2, 52.6)	<0.0001
IHC Sclerostin	0.002 (0, 0.007)	0.002 (0, 0.01)	0.7
PTH	407 (178, 950)	94 (49, 158)	<0.0001
Vitamin D	21.9 (13.4, 29.1)	25.5 (23.5, 29.7)	0.06
Intact FGF23	1201 (301, 5796)	94.5 (64, 140)	<0.0001
c-terminal FGF23	1879 (705, 6960)	197 (101, 344)	<0.0001
Calcium, mg/dL	9.25 (8.6, 9.7)	9.4 (9, 9.8)	0.1
Phosphate, mg/dL	6.4 (5.3, 7.9)	4.8 (4, 5.3)	<0.0001

IHC=Immunohistochemistry

SA-PO472

Real-World Utilization of Prescription Medications to Manage Pain in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a rare inherited disease characterized by progressive kidney enlargement and leads to end stage renal disease. Symptoms of ADPKD include chronic and transient types of pain in more than 80% of patients which can range in severity from mild to disabling. Understanding utilization of pain medications is important given pain has been linked to lower quality of life. Study aims to characterize management of pain through use of prescription medications.

Methods: Patients diagnosed with ADPKD (ICD-9/10 codes 753.12, 753.13, Q61.2, or Q61.3) were selected from Optum Clinformatics 2007-2017 US research database which is comprised of 7 million commercial and Medicare Advantage beneficiaries. Patients were aged 18 years or older, with continuous medical and pharmacy benefits for 6 months pre-index date (baseline period) and at least 6 months post-index date. The index date was the date of ADPKD diagnosis. Descriptive analyses described baseline patient characteristics, comorbidities, and utilization of pain medications by drug class during one-year post index-date. Included pain medications were selected per literature assessment of common pharmacologic treatments for the management of non-neuropathic and neuropathic pain syndromes.

Results: 8,984 ADPKD patients met study inclusion criteria. Mean age was 57 years (SD=17) and 50% male. Mean follow-up time was 36 months (SD=27). At baseline, the mean Charlson comorbidity score was 1.86 and common medical comorbidities included hypertension (65%), diabetes (25%), chronic pulmonary disorder (14%), depression (9%), and anxiety (8%). Seventy percent (N=6,285) received at least one prescription for a medication commonly used to treat pain during one-year post index. Opioids were used by 50% of patients, followed by corticosteroids (31%), hypnotics including benzodiazepines (28%), antidepressants (20%), NSAIDS (18%), and anticonvulsants (11%).

Conclusions: Results show pharmacologic treatment of pain is common in patients with ADPKD with high use of opioids, corticosteroids, hypnotics, antidepressants, and NSAIDS. Use of NSAIDs in this population is relatively contraindicated suggesting higher severity of pain in this population and warrants further investigation.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

SA-PO473

AD(H)PKD – A Prospective Cohort Study on the Use of Tolvaptan in ADPKD

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Background: The approval of tolvaptan as the first targeted therapy of autosomal-dominant polycystic kidney disease is a significant progress in the treatment of this disease. But how is this therapy managed in the real-life setting? How is it accepted by patients taking into account the consecutive polyuria?

Methods: To answer these questions, we initiated the AD(H)PKD registry which enrolls ADPKD patients that have not reached ESRD yet and present with the question whether tolvaptan would be a treatment option. We collect data on a yearly basis including lab values, kidney volume, quality of life, adherence, genotype, extrarenal manifestations, comorbidity, side effects and complications.

Results: Since the start of the study at the end of 2015 until May 2018 more than 450 patients could be enrolled. Here, we present - apart from the general characterization of the cohort – first data regarding the use of tolvaptan in the real-life setting. The urine volume increases to 5-7.5 liters in the majority of patients on tolvaptan. The largest increase occurs when starting the first dose step (45/15 mg), whilst the further uptitration (60/30 and 90/30 mg) only shows a minor additional effect on urine output. The same holds true for urine osmolality. Adherence to the therapy is currently about 80%; most patients that discontinue tolvaptan do so early after initation with polyuria-related events being the most common reason. More than 75% of patients report little to no problems with the therapy in everyday life. Patients skip a dose 1-2x per month on average and do so mainly due to professional and leisure-time activities.

Conclusions: The AD(H)PKD study continues successful enrolment and allows for a first insight into patient-reported outcomes like quality of life and feasibility of the therapy. The adherence of about 80% confirms the data obtained in TEMPO 3:4. Furthermore, AD(H)PKD provides the first systematic data on urine volume and osmolality in the real-life setting. These results will be very helpful for guiding management of ADPKD patients and patient counselling in the future.

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SA-PO474

An Analysis of Novel Quantitative MRI Parameters to Evaluate Cystic Burden in Autosomal-Dominant Polycystic Kidney Disease

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Background: In ADPKD, parameters that correlate with severity of disease are of crucial importance in guiding the management. To date, these rely primarily on genetics, clinical evaluation and kidney volumetry (TKV). Whilst TKV has been shown to be a very useful tool to predict future outcome, measuring the cyst fraction would be favorable. However, this is currently not feasible in the everyday clinical setting. Here, we present a novel approach employing MRI T2 mapping.

Methods: 141 ADPKD patients from the AD(H)PKD-cohort and 10 healthy controls underwent MRI (1.5T system). HtTKV was calculated on coronary T2-weighted images using semi-automatic segmentation. Renal T2 relaxation times [ms] were generated using a Gradient-Spin-Echo (GraSE) T2 mapping sequence. Cyst fractions and mean T2 relaxation times (kidney-T2) were calculated using a plugin in Osirix. For analysis of T2-times of the remaining renal parenchyma (parenchyma-T2) a single ROI was chosen manually in 3 slices of each kidney and the results were averaged. Based on the cyst fraction patients were separated into three groups (<35%, 36-70%,> 70%).

Results: Obtaining parenchyma-T2 required 6-10fold less time than kidney-T2 or htTKV by semiautomatic segmentation (0,78±0,14 vs. 4,78±1,17 min, $p<0,001$, 0,78 ±0,14 vs. 7,59±1,57 min, $p<.001$). Importantly, parenchyma-T2 showed a similarly strong correlation to the cyst fraction ($r=0,77$, $p<0,001$) as kidney-T2 ($r=0,77$, $p<0,001$) and resulted in the clearest separation of patient groups. HtTKV showed only a moderate correlation to cyst fraction ($r= 0,48$, $p<0,001$) and did not allow for a clear group separation. Limiting the analysis to CKD stage 1 ($n = 47$) increased this discriminatory power whilst maintaining a similar correlation to the cyst fraction (parenchyma-T2: r=0,81; kidney-T2: r=0,79; htTKV: $r = 0,48$, $p<0,001$ for all).

Conclusions: Renal T2-mapping allows the determination of novel imaging parameters which show a high correlation to the cyst fraction. Whilst currently used methods for measuring TKV and cyst fraction are time-consuming, parenchyma-T2 can be measured within one minute. The high correlation with cyst fraction makes this parameter a promising biomarker, the power of which regarding disease progression will now be examined.

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SA-PO475

Acute Tolvaptan Treatment Has No Immediate Effect on Renal Plasma Flow or Glomerular Filtration Rate in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease ADPKD is a common genetic disorder, characterized by formation of cysts in the kidneys, causing gradual renal failure. Tolvaptan is a vasopressin 2 antagonist that seems to reduce the decline in glomerular filtration rate (GFR) in ADPKD. The mechanisms are not fully understood and could, at least partly, be related to changes in renal plasma flow (RPF). The purpose of this randomized, cross-over, double-blind, placebo-controlled study was to investigate if acute tolvaptan treatment increases RPF and/or GFR in patients with ADPKD.

Methods: We studied 18 ADPKD patients (chronic kidney disease stages 1-3) on two separate occasions after a single dose of tolvaptan 60 mg or placebo. Two hours after treatment, RPF and GFR were measured by 99-mTc-DTPA renography. Blood pressure was measured every fifteen minutes throughout the day by Mobil-O-Graph®. Renal vascular resistance (RVR) was estimated by the equation mean arterial pressure/RPF.

Results: 99-mTc-DTPA renography showed a similar RPF after tolvaptan treatment and placebo treatment (673 ±262 ml/min vs. 650 ±209 ml/min p = 0.571). GFR estimated by 99-mTc-DTPA renography was also unchanged after tolvaptan (78 ±26 ml/min after tolvaptan vs. 79 ±21 ml/min after placebo p = 0.774). During renography, after tolvaptan intake, the brachial systolic blood pressures dropped significantly (135 ±13 mmHg after tolvaptan vs. 141 ±19 mmHg after placebo p = 0.043). We found no significant change in brachial diastolic, central systolic or central diastolic blood pressure. Estimated RVR during renography was unchanged after tolvaptan treatment (0.20 ±0.12 mmHg/ml/min after tolvaptan vs. 0.20 ±0.08 mmHg/ml/min after placebo p = 0.908).

Conclusions: Our results suggest that acute tolvaptan treatment has no immediate effect on RPF and GFR. Our results do not support the hypothesis that the effect of tolvaptan on ADPKD progression is mediated by changes in renal hemodynamics.

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SA-PO476

The Impact of Tolvaptan on Glomerular Filtration Rate in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Tolvaptan, a V2 receptor antagonist that induces aquaresis, has been shown through placebo-controlled studies to slow the decline in kidney function of patients with autosomal dominant polycystic kidney disease (ADPKD). Polyuria is a significant side-effect that can be attenuated by reducing daily sodium intake. In a cohort of ADPKD on tolvaptan, we aimed to identify the determinants of polyuria, to evaluate the impact of dietary counselling on the natriuresis and to compare the decline of estimated glomerular filtration rate (eGFR) before and after tolvaptan.

Methods: Retrospective study of 29 patients with ADPKD on tolvaptan. Serum creatinine level and 24-hour urine collection with volume and natriuresis were obtained before tolvaptan initiation. Patients had individual nutrition counselling to reduce their sodium intake. Tolvaptan was introduced after the nutrition counselling with serum creatinine level and 24-hour urine collection obtained on treatment. Polyuria was arbitrary defined as a urine volume of >5L/d. We used linear regression model and generalized estimation equations to analyse the data.

Results: The average of age and eGFR were respectively 44±11 years and 60±25 mL/min/1.73m^2. The urinary volume increased from 2.5 to 5.2L/d (95%CI: 4.6 to 5.8) on tolvaptan. Dietetic counselling resulted in a reduction of natriuresis (147 mmol/d (95%CI: 129 to165) to 131mmol/d (95%CI: 114 to 184)) (p=0.028). For each baseline increment of 10 mmol of daily sodium intake the odds ratio of polyuria was 3.4 (95%CI: 2.7-4.5). After adjusting for tolvaptan dose, an increase in 100 mmol of sodium intake was associated with an additional urinary volume of 1.1 L/d (95%CI: 0.6 to 1.6). The annual rate of eGFR loss was -5.5 ml/min/1.73m^2/year (95%CI: -8.2 to -2.7) before tolvaptan and -1.6 ml/min/1.73m^2/year (95%CI: -3.5 to 0.2) on tolvaptan. This slower rate of decline was statistically significant (p=0.033).

Conclusions: Natriuresis before tolvaptan is the major determinant of the polyuria on tolvaptan, but natriuresis can be significantly reduced by dietetic counselling. In this small cohort, we observed a slower decline in renal function after tolvaptan, as compared to the annual rate of decline before treatment with tolvaptan.

SA-PO477

Association Between Initial Dose of Tolvaptan and Reduction of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease

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Background: It is occasionally difficult to increase dosage of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD) treatment. The reason of difficulty in increase of tolvaptan dosage is mainly limitation of water intake. Therefore, the effect of lower tolvaptan dose is one of major concerns in ADPKD treatment. Despite that TEMPO3:4 trial and REPRISE trial revealed efficacy of high dose tolvaptan among ADPKD patients, dose-dependent efficacy of tolvaptan remains unclear.

Methods: We selected ADPKD patients who underwent tolvaptan treatment from 2014 to 2017 in our department. The association between averaged dose of tolvaptan during the first six months after the initiation of tolvaptan treatment and change rate of total kidney volume after the treatment. Total kidney volume was estimated by abdominal MRI.

Results: The median age of 10 male and 14 female patients was 50 years (IQR, 45 to 65 years). The total kidney volume, height-adjusted total kidney volume, and annual change rate were 1024mL (918 to 1819mL), 673mL/m (606 to 1137mL/m), +10.7% (+7.7 to +26.6%), respectively. Serum creatinine level was 0.9mg/dL (0.74 to1.42mg/dL), and eGFR was 52mL/min/1.73m^2 (37.7 to 71.8 mL/min/1.73m^2). CKD G2, G3a, G3b and G4 were 11 (44%), 4 (16%), 6 (24%), and 4 (16%) while Mayo classification 1A, 1B, 1C, 1D, and 1E were 0 (0%), 14 (58%), 3 (13%), 4 (17%), and 3 (13%). The annual rate of total kidney volume after tolvaptan treatment for six months was significantly lower than that of pretreatment level by -9.6% (-29.1 to +3.2%) ($P<1x10^{-5}$). When all the patients were divided into two groups according to median of difference between annual total kidney volume change before and six months after tolvaptan treatment, averaged tolvaptan dose during the first six months of tolvaptan treatment was higher in a group with stronger inhibition of kidney enlargement than a group with weaker inhibition of kidney enlargement (P=0.05). Mayo classification and CKD GFR stage were similar between the stronger and weaker inhibition groups.

Conclusions: Early effect on inhibition of total kidney volume growth may be associated with initial tolvaptan dose during the first six months after the initiation of tolvaptan treatment.

SA-PO478

Clinical Features Expecting High Efficacy of Tolvaptan in ADPKD Patients

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Background: Clinical efficacy of tolvaptan is variable in individual ADPKD patient. In our facility, we manage 120 ADPKD patients at present, and adapt 49 patients to the tolvaptan therapy. Among the cases, 40 patients have been proceeded more than one year after induction to the therapy, they are enabled to be examined the efficacy of tolvaptan. When the effectiveness would be defined as the reduction of total kidney volume (TKV) or the annual expansion rate of kidney volume (kidney growth rate: KGR) being less than 5%, tolvaptan showed approximately 70% of effectiveness in our facility. In this study, we retrospectively studied common clinical features in ADPKD patients who showed higher efficacy to tolvaptan by primarily focusing on KGR.

Methods: Forty ADPKD patients who had been treated with tolvaptan for at least one year were included in this study. KGR was calculated by CT-based total kidney volume (TKV) at one-year prior, just before, and one-year passed to the therapy. Response to tolvaptan was determined by ΔKGR (subtraction of pre-KGR from post-KGR), and negative value of ΔKGR indicates that the increase in TKV was inhibited by tolvaptan. Enrolled patients were stratified into 3 groups by ΔKGR value, and multiple clinical parameters were compared between 1st tertile group (1TG, lowest ΔKGR indicating highly effective) and 3rd tertile group (3TG, highest ΔKGR indicating poorly effective).

Results: ΔKGR values in 1TG and 3TG were -16.9% and 13.3%, respectively. Baseline values of TKV, KGR, systolic blood pressure (SBP), body mass index (BMI) and eGFR were significantly different between 1TG and 3TG (median TKV: 2005 mL vs 2534 mL, median KGR: 18.4% vs 3.0%, SBP: 123.1±16.5 mmHg vs 133.9±17.7 mmHg, BMI: 22.5±4.0 vs 26.3±7.4, eGFR: 57.1±23.7 mL/min vs 40.5±14.1 mL/min).

Conclusions: Present study may indicate that ADPKD patients who show less TKV, higher KGR, lower blood pressure, not-obese and renal function is not severely damaged would be expected higher efficacy of tolvaptan.

SA-PO479

Tolvaptan (TLV) in Children and Adolescents with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Design of a Two-Part, Randomized, Double-Blind, Placebo (PBO)-Controlled Trial

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Background: TLV slows ADPKD progression in adults; its value in affected children and adolescents remains unknown. The first trial to assess TLV in pediatric ADPKD is currently ongoing (NCT02964273). We present the unique features of the trial population and its design.

Methods: This multicenter trial comprises two phases: Phase A is one year, randomized, double-blind, and PBO-controlled, Phase B is a two year open-label extension for subjects who completed Phase A. As formal diagnostic criteria for pediatric ADPKD are not developed, an advisory panel agreed eligibility would be based on family history/genetic criteria and would require ≥ 10 renal cysts measuring ≥ 0.5 cm on MRI to warrant treatment. Subjects (n=60) are allocated into 4 groups by gender and age (12–14y;15–17y). Subjects aged 4–11y may enroll. TLV is initiated at a weight-adjusted split dose ≤ 67% of the adult starting dose to allow for acclimation to excess diuresis; TLV is up-titrated after 1 wk to approximate the weight-adjusted starting dose for adults. Down-titration is permitted per tolerance. Assessments include spot urine osmolality and specific gravity (co-primary endpoints), total kidney volume, eGFR, PD parameters (urine volume, fluid intake and fluid balance, serum sodium, serum creatinine, and free water clearance), PK parameters, and generic pediatric QoL assessments. Safety parameters include AEs, changes in creatinine, vital signs, and lab values. Subjects are tested for ALT/AST, alkaline phosphatase and total bilirubin during screening and for ALT/AST monthly during treatment. Liver function tests are reviewed by investigators, and by independent hepatic adjudication and independent data monitoring committees. Stringent monitoring and intervention rules ensure rapid response to any potential hepatic signals.

Results: Pending

Conclusions: Kidney enlargement is continuous in ADPKD; cysts expand years before a reduction in GFR is apparent. This trial assesses the tolerability of TLV and begins to test the hypothesis that early treatment with a disease-modifying agent might be beneficial. Available interim data will be presented.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Rockville, MD, USA

SA-PO480

Canadian Real-Life Assessment of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease (ADPKD): C-MAJOR Study and Hepatic Safety Monitoring Program

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Background: Tolvaptan is the only treatment slowing renal function decline, kidney enlargement and progression to end-stage renal disease in ADPKD. Health Canada mandated a patient registry of long-term clinical outcomes and a hepatic safety monitoring and distribution program (HSMDP) to mitigate the risk of liver injury. The objectives were to describe the baseline characteristics, quality of life (QoL), adherence, liver profile elevation rates and overall safety profile of patients enrolled in the real life setting of these two programs.

Methods: This is the 3rd interim analysis of C-MAJOR, the Canadian, non-interventional registry of ADPKD patients treated with tolvaptan and the 1st analysis of the HSMDP documenting the appropriate laboratory monitoring of hepatic function.

Results: 1143 and 250 patients were included in the HSMDP and C-MAJOR, respectively. At tolvaptan initiation, hypertension (77%), hepatic cysts (63%), and renal pain (21%) were the most common ADPKD manifestations. Patients presented with chronic kidney disease (CKD) Stage 1 (16%), 2 (28%), 3a (24%), 3b (20%) and 4 (8%) and with family history of ADPKD (77%) and family history of early ESRD (36%). At treatment initiation, 87 % of patients were considered at high risk of disease progression as per the Mayo classification (1C, D or E). QoL was assessed in newly initiated tolvaptan patients. Although not significantly different, progressively severe ADPKD-Pain and Discomfort Scale and Impact Scale scores in all domains were observed for increasing CKD stage. Over a mean (SD) follow-up of 64.1 (43.0) weeks, 3.1% of the 941 patients on tolvaptan experienced an elevation of LFT >3 X ULN. No cases of drug-induced liver injury were reported. The 6, 12 and 24-month treatment persistence rates on tolvaptan were 89.2%, 83.9% and 77.9% respectively. 47% of patients experienced an adverse event, most commonly nocturia (12%), polydipsia (9%), hypertension (8%), dizziness (7%), polyuria (6%) and fatigue (5%).

Conclusions: This interim report on real-life utilization of tolvaptan in Canada provides evidence of advanced disease at treatment initiation. The safety profile and persistence rate are similar to that reported in clinical trials. The liver safety evidence demonstrates that the HSMDP is effective in mitigating the risks to the patients.

Funding: Commercial Support - Otsuka Canada Pharmaceutical Inc.

SA-PO481

Gender-Specific Differences in Baseline Fluid and Solute Intake in the PREVENT-ADPKD Study

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Background: Adequate hydration may slow the postnatal growth of renal cysts in autosomal dominant polycystic kidney disease (ADPKD) by attenuating the release of arginine vasopressin (AVP). However, the efficacy, safety and feasibility of this approach, and whether baseline fluid and dietary solute intakes vary by gender are not known.

Methods: PREVENT-ADPKD is a 3-yr multi-centre randomized controlled trial determining the effect of Prescribed Fluid Intake (sufficient to reduce urine osmolality to ≤270 mOsmol coupled with reduced dietary solute intake) on the progression of height-corrected total kidney volume (Ht-TKV) compared to Usual Fluid Intake in ADPKD patients (eGFR≥30ml/min/1.73m^2; Mayo Class 1B-1E). Recruitment was completed in May 2018.

Results: Of 1571 patients assessed for eligibility at 13 sites in Australia, 1295 were excluded due to ineligibility (n=1144) or declined to participate (n=151). The remaining 276 patients consented to the study, of whom 89 failed run-in (Mayo Subclass 1A, n=37; atypical kidneys, n=3; cannot do MRI, n=5; eGFR<30, n=7; pregnancy, n=2; non-compliance, n=31; and other exclusion criteria met, n=4) and 187 were randomised into Usual Fluid Intake (n=93) or Prescribed Fluid Intake (n=94). The median age of the randomised cohort was 43 yrs (range: 19-67; 94 women; 72% caucasian). At baseline, men had worse clinical characteristics of ADPKD (higher blood pressure, Ht-TKV and serum creatinine; P<0.001) but reported less kidney pain (P=0.03). Baseline 24hr urine volume did not differ by gender (P=0.85), whereas men had higher 24hr urine osmolality (26.6%), 24hr urine sodium excretion (31.0%), serum osmolality (1.7%) and serum copeptin (biomarker of AVP release) (116.1%) compared to women (P<0.001). Ninety percent of the cohort consumed caffeinated drinks but this did not differ by gender.

Conclusions: Baseline fluid intake is not affected by gender, but dietary sodium intake and AVP release are higher in men compared to women with ADPKD. These data support the importance of targeting both fluid and dietary solute intake to synergise the possible benefits of the intervention in PREVENT-ADPKD.

Funding: Commercial Support - Danone Nutricia Research, Private Foundation Support, Government Support - Non-U.S.

SA-PO482

Random Daytime Spot Urine Correlates with Twenty-Four Hour Urine Osmolality in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Urine osmolality (UOsm) is a surrogate measure of hydration and dietary solute intake, regulated by levels of circulating arginine vasopressin (AVP). Monitoring UOsm may be useful to gauge adherence to fluid and diet prescriptions in autosomal dominant polycystic kidney disease (ADPKD). Traditionally, UOsm has been determined by 24hr urine collection but patients find this method cumbersome, and hence we investigated if spot urine could serve as an alternative method. The aim of this study was to determine the relationship between random daytime spot UOsm and 24hr UOsm in patients with ADPKD.

Methods: Random spot urine was collected prospectively from ADPKD patients (18-65 years, eGFR≥30 mL/min/1.73m^2) during the Screening Visit of the PREVENT-ADPKD study (a randomised controlled trial investigating the efficacy of prescribed fluid intake on kidney cyst growth). Urine specific gravity (USG) and serum copeptin (a biomarker of AVP release) were also analysed at the study visit, and patients then performed two 24hr urine collections over the subsequent 12 weeks.

Results: Seventy-nine participants were included (age:43±11 ys; 54% male). The mean spot UOsm was 491±196 mOsmol/L and correlated moderately with the mean 24hr UOsm (424±173 mOsmol/L; r=0.56; P<0.001). In contrast, the association between spot UOsm to urine creatinine ratio and the mean 24hr UOsm was weak (r=0.16, P=0.03). As expected, spot UOsm predicted the USG (P<0.001), and the latter was also positively correlated with the mean 24hr UOsm (r=049, P<0.001). Spot UOsm had a weak association with serum copeptin (median 4.2, range 0.9-28.1 pmol/L; r=0.26; P<0.001).

Conclusions: These data suggest that spot urine collected randomly during the day (either at a clinic visit for measurement of UOsm or by patient self-monitoring for USG)

may be an alternative method to estimate 24hr UOsm in patients with ADPKD. Further prospective studies and the outcome of the PREVENT-ADPKD trial are required to validate these findings.

Funding: Commercial Support - Danone Nutricia Research, Private Foundation Support, Government Support - Non-U.S.

SA-PO483

A Randomised Feasibility Trial of High vs Ad Libitum Water Intake in Autosomal Polycystic Kidney Disease

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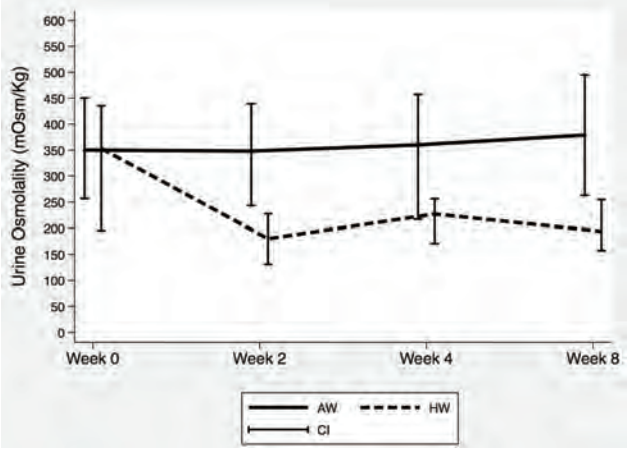
Background: High water intake is a rational therapeutic approach in Autosomal Dominant Polycystic Kidney Disease (ADPKD) and may have similar benefits to tolvaptan, but the efficacy of high water intake in slowing ADPKD progression has not been assessed. It is not known whether a randomised trial of high water intake in ADPKD would be feasible.

Methods: In a single-centre, open label randomised controlled feasibility trial, we assigned adult ADPKD patients with an eGFR≥20ml/min/1.73m2 to either 1) individualised daily fluid prescription with target urine osmolality ≤270mOsm/kg (HW), or 2) drinking to thirst (AW), over 8 weeks. Co-primary feasibility endpoints were the recruitment rate and separation between treatment arms in urine osmolality.

Results: 42 participants (57% female, age 46±13 years) were randomised (1:1) to HW (n=21) and AW (n=21) at a recruitment rate of 1 patient every 10 days. Baseline characteristics did not differ between trial arms (eGFR 68.4 (35.9-107.2) vs 75.8 (35.9-107.2) ml/min respectively). Significantly more HW patients achieved the target uOsm (14/21, 67%) compared to the AW group (5/21, 24%) during the 8 week treatment period ($p<0.001$), with uOsm significantly lower throughout follow-up in the in the HW group (Figure, $p=0.02$). There were no significant differences in CKD-EPI eGFR between arms, and no acute effects on ^{51}Cr-EDTA GFR.

Conclusions: Rapid recruitment to the trial, compliance with prescribed fluid intake, and separation between trial arms in uOsm suggest that a large-scale trial of high water intake in ADPKD is feasible.



Change in urine osmolality over time by treatment group

SA-PO484

Smart Water Bottle Technology and Adherence to Fluid Prescription in ADPKD Patients

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Background: The Vasopressin (V) V2 receptor antagonist, Tolvaptan, slows cyst growth and loss of kidney function in autosomal dominant polycystic kidney disease (ADPKD). Water intake inhibits V secretion and may have similar benefits. Using smartphone technology, the water bottle (HidrateSpark© (SB)) reminds individuals to drink at specific times and documents volume and time of fluid intake. We sought to determine if SB and dietary recommendations (DR) improved fluid prescription adherence versus DR alone.

Methods: SB was tested to known volumes for accuracy and 24-hour urine volume (24UV) (mean % error= -3.69%, p=NS), precision (relative uncertainty=0.0035), limit of detection (15 mL), between bottle reproducibility (p=0.94), and inter and intra-operator reliability (0.005% variability, p=0.97; p=0.216) were calculated. Subjects were randomized to receive DR or DR/SB and prescribed a 20% increase in fluid intake from their most recent 24UV or 3 liters/day, whichever was greater. All subjects received DR at 6 weeks and completed 24UV at 6 and 12 weeks. DR and DR/SB groups were analyzed for significance utilizing chi-square analysis methods comparing the proportion that met fluid goals and a t-test comparing mean fluid intake.

Results: With 36 subjects enrolled, 15 DR and 15 DR/SB completed the study. Target fluid intake in DR and DR/SB were 3460.88±416.3 and 3661.5±752.5 mL (p=NS). At 6 weeks, 40 and 67% of DR and DR/SB subjects met fluid goals (p=0.143). At week 12, 40 and 80% of DR and DR/SB subjects met fluid goals ($p<0.03$). At 6 and 12 weeks, DR/SB fluid intake was greater than DR (p=0.026; p=0.006). DR/SB subjects used SB 88.25% and 80.5% of days between 0-6 and 6-12 wks. DR/SB patients met or exceeded their fluid prescription on 41% of days.

Conclusions: DR/SB subjects attained their fluid prescriptions more often than DR subjects. Additionally, DR/SB patients displayed greater adherence and fluid intake with longer use of the bottle. However, day-to-day adherence was less than ideal. This indicates that use of a smart water bottle increases hydration, provides the potential for ongoing feedback, and can potentially lead to sustained behavioral change in ADPKD patients.

SA-PO485

Effect of Somatostatin Analogues on the Vasopressin Pathway in Patients with ADPKD

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Background: The vasopressin V2 receptor antagonist tolvaptan slows the rates of total kidney volume growth and GFR decline in ADPKD, but its effect is limited and aquaretic side effects hamper wide spread clinical use. Therefore somatostatin analogues are of interest, which also interfere with cyst formation. Interestingly, several studies have suggested that somatostatin is involved in renal water handling, indicating that there may be an interaction between the somatostatin and vasopressin pathways. We therefore investigated if the somatostatin analogue lanreotide has an effect on vasopressin levels and aquaresis in patients with ADPKD.

Methods: Patients were included who participated in the DIPAK-1 study, a randomized, open-label controlled clinical trial to test the efficacy and safety of the somatostatin analogue lanreotide in later stage ADPKD. Patients were invited for a baseline visit, and randomized to receive either lanreotide or standard care in a 1:1 ratio. Blood and 24 hour urine samples were collected at baseline and after 12 weeks. Free water clearance (FWC) was calculated as 24 hour urine volume-((Urine osmolality*24 hour urine volume)/plasma osmolality) and fractional free water clearance (FFWC) as (FWC/eGFR)*100%.

Results: Overall, 305 ADPKD patients were included, 53% female, 48±7 years of age, with an eGFR of 50±11 ml/min/1.73m^2. At baseline, there were no differences in plasma copeptin levels (a surrogate for vasopressin), 24 hour urine volume, FWC and FFWC between patients randomized to lanreotide (n=153) or standard care (n=152). From baseline to week 12, we observed no differences in change in plasma copeptin, 24 hour volume, FWC and FFWC between patients receiving lanreotide or standard care (-0.93±13.5 vs. -0.07±5.58 pmol/L, p=0.48; -0.02±0.6 vs. 0.07±0.7 L/24hr, p=0.25; 0.09±0.6 vs. 0.2±0.8 L/24hr, p=0.39 and 0.2±1.3 vs. 0.3±1.7 %, p=0.79 respectively).

Conclusions: The somatostatin analogue lanreotide does not affect vasopressin levels or aquaresis in patients with ADPKD. Our data therefore do not support an effect of somatostatin on the vasopressin pathway. An effect of lanreotide on vasopressin V2 receptor antagonist induced renoprotection and polyuria is therefore not to be expected.

Funding: Commercial Support - IPSEN pharmaceuticals, Thermo Fisher Scientific

SA-PO486

Two Year Open Label Extension Study of Pasireotide LAR in Polycystic Liver and Kidney Disease

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Background: Mass symptoms from liver (LV) & kidney (KV) volumes negatively impact quality of life in ADPKD & ADPLD patients. The SST analog Pasireotide LAR (Pas LAR) has a broader binding profile & higher affinity to SST receptors with potential for greater efficacy than octreotide or lanreotide. In our one year randomized controlled trial Pas LAR signifiantly reduced LVs and KVs but not GFR decline.

Methods: Pas LAR was offered to all participants every 28d for an additional 2 yrs. Changes beyond yr 1 in all subjects on continued or beginning (placebo in year 1) PasLAR for another 2 yrs were assessed. Using MRI, % changes in LV in placebo group before (yr 1) & after (yrs 2-3) cross-over to active treatment were assessed and effects of Pas LAR for 3 years. Annualized % changes in LV in treatment arm at yr 3 compared to the placebo arm during yr 1 & changes in KV from baseline at 12 & 36 mo in ADPKD cases were also assessed.

Results: Of 41 participants who completed LV measurements at 12 mo, 24 had LV and 15 had KV data at end of yr 3. Among 6 given placebo at baseline, the difference in the rate of change in LV baseline to yr 1 (5.4%) vs in the OLE_{on} period from yr 1 to OLE_{end} (-2.4%) was significantly decreased (P=0.037). Among the 4 patients given placebo at baseline with KV available, the difference in the rate of change in KV baseline to yr 1 (6.0%) vs. in the OLE_{on} period from yr 1 to OLE_{end} (-1.2%) decreased (P=0.043). Similarly, differences in the rate of change in LV of patients on placebo baseline to yr 1 (n=6, 5.4%) vs those from the Pas LAR group baseline to OLE_{end} (n=18, -0.3%) were lower (P=0.046). Differences

in the rate of change in KV of patients on placebo baseline to yr 1 (n=4, 6.0%) vs those from the treatment group baseline to OLE_{end} (n=11, 0.2%), (P=0.068). Of 17 who discontinued the study during OLE_{on} reasons included 6 hepatectomies (2 later returned to OLE_{on}), 2 had liver transplants, 7 with hyperglycemia.

Conclusions: Over three years Pas LAR continued to significantly slow the progressive increase in LV & TKV growth rates to a lesser extent, but participants experienced a higher frequency of AEs (hyperglycemia and diabetes).

Funding: NIDDK Support, Commercial Support - Novartis, Private Foundation Support

SA-PO487

Pancreatic Cysts and Intraductal Papillary Mucinous Neoplasm in Autosomal Dominant Polycystic Kidney Disease

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Background: Pancreatic Cyst lesions in ADPKD are primarily cysts. They are recognized increasingly, with isolated reports of intraductal papillary mucinous neoplasia (IPMN).

Methods: Tertiary care center retrospective study to determine prevalence, number, size, and location of pancreatic abnormalities (pancreatic cyst lesions [PCLs], IPMN, and not-otherwise-specified abnormalities) with abdominal magnetic resonance imaging (MRI) of genotyped ADPKD patients (1998 - 2013) and compared with age- and sex-matched non-ADPKD controls. We evaluated presentation, investigation, and management of all IPMNs among individuals with ADPKD (1997- 2016), for natural history and management of pancreatic abnormalities.

Results: Abdominal MRIs (104 with and 167 without gadolinium) were examined for 271 genotyped ADPKD patients. At least 1 PCL was noted in 19% of ADPKD patients (n=52) compared with 10.2% of controls (n=28) (*P*=.03). Mean (SD) age at diagnosis was 42(12) years for ADPKD vs 50(9) years (controls) (*P*<.001). Thirty-seven (71%) had a solitary PCL; 15 (28%) had multiple. PCL prevalence did not differ by genotype. IPMNs were detected in 1% of ADPKD cases. Among 12 IPMN patients (7 branch duct; 5 main duct or mixed type) monitored for ~140 months, 2 with main duct IPMN required Whipple resection, and 1 patient died of complications from small-bowel obstruction after declining surgical intervention.

Conclusions: With MRI, PCLs were detected in 19% and IPMNs in 1% of 271 ADPKD patients with proven mutations, without difference across genotypes. PCLs were asymptomatic and remained stable in size. No malignant transformation occurred among 12 IPMN patients.

SA-PO488

Epidemiology of Autosomal Dominant Polycystic Kidney Disease (ADPKD) in Olmsted County

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Background: ADPKD is the most common inherited kidney disease. A prior study in Olmsted County estimated an incidence of ADPKD of 1.38 per 100,000 during 1935–1980; however, contemporary data on the incidence of ADPKD are scarce. We aimed to determine the incidence of ADPKD in Olmsted County, MN during 1980-2016.

Methods: Mayo Clinic and Olmsted Medical Center (OMC) deliver most health care to Olmsted County residents. We searched diagnostic codes and the Mayo Clinic and OMC radiology databases to identify subjects and all medical records were reviewed to validate ADPKD diagnoses using the following criteria. Diagnosis of definite ADPKD was based on radiographic findings plus family history of ADPKD or genetic testing; likely ADPKD, on >10 cysts in each kidney without advanced CKD or different renal cystic diseases; possible ADPKD, on cyst number exceeding the 97.5 percentile in kidney donors of the same sex and age. Incidence of ADPKD during 1980-2016 and point prevalences for the year 2010 were calculated.

Results: We reviewed medical charts and abdominal images and/or radiology reports of 1,231 subjects with diagnostic codes of cystic disease during 1980-2016, and the medical charts and abdominal CT or MR scans of 2,765 subjects with multiple cysts from radiology databases during 1997-2016. 364 patients with incident ADPKD (85 definite, 45 likely, 234 possible) were identified. Overall age and sex adjusted annual incidence rates of definite ADPKD were 1.79 (95% CI: 1.40, 2.17) and those of definite or likely ADPKD 3.06 (2.52, 3.60) per 100,000 person-years. The peak incidence rate of definite and likely cases was 5.27 (3.07, 8.44) in the 60-69 year age group. Incidence rates of possible ADPKD increased markedly after 1997 when CT and MRI became available electronically. On January 1, 2010, the overall age and sex adjusted prevalence of definite ADPKD was 47.0 (35.4, 58.5), definite or likely ADPKD was 68.0 (53.9, 82.1) and definite, likely or possible ADPKD was 123.9 (104.6, 143.2) per 100,000 population.

Conclusions: The incidence of definite or likely ADPKD was 2.22 times higher than in the 1935-1980 study likely due to more comprehensive ascertainment of the population. Genetic testing will be necessary to determine how many of the patients classified as possible cases have ADPKD or another genetic renal cystic disease.

SA-PO489

Prediction of Autosomal Dominant Polycystic Kidney Disease (ADPKD) Outcomes at Birth

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Background: The identification of high-risk ADPKD patients at birth may help them to receive appropriate medical attention.

Methods: We developed logistic, tree and random forests models for reaching CKD stage 3b progression endpoint (GFR<45 ml/min/1.73m^2) based on data collected by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease study (CRISP; 241 ADPKD adults). We validated these models using data collected by the HALT-A study (558 ADPKD adults). In addition to the GFR endpoint and age, analyzed variables included race, gender, birth weight, gene type and mutation strength-based indices (data available at birth).

Results: The logistic regression model yielded area under an ROC curve (AUC) 0.786 (95% CI: 0.7231, 0.8491; p<0.001). The tree model pruned to the optimal complexity parameter of 0.038 had a similar prognostic ability as the logistic model (their 95% CI of AUC overlapped). Random forests grown by 1000 bootstrap replicate samples of a size of 196 samples with replacement improved the prognostic ability of the factors available at birth and reached AUC 0.91 (95% CI:0.8689, 0.9467; p<0.001). Validation of these models in HALT-A cohort revealed much lower AUC for the logistic regression model (AUC 0.537), the tree model (AUC 0.552), as well as random forests (AUC 0.612). This likely occurred in part due to overfitting during analyses of CRISP data.

Conclusions: The data available at birth have modest value in prediction of advanced CKD outcomes based on information collected in the CRISP and HALT-A studies. Our analyses also demonstrate an essential role of predictive model validation using independent cohort datasets.

Funding: NIDDK Support

SA-PO490

Defining the Prevalence and Clinical Characteristics of Atypical Polycystic Kidney Disease (PKD)

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Background: The Mayo Clinic Imaging Classification is now widely used for risk assessment of autosomal dominant polycystic kidney disease, but requires exclusion of cases with atypical kidney imaging. Here, we report the first systematic study to define the prevalence and clinical correlates of atypical PKD.

Methods: We reviewed all patients seen at the Toronto General Hospital PKD Clinic between 5/2007 to 10/2017 for their clinical, genetic, and MRI/CT results. Atypical PKD was classified as: (i) unilateral, (ii) segmental, (iii) asymmetric, (iv) lopsided, (v) mild lopsided, (vi) unilateral or bilateral atrophy, or (vii) segmental sparing.

Results: 7.6% (n=36) of 472 patients reviewed displayed imaging patterns consistent with atypical PKD. Compared to patients with a typical imaging pattern, they were older with normal renal function and displayed a high rate of no mutation detected (see Table).

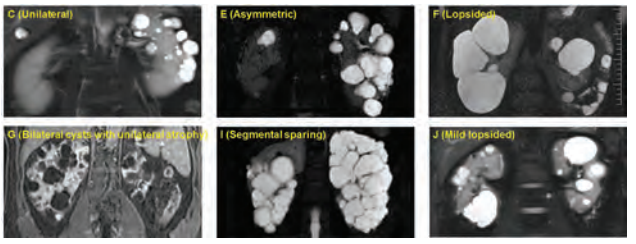
Conclusions: Atypical PKD is generally associated with mild kidney disease and needs to be vigorously excluded from kidney volume-based risk assessment. The etiologies of these cases are likely heterogeneous, but many may be underpinned by somatic mosaicism which can be unravelled by Next Generation Sequencing.

Characteristics of cohort

	Total (n=472)	Typical (n=436)	Atypical (n=36)
Age, mean [range]	43 [16-78]	43 [16-78]	54 [20-74]
Male:Female	213:259	191:245	22:14
Positive family history, n (%)	331 (70.1)	320 (73.4)	11 (30.6)
Mutation class, n (%)			
PKD1 PT	167 (35.4)	165 (37.8)	2 (5.6)
PKD1 in-frame indel	16 (3.4)	16 (3.7)	0 (0)
PKD1 NT	100 (21.2)*	98 (22.5)	2 (5.6)
PKD2	122 (25.8)*	117 (26.8)	5 (13.9)
NMD	68 (14.4)	41 (9.4)	27 (75.0)
sCreat at last follow-up, median (IQR), umol/L	89 (70-122)	89 (71-126)	81 (70-103)
eGFR at last follow-up, median (IQR), mL/min	80 (51-101)	79 (49-102)	82 (69-99)
TKV, median (IQR), mL	1139 (625-2002)	1151 (609-2101)	1088 (763-1362)

*one patient had bilineal (PKD1 NT/PKD2) inheritance;

PT: protein-truncating; NT: non-truncating; NMD: no mutation detected; IQR: interquartile range



SA-PO491

PROPKD Score Predicts Kidney Decline in Australian Patients with Autosomal Dominant Polycystic Kidney Disease in Clinical Practice

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Background: The PROPKD score was recently developed from a single-country cohort study to enable risk stratification of progression to end-stage kidney disease in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). The aim of this study was to validate whether the PROPKD score predicts kidney function decline in clinical practice amongst Australian ADPKD patients.

Methods: A cross-sectional study was conducted of 39 unrelated individuals with genetically confirmed ADPKD encountered by the Queensland Conjoint Renal Genetics Clinic Service between 1st January 1994 to 31st May, 2018. Clinical and genetic factors were examined using the PROPKD score, to assess its relationship with kidney function decline prediction over a three year period.

Results: Of the 39 individuals in this study, 15 patients were low risk, 17 were intermediate risk and 7 were high risk. The median age for the low risk group commencing renal replacement therapy (RRT) was 60 years, 54.5 years for the intermediate risk group, and 55.3 years for the high risk group. Of those who commenced RRT, 1 was high risk, 6 were intermediate risk and 1 was low risk. One high risk patient underwent pre-empt live transplant at 48 years. The median change in estimated glomerular filtration rate (CKD-EPI) in the low risk group was 1.5ml/min/1.73m^2/yr, 12.5 ml/min/1.73m^2/yr in the intermediate risk group and 15 ml/min/1.73m^2/yr in the high risk group ($p<0.001$). There were no deaths from this cohort.

Conclusions: The PROPKD score accurately predicts kidney function decline in patients with ADPKD in this Australian cohort in clinical practice. This prediction tool may enable future personalised clinical prognostication and therapeutic management of ADPKD, as well as for potential participants to be identified for clinical trials.

SA-PO492

Disease Symptoms and Poor Quality of Life (QoL) in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Preserved Kidney Function

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Background: ADPKD is a hereditary progressive disease in which enlarging kidney cysts impair function and lead to kidney failure. In general, patients in early-stage chronic kidney disease [CKD] (eg, stages 1 and 2) tend to have normal QoL, but there is variability in disease burden with early-stage ADPKD. A subgroup of patients within an observational study had significant disease burden prior to renal function decline. We examine the characteristics of this subgroup.

Methods: Data were from a multi-center, longitudinal, observational study of 3,409 adult ADPKD patients (NCT01430494) with 990 and 956 patients in CKD stages 1 and 2, respectively. A subgroup of patients in stages 1 or 2 (n=42) was identified based on poor scores (≥3 points) on 2 of 3 ADPKD-Impact scale (ADPKD-IS) subscales (physical, emotional, fatigue). We examined associations of poor ADPKD-IS scores with clinical outcomes (eg, albuminuria, kidney stones, urinary tract infection [UTI]), biomarkers (eg, height-adjusted total kidney volume, estimated glomerular filtration rate, abdominal girth), and patient-reported outcome (PRO) measures (ADPKD-Urinary Impact Scale, SF-12v2® Health Survey, Brief Pain Inventory). Analyses used χ^2 tests, receiver operating characteristic (ROC) curves, and Cohen's *d* effect sizes for mean differences.

Results: Patients in the poor ADPKD-IS subsample were more likely than other early-stage CKD patients to have albuminuria, hematuria, kidney pain, kidney stones, and UTI (all p <.05). ROC analyses found that biomarkers did not distinguish between the poor ADPKD-IS subgroup and other early-stage patients: all areas under the curve (AUC) ≤.60, all p >.05. All PRO scores accurately differentiated the poor ADPKD-IS subgroup from the remaining early stage sample: AUCs from .83 to .95 (all p <.0001), with large mean sample differences (all $d \geq 1.6$).

Conclusions: A subgroup of ADPKD patients in early-stage CKD experience poor symptomatology and QOL. These patients are more likely to have albuminuria, hematuria, kidney pain, kidney stones, or UTI.

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SA-PO493

Patient-Reported Outcomes (PROs) as Predictors of Healthcare Utilization (HCU) and Work Outcomes in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a rare progressive hereditary disease where cysts in the kidneys reduce renal function, often leading to kidney failure. ADPKD is associated with deficits in patients' quality of life (QoL) and functioning. We examine if PROs predict HCU and work outcomes in ADPKD patients.

Methods: In a global, multi-center, longitudinal, observational study of 3,409 ADPKD patients (NCT01430494) data collection at baseline and every 6 months (up to 30 months) included measures of ADPKD-associated symptoms and health burden (ADPKD-Impact Scale [ADPKD-IS], ADPKD-Urinary Impact Scale [ADPKD-UIS]), generic QoL (SF-12v2® Health Survey [SF-12v2]), and pain (Brief Pain Inventory-Short Form [BPI-SF]) as well as HCU and work outcomes. Separate logistic regression models examined each PRO as a predictor of dichotomous HCU (0, ≥1 hospitalization) and work outcomes (0, ≥1 sick days). Ordinary least squares regression examined each PRO as a predictor of continuous work outcomes (sick days, work effectiveness). Baseline to month 18 data were used for this analysis.

Results: The likelihood of ≥1 hospitalization in the previous 6 months was significantly predicted by worse baseline scores on ADPKD-IS fatigue, emotional, and physical scales (Odds ratios [ORs] from 1.55 to 1.77), ADPKD-UIS frequency, nocturia, and urgency scales (ORs from 1.32 to 1.43), SF-12v2 physical and mental component summaries (ORs: 0.97, 0.96), and BPI-SF pain severity and pain interference scales (ORs: 1.11, 1.16), all P <.05. The likelihood of ≥1 sick day in the previous 6 months was significantly predicted by worse scores on ADPKD-IS and ADPKD-UIS scales (ORs from 1.24 to 1.76), SF-12v2 summaries (ORs: 0.95, 0.96), and BPI-SF scales (ORs: 1.25, 1.26), all P <.001. Worse scores on PROs predicted a higher number of work days missed (all P <.001), while worse scores on ADPKD-IS and ADPKD-UIS scales, SF-12v2 summaries, and the BPI-SF pain interference scale predicted lower work effectiveness (all P <.05).

Conclusions: ADPKD-associated symptoms, QoL, and pain PROs were predictive of ADPKD patients' HCU and work outcomes. These findings support the inclusion of PROs in clinical studies and practice with ADPKD patients.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

SA-PO494

Patient and Caregiver Beliefs, Attitudes, and Perspectives on Genetic Screening and Testing for Autosomal Polycystic Kidney Disease

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Background: Predictive genetic screening and testing is available for accurate and early diagnosis of hereditary autosomal polycystic kidney disease. However, the complex ethical and psychosocial implications can make decision-making challenging and data on patients' perspectives are limited. We aimed to describe patient and caregiver perspectives on the value and risks of genetic screening and testing for autosomal polycystic kidney disease (ADPKD).

Methods: 154 participants (120 patients and 34 caregivers) from 8 centres in Australia, France and Korea participated in 17 focus groups. Transcripts were analysed thematically.

Results: We identified five themes: *financial constraints* (insecurity in the inability to obtain life insurance, self-doubt in limited work opportunities, financial barrier of test); *futility in unpredictability* (accepting erratic and diverse manifestation of disease, inevitable disease progression, daunted by perplexity of results); *lacking autonomy and support in decisions* (overwhelmed by ambiguous information, medicalising family planning, appeasing the family, financial barrier); *seizing control of wellbeing* (gaining confidence through disease management, reassurance in family resilience, hope for health innovations to benefit the next generation, minimalising regret with preparation); and anticipating impact on quality of life (comforted by lack of symptoms, decisional uncertainty in risk of inheriting PKD, judging the value of life with PKD in family planning, guilt in foetal testing or abortion).

Conclusions: For patients with ADPKD, genetic screening or testing provides an opportunity for them to take ownership of their health through family planning and preventive measures. However, they are also concerned and uncertain about the accessibility of these services, psychological sequelae of testing, and potential financial consequences. Patient-centred genetic counselling and education that addresses patients' concerns may support informed decision-making about genetic testing and screening in ADPKD.

SA-PO495

Patient-Reported Disease Burden and Urinary Impact in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is an inherited disease leading to kidney enlargement, worsening of kidney function, and quality of life impacts. ADPKD patients experience symptoms consistent with urine concentration deficits, such as polyuria, nocturia, urinary frequency and urgency. Combined with tolvaptan (TLV) therapy those symptoms may be accentuated.

Methods: In a randomized, placebo-controlled, double-blind clinical trial (NCT01451827) urinary burden, and health-related quality of life (HRQoL) were assessed over 8 weeks. Urinary burden was measured by number of voids and 24h urine volume. HRQoL measures included the ADPKD Impact Scale (ADPKD-IS), ADPKD Urinary Impact Scale (ADPKD-UIS), and SF-12v2 Physical and Mental Component Summary (PCS and MCS).

Results: A total of 177 subjects enrolled in the clinical trial. 134 subjects were randomized to various doses of TLV in several formulations (50-120mg/day, pooled) and 42 subjects to placebo (PLC). Mean number of voids were similar for TLV and PLC subjects at baseline (daytime: 6.4 vs 6.2; nighttime: 1.5 vs 1.6) but increased in the TLV group by Week 8 (daytime: 10.1 vs 6.9, p=0.0002; nighttime: 2.4 vs 1.5, p≤0.00001). Mean 24h urine volume at baseline was similar between TLV and PLC subjects (2.3L vs 2.4L) but increased in the TLV group through Week 8 (6.1L vs 2.9L, p<0.0001). Compliance was 98% for TLV vs 97% for PLC.

Conclusions: Baseline urinary burden is low with subjects reporting only minimal bother/impact during daytime and slightly higher burden associated with nocturia. With tolvaptan treatment, the urine volume doubled and number of voids increased by over 50% with intermediate increases in patient-reported urinary burden during daytime and nighttime. Overall HRQoL showed no noticeable change during the study duration even with increased urinary burden.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Mean HRQoL

		TLV		PLC		p-value
		Baseline	Week 8	Baseline	Week 8	
ADPKD-IS	Physical	1.4	1.5	1.4	1.4	0.91
	Fatigue	1.7	1.8	1.6	1.6	0.30
	Emotional	1.6	1.6	1.8	1.6	0.06
ADPKD-UIS	Frequency	1.3	2.1	1.2	1.3	<0.0001
	Urgency	1.2	2.0	1.1	1.1	<0.0001
	Nocturia	1.5	2.6	1.5	1.6	<0.0001
SF-12v2	PCS	52.0	51.4	50.1	50.6	0.51
	MCS	52.4	51.1	52.4	51.7	0.67

SA-PO496

Patients Values and Preferences About Renal Cysts: A Survey

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Background: Renal cysts are a common incidental finding on radiographic imaging. While most cysts are indolent, individuals with such cysts are frequently monitored for interval growth and potential malignant transformation, which is ultimately rare.

Methods: We are deploying a cross-sectional survey to patients who have billing code for renal cysts and those who do not in the Greater Plain Collaborative (GPC) de-identified dataset. We developed and prepiloted a survey that assesses patients values and preferences about renal cysts. Here we present preliminary results from the University of Kansas Medical Center.

Results: To date, there have been 71 respondents. The mean age was 61 (range 30-82) years. 4% were Asian, 3% were black, 91% were white and 56% were female. The majority of respondents were college graduates (33%) or possessed post graduate degrees (37%). 72% of people reported no family history of kidney disease, and 66% of respondents (47 people) reported being told by a doctor that they have a kidney cyst. Of those with a renal cyst, 24 reported having one cyst. 39 people reported having no treatment plan for their cyst(s), and of those who reported having a treatment plan (n=15), all reported follow-up visits providing a sense of security and reassurance. 12 of these 15 reported that they would worry more about the cyst(s) if there were no follow-up. 15 people with renal cyst(s) reported seeing their primary care physician for their cyst, and 30 people reported seeing a nephrologist for their cyst(s). Of those with a renal cyst, 34 felt their doctor considered their values and opinions regarding follow-up imaging for renal cyst(s). 29/71 respondents wanted to know more about their cyst(s), and 23/29 specified wanting to know more about how often it should be imaged, if there are treatments, and the risk of progression to cancer. 20/71 people reported feeling anxious or would feel anxious about their renal cyst(s)

Conclusions: There is wide variability in patient values and preferences regarding renal cysts and their follow-up. While some expressed concerns about the risk of progression to cancer, others were not worried at all. It is unclear if this correlates to knowledge about prognosis of renal cysts or perceived risk. Guidance on this topic is needed and could help physicians and patients with shared decision making regarding renal cyst management.

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SA-PO497

Composite End Points in ADPKD Studies: A Guide for Best Practices

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Background: There is considerable inconsistency in the outcomes reported in Autosomal Dominate Polycystic Kidney Disease (ADPKD) and how they are measured. In this article, we aim to highlight the appropriateness of different outcomes to be included as a component in composite outcomes

Methods: We developed guidance including a summary table for components of the composite end points in ADPKD. We utilized the results of a systematic review and discussions among the Polycystic Kidney Disease Outcome Consortium (PKDOC) composite endpoint subcommittee. The subcommittee consists of Scientists, clinicians, methodologists, manufacturers, patients, advocacy groups representatives, and critical path institute representatives, all with experience in ADPKD. The investigators assessed the face validity of the suggested guidance and used an iterative approach of feedback, revision, and testing.

Results: Table 1 summarizes outcomes that are reported in ADPKD studies and the different ways they can be measured. It also explores pros and cons for including them as part of a composite outcome for ADPKD studies.

Conclusions: Composite end points will continue to be used in ADPKD studies and may be more utilized in-light of new approved treatments. Understanding the unique considerations about the different components and their use in ADPKD studies is essential in developing high quality evidence that will appropriately assess the short and long term effects of different interventions.

Table 1

Endpoint	Feasibility of collecting data	Event frequency	Acceptability to regulators	Previous body of evidence in a clinical area	Comments
Death	Yes	Rare	Yes	Commonly reported as a component of a composite	- Likely more appropriate to use overall mortality -Disease specific mortality requires clear definitions. - Death rate will depend on baseline risk of mortality in the population of interest, which is low in ADPKD -Should be considered but may not apply in all cases (e.g. children).
ESRD including preemptive transplant	Yes	Varies depending on genotype, rate of progression and comorbidities	Yes	Commonly reported as a component of a composite	Enrichment strategies are useful to increase the event rate of the outcome. -Clear definitions of ESRD are necessary.
Hospitalization	Yes	Varies; Can be affected by patients' history	Yes	Reported as an outcome but not often part of a composite	Hospitalization due to disease specific interventions or complications should be very clearly defined and adjudicated
Worsening kidney function	Yes	Varies/Frequent	Yes	Commonly reported as a component of a composite	-Reported using different measures (e.g. doubling of serum Cr, 50% reduction in eGFR, reduction of eGFR beyond a certain threshold) -Important to note that the pattern of treatment effects on GFR must be examined, specifically acute effects on eGFR -Need to be aware of hyperfiltration as a potential confounder to the results of kidney function
Hypertension	Complicated if agent affects BP and by concomitant anti-hypertensive use	Frequent	Accepted surrogate	Reported as an outcome but not often part of a composite	-could be unreliable unless very clearly defined. -Reported using different measures (e.g. SBP, DBP, worsening hypertension as defined by "intensified therapy") - It is important to include the actual BP value
Chronic or acute pain / Medication	? lack of reliable and responsive tools to assess pain and identify cause	Varies/Frequent	Yes when using validated tools	Reported as an outcome but not part of a composite	-Reported using different measures (e.g. significant kidney pain necessitating medical leave, pharmacologic treatment or invasive intervention) -Challenging to distinguish Kidney pain

SA-PO498

Identifying Patient-Important Outcomes in Polycystic Kidney Disease: An International Nominal Group Technique Study

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Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) are at increased risk of premature mortality, morbidities, and complications, which severely impair quality of life. However, patient-centered outcomes are not consistently reported intrials in ADPKD, which can limit shared decision-making. We aimed to identify outcomes important to patients and caregivers and the reasons for their priorities.

Methods: Patients with ADPKD and their caregivers were purposively selected from eight centers across Australia, France and Republic of Korea. Participants identified ranked and discussed outcomes for trials in ADPKD. We calculated an importance score (0-1) for each outcome and conducted thematic analyses.

Results: Across 17 groups, 154 participants (121 patients, 33 caregivers) aged 19 to 78 (mean 54.5 years) identified 55 oucomes. The 10 highest ranked outcomes were: kidney function (mean importance score 0.36), end stage kidney disease (0.32), survival (0.21), cyst size/growth (0.20), cyst pain/bleeding (0.18), blood pressure (0.17), ability to work (0.16), cerebral aneurysm/stroke (0.14), mobility/physical function (0.12), and fatigue (0.12). Three themes were identified: threatening sembalance of normality, inability to control, and making sense of the diverse risks.

Conclusions: For patients with ADPKD and their caregivers, kidney function, delayed progression to end stage kidney disease and survival were the highest priorities, and were focused on achieving normality, and maintaining control over health and lifestyle. Implementing these patient-important outcomes may improve the meaning and relevance of trials to inform clinical care in ADPKD.

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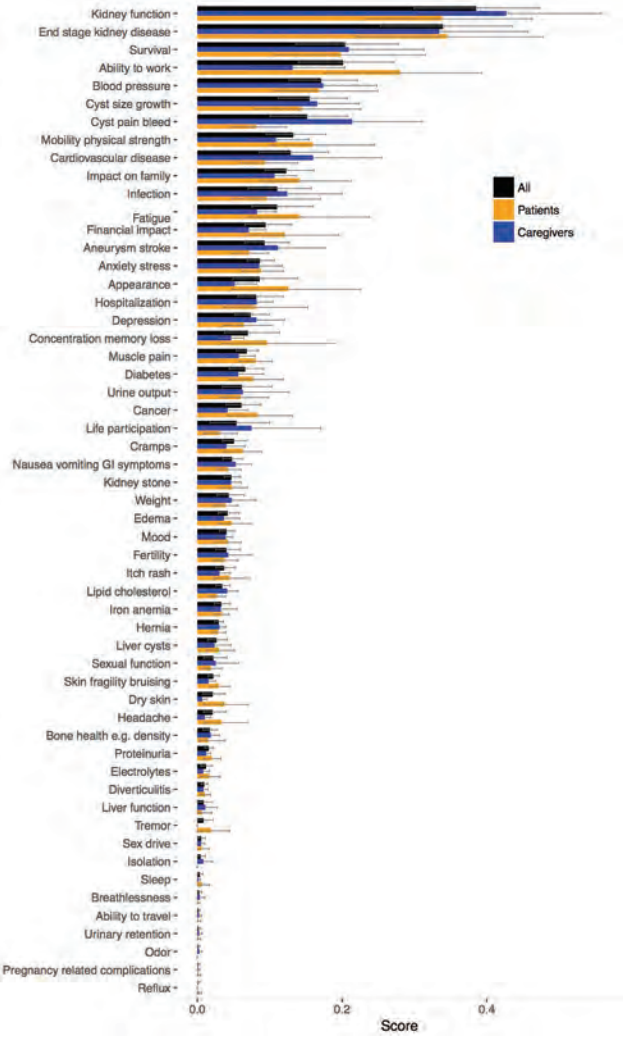

Mean importance score by patient status

SA-PO499

Description and Variability of Dietary Intake of Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Nutrition counseling is imperative for Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients; proper intake of protein and sodium can delay cyst growth and reducing diet acid load may delay progression of disease. Little has been published describing the diet of ADPKD patients. Food records collected over 3 days are standard practice to account for daily variations in intake. However, it is unknown how much nutrient intakes vary and if three days of food records are necessary. The objective of this project was to describe the diet of ADPKD patients and to understand how much nutrient intake varies daily.

Methods: Three-day food records were collected in a genetic disorder nephrology clinic at University of Chicago Medicine. A Registered Dietitian provided food record instructions and analyzed the record with National Data Research System, 2017. Potential Renal Acid Load (PRAL) and the variability of nutrient intake between three days of food record for a single patient were calculated.

Results: A total of 22 patients were included in analysis with a mean age of 48.18years, BMI of 26.6kg/m^2 and GFR of 58.29ml/min (n=15); 91% were Caucasian. See table for dietary analysis results and day-to-day variability.

Conclusions: ADPKD patients are consuming excess protein, sodium, saturated fat and cholesterol; whereas potassium, calcium and fiber intake is inadequate. These results showcase the importance of nutrition counseling for ADPKD patients. Nutrient intake varies greatly from day to day, highlighting the importance of capturing more than a single day when assessing diet.

Average Nutrient Intake and Daily Variability

	Average Intake	Variability
Calories	1929	29%
Protein	81g	42%
Fat	85g	41%
Carbohydrate	209g	37%
Sodium	2770mg	42%
Potassium	2663mg	35%
Phosphorus	1257mg	38%
Magnesium	332mg	33%
Calcium	930mg	47%
Cholesterol	334mg	56%
Fiber	22g	36%
% Calories from Saturated Fat	13%	42%
% Calories from Added Sugar	2%	63%
Potential Renal Acid Load (PRAL)	9.09 mEq/day	126%

SA-PO500

Survey of Contemporary Management of ADPKD Highlights Need for Improved Knowledge Translation

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Background: Recent years have witnessed a paradigm shift in the management of ADPKD, including novel biomarkers of disease progression such as total kidney volume (TKV), refined blood pressure (BP) targets, and repurposed drugs such as Tolvaptan. We sought to identify clinician's familiarity with and usage of these new management tools in contemporary-real world practice.

Methods: An online survey of 20 questions was disseminated to 71 nephrologists across British Columbia. The survey consisted of multiple choice questions regarding: clinician demographics, sources of information regarding ADPKD care, self-identified needs for optimal management of ADPKD, types of renal prognostication tools used, imaging tests and frequency of follow up imaging, blood pressure targets, and understanding of Tolvaptan utility.

Results: A total of 22 nephrologists (28%) completed the questionnaire. 89% of respondents are assessing risk of renal progression before GFR decline in their ADPKD patients, with a variety of tools being used. 90% of respondents obtain additional imaging after diagnosis in some or all of their ADPKD patients, but only 40% report use of imaging to assess risk of renal progression. 1 in 5 respondents are confident in their ability to interpret metrics of kidney size in ADPKD. 60% of nephrologists have been approached by patients about Tolvaptan, but 55% of respondents were not confident or only somewhat confident in their ability to identify which patients would benefit from treatment with Tolvaptan. Only 30% of respondents use the HALT-PKD BP target of <110/75 with the remainder using higher BP targets. The necessity for clear treatment guidelines and algorithms was identified by 25% of clinicians as the greatest unmet need.

Conclusions: The results of this survey indicate that there is variability in practice patterns, usage and familiarity with evidence-based ADPKD management tools among clinical nephrologists. Although only a minority of clinicians are confident in their ability to use these new tools and treatments appropriately, the vast majority show interest in further education. This emphasizes a need for ongoing efforts to translate these developments in ADPKD care into routine clinical practice.

SA-PO501

Standardized Image Acquisition and Measurement Methods Yield Accurate Total Kidney Volume Assessment in Polycystic Kidneys via CT or MRI

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Background: Total Kidney Volume (TKV) assessment is a robust tool for predicting renal prognosis in autosomal dominant polycystic kidney disease (ADPKD) but is difficult to obtain outside of research settings or large academic centers. Bringing TKV measurement into routine clinical practice requires imaging protocols that are widely available and interpretation methods that are feasible for clinical radiologists.

Methods: 30 participants >18 years of age with a diagnosis of ADPKD were recruited. Participants underwent 3 scans; an MRI, a low-dose CT (LD) scan and an ultra-low dose CT scan (ULD). The ULD was also reconstructed via model based iterative reconstruction (MBIR) yielding a 4th image set. The images from the 4 modalities were analyzed with three standardized TKV measurement equations and compared to the gold standard method of MRI manual planimetry. Images were interpreted by radiologists using detailed measurement instructions, but without any formal training in TKV. Accuracy, variation and reproducibility of the different imaging modalities and measurement techniques was assessed.

Results: All imaging modalities (LD, ULD and MBIR) as well as all measurement equations ('Traditional ellipsoid', 'Mayo ellipsoid' and the 'mid-slice method') had excellent correlation with the gold standard with r^2 values for all being over 0.97. Variation was within ranges reported in previous analyses of TKV measurement, although un-reconstructed ULD and the mid-slice method showed higher variability. Intraclass Correlation Coefficients were >0.98 for all methods, demonstrating high reproducibility. The standardized measurement methods had interpretation times of 5 minutes compared to 45 minutes for the gold standard. The ULD CT scan had a mean effective radiation dose of 0.88 mSv, a value approaching average exposure for an abdominal x-ray series.

Conclusions: Accurate and reproducible TKV measurements can be obtained using time saving interpretation methods and readily available image acquisition methods including abbreviated CT protocols with minimal radiation exposure. These results confirm the accuracy of a variety of standardized TKV measurement methods which may facilitate the implementation of TKV assessment in routine clinical use across diverse practice settings.

SA-PO502

Using Segmental Bioelectrical Impedance Analysis to Predict Abdominal Cystic Organ Volumes in Autosomal Dominant Polycystic Kidney Disease

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Background: Increased abdominal cystic organ volume are risk factor for pressure-related complications and malnutrition in autosomal dominant polycystic kidney disease (ADPKD). However measuring actual abdominal cystic organ volume can be difficult in routine practice. Bioelectrical impedance analysis (BIA) are non-invasive, easy-to-use tool which can be applied in outpatient clinic. In this study, we evaluated the association of segmental BIA parameters with abdominal cystic organ volume in ADPKD patients.

Methods: In this single center, cross-sectional study, segmental BIA (Inbody S10) were measured and height-adjusted total kidney and liver volume (htTKLV) were calculated using recent CT scan in all patients.

Results: A total of 288 patients were included in the study and 47.9% were female. The mean age was 48.3±12.2 years and the mean estimated glomerular filtration rate (eGFR) was 65.3±25.3 mL/min/1.73m^2. The median values of htTKLV were 1,776 mL/m (IQR 1,361–2,381 mL/m). The highest correlation between BIA parameters and nature log value of htTKLV (ln htTKLV) was observed for the ratio of extracellular water to total body water (ECW/TBW) of trunk (ECW/TBW_{TR}) (r=0.466), followed by whole-body (ECW/TBW_{WB}) (r=0.407), lower extremity (ECW/TBW_{LE}) (r=0.385), and phase angle of trunk (PhA_{TR}) (r=0.215). The phase angle of lower extremity (PhA_{LE}) correlated negatively with ln htTKLV (r=-0.279). To exclude the effect of renal function on BIA, the subgroup analysis of patients with eGFR ≥45 mL/min/1.73 m^2 were conducted and correlations were similar. In the Receiver-operating characteristics analysis to predict the significant htTKLV (defined as ≥2,400 mL/m, the value known to increase 8.7 fold of malnutrition risk from previous study), ECW/TBW_{TR} showed the largest area under curve (0.726) with the following order; ECW/TBW_{WB} (0.697), ECW/TBW_{LE} (0.683), PhA_{LE} (0.637) and PhA_{TR} (0.601). The cut off value of ECW/TBW_{TR} to predict significant htTKLV was ≥0.387 with sensitivity of 57.7% and specificity of 76%.

Conclusions: Among segmental BIA parameters, ECW/TBW_{TR} showed highest correlation with htTKLV. Using the cut off value of ECW/TBW_{TR} ≥0.387, significant htTKLV values of ≥ 2,400 mL/m can be detected with sensitivity of 57.7% and specificity of 76%.

SA-PO503

Alteration of Tubular Secretion in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney disease. Glomerular filtration rate (GFR) typically remains normal during early stages of disease; however the impact of ADPKD on other kidney functions is less certain. We compared proximal tubular solute clearance in 124 ADPKD patients from the Baltimore PKD Center to that of healthy controls and individuals with non-ADPKD chronic kidney disease (CKD).

Methods: We used liquid chromatography-mass spectrometry to quantify serum and urine concentrations of ten secretory solutes and calculated solute fractional excretions relative to creatinine. For 31 ADPKD patients with normal estimated GFR (eGFR), we compared fractional excretions with 25 healthy individuals. For 93 ADPKD patients with impaired eGFR, we compared fractional excretions with 91 general CKD patients from the Seattle Kidney Study matched by age, race, gender, and eGFR stage. We used linear regression to compare relative differences in fractional excretions adjusted for eGFR, age, gender, and body mass index. Among ADPKD patients we used linear regression to assess associations of fractional excretion with height adjusted kidney volume, determined by magnetic resonance imaging.

Results: The fractional excretions of most secretory solutes were lower in PKD patients compared with healthy controls and general CKD patients. Associations for six solutes were significant after accounting for multiple comparisons (Table). None of the secretory solutes were associated with kidney volume.

Conclusions: Secretory solute excretion is lower in ADPKD patients compared with healthy controls and general CKD patients independent of eGFR.

Funding: NIDDK Support

Secretory solute	Fold-difference ADPKD (eGFR ≥90 ml/min/1.73m2) versus healthy** [95% CI]	p-value	Fold-difference ADPKD (eGFR<90 ml/min/1.73m2) versus CKD** [95% CI]	p-value	Difference in height-adjusted kidney volume (cm3/m)** [95% CI]	p-value
Cinnamoylglycine	0.57 (0.41, 0.78)	0.0006*	0.63 (0.46, 0.86)	0.003*	200 (-227, 627)	0.36
Hippurate	0.66 (0.51, 0.86)	0.002*	0.40 (0.32, 0.51)	<0.0001*	59 (-362, 480)	0.78
Indoxyl sulfate	0.84 (0.67, 1.05)	0.13	0.96 (0.81, 1.15)	0.68	-110 (-494, 275)	0.58
Isovalerylglycine	0.57 (0.42, 0.76)	0.0001*	0.51 (0.42, 0.60)	<0.0001*	-28 (-491, 434)	0.91
Kynurenic acid	1.46 (1.09, 1.97)	0.01	1.11 (0.95, 1.29)	0.18	-34 (-379, 311)	0.85
Pantothenic acid	1.04 (0.72, 1.51)	0.82	1.20 (0.96, 1.49)	0.11	-109 (-513, 296)	0.6
P-cresol sulfate	0.63 (0.49, 0.80)	0.0003*	0.87 (0.73, 1.04)	0.13	-355 (-721, 12)	0.06
Pyridoxic acid	0.81 (0.64, 1.02)	0.08	0.73 (0.60, 0.89)	0.001*	-355 (-721, 12)	0.82
Tiglylglycine	0.59 (0.43, 0.79)	0.0005*	0.57 (0.48, 0.67)	<0.0001*	57 (-405, 520)	0.81
Xanthosine	0.08 (0.06, 0.13)	<0.0001*	0.27 (0.21, 0.35)	<0.0001*	506 (-6, 1018)	0.05

*denotes statistical significance at Bonferroni p-value threshold <0.005

**Adjusted for age, gender, body mass index, eGFR

SA-PO504

Arterial stiffness Is Independently Associated with Total Kidney Volume in Children and Young Adults with ADPKD

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Background: Large-elastic artery stiffness is independently associated with both impaired kidney function and future decline in estimated glomerular filtration rate (eGFR) in chronic kidney disease. In patients with autosomal dominant polycystic kidney disease (ADPKD), an increase in total kidney volume (TKV) precedes the decline in kidney function and is a prognostic marker of future kidney function decline. We hypothesized that large-elastic artery stiffness, measured as carotid-femoral pulse-wave velocity (CFPWV), would be independently associated with height-adjusted TKV (htTKV) in children and young adults with ADPKD and preserved kidney function.

Methods: 51 non-diabetic children and young adults (6-25 years) with ADPKD and eGFR >90 ml/min/1.73m^2 with baseline data from an ongoing clinical trial underwent measurement of CFPWV and htTKV (by magnetic resonance imaging). The cross-sectional association of CFPWV with htTKV was evaluated using multiple linear regression models.

Results: Mean±s.d. age was 19±5 years, median htTKV was 371 (274, 509) ml/mm, and median CFPWV was 515 (455, 569) cm/sec. htTKV was greater in participants with CFPWV above the median (455 [308, 969] ml/m) compared to below the median (309 [267, 397] ml/m; p<0.0001). After adjustment for age, sex, race/ethnicity, systolic blood pressure, eGFR, and overweight/obesity, greater CFPWV was associated with larger htTKV (β-estimate: 11.27; 95% Confidence Interval: 1.0, 21.6, per 10 unit increase in CFPWV; p<0.05).

Conclusions: In children and young adults with ADPKD, CFPWV is independently associated with increased htTKV, an important predictor of progression in early-stage disease. Targeting arterial stiffness may be a novel strategy to slow kidney growth in children and young adults with ADPKD.

Funding: NIDDK Support

SA-PO505

Overweight and Obesity Are Independently Associated with Total Kidney Volume in Children and Young Adults with ADPKD

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Background: Similar to the general population, body-mass index (BMI) in individuals with autosomal dominant polycystic kidney disease (ADPKD) has been increasing over recent decades. We recently reported that overweight and obesity are predictors of progression in adults with early-stage ADPKD who participated in the HALT-PKD study. We hypothesized that overweight and obesity would be also be independently associated with height-adjusted total kidney volume (htTKV) even earlier in the course of the disease (children and young adults).

Methods: 51 non-diabetic children and young adults (6-25 years) with ADPKD and estimated glomerular filtration rate (eGFR) >90 ml/min/1.73m^2 with baseline data from an ongoing clinical trial were classified as normal weight (<85th BMI percentile for age, sex, and height in children; BMI of 18.5-24.9 kg/m^2 in adults; ref; n=37), or overweight/obese (≥85th BMI percentile in children; BMI ≥25.0 in adults; n=14), using body weights adjusted to remove the contribution of kidneys. The cross-sectional association of overweight/obesity with htTKV by magnetic resonance imaging was evaluated using multiple logistic regression models.

Results: Mean±s.d. age was 19±5 years and median htTKV was 371 (274, 509) ml/m. htTKV was greater in the overweight/obese group (532 [421, 969] ml/m) compared to the normal weight group (316 [258, 428] ml/m; p=0.01). After adjustment for age, sex, race/ethnicity, systolic blood pressure, eGFR, and glucose, overweight/obesity was associated with increased odds of htTKV above the median compared to normal weight (Odds Ratio: 25.6; 95% Confidence Interval: 2.1, 333.3).

Conclusions: In children and young adults with ADPKD, overweight and obesity are independently associated with increased height-adjusted total kidney volume, an important predictor of progression in early-stage disease. Maintaining ideal body weight may be an important strategy to slow kidney growth in children and young adults with ADPKD.

Funding: NIDDK Support

SA-PO506

Nephrolithiasis as a Risk Factor for Kidney Disease Progression in ADPKD

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Background: Kidney stones are a frequent complication among patients with autosomal dominant polycystic kidney disease (ADPKD). Previous studies have shown a higher risk of incident chronic kidney disease in persons with a history of kidney stones, but these studies did not examine patients with ADPKD. Thus, we hypothesized that a history of kidney stones may affect the rate of kidney function decline or increase in height corrected total kidney volume (HtTKV) in patients with ADPKD.

Methods: We assessed the association between a history of nephrolithiasis and annual rate of eGFR decline or % increase HtTKV using linear regression in 898 HALT-PKD study participants. To better ensure the temporal relation between nephrolithiasis and kidney function decline, we required that eGFR measurements were at least 180 days after the date of the kidney stone ascertainment. Analyses were adjusted for age, sex, body mass index, randomization group, baseline eGFR, systolic blood pressure, albumin excretion and genotype.

Results: A total of 898 subjects (mean age 43±10 years), comprising 789 non-stone forming (NKS) subjects and 109 subjects (46 with eGFR > 60 and 63 with eGFR 25-60 ml/min/1.73m^2 at baseline) with kidney stones (KS) and complete data were included in the analysis of eGFR decline. Baseline eGFR was 70±26 ml/min/1.73m^2 in the NKS group and 70±28 ml/min/1.73m^2 in the KS group (p= 0.9). Stone forming patients had a significantly faster yearly rate of kidney function decline of -5.3 ±8.3 ml/min/1.73m^2 vs. NKS -3.6±4.1 ml/min/1.73m^2 after adjustment for all variables (p<0.001). A total of 435 subjects (mean age 37±8.3 years), comprising 389 NKS (HtTKV 710±413 ml) and 46 KS (HtTKV 727±449ml) were included in the analysis of kidney volume progression. There was no significant difference in the rate of increase in HtTKV between the NKS and KS groups.

Conclusions: The presence of kidney stones was associated with more rapid loss of kidney function, thus may be a risk factor for more rapid kidney disease progression in ADPKD. As there were fewer subjects and imaging measures over the course of the HALT-PKD study this may confound ability to detect an effect of kidney stones on the rate of increase in HtTKV.

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SA-PO507

Serum Micro RNA Levels and Disease Progression in ADPKD

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Background: The rate of kidney disease progression is highly variable among patients with autosomal dominant polycystic kidney disease (ADPKD). Unfortunately, there is currently no biomarker that accurately predicts disease progression especially in the early stages of disease while kidney function is normal. Changes in circulating micro RNA (miR) levels occur in patients with chronic kidney disease and also in patients with acute kidney injury. We hypothesized that a signature of miRs may distinguish ADPKD patients at increased risk for faster kidney disease progression.

Methods: Forty-six serum samples from HALT ADPKD study participants were analyzed, 23 from fast progressors (eGFR decline > 3.4 ml/min/1.73m^2/year) and 23 from slow/normal progressors (eGFR decline ≤ 3.4 ml/min/1.73m^2/year). Subjects were matched by sex, gene mutation, mutation type and age (± 5 years). Serum miRs were analyzed by RNASeq and human mature miRNA sequences were mapped to miRBase 21.

Results: The baseline characteristics and eGFR decline rate for both groups are shown in Table 1. The differentially expressed miRs in the fast compared to slow progressors included miR 1246, miR 6785-5p and miR 323a-3p which were significantly up-regulated in the fast progressors while miR 93, miR 451a and miR 106-5p were down regulated. Pathways associated with up-regulated miRs included adherens junction, renal cell carcinoma and AMP kinase signaling and those associated with down-regulated miRs included TGF-β and mTOR signaling, focal adhesion and extracellular matrix interaction.

Conclusions: The results indicate that aberrant expression of serum miRs occurs in ADPKD patients with fast disease progression. These may indicate further disruption of key pathways in patients with faster kidney disease progression. Future validation in a large cohort will be necessary to fully chracterize the key signature of discriminatory miRs.

Funding: NIDDK Support, Private Foundation Support

Table 1 Characteristics of ADPKD Population for RNAseq

Characteristic	Fast progressors	Slow progressors
Baseline age years (SD)	35 (8)	40 (8)
Baseline eGFR (SD) (ml/min/1.73m2)	67.6 (22.5)	92.7 (22.9)
Decrease in eGFR/year (SD) (ml/min/1.73m2)	-9.2 (3.9)	-1.3 (2.0)

SA-PO508

Urinary Epidermal Growth Factor/Monocyte Chemotactic Peptide 1 Ratio Predicts Outcome in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited condition leading to end stage renal disease, but it is difficult to predict the rate of disease progression. Total kidney volume (TKV) is an independent prognostic marker of renal function decline and is used to define the Mayo classification. Urinary Epidermal Growth Factor/Monocyte Chemotactic Peptide 1 ratio (uEGF/MCP1) has been shown to be a prognostic biomarker in IgA nephropathy. In this study, we tested the role of uEGF/MCP1 in predicting outcome of ADPKD patients according to the Mayo classification.

Methods: A cohort of 46 (32 F, 14 M) patients with ADPKD consecutively enrolled was evaluated. Urinary EGF and MCP1 levels were measured by ELISA. TKV calculation and Mayo classification were based on MRI measurements. The Mayo classification was used for the prediction of the eGFR at 10 years to calculate the ΔT0-T10. The outcome was defined as follows: Mayo Classes 1A-1B patients were classified as "non-progressors", whereas 1C-1E patients were classified as rapid disease "progressors" (corresponding to a predicted eGFR decrease ≥2.5 mL/min/1.73 m2 per year).

Results: Clinical data at baseline (T0) were the following: age 44±13 years, eGFR 71±32 ml/min/1.73 m^2, TKV 1239 (731–2287) ml, uEGF/MCP1 58.5 (16.8–127.1), Mayo Class (no.) 1A (3), 1B (10), 1C (13), 1D (16), 1E (4), progressors/non-progressors (no.) 33/13. uEGF/MCP1 at T0 was significantly different across Mayo Classes (p=2.14e-05) showing a trend towards a reduction in Class 1E and correlated with the predicted variation of eGFR at 10 years (ΔT0-T10, r =-0.405, p=0.004). In addition, both urinary EGF (r=-0.313, p=0.027) and MCP1 (r=0.404, p=0.004) correlated with the ΔT0-T10. In a multivariate analysis including adjustment for age and sex we found that uEGF/MCP1 at T0 is an independent predictor of outcome (OR 0.98; 95% CI: 0.97-0.99, p=0.005) and this model showed an area under the ROC curve of 0.90 (95% CI: 0.81-0.98), achieving a specificity of 0.92 and a sensitivity of 0.82.

Conclusions: These findings show that uEGF/MCP1 can be used as a reliable and non-invasive biomarker for the estimation of disease progression in patients with ADPKD.

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SA-PO509

Identifying Urine Biomarkers of Disease Progression in Pediatric Autosomal Dominant Polycystic Kidney Disease Patients

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease. Though children with ADPKD show normal renal function, rapid cyst development is already occurring. In this study, we aimed to identify urine biomarkers of disease progression in the pediatric ADPKD population.

Methods: Urine samples from 70 ADPKD patients aged 8-26 years were collected at baseline. Following collection at baseline, 37 patients were randomized to a pravastatin treatment group and 33 to a placebo group. Metabolomic analysis of urine was performed using targeted liquid chromatography-mass spectrometry. Within the treatment and placebo groups, differences between biomarkers at baseline and 36 months were evaluated. Metabolites with a P value < 0.05 were identified as significant. Pathway analysis was conducted on significant metabolites.

Results: Within the pravastatin treatment group, 27 metabolites were uniquely and significantly changed. Metabolites involved in glutamine metabolism (glutamic acid, α-ketoglutarate) and pyruvate metabolism (dihydroxyacetone phosphate, acetylphosphate) were all decreased at 36 months. Interestingly, ascorbic acid, a metabolite with antioxidant properties, was increased by 59% at 36 months in the treatment group. Within the placebo group, 37 metabolites were uniquely and significantly changed. Metabolites of the citric acid cycle (oxaloacetic acid, malic acid, cis-aconitic acid, citric acid, pyruvic acid) were decreased, and literature confirms that citric acid cycle activity is decreased in patients with CKD. Trimethylamine N-oxide (TMAO) is a marker of atherosclerotic risk and it has been shown to be elevated in the plasma of patients with CKD, in part due to decreased renal clearance. Our results were consistent with this finding as we found metabolites involved in the TMAO pathway (betaine, choline, and TMAO) to be decreased in the placebo group at 36 months.

Conclusions: Progression of ADPKD was associated with a decline in the renal clearance of citric acid cycle and betaine metabolism intermediates, preceding any loss of renal function. Future work involves correlating urine metabolites to plasma metabolites in order to identify biomarkers that may be able to risk stratify patients over the course of the disease.

Funding: NIDDK Support

SA-PO510

Plasma Metabolomics to Identify Biomarkers and Altered Pathways in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease. Though children with ADPKD show normal renal function prior to adulthood, rapid cyst development is already occurring. In this study, we aimed to identify plasma biomarkers of disease progression in the pediatric ADPKD population.

Methods: Plasma samples from 81 ADPKD patients aged 8-22 years were collected. Samples from healthy children (60 subjects, aged 1-3 years) served as a control. Metabolomic analysis was performed using liquid chromatography-mass spectrometry and differences in biomarkers between healthy subjects and ADPKD patients were evaluated. Additionally, longitudinal analysis of the ADPKD patients was completed over 36 months. Metabolites with a P value < 0.05 and a fold change of 50% or greater were identified as significant. Pathway analysis was conducted on significant metabolites.

Results: Cardiovascular risk markers and intermediates of the methionine cycle (uric acid, allantoin, cysteine, S-adenosyl-homocysteine, methionine sulfoxide), intermediates of the Krebs cycle and glycolysis (pyruvate, α-ketoglutarate, D-glyceraldehyde-3-phosphate), and bile acids (deoxycholic and cholic acids) were increased in plasma in ADPKD patients. An increase in intermediates of tryptophan metabolism (kynurenine, 3-hydroxykunurenine, xanthurenic acid and anthranilic acid) was accompanied by a decrease in nicotinamide in patients with ADPKD. The concentration of pipecolic acid, a diagnostic marker for peroxisome biogenesis disorders such as the renal cystic disorder Zellweger syndrome, was also significantly higher in ADPKD patients. Longitudinal analysis of ADPKD patients showed the above metabolites remained changed at 36 months. For the tryptophan pathway, changes became more pronounced.

Conclusions: Kynurenine metabolism is elevated in children with ADPKD suggesting that its direct targeting via, for example inhibition of the pathway's regulating enzyme indolamine-2,3-dioxygenase (IDO1), could prevent progression of the disease. Markers of cardiovascular risk were increased in pediatric ADPKD patients compared to healthy subjects. Qualification of these as markers for disease progression could help to risk stratify patients and help identify molecular targets for further therapeutic developments.

Funding: NIDDK Support

SA-PO511

Proteomic Differential Study Associated to Autosomal Dominant Polycystic Kidney Disease in Mouse Embryonic Models

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Background: The autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease characterized by the formation of cysts along the nephrons that can lead to renal failure. It is associated with other extrarenal manifestations such as the formation of hepatic or pancreatic cysts, aneurysms, etc. ADPKD is caused by mutations in the PKD1, PKD2 and GANAβ genes. Mouse models of ADPKD with homozygous variants in PKD1 or PKD2 genes present cystogenesis from day 15.5 of gestation and die during embryonic development typically around day 17. The study of these models at embryonic ages could be useful to investigate the molecular mechanisms involved in the onset of cyst formation.

Methods: In order to identify proteins and pathways involved in cystogenesis, we compared the proteome of double mutants vs. healthy mouse embryos kidney. Embryo kidneys were removed at day 15.5 and 16.5 from two animal models of ADPKD with germline mutations in the PKD1 ($PKD1^{del2\text{-}4}$) and PKD2 ($PKD2^{\Delta 11\text{-}13}$) genes as well as wild type animals. A combined study of two mass spectrometry technologies was carried out: LC-MALDI using a MALDI TOF-TOF 4800 and LC-MS / MS using a MALDI-TripleTOF 6600. The differential proteome of double mutants and healthy mice was identified and their involved pathways were analyzed with Reactome.

Results: We identified 1 protein in E15.5 PKD1 double mutant model not detected in healthy embryo, 6 in E16.5 PKD1, 2 in E15.5 PKD2 and 19 in E16.5 PKD2. We also identified 37 proteins in E15.5 PKD1 models only detected in healthy individuals; 20 in E16.5 PKD1; 20 in E15.5 PKD2 and 5 in E16.5 PKD2. These proteins are involved in different pathways such as metabolism, signal transduction, transcription and immune system as well as development biology, vesicle-mediated transport, hemostasis or cell cycle among others.

Conclusions: Our results would contribute to improve the knowledge on the molecular mechanisms underlying the processes of cystogenesis, as well as to identify possible therapeutic targets.

SA-PO512

Proteomic Analysis for the Identification of the PKD1 Related Signaling Pathways and Direct Targeting of Polycystic Kidney and Liver Disease: Few Cysts Remain Uncontrolled

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Background: Different mechanisms have been related to the pathogenesis of renal and hepatic cystogenesis but the identification of **the proteome signature for the identification of the cystogenic fingerprint and consequent treatment approaches has never been develop up to date.**

Methods: We inactivated Pkd1 (*$Pkd1^{cond/cond}$TamCre)* gene at postnatal day 10/11 (cystic window) and postnatal day 15/16 (non-cystic window) and recollected organs at day 30 for kidney (cystic kidney proteome or CKP) and liver (cystic liver proteome or CLP) proteome analysis by **mass spectrometry MALDI-TOF. We refined the renal and hepatic cystogenic proteome** (Reactome, KEGG, FunRich, String) by the identification of 34 specific proteins related to the liver phenotype (26 up and 8 down) and 22 to the kidney phenotype (16 up and 6 down).

Results: As expected, the major **pathways related to CKP and CLP are** signal transduction, immune system, metabolism and metabolism of proteins. Interestingly, vesicle-mediated transport and cell cycle pathways are specifically related to CLP and, in contrast, extracellular matrix organization and developmental biology pathways are specific of CKP. Based on this and previous results, approach treatment of PKD animals allowing us to inhibition of liver cystogenesis and significantly reduction of kidney cystic index and volume, recovering physiological parameters of kidney and liver function. In addition, we combined our molecules with known therapies for ADPKD (Tolvaptan) showing recovery of kidney and liver physiological parameters, although THP-positive nephron segment and a low portion of DBA positive remain cystic. This indicates the need of continuing puzzling out the remaining cysts for further treatments.

Conclusions: We described a list of **new signaling pathways and possible targets** for the development of specific therapeutic approaches **for renal and hepatic phenotypes related to ADPKD**. This data opens a new understanding of the molecular basis of the disease based on an organ specific protein profile of cystogenesis.

SA-PO513

Exploring KIM-1 as a Marker for Kidney Disease in ADPKD: Analysis from the HALT-PKD Studies

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Background: Cyst compression of renal tubules and intrarenal microvasculature play a vital role in progression of autosomal dominant polycystic kidney disease (ADPKD) and may induce kidney injury molecule-1 (KIM-1). We hypothesized that urinary KIM-1 is a marker of disease progression in ADPKD.

Methods: We measured baseline and 48-month urinary KIM-1/urinary creatinine (UKIM-1/Cr) of participants in the HALT-PKD studies. We evaluated whether UKIM-1/Cr predicted decline in eGFR in studies A and B (n=738) or increase in height-adjusted TKV (TKV) in study A (n=283) and whether intensive, compared to standard, blood pressure (BP) control lowered UKIM-1/Cr over 48 months in study A (n=101).

Results: Higher baseline UKIM-1/Cr was associated with decline in eGFR in unadjusted analysis (β-estimate for eGFR slope=-0.04, 95% C.I. -0.06- -0.01, P=0.0006). After adjusting for demographics, PKD1 genotype, SBP, DBP, BMI, baseline eGFR, urinary albumin/Cr ratio (UACR), and TKV, baseline UKIM-1/Cr was associated with slightly greater kidney function decline (β-estimate = -0.03, 95% C.I. -0.05- -0.003, P= 0.03). In linear mixed model regression analysis, baseline UKIM-1/Cr was associated with increased TKV over time in the multivariate model (β-estimate= 0.10, 95% C.I. 0.002-0.20, P=0.05). Intensive, compared to standard, BP control was not associated with lower UKIM-1/Cr levels. However, after adjusting for interaction with baseline UACR, intensive BP control was associated with lower KIM-1 in the multivariate model (β-estimate= -0.27, 95% C.I. -0.52- -0.011, P= 0.04). This persisted after adjustment for renal blood flow and inflammatory markers (Table).

Conclusions: UKIM-1/Cr was associated with slightly greater decline in kidney function in ADPKD and intensive BP control was associated with lower UKIM-1/Cr over 48 months. Further studies are needed to determine what role KIM-1 plays in ADPKD progression.

Effect of intensive vs standard BP control on UKIM-1/Cr in study A:

Odds ratio (CI)	P value
-0.32 (-0.58 to -0.06) *	0.02
-0.33 (-0.59 to -0.06) #	0.02

*adjusted for demographics age, male gender, PKD1 genotype, SBP, DBP, BMI, baseline eGFR, baseline UACR, baseline TKV, and baseline renal blood flow

#: Variables in * + high sensitivity CRP (hs-CRP), interleukin-6 (IL-6)

SA-PO514

Assessment of Endocannabinoid System as a Biomarker for Progression of ADPKD

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Background: Endocannabinoids (eCBs) are endogenous lipid ligands of the cannabinoid-1 receptor (CB1). In the renal vasculature, CB1 is involved in the regulation of renal blood flow and hemodynamics via NO release. Expression of CB1 and main eCBs are significantly increased in the fibrotic kidney where they modulate inflammation and fibrosis, another pathophysiological mechanism of autosomal dominant polycystic kidney disease (ADPKD).

Methods: Plasma from children and young adults with ADPKD and normal renal function were collected during an interventional trial at 0, 18 and 36 months. A single serum sample from adult ADPKD patients was collected at baseline of a cross-sectional trial (n=71, eGFR >60 mL/min per 1.73m^2). All patients had available measures of total kidney volume (normalized to height (HtTKV) in pediatric patients or to body surface area (TKV/BSA) in adult patients) and left ventricular mass index (LVMI). Analysis of fourteen eCBs was performed using a liquid chromatography tandem mass spectrometry with online extraction. Statistical analysis was performed using SPSS v. 24.

Results: In children and young adults, plasma AEA (n=118, cross-sectional) correlated with HtTKV. The association was independent of the treatment group but highly dependent on child's age. After control for age and sex, linoeyl ethanolamide was positively correlated with HtTKV and cardiovascular LVMI. In 11 placebo treated pediatric patients with available samples at 0 and 36 months, the change in concentration of O-arachidonoyl ethanolamide positively correlated with ΔHtTKV (r=0.659) adjusted for age and sex. In adult ADPKD patients, plasma palmitoyl- (r=0.379) and stearoyl-ethanolamide (r=0.426) positively correlated with TKV/BSA, after control for age and sex. AEA also increased with disease progression; significant negative correlation between the renal function as measured by eGFR and AEA (r=-0.395) was observed.

Conclusions: Our results showed that an overall increase of the circulating endocannabinoids is present in patients with ADPKD, with manifestations already present early in the disease, in children with ADPKD and normal kidney function. Thus, eCBs should be evaluated for their potential as biomarkers of ADPKD severity and progression and in mechanistic studies evaluating CB1's role in mediating renal fibrosis.

Funding: NIDDK Support

SA-PO515

NADPH Oxidase (NOX4) and Mitochondrial Injury Contribute to Oxidative Stress and Endothelial Dysfunction in Young Normotensive Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Endothelial dysfunction (ED) is an independent predictor of cardiovascular (CV) events. In ADPKD, ED and oxidative stress (OS) develop early on, preceding hypertension (HTN) and renal function decline. However, the mechanisms responsible remain unknown. We hypothesized that NOX4 and mitochondrial injury contribute to OS and ED preceding HTN in young normotensive ADPKD patients.

Methods: We prospectively measured plasma levels of homocysteine (Hcy), 8-isoprostane, NOX4 and the mtDNA genes cytochrome-c oxidase-3 (COX3) and nicotinamide adenine dinucleotide (NADH) dehydrogenase subunit-1 (ND1), in young, normotensive (without BP medication) ADPKD patients, and age/gender-matched healthy volunteers (HV) (n=10, each). Total kidney volume (TKV) and Renal Blood Flow (RBF) were evaluated by MRI.

Results: BP levels were higher in ADPKD, and HtTKV was twofold higher in ADPKD vs. controls. Yet, eGFR and RBF were similar between the groups (Table). Plasma Hcy, 8-isoprostanes and NOX4 were higher in ADPKD (Figure), and correlated directly with HtTKV ($p<0.05$, figure), but the correlation with RBF was not significant. Plasma mtDNA levels were lower in ADPKD vs controls, and correlated inversely with HtTKV (R^2 0.397 and 0.392 respectively).

Conclusions: Early ADPKD is associated with elevated Hcy, 8-isoprostane, and NOX4, and decreased mtDNA levels, which precede the reduction in RBF and the development of HTN, and are associated with disease severity. These findings suggest that NOX4 and mitochondrial abnormalities contribute to oxidative stress, endothelial dysfunction, and possibly the development of HTN and disease progression in ADPKD

Funding: Private Foundation Support

Table

	HV	ADPKD	*p value*
Number of patients	10	10	N/A
Gender (Female/Male)	6/4	6/4	N/A
Age (years)	23.2 ± 3.2	22.5 ± 3.2	N/A
Systolic blood pressure (mmHg)	114.6 ± 9.0	123.6 ± 11.0	**0.008**
Diastolic blood pressure (mmHg)	70.2 ± 8.4	77.3 ± 8.3	0.063
Serum creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.2	0.494
eGFR-CDK-EPI (ml/min/1.73m²)	104.9 ± 19.3	110.6 ± 12.4	0.411
HtTKV (mL/m)	179 (160 - 189)	347 (270 - 460)	**<0.001**
RBF (cc/min/1.73m²)	624 ± 100	619 ± 79	0.903

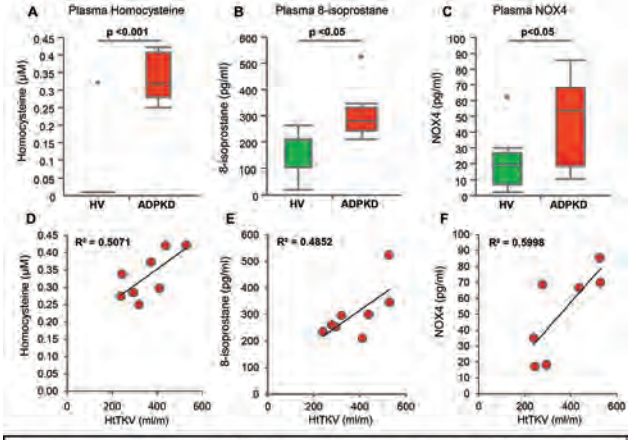

Figure. Top: Plasma levels of Hcy (A), 8-isoprostane (B) and NOX4 (C) in ADPKD patients and HV. Top and bottom boxes are estimated 75th and 25th percentiles, respectively. Vertical lines extend from the 75th percentile to the highest and from the 25th percentile to the lowest data points. Bottom: HtTKV correlated directly with plasma Hcy (D), 8-isoprostane (E), and NOX4 (F).

SA-PO516

ELiSA, a Phase 2 Clinical Study with the Novel Vasopressin V2 Receptor Antagonist Lixivaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most prevalent inherited genetic diseases of the kidney in humans. Recent advances established vasopressin V2 receptor inhibition as a clinically validated mechanism of action for the treatment of ADPKD; however, safe and effective disease-modifying therapies for ADPKD are still lacking. Here we describe a first-in-patients clinical study with lixivaptan, a potent, selective vasopressin V2 antagonist, in patients with ADPKD.

Methods: ELiSA (Evaluation of Lixivaptan in Subjects with ADPKD) is a phase 2, open-label, multicenter clinical study of lixivaptan in patients with ADPKD to be conducted at up to 15 clinical sites in the United States. Eligible patients will include adults aged 18–60 years with relatively preserved kidney function (chronic kidney disease CKD1 and CKD2; n = 16) or moderately impaired renal function (CKD3; n = 16). Two doses of lixivaptan, administered for 7 days, will be tested in eight patients within each patient group.

Results: The primary objectives of the ELiSA study are to characterize the safety, tolerability and pharmacokinetic profile of lixivaptan and its major metabolites following multiple doses in ADPKD patients with various degrees of kidney function impairment. The secondary objectives are to characterize the effect of lixivaptan on pharmacodynamic markers that have been shown to correlate with the clinical activity of vasopressin antagonists in the treatment of ADPKD, including urine osmolality, urine output, serum creatinine, plasma copeptin and total kidney volume.

Conclusions: The ELiSA clinical study is an important milestone toward the potential approval of lixivaptan as a safe and effective therapy for the treatment of ADPKD in a broad patient population. Study results will inform the design and execution of an upcoming pivotal registration study with lixivaptan for the treatment of ADPKD.

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SA-PO517

Soluble Urokinase Plasminogen Activator Receptor Levels Predict Renal Function Decline in Autosomal Dominant Polycystic Kidney Disease

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Background: Levels of soluble urokinase-type plasminogen activator receptor (suPAR), a signaling molecule and marker of immune activation, have been shown to predict incident kidney disease. Patients with autosomal dominant polycystic kidney disease (ADPKD) experience progressive but highly variables rates of decline in renal function, with highly heterogenous outcomes. Whether suPAR levels are predictive of decreasing kidney function in patients with ADPKD independently of known prognostic factors such as proteinuria and kidney volume, is unknown.

Methods: SuPAR levels were measured in a subset of 479 patients with ADPKD (mean age 39, 52% male, 80% Caucasians) enrolled in the TEMPO 3:4 trial and randomized to the placebo arm. All subjects randomized into the placebo arm with plasma samples that were available were included. Patients underwent scheduled follow-up for 3 years, with repeated measurements of height-adjusted kidney volume (htTKV), urine albumin-creatinine ratio (UACR), and Cockcroft-Gault calculated estimated glomerular filtration rate (eGFR). Linear mixed models for repeated measures were used adjusting for age, gender, baseline eGFR, UACR and htTKV to examine the association between baseline suPAR levels stratified by tertiles and follow-up eGFR measures.

Results: At baseline, the median suPAR level was 2544 pg/mL [IQR 2125-3221], with 32% of subjects having suPAR levels≥3000 pg/mL, while median eGFR was 78 [IQR 62;96] and htTKV 853 mL/m [IQR 623-1151]. Baseline suPAR levels were weakly associated with htTKV (β 0.15 95%CI[0.00;0.29] independently of eGFR, UACR, gender, age and hypertension. Patients in the first, second and third tertiles of suPAR had a 10%, 15% and 23% decrease in eGFR (P<0.001), and a 18%, 18% and 17% increase in htTKV at 3-years follow-up (P=0.6). The associations did not differ according to gender and was independent of age, baseline UACR and eGFR.

Conclusions: SuPAR levels were associated with decline in renal function in patients with ADPKD. Whether suPAR can be used as a prognostic marker to identify patients at high risk of decline in renal function that would benefit from early therapeutic intervention remains to be determined.

Funding: NIDDK Support

SA-PO518

Preeclampsia an Under Recognised Cause of AKI in Pregnancy

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Background: Obstetric acute kidney injury (AKI) constitutes about 8-12% of all AKI in developing countries, with blood loss and sepsis as the main causes. Reliance on clinical parameters alone may lead to underestimation of the prevalence of preeclampsia (PE) in those with AKI, and use of biomarkers may help identify more cases.

Methods: All patients with obstetric AKI referred to the nephrology unit from September 2015 to August 2017 were evaluated. PE was diagnosed as clinical (cPE) in the presence of new onset of hypertension and proteinuria (≥ 1+ on dipstick) or hypertension and end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman; and serological (sPE) on the basis of soluble fms-like tyrosine kinase(FLT1)/placental growth factor (PIGF) ratio of > 85 (<34 weeks of gestation) and > 110 (≥34 weeks of gestation) when clinical findings were indeterminate. Patients with pre-existing CKD or known systemic illnesses were excluded. We evaluated 6-month maternal and fetal outcomes in all patients.

Results: Out of a total of 73 patients seen during the study, 64 (87.7%) were seen in third trimester/postpartum period. The mean age was 26.38±3.92 (range 19-38) years. Thirty-six (49%), 34 (47%), and 57 (78%) patients had evidence of blood loss, sepsis and HUS respectively. cPE was diagnosed in 19 (30%) cases, and an additional 11 (17%) showed evidence of sPE. Fourteen (47%), 11 (37%) and 27 (90%) patients with PE had haemorrhage, sepsis and of HUS respectively. A total of 5 (17%) patients died, and 10 (33%) failed to recover from AKI. Only 6 (20%) had a successful fetal outcome.

Conclusions: Use of clinical criteria alone leads to under-diagnosis of PE in patients with obstetric AKI in developing countries. Sepsis, blood loss and AKI mask the clinical manifestations.

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SA-PO519

Effect of Spironolactone in Ischemic AKI in Critically Ill Cancer Patients: A Pilot Study

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Background: Acute kidney injury (AKI) is a common complication in critically ill patients, about 30% of cases occur after major surgery caused by hypoperfusion. Cancer

patients who undergo major surgery have a greater AKI risk, due to factors associated with cancer or its treatment. Previous animal studies from our laboratory showed that mineralocorticoid receptor blockade with spironolactone, after renal ischemia/reperfusion prevents AKI. In this pilot study, we explored the tolerance and effectiveness of spironolactone for AKI prevention in critically ill cancer patients after major surgery.

Methods: We included 24 patients in a randomized, double-blinded, placebo-control trial. Patients received either spironolactone 25 mg or placebo, at 0, 24, and 48 h after surgery and were followed for five days. Our outcomes were AKI defined by KDIGO criteria, urinary biomarkers, hyperkalemia, lactate clearance, and days with vasopressor use.

Results: There were no differences between groups at inclusion. In spironolactone group, 6/12 patients developed AKI compared to 7/12 patients in placebo group (p=0.682). Spironolactone did not alter potassium, lactate clearance, or days with vasopressor. We analyzed the percentage change in biomarkers obtained at 48 h compared to the baseline level. We found that NGAL decrease and KIM1 increase significantly in spironolactone group.

Conclusions: In this exploratory study, we observed that spironolactone was well tolerated, although it did not reduce the incidence of clinical AKI in relation with the sample size, the significant decrease in urinary NGAL in the group treated with spironolactone suggests a decrease in tubular damage. These data can be useful in the design of larger controlled studies.

Variable	Spironolactone (n=12)	Placebo (n=12)	p value
Male gender	6	5	1.00
Age	58±13	55±17	0.61
Baseline creatinine(mg/dl)	0.75±0.2	0.78±0.3	0.80
NGAL % change	-68(-84 to 75)	+57(-32 to 130)	0.03
Hsp72 % change	-26(-88 to +340)	-44(-77 to +44)	0.76
KIM1 % change	+159(+48 to +315)	-33(-49 to +21)	0.00
Maximum potassium level	4.3 ±0.5	4.4±0.1	0.50
Decrease in lactate	-3 (-2 to-4)	-2 (-2 to-5)	0.84
Days with vasopressor	0 (0-3)	1 (0-3)	0.59
1-year mortality	1	2	1.00
6-monts GFR<60ml/min	1	3	0.38
Statistical analysis: x2 or Fisher exact test for categorical data and Mann-Whitney U test for continuous data.			

SA-PO520

Rate of AKI with Epithelial Growth Factor Tyrosine Kinase Inhibitors

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Background: Epithelial growth factor receptor (EGFR) mutations are found in several tumors, especially non-small cell lung cancer (NSCLC), occurring in 10-15% of NSCLC in Europe and 30-40% in Asia. Renal dysfunction is rare with EGFR TKIs. In phase III clinical trials, one patient on erlotinib had any grade renal failure and 1.5% of patients treated with gefitinib had an elevated creatinine (Cr). EGFR is expressed throughout the mammalian kidney and EGF and EGFR ligands are involved in renal development. In animal models, EGFR activation, and reductions in EGFR or EGFR TKI activity are associated with both benefit and harm to renal function, depending on the model of renal injury. The purpose of this this study is to determine the rate of acute kidney injury (AKI) with the use of EGFR TKIs at a single center.

Methods: Retrospective data was collected on all adult patients at our institution who received any EGFR TKI from 1/1/2014-12/31/2016. Demographic data, baseline Cr (Cr within 30 days prior to treatment) and peak Cr after each treatment cycle were collected. AKI was defined as an increase in Cr ≥1.5x baseline. Incomplete recovery of renal function was defined as a last Cr ≥25% of baseline. All statistical analyses was conducted using R version 3.4.4. A p-value of <0.05 was considered statistically significant.

Results: Analyses was performed on 1831 observations in 503 patients. Of 503 patients, AKI occurred in 121 (24%). Of these, 103(85%) had incomplete recovery of renal function. The average time from baseline to last Cr was 314.8 days. Overall, 85% of patients were treated for lung cancer. AKI occured in 26% of lung cancer patients and 92% of all patients with AKI had underlying lung cancer (p=0.001). Overall, 385 (77%) patients were treated with erlotinib. AKI occured in 28% of patients treated with erlotinib and 89% of all patients with AKI had received erlotinib (p=0.002). Overall, the group was largely white (67%), non-Hispanic (91%) and female (70%), with no significant differences between those with and without AKI.

Conclusions: The rate of AKI with any EGFR TKI was 24%. On follow up, 85% of patients never returned to within 25% of their baseline Cr. AKI rates were significantly higher in lung cancer patients and with erlotinib use. Retrospective data with it attendant limitations cannot assign causality or define mechanisms. This relationship needs further examination.

SA-PO521

Immune Interstitial Nephritis Complicating Treatment of Lung Cancer

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Introduction: Immune check point inhibitors (ICPIs) have revolutionized the treatment of cancer therapy in the modern era. Amongst these, Nivolumab targeting programmed-death-1 (PD-1) and its ligand (PD-L1) is increasingly being used for treatment of metastatic melanoma, non-small cell lung cancer, and renal carcinomas. The advent of these novel biologics, also brought with them the unique spectrum of immune mediated adverse effects. We describe a case of nivolumab induced immune nephritis and stress the importance of renal surveillance, as early recognition and treatment can prevent irreversible renal damage.

Case Description: An 82-yr-old female with metastatic squamous cell carcinoma of lung was admitted to the hospital due to Acute kidney injury (AKI) (creatinine 3.3 mg/dl), found on routine labs. Her chemotherapy was recently changed from paclitaxel to nivolumab due to non-response to paclitaxel as well as positive PD-1 mutation. Urinalysis showed persistent pyuria with 1% eosinophils and renal ultrasound was unremarkable. Renal biopsy done to further evaluate, revealed diffuse mononuclear infiltrate, predominantly plasma cells in the tubulointerstitial compartment with severe tubulitis. Patient was diagnosed with nivolumab induced immune tubulointerstitial nephritis. Her kidney function gradually improved to creatinine of 1 mg/dl, with withdrawal of nivolumab and short course of steroids. Our case spotlights the immune mediated injury and warrants renal monitoring while on ICPIs.

Discussion: Nivolumab is an IgG4 fully humanized monoclonal antibody, precisely a PD-1 inhibitor. Nivolumab is highly effective in treating melanoma, lung and renal cancers. As the use of these ICPIs is widening, prevalence of immune adverse effects is also spiraling. The incidence of AKI associated with these ICPIs was found to be 2.2 % per Cortazar et al, however recent studies showed higher incidence of 9.9 – 29 %. Clinical awareness regarding these unfamiliar immune side effects of ICPIs should be raised, as timely diagnosis and early intervention plays a crucial role in the management of these complications. Renal surveillance every two weeks is recommended while on ICPIs and withdrawal of offending agent is based on the severity of AKI and cancer prognostic risk. Multidisciplinary approach and close alliance between oncologists and nephrologists is advocated for optimal clinical outcomes.

SA-PO522

Outcome and Possible Mechanism of Acute Tubulointerstitial Nephritis

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Background: Acute tubulointerstitial nephritis (ATIN) is an important cause of acute kidney injury (AKI) and often described as a potentially reversible disease. Some previous guidelines or studies recommended corticosteroid usage, but the role of steroids remains controversial and underlying mechanisms remain unresolved. The study purpose was to evaluate the steroid effect and the possible mechanism of ATIN.

Methods: A total of 82 adult patients with biopsy-proven ATIN except combined glomerulonephritis, pyelonephritis, and vasculopathy from three tertiary referral centers were recruited between 2001 and 2017. Renal recovery was defined as improvement in Cr level to 1.3 mg/dL or ≥ 50% decrease of the peak Cr. The effect of corticosteroid therapy was determined using multivariate logistic model.. Plasma and urine inflammatory cytokines at the time of biopsy were analyzed using a multi-analyte flow assay kit (n=33).

Results: Causes of ATIN included unknown (74.4%), drugs (17.1%), autoimmune (6.1%), and obstructive disease (2.4%). In drug-induced ATIN, herbal medication was the most common cause (35.7%), and followed by NSAID (28.6%), antibiotics (28.6%). Overall, 76.8% of ATIN patients experienced renal recovery once or more. 59.8% of patients encountered renal recovery status at 6 months post-biopsy. 23.2% of the patients were dependent on dialysis at final follow-up. Among a total of 82 patients with unknown and drug-induced ATIN, 24 patients (82.9%) were treated with corticosteroid. There were no significant difference in renal recovery, ESRD progression, and mortality between steroid-treated and non-treated groups. In both Cox regression for renal recovery and logistic regression for renal recovery at 6 months post-biopsy, steroid use was not significant factor. Among several inflammatory cytokines, monocyte chemotactic protein 1 and interleukin-8 levels were markedly elevated in both plasma and urine; and interleukin-18 levels were high in plasma alone

Conclusions: Steroid use may not determine the overall outcome of ATIN. Therefore, targeting therapy based on the pathophysiology of ATIN should be investigated to improve overall outcomes. The present cytokine results will be helpful to develop a novel targeting therapy for ATIN.

SA-PO523

AKI Due to Methotrexate-Induced Crystal Nephropathy with Electron Microscopy

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Introduction: High dose methotrexate (MTX) (infusion of 1.5 to 8.0 gm/m2) is a key component of regimens for treatment of primary central nervous system lymphoma (PCNSL). 90% of MTX and its metabolites are excreted via the kidney. They are poorly soluble in acid pH and need intense hydration and alkalization of the urine (pH > 7) to reduce the risk of acute kidney injury (AKI) to less than 5%. Here, we present a case of AKI due to MTX-induced crystal nephropathy with by electron microscopy.

Case Description: A 53 years old male presented with frontal headaches. Imaging study followed by brain biopsy confirmed the diagnosis of PCNSL. Patient had normal baseline serum creatinine of 0.91 mg/dL prior to two infusions of high dose MTX 3.5 gm/m2 on 3/7/18 and 3/21/18. MTX and serum creatinine levels peaked at 12.3 mmol/L on 3/24/18 and 5.82 mg/dl on 3/28/18 respectively. Patient developed AKI in spite of maintaining intensive hydration, urine pH between 8 and 9 with the use of crystalloid solution of sodium bicarbonate and an adequate urine output of approximately 100 mL/hour. The urine sediment showed brownish crystals. Kidney biopsy done on 4/3/18, revealed light

microscopy diffuse severe acute tubular epithelial cell injury (acute tubular necrosis, ATN) with tubular lumen MTX crystals also present by electron microscopy (image 1). After discontinuing MTX, the serum creatinine gradually improved to a level of 2.1 mg/dL on the day of discharge on 4/21/18.

Discussion: supersaturation is the initial step in crystallization of MTX in the renal tubular lumens, may occur despite maintaining adequate urine output and urine alkalization and leads to MTX-induced crystal nephropathy. We report a case of MTX-induced crystal nephropat, renal biopsy morphologic features of nephrotoxic ATN and MTX crystals both by light microscopy and electron microscopy.

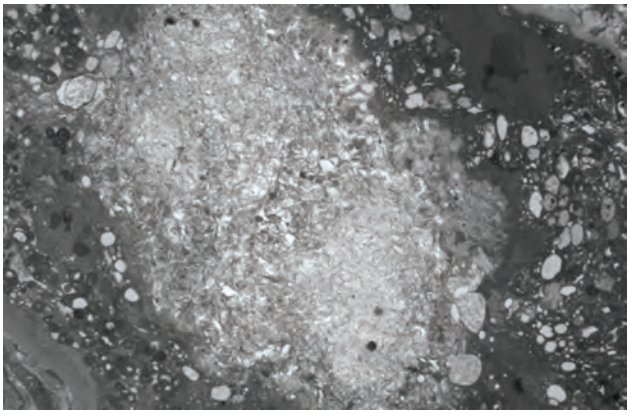

IMAGE 1

SA-PO524

Severe AKI Due to Minocycline-Associated Heme Pigment Nephropathy

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Introduction: Minocycline-associated acute kidney injury (AKI) is rarely reported in the literature. We present a patient with two separate episodes of minocycline-induced hemolytic anemia with severe AKI due to heme pigment nephropathy.

Case Description: A 45-year-old woman with a history of recurrent acne resumed minocycline after a six-month hiatus from taking the drug. She developed acute nausea, vomiting and dark urine within hours of drug administration, and presented to the hospital. She was noted to have AKI (SCr peaked at 5.8 mg/dL) and acute hemolytic anemia (Hemoglobin decreased from 14 to 10 g/dL; LDH 2335 U/L; haptoglobin < 15 mg/dL). A UA was positive for 1+ protein and gross blood with RBC 2-5/HPF. A kidney biopsy showed acute tubular injury with multifocal pigmented casts with negative immunostaining for myoglobin. There was no evidence of thrombotic microangiopathy. Her minocycline was held and her AKI and anemia resolved without additional therapy. One year after this episode, she was restarted on minocycline for recurrent acne, and again experienced nausea, vomiting, diarrhea and back pain within few hours of the first minocycline dose. She presented to the hospital where she developed anuric AKI (peak SCr 8.0 mg/dL), hemolytic anemia (Hgb of 11.0 g/dL; LDH 3000 U/L; haptoglobin < 15 mg/dL) and thrombocytopenia (Plts 40,000/μL). She was started on plasma exchange therapy due to an initial concern for TTP. A repeat kidney biopsy was not performed. She again had rapid and full recovery of AKI, hemolytic anemia and thrombocytopenia with holding minocycline. .

Discussion: Minocycline-induced hemolytic anemia is rare, with only 1 published case of hemolytic anemia and hemoglobulinuria. An FDA Adverse Events reporting system search revealed 5 cases of anemia and 1 case of anuria attributed to minocycline. AKI was more frequently recorded (48 cases). This is the first report of biopsy-proven heme pigment nephropathy associated with minocycline.

SA-PO525

Effectiveness of Inactivated Hantavirus Vaccine on the Disease Severity of Hemorrhagic Fever with Renal Syndrome

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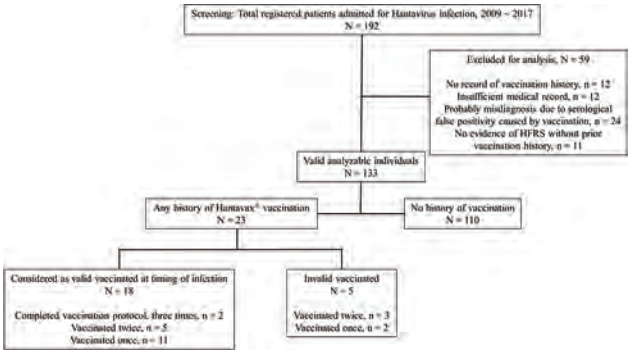
Background: An inactive Hantaan virus vaccine (iHV) has been broadly used as a preventive strategy in the South Korean army. After the vaccination program, the overall incidence of Hantavirus cases was reduced. However, hundreds of new HFRS cases occur annually. Furthermore, few studies have demonstrated the efficacy of the iHV's in field settings. This study aimed to evaluate the vaccine efficacy on HFRS severity.

Methods: From 2009 to 2017, we registered all reported Hantavirus cases in the South Korean army hospitals along with the patients' vaccination history. We retrospectively classified HFRS patients into both groups according to their vaccination records: no history of iHV vaccination and valid vaccination. To evaluate the vaccine efficacy on the severity of renal injury, acute kidney injury (AKI) ≧ stage 3 and event of dialysis were investigated.

Results: We assessed the effect of the vaccine on severity in 18 and 110 HFRS patients with and without valid vaccination history, respectively. In the valid-vaccination group, six of 18 patients (33.3%) had stage 3 AKI, compared to 60 of 110 (54.5%) HFRS patients in the non-vaccination group. The vaccine efficacy against HFRS progression (VE_p) was 58.1% (95% confidence interval [CI]: -31.3–88.0%).

Conclusions: The vaccine efficacy against the progression of HFRS in this case-control study failed to show a statistically significant result. However, different severity profiles were observed between the vaccinated and none-vaccinated groups. More studies with large vaccinated populations are needed to demonstrate the effectiveness of the vaccine in patients with HFRS.

Funding: Government Support - Non-U.S.



	No Vaccination Group (n = 110)	Valid Vaccination Group (n = 18)	Vaccination Effectiveness on Progression (VE_p)
HFRS with KDIGO-AKI stage 3, n (%)	60 (54.5%)	6 (33.3%)	58.1% (-31.3%, 88.0%)
HFRS with renal replacement therapy, n (%)	25 (22.7%)	2 (11.1%)	57.3% (-102.1%, 95.5%)

SA-PO526

Eculizumab Safety: 5-Year Experience from the Global aHUS Registry

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Background: Eculizumab (ECU) is approved for treatment of atypical hemolytic uremic syndrome (aHUS), a rare and life-threatening disease. The Global aHUS Registry was initiated in 2012 and has recruited both ECU- and non-ECU-treated adult and pediatric patients (pts).

Methods: This observational, multinational Registry (NCT01522183) evaluates safety and effectiveness of ECU in pts with aHUS, while also assessing clinical characteristics at enrollment and follow-up visits every 6 months thereafter, irrespective of disease management. Herein, we report baseline characteristics and targeted safety events from adult and pediatric pts who were "ever treated" (ET) vs "never treated" (NT) with ECU in the first 5 years of the Registry through the study cut-off date of January 26, 2017.

Results: Overall, N=1321 pts (ET, n=865; NT, n=456) have been enrolled. In ET patients, mean (SD) ECU exposure was 2.17 (1.56) years in adults and 2.72 (1.74) years in children. At baseline, ET pts had greater rates of organ involvement (renal: 79.2% vs 23.7%; gastrointestinal: 35.0% vs 9.9%; cardiovascular: 28.3% vs 8.6%; CNS: 25.9% vs 7.9%; and pulmonary: 15.0% vs 6.4%), and poorer quality of life (lower median Functional Assessment of Chronic Illness Therapy–Fatigue scores: 30 vs 41), compared with NT pts, respectively. Prespecified targeted safety events reported for 801 adult and 464 pediatric pts are presented in the Table. No differences in event rates between ET and NT pts were observed, except for serious infections in pediatric pts, which were more common in ET vs NT.

Conclusions: Five-year data from the Global aHUS Registry reveal no new safety signals with ECU treatment in either adult or pediatric ET pts, confirming ECU's safety profile and, therefore, its positive benefit:risk ratio in a real-world setting.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

Table. Prespecified, Targeted Safety Events After 5 Years in the Global aHUS Registry

	Adult Patients (n=801)		Pediatric Patients (n=464)	
	Ever treated with ECU (n=529)	Never treated with ECU (n=272)	Ever treated with ECU (n=328)	Never treated with ECU (n=136)
Serious infection				
Pts with event (n)	46	14	32	2
Events (n)	86	26	46	3
Events/100 pt-yrs	7.48	6.17	5.15	1.12
95% CI	5.98, 9.24	4.03, 9.04	3.77, 6.87	0.23, 3.28
Sepsis				
Pts with event (n)	14	8	1	0
Events (n)	19	12	1	0
Events/100 pt-yrs	1.65	2.85	0.11	0.00
95% CI	0.99, 2.58	1.47, 4.98	0.00, 0.62	0.00, 1.12
Malignancy				
Pts with event (n)	3	5	1	0
Events (n)	4	6	1	0
Events/100 pt-yrs	0.35	1.42	0.11	0.00
95% CI	0.09, 0.89	0.52, 3.10	0.00, 0.62	0.00, 1.12
Hepatic impairment				
Pts with event (n)	6	1	2	0
Events (n)	7	1	2	0
Events/100 pt-yrs	0.61	0.24	0.22	0.00
95% CI	0.24, 1.25	0.01, 1.32	0.03, 0.81	0.00, 1.12
Infusion reaction				
Pts with event (n)	4	0	5	0
Events (n)	6	0	7	0
Events/100 pt-yrs	0.52	0.00	0.78	0.00
95% CI	0.19, 1.14	0.00, 0.71	0.32, 1.62	0.00, 1.12
Meningococcal infection (nonfatal)*				
Pts with event (n)	1	0	2	0
Events (n)	1	0	2	0
Events/100 pt-yrs	0.09	0.00	0.22	0
95% CI	0.00, 0.48	0.00, 0.71	0.03, 0.81	0.00, 1.12
Deaths, n (%)†	25 (4.7)	27 (9.9)	6 (1.8)	0

*In adults, reported as probably related to ECU; the patient recovered without treatment interruption. In pediatric patients, one case was possibly related and one case was unlikely related to ECU. Both recovered, one without and one with ECU treatment interruption.
†One adult patient death occurred after a meningococcal meningitis event. Meningitis was reported as probably related to ECU treatment, but the cause of death was reported as unknown and no further details are available for this patient; 2 pediatric deaths (viral pneumonia followed by respiratory arrest; suspected sepsis) were deemed possibly related to ECU.

SA-PO527

Differences in Cardiovascular and Renal Complication Rates in Thrombotic Microangiopathies with and Without Hemolytic Uremic Syndromes

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Background: Pathophysiologic differences between different thrombotic microangiopathies (TMAs) might predispose to varying complications. We sought to study if there is a difference in the incidence of cardiovascular and renal complications between hemolytic uremic syndrome (HUS)-TMA and non-HUS TMAs.

Methods: We queried the United States National Inpatient Sample years 2005 to 2014 to identify hospitalizations in adult patients (age≥18 years) complicated by either HUS-TMA or non-HUS TMA using ICD-9 codes 283.11 (HUS) and 446.6 (TMA). In this cohort, we analyzed differences in the rates of acute myocardial infarction (AMI), heart failure (HF), stroke or transient ischemic attack (TIA), acute kidney injury (AKI), plasmapheresis and hemodialysis requirement, and in-hospital mortality.

Results: Out the weighted 59,166 cases in our study (mean patient age 50 years, 64% women), HUS-TMA was present in 24.5% (N=14,508) and non-HUS TMA in 75.5% (N=44,658). Patients with non-HUS TMA were older than those with HUS-TMA (mean age 50 years vs 48 years, p<0.001) but had similar gender distribution (women: 64.5% vs 62.9%, p=0.171). Compared to HUS-TMA, non-HUS TMA had higher rates of AMI (5.3% vs 4.2%, p=0.017), stroke/TIA (8.2% vs 3.0%, p<0.001), and plasmapheresis use (39.2% vs 30.9%, p<0.001). Compared to non-HUS TMA, HUS-TMA had higher rates of AKI (58.2% vs 36.4%, p<0.001), CHF (15.7% vs 12.5%, p<0.001), and HD requirement (41.6% vs 16.7%, p<0.001). In-hospital mortality was higher with non-HUS TMA (10.2%) than with HUS-TMA (8.5%, p=0.011).

Conclusions: In this large study of TMAs, HUS-TMAs were associated with more renal complications and non-HUS TMAs with more cardiovascular complications. The microvascular derangements in non-HUS TMA might be responsible for the higher incidence of AMI and stroke/TIA, whereas fluid balance disturbances from renal failure might contribute to increased heart failure with HUS-TMA. The high complication rates and mortality associated with these conditions necessitate further research into identifying underlying mechanisms and developing appropriate therapeutic strategies.

SA-PO528

The Risk Factors Analysis of Idiopathic Membranous Nephropathy Complicated with AKI

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Background: Idiopathic membranous nephropathy (IMN) is the most conmon pathological types for nephrotic syndrome. In Chinese population, the proportion of IMN in primary glomerular disease increased obviously in recent years. Acute kidney injury(AKI) is a common complication of IMN. The risk factors of IMN complicate with AKI were unknown.

Methods: We collected the clinical data of 129 IMN patients diagnosed by renal biopsy from March 2011 to October 2015 in the First Affiliated Hospital of Guangxi Medical University, including 35 IMN patients complicated with AKI (AKI group) and 94 IMN patients without AKI (Non-AKI group). The age, blood pressure, BMI, blood homocysteine, blood 25(OH) vit-D3, 24h urinary protein, many other laboratory parameters and pathological parameters were compared between these two group. Single factor analysis and multivariate analysis were conducted to explore the independent risk factors of AKI.

Results: The age, systolic blood pressure(SBP), blood homocysteine, blood 25(OH) vit-D3, 24h urinary protein, blood IgG and blood IgG/C3 showed significant statistically differences between these two group (P <0.05). In AKI group, age, SBP, 24h urinary protein, blood homocysteine was higher than those in non-AKI group, but blood 25(OH) vit-D3, blood IgG, blood IgG/C3 was lower than those in non-AKI group. The SBP, level of blood homocyhsteine, level of low-density lipoprotein cholesterol, and level of 24 urinary protein was positively correlated with the occurrence of AKI (P<0.05). However, the level of 25(OH) vit-D3, blood IgG and blood IgG/C3 was negatively correlated with the occurrence of AKI (P <0.05). In multivariate analysis, high blood homocysteine, high 24h urinary protein, hypertension, high pathological stage was the risk factors of AKI.

Conclusions: The IMN patients, with advancing age, higher SBP, higher serum homocysteine, lower serum 25(OH) vit-D3, lower IgG/C3 and higher pathological stage were more prone to complicate with AKI.

Funding: Government Support - Non-U.S.

SA-PO529

Randomized Controlled Trial of Omega 3 Fatty Acids to Reduce Contrast-Induced Nephropathy in CKD Patients Undergoing Coronary Angiography

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Background: Contrast-induced nephropathy (CIN) is a leading cause of acquired acute kidney injury and has been associated with prolonged hospitalization and adverse clinical outcomes. The results of studies investigating the effects of antioxidants on the prevention of CIN remain inconsistent. Omega 3 fatty acids have been shown to reduce inflammatory markers and oxidative stress, improve endothelial function, and reduce kidney dysfunction following reperfusion injury and chronic renal insufficiency in animal models. This pilot study aimed to determine the effects of omega 3 fatty acids on CIN prevention in patients with chronic kidney disease (CKD) undergoing coronary angiography

Methods: 67 patients were assigned to the N-acetylcysteine (NAC) and 63 patients were assigned to the omega 3 fatty acids (omacor ®). Both drugs were administered orally twice per day on the day prior to and on the day of contrast administration, for a total of 2 days. The primary endpoint was the occurrence of CIN, defined as an increase in baseline serum creatinine levels of > 0.5 mg/dl (44 μmol/l) or > 25% increase in serum creatinine levels from baseline levels 48–72 h following contrast administration. The secondary endpoints were: the need for renal replacement therapy, death, and length of hospitalization after contrast administration

Results: Of the 130 CKD patients enrolled in this study, 10 (7.7%) experienced an increase of at least 0.5 mg/dl (44 μmol/l) in serum creatinine levels 48 h after administration of the contrast agent, including 5 of the 67 patients in the NAC group (7.5%) and 5 of the 63 patients in the omega 3 fatty acids group (7.9%; P = 0.919). There were no significant differences in the need for renal replacement therapy or in the mortality rate between both groups

Conclusions: Short-term prophylactic omega 3 fatty acid treatment with hydration does not reduce CIN in CKD patients undergoing coronary angiography

Funding: Government Support - Non-U.S.

Primary and secondary endpoints

Outcome	NAC (N=67)	Omega 3 fatty acid (N=63)	P-value
Primary endpoint			
Increase in creatinine > 44 μmol/l	5 (7.5%)	5 (7.9%)	0.919
Increase in creatinine > 25%	6 (9.1%)	9 (14.3%)	0.358
Secondary endpoints			
renal replacement therapy	2 (3.0%)	6 (9.5%)	0.121
death	2 (3.0%)	4 (6.3%)	0.361
hospitalization(days)	6.70 ± 8.73	6.16 ± 7.82	0.714

SA-PO530

Are the Iodinated Contrast Media Dangerous? Influence of Iodinated Contrast Media on Renal and Thyroid Gland in Patients with CKD

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Background: The aim of our study was to assess the risk and incidence of CIN in patients with CKD, the impact of iodine CM on the endocrine function of the thyroid gland and the impact of renal impairment on the risk of contrast-induced hypothyroidism or hyperthyroidism.

Methods: We included 75 patients(pts). The first CKD-Group: 36pts with eGFR<60ml/min. (mean age 69.4±11, male-72.2%). The second RRT-Group: 20pts chronically dialysed (mean age 63.7±12.2, male-50%). The control group: 19pts with eGFR>60 ml/min, (mean age 48.2±18.0, male-57.9%). CIN prevention were conducted among all patients: hydration and N-acetylocysteine. All patients received iomeprol or iohexol. Patients were monitored for 6 months after the administration of CM (48 hours, 14 days and 6 months

after contrast administration). Creatinine, urea, eGFR, cystatin C, TSH, free-T3(fT3), free-T4(fT4), reverse-T3(rT3), were monitored. The results were statistically analyzed. Study was approved by the Ethics Committee.

Results: AKI was found in 2.7% in test group (3 pts). In the CKD group, the mean creatinine was 1.65mg / dl (1.33-2.28), eGFR 39.91 ± 12.89, cystatin C 2.17mg / dl ± 0.83, urea 67.7mg / dl ± 27.55. Increase in creatinine value was not statistically significant (ΔCREA 0.2 p = 0.8, Δcystatin C-0.04, p = 0.891, and ΔeGFR = 0.62, p = 0.912 within 48 hours after administration of CM. In the CKD group two weeks after administration of CM a decrease fT3, ΔfT31CKD -0.39 ± 0.77 p1CKD = 0.004. changes fT3 persisted during the 6 months follow-up (ΔfT32CKD = -0.36 ± 0.91 p2CKD = 0.023). The changes of ΔfT3 were no correlation with dose of CM and eGFR. In the group of RRT a change of ΔfT41RRT 1.58 ± 2.56 p1RRT = 0.013 was observed after 2 weeks, which maintained for 6 months (ΔfT42RRT 2.0 ± 3.38 p2RRT = 0.016). In the control group the changes were minimal and not statistically significant. No thyroid dysfunction was observed.

Conclusions: Adverse effects of intravenous administration of iodine contrast are rare. CIN in the group with CKD is 2.7%. CM have no adverse effect on kidney and thyroid function among patients with good function of these organs. CKD is not a risk factor for contrast-induced hyperthyroidism or hypothyroidism. Changes in thyroid hormones were statistically significant but asymptomatic. CM are not so dangerous. Further research is needed.

SA-PO531

New Perspectives on Bothrops-Induced AKI: Novel Biomarkers and Coagulation Disturbances

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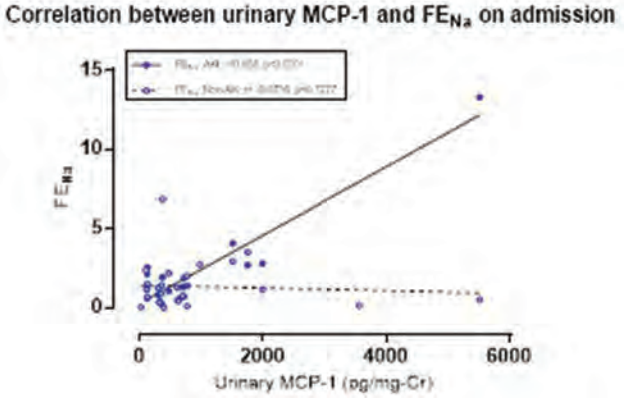
Background: *Bothrops sp* is the most common snake genus associated with acute kidney injury (AKI) in Latin America. We evaluated novel biomarkers and coagulation disturbances among patients with *Bothrops* venom-induced AKI.

Methods: This is a prospective study of patients with snakebite (*Bothrops*)-induced AKI admitted to a referral emergency hospital in Fortaleza city, Brazil, from December 2015 to December 2016. Biomarkers were measured in blood (sNGAL) and urine (uNGAL, uMCP-1, uKIM-1, VCAM-1 and IL-6) using ELISA.

Results: 63 patients were included, and 22 (34.9%) developed AKI. The age, time elapsed between snakebite and administration of antivenom, number of administered antivenom vials, gender distribution and severity of the envenomation were similar in the groups. The biomarkers uMCP-1 and uNGAL were significantly higher in the AKI group: uMCP-1 (471.2 ± 60.40 vs. 288.8 ± 41.42pg/ml; p=0.014) and uNGAL (15.27 ± 1.28 vs. 10.29 ± 1.06ng/ml; p=0.006). The activated partial thromboplastin time (APTT) on admission, was significantly longer in the AKI group (p=0.011). Urinary proteinuria correlated highly with two specific urine biomarkers: uMCP-1 (r=0.5242, p=0.0003) and uNGAL (r=0.4938, p=0.0008). The fractional excretion of sodium (FE_{Na}) also strongly correlated with uMCP-1 (r=0.8696, p<0.0001) and uNGAL (r=0.6833, p<0.0001). The correlation between FE_{Na} and uMCP-1was largely confined to the AKI-group (Figure 1). The FE_K also positively correlated with uMCP-1 (r=0.5775, p<0.0001) and uNGAL (r=0.5647, p=0.0001).

Conclusions: Coagulation abnormalities seem to be a pivotal factor in AKI development in *Bothrops*-induced AKI. The higher levels of uMCP-1 and uNGAL could represent early tubular and glomerular dysfunction caused by snakebite venom, and the abnormalities in fractional excretion of electrolytes point to tubular transport dysfunction.

Funding: Government Support - Non-U.S.



SA-PO532

Ex Vivo MSC Therapy for Subjects with AKI

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Background: Mesenchymal stromal cells (MSCs) are known to secrete potent molecules and extracellular vesicles contributing to immunomodulation and wound healing. There is a good deal of interest in MSC based approaches for the treatment of human kidney injury driven by evidence that MSCs repair the kidney by paracrine and endocrine mechanisms (Humphreys & Bonventre, 2008). Though clinical trials using MSCs as infusion therapeutics have been successful in demonstrating safety, clear clinical benefit has not consistently been realized. Lack of clinical effectiveness may be due to ineffective dosing of MSCs and short exposure times of the infused cells. Sentien Biotechnologies has pioneered a new way to control the delivery of MSC secreted factors by using an ex vivo cell therapy approach as a novel route of extracorporeal administration. Sentien's lead product consists of a continuous flow bioreactor with MSCs immobilized on the extraluminal side of a hollow fiber membrane. Patient's blood flows through the lumen of the hollow fibers and are conditioned by MSC secreted factors, allowing for the blood cells and MSCs to sense their environment and react to it.

Methods: In vitro studies were performed to assess MSC function within Sentien's reactors. The technology was also tested as a continuous ex vivo therapy in an ischemia/reperfusion dog model of Acute Kidney Injury (AKI). Toxicological studies were performed in healthy dogs. A multi-center, randomized, placebo-controlled double-blind study of extracorporeal MSC therapy has begun in human subjects with AKI receiving continuous renal replacement therapy.

Results: In vitro studies showed that MSCs are viable and responsive in the biorector. In a dog model of AKI, an increase in survival was observed in the treated animals. Additionally, toxicological studies verified a pharmacokinetic and pharmacodynamic response to MSCs that was consistent with a potent immunomodulatory mechanism of action. Preliminary results from the ongoing clinical trial will be presented.

Conclusions: Ex vivo MSC therapy using this reactor technology has promise for other clinical applications requiring systemic immunotherapy for tissue repair and regeneration.

Funding: NIDDK Support

SA-PO533

The Effect of Fluid Resuscitation with Normal Saline versus Ringer's Acetate on Renal Function and Host Defense in Severe Sepsis/Septic Shock Patients: A Randomized Controlled Trial

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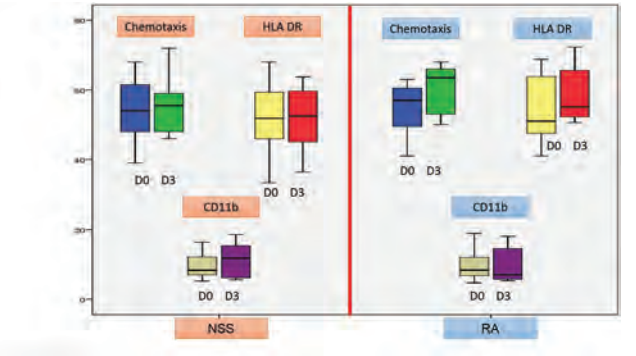
Background: Recent large observational studies in severe sepsis showed that Normal Saline (NSS) might worsen acute kidney injury (AKI) determined by serum creatinine. In animal model with sepsis, NSS could impair monocyte/neutrophil functions, the main host defense mechanism during sepsis, and this impairment might cause renal dysfunction.

Methods: NSS or RA was utilized for volume expansion during fluid resuscitation phase for 72 hours. The treatment followed the recommendations for fluid therapy provided by the Surviving Sepsis Campaign. Blood and urine samples were collected at 72 hrs. Primary outcome was median difference of uNGAL levels on day 3. Secondary outcomes were difference of monocyte HLA-DR (mHLA-DR)expression, neutrophil chemotaxis activity, and CD11b expression on day 3, and maximum AKI state on day 7.

Results: Fifty-nine patients were recruited, 29 and 30 for NSS and RA, respectively. The volume of resuscitation during the first 6 hours were comparable (NSS=1000 (1000,2000) mL, RA=1000 (700,1500) mL, p=0.38). Patients receiving NSS became more acidic than RA. There was no significant difference in renal function between both groups at baseline. The median uNGAL levels were not different between groups (NSS=111 (36.4, 262.2) ng/mL, RA= 32.7 (8.85, 178.1) ng/mL, p=0.59), mHLA-DR expression, neutrophil chemotaxis, and CD11b expression on day 3 were no improvement in NSS groups. But there were significant improvement in chemotaxis (p=0.024) and mHLA-DR expression (p=0.036) in RA group. The maximal AKI state determined by serum creatinine on day 7 were not different (NSS=24.1%, RA=26.7%, p=0.82).

Conclusions: Our study showed that there was significant improvement of immunoparalysis status (increased HLA-DR and chemotaxis activity) in RA group. No significant difference in tubular dysfunction between groups. (But lower trends of uNGAL and L-FABP in RA group.)

Funding: Government Support - Non-U.S.



SA-PO534

Balanced Crystalloids vs Normal Saline and Risk of AKI in Critically Ill Patients: A Systematic Review and Meta-Analysis

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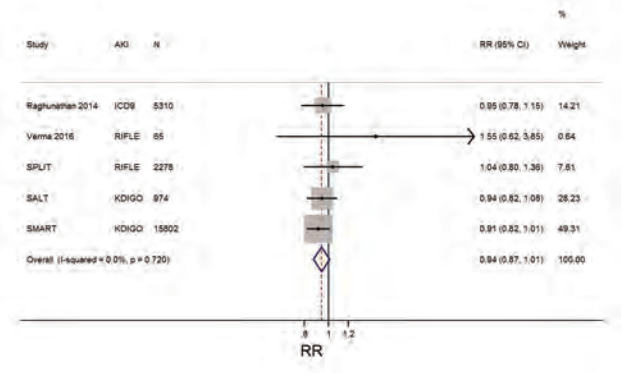
Background: In both animals and in vitro human studies, the high chloride content of normal saline (NS) has been linked with adverse pathophysiological effects. Emerging evidence, including a recent large clinical trial, suggests that balanced fluids (e.g. lactated Ringer or Plasma-Lyte A) may result in fewer adverse renal outcomes. However, whether NS is associated with a higher incidence of AKI when compared to balanced crystalloids in critically ill adults remains controversial.

Methods: A meta-analysis of RCTs and observational studies that enrolled critically ill patients receiving balanced crystalloids or NS in an ICU setting was conducted. Electronic databases (PubMed, EMBASE, Cochrane) were searched from inception until April 2018. Relative risks (RR) and 95% CIs were pooled using the random effects model in STATA. The primary outcome was AKI, as defined by the individual study. The secondary outcome was the requirement for renal replacement therapy (RRT).

Results: Five studies with a total of 24,429 patients met the eligibility criteria and were included. The definition of AKI was based on KIDGO criteria, RIFLE criteria or ICD-9 code. The risk of AKI with balanced crystalloids was not significantly different when compared to NS (RR 0.94; 95% CI, 0.87, 1.01, p=0.08) (Figure 1), but there was a trend toward a more favorable outcome. There was also no difference between the two groups in new RRT requirements (RR 0.98; 95% CI, 0.87, 1.09, p=0.65).

Conclusions: Although there is a trend toward less detriment to renal function with balanced crystalloids, the current evidence insufficiently supports their use over NS for fluid resuscitation to decrease the risk of AKI or RRT requirement in critically ill patients in the ICUs. Current studies are limited by the inconsistent definition of AKI. Therefore, additional clinical trials adopting a standardized AKI definition are needed to further clarify the ideal resuscitation fluid for critically ill patients.



SA-PO535

AKI Evaluation and Mortality Risk on Mexican Patients

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Background: AKI prevalence in Mexico is unknown and mortality rates are estimated 16 – 18%, its presence increases the risk of death in critically ill patients and is associated with high morbidity and mortality. In Mexico, limited data including early RRT, AKI biomarkers, furosemide response and risks factors of AKI progression, remains AKI treatment controversial. This study aimed to evaluate characteristics and risk factors of AKI and predict RRT and renal function recovery.

Methods: We analyze a single center AKI cohort of 112 Mexican patients. Serum creatinine assay was done to diagnose AKI. Demographics, clinical and biochemical profiles, risk factors for AKI and RRT prescription was assessed and reported during diagnosis and discharge. Outcome measures were renal recovery, mortality and causes of death.

Results: Mean age was 56.81 ± 18.38 years, 73% on AKI stage 3, mixed causes (60%) and pre-renal AKI (26%) were the most frequent forms. Main etiologies were cardiovascular disease (30%) and sepsis (24%). Of 112 patients, 49% initiate RRT and 55% had renal recovery. Global mortality rate was 48% mainly due to cardiovascular disease. We observed significant differences between (p=0.05) in serum creatinine admission OR=01.65 (1.47-1.83) and fluid balance OR=1.56 (1.45-1.69) as risk factors for RRT and furosemide response OR 9.16 (4.03-39.96) as renal recovery factor.

Conclusions: This was the first study that evaluate AKI risk factors, allowing RRT therapy and enhance renal recovery. Our findings support the furosemide stress test response strongly allows the adequate risk stratification, and can be used for early RRT initiation and might prolong time to renal recovery. Further studies are needed to determine if at the time of admission measurement of AKI biomarkers, may significantly improve the ability to predict hard outcomes (RRT, renal recovery and death).

Funding: Government Support - Non-U.S.

SA-PO536

AKI in a Developing Country: Clinical Course, Renal Recovery and Patient Outcome

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Background: Acute Kidney Injury (AKI) is an important determinant of outcome in hospitalized patients. Moreover, there is a risk for future development of Chronic Kidney Disease (CKD). Though the long-term impact of AKI has been studied in developed countries, there is a paucity of data in this area from the Indian subcontinent. This single-centre study aimed to assess the pattern, clinical spectrum and long-term outcome of AKI.

Methods: In this prospective observational cohort study, detailed demographic and clinical data at presentation, during hospital stay and follow-up at 1, 3, 6 and 12 months after discharge were obtained prospectively for a cohort of patients with AKI. Both community (CAAKI) and hospital acquired AKI (HAAKI) were included. Patient with preexisting CKD were excluded. Outcome variables were in-hospital mortality, renal function at discharge and on long-term follow-up.

Results: Of the 476 patients, majority of the cases, 395 (83%) were CAAKI. The mean age was 44.8 ± 18.7 years. Etiology groups included medical (84%), surgical (10%) and obstetric (6%) with sepsis (176/476; 36.9%) being the most common cause of AKI. The in-hospital mortality rate was 38%. Age >60 yrs (HR = 1.51; 95% CI, 1.11 – 2.07), oliguria (HR = 1.48; 95% CI, 1.05 – 2.10) and need for ventilator (HR = 2.45; 95% CI, 1.36 – 4.41) and/or inotropes (HR = 14.4; 95% CI, 6.28 – 33.05) were predictors of mortality. At discharge, 146 (30.7%) patients had complete renal recovery, while 149 (31.3%) had partial renal recovery. Oliguria ($p < 0.001$), hypoalbuminaemia ($p = 0.001$) and need for renal replacement therapy (RRT) ($p = 0.01$) were significantly associated with partial recovery. Of the 295 patients on follow-up, 211 (71.5%) patients had normal renal function, 4 (1.4%) died and 33 (11.2%) lost to follow up; 41(14%) patients developed CKD while 6 (2%) were dialysis dependent. The need for RRT during hospital stay was the single most important factor predicting the risk of CKD (OR 1.77, 95% CI, 1.12-2.78).

Conclusions: In conclusion, our data shows that AKI in hospitalized patients still has high mortality. Though a fairly good percentage of cases recovered, there is a definite risk of CKD development, especially in patients who required RRT during hospitalization.

SA-PO537

Recovery from AKI-Requiring Dialysis in Hospital Survivors Discharged to a Rehabilitation Facility

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Background: Acute kidney injury-requiring dialysis (AKI-D) occurs in about 5% of hospitalized patients and is associated with poor outcome. Little is known about the incidence of AKI-D recovery following hospital discharge. We aim to examine AKI-D recovery in hospital survivors transferred to an affiliated rehabilitation facility (Select) with need of hemodialysis (HD) for AKI.

Methods: Single-center, retrospective cohort study of 42 patients who were admitted to the University of Kentucky Hospital (8/2015 to 3/2018), suffered from AKI-D and were transferred to Select with ongoing need for HD. Kidney recovery was defined as the patient being alive and no longer requiring HD support. Kidney recovery was assessed at the time of discharge from Select and from Select discharge until the end of the observation period (5/2018). Multivariable logistic regression models were performed to assess clinical characteristics associated with kidney recovery.

Results: Mean (SD) age was 61.4 (9.6) years; 61.9% were males and 90.5% whites. A total of 29 out of 42 patients (69%) recovered kidney function by the time of discharge from Select. Of these, 5 (17%) died after Select discharge (median follow-up 9.1 months). A total of 5 (12%) patients died during their stay at Select. Of the 8 (19%) patients that were discharged from Select with HD-dependent status, 3 (38%) died and only 1 recovered kidney function (median follow-up 16.5 months). The total number of hospital dialysis days was independently associated with kidney recovery at Select discharge (OR 0.81, 95% CI 0.68–0.98, p=0.027) and the number of intradialytic hypotension events during the stay at Select was associated with death or HD-dependent status at follow-up (OR 1.24, 95% CI 1.02–1.51, p=0.034).

Conclusions: At least 2 out of 3 patients transferred to a rehabilitation facility with AKI-D diagnosis recovered kidney function no longer requiring HD by the time of discharge. Dialysis-specific characteristics such as total days and intradialytic hypotension events may play a key role in the development of risk prediction models and 'best clinical practices' to promote kidney recovery in this susceptible population.

SA-PO538

Long Term Outcomes of Acute Tubular Necrosis and Acute Tubulointerstitial Nephritis

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Background: Renal damage of acute tubular necrosis (ATN) and acute tubulointerstitial nephritis (ATIN) are considered reversible. However, the prevalence and long-term outcome of ATN and ATIN were unknown.

Methods: We included 4690 adult patients who had underwent kidney biopsy in two tertiary hospital in Korea during 1979-2017. We excluded patients with biopsy confirmed end stage renal disease (ESRD), previous kidney transplantation, malignancy, and inadequate biopsy specimen.

Results: Mean age was 39.0±15.5 years and 55% was male. Primary glomerulonephritis (PGN) was 3466 (65.4%), secondary glomerulonephritis (SGN) was 1088 (20.5%), and ATN or ATIN was 136 (2.6%). Patients with ATN or ATIN were significantly older compared than PGN or SGN (P<0.001) and had lower eGFR (P<0.001; 31.9±28.0, 74.5±36.6, and 70.9±38.5ml/min/1.73m^2, respectively). Mortality was the highest in patients with SGN (18.0%). Mortality in patients with PGN was 8.7%, and ATN or ATIN was 7.4% (P<0.001). The incidence of ESRD was much lower in patients with ATN or ATIN (2.9%) compared than PGN (14.4%) or SGN (15.0%) (P=0.001). During 156.8 ± 101.8 months follow up period, the adjusted risk of mortality was higher in patients with SGN compared than PGN (RR 2.156; 95% CI, 1.795-2.590). However, risk of mortality was not significantly different between PGN and ATN or ATIN. The adjusted risk of ESRD was significantly lower in patients with ATN or ATIN (RR 0.100; 95% CI, 0.037-0.268) compared than PGN, and the risks of ESRD was not different between PGN and SGN during 155.3±105.8 months.

Conclusions: The risk of long-term mortality was not different between PGN and ATN or ATIN. Although the risk of ESRD was significantly lower in patients with ATN or ATIN compared than GN, 2.9% of ATN or ATIN patients progressed to ESRD.

SA-PO539

AKI in Patients with Hip Fracture: A Single Centre Experience

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Background: Hip fracture is the most common serious injury in the elderly associated with high morbidity and mortality. These patients are high risk of developing acute kidney injury (AKI). We evaluated the incidence of AKI occurring anytime during admission and impact on length of stay (LoS) and mortality in patients admitted with hip fracture. St Helier Hospital Hip Fracture Unit is the best performing and second busiest in London according to the Department of Health's Best Practice Tariff. We sought to establish if this good practice translated to reduced AKI incidence and improved outcomes.

Methods: This is a retrospective observational study of patients presenting to St Helier Hospital Hip Fracture Unit between January 2015 and December 2016. Patients were identified from the National Hip Fracture Database. AKI was identified from electronic pathology alerts and defined according to Kidney Disease Improving Global Outcomes criteria.

Results: 861 patients presented with hip fracture; 246 males (28.6%) and 615 females (71.4%). Mean age was 83.4 years (60-104 years) and median LoS was 23 days (IQR 11-27 days). 16.4% (141) patients developed AKI; 11.1% (96) with AKI stage 1, 3% (26) with AK1 stage 2 and 2.6% (19) with AKI stage 3. AKI was associated with increased LoS. Death was adjusted for by assigning median LoS to those who died. Median LoS was 31 days (IQR 16-36 days) in patients with AKI compared to 22 days (IQR 11-25 days) without AKI. Patients who developed AKI were less likely to be discharged home. 31.9% patients with AKI were discharged to their own home compared with 41.7% of patients without AKI. AKI was associated with increased unadjusted mortality. Patients with AKI had a 30 day mortality of 16.3% compared with 4.4% in patients without AKI. 30 day mortality was 15.6%, 19.2% and 15.8% in patients with AKI stage 1, 2 and 3, respectively. Patients with AKI had an inpatient mortality of 16.3% compared with 3.75% in patients without AKI. Inpatient mortality was 13.5%, 19.2% and 26.3% in patients with AKI stage 1, 2 and 3, respectively.

Conclusions: The incidence of AKI at our unit (16.4%) is significantly lower than previously published data (24%) but despite this, it is associated with increased LoS and mortality. This suggests early and intensive ortho-geriatrician and multi-disciplinary team input can improve AKI incidence and also outcomes in these patients.

SA-PO540

Temporal Trend of Utilization of Palliative Care Encounters in Hospitalized Patients with Dialysis Requiring AKI - A Nationwide Analysis

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Background: Dialysis requiring AKI (AKID) is major cause of in-hospital morbidity and carries high rate of mortality. We sought to investigate the temporal trend of the utilization of palliative care (PC) in hospitalized patients with AKID in United States.

Methods: We conducted a retrospective study using the national inpatient sample from 2005 to 2014, to identify hospitalized patients complicated by AKID. The outcomes were the temporal trend and factors associated with utilization of PC in hospital. Multivariate logistic analysis was conducted to calculate odds ratios, adjusting for demographics, hospital characteristics, comorbidities and code status. Analysis was performed using Stata 14.0.

Results: A cohort of 808,159 patients was identified from 2005 to 2014, of whom 5.88% had palliative care consult referral. The incidence of palliative care contact increased from 0.41% in 2005 to 12.38% in 2014 (aOR 1.18, p<0.01). Patients who received palliative care contact, compared to who did not, were older (65.37 vs 62.50, p<0.01) and more likely to die in hospital (75.00% vs. 25.62%, p<0.01). Factors associated with more frequent PC referral included more cormobidities, Caucasian race (compared to other minorities), teaching hospitals, larger hospitals, hospitals region other than Northeastern area, Medicaid insurance and do not resuscitate status (shown in Table 1).

Conclusions: The use of palliative care consultation for patients with AKID who are admitted to hospitals, based on the NIS, is approximately 5.88%. Race, insurance status, hospital size, location and teaching status all were associated with differential rates of referral. There was a significant increase in palliative care use observed from 2005 to 2014.

Table 1

Predictors for Palliative Care	aOR	95% CI	P
AGE	1.01	1.01-1.01	<0.01
Female	0.98	0.93-1.03	0.43
Race			
Caucasian	Reference		
African American	0.68	0.62-0.75	<0.01
Hispanic	0.67	0.60-0.74	<0.01
Asian	0.70	0.59-0.83	<0.01
Charlson Comorbidity Index			
1 to 3	Reference		
4 to 6	1.18	1.10-1.26	<0.01
More than 6	1.60	1.47-1.74	<0.01
Teaching Status			
Non-Teaching	Reference		
Teaching	1.31	1.17-1.46	<0.01
Hospital Bedsize			
Small	Reference		
Medium	1.29	1.09-1.52	<0.01
Large	1.68	1.45-1.95	<0.01
Region			
Northeast	Reference		
Midwest	1.25	1.01-1.55	0.04
South	1.19	0.97-1.47	0.09
West	1.62	1.33-1.98	<0.01
Insurance			
Medicare	Reference		
Medicaid	1.17	1.07-1.28	<0.01
Private Insurance	1.06	0.98-1.14	0.13
Self-Pay	1.28	1.11-1.47	<0.01
DNR	10.49	9.62-11.45	<0.01

SA-PO541

Prognostic Tool in Dialysis Treated AKI

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Background: AKI is a common condition in hospitalized patients, having a mortality which may exceed 50%. Although dialysis may extend life in some subjects with AKI, elderly patients, with multiple comorbidities have a significantly shortened life expectancy. Attempts to identify prognostic models for a more accurate estimation of survival for AKI which was treated by dialysis were not successful. Utility of the "surprise" question to identify chronic dialysis patients with high mortality was reported, but studies on general population of seriously ill patients this question performs poor to modest predictive tool. The aim of our study was to identify the sensitivity of the "surprise" question in patients with unscheduled in-hospital started dialysis.

Methods: Prospective cohort study of all AKI patients who were treated by hemodialysis between January 1st, 2013 and December 31, 2017 in our center. During this period nephrologists had to answer the "surprise" question (Would I be surprised if this patient died in the next 6 months?) regarding every patient with AKI at the day of the first dialysis.

Results: The cohort included 475 patients**,** 60% males, 60% diabetics, aged 72.8 ± 12.2 (Range 20.6-98.7). In 31% of cases patients suffered from AKI and in 69% from Acute on Chronic Kidney Disease. In 41%, patients started dialysis in an ICU. The 30- days-all- cause mortality was 37% and the 6-months mortality rate 53%. The 7-days mortality was 20%. The Positive Predictive Value of the "surprise" question was 65%, the Negative Predictive Value 58% with a Sensitivity 58% and Specificity 65%.

Conclusions: The "surprise" question showed a weak predictive value for death in AKI patients treated by dialysis. Since patients requiring dialysis have a poor general prognosis, we need more sensitive instruments to choose the right patient for the right treatment avoiding unnecessary and futile treatments.

SA-PO542

AKI Outcomes as a Quality Paradigm: A Health Systems Approach

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Background: Acute kidney injury (AKI) affects 1-in-3 hospitalized patients; survivors face long-term consequences including high risk of re-admissions, end-stage renal disease (ESRD), or mortality. Retrospective studies estimate that only 15-20% of patients receive follow-up renal care within one year of discharge. At a large tertiary care health system, we operationalized and implemented a quality improvement program (QIP) to track discharge disposition and post-discharge follow-up renal care of all AKI consults.

Methods: By combining billing data and health-system wide informatics, we considered all non-ESRD, non-transplant hospitalizations receiving renal consults for each calendar quarter. The first hospitalization with an AKI renal consult in each quarter was considered as the index event. Discharge dispositions included expired/hospice, inter-facility transfers (long-term acute care/acute care), home with self-care or home-health, nursing home, and others. All survivors except inter-facility transfers were considered eligible for renal follow-up metric defined as any renal contact within 90-days of discharge (office visits, chronic dialysis visits, or renal follow-up during readmission). We also tracked all-cause 90-day re-admissions. Chi-square and Kruskal-Wallis test was used for comparison across quarters.

Results: Between 10/2015 and 12/2017 (9 quarters) we identified 2,383 AKI consults (60% male, 64% White). Overall, 22% expired/discharged to hospice (18% to 25% across quarters; p = 0.70); 12% inter-facility transfers; and 66% were eligible for renal follow-up metric (23% home with self-care; 18% home with home-care; 23% rehab-nursing home; 2% others). Of the eligible patients, 42% met the metric (range from 39% to 49% across quarters p=0.09); renal office visits occurred in 29% (range across quarters 22% to 37%), with a median time to renal visit of 31 days (q1, q3, 18, 49). Overall 90-day re-admission rate was 40% (range 35 to 46% across quarters; p=0.29), with median time to re-admission of 17 days (q1, q3, 7, 42).

Conclusions: This is the first report of operationalizing system-wide AKI metrics in real-time and can inform optimal strategies to improve post-discharge care in AKI. Such informatics-based QIP have the potential to plan and implement targeted resource allocation and improve patient and process outcomes.

Funding: Clinical Revenue Support

SA-PO543

Integrating Electronic Alerts and Clinical Decision Support Systems to Improve Diagnosis and Management of AKI

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Background: Acute kidney injury(AKI) is a common clinical event with severe consequences. It is associated with prolonged hospital stay, increased risk of mortality and progression to chronic kidney disease. It is often underrecognized and underdiagnosed as seen in studies with significant discrepancy in incidence based on methods (administrative data vs chart review). Early, accurate diagnosis and correct management can improve the standard of care and patient outcomes

Methods: This is preliminary data from an ongoing prospective intervention study across all non-nephrology, non-intensive care patients (6 mo-18yrs) at Seattle Children's Hospital. Our aim was to see if an electronic-alert (e-alert) combined with a clinical decision support system (CDSS) can improve detection and outcome of AKI. We developed an automated real-time e-alert using Kidney Disease Improving Global Outcomes (KDIGO) criteria. E-Alert with stage of AKI was sent as a text page to the contact provider in a patient's electronic health record. It was linked to a CDSS providing basic guidelines on AKI management. The CDSS did not place orders or consults automatically.

Results: 83 AKI alerts were recorded across both phases(Table). Both groups had similar baseline characteristics including age, admitting service, history of transplant or past AKI. There was significant difference in the recognition and documentation of AKI (41%, pre-alert phase vs 80%, alert phase, p<0.005). More renal consults were obtained for severe AKI (≥KDIGO Stage 2) in the alert phase (86.6% vs 36.3%, p<0.005). A higher proportion of patients in alert phase showed return to a baseline kidney function by discharge. Data on follow up and long term outcome is awaited.

Conclusions: Our study shows that AKI remains under diagnosed. E-alerts improve the recognition of AKI, enabling providers to intervene early. They encourage nephrology consultation for severe AKI. This may improve outcomes of children with AKI

Key differences between the study phases

	Pre-alert phase (43 episodes in 41 admissions)	E-alert phase (40 episodes in 38 admissions)
History of transplant, n	BMT = 6 Heart = 5 Liver = 0	BMT = 7 Heart = 5 Liver = 1
Previous AKI, n (%)	20 (48%)	21 (58%)
AKI severity, n (%)	Stage 1= 31 (72%) Stage 2/3= 12 (28%)	Stage 1= 25 (62.5%) Stage 2/3= 15 (37.5%)
AKI documented, n (%)	18 (41.8%)	32 (80%)*
Renal consult for AKI Stage 2 or 3, n(%)	4 (33.3%)	13 (86.6%)*
Return of kidney function to baseline at discharge, n(%)	20 (48.7%)	23(63.8%)

* p<0.005

SA-PO544

Real Time Utilization of TIMP2*IGFBP7 in ICU Patients: A Quality Initiative

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Background: Little is known about the real-time clinical use of urinary [tissue inhibitor of metalloproteinase-2]*[insulin-like growth factor binding protein 7] (Nephrocheck, Astute Medical) (NC) in mixed ICU patients at risk for acute kidney injury (AKI).

Methods: We conducted a single center before and after quality initiative assessing outcomes in ICU patients at risk for severe AKI (defined as elevated cardiovascular or pulmonary SOFA score or having KDIGO Stage 1 AKI). We compared 70 retrospective patients who had NC measured but never clinically reported with 60 prospective patients who had NC reported with clinical guidance about their severe AKI risk. We assessed patient outcomes including maximal AKI stage, need for RRT, nephrotoxin exposure and need for nephrology consult.

Results: There was no difference in age, race, gender, baseline hypertension, diabetes, CKD, baseline serum creatinine (SCr) between the retrospective and prospective cohorts. Compared to prospective patients, retrospective patients had higher APACHE II scores(p<0.001), but there was no difference in the need for vasoactive medications(p=0.87). On the day the biomarker was measured both SCr and NC were higher in the prospective cohort.(Table) Despite higher NC values in the prospective cohort there was no difference in the development of Stage 2/3 AKI (p=0.72) or the need for RRT (p=0.68). There was a trend toward decreased mortality in the prospective group (p=0.08). The prospective cohort was more likely to have a nephrology consult in the 24 hours following NC measurement. Prospective patients with a NC>2.0 (n=19) were less likely to be exposed to a nephrotoxins (NSAIDs, Aminoglycosides, amphotericin, r adiocontrast and diuretics) over the first 48 hours compared to retrospective patients with NC>2.0 (n=12)(p<0.01).

Conclusions: Real-time NC measurement decreases nephrotoxin exposure in at risk patients, increases nephrology-based care and improves ICU patient outcomes.

TIMP2*IGFBP7 Outcomes

Variable (either median(IQR) or n(%))	Retrospective Cohort (n=70)	Prospective Cohort (n=60)	p-value
Baseline Serum Creatinine (mg/dl)	1.0 (0.7 - 1.4)	1.0 (0.7 - 1.3)	0.93
Serum Creatinine on Day of NC Measurement	1.1 (0.7 - 1.7)	1.4 (1.0 - 2.1)	0.012
Nephrocheck value	0.33 (0.1 - 1.6)	0.74 (0.24 - 2.3)	0.06
Reached Stage 2 or 3 AKI	18 (24%)	17 (28%)	0.72
Inpatient Mortality	16 (23%)	7 (11%)	0.08
Nephrology Consult within 24 hour of NC measurement	4 (5.7%)	11 (18%)	0.03

SA-PO545

AKI Awareness Among Hospitalized Survivors of AKI

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Background: Low health literacy (HL) has been linked to poor patient awareness of health conditions, particularly chronic kidney disease (CKD). Little is known about patients' awareness of AKI, and the role of HL. Using data from the Change AKI study, we examined the association of patient and clinical factors with AKI awareness among hospitalized survivors.

Methods: The Change AKI Study is an ongoing pilot study of an AKI educational intervention for hospitalized survivors of AKI at Duke University Hospital, seen in consultation by an inpatient nephrology service, and enrolled beginning in 2017. All participants completed baseline and 1-month surveys of AKI-related risk factors and awareness. We defined adequate HL at baseline as a Rapid Estimation of Health Literacy Measure (REALM-SF) score ≥7. The primary outcome was baseline AKI awareness, defined as a "yes" response to the question "Before right now, did anyone in the hospital tell you that you had acute kidney injury?" We used multivariate logistic regression to examine the association of HL with baseline AKI awareness, adjusted for patient demographic (age, sex, race, education) and clinical (severity of AKI, need for dialysis, baseline CKD) factors. In a *post hoc* analysis, we examined the association of discharge-related factors (AKI in discharge summary, instructions, or schedule follow-up care) with AKI awareness at follow-up among those previously unaware at baseline.

Results: Among 61 AKI survivors, 46% were aware of their AKI diagnosis at baseline and 78% had adequate HL. HL was not associated with AKI awareness (odds ratio 2.25, 95% confidence interval 0.61-8.31), even after accounting for demographic or clinical

factors. Of 45 participants at follow-up, 20% and 68% had AKI mentioned in their discharge instructions and summaries, respectively. Only 37% had scheduled follow-up care for AKI. Of 30 participants who were unaware at baseline, 43% were aware at follow-up; discharge-related factors were not associated with new AKI awareness.

Conclusions: AKI awareness in hospitalized patients seems unrelated to HL, demographic or clinical factors. Discharge-related educational and follow-up processes are suboptimal and need improvement. Multifactorial interventions targeting AKI awareness need further investigation.

Funding: NIDDK Support

SA-PO546

Nephrology Consultation After AKI Can Improve Patients' In-Hospital Survival

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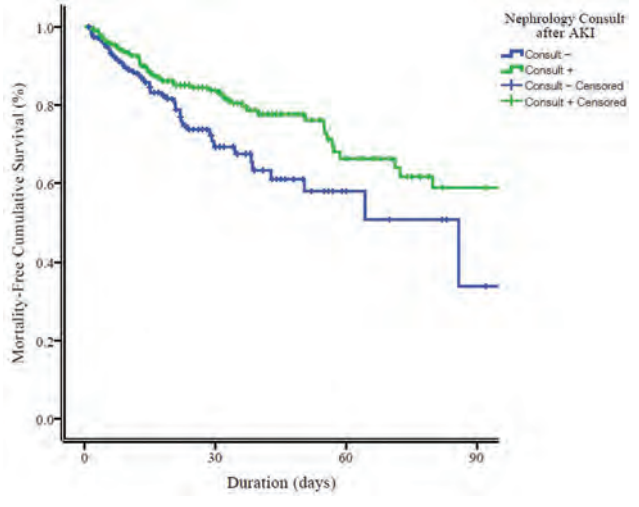
Background: The significance of nephrology consultation in patients with acute kidney injury (AKI) is not well established.

Methods: We enrolled a total of 20,914 patients who were admitted to the Seoul National University Bundang Hospital from January 1, 2013 to December 31, 2013. All clinical and laboratory data were retrieved retrospectively from the electronic medical record database.

Results: In total, 2,603 (12.4%) patients had AKI during admission (8.7% AKI stage 1, 2.1% AKI stage 2, 1.6% AKI stage 3). Among the 2603 patients with AKI, 446 (17.1%) patients were referred to nephrologists for consultation. Patients who were referred to nephrologists showed characteristics of older age (68.7 ± 14.6 vs. 66.3 ± 15.7 years old, P = 0.0002), male preponderance (60.8% vs. 55.6 %, P = 0.045), more surgical operation (39.7% vs. 29.6%, P < 0.001), more ICU care (51.8% vs 24.1%, P < 0.001), increased baseline creatinine level (1.51 ± 1.58 vs. 1.05 ± 1.28, P < 0.001), high comorbidity score (0.89 ± 1.00 vs. 0.67 ± 0.75), and more advanced AKI stage (eg. AKI stage 3, 33.6% vs. 9.0%, P < 0.001). Overall, patients who were referred to nephrologists for consultation showed similar survival rate compared with patients who were not consulted to nephrologist (log-rank P = 0.223, HR 1.190 (0.899-1.575). After propensity score matching (1:1, n= 359 in both group), both group showed comparable clinical characteristics, and nephrology consulted patients showed better survival outcomes (log-rank P = 0.07, HR 0.614 (0.428-0.881). The time from AKI to nephrology consultation and time to answer after consultation did not significantly affect patient survival.

Conclusions: Patients with AKI who were consulted to nephrologists have a better survival prognosis than those who were not. AKI patients should be encouraged to be consulted to nephrologists for appropriate management and improvement of clinical outcomes.



Propensity Score Matched Patients Survival after AKI according to the Nephrology Consultation.

SA-PO547

Provider-Level Exposure to AKI Alerts in an Ongoing Randomized Trial

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Background: Electronic alerts for acute kidney injury (AKI) are increasingly considered in clinical care because of the potential harms that may come from missed diagnoses of AKI. Alert fatigue, however, may reduce the effectiveness of AKI alerts.

Methods: The Electronic Alerts for AKI Amelioration (ELAIA-1) trial began in March 2018 and will randomize 6,030 patients to real-time, electronic health record-based AKI alerts or usual care across 6 hospitals. Alerts fire when the electronic health record is opened by an MD, NP, or PA while AKI diagnostic criteria are met. In this preliminary analysis, we describe the differential exposure to AKI alerts at the provider level.

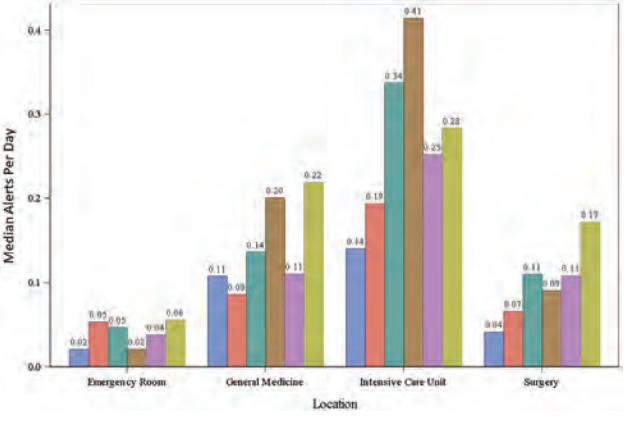
Results: Two months into the study, 10,665 alerts had fired for 217 patients with AKI over a six-week period, at a median of 30 (IQR 13-72) alerts per patient. At the patient level, the median alert duration was 1.1 (0.5-2.9) days. A total of 996 unique providers were exposed to alerts with a median of 0.09 (.05-0.31) alerts per day per provider. Fellows received the most alerts per day while attending physicians and PAs received the fewest. Alert burden was highest in the ICU (Figure) and substantially lower in the hospital wards and emergency department.

Conclusions: Despite the large total number of alerts, provider alert burden was generally low. Fellows experienced the highest median number of alerts per day, a potential signal for higher risk of alert fatigue. Providers caring for patients in the ICU may also be at higher risk of alert fatigue.

Funding: NIDDK Support

Exposure to AKI Alerts by Provider Type

Provider	Unique Providers	Alerts Per Day, Median (IQR)	Alerts Per Day (Max)
Attending	450	0.08 (0.04 - 0.16)	3.77
Fellow	119	0.21 (0.08 - 0.49)	2.35
Resident	416	0.12 (0.04 - 0.40)	4.59
Physician Assistant	93	0.10 (0.02 - 0.29)	3.64
Nurse Practitioner	58	0.14 (0.06 - 0.33)	3.29



SA-PO548

Focused Ultrasound in Nephrology: A Nephrology Fellow's Perspective

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Background: The portable bedside ultrasound has recently been widely used in clinical practice. The time efficient bedside evaluation is invaluable in managing a patient. Focused Assessment with Sonography for Trauma (FAST) exam is a standard now in Emergency Medicine. Renal fellows are also being encouraged by training programs to use this evolving tool to improve patient care. So we performed a series of case studies to assess usefulness of portable bedside sonography on acute renal consults, termed Focused Ultrasound in Nephrology (FUN)

Methods: 14 patients were studied by a renal fellow and subjected to FUN. All patients had Acute Kidney Injury with an initial impression of pre, post or intra-renal etiology. Volume status was defined by physical exam. Bedside FUN was performed on the same day to see if it changed management. FUN is a quick 4 point bedside ultrasound on initial assessment of patients using a Philips Lumify portable ultrasound. 4 points chosen were bilateral lung scans at mid-axillary lines to look for lung B-lines, IVC for >50% collapsibility on inspiration and bladder scan for distension. Extra 2 point kidney ultrasound to look for kidney size and hydronephrosis was excluded because of lack of training.

Results: 5 out of 14 patients' management was changed on the basis of FUN: 6 scan findings validated the physical exam and 3 did not benefit from the study. 3 patients who were initially rendered euvolemic on physical exam, received IV diuretics when found to have significant lung B-lines (>3) with non-collapsing IVC by FUN. 2 patients who were initially rendered euvolemic had a change in diagnosis to pre-renal and received volume expansion when found more than 50% IVC collapsibility without significant lung B lines. In 3 cases bladder distension was picked up earlier at bedside and later confirmed by a sonogram performed by radiology.

Conclusions: We propose a 4-6 point FUN exam by fellows on acute renal consults. It is a real time assessment of intravascular volume status (pre-renal), pulmonary congestion, bladder obstruction (post-renal) and renal anatomy. Minor training is needed but potential benefits far outweigh the limitations of bedside FUN.

SA-PO549

Comparison of Effectiveness of Renal Ultrasonography in the Work-up of AKI Before and After the Introduction of a Risk Stratification Model

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Background: In 2010, Licurse et al, created the Licurse Model for risk stratification of patients according to the probability of having an obstructive cause of acute kidney injury (AKI). The researchers suggested that renal ultrasonography (RUS) findings do not change the management of patients with AKI in most cases. They found that performing RUS only in patients with a higher pre-test probability of urinary tract obstruction conserves resources. They constructed a model consisting of seven variables, which stratified patients with AKI into low, medium, and high risk of obstructive cause of AKI.

Methods: We conducted a retrospective chart review project looking at a total of 482 patient charts, who had RUS performed in the work up of AKI from Jan. 2012 to Mar. 2018 at Staten Island University Hospital. In the months of Oct. 2017 through Dec. 2017 we performed an intervention, which consisted of educating the house staff regarding the appropriate use of a RUS in the work up of AKI. We compared the percentage of patients who met the criteria of the Licurse Model for ordering RUS, had positive findings on RUS, and had a change in clinical management based on the RUS findings before and after our intervention.

Results: We found that the percentage of patients who had RUS in the work up of AKI was 49.9% before the intervention, compared to 49.3% after the intervention, P-value 0.936. The percentage of patients who had a change in clinical management based on RUS findings was 7.23% before the intervention, and 6.17% after the intervention, P-value 0.734.

Conclusions: Our results show that there was no improvement in the effectiveness of RUS for the work up of AKI after the intervention at our facility. Our intervention consisted of educating the resident physicians, and a small number of the attending physicians about the proper use of RUS for the work up of AKI.

SA-PO550

Absence of Hydronephrosis Does Not Exclude Obstructive Nephropathy

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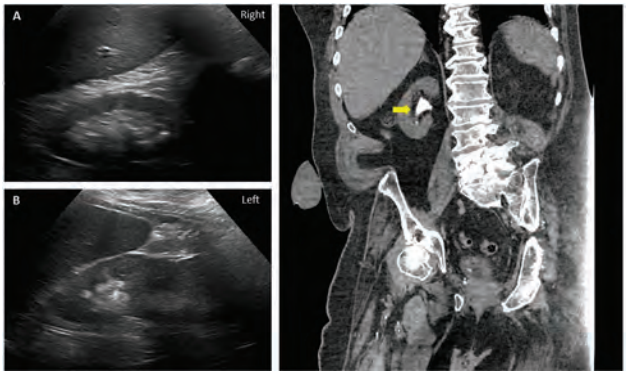
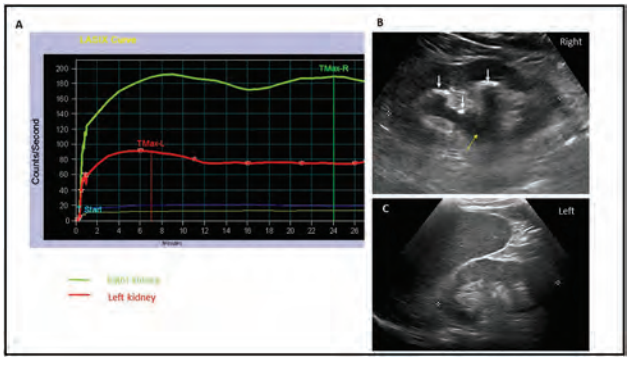
Introduction: Clinicians should be aware of the pitfalls associated with diagnostic renal imaging.

Case Description: A 63-year-old man with a history of nephrolithiasis and neurogenic bladder requiring chronic indwelling urinary catheter was admitted for urinary tract infection and acute kidney injury (AKI) with a serum creatinine of 3.6 mg/dL (baseline ~1.9-2.2). Bedside renal sonogram did not demonstrate hydronephrosis or nephrolithiasis [Figure-1A,B]. Non-contrast CT scan of the abdomen also was negative for hydronephrosis but showed a 2.6 cm staghorn-appearing calculus in the right kidney [Figure-1C]. As the patient appeared dehydrated, he was treated with intravenous hydration along with antibiotics. However, renal function continued to worsen. Because of high index of suspicion for obstructive nephropathy, a radioisotope-lasix renogram was performed, which demonstrated complete obstruction on the right [Figure-2A]. Moreover, right kidney had a differential function of ~70%, which explains AKI with unilateral obstruction. Interestingly, a repeat renal sonogram demonstrated mild hydronephrosis and calculus in the right kidney [Figure-2B,C]. Serum creatinine improved significantly after nephrostomy tube placement, reaching baseline in a few days.

Discussion: Renal imaging can be negative for hydronephrosis in the setting of volume depletion. It should be repeated after volume repletion if the index of suspicion for obstructive nephropathy is high. Radioisotope renography is beneficial in selected cases. Early diagnosis is crucial for timely intervention and prevention of irreversible renal injury.





SA-PO551

Association of Body Mass Index with Outcomes in a Critically Ill Population on Renal Replacement Therapy

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Background: The prevalence of obesity is rising in the critically ill population. Acute kidney injury (AKI) is a common complication seen in the intensive care unit (ICU) with 5% requiring renal replacement therapy (RRT). Limited data exists on the association of body mass index (BMI) and outcomes in patients on RRT in the ICU. In our study, we investigated the impact of very high and very low BMI on mortality rates.

Methods: We conducted a secondary analysis of the Acute Renal Failure Trial Network (ATN) database, which compared less-intensive to more-intensive RRT dosing in the ICU population with AKI. Weights >128.5kg, which exceeded the max dosing capabilities of the Prisma machine at the time, were excluded. In this analysis, patients were categorized into BMI quintiles; Q1 (<23.5kg/m^2, n=173), Q2 (23.5-26.2kg/m^2, n=174), Q3 (26.21-28.39kg/m^2, n=173), Q4 (28.4-32.77kg/m^2, n=174) and Q5 (≥32.78kg/m^2, n=174). Q3 was the comparison value. Our primary endpoint was 60-day mortality. Logistic regression was used to adjust for demographics, SOFA score, Charlson score and treatment strategy.

Results: Participants were mainly white (79%) males (70%) with a mean age of 60 ± 15.3 and overall mortality rate of 52%. Those in the highest quintile of BMI had a lower mortality rate (mortality rate 44% vs. 53%, 59%, 51% and 56% in quintiles 1,2,3 and 4, respectively). However, compared to quintile 3, those in the highest quintile did not have significantly lower odds of mortality in unadjusted or adjusted models. Compared to quintile 3, lower quintiles of BMI did not have a significant association with mortality.

Conclusions: Very high and very low BMI was not associated with an increased risk of mortality in critically ill patients requiring RRT. The small number of patients per quintile limited the power of this study. Larger studies analyzing the impact of BMI on mortality in critically ill patients with AKI is needed.

Multivariate analysis for 60-day ICU mortality

	Odds Ratio (95% CI)		
	Unadjusted Model 1	Model 2	
Q1	1.0 (0.69-1.6)	1.1 (0.7-1.7)	1.2 (0.7-1.9)
Q2	1.3 (0.88-2.0)	1.3 (0.9-2)	1.3 (0.8-2.1)
Q3	REF	REF	REF
Q4	1.2 (0.78-1.8)	1.2 (0.8-1.9)	1.3 (0.9-2.1)
Q5	0.7 (0.5-1.11)	0.8 (0.5-1.2)	0.8 (0.5-1.0)

Model 1: Age, race, gender

Model 2: SOFA score, Charlson score, Treatment strategy + Model 1

SA-PO552

Analysis of Survival After Initiation of Continuous Renal Replacement Therapy in Patients with Extracorporeal Membrane Oxygenation

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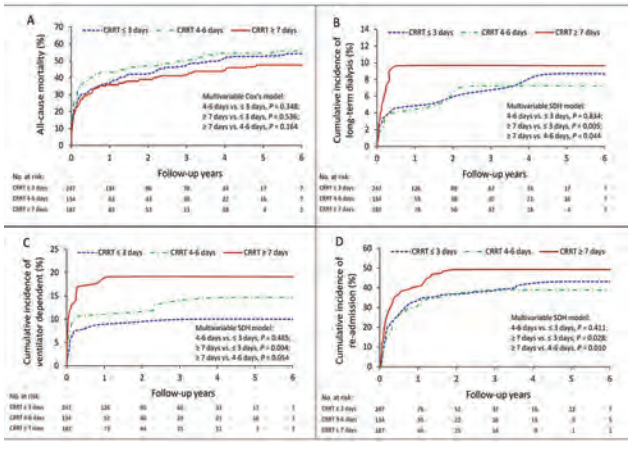
Background: No study has specifically investigated the duration of continuous renal replacement therapy (CRRT) in patients who suffered acute kidney injury during extracorporeal membrane oxygenation (ECMO) support. However, there are concerns that prolonged CRRT may be futile.

Methods: A retrospective population-based cohort study using Taiwan National Health Insurance Research Database data collected between January 1, 2007 and December 31, 2013. Patients who received ECMO and CRRT during the study period were included. We divided the patients into three groups based on the duration of CRRT received: ≤ 3 days, 4–6 days, and ≥ 7 days.

Results: The overall survival after discharge did differ significantly among the three CRRT groups. The patients who received CRRT ≥ 7 days had a higher risk of ESRD than did those who received CRRT ≤ 3 days (adjusted hazard ratio [aHR] 3.46, 95% confidence interval [CI] 1.47–8.14) and between 4 and 6 days (aHR 3.10, 95% CI 1.03–9.29). The incidence of ventilator dependent was higher in the patients with CRRT ≥ 7 days than in those with ≤ 3 days (aHR 2.45, 95% CI 1.32–4.54). The CRRT ≥ 7 days group also exhibited a higher readmission rate than did the 4–6 days and ≤ 3 days groups (aHR 1.43, 95% CI 1.04–1.96 and aHR 1.67, 95% CI 1.13–2.47, respectively).

Conclusions: Our study found similar long-term survival but increased long-term ESRD and ventilator dependency among the ECMO patients who underwent CRRT for 7 days or more. These results offer reason to be concerned that this aggressive form of life support may maintain patient survival but do so at the cost of long-term disabilities and, consequently, a lower quality of life

Funding: Private Foundation Support



SA-PO553

Platelet Decrease Following Continuous Renal Replacement Therapy (CRRT) Initiation Predicts Mortality in Patients with Severe AKI

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Background: Thrombocytopenia is common in critically ill patients and is associated with increased mortality. Recent data suggest that CRRT is associated with decreased circulating platelet levels, possibly due to consumptive platelet-filter interactions. The impact of this platelet decrease on mortality is unclear. The purpose of this study was to examine the impact of platelet decrease following CRRT initiation on in-hospital mortality.

Methods: We conducted a retrospective analysis of adult patients initiated on CRRT at the University of Colorado Hospital between July 2015 and September 2016. Patients who died < 24 hours after CRRT initiation were excluded. Patients were categorized based on the percentage decrease from pre-CRRT levels to nadir following CRRT initiation: (1) no decrease (platelet increase from baseline), (2) mild decrease (0-50% decrease), and (3) severe decrease (>50% decrease). The primary outcome was in-hospital mortality. Logistic regression was used to adjust for SOFA score (excluding platelet component), body mass index (BMI), gender, and baseline platelets.

Results: A total of 154 cases met inclusion criteria. Platelet counts decreased in 101 (65.6%) patients and 38 (24.7%) had a decrease of >50%. In-hospital mortality occurred in 72 (46.7%) patients. Patients with a severe decrease in platelets were 3.16 times more likely to die in the hospital compared to patients with an increase in platelets after adjusting for confounders (Table 1). In this study, <50% platelet decrease was not associated with mortality.

Conclusions: Platelet consumption following CRRT initiation is common, and a severe decrease is independently associated with mortality after adjusting for confounders. The mechanism of platelet decrease and its impact on mortality in patients requiring CRRT merits further study.

Funding: Other NIH Support - T32 DK 007135

Table 1. Effect of platelet decrease in final multivariate model for in-hospital mortality

Variable	OR (95% CI)	p value
Platelet Decrease > 50%*	3.16 (1.11 - 8.99)	0.003
Platelet Decrease 0-50%*	1.59 (0.64 - 3.95)	0.3

*Platelet decreases are in comparison to patients with an increase in platelets following CRRT initiation. The model was also adjusted for SOFA score (minus platelet component), Gender, BMI, and baseline platelets.

SA-PO554

Continuous Renal Replacement Therapy Is Associated with Acute Myocardial Injury in Critically Ill Patients

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Background: Intermittent renal replacement therapy induces cardiac stunning in chronic hemodialysis (HD) and acute kidney injury (AKI) patients. In chronic HD, recurrent stunning contributes to heart failure and cardiac death, with ultrafiltration and intra-dialytic hypotension being the principal determinants of this injury. Continuous renal replacement therapy (CRRT), with its lower ultrafiltration rates and improved hemodynamic profile, should protect against cardiac stunning in AKI. We assessed whether CRRT is associated with cardiac stunning in critically ill patients with AKI.

Methods: We prospectively measured cardiac function using global and segmental longitudinal left ventricular (LV) strain derived from transthoracic echocardiography in 11 critically ill patients who were started on CRRT for AKI. We compared measurements at 4, 8 and 24 hours to baseline immediately prior to initiation of CRRT, with each patient serving as their own control. We also recorded blood pressure, heart rate, dose of vasoactive medications and ICU mortality.

Results: 10/11 patients developed new regional cardiac stunning, with 8/11 within 4 hours of starting CRRT, despite stable hemodynamics. The number of affected LV segments varied from 1 to 11 (out of 12). The stunning occurred both in patients with preserved and impaired baseline cardiac function, and 7/11 patients died in the ICU.

Conclusions: Initiation of CRRT in critically ill patients with AKI is associated with cardiac stunning despite stable hemodynamics. This mechanism may explain lack of clinical benefit of CRRT over intermittent modalities and warrants further investigation to improve cardiovascular outcomes in critically ill patients with AKI.

SA-PO555

The Impact of Early Initiation of Continuous Renal Replacement Therapy in Critically Ill Patients with AKI

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Background: The acute kidney injury (AKI) in ICU patients is one of a risk factor for mortality ICU patients. Continuous renal replacement therapy (CRRT) widely used in various situation, but the optimal timing for initiation of CRRT in critically ill patients with AKI remains controversial. The purpose of this study is to investigate the impact of early, preemptive initiation on outcomes of AKI patients in ICU compare to classic, delayed initiation.

Methods: This is two center retrospective review from 2014 to 2017. Any type of stage IV cancer patients, CRRT duration less than 24 hours, end-stage renal disease with hemodialysis or peritoneal dialysis or kidney transplanted patients were excluded. The primary clinical outcome variables were 90-day Mortality and Renal recovery. Renal recovery was defined by creatinine clearance (≥15 mL/minute) with no need for renal replacement therapy at 90 days.

Results: Total 1152 patients are included, 583 patients were analyzed. Compare to delayed initiation group, early initiation group had lower eGFR(80 vs 52 mL/min/1.73m^2, p<0.001), more chronic kidney disease patients which is defined eGFR lower than 60 mL/min/1.73m^2 (59 vs 19%, p<0.001), more extra-corporeal membrane oxygenation application (1 vs 8%, p=0.005), longer survival period (42.2 vs 58.01 days, p=0.03), severe inflammatory/infectious condition (leukocytosis and higher C-reactive protein level). Ventilator care and higher APACHE-II score, classic initiation of CRRT were risk factors for non-real recovery at 90day. Elderly, CKD, underlying liver disease, higher APACHE-II score, ECMO, and delayed initiation were risk factors for 90-day mortality.

Conclusions: Delayed initiation of CRRT was independently associated with 90-day mortality. They showed lower renal recovery than the non-classic group. Delayed initiation of CRRT was independently associated with greater odds of non-renal recovery. Initiating CRRT in critically ill patients with AKI should not be delayed until fulfillment of classic indications.

SA-PO556

Modified APACHE II and SOFA Scores in Patients Requiring Continuous Renal Replacement Therapy

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Background: Based on the worse outcomes of intensive care unit patients, acute physiology and chronic health evaluation II (APACHE II) and sepsis-related organ failure assessment (SOFA) scores have been frequently used to predict mortality. Nevertheless, these prediction models have not been optimized to the patients receiving continuous renal replacement therapy (CRRT) because of acute kidney injury.

Methods: A total of 828 patients who underwent CRRT from June 2010 to December 2015 were retrospectively reviewed. All the components of APACHE II and SOFA were collected at the time of starting CRRT. End-points were 7-day and 30-day mortality. Based on the restricted cubic spline results, modified scores were assigned to each variable. Additionally, abbreviated model including the best predictable variables alone was developed after stepwise selection analysis.

Results: The prediction powers indicated by c-statistics were 0.683 and 0.668 for 7- and 30-day mortality by APACHE II; and 0.683 and 0.660 for 7- and 30-day mortality by SOFA. After modification of these models, the prediction powers increased up to 0.765 for APACHE II and 0.775 for SOFA. Using multivariate stepwise analysis, the respiratory rate, FiO2, bilirubin, pH, and inotropics used were selected in the abbreviated 7-day mortality model (c-statistics = 0.765). For a 30-day mortality model, AaDO2, respiratory rate, Glasgow coma scale, hematocrit, whole blood cells, bilirubin, potassium, and inotropics used were selected (c-statistics = 0.771).

Conclusions: Modified APACHE II and SOFA models are better than the originals in predicting mortality of patients receiving CRRT, which may ultimately be helpful in clinical practice.

SA-PO557

Hypotension within One-Hour from Starting CRRT Is an Independent Predictor for In-Hospital Mortality

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Background: In-hospital mortality in critically ill patients who require renal replacement therapy is high. Patients who receive CRRT may be at higher risk for hemodynamic instability that can have implications in terms of renal recovery and mortality.

Methods: This is a retrospective analysis of a cohort of patients admitted to the ICUs at a tertiary care hospital from December 2006 through November 2015 who underwent CRRT. The primary outcome was in-hospital mortality. Multivariate logistic regression was performed to identify independent predictors of in-hospital mortality. Hypotension within the first hour of CRRT initiation was defined as: MAP <60 mm Hg, SBP <90 mm Hg or a decline in SBP >40 mm Hg from baseline, a positive fluid balance more than 500 ml or increased vasopressor requirement.

Results: The analysis included 1,743 patients, 345 (19.8%) with ESRD and 1,398 (80.2%) with AKI. The median age was 63 (IQR 53-73) years with 699 (40%) female, median Charlson comorbidity index 5 (IQR 3-7) and median SOFA on the day of CRRT initiation was 12 (IQR 9-14). Overall in-hospital mortality occurred was 50%. Hypotension within one hour of CRRT initiation occurred in 64% of the patients. Predictors of in-hospital mortality in univariate analysis included: SOFA score (OR 1.13 per 1 unit increase, 95% CI:1.10-1.16), mechanical ventilation (OR 1.6, 95% CI:1.2-2.1), hypotension within 1 hour (OR 1.6, 95% CI:1.3-1.9), AKI compared to ESRD (OR 1.9, 95% CI:1.5-2.5) and modified shock index (OR 2.1 per 1 unit increase, 95% CI:1.7-2.7). Hypotension within one hour of CRRT initiation remained an independent predictor of in-hospital mortality (OR 1.45, 95% CI:1.15- 1.82, p=0.001), after adjusting for age, gender, SOFA score, mechanical ventilation, fluid balance between ICU admission and CRRT initiation, modified shock index, Charlson comorbidity index, AKI vs ESRD, ICU type, creatinine closest to CRRT initiation and ICU day number when CRRT was initiated.

Conclusions: Hypotension occurs frequently in patients receiving CRRT despite being chosen as a modality with better hemodynamic tolerance. Hypotension during the first hour after initiating CRRT is a significant independent risk factor for in-hospital mortality. Further studies are required to help understand this phenomenon given its implications for in-hospital mortality.

SA-PO558

Predictive Factors for Successful Discontinuation of Continuous Renal Replacement Therapy in AKI

Song in Baeg, Hyo jin Boo, Minjung Kim, Eun jeong Lee, Jung eun Lee, Wooseong Huh, Dae Joong Kim, Yoon-Goo Kim, Ha Young Oh, Hye Ryoun Jang. *Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.*

Background: Although continuous renal replacement therapy (CRRT) is the standard treatment for severe acute kidney injury (AKI) in critically ill patients, there is no practical consensus for discontinuing CRRT. In this retrospective study, predictive factors for successful discontinuation of CRRT was investigated.

Methods: Adult patients (≥18 years) who received CRRT at Samsung Medical Center from June 2007 to June 2017 were included (n=4166). Patients with preexisting end stage renal disease (ESRD), patients who progressed to ESRD within 1 year after CRRT discontinuation or died within 7 days were excluded. Successful discontinuation of CRRT was defined as no requirement of RRT for 7 days after discontinuing CRRT. Patients were divided into the failure group and the success group. Clinical information and laboratory results were collected via electronic medical records.

Results: A total of 1158 patients were analyzed. There were no differences in comorbidities. The duration of CRRT was longer in the failure group. Mean arterial pressure (MAP) on discontinuation day (D0) was lower in the success group (failure vs. success, 80.86±12.56 vs. 78.95±12.51 mmHg, p=0.010). Urine output on the day before discontinuation (D-1) (140 vs. 648 mL/day, p<0.001) and D0 (253 vs. 1298 mL/day, p<0.001) and the proportion of patients who received vasopressors on D-1 (26.6% vs. 43.1%, p<0.001) and D0 (19.1% vs. 34.8%, p<0.001) were higher in the success group. Serum potassium on D0 was lower in the success group (4.02±0.45 vs. 3.88±0.46 mmol/L, p<0.001). Multivariable analysis showed that urine output on D0 (odds ratio [OR], 1.621; 95% confidence interval [CI], 1.468 to 1.789; p<0.0001), difference in HCO_3 between D0 and D-1 (OR, 1.070; CI, 1.009 to 1.135; p=0.0231) and vasopressor use on D0 (OR, 2.306; CI, 1.348 to 3.946; P=0.0023) were significant predictive factors for successful discontinuation of CRRT. MAP on D0 (OR, 0.980; CI, 0.969 to 0.992; p=0.0007) and serum potassium on D0 (OR, 0.592; CI, 0.732 to 0.809; p=0.001) were also significant predictive factors.

Conclusions: Our study showed that greater urine output, maintenance of adequate blood pressure with vasopressors, and lower normal range of serum potassium on discontinuation day were associated with successful discontinuation of CRRT.

SA-PO559

CVVH Yields Better Renal Outcomes Than Intermittent Hemodialysis Among Traumatic Intracranial Hemorrhage Patients with AKI: A Nationwide Population-Based Retrospective Study in Taiwan

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Background: Traumatic intracranial hemorrhage (TICH) patients with acute kidney injury (AKI) were reported to have a high mortality rate. Renal replacement therapy (RRT) is indicated for patients with severe kidney injury. This study aimed to compare the effects of different RRT modalities in terms of chronic dialysis rate among adult TICH patients with AKI.

Methods: A retrospective search of computerized hospital records from 2000 to 2010 for patients with a discharge diagnosis of TICH was conducted to identify the index cases. We collected the data of TICH patients with increased intracranial pressure combined with severe AKI who received intermittent hemodialysis (IHD) or continuous veno-venous hemofiltration (CVVH) as RRT. The outcome was dialysis dependence between 2000 and 2010.

Results: From a total of 310 patients who were enrolled in the study, 134 (43%) received CVVH and 176 (57%) received IHD. The risk of dialysis dependency was significantly lower in the CVVH group than in the IHD group (adjusted hazard ratio: 0.368, 95% CI, 0.158–0.858, P = 0.034). Diabetes mellitus and coronary artery disease were risk factors for dialysis dependency. CVVH compared with IHD modality was associated with lower dialysis dependency rate in TICH patients combined with AKI and diabetes mellitus and those with an injury severity score (ISS) ≥16.

Conclusions: CVVH may yield better renal outcomes than IHD among TICH patients with AKI, especially those with diabetes mellitus and an ISS ≥16. Therefore, the beneficial impact of CVVH on TICH patients needs to be clarified in a large cohort study in future.

SA-PO560

AKI in Patients Requiring Extracorporeal Membrane Oxygenation

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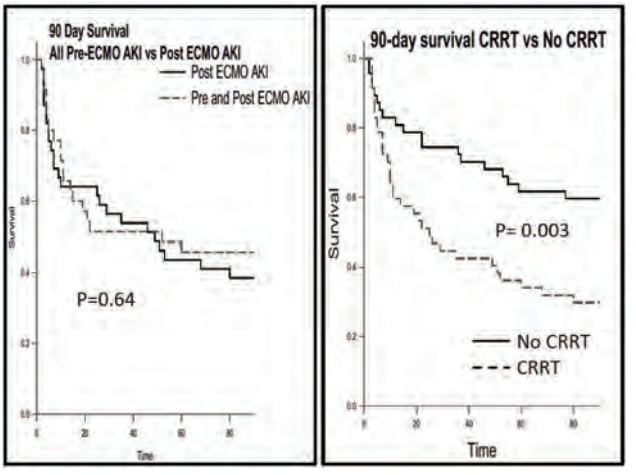
Background: There is limited published data on the outcomes in those with AKI after extracorporeal membrane oxygenation (ECMO) cannulation.

Methods: We performed a single center retrospective study of patients who underwent ECMO cannulation between 1/2015 and 7/2017. We excluded patients with pre-existing End Stage Renal Disease (ESRD) and those who died within 24 hours of ECMO initiation. AKI was defined by the KDIGO criteria within 7 days of ECMO cannulation. Survival analyses were performed using the log-rank test.

Results: We found 117 patients but excluded 23(18 of whom died within 24 hours of ECMO). Of the remaining 94 patients 76(81%) received veno-arterial (VA-ECMO) and 18 received Veno-venous (VV-ECMO). Of the 94 patients, 13(13.8%) did not experience AKI during their entire hospital stay. AKI prior to ECMO cannulation occurred in 42(44%) patients and 39(41%) patients only developed AKI after ECMO. Of those with AKI(n=81), 16 developed Stage 2 AKI, 51 developed Stage 3 AKI of which 47(50%) received renal replacement therapy (RRT). AKI rates were not different across VA and VV ECMO(p=0.15). Patients with any AKI were more likely to die at 30 and 90 days compared to those without any AKI(p<0.01 for both). Figure A demonstrates no difference in 90 day mortality between those with pre-ECMO AKI compared to those with post-ECMO AKI (p=0.64). Those who did receive RRT(n=47) did not have significantly different pHs, hemoglobin or other pre-ECMO co-morbidities (CKD, CHF, Diabetes) compared to those without RRT(n=47). In a multivariate model the presence of pre-ECMO vasopressors was an independent predictor for the need for RRT(OR(95%CI) 4.59(1.10-19.2)p=0.037). Patients requiring RRT had increased 90-day mortality compared to those without RRT(p<0.003) Figure B.

Conclusions: AKI is common in the setting of ECMO. While there was no difference in mortality in those with pre versus post ECMO AKI, AKI requiring RRT significantly decreases patient survival at 90 days.



SA-PO561

Inhibition of PARP1 Attenuates Rat Renal Ischemia Reperfusion Injury

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Background: Renal ischemia reperfusion injury (IRI) generates superoxide and other reactive species and induces PARP1 activation to repair ROS-mediated DNA strand breaks. However, PARP1 activation depletes NAD^+ and ATP, and promotes pro-inflammatory signal transduction, all of which can exacerbate IRI. We hypothesized that inhibiting PARP1 would decrease/prevent NAD^+ depletion and reduce IR-induced acute kidney injury (AKI).

Methods: We evaluated the ability of a novel and selective PARP1 inhibitor, Cmpd A to boost NAD^+ and mitochondrial respiration in control and cisplatin challenged human proximal tubule cells (PTC). Sprague-Dawley rats underwent a 50 minute bilateral IR and were administered Cmpd A (or vehicle), twice daily at 0.1, 0.3, 1, 5, or 15 mg/kg by intravenous injection for 2 days, beginning at 4 hours post reperfusion. Cmpd A activity was assessed by measuring renal PAR levels, NAD^+ and its breakdown products, by ELISA or mass spectrometry. Renal injury biomarkers were measured in plasma at 24 and 48 hr post reperfusion and tubular injury was evaluated by histopathology. Gene expression analysis for inflammatory mediators and *Vegfa* were assessed using Nanostring technology.

Results: Cmpd A treatment increases NAD^+ levels by 35% and enhances mitochondrial respiration under normal PTC culture conditions while preventing nephrotoxin-induced NAD^+ depletion when PTC are treated with cisplatin. In the rat model of IR-AKI, Cmpd A lowers plasma creatinine and BUN dose dependently at 24 and 48 hr post injury. This translates to improved renal function via increased creatinine clearance and normalization of fractional excretion of Na^+ (FENa). Assessment of kidney histopathology at 48 hr post reperfusion revealed that Cmpd A normalizes renal tubular architecture. In addition, Cmpd A treatment reduces IR-induced upregulation of inflammatory mediators and restores the downregulation of *Vegfa* gene expression.

Conclusions: Dosing of a selective PARP1 inhibitor after an ischemic AKI event in rats recovers renal and tubular function. Mechanistically, our data suggest that this effect is mediated by a reduction of pro-inflammatory signaling, preservation of *Vegfa* and increase of NAD^+ levels.

Funding: Commercial Support - Astellas

SA-PO562

The Protective Effect of Klotho Against Contrast-Associated AKI via the Anti-Oxidative Effect

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Background: Contrast-associated acute kidney injury (CA-AKI) is defined as AKI caused by the supplementation of iodinated contrast agents, and oxidative stress is one of its main factors. Klotho, an anti-aging gene, shows anti-oxidative activity and is expressed in renal tubular cells. We investigated the protective effect of klotho against CA-AKI via the anti-oxidative effect.

Methods: We used NRK-52E cell lines and iopamidol as the contrast agent. Experiments were performed after cell cultures were divided into one of three groups: the control, iopamidol, and iopamidol+recombinant klotho (rKL) groups. Moreover, the siRNA-mediated knockdown of *klotho (siklotho)* was also done to reveal the endogenous klotho effect. Cell viability and oxidative stress were measured, and real-time PCR and western blotting were performed. We also designed a CA-AKI mouse model with ketorolac, L-NAME and iopamidol, and performed experiments similar to our *in vitro* experiments.

Results: The viability of the NRK-52E cells significantly decreased, but oxidative stress significantly increased after 200 mgI iopamidol was supplemented for 1h compared to the controls. Protein and mRNA expressions of klotho also significantly decreased, while apoptotic markers (Bax/Bcl_2, cleaved caspase3) increased significantly after iopamidol injection. However, the decrease in cell viability after iopamidol supplementation was significantly attenuated after the cells were exposed to rKL, and rKL mitigated the elevated apoptotic markers and oxidative stress under iopamidol injection. Additionally, the apoptotic markers and oxidative stress were significantly upregulated in the group of iopamidol-treated *siklotho* compared to the iopamidol-treated NTC group. Our *in vivo* study results showed similar trends to our *in vitro* experiments.

Conclusions: This study showed that klotho can protect against CA-AKI via the anti-oxidative effect. These findings provide new insight into the mechanisms behind the protective effect of klotho in CA-AKI.

Funding: Government Support - Non-U.S.

SA-PO563

Increased Soluble Guanylyl Cyclase Activity in Ischemia/Reperfusion Induced AKI Suppresses PGC-1a and Mitochondrial Biogenesis

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Background: Acute Kidney Injury (AKI) can result from numerous causes such as ischemia/reperfusion (I/R) injury. We have shown that mitochondrial biogenesis (MB) is persistently suppressed following diverse injuries and that stimulation of MB, by targeting PGC-1a, the master regulator of MB, promotes recovery of renal function. Soluble guanylyl cyclase (sGC) is a heterodimer that catalyzes the production of cGMP from guanosine triphosphate (GTP). cGMP can be increased by sGC activity or by pharmacological inhibition of phosphodiesterases (PDE) 3 and 5, enzymes that degrade cGMP. Although inhibition of PDE3 and 5 induces MB and promotes renal recovery in AKI models, the role of sGC in AKI has received minimal attention.

Methods: Mice underwent bilateral I/R and were euthanized 24 h later. Kidney function was determined by serum creatinine (SCr). Cell signaling was measured using RT-qPCR and immunoblot analysis. sGC enzyme activity was determined by measuring cGMP in renal cortical homogenates.

Results: SCr increased 10-fold to 1.8 mg/dL 24 h after I/R injury. While renal cortical protein expression of the sGC subunits was not altered, sGC activity increased 1.6-fold in I/R mice compared to sham mice. Increased cGMP activated protein kinase G (PKG). In turn, phosphorylated p38, a target of PKG, increased in I/R mice. Phosphorylated FOXO1, a target of activated p38, also increased, inhibiting FOXO1 translocation into the nucleus. PGC-1a mRNA, a transcriptional target of FOXO1, decreased 24 h after I/R.

Conclusions: I/R injury initiates a signaling pathway comprised of sGC-cGMP-PKG-p38-FOXO1-PGC-1a and resulted in decreased PGC-1a transcription. These results are consistent with previous findings demonstrating decreased PGC-1a in various forms of AKI and the suppression of MB.

Funding: Other NIH Support - National Institutes of Health National Institute of General Medical Sciences, Veterans Affairs Support

SA-PO564

Adipose Stem Cell-Derived Exosomes Afford Effective Survival Benefits and Functional Rescue from Severe, Progressive IRI-Induced AKI in Rats

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Background: Bone marrow and Adipose-derived Mesenchymal Stem Cells (M/ASCs) are effective for prevention of Acute Kidney Injury (AKI). Yet when MSCs are given 48 hrs post-insult, a time at which severe clinical AKI is diagnosed and when no rescue therapy is currently available, they are ineffective or potentially damaging because the introduction of large cells (~50μm) into the compromised microvasculature may impair renal function. M/ASCs' renoprotection is mediated by their paracrine release of anti-inflammatory and trophic cytokines and their exosomes. Exosomes signal, post uptake by target cells, through the lateral transfer of mRNAs, miRNAs, DNA, proteins, and lipids. Since ASC-derived exosomes can prevent AKI we tested whether their small size and ability to move through the compromised renal microvasculature might allow them to provide effective rescue therapy for late stage AKI.

Methods: Exosomes from Sprague Dawley (SD) rat ASCs were isolated post 24 hr culture in SFM, purified using the ExoQuick-TC kit, and characterized for size, protein and gene expression of relevant markers. I/R AKI (52 min bilateral renal pedicle clamp) was induced in female SD rats. If the SCr value on D2 was greater than that on D1, then rats were administered via left carotid artery either 1 ml of Vehicle (PBS; n=8), Exosomes (200 μg protein-equivalent; ~4x10e10 exosomes; n=6), or ASCs (2x10e6 ASCs; n=6) on D3.

Results: 1e6 ASCs secrete ~ 4.9x10e10 exosomes and other microvesicles (mode 136.7 nm) and >95% express CD44 and CD29, and carry mRNAs of renoprotective genes expressed in ASCs. While both ASC and exosome administration improved survival over PBS, renal function only showed significant and sustained improvement in exosome-treated rats.

Conclusions: ASC-derived exosome therapy 3 days post progressive AKI, when renal blood flow is significantly impaired and when most clinical AKI is diagnosed, is superior to ASC therapy, likely due to their ability to deliver their renoproetective cargo into the compromised renal microcirculation. These data have, we posit, significant translational promise for the development of an effective rescue therapy for advanced AKI.

Funding: Commercial Support - SCT

SA-PO565

Transfer of Healthy Isolated Mitochondria in Established Injury Reduces Progression to Fibrosis

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Background: Ischemia induces altered bioenergetics with increased mitochondrial swelling and reactive oxygen species (ROS) and ultimately degradation of cellular function. Therapeutic interventions that target to improve mitochondrial health to repair, reprogram or replace mitochondria to restore respiratory functions are beneficial for prevention and/or treatment of established disease.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 mice were i.v. injected with isolated mitochondria (50mcg, from healthy non-ischemic mouse liver). 1d, 3d or 5d after unilateral IRI. Nephrectomy of contra-lateral control kidney was done on day 13. Change in fibrosis genes were measured by RTPCR and histology changes with Masson trichrome and picrosirius red were done on day 14. For *in vitro* studies, PT cells (TKPTS) were treated with 10 or 20 mcg of isolated mitochondria 1d prior to analysis that included measurement of ATP levels, mitochondrial functions (Seahorse analyzer), cytokines (RTPCR), immunofluorescence microscopy (uptake efficiency) and flow cytometry (mitotracker dyes).

Results: *In vivo* studies demonstrated treatment of mice with 50 mcg of mitochondria at 1d, 3d or 5d after IRI significantly protected compared to vehicle treated mice after IRI [Day 14 PCr (0.6±0.04 (+1d) vs 0.68±0.18 (+3d) vs 0.57±0.18 (+5d) vs 1.54±0.16), $p<0.05$]. Transfer of labeled isolated mitochondria (mitotracker dye) signal was found in spleen (in macrophages) and kidney (in PT, identified with anti-CD13 antibody [labels brush border]). The +3d mitochondria treated kidneys had significantly lower levels of Acta and Col3a1 and significantly higher PGC1α gene expression compared to vehicle treated mice at day 14. *In vitro* studies demonstrate that treatment of TKPTS with mitochondria had significantly higher levels of ATP, higher basal oxygen consumption rate and spare respiratory capacity measured by Seahorse analyzer.

Conclusions: Our current study demonstrates that up take of healthy mitochondria by PT helps maintain bioenergetics through upregulation of mitochondria biogenesis gene, PGC1α. Treatment to mice with established AKI with mitochondria attenuates progression to fibrosis compared to vehicle treated mice. Mitochondria could be used as a therapeutic modality to lessen progression of AKI to CKD.

Funding: Other NIH Support - ASN Foundation Grant

SA-PO566

Kidney Injury Under Oxidative Stress Release CD36 and CD47 Microparticles

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Background: Kidney epithelial cell damage is the major cause of acute kidney injury (AKI). Thrombospondin 1 (TSP-1) is released by renal epithelial cells and mediates kidney damage in murine ischemia reperfusion injury (IRI). TSP-1 exerts its inflammatory modulating effects through signaling of CD36 (pro-inflammatory) and CD47 (anti-inflammatory) ligands. Given that CD36 reduces angiogenesis, and stimulates VEGF induced migration and apoptosis, whereas CD47 stimulate angiogenesis, these ligands may play a role in epithelial to endothelial cross-talk. We hypothesized that in both *in vivo* murine models of IRI and *in vitro* models of oxidative stress to human renal epithelial cells (h-RPTEC), CD36 and CD47 proteins will be released as MP significantly when compared to control.

Methods: h-RPTEC line was used and oxidative stress (induced by adding 0.03 mM of H_2O_2 for 1hr) was evaluated for MP release and apoptosis compared to controls. IRI was performed in C57BL/6 mice by renal pedicle clamp for 30 minutes followed by reperfusion compared to sham. Animals were euthanized at 48 hrs. Histology was performed by standard techniques to evaluate kidney damage. Citrate poor plasma was collected at 0, 12, 48 hrs to measure urea (BUN). MP were measured with flow cytometry and were reported at 10^5 /ml and analyzed by flow jo software. Unpaired t test Welch's correction were used for comparisons.

Results: h-RPTEC contained CD36 and CD47 receptors in the cellular membrane, confirmed by immunohistochemistry. Upon exposure to H_2O_2, cell viability study showed 25% apoptotic, 15% in necrotic and 60% viable. A a significant increase of release of MP was observed for CD36 vs control (2.7 $X10^5$ MP/ml vs. 0.73 $X10^5$ MP/ml; p=0.001); and for CD47 vs control (31.84 10^5 MP/ml vs 2.51 10^5 MP/ml; p=0.001). For *in vivo* studies, compared to sham, IRI mice showed that MP containing CD36 were released at 12 hr and remained elevated at 48 hr. In contrast, CD47 showed an increase at 12 hrs and returned towards baseline by 48 hr. Analysis of percent expression showed that CD36 expression increased with time compared with CD47.

Conclusions: In murine and in vitro models of oxidative stress CD36 and CD47 are released as MP. Given the role of TSP-1 and other thrombomodulins in AKI, MP may serve as ligands to both potentiate epithelial cell injury as well as mediate cross-talk between epithelium and endothelium.

Funding: Clinical Revenue Support

SA-PO567

Microparticles Can Phenotype Ischemic and Nephrotoxic AKI

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Background: Acute tubular necrosis is the major cause of acute kidney injury (AKI), occuring due to ischemia reperfusion injury (IRI) or nephrotoxicity (NT); however, it cannot be differentiated by biochemical or histological parameters. Although biomarkers allow earlier identification of AKI, they cannot discriminate cause-specificity, leading to impediment in translating novel therapies. Our prior work confirmed that CD10, CD13 and CD146 proteins on renal epithelial cells are released as microparticles (MP) upon exposure to oxidative or inflammatory stress. We evaluated whether these MP can discriminate IRI or NT in murine models.

Methods: In C57BL/6 mice, IRI was performed by clamping both renal pedicles for 30 minutes followed by reperfusion and NT was induced by injecting intraperitoneal (IP) Cisplatin at 20 mg/kg. Sham mice underwent surgery without clamp in IRI and IP normal saline in NT. Mice were euthanized at 48 hrs and examined by standard techniques for renal histology. Citrate poor plasma was collected at 0, 12, 48 hrs. Blood urea nitrogen (BUN), neutrophil gelatinase associated lipocalin (NGAL); and MP containing CD10, CD13 and CD146 were measured using flow cytometry and analyzed by flow jo software. MP were expressed as 10^5/ml, and compared within each model over time, and across models by Chi-square tests.

Results: AKI was confirmed in IRI and NT samples by histology, BUN and NGAL levels at 48 hrs. In IRI (48 hrs), CD10 and CD13 MP increased by 1.77 and 1.5 fold respectively, but CD146 declined by 1.7 fold from baseline. In contrast, NT model showed decline of MP quantity at 48 hrs relative to baseline in CD10, CD13 and CD146 by 1.5, 1.5 and 3.6 fold respectively. When examined across the models, then proportion of MP released at 48 hrs in IRI were 64% CD10, 6% CD13 and 30% CD146. Interestingly NT model showed distinctly different proportions: 6% CD10, 18% CD13 and 76% CD146 quantitatively. ($p<0.0001$ for comparison across models)

Conclusions: Despite similar biochemical, histological and biomarker parameters, MP quantity changed over time differently in each model. More importantly, the pattern of MP proportions almost switched across IRI and NT models, allowing discrimnation of ischemic and toxic cell injury. MP measured in plasma can phenotype AKI based on cause-specificity and can lead to development of novel diagnostic or therapeutic strategies.

Funding: Other NIH Support - Intramural funds, Clinical Revenue Support

SA-PO568

β-Hydroxybutyrate Attenuates Renal Ischemia-Reperfusion Injury Through Its Anti-Pyroptotic Effects via Epigenetic Mechanism

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Background: An endogenous ketone, β-hydroxybutyrate(β-OHB) is used as an energy source in various organs including kidney and has therapeutic benefits against stress conditions. In this study, we evaluated its protective effects and potential mechanisms in renal ischemia/reperfusion injury(IR).

Methods: Male C57BL/6J mice undetook heminephrectomy and separated into 4 groups: saline-treated sham-operated mice (Sham: n=6), β-OHB-treated sham mice (Sham+β-OHB ; n=6), saline-treated mice with IR (IR; n=8), β-OHB-treated mice with IR (IR+β-OHB; n=8). In IR injury mice were subject to clamping of both renal arteries and veins for 45 min and to reperfusion. β-OHB was administered continuously by osmotic mini-pump at the dose of 8 mg/h. Kidneys were harvested 24 h after IR injury, and functional and molecular parameters were evaluated. In vitro studies, HK-2 cells were incubated for 1 h with mineral oil to induce hypoxic injury, and incubated for 24 h after medium replacement. These HK-2 cells were treated with various doses of β-OHB and molecular parameters were evaluated.

Results: In IR mice, blood urea nitrogen, serum creatinine levels, and renal tissue injury scores were significantly higher than those in control mice. These values were significantly lowered in IR+β-OHB group. β-OHB treatment significantly reduced the TUNEL-positive cell number and increased FOXO3 and its downstream target molecule, apoptosis repressor with caspase recruitment domain (ARC) expressions. Although β-OHB unchanged the apoptotic markers, it decreased the expressions of caspase-1, the proinflammatory cytokines interleukin (IL)-1β and IL-18 in IR-injured kidneys, indicating that β-OHB blocked pyroptotic cell death rather than apoptotic cell death. In HK-2 cell subject to hypoxic insult, β-OHB reduced the number of cell death through the inhibition of pyroptosis pathway in FOXO3-dependent fashion. Histone acetylation deceased in IR mice and in hypoxic HK-2 cells through the inactivation of histone acetyltransferase activity. This reduction was ameliorated by β-OHB through the inactivation of histone deacetylase.

Conclusions: β-OHB attenuates renal IR injury by its anti-pyroptotic effect through its epigenetic effects on FOXO3 expression.

SA-PO569

Regulation of Fibronectin Splicing with Antisense Oligonucleotides in an Aristolochic Acid Model of AKI to CKD

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Background: Extra Domain A Fibronectin (EDA+FN) is an active glycoprotein present at sites of fibrosis and is produced through post transcriptional alternative splicing of mRNA. Bonventre et al have previously described an early peak at 3 hours with significant fall in EDA+FN at 6 weeks post ischaemia reperfusion injury. We developed a murine model of aristolochic acid nephropathy (AAN) exhibiting acute to chronic progression and investigated the effects of RNAse H-Independent ASO on EDA+FN expression and subsequent impact on markers and mediators of tubulointerstitial fibrosis.

Methods: In a short model of AAN, CD1 mice aged 10 weeks received subcutaneous (SC) PBS (n=6), RNAse H-independent negative control (NC-ASO, n=6) or target antisense (T-ASO, n=6) at 50mg/kg at day -1 followed by one dose of intraperitoneal (IP) AA 3.5mg/kg on day 1 for each arm, mice culled at day 3. In the long model they were injected with IP AA 3.5mg/kg on days 1 and 5 followed by SC PBS (n=6) or 50mg/kg NC-ASO (n=12) or T-ASO (n=12) at day -1 and 3 and then weekly injections until day 96. Whole kidney tissue was extracted and RNA analysis undertaken using RT PCR.

Results: In the short model KIM1, CD68 and EDA + FN mRNA expression was significantly increased at 48 hr post AA compared to Day 0 ($p<0.05$). T-ASO reduced EDA+FN mRNA significantly compared to NC-ASO ($p<0.0001$) with no effect on CD68 or KIM1. TGFβ1 expression was downregulated by T-ASO ($p<0.05$). In PBS arm of the long model at day 96, compared to day 0 there was statistically significant increase in mRNA expression of EDA+FN, EDA-FN, TGFβ1, LTBP1, MMP2, MMP9, αSMA, KIM1 and Coll1a1. At day 96, T-ASO resulted in significant knock down of mRNA expression of EDA+FN, TGFβ1and LTBP1 compared against NC-ASO with no effect on expression of αSMA, Coll1a1, MMP2 or KIM1.

Conclusions: In this model of AAN we have demonstrated increased mRNA expression of EDA+FN in the early phase but also sustained at day 96. We have demonstrated the ability to knockdown EDA+FN mRNA at both time points and also noted knockdown of TGFβ1 and LTBP1 mRNA with our target antisense suggesting a functional interaction. Antisense did not have an effect on markers of AKI or other mediators of fibrosis. Further analysis of samples with immunohistochemistry will help determine whether T-ASO has an impact on attenuation of fibrosis in this model.

SA-PO570

Inhibition of CXCR3 Expression Through Blockade of STAT3 Alpha Signaling Down-Regulates Inflammation of Renal Ischemia-Reperfusion Injury

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Background: Signal transducer and activator of transcription 3 (STAT3) is the main mediator of interleukin 6 (IL-6)–type cytokine signaling. Although it exists in two isoforms: the full-length STAT3α and the truncated STAT3β, their role in acute kidney injury is not clarified. We investigated their relative function through inhibiting STAT3α in ischemia-reperfusion (IR)-induced renal inflammation.

Methods: IR injury was induced in B6 wild type mice. Stattic (a nonpeptide small molecular inhibitor of STAT3 activation and dimerization) was treated 3 hours prior to IR injury. We quantified intrarenal cytokine expression using real-time PCR and performed FACS analysis. We cultured human tubular epithelial cells (TECs) in hypoxic condition and evaluated the effect of Stattic treatment. We detected the isoforms of phosphorylated STAT3 using western blot analaysis.

Results: IR injury produced more severe tubular damage in control group than in Stattic-treated mice (serum creatinine, 2.2±0.1 versus 1.6±0.1 mg/dL, $p<0.05$). Although inflammatory cytokines/chemokines, such as IL-6, total STAT3, STAT3α, CXCR3, IL-10 and TGF-β were increased by IR injury in control group, they were attenuated in Stattic-treated mice. Apoptosis of TECs and infiltration of mononuclear cells and macrophages were decreased and the expression of STAT3α as well as total STAT3 was reduced in Stattic-treated mice. These findings were supported by in-vitro study with human TECs. Whereas the level of pSTAT3α was elevated in the hypoxia-conditioned TECs and it was decreased in Stattic-treated cells, the level of pSTAT3β was not changed in both cell groups. The expression of CXCR3 was decreased in accordance to the STAT3α decrease and the supernatant levels of IL-6 and IL-8 were decreased in Stattic-treated cells.

Conclusions: We demonstrated that the activation of STAT3 is associated with progression of IR injury and the α-isoform may contribute as major player. These mechanisms of STAT3/CXCR3 signaling according to each isoforms suggest a novel strategy for management of AKI with STAT3 inhibitor.

SA-PO571

PHD Inhibition Reduces Reactive Oxidative Stress in In Vitro Ischemia Model

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Background: Hypoxia-inducible factor (HIF) is widely accepted to mediate the protection by hypoxic preconditioning in both *in vitro* and *in vivo* ischemia models but the underlying mechanism remains unknown. Prolyl hydroxylase domain proteins (PHDs) serve as main HIF regulator via hydroxylation of HIF-α leading to its degradation. Several PHD inhibitors, including enarodustat are now under clinical trials as treatment for renal anemia and the beneficial effect might go far beyond.

Methods: We investigated the role of PHD inhibition in oxygen-glucose deprived (OGD) model of human renal tubular cells (HK2) as an *in vitro* model of renal ischemia. Enarodustat or siRNA knockdown of PHD isoforms was used to study the impact of PHD inhibition on cytoprotection and ROS. Cell viability and ROS were measured using the Muse™ Count & Viability Assay Kit and Oxidative Stress Kit according to the manufacturer's instructions. mRNAs for antioxidative genes (GPX1, catalase, SOD1, SOD2, HO-1 and NQO1) were quantified by real-time PCR. Specific effects of HIF isoforms and respective antioxidative genes were studied using siRNA knockdown series. The role of autophagy was evaluated with Atg7-KO cells.

Results: Enarodustat treatment and siRNA knockdown of PHD2, but not of PHD1 or PHD3, significantly increased cell viability and reduced reactive oxygen species (ROS) levels by HIF stabilization. These effects were offset by simultaneous knockdown of HIF-α isoforms. HIF-1α alone could confer protection in both viability and ROS levels, while the contribution of HIF2 was only evident in combination with HIF1, with a larger role in viability. As candidate mechanisms for ROS elimination, we examined the role of autophagy and antioxidants. Autophagy reduces ROS by degrading damaged mitochondria in several models. However, in our OGD model cell death and ROS were not increased in Atg7-KO cells. Next we measured the mRNA levels of antioxidants and among them superoxide dismutase 2 (SOD2) and heme oxygenase-1 (HO-1) are significantly increased in enarodustat-treated cells. While SOD2 knockdown had little effect, HO-1 knockdown partially abrogated the cytoprotection and ROS reduction by PHD inhibition.

Conclusions: HIF stabilization by PHD inhibition increased cell viability and decreased ROS levels, and HO-1 partially mediated the effect.

SA-PO572

Hypoproteic Diet During Pregnancy and/or Lactation Differentially Affects the Response of the Offspring to an Episode of AKI

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Background: Protein restriction during pregnancy induces morpho-functional alterations related to deficient nephrogenesis. We studied the renal functional and morphological significance of protein restriction during pregnancy (Preg), lactation (Lact) or both, in the adult stage of the offspring and their repercussion on the AKI severity.

Methods: Female rats were randomly assigned to the following groups: C = standard diet, (SD) during Preg and Lact; CR = SD during Preg and protein restriction diet (PR) during Lact; RC = PR during Preg and SD during Lact and RR = PR during Preg and Lact. Three months after birth, at least twelve male offspring of each group underwent randomly to bilateral renal ischemia for 45 min (IR) or sham surgery. Thus, eight groups were studied 24 h after reperfusion: C, C+IR, CR, CR+IR, RC, RC+IR, RR and RR+IR.

Results: The CR, RC, and RR groups exhibited a significant reduction by ≈ 15% in the nephron number that was associated with a reduction in renal blood flow (RBF). In spite of this, glomerular hypertrophy was observed together with a significant reduction in endothelin, angiotensinogen and their receptors, as well as catalase and GPx mRNA levels. In the next table appears the % change in renal function and vasoactive factors mRNA levels after the IR injury compared to their respective control group.

Conclusions: During basal conditions, the lesser nephrons observed in the offspring of protein-restricted mothers was associated with glomerular hypertrophy and reduced expression in vasoconstrictor factors. The ischemic insult in these groups induced a differential vasoconstrictor response that allowed a faster recovery in RBF, as compared to control group. These results suggest that CR, RC and RR groups respond better to an ischemic insult and most likely to the long-term consequences of AKI.

Funding: Government Support - Non-U.S.

	mRNA levels									
Group	δ RBF	δ Protei-nuria	δ Endo-thelin	δ ETa	δ ETb	δ Angitensi-nogen	δ AT1	δ eNOS	δ Cat	δ GPX
C	-41±3*	440±61*	46±40	7±4	-58±15*	-67±14*	-76±2*	51±28	-50±18*	-69±6*
CR	-22±9	250±81*	107±34	188±39*+	-26±14	501±217+	-23±16+	73±13	-52±9*	-36±10*
RC	1±8+	193±47*+	162±65	54±35	-20±14	2612±293*+	39±17+	17±16	-63±9*	-23±12+
RR	3±8+	112±23+	172±46	119±48	-10±13	-95±3.6	16±12+	24±41	-64±8*	-36±15

Prot = proteinuria, Cat=catalasa, GPX= Glutathione peroxidase.
* $p<0.05$ vs. their respective group without IR. + $p<0.05$ vs. control group.

Percentage change in functional, vasoactive factor and antioxidant response against an AKI episode

SA-PO573

Hypoxia Induces Ligand-Receptor Interactions to Mediate Exosome Targeting to Endothelial Cells in AKI

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Background: Intravenous (i.v.) injection of exosomes derived from human endothelial colony forming cells (ECFCs) leads to selective targeting of the kidneys after ischemic injury in mice, along with increased miR-486-5p levels. Mechanisms mediating recruitment of exosomes are unclear. We previously showed that exosomes express CXC chemokine receptor type 4 (CXCR4), and a neutralizing antibody to stromal cell-derived factor (SDF)-1α prevented exosome uptake into normoxic endothelial cells. Here, we determined if exosomes transfer miR-486-5p to endothelial cells and nephron segments after kidney ischemic injury, and further explored the role of the CXCR4/SDF-1α interaction.

Methods: Ischemia-reperfusion kidney injury was induced in mice by renal vascular clamp, with or without i.v. infusion of ECFC exosomes. Kidneys were removed 30 min after reperfusion, and endothelial cells were isolated by enzymatic digestion and sorting using CD31-labeled magnetic beads, followed by PCR for miR-486-5p. Proximal tubules and glomeruli were microdissected. Human umbilical vein endothelial cells (HUVECs) were exposed to hypoxia to study the role of CXCR4/SDF-1α interaction.

Results: Infusion of ECFC exosomes increased kidney cortical levels of miR-486-5p at 30 min after reperfusion ($P<0.05$; n=4). Exosomes significantly increased miR-486-5p levels in endothelial cells, proximal tubules, and glomeruli ($P<0.05$ vs ischemia-reperfusion alone; n=4). PKH26-labeled exosomes were detected mainly in the tubulointerstitial compartment of the kidney 30 min after infusion. In HUVECs, hypoxia increased secreted levels of SDF-1α and enhanced exosome uptake. Incubation with neutralizing antibody to SDF-1α or the CXCR4 inhibitor Plerixafor blocked exosome uptake into hypoxic HUVECs (n=4). Hypoxia also increased uptake of exosomal-derived Cy3-labeled miR-486-5p, which was inhibited by either neutralizing antibody to SDF-1α or Plerixafor (n=4).

Conclusions: ECFC exosomes target endothelial cells, proximal tubules, and glomeruli in ischemic kidneys, with transfer of miR-486-5p. Selective targeting of ischemic kidneys by exosomes may involve an interaction of exosomal CXCR4 with hypoxia-induced SDF-1α in endothelial cells. These data provide further support for the promising therapeutic potential of ECFC exosomes in human acute kidney injury.

Funding: Government Support - Non-U.S.

SA-PO574

Fibroblast mTORC2/PPARγ-Dependent HGF Production Protects Against Tubular Cell Death and AKI

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Background: Kidney interstitial fibroblasts play a crucial role in dictating tubular cell fate and the outcome of acute kidney injury (AKI). However, the underlying mechanisms remain to be further determined.

Methods: Mouse model with inducible Rictor gene deletion in fibroblast was generated. Kidney ischemia/reperfusion injury was employed to induce acute kidney injury in mice.

Results: Here, we found that Rictor/mTORC2 signaling was activated in mouse kidney interstitial fibroblasts after ischemia/reperfusion injury (IRI). Ablation of Rictor in fibroblasts led to more severe kidney dysfunction and morphological damage in mice after IRI compared to their littermate controls. More tubular cell apoptosis and inflammatory cell accumulation were detected in the knockout kidneys after IRI. In *in vitro*, a co-culture system between fibroblasts and tubular cells was generated. Blockade of Rictor/mTORC2 signaling in fibroblasts with Rictor gene ablation or pharmacological inhibition facilitated staurosporine-induced tubular cell death. In addition, blocking fibroblast mTORC2 signaling could downregulate its peroxisome proliferator-activated receptor gamma (PPARγ) and hepatocyte growth factor (HGF) expression, as well as attenuate c-met signaling activation in tubular cells. Moreover, activation of fibroblast PPARγ could augment HGF expression and attenuate tubular cell death. Notably, in mouse kidneys, ablation of fibroblast Rictor reduced the PPARg and HGF expression. The tyrosine phosphorylation of HGF receptor c-met was also diminished in the knockout kidneys after IRI.

Conclusions: Together, these data suggests that Rictor/mTORC2 signaling activation in kidney interstitial fibroblasts may protect against tubular cell death and dictate the outcome of acute kidney injury through PPARγ-stimulated HGF production.

Funding: Government Support - Non-U.S.

SA-PO575

Cultured Renal Tubular Epithelia in Migration Develop 3 Forms of Filopodia Having an Inherent Short Diameter: A Scanning Electron Microscope (SEM) Study

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Background: Renal tubular epithelial regenerate themselves after severe injuries as exemplified in acute kidney injury (AKI), when cell migration plays a crucial role. Studies have demonstrated that formations of filopodia are pivotal in cell migration. However, ultrastructure of cells with filopodia in migration largely remains to be seen. In this study, we use scanning electron microscope (SEM), and report fine ultrastructural images of filopodia that tubular epithelia form in cell migration.

Methods: Rat renal epthelialia, NRK-52E, were grown to confluence, and then, scratched or subcultured. At various time points until the next 100% confluence, they were fixed and subjected to SEM analysis. Filopodia were found in the specimens almost without exceptions. 20 different areas were randomly picked up to measure the short and long diameters of filopodia.

Results: Major findings of this study were 1) Filopodia were classified into 3 groups: having A(32±9)nm, B(108±16) nm, and C(155±21) nm short diameters. 2) Typically, the ratio of the short diameter to the long diameter in A, B, and C were 1:70, 1:150, and 1:400, respectively. 3) Group C filopodia were the major one when the cells were directionally migrating at >70% confluence. Interestingly, Group C filopodia was seen after the cells were grown to confluence (Figure). Appearances of Group A filopodia were rare.

Conclusions: Our ultrastructural study identified 3 forms of filopodia, although reciprocal relationship among them remained to be elucidated. Each one was associated with cell migration. We propose a hypothesis that group C filopodia play a role in learning the position of a cell in relation to adjacent ones.

SA-PO576

3D Organellar Morphological Dynamics in Kidney Tissue Using SIM Super-Resolution Microscopy

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Background: Organellar dynamics, mitochondrial morphology, endoplasmic reticulum (ER) morphology and autophagosome formation, are key components in the pathology of kidney disease. Imaging organellar dynamics in isolated cells has been a cornerstone to our understanding of cellular biology. Visualizing changes in these organelles in kidney tissue, however, remains difficult and largely limited to electron microscopy (EM), which provides a very narrow two dimensional image of the cellular/organellar structure. Thus, our understanding of organelle structure *in vivo*, and how this structure changes with disease, remains limited. Here, we investigate whether structured illumination microscopy (SIM) could be used to visualize three dimensional organellar dynamics in kidney tissue.

Methods: Human biopsies or kidneys from sham, aristolochic acid- or ischemic reperfusion-injured C57BL/6 mice were fixed and paraffin embedded following standard protocols. Sections of the kidneys were mounted on silane-treated coverslips and stained for intracellular organelles markers, and then imaged by Nikon N-SIM microscope. Kidney tissue was co-stained for markers of kidney injury, such as kidney injury molecule 1 (KIM-1)

and markers of the cell cycle. Changes in organelle structure were quantified with Imaris software.

Results: SIM reveals a dramatic increase in the number and size of autophagosomes in injured tubular cells marked with KIM-1. Likewise, the ER morphology is significantly altered in injured kidneys. Mitochondrial morphology was found to be far more complex than suggested by EM. 3D rendering of the mitochondria demonstrates that within one cell in uninjured kidneys the mitochondrial network is nearly continuous. After injury, this network breaks down into many smaller mitochondria. Importantly, SIM analysis of human kidney tissue exhibits dramatic changes in mitochondrial and other organelle structures.

Conclusions: SIM imaging provides a novel approach to analyze organellar dynamics and interfaces of organelles in kidney tissue and enables a 3D morphological analysis. KIM-1 staining is associated with increased autophagy and mitochondrial fragmentation. When combined with Injury or other markers SIM imaging can help delineate the pathways involved in organelle dynamics *in vivo* in human disease or animal models.

SA-PO577

A Novel 3D Cell Model That Mimics Renal Tubular Injury and Repair

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Background: Acute kidney injury (AKI) is a major health problem with high morbidity and mortality. Despite decades of research, there is still no specific therapy for AKI. To develop targeted therapies to prevent or treat AKI, a basic prerequisite is a clear understanding of how cells repair injured kidney. When epithelial cells in the proximal portion of the nephron are damaged they rapidly proliferate to repair the damage to the kidney. Here, we developed a novel 3D culture model of AKI and, in a key insight, looked for genes that were involved in injury and repair.

Methods: A mosaic MDCK cysts were cultured in Matrigel and damaged at Day 7. During cysts repairing, total RNA of MDCK cells at indicated stages were extracted, purified and concentrated. After microarray analysis, genes that significantly expressed were selected, and verified in mouse ischemic reperfusion injury model at multiple time points by qRT-PCR.

Results: In our 3D culture system, cysts with monolayer of highly polarized cells were formed at Day6. Sectional cells in mosaic cyst could be induce apoptosis by oligomerization of a membrane localized, truncated form of caspase 8 and thereby cause damage to the cysts. Intriguingly, the remaining cells in the damaged cysts were able to re-enter the cell cycle, and restore the cysts to their pre-apoptotic state. Microarray analysis highlights a cascade of temporal-specific gene expression patterns related to tubular injury/repair. Seven genes that involved in cell junction and adhesion were selected and verified in animal AKI model. Three of those genes were significantly upregulated at 24h after IRI, two of those genes were dramatically reduced after IRI, and one gene's expression has no change before 48h.

Conclusions: Using this 3D cell model of AKI, we have generated a list of gene candidates. Seven genes that related to cell junction and adhesion were identified, and expression patterns were similar between cell and mouse AKI model at multiple time points.

Funding: Government Support - Non-U.S.

SA-PO578

Mitigation of AKI in Mice Using DNase I Inhibitor

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Background: Our previous studies showed that genetic inactivation of the most active kidney apoptotic endonuclease, DNase I, was partially protective against tubular epithelial cell death induced by hypoxia-reoxygenation or cisplatin. Our recent discovery of the first pharmaceutically meaningful DNase I inhibitor, IG-17, provides an opportunity for the development of first anti-DNase drug mitigating acute kidney injury (AKI).

Methods: *In vitro* experiments using kidney tubular epithelial NRK-52E cells showed that IG-17 was able to suppress DNase activity inside the cells, and provided partial protection against hypoxia-reoxygenation, cisplatin or hemin toxicity measured using LDH release assay and TUNEL.

Results: The absence of IG-17 toxicity in mice at 1, 5 or 25 mg/kg was shown by 14 blood plasma assays for organ function. AKI experiments were done in male and female mice subjected to bilateral kidney 50-min ischemia followed by 24-h reoxygenation, or injected with cisplatin (20 mg/kg, IP), or glycerol (50% solution, 8 ml/kg, IM). Kidney failure was measured by serum creatinine and BUN. Structural kidney damage was assessed by acute tubular necrosis and TUNEL. In all three *in vivo* models, SC or IP injections of IG-17 (5 mg/kg) were either partially (ischemia-reperfusion, cisplatin) or fully protective (glycerol).

Conclusions: The results of this study suggest that IG-17 has a promise as the first non-toxic anti-DNase agent for mitigation of AKI.

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SA-PO579

Inhibition of BRD4 with MS417 Lessens the Inflammatory Response Following Ischemia Reperfusion Injury

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Background: A key regulator of the immune and inflammatory response is the NFκB// Rel protein family. A variety of stimuli, including ischemia reperfusion injury (IRI), activate the NFκB signalling cascade which stimulates the transcription of genes primarily involved in immune and inflammatory response. A key regulator of NFκB transcription is BRD4 which binds to acetylated RelA leading to the recruitment and activation of CDK9, subsequently resulting in the phosphorylation of RNA polymerase II and the transcriptional activation of NFκB target genes. The key role of BRD4 in transcription has led to the development of small molecule inhibitors that competitively bind to the acetylated RelA. One inhibitor, MS417, has shown promise in attenuating injury in different models of kidney injury, but has yet to be analyzed in a model of ischemia reperfusion injury.

Methods: Male C57BL/6 mice were treated with 1 μM of MS417 or vehicle via oral gavage daily for 7 days before unilateral IR was performed by clamping off the renal artery for 45 minutes followed by reperfusion. Daily treatment was continued until the time of sacrifice when tissue was collected for immunohistochemistry (IHC) and PCR analysis. Fixed kidney tissue was paraffin-embedded, sectioned, stained with periodic acid–Schiff (PAS) and scored for glomerular injury as well as for infiltrating neutrophils in a blinded manner. RNA was extracted from snap-frozen kidney tissue and was reverse transcribed into cDNA which was subsequently used in quantitative polymerase chain reaction.

Results: IHC staining for tubular injury and neutrophil infiltration showed a marked increase in the control group (treatment with saline) when compared to shams (no IRI). Treatment with MS417 prior to IR resulted in a lower trend in both injury and neutrophil infiltration. Administration of MS417 further suppressed the increase of the transcript levels of the proinflammatory markers C-C Motif Chemokine Ligand 2, Interleukin-1β, and Interleukin-6 by approximately 50%.

Conclusions: Treatment with the BRD4 inhibitor, MS414, prior to IR resulted in reduced tubular injury and neutrophil recruitment as well as reduced expression of proinflammatory genes. Further analysis of MS417's specificity and role in lessening the inflammatory response following IR is required.

SA-PO580

PMMA-Based Continuous-Adsorbitive-Hemofiltration Abrogated Complement Activation and Tubular Senescence-Associated Secretory Phenotype (SASP) in LPS-Induced AKI

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Background: During sepsis-induced AKI, inflammatory mediators could induce a maladaptive response in tubular epithelial cells (TEC). Hemofeel (TORAY, Japan) is a PMMA membrane based hemofilter indicated for blood purification therapies in continuous modality (CRRT), combining filtration and adsorption.

Methods: After 3h from LPS infusion, 8 pigs (female, 40-50 Kg) were treated with PMMA-CVVH (CH-1.8 W series), working in post-dilution modality (time =7 hours; Qb= 150 ml/min; Effluent rate =2000 ml/h; Substitution Rate = 2000 ml/h; UF rate = 0 ml/h). 8 control pigs received no treatment and developed endotoxemia-induced oliguric AKI. Renal biopsies were collected at 24h and analyzed by IHC and IF. Systemic Complement activation was evaluated by Wieslab kit. In vitro, tubular epithelial cells (TEC) were stimulated with LPS (4μg/ml) for 24h and then analyzed for SASP markers (p53, p21, cyp1b1, Klotho) by qPCR.

Results: A significant activation of Complement classical and alternative pathways was observed at 3h and 24h after LPS infusion. Histological and Confocal analysis revealed extensive Pentraxin-3 and collagen deposits at the interstitial level, along capillaries with diffuse glomerular thrombi compared to healthy pigs (T24LPS vs T24CTR, $p < 0.05$). Interestingly, we found significant TEC senescence with increased $p16^{INK4a}$ expression (IHC T24LPS vs T24CTR $p < 0.05$). PMMA-CVVH treatment significantly reduced Complement activation and antagonized SASP by restoring $p16^{INK4a}$ basal expression (T24LPS vs T24PMMA $p < 0.05$). In accordance, LPS stimulation of TEC (24h) in vitro induced accelerated senescence by up-regulating p53, p21, cyp1b1 (2-DDCT: LPS: 4.3 ± 0.63 vs Basal: 1 ± 0.00, $p < 0.05$) and reducing Klotho expression ($p < 0.05$).

Conclusions: Endotoxemia can induce AKI with systemic Complement activation leading to the development of SASP phenotype in TEC. PMMA treatment might be a new therapeutic approach to prevent Complement activation in LPS-induced AKI.

SA-PO581

The Stabilizing Effect of Dipeptidyl Peptidase-4 Inhibitors on the Epithelial Barrier in the Colistin-Induced Tubular Injury

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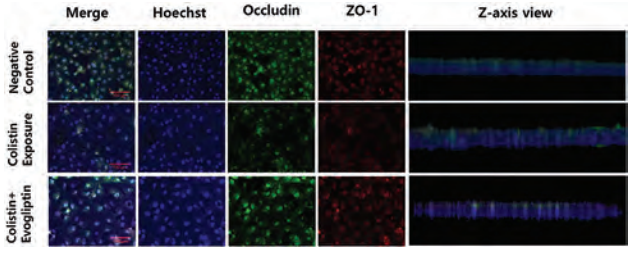
Background: Recently, dipeptidyl peptidase-4 inhibitors (DPP4i) have been identified to have some pleiotropic effects in different kidney diseases including diabetic kidney disease, ischemic acute kidney injury. In terms of pathophysiology, few studies have examined the effects of DPP4i on the epithelial barrier in drug-induced acute kidney injury. The increased tubular epithelial cell permeability and barrier dysfunction have been shown in previous studies regarding colistin-induced nephrotoxicity. This study was performed to evaluate the renoprotective effect of DDP4i in colistin-induced tubular injury using a two-layered kidney-on-a-chip device.

Methods: The kidney-on-a-chip device consists of upper and lower channels mimicking intraluminal space and interstitial space. Kidney tubular epithelial cells were seeded into upper channel and exposed to colistin at a concentration of 400 μg/ml for 48 hours under physiological shear stress condition (1 dyn/cm^2). Evogliptin (Suganon®, Dong Ah Pharm., Korea) was administered to the lower channel at a concentration of 50 nM for 48 hours. Transmembrane permeability, tight junction protein expression, cell viability, and tubular injury marker, kidney injury molecule-1 (KIM-1), in outlet-collected media were evaluated in evogliptin-treated and control groups.

Results: After colistin treatment, transmembrane permeability increased from 6.75% to 51.5%, but evogliptin decreased transmembrane permeability to 34.6%. In addition, the fluorescence intensity of tight junction proteins, occludin and ZO-1, which were reduced by 56.2% and 44.5% after colistin exposure, were maintained during the treatment with evogliptin. The dead cell percentage and KIM-1 level were slightly decreased in evogliptin-treated groups.

Conclusions: We identified some renoprotective effects of the DPP4i on the epithelial barriers in short-term colistin-induced tubular injury. Further studies are required for the cytoprotective effect in long-term colistin injury models.



SA-PO582

Exercise Attenuates Ischemia–Reperfusion-Induced AKI

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Background: Aerobic (endurance) and strength (resistance) exercise have both been proven to be beneficial for patients with chronic kidney disease. Acute kidney injury continues to be the leading cause of death among critical care patients. We hypothesized that there is cross-talk between muscles and the kidneys and that exercise could attenuate the renal damage caused by ischemia–reperfusion. In this study, we assess the impact of exercise in rats submitted to renal ischemia–reperfusion injury (IRI).

Methods: Wistar rats were divided into two groups: Exer+IRI (n = 7), in which rats were submitted to a standardized protocol consisting in a treadmill run at up to 60% of the maximum calculated speed and climbing of a standardized ladder (30 min of running+10 climbs with tail weights, 5 times a week for 8 weeks), followed by bilateral clamping of the kidney hila (30 min) and subsequent reperfusion; and control+IRI (n = 6) in which the protocol consisted in a treadmill run at the lowest speed (30 min, 5 times a week for 8 weeks: control condition), bilateral clamping of the kidney hila (30 min), and subsequent reperfusion. All studies were performed 48 h after reperfusion. Data are mean ± SEM.

Results: Serum levels of urea were higher in control+IRI rats than in Exer+IRI rats (143 ± 43 vs. 92 ± 12 mg/dl), as were urinary levels of NGAL (46 ± 10.6 vs. 24 ± 5.6 μg/mg urinary creatinine, $p < 0.05$). In kidney tissue, protein expression of Toll-like receptor 4 (TLR4) was higher in control+IRI rats than in Exer+IRI rats (105 ± 2.4 vs. 67 ± 1.9%; $p < 0.01$). Renal protein expression of Klotho was lower in control+IRI rats than in Exer+IRI rats (99.5 ± 1.6 vs. 134 ± 6.7%; $p < 0.01$) as was protein expression of manganese superoxide dismutase (98.8 ± 2.2 vs. 122 ± 5.7%, $p <0.01$). Renal apoptosis (determined by TUNEL) was lower in Exer+IRI rats than in control+IRI rats (3.7 ± 0.8 vs. 11.5 ± 5.0 positive cells/0.087 mm^2; $p < 0.05$). Acute tubular necrosis was more extensive in control+IRI rats than in Exer+IRI rats (5.3 ± 0.6 vs. 3.8 ± 0.4, $p < 0.05$), most control+IRI rats presenting damage in >50% of the tubular area, compared with <50% for the Exer+IRI rats.

Conclusions: Exercise attenuates renal IRI by decreasing TLR4 expression and is renoprotective in a Klotho-dependent manner. (FAPESP)

Funding: Government Support - Non-U.S.

SA-PO583

Renal Hypercoagulability Is Front and Center in Ischemic Injury

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Background: The transition of acute kidney injury (AKI) to chronic kidney disease (CKD) is common and misunderstood. We hypothesize that widespread renal clotting impairs reperfusion following renal ischemia in rats. This renal response is manifested as no-reflow in the microcirculation, causing swaths of renal micro ischemia, inflammation, apoptosis and fibrosis.

Methods: SD rats (n = 5/group) were subjected to 50 minutes of renal ischemia and then to 6 days of reperfusion. We used RNAseq comprehensive transcriptome analysis and measured 12,159 renal transcripts in sham and ischemic rats. The data were analyzed with established informatics tools.

Results: Renal ischemia activated the intrinsic renal clotting system and clotted renal microvessels. This response to injury included prothrombotic stimulation manifested by renal tubular activation of tissue factor (up 1.9 fold; $p<0.002$), and inhibition of tissue factor pathway inhibitor (down 1.44 fold, $p = 0.008$). Moreover, all three chains of renal fibrinogen were upregulated (up to 33 fold; 2.2E-10) and circulating fibrinogen also surged: 140±30 to 719±29 mg/dl, $p<0.0024$. Renal plasminogen was not expressed. There was major inhibition of fibrinolysis represented by activation of plasminogen activator inhibitor (up 5.6 fold; p = 1.7E-7), lack of response in renal urokinase and tisue plasminogen activator, and inhibition of plasminogen activator kallikrein (down 10 fold, p = 1.85E-6). In addition the thrombin receptor F2rl1 was activated 2 fold ($p<0.0001$). Complement component C1qa,b,c increased 3 fold ($p <0.0001$), C3 (up 5 fold p= 1.2E-5), and C4 a,b (up 12.56 and 20 fold respectively, p = 1.9E-13). These renal mRNA changes were associated with similar responses in renal cognate proteins and fibrin deposition. Kegg pathway analysis confirmed differential expression in ischemia of coagulation and complement pathways P=2.68 x 10-3.

Conclusions: We suggest the renal pro-thrombotic and fibrinolytic balance is essential to protect and assure competent blood flow. In renal injury, this balance is disrupted in favor of hypercoagulability. The risk to renal microthrombosis is further enhanced by complement activation and inhibition of a robust renal fibrinolytic system. We propose that in ischemic AKI the most optimal option is to re-activate fibrinolysis, anticipating that anti-coagulant agents are unlikely to be effective.

Funding: Veterans Affairs Support

SA-PO584

High Throughput Metabolic Flux Analysis of Intact Kidney Tissue Reveals Abnormal Mitochondrial Respiration During AKI to CKD Transition

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Background: Mitochondrial dysfunction has been implicated in the pathogenesis of multiple renal diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD). However, knowledge about mitochondrial function during AKI to CKD transition is limited. The assessment of basal oxygen consumption rates (OCR) and the responses to electron transport chain inhibitors and uncoupling agents represent the first steps in evaluating cellular mitochondrial function. In order to avoid artifacts associated with tissue disruption or primary cell culture, we developed a novel method that permits the measurement of OCR in intact kidney tissue slices and investigated mitochondrial function during AKI to CKD transition.

Methods: 9-12 week-old C57/BL6 male mice were subjected to unilateral ischemia reperfusion injury (IRI) induced by 30 minutes of renal pedicle clamping. Kidneys were analyzed immediately after clamp removal (no-reperfusion) and at 24 hours, day 3, day 7 and day 21 post IRI. After removal of the kidney capsule, a portion of the kidney was used for DNA, RNA and histologic analysis. The remainder of the kidney was submerged in oxygenated modified Ringers solution. 1mm punch-biopsies were obtained from 100 μm vibratome sections of kidney pole tissue and loaded into an islet capture plate. OCR and extracellular acidification rates (ECAR) were analyzed with a Seahorse XF^{e}24 metabolic flux analyzer.

Results: Basal OCR and ECAR rates were significantly reduced immediately following IRI and recovered incompletely by day 3 post IRI. Day 7 and day 21 were characterized by a further reduction in OCR and ECAR below day 3 levels. The reduction in OCR correlated with significantly diminished mitochondrial DNA and gene expression levels and the development of fibrosis at day 7 an day 21. Similarly reduced ECAR values were associated with reduced glycolytic gene expression.

Conclusions: Here we present a novel approach for high throughput monitoring and analysis of mitochondrial respiration in intact kidney tissue sections. Our data indicate that AKI to CKD transition is associated with reduced mitochondrial respiration and glycolysis rates. A detailed protocol of this method will be presented at the meeting.

SA-PO585

Lipopolysaccharide Causes Renal Biotin Uptake Inhibition via a Transcriptional Mechanism

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Background: Biotin (vitamin B7), a water-soluble vitamin, is indispensable for normal human health and its deficiency is associated with various severe clinical conditions. Renal proximal tubule epithelial cells are critical to maintaining normal body biotin homeostasis by mediating its reabsorption via a specific carrier mediated process (sodium-dependent multivitamin transporter [SMVT]). Although it has also been shown that lipopolysaccharides (LPS) can cause intestinal biotin deficiency by inhibiting its absorption, very little is known about the effect of inflammation and LPS on the kidney biotin uptake process.

Methods: Given the major role of inflammation in kidney disease and injury we sought to assess the effect of LPS exposure on renal biotin transport. We evaluated the impact of LPS on renal biotin uptake, expression, promoter activity and transcriptional regulation using *in vitro* (human proximal tubule kidney epithelial HK2 cells) and *in vivo* (mice) models subjected to LPS for 72 hours.

Results: The HK2 cells treated with LPS from gram negative E. coli (10 μg/ml) exhibited a significant inhibition in carrier-mediated biotin uptake, compared to controls. This inhibition was associated with a significant reduction in SMVT protein, mRNA and hnRNA expression levels. Similar inhibition of SMVT protein, mRNA and hnRNA expression levels were also observed in mice injected with LPS (2 mg/kg body weight). Additionally, we found that *SLC5A6* (biotin) promoter activity was attenuated following LPS treatment of HK2 cells. This was associated with a significant reduction in the mRNA expression levels of activator protein-2 (AP-2), a transcription factor which drives the *SLC5A6* promoter activity, in both of our *in vitro* and *in vivo* models.

Conclusions: This study shows for the first time that LPS inhibits renal biotin uptake via a transcriptionally-mediated mechanism. The potential clinical impact of these findings and possible role of biotin therapy in kidney injury caused by LPS remains to be determined.

Funding: NIDDK Support, Veterans Affairs Support

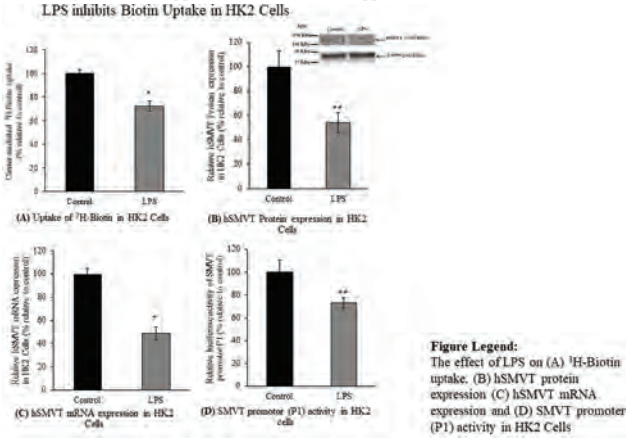

Figure Legend: The effect of LPS on (A) ³H-Biotin uptake. (B) hSMVT protein expression (C) hSMVT mRNA expression and (D) SMVT promoter (P1) activity in HK2 Cells

SA-PO586

Lack of DJ-1 Amplifies Sepsis-Associated AKI and Increases Daxx-Mediated Parenchymal Apoptosis

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Background: Sepsis is frequently complicated by acute kidney injury (AKI). AKI in sepsis is associated with increased morbidity and mortality. Studies of sepsis-induced AKI suggest that uncontrolled inflammatory responses to tubular injury can further worsen renal damage. DJ-1 is a known anti-oxidant protein that is expressed in the brain, kidney, and immune cells. The role of DJ-1 in sepsis is not clear. AKI is one of the common sepsis-associated pathologies, and there is no data on the role of DJ-1 in sepsis-associated AKI.

Methods: Wildtype and DJ-1 knockout mice both on B6 background were administered 6.5 mg/kg LPS (i.p.) and tissues were harvested 24 hours later. Renal function and injury, as well as markers for inflammation were studied. Inner Medullary Collecting Duct cells (iMCD3) were used to study activation as well as cytotoxic serum responses.

Results: Compared to WT mice, DJ-1$^{(-/-)}$ mice were more susceptible to LPS-induced AKI as indicated by higher plasma creatinine (WT LPS 0.61 ± 0.11 Vs DJ-1$^{(-/-)}$ LPS 0.87 ± 0.23; p= 0.0006) and Kidney Injury Marker-1 (KIM-1). Markers of renal inflammation (s100A8 and s100A9) and Reactive Oxidant/Nitrogen Stress (ROS/RNS) were increased in renal tissue of DJ-1 deficient mice. The increased oxidative stress was associated with induction of Daxx-mediated apoptosis in the kidney. We demonstrate a protective effect of DJ-1 against LPS serum toxicity with *in vitro* studies on IMCD3 cells.

Conclusions: Our data suggests DJ-1 plays an important protective role in against sepsis-associated renal inflammation and injury, through ROS/RNS control, and by preventing Daxx-dependent apoptosis.

Funding: Other NIH Support - T32 DK072922

SA-PO587

Severity and Frequency of Tubule Injury Induced by Ischemia-Reperfusion Determines Prognosis of AKI

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Background: Ischemia is a common etiology in human acute kidney injury (AKI), which is an underestimated, yet significant predisposing factor for development of chronic kidney disease (CKD). However, a systematic and explicit reference standard is lacking for researchers when IRI models with divergent outcomes are to establish. Also, the biomarkers reflecting AKI to CKD progression are particularly lacking. The purpose of the current study was to establish suitable mice models simulating different clinical situations of renal ischemia patients, investigating the time and frequency effect of ischemia on AKI and subsequent AKI to CKD progression and exploring the potential function of noninvasive biomarkers KIM-1 and NGAL in predicting the renal outcome and prognosis.

Methods: Male C57BL/6J mice were subjected to different durations and episodes of ischemia attack for the UIRI (Unilateral Ischemia-Reperfusion Injury). We collected and analyzed the kidney samples at different time point post-ischemia. The concomitant changes of tubular injury biomarkers KIM-1 and NGAL in blood and urine along with different disease progression pattern were also investigated.

Results: We found that short-term duration of ischemia induced mild and reversible AKI in mice, while long-term duration of ischemia led to severe and progressive AKI. Repeated attack of moderate ischemia reperfusion injury could be applied to establish a model of AKI on CKD in mice. Furthermore, levels of KIM-1 and NGAL restored completely in reversible AKI, while they remained increased in progressive AKI. To be specific, levels of NGAL presented an increasing tendency till the chronic phase of the disease, while levels of KIM-1 merely peaked at the acute phase then suffered a subsequent decrease although still significantly higher than basal values.

Conclusions: In conclusion, different severity and frequency of ischemia injury dictate the divergent outcomes of ischemia-induced AKI. Both KIM-1 and NGAL enable noninvasive and early detection of AKI, also NGAL may better reflecting and predicting the process of AKI to CKD progression.

Funding: Government Support - Non-U.S.

SA-PO588

PBI-4050 Reduces Systemic Inflammation, Electrolyte Disturbances, and Renal Injury in Mice with Sepsis-Induced AKI: Role of GPR84

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Background: PBI-4050, Prometic Biosciences Inc.'s lead drug candidate, exerts anti-inflammatory and anti-fibrotic effects in several diabetic and non-diabetic models of kidney injury through modulation of GPR40 and GPR84 fatty acid receptors. Primarily in macrophages and fibroblasts, we have shown that the pro-inflammatory GPR84 receptor is induced in cultured human renal cells including proximal tubule epithelial cells (hPTEC) and podocytes (hPod) stimulated with bacterial lipopolysaccharides (LPS). We therefore queried the impact of PBI-4050 in a model of endotoxemia-induced AKI and evaluated the role of GPR84 in this regard.

Methods: Eight-week old male C57BL/6 mice were treated with PBI-4050 (200 mg/kg BW, p.o.) for 14 days followed by LPS (10 mg/kg, i.p.)-challenge and sacrificed 24 hours later.

Results: AKI was confirmed as LPS led to a rapid rise in plasma creatinine and urea, which were significantly decreased in PBI-4050-treated mice. LPS-induced hyperphosphatemia, hyperkalemia, hypocalcaemia and hypoglycemia, were also significantly improved by PBI-4050. Circulating levels of several major pro-inflammatory cytokines, including IL-1β, IL-6, MCP-1, TNFα, CXCL-1 and Rantes (CCL5) correlated with creatinine levels, and were significantly decreased by PBI-4050 in LPS mice. Moreover, PBI-4050 reduced LPS-induced albuminuria and albuminemia. Histological assessment revealed tubular cell injury was reduced and PT-megalin expression improved with PBI-4050, as was peri-glomerular and tubulointerstitial α-SMA expression. In a pilot study, GPR84$^{-/-}$ mice challenged with 24 hours LPS showed modest yet significant improvements in renal function. LPS caused GPR84 induction in cultured hPTECs and hPODs. PBI-4050 treatment in LPS-stimulated hPTEC and hPods decreased pro-inflammatory gene expression including MCP-1, IL-6 and IL-8.

Conclusions: Taken together, PBI-4050 improves systemic inflammation and indicators of glomerular and tubular injury in a model of LPS-induced AKI partly through GPR84 and may directly target specific renal cell types including PTEC's and podocytes.

Funding: Commercial Support - Prometic Life Sciences Inc.

SA-PO589

Ceria-Zirconia Nanoparticles as an Enhanced Multi-Antioxidant Attenuates Apoptosis of Human Kidney Proximal Tubular Epithelial Cells in Hypoxia

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Background: Hypoxia is an important cause of acute kidney injury (AKI) in various conditions because kidneys are one of the most susceptible organ to hypoxia. Various mechanisms have been introduced as mediators of the AKI caused by hypoxia, including calcium overload, endoplasmic reticulum stress, complement system activation, and reactive oxygen species (ROS). ROS play an important role in hypoxia induced AKI by affecting the function of cellular DNA, proteins, and lipids. The use of antioxidants can benefit the control and prevention of hypoxia induced AKI. Ceria-Zirconia nanoparticles (CZ NPs) exhibit superoxide dismutase and catalase mimetic activities. We investigated the effect of CZ NPs in cultures of hypoxia exposed human proximal tubular epithelial cells.

Methods: CZ NPs with size 2-3nm were synthesized using non-hydrolytic sol-gel reaction. To investigate the catalytic effect of CZ NPs, reactive oxygen species (ROS) production was measured using DHE, DCF-DA and amplex red assay. Cellular survival rate and cytotoxicity were measured with 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Cellular signaling pathway were studied by real time polymerase chain reaction and Western blot analysis.

Results: Cell survival was reduced in a dose-dependent manner for 24h after hypoxia exposure. Hypoxia caused a significant increase in ROS production 24 h after hypoxia. The extent of the effect of hypoxia on ROS levels was significantly reduced by CZ NPs treatment. CZ NPs downregulated proinflammatory markers and reduced caspase 3/7 activity in hypoxic HK-2 cells. CZ NPs also improved the survival of HK-2 cells in response to hypoxia.

Conclusions: CZ NPs have the potential as a therapeutic medicine for preventing ROS-related hypoxia induced AKI

SA-PO590

NADPH Oxidase 4 Mediates TGF-β1/Smad Signaling Pathway Induced AKI in Hypoxia

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Background: Hypoxia is an important cause of acute kidney injury (AKI) in various conditions because kidneys are one of the most susceptible organ to hypoxia. Reactive oxygen species (ROS) plays an important role in hypoxia induced AKI. Among various sources of ROS, nicotinamide adenine dinucleotide 3-phosphate (NADPH) oxidase (Nox) is the major intracellular non- mitochondrial ROS source. Because among seven Nox families, Nox4 is the most abundant in the human kidney, changes of Nox4 expression in hypoxia are predicted to affect the progression of AKI by altering the intracellular ROS level in the kidney. Based on these observations, we investigated the role of Nox4 and the benefits of Nox4 inhibition in hypoxia induced AKI.

Methods: The hypoxic injury induced in HK-2 cells by hypoxia chamber and $CoCl_2$. Reverse transcription polymerase chain reaction for Nox4 and TGF-β1 was performed. Western blotting for Nox4 and Smad pathway were done. ROS production was detected using a DHE stain and Amplex red assay. HK-2 cells were transfected with siNox4 and pretreated with GKT137831(most specific Nox1/4 inhibitor). ELISA has been used to measure TGF-β1 levels. The effect of treatment with TGF-β1 type 1 tyrosine kinase inhibitor SB431542 on Nox4 expression was observed.

Results: Expression of Nox4 in cultured human renal proximal tubular epithelial cells (HK-2) was significantly increased by hypoxic stimulation. TGF-β1 was endogenously secreted by hypoxic HK-2 cells. SB4315432 (a TGF-β1 receptor I inhibitor) significantly inhibited Nox4 expression in HK-2 cells through the Smad-dependent cell signaling pathway. Silencing of Nox4 using *Nox4* siRNA and pharmacologic inhibition with GKT137831 reduced the production of ROS and attenuated the apoptotic pathway. In addition, knockdown of Nox4 increased cell survival in hypoxic HK-2 cells and pretreatment with GKT137831 reproduce these results.

Conclusions: This study demonstrates that hypoxia induces HK-2 cell apoptosis through a signaling pathway involving TGF-β1 via Smad pathway induction of Nox4-dependent ROS generation. Therapies targeting Nox4 may be effective against hypoxia-induced AKI.

SA-PO591

Ischemia Time Effects Long-Term Kidney Function in a Murine Model of Unilateral Ischemic AKI

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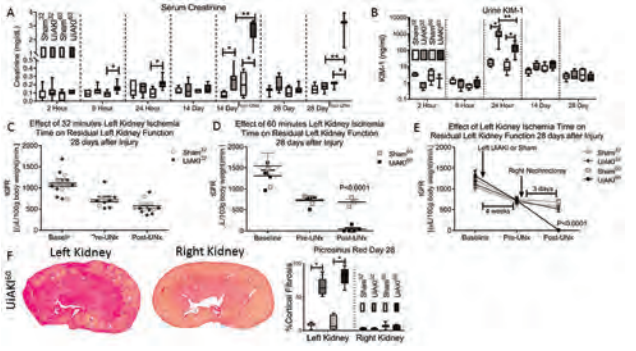
Background: The duration of ischemia that allows for complete recovery remains undetermined. Parekh performed a prospective study in patients undergoing unilateral ischemia-reperfusion acute kidney injury (UiAKI) for partial nephrectomy, and evaluated histological, serum and urine biomarker changes. Their findings suggested that while there was evidence of acute biomarker and histological injury, the injury was short-lived and did not correlate with ischemia times. This study has been utilized clinically to reassure against long-term renal damage following prolonged ischemia, but did not include outcomes beyond the immediate post-operative period.

Methods: Adult male C57BL/6 mice underwent UiAKI or sham procedure on the left kidney for 32 or 60 minutes. Serum and urine biomarkers were evaluated at 2, 6, and 24 hours, and 14 and 28 days. Transcutaneous glomerular filtration rate (tGFR) was measured serially. Additional 14 and 28 day groups underwent healthy unilateral nephrectomy 3 days prior to sacrifice in order to unmask any compensatory hyperfiltration.

Results: tGFR and histological outcomes demonstrated significant functional impairment and fibrosis despite reassuring serum biomarkers at the 14 and 28 day time-points.

Conclusions: Ischemia time correlates with functional impairment and fibrosis despite reassuring urine and serum biomarkers. Efforts to limit ischemia time in renal-sparing surgery remain warranted.



(A) Serum creatinine and (B) Urine KIM-1 were reassuring at the day 14 and 28 time-points (without nephrectomy), while functional assessment of glomerular filtration rate and histological outcomes demonstrated higher degrees of injury proportional to the ischedmia time. Specifically, 32 minutes of ischemia did not impair GFR 28 days later (C) and (E) while 60 minutes of ischemia resulted in nil function of the injured kidney (D) and (E). Picrosirius Red staining demonstrated increased fibrosis in the left injured kidney for both the 32 and 60 minute ischemia times (F). n = 5-7, $p < 0.05$.

SA-PO592

Metabolomic Alterations in a Mouse Model of Cisplatin-Induced AKI

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Background: Cisplatin-induced acute kidney injury (AKI) occurs in approximately 1/3 of patients receiving cisplatin therapy, but the reason why only certain patients develop AKI is unknown. AKI is currently diagnosed by increases in serum creatinine (SCr), but nephrotoxicity develops prior to detectable rises in SCr. Discovery of novel predictive/diagnostic markers of AKI is necessary and may help explain the differential susceptibility of cisplatin patients to AKI. FVB mice have shown greater susceptibility to cisplatin AKI than C57BL/6 mice. These two strains were used to model the variability of cisplatin nephrotoxicity observed in humans. We aim to: 1) Determine the differences in expression of renal transporters and enzymes involved in cisplatin disposition these mouse strains; 2) Investigate metabolic differences between FVB and C57BL/6 mice using metabolomics, with the aim of biomarker discovery.

Methods: FVB and C57BL/6 strains were treated with 15 mg/kg cisplatin or saline by intraperitoneal injection. Mice were sacrificed 1 and 3 days following treatment, and blood, urine, and kidneys were collected. Gene expression was assessed using RT-PCR. Liquid chromatography-mass spectrometry was used for untargeted metabolomics.

Results: Renal expression of transporters Oct2 and Oat1, and metabolizing enzyme Ggt1 were higher (+20%, $p<0.05$; +38%, $p<0.01$; +45%, $p<0.05$) in untreated FVB mice compared to C57BL/6. Principle component analysis (PCA) of plasma and kidney samples from untreated FVB and C57BL/6 showed visual separation based on mouse strain. PCA of day 3 plasma and kidney samples separated cisplatin and saline groups for both strains. Multivariate analysis revealed uremic toxins indoxyl sulfate, phenyl sulfate and p-cresyl sulfate to be altered in cisplatin AKI.

Conclusions: FVB mice exhibited increased expression of various renal transporters and enzymes involved in cisplatin disposition, as compared to C57BL/6. PCA clustering of plasma and kidney samples from untreated mice indicates baseline metabolic differences between the strains, while separation by treatment (saline vs. cisplatin) suggests that cisplatin administration alters the metabolic profile of the mice. Future work will further characterize metabolic changes associated with cisplatin AKI. Our data suggests possible mechanisms why FVB mice are more susceptible to cisplatin AKI compared to C57BL/6 mice.

Funding: Government Support - Non-U.S.

SA-PO593

Coenzyme Q-10 Protects Against Radiocontrast-Induced AKI by Regulating Heme Oxygenase-1 (HO-1) and Inducible Nitric Oxide Synthase (iNOS)

Sheila M. Fernandes,[2,1] Maria De Fatima Vattimo,[2,1] Cassiane D. da Fonseca,[2,1] Mirian Watanabe,[2,1] Karina B. Peres,[2,1] Carolina F. Vasco.[3] *[1]EEUSP, São Paulo, Brazil; [2]Universidade de São Paulo (USP), São Paulo, Brazil; [3]Universidade de São Paulo, São Paulo, Brazil*.

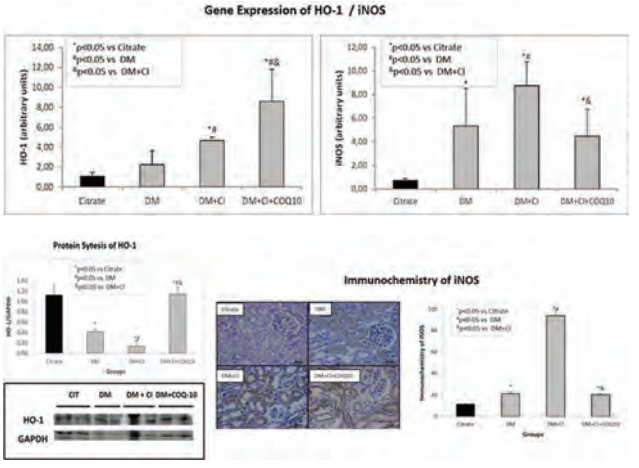
Background: Radiocontrast agents are thought to induce acute kidney injury in part through increased production of reactive oxygen species. Recently, we reported that IC reduced inulin clearance and increased urinary peroxides, nitric oxide and TBARS with consumption of antioxidant reserve, that were significantly attenuated by COQ-10 (Vattimo MFF, JASN 2016). The aim of this study is to examine if the renoprotective effect of COQ-10 is mediated by heme oxygenase-1 (HO-1) and inducible nitric oxide synthase (iNOS) in diabetic rats.

Methods: Adult male Wistar rats, randomized into 4 groups: Citrate - citrate buffer (streptozotocin vehicle); DM (streptozotocin, 65 mg/kg, iv).; DM+IC - DM animals that after 4 weeks received iodinated contrast (IC, 6 ml/kg, ip); DM+IC+CO-Q10 - DM preconditioned animals (COQ-10, (10 mg/kg, ip). Were evaluated gene expression and protein syntesis of heme oxygenase-1 (HO-1) and inducible nitric oxide synthase (iNOS) in CI-AKI in diabetic rats treated with COQ-10.

Results: Treatment with IC significantly incresed gene expression and reduced protein syntesis of HO-1 in diabetic rats compared the DM group. COQ-10 induced an elevation in gene expression and in the protein syntesis of HO-1. IC led to a increasing the levels of gene expression and protein syntesis of iNOS in the kidney rats diabetic. Treatment with COQ-10 was able to attenuate the increase in iNOS protein levels observed in DM+CI group.

Conclusions: The data highlighted that the regulation of HO-1 and iNOS can be point out as the mechanism involved in the renal protective effect of the COQ10 in the CI-AKI in diabetic rats, probably due to its anti-oxidative and anti-nitrosative effective.

Funding: Government Support - Non-U.S.



SA-PO594

Heme Oxigenase-1 (HO-1) and Inducible Nitric Oxide Synthase (iNOS) Modulate by Resveratrol in Contrast-Induced AKI in CKD Rats

Sheila M. Fernandes,[5,4] Maria De Fatima Vattimo,[5,4] Mirian Watanabe,[2,4] Karina B. Peres,[3,4] Daniel M. Martins,[1] Carolina F. Vasco.[6] Experimental lab on animal models *[1]University of São Paulo, Carapicuíba, Brazil; [2]University of Sao Paulo, Sao Paulo, Brazil; [3]EEUSP, São Paulo, Brazil; [4]Escola de Enfermagem da USP (EEUSP), Universidade de São Paulo (USP), São Paulo, Brazil; [5]Universidade de São Paulo (USP), São Paulo, Brazil; [6]Universidade de São Paulo, São Paulo, Brazil*.

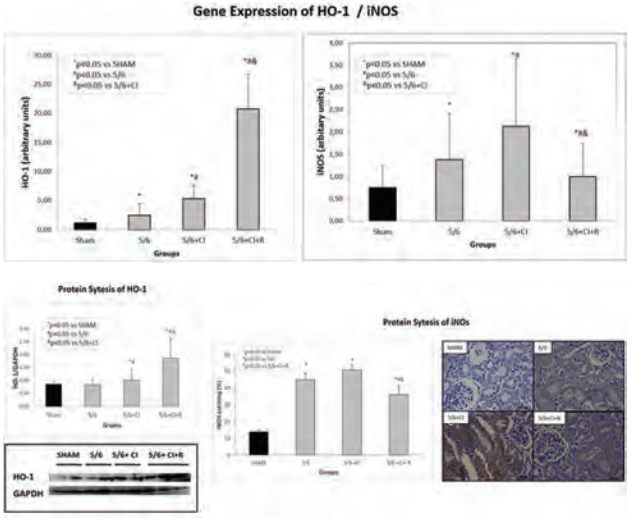
Background: Iodinated contrast (IC)-induced acute kidney injury (AKI) is an important complication in patients with chronic kidney disease (CKD). In previous studies, we demonstrated a protective effect of Resveratrol (R) treatment demonstrated improvement of renal function in IC-AKI by renal hemodynamic modulation in CKD rats (VATTIMO MFF, JASN 2016). The aim of this study was to evaluate the potential renoprotective effect of resveratrol as anti-oxidate and anti-nitrosative by modulation of heme oxygenase-1 (HO-1) and nitric oxide induced synostosis (iNOS) in rats with CKD treated with IC.

Methods: Wistar, adult, male rats were randomized in four groups. Sham (control group), 5/6 (CKD model: 5/6 nefrectomy), 5/6+IC (CKD model + IC, 6ml/Kg, intraperitoneal- i.p., single dose), 5/6+IC+R (CKD model + R, 25 mg/Kg, intraperitoneal, single dose + IC, i.p, single dose, 30 minutes after R). Gene expression and protein syntesis of HO-1 and iNOS in renal tissue were evaluated.

Results: Treatment with IC significantly incresed gene expression and protein synthesis of HO-1 in 5/6 + IC rats compared to the 5/6 (DRC model) group and treatment with Resveratrol induced an additional elevation in gene expression and in the protein synthesis of HO-1 in 5/6 + IC + R rats. The levels of gene expression and protein synthesis of iNOS also to increase in the kidney of 5/6+IC group. 5/6 + IC + R reduced iNOS protein levels compared to 5/6 + IC rats.

Conclusions: These results demonstrate that Resveratrol influence renal HO-1 and iNOS expression after IC-induced AKI in CKD rats and may contribute to better outcomes in this setting by involvement in the modulation of oxidative and nitrosative stress.

Funding: Government Support - Non-U.S.



SA-PO595

Renal Epithelial Cells Reprogram Metabolism to Adapt to Sepsis

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Background: Adaptive metabolic reprogramming may play a key role in the development of sepsis induced acute kidney injury (AKI). Like monocytes, renal tissue shifts metabolism toward glycolysis early after cecal ligation and puncture. In monocytes, this shift is driven by the hypoxia inducible factor (HIF-1a) though expression of pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase kinase (PDHK), whereas return to oxidative phosphorylation (OXPHOS) is driven by the activation of Sirtuin 1 (Sirt1). We hypothesized that human kidney 2 cells (HK2) follow the same biphasic reprogramming as an adaptive mechanism to sepsis.

Methods: HK2 were cultured in serum containing media and plated in XF24 microplates and 6-well plates for Seahorse and immunoblotting (WB) respectively at 21% O_2. Cells were treated with vehicle or sepsis mix (SM=LPS+HMGB1). We measured oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) as surrogates of glycolysis and OXPHOS, respectively at 3 and 24 hours after treatment. HIF-1a, PDHK, Sirt1 and b-Actin were identified by WB at 3, 6, and 24h.

Results: SM induced a decline in ECAR and an increase in OCR at 24h (Fig 1), suggesting that utilization of glycolysis decreases, and utilization of OXPHOS increases by 24h of SM. SM induced an increase in HIF-1α levels at 3h, with a late decrease by 24h. Protein levels of the downstream HIF-1α target, PDHK also increased from 3 to 6h, followed by a similar decline by 24h. SM induced a delayed increase in Sirt1 by 24h, with an early suppression at 3h (Fig 2).

Conclusions: Our study shows that in response to SM, HK2 cells shift metabolism by decreasing the use of glycolysis and increasing the use of OXPHOS by 24h. Increased expression of drivers and mediators of glycolysis early (3h) after SM, followed by a late (24h) decline in glycolysis concomitant with increased expression of drivers of OXPHOS, suggests a biphasic HK2 response to inflammation, reminiscent of that of monocytes.

Funding: Other NIH Support - 1K08GM117310-01A1

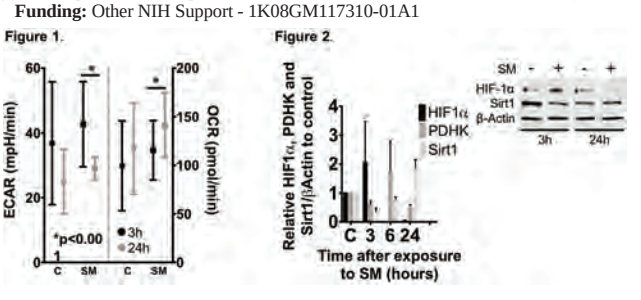

Fig 1. Change in glycolysis and OXPHOS from 3 to 24h after exposure to SM **Fig 2.** Protein expression of drivers of glycolysis and OXPHOS in HK2 cells after SM

SA-PO596

Cyclophilin A Promotes AKI and Inflammation Following Renal Ischaemia/Reperfusion Injury

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Background: Cyclophilins are enzymes that regulate protein folding. During various pathological conditions, cyclophilin A (CypA) has been shown to promote leukocyte recruitment and inflammation. However, the contribution of CypA in acute kidney injury (AKI) and renal fibrosis is poorly understood. The aim of this study was to determine the role of CypA in renal tubular damage, inflammation, and fibrosis using the: (1) renal ischaemia/reperfusion injury (IRI), and (2) unilateral ureteric obstruction (UUO) models.

Methods: Groups (n=10) of wild type (WT) and CypA-/- mice on the 129 background were subjected to either: (1) bilateral renal IRI (19min at 37°C) and killed 24 hours post reperfusion, or (2) UUO surgery and killed on day 7. Controls were sham operated.

Results: Renal IRI induced AKI with a >6-fold rise in serum creatinine (sCr) in WT mice (41±13.8 vs 6.3±1.7umol/L in sham; P<0.0001) and marked tubular damage based on the tubular injury score, increased KIM-1 mRNA levels, and tubular cell death (TUNEL+ cells; all P<0.0001 vs sham). CypA-/- mice were protected from renal dysfunction with a 50% improvement of sCr (20.7±3.5umol/L; P<0.0001), less histologic tubular damage (P<0.01), lower KIM-1 mRNA levels (P<0.01), and less tubular cell death (P<0.001). Renal IRI caused upregulated mRNA levels of inflammatory molecules (TNF-α and IL-36-α; P<0.05), and neutrophil infiltration (Ly6G+ cells; P<0.0001). CypA-/- mice had a clear reduction in inflammatory molecules (P<0.05) and less infiltrating neutrophils (P<0.001). UUO in WT mice resulted in significant renal fibrosis (3-fold increase in collagen IV deposition by immunostaining; P<0.001 vs sham), with significant infiltrates of macrophages (F4/80+ cells), T cells (CD3+ cells) and neutrophils (Ly6G+ cells) (all P<0.0001 vs sham). CypA-/- mice were not protected from renal fibrosis or leukocyte infiltration in the UUO model.

Conclusions: CypA contributes to leukocyte infiltration and inflammation leading to AKI following IRI. In comparison, the leukocyte infiltration and renal fibrosis seen following the less severe tubular injury in UUO does not require CypA. This contrast may relate to differences in CypA release/secretion by tubular cells in the two models.

SA-PO597

Preexisting CKD Impairs Recovery from AKI in Female Rats

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Background: We previously demonstrated that male rats with preexisting CKD exhibit impaired recovery from AKI and the subsequent development of *de novo* mechanisms of CKD progression. The goal of this study was to determine if impaired recovery from AKI is also observed in female rats with preexisting CKD.

Methods: We induced two levels of CKD in 10-12 week old male and female Sprague-Dawley rats by performing either 50% renal mass reduction via a right uninephrectomy (UNX, n=14, 6 females) or 75% renal mass reduction via a right UNX + surgical excision of 1/2 of the left kidney (3/4 NX, n=12, 6 females). Two weeks later, rats were subjected to 35 minute ischemia-reperfusion (IR)-induced AKI. Blood samples were obtained prior to IR and at 48 hours and 7, 14 and 28 days post IR to assess plasma creatinine (P_{Cr}). A 24-hour urine collection was performed in a subset of rats prior to IR and at 28 days post IR to assess proteinuria. At the end of the study, renal pathology and tubular vimentin expression were assessed.

Results: The severity of AKI, based on P_{Cr} levels 48 hours post AKI, was similar between UNX vs. 3/4 NX groups. The severity of AKI was lower (P<0.05) in females vs. males with 3/4 NX (1.9±0.3 vs. 3.3±0.3 mg/dl) but not significantly different between females vs. males with UNX (1.7±0.6 vs. 2.7±0.4 mg/dl). While minimal injury and vimentin expression (0.7±0.2) was observed in females with UNX, females with 3/4 NX exhibited greater (P<0.05) tubular vimentin staining (1.3±0.3), tubular injury and fibrosis 28 days post IR. Moreover, recovery of P_{Cr} over 28 days post IR was delayed in females with 3/4 NX vs. UNX. Finally, female rats with 3/4 NX developed substantial (P<0.05) increases in proteinuria 28 days post IR as compared to pre-IR levels (195±57 vs. 62±20 mg/day) while proteinuria was similar at 28 days post IR vs. pre-IR in female rats with UNX (21±4 vs. 23±5 mg/day). Males with 3/4 NX exhibited impaired recovery from AKI and the development of proteinuria 28 days post AKI as compared to males with UNX.

Conclusions: These data support previous studies documenting resistance to IR-induced AKI in female vs. male rats. However, our data indicate that preexisting CKD of greater than 50% renal mass reduction predisposes female rats to impaired recovery from AKI and the subsequent development of mechanisms of CKD progression, similar to male rats.

Funding: Private Foundation Support

SA-PO598

Double-Negative T-Cells That Express PD-1 Are Early Responders During Ischemic AKI

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Background: Unconventional T cells (e.g. Tregs and γδT cells) are increasingly recognized for their roles in maintaining homeostasis and protecting non-lymphoid tissues against injury/stress. CD4-CD8- double negative (DN) αβT cells are abundant in mouse and human kidneys, actively dividing in steady state and involved in protecting against ischemic AKI. However, there is less knowledge about DN T cells residing in kidney are known.

Methods: C57BL/6J (WT), B6.129P2-B2mtm1Unc/J (β2m KO), B6.129S2-H2dlAb1-Ea/J (MHC II KO), B6.129P2-H2-K1tm1Bpe H2-D1tm1Bpe/DcrJ (KD KO) and Nu/J mice were used for this study, n=3-7/group. Human kidney samples were from nephrectomies for renal cancers. Kidney lymphocytes were isolated and analyzed by flow cytometry.

Results: Our data demonstrates that kidney DN T cells are thymus-derived as lack of thymus significantly reduced the absolute count of DN T cells in kidney (WT, $2.2x10^4$ vs. Nu/J, $0.24x10^4$, P<0.05) and also comprised of two (PD-1^+ and NK1.1^+) subsets whose development and homeostasis are dependent on non-classical MHC class I molecules. Development of the NK1.1^+ subset is restricted by β2m-dependent non-classical MHC molecules as the frequency of NK1.1^+ DN T cells was significantly reduced in β2m KO (10.3±2) but not in KD-deficient mice (21.5±2) then WT mice (23.1±3, P<0.001). In contrast, homeostasis but not development of the PD-1 subset is regulated by β2m-dependent non-classical MHC molecules as the frequency of PD-1^+ DN T cells was significantly higher in β2m KO (70.2±5) then WT mice (44.2±3 P<0.001). DN T-cells are present in kidney of β2m KO mice, but lose their phenotypic activation (>60%, P<0.001), spontaneous steady proliferation (>40%, P<0.05) and undergo apoptosis. DN T cells retained in kidneys of β2m KO mice are mostly PD-1^+ and remain functionally responsive to external stimuli as indicated by their rapid activation and expansion in response to ischemic AKI. Both normal human kidney and cancer samples express the PD-1^+ (% normal, 39.5±8 vs. tumor, 47.9±7.8) and NK1.1^+ subsets (% normal, 26.2±8.4 vs. tumor, 23.0±8.3).

Conclusions: These findings demonstrate that kidney DN T cells, particularly PD-1^+ DN T cells, are early responders of the renal immune surveillance system utilizing recognition/activation/regulation mechanisms that differ from conventional T cells.

Funding: NIDDK Support

SA-PO599

Targeting Enhancer of Zeste Homolog 2 Protects Against AKI

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Background: Despite the established oncogenic and profibrotic functions of enhancer of zeste homolog 2 (EZH2), a methyltransferase that induces histone H3 lysine 27 trimethylation (H3K27me3), its role in acute kidney injury (AKI) remains unclear.

Methods: In this study, we examined the effect of EZH2 inhibition on acute kidney injury in murine models induced by induced by either ischemia-reperfusion (IR) or folic acid (FA).

Results: We demonstrated that EZH2 and H3K27me3 were upregulated in the murine kidney with AKI in both models. Pharmacologic inhibition of EZH2 with 3-deazaneplanocin A (3-DZNeP) inhibited tubular injury in both models as demonstrated by a decrease in renal dysfunction, reduced neutrophil gelatinase-associated lipocalin expression and a lower rate of renal tubule cell death. Injury to the kidney resulted in reduced expression of E-cadherin and ZO-1, whereas EZH2 inhibition largely preserved their expression. Moreover, 3-DZNep was effective in counteracting the increased expression of matrix metalloproteinase (MMP) -2 and -9 as well as the phosphorylation of Raf-1 and ERK1/2 in the injured kidney. Conversely, blocking EZH2 reversed the decrease of tissue inhibitor of metalloproteinase (TIMP)-2 and -3 and Raf kinase inhibitor protein (RKIP) in the kidney after acute injury. Similarly, oxidant injury to cultured kidney proximal tubular epithelial cells caused a decrease in the expression of E-cadherin, ZO-1, TIMP-2/-3, and RKIP as well as an increase in the expression of MMP-2/9 and phosphorylation of Raf-1 ERK1/2. Blocking EZH2 with 3-DZNep or SiRNA hindered these responses.

Conclusions: These results suggest that targeting EZH2 protects against AKI through a mechanism associated with the preservation of adhesion/junctions, reduction of matrix metalloproteinases and attenuation of the Raf-1/ERK1/2 pathway.

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SA-PO600

Deciphering the Role of Angpt4-Tie2 Signaling in the Kidney

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Background: The angiopoietin-Tie2 signaling pathway is fundamental for vascular development and has been linked to numerous kidney diseases including diabetic nephropathy and sepsis-related AKI. The pathway is composed of two receptors, Tie1 and Tie2, and three ligands, Angiopoiein-1, Angiopoietin-2 and Angiopoietin-4 (Angpt-4). Among the ligands, Angpt-4 has been poorly characterized. While Angpt4 has been suggested to act as a Tie2 agonist and seems to be highly regulated by hypoxia, its physiological role remains elusive. Moreover, the study of Angpt-4 function is currently challenging due to the lack of knockout transgenic model. In order to decipher its physiological role, we have developed a new Angpt4 mouse model.

Methods: We generated a new reporter and conditional allele for Angpt4 in mice. Using the X-gal chromogenic substrate of the β-galactosidase, this model allows us to characterize high-resolution expression pattern of Angpt-4. To identify the cell type expressing Angpt-4, we performed immunohistochemical staining on tissue sections using antibody coupled with the alkaline phosphatase enzyme. Global and timed deletion of Angpt4 was accomplished using ubiquitous and tetON inducible Cre-deletor lines.

Results: X-gal staining reveals strong expression restricted to the vasculature of organs including the kidney, adrenal glands, gonads, and mesentery. In the kidney, X-gal staining is found in the renal and interlobular arteries. Using an antibody against Transgelin (SM22), a marker of smooth muscle cells, we show Angpt-4 co-localizes with vascular smooth muscle cells in the kidney. Global KO mice survive to birth and renal function testing is underway.

Conclusions: Our data demonstrate a highly specific vascular pattern of expression for Angpt-4 in smooth muscle cells of the vascular wall. These observations suggest that Angpt-4 may have a role in arterial function with potential impact in the pathology of renal ischemia as Angpt-4 has been shown to be regulated by hypoxia.

SA-PO601

Targeting IL-17 Activity Protects from Salt Sensitive Progression of CKD Following AKI

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Background: Patients surviving AKI have a higher risk for chronic kidney disease (CKD). Previous studies in rats demonstrate that inhibition of T-cell activity (e.g., using mycophenolate or losartan) following recovery from AKI attenuates the subsequent development ofproteinuria, inflammation and fibrosis. Th17 cells, characterized by IL-17 secretion, are the predominant T helper subset associated with the AKI-to-CKD transition. Blockade of IL-17 activity using IL-17Rc receptor antagonist significantly decreased fibrosis and neutrophil recruitment in post ischemic rats compared to vehicle treated controls but other parameters of AKI-CKD transition have not been evaluated.

Methods: Male Sprague Dawley rats were subjected to unilateral I/R (40min) and allowed to recover for 5 weeks on low salt diet (0.4%). Rats were subjected contralateral nephrectomy UNx and elevated dietary NaCl (4%) for 4 additional weeks to hasten CKD. The rats were injected anti-IL-17 (5 mg/kg) or IgG control during the exposure to high salt diet and blood pressure measured by telemetry.

Results: Renal hypertrophy was evident in post-AKI IgG-treated rats relative to sham (~14%), which was significantly attenuated by IL-17 neutralizing antibody ($p<0.05$). There was a significant increase in the levels CD4+IL17+ cells and CD4+IFNγ+ cells in kidney of post AKI rats which was significantly reduced by IL-17 neutralizing antibody (IL17: IgG 17847±3787 and IL-17 7360±1680; p£0.05; IFNγ+: IgG 2703±495 and IL-17 1083±314; cells/g tissue p£0.05). Histological examination demonstrated that anti-IL17 antibody treatment reduced the level of renal fibrosis as indicated by picrosirius red staining. In addition, m-RNA expression of Kim-1 and Tgf-bwas reduced by 25% and 42% respectively. Mean arterial blood pressure was significantly attenuated by ~ 12 mm Hg in post-ischemic rats treated with anti-IL17 relative to vehicle treated post-AKI rats.

Conclusions: These data suggest that enhanced expression of CD4+IL-17 cells contribute to renal inflammation, fibrosis and hypertension in CKD following AKI.

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SA-PO602

Hypoxic Preconditioning Suppresses Renal Inflammation in Ischemic and Septic AKI

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Background: Prolyl-hydroxylases (PHDs) have emerged as safeguards of cellular metabolism through their oxygen sensing function, which enables them to regulate the activity of hypoxia-inducible factors (HIF). We previously reported that activation of HIF signaling via pharmacologic inhibition of PHDs (PHI) protects against kidney ischemia reperfusion injury (IRI). Here, we investigated whether HIF activation through exposure to normobaric hypoxia mimics the renoprotection induced by PHI. Using an unbiased metabolomic approach, we identified conserved metabolic responses between these interventions.

Methods: C57BL/6 male mice aged 8-10 weeks were subjected to normobaric hypoxia (8% O_2) for 48 hours prior to induction of AKI via unilateral renal artery clamping (IRI) or LPS administration. Untargeted metabolomic screening by a GC/MS and LC/MS based platform was performed in sera from mice treated with PHI or exposed to acute hypoxia.

Results: Pre-ischemic exposure to normobaric hypoxia attenuated kidney injury at day 3 post IRI as indicated by improved kidney histogical scores and a 2.3-fold reduction of *Kim1* mRNA levels in kidney homogenates compared to normoxic controls (n=7-8, P=0.0002). Furthermore, hypoxic preconditioning suppressed the expression of pro-inflammatory genes *Vcam1* and *Tnf*α by 2.6-fold (n=7-8, P<0.0001) and diminished the infiltration of $Ly6B.2^{+ve}$ cells in injured kidneys by 85% (P<0.0001) compared to controls. In a septic model of AKI induced by LPS, hypoxic preconditioning suppressed the transcripts of *Tnf*α and *Il-6* by 2.3- and 5-fold respectively (Day 1 post LPS, n= 11-14; p < 0.009). Comparative untargeted metabolomic analysis revealed that exposure to hypoxia and pharmacologic PHD inhibition led to significantly overlapping alterations in serum metabolome. For instance, serum levels of α-ketoglutarate, a TCA cycle metabolite, were reduced by 60% in the setting of hypoxic preconditioning (n=8, P <0.0001) and by 36% with PHD inhibition (n=8, P = 0.004) compared to their corresponding controls.

Conclusions: Our data demonstrate that exposure to normobaric hypoxia attenuates kidney inflammation in both IRI-and sepsis-induced AKI. Furthermore, PHD inhibition induced by exposure to hypoxia or pharmacologic means lead to metabolic reprogramming, which may play a critical role in regulating inflammatory responses in the context of AKI.

Funding: NIDDK Support

SA-PO603

Conditional Histone Deacetylase-2 Knockout Within Renal Tubular Cells Is Protective in Renal Ischemia-Reperfusion Injury

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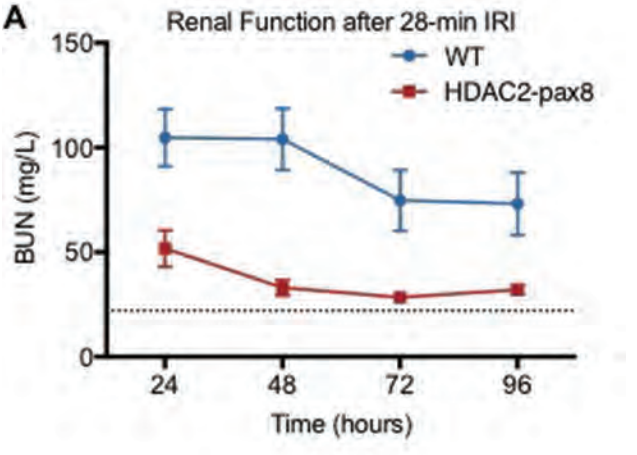
Background: Ischemia/reperfusion injury (IRI) is a major source of morbidity in renal transplantation and other surgical scenarios. In renal transplantation, IRI contributes to poor outcomes and early graft loss. Histone deacetylases (HDACs) regulate diverse cellular processes. We have previously shown that the class I HDACs 1 and 2 have reciprocal effects on renal ischemia-reperfusion injury (IRI) with HDAC1 deletion increasing vulnerability and HDAC2 protection providing profound protection. A more thorough understanding of the mechanism of this protection, including the site of action, is critical to develop specific targeting in IRI.

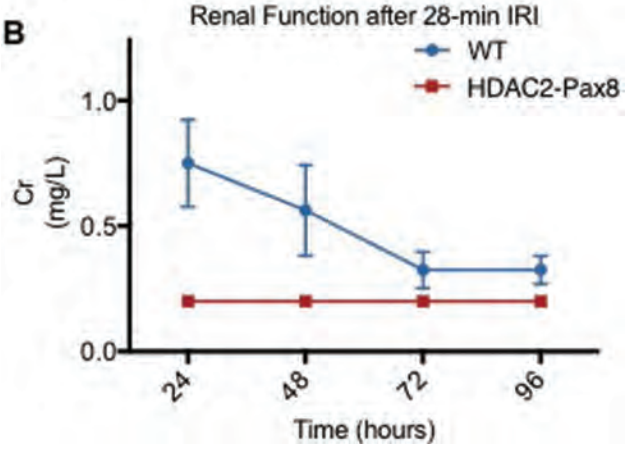
Methods: Renal tubule-specific tamoxifen-inducible HDAC-2 knockout (HDAC2-pax8), and tamoxifen-treated WT female (WT) control mice were used. Mice were subjected to warm renal IRI through unilateral clamping of the renal pedicle and contralateral nephrectomy under strict temperature control. Creatinine and BUN were examined at 24-, 48-, 72-, and 96-hours post-IRI.

Results: HDAC2-pax8 mice had significant protection from renal injury after renal IRI versus WT mice, as shown by decreased elevations in BUN and Cr post-injury (Figure 1, $p<0.005$).

Conclusions: Renal tubule-specific HDAC2 deletion is protective in a standardized model of renal warm IRI. We have now moved from showing efficacy with pan-HDAC inhibition to kidney-specific inhibition and now to proximal tubule-specific inhibition. This finding has important translational potential and provides guidance for identifying renal-specific targets for clinical use.

Funding: NIDDK Support, Other U.S. Government Support





SA-PO604

Renal Tubular Epithelial Cell Proliferation Inhibition by C-Reactive Protein and Myeloid Derived Suppressor Cells

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Background: Re-establishment of renal function after acute kidney injury (AKI) largely depends on the recovery of injured renal tubular epithelial cells (RTEC). However, the inflammatory response that accompanies AKI complicates RTEC recuperation. In a series of studies, we showed that C-reactive protein (CRP), a well-known biomarker of inflammation, plays a causal role in AKI *i.e.* human CRP transgenic mice (CRPtg) subjected to renal ischemia-reperfusion have more severe AKI compared to CRP knockout mice. Notably, for CRPtg the exacerbation of AKI is accompanied by increased renal infiltration by myeloid derived suppressor cells (MDSC), and depletion of human CRP blunts both MDSC infiltration and renal injury. In the present study we explored the CRP → MDSC → RTEC axis.

Methods: To determine the direct impact of human CRP on MDSC functions and RTEC health, and to establish whether MDSCs can suppress RTEC proliferation, primary mouse RTECs were isolated and mouse MDSCs were generated from bone marrow (BM-MDSC) and studied *in vitro* using microscopy, flow cytometry, and co-culture assays.

Results: We first confirmed that BM-MDSCs ($CD11b^+CD11c^-F4/80^-Ly6C^+Ly6G^+$ cells with an immature nuclear morphology) effectively suppressed the proliferation of CD3ε/CD28-stimulated $CD4^+$ T cells and that this BM-MDSC suppressive action is enhanced by human CRP. When human CRP was added to freshly isolated bone marrow, human CRP increased the proportion of BM-MDSCs ultimately generated and also increased the proportion of BM-MDSCs entering S phase. Co-cultures with BM-MDSCs in transwells inhibited the cell cycling of primary RTEC monolayers.

Conclusions: Our results show that human CRP promotes the generation of MDSCs from bone marrow precursors and enhances their ability to suppress target-cells. Our initial evidence suggests BM-MDSCs suppress primary RTEC cell cycling in a contact-independent manner. These new *in vitro* data align with our earlier observation that AKI is worsened in CRPtg. We hypothesize that in CRPtg with AKI, human CRP enhances the noxious effects of renal infiltrating MDSCs, thereby promoting inhibition of RTEC and delaying their recovery. Ongoing work investigates whether human CRP enhances the MDSC-mediated suppression of RTEC proliferation and whether this effect requires MDSC expression of CRP receptor(s).

Funding: NIDDK Support

SA-PO605

Impact of Ciprofloxacin on Renal Tubular Epithelial Injury Through the Interaction of Autophagy and Apoptosis

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Background: Autophagy and apoptosis play an important role in renal tubular epithelial injury by hypoxia, nutrient deprivation, and oxidative stress. Recent research reported that antibiotics might contribute to ischemic renal injury characterized by both apoptosis and inflammation, but the mechanism remains unclear. Therefore, we investigated the impact of ciprofloxacin on renal tubular epithelial injury through the interaction of autophagy and apoptosis.

Methods: We used MDCK cells, a model for renal distal tubular epithelial cells. We performed TUNEL assay to identify the effect of ciprofloxacin for cell viability under nutrient deprivation for 48 hours (hrs). We assessed apoptosis and autophagy markers to investigate the effect of ciprofloxacin through the interaction between apoptosis and autophagy.

Results: In the TUNEL assay, the ratio of apoptotic cells/total cells was significantly lower in the ciprofloxacin group (100 ug/mL) than in the control group (0 ug/mL) (7.17 ± 1.25 vs. 20.41 ± 1.04, $P < 0.001$). Among apoptosis markers, the ratio of pBax/Bax was reduced at 6 hr, and pBcl-2/Bcl-2 was increased at 12 hr in the ciprofloxacin group compared with the control group. In the MAPK pathway, located further upstream of Bax and Bcl-2, the ratio of pJNK/JNK, pp38/p38, and pERK/ERK was decreased at 12 hr in the ciprofloxacin group compared to the control group. The ratio of cleaved caspase 3/caspase 3, the final effector caspase, was decreased at 36 hr in the ciprofloxacin group compared with the control group. Among autophagy markers, the level of Beclin-1 was increased at 6 hr in the ciprofloxacin group compared with control group, and the level of LC3B was increased after 12 hr. Finally, activation of autophagy by ciprofloxacin during apoptosis by nutrient deprivation might cause recovery of renal tubular epithelial injury.

Conclusions: Ciprofloxacin can help to restore cell viability against renal tubular epithelial injury under nutrient deprivation condition, and the cell viability by ciprofloxacin might be associated with the crosstalk of autophagy and apoptosis. Therefore, ciprofloxacin is helpful to increase cell viability through activation of autophagy under ischemic renal injury.

SA-PO606

5-HT1F Receptor Mediates Renal Vascular Homeostasis and Mitochondrial Biogenesis

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Background: Acute kidney injury (AKI) is a devastating disease with no treatment options. After AKI, there is a marked reduction in renal vasculature. Thus, promoting vascular recovery following AKI could facilitate renal repair as the vasculature is responsible for carrying oxygen and nutrients to extravascular tissues. Our laboratory has shown that stimulating mitochondrial biogenesis (MB) through the $5\text{-}HT_{1F}$ receptor stimulates recovery from AKI. In contrast, $5HT_{1F}$ receptor knockout mice have decreased MB and poor renal recovery. Importantly, induction of MB has been linked to increased angiogenesis. Thus, we hypothesized that the $5HT_{1F}$ receptor plays a role in vascular homeostasis and mediates MB in renal endothelial cells.

Methods: Primary human glomerular endothelial cells (HEC) and mouse glomerular endothelial cells (MEC) were treated with the $5\text{-}HT_{1F}$ receptor agonists LY344864 or lasmiditan (0-500 nM) for 24 or 72h. Mitochondrial respiration using Seahorse analysis, mitochondrial proteins using immunoblot analysis and mitochondrial copy number using qPCR analysis was determined. Immunohistochemical analysis for CD31 was performed on paraffin embedded kidney sections.

Results: We determined that HEC and MEC express the $5\text{-}HT_{1F}$ receptor. Treatment of HEC and MEC with LY344864 or lasmiditan induced MB, as evidenced by maximal mitochondrial respiration, a marker of MB. HEC that were treated with lasmiditan or LY344864 had increased expression of nuclear- and mitochondrial-encoded proteins (PGC1α, TFAM, NDUFS1, COX-1, and VDAC) and mitochondrial DNA copy number, confirming MB and increased mitochondrial content. Lastly, $5\text{-}HT_{1F}$ receptor knockout mice had decreased renal vascular content, as immunohistochemical analysis revealed decreased $CD31^+$ renal endothelial cells.

Conclusions: Stimulation of $5\text{-}HT_{1F}$ receptor with LY344864 and lasmiditan induces MB in HEC and MEC, *in vitro*, and $5\text{-}HT_{1F}$ receptor mediates vascular homeostasis, *in vivo*. We propose that inducing MB in endothelial cells after AKI could restore vascular function and stimulate renal repair and recovery.

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SA-PO607

Abnormal Uromodulin Glycosylation in AKI and Its Interaction with Protein in Lectin Pathway of Complement

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Background: Uromodulin (UMOD) is a glycoprotein with a carbohydrate content, nearly 30%. It might protect against urinary tract infection and kidney stones, have roles in kidney injury and innate immunity. Many functions were glycosylation dependent. Mannose binding lectin (MBL) and collectin 11 (CL-11) were the initiated protein of lectin pathway (LP) with a carbohydrate-recognition domain (CRD). In the present study, we measured the glycosylation of acute kidney injury (AKI) patients and the binding affinity of UMOD to lectin pathway protein in modified glycosylation of uromodulin

Methods: 10 AKI patients and 10 healthy control recruited for this study after matched their age and gender. After purified the UMOD with diatomaceous earth, structure of the protein glycosylation chains was analyzed using matrix assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS). Different kinds of glycosidase digested UMOD to make glycan-deficient protein. Binding affinity of uromodulin to MBL and CL-11 were probed by ELISA

Results: The profile of MALDI-TOF-MS N-glycans released from uromodulin healthy control showed more complex N-glycan structures. The amount of high mannose and core fucosylation were increase in the AKI patients compare with those healthy control ($P<0.05$). Native uromodulin could bind to CL-11 (Ca^{2+} independent) and MBL(Ca^{2+} dependent). The binding activity of UMOD to CL-11 was significantly decreased by digesting the protein with fucosidase and neuraminidase. Digested by EndoH could decrease the binding activity as well, while the decrease was slightly.

Conclusions: Abnormal glycosylation of UMOD could be observed in AKI patients. UMOD bind to lectin pathway protein, and this interaction was dependent on glycan structure of UMOD.

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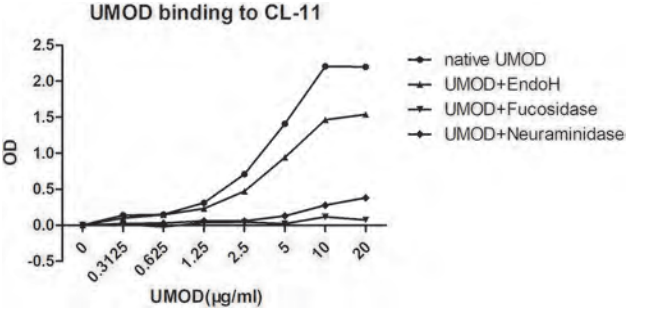

SA-PO608

Hes1, a Newly Identified Downstream Mediator of α7nAChR on Macrophages in the Cholinergic Anti-Inflammatory Pathway, Plays a Protective Role in AKI

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Background: The cholinergic anti-inflammatory pathway (CAP) links the nervous and immune systems and modulates innate and adaptive immunity. Activation of the CAP by vagus nerve stimulation (VNS) exerts protective effects in a wide variety of clinical disorders including rheumatoid arthritis and Crohn's disease. The CAP involves splenic alpha7-nicotinic acetylcholine receptor (α7nAChR)-positive macrophages although their detailed role *in vivo* has yet to be established.

Methods: RNA-seq using peritoneal macrphages from WT and α7nAChRKO mice was performed after nicotine and/or LPS treatment. Kidney IRI (bilateral, 26 mins) was used as an acute kidney injury model and was performed 24 hr after VNS (left side, 5 Hz, 50 μA for 10 min) treatment or adoptive transfer of treated-macrophages. Kidney injury was evaluated 24 hr later using plasma creatinine, kidney Kim-1 mRNA expression and histology (H&E). TNF level in the media was measured by ELISA and RAW 264.7 cells were used as macrophages for the experiments requiring modifications of gene expression.

Results: Adoptive transfer of $1x10^5$ nicotine-treated peritoneal macrophages from $\alpha7nAChR^{+/+}$ (α7WT; progeny control) but not from $\alpha7nAChR^{-/-}$ (α7KO) mice protected kidneys of recipient mice from IRI, showing the importance of α7nAChR on macrophages. Nicotine-induced genes whose expressions were lower (<1/2 compared to $\alpha7nAChR^{+/+}$-derived cells) in $\alpha7nAChR^{-/-}$-derived peritoneal macrophages were extracted by RNA-seq. We focused on hairy and enhancer of split-1 (Hes1), a basic helix-loop-helix (bHLH) transcription factor that acts as a transcriptional repressor of genes that require a bHLH protein for their transcription. VNS induced Hes1 expression in peritoneal macrophags. siRNA against Hes1 inhibited nicotine-induced TNF suppression, and Hes1 overexpression suppressed LPS-stimulated TNF induction in RAW 264.7 cells. Hes1 overexpression in RAW 264.7 cells mainly induced macrophage M2 markers (anti-inflammatory). Lastly we found that adoptive transfer of Hes1-overexpressing RAW 264.7 cells protected the kidney from IRI.

Conclusions: These data demonstrate that Hes1 is a new downstream signaling molecule of α7nAChR in the CAP.

Funding: NIDDK Support

SA-PO609

Influence of Renal Ischemia-Reperfusion Injury on Renal Neutrophil Gelatinase-Associated Lipocalin Receptor (24p3R) in Rats

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Background: The neutrophil gelatinase-associated lipocalin (NGAL) receptor (24p3R) is expressed in distal nephron, and contributes to the endocytosis of NGAL in urine. This study was undertaken to evaluate an influence of renal ischemia-reperfusion injury on 24p3R.

Methods: Unilateral renal pedicle was clamped for 0, 10, 20, 30, or 45 min in male Wistar rats. Urine was collected for 24hours after reperfusion, and ischemic kidney was obtained.

Results: Renal NGAL mRNA expression and urinary NGAL excretion elevated in rats with renal ischemia for more than 20min. On the other hand, renal mRNA expressions of 24p3R, and megalin and cubilin which are expressed in proximal nephron and uptake NGAL in urine, decreased in animals with renal ischemia for more than 20min. Renal protein expressions of 24p3R and megalin decreased in rats with renal ischemia for 30 and 45min.

Conclusions: This study showed for the first time that renal 24p3R decreased in response to renal ischemia. As NGAL in urine is reabsorbed by the megalin-cubilin complex at the proximal nephron and by the 24p3R at the distal nephron, the down-regulations of these proteins might contribute to the elevated urinary NGAL excretion in rats with renal ischemia-reperfusion injury.

SA-PO610

Lipopolysaccharide Induces Filtrate Leakage from Tubular Lumen to Interstitial Space via Proximal Tubular TLR4-Dependent Pathway in Mice

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Background: We previously reported by using intravital imaging technique that lipopolysaccharide (LPS) slowed proximal tubular flow rate in an early phase of endotoxemia. However, the mechanism by which LPS reduced tubular flow rate was unclear. Hereby, we hypothesized that LPS might disrupt tight junction in proximal tubular cells and induce leakage of filtrate through a Toll-like receptor 4 (TLR4)-dependent mechanism.

Methods: Tubular flow rate was determined by the timing of the appearance and disappearance of intravenously injected dyes in the early segments of proximal tubules in mice under 2-photon laser microscopy observation.

Results: LPS at 5 mg/kg did not change the inflow rate of filtrate into the proximal tubules, which reflect unchanged GFR, and significantly reduced the outflow rate from the proximal tubules at 6h. LPS at 15 mg/kg reduced both inflow and outflow rate. Both dosages of LPS induced oliguria. LPS (5 mg/kg) induced paracellular leakage of FITC-inulin and reduced tight junction mRNA expression (occludin and cldn2). LPS also increased water content, interstitial hydrostatic pressure and Na^+/K^+ ratio in the kidney, indicating the accumulation of extracellular fluid in the interstitium. These changes were diminished by the conditional knock out of TLR4 in proximal tubules. Furthermore, denuding renal capsule further slowed tubular flow down, suggesting that increasing interstitial pressure might counteract the leakage.

Conclusions: Our results suggest that LPS disrupted tight junction of proximal tubular cells via a TLR4-dependent mechanism, resulting in paracellular leakage of filtrate to interstitium in an early phase of endotoxemia in mice.

Funding: Government Support - Non-U.S.

SA-PO611

Clinician Attitudes Toward Implementation of Precision Medicine

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Background: Advancements in understanding the genetic basis of CKD & pharmacogenomic drug dosing are facilitated by the discovery of genetic predictors. We implemented precision medicine testing in our renal clinics to assess CKD progression risk and hypertension drug dosing.

Methods: Physicians on nephrology services (N=42) were surveyed about their knowledge, attitude & willingness to act on genetic testing results. A 26 question survey was graded on a LIKERT scale from "strongly agree" to "strongly disagree." Respondents were stratified according to knowledge & attitude. Statistics were calculated with a Fisher's exact test. We hypothesized clinicians who agreed sufficient evidence was available to support implementation would have more positive attitudes & greater willingness to act on genetic data.

Results: Respondents were grouped as those who agreed there is sufficient evidence to implement genetic testing (supporters N=14) & those who disagreed (nonsupporters N=28). Compared to nonsupporters, supporters agreed that: 1) genetic testing helps them better identify etiology of CKD (p=0.05), 2) the presence of 2 *APOL1* risk alleles impacts their management of focal segmental glomerulosclerosis (p=0.05), 3) testing could change their choice of antihypertensives (p=0.01) and 4) testing will help to delay the progression of CKD (p=0.006). Most respondents agreed (98%) that a patient's genetic profile can influence their response to antihypertensives. We assessed the attitude of clinicians toward genetic testing by asking "whether a discussion of genetic test results is too time-consuming for an encounter". Clinicians who agreed (negative attitude N=19) & those who disagreed (positive attitude N=23) showed differences in their willingness to act on genetic data. Those who felt there is sufficient time to discuss results also agreed that genetic testing of CKD patients provides information that changes their dialysis preparation strategies (p=0.02).

Conclusions: Physicians with greater awareness of the evidence supporting implementation of genomic testing appear to be more likely to act on the genomic results.

Funding: Clinical Revenue Support

SA-PO612

A Novel Nomogram to Predict the Reliability of Estimated Glomerular Filtration Rate Formula in Oncology Patients

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Background: Formulae of estimated glomerular filtration rate (eGFR) based on serum creatinine (Scr) are routinely used for drug dosage in oncology patients, however, they are inaccurate in some populations. Our aim was to identify population characteristics where eGFR formulae performed poorly and thereby build a nomogram to predict the reliability of estimates.

Methods: Measured GFR (mGFR) using isotope from 444 oncology patients were compared with eGFR from four formulae (Cockcroft-Gault, de-indexed MDRD, de-indexed CKD-EPI and Wright). Multivariate logistic regression was applied to identify characteristics associated with inaccurate eGFR and construct a predictive nomogram.

Results: The Cockcroft–Gault formula exhibited estimates with lowest bias and highest precision. Nonetheless, it was still unreliable in a relevant proportion of patients. The percentage of patients within 30%, 20%, and 10% of the accurate percentage error (APE) was seen in only 62.8%, 47.7% and 24.8% of patients respectively. Inaccuracy was

found in overweight patients or in patients with BUN/Scr ratio greater than 20 or with eGFR greater than 60 ml/min/1.73m^2. A novel nomogram was constructed to help oncologists to predict the risk of inaccuracy of eGFR. The calibration curve showed good agreement.

Conclusions: Our results suggest that all eGFR formulae tend to overestimate the eGFR in oncology patients. Our nomogram may assist oncologists in decision-making when mGFR is needed.

SA-PO613

Mechanism of Difference in Plasma and Urinary Clearance Glomerular Filtration Rate (GFR) Determinations

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Background: It is well established, but not understood, that plasma clearance GFRs exceed urinary clearance GFRs for the same filtered marker, often by 5-10%. Therefore, the present studies were undertaken to determine the role of proximal tubule endocytosis in reducing urinary excretion of filtration markers.

Methods: To visualize and quantify the effect of PTC uptake on reducing urinary GFR determinations freely filterable fluorescently labeled dextrans, inulin and small molecular weight proteins were investigated. All had a glomerular sieving coefficient of 1.0, and given by bolus intravenous administration. Ratiometric analysis of 2-photon images and urinary quantification of neutral (TRITC) and negatively charged (FITC) markers was used to quantify PTC uptake and the effect of charge on PTC uptake.

Results: Intravital 2-photon imaging revealed PTC endocytic uptake of freely filtered GFR markers was rapid, dose and time dependent. pH mediated quenching of FITC fluorescence resulted in a pseudo-reduction in apparent PTC uptake of FITC labeled markers. Neutrally charged fluorescent markers were internalized by PTC $S_2 > S_1$. Negatively charged FITC dextrans and inulins were preferentially taken up versus a neutral TRITC inulin, particularly in S_1 PTC. Two-photon imaging demonstrated that a negative charge increased PTC uptake, as the injected ratio of FITC /TRITC inulin was increased from 0.504 to 0.729 +/- 0.056 for a 45% increase in negatively charge inulin uptake. On the other hand, the urine FITC/TIRTC ratio decreased 38.7% +/-0.1%, consistent with increased PTC endocytosis of negatively charged inulin.

Conclusions: PTC reabsorbed filtration markers, including inulin, in a dose and time dependent fashion via endocytosis. PTC uptake explains in part the reduction in urinary compared to plasma GFR clearance. Finally, a negative charge on these molecules increases uptake by PTC, especially in the S1 segment.

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SA-PO614

Renal and Dialytic Clearances of Uremic Solutes

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Background: Many uremic solutes are protein bound and removed by proximal tubular organic anion transporters (OATs) rather than filtration.

Methods: In 4 subjects undergoing right heart catheterization, samples were obtained from the right renal vein and the inferior vena cava below the renal veins.Total and ultrafiltrate concentrations of uremic solutes were measured utilizing MS-HPLC.

Results: Renal extraction ratio (removal across the renal vascular bed) and renal excretion fraction (renal clearance of solute relative to creatinine) varied greatly. HA and PAG exhibited the highest renal extraction ratios and excretion fractions approximating values reported for para-amino-hippurate (PAH). The dialytic clearance of these solutes exhibited the same pattern but never exceeded estimated creatinine clearance. Highly bound solutes (IS, PCS) exhibited low renal extraction and low renal excretion fractions. KA was an anomaly. Though highly bound, renal extraction and excretion were higher than expected, possibly related to pKa or other unique properties of this solute.

Conclusions: The findings suggest that endogenous hippurate clearance might provide a measure of effective renal plasma flow. The finding that uremic retention solutes such as IS, PCS, and KA, known to bind to OAT receptors on vascular endothelium where they act as transcription factors, are also tightly bound to albumin suggests that protein binding serves to deliver solutes to receptors in a manner analogous to the delivery of hormones, bound to carrier proteins, from an endocrine source to distant receptors.

Funding: Private Foundation Support

Protein binding, extraction, and excretion of Uremic Retention Solutes

	Protein Binding	Extraction Ratio	Excretion Fraction	Hemodialyzer Clearance*
Hippuric acid (HA)	0.68	0.79 +/- 0.16**	4.12 +/- 1.64	108
ϕ acetyl glutamine (PAG)	0.08	0.68 +/- 0.09	3.69 +/- 0.65	168
Kynurenic acid (KA)	> 0.95***	0.43 +/- 0.11	2.01 +/- 0.24	41
Indoxyl sulfate (IS)	0.91	0.11 +/- 0.20	0.72 +/- 0.14	26
p-cresyl sulfate (PCS)	0.92	0.06 +/- 0.14	0.24 +/- 0.03	18
Indole 3 acetic acid (I-3A)	0.60	0.05 +/- 0.12	0.08 +/- 0.06	70
ϕ sulfate (PS)	0.51	0.01 +/- 0.13	0.28 +/- 0.07	49
Kynurenine (KY)	0.39	0.35 +/- 0.07	0.01 +/- 0.01	96

*In ESRD patients(PLoS ONE 13(2): e0192770) **Mean +/- SD *** Minimum estimate based on levels below the limit of detection, 0.002

SA-PO615

The Pathophysiology of Augmented Renal Clearance Similarly Affects Hepatic Clearance in Critically Ill Trauma Patients

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Background: In trauma, the systemic inflammatory response and intensive care therapy leads to a hypermetabolic state described as Augmented Renal Clearance (ARC). Literature has shown an association between ARC and sub-therapeutic antibiotic concentrations and suggests worst clinical outcomes. We examined whether hepatic clearance is also augmented in trauma by measuring Dilantin levels (DL), a drug primarily metabolized by the liver.

Methods: A retrospective review of the trauma registry at our level 1 trauma center was conducted from 2009 to 2014 for adults admitted for traumatic brain injury receiving Dilantin. Patients with acute kidney injury were excluded. GFR was estimated using CKD-Epi formula. DL were corrected for hypoalbuminemia (<3 g/dL) and compared between ARC patients (eGFR ≥ 130) and those without (nARC) at 24, 48 hours, and 72 hours.

Results: There were a total of 98 nARC (eGFR= 97.4) and 20 ARC patients (eGFR=133.3) all of which dosed similarly. ARC patients were younger, had lower creatinine and DL at 72 hours. At 48 and 72 hours the correlation comparing eGFR to DL is negative ($p<.05$). At 48 hours ALT levels were significantly higher ($p<0.05$).

Conclusions: ARC patients had lower DL at 24 and 48 hours, and DL correlated negatively with GFR augmentation. ALT and AST levels were higher in the ARC patients possibly due to increased hepatic function. In ARC, hepatic clearance may also be augmented raising issues of drug dosing regardless of renal or hepatic metabolism.

Descriptive statistics comparing ARC vs non-ARC patients

	non-ARC (n=a98)	ARC (n=20)	
	mean	mean	P-value
Age	53.45	30.2	<.001
Creatinine at 48 hours	0.86	0.63	<.001
Dilantin level at 72 hours	12.24	9.32	0.007
GFR on admission	89.93	125.40	<.001
GFR at 24 hours	94.54	134.10	<.001
GFR at 48 hours	97.94	133.30	<.001
Average GFR	94.01	130.94	<.001
ALT at 48 hours	23.35	38.92	<.05

SA-PO616

Probability of Target Attainment Estimated by Residual Blood Sampling Agrees with Intensive Sampling Predictions

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Background: Patients with critical illness and multiple organ failure have altered pharmacokinetics and are at risk of over- or under- dosing. Patient-specific estimates of target attainment require timed and repeated phlebotomy. This additional loss of blood is undesirable and, in a research setting, requires individual informed consent. Blood tests ordered for clinical purposes rarely consume the entire sample volume. We hypothesized that residual blood samples could be used to estimate target attainment in critically ill patients.

Methods: We adapted Bayesian population-pharmacokinetic statistical tools to accommodate the sparse sampling and irregular timing of clinical samples. This method incorporates dosing history, a priori estimates of population heterogeneity, other available clinical information, and patient-specific measurements of piperacillin concentration in residual blood samples to estimate patient-specific probability of target attainment. We compared these estimates to a gold-standard estimate of target attainment using intensive repeated sampling in ten patients.

Results: There was excellent agreement between the two methods. Just one of ten subjects was misclassified as having failed to meet target exposure, and that was in a subject whose residual sample was obtained 72 hours prior to intensive sampling for the gold-standard estimate. Excluding this subject, the correlation between the residual and gold-standard estimate of drug exposure was 0.91 (95% CI: 0.62, 0.98). No subjects were misclassified as having attained target exposures when they had not.

Conclusions: Although this was a small sample, consistent results in this subtype of patient demonstrates that residual blood sampling may be useful for the estimation of antibiotic target attainment. As a result, residual blood sampling may be an efficient use of patient blood, a scarce resource, for pharmacokinetic measurements and therapeutic drug monitoring. Overall, residual blood sampling would reduce blood loss and potentially lower requirements for blood transfusion during a prolonged hospital stay. In addition, use of residual blood sampling may increase research participation, as it would allow for the avoidance of additional venipuncture which is often a common barrier to consent.

Funding: Commercial Support - Baxter Healthcare

SA-PO617

Prevalence and Adverse Outcomes Associated with Opioid Prescriptions Across the Range of eGFR

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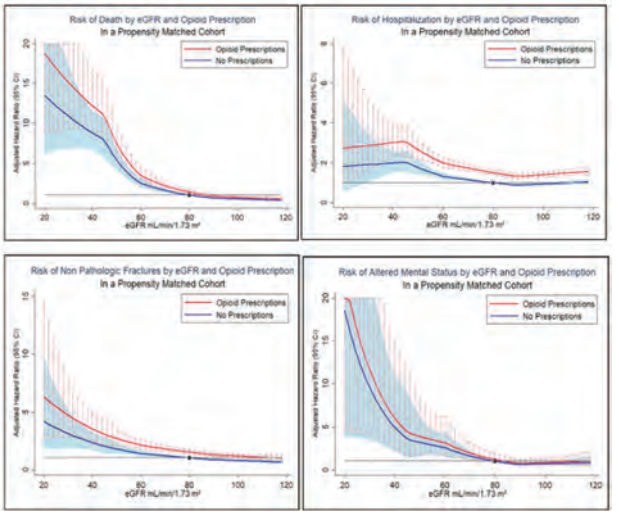
Background: Kidney disease limits therapeutic options for pain control given the relative contraindication to non-steroidal antiflammatory drugs. The goal of this study was to assess the prevalence and safety of prescription opioid use across the range of eGFR in a U.S. outpatient population.

Methods: Using electronic medical records from the Geisinger Health System, we described trends in opioid prescriptions by CKD stage between 2011 and 2016. In a cohort matched on propensity for ≥2 opioid prescriptions during a 2-year baseline period (2011-2013) we used Cox proportional hazards regression to evaluate the association between opiate prescription compared to no opiate prescription and death, total hospitalizations, non-pathologic fracture, and presentations for altered mental status, as well as whether associations differed by eGFR level.

Results: Opioid prescriptions increased over time, particularly among patients with eGFR < 30 ml/min/1.73m². For example, 43.5% patients with eGFR < 30 ml/min were prescribed opioids in 2011 compared to 46.4% in 2016 (p for trend < 0.001). Among 22,261 patients receiving at least two opiate prescriptions during the baseline period, a suitable match was found for 5,337 based on 23 clinical and demographic covariates. Patients with opioid prescriptions had significantly increased risk for death (HR 1.39, 95% CI 1.16-1.67), hospitalization (HR 1.51, 95% CI 1.39-1.63), and non-pathologic fracture (HR 1.51, 95% CI 1.33-1.72) compared to their counterparts for all levels of eGFR (p >0.05), but differences in altered mental status were not statistically significant (HR 1.22, 95% CI 0.79-1.88) (**Figure**).

Conclusions: Opioid prescriptions are common in patients with CKD and are associated with higher risk for death, hospital admissions and non-pathologic fracture.

Figure. Adjusted hazard ratios for (A) death, (B) hospitalization, (C) non-pathologic fracture and (D) altered mental status comparing those with and without opioid prescriptions in the baseline period across different levels of eGFR.



SA-PO618

G-Protein Signaling and Kappa Opioid Mediated Aquaresis

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Background: Kappa opioid agonists act centrally to inhibit antidiuretic hormone (ADH) secretion and increase renal sympathetic nerve activity. Together, these effects lead to a water diuresis. However, the signaling pathway by which kappa opioid receptor (KOR) activation produces these effects remains unknown. In prior studies, we have shown that activation of opioid receptor like one (ORL1) by the ligand nociceptin produces a marked diuresis in rats by a downstream G-alpha z protein pathway that inhibits ADH secretion. These studies investigated whether central G-alpha protein signaling pathways also contribute in producing the diuretic and/or antinatriuretic response to central administration of the kappa opioid agonist, U-50488H.

Methods: Sprague Dawley rats were implanted with an intracerebroventricular (i.c.v.) cannulae and pretreated with vehicle or pertussis toxin (PT), which inhibits the Gi/o family of proteins except for Gz. After 48-hrs pretreatment, rats were instrumented with cannula in the femoral artery, vein, and bladder and infused i.v. with isotonic saline (55 µl/min). After stabilization, blood pressure (BP), heart rate (HR), and urine output (V) was collected in conscious rats before (control) and for 90-min after (10-min collections) i.c.v. U-50488H (n=6).

Results: In vehicle pretreated rats, i.c.v. U-50488H produced a marked increase in V (max Δ, 101±8 ul/min) and decrease in urinary sodium excretion (UNaV; max Δ, 5±0.5 ueq/min). The diuretic response produced by U-50488H was significantly ($p<0.05$) blunted by pretreatment with PT (max Δ, 57±3 ul/min). In contrast, PT did not alter the decrease in UNaV. U-50488H did not alter BP or HR in either group. To explore which G-alpha proteins may participate in mediating the kappa diuresis, separate rats were pretreated i.c.v. (24-hrs) with an oligodeoxynucleotide (ODN), which selectively targeted a specific G-alpha protein. In these studies, pretreatment of groups of rats (n=6/group) with a single ODN for either Gi1, Gi2, Gi3, Go, or Gz, failed to blunt the maximal diuresis as compared to the increase in V produced by i.c.v. U-50488H in scrambled ODN treated rats.

Conclusions: These results demonstrate that central kappa opioids produce a pertussis toxin sensitive diuresis, but not antinatriuresis. This suggests that a combination of Gi/o proteins may be required to produce the aquaretic effects of kappa opioid agonists.

Funding: Other NIH Support - NIH NIGMS COBRE 5P30GM106392

SA-PO619

Ouabain Regulated Phosphoproteome Reveals Molecular Mechanisms Behind Na,K-ATPase Control of Cell Adhesion, Proliferation, and Survival of Renal Cells

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Background: Ouabain, a Na,K-ATPase ligand, triggers calcium release and Erk phosphorylation. Ouabain protects from apoptosis and stimulates proliferation and cell contact in primary and immortalized kidney epithelial cells. However, the mechanisms that connect the calcium and Erk signaling with the downstream effects are unknown.

Methods: We have performed a proteomic and phosphoproteomic study on COS cells, derived from embryonic monkey kidney. Cells were treated with ouabain for 10 and 20 min in concentrations that do not increase $[Na^+]_i$. Hierarchical clustering was applied to describe the temporal pattern of phosphorylation events. Gene ontology analysis was then used to examine whether phosphorylation events with different temporal patterns regulate distinct cellular processes. To verify the significance of identified proteins, siRNA studies were performed on primary rat proximal tubule cells.

Results: We identified 1941 ouabain-regulated sites that were either phosphorylated or dephosphorylated in a transient or sustained manner. The state of phosphorylation for proteins associated with cell adhesion and proliferation was prominently altered by ouabain. Analysis of protein-protein interaction networks showed a high connectivity of phosphoproteins that regulate cell adhesion and cell proliferation. Protein kinases and calcium dependent protein kinases were enriched among the proteins where the phosphorylation state is regulated by ouabain. Downregulation of protein expression by siRNA showed that CaMKK1 and CaMK2γ are essential for ouabain protection from apoptosis caused by serum deprivation or exposure to high glucose

Conclusions: This study represents a major advancement in the understanding of the dual function of Na,K-ATPase as an ion pump and as a signal transducer. It offers an insight into the role of ouabain for kidney growth and development and for protection against apoptosis.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO620

Prescribing and Safety of Direct-Acting Oral Anticoagulants Compared to Warfarin in Atrial Fibrillation Patients on Chronic Hemodialysis

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Background: ESRD patients on hemodialysis (HD) were excluded from safety and efficacy studies of direct-acting oral anticoagulants (DOACs) in atrial fibrillation (AF). The objective of this study was to evaluate prescribing, dose selection, and safety outcomes of DOACs compared to warfarin in AF patients on chronic HD. Secondary objectives were to evaluate major ISTH bleeding and clinically relevant non-major bleeding (CRNMB).

Methods: This was a retrospective study of AF patients on outpatient HD and oral anticoagulation (OAC) with warfarin or DOAC from April 2010-April 2016. Records were obtained from metro area CHI Health System and Dialysis Clinics Inc. Data was analyzed using descriptive statistics, ANOVA and chi-square.

Results: 91 patients were included (52% male, 79% white, mean age 69). Average CHA_2DS_2Vasc was 4.6 and HASBLED was 3.8. Warfarin was the initial OAC in most patients (n=76), mean dose 29mg/week. 15 patients were initially on DOACs: apixaban 2.5mg (n=7), apixaban 5mg (n=5), dabigatran 75mg (n=2), and dabigatran 150mg (n=1). Of 14 patients whose initial OAC was switched, 12 switched to apixaban 5mg or 2.5mg. Initial apixaban was dosed appropriately in most patients (83%) compared to apixaban switches (42%) where 9 on low dose did not meet dose reduction criteria. HASBLED scores were higher in switched patients not dosed appropriately (4 vs. 3.2, p=0.156). 26 patients experienced a bleed, with significantly more bleeding in warfarin compared to DOAC (31% vs 28%, p=0.022) patients. Most major bleeds (n=7), CRNMB (n=12), and major plus CRNMB (n=1) occurred with warfarin alone. Bleeding in DOAC patients: 1 on warfarin to dabigatran 75mg (major), 1 on warfarin to apixaban 2.5mg (major), 2 on apixaban 2.5mg (CRNMB), 1 on warfarin to dabigatran 150mg (major and CRNMB), and 1 on dabigatran 150mg to apixaban 5mg (major and CRNMB).

Conclusions: More HD patients were prescribed warfarin initially and more of these patients experienced a bleed. More prescribers selected appropriate dose apixaban as the initial DOAC or switched to it as low dose when dose reduction criteria were not met.

Bleeding occurred in DOAC patients with prior warfarin therapy, switching between DOACs, and maintained on the initial DOAC. Larger studies evaluating DOAC prescribing and impact on safety in AF patients on chronic HD are warranted.

SA-PO621

Increasing Use of Direct Oral Anticoagulants Among Hemodialysis Patients with Medicare Prescription Drug Coverage

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Background: For decades, warfarin was the only agent to be used for long-term anticoagulation. Since 2010, a series of direct oral anticoagulants (DOACs) have been approved by the United States Food and Drug Administration, including dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. The efficacy and safety of DOACs in hemodialysis (HD) patients is poorly understood. We assessed trends in utilization of warfarin and DOACs among HD patients in 2011-2015.

Methods: We analyzed data from the United States Renal Data System. For each calendar month from January 2011 to December 2015, we identified patients who underwent HD and were enrolled in Medicare Part C or D; we also assessed whether HD was delivered in a facility or at home. From pharmacy claims, we identified whether each patient possessed a supply of warfarin, rivaroxaban, apixaban, or edoxaban. We estimated percentages of patients with a supply of any anticoagulant, any DOAC, and individual DOACs. We fit logistic generalized estimating equations of DOAC use, with adjustment for age, race, sex, primary cause of end-stage renal disease (ESRD), and dialytic setting.

Results: Monthly sample sizes increased from roughly 249,000 in January 2011 to 311,000 in December 2015. During this era, the percentage of patients using any anticoagulant steadily increased from 9.2% to 10.2%. However, the percentage of patients using warfarin reached an apex of 9.4% in December 2013 and subsequently fell to less than 9.0% in late 2015. Concurrently, the percentage of patients using any DOAC increased from 0.1% to 1.3%. By December 2015, 11.6% of patients using an anticoagulant were DOAC users and 93.0% of patients using a DOAC were apixaban users. Among patient-months with anticoagulant use in 2015, positive predictors of DOAC use were older age and Asian (versus white) race; negative predictors were black (versus white) race and glomerulonephritis and polycystic kidney disease (versus diabetes) as the primary cause of ESRD. Relative to in-center hemodialysis, home hemodialysis was associated with 18% lower odds of DOAC use, but the association was not statistically significant ($P = 0.09$).

Conclusions: Among hemodialysis patients, warfarin use is decreasing, DOAC use is increasing, and apixaban dominates DOAC utilization. Direct comparisons of warfarin and apixaban are urgently needed.

Funding: Commercial Support - NxStage Medical, Inc.

SA-PO622

Prevalence and Outcomes Associated with NSAID Use in Patients with CKD

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of incident acute kidney injury and chronic kidney disease (CKD). The effect of NSAIDs on the rate of CKD progression is still uncertain. The purpose of this study is to measure the prevalence of NSAID use in CKD patients under the care of a nephrologist compared to a primary care physican (PCP) and evaluate the impact of NSAID use on CKD progression.

Methods: This is a single center, retrospective study of patients with CKD stage 3 to 5 over a 1 year period. Patients 18 years or older with GFR < 60 mL/min (2 occasions), an office visit with nephrologist or PCP and an active NSAID prescription were included. We excluded hospitalized patients, transplant recipients, AKI episodes or dialysis dependency. We evaluated the change in GFR pre and post NSAID prescription over 1 year compared to non-NSAID users and compared nephrology to PCP care. Multivariate logistic regression identified potential co-variates of GFR change.

Results: Of the 2,157 patients included in the study, 12.2% had an NSAID prescription; 9.6% vs. 15% for patients receiving care from a nephrologist or PCP (p<0.001). Table 1 describes baseline demographics. GFR change was -3.9 vs. -3.7 mL/min/1.73 m^2 (p=NS) for NSAID users and non-users, respectively. In patients managed by a nephrologist, GFR change was -4.94 vs. -4.21 mL/min/1.73m^2 (p=NS) in users and non-users, while GFR change for patients managed by a PCP was -3.18 vs. -3.05 mL/min/1.73m^2 (p=NS) in users and non-users, respectively. Age (p<0.001), diabetes (p=0.02) and hepatitis C (p=0.001) were significantly associated with GFR change.

Conclusions: NSAIDs are prescribed to more than one out of every ten patients with CKD; more often by PCPs than nephrologists. Over 1 year, there was no statistically significant GFR change for NSAID users compared to non-users. Further long term studies are warranted to confirm safety of this medication class.

Baseline Demographics

Variable	Nephrology (n = 1,123)	Primary Care (n = 1,034)
Age, mean (IQR)	64 (56-75)	73 (65-82)
Male gender, n(%)	619 (55.1)	539 (52.1)
Race, n(%)		
African American	113 (10.1)	50 (4.8)
American Indian or Alaskan	4 (0.4)	4 (0.4)
Asian	154 (13.7)	115 (11.1)
Other	207 (18.4)	116 (11.2)
Unknown	19 (1.7)	8 (0.8)
White	626 (55.7)	741 (71.7)
Comorbidities, n(%)		
HIV	77 (6.9)	11 (1.1)
Hypertension	825 (73.5)	752 (72.7)
Chronic lung disease	20 (1.8)	13 (1.3)
Peripheral artery disease	57 (5.1)	54 (5.2)
Diabetes	335 (29.8)	269 (26)
Dementia	23 (2)	19 (1.8)
Hepatitis C	49 (4.4)	18 (1.7)
Cerebrovascular disease	3 (0.3)	9 (0.9)
eGFR (mL/min/1.73m2), n(%)		
30-59	631 (63)	918 (88.8)
15-29	239 (21.3)	75 (7.3)
< 15	176 (15.7)	41 (4)
Baseline eGFR (mL/min/1.73 m2), mean (IQR)	34 (23-47)	45 (40-54)

SA-PO623

Cause Specific Mortality Attributable to Proton Pump Inhibitor

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Background: Proton pump inhibitors (PPI) are widely used; and their use is associated with increased risk of adverse events and death. However, a detailed analysis of the cause of the death distribution among users of PPI is not available. In this work, we aimed to characterize the cause of death among users of PPI.

Methods: A cohort of 325,307 new users of PPI or H2 blockers was built. Cause of death data from National Death Index was used to examine the association between PPI and cause specific morality. Multiple survival models including proportional hazards models, accelerated failure time models, and additive hazard models were used. we used an instrumental variable approach based on clinicians' prescribing behavior and high-dimensional propensity score in domains including diagnoses, procedures, medications and laboratory results to account for measured and unmeasured confounders, respectively. For each outcome, model-covariate combination with smallest Brier score was selected and the survival possibility for the cohort was calculated.

Results: During 10 years of follow up, PPI use was significantly associated with all-cause mortality, and mortality from circulatory, and genitourinary causes. Compared to users of H2 blockers, event rate per 1000 persons attributable to PPI use was 5.44 (17.57, 33.43), 9.91 (3.94, 15.79) and 5.17 (2.83, 7.51) for all-cause, circulatory and genitourinary mortality, respectively. The excess death accounted for 6.94% (4.85, 9.03), 7.15% (2.90, 11.17) and 32.58% (19.34, 43.56) of all the all-cause, circulatory, and genitourinary mortality in PPI users. Further analyses within the circulatory and genitourinary causes showed PPI use was associated with 8.07 (3.29, 12.77) and 3.66 (1.95, 5.46) excess death per 1000 persons from coronary artery disease and chronic kidney disease, which accounted for 10.22% (4.27, 15.72) and 35.97% (21.07, 48.23) of the related deaths. Death from acute kidney injury was not associated with PPI use (excess death 0.61 (-0.27, 1.51) and population attributable fraction 29.32% (-15.42, 56.11)).

Conclusions: In this work, we used advanced statistical methodologies to map the cause of death distribution among users of PPI. Our findings suggest that PPI use is associated with increased mortality from circulatory and genitourinary causes, but not other causes of death. PPI should only be used when medically indicated.

Funding: Veterans Affairs Support

SA-PO624

Retrospective Population Scale Analysis Reveals Associations of Proton-Pump Inhibitor Use with Kidney Related Disorders

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Background: Proton pump inhibitors (PPIs) are one of the most widely prescribed and sold drugs globally. Recent studies have revealed associations between PPI use and acute kidney injury (AKI), chronic kidney disease (CKD), and end stage renal disease (ESRD). The growing concern over potentially serious adverse events (AE) associated with their use warrants an evaluation of post marketing surveillance.

Methods: This is a retrospective study of 9.5 million voluntary adverse event (AE) reports to the FDA Adverse Event Reporting System (FAERS) from January 2004 to August 2017. Two cohorts were constructed from these reports: (1) PPI (n=665,735) and (2) histamine receptor antagonists (H2RA) (n=124,251) cohorts. Any report of patients taking concurrent nephrotoxins or where age was not reported was excluded resulting in 150,361 PPI and 29,115 H2RA AE reports. Outcomes were CKD, AKI, ESRD, nephrolithiasis and electrolyte disorders (hypomagnesemia, hypocalcemia and hypokalemia) defined by coding data. Frequencies of all reported AEs and corresponding odds ratios (OR) were calculated in each cohort.

Results: Patients who received PPIs had a significant increase in the number of reports for CKD OR 1.87 95% CI [1.3, 2.7], AKI 1.23 [1.1, 1.4], nephrolithiasis 2.16 [1.6, 2.9], hypomagnesemia 2.62 [2, 3.4], and hypocalcemia 1.95 [1.5, 2.5]. There was no significant difference in the frequency of hypokalemia 1.15 [0.91, 1.5] and ESRD 7.17 [0.99, 52]. Significant increases in CKD reports were identified for omeprazole 1.89 [1.3, 2.8], esomeprazole 1.95 [1.3, 2.9], dexlansoprazole 10.65 [3.3, 35]. Omeprazole and pantoprazole were significantly associated with increased AKI reports, 1.54 [1.4, 1.7] and 1.64 [1.4, 1.9], respectively whereas esomeprazole had a decrease in AKI reports 0.85 [0.75, 0.96].

Conclusions: In this study, we replicated the association between PPI exposure and the increased risk of AKI, CKD and electrolyte abnormalities from the AE reports in the FAERS database. To our knowledge this is the first large scale study showing a significant association of PPI use with nephrolithiasis. We found differences in AE reporting risk for individual PPIs. Further studies evaluating individual drug effects are warranted to confirm these findings.

SA-PO625

Does Desmopressin Decrease Kidney Biopsy Bleeding Risk in Patients with CKD?

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Background: Kidney biopsy, the gold standard for diagnosing kidney disease, is associated with bleeding risk. Desmopressin is routinely prescribed to improve platelet function and decrease bleeding risk of kidney biopsy. It is not known if desmopressin decreases the risk of clinically significant bleeding (defined as post-biopsy hematoma, decrease in hemoglobin or need for RBC transfusion) in patients with CKD.

Methods: Retrospective review of consecutive percutaneous kidney biopsies performed at Stroger hospital between January 2014 and March 2018. CKD was defined as eGFR < 60ml/min/1.73 m^2. All biopsies were performed under real-time ultrasound guidance. Patients with bleeding time > 10 minutes were excluded from the study.

Results: 323 kidney biopsies were performed during the study period of which 217 had CKD. As compared to patients who did not receive desmopressin, administration of desmopressin did not decrease the risk of post-biopsy hematoma (18.94% in desmopressin group vs 19.44% in non-desmopressin group; p = 0.90) or need for blood transfusion (p=0.08). The mean decrease in hemoglobin was statistically significant in the desmopressin group than the non-desmopressin group (0.79 g/dl vs 0.46 g/dl; p = 0.0001) but not clinically significant. Both groups had adequate number of glomeruli on biopsy.

Conclusions: Routine administration of desmopressin in patients with CKD did not reduce the risk of clinically significant post-biopsy bleeding.

Clinical features and outcomes of kidney biopsy in patients with CKD

	Desmopressin (n=88)	No Desmopressin (n=129)	P value
Age	50.66 (13.42)	48.85 (13.83)	0.32
BMI	28.82 (6.2)	30.72 (6.32)	0.02
Serum creatinine	4.02 (2.51)	2.80 (1.46)	0.0001
Baseline hemoglobin	10.07 (1.45)	11.32 (1.81)	0.0001
Systolic BP	135 (15)	136 (16)	0.6
Platelet count	213.12 (71.91)	239.89 (85.28)	0.01
Bleeding time	7.10 (2.88)	4.61 (1.87)	0.0001
Number of passes	2.52 (0.79)	2.69 (1.11)	0.22
Number of glomeruli	21.40 (9.66)	17.92 (8.78)	0.005
Mean hemoglobin decrease	0.79 (0.63)	0.46 (0.54)	0.0001
Gross hematuria	9 (11.39%)	4 (3.10 %)	0.0001
Post-biopsy hematoma	14 (18.91%)	21 (19.44%)	0.90
RBC transfusion	5 (6.03%)	1 (0.007%)	0.08

SA-PO626

Use of Urinary Exosomes to Confirm Pharmacological Activity of CXA-10 on Nrf2 and Heat Shock Response Gene Expression in the Kidney of Patients with CKD

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Background: CXA-10 is an electrophilic nitrated fatty acid being developed for focal segmental glomerular sclerosis. In animal studies, CXA-10 modulated several pathways including activation of nuclear factor E2-related factor 2 (Nrf2) and heat shock response (HSR). Urinary exosomes are small cell-derived vesicles shed from kidney cells that carry mRNA and proteins. Genetic material in urinary exosomes reflects gene activation in the kidney. The purpose of this study was to examine the ability of CXA-10 to induce Nrf2- and HSR-dependent gene expression in blood and kidney of subjects with chronic kidney disease (CKD).

Methods: This was a multicenter, open-label, single-dose study of CXA-10 in subjects with moderate and severe CKD. Four subjects received a 1-hour infusion of 0.34 mg/kg and 8 subjects received a 1-hour infusion of 0.68 mg/kg CXA-10. Gene expression assessments were conducted from predose to 96 hours postdose as the time course of responses was unknown. Whole blood and urine samples were collected for analysis of target genes by qRT-PCR in isolated PBMCs and exosomes, respectively. Target genes were from the Nrf2 pathway, NAD(P)H quinone dehydrogenase 1 (NQO1) and Heme Oxygenase 1 (HMOX-1) and the heat shock pathway, Heat Shock Protein Family A and 1B (HSPA1A/B).

Results: Gene expression increased after CXA-10 dosing for all target genes. Maximum gene expression per subject showed a dose-response relationship for NQO1 and HSP1A/B in both PBMCs and urinary exosomes. Gene expression response, defined as ≥3-fold increase from baseline, was exhibited in 10 subjects (83.3%) for ≥1 target gene. PBMC gene expression response was observed in 8 subjects (66.7%) and urinary exosome gene expression in 6 subjects (50%). HSPA1A/B showed the highest level of induction in both PBMCs and urinary exosomes.

Conclusions: A single IV dose of CXA-10 increases cellular protective Nrf2- and HSR-related genes in subjects with CKD. This study demonstrates the first human translation of the pharmacological actions of CXA-10 that have been previously characterized in vitro and in animal models. To our knowledge, this is the first use of urinary exosomes to demonstrate the pharmacological action in the target organ of a novel drug in clinical development.

Funding: Commercial Support - Complexa, Inc.

SA-PO627

Tumor Lysis Syndrome Linked to Anticancer Agents: An Analysis Using the FDA Adverse Event Reporting System

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Background: Tumor lysis syndrome (TLS) is an oncologic emergency that can lead to severe renal impairment, cardiac arrhythmias, seizures, and death. We used the Food and Drug Administration Adverse Reporting System (FAERS) database to identify associations between anticancer agents and TLS.

Methods: Reports of TLS were retrieved from the FAERS database. Reporting odds ratios (RORs) were used to estimate associations between TLS and old and new anticancer agents or their combinations.

Results: We identified 1,615 TLS cases from among 4,330,807 case reports from the first quarter of 2004 through the first quarter of 2014. Statistically significant risk signals were detected for 56 of 64 anticancer agents. Bortezomib (BOR), a drug used for multiple myeloma (MM), had a high ROR and large number of TLS events relative to that of molecular-targeted drugs (161 TLS events, ROR = 28.89, 95% CI: 24.53–34.02). However, MM is a disease considered low-risk for TLS. We analyzed regimens containing novel MM drugs (e.g., BOR, lenalidomide, and thalidomide). Of those drugs, TLS was more frequently reported for BOR-containing treatments than for other MM treatments (Fig. 1).

Conclusions: Although the risk of TLS is generally considered low for MM patients, careful evaluation of TLS risk is recommended for those receiving BOR-containing therapy.

Funding: Government Support - Non-U.S.

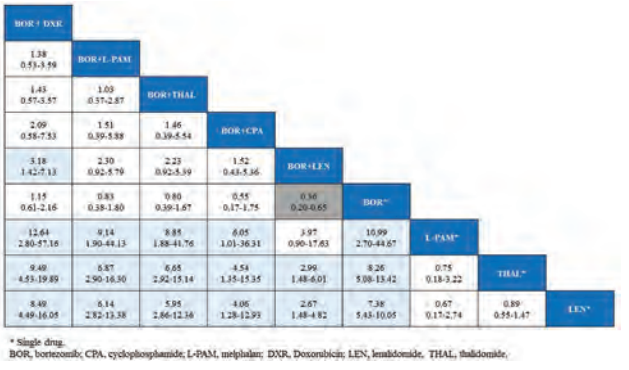

Fig. 1 Estimates of TLS risk in MM chemotherapy regimens. Chemotherapy drug combinations are in blue cells. Values listed are for the TLS risk of column-defined combinations relative to that of row-defined combinations. For RORs in the opposing direction, reciprocals of the listed values must be used. ROR values > 1 favor the column-defined combinations. Light blue and gray cells indicate statistical significance. Ranges represent 95% confidence intervals.

SA-PO628

The Pharmacokinetics of Meropenem and Piperacillin/Tazobactam in Haemodiafiltration

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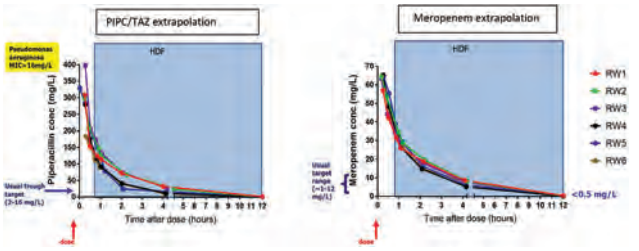
Background: Meropenem and piperacillin/tazoobactam (PIPC/TAZ) are commonly used in the treatment of sepsis. Their effectiveness is dependent upon time above minimium inhibitory concentration (MIC). Dosing practices in haemodiafiltration (HDF) rely on extrapolation from intermittent haemodialysis (IHD) or continuous renal replacement therapies and may lead to subtherapeutic concentration due to fundamental differences in membrane characteristics, duration of therapy and blood flow rates.

Methods: We performed an open label pilot study on 6 stable haemodialysis patients. HDF prescription was based upon our local intensive care practice. Patient characteristics, bioimpendance and any deviation from prescription were documented. Meropenem (1g) was administered 1 hour prior to commencement of HDF. 12 blood samples were taken (baseline, pre, post membrane during HDF and 1 hour post cessation). This was repeated with PIPC/TAZ (4.5g) 1 week later. Samples were analysed by validated chromatography. Pharmacokinetic modelling analysis was performed on each of the samples using non-compartmental methods. Extrapolation of plasma concentrations to 12 hrs was approximated assuming an exponential decline, given by; $C_{p(t)} = C_{p0} \times e^{-kt}$ were Cp(t) is the plasma concentration at time (12 hrs post=dose in this case),C_{p0} is the plasma concentration at time 0, and *k* is the terminal phase rate constant.

Results: Participants were mostly male with a mean age of 63.8±14 yrs. Haemodiafiltration clearance (HDCL) ranged from 8.9-10.8 L/h for meropenem and 9.6-19.1 L/h for PIPC/TAZ with an area under the plasma concentration-time curve during HDF (AUC_{HDF}) of 83-99 and 195-351 mg/L*h respectively. Fig 1 shows approximation of the PIPC/TAZ and meropenem data assuming the HDF continued for 12 hours without repeated dosing.

Conclusions: Meropenem and PIPC/TAZ removal during HDF is substantial with potential subtherapeutic concentration after a relatively short period.



SA-PO629

Meropenem Renal Kinetics in Human Kidney Biopsies

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Background: Urinary tract infection is the most common bacterial infection. Usually it has good prognosis even though some cases can have serious complications. Last decades multi-resistant bacterial strains are arising but development of antibiotics has declined. Meropenem is a broad-spectrum antibiotic with activity against many bacteria including multi-resistant strains; however, its renal tissue kinetics is unknown.

Methods: We conducted a descriptive study in humans with indication of kidney biopsy. Meropenem was infused over 30 minutes one hour before biopsy performed and was evaluated the plasmatic concentration after meropenem infusion (T1), 60 minutes (T2) and 120 minutes (T3). Also meropenem concentration in the kidney sample was measured. It was used a fluorescent biosensor for B-Lactams antibiotics to measure levels of meropenem.

Results: In 14 patients, 64% women, body mass index was 26.3 ±2.9, eGFR was 57.5 ±44.1 ml/min/1.73m^2 and plasma albumin 3.8 ±0.9 g/dL. Kidney biopsy was done at 68.9 ±20.3 minutes after meropenem infusion; the second plasma sample was obtained at 82.1 ±21.2 minutes and the third at 149.6 ±31.5 minutes. Meropenem concentrations at T1, T2 and T3 were 45.9 ±10, 20.7 ±13, 16.6 ±13 μg/mL respectively. Mean kidney sample weight was 5.9 ±3.0 mg and meropenem concentration was 3.1 ±1.9 μg/mL. For each patient a decay curve was constructed and meropenem plasma concentration was estimated at the biopsy time. The ratio of meropenem concentration between plasma and renal tissue (mP/mK) was 14 ±10% with a range of 3.8% – 34.8%. Meropenem excretion occurs predominantly by glomerular filtration, thus plasma concentration and glomerular filtration rate determine the filtered load, modifying the urinary concentration and keeping the (mP/mK) ratio constant over time. The absence of linear correlation between (mP/mK) ratio and eGFR supports this idea. With the standard meropenem doses and normal renal function, we estimate that is possible treating with bactericide effect to bacteria with MIC90 <0.76 μg/mL.

Conclusions: With standard meropenem doses is possible achieve adequate concentration in renal parenchyma to treat, with bactericide effect, most frequent uropathogens. Nevertheless, for resistant bacteria is necessary increase the dose or consider another antibiotic. Renal failure does not avoid achieving adequate meropenem renal tissue concentrations.

Funding: Private Foundation Support

SA-PO630

Pharmacokinetics of Intraperitoneal Cefazolin and Ceftazidime in Automated Peritoneal Dialysis Patients with Peritonitis

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Background: The current peritoneal dialysis (PD) guideline suggested that intraperitoneal (IP) antibiotics should be administered only in a long dwell (≥6 hours). We previously showed that IP cefazolin and ceftazidime during short-dwell cycling PD (<2-hour) could provide adequate plasma concentration for up to 24 hours in non-peritonitis patients. This study was aimed to evaluate bioavailability, as well as plasma and dialysate concentration of IP cefazolin and ceftazidime during short-dwell cycling PD in patients with peritonitis.

Methods: PD patients with peritonitis were enrolled. Cefazolin and ceftazidime (2,500 mg each) were added in a 5-liter bag containing 2.5% dextrose PD fluid, placed on the warmer of PD cycling machine. Another 5-liter bag of PD fluid was connected to the machine, off the warmer. Patients underwent 5 exchanges of 2-liter PD fluid over 10 hours by the PD cycling machine without last fill or additional dwell. Antibiotics concentrations were determined by high-performance liquid chromatography.

Results: Six PD patients with peritonitis participated in this study. The IP bioavailability of cefazolin and ceftazidime were 50.3±16.4% and 56.6±18.4%, respectively. Plasma cefazolin and ceftazidime levels exceeded the minimum inhibitory concentration (MIC) of 8 mg/L within the first hour (cefazolin 37.0±6.5 and ceftazidime 21.4±5.7 mg/L), peak at 10 hours (100.1±4.0 and 54.0±14.5 mg/L) and then sustained well above the MIC at 24 hours after the infusion (82.3±3.2 and 40.2±10.5 mg/L). Dialysate cefazolin and ceftazidime levels were also sustained above the MIC throughout the PD session in all patients.

Conclusions: The IP cefazolin and ceftazidime during short dwells in peritonitis patients provided sufficient bioavailability as well as adequate plasma and dialysate concentrations. This regimen should be one of the standard regimens for treatment of peritonitis in PD patients.

Funding: Government Support - Non-U.S.

SA-PO631

The Distribution Profile of Anti-Sense Oligonucleotides Indicates That Proximal Tubular Targets Should Be Prioritized in Renal Disease

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Background: Antisense oligonucleotides (ASOs) are predominantly taken up by the liver and kidneys, which makes them a potentially attractive modality for the treatment of renal disease. However, it is not clear to what extent ASOs reach the different compartments of the kidney. The biodistribution of ASOs is dependent on plasma protein binding, which delays urinary excretion, but may also facilitate uptake into proximal tubular cells (PTCs).

Methods: We investigated the tissue exposure and distribution of a phosphorothioate cEt gapmer ASO in three different renal disease models: the diabetic BTBR*ob/ob*, the 5/6 nephrectomy and the adenine diet mouse models. Mice were subcutaneously administered weekly doses of 3, 10 or 30 mg/kg ASO and followed for between 2 and 12 weeks.

Results: In all treated animals, renal tissue ASO exposure and significant knockdown of the target gene were achieved. Detailed analysis of the ASO distribution and knockdown revealed that the primary site of action is the PTCs, whereas knockdown in the glomerular compartment required higher doses. Uptake of ASOs in distal tubules was only detected in the adenine model in which PTCs were severely injured.

Conclusions: These results indicate that ASOs can primarily be used for treatment targets in PTCs, while targets in the distal tubule will require facilitated delivery for efficient knockdown.

Funding: Commercial Support - AstraZeneca

SA-PO632

Identification of Patients with High Probability of Not or Poorly Responding to Mycophenolic Acid Prodrugs

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Background: The antiproliferative agent mycophenolic acid (MPA) exerts its immunosuppressive effect by a selective inhibition of inosine 5'-monophosphate dehydrogenase (IMPDH), the rate-limiting enzyme of purine metabolism. The isoenzyme IMPDH2 predominates in activated lymphocytes, and its inhibition by MPA is part of standard immunosuppressive therapy in transplant medicine. Previously, factors which might explain differences in MPA efficacy and tolerability among patients have been studied: polymorphism rs11706052 in the IMPDH2 gene has been identified to reduce the antiproliferative effect of MPA on lymphocytes; data on therapeutic drug monitoring using MPA trough levels and IMPDH activity were not conclusive. Yet, whether a combination of

pharmacogenomic, pharmacokinetic and pharmacodynamic factors explain the differences in response to MPA therapy and drug tolerance remains to be elucidated.

Methods: This was designed as a prospective study of kidney transplant patients with and without biopsy-proven rejection (BPR). Both groups were tested for the presence of SNP rs11706052. In addition, MPA trough levels in plasma were measured by high performance liquid chromatography and IMPDH enzyme activity in peripheral blood mononuclear cells was tested by liquid chromatography–mass spectrometry. Correlations between BPR and the presence of rs11706052, MPA trough levels, IMPDH activity as well as the IMPDH/MPA ratio (assuming that a higher IMPDH activity requires higher MPA trough levels for an adequate immunosuppressive effect) were examined.

Results: Preliminary results from 50 kidney transplant recipients with biopsy-proven rejection and 100 controls without rejection suggest 1.) IMPDH activity was significantly higher in patients with BPR compared to patients with a stable graft function over 12 months with no immunological complications, 2.) no correlation between IMPDH activity and MPA levels, BPR and the IMPDH/MPA ratio, 3.) no influence of rs11706052.

Conclusions: This is the clinical extension of our previous in vitro study, which has shown that the polymorphism rs11706052 reduces the immunosuppressive effect of MPA. This prospective study investigates the susceptibility to reject kidney allografts using a combined pharmacogenomic, pharmacokinetic and pharmacodynamic approach.

SA-PO633

Tacrolimus Troughs and Doses in African American, Asian, Caucasian, and Hispanic/Native American Kidney Transplant (tx) Recipients

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Background: TAC is an immune suppressant with a narrow therapeutic index and high inter-individual pharmacokinetic (PK) variability. African Americans (AA) have lower troughs and higher dose requirements primarily due to the *CYP3A5*1* allele that results in CYP3A expression. Caucasians have higher troughs and lower dose requirements due to the loss of function variants *CYP3A5*3* and *CYP3A4*22.* TAC trough and genotype relationships for Asian and Hispanic/Native Americans are not well described.

Methods: 2739 adult kidney tx recipients enrolled in the multicenter DeKAF Genomics and the GEN03 genome wide association studies (GWAS) who received TAC maintenance and had TAC troughs available in the first 6 mo posttx were studied. Race was identified and confirmed through principal component analysis using the GWAS. We tested the association between genetic variants (CYP3A5*3, *6 and *7, CYP3A4*22) and dose-normalized TAC troughs in each population adjusting for center, age and gender

Results: The allele frequency of CYP3A5*3 differed between the groups; 0.30, 0.72, 0.92, 0.84 in AA, Asian, Caucasian and Hispanic/Native Americans, respectively. The median (IQR) TAC dose-normalized trough, dose and trough by population are in the table. CYP3A5*3 was highly significant in all groups (p = 3.3E-09 to 4.9E-127). CYP3A5*6 and *7 were associated with troughs in the AA group (p=2.0E-12 and 1.3E-24) and CYP3A4*22 in the Caucasian group (2.2xE-22).

Conclusions: The Hispanic/Native American group had the highest dose-normalized TAC trough and the AA the lowest. The most rapid TAC metabolism occurs in AA followed by Asians, Caucasians and Hispanic/Native Americans. Genetic variants that influence TAC metabolism are highly significant and vary by race. This data suggest that additional variants may be present in the Asian and Hispanic/Native American groups which impact CYP3A4 and 5 substrate metabolism.

Race	TAC dose-normalized trough	TAC Daily Dose	TAC trough
African American (n=516)	0.77 (90.52-1.19)	8.0 (6.0-12.0)	6.8 (4.9-8.9)
Asian (n=91)	1.50 (0.98-2.53)	6.0 (3.5-8.0)	6.7 (6.7-10.6)
Caucasian (n=2055)	1.55 (1.02-2.40)	5.0 (4.0-8.0)	8.4 (6.5-10.3)
Hispanic/Native American (n=77)	1.73 (1.06-2.67)	5.0 (3.0-8.0)	8.3 (6.3-10.3)

SA-PO634

Safety and Single Ascending Dose Pharmacokinetic Study of DUR-928 in Patients with CKD versus Matched Control Subjects

Jaymin C. Shah, David J. Ellis, Andrew R. Miksztal, Wei Qi Lin. *DURECT Corporation, Cupertino, CA.*

Background: DUR-928 ((5-cholesten-3β,25-diol 3-sulfate (25HC3S)) is an endogenous intracellular sulfated oxysterol that has been shown to regulate lipid metabolism, inflammatory response, and cell survival. This first-in-class investigational product is being developed for the treatment of various liver and kidney diseases. Animal ADME studies have shown that ≈ 17% of DUR-928 is eliminated through the urine. This study was to evaluate the impact of renal impairment in chronic kidney disease (CKD), on the safety and pharmacokinetics (PK) of DUR-928.

Methods: The study was a Phase 1b, open label, single ascending dose study to evaluate the safety and PK of IM injected DUR-928 in patients with moderate and severe kidney function impairment (Stage 3 and Stage 4 CKD) and matched control subjects (MCS), matched by age, BMI, and gender, with normal kidney function. The two doses of DUR-928 in the study were 30 mg and 120 mg. Biomarkers were also examined. All study subjects were followed through 7 days post dosing.

Results: Eleven CKD patients (Stage 3 (N=8), Stage 4 (N=3)) and six MCS completed the study. A total of 13 TEAEs were reported by 8 participants, mostly mild and none were severe. A clinically non-significant decrease (≈ 10%) in exposure was observed in CKD patients as compared to MCS at both dose levels of DUR-928. The AUC values for 30 and 120 mg doses in CKD patients were 1061 and 4304 ng*hr/mL vs. 1138 and 4766 ng*hr/mL in MCS. Similarly, the C_{max} values for 30 and 120 mg doses in CKD patients were 281 and 890 ng/mL vs. 345 and 997 ng/mL in MCS. The plasma half-life ($T_{½}$) was in the range of 1.5 to 2 hours. Participants with elevated levels of CK-18 (markers of cell death) or bilirubin at baseline showed considerable reduction of these markers at 12 or 24 - 48 hours after a single IM injection of DUR-928.

Conclusions: Single IM doses of DUR-928 in CKD patients were found to be well tolerated. Kidney function impairment did not impact the PK of DUR-928. These data support further evaluation of DUR-928 in patients with kidney disease.

SA-PO635

Evaluation of the Antioxidant Effects of Benzbromarone in Angiotensin II Induced Hypertension Model

Daisuke Kadowaki,[1] Yuki Narita,[2] Shigeyuki Miyamura,[1] Kohei Uchimura,[3,4] Kenichiro Kitamura,[4] Toru Maruyama,[2] Sumio Hirata,[2] Hakaru Seo.[1] *[1]School of Pharmacy, Sojo University, Kumamoto, Japan; [2]School of Pharmacy, Kumamoto University, Kumamoto, Japan; [3]Washington University in St. Louis, Saint Louis, MO; [4]University of Yamanashi School of Medicine, Chuo, Japan.*

Background: Uric acid exerts an important antioxidant effect against external oxidative stress under physiological conditions. However, oxidative stress induced by hyperuricemia is closely associated with the renin-angiotensin system, as well as the onset and progression of cardiovascular disease (CVD) and chronic kidney disease (CKD). Furthermore, uric acid locally activates the renin-angiotensin system, thus producing angiotensin II and subsequently increasing intracellular oxidative stress. Benzbromarone has been reported to suppress uric acid reabsorption via uric acid transporter 1 inhibition in renal tubular cells. In this study, we evaluated the antioxidant effect of benzbromarone from several perspectives *in vitro* and *in vivo*.

Methods: First, the direct radical-trapping capacity of benzbromarone was measured by chemiluminescence assay and electron paramagnetic resonance spectroscopy *in vitro*. Second, the intracellular antioxidant activity of benzbromarone was evaluated using endothelial cells. Finally, the antioxidant effects of benzbromarone were evaluated *in vivo* via oral administration of benzbromarone for 4 weeks to model rats with angiotensin II– and salt-induced hypertension.

Results: benzbromarone showed direct radical scavenging capacity against the superoxide anion radical *in vitro*. In addition, benzbromarone inhibited reactive oxygen species production that was induced by angiotensin II or uric acid in endothelial cells. In *in vivo* study, benzbromarone did not alter plasma uric acid levels or blood pressure, but significantly reduced the levels of advanced oxidation protein products, which are oxidative stress markers. Furthermore, dihydroethidium staining of the kidney revealed a reduction in oxidative stress after benzbromarone administration.

Conclusions: These findings suggest that benzbromarone possesses the ability directly to scavenge radicals and may act as an antioxidant against uric acid and angiotensin II-induced oxidative stresses in endothelial cells or angiotensin II induced hypertension.

SA-PO636

C-PAM, a Novel Iron Oxide-based Oral Drug, Efficiently Lowers Serum PI

Susanne E. Wagner,[2] Jörg Schnorr,[1] Monika Ebert,[1] Nicola Stolzenburg,[1] Matthias Taupitz.[1] *[1]Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Wagner MSL Management, Mahlow, Germany.*

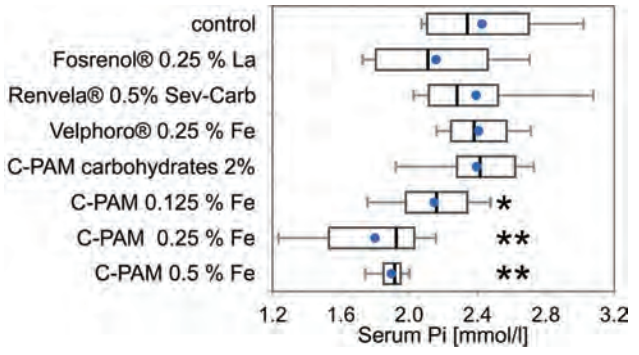
Background: C-PAM is a novel compound designed for use as a serum Pi-lowering oral drug. It is composed of iron (Fe) oxide nanoparticles with a maghemite structure, mannitol, inulin, and Arabic gum. In previous analytical tests, C-PAM had a superior Pi-binding capacity compared to major approved Pi-binders. The hypothesis of this experimental in vivo study is that C-PAM more efficiently lowers serum Pi compared to those Pi-binders.

Methods: Healthy male Sprague-Dawley rats with a starting weight of 250 g were treated with drug co-feeding for 4 weeks (n=8 rats per group). C-PAM was added to Altromin standard 1320 diet (containing 0.6 wt% free adsorbable Pi) at 0.125, 0.25, and 0.5 wt% Fe. For comparison, three groups received Fosrenol® at 0.25 wt% La, Renvela® at 0.5 wt% sevelamer carbonate, and Velphoro® at 0.25 wt% Fe. As controls, one group received standard diet only and one group the carbohydrate components of C-PAM (mannitol, inulin, Arabic gum) at 2.0 wt%. Blood was sampled at the end of the 4-week study period and analyzed for serum Pi and standard parameters of hematology and clinical chemistry. For histopathology, HE and iron stains of liver, spleen, heart, lung, kidney, stomach, duodenum, jejunum, ileum, colon, and intestinal lymph nodes were assessed. Student's t-test was used for statistical analysis.

Results: At all doses investigated, C-PAM reduced serum Pi significantly (0.125 wt%: $p < .05$, 0.25 and 0.5 wt%: $p < .01$). None of the other products tested or the carbohydrate components of C-PAM had a significant serum Pi lowering effect (figure). For C-PAM, except serum Pi, there was no effect on hematology and clinical chemistry parameters. No histopathologic changes were observed.

Conclusions: Even at a low dose, C-PAM effectively reduces serum Pi in healthy rats and thus is superior to three major approved products.

Funding: Government Support - Non-U.S.



In vivo efficacy of C-PAM in lowering serum Pi at three different doses compared with three approved products, the carbohydrate components of C-PAM only, and with a control group (*p<.05; **p<.01).

SA-PO637

C-PAM, a Novel Serum Phosphate-Lowering Oral Drug with Dual Mode of Action, Prevents Serum Phosphate Rise After Drug Skip

Matthias Taupitz,[1] Jörg Schnorr,[1] Nicola Stolzenburg,[1] Franziska Rausch,[1] Monika Ebert,[1] Susanne E. Wagner.[3] *[1]Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Wagner MSL Management, Mahlow, Germany.*

Background: In ESRD patients, medications based on Pi-binders to control serum Pi require regular oral drug intake with each meal. Such a regimen is not conducive to adequate compliance, and occasional drug skipping is one reason why <20% of patients have serum Pi levels within the KDOQI® recommended target range. C-PAM is a novel compound consisting of iron oxide nanoparticles with a maghemite structure, mannitol, inulin, and Arabic gum. C-PAM showed superior Pi-binding in earlier analytical tests and better serum Pi-lowering in experimental in vivo studies, both compared to major approved drugs. The hypothesis for this experimental study was that, for C-PAM, a 1-day drug skip does not significantly increase serum Pi.

Methods: Healthy male Sprague-Dawley rats (CD Charles River) with an initial weight > 320 g were treated with drug co-feeding for 4 weeks (n=8 rats per group). Group A: C-PAM added to Altromin standard 1320 diet (0.47% digestable Pi) at 0.75 wt% total drug substance. Group B: Renvela® at 1.5 wt% total drug substance. Blood was sampled at the end of each week (W1 to W4) for analysis of serum Pi. During one day before W3 blood sampling, rats received the standard diet only. After W4 sampling, rats were sacrificed and the intestine was analyzed for NaPi2b expression using PCR. For statistical analysis student's t-test was used.

Results: Serum Pi was as follows [mmol/l]: C-PAM: BL 2.31±.21; W1 2.13±.21; W2 2.15±.27; W3 (after drug skip) 2.29±.20; W4 1.92±.20. Renvela®: BL 2.60±.25; W1 1.89±.24; W2 1.93±.44; W3 (after drug skip) 2.56±.27; W4 1.87±.13. After drug skip the rise was 7% (n.s.) and 33% (p<.01) resp. After drug skip the values were -10% and +1% resp. compared to age matched controls (n.s.). PCR analysis showed less expression of NaPi2b (ΔΔCt) in the proximal jejunum in the C-PAM group (3.08±.05) compared to the Renvela group (5.30±2.56, p<.05).

Conclusions: C-PAM effectively reduces serum Pi at a low dose and is robust against a 1-d drug skip, which is because of its dual mode of action combining highly effective Pi binding with an effect on NaPi2b transporters. If C-PAM is equally effective in the clinical setting, treatment of ESRD patients may be impoved by a significantly lower pill burden with better maintainance of serum Pi within the KDOQI® recommended target range.

Funding: Government Support - Non-U.S.

SA-PO638

Effect of Serum Parathyroid Hormone on Tacrolimus Therapy in Kidney Transplant Patients: A Possible Biomarker for a Tacrolimus Dosage Schedule

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Background: The mechanism responsible for the decreased extra-renal CYP3A activity in chronic kidney disease (CKD) patients remains unknown. Using an animal model, we previously found that elevated levels of serum intact parathyroid hormone (iPTH) caused a reduced CYP3A activity. The purpose of this study is to investigate whether serum iPTH levels affects the pharmacokinetics of tacrolimus, a CYP3A substrate, and its dosage schedule in kidney transplant recipients.

Methods: Thirty-four patients who were recipients of kidney transplantation between April 2014 and March 2016 and were administrated prolonged-release tacrolimus (Graceptor®, Astellas Pharm Inc.) once daily were the subjects of this study. Among the 34 patients, 22 patients had received the concomitant CYP3A substrate drug. To clarify the role of iPTH on the pharmacokinetics of tacrolimus, we performed the analysis using 12 patients who had not been administered concomitant CYP3A substrate drug.

Results: To investigate the relationship between serum iPTH levels and tacrolimus trough levels, we monitored the serum iPTH levels in patients before kidney transplantation. At this time point, serum iPTH levels in these subjects were increased, but with large deviations due to the difference in the patients' background such as the causes of and the progression of renal failure and complications. Therefore, we examined the correlation between serum iPTH levels and trough levels after the first oral administration of tacrolimus at 4 days before kidney transplantation. A significant positive correlation between serum iPTH level and the initial trough level for tacrolimus was found. This indicates that the tacrolimus trough level before transplantation was higher in patients with high serum iPTH levels as compared to patients with low iPTH values. These data suggest that CYP3A activity might be lower in patients with high serum iPTH levels, as was observed in the previous animal study, and that the initial trough level of tacrolimus could be predicted from serum iPTH levels before kidney transplantation.

Conclusions: Monitoring serum iPTH levels could predict the trough level for the initial administration of tacrolimus, and may serve as an index for the initial dose of tacrolimus in kidney transplantation patients.

SA-PO639

Rhein Attenuates D-Galactose Induced Renal Aging via Regulation of mTOR-Mediated Autophagy

Yue Tu, Diping Chen, Yihuang Gu. *Department of TCM Health Preservation, Nanjing University of Chinese Medicine, Nanjing, China.*

Background: In recent years, traditional Chinese herbal medications (TCHMs) are found to possess potent anti-aging activities. Rhubarb, derived from the root of *Rheum palmatum*, has been found to have anti-aging pharmacological effect. Rhein, a bioactive constituent of rhubarb, plays a vital role in its pharmacological effect. However, the potential mechanism of rhein in anti-aging remains unclear. Autophagy and its related signaling pathway mTOR play the important roles in aging.

Methods: *In vitro*, D-galactose (D-gal) was used to induce renal cellular aging in NRK-52E cells, following treating with or without rhein or vitamin E (VE). To measure renal cellular aging, the klotho protein expression was detected, and the senescence-associated-β-galactosidase (SA-β-gal) staining were observed. To study the changes of autophagy in the aging effects, several key autophagic markers protein expressions, including LC3 I/II, beclin1, SQSTM1/p62 and phospho-p62 (p-p62), were detected. Further, the changes of key protein expressions in mTOR signaling, including mTOR, and phospho-mTOR (Ser2448 and Ser2481), were detected in the same condition. The changes of the key protein expressions in mTOR-mediated autophagy were detected in NRK-52E cells exposed to D-gal and rhein or VE with or without mTOR inhibitor rapamycin (RAP) and mTOR activator MHY1485. *In vivo*, SD rats were divided into Normal, D-gal, Rhein-low dose, Rhein-high dose, VE, RAP and MHY1485 groups. The renal aging and mTOR-mediated autophagy related protein expressions and SA-β-gal staining were detected.

Results: Results showed that, renal tubular cellular aging *in vitro* and renal aging *in vivo* both induced by D-gal could be ameliorated by rhein and VE by inducing klotho protein expression, and attenuating the positive area of SA-β-gal staining. Rhein and VE could regulate mTOR-mediated autophagy by reducing autophagic related protein expressions and increasing mTOR signaling related protein expressions both *in vitro* and *in vivo*.

Conclusions: In this study, we demonstrated that rhein, similar to VE, could alleviate renal aging via regulating mTOR-mediated autophagy. These findings suggest that targeting autophagy and related signaling pathways may provide new strategies in the age-associated renal damage of the elderly patients.

Funding: Government Support - Non-U.S.

SA-PO640

Effect of CKD on Fexofenadine Disposition in Humanized OATP1B1/1B3 Mice

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Background: Patients with chronic kidney disease (CKD) often experience variable responses to drug therapies evidenced by their elevated incidence of adverse drug reactions. Cytochrome P450s (CYPs) and drug transporters are major contributors to drug disposition, as they mediate drug metabolism and removal from blood, respectively, to facilitate non-renal excretion. Rodent models of CKD exhibit reduced CYP expression and activity. However, the impact of CKD on drug transporters, namely organic anion transporting polypeptides (OATPs), is not well elucidated. Fexofenadine is a commonly used transporter probe ideal to study non-renal clearance since it is not metabolized and not eliminated in the urine. Multiple studies have documented significantly increased fexofenadine exposure in CKD patients, although the mechanism is unclear. This study investigated the effects of CKD on hepatic drug transporter activity in a humanized hepatic OATP1B1/1B3 mouse model by evaluating the liver distribution fexofenadine. It was hypothesized that CKD would decrease the activity of these transporters, as shown by a reduction in hepatic fexofenadine distribution.

Methods: CKD was induced in humanized OATP1B1 and OATP1B3 FVB/N mice by feeding chow supplemented with 0.2% adenine (n=6) for a total of 28 days while controls (n=6) received standard chow. Blood and organs were collected at sacrifice and plasma creatinine concentrations and the liver to plasma ratio of fexofenadine ($L:P_{FEX}$) were measured using ultra performance liquid chromatography coupled to mass spectrometry.

Results: Plasma creatinine was two-fold higher in adenine-fed mice compared to controls (p=0.0011). L:P_{FEX} was reduced by 15%, indicating a modest decrease in hepatic fexofenadine liver distribution (p=0.1870).

Conclusions: Induction of CKD did not significantly alter the liver distribution of fexofenadine in the humanized hepatic OATP1B1/1B3 mouse model. Further analysis into expression levels of these transporters, and other hepatic transporters such as P-glycoprotein, will provide further insight into the impact of CKD on drug transporters and distribution of fexofenadine in the liver.

Funding: Government Support - Non-U.S.

SA-PO641

Activity of Brincidofovir (BCV) Against Murine Polyoma Virus (MuPyV) in a Mouse Infection Model

Odin Naderer,[1] Heidi Colton,[1] Ge Jin,[2] Matthew D. Lauver,[2] Aron Lukacher.[2]
[1]Chimerix, Durham, NC; [2]Pennsylvania State University, Hershey, PA.

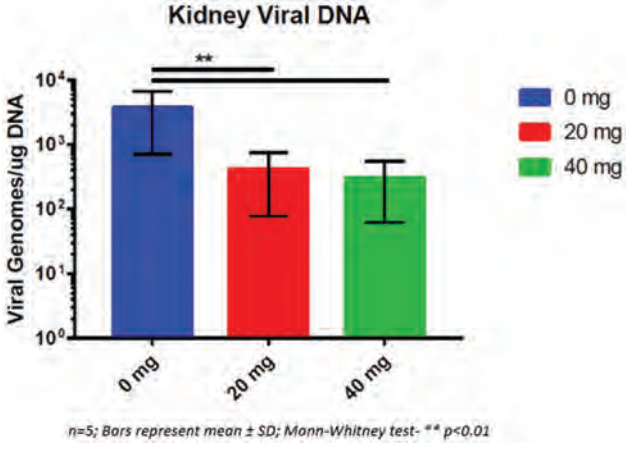
Background: BK virus (BKV) is a ubiquitous polyomavirus which can result in up to 10% of kidney transplant recipients to develop BKV-associated nephropathy and organ loss. As no antivirals are available, the current treatment paradigm is reduction of immunosuppression which can risk organ rejection. An active antiviral capable of reducing BK viral burden while maintaining optimal immunosuppression could have a substantial impact on the survival of existing kidney grafts and avoid re-transplantation. BCV is a lipid conjugated nucleotide analog of cidofovir (CDV) with potent antiviral activity against BKV in vitro (EC_{50}= 0.02 uM) without CDV-associated nephrotoxicity. In this study, we assessed the in vivo antiviral activity of BCV against a murine polyomavirus (MuPyV) which infects the kidney in a mouse model.

Methods: Fifteen C57BL/6 mice (8–12 weeks old) were randomized 1:1:1 to placebo, BCV 20mg/kg or BCV 40mg/kg IP twice weekly. Treatment was given on Day -7, Day -3, Day 1, and Day 4. Mice were inoculated in hind footpads with 1.0×10^6 PFU of MuPyV on Day 1. qPCR of kidney and spleen were performed at Day 5 (Termination).

Results: All mice tolerated all BCV IP doses to termination. BCV 20 mg/kg or higher delivered IP decreased viral load in the kidney by ~1 log.

Conclusions: BCV demonstrated antiviral activity in mice infected with MuPyV in this prophylaxis model. Evaluation of BCV activity in a post -infection treatment model of MuPyV is warranted to support BCV as a potential treatment for BKV.

Funding: Commercial Support - Chimerix



SA-PO642

Brincidofovir (BCV) Demonstrates Antiviral Activity Against Murine Polyoma Virus (MuPyV) in a Mouse Model of Acute Infection

Odin Naderer,[1] Heidi Colton,[1] Ge Jin,[2] Matthew D. Lauver,[2] Aron Lukacher.[2]
[1]Chimerix, Durham, NC; [2]Pennsylvania State University, Hershey, PA.

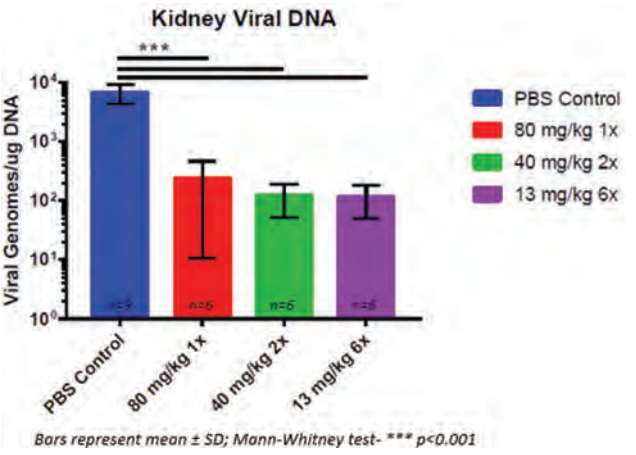
Background: BK virus (BKV) is a ubiquitous polyomavirus which can result in up to 10% of kidney transplant recipients to develop BKV-associated nephropathy and organ loss. As no antivirals are available, the current treatment is reduction of immunosuppression which can risk organ rejection. An active antiviral capable of reducing viral burden while maintaining immunosuppression could have a substantial impact on the survival of existing kidney grafts and avoid re-transplantation. BCV is a lipid conjugated nucleotide analog of cidofovir (CDV) with potent antiviral activity against BKV in vitro (EC_{50}= 0.02 uM) without CDV-associated nephrotoxicity. In this acute infection-treatment model study, we assessed the antiviral activity of BCV against MuPyV which infects the kidney.

Methods: Twenty-seven C57BL/6 mice (8–12 weeks old) were assigned to one of three treatment groups (n=6/group) or three corresponding placebo groups (n=3/group). For the treatment groups, BCV 80 mg/kg was delivered over a one-week period as a single dose or through divided doses: BCV 80mg/kg IP on Day 1; BCV 40mg/kg IP on Days 1 and 4; or BCV ~13 mg/kg IP on Days 1-6. Mice were inoculated in hind footpads with 1.0×10^6 PFU of MuPyV on Day 1. qPCR of kidney and spleen were performed at Day 7. Placebo groups were pooled for analysis.

Results: All mice tolerated all BCV IP doses to termination. All animals that received BCV had kidney viral loads 2-logs lower than animals that received placebo.

Conclusions: BCV reduced the viral load in the kidneys of mice acutely infected with MuPyV in this model. Further evaluation of BCV activity in immunocompromised mice with chronic MuPyV is planned to further explore BCV as a potential treatment for BKV.

Funding: Commercial Support - Chimerix



SA-PO643

Characterization of GFB-8438, a Potent and Selective TRPC5 Inhibitor Under Evaluation for the Treatment of FSGS

Maria Beconi, Mark Ledeboer, Maolin Yu, Matthew Daniels, Goran Malojcic, Marie F. Coeffet-LeGal, Xin-Ru Pan-Zhou, Peter H. Mundel, Jean-Christophe P. Harmange. *Goldfinch Bio, Cambridge, MA.*

Background: The predominant role of podocyte in the development of FSGS is well established. One of the central mechanisms leading to FSGS is the disruption of the podocyte actin cytoskeleton via Rac1 activation. TRPC5 has been identified as a key regulator of Rac1 activation in podocytes and its role was reinforced by the antiproteinuric effect of two TRPC5 small molecule inhibitors in two models of FSGS (Zhou et al, 2017). Here we present the preclinical characterization of GFB-8438, a potent and selective inhibitor of TRPC5. Metabolism, pharmacokinetic and the pharmacology of GFB-8438 will be discussed.

Methods: High throughput screening of a structurally diverse compound collection followed by lead optimization yielded several potent TRPC5 inhibitors. GFB-8438 inhibitory activity against TRPC5 and selectivity across other TRP channels were determined using FLIPR based assays and electrophysiology. Additional profiling was conducted using standard receptor and kinase panels. In vitro routes and clearance mechanisms across species and drug-drug interaction (DDI) potential were evaluated using standard ADME assays. The pharmacokinetic profile was characterized in rats and dogs at 1 mg/kg iv (solution) and at 3, 10, 30 and 100 mg/kg po (suspension). The in vivo efficacy was evaluated in a uni-nephrectomized DOCA-salt rat model of FSGS. PK/PD relationships were derived.

Results: GFB-8438 is a potent TRPC5 inhibitor with high selectivity against TRPC6. Further profiling in standard receptor and kinase panels did not reveal any off-target activities. GFB-8438 is metabolized primarily by oxidation and renal clearance is predicted to be low. Oral bioavailability in rats and dogs is acceptable, with favorable human PK projections given the low rate of hepatic metabolism. When dosed to DOCA-salt rats (single daily dose for 21 consecutive days), GFB-8438 reduced the rate of albuminuria progression without affecting the blood pressure. Rate of albuminuria reduction correlated well with exposure.

Conclusions: GFB-8438 is a potent and selective TPRC5 inhibitor with favorable DMPK and pharmacology characteristics under evaluation for the treatment of FSGS. Characterization in toxicology models is ongoing.

Funding: Commercial Support - Goldfinch Bio

SA-PO644

Preclinical Safety and Scalability of VIS649 Production for Clinical Trials for the Treatment of IgA Nephropathy

Veronica M. Miller, Susan E. Sloan, Emily A. Helger, James R. Myette, Pat Vollmer, Kristy J. Szretter, Ketan Deotale, Brian J. Pereira. *Visterra, Inc., Waltham, MA.*

Background: IgA Nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide, with no disease-specific therapies currently available. VIS649 is a humanized IgG2 monoclonal antibody targeting the cytokine named A Proliferation Inducing Ligand (APRIL) that is implicated in the pathophysiology of IgAN. To demonstrate the feasibility of generating a commercially available VIS649 treatment, the preclinical effects, potency and safety attributes of VIS649 materials that were produced using a range of scaled down bench-top and scaled up manufacturing processes were compared.

Methods: VIS649 was first produced in-house using a CHO cell line – Batch 1, followed by small scale production at a CRO using a pool of CHO clones (Batch 2) and finally at a larger-scale manufacturing plant using CHO cells from a research cell bank (Batch 3). Each batch of VIS649 was then assessed for preclinical safety and efficacy in

non-human primates (NHPs). In addition, *in vitro* analytical assays were used to compare the batches including APRIL binding (ELISA), and engagement with immune factors and receptors (complement, FcRI, FcRII and FcRIII binding by Octet). Finally, because glycans can influence the half-life and metabolism of immunoglobulins the glycan profile of each batch was assessed using MS, HPLC and CE methods.

Results: VIS649 synthesized at each scale was found to produce equivalent maximal reductions in circulating IgA levels (~70%) in the NHP studies. Furthermore, *in vitro* assessments confirmed that the three batches of VIS649 had similar binding to APRIL, as well as minimal FcRI, II, III and complement binding. Observed minor changes in glycans were not found to impact *in vivo* or *in vitro* VIS649 activity.

Conclusions: These data confirm that VIS649 production can be consistently scaled from small to larger scale manufacturing, while retaining important potency, purity and safety characteristics. These results support that large-scale production of VIS649 will be suitable for use in clinical trials to assess both safety and efficacy in IgAN patients.

Funding: Commercial Support - Visterra Inc.

SA-PO645

Crotamine, a Cell Penetrating Peptide, Targeting Renal Proximal Tubular Epithelial Cells: A Potential Future for Kidney Gene Therapy

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Background: Activated proximal tubular epithelial cells (PTECs) play a crucial role in progressive tubulointerstitial fibrosis in native and transplanted kidneys. Active targeting of PTECs by non-viral gene delivery vectors such as cell penetrating peptides (CPPs) might be useful to influence the expression of genes in these cells, however most CPPs are not very cell type specific. Crotamine, isolated from the venom of rattlesnake, is characterized as CPP due to its ability to cross lipid cell membranes. Crotamine is also able to form complexes with DNA molecules and contains a nuclear retention motif, which helps to deliver DNA cargo into the nucleus enabling its use as a cell transfection agent. The ability of crotamine to internalize and carry molecules into cells is dependent on proteoglycans present on the cell membrane.

Methods: Crotamine was administered intraperitoneally to 14 week-old mice for 21 consecutive days. Main organs and body weight, food and water intake and renal function biomarkers were assessed. Fluorescently-labeled Cy3-crotamine was injected to track its localization throughout the kidney. Kidney was collected for immunohistochemistry assays. Crotamine binding, uptake and reporter gene expression was assessed in PTEC cell line.

Results: We demonstrated the safety of long-term crotamine administration and after injection into mice, crotamine passes the glomerular filter, is selectively taken up by PTECs, and subsequently localized into the nuclei of these cells. *In vitro* we could show that the binding and uptake of crotamine into PTEC cell line is mediated via the heparan sulfate side chains of syndecan-1, a major proteoglycan on these cells. *In vitro* we also showed efficient gene-delivery and reporter gene expression in this cell line.

Conclusions: This study shows the in vivo applicability of using crotamine as PTEC specific gene delivery nanocarrier and might be a prototypic example of the next generation kidney specific non-viral gene delivery vectors to modulate aberrant gene expression in PTECs in kidneys in order to slow down progressive tubulointerstitial fibrosis. Support: FAPESP/Capes.

Funding: Government Support - Non-U.S.

SA-PO646

Unbiased Interrogation of Clinically-Indicated Biopsies Identifies Discoidin Domain Receptor Inhibition as Target for Anti-Fibrotic Therapy: Cell, Animal, and Pharmacological Intervention Studies

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Background: Regardless of etiology, most forms of kidney disease are characterized by advancing fibrosis, the extent of which correlates closely with declining kidney function. As such, fibrogenesis may be a final common pathway in kidney disease progression so that strategies to temper it may attenuate the loss of function in a broad range of kidney diseases. While most efforts at developing anti-fibrotic drugs have focused on inhibiting transforming growth factor-beta (TGF-beta) or connective tissue growth factor (CTGF), other yet unidentified mediators may also be importamt targets for therapeutic development.

Methods: RNA was extracted from 14, -80C degrees frozen, clinically-indicated kidney transplant biopsies and subjected to RNASeq analysis. Clinical data including sequential eGFR values were also collected.

Results: In addition to TGF-ß and CTGF we also found that the abundance of discoidin domain receptor (DDR) mRNA correlated closely with both the extent of fibrosis (rho=0.6, p=0.01) and rate of eGFR decline (rho=0.6, p=0.01). Since DDR is a receptor tyrosine kinase that is activated by binding to fibrillary collagen, we exposed NRK-49F renal fibroblasts ($p<0.05$) to type I collagen and noted that this not only led to DDR phosphorylation but also induced the de novo synthesis of collagen, identified by the incorporation of 3H-proline. We next synthesized a DDR inhibitor, 6j (Wang et al., J. Med. Chem. 2016, 59, 5911–5916), showing that it dose-dependently reduced DDR phosphorylation and 3H-proline incorporation in renal fibroblasts ($p<0.05$) in response to collagen I. We then conducted in vivo proof-of-concept studies in the unilateral ureteric obstruction (UUO) model of kidney fibrosis showing robust reduction in collagen III deposition at 50 mg/kg/day ($p<0.05$) at 7 days.

Conclusions: Merging unbiased transcriptomic analysis of clinically-indicated kidney biopsies with histopathological and clinical data can identify novel mediators of fibrogenesis. The pathophysiological relevance of the so-derived targets can then be assessed by in vitro and in vivo models as a prelude to the development of new therapies for human use that aim to slow, arrest or potentially even reverse the progression of CKD.

Funding: Commercial Support - Fibrocor Therapeutics, Private Foundation Support

SA-PO647

Dexamethasone-Loaded Macrophage-Derived Microvesicles: A Novel Approach for Enhanced Anti-Inflammatory Efficacy for Renal Disease

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Background: Although glucocorticoids are the mainstays in the treatment of renal disease, the dose dependent side effects have largely restricted their clinical use. Microvesicles (MVs) are nano-sized extracellular vesicles with a membrane lipid bilayer that are shed by cells and efficiently entering other cells. Here, we investigated whether macrophage-derived MVs can function as efficient carriers of dexamethasone (DEX), and the anti-inflammatory efficacy of the novel DEX delivery system was assessed in both in vitro and in vivo models of renal disease.

Methods: MVs were prepared from the supernatants of RAW 264.7 cells treated with DEX by centrifugation. In vivo, the therapeutic potential of DEX-packaging MVs (MV-DEX) was assessed in LPS and Adriamycin (ADR) induced nephropathy model. In vitro, the therapeutic efficacy was assessed in glomerular endothelial cells (GECs).

Results: The mean diameter of MV-DEX was 140.7±4.8 nm and the average drug content was $6.2\mu g/1\times10^{10}$ MVs. Compared with GECs without LPS stimulation, more MVs were accumulated in the inflamed GECs. Consistently, the higher renal radiance signal of DID-labelled MVs was observed in LPS and ADR model. The extent of average radiance was positively correlated with renal TNF-α or IL-6 protein levels. In vitro, we found that the mRNA levels of proinflammatory cytokines, protein expression of NF-κB p65 and p-p65, and levels of TNF-α and IL-6 in the supernatants were significantly inhibited by MV-DEX treatment. Inflammation was blunted with free DEX, however, to a much lesser extent than with MV-DEX therapy. In LPS model, treatment with MV-DEX increased the animal survival rate. In ADR model, albuminuria, glomerulosclerosis and foot process effacement were remarkedly ameliorated with MV-DEX threatment. In both models, the mRNA levels of proinflammatory cytokines, protein expression of p65 and p-p65, and infiltration of inflammatory cells were inhibited after MV-DEX treatment. Interestingly, MV-DEX treatment showed better therapeutic efficacy than free DEX both in vivo and in vitro.

Conclusions: Our studies firstly demonstrated that macrophage-derived MVs could efficiently deliver DEX into inflamed kidney and exhibit a superior ability to suppress renal inflammation compared to routine DEX therapy.

SA-PO648

Safety and Efficacy of a New Biomimetic Sorbent Hemoperfusion Device in Removing Bacteria from Hemodialysis Patients with Blood Stream Infections - Results of a Multicenter First-in-Human Study

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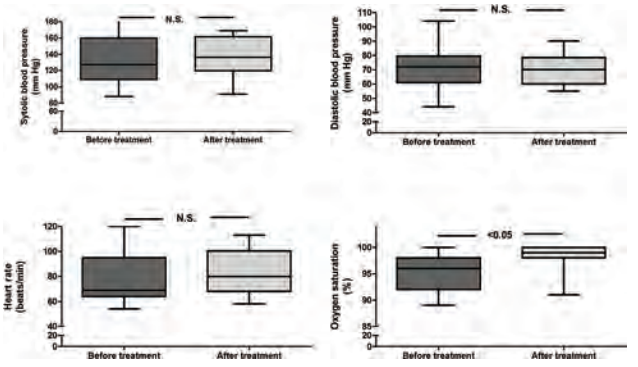
Background: Prompt reduction of bacterial load improves survial of bacteremic patients, so strategies above and beyound antibiotics are invesitagted. Binding of bacteria to heparan sulfate can be used to remove bacteria from the circulating blood by mimicking heparan sulfate grafting heparin to beads packed in a column. This device, the Seraph® 100 Blood Filter (Seraph), also removes toxins, and cytokines. Aim of this multicenter first in human study was to asses safety and efficacy of the Seraph in hemodialysis patients with bacteremia.

Methods: Fifteen (3F/12M, median age 75 [66-79] years) patients were included (www.clinicaltrials.gov. NCT02914132). The Seraph was placed in series, upstream from a dialyzer during a single four hour dialysis session. Vital signs as well as coordinates of the hemodialysis and a detailed laboratory analysis were performed. Efficacy was evaluated by measuring time to positivity in the blood cultures taken before and after the Seraph at several time points. Patient follow up was 14 days.

Results: As the last patient was enrolled before the abstract deadline complete data are only available in 14 patients. Vital signs remained stable and peripheral oxygen saturation improved during treatment unrelated to fluid removal. In patients with bacteremia at the time of treatment despite an adequate dose on antibiotics (4 out of 15), Seraph lead to a decrease in bacterial count.

Conclusions: Seraph treatment is well tolerated by hemodialysis patients, and can quickly remove bacteria from blood. It's rapid, broad-spectrum binding and inherent blood compatibility suggest future use as a prophylactic, or at the first sign of bloodstream infection, even before pathogen identification. Improvement of oxygen saturation during treatment deserves further investigation.

Funding: Commercial Support - ExThera Medical



SA-PO649

Urinary Exosomes Identify Inflammatory Pathways in Vancomycin Induced AKI

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Background: Vancomycin is used as a first line empiric therapy for gram positive organisms such as resistant Staphylococcus species. Vancomycin-induced acute kidney injury (VAN-AKI) has been reported in up to 43% of patients, especially in those targeting higher trough concentrations. The mechanism of injury in humans remains not well understood with recent evidence pointing to cast nephropathy. In this study, we investigate the protein contents of urinary exosomes in patients with VAN-AKI to further elucidate mechanisms of injury.

Methods: Urine samples from 10 patients with VAN-AKI who were enrolled in the DIRECT study and 12 healthy control urine samples from the UAB-UCSD O'Brien Center Biorepository were included in the analysis. Exosomes were extracted using solvent exclusion principle and polyethylene glycol induced precipitation. Protein quantification was analyzed by high throughput liquid chromatography/mass spectrometry. Significant proteins were determined by Pi score >1, which accounts for both fold change and t-test significance. Western blotting is currently being conducted as validation of proteomic findings.

Results: Subjects were male with a mean age of 40.8±18.3 years, BMI of 26.6±7.0, and a distribution of comorbidities. The mean peak serum creatinine was 3.7±1.4 mg/dL and time to kidney injury was 4.0±3.0 days. At discharge, 90% of patients demonstrated none or partial recovery; 33% experienced full recovery by day 28. Twelve samples were included in the final proteomic analysis and revealed 2009 proteins in all samples and 251 proteins significantly associated with VAN-AKI (Pi score >1). The top discriminatory proteins were fibrinogen, complement C3, complement C4, galectin-3-binding protein, alpha-2 macroglobulin, immunoglobulin heavy constant mu and serotransferrin. Galectin-3 binding protein binds glycoproteins such as serotransferrin and alpha 2 macroglobulin and up-regulation has been previously correlated with inflammation, fibrosis and rapid kidney function decline. Fibrinogen upregulation and complement activation have been demonstrated after ischemia reperfusion injury.

Conclusions: Urinary exosomes reveal up-regulation of inflammatory proteins after nephrotoxic injury in VAN-AKI.

Funding: NIDDK Support, Private Foundation Support

SA-PO650

Attenuation of Renal Ischemic Reperfusion Injury in Rats with DUR-928, a Novel, First-in-Class Therapeutic in Development for Renal Disease

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Background: DUR-928 (5-cholesten-3β,25-diol 3-sulfate) is a first-in-class, endogenous sulfated oxysterol that regulates lipid metabolism, inflammatory response, and cell survival. It has been reported that this molecule protects against acute organ injury, including the kidney, and improved survival, from LPS-induced endotoxin shock and acetaminophen overdose/toxicity mouse models when administered at doses of 25-50 mg/kg by intraperitoneal (IP) injection.

Methods: In this study, the potential therapeutic effect of DUR-928 was investigated in a rodent model of acute kidney injury (AKI) induced by renal ischemia/reperfusion (I/R) injury. Renal ischemia was achieved by transient occlusion of the left kidney in adult male Lewis rats (9-11 weeks of age) for 50 minutes. At reperfusion, the right kidney was removed. Rats were randomized into three treatment groups (N=6 rats/vehicle control; N=11-12 rats/DUR-928) for IP administration of DUR-928 (25 mg/kg/day) or vehicle control. Three or four daily IP injections of DUR-928 or vehicle control were administered and rats were followed through 7 days of observation after I/R injury.

Results: On Days -2 (Baseline), 3 and 7 after surgery, serum creatinine (sCr) and blood urea nitrogen (BUN) were measured to evaluate renal function. Induction of I/R injury in rats was successfully achieved. sCr and BUN levels peaked significantly on Day 3 compared to Baseline. Improvement of these measures was observed on Day 7 due to spontaneous self-recovery that is characteristic of this I/R injury model. IP administration of 4 daily doses of 25 mg/kg DUR-928 resulted in significant reductions in sCr and BUN compared to vehicle-treated rats on Day 3, suggesting improved renal function. DUR-928 treatment resulted in a 63% reduction in sCr (118.4±85.9 mg/dL versus 317.3±296.6 mg/dL; $p<0.05$) and a 57% reduction in BUN (23.4±14.8 mg/dL versus 54.0±27.7 mg/dL; $p<0.05$) compared to vehicle. Similar results were found with 3 daily doses of DUR-928, with a 43% reduction in sCr ($p=0.05$) and 45% reduction in BUN ($p<0.05$), compared to vehicle.

Conclusions: The current study highlights the potential of DUR-928 to attenuate kidney injury in an acute setting and supports the continued evaluation of DUR-928 in renal disease.

Funding: Commercial Support - DURECT Corporation

SA-PO651

Multipronged Systems Approach to Enhance Medication Safety in Patients with CKD

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Background: In the United States, 1 in 7 people have chronic kidney disease (CKD), over 650,000 people have end stage renal disease (ESRD). Patients with CKD experience polypharmacy with ESRD patients taking average 10-12 prescriptions. Pharmacokinetic differences in CKD/ESRD patients require increased awareness and dose adjustment to minimize adverse events from prescription and OTC medications or herbal supplements. Kaiser Permanente Northern California (KPNC) is an integrated health care system that provides care to 4.3 million members with over 300,000 CKD patients through 21 medical centers.

Methods: In 2016, a workgroup was formed to improve medication safety for patients with CKD. The workgroup comprises of nephrologists, pharmacists and pharmacy informatics across the region. The work group met monthly via web conferencing. The workgroup outreached to relevant stakeholders and decision-makers between meetings. Leveraging Electronic Medical Record (EMR) and the expertise of the members, the workgroup used a multipronged systems approach to identify gaps and developed standardized protocols. The work group also optimized processes to enhance medication safety in CKD and to reduce acute kidney injury (AKI).

Results: In the inpatient setting, the work group standardized protocols for antibiotic dosing, created order sets to minimize use of nephrotoxic agents including elimination of sodium phosphate enema use, and implemented calcineurin inhibitor drug interaction alerts. Additionally, EMR alerts are being placed for outpatient prescriptions that require dose adjustment or are contraindicated in CKD. In the home setting, herbal supplements and OTC medications tip sheet was produced for patient education and kidney protection.

Conclusions: In an integrated healthcare system such as KPNC, creation of an integrated nephrology pharmacy workgroup may help develop objectives and provide implementation strategies to reduce potential adverse medication events in patients with CKD.

Funding: Private Foundation Support

SA-PO652

Efficacy of Teriparatide and Denosumab on Bone Mineral Density in Dialysis Patients: A Meta-Analysis

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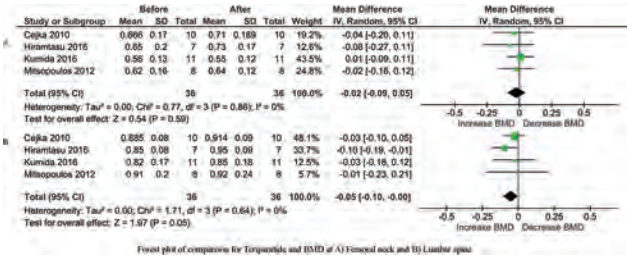
Background: Teriparatide and denosumab are therapeutic agents proven to increase bone density and prevent fracture in patients with osteoporosis. Evidence of efficacy of these agents in end-stage renal disease (ESRD) is still lacking. This meta-analysis evaluated the effect of Teriparatide and denosumab on bone mineral density (BMD) and biochemical testing in ESRD patients on dialysis.

Methods: We comprehensively searched the databases of MEDLINE, EMBASE, and Cochrane Databases. The inclusion criteria were published studies using denosumab or teriparatide in dialysis patients with low bone mass for at least six months. The primary outcome was BMD at the femoral neck, lumbar spine, and radius. The secondary outcome was parathyroid hormone (PTH), calcium, phosphorus, and bone-specific alkaline phosphatase (BSAP). A random-effects meta-analysis was performed to compare the change in outcome at baseline and after denosumab or teriparatide was given.

Results: Four studies using teriparatide were included in the meta-analysis of BMD. Overall, there was no significant change in BMD at the femoral neck ($p=0.59$), lumbar spine ($p=0.05$), or radius ($p=0.23$). There was also no significant change in calcium ($p=0.33$), phosphorus ($p=0.23$), PTH ($p=0.46$), and BSAP ($p=0.86$). Four studies using denosumab were included in the meta-analysis. There was a significant decrease in PTH with a standardized mean difference of 2.22 (95% CI: 0.13 to 4.31). No significant change in calcium ($p=0.37$), phosphorus ($p=0.43$), and BSAP ($p=0.15$) was found. There was not enough study to assess the effect on BMD.

Conclusions: Current evidence does not support the use of denosumab or teriparatide in dialysis patients with low bone mass. More studies are needed to evaluate efficacy and safety of these therapeutic agents for osteoporosis in this population.



Forest plot of comparison for Teriparatide and BMD at A) Femoral neck and B) Lumbar spine

Forest plot of comparison for Teriparatide and BMD at A) Femoral neck and B) Lumbar spine

SA-PO653

Bone Mineral Density and Handgrip Strength in Early CKD: Cross-Sectional Analysis of CARTaGENE

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Background: Bone mineral density (BMD) and handgrip strength (HGS) are associated with adverse outcomes in general and advanced CKD populations. However, how early CKD impacts these two parameters has not been well studied.

Methods: Cross-sectional analysis of CARTaGENE, a population-based health survey of 40 to 69 years old individuals from Quebec. Individuals with data on estimated glomerular filtration rate (eGFR) over 30 ml/min/1,73m^2, BMD and HGS were included. BMD was measured by quantitative ultrasound at the calcaneus and HGS by a hand dynamometer. Early CKD was expressed continuously (eGFR) and categorically (KDIGO stages). Association between CKD, BMD and HGS was assessed with linear regression in univariate and multivariate models adjusted for demographics, comorbidities and medication. BMD results were stratified for sex because of an interaction between CKD and sex.

Results: We included 15,721 individuals (51% male with a mean age of 54 years and a mean eGFR of 88 ml/min/1.73m^2). 47% of individuals had G2 CKD and 4% G3 CKD. Mean BMD t-score was 0.19 in non-CKD individuals, 0.22 in G2 CKD and 0.08 in G3 CKD (G3 vs G1-G2 p=0.01). Mean HGS was 68kg in non-CKD individuals, 69kg in G2 CKD and 64kg in G3 CKD (G3 vs G1-G2 p<0.001). In univariate analysis, eGFR was not associated with HGS, but was positively associated with BMD in men and negatively in women. In adjusted models, eGFR was negatively associated with both HGS and BMD (Table). G2 and G3 CKD were associated with higher HGS compared to non-CKD. G2 CKD was associated with increased BMD in both men and women while G3 CKD was associated with increased BMD in men only.

Conclusions: In a large population of 40 to 69 years old individuals and in contrast to advanced CKD, early CKD is not associated with a decrease in BMD and HGS.

Funding: Government Support - Non-U.S.

	BMD			HGS
	Men	Women	Interaction	Men & Women
Univariate				
eGFR (per 10 ml/min/1.73m²)	-0.03 (-0.04, -0.01)*	0.04 (0.02, 0.05)**	< 0.001	-0.18 (-0.44, 0.08)
CKD stage 2 (vs stage 1)	0.08 (0.02, 0.13)*	-0.02 (-0.07, 0.03)	0.006	1.8 (1.1, 2.6)**
CKD stage 3 (vs stage 1)	-0.05 (-0.19, 0.10)	-0.16 (-0.29, -0.03)*	0.26	-3.6 (-5.6, -1.5)**
Fully adjusted[a]				
eGFR (per 10 ml/min/1.73m²)	-0.08 (-0.09, -0.06)**	-0.03 (-0.05, -0.01)*	< 0.001	-1.5 (-1.6, -1.3)**
CKD stage 2 (vs stage 1)	0.16 (0.11, 0.22)**	0.09 (0.04, 0.14)**	0.04	3.8 (3.4, 4.4)**
CKD stage 3 (vs stage 1)	0.14 (0.00, 0.28)*	0.05 (-0.09, 0.18)	0.33	2.8 (1.4, 4.0)**

[a]Adjusted for age, gender, race, body mass index, menopause status, hormonal replacement therapy, calcium, vitamin D and bisphosphonates usage.
* p < 0.05
** p < 0.001

SA-PO654

Effect of Denosumab on Trabecular Bone Score (TBS) in De Novo Kidney Transplant Recipients (KTR)

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Background: Kidney transplant recipients (KTR) are at high risk to lose bone mass in the first year after transplantation. The trabecular bone score (TBS) represents a recently developed parameter of lumbar spine bone texture that correlates with the occurrence of fractures. The utility of the TBS and its response to anti-resorptive treatment with denosumab in the first year after kidney transplantation is not known.

Methods: Post-hoc analysis of 1-year changes in TBS in 44 de novo KTR (mean age 50.6±12.6 years; 28 [64%] were male; mean baseline eGFR 54.1±16.5 ml/min/1.73 m^2) which were randomized 1:1 to denosumab or no treatment, and correlation with 1-year areal bone mineral density (aBMD) changes at the lumbar spine and total hip as assessed by dual energy X-ray absorptiometry (DXA), and peripheral bone microarchitecture as assessed by high-resolution peripheral quantitative computed tomography (HRpQCT).

Results: The baseline TBS in KTR amounted to 1.312±0.101 which was reduced compared to an age-matched normal control population (1.464±0.071). There was a significant correlation between TBS and aBMD at the lumbar spine (Spearman's ρ=0.56; p<0.001) and total hip (ρ=0.33; p<0.05). The TBS also correlated with HRpQCT-derived total (ρ=0.49; p<0.05) and trabecular volumetric BMD at the tibia (ρ=0.57; p<0.01), whereas no such correlation was found at the radius. Denosumab treatment led to an increase in TBS, paralleling the BMD changes at the lumbar spine. More denosumab-treated than control KTR showed an increase in TBS at 6 months (91% vs. 55%; p<0.01) and 12 months (87% vs 71%; p=ns). TBS increased more in denosumab-treated than control KTR (+4.0% vs +1.5%) in the first 6 months, but changed little (-0.4% vs +0.6%) in the subsequent 6 months.

Conclusions: The TBS represents a valuable parameter which provides additional data on bone health in KTR. The increase in TBS in denosumab-treated de novo KTR suggests that denosumab may improve bone microarchitecture in KTR.

Funding: Government Support - Non-U.S.

SA-PO655

AKI Followed by Complete Recovery Is Associated with Increased Bone Fracture Risk

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Background: Acute kidney injury (AKI) affects multiple organ systems, including bone mineral metabolism. Fracture risk is increased among dialysis-requiring AKI patients. The relationship between fracture risk and AKI with complete recovery has not been characterized. We investigated fracture risk following an admission complicated by non-dialysis requiring AKI with complete recovery in a propensity score-matched cohort of cases and controls.

Methods: We identified 1139 AKI cases (AKI Network definition) with complete recovery at discharge, defined by creatinine <1.10 times the pre-admit baseline value, during a hospitalization between January 1, 1999 and December 31, 2009 from an integrated health care delivery system. We matched 1139 controls (no AKI during index admission) based on a propensity score including age, sex, race, prior inpatient visits, baseline creatinine, all comorbidities in the Charlson index, and season of admission. The primary outcome was incident bone fracture following discharge. Cox proportional hazards models were adjusted for prior fracture and body mass index (BMI) and censored for death.

Results: Baseline characteristics among cases and controls were similar: age 62 ± 17 years, 45% female, 92% white, creatinine 0.9 ± 0.2 mg/dL. During a median [IQR] follow-up of 63 [10-87] months, 294 (26%) AKI cases and 169 (15%) controls had a bone fracture. Those with AKI followed by complete recovery had a two-fold increased hazard of bone fracture (HR 2.13 [95% CI, 1.76-2.58]; p=<0.0001). After adjusting for prior fracture and BMI the association persisted but was somewhat attenuated (HR 1.49 [95% CI, 1.23-1.80]; p<0.0001).

Conclusions: Hospitalized patients whose course was complicated by non-dialysis requiring AKI with complete kidney function recovery had an increased risk of fracture following discharge compared to propensity score-matched controls. These data suggest alterations in bone mineral metabolism during AKI may be associated with long-term risk of fracture even if serum creatinine returns to baseline. Further studies investigating bone and mineral metabolism pathophysiology and AKI are warranted.

Funding: Veterans Affairs Support

SA-PO656

The Relationship Between Density Measurements and Histomorphometric Parameters of Cortical Bone of Patients in the Early Stages of CKD

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Background: Cortical bone comprises a compact tissue, which is denser, less porous and metabolically active than trabecular bone. These differences give to the cortical bone a mechanical function while the mineral homeostasis is the main role of the trabecular bone. In order to evaluate these tissues, bone biopsy is the gold standard tool, but it is an invasive and expensive method. In this context, the possibility of using a non-invasive technique is clinically relevant. Quantitative computed tomography of the vertebrae (QCT) is effective for evaluating trabecular bone when compared to structural histomorphometric parameters of patients with chronic kidney disease (CKD). This relationship has not yet been fully evaluated in cortical bone. We investigated the relationship between vertebrae density measured by QCT and structural histomorphometric parameters of cortical bone of patients in the early stages of chronic kidney disease.

Methods: A post-hoc analysis of a cross-sectional study with 50 CKD stage 2-5ND patients undergone QCT and bone biopsy. Undecalcified bone samples from iliac crest was submitted to histomorphometric analysis using the Osteomeasure software (Osteometrics Inc., Atlanta, GA, USA). The histomorphometric parameters analyzed were: Ct.Po (cortical porosity) and Ct.Th (cortical thickness). The cortical bone density, expressed in Hounsfield Units (HU), was obtained by QCT from the thoracic vertebrae at the aorta root.

Results: Patients were 52±10years, 68%male and 30%diabetes mellitus. Laboratorial data included eGFR34±16 mL/min/1.73m^2, ionized calcium 1.30±0.06mmol/L, phosphorus 3.8±0.7mg/dL, alkaline phosphatase 116(71.5;160.5)U/L; iPTH 83(53.5;167.5)pg/mL, 25OHD30.8±10.1ng/dL and 1,25OH$_2$D 35.8(30;47.5)pg/mL. Regarding cortical histomorphometric parameters, cortical porosity was 4.6%(2.6;6.6) and cortical thickness was 578.4±151.8µm. The cortical bone density was 379.0 HU(344.7;411.4). There was no correlation between cortical porosity and cortical density(p=0.67) or cortical thickness and cortical density(p=0.41).

Conclusions: Cortical bone density measured by quantitative computed tomography is not associated to structural histomorphometric parameters of cortical bone of patients in the early stages of chronic kidney disease.

Funding: Government Support - Non-U.S.

SA-PO657

Etelcalcetide in the Treatment of Secondary Hyperparathyroidism in Patients Uncontrolled with Cinacalcet – Results from a Prospective Study

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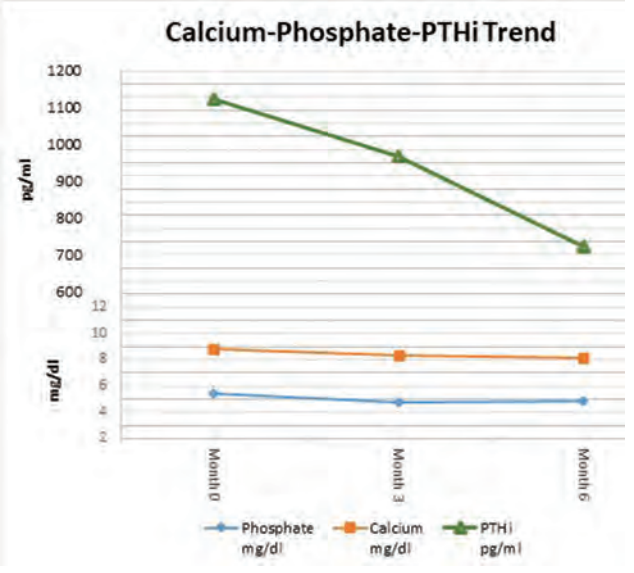
Background: Secondary hyperparathyroidism (sHPT) is associated with increased risk of fractures, vascular calcifications and all-cause mortality. Etelcalcetide is a new calcimimetic with a pharmacokinetic profile that allows thrice weekly intravenous(IV) dosing after hemodialysis(HD), recently approved for sHPT treatment. There is scarce clinical experience with this agent with respect to its efficacy in patients with sHPT that is uncontrolled with cinacalcet.

Methods: We conducted a prospective cohort study in prevalent HD patients in DaVita clinics in Portugal who had uncontrolled sHPT under cinacalcet treatment for at least 3 months. Inclusion criteria included mean intact PTH(iPTH) levels above 800 pg/mL and total calcium(Ca) above 8.3 mg/dL in the previous 3 months. After 1 week of cinacalcet washout, etelcalcetide 5mg IV/HD was initiated. iPTH, Ca and phosphorus were followed; FGF-23 and sclerostin levels were analyzed before the start of etelcalcetide and after 6 months.

Results: Thirty-four patients participated in the study; mean age was 60.7(SD ± 12.3) years; median time on HD was 82.5(7-296) months and median cinacalcet dose was 180(90-840) mg/week. Median etelcalcetide dose remained at 5mg/HD at 3 and 6 months. Evolution of biochemical parameters is represented in the figure. Over 6 months of etelcalcetide treatment, serum FGF-23 decreased from 39.3(23.0-43.3) pmol/L to 29.1(11.5 -115.6) pmol/L and sclerostin increased from 37.2(5.8 – 200.7) pmol/L to 71.7(28.2- 185.5) pmolL (p<0.0001).

Conclusions: Etelcalcetide was efficacious in improving sHPT control in this group of patients and significantly increased plasma sclerostin concentration. This is the first study describing the impact of etelcalcetide treatment on plasma sclerostin levels.



SA-PO658

Superior Effects of Etelcalcetide Compared to Cinacalcet on Increasing Bone Mineral Density in Patients Receiving Hemodialysis with Secondary Hyperparathyroidism

Satoshi Funakoshi,[3] Jyunichiro Hashiguchi,[3] Tayo Kawazu,[3] Kenji Sawase,[3] Yuko Maruyama,[3] Yoko Obata,[1] Tomoya Nishino,[2] Takashi Harada.[3] *[1]Nagasaki University Hospital, Nagasaki, Japan; [2]Nagasaki University School of Medicine, Nagasaki, Japan; [3]Nagasaki Kidney Hospital, Nagasaki, Japan.*

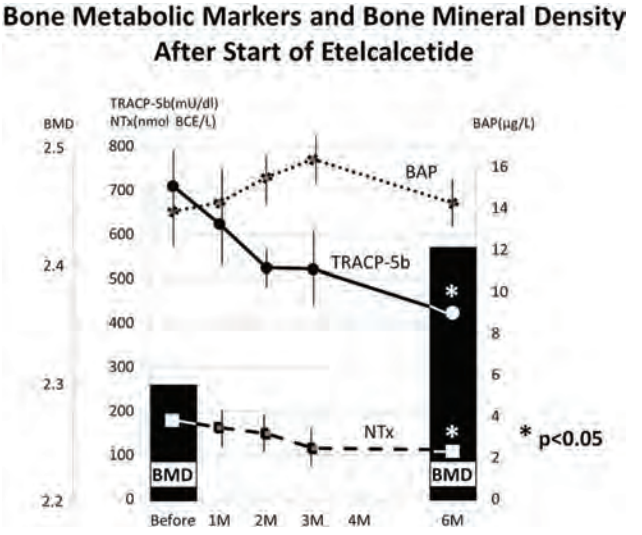
Background: Etelcalcetide hydrochloride (ET) is a novel peptide calcimimetic agent that has a similar mechanism of action as cinacalcet hydrochloride (CT). Clinical trials have demonstrated the safety and efficacy of ET in hemodialysis (HD) patients. In this study we evaluated the efficacy of ET on increasing bone mineral density (BMD) in HD patients with secondary hyperparathyroidism (SHPT).

Methods: Ten HD patients with SHPT (M/F: 6/4, mean age: 61.9 years, mean HD duration: 10.3 months) who received oral CT were enrolled in this study after their informed consent was obtained. Various doses of oral CT were converted to 5mg of intravenous ET, and bone resorption markers; TRCP-5b, NTx and bone formation marker; BAP were compared in each patient. BMD was assessed 6 months after conversion to ET treatment by digital image processing (DIP).

Results: As shown in figure, significant declines (p<0.05) were observed in serum levels of TRCP-5b and NTx (from 710.0 ± 289.0 to 420.9 ± 221.1 mU/dL, from 179.6 ± 35.5 to 112.1 ± 26.1 nmol BCE/L, respectively). On the other hand, there was no significant change in serum BAP level. Notably, BMD was significantly increased 6 months after ET treatment was started (p<0.05).

Conclusions: In our study, significant decrease of bone resorption markers, TRCP-5b and NTx, along with no alteration of BAP as a bone formation marker may explain the significant increase in BMD in HD patients with SHPT.

Funding: Private Foundation Support



SA-PO659

Denosumab: Is It Safe to Use in CKD?

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Background: Denosumab is a monoclonal antibody directed against receptor activator of RANK ligand used to treat osteoporosis. It has been promoted as safe to use in Chronic Kidney Disease (CKD) as it does not appear to accumulate in kidney failure and because of the experience in a small number of patients with CKD 3-4 enrolled in RCTs. There is no evidence for use in CKD 5. Case reports show patients with severe CKD are at higher risk of developing hypocalcemia following Denosumab. This may be due to hyperparathyroidism and vitamin D deficiency. In this case series we have examined the incidence of hypocalcemia following Denosumab treatment and tried to identify any risk factors.

Methods: Patients with CKD stages 3-5 attending our service treated with Denosumab in the last 5 years were included. Retrospective data was collected using an electronic patient database. Data collected included Corrected calcium levels prior to and after dosing, vitamin D and Parathormone (PTH) levels prior to dosing.

Results: 14 patients were identified; 9 had a functioning renal transplant and 1 patient was on hemodialysis. 4 patients were male and 10 female. Mean duration of treatment was 2.2 years. Average eGFR was 27 ml/min/1.73m2. Mean patient age was 60 years (range 44-84). Mean BMI was 25 (range 19-36). 11 patients were on oral steroids. The average calcium prior to dosing was 2.35 mmol/l (2.12 to 2.54) falling to 1.98mmol/l (1.58-2.22) after dosing. 9 patients achieved their lowest calcium at 1 week, 2 at 4 weeks and 3 at 8 weeks. Average PTH level prior to dosing was 153ng/l (42-371) and after was 888ng/l (155-1990). 5 patients developed severe hypocalcemia (corrected calcium less than1.9mmol/l), average prior calcium in this group was 2.39mmol/l (2.22 – 2.54) falling to 1.77mmol/l (range 1.58 – 1.86). The average prior PTH was 206ng/l, rising to 1171ng/l after denosumab. Four patients did not have Vitamin D checked before dosing.

Conclusions: Denosumab will cause a small but not clinically significant reduction in serum Calcium in most patients with CKD. Severe hypocalcaemia can result if Vitamin D levels are unknown or in higher PTH levels. eGFR does not seem to correlate with the risk of hypocalcaemia. The biochemical abnormalities associated with CKD should be corrected, specifically, calcium, phosphate, PTH and vitamin D. Densoumab is the preferred treatment in CKD 4/5 however its use should be avoided in severe hyperparathyroidism and vitamin D deficiency.

SA-PO660

Proton Pump Inhibitors, But Not Histamine-2 Receptor Antagonists, Associate with Hip Fracture Risk Among Patients on Hemodialysis

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Background: An association between proton pump inhibitor (PPI) use and hip fracture risk has been described in the general population, where the primary causative hypothesis focuses on impaired gastrointestinal calcium absorption. The impact of acid suppressor use on hip fracture risk in a high-risk subset, patients with end-stage kidney disease requiring hemodialysis, is unknown and could help further distinguish the reason for increased susceptibility among PPI users.

Methods: Using the U.S. Renal Data System (USRDS), we identified all hip fracture events recorded between 2009 and 2014 among hemodialysis-dependent patients. Eligible cases were matched on index date with 10 controls. We identified PPI and histamine-2 receptor antagonist use from Medicare Part D claims covering 3 years prior to index date and stratified according to proportion of days covered by filled prescriptions. Using logistic regression with multiple imputation for missing data, we estimated unadjusted and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: We studied 4,551 cases and 45,510 controls. Cases were older, more likely to be female and Caucasian, and had shorter dialysis vintage; fewer were obese. A larger proportion of cases had any prior PPI (70% *vs.* 63%) or histamine-2 receptor antagonist (25% *vs.* 23%) use. Use of PPI was associated with higher risk of hip fracture (adjusted OR 1.19, 95% CI 1.11-1.28). This association remained within subgroups of low, moderate, and high PPI use, yielding adjusted ORs of 1.16 (1.06-1.27), 1.21 (1.11-1.31), and 1.20 (1.09-1.32), respectively.

Conclusions: Conclusion: Among patients with end-stage kidney disease on hemodialysis, PPIs, and not histamine-2 receptor antagonists, were associated with hip fracture events.

Funding: Private Foundation Support

SA-PO661

Selective Serotonin Reuptake Inhibitors Associate with Hip Fracture Risk Among Patients on Hemodialysis

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Background: Selective serotonin reuptake inhibitor (SSRI) use has been associated with hip fracture risk in the general population. Patients with end-stage renal disease on hemodialysis (HD) are a unique, high-risk subset with distinct metabolism and bone pathology, and the impact of SSRI use on hip fracture risk in this subset remains unexplored.

Methods: Using the U.S. Renal Data System, we identified all hip fracture events recorded between 2006 and 2014 among HD-dependent patients. Eligible cases were matched on index date with 10 controls; all were required to have >1 year of Medicare Parts A & B coverage. To study cumulative long-term exposure, we further required >3 years of part D coverage. We defined and stratified SSRI use by the proportion of days covered by filled prescriptions in the 3 years prior to index. In a separate study of short-term exposure, we selected subjects with >18 months of Part D coverage and required no prior antidepressant use for 1 year (months 7-18). We defined SSRI use by filled claims in the 6 months prior to index. Using conditional logistic regression, we estimated unadjusted and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: In the long-term study, we identified 4,551 cases and 45,510 controls. Compared to controls, a larger proportion of cases had any prior SSRI (37.2% *vs.* 27.6%) use. Use of SSRIs was associated with increased hip fracture risk (adjusted OR 1.30, 95% CI 1.20-1.40). The subgroups of low, moderate, and high SSRI use yielded adjusted ORs of 1.27 (1.15-1.41), 1.32 (1.19-1.45), and 1.31 (1.16-1.47), respectively. In the short-term study, we examined 4,354 cases and 43,540 controls. Increased hip fracture risk was also associated with short-term use of SSRIs (adjusted OR 1.51, 95% CI 1.29-1.76).

Conclusions: Compared to long-term SSRI use, the stronger association of short-term use with increased hip fracture risk in HD-dependent patients may suggest an acute mechanism potentially related to falls.

Funding: Private Foundation Support

SA-PO662

Association Between Malnutrition-Inflammation Complex Syndrome (MICS) and the Risk for Bone-Vascular Events in Patients Receiving Maintenance Hemodialysis: The Q-Cohort Study

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Background: Malnutrition-inflammation complex syndrome (MICS) is highly prevalent in hemodialysis patients and increases the risk for morbidity and mortality. MICS is supposed to affect bone-vascular system. However, it is unknown whether MICS increases the risk for both bone fracture and cardiovascular events in maintenance hemodialysis patients. To determine the association between MICS and those risks, we analyzed the data of the Q-Cohort Study, a multicenter, prospective, observational study.

Methods: A total of 2887 hemodialysis patients were included in the analysis. As a simple indicator for MICS, we newly developed a score (0-12) reflecting MICS by semi-quantitatively scaling the following five baseline parameters and adding up the scores of each parameters; age (0-3), serum levels of albumin (0-3), creatinine (0-3), and C-reactive protein (0-2), and body mass index (0-1). The main outcomes were the incidence of bone fracture, cardiovascular events, and all-cause death. The main exposure was MICS score. Patients were divided into four groups based on the MICS score; 0-3, 4-5, 6-8, and 9-12). Risk estimates for each outcome were calculated by Cox proportional hazards model with multivariable adjustments.

Results: During the median follow-up period of four years, 134 patients developed bone fracture, 519 patients developed cardiovascular events, and 482 patients died of any cause. The average MICS score was 5.16. Patients in the highest MICS score group (9-12) showed an increased risk for bone fracture, cardiovascular events, and all-cause mortality (HR [95%CI]; 2.14 [1.08–4.02], 2.17 [1.52–2.96], and 5.07 [3.37–7.63], respectively) compared with the lowest MICS score group (0-3). We also confirmed the internal validity of our MICS score by applying bootstrap resampling. A principal analysis also confirmed that the five parameters of the MICS score increased the risk for the three outcomes examined in our patients.

Conclusions: A higher MICS score was associated with the increased risk for bone fracture and cardiovascular events in patients receiving hemodialysis.

SA-PO663

Effectiveness of Elcatonin in Osteoporosis Patients Undergoing Hemodialysis

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Background: Osteoporosis is a very serious risk factor for fractures that are related to patient mortality, Quality of Life worsening, and hospitalization in hemodialysis(HD) patients. In particular, treatment methods are very limited in HD patients compared with normal population. Therefore, most dialysis patients will not be able to treat osteoporosis, which can lead to bone fractures. On the other hand, elcatonin inhibits bone resorption and causes bone bone mineral density(BMD) elevation, but it is difficult to maintain bone mass and strengh. Although this medication reduces osteoporosis-induced pain, it is known to increase bone mass in some studies, and it can also be used in dialysis patients

Methods: We retrospectively studied 32 elecatonin-treated HD patients and 178 untreated HD patients. The follow up period was from 2005 to 2017, and the study was conducted at a single center. Osteoporosis was defined by WHO criteria (T score <-2.5). Elcatonin treatment group was diagnosed with osteoporosis, and 20 units were injected intramuscularly once a week after the patient 's consent was obtained. The primary outcome were Incidence of bone fracture, changes in BMD. Secondary outcomes was reduction of bone pain

Results: Fractures were observed in 7 patients (21%) in the Elcatonin group and 9 (11%) in the control group, but there was no statistical significance(p-value = 0.088). In 2013, the BMD in the Elcatonin group was 0.689 ± 0.039 which was statistically significantly lower than that of the control group of 0.937 ± 0.181(p-value <0.001). Also, in 2018, the BMD of the elcitonin group was 0.724 ± 0.08, which was statistically significantly lower than that of the control group of 0.9672 ± 0.186(p-value <0.001). There was no significant difference in reduction of bone pain between the two groups

Conclusions: Elcatonin was not effective in reducing the frequency of fractures or reducing bone pain in hemodialysis patients. Rather, the Elcatonin group had a further decrease in BMD compared with the control group. It is possible that the results have been observed to be worse because the Elcatonin group has been used on existing osteoporosis patients. However, Elcatonin seems to be ineffective in HD patients because it causes pain, increases drug costs and is not effective in treating osteoporosis.

SA-PO664

Bone Mineral Density in Patients with CKD: Hip Is More Affected Than Spine

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Background: Patients with chronic kidney disease (CKD) have a higher risk of fracture than the general population. Osteoporosis is a co-prevalent disease, twice as common in this population, and dual-energy X-ray absorptiometry (DXA) has been recognized to predict fracture in CKD. We hypothesized that low bone mineral density (BMD) will be more

prevalent as kidney function decreases and will be associated with biomarkers of mineral and bone disease.

Methods: We investigated the features of BMD in patients with CKD stages 1-5, in a decade observation. DXA obtained from January 1st 2007 to Dec 31st 2017, clinical, demographic and biochemical data at the time of image acquisition were recorded. A total of 1,172 patients were enrolled into this study (81.3% women, 79.9 % white, and 8.6% diabetic).

Results: Osteopenia and osteoporosis in at least one site (total hip or spine) were found in 32.7% and 20.0% of patients, respectively. As CKD progresses, the percentage of patients with normal BMD decreases whereas the percentage of osteopenia and osteoporosis increases, which was mostly due to the total hip involvement. Older age and hyperparathyroidism (PTH>65pg/ml) were independently risk factors for osteopenia/osteoporosis at total hip. Regarding spine, female gender, older age and higher iCa were independently associated with the risk of osteopenia/osteoporosis in the entire population. The odds ratios for osteoporosis/osteopenia at the hip were 1.14 (95% CI: 2.10-3.85) and 1.05 (95% CI: 1.87-3.35) for patients with eGFR <15 and 15-30 ml/min/1.73m^2, respectively. None eGFR category was significantly associated with the risk of osteoporosis/osteopenia at the spine.

Conclusions: We confirmed the risk factors for low BMD already described for the general population, and demonstrated the association with impaired renal function and the more expressive hip involvement than spine. In addition, hyperparathyroidism seems to be an additional, and sizable risk factor in this population.

SA-PO665

Bone Loss in Kidney Transplant Recipients and Patients on Dialysis Treated with Nocturnal Hemodialysis, Conventional Hemodialysis, and Peritoneal Dialysis

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Background: Patients on dialysis have an increased risk of fractures due to mineral bone disorder. This disturbed mineral metabolism is improved by nocturnal hemodialysis, an intensified hemodialysis regimen, and completely normalized by kidney transplantation. This study therefore had two aims: to compare bone loss and its determinants in kidney transplant recipients and patients on dialysis, and to compare bone loss between patients on nocturnal hemodialysis, conventional hemodialysis, and peritoneal dialysis.

Methods: In this prospective observational study, we measured trabecular bone mineral density at the thoracic spine with computed tomography annually for up to 3 years in 45 incident kidney transplant recipients and 78 patients on dialysis (30 on nocturnal hemodialysis, 28 on conventional hemodialysis, and 20 on peritoneal dialysis), who were all transplantation candidates. We used mixed models to compare bone loss between treatment groups and used logistic regression to assess determinants of significant bone loss.

Results: Overall, mean age was 51 ±13 years, and 80 (65%) were male. Bone mineral density remained stable in kidney transplant recipients (change 1.9, 95% confidence interval -1.4; 5.2 mg/cm^3 per year), while it decreased in patients on dialysis at a rate of -6.4, 95% confidence interval -9.2; -3.7 mg/cm^3 per year (P<0.001 for difference). In kidney transplant recipients, determinants of significant bone loss were female sex and over 50 years old (P=0.01), higher baseline bone mineral density (P=0.01), and no calcium supplementation (P=0.03). In patients on dialysis, determinants were female sex (P=0.01) and low parathyroid hormone levels (P=0.03). In patients on dialysis, bone loss was similar in patients on nocturnal hemodialysis, conventional hemodialysis, and peritoneal dialysis (P=0.92 for differences).

Conclusions: After kidney transplantation patients have stable trabecular bone mineral density, while patients who remain on dialysis lose substantial amounts of trabecular bone. This loss is similar in treatment with nocturnal hemodialysis, conventional hemodialysis, and peritoneal dialysis. Whether this is due to oversuppression of parathyroid hormone needs further study.

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SA-PO666

Variability and Facility Predictors of Cinacalcet Prescription Among US Hemodialysis Facilities

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Background: Calcimimetic drugs used to treat secondary hyperparathyroidism (SHPT) are being considered for inclusion in the ESRD bundled payment system. Understanding of utilization patterns of calcimimetics across dialysis facilities may help align financial incentives with clinical goals. The objective of our study was to describe the distribution of cinacalcet prescription across dialysis facilities and to explore factors that may influence utilization of cinacalcet.

Methods: We used monthly cross-sectional data from the Dialysis Outcomes and Practice Patterns Study in 2014 to characterize the distribution of cinacalcet prescription across 203 US hemodialysis facilities (10,521 patients). Based on associations with PTH levels from patient-level analyses, we used linear mixed-effects regression to estimate the association between three facility-level exposures – % black, % <65 years old, % having a dialysis vintage ≥3 years – and the prevalence of cinacalcet prescription, adjusting for facility- and patient-level potential confounders.

Results: The average unadjusted mean percentage of patients in each facility prescribed cinacalcet was 23.0% in June 2014 (median, 21.9%; IQR, 12.8-30.5%). The percentage of patients in each facility prescribed cinacalcet in June 2014 was strongly and positively associated with the percentage of patients in the facility who were black, <65 years old, and had a dialysis vintage ≥3 years, adjusting for patient case-mix and dialysis chain affiliation (Figure).

Conclusions: Given these systematic differences of cinacalcet use across dialysis facilities, facilities treating proportionally more patients who are black, under age 65, and having ≥3 years on dialysis may bear disproportionally greater financial burden for treating patients with SHPT after calcimimetics are added to the ESRD bundle. Additional studies evaluating the differential financial impact on facilities of adding calcimimetics to the bundle are warranted.

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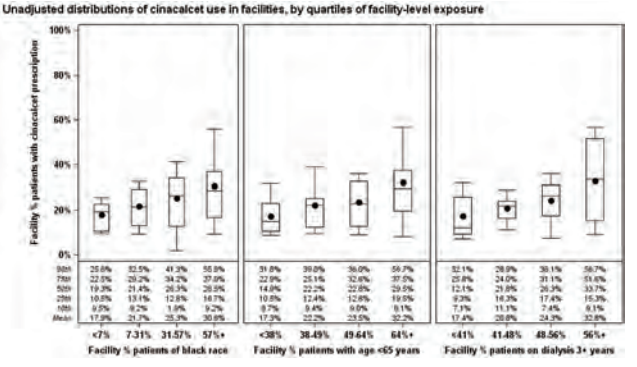

SA-PO667

The Effects of Lanthanum Carbonate on Bone Metabolic Markers and Bone Mineral Density in Incident Hemodialysis Patients

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Background: Abnormal bone turnover is a risk factor for cardiovascular disease in hemodialysis (HD) patients. Lanthanum carbonate (LC) is widely used as one of calcium-free phosphate binders and some clinical trials reported the effect of LC on vascular calcification in HD patients. We previously conducted a randomized controlled trial which focused on the effect of LC on coronary artery calcification compared with calcium carbonate (CC) in patients after initiating HD. The aim of the present study was to investigate the effect of LC on bone metabolic markers and bone mineral density (BMD) compared with CC in subjects new to HD.

Methods: We conducted a post hoc analysis from our previous randomized controlled trial. We measured osteocalcin (OC), bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP-5b), and sclerostin in serum at baseline, 12, and 18 months. The measurement of BMD at lumbar spine and femoral neck was performed at the same time. The patients who did not have the data of bone metabolic markers were excluded from this study. Finally, 65 subjects were included in the present study.

Results: Serum OC, BAP, TRACP-5b, and sclerostin levels were comparable between the two groups at baseline. Serum OC levels in the LC group were significantly higher than those in the CC group at 18 months [LC vs CC, 30.0 (18.9-53.2) pg/mL vs 21.7 (15.3-28.3) pg/mL, p = 0.015]. Serum BAP and TRACP-5b levels tended to be higher in the LC group than in the CC group at 18 months [LC vs CC; BAP, 11.9 (8.1-18.5) vs 9.5 (8-12.9) μg/L, P = 0.174; TRACP-5b, 456.0 (228.0-644.0) vs 326.5 (183.3-487.5) mU/dL, P = 0.158, respectively]. Serum sclerostin levels were not different between the two groups. Although serum phosphate levels were comparable between the two groups, serum calcium levels tended to be lower and intact parathyroid hormone levels tended to be higher in the LC group than those in the CC group at 18 months. BMD at both lumbar spine and femoral neck were comparable between the two groups.

Conclusions: In the present study, bone formation and resorption markers were higher in the LC group than in the CC group. Our findings suggested that the treatment of LC was able to maintain proper bone turnover compared with calcium-containing phosphate binders in incident HD patients.

SA-PO668

Etelcalcetide Utilization Pattern in a Mid-Size Dialysis Organization

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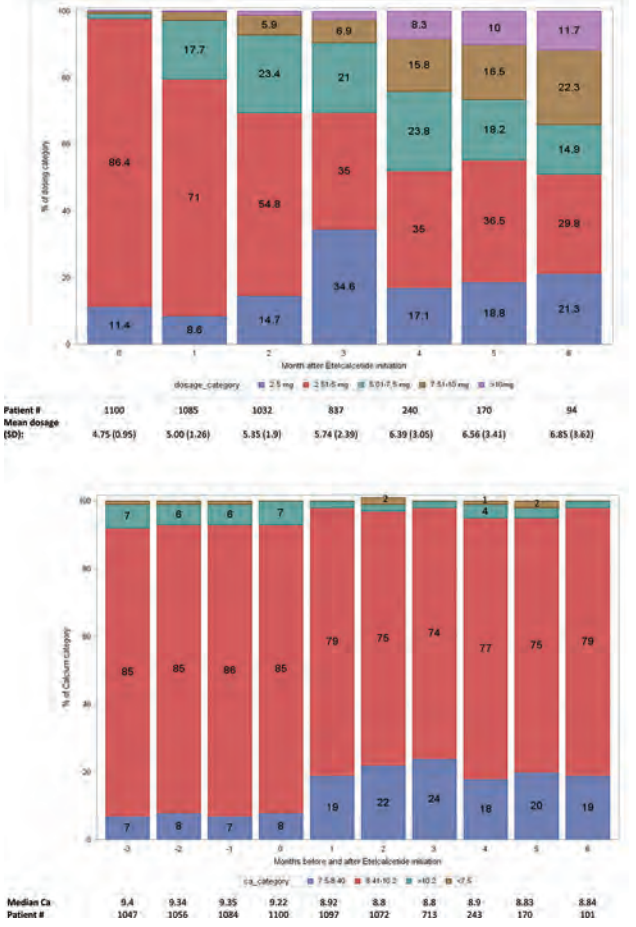
Background: Etelcalcetide is a new calcimimetic agent just entered into clinical practice. The aims of this study are to describe the initial etelcalcetide doses, titration and changes of three key laboratory indices for secondary hyperparathyroidism (SHPT) management.

Methods: This retrospective cohort study included all US ESRD patients ≥18 years, who had received in-center hemodialysis at US Renal Care centers and initiated etelcalcetide between 2/2017 and 2/2018. Every patient was followed from etelcalcetide initiation date until the earliest date of 6 months, death, transplantation, parathyroidectomy, termination of follow-up. Descriptive analyses (mean, median and %) for etelcalcetide dosage, 3 key laboratory indices for SHPT management (parathyroid hormone (PTH), corrected calcium (cCa) and phosphorus (P)) were presented at baseline period and during follow-up.

Results: A total of 1,100 patients initiated etelcalcetide, and the mean (SD) age was 58.7±13.8 years. A total of 86.4% of patients initiated etelcalcetide at 5mg, and 11.4% at 2.5mg three times a week (TIW). The mean (SD) monthly dosage increased from 5.0±1.3 mg at the first month to 6.9±3.6 mg at the 6th month (**Figure 1A**). After etelcalcetide initiation, the proportion of patients achieved a PTH goal of <600 increased from 19% to 51%. During follow-up, 19-24% of patients had at least one cCa level <8.4mg/dL, with <2% (of 1,100) had cCa <7.5 mg/dL (**Figure 1B**). The median P level remained between 5.5-5.7 mg/dL during follow-up.

Conclusions: We found the vast majority of patients were initiated on etelcalcetide at a dose of 5 mg TIW consistent with approved prescribing information. The prevalence of serious hypocalcemia was low, with less than 2% of patients ever having cCa levels <7.5 mg/dL.

Funding: Commercial Support - Amgen, Thousand Oaks



SA-PO669

Etelcalcetide from Controlled Trial to Bedside

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Background: Cinacalcet reduces high PTH levels (SHPT) in dialysis patients. Relevant complaints associate cinacalcet: nausea, vomiting, hypocalcemia. Therefore, clinicians are forced to reduce dose or discontinue cinacalcet with consequent poor PTH control. Etelcalcetide in randomized trials resulted non inferior to cinacalcet at lowering PTH. Common adverse events are hypocalcemia and gastrointestinal symptoms. This pilot observational multicenter study was conducted to evaluate efficacy and occurrence of side effects of etelcalcetide in a "real world" setting that is different from randomized controlled trials.

Methods: Patients on thrice weekly maintenance hemodialysis, stable doses of phosphate binders, calcitriol or active vitamin D were evaluated. Investigator were free in prescriving starting dose and etelcalcetide increments. Biochemistry and side effects were recorded after etelcalcetide. Clinician's satisfaction was evaluated by questionnaire.

Results: n.73 patients (mean age:61±13 years; males:62 %; diabetics:25 %;dialysis vintage:78±52months) received etelcalcetide. Many patients (83%) were treated with cinacalcet (median daily dose:30 mg). Cinacalcet-dependent gastrointestinal side effect were 49%; episodes of hypocalcemia were 4. No changes were observed in phosphate binder, vitamin D sterols and ESA doses, and serum hemoglobin concentration. Further results are reported in table.

Conclusions: The study shows that in high-risk dialysis patients, lower doses of etelcalcetide than that reported before reduce PTH with minimal gastrointestinal discomfort and low occurrence of hypocalcemia requiring drug discontinuation. The effect on PTH seems dose dependent. Almost all participating clinicians regarded etelcalcetide as very handy medication. Larger study and longer follow-up in "real world" setting are mandatory.

*p<0.01 Vs baseline; **p<0.02 Vs baseline	BASELINE	30 DAYS AFTER ETELCALCETIDE	60 DAYS AFTER ETELCALCETIDE	90 DAYS AFTER ETELCALCETIDE
WEEKLY ETELCALCETIDE DOSE(mg)	13±4	15±5*	17±9*	21±17*
SERUM PTH (pg/dl)	630 (443-973)	518(312-874)	437(241-1173)*	459(216-675) *
30% PTH DECREASE (% OF CASES)		45	65	71
MEDIAN SERUM CALCIUM (mg/dl)	9,1 (8,7-9,6)	8,7 (8,1-9,2) *	8,9 (8,0-9,2)	8,1 (7,2-9,0) *
EPISODES OF HYPOCALCEMIA DUE TO ETELCALCETIDE (≤7.5 mg/dl; percentage)	4,0 (during therapy with cinacalcet)	6,8**	8,2**	5,5**
ETELCALCETIDE WITHDRAWAL BY HYPOCALCEMIA (CASES)		1	2	0
SERUM PHOSPHORUS (mg/dl: median)	5,2 (4,4-6,0)	5,1 (4,5-5,8)	5,0 (3,9-6,5)	4,4 (3,1-6,1)
CLINICIAN'S SATISFACTION WITH RESULTS (%)		56	62	78

*p<0.01 Vs baseline; **p<0.02 Vs baseline

SA-PO670

Daily versus Post-Dialysis Administration of Calcimimetics for the Treatment of Secondary Hyperparathyroidism in Hemodialysis Patients: An Interventional, Multi-center Study

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Background: Treatment of secondary hyperparathyroidism (SHPT) in patients on hemodialysis (HD) may be hampered by poor medication adherence. The aim of this study was to assess the effectiveness of supervised, post-HD administration of calcimimetics in controlling mineral bone disorder (MBD) in patients on maintenance HD.

Methods: This was a multi-center prospective study that included adults treated at DaVita HD facilities in Saudi Arabia with HD vintage ≥6 months and proven SHPT. Patients with previous parathyroidectomy, baseline corrected calcium <8.4 mg/dL, tertiary HPT, and patients having other causes of hyper- or hypo-calcemia were excluded. As of Nov 1, 2017, study patients were shifted from daily dosing of calcimimetics to three weekly doses taken at the end of each HD session. Intact parathyroid hormone (iPTH), serum calcium, phosphorus, alkaline phosphatase levels, dosage of phosphate binders (calcium carbonate/sevelamer), and vitamin D analog were compared at baseline and 6 months after initiation of thrice-weekly calcimimetic dosing.

Results: A total of 73 HD patients switched to receive calcimimetics after dialysis. After 6 months, there was a significant reduction in both calcimimetic dose (p=0.005) and iPTH (p=0.013). Despite the absence of any significant change in serum calcium, phosphorus, or alkaline phosphatase, there was an increase in calcium carbonate dose (p<0.009) and a reduction in sevelamer dose (p<0.011)

Conclusions: Compared to daily dosing, supervised calcimimetic dosing after HD was more effective in controlling SHPT. Evaluation in large-scale randomized controlled studies is recommended.

Funding: Commercial Support - DaVita

Effects of alternate dose of cinacalcet on laboratory values and dosage of medications

	Baseline	After 6 months	P value
Serum phosphate, mean ± SD	5.5±1.52	5.83±1.3	0.135
Serum calcium, mean ± SD	9.2±0.8	9.3±0.74	0.62
Alkaline phosphatase, median (IQR)	133 (138)	125 (125)	0.314
iPTH, median (IQR)	1213 (784)	849 (1028)	0.013
Calcium carbonate dose, median (IQR)	3 (3)	6 (6)	0.009
Sevelamer dose, median (IQR)	6 (6)	6 (6)	0.011
Paricalcitol dose, median (IQR)	15 (12.5)	15 (10)	0.981
Cinacalcet dose, median (IQR)	60 (30)	90 (60)	0.005

SA-PO671

Conversion from Cinacalcet to Etelcalcetide in a Mid-Size Dialysis Organization: Real-World Therapeutic Conversion

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Background: There are two FDA approved calcimimetics available in the United States, intravenous etelcalcetide and oral cinacalcet. There is limited data to guide therapeutic conversion from cinacalcet to etelcalcetide in a real-world hemodialysis (HD) setting. Here we describe our experience with conversion from cinacalcet to etelcalcetide HD patients in a mid-size dialysis provider organization.

Methods: Data from 1264 in-center hemodialysis patients treated with cinacalcet from 60 dialysis centers from December 2017 to April 2018 are reported. Conversion from cinacalcet to etelcalcetide occurred in February 2018. All patients started etelcalcetide at 2.5 mg IV three times a week regardless of previous cinacalcet dose after a 7 day wash out period. Etelcalcetide doses were subsequently adjusted monthly to achieve a target iPTH of 150-700 pg/mL and an adjusted calcium of 8.0-10.2 mg/dL.

Results: The percentage of patients with an adjusted calcium reaching the target iPTH declined temporarily, but increased in month 1 and 2 after conversion. Monitoring in all patients treated with etelcalcetide, recorded the following adverse events (AEs) profiles: 4% of patients experienced nausea/vomiting and 24% hypotension. No severe AEs were reported.

Conclusions: In this real-world dosing conversion from cinacalcet to etelcalcetide aggregated biochemical targets after converting all patients to etelcalcetide 2.5 mg IV three times a week regardless of previous cinacalcet dose showed a decrease in percentage of patients reaching iPTH targets during conversion month with improving iPTH results in the subsequent two months post conversion. Side effect profile was unchanged compared to commonly reported AEs.

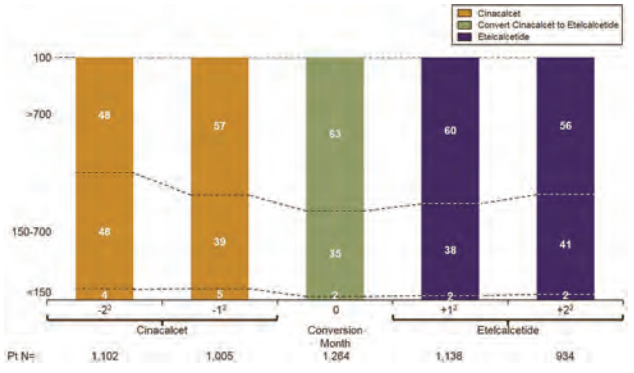

Figure: Proportion of Converted Patients by iPTH Ranges

SA-PO672

Uremic Periodontitis: Bacterial Dysbiosis and Immune Dysfunction

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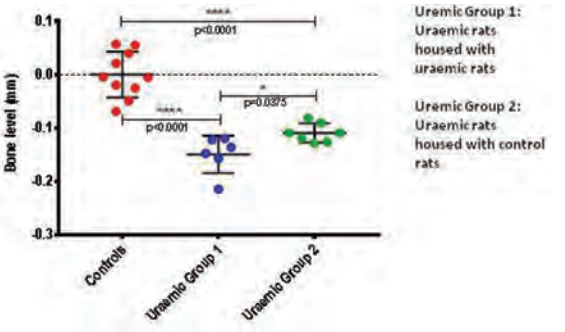
Background: Patients with CKD have a high incidence of periodontitis, which acts as a marker for increased mortality in these individuals. We sought to establish whether this represents a causal association, and to understand the mechanisms responsible.

Methods: Two models of CKD were used in wild-type Wistar rats: feeding with 0.75% adenine and subtotal nephrectomy. Of the uremic animals, half were housed with other uremics whilst half were housed with controls. The oral microbiome was assessed using next-generation sequencing and culture-based methods. Periodontal bone loss was measured as the distance between the cemento-enamel junction and the alveolar bone ridge, supplemented by immunohistochemistry, micro-CT imaging and scanning electron microscopy.

Results: In both models of CKD, uremic rats displayed significantly more periodontal bone loss than controls (alveolar bone level > 0.1mm lower in uremics, p<0.0001). These animals displayed substantial oral dysbiosis compared to controls, including a reduction in cultured bacterial counts (log 5.95 vs log 6.21, p=0.05), increased alpha diversity (Inv Simpson index 10.3 vs 6.46, p=0.03), a decline in health-associated phylum Firmicutes (55.2% vs 66%, p=0.05) and genus Streptococcus (29.8% vs 45.8%, p=0.004), and an increase in disease-associated Gammaproteobacteria (29.6% vs 19.4%, p=0.038). Histology and imaging confirmed bone disease associated with IL-17 driven inflammation. Significantly, uremic rats housed with healthy controls demonstrated milder bone loss than those housed with other uremics (p=0.037).

Conclusions: This work proves for the first time that periodontitis can be caused by uremia. A key role for bacterial dysbiosis is suggested from the fact that periodontal disease was partially reversed in uremic animals housed with controls. We propose that oral bacterial dysbiosis induces Th17-driven inflammatory periodontal bone loss.



The mean of the bone levels of the control rats has been used as a baseline. Negative values of alveolar bone level indicate bone loss relative to this baseline. Each circle represents the mean bone level for an individual rat with horizontal lines representing the mean bone levels per group +/- SD.

SA-PO673

The Ability of Intact Parathyroid Hormone and Total Alkaline Phosphatase to Predict Bone Turnover in Patients with Renal Osteodystrophy

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Background: Bone turnover (BT) markers reflect bone cell activity and are useful in the diagnosis and management of chronic kidney disease-mineral and bone disorders. Bone biopsy (BB) is considered gold standard for diagnosing renal osteodystrophy, although it should be reserved just for certain patients. The objective of this study was to evaluate the predictive value of intact parathyroid hormone (iPTH) and total alkaline phosphatase (tALP) as BT markers.

Methods: This was a cross-sectional retrospective diagnostic test study. Two hundred and eleven patients were assessed through BB and serum levels of iPTH and tALP. iPTH assays were performed using the same methodology (chemiluminescence: NR: 15-65 pg/mL). For the tALP analysis, an index representing the ratio between tALP and the maximum reference value for the method was used, since there are tests with different methodologies. According to histological diagnosis, the patients were divided into high turnover (HT), those with fibrous osteitis and mixed disease, and low turnover (LT), those with adynamic bone disease and osteomalacia. An analysis was conducted in order to derive the area under the receiver operating characteristic (ROC) curve (AUROC) to determine the diagnostic ability of BT as a biomarker.

Results: Patients (48.9 years) had been on hemodialysis for 9.5 years, of whom 84% and 16% were classified as HT and LT, respectively. The median serum level of iPTH was 1296 in the HT patients, and 116 in LT patients. The median tALP index was 1.82 for the HT and 0.9 for the LT patients. To predict HT, the iPTH presented an AUROC of 0.908, with a cutoff value of 363 with a sensitivity of 82.5% and a specificity of 88%; while the tALP index demonstrated an AUROC of 0.747, with a cutoff value of 1.01, with a sensitivity of 72.3% and a specificity of 65%. To predict LT, the iPTH and tALP index were not good markers, with an AUROC of 0.092 and 0.253, respectively. Limitations**:** Histomorphometry and bone alkaline phosphatase were not performed; Predominance of severe secondary hyperparathyroidism.

Conclusions: Our results have demonstrated that the iPTH and tALP were excellent predictors for HT, but it was evident that iPTH was far superior.

SA-PO674

Twenty-Four Hour Urine Testing in Kidney Stone Formers: A Veterans Health Administration Study

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Background: The American Urological Association recommends 24-hour urine testing in stone formers to prevent recurrent stones. However national practice patterns of

metabolic evaluation which utilize urine testing remain uncharacterized. To address this, we identified stone formers in the national Veterans Health Administration (VHA) database and assessed the characteristics of those who received 24-hour urine testing and the timing and frequency of testing.

Methods: We defined stone formers as those with one or more inpatient ICD-9 codes for stones, two or more outpatient ICD-9 codes for stones, or one or more CPT codes for stone procedures in 2007-13 using the national VHA database. We defined a 24-hour urine test as having a 24-hour urine calcium, oxalate, citrate or sulfate measurement. We compared demographics and clinical characteristics among Veterans who received testing and those who did not. We determined the timing and frequency of 24-hour urine testing and evaluated whether urine testing varied geographically. We assessed factors associated with 24-hour testing using multivariable regression.

Results: We identified 130,489 individuals with a stone encounter between 2007-2013. Within this stone cohort, 13.3% (19,288 individuals) underwent 24-hour urine testing. These individuals were younger, had fewer comorbidities, and were more likely to be seen on an outpatient basis. In addition, those with 24-hour urine testing had more stone procedures than those who did not (3.0 ± 2.8 vs. 2.3 ± 2.1, p <.001). The majority of testing occurred within 1 year of a stone encounter. There was considerable geographic variation in the utilization of 24-hour urine tests, ranging between 1% and 40% across VA facilities, with the most frequent testing in the western United States.

Conclusions: We found high facility level variation in 24-hour urine testing among stone formers. Our results suggest that in addition to patient risk, physician practice patterns influence the use of 24-hour testing in urinary stone disease. Comparative effectiveness research could help to define the role of 24-hour urine testing in the evaluation and management of kidney stones.

Funding: Private Foundation Support

SA-PO675

Prevalence of Kidney Stones in Cystic Fibrosis

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Background: Cystic fibrosis (CF) may predispose patients to urinary stone disease (USD) via several proposed mechanisms including antibiotic exposure and intestinal malabsorption. Prevalence of USD in patients with CF was estimated at 2-6% in studies with mean age 16-27 years. These data are limited by small sample sizes and single-center settings. The CF Foundation Patient Registry (CFFPR) began collecting prevalence data on USD in 2006.

Methods: We studied 29,396 patients in the CFFPR living in 2016 to calculate age-stratified prevalence of USD.USD was assessed by trained CF clinic staff at each encounter. For 15,531 patients age 18 or older we examined associations between age, BMI, demographics, CFTR mutation class, other clinical parameters, and prevalent USD using multivariate logistic regression.

Results: Overall prevalence of USD was 3.1% (95% CI 2.9-3.3%). Prevalence under age 18 years was 0.4% (0.3-0.5%), 18 to 24 years, 3.1% (2.7-3.6%), 25 to 34 years, 6.4% (5.8 -7.1%), 35 to 44 years, 7.5% (6.5-8.5%), and 45 years and older, 6.7% (5.8-7.8%). Mean age of all patients was 21.3 years. We also calculated prevalence for age ranges 20-29, and 30-39 years to compare with published NHANES data for the general population. Stone prevalence was 4.8% and 7.1% in in CF patients within these two age cohorts, respectively, compared to 3.4 and 6.4% in NHANES. Multivariate adjusted odds ratios for stone prevalence were significant for female sex, OR 1.4 (95% CI 1.2-1.7), severe CFTR mutations, OR 1.8 (1.2-2.5), diabetes, OR 1.2 (1.0-1.5), hypertension, OR 1.4 (1.0 -1.9), and chronic macrolide therapy, OR 1.3 (1.1-1.6). BMI was not associated with USD.

Conclusions: USD prevalence in CFFPR may be higher than in the general population and increased with age. Some risk factors for stone disease in the general population appear significant for adult patients with CF, including hypertension and diabetes. However, BMI did not show the same relationship. Several novel associations with USD in CF patients also were identified, including a greater prevalence in women. This study is limited by the method of USD assessment; it is possible patients with more severe CF had higher rates of reported asymptomatic stones incidentally diagnosed due to more frequent imaging. As life expectancy of people with CF increases, the prevalence of USD may also increase.

Funding: Private Foundation Support

SA-PO676

Correlation of Papillary Grading and Metabolic Parameters in Calcium Stone Formers

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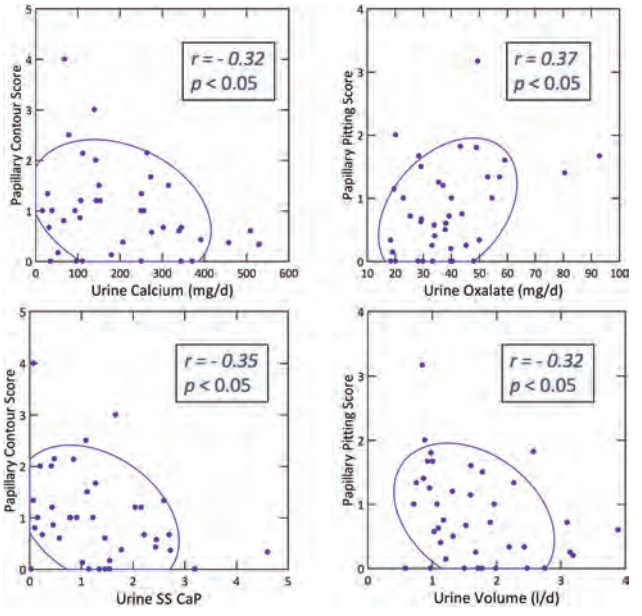
Background: Papillary grading has emerged as a novel technique to standardize ureteroscopic findings, but its relationship to stone pathogenesis is poorly understood. As 24-hour urine metabolic risk parameters predict stone type and likelihood of recurrence, we sought to determine whether papillary grading correlates with these parameters.

Methods: Patients' endoscopic findings during stone procedures were graded by two urologists at a single academic institution using a previously described renal papillary grading system. This system quantifies the degree of Randall's plaque (RP), pitting, plugging, and loss of contour, yielding a summary score for each papillum. Composite scores were generated by averaging all papillary scores from a single kidney. Patients were included if they had calcium based stones and completed two 24-hour urine collections with paired serum studies prior to treatment. Pearson correlations were used to determine relationships between individual components of the score, total score, and average across the categories as related to urinary metabolic risk factors.

Results: 41 patients (43% Male, 63% Caucasian) were included. The mean age was 52.1 yrs (±7.5) and mean BMI was 30.8 (±4.0) kg/m2. Contour was inversely related to 24 hr urine calcium (P<0.05) and calcium phosphate supersaturation (SSCaP) (p<0.05). Pitting is directly related to 24-hr urine oxalate (p<0.05) and inversely related to urine volume (p<0.05) (Figure). No significant correlations were found for urine pH or 24 hr urine citrate. Significant differences in RP scores (AA 0.53, C 1.35, p<0.003), but not the other grading components, were noted across racial groups.

Conclusions: Papillary grading correlates with 24 hr urine volume, calcium, oxalate, and SSCaP. Racial differences in RP burden suggest differing mechanisms of calcium lithogenesis by race which warrants further study.

Funding: NIDDK Support



SA-PO677

Prevention of Recurrent Stones and CKD in Kidney Stone Formers: What Are the Goals for Biochemical Parameters in Urine Collections?

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Background: The evidence of effective prevention of recurrent stone formation and CKD in kidney stone formers (KSF) through the treatment of biochemical abnormalities present in repeated 24h urine collections (24UC) is scarce. Our aim was to analyze the association between metabolic control (assessed by yearly 24UC) and kidney stone recurrence rates and decline in eGFR in KSF attending a nephrolithiasis clinic.

Methods: Single-center cohort study of KSF with at least three 24UC and ≥2 years of follow-up. Exclusions: primary hyperparathyroidism, eGFR >30 mL/min/1.73m^2. Medical data, including chemistry of 24UC, were compared using analysis of variance and general linear modelling.

Results: Of 220 KSF, 63% had absorptive hypercalciuria and 64% hipocitraturia (median follow-up of 4 yrs [IQR 4-5.2 yrs]). All KSF with hypercalciuria received chlortalidone. 24UC abnormalities display a trend to improve along time in all the cohort. Stone recurrence (≥2 episodes, 35% of KSF) was associated with higher urinary Ca/Cr index compared with KSF free of stone recurrence at follow up with treatment (yearly mean 24UC Ca/Cr 0.15±0.08 Vs. 0.12±0.05 respectively, p=0.02). Inappropriate eGFR decline (>2 mL/min/year) not related to obstruction or AKI episodes was observe in 13% of KSF and was associated with lower citraturia (yearly median citrate 192 mg/24UC [IQR 153-290] Vs 354 mg/24UC [IQR 237-541], p=0.003). Other parameters of the 24UC (volume recollected, Na, oxaluria, or uricosuria) were not associated with recurrence or eGFR decline.

Conclusions: Among 24UC yearly measurement; a very low Ca/Cr index was effective preventing stone recurrence in KSF. Low citrate excretion predicted an inappropriate eGFR decline, even before treatment.

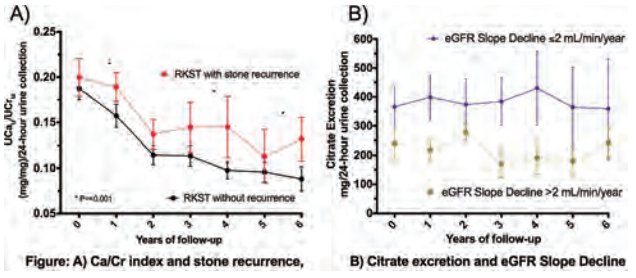

Figure. Association between repeated urinary chemistry of yearly 24-hour collections and renal outcomes. A) Calciuria/creatinuria index and stone recurrence. B) Citrate excretion and eGFR Slope Decline.

SA-PO678

Manifestations of Kidney Stone Recurrence and Their Prediction by Risk Factors

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Background: The relationship between symptomatic and radiographic kidney stone recurrence is unclear. Risk factors may also differ in their association with symptomatic and radiographic recurrence.

Methods: First-time symptomatic stone formers were recruited from 2009 to 2013 in MN and FL. Baseline and 5-year follow-up visits included CT scans, surveys, and medical record review. At 5 years, symptomatic recurrence was identified by clinical care (medical record) and self-report (survey); radiographic recurrence was identified by new stone, stone growth, or stone disappearance between CT's. A Recurrence of Kidney Stone (ROKS) score summed risk factors for recurrence (young age, male gender, high BMI, family history of stones, pregnancy, asymptomatic or suspected stone prior to first episode, history of a brushite/struvite/uric acid stone, no history of COM stone, pelvic/lower pole stone, no uterovesical junction stone, number of stones in kidney, and diameter of largest kidney stone). The 5-year incidence of recurrence and its association with ROKS score was compared.

Results: There were 175 stone formers studied (55% had an asymptomatic kidney stone at baseline). By year 5, 19% had symptomatic recurrence (clinical care), 25% had symptomatic recurrence (self-report), 35% had a new stone, 24% had stone growth, and 26% had stone disappearance. Of those with an asymptomatic stone, 47% had stone disappearance, and 50% of those had a concurrent symptomatic recurrence. Symptomatic recurrence by clinical care versus self-report was more strongly associated with new stone (OR=4.8 95% CI [2.2-10.6] versus 1.9 [1.0-3.9]) or stone disappearance (OR=3.9 [1.8-8.5] versus 2.0 [1.0-4.2]). The ROKS score associated more strongly with radiographic recurrence than only symptomatic recurrence (Table).

Conclusions: Clinical care is more strongly associated with recurrence than self-report. Half of first-time stone formers have an asymptomatic stone. By 5 years, half of these stones will have passed with symptoms occurring half the time (Rule of Halves). While symptomatic recurrence is more clinically relevant, asymptomatic radiographic recurrence is better predicted by risk factors.

	Symptomatic recurrence: clinical care only	Symptomatic recurrence: clinical care or self-report	Radiographic recurrence: new stone, stone growth or stone disappearance	Symptomatic or radiographic recurrence
5-year rate	19%	30%	59%	67%
OR (95% CI) per standard deviation of ROKS score	1.7 (1.1, 2.5)	2.1 (1.5, 3.1)	3.7 (2.4, 5.8)	3.6 (2.3, 5.5)

SA-PO679

Rotating Shift Work and Kidney Stones

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Background: Related to circadian rhythm, which is the 24-hour periodicity of physiologic processes, there is diurnal variation in excretion of urinary factors, including factors associated with kidney stone risk. Rotating shift work disrupts circadian rhythm but has not been evaluated as a risk factor for kidney stones. We examined rotating shift work with risk of incident kidney stones and 24-hour urine composition in the Nurses' Health Study II.

Methods: We conducted a prospective analysis of 101,983 Nurses' Health Study II participants who provided information on rotating shift work and kidney stones. We used multivariate adjusted Cox proportional hazards models to compare current (1 to 9 months, or 10 or greater months) and past rotating shift work to no rotating shift work. In a separate analysis, we used multivariate adjusted Cox proportional hazards models to compare cumulative shift work exposure to no shift work. We also analyzed rotating shift work in 24-hour urine collections from 3811 participants. We used ANOVA to compare urinary factors by rotating shift work duration.

Results: In 22 years of follow-up, there were 3,281 incident kidney stones. Compared with no rotating shift work, the multivariate adjusted relative risks for incident kidney stone were 1.16 (95% CI 0.92 to 1.46) for 1 to 9 months current rotating shift work, 1.12 (95% CI 0.92 to 1.34) for 10 months or greater current rotating shift work, and 1.12 (95% CI 1.04 to 1.20) for past rotating shift work. Compared with no rotating shift work, participants with the highest exposure of cumulative rotating shift work, 10 years or greater, the multivariate adjusted risk for incident kidney stone was 1.19 (95% CI 1.06 to 1.34). There were no substantial differences or trends in the urine composition profiles when comparing 24-hour urine collections for participants who had no rotating shift work, 1 to 4 months, 5 to 14 months, and 15 months or greater of rotating shift work during the collection period.

Conclusions: Rotating shift work was associated with a slightly higher risk of incident kidney stone compared with no rotating shift work. There were no differences in urine composition based on rotating shift work.

Funding: NIDDK Support

SA-PO680

Stone Frequency Determines Health-Related Quality of Life (HRQoL) in Cystine Stone Formers (CSF)

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Background: CSF have lower HRQoL compared to US Standard Population. We have shown previously that HRQoL results need to be controlled for the last stone event and comorbidities. We now show the first longitudinal HRQoL domain profiles for baseline and two yearly follow-ups.

Methods: CSF were enrolled from the RKSC registry. HRQoL was measured with the generic non-disease specific SF-36v2. Results were calculated as norm-based scores (NBS) based on US Standard Population (Domain score mean = 50). We selected 3 stone frequency groups (SFG): low (stone-free during observation period), medium (minimum of one stone event between 31 - 365 days) and high (stone event always present within 30 days of the survey), and compared the groups' HRQoL at baseline and second follow-up.

Results: We scored 386 surveys. 78 participants (32 males and 46 females) were compared at baseline and 2 follow-up assessments. Mean age was 45 years (male 44/ female 46). Repeated measure ANOVA showed no difference within each SFG over time (Fig 1). However, domain scores were significantly different between SFG's ($p<0.05$) at each time point, with low>medium>high stone frequency. Whether surgical intervention was required, and type, were not predictors of HRQoL outcomes. Better HRQoL tracked with lower cystine excretion per liter on 24h urine collections; lower cystine capacity and higher citrate doses were underpowered (NS).

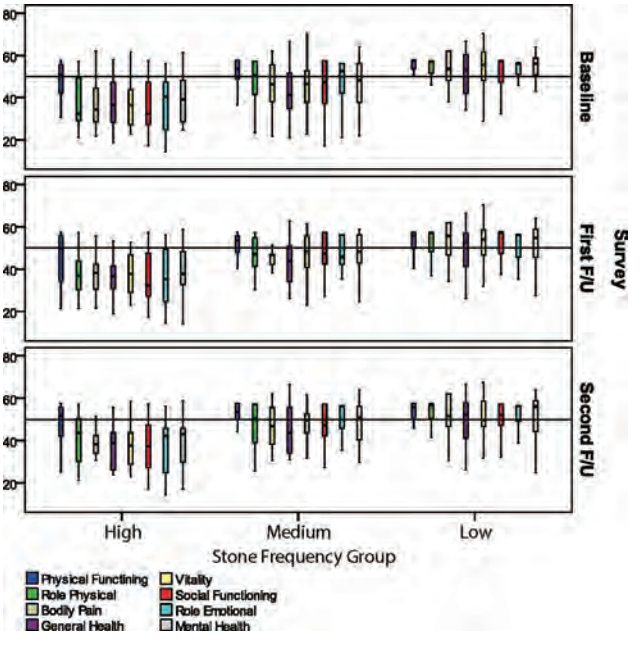
Conclusions: CSF with high stone event rates experience worse HRQoL over time, while CSF with no stone events achieved better HRQoL than US standard. Clinnical data suggest that the high SFG is undertreated.

Funding: NIDDK Support

Clinical Data

Stone Frequency Group	Cystine/liter*	Citrate use (mg/d)	Cystine Capacity
High	463 (370), 11	51 (40), 10	110 (245), 8
Medium	270 (124), 21	68 (27), 13	41 (130), 16
Low	231 (100), 15	69 (31), 11	26 (96), 10

mean (SD), n; *p=0.015



SA-PO681

Vascular Calcifications in Patients with Calcium and Uric Acid Kidney Stone Composition

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Background: Kidney stone disease has been associated with incident cardiovascular events, as well as with vascular calcifications. It is not known whether the likelihood and extent of vascular calcifications differ in patients with different types of stone composition.

Methods: We retrospectively evaluated CT scan images of patients who underwent at least one kidney stone composition analysis during the 2015-2018 period. Kidney stones were analyzed by Fourier-transform infrared spectroscopy and categorized as follows: calcium stones (≥50% calcium oxalate or calcium phosphate), uric acid stones (any uric acid). A calcification score was calculated from the CT scan images at the abdominal aorta and expressed as calcium volume. The radiologist who performed the calcification score evaluation was not aware of the stone composition group of the patients. For patients who underwent multiple kidney stone composition analyses and/or CT scans, information on vascular calcification was obtained from the CT scan closest in time to a kidney stone composition analysis.

Results: We enrolled 30 patients with at least one kidney stone composition analysis in the observation period who had undergone at least one CT scan examination at our Institution. Average age was 56±16 years, 16 (53%) were males. Patients with uric acid stones had significantly higher values of calcification at abdominal aorta (975 mm^3, 95% CI –3, 1,953 mm^3; p=0.05). However, such differences attenuated after adjustment for age (370 mm^3, 95% CI –598, 1,337 mm^3; p=0.44).

Conclusions: Patients who form uric acid stones seem to have worse calcifications at abdominal aorta compared with those who form calcium stones; however, this association could be at least in part mediated by differences in age between groups.

SA-PO682

Nephrolithiasis in HIV+ Patients with CKD: A Case Series

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Background: Nephrolithiasis and CKD are highly prevalent in the HIV+ population, independent of each other. The association between some anti-retroviral therapy (ART) and both nephrolithiasis and CKD, respectively, has been demonstrated. However, amongst HIV+ patients, there are limited data on the relationship between nephrolithiasis and CKD progression. It is unknown if HIV+ patients have risk factors for nephrolithiasis beyond ART. We describe a series of HIV+ patients with a history of nephrolithiasis in a CKD clinic.

Methods: In a CKD clinic of HIV+ patients (n = 55), we identified those with history of nephrolithiasis by radiology or self-report. Data was collected on demographics; co-morbidities; HIV control; age at first stone; urologic interventions; ART; creatinine trends; urine chemistries; and stone composition.

Results: The prevalence of nephrolithiasis was 21.8% (n = 12). Sixty-seven percent were black; 92% male; 75% had HTN; 8%, DM. At the initial CKD appointment, median age was 53; baseline creatinine, 1.5 mg/dl (IQR, 1.2-1.8); eGFR, 49 ml/min/1.73m^2; UPCR, 1.02 (IQR, 0.37-1.89). Ninety-two percent had an undetectable viral load (VL). Eighty-three percent had taken tenofovir disoproxil fumarate (TDF); 50%, atazanavir; 17%, indinavir. The majority had their first stone after HIV diagnosis (58%) and 42% of first episodes were between ages 51-60. After the first stone, there was a generalized upward creatinine slope in 75% of patients (n = 9). Only one patient had data on stone composition, and two, urine chemistry.

Conclusions: There was a high prevalence of nephrolithiasis among HIV+ patients in a CKD clinic. Most patients had their first stone after HIV diagnosis and experienced an upward slope in creatinine after this. Nearly all had early CKD with sub-nephrotic proteinuria and undetectable VL. While most patients had exposure to ART that might increase stone risk, we cannot infer that this entirely accounts for the high prevalence. Studies show that proximal tubule cells are a reservoir for HIV. This could be a potential risk factor for stones by altering urine chemistry. Controlled studies are needed to describe urine chemistries in HIV+ patients with nephrolithiasis as well as the association between nephrolithiasis and CKD progression.

SA-PO683

Independent Effects of Age and Kidney Function on Urine pH in Stone Forming Patients

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Background: We have found that normal women (W) have higher urine pH (UpH) than men (M) fed identical diets in a clinical research center. Prevalence of high UpH-dependent phosphate stones decreases with age while that of uric acid stones – signifying low UpH - increases. We sought to determine if UpH falls with age in a large population of stone formers (SF), and if so to quantify the independent effects of sex, falling renal function, and age itself.

Methods: From a large dataset of 12839 SF patients with pretreatment 24 hour urine collections and matching serum collections (Litholink) we selected 7891 (3605 F) SF without markers of systemic disease, infections, or missing lab values. The final dataset was used to model UpH using continuous generalized linear models with urine potential renal acid load (uPRAL) calculated from urine charge balance, age, creatinine clearance (CCr) and their appropriate cross products. To directly compare the effect sizes of CCr and age, we treated both as categorical variables in a separate analysis.

Results: UpH in W was higher than M at all ages and UpH declines with age and CCr via separable effects. uPRAL, age, and CCr are all significant ($p<.01$) predictors of UpH (Table), and the effect of uPRAL is conditioned by both CCr and age. The observed sex difference is fully accounted for after adjustment in both the continuous and categorical models of UpH.

Conclusions: Age and CCr exert separate effects on UpH in SF patients. Of the two, age is the more important predictor with an effect size approximately twice that of CCr. UpH is most strongly conditioned by uPRAL with effects that are mediated by age and kidney function.

Funding: NIDDK Support

	CONTINUOUS		CATEGORICAL (CCR+AGE)	
	Fisher's F	EFFECT	Fisher's F	EFFECT
CONSTANT	----	6.50	----	6.17
uPRAL	5960	-0.15	6376	-0.16
AGE	764	-0.08	87.7	-0.24±0.01 #
CCR	21	0.005	17.4	0.11±0.01 #
SEX	5.2*	M=0.034	2.0**	M=-0.0063
SEX*uPRAL	21	M=0.01	15.3	M=0.005
AGE*uPRAL	----	----	12.0	H=-0.12; L=-0.17 +
CCR*uPRAL	----	----	18.8	H=-0.13; L=-0.19
SEX*AGE	8	M=-0.01	2.4*	----
MULTIPLE R^2	0.463	----	0.484	

All effects have significance p<.01 unless marked. All effects per 10 unit change unless marked. #, Coefficient and SE of linear contrast across hexiles. *, p <.05. **, P= NS, forced in for cross products. +, largest effects not in order, interval describes the range of effects only. All models fully adjust sex difference.

SA-PO684

Correlation of Vitamin D and Insulin Resistance Among Calcium Kidney Stone Formers

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Background: Existing evidence suggest that vitamin D could play a role in the pathogenesis of type 2 diabetes, by affecting insulin sensitivity. However, the interaction of 25(OH)-vitamin D (25D) with insulin sensitivity has not been examined in calcium kidney stone formers, a unique population whose 1,25(OH) vitamin D (1,25-D) action seems to be hyperactive.

Methods: Prevalent non-diabetic calcium kidney stone formers from 2015 to 2018 were enrolled in this study. We assessed the association between serum 25D and insulin resistance measured by Homeostatic model assessment insulin resistance {HOMA IR = (fasting glucose (mg/dl) × fasting insulin (mU/L)/(405)} using univariate analysis and multivariate regression model adjusting for demographics and important clinical covariates. P values less than 0.05 were considered significant.

Results: A total of 94 non-diabetic calcium kidney stone formers were enrolled in this study. Among them, 51% were male, 86% were Caucasian, 38% had history of hypertension, and 29% had history of dyslipidemia. Mean age was 54 years, mean creatinine clearance (CrCl) was 131 ml/min, mean body mass index was 31.3 kg/m^2, mean serum 25D was 28 ng/ml, mean serum 1,25D was 52 pg/ml and mean serum parathyroid hormone level was 66 pg/ml. The mean HOMA IR was calculated at 8.1. In univariate analysis, 25D had no significant association with HOMA-IR (p=0.68), however, hypertension, dyslipidemia, CrCl and BMI associated significantly with HOMA-IR ($p<0.05$). After adjusting for demographics, 25D again did not associate significantly with HOMA-IR (p=0.33), but the associations between HOMA-IR and hypertension, dyslipidemia, CrCl and BMI remained significant ($p<0.05$). Finally, after adjusting for demographics, hypertension, dyslipidemia, CrCl, BMI and serum uric acid, the association between 25D and HOMA-IR remained insignificant (p=0.14). Like 25D, serum 1,25D levels had no association with HOMA-IR in univariate and multivariate analyses.

Conclusions: Unlike the general population, low serum 25D levels, had no significant association with insulin-resistance measured by HOMA IR in calcium kidney stone formers.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO685

Unmet Need in Enteric Hyperoxaluria: Clinical Characteristics and Stone Burden in Patients from ALLN-177 Studies

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Background: Hyperoxaluria (HOx) is a serious metabolic disorder and a key risk factor for progression of kidney stone (KS) disease and other renal complications. Patients with malabsorptive gastrointestinal (GI) conditions (e.g., bariatric surgery, Crohn's disease) can develop what is called enteric HOx (EH) due to over-absorption of oxalate (Ox). Standard

of care interventions are non-specific, and many have persistently high urine Ox (UOx) levels. The existing KS burden in patients with EH has not been described.

Methods: Baseline data on33 patients with EH enrolled in 3 Phase II studies of ALLN-177 (an oral, non-absorbed, Ox-specific enzyme therapy) were analyzed. Medications, 24-hr urine parameters, KS history, and dietary Ox were assessed in all 3 studies; computed tomograms (CT) were obtained in 2 studies to define silent KS burden (active renal colic was exclusionary).

Results: Mean age was 64 (range 41-82) and 57.6% were female. The enteric condition was bariatric surgery in 24 (73%), Crohn's in 5 (15%), pancreatic insufficiency in 2 (6%) and 'other' disease in 2 (6%). Mean (SD) dietary Ox was 185±138 mg/d, urine volume 1.9± 0.8 L/d and UOx 102±55 mg/d. Twenty-one (64%) subjects overall were on calcium and/or citrate supplements, thiazides, allopurinol and/or pyridoxine. Among the 28 participants who provided KS medical history, 93% had at least one KS episode in past 5 years. Among the 20 participants who had a CT scan, 16 (80%) had at least one KS and 8 (40%) had KS in both kidneys; on average participants had 3 KS. Notably, 4 (20%) had KS >10 mm and 8 (40%) had KS 5-10 mm in size.

Conclusions: Despite standard interventions, patients with EH had persistently high UOx. In addition, a substantial KS burden was found on CT; many patients had multiple KS, including some with larger KS that could require urological intervention. Both HOx and KS burden are risk factors for progressive loss of kidney function. Our analysis highlights a significant unmet need in the EH population, and the current ALLN-177 development program is focused on addressing this.

Funding: Commercial Support - Allena Pharmaceuticals

SA-PO686

Analysis of Gut Microbiome Alterations in Hyperoxaluric Patients

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Background: About 60–80% of kidney stones are composed of calcium oxalate (CaOx); idiopathic CaOx kidney stones (CaOPx), primary hyperoxaluria (PH) and enteric hyperoxaluria (EH) are diseases predisposing to stones. *Oxalobacter formigenes (Oxf)* is a human gut commensal that depends on oxalate for its carbon and energy, and may be protective against CaOx stones. We hypothesize that the microbiome community structure differs between patients with CaOx, PH, EH and normal subjects (NS). We also expect that *Oxf* isolates from PH patients will result in further reduction in urinary oxalate when compared to *Oxf* reference strain CC13, in a germ-free (GF) mouse model.

Methods: We collected fecal specimens from 34 subjects (mean age: 39.1 ± 11.9 years) with PH (n=6), CaOPx (n=10), EH (n= 5) and NS (n=13) in a cross-sectional observational study, and tested fecal samples from the groups by: 1)16S rRNA sequencing to determine the microbiome community structure, 2)PCR and qPCR for *Oxf* colonization and, 3) culturing in high oxalate selective media for indication of *Oxf* presence and subsequent isolation. We isolated *Oxf* from 4 PH (*Oxf* PH) subjects. We gavaged a growing culture of PH *Oxf* (n=6), *Oxf* reference strain CC13 (*Oxf* CC13) (n=5), and sham (n=6) into adult C5B6 GF mice, observing them for 4 weeks. We collected urine from mice for 48 hours before sacrifice to be tested for oxalate and creatinine (Uox/cr).

Results: *Oxf* was detected in 6 (46%) of 13 NS, 1 (10%) of 10 CaOPx, 0 (0%)of 4 EH, and 5 (83%) of 6 PH. Microbiome analysis revealed that the 4 groups differed in beta diversity, based on Bray-Curtis dissimilarity (p=0.08). Alpha diversity analysis trended toward lower Shannon and phylogenetic diversity index in the CaOPx and EH subjects compared to PH and NS. Introducing the PH *Oxf* to GF mice led to lower Uox/cr than in uninoculated controls (0.68 ± 0.14, and 2.26 ±0.49, respectively, p=0.04 by Mann-Whitney U test), but not significantly different from the *Oxf* CC13-innoculated mice (0.68 ± 0.14, and 0.91 ±0.24, respectively, p=0.26 by Mann-Whitney U test).

Conclusions: These studies provide evidence of differences in *Oxf* colonization rates and in microbiome composition in patients with CaOx stones and show the functional capacity of a PH *Oxf* strain to ameliorate hyperoxaluria. Studies to expand these patient groups are on-going.

Funding: NIDDK Support, Private Foundation Support

SA-PO687

Pharmacokinetics and Pharmacodynamics of SNF472 in Calciphylaxis Patients: Results from a Phase 2 Clinical Trial (SNFCT2015_04)

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Background: SNF472 is a selective calcification inhibitor that interferes in the formation and growth of hydroxyapatite crystals. It is being developed for the treatment of calciphylaxis (CUA), a severe form of vascular calcification that affects the small vessels under the skin in patients with end-stage renal disease on hemodialysis (HD).

Methods: This was an open label, single arm trial investigating the effect of SNF472 on top of standard of care in the treatment of CUA in HD patients. Patients were treated for 12 weeks with intravenous 6-9 mg/kg of SNF472 three times per week during each dialysis session. The dose (400, 450, 700 or 900 mg) was adjusted by body weight categories. SNF472 levels were measured in plasma samples obtained pre-HD (baseline) and at the end of SNF472 infusion on the first and the last treatment sessions. Another aliquot of plasma was used to measure ex-vivo the propensity of plasma to induce calcium phosphate (CaP) crystallization as a pharmacodynamic (PD) measurement.

Results: The study enrolled 14 patients with 11 completing the treatment. The maximum SNF472 concentration in plasma was 29.1 ± 19.1 μM in week 1 and 26.3 ± 21.3 μM in week 12. There was no accumulation of SNF472 or any effect of repeated administration for up to 12 weeks in the exposure to the compound, confirming the results of a previous phase 1b trial in HD patients. The ex-vivo induction of CaP crystallization was inhibited up to 65 ± 14% after treatment with SNF472 (week 1) and up to 60 ± 29% at week 12. No differences attributable to the doses tested were observed concerning the PD effect, as all doses were on the plateau of the effect. These results were in accordance with the previous data seen in the Phase 1b trial. No inhibition of crystallization was evidenced in one patient that did not present detectable SNF472 levels (<0.76 μM) after treatment at week 12, showing a relationship between SNF472 circulating levels and PD.

Conclusions: These results suggest that the administration of SNF472 to CUA patients on HD allows to attain potentially therapeutic levels, as evidenced by both its circulating levels and the inhibition of ex-vivo calcification induction.

Funding: Commercial Support - Laboratoris Sanifit

SA-PO688

The Novel Bone Alkaline Phosphatase Isoform B1x in Serum Identifies Patients with Calciphylaxis on Vitamin K Antagonist Treatment

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Background: The novel bone alkaline phosphatase (BALP) isoform B1x is only detectable in serum from patients with advanced chronic kidney disease (CKD) or end-stage renal disease. B1x has been proposed as a marker for low bone turnover, furthermore, B1x activity increases in calcifying vascular smooth muscle cells. Vitamin K antagonists (VKA) prevent activation of the potent vascular calcification inhibitor matrix Gla protein. VKA is associated with an increased risk for calciphylaxis (calcific uremic arteriolopathy, CUA), a rare and often fatal complication associated with severe calcification of arterioles. The objective was to study the appearance of B1x in serum from CKD patients with CUA.

Methods: Seventeen CKD patients with CUA (15 on hemodialysis, 1 transplanted, 1 pre-dialysis) were recruited from the European Calciphylaxis Network. Serum total ALP was determined by a kinetic assay and the BALP isoforms (B/I, B1, B1x and B2) by high-performance liquid chromatography. Fetuin A, intact parathyroid hormone (iPTH), total BALP (ELISA), C-reactive protein, sclerostin, C-terminal fibroblast growth factor 23, tartrate-resistant acid phosphatase type 5b (TRAP5b), osteoprotegerin, 25-OH vitamin D, total calcium (Ca) and phosphate were also assessed.

Results: B1x was detected in 10 patients (56%). These patients were more often treated with VKA (7 VKA patients B1x positive, vs 1 VKA patient B1x negative), had a more frequent history of myocardial infarction, lower total ALP (P=0.025), lower BALP (P=0.025), lower BALP isoform B1 (P<0.001) and lower total Ca (P=0.014) in serum. There was a tendency towards lower iPTH and lower TRAP5b (P=0.055 for both).

Conclusions: Patients with B1x were more often treated with VKA. Circulating bone markers indicate an association of B1x with low bone turnover. We hypothesize that VKA induce a specific subtype of vascular calcification, which is different from non-VKA-users. Based on the BALP isoform analysis, subgroups of CUA could be identified, which might also reveal differences in terms of bone metabolism.

Funding: Commercial Support - Amgen, Government Support - Non-U.S.

SA-PO689

Improvements in Calcific Uremic Arteriolopathy Wound Healing During SNF472 Treatment Assessed with the BWAT-CUA

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Background: Calcific uremic arteriolopathy (CUA/calciphylaxis) in patients with end-stage renal disease is a severe form of vascular calcification characterized by painful necrotic skin ulcers and very high mortality. No approved therapies are available. The investigational drug SNF472 is an intravenous formulation of myo-inositol hexaphosphate that inhibits formation and growth of hydroxyapatite crystals, the final common step in the pathophysiology of vascular calcification. A recent open-label, single-arm, 12-week Phase 2 trial of SNF472 in patients with CUA receiving hemodialysis demonstrated statistically and clinically significant improvements from baseline to end-of-study in wound healing, pain, and wound-related quality of life (NCT02790073).

Methods: 14 patients with CUA were treated with SNF472 thrice weekly during each hemodialysis session for up to 12 weeks. We assessed effect on wound healing with the Bates-Jensen Wound Assessment Tool (BWAT), a 13-item, objective, quantitative tool originally developed and validated for the assessment of pressure ulcers. Based on the expert opinion of specialists in plastic surgery, wound care, and nephrology (all experienced in the care of patients with CUA) we derived a targeted modification of the BWAT using 8

items focused on prototypical features of CUA lesions: necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema, peripheral tissue induration, and granulation tissue.

Results: Mean (SE) BWAT-CUA improved from 21.2 ± 2.0 at baseline to 14.9 ± 1.4 at Week 12 ($p<0.002$). Among the individual BWAT items, the largest improvements were observed for peripheral tissue induration, skin color surrounding wound, and granulation tissue.

Conclusions: BWAT-CUA is an objective and quantitative tool targeted for evaluation of CUA lesions and will be used in the upcoming Phase 3 randomized controlled trial of SNF472 for CUA.

Funding: Commercial Support - Sanifit

SA-PO690

National Trends in Hospitalization in the US Calciphylaxis Population from 2007 to 2014

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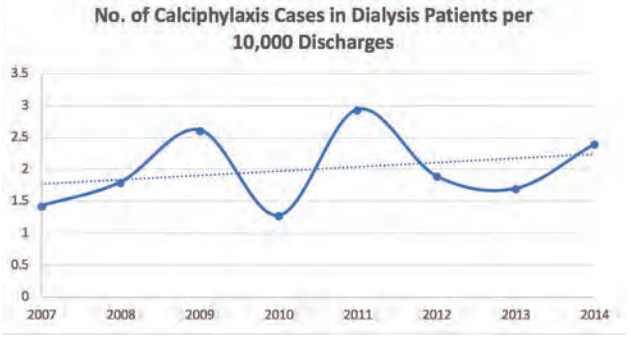
Background: Calciphylaxis is a rare syndrome of vascular calcification characterized by occlusion of microvessels in the subcutaneous adipose tissue and dermis, resulting in painful, ischemic skin lesions. The definitive diagnosis is made by confirming the presence of calcified dermal arterioles on a skin biopsy in a patient with clinical suspicion for calciphylaxis. In this study we describe the trends and patient distribution and characteristics of calciphylaxis in the US inpatient population from 2007-2014.

Methods: We included all adult discharges from the National Inpatient Sample (NIS) from 2007-2014, from large (>=325 beds) teaching hospitals, excluding cases with missing data on age, gender, or inpatient mortality. We used a previously published algorithm to identify patients with calciphylaxis from the NIS. This algorithm applies the ICD-9-CM diagnosis code 275.49 "Other Disorders of Calcium Metabolism" in combination with the ICD-9 code 86.1.

Results: We identified 1576 probable calciphylaxis discharges from 2007 to 2014, with 69% patients on dialysis of which 90% where patients on HD, 54.8% were white and 70.5% were females. Mean age was 59 years (95% CI: 57 to 61 years). 35% belonged in the lowest income quartile and 17% belonged to the upper quartile in the US. Most patients were located in the Southern (39.8%) and Midwest (29%) Region of the US. 49% of the patients had DM, 19% were obese, 78% had HTN and 26% had A-Fib. Overall inpatient mortality was 7.9%. The median length of stay was 11 days (range 0-98) and mean hospitalization cost was $31467 ±$2127. We found that 63% patients were discharged to rehab, skilled nursing facility or home with nurse care and 37% went home.

Conclusions: Calciphylaxis was more prevalent in females. One third of the patients belonged to the lowest income quartile. Most of the patients with calciphylaxis were located in the Southern and Midwest Region. Most of the patients were discharged to rehab, skilled nursing facility or home with nurse.



SA-PO691

Modeling Decision Making for IV Vitamin D Titration in Patients on Hemodialysis (HD)

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Background: Studies in HD often focus exclusively on parathyroid hormone (PTH) as the driver of intravenous (IV) vitamin D titration. We hypothesized that a constellation of mineral metabolism (MM) laboratories (labs), including calcium (Ca), phosphorus (Pi) and PTH, influence titration.

Methods: We retrospectively studied 62,284 decisions in 5442 patients initiating in-center HD between 2006-2008 in Dialysis Clinic, Inc. facilities with non-missing data. We used multinomial transition mixed models to predict increase, decrease or no change in IV vitamin D based on monthly albumin-corrected Ca, Pi, and PTH using piecewise linear functions with knots at 8.0 and 10.2 mg/dl for Ca, 3.5 and 5.5 mg/dl for Pi, and 150 and 300 pg/ml for PTH, 3 sets of lagged monthly lab values, and interactions between current labs to capture a fully integrated lab phenotype. Adding piecewise functions and lab interactions improved fit as reflected in AIC (66,282 vs. 80,084).

Results: Participants contributed a mean ± SD of 9.3 ± 8.5 treatment months. The PTH threshold at which IV vitamin D is more likely to be increased than decreased is the intersection of solid (probability of increase) and dashed (probability of decrease) lines (Figure). This threshold PTH is higher when Ca and Pi were higher, demonstrating that Ca and Pi influence providers' effective PTH titration goal. Titration or addition of alternative therapies, such as cinacalcet, are not depicted here, but are also impacted by integrated lab phenotypes (data not shown).

Conclusions: Prescribers consider multiple lab dimensions when titrating IV vitamin D. Comparative effectiveness studies and trials in MM may be improved by appropriately capturing complex lab phenotypes that contribute to decision-making.

Funding: NIDDK Support

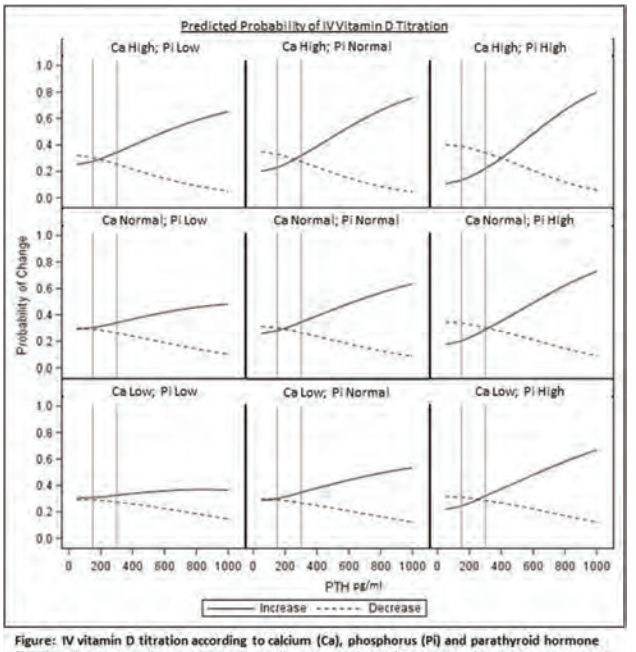


Figure: IV vitamin D titration according to calcium (Ca), phosphorus (Pi) and parathyroid hormone (PTH) levels. Presented probabilities depict decisions at 12 months post HD initiation among users of IV vitamin D sterols alone when Ca is 8.0 (low), 9.0 (normal) or 10.7 mg/dl (high), Pi is 3.0 (low), 4.5 (normal) or 6.5 mg/dl (high), PTH is 100-1000 pg/ml and lagged lab values are the same as current labs. Increase is depicted by solid lines, decrease by dashed lines. No change is not depicted.

SA-PO692

Free 25(OH) Vitamin D and Mortality Among Hemodialysis Patients

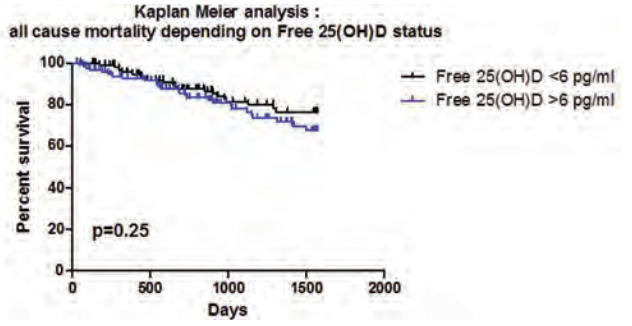
Etienne Novel-Catin,[1] Laetitia Koppe,[1,4] Anaïs Bouchara,[1] Marie-christine Carlier,[1] Myriam Pastural,[3] Granjon Samuel,[2] Jean-christophe Szelag,[3] Maurice Laville,[1] Denis Fouque,[1,4] Solenne Pelletier.[1] *[1]University Center Hospital - Lyon Sud, Saint Priest, France; [2]Cerballiance laboratory, Lyon, France; [3]AURAL, LYON, France; [4]CarMeN laboratory INSERM U1060, F-69621 Villeurbane, France.*

Background: Most of the circulating 25-(OH) vitamin D (abbreviated 25(OH)D) is bound to proteins. Free vitamin D represents only 1% of the circulating vitamin D. There is abundant evidence that this free faction is the bioactive form of vitamin D. Total 25(OH) D deficiency has been associated with early mortality and cardiovascular events (CV) in chronic kidney disease (CKD) patients. The aim of the present study was to investigate a potential association between serum free 25(OH)D levels and i) other biochemical parameters of mineral metabolism, (ii) CV events and (iii) mortality.

Methods: 253 patients undergoing maintenance hemodialysis (HD) were included. Serum free 25(OH)D measurement by ELISA (Diasource® Leuven, Belgium) as well as routine biochemistry tests were performed. Enrolled patients were prospectively monitored for cardiovascular (CV) events and mortality.

Results: During a mean study period of 2.5 years, 48 patients died and 60 suffered from a CV event. Median serum free 25(OH)D was 6.01 pg/ml [4.67 – 7.39] and median total 25(OH)D was 32.2µg/l [24.8-39.9]. Free 25(OH)D was strongly associated with total 25(OH)D ($r= 0.77$, $p < 0.01$). Free 25(OH)D was positively associated with serum calcium levels ($r= 0.29$, $p<0.01$) and negatively with serum PTH ($r= - 0.19$, $p<0.01$). Kaplan-Meier analysis showed no significant association between below median free 25(OH) and all-cause mortality (log rank, $p=0.25$, see figure 1) nor CV events (log rank, $p=0.91$).

Conclusions: This is the first study reporting survival depending on free 25(OH)D status in maintenance dialysis patients. It shows that free 25(OH)D levels are not associated with mortality nor cardiovascular events among maintenance HD patients. Our data concur with precedent results showing that bioavailable vitamin D is positively associated with calcium levels and negatively associated with serum PTH.



SA-PO693

Relationship Between Bioelectrical Impedance Body Composition and CKD-MBD in Dialysis Patients

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Background: Recent studies have assessed body composition through multifrequency bioelectrical impedance analysis (MF-BIA). However, none has employed this technique to test the associations of CKD-MBD with body composition. As recent experimental studies have linked hyperparathyroidism with an increase in energy expenditure, it is important to validate this hypothesis in a clinical scenario.

Methods: In a transversal study, we evaluated 160 prevalent dialysis patients (hemodialysis, HD = 99; peritoneal dialysis, PD = 61) through whole-body and segmental composition and correlated MF-BIA with CKD-MBD parameters.

Results: Patients were 49 years old (range 18-90), with BMI = 24.6 kg/m^2 (13.3-49.3), fat mass (FAT) = 17.8 kg (1.1-61.5), muscular mass (MUSC) = 25.6 kg (10.1-45.4), bone mineral content (BMC) = 2.78 kg (2.43-3.30). In PD patients, serum 25 vitamin D correlated with MUSC (r= 0.41 p = 0.002) and BMC (r = 0.42 p =0.002). Alkaline phosphatase correlated negatively with FAT (r = - 0.30. p 0.02). No significant correlations were found for parathormone, calcium, phosphate or albumin. In HD patients, we did not find any significant correlation between MF-BIA and CKD-MBD parameters.

Conclusions: Assuming the accuracy of MF-BIA, in PD patients, higher serum vitamin D levels were associated with lower risk of sarcopenia and low bone mineral density, whereas higher alkaline phosphatase was linked with lower fat mass. Future prospective studies should evaluate whether cholecalciferol supplementation and hyperparathyroidism control could improve muscle, bone and fat masses in these patients.

Funding: Government Support - Non-U.S.

SA-PO694

Efficacy of High versus Conventional Dose of Ergocalciferol Supplementation on Serum 25-Hydroxyvitamin D and Interleukin-6 Levels in Hemodialysis Patients with Vitamin D Deficiency

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Background: Vitamin D deficiency alters innate and adaptive immune function, which will increase inflammatory cytokines production. Long-term dialysis is chronic inflammatory state and it has high prevalence of vitamin D deficiency. Trials examining the efficacy, and dosage of ergocalciferol supplementation in end stage renal disease (ESRD) on hemodialysis have been limited.

Methods: A multicenter, randomized, controlled trial was conducted in ESRD on hemodialysis with serum 25-hydroxyvitamin D (25[OH]D) level < 30 ng/mL. The conventional-group (N=35) and the high-dose group (N=35) were treated with ergocalciferol according to the K/DOQI guidelines and double dosage of ergocalciferol from the recommendation for 8 weeks, respectively. The main outcomes were measured by serum 25[OH]D, IL-6, calcium, and phosphorus levels.

Results: At the end of 8-week, there was a statistically significantly greater increase of mean serum 25[OH]D levels in the high-dose group compared with the conventional-dose group (17.8 ng/mL [95%CI 15.8 to 19.7] vs. 9.2 ng/mL [95%CI 7.4 to 11.1], P<0.001) and the high-dose group had also higher achievement of vitamin D sufficiency (25[OH]D level >30 ng/mL) than the conventional-dose group (97.4% vs. 76.4%, P=0.012). A trend toward lower serum IL-6 levels in the high-dose group (-0.45 pg/mL [95%CI -3.57 to 2.68], P=0.772) and there was a statistically significance lower serum IL-6 levels in the subgroup who had baseline serum 25[OH]D levels < 20 ng/mL (-2.67 pg/mL [IQR -6.56 to -0.17], P=0.039). There were no differences between the two groups in changes in serum calcium, phosphorus levels, and adverse events.

Conclusions: Oral high-dose ergocalciferol supplementation has achieved higher vitamin D sufficiency than standard recommendation dose in ESRD patients on dialysis with vitamin D deficiency. It might also be benefit on reduction of the inflammatory cytokine in group of patients with baseline serum 25[OH]D levels < 20 ng/mL.

SA-PO695

Evaluation of Long Term Supplementation with Cholecalciferol on the Levels of 25-Hydroxyvitamin D (25[OH]D) and on Bone Turnover Biomarkers of Chronic Hemodialysis Patients

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Background: We addressed the safety of long term supplementation with cholecalciferol in maintenance hemodialysis patients along with its effect on markers of bone and mineral metabolism.

Methods: Sixty stable hemodialysis patients, initially, received a dose of 1200 IU of cholecalciferol orally, once daily, every 48 hours, for 18 months. This dose was, subsequently, increased to 1200 IU, once daily for another 6 months. 25[OH]D levels were measured at 0, 4, 12, 18, and 24 months along with Ca, P, ALP, iPTH, HbA1c levels and BMI. Additionally, all patients had a T – score evaluation by dual – energy x – ray absorptiometry (DXA) at the beginning of the study and after 12 and 24 months.

Results: All patients proved to be 25[OH]D deficient, regardless that measurements were done during the summer period (increasd sunlight). There was no correlation of the low 25[OH]D levels with age, sex, time on hemodialysis and HbA1c levels, but they did correlate to BMI, implicating diet as a source of 25[OH]D. Likewise, we observed no correlation with the administration of phosphate binders, statins or vitamin D receptor activators. Alternate day supplementation improved 25[OH]D levels, which evolved from the deficient level to stage of insufficiency (p<0.01). Daily administration – after 18 months – was achieved by 46 patients (76%). Annual screening of bone density revealed gradual amelioration of T – score (p<0.01). No significant changes of the other markers were observed.

Conclusions: In conclusion, the very low levels of calcidiol in dialysis patients should draw considerable attention. A "safe" threshold of 20 ng/ml was achieved by choosing the alternate day supplementation of 1200 IU of cholecalciferol, with no particular financial burden and succeeding compliance. The positive effect on bone density which was shown in this long term study regards more extended research. Although supplementation with calcidiol is not considered to be an essential treatment, yet, we consider that there are sufficient data to support long term supplementation of 25[OH]D for maintenance dialysis patients.

SA-PO696

Paricalcitol and Renal Anemia: A Novel Association Beyond Inflammation

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Background: The utilization of the paricalcitol (a selective vitamin d receptor activator) for the control of the secondary hyperthyroidisms (SHPT) and its antinflammatory properties have been associated with a better response to the erythropoietic stimulating agents(ESA). Whether the effect of the paricalcitol is directly associated with the erythropoiteic process and its influence on endogenous erythropoietin production is unknow. **Objective:** To evaluate the influence of the paricalcitol on the novel parameters associated with the erythropoiesis in anemic hemodialysis patients.

Methods: These are the results of the secondary objective of the MIR-EPO trial (EudraCT: 2009-015511-40). Study subjects were allocated to those treated with paricalcitol (group A: N=23) and those without it (group B, N=8). Plasma factors associated with inflammatory anemia (interleuquin-6 and hepcidin) and accelerated red blood cells death (eryptosis: soluble alpha-Klotho levels) were evaluated. Plasma erythropoietin and its main transcriptional factor: hypoxia inducible factor 2-alpha (HIF-2a)) were also evaluated during the evaluation period (from month 3 to 6).

Results: Five patients (22%) under paricalcitol stopped ESA by protocol (*P*=0.06). Lower IL-6 and higher s-klotho levels were observed in those under paricalcitol. Erythropoietin levels (median) increased significantly from 10 to 20 mUI/ml in patients under paricalcitol. The percentage of patients who increased HIF-2a at M6 with respect to M3 (35%) was also significantly only in the group A (*P*=0.01). After adjusting by IL-6 levels, HIF-2a increased in the group A (0.40 pg/ml,$_{log}$ *P*=0.030), but did not change in the group B (-0.31 pg/ml,$_{log}$ *P*=0.340). Free serum iron and transferrin saturation index changes correlate negatively with changes on IL-6 and positively with s-Klotho changes.

Conclusions: The use of the paricalcitol may improves the erythropoiesis process through direct effect on erythropoietin/HIF-2a axes stimulation. Our results suggest an important influence of the vitamin D selective activation on iron metabolism, erythropoietin synthesis and could be on eryptosis process. Larger controlled studies are needed to confirm these findings for potential benefit of the paricalcitol for renal anemia control.

SA-PO697

Renal Complication and Mineral Ion Abnormalities in Patients with Jansen Metaphyseal Chondrodysplasia

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Background: Jansen metaphyseal chondrodysplasia (JMC) is a rare disease that is caused by heterozygous, activating mutations in the PTH/PTHrP receptor (PTHR1). Expression of PTHR1 mutants in growth plate chondrocyte impairs their maturation leading to marked skeletal abnormalities. Because the PTHR1 is also expressed in kidney and bone, JMC patients can develop PTH-independent hypercalcemia, hypophosphatemia, and high bone turnover, and thus nephrocalcinosis and impaired renal function. Long-term outcome of multiple JMC patients was recently reported (Saito et al., JCEM, 2018). We now emphasize the renal abnormalities associated with JMC.

Methods: Clinical and laboratory findings in 24 patients with JMC due to five different PTHR1 mutations (H223R, T410P, T410R, I458R, and I458K).

Results: During the first 2 weeks of life, calcium levels were normal in most patients. During childhood hypercalcemia was severe (11.8±1.4 mg/dL), but improved by adulthood (10.0±1.0 mg/dl). Phosphate and PTH levels were at the lower end of normal ranges. Urinary Ca/Cr (mg/mg) were consistently elevated (children, 0.8±0.4; adults, 0.3±0.2; normal:<0.2). Growth was severely impaired resulting in adult heights well below the 3rd percentile; furthermore, scoliosis and other skeletal deformities were noted. Most young JMC patients had nephrocalcinosis, but normal renal function. Two middle-aged patients revealed continuously worsening renal function, probably secondary to stag horn renal calculi, recurrent UTIs, and urinary tract obstructions.

Conclusions: Activating PTHR1 mutations are associated with persistently increased urinary calcium excretion, which is caused by the PTH-independent hypercalcemia. Hypercalciuria contributes early in life to nephrocalcinosis, which leads in adults to a decline in renal function. Treatment with bisphosphonates to reduce bone resorption may limit calcium excretion to slow the progression of chronic kidney disease. Although an inverse PTH agonist, namely [L11,dW12,W23,Y36]PTHrP(7–36), reduced basal cAMP signaling of the mutant PTHR1s in vitro, it remains to be determined whether such peptides have therapeutic potential.

Funding: Other NIH Support - National Institutes of Health; DK11794 (PO1); AR066261 (P30)

SA-PO698

Risk Factors Associated with Hyperparathyroidism in Maintenance Hemodialysis Patients

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Background: The severity and progression of hyperparathyroidism (HPT) are different among individuals with end-stage-renal disease. Factors other than decreased 1,25-OH-D level and phosphate retention likely participate in the severity and progression of HPT. The present study identified risk factors associated with the progression of HPT as well as factors associated with parathyroid hormone (PTH) levels above the KDIGO's recommended range in maintenance hemodialysis patients.

Methods: Five hundred and one patients were included. Exclusion criteria were previous parathyroidectomy or taking calcimimetic. Changes in PTH levels over 24 months were categorized into 4 patterns as follows, "progression" (increase in PTH levels >= 50%), "reduction" (decrease in PTH levels > 50%), "fluctuation" (changes in PTH levels >= 50% in BOTH directions) and "stable" (changes in PTH levels < 50% in either directions).

Results: 29% of PTH values were > 9 times, 22% were < 2 times and 49% were between 2-9 times of the upper normal limit (UNL). Progression of HPT occurs in 32%, reduction in 19%, fluctuation in 21% and stable in 28% of the patients. The progression group was more likely to have PTH levels > 300 pg/mL, whereas the fluctuation and reduction groups were more likely to have PTH levels <= 300 pg/mL. Factors associated with the progression of HPT were younger age, non-diabetics, suboptimal insurance program (limited access to non-calcium binders and newer drugs), higher PTH levels and higher serum phosphate. Factors associated with PTH levels > 9 times the UNL were younger age, not having DM, CVD and DLP, prolonged dialysis vintage, suboptimal insurance program, higher active vitamin D dose, higher serum phosphate, albumin and creatinine.

Conclusions: Young healthy patients (not having CVD risks including DM and DLP) with better overall health status (higher serum albumin, phosphate and creatinine) are likely to experience the progression of HPT overtime. Prolonged dialysis vintage and suboptimal insurance program also play substantial roles in the increase in PTH level above the KDIGO's recommended range.

Funding: Government Support - Non-U.S.

SA-PO699

Association of Secondary Hyperparathyroidism with Thymic Atrophy in Patients with CKD

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Background: Immune aging, including thymic atrophy, is accelerated in patients with chronic kidney disease (CKD) and can lead to cardiovascular and infectious diseases. However, the mechanism of thymic atrophy is not well understood. Mineral and bone disorders (MBD) affect mortality through bone-related factors and blood vessel calcification; parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) also affect immune cells and possibly thymic atrophy.

Methods: We examined the cross-sectional association between thymic atrophy, evaluated as the number of $CD3^+CD4^+CD45RA^+CD31^+$ cells [recent thymic emigrants (RTE)/μL], and MBD-related factors (PTH, FGF23, and alkaline phosphatase) in patients with non-dialysis-dependent CKD.

Results: This study enrolled 125 patients with CKD (median eGFR, 17 mL/min/1.73 m^2). Age (r = –0.46) and male sex (r = –0.34) correlated negatively and eGFR (r = 0.27) correlated positively with RTE. In terms of MBD-related factors, corrected calcium (r = 0.27) correlated positively whereas PTH (r = –0.36) and alkaline phosphatase (r = –0.20) correlated negatively with RTE. In contrast, FGF23 and phosphorus were not correlated with RTE. Multivariate non-linear regression analysis adjusted for age, sex, eGFR, diabetes, corrected calcium, phosphorus, vitamin D supplementation, and use of phosphate binder indicated a negative association between PTH and log-transformed RTE (P = 0.030, P for non-linearity = 0.124). However, FGF23 and alkaline phosphatase were not associated with RTE.

Conclusions: Secondary hyperparathyroidism appears to be related to thymic atrophy, contributing to immune abnormalities in patients with CKD. Our findings may partially explain the mechanism through which PTH is associated with mortality.

SA-PO700

Serum 1,25-Dihydroxyvitamin D Concentrations in Maintenance Hemodialysis Patients: In the Era of CKD-MBD Guideline

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Background: In hemodialysis (HD) patients, serum levels of 1,25-dihydroxyvitamin D (1,25D), an active form of vitamin D, are low; however, 1,25D, even in low, was reported to play an important role in HD patients (Ando R et al, J Jap Soc Dial Ther 1996). Currently, little is known about serum 1,25D concentrations in HD patients, particularly in the era of CKD-MBD guideline. We measured serum 1,25D concentrations in stable HD patients, and examined their association with clinical factors.

Methods: A total of 89 HD patients (71±11 year-old, 48 males, HD duration 9.4±7.4 years, 36 with type 2 diabetes) were examined. Serum 1,25D was measured by a 1,25D RIA kit (Ishimura E et al. Kidney Int 1999), and intact PTH by a Elecsys PTH IRMA assay (Kurajoh M et al. Osteoporos Int 2008).

Results: Serum 1,25D concentrations were 14.4±8.0 pg/ml, being lower compared to those of healthy subjects. Serum 1,25D concentrations were significantly higher in males than in females (p=0.045). They were tended to be negatively correlated with age (r=-0.034, p=0.083) and HD duration (r=-0.042, p=0.055). Serum 1,25D concentrations were significantly, negatively associated with intact PTH (r=-0.085,p⟨0.001), although they were not with serum calcium or phosphate. There were no significant differences in serum 1,25D between patients with (n=65) and without vitamin D treatment, and between those with (n=12) and without calcimimetics. However, serum 1,25D concentrations in patients with intravenous treatment of maxiacalcitol, an active form of vitamin D, (n=12) were significantly higher than those without (p=0.045). In a multiple regression analysis after adjustment of age, gender, HD duration, and vitamin D treatment, serum 1,25D concentrations were significantly, independently associated with serum intact PTH (β=-0.310, p=0.003) (R^2=0.200, p=0.002).

Conclusions: These results indicate that serum 1,25D, even in low, is significantly associated with intact PHT. The results also suggest that, even in the era of CKD-MBD guidelines, a clinical importance of serum 1,25D concentrations may be re-considered for the assessment of CKD-MBD, particularly in regards to prevention of secondary hyperparathyroidism. Intravenous, rather than oral, vitamin D treatment may be useful for treatment of secondary hyperparathyroidism.

SA-PO701

Secondary Hyperparathyroidism: Are KDIGO Guidelines for PTH Testing Being Followed?

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Background: KDIGO recommends that patients with chronic kidney disease (CKD) undergo parathyroid hormone (PTH) testing beginning in CKD stage 3 followed by testing in stage 4 (every 6-12 months) and in stage 5 (every 3-6 months). KDIGO also suggests a role for 25-hydroxyvitamin D [25(OH)D] testing, although frequency is not specified. Adherence to these guidelines is unknown.

Methods: Using the 2007-2015 20% Medicare sample, we identified a cohort of patients with stage 3, 4, or 5 CKD. CKD stage was determined by presence of two or more claims with ICD-9-CM codes for CKD. Only patients with 30 or more days of follow-up were included. Frequency of 25(OH)D and PTH testing was identified using laboratory procedure codes. Factors associated with PTH testing by each CKD stage were then determined using separate logistic regression models.

Results: A total of 381,332 (stage 3), 86,875 (stage 4), and 14,401 (stage 5) CKD patients were identified. Over mean follow-up of 2.3 ± 1.8 (stage 3), 1.3 ± 1.3 (stage 4), and 0.7 ± 0.9 (stage 5) years, 54% of stage 3, 61% of stage 4, and 70% of stage 5 patients were not tested for 25(OH)D deficiency; corresponding percentages for PTH were 66%, 56%,

and 52%, respectively (**Table**). Factors inversely associated with PTH testing were older age and presence of most comorbid conditions.

Conclusions: Testing for 25(OH)D deficiency was relatively infrequent. PTH testing was undertaken less than half as often as is recommend by KDIGO guidelines. This is potentially concerning, especially since recent data indicate it can be challenging to achieve PTH targets even with routine testing. How the uncertainty over optimal PTH targets in CKD, as discussed in the current KDIGO guidelines, will affect future testing patterns, should be studied.

Funding: Commercial Support - OPKO Pharmaceuticals, LLC

Table. Participant characteristics and frequency of 25(OH)D and PTH testing over follow-up

	CKD stage 3	CKD stage 4	CKD stage 5
	N = 381,332	*N* = 86,875	*N* = 14,401
Follow-up time, mean ± SD years	2.3 ± 1.8	1.3 ± 1.3	0.7 ± 0.9
Age, mean ± SD years	76.1 ± 10.7	77.2 ± 11.6	73.5 ± 13.0
Female, %	57.4%	58.1%	55.0%
Race, %			
White	80.7%	76.4%	63.2%
Black	12.5%	16.0%	25.4%
Asian	2.3%	2.4%	3.6%
Hispanic	2.4%	2.8%	4.4%
Other	2.1%	2.3%	3.4%
Comorbid conditions, %			
Heart failure	30.9%	46.9%	41.9%
Stroke/transient ischemic attack	16.0%	19.9%	18.8%
Chronic obstructive pulmonary disease	26.8%	31.3%	25.9%
Diabetes	48.0%	57.3%	60.7%
Hypertension	90.2%	94.6%	95.7%
25(OH)D testing over follow-up			
No testing	53.9%	61.4%	69.9%
1 or more tests	46.1%	38.6%	30.1%
PHT testing over follow-up			
No testing	65.6%	56.0%	51.7%
1 or more tests	34.4%	44.0%	48.3%

CKD: chronic kidney disease, PTH: parathyroid hormone

SA-PO702

Diagnosis of Renal Osteodystrophy by Bone Histomorphometry in Chronic Hemodialysis (HD) Patients

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Background: Management of secondary hyperparathyroidism has been evolving and requires more investigations. Currently, the relatively "wide" recommended target for intact parathyroid hormone (iPTH) level has proved to be reasonable only in limited circumstances. This study was conducted to determine the prevalence of various types of renal osteodystrophy in Thailand and to investigate the correlation between bone markers and bone histomorphometry to suggest an optimal iPTH level.

Methods: 22 chronic HD patients participated in this cross-sectional study. iPTH, serum calcium, phosphate and 25-hydroxyvitamin D and bone turnover markers including tartrate-resistant acid phosphatase-5b (TRAP-5b) and bone specific alkaline phosphatase (B-ALP) were measured. Double tetracycline-labeled iliac crest bone specimens were evaluated for static and dynamic parameters by using specialized program (Osteomeasure®). The types of bone histomorphometry were classified based on turnover (T), mineralization (M), and volume (V) classification.

Results: Mean age and iPTH were 48±10 years and 523±238 pg/mL, respectively. Median dialysis vintage was 64 months. Adynamic bone disease was the most common bone abnormalities (50%), followed by osteitis fibrosa (40.9%) and mixed uremic osteodystrophy (9.1%). No evidences of osteomalacia and aluminum bone disease were detected. iPTH at the cutoff of 484.5 pg/mL predicted high bone turnover with an area under the receiver operating characteristic curve (AUROC) of 0.86 (95 % CI 0.70-1.0) with the sensitivity and specificity of 0.82 and 0.82 respectively.

Conclusions: Adynamic bone disease remains the most common bone disease among chronic HD patients in Thai population, albeit iPTH levels were close to the upper limit target of KDIGO guideline. Our study suggested that bone biopsy is required as an accurate diagnostic tool and providing guide for the treatment of chronic HD patients with renal osteodystrophy.

Funding: Government Support - Non-U.S.

Bone Biomarker	AUROC	95%CI	P-value	Best cutoff	Sensitivity	Specificity
iPTH	0.86	0.704-1.0	0.004	484.5	0.818	0.818
TRAP-5b	0.727	0.501-0.953	0.071	2.674	0.636	0.91
B-ALP	0.633	0.348-0.919	0.327	26.944	0.6	0.667
FGF-23	0.388	0.143-0.634	0.375	2.643	0.222	0.846

AUROC of Bone Biomarker to Distinguish High and Low Bone Turnover

SA-PO703

Parathyroidectomy (PTX) and Anemia in a Cohort of Italian Dialysis Patients

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Background: Secondary hyperparathyroidism (SHP) negatively affects endogenous erythropoietin (EPO) synthesis, bone marrow erythroid progenitors, and red cell survival, thus contributing to anemia. PTX is generally thought to be followed by improved anemia control. However, low turnover bone disease (LTBD), a common finding after PTX, could negatively affect anemia. We compared anemic status and EPO therapy in two prevalent populations of dialysis patientswho received or not PTX

Methods: We enrolled both hemo- and peritoneal dialysis patients, aged ≥18 y, from 149 Italian dialysis units. The control group (C) was selected to be comparable to the prevalent population of PTX patients for age, sex and dialysis duration. Local EC approved the protocol (N° 888/09).

Results: We obtained data of 527 PTX patients (age: 57.90±12.52 yo; M/F = 44/56%; D time: 14.5±8.4 y) and 432 C patients (age 58.9±16.5 y.o.; M/F = 45/55 %; D time 11.7±2.6 y). PTH levels were lower in PTX (181.9±292.5 vs 333.7±293.7 pg/ml; p<.01), with 17 % and 35% respectively at KDOQI target (p<.001). In particular, cases with values <150pg/ml were 60% and 20% in the PTX and C groups respectively (p<.001). PTX patients were similarly less at target for Ca (50.9 vs 57.6, p<.001) and P (55.3 vs 58.8%; p<.05). Hemoglobin levels (PTX=11.3±1.1vs C=11.3±1.1 mg/dl), hsCRP (PTX 2.82±4.93 vs C=2.59±5.39 mg/dl) and ESR (PTX=32.29±23.98 vs C=36.46±24.49 mm/hr) were similar in the two groups. Ferritin values were higher in the C group (443.1±363.39 vs 339.84±336.9mg/dl; p<.0001). Patients receiving ESA (either epoietin or darbepoietin) were significantly higher in the PTX group (80.9% vs 70%, X^2=15.2; p<.001) while average doses of EPO (expressed as mean darbepoietin considering 1 mcg darbepoietin = 200 IU epoietin), were not different (PTX 0.34±0.25 vs C 0.33±0.25mcg/Kg/weekly).

Conclusions: Our data suggest that, in the long term, PTX does not associate with improved anemia. This is possibly due, in our population, to worse biochemical control of SHP, most frequently showing low PTH (indicative of LTBD). In conclusion, it seems thatit is more important the biochemical control of SHP than neck surgery to improve anemia in dialysis.

Funding: Commercial Support - Unrestricted grant by Amgen

SA-PO704

Clinical Outcomes and Costs of Parathyroidectomy in CKD Patients

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Background: Cinacalcet (CT) for treatment of secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) was withdrawn in August 2016 from the Australian Pharmaceutical Benefits Scheme. We aimed to audit parathyroidectomy (PT) for SHPT in CKD, and, to compare PT costs to those of CT therapyin one tertiary Australian centre.

Methods: A retrospective audit of CKD patients with SHPT at a tertiary Australian centre who underwent PT between 1/1/11 and 31/6/17 (n=44) (HREC/17/QRBW/231). Median wait time to renal transplant in Australia is 2.4yrs (range 1.3-4.1yrs) thus centre-specific total cost of 2.4yrs of CT therapy 60mg/day was calculated and compared to the total cost of PT based on hospital records, length of stay (LOS) and peri-operative complications (Cx).

Results: 34 and 11 PT were performed respectively in the 67months pre & 11months post August 2016. Median age and body mass index of patients undergoing PT were 51.5yrs (range 24-79yrs) and 29 (range 22-55). 30/34 patients were on dialysis. 5/34 patients were treated according to centre-specific pre-operative protocol. 18/34 patients were treated as per protocol post-operatively. 23/34 patients experienced post-operative Cx/s; ≥2 Cx in 52%. The median LOS post-PT was 6.5days (range 2-35days) with 32% of patients admitted to the intensive care unit. There was a 23.5% re-admission rate within 28 days of PT. All-cause mortality was 5% at 12months post-PT. A median of 5 outpatient reviews (range 0-37) were required before patients had two consecutive post-operative serum calcium results in normal range whilst on oral therapy. The median follow-up of patients post-PT was 25.5 months. The mean cost of CT ($13,149/patient) was less than the mean total cost of PT ($23,062/patient; range $11,375-53,279/patient). The median postoperative LOS was 7.51days (range 3.47-35.74days).

Conclusions: PT for SHPT in CKD patients is associated with a significant Cx, protocol non-adherence, re-admission rate and cost. There has been an overall increased annual rate of PT for SHPT in CKD patients. Further, we identified CT to be more cost-

effective than PT as a treatment approach in CKD patients with SHPT. Optimised patient selection, protocol review and clinician engagement is indicated to guide best treatment for patients.

SA-PO705

An Examination of Multiple Explanations for Secondary Hyperparathyroidism

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Background: We have advanced the tradeoff-in-the-nephron hypothesis to explain the evolution of secondary hyperparathyroidism (SHPT) in CKD (*Nutrients* 2017;9:pii:E427). The hypothesis states that a high phosphate (P) concentration in the cortical distal nephron ($[P]_{CDN}$) limits availability of calcium (Ca) for reabsorption and necessitates high [PTH] for maintenance of normocalcemia. With assumptions, P excreted per volume of filtrate (E_p/C_{cr}) is a surrogate for $[P]_{CDN}$ to which [PTH] can be compared. In the present study, we used contemporaneous data to assess our hypothesis and others.

Methods: Fasting specimens of serum (s), plasma, and urine (u) were obtained from 30 patients with stages 3 or 4 CKD (mean eGFR 29.5 mL/min/1.73m^2). Concentrations of creatinine ([cr]), P, Ca, and ionized calcium ($[Ca]_i$) were measured with standard methods. [PTH]1-84 and intact [FGF23] were measured with ELISAs (Scantibodies and Immutopics), [25OHD] with an enzyme immunoassay (immunodiagnosticsystems), and $[1,25(OH)_2D]$ with a radioimmunoassay (Labcorp). E_p/C_{cr} and E_{Ca}/C_{cr} were calculated as $[P]_u[cr]_s/[cr]_u$ and $[Ca]_u[cr]_s/[cr]_u$. Simple linear regressions were performed to examine theories of SHPT (see table).

Results: [PTH] varied directly with 100/eGFR, E_{Ca}/C_{cr}, [FGF23], and E_p/C_{cr}. Other regressions were not significant.

Conclusions: The *direct* relationship of [PTH] to E_{Ca}/C_{cr} undermines the theory of skeletal resistance to PTH. The relationship to [FGF23] probably reflects dependence of FGF23 synthesis on PTH (*Kidney Int* 2017;92:165). The regression of [PTH] on E_p/C_{cr} supports the tradeoff-in-the-nephron hypothesis. The regression also explains the inverse relationship of [PTH] to eGFR and the historic observation that influx of P determines [PTH] in CKD. Our data do not support other explanations for SHPT.

Funding: Veterans Affairs Support, Commercial Support - Sanofi-Genzyme

EXPLANATION FOR INCREASED PTH SECRETION	REGRESSION(S) EXAMINED	R2	p
CKD causes SHPT	[PTH] on 100/eGFR	0.33	≤ 0.001
Original tradeoff hypothesis (in plasma)	[PTH] on [Ca]i;[PTH] on [P]s	0.06; 0.09	0.21; 0.11
Skeletal resistance to PTH	[PTH] on [Ca]i; [PTH] on ECa/Ccr	0.06; 0.12	0.21; 0.015
Deficiency of 1,25(OH)2D	[PTH] on [1,25(OH)2D]	0.03	0.34
Direct effect of hyperphosphatemia	[PTH] on [P]s	0.09	0.11
Parent vitamin D insufficiency	[PTH] on [25OHD]	0.001	0.85
Loss of suppression by FGF23	[PTH] on [FGF23]	0.13	0.05
Tradeoff in the nephron	[PTH] on EP/Ccr	0.28	0.003

SA-PO706

Cost Effective Model for Bone Mineral Disease Management in Hemodialysis Population in Qatar

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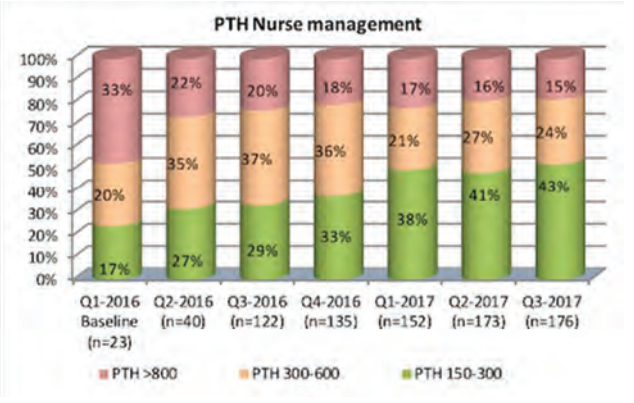
Background: Hemodialysis population have multiple comorbidities with high morbidity and mortality. High calcium level contributes to vascular calcification and increased cardiovascular mortality in the dialysis population. Hypercalcemia, hyperphosphataemia and high parathyroid hormone level are related to vascular calcification and increased cardiovascular mortality. On our annual report we found suboptimal MBD results in 2015. That is why a change was needed.

Methods: BMD team consisted of 2 part-time nurses and a nephrologist who provided extensive training for 2 months to work almost independently. We started April 2016 and followed theses target for calcium. We followed this available target for calcium (<2.37 mmol/L), phosphorus (<1.75 mmol.) And PTH (150-600 pg/mL) or >800 pg/mL (negative outcome). Nurse review the results within 4 days after blood extraction with the nephrologist and prescription were written simultaneously (physician prescription is mandatory), Data collection was done under IRB approval.

Results: all first-floor patient's (176/380) were included. Over a short period, we were able to achieve our targets. There was statistically significant difference in the number of patients in target range for PTH in interventional group compared with standard care group in the ground floor (43% versus 17%), (P value <0.005), and PTH less than 800(15% versus 83%),(P Value 0.0006). Through proper accounting for medicine dispensing, we were able to reduce number of prescription and pill burden. Reduced number of sevelamer tablets estimated at 4.5 tablets/Week/Patient (average of 30 tablets/week/patient in the new model versus 34.5 in the standard of care) with annual course surfing estimated at 60,000 $. Cinacalcet consumption dropped from 430 mg/week/patient to 370mg/week/patient with an annual cost saving of 125000 US dollars.

Conclusions: MBD nurse manager model in dialysis was successful to achieve, exceed and maintain patients within benchmark for calcium, phosphorus, and PTH.



SA-PO707

Determinants of Secondary Hyperparathyroidism Progression in CKD Patients

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Background: Secondary hyperparathyroidism (SHPT) is a common complication in patients with CKD and should be early identified and managed. However, it is still unknown which factors are associated with SHPT progression.

Methods: Electronic charts of all nephrology outpatients clinic (n=1,170) in the period between Jan-2017 and Dec-2017 with CKD stages 3 and 4 were included. Estimated glomerular filtration rate (eGFR) based on CKD-EPI equation and biochemical parameters were assessed. Patients were divided in two groups: those who exhibited SHPT (final PTH > 150 pg/ml; n= 279) and those who did not (n = 891).

Results: Patients who developed SHPT had lower basal calcium (9.45 ± 0.6 vs. 9.57 ± 0.5 mg/dl), eGFR (24±7 vs. 34±11 ml/min, p=0.002) and 25 vitD (25±10 vs. 27±10 ng/dl, p=0.002), despite a trend for a higher prevalence of cholecalciferol supplementation (77 vs. 72%, p=0.07). They also had higher phosphate (3.68 ± 0.7 vs. 3.52 ± 0.7 mg/dl, p=0.001) and eGFR loss (3.3±6 vs. 1.0±7.6 ml/mi, p=0.0001). No association was found for age or gender. Multivariate analysis disclosed that SHPT progression was associated with more rapid progression of CKD, as well as lower vit D and higher phosphate at baseline.

Conclusions: Our data suggest that patients with faster progression of SHPT present lower eGFR and 25 vitD and higher phosphate, even within the reference range. These patients should be closely monitored and future prospective studies might show whether interventions such as phosphate restriction and more vigorous cholecalciferol supplementation could change the SHPT natural history.

SA-PO708

A Qualitative Analysis of the Medical Record of a National Cohort of Patients with Advanced Kidney Disease Not Treated with Maintenance Dialysis in the US Department of Veterans Affairs

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Background: Although it is widely recognized that not all patients with advanced chronic kidney disease (CKD) will choose to receive maintenance dialysis, little is known about the clinical context in which these decisions occur.

Methods: We performed an in-depth qualitative analysis of the electronic medical records of a national cohort of 851 patients with advanced CKD and in whom there had been a decision not to initiate maintenance dialysis in the Veterans Affairs (VA) healthcare system between 2000-2011. We used inductive content analysis to identify clinical events, care processes, healthcare interactions and documented concerns of patients and providers relevant to the decision not to pursue dialysis

Results: Overall, 66.6% of cohort members were white and 61.3% were aged ≥75 years. We identified three major dynamics relevant to understanding the context in which decisions not to pursue dialysis unfolded: 1) *Perseveration about dialysis*, which reflected circumstances in which some patients had refused dialysis but providers did not readily accept this decision and seemed rooted to the possibility of starting dialysis. Providers repeatedly questioned patients' preferences, questioned patients' competency to make this decision, increased opportunities for patients to initiate dialysis, and proceeded as if patients would change their minds about dialysis; 2) *Not candidates for dialysis*, which reflected circumstances in which providers deemed some patients not to be candidates or appropriate for dialysis on the basis of patients' characteristics and expected prognosis rather than on patients' values and preferences; and, 3) *Nothing left to offer*, which reflected providers' tendency to view that they had little else to offer when patients did not receive dialysis and pressed patients to enter hospice care, often before patients were ready.

Conclusions: Our findings reveal the all-or-nothing approach to caring for patients with advanced CKD who did not pursue maintenance dialysis. Greater efforts are needed

to develop patient-centered models of care for advanced CKD capable of supporting those who do not to start dialysis.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO709

Association Between eGFR and Cognitive Performance

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Background: Moderate to severe chronic renal failure is known to be associated with cognitive impairment; however, few studies have looked at the impact of subclinical kidney dysfunction on cognition. This study aimed at investigating the association between cognition and eGFR in a population-based cohort.

Methods: We evaluated cardiovascular, renal and cognitive profiles in randomly selected individuals from the general population between the ages of 40 and 69 years. Cognitive function was quantified by computer-based testing of reaction time, paired associates learning (memory), and verbal-numerical reasoning. eGFR was estimated using the CKD-EPI equation. We used multivariate analysis to study the association between eGFR and cognition, while adjusting for confounders, including age, gender, income, education, smoking, hypertension, dyslipidemia, diabetes, body mass index, cardiovascular diseases, alcohol intake and psychoactive medication use.

Results: A total of 15 897 patients had cognitive testing and eGFR measurements performed during the same clinic visit. Mean eGFR was 88.0± 14.6 ml/min/1.73m^2. After adjusting for age, gender, income, education, alcohol intake and known cardiovascular risk factors, lower eGFR was significantly associated with poorer performance on reaction time testing, paired associates learning (memory), and verbal-numerical reasoning. These associations remained significant after further adjustment for use of psychoactive medications (cf. table).

Conclusions: Subclinical renal dysfunction may be associated with impaired cognitive performance, independently of known risk factors for cognitive decline.

Funding: Government Support - Non-U.S.

Table - Association between eGFR and cognitive function.

	Quartile	Adj. eGFR* (SD) ml/min/1.73m^2	Adj. p-value*
Reaction time	Q1	90.4 (5.2)	< 0.001
	Q2	88.5 (5.6)	
	Q3	87.0 (6.0)	
	Q4	85.6 (6.1)	
Memory	Q1	89.2 (5.7)	< 0.001
	Q2	88.2 (5.9)	
	Q3	87.3 (6.0)	
	Q4	86.3 (6.1)	
Reasoning	Q1	88.4 (5.7)	< 0.001
	Q2	88.2 (5.8)	
	Q3	88.0 (5.9)	
	Q4	87.5 (6.2)	

*Adjusted for age, gender, income, education, smoking, alcohol intake, hypertension, dyslipidemia, body mass index, diabetes, history of cardiovascular disease, including stroke, and psychoactive medication use. The first quartile (Q1) corresponds to best cognitive performances while that of the fourth quartile (Q4) relates to worst cognitive performances.

SA-PO710

Trajectories of Distress in Older Patients at Initiation of Haemodialysis

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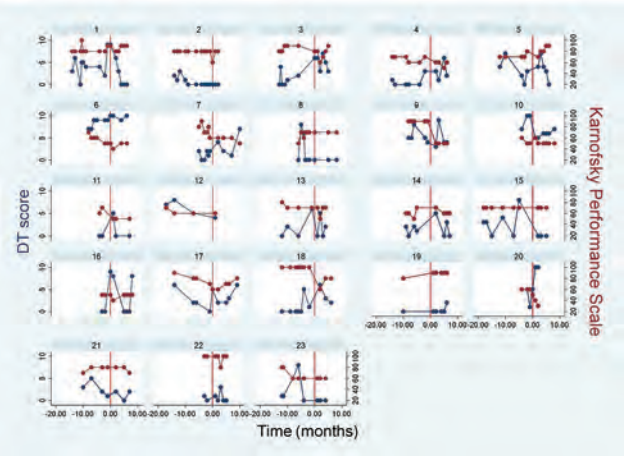
Background: Previous studies examined trajectories of functional status (Kurella Tamura et al, 2010; Murtagh et al, 2011) and trajectories of quality of life (da Silva Gane et al, 2012) at dialysis initiation. We compared trajectories of functional status and distress in older patients before and after dialysis initiation.

Methods: We obtained records for 316 CKD4/5 patients aged <70 with ≥3 DTs and KPSs in their patient record. 23 started haemodialysis during the study period. Linear regression analysed distress, KPS and other factors of interest at baseline. Multi-level regression analysed changes in DT and KPS score over time. Visual Graphical Analysis (VGA) assessed the trajectories of patients who started dialysis in the study period.

Results: For each 10% loss of functional performance on the KPS, DT score fell by 0.47 (p<0.001). The relationship between DT scores and factors such as gender, eGFR and age, was not statistically significant. We identified 5 categories of DT trajectory: 1: increase in distress around the time of starting dialysis, returning to baseline levels of distress (psychological adaptation) after a couple of months 2: increase in distress around the time of starting dialysis, but with no return to baseline 3: unaffected by the start of dialysis – reported no distress at all 4: unaffected by start of dialysis because they were so distressed all the time that dialysis made no difference to their DT scores 5: unaffected by start of dialysis but experienced a rise in distress at other times.

Conclusions: A majority of participants experienced a rise in DT score around start of dialysis, and for some this did not return to baseline even after six months. However low eGFR was not associated with higher levels of distress. How do we reconcile this? We found an association between functional status and distress, suggesting that the distressing aspects of dialysis initiation may be unrelated to declining kidney function, instead due to the impact of haemodialysis on their previous life.

Funding: Private Foundation Support



SA-PO711

Impact of Effective Treatment of Hyponatremia in Geriatric Patients

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Background: Hyponatremia is highly prevalent in old age and associated with increased morbidity and mortality. Until now it is not known whether effective treatment of frequently perceived asymptomatic hyponatremia in the geriatric population has an impact on patient outcome. Here, we investigate the effect of inpatient treatment of patients with hypotonic hyponatremia on neurocognitive and motor performance using a comprehensive geriatric assessment (CGA).

Methods: 150 geriatric patients with serum [Na^+] <130 mEq/L on admission and complete diagnostic datasets were enrolled. The results of the CGA on admission as well as the change of individual CGA tests until discharge were compared to a matched (sex, age, Barthel index of activities of daily living [ADL]) control group.

Results: Both groups were similar with respect to comorbidities and clinical characteristics. There were no differences in the individual assessments (ADL, Tinetti's Mobility Assessment, Timed Up and Go-Test, Mini-Mental State Examination [MMSE], handgrip strength, Geriatric Depression Scale, Clock-drawing Test, and Esslinger Transfer Scale) at baseline (i.e. upon admission). A small but highly significant improvement as compared to the control group between baseline and time of discharge was observed with regard to ADL (mean(SD): 14.3(17.12)] vs. 9.84(14.67); P=0.002) and MMSE (mean(SD): 1.43(3.71) vs. 0.72(2.17); P=0.002) in the primary analysis group and this improvement was attributable to those patients in which serum [Na+] was increased by >5 mEq/L whereas no improvement was seen in those in which serum [Na+] was increased by only ≤5 mEq/L. However, regression analyses were not able to confirm a statistically significant association between effective [Na+] increase and CGA outcome within the primary analysis group. With respect to the subgroup of euvolemic hyponatremia, only changes of MMSE results were significantly different.

Conclusions: With the most robust changes observed with ADL and MMSE, the results of this prospective observational study suggest a true impact of treating hyponatremia on quality of life and neurocognitive function. However, the detected differences are small and further investigations are needed to prove their clinical relevance.

Funding: Commercial Support - Otsuka

SA-PO712

Patiromer and Maintenance of RAASI Therapy in Hyperkalemic Medicare Patients

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Background: Continuing RAASI is critical for patients (pts) with high cardiovascular risk. Patiromer (PAT) is a Na-free non-absorbed K^+-binder approved for hyperkalemia (HK) treatment in Oct 2015. PAT has been shown to reduce recurrent HK and allow pts to maintain RAASI. This retrospective cohort study evaluated RAASI utilization among Medicare Advantage pts with HK.

Methods: RAASI utilization was evaluated from a large, de-identified national health insurance claims database from 1/1/16 to 3/31/17. Three HK cohorts were identified based on: dispensed a K^+-binder, either 1) patiromer [PAT cohort] or 2) SPS [SPS cohort], or 3) HK diagnosis code without a K^+-binder dispensed (HK cohort). Pts were included who had a pre-index serum K^+ ≥5.0 mEq/L and were continuously exposed to RAASI for ≥6 months pre-index (ie, date of first K^+-binder dispensing or HK diagnosis). We evaluated RAASI continuation and down-titration (the latter assessed for lisinopril, losartan, and valsartan) within 1, 3, and 6 months post-index.

Results: Pre-index pt characteristics and sample sizes are listed in the **Table**. At 6 months post-index RAASI continuation rates were 87%, 72%, and 57% (**Figure**) and down-titration rates were 11%, 11%, and 9% in the PAT, SPS, and HK cohorts, respectively.

Conclusions: The highest RAASI continuation rate was observed in the PAT cohort across all time intervals, and down-titration rates in all 3 cohorts were low (~10%). Further study is warranted to fully elucidate these findings in early patiromer users.

Funding: Commercial Support - Supported by Relypsa, Inc., a Vifor Pharma Group Company

Cohort	Patiromer	SPS	HK
Sample Size	N=82	N=1,449	N=4,988
Age (years), median (Q1, Q3)	71 (67, 79)	75 (69, 82)	75 (69, 81)
Female, %	48	50	50
CKD, %	62	47	49
eGFR (mL/min/1.73m²), median (Q1, Q3)	35 (22, 48)	42 (27, 65)	54 (35, 78)
CHF, %	16	20	24
Diabetes, %	50	45	56
Serum K⁺ (mEq/L), median (Q1, Q3)	5.5 (5.3, 5.7)	5.8 (5.5, 6.1)	5.5 (5.2, 5.7)

Table: Pre-Index Patient Characteristics and Sample Sizes by Cohort.

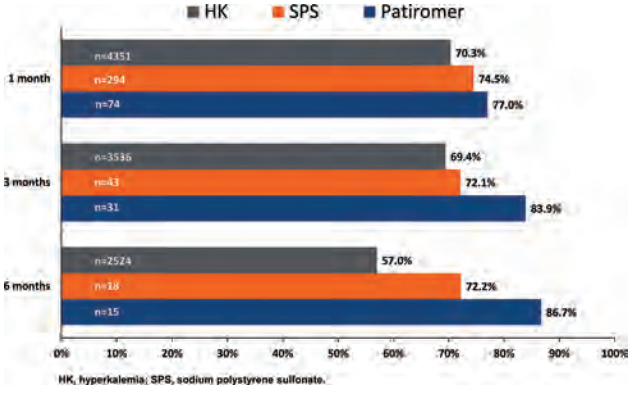

Figure: RAASI Continuation Rates at 1, 3, and 6 Months Post-Index by Cohort.

SA-PO713

Discharge Destination and Disparities in Dialysis Patients' Post-Acute Care

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Background: Post-acute care (PAC) goals emphasize functional recovery and reduced re-hospitalization, and PAC use has increased markedly since 2000. However, a recent concern is that lack of evidence-based guidelines for PAC decision-making creates opportunities for disparities in care, as in black/white disparities in PAC post-arthroplasty (JAMA 2018) and in PAC services among older community residents (JAGS 2017). Home health (HH) and skilled nursing facility (SNF) are most used but include substantially different levels of patient support (HH higher) and cost (HH lower). The inpatient rehabilitation facility (IRF) emphasizes physician involvement and care coordination, and IRF cost is higher. Outcomes following IRF may be superior to those following SNF for comparable patients with hip fracture and stroke diagnoses. Using Medicare claims data in USRDS files, we examined dialysis patient PAC patterns after lower-extremity amputation (LEA), fracture, and stroke, conditions for which kidney patients and blacks are at increased risk.

Methods: Prevalent dialysis patients with Medical Evidence data and Medicare Part A/B coverage, who were hospitalized at least once 11/2011-12/2012 followed by one or more PAC provider claims in 2012, were the study cohort (n=85,242). We identified IRF providers by matching CMS Certification Numbers with USRDS facility IDs in a provider crosswalk file. USRDS maintains HH and SNF analysis files. Dialysis patients' receipt of HH, SNF and IRF following LEA (n=10,290), fracture (n=10,119), and stroke (n=5,537) was observed in claims data.

Results: Median (IQR) age was 66 (58, 75) for HH users, 72 (63, 80) for SNF users, and 69 (60, 77) for IRF users. Women were 50% of HH and SNF users and 45% of IRF users; blacks were 32% (HH), 29% (SNF), and 30% (IRF). The percentage of dialysis patients with LEA, fracture and stroke was larger among IRF users than among SNF users, but SNF use far exceeded IRF use. Among those who received IRF services, blacks accounted for 39% of those with LEA and 31% of those with stroke, but only 17% of all IRF patients with fracture.

Conclusions: Equity is needed in PAC choices, and the challenge of "who belongs where" when multiple PAC options are available calls for well-designed studies of patients' rehabilitation needs and outcomes during an extended window of patient experience.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO714

Health Outcome Priorities of Older Adults with Advanced CKD and Concordance with Their Nephrology Providers' Perceptions

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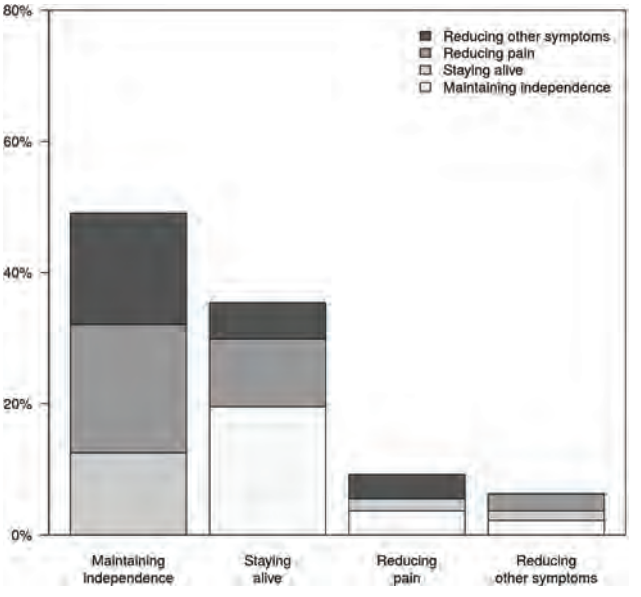
Background: Nephrology providers must understand their patients' priorities before recommending treatments, especially in older adults, for whom the tradeoffs in risks and benefits become more salient. We therefore elicited the health outcome priorities (HOPs) of older adults with advanced non-dialysis-dependent CKD; examined the association between priorities, self-reported health, and acceptance of common end-of-life scenarios; and measured concordance between patients' priorities and providers' perceptions of these priorities.

Methods: Patients ≥ 60 years old with non-dialysis-dependent CKD stages 4-5 recruited from a US nephrology clinic completed a validated HOP tool, self-rated health question, and end-of-life scenarios tool. For each enrolled patient, the nephrology provider completed the same HOP tool.

Results: Among 271 patients, 46% women, with median age 71, 49% chose maintaining independence as their top HOP, followed by staying alive (35%), reducing pain (9%), and reducing other symptoms (6%) (Figure). 49% ranked staying alive as their 3rd or 4th priority. There was no association between patients' self-rated health and top priority ranking (P=0.33), but for 6 of 13 common end-of-life scenarios (e.g., "are an emotional or financial burden to family"), reported acceptance significantly differed by top HOP. Patient-provider concordance on HOPs was overall poor (weighted kappa <0.1 for all 4 choices at any rank).

Conclusions: Nearly half of a group of older adults with advanced CKD ranked maintaining independence as their top HOP. Almost as many ranked staying alive as their last or second-to-last HOP. Nephrology providers demonstrated limited knowledge of their patients' priorities.

Funding: Private Foundation Support



Patients' 1st (main bars) and 2nd (sub-bars) HOP choices

SA-PO715

Factors Associated with Fractures in Octogenarian Patients with CKD

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Background: Fracture risk is increased in chronic kidney disease (CKD), and is associated with a higher mortality rate, mainly in the elderly patients. However, little is known regarding the factors associated with fracture risk in octogenarian patients with CKD

Methods: This study investigates the associations among bone turnover markers, cognition, comorbidities and prevalent fractures in a cohort of octogenarian CKD patients. The comprehensive geriatric assessment was applied by a geriatric and nephrologist team, and data obtained in two occasions were extracted from electronic charts including estimated glomerular filtration rate (eGFR) based on CKD-EPI equation, biochemical and demographic data, modified mini-mental state examination (MMSE), and Charlson Comorbidity Index (CCI). The median time between assessments was 174 days.

Results: The fracture prevalence was 26.5% in a sample of 49 patients (67% men, age 83±7 years). We did not find differences regarding age, gender, eGFR, proteinuria, calcium, phosphate PTH, serum vitamin D, supplementation of cholecalciferol, use of omeprazole, diuretic and calcitriol between those with and without fractures (p>0.05). However, patients

who had fracture had higher comorbidity - CCI >7 (92% *vs.* 8%; p=0.031) and lower MMSE scores (15±9 *vs.* 23±5; p=0.018). During the follow-up, we observed that patients with fracture had a rapid loss of renal function (eGFR -0.016 ± 0.040 *vs.* 0.019 ± 0.052 ml/min/1.73m^2/month, p=0.017).

Conclusions: Elderly patients with CKD who experience fractures are usually marked by more comorbidities, more cognitive deficits, and greater loss of renal function. A closing monitoring of falls and a multidisciplinary care is warranted to minimize fractures and understand the mechanisms of deteriorating renal function.

SA-PO716

Quantitative Gait Abnormalities and Risk of Falls in CKD

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Background: Physical function is impaired in people with chronic kidney disease (CKD), leading to a high risk of falls and the development of disability. It is not known whether gait abnormalities are present which may explain their risk of falling.

Methods: Quantitative and clinical gait assessments and kidney function measurement were performed in 330 community dwelling adults aged 65 years and older. Fall history was obtained every two months by standardized telephone questionnaire. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2. Cox proportional hazards models adjusted for demographics, comorbidities, and history of falls were created to examine the risk of falls.

Results: Participants with CKD had slower gait speed, as well as gait cycle abnormalities including shorter stride length and greater time in the stance and double-support phases. Cadence and stride length variability did not differ between CKD and non-CKD. Among people with CKD, lower eGFR was significantly associated with the severity of gait cycle abnormalities (per 10 mL/min/1.73m^2 lower eGFR: 3.6 cm (95% CI 1.4-5.8) shorter stride length; 0.7% (95% CI 0.3-1.0) greater time in stance phase; 1.1% (95% CI 0.5-1.7) greater time in double-support phase) after adjustment for demographics and comorbidities, and these abnormalities mediated the association of lower eGFR with slower gait speed. The associations with eGFR remained significant after adjustment for measures of cognitive function, muscle strength, and sensory neuropathy. On clinical gait exam, consistent with the quantitative abnormalities, short steps and marked sway or loss of balance with straight or tandem walking were more common among participants with CKD, yet the majority had no identifiable gait phenotype. A gait phenotype defined by these abnormal gait signs was associated with the risk of incident falls among participants with CKD (compared with non-CKD without gait phenotype: HR 1.8 (95% CI 1.2-2.9, p=0.01) for CKD with phenotype, HR 0.9 (95% CI 0.6-1.5, p=0.72) for CKD without phenotype).

Conclusions: The association of CKD with slow gait speed is explained by more proximal changes in gait. A newly identified gait phenotype predicts fall risk among older adults with CKD.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging

SA-PO717

Is Healthy Aging Associated with Preserved Kidney Function?

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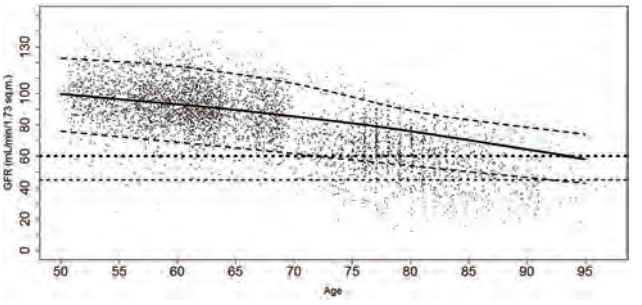
Background: Studies of kidney function based on creatinine in older adults have indicated a wide variation in age-related GFR decline and that healthy persons age with a well-preserved GFR. However, estimated GFR from creatinine is problematic in this age group because of confounding by sarcopenia. We investigated variation of measured GFR in the general population to study whether healthy ageing is associated with a stable GFR.

Methods: We measured iohexol clearance in three European cohorts (AGES-II-Reykjavik Study, Berlin Initiative Study and Renal Iohexol Clearance Survey (RENIS)) representative of the general population aged 50 to 97 years. The iohexol assays were calibrated across cohorts. We also registered the most important prevalent diseases representing risk factors for chronic kidney disease (diabetes, hypertension, cardiovascular disease and cancer). We predicted the median, 2.5th and 97.5th percentiles of cross-sectional GFR by age for persons without these risk factors using generalized additive quantile mixed models.

Results: We included 3002 persons. For persons > 90 years, the maximum observed GFR was 78 mL/min/1.73 m^2. For a person free from diabetes, hypertension, cardiovascular disease and cancer, the predicted 2.5th, 50thand 97.5th percentiles of GFR uniformly declined across the investigated age range. At 90 years, the predicted GFR values at these percentiles were 47, 64 and 78 mL/min/1.73 m^2, respectively. The 2.5th percentile crossed the 60 mL/min/1.73 m^2 level at 71.5 years and the 45 mL/min/1.73 m^2 level at 91.6 years (Figure).

Conclusions: Persons without the most important risk factors for chronic kidney disease are not exempt from age-related GFR decline. This indicates that GFR decline in these persons is caused by general ageing rather than by kidney disease.

Funding: Government Support - Non-U.S.



Points are individual measurements of GFR. Line (dashed lines) are predicted median (2.5th and 95th percentiles) under the statistical model for a person without diabetes, hypertension, CVD or cancer. Dotted horizontal lines indicate 45 and 60 ml/min/1.73 m^2.

SA-PO718

Differential Impact of Self-Reported and eGFR-Based CKD on the Outcomes of Community-Dwelling Elderly

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Background: Awareness of CKD has been low among affected patients, particularly elderly. However, whether such awareness is synonymous with the presence of laboratory-diagnosed CKD is currently unclear.

Methods: We retrospectively enrolled 2932 community-dwelling old adults (≥65 years) who received health examinations between 2013 and 2016 from a regional hospital. Clinical information and geriatric syndromes including depression, cognitive impairment, fall, quality of life, and visual disturbance were evaluated during medical interview. We compared differences in clinical features between those with and without self-reported or estimated glomerular filtration rate (eGFR)-based CKD and investigated their influences and interactions on the risk of CKD complications and geriatric syndromes.

Results: Among 2932 elderly (mean 73.4 years), 93 (3%) reported having CKD by history, while 585 (20%) had an eGFR <60 mL/min/1.73m2 persisted over 3 months. The prevalence of body mass index, waist circumference, and the incidence of fall differed only between those with and without eGFR-based CKD, but not self-reported CKD. A synergistic effect was found between self-reported and eGFR-based CKD regarding the CKD complication severity, including malnutrition (albumin), anemia (hemoglobin), dyslipidemia (serum cholesterol), and geriatric syndromes (cognitive and quality of life impairment) (Fig 1). Those with self-reported without eGFR-based CKD had specific features differing from others (Fig 2). Multivariate regression analyses showed that self-reported CKD exhibited better predictive efficacy for lower serum albumin and hemoglobin than eGFR-based CKD, while the latter outperformed the former for predicting lower serum cholesterol and a higher risk of cognitive impairment.

Conclusions: Among older adults, self-reported CKD may not be a surrogate for laboratory-diagnosed CKD and has an independent effect on CKD-related complications.

Funding: Clinical Revenue Support

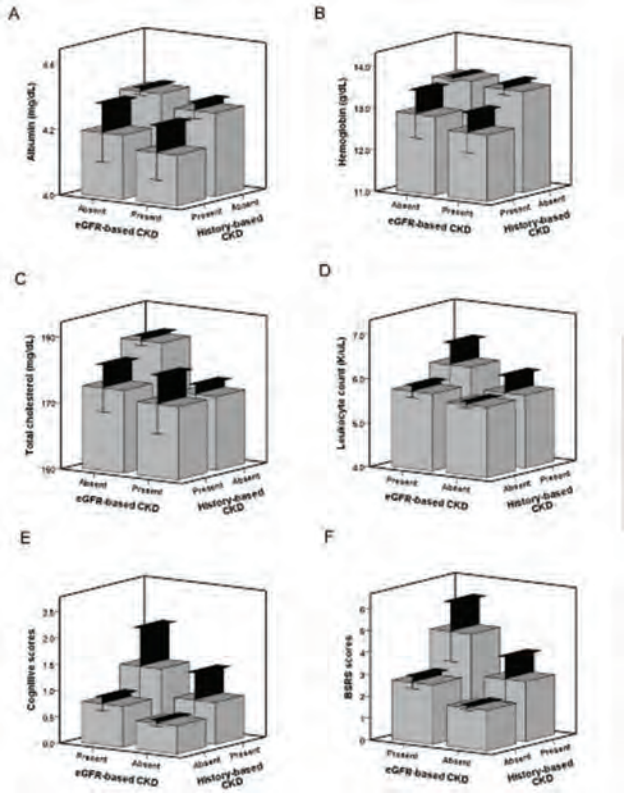

Fig 1

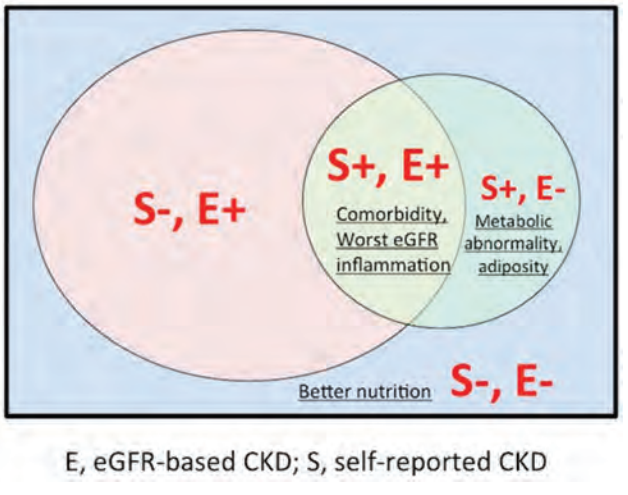

Fig 2

SA-PO719

A Census of Skilled Nursing Facility Utilization in Medicare Dialysis Patients

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Background: The size of the dialysis patient population that resides in a skilled nursing facility (SNF), either for short-term rehabilitation or long-term custodial care, is unclear. Medicare Part A covers SNF care only in specific circumstances, thus complicating interpretation of Medicare claims analysis. However, Yun *et al* (*Health Serv Outcomes Res Methodol*, 2010) proposed an algorithm that collects data from Part A claims for SNF care and Part B claims for physician visits in a SNF to identify Medicare beneficiaries who reside in a SNF. We implemented this algorithm in Medicare dialysis patients to identify an ongoing census of SNF utilization.

Methods: We analyzed data from the United States Renal Data System. For each calendar month from January 2013 to September 2015, we identified patients who underwent outpatient dialysis and carried Medicare Parts A and B as primary payer. According to the algorithm proposed by Yun *et al*, we ascertained 3 classes of claims among these patients: (1) Medicare Parts A claims submitted by a SNF; (2) Medicare Part B claims submitted by physicians, with place of service code 31 (SNF), 32 (nursing facility), or 33 (custodial care facility); (3) Medicare Part B claims submitted by physicians, with a *Current Procedural Terminology* code indicating evaluation or management of a nursing facility patient. In each calendar month, we estimated the percentage of patients residing in a SNF, and further classified patients as short-term or long-term residents.

Results: Monthly counts of Medicare dialysis patients increased from approximately 306,600 patients during the first quarter of 2013 to approximately 315,600 patients during the third quarter of 2015. The mean percentage of Medicare dialysis patients residing in a SNF during a month was 8.57%, with a range from 8.24% to 8.90%. Concurrently, the mean percentage of patients residing in a SNF for short-term care was 4.91%, whereas the mean percentage of patients residing in a SNF for long-term care was 3.66%. In the subset of patients with age ≥75 years, the mean percentage of patients residing in a SNF during a month was 14.85%, with 8.70% in a SNF for short-term care and 6.16% in a SNF for long-term care.

Conclusions: During any month, slightly more than 85 of every 1000 Medicare dialysis patients reside in a SNF, with a ratio of approximately 4 to 3 for short-term versus long-term care.

Funding: Commercial Support - NxStage Medical, Inc.

SA-PO720

Proteinuria Selectivity Index as a Predictor for Response to Therapy in Nephrotic Syndrome

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Background: The nephrotic syndrome (NS) is defined by heavy proteinuria due to abnormal increase of glomerular permeability and following hypoalbuminemia, hyperlipidemia and edema. Clinical manifestation of NS is highly variable due to the response to therapy. Selectivity index (S.I.) that commonly used for initial examination to differentiate minimal change disease (MCD). However, clinical application of S.I. is controversial for reliability. In present study, we evaluated clinical examinations including S.I. and prognosis of NS.

Methods: We retrospectively analysed 66 cases with NS who underwent renal biopsy in our hospital from 2013 to 2017. The clinical features at the time of renal biopsy, remission rate of initial therapy, and relapse rate of during the course of medication were evaluated in each primary glomerulonephritis.

Results: Of the 66 cases of NS, 47 cases were caused by primary glomerulonephritis. The incidence of MCD, idiopathic membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis (MPGN) were 55%, 32%, 9%, and 4%, respectively. Prevalence of each causal disease of NS was similar to data of Japanese renal biopsy registry. At the time of renal biopsy, levels of proteinuria (6.9g/day), degree of hypoalbuminemia (1.6 g/dL) and dyslipidemia in MCD were most severe as compared with other primary glomerulonephritis (P=0.02). Complete remission rate of initial therapy in each primary glomerular disease were 96% for MCD, 57% for MN, 50% for FSGS and 50% for MPGN, respectively. However, 42.3% patients with MCD recurred during the course of immunosuppression therapy, despite high frequency of remission. Of note, patients with 67% of MN and 75% of FSGS indicated high S.I. (less than 0.2). There was the trend that in cases with high S.I. patients with MN and FSGS indicated high remission rate by initial therapy.

Conclusions: Although levels of proteinuria and degree of hypoalbuminemia were most severe in MCD, remission rate of MCD was high by initial therapy. The recurrence rate is also high in patients with MCD. The high S.I. may be useful to expect response to initial therapy in patients with MN and FSGS.

SA-PO721

Clinical Outcomes and Effects of Treatment in Older Patients with Idiopathic Membranous Nephropathy

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Background: Membranous nephropathy (MN) is the most common primary glomerular disease diagnosed in older patients. However, few reports describe the clinical outcomes in older patients with idiopathic MN.

Methods: The outcomes of 135 patients with histologically proven MN were analyzed. 'Older' was defined as 60 years of age or older at the time of the renal biopsy. The rates of complete remission (CR), progression to end-stage renal disease (ESRD) and infection were compared between older and younger patients.

Results: The cumulative event rate for achieving CR was inferior (P = 0.012) and that for requiring renal replacement therapy was higher (P = 0.015) in older patients, and they had a greater risk of infection (P = 0.005). Older age was a significant predictor of a lower rate of CR from proteinuria (adjusted odds ratio [OR] = 0.51, 95% confidence interval [CI] 0.26–0.98), and was a robust predictor of infection (adjusted OR = 5.27, 95% CI 1.31–21.20). Conservative treatment was associated with a lower remission rate (P = 0.036) and corticosteroid treatment was less effective in achieving CR (P = 0.014),

in preventing progression to ESRD (P = 0.013) and in reducing infection (P = 0.033) in older patients. Cyclosporine treatment had comparable clinical outcomes with regard to CR, ESRD progression, and infection.

Conclusions: Older age was independently associated with inferior rates of CR and greater risk of infection. Treatment modalities affected the outcomes of older patients differently in that cyclosporine treatment is predicted to be more useful than corticosteroids in this population.

SA-PO722

Histological and Clinical Patterns in Glomerular Diseases of the Elderly: A Monocentric Study

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Background: Renal biopsy is an essential instrument for diagnosis of glomerular disease: according to data described in literature, this tool is overlooked in the elderly patients, which represent 15% of renal biopsies

Methods: Our Division is the regional hub of renal diseases in Sardinia, covering around 1.6 million of inhabitants, of whom 217.000 are eldery. We retrospectively reviewed histological and clinical data of all biopsy proven glomerular disease performed on ≥65 y/o patients from 2000 to 2016.

Results: 227 patients, with a mean age of 73.62 ± 6.41 years, were included in our analysis. 61.2% of them were younger than 75 y/o and 3.5% were older than 85 y/o (with 3 patients > 99 y/o). The annual incidence of biopsy proven glomerular diseases in the elderly population increased progressively in the considered period, from 4 cases/100.000 exposed in 2000 to 11.5 cases/100.000 in 2016. Membranous Nephropathy was the most recurrent histological diagnosis (23.8%), followed by Minimal Change Disease (13.2%), AL amyloidosis (9.3%) and MPO-ANCA vasculitis (9.3%). Our analysis showed few significative differences when patients were classified according their age (65-74, 75-84 and ≥85 years old): diabetic nephropathy was more frequent in the third group (p 0.001) and MPO-ANCA vasculitis were more frequently diagnosed in group 1 and 2 than in group 3 (p 0.05). Interestingly, incidence of MGRS and malignant clones with renal involvement rose from no cases in 2000-2003, to a peak of 33% in 2013

Conclusions: Incidence of glomerular diseases is increasing, likely due to more comprehensive indications to renal biopsy from 2000 to 2016. Histological patterns revealed a substantial homogeneity in among the three subgroups analyzed. Coherently, most of patients benefited of a specific treatment. Renal biopsy is, therefore, an irreplaceable tool even in a selected elderly population

Annual number of new biopsy proven diagnosis of glomerular disease in elderly patients at Ospedale Brotzu Nephrology Department (2000-2016)

SA-PO723

Functional Decline and Associated Risk Factors in a Survivor Cohort of Older Dialysis Patients

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Background: At least 50% of older adults undergo functional decline or die within the first 6 months of dialysis. Little is known about functional decline in older adults who survive the first 6 months of dialysis. We sought to identify risk factors for functional decline, as measured by Short Form-12 physical component score (SF-12 PCS) change, in a survivor cohort of older dialysis patients.

Methods: We conducted a retrospective study of 3,284 adults aged ≥ 65 years with ≥ 6 months of hemodialysis and complete SF-12s in 2012 and 2013. We calculated PCS change as second minus first PCS for individuals with PCSs ≥ 300 days apart. Using a multivariable linear regression, we modeled PCS change and adjusted for baseline age, gender, race, Medicaid status, access type, Kt/V, albumin, hemoglobin, time on dialysis, Charlson index, hospitalization rate, and days between PCSs. In post hoc analysis, we compared individuals in categories: clinically relevant (CR) PCS decline or increase (PCS change > 3) and no CR change.

Results: Of 3,284, 801 (24.4%) died and an additional 1,112 (33.9%) did not have 2 PCSs ≥ 300 days apart. Our analytic cohort included the remaining 1,371 (41.7%) who had 2 PCSs ≥ 300 days apart (mean 399 ± 74 days), mean time on dialysis 6.1 ± 3.1 years, and mean PCS change -0.9 ± 9.6. Cohort members with time on dialysis < 5 years had significant but modestly smaller decline in PCS compared to those with ≥ 5 years (p=0.03) (Table), but the regression did not reveal any significant associations between patient characteristics and PCS change. The proportion with CR PCS decline, increase, or no CR change were 39.3% (n=539), 32.2% (n=442), and 28.4% (n=390), respectively. Mean hospitalization rate was highest among those with CR PCS decline (2.0 ± 3.7) compared to those with CR increase (1.7± 3.5) or no CR change (1.4 ± 2.6) (p<0.05).

Conclusions: In this survivor cohort, nearly 25% died and 40% of those who did not die had CR PCS decline within 2 years. Although age, race, time on dialysis, and access type were not associated with SF-12 PCS change, one potential risk factor for CR PCS decline is recurrent hospitalizations.

Funding: Other NIH Support - Kl2TR001115, R03AG050834, P30AG028716

Mean Time on Dialysis and Relation to SF-12 PCS Change

	Time on Dialysis (years)	SF-12 PCS Change
Time on Dialysis < 5 Years (46%, n=628)	3.9 ± 0.7	-0.3 ± 9.5
Time on Dialysis ≥ 5 Years (54%, n=743)	7.9 ± 3.1	-1.5 ± 9.7

(Mean ± SD)

SA-PO724

Preliminary Satisfaction and Acceptability Ratings of a Supportive Care Video Decision Aid for Elderly Patients with Advanced CKD

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Background: The benefits of dialysis remain uncertain for elderly and frail patients with advanced chronic kidney disease (CKD). Recent studies have not shown an improvement in survival or quality of life for many such patients on dialysis, thus making supportive kidney care a viable option. Furthermore, decision aids to promote informed decision making about supportive care are lacking. As part of a randomized controlled trial (RCT) to test preliminary efficacy of a video decision aid on knowledge of supportive care among elderly patients with advanced CKD, we explored satisfaction and acceptability ratings among participants who received video education.

Methods: Eligible patients are age ≥ 65 years, English-speaking, and receive primary nephrology care at a large medical center in Boston, MA. The video was developed in an iterative process by a national panel of nephrologists with an expertise in shared decision making in this patient population. The video includes images of patients undergoing hemodialysis, peritoneal dialysis or no dialysis.

Results: A total of 64 out of eligible 100 patients have enrolled in the RCT and 43.8% (n=28) have been randomized to video education. Satisfaction and acceptability ratings of the video decision aid are displayed in Table 1.

Conclusions: Most patients who have received the video decision aid thus far in the RCT report high satisfaction and acceptability ratings. These findings contradict historical beliefs that patients are fearful or averse to learning about supportive care. Future research will determine whether a supportive care video decision aid improves supportive care knowledge for elderly patients with CKD.

Funding: NIDDK Support

Table 1. Satisfaction and acceptability ratings of a supportive care video decision aid

Question	Very N (%)	Somewhat N (%)	A little N (%)	Not N (%)
How satisfied were you with this video?	17 (60.71%)	9 (32.14%)	1 (3.57%)	1 (3.57%)
How helpful was the video in forming your preferences for end-stage renal disease care?	17 (60.71%)	7 (25.00%)	2 (7.14%)	2 (7.14%)
How comfortable were you when you watched this video?	21 (75.00%)	6 (21.43%)	0	1 (3.57%)
	Definitely N (%)	Probably N (%)	Probably not N (%)	Definitely not N (%)
Would you recommend this video to other people who are thinking of making similar decisions?	18 (64.29%)	8 (28.57%)	2 (7.14%)	0

SA-PO725

Effect of Pentoxifylline on Pericyte in Aging Mice Kidney

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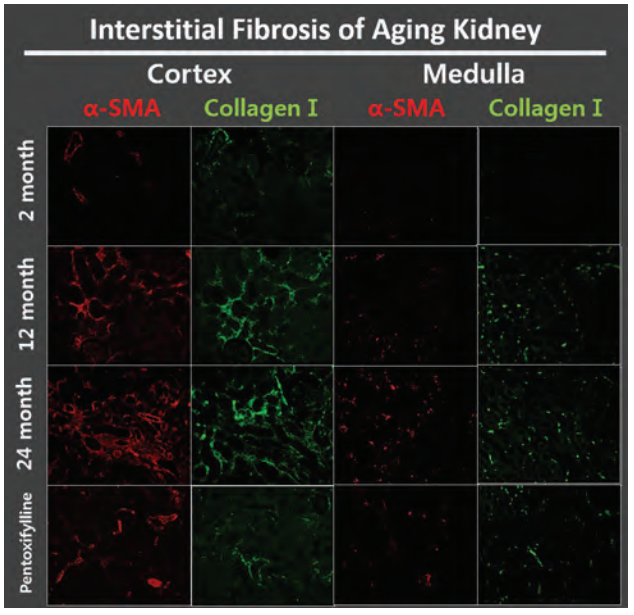
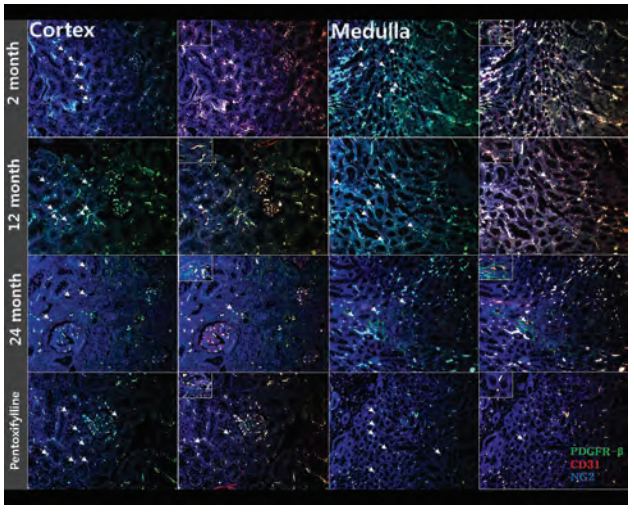
Background: In aging kidney, oxidative stress and inflammation lead to a decrease in renal function. Recent studies related to the aging process of the kidneys have shown that pericyte is a progenitor cell of myofibroblast, and the relationship between renal fibrosis and pericyte has been reported. In this study, we investigated the effect of pentoxifylline on pericyte.

Methods: 2, 12, and 24-months-old mice were assigned to control group. (Each group consisted of 7 mice) Seven 18-month-old mice were treated with pentoxifylline for 6 months. Pericyte was confirmed by PDGFR-beta and NG2 double stain.

Results: Abundant microvascular density was detected in kidney of 2 and 12-months-old young mice. In 24-months-old mice kidney, CD31 stain decreased and collagen I stain increased which means progression of renal fibrosis. In the Pentoxifylline group, the collagen I stain was significantly decreased and the microvascular density was increased compared to the 24 months group. In the 24-months group, the pericyte marker was significantly decreased and the endothelial contact was disappeared. However, the pericyte was not decreased in the pentoxifylline group and maintained their perivascular location.

Conclusions: Pentoxifylline attenuates tubulointerstitial fibrosis in aging mice kidney via pericyte.





SA-PO726

Serum Stem Cell Factor Level Predicts Declined Kidney Function in Healthy Adults

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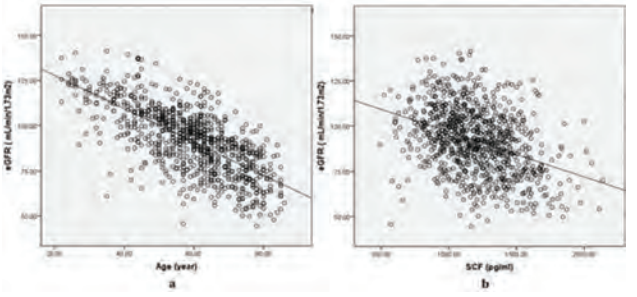
Background: Stem cell factor (SCF), the ligand of mast cells' c-kit receptor, actively participates in the organ reconstruction and fibrosis in various diseases. Recent studies also revealed that SCF plays an important role in kidney diseases, including nephrotoxic nephritis and crescentic glomerulonephritis. However, it remains unclear whether SCF play a role in the ageing of kidney. This study was designed to investigate the relationship between serum SCF level and the function of kidney aging.

Methods: In this study, we collected the data of serum SCF, estimated glomerular filtration rate (eGFR) calculated by CKD-EPI equation and other biological indicators in a Chinese Han and investigated the relationship of SCF and the renal function in the aging process, so as to search new biomarkers of kidney aging. The levels of serum SCF (R&D Systems, Min., U.S.A) were tested by enzyme-linked immunosorbent assay (ELISA). Then correlation analysis, redundancy analysis and multiple linear regression were done to select potential indicators to estimate renal function decline. We divide subjects into youth (age<45), middle-aged (45≤age<60), young elderly (60≤age<75) and elderly (age≥75) groups. SCF levels were compared among different age groups and genders using one-way ANOVA (P<0.05) and student t test (P<0.05) respectively.

Results: 1. Demographic features Initially, 1,368 volunteers were enrolled. After the screening, 892 healthy participants of mean age 59.0 ± 13.4 years were finally enrolled. 2. **Age and SCF level are predictors of eGFR**. The final relationship between eGFR and SCF level was expressed as: eGFR = 154.486 – (0.846 × age) – (0.011 × SCF level). Fig. 1. Associations of predictive variables with the estimated glomerular filtration rate (eGFR).

Conclusions: In conclusion, we investigated the relationship between SCF and eGFR in the ageing process of kidney, and revealed that SCF is closely related with eGFR. Finally, we constructed an eGFR estimated equation for kidney aging.



SA-PO727

Impact of Aging on Kidney and Gut Cross-Talk in AKI

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Background: Recently, the high incidence of acute kidney damage (AKI) and the mortality rate in elderly population are important healthcare burdens. Although, experimental studies showed that interaction between the kidney and the remote organ (lung, heart, bowel, etc.) could significantly affect the outcome of AKI, the impact of aging on the remote organ effects of AKI are still unknown. Here, we investigated the effects of aging on AKI outcomes, especially kidney and gut crosstalk in animal models.

Methods: In old (10mo) and young (2mo) C57BL/6 mice, 25min bilateral ischemia reperfusion injury (IRI) was applied, and then expression of inflammatory cytokines as well as functional and histological changes of kidney and colon were examined on day 1 and 3 after IRI. Intestinal barrier integrity was assessed by permeability to FITC-dextran.

Results: There was no significant difference in renal function between old and young mice on day1 post IRI, but the mRNA expression of IL-6, TNF-α, IL-12 and IFN-r was significantly higher in the kidneys of old mice than in young mice on day 1, and the expressions of TNF-α and IL-12 were also increased in old mice on day3. The balance of the M1/M2 markers (iNOS/mannose receptor) skewed towards M2 phenotype on day3 post IRI in young mice, however it was significantly blunted in old mice. Interestingly, this intrarenal inflammatory milieu in old mice was similarly observed in the colon. In the aged colon, TNF-α and IL-12 mRNA expression was significantly higher and mannose receptor and arginase-1 expression was lower than in young mice on day3 post IRI. Increased inflammatory cytokines in the colon were accompanied by an increase in TUNEL-positive apoptotic colon epithelial cells and increased permeability of the colon in old mice. The AKI-induced "leaky gut" showed a strong positive correlation with high TNF-α expression in mesenteric lymph nodes, suggesting that persistent inflammation of the kidney after IRI in old mice contributes to increased colon inflammation and permeability.

Conclusions: We conclude that AKI in old mice results in a more M1-related inflammation in the kidney and colon, and worsens AKI-induced "leaky gut". These results suggest that strategies for targeting intestine might provide novel therapeutic opportunities for reducing poor outcomes in elderly patients with AKI.

SA-PO728

Cystatin C and Cystatin C-Based GFR Markers for Prediction of Mortality in Elderly Patients with CKD

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Background: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C is an accurate marker of kidney function and also has prognostic utility in CKD patients. The aim of our study was to determine the prediction of cystatin C and cystatin-C based markers of kidney function (eGFR) on long-term survival in elderly CKD patients.

Methods: In our study 58 adult Caucasian patients, older than 65 years (50% women; mean age 73 years; range from 65 to 85 years), were included. Patients with known malignancy, thyroid disease and/or on steroid therapy were not enrolled in the study. In each patient ^{51}CrEDTA clearance, serum cystatin C (immunonephelometric method) and eGFR using two cystatin C-based formulas (CKD-EPI cystatin and FAS cystatin) were determined on the same day and patients were then followed for 12 years or until their death.

Results: The mean values: ^{51}CrEDTA clearance 53.3±17.4 ml/min/1.73m^2, serum cystatin C 1.79±0.5 mg/l, CKD-EPI cystatin 36.1±13.6 ml/min/1.73m^2, FAS cystatin 40.1±11.7 ml/min/1.73m^2. In the follow up period of 12 years 48 (83%; 24 women and

24 men) of our elderly CKD patients died. Cox regression analysis showed different hazard ratios (HR) for death: for ^{51}CrEDTA clearance HR was 1.024 (95% CI 1.001-1.042; P=0.009), for serum cystatin C HR was 2.021 (95% CI 1.264-3.229; P=0.003), for CKD-EPI cystatin HR was 1.034 (95% CI 1.008-1.062; P=0.01), for FAS cystatin HR was 1.041 (95% CI 1.010-1.071; P=0.008).

Conclusions: Our results show that in elderly CKD patients the highest hazard ratio for all-cause mortality has serum cystatin C compared to the cystatin C-based markers of kidney function (eGFR).

SA-PO729

Chloride Channel Accessory 1 Protein Could Be a Novel Regulatory Factor in Aging-Related Changes in the Kidney

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Background: We have reported that aging induces kidney fibrosis, albuminuria and impairs clearance function in mice (Sataranatarajan K, Aging Cell, 2012). The underlying mechanisms are not well understood. In the current study, we took an unbiased discovery approach to identify potentially novel mechanisms.

Methods: We performed RNA Seq on renal cortical samples from C57BL6 male young mice (5 months old, n=4) and old mice (30 months old, n=3). Next, we directly verified changes in mRNAs that showed the maximum increase by performing qRT-PCR. We studied changes in renal cortical chloride channel accessory protein 1 (CLCA1) protein expression by immunoblotting (male and female young and old mice, n=6 to 10 per group). To study if changes found in mice were evolutionarily conserved, we studied kidney tissue from non-human primate marmosets (young 3 yrs of age, old 16 yrs of age, male and female, n=8-10 per group).

Results: On RNA Seq, we found CLCA1 as one of the mRNAs that showed most significant increase in old vs. young mice (p=7.6E-27). We performed qRT-PCR to directly test the status of CLCA1 mRNA; we confirmed a 10-fold increase in renal cortex of old male mice compared to young mice. Immunoblotting showed a 2-fold increase in CLCA1 protein in renal cortex of old male mice but not old female mice. We have reported that renal hydrogen sulfide (H2S) generation is reduced in aging mice; administration of sodium hydrosulfide (NaHS, a source of H2S) to 19 month-old mice for 5 months ameliorates aging-related kidney changes in mice (Lee HJ, GeroScience, 2018). NaHS administration decreased renal cortical CLCA1 expression by 40% compared to untreated Control old mice. On immunohistochemistry CLCA1 was expressed mostly in the tubules in young marmosets. Renal cortical CLCA1 expression was increased 2-fold in old male and female marmosets.

Conclusions: Increase in renal cortical CLCA1 expression correlates with aging-related kidney dysfunction in male mice; it appears to be evolutionarily conserved from mice to marmosets. CLCA1 activates Ca^{++}-dependent chloride channel TMEM16A that is expressed in kidney proximal tubules and podocytes. Mechanisms by which CLCA1 contributes to renal aging need to be explored.

Funding: Veterans Affairs Support

SA-PO730

Loss of Asparaginyl Endopeptidase Accelerates Cellular Senescence and Boosts Age-Related Renal Interstitial Fibrosis

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Background: Asparaginyl endopeptidase (AEP) is highly expressed in the renal tubuli while significantly declined in the elderly ones. AEP exhibits anti-fibrotic effect in the mouse model of unilateral ureteral obstruction. The role of AEP in the age-related fibrosis is obscure.

Methods: We compared the level of renal interstitial fibrosis and renal tubular senescence in the wild-type (wt) and AEP knockout (*AEP$^{-/-}$*) mice at different ages. We established stable AEP-knockdown HK2 cell line (HK2-shAEP) and analyzed the cellular senescence. Then, we co-cultured HK2-shAEP with fibroblasts and assessed the activated indexes of fibroblasts. We also evaluated the lysosomal pH and change of autophagy upon AEP downregulation.

Results: Renal tubular senescence was obvious from the 3rd months in *AEP$^{-/-}$* mice with significant accumulation of Fibronectin and Collagen I/III in the renal interstitial area. Levels of serum creatinine and urea nitrogen were 2 times higher than that in wt mice at the 6th months. *In vitro*, AEP knockdown induced the cell cycle arrested at G1/S with increased expression of β-Gal, p21^{cip1} and p16^{ink4a}. HK2-shAEP cells expressed and secreted more pro-fibrotic cytokines, including TGF-β1, CTGF and PAI-1. Co-culture with HK2-shAEP promoted the differentiation, migration and proliferation of fibroblasts. Blocking the senescent signaling via downregulating p21^{cip1} or p16^{ink4a} could reverse the accelerated senescence and pro-fibrotic effects of HK2-shAEP cells. Assessment of autophagy and lysosomal PH showed that knockdown of AEP led to impaired autophagy flux and disturbance of lysosomal homeostasis, accompanying with accumulation of ROS. Autophagy inducer rapamycin or anti-senescence agent spermidine could reverse the senescent state of HK2-shAEP cells. *in vivo*, both spermidine and genetical mutant of p53 alleviated renal interstitial fibrosis of *AEP$^{-/-}$* mice.

Conclusions: The study defines the role of AEP in regulation of autophagy via maintainance of lysosomal hemostasis in renal tubuli. Loss of AEP accelerates tubular senescence and boosts aged-related interstitial fibrosis. Therefore, our finding highlights AEP as a potential biomarker of age-related kidney diseases and therapeutic target.

Funding: Government Support - Non-U.S.

SA-PO731

Marmoset - A Non-Human Primate Model to Study Aging Associated Changes in the Kidney

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Background: Because of the genetic distance between rodents and humans an appropriate primate model to study kidney aging is needed. We evaluated whether the marmoset can fill this need by studying kidney parameters in healthy young and aged marmosets of both sexes.

Methods: We studied 4 young male (average age 3 years) and 4 young female (average age 2.8 years) marmosets, and, 5 aged male (average age 16.1 years) and 5 aged female (average age 15.9 years) marmosets. We examined structural changes in the kidney by H and E and PAS stains. Immunoblotting was employed to study changes in the expression of proteins. Measurement of urinary albumin and protein was by ELISA and Bio-Rad assay, respectively.

Results: Aging was associated with glomerulosclerosis, tubulointerstitial fibrosis and arteriolosclerosis constituting nephrosclerosis in both sexes; patchy areas of interstitial nephritis were seen. The renal cortical content of matrix proteins laminin, type III collagen, and fibronectin was increased on immunoblotting. Functionally, aging resulted in an increase in urinary albumin to creatinine ratio and protein to creatinine ratio in association with reduction in kidney expression of nephrin. There was a robust correlation between histologic markers of fibrosis and albuminuria and proteinuria. We explored signaling pathways as potential mechanistic events. Aging in males, but not in females, was associated with reduced renal cortical activity of AMP-activated protein kinase (AMPK) and a trend toward activation of mechanistic target of rapamycin complex 1 (mTORC1); upstream of AMPK and mTORC1, Akt and insulin–like growth factor 1 receptor were activated. In both sexes, aging promoted renal cortical expression transforming growth factor β-1 and phospho-Smad3. Since kidney fibrosis is associated with deficiency of hydrogen sulfide synthesis in renal disease, we examined its status in aging marmosets. While the expression of cysthathionine β-synthase, an enzyme involved H_2S synthesis, was reduced in both aged males and females, decreased H_2S generation was seen only in the males.

Conclusions: Our studies show that the marmoset is a valid model to study kidney aging; some of the signaling pathways involved in renal senescence differ between male and female marmosets.

Funding: Veterans Affairs Support

SA-PO732

Sirt1-Induced Hypoxia-Inducible Factor-1α Deacetylation Attenuates Tubulointerstitial Damage in Aged Kidney

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Background: Although it is well known that the expression and activity of Sirt-1 are decreased in the aged kidney, the role of interaction between Sirt-1 and hypoxia-inducible factor (HIF)-1 is largely unknown. Here, we investigated whether HIF-1α could be a deacetylation target of Sirt-1 and the effect of their interaction on age-associated renal injury.

Methods: Five-week-old (young) and 24-month-old (old) male C57Bl/6J mice were assessed for their age-associated changes. To clarify the underlying mechanisms, HK-2 cells were exposed to hypoxia. The effect of chronic activation of HIF-1α was investigated using tubular cell-specific HIF-1α transgenic mice.

Results: Kidneys from aged mice showed increased infiltration of CD68 positive macrophages, higher expression of extracellular matrix (ECM) proteins, and apoptosis than young controls. They also showed decreased expression of Sirt-1 along with increased acetylated HIF-1α. Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 level, which is regulated by HIF-1α, was significantly higher in aged mice suggesting that HIF-1α activity is increased. In HK-2 cells, Sirt-1 inhibitor sirtinol or siRNA-mediated knock-down of Sirt1 enhanced apoptosis and ECM accumulation whereas Sirt1 over-expression induced the opposite changes. During hypoxia, Sirt-1 was down-regulated, which allowed the acetylation and activation of HIF-1α. Resveratrol, a Sirt1 activator, effectively prevented hypoxia-induced production of ECM proteins, mitochondrial damage, reactive oxygen species generation, and apoptosis. The findings that Sirt1-induced deacetylation of HIF-1α inhibits HIF-1α activity were also confirmed by Sirt1 over-expression under hypoxic condition and by resveratrol treatment or Sirt1 over-expression in HIF-1α transfected HK-2 cells. Finally, we confirmed chronic activation of HIF-1α promoted apoptosis and fibrosis using tubular cell-specific HIF-1α transgenic mice.

Conclusions: Taken together, our data suggest that Sirt-1-induced deacetylation of HIF-1α may have protective effects against tubulointerstitial damage in aged kidney.

Funding: Government Support - Non-U.S.

SA-PO733

Podocyte-Specific Knockout of the Transcriptional Factor C/EBPα Aggravates Podocyte Senescence and Kidney Injury in Aging Mice

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Background: CCAAT/enhancer binding protein α (C/EBPα) is a widely expressed transcriptional factor, participating in regulation of metabolism, inflammation and differentiation. We have previously showed that C/EBPα expression was suppressed in glomerular cells, particularly in podocytes, in focal segmental glomerulosclerosis (FSGS), and have demonstrated its anti-inflammatory effects in FSGS in *vivo* and in *vitro*. And as terminally differentiated cells, podocytes are vulnerable to stress and play a central role in kidney aging. However, the specific role of C/EBPα in kidney aging remains undefined.

Methods: By crossing floxed C/EBPα mice with Pod-Cre mice, we generated podocyte-specific C/EBPα knockout mice. Both the homozygous transgenic mice (KO) and their wild-type littermates (WT) were sacrificed at 3 and 20 months of age as young and aging groups, respectively. Immortalized mouse podocyte line with transient C/EBPα overexpression and induced senescence by adriamycin (ADR) were used for in vitro experiments.

Results: KO-Young kidneys showed little morphological or gene expression change except reduced C/EBPα compared to WT-Young kidneys. In WT-Aging mice, foot process effacement, positive senescence-associated β-galactosidase (SA-β-Gal) staining accumulation in podocytes, glomerulosclerosis and tubular basement membrane thickening occurred, accompanied by epithelial-mesenchymal transdifferentiation and AMPK-SIRT1-PGC1α-mitochondria axis inhibition in tubular cells. These were aggravated in KO-Aging mice, as well as significant albuminuria and decreased podocyte markers occurred. In ADR induced senescent model in cultured podocytes, C/EBPα was down-regulated, and vimentin, CTGF, VEGFA and IL-6 increased. These phenotypes was rescued by C/EBPα overexpression.

Conclusions: These findings suggest that loss of C/EBPα accelerates podocyte senescence, aggravating glomerulosclerosis and tubular injury in aging mice. Targeting C/EBPα in podocytes may be a novel strategy for improving kidney aging.

Funding: Government Support - Non-U.S.

SA-PO734

Hospitalizations within the First Year and Survival in Patients Aged Above 80 Who Start Dialysis in Emergency

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Background: Implementation of dialysis in octogenarians is a debated question on account of an unfavourable short-term prognosis. We therefore analyzed what is the impact of planned implementation versus emergency dialysis on first year hospitalizations and survival in this population.

Methods: During the past 16 years, all patients who started maintenance dialysis in our unit were reviewed. Patient's demographic and clinical characteristics were collected. Emergency implementation of maintenance dialysis was defined as no prior referral to a nephrologist one month before starting dialysis.

Results: From 2000 to the end of 2016, 684 patients started maintenance dialysis in our unit, of whom 96 were aged 80 and above. Mean age was 83 ± 2.4 years. Hemodialysis and peritoneal dialysis were implemented in 78 and 18 patients respectively. There were 66% male, 33 % diabetic and median eGFR at start of dialysis was 8± 3 ml/min. Emergency dialysis was implemented in 44% of the patients. Overall mean survival was 33 ± 3 months. One-year mortality was 36.4% in referred patients who had emergency dialysis and 11.5% patients with planned dialysis. One-year mean survival was 334±12 days in patients with planned dialysis implementation versus 274± 21days in those who had emergency dialysis ($p< 0.004$). In a multivariate analysis including prior referral, age, gender, comorbidity score and dialysis modality, one-year survival was only associated with prior referral (HR: 0.36; 95% CI. 013-0.98). In patients with planned dialysis implementation, one -year hospitalization-free days were 269±108 versus 212± 136 days in those who had emergency dialysis ($p< 0.03$).

Conclusions: Prior referral to nephrologists substantially increase one-year hospitalization-free days and survival after dialysis implementation in ESKD patients aged above 80.

SA-PO735

Risk of the Dialysis Disequilibrium Syndrome in Japanese Elderly

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Background: In Japan, there is an increased number of elderly patients with end-stage renal disease (ESRD). Elderly patients are more likely to develop a dialysis disequilibrium syndrome (DDS). To improve their quality of life, recognizing the mild symptoms of DDS is necessary. High level of blood urea nitrogen and severe metabolic acidosis are regarded as risk factors of DDS, but the accurate incidence of them remains unclear in Japan. Here, we aim to evaluate the incidence and risk of mild to severe DDS for the well-managed ESRD patients in a single facility.

Methods: A total of 75 ESRD patients aged over 65 years were included, who had undergone scheduled hemodialysis after arteriovenous fistula creation at our hospital from 2015 through 2017. The DDS, or primary outcome, is defined as the mild to severe symptoms developing at the first dialysis treatment like headache, nausea and/or vomiting, appetite loss, muscle cramp, psychomotor agitation, and convulsions. Demographics and clinical data obtained before first dialysis were assessed as covariates to calculate the adjusted odds ratio in the multivariate analysis.

Results: The DDS was observed in 23 of 75 patients of interest. Headache was the most common symptom of them. Logistic regression model revealed that low level of eGFR, excessive fluid removal, and non-medication of sodium bicarbonate were independently associated with DDS in the ESRD elderly. Oral sodium bicarbonate was administered to 36 patients. Significant difference was found in serum [HCO_3^-] between two groups with and without oral sodium bicarbonate (median 19.7 mEq/L [IQR: 13.1 - 29.1] vs. median 17.0 mEq/L [IQR: 6.70 - 27.7], $P = 0.015$) using Mann-Whitney U test. These suggested that efficient dose of bicarbonate were taken in the ESRD patients. After adjustment for covariates, oral sodium bicarbonate for preventing metabolic acidosis significantly reduced the incidence of primary outcome (adjusted odds ratio 0.21 [95%CI: 0.06 - 0.77], $P = 0.019$).

Conclusions: At the first dialysis treatment for the ESRD elderly, we should pay attention to metabolic acidosis as a risk developing DDS. The effectiveness of oral sodium bicarbonate is necessary to be examined by prospective studies.

SA-PO736

Outcomes Among Those Receiving Veterans Affairs (VA) Insurance in the United States

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Background: Recent policy initiatives seek to address barriers to subspecialty care for veterans based on clinic wait times and geographic distance through a mechanism of outsourcing to community providers. Due to limited Veterans Health Care Service (VAHCS) capacity to provide care to those with end-stage kidney disease (ESKD), we set out to describe characteristics, trends and important healthcare outcomes among Veterans Affairs (VA) insured patients from 1995-2012.

Methods: United States Renal Data System (USRDS) combined with United States (US) census data was used to compare baseline characteristics and adjusted outcomes for mortality and transplantation among those initiating maintenance renal replacement therapy receiving VA insurance.

Results: A total of 32,035 VA insured patients initiated maintenance RRT over the time period of 1995-2012 with follow up extending to June 30th, 2014. Compared to 1995-1996, overall incidence of RRT initiation increased in a linear fashion (IR 1.94, 2011-2012). Subgroups experiencing the greatest increase included those > 65 years of age (IR 2.16), female (IR 2.54), and white patients (IR 2.35). Compared to 1995 - 2004, VA insured patients initiating between 2005 – 2012 were more likely to be 40-64 years of age (51.3% vs. 50%), > 65 years of age (47.3% vs. 46.4%), and less likely to be female (8.4% vs. 9.4%) or Hispanic (8.7% vs. 10.9%). No difference in mortality hazard was observed in demography adjusted models (AHR 1.03; CI 0.99 – 1.08), however, VA insured patients were more likely to be listed for (AHR 1.23; CI 1.10 – 1.37) and to receive kidney transplantation (AHR 1.19; CI 1.03 – 1.38).

Conclusions: In conclusion, VA insured patients initiating RRT has increased significantly in recent years. While older patients are increasingly likely to have initiated RRT in recent years, the finding of no mortality difference in adjusted models is reassuring.

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SA-PO737

Impact of Hemodialysis Hours on Outcomes in Elderly Hemodialysis Patients

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Background: Longer treatment time is associated with improved outcomes in hemodialysis (HD) patients. Longer treatment times pose additional challenges in the elderly, who are more likely to suffer from conditions like arthritis which make sitting for long periods uncomfortable. The aim of this study is to determine whether or not a mortality benefit exists with longer treatment time in elderly (age ≥ 65 years) HD patients.

Methods: Data was obtained from the Australia and New Zealand Dialysis & Transplant Registry. Incident patient on thrice weekly HD were included if they were ≥65 years of age at HD commencement. Subjects entered the analysis at 90 days after start of HD. The exposure of interest was treatment time (hours per HD session) at HD commencement categorised into 5 groups. The primary outcome was all-cause mortality. Censoring events were transplantation, switch to another dialysis modality, recovery of kidney function, or loss to follow up. Cox regression models adjusting for age and treatment time and age interaction were assessed.

Results: 8992 subjects were included in the analysis with 30541 person-years of data. The incidence rate of death was 16 per 100 person-years. The risk of death decreased with increasing duration of dialysis. However, inclusion of age in the model attenuated this association. The interaction of age and hours was not significant (p=0.895). Inclusion of gender in the model did not alter associations.

Conclusions: Longer treatment times are associated with reduced risk of mortality in a dose-response relationship. However, once adjusted for age, there is no longer a significant mortality benefit to longer hours. This suggests that in the elderly, longer dialysis hours may not reduce mortality risk, and other factors such as quality of life should be considered in a dialysis prescription.

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age	1.03 (1.02-1.04)	<.001	1.05 (1.04-1.06)	<.001
Treatment Time				
<4 hours	1.00		1.00	
4 to <4.5 hours	0.85 (0.77-0.95)	0.004	0.95 (0.60-1.50)	0.834
4.5 to <5 hours	0.72 (0.64-0.81)	<.001	0.90 (0.37-2.18)	0.820
5 to <5.5 hours	0.70 (0.62-0.78)	<.001	0.92 (0.25-3.37)	0.897
>5.5 hours	0.57 (0.36-0.90)	0.016	0.86 (0.15-4.90)	0.866

SA-PO738

Associations of Cognitive Function and Education Level with All-Cause Mortality in Adults on Hemodialysis: The COGNITIVE-HD Cohort Study

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Background: Cognitive impairment is common in dialysis patients and is associated with lower education levels. Associations of cognitive impairment and education with mortality in dialysis patients are understudied. We aimed to assess the association between cognitive function and all-cause mortality in adults on hemodialysis, and the independent and interactive effects of education.

Methods: We recruited adult hemodialysis patients from 20 centers in Italy, assessing their cognitive function on 5 domains (memory, attention, executive function, language, perceptual-motor function) with 10 neuropsychological tests, and their self-reported education. We examined associations of cognition (any domain impaired, number of domains impaired, global score from principal components analysis of all tests) and education with all-cause mortality in multivariable Cox models.

Results: Of 958 patients, 676 participated (70.6%). Patients' median age was 70.9 years (IQR: 59.9-78.1) and 262 (38.8%) were female. Education levels were 338 (50.0%) primary/less, 163 (24.1%) lower secondary, 175 (25.9%) upper secondary/higher. Of 664 with data, 527 (79.4%) were impaired on at least 1 domain. Median follow-up was 3.3 years (IQR: 1.9-3.6) and there were 206 deaths in 1874.2 person-years. Adjusted HR (95% CI) for cognition were: 1.77 (1.07-2.93) for any impairment (referent: none, N=630); 1.48 (0.82-2.68) for 1 domain impaired, 1.88 (1.01-3.53) for 2 domains, 2.01 (1.14-3.55) for 3 or more (referent: none, N=564); 0.68 (0.51-0.92) per standard deviation increase in global cognitive score (N=429). Adjusted education HR (95% CI) were 0.94 (0.61-1.45) for lower secondary and 1.49 (1.02-2.18) for upper secondary/higher (referent: primary/less, N=630). The cognition-by-education interaction was not significant (p=.691).

Conclusions: Cognitive impairment appears to predict mortality in hemodialysis patients.

Funding: Commercial Support - Diaverum (renal services provider), Government Support - Non-U.S.

SA-PO739

Validation of Indices Predicting 6 Month Mortality for Incident Dialysis Patients Over 75

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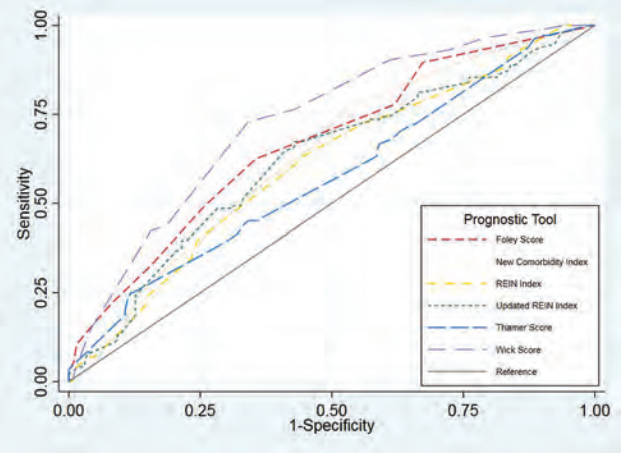
Background: Prognosis is one of the pinnacles of shared decision making. Much research has been done in the development of valid prognostic tools for mortality in patients on dialysis, however the performance and clinical applications of these tools in elderly incident dialysis patients remains to be determined. We aimed to find the best performing prognostic tool for short term mortality in elderly incident dialysis patients.

Methods: Six validated indices (Foley, NCI, REIN, newREIN, Thamer, and Wick) were identified in a systematic review for short term mortality prediction in incident dialysis patients. We applied these indices to an established cohort of 349 incident dialysis patients who were >75y old and used each to predict 6 month mortality. Variables were extracted from the medical record, and missing variables were imputed. Models were compared using the c-statistic, i.e. area under the receiver operating characteristic curve (ROC). Sensitivity and specificity were also calculated.

Results: The average age of our population was 81.5 years, 65.9% male, median survival was 351 days. The ROC ranged from 0.57 to 0.73, with the Foley and Wick indices performing the best, see Figure 1. The following cutoff scores yielded a specificity of >50% and >90% respectively in predicting mortality: Foley 7 and 10, NCI 4 and 10, REIN 4.2 and 8.2, REIN_new 12.1 and 16.4, Thamer 4.2 and 6.5, Wick 6 and 10. Sensitivity ranged from 45.8-76.4 for 50% mortality prediction with Wick having highest sensitivity and 9.0-22.0 for 90% mortality with Foley having highest sensitivity.

Conclusions: Most of the indices can predict which patients are more likely than not to die within 6 months of dialysis start with acceptable sensitivity and specificity. Higher cutoff scores can be used to predict death with high specificity (>90%) but at the considerable loss of sensitivity. The Wick and Foley indices performed best.

Funding: NIDDK Support, Other NIH Support - NIA K23 award, Private Foundation Support



SA-PO740

Prognosis in Shared Decision Making for Advanced CKD: A Qualitative Study

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Background: Prognostic information is key to shared decision making. Efforts are underway to enhance and implement prognostic tools for prediction of CKD progression and mortality. Whether patients are receptive and value such individualized risk predictions is unclear.

Methods: Semi-structured telephone or in-person interviews were conducted following routine visits to a multidisciplinary CKD clinic. Each patient was asked about his or her perspectives and experiences related to sharing dialysis risk prediction and prognosis with patients. Interviews were audiotaped, transcribed verbatim, and analyzed. Our team engaged in line-by-line, open, axial, and selective coding followed by content analysis.

Results: We enrolled 19 patients stage 3b-5, age 67-89 (avg. 78.57), 74% men. Often patients dreaded the possibility of starting dialysis, considering it a "last resort." Most patients understood that dialysis would impose significant limitations on their freedom. Almost all patients reported that they wanted to receive (or would not object to) a prediction of their risk of progressing to dialysis, even if it would be "kinda scary." Patients reported this could help them "plan for the future" and motivate them to adhere to preventive measures, but noted that the prediction might be upsetting to some. There was less agreement about the value of receiving a life expectancy prediction. Patients suggested that it should be offered only when a patient requests it or agrees to it. A life expectancy prediction would help patients "make an informed decision" about how to treat their CKD, and help them make preparations for the end of life if needed. We identified that several patients conflated the risk of progression to dialysis with the risk of death, equating refusing dialysis with rapid death.

Conclusions: This prospective patient-centered qualitative study confirms previous survey results suggesting that CKD patients are interested in prognostic information. Furthermore our findings add context and depth to the value of risk prediction in the clinical encounter and suggest ways in which to address individualized prognosis with patients. This can help further the development of intuitive shared decision making tools to relay this information to the patients who want it.

Funding: NIDDK Support, Other NIH Support - NIDDK K23 award, NIA K23 award, Private Foundation Support

SA-PO741

Factors Affecting Mortality in the Very Elderly on Haemodialysis – A Single Centre Study

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Background: The number of elderly patients currently managed on haemodialysis (HD) is increasing. We aimed to determine the outcome of very elderly patients (over the age of 85 years) on HD and to identify any factors associated with mortality in this group.

Methods: Data were retrospectively collected from a single UK centre over 11 years (2003-2014). HD dependence was defined as those requiring HD for more than 90 days. All patients starting HD at the age of 85 years or over were included. Demographics, reasons for starting HD, access at initiation and co-morbidities were recorded. The Davies Co-morbidity Score (DCS) was used to quantify co-morbidities in patients. Outcomes were of death, recovery of function and continued HD. Chi-square tests were used for categorical analysis of DCS.

Results: Of 149 patients, 144 were included (5 excluded due to lack of data). Age ranged from 85 to 98 years (modal age 85.04). 73.6% were male. Time on HD ranged from 95 - 2598 days (median 546 days). Overall mortality at 1-year was 18.8% (18.2% for 85-90 years and 25% for over 90 years). 74.3% started HD with a line and 25.7% with an arterio-venous fistula (AVF): A higher 1-year mortality (16.7%) was seen in the former group compared to the latter (2.1%). Overall 72.2% were non-diabetic (ND) with mortality at 1-year being 16.0% compared to 2.8% in diabetic patients. Mortality according to DCS is shown in Table 1. There was no significant difference in 1-year mortality between DCS groups (p >0.05).

Conclusions: Our HD cohort demonstrates better overall 1-year survival than that of the UK Renal Registry 2015 (71% in 85+ years). Type of HD access was the most important factor affecting mortality. Though the reasons for this are varied, HD via a line may reflect a more acute decline in renal function. DCS and diabetes were not independent predictors of mortality in this cohort. It may be that, in this age group, traditional markers of renal progression are no longer relevant. Further work is needed to look at other markers of survival and HD benefit in this age group, such as frailty and quality of life scores, to aid decision making with regards to HD in the very elderly.

Table 1

Davies Co-morbidity Score	1-year Mortality (%)
0	0.7
1	16.0
2	2.1

SA-PO742

Prognostic Value of a Geriatric Assessment in Older Patients Starting Dialysis

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Background: A geriatric assessment (GA) is a structural method for identifying frail patients. The prognostic value of a GA in end-stage kidney disease (ESKD) is not known. The subject of the GOLD (Geriatric assessment in OLder patients starting Dialysis) Study was to assess the relation of GA at dialysis initiation with poor outcome.

Methods: Patients ≥65 years old were included just prior to dialysis initiation. All underwent a GA, including assessment of ADL, instrumental (i)ADL, mobility, cognition, mood, nutrition, comorbidity, and a frailty screening (Fried Frailty Index, FFI). Quality of life (QoL) was scored with the visual analogue scale of the EuroQol-D5 (ranging from 0 [poor] to 10 [good]). Outcome measures were 6-and 12-months mortality, and 6-month hospitalization and change in QoL. Mortality was assessed with cox-regression and hospitalization with logistic regression, adjusting for age, sex and comorbidity.

Results: 192 patients were included, mean age 75±7 years, of whom 48% had ≥ 3 geriatric impairments and were considered frail. Mortality rate was 8% and 15% for 6-and 12-months. ADL, depressive symptoms and malnutrition were significantly related to 1-year mortality. Compared to non-frail patients, 1-year mortality risk was higher in patients with ≥ 3 impairments (HR 2.61 [95%CI 1.14-5.98]). Frailty was associated with lower baseline QoL (6.0±1.4 vs. 6.6±1.4, p=0.01), but not with 6-month change (overall improvement +0.3±1.4, p<0.01). Depressive symptoms, ADL and iADL were associated with hospitalization, but overall GA was not. Screening for frailty with the FFI resulted in 44% frail patients and FFI was related to mortality (HR 4.5 [95%CI 1.44-14.36) and hospitalization (OR 1.93 [95%CI 1.00-3.72]).

Conclusions: Geriatric impairment at dialysis initiation is related to mortality, hospitalization and QoL. A GA offers the advantage of both risk assessment and identification of potential targets for intervention and improving QoL. Whether these results contribute to decision-making in the pre-dialysis population should be the subject of further research.

Funding: Private Foundation Support

SA-PO743

Quality of Life After Initiation of Dialysis or Maximal Conservative Management

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Background: Maximal conservative management (MCM) may be an appropriate option for dialysis in some elderly patients with end stage kidney disease (ESKD). Whether MCM offers a better quality of life (QoL) compared to dialysis is not known. In the GOLD (Geriatric assessment in OLder patients starting Dialysis) Study the trajectory of QoL was assessed in patients starting dialysis or MCM.

Methods: Patients ≥65 years old were included just prior to dialysis initiation or after decision for MCM. Baseline data included demographics, QoL (EuroQol-D5 visual analogue scale [VAS], 0[poor]-10[good]) and geriatric impairment: mobility, (instrumental) ADL, mood, cognition, nutrition and comorbidity. Six-months follow-up data included QoL, mortality and hospitalizations. In both groups, logistic regression was used to assess the relation between impairment and deterioration of QoL (≥1 point), adjusting for age, sex, comorbidity and baseline QoL.

Results: The cohort comprised 192 dialysis (23% PD) and 88 MCM patients. The MCM patients were older (mean age 82±6 vs. 75±7 years, p< 0.01) and mean kidney function was better (eGFR 11.5±4.0 vs. 8.0±2.9 ml/min/1.73m^2, p<0.01). In both groups, poorer QoL was significantly associated with impairment in (i)ADL, mobility and mood; in dialysis patients also with comorbidity. Baseline QoL did not differ between dialysis and MCM (6.3±1.3 vs.6.3±1.4 respectively; p=0.91) and change in QoL was +0.3±1.4 (p< 0.01) and -0.4±1.4 (p<0.01) respectively. At 6 months follow-up, 8% of patients starting dialysis had died and Qol in 23% deteriorated, while 40% showed improved QoL. This was 18%, 31% and 15% respectively in MCM. Impairments were not associated with deterioration in QoL in both groups. Hospitalization differed relevantly (24% in MCM vs. 51% in dialysis; p< 0.01).

Conclusions: QoL was comparable for patients starting dialysis and MCM. Small improvement of QoL after dialysis start was seen. For MCM, QoL slightly decreased after six months. Geriatric impairment is associated with baseline QoL, but not with deterioration after start of dialysis or MCM.

Funding: Private Foundation Support

SA-PO744

Identification and Prioritization of Quality Indicators for Conservative Kidney Management

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Background: Conservative kidney management (CKM) is comprehensive patient-centred care for individuals with end-stage renal disease (ESRD) without renal replacement therapy. CKM focuses on delaying progression of kidney disease, symptom management, and frequent communication and support. Currently there is no consensus as to what constitutes high quality CKM. We aimed to develop a consensus-based set of quality indicators (QIs) for the conservative management of ESRD.

Methods: A nominal group technique study of patients and caregivers was used to identify and prioritize QIs for CKM, guided by QIs reported in the literature. A Delphi process with healthcare providers was used to rate the QIs using a 9-point Likert scale, in a series of four rounds, until consensus was reached based on pre-specified criteria. Consensus for the QIs in the Delphi process was met if the mean rating on the Likert scale was ≥7.0 and percent agreement was >75%.

Results: Sixteen patients and caregivers from Calgary, Canada participated in two nominal group meetings. Ninety-one multidisciplinary healthcare providers from 10 countries took part in the Delphi process. Patients and caregivers prioritized QIs focused on quality of dying and access to CKM personnel. Healthcare providers prioritized 99 QIs (out of a total 160) that met consensus criteria for inclusion. Nearly all (98.7%) participating healthcare providers indicated that quality of CKM delivery was important to measure, though less than a third (32.1%) measured quality in their provision of CKM. The most highly rated QI in the Delphi process was the "percentage of patients that die in the place they desire." There were several limitations as participants were largely from high-income, English-speaking countries, and most had structured CKM programs in place.

Conclusions: Quality of CKM care is important to patients, caregivers, and healthcare providers, though differences in priorities were noted. CKM programs and healthcare providers can use this international consensus-based QI list to evaluate and modify their CKM program delivery.

SA-PO745

Patient-Reported Experiences of a Shared Decision-Making Process on Dialysis or Conservative Care

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Background: Older patients approaching end-stage renal disease face the decision whether to start dialysis, or conservative care (CC)—which is argued to be a reasonable treatment option, particularly in the oldest old and those with severe comorbidity. Shared decision-making has been recommended to align treatment plans with the patient's values and preferences. Little is known regarding experiences of patients with such decision-making process.

Methods: We developed a questionnaire in collaboration with the Dutch Kidney Patients Association to assess older patients' experiences of their decision-making process on choosing dialysis or CC. We included 99 patients with stage 4/5 CKD and aged ≥70 years, who had chosen dialysis (n=75) or CC (n=24). A shared decision-making process had been initiated by a multidisciplinary team when the estimated glomerular filtration rate fell below 20 mL/min/1.73m^2, and included in-depth discussions in which oral and/or written information was given about dialysis and CC.

Results: Overall, patients stated to be satisfied with the decision-making process (median score on a 11-point Likert scale; dialysis group: 8.0 vs. CC group: 9.0; p = 0.06), as well as with their treatment decision (8.0 vs. 9.0; p = 0.07). Most felt they had enough time (79% vs. 87%) and information (80% vs. 73%) to make a decision, although factors as more time, information, and deliberation were mentioned as potential improvements. Patients choosing dialysis reported life prolongation and feeling of lack of choice as important

reasons for their decision, whereas quality of life and treatment burden were important reasons in choosing CC. 53% of the patients in the dialysis group considered their own opinion as most important in their treatment choice compared to 95% in the CC group (p = 0.003). More patients in the dialysis group felt forced by the situation to make a decision (32% vs. 4%; p = 0.01), or still doubted their treatment decision (17% vs. 0%; p = 0.03).

Conclusions: In this small Dutch sample, older kidney patients reported to be overall satisfied with a shared decision-making process on choosing dialysis or CC, although some had important recommendations for improvement. Patients had contrasting reasons for their treatment choice. Patients choosing CC experienced more autonomy and ownership in their decision-making.

Funding: Commercial Support - Roche; Zilveren Kruis Health Insurance, Private Foundation Support

SA-PO746

Shared-Decision Making and Renal Supportive Care: A Patient-Centered Clinical Trial

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Background: End-of-life (EOL) care planning in ESRD patients occurs infrequently, contributing to decreased quality of care and patient suffering. ESRD patients are much more likely to receive intensive care and less likely to receive hospice than other chronic conditions. The SDM-RSC study sought to create an easily replicable patient-centered model for EOL care planning discussions in dialysis units and to determine impacts on hospice use, EOL advanced planning, and to assess effect on patient quality of life.

Methods: We selected participants who were receiving maintenance hemodialysis and had poor prognoses using a validated prognostic instrument. Social workers and nephrologists received separate ACP training prior to inception of the intervention. Nephrologists participated in a one-hour training session that included reviews of mortality rates and ACP for hemodialysis patients. The social worker received a one-day training session and four additional telephonic "booster" sessions over two years. The intervention visit consisted of an initial patient and family meeting involving a dialysis social worker, and nephrologist; followed by ongoing contacts by the social worker and hospice contacts to dialysis units. We examined clinic-level data using an interrupted time-series design to assess changes in hospice usage over time.

Results: We recruited 125 participants from 18 dialysis units in 3 states. Our sample was 51% male, median age=70, 12% African-American, 14% American Indian, 46% White; and 37% Hispanic ethnicity. Overall clinic-level hospice usage did not vary significantly between pre- and post-intervention periods (observed average rate=25%). In participants that died during the study period, 48% stopped dialysis prior to death and 43% received hospice services. Of enrolled participants with follow-up, 75% had completed a healthcare proxy; 63% completed Medical (or Physician) Orders for Life-sustaining Treatment (MOLST/POLST). Quality of life indicators did not change significantly within 6 months of the initial meeting.

Conclusions: Clinic level effects of the intervention were not observed. There were important changes in EOL care planning for individuals, including completion of advanced care planning documents. The SDM-RSC intervention used existing staff at clinics making it practical to replicate.

Funding: Other U.S. Government Support

SA-PO747

Palliative Care Use and Patterns of End-of-Life Care in Hospitalized Patients with Calciphylaxis

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Background: Calciphylaxis (CUA) is a rare debilitating condition that is associated with poor quality of life and significant morbidity and mortality. Given that palliative care referrals are scarce in this population, we investigated the frequency of palliative care referrals and patterns of end-of-life (EOL) care in hospitalized CUA patients.

Methods: We included patients with CUA (confirmed by skin biopsy or clinical diagnosis via chart review) who were admitted to a large health care system in Boston, MA and died between 1/2014-4/2018. Terminal admissions were identified by chart review and outcomes included palliative care consultation, opiate use, receipt of cardiopulmonary resuscitation, mechanical ventilation, tube feeds, and vasopressor therapy, hospice referral, and place of death.

Results: Thirty CUA patients were identified. Seven percent had chronic kidney disease and 87% received dialysis. The median age at diagnosis was 60(15) years, 53% were female and 80% were White. The median Charlson Comorbidity Index score was 6(3) and median follow-up time was 63(104) days. Outcomes are displayed in Table 1.

Conclusions: Among CUA patients that died during the study period, less than half received palliative care consults and many patients received intense care prior to death. Furthermore, a minority of patients were referred for hospice care prior to death. Our data highlights the need for improved integration of palliative care to decrease care intensity and improve quality of EOL care for this seriously ill patient population.

Outcomes in Terminal Admissions

Outcomes	Terminal (N = 30)
Palliative care consultation	14 (47%)
Opiate use	25 (83%)
Cardiopulmonary resuscitation	5 (17%)
Mechanical ventilation	11 (37%)
Tube feeds	5 (17%)
Vasopressor therapy	10 (33%)
Hospice referral	8 (27%)
Place of death	
Inpatient ward	7 (23%)
Intensive care unit	13 (43%)
Inpatient hospice	4 (13%)
Unknown	6 (20%)

SA-PO748

In-Center Extended-Hour Hemodialysis Can Be Effective in Improving the Mortality of Elderly Dialysis Patients

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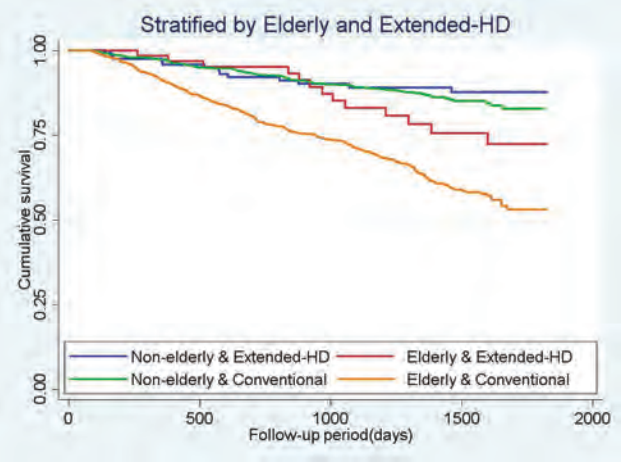
Background: Amid the global problem of aging among dialysis patients, it has become more difficult to improve prognosis among dialysis patients. Despite previous reports that the extended-hour hemodialysis (HD) can reduce the risk of death, the impact of this treatment on elderly patients remains unclear. The aim of this study is to investigate the effect of extended-hour HD on elderly patients, using largest cohort of incident extended-hour HD in Japan.

Methods: Multicenter retrospective cohort study; we included 205 consecutive patients who had received in-center extended-hour HD since the initiation of HD in 4 facilities during Oct. 2008 to Sept. 2017 (extended-HD). We also included 1382 consecutive patients who initiated conventional HD in 17 facilities during Oct. 2011 to Sept. 2013 as the control group (conventional). Each treatment group was divided into two age subgroups (over or less than 70 years old). We compared the risk for mortality during the first 5 years of follow-up among the treatment groups and age subgroups.

Results: The mean age was 63.3±14 years in extended-HD and 68.1±13 years in conventional. The crude mortality in the extended-HD group was 3.9 deaths per 100 patient-years compared with 7.9 deaths per 100 patient-years in the conventional group. Extended-HD was associated with a 37% reduction in mortality after adjustment for age, sex, body mass index, diabetes, and cardiovascular disease (95% confidence interval (CI): 5-58%). In the subgroup analyses, elderly dialysis patients (>70 years old) treated with extended-HD had a 48% lower adjusted mortality than that of conventional (95% CI: 10-71%).

Conclusions: Especially for the elderly, treatment with extended-hour HD was associated with a lower risk of mortality compared to conventional HD.

Funding: Government Support - Non-U.S.



SA-PO749

Single Measurements of Fibroblast Growth Factor 23 and Clinical Risk Prediction in CKD

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Background: Elevated fibroblast growth factor 23 (FGF23) levels are independently associated with a number of adverse outcomes in patients with chronic kidney disease (CKD) at the population level, but it is unknown if FGF23 testing can improve individual clinical risk prediction.

Methods: In 3879 participants in the Chronic Renal Insufficiency Cohort Study, we tested whether addition of a single baseline measurement of FGF23 testing to standard clinical risk predictors (Figure) significantly improves prediction of all-cause mortality, incident end-stage renal disease (ESRD), heart failure (HF) admission, and atherosclerotic events over periods of 3 (primary analysis), 5, and 8 years of follow-up. We assessed changes in C index, integrated discrimination improvement (IDI), relative IDI, and category-based net reclassification index (NRI). We also compared the incremental utility of FGF23 versus an analogous model using serum phosphate concentration.

Results: The base model best predicted incident ESRD and HF (Figure). The addition of FGF23 improved prediction of all-cause mortality and HF admissions by change in C index, IDI, and relative IDI (NRI trended towards significance), but not incident ESRD or atherosclerotic events (Figure). The years 5 and 8 results were qualitatively similar to the 3-year results. FGF23 outperformed phosphate for all outcomes.

Conclusions: In CKD, single measurements of FGF23 improves prediction of risks of all-cause mortality and HF admissions but not ESRD or atherosclerotic events. Future studies are needed to evaluate the predictive utility of repeated FGF23 testing.

Funding: NIDDK Support

Candidate variables included in base model

Candidate Variables			
Demographics	**Medical History**	**HTN Burden**	**Lab Values**
Age	Diabetes	Number of antihypertensive medications	Estimated GFR
Sex (male vs female)	Coronary artery disease	Systolic blood pressure	Albumin-to-creatinine ratio
Race (Black vs non-Black)	Heart failure		Serum albumin
Ethnicity (Hispanic vs non-Hispanic)	Stroke		Total cholesterol
	Smoking history		

FGF23 Model Discrimination Summary

Outcome	C Index		ΔAUC (95% CI)	IDI (95% CI)	Relative IDI (95% CI)	NRI (95% CI)
	Base Model	Base Model + FGF23				
All-cause Mortality	0.746	0.763	0.017 (0.001, 0.033)	0.021 (0.006, 0.036)	32.7% (8.54%, 56.9%)	0.039 (-0.002, 0.079)
ESRD	0.909	0.909	0.0003 (-0.001, 0.002)	0.0004 (-0.001, 0.001)	0.11% (-0.12%, 0.34%)	0.001 (-0.006, 0.008)
HF Admission	0.838	0.846	0.008 (0.0004, 0.016)	0.019 (0.004, 0.039)	10.0% (1.82%, 18.3%)	0.005 (-0.030, 0.037)
Atherosclerotic Event	0.752	0.754	0.002 (-0.006, 0.010)	0.004 (-0.003, 0.012)	5.02% (-3.03%, 13.1%)	0.006 (-0.018, 0.030)

SA-PO750

Even Low-Grade Proteinuria Increases Progression to Renal End-Points in Non-Diabetic Hypertensive Veterans

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Background: Proteinuria is an indicator of renal injury but there is little quantitative information about the predictive value of low concentrations of urine protein in patients without diabetes. We hypothesized that incremental risk would accrue with increasing proteinuria in hypertensive, non-diabetic patients.

Methods: A cohort of 153,848 hypertensive non-diabetic patients in the VA national database (VINCI) and recorded urinalysis was categorized as 'no proteinuria' or by first recorded urine protein (dip-stick: ≤30, 31-100, and >100 mg/dl) and by CKD stage. Endpoints included ESRD and all-cause mortality. Baseline characteristics were compared using ANOVA, Chi square tests and non-parametric tests. Adjusted Cox regression, and Kaplan Meier analyses were conducted to compare risks.

Results: Proteinuric groups had accelerated progression to ESRD and combined renal endpoint, and had increased all-cause mortality (Logrank P<0.01). Proteinuria < 30 mg/dl was associated with renal endpoint and had a relatively smaller effect than higher grades proteinuria. Younger age, higher CKD stage, prior diagnosis of AKI, or use of ACEI, ARB or β-blocker at first proteinuria were associated with higher risk of progression and all-cause mortality.

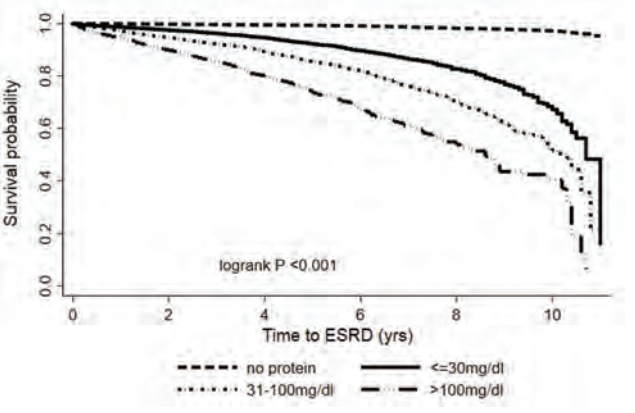
Conclusions: We conclude that, in non-diabetic Veterans with hypertension, even low concentrations of proteinuria predict renal failure and mortality and should not be ignored. Early identification of proteinuria as a risk will permit research regarding novel mechanisms of progression and may define interventions to delay progression and lower mortality.

Funding: Veterans Affairs Support

Adjusted Hazard ratios for Renal Endpoints

Proteinuria group (ref=no protein)	ESRD HR (CI)	Mortality HR (CI)	Composite¥ HR (CI)
<=30mg/dl	3.8 (3.4-4.2)	1.6 (1.5-1.7)	1.6 (1.5-1.7)
31-100mg/dl	4.6 (4.1-5.2)	1.7 (1.6-1.8)	1.7 (1.6-1.8)
>100mg/dl	4.7 (4.1-5.5)	1.6 (1.5-1.7)	1.6 (1.5-1.8)

¥ ESRD, mortality, or dialysis. All P values <0.01. Mean BMI=28.6; mean age=66.1 years. Covariates not shown.



SA-PO751

The Kidney Failure Risk Equation Predicts Progression to Hemodialysis in Cancer Patients with CKD

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Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for progression to hemodialysis (HD) in a cohort of cancer patients with CKD.

Methods: Among 397 outpatients with cancer referred to nephrology evaluation (2009-12), 202 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The primary endpoint was defined as progression to HD during follow up. The Cox regression was used to examine the association between the baseline features and progression to HD.

Results: Throughout a mean follow up period of 3.7±2.3 years, 10% of patients progressed to HD. Patients baseline features data are shown in Table 1. In the Cox regression analyses, the risk of HD estimated by the 4-variable Kidney Failure Risk Equation (aHR=1.05; 95% CI 1.03-1.06, p<0.001) was the strongest predictor of HD in our population after adjusments for CKD etiology.

Conclusions: In this cohort, traditional risk factors as hypertension, diabetes and albuminuria were associated with a greather risk of hemodialysis in univariated analysis. Beyond, the Kidney Failure Risk Equation was a good instrument for identifying a high risk of progression to HD among cancer patients with CKD.

Table 1. Baseline Features

	Hemodialysis (n=19)	No Hemodialysis (n=183)
Age (yr)	65±9	66±12*
Male (%)	63	72
Solid Tumors (%)	89	85
Metastasis (%)	32	26
Hypertension (%)	95	74*
Baseline eGFR (ml/min/1.73m2)	23±14	40±14
Albuminuria > 300 mg/g	80	25*
5yr Kidney Failure Risk (%)	51±37	7±12*
Diabetic Nephropathy (%)	37	14*
Obstructive Nephropathy (%)	21	16
Follow up (yr)	4,6±2	3,8±2

Results are expressed as mean±SD and percentage. * < 0.05 vs Hemodialysis group

SA-PO752

Validation of the Kidney Failure Risk Equation in Primary Care Clinics in Southeast Asia

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Background: Patients with chronic kidney disease (CKD) are at high risk of progression to end stage kidney disease (ESKD). The Kidney Failure Risk Equation (KRFE) was developed to accurately predict the progression of CKD to kidney failure. However, it has not been validated in primary care clinic settings in Asia. The objective of this study was to validate the predictive utility of KFRE for ESRD risk, and compare it with that of eGFR alone in polyclinics in Singapore.

Methods: Electronic health records were extracted from 9 government clinics on 117,528 patients aged 40 years or older visiting clinics during 1st Jan 2010 to 31st Dec 2012 with at least one measurement of serum creatinine or proteinuria. All patients with CKD-EPI estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 and proteinuria had KFRE evaluated using the 4-variable equation (age, sex, eGFR, ACR). ESRD was determined by linkage with Singapore Renal Registry. Area under the operating characteristics curves (AUC) was used to calculate the predictive utility for 5-year risk of ESRD with KFRE versus eGFR alone.

Results: A total of 17271 participants had eGFR <60 ml/min/1.73m^2 of whom 49% were men, 80% were Chinese, 12% were Indian and 4% were Malays. After a mean follow-up of 5 years, a total of 491 (2.8%) patients developed ESRD. The AUC (95% confidence interval) for KFRE and eGFR alone was 0.93 (0.92-0.94) and 0.89 (0.88-0.91), respectively.

Conclusions: The KFRE showed excellent predictive utility, which was better than eGFR alone for ESRD risk in this multi-ethnic population. We provided several thresholds below for the clinical decision making and implementation in primary care clinics in Singapore and possibly other Asian countries.

Funding: Government Support - Non-U.S.

Table. Summary statistics of different thresholds to assess discrimination for ESKD.

	KFRE AUC (95% CI): 0.93 (0.92-0.94)				CKD-EPI eGFR ml/min/1.73m^2 AUC (95% CI): 0.89 (0.88-0.91)	
Threshold	≥1.9%	≥3%	≥10%	≥15%	≤30	≤45
Cumulative number (%) of people	2534 (14.67%)	1652 (9.57%)	356 (2.06%)	170 (0.98%)	1958 (11.34%)	7813 (45.24%)
Sensitivity	0.84	0.74	0.40	0.24	0.70	0.94
Specificity	0.87	0.92	0.99	0.99	0.90	0.56
Negative predictive value	0.16	0.22	0.56	0.68	0.18	0.06
Positive predictive value	0.99	0.99	0.98	0.98	0.99	0.99

SA-PO753

Validation and Assessment of Kidney Failure Risk Equations in Korean Population

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Background: Predicting the risk of chronic kidney disease (CKD) may facilitate early and appropriate nephrology care of CKD patients. Previously, kidney failure risk equations were developed in Canadian population and validated in more than 30 countries spanning 4 continents. However, there is no validation data in Korean population. Thus, we attmped to evaluate the accuracy of the risk equations in Korean population and to adjust the equation.

Methods: SNU cohort, including 1315 patients with CKD in Seoul National University Hospital (SNUH) and Seoul National University Boramae Medical Center (SNUBMC), were studied. These cohorts collected data from 2001 through 2016. With the risk factors from the original risk equations, hazard ratios were estimated in SNU cohort and used to adjust the equation. The time horizon for risk prediction was 5 years. We used three risk prediction equations, 4-variable, 6-variable and 8-variable equations. Then, these three equations were evaluated using AUROC for the goodness of a predictor, integrated discrimination improvement (IDI) for discrimination, and net reclassification improvement (NRI) at 5 years.

Results: The mean age of the study population was 58 years, and the mean baseline eGFR was 73 mL/min/1.73m2. The three risk prediction equations showed great performance of prediction (AUROC, 0.91; 95% CI, 0.88-0.94 at 4-variable equation, 0.91; 95% CI, 0.88-0.94 at 6-variable equation, 0.91; 95% CI, 0.89-0.94 at 8-variable equation). Using DeLong test, 4-variable equation and 6-variable equation were compared with at 8-variable equation. There was no improvement in performance with 8-variable equation (4-variable equation vs 8-variable equation, p=0.068 and 6-variable equation vs 8-variable equation, p=0.080)

Conclusions: Adjusted Kidney failure risk equation showed high performance of prediction in Korean population. However, further verification in a larger cohort may be necessary in the future.

Table 2. 5-years risk models

Model 3	$1-0.9240e^{(-0.2201\times(Age/10-7.036)+0.2467\times(Male-0.5642)-0.5567\times(eGFR/5-7.222)+0.4510\times(logACR-5.137))}$
Model 4	[illegible]
Model 6	[illegible]

SA-PO754

Validation of Predictive Model for Progression of CKD to ESRF in Singapore

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Background: Risk stratification of chronic kidney disease (CKD) patients allows clinicians to individualize treatment and improves resource allocation on the national level. Tangri et al *(JAMA. 2011 Apr 20;305(15):1553-1559)* proposed and validated a predictive model for progression of chronic kidney disease to kidney failure in a Canadian population and subsequently in a meta-analysis of multinational cohorts. As accuracy of the prediction model may vary among different populations, we aim to validate this prediction model in a Singapore CKD cohort and to determine if a calibration factor is required.

Methods: The study population was derived from newly referred patients to Department of Renal Medicine at Singapore General Hospital (SGH), Singapore in 2009. Eight variables based on the most accurate model in the Tangri et al study were obtained within 90 days of the initial visit. Primary outcome measure is kidney failure in 5 years and time to kidney failure was defined from initial renal medicine visit to kidney failure.

Results: Out of 2216 patients reviewed, 795 were included in the analysis. The mean age is 65.8 years old, mean eGFR is 34.5ml/min/1.73m^2. Majority are Chinese (74.6%) with 15.5% Malay, 6.2% Indian, 1.1% Eurasian and 0.6% others (2 Thais, 1 Filipino, 1 Indonesian and 1 Arab). Six hundred and forty (80.4%) are on angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Four hundred and ninety-seven (62.4%) have diabetes mellitus. Two hundred and twelve (26.7%) reached kidney failure. Mean time to renal failure is 1288 days (3.5 years). Both the 8-factor (age, gender, estimated glomerular filtration rate (CKD-EPI) (eGFR), albuminuria (ACR), serum albumin, serum phosphate, serum bicarbonate and serum calcium) and 4-factor (age, gender, eGFR and ACR) model are accurate (C-index 0.863 and 0.865 respectively) in predicting risk of kidney failure with the 8-factor model outperforming the 4-factor model (adequacy index of 98.8% vs 97.2%)

Conclusions: The predictive model developed by Tangri et al is accurate in predicting the progression of CKD to ESRF in 5 years in the Singapore CKD population.

SA-PO755

Underperformance of ESRD Prediction Equations in a Contemporary Diverse Adult Population with Advanced CKD

Sijie Zheng,[1] Leonid Pravoverov,[2] Victor Shiau,[3] Rishi V. Parikh,[2] Nhi Tan,[5] Joanna Mroz,[1] Thida C. Tan,[3] Tracy Y. Jonelis,[4] Alan S. Go.[3] [1]*The Permanente Medical Group, Oakland, CA;* [2]*Kaiser Permanente, Walnut Creek, CA;* [3]*Kaiser Permanente Northern California, Oakland, CA;* [4]*The Permanente Medical Group, Inc, San Francisco, CA;* [5]*Kaiser Oakland Medical Center, OAKLAND, CA.*

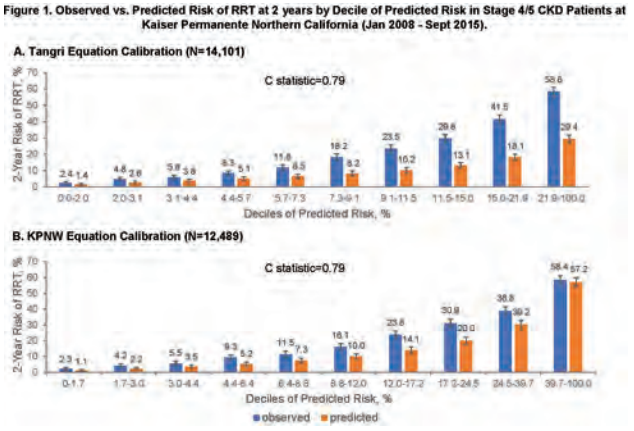
Background: Two risk prediction models (Tangri, KPNW) have been proposed for risk stratification for transition to ESRD in adults with CKD 3-5. We evaluated the performance of these models in an ethnically diverse advanced CKD population.

Methods: We identified all adult members of Kaiser Permanente Northern California (KPNC) with Stage 4-5 CKD between Jan. 2008-Sep. 2015. Receipt of RRT through Sep. 2016 was ascertained from an internal ESRD registry. Data on patient characteristics and lab results were obtained from electronic health records. We examined model discrimination (c statistic) and calibration (observed vs. predicted risk) for initiating RRT at 1, 2 and 5 years for the Tangri equation and at 2 years for the KPNW equation.

Results: In 17,586 adults with CKD 4-5, mean age was 73.7 years, 53% were women, and 49% were persons of color. The 1-, 2- and 5-year crude risks for RRT were 8.8% (95%CI:8.3-9.2%), 20.1% (19.5-20.8%) and 37.9% (36.9-38.8%), respectively. For Tangri, we found lower discrimination at 1 year (c=0.80 KPNC, c=0.86 Tangri), and 5 years (c=0.76 KPNC, c=0.84 Tangri), with substantial underestimation of actual absolute risk (Figure 1A). Similarly, for the KPNW model, we observed lower discrimination (c=0.79 KPNC, c=0.96 KPNW) and underestimation of actual risk (Figure 1B).

Conclusions: In a large, ethnically diverse CKD 4-5 population, Tangri and KPNW prediction models exhibited both lower discrimination and significant underestimation of absolute RRT risk. Given that most ESRD cases are derived from CKD 4-5 patients, more accurate prediction models are needed to help tailor management.

Funding: Private Foundation Support



Observed vs. Predicted Risk of RRT at 2 years by Deciles of Predicted Risk in Stage 4/5 CKD Patients at Kaiser Permanente Northern California (Jan. 2008-Sep. 2015).

SA-PO756

Clinical Utility of the Kidney Failure Risk Equation in Determining Timing of Predialysis Education

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Background: The Kidney Failure Risk Equation (KFRE) has been validated to predict decline in chronic kidney disease (CKD) and proposed as a tool for dialysis planning. Timing of predialysis education is known to impact short- and long-term outcomes on dialysis. Current guidelines recommend it occurs within 12 months before initiation but little evidence exists to guide the timing of this referral. Our aim was to assess and validate the efficacy of the KFRE in predicting optimal timing for dialysis education.

Methods: A 2 year risk of end stage kidney disease (ESKD) was calculated using the 4-variable KFRE in a cohort of patients with CKD stages 3-5 and compared to eGFR with respect to predictive efficacy. The sensitivity and specificity of the test using KFRE thresholds of 10 and 20% as well as eGFR of 15 and 20 ml/min/1.73 m^2 were examined, reflecting KFRE risk suggestions and eGFR cut-offs currently used for referral to predialysis education. In patients who developed ESKD and commenced dialysis we searched retrospectively for an association between KFRE and time from predialysis education to initiation (dependent variable) using linear regression.

Results: Of 294 patients included in the analysis, 106 progressed to ESKD over the 2 year follow-up period. The area under the receiver operating curve for KFRE was 0.97 [95% confidence interval (CI) 0.96-0.99]) and 0.93 for eGFR (95% CI, 0.90-0.97). Using a KFRE threshold of 10% the sensitivity was 82% and specificity 97% and at 20% the sensitivity decreased to 57% but specificity was maintained (98%). Use of eGFR cut-offs of 20 and 15 ml/min/1.73 m^2 resulted in lower sensitivity (56% and 18% respectively) but equivalent specificity (97 and 99% respectively). There was a weak, positive association between KFRE risk and longer time from dialysis education to initiation (r^2 = 0.072, p = 0.016).

Conclusions: The KFRE can be considered validated in our population as a good predictor of ESKD and modestly superior to eGFR. A threshold KFRE risk of 10% over 2 years appears to be a more useful guide than eGFR for timely referral to predialysis education. However, this was not observed at a higher threshold, suggesting that other factors may impact on the rate of progression to dialysis. KFRE requires ongoing evaluation for decision-making nearing ESKD.

SA-PO757

Predicting Incidence of CKD G3+ (eGFR <60 mL/min/1.73 m2) in the General Population

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Background: Risk-based treatment strategies are one method of delivering personalized medicine. Valid risk scores are needed for the prediction of CKD G3+, which may prompt albuminuria testing in those who are not already advised to undergo screening because of diabetes, hypertension, or history of cardiovascular disease (CVD).

Methods: Among 26 general population and high-risk population cohorts (N=2.1 million participants) with eGFR ≥60 ml/min/1.73 m^2, we estimated risk factors of incident eGFR <60 ml/min/1.73 m^2 (CKD G3+) and eGFR <30 ml/min/1.73 m^2 (CKD G4+). We derived a risk score using random-effects meta-analyzed sub-hazard ratios from all cohorts, and random-effects meta-analyzed re-fit subhazards from the six cohorts with frequent creatinine measurements. Risk factors evaluated included age, sex, race, baseline eGFR, history of CVD, diabetes, smoking status, hypertension, and body-mass index. Albuminuria was modeled in people with and without diabetes separately due to differences in data availability.

Results: Mean age of participants was 54 years, 53% were female, and mean baseline eGFR was 91 ml/min/1.73 m^2. Over a mean follow-up of 4.5 years, there were 152,968 events of incident eGFR <60 ml/min/1.73 m^2 and 31,631 events of incident eGFR <30 ml/min/1.73 m^2. All risk factors listed in the methods were statistically significant. Applying the risk score to NHANES 2011-2016, the 10th and 90th percentiles of 5-year risk of incident eGFR <60 ml/min/1.73 m^2 were 0.04% and 3.7% for those aged 18-39 years, 0.6% and 21.9% for 40-59 years, 6.9% and 64.4% for 60-79 years, and 29.3% and 84.6% for ≥80 years. Corresponding estimates of incident eGFR <30 ml/min/1.73 m^2 were 0.01% and 0.02%, 0.09% and 1.3%, 0.6% and 5.1%, and 1.4% and 7.8%, respectively. Specific equations for patients with diabetes as well as incorporating albuminuria, when measured, provide better personalization.

Conclusions: A risk score for CKD incidence developed from risk factors available in electronic health records had a 10-100 fold risk gradient and could help guide screening and prevention.

Funding: NIDDK Support, Private Foundation Support

SA-PO758

Random Survival Forest Identifies Key Factors Predicting CKD Progression: The CRIC Study

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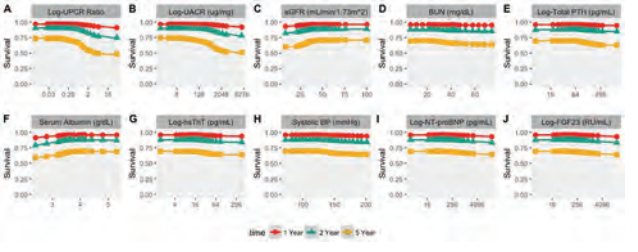
Background: Increasing numbers of clinically-available and novel factors bring opportunities to improve CKD risk prediction, as well as statistical challenges of multiple comparison, nonlinearity, variable interactions, and missing data. We applied the machine learning technique of random survival forest (RSF) to identify factors associated with CKD progression.

Methods: We studied 3,939 subjects in the Chronic Renal Insufficiency Cohort and followed them for the composite survival outcome of eGFR halving or incident ESRD for 12 years. We used 73 clinically-available and 25 novel baseline variables as exposures, which covered a broad spectrum of socio-demographics, comorbidities, physical and laboratory measurements and medications. We applied the RSF approach with 1000 bootstrap iterations and log-rank splitting rule. We calculated statistics of variable importance and minimal depth to rank predictors according to their impact on prediction accuracy. We also graphed the adjusted relationships of CKD progression and the top 10 strongest predictors.

Results: After setting the outliers to missing, we included 3,921 individuals in the analysis. Missing data were imputed and variable interactions were incorporated in the RSF algorithm. The 98-predictor RSF model yielded a low prediction error of 14.2% (1 minus Harrell's C-index). The top 10 predictors identified with highest variable importance values and smallest minimal depths are urine protein/creatine ratio, urine albumin/creatinine ratio, eGFR, serum urea nitrogen, parathyroid hormone, serum albumin, high sensitivity troponin T, systolic blood pressure, NT-proBNP, and FGF-23. The relationships of the predicted survival at 1-, 2-, and 5-years and the 10 factors are shown in the partial dependence plots.

Conclusions: We identified and ranked variables that are most important to CKD progression from among 98 clinically-available and novel factors using the RSF method. Utilizing high-dimensional data enabled us to predict outcomes with a low error rate.

Funding: NIDDK Support



Partial dependence plot

SA-PO759

Mediation of the Association Between Particulate Matter Air Pollution and Renal Disease by Diabetes

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Background: Evidence suggests that elevated levels of fine particulate matter of <2.5 µm in aerodynamic diameter ($PM_{2.5}$) are associated with increased risk of kidney disease. However, $PM_{2.5}$ is also associated with risk of diabetes, which is a major driver of CKD. Whether and to what extent the association of $PM_{2.5}$ and CKD is mediated by diabetes is unknown.

Methods: Databases from the Environmental Protection Agency (EPA) and National Aeronautics and Space Administration (NASA) were linked with those from Department of Veterans Affairs. Inverse odds ratio-weighted estimations for mediation analyses were undertaken to quantitate the proportion of the association between $PM_{2.5}$ and risk of CKD outcomes that is mediated by diabetes. CKD outcomes included incident eGFR < 60 mL/min/1.73m^2, incident CKD, incident eGFR decline ≥ 30%, and time until end stage renal disease (ESRD) or eGFR decline ≥ 50%.

Results: In a cohort of 2,444,157 United States Veterans followed for a median of 8.5 years, using EPA data, the proportion of the association (between $PM_{2.5}$ and risk of CKD outcomes) mediated by diabetes was 4.7%, 4.8%, 5.8%, and 16.5% for risk of incident eGFR less than 60 mL/min/1.73m^2, risk of incident CKD, risk of eGFR decline of 30% or more, and risk of ESRD or eGFR decline ≥50%, respectively. Results were consistent when exposure was defined according to NASA data.

Conclusions: Our findings demonstrate that a small proportion of the association between $PM_{2.5}$ and CKD was mediated by diabetes, suggesting that the presence of other mediators or a direct effect between $PM_{2.5}$ and CKD may drive the association between $PM_{2.5}$ and CKD.

Funding: Veterans Affairs Support

SA-PO760

Improvement in Glomerular Filtration Rate Among CKD Patients: Findings from the CRIC Study

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Background: Improvement of eGFR has been observed in approximately 10% of participants in numerous CKD cohorts. Among those with improving eGFR, a counterintuitive association with increased risk of coronary heart disease and death compared to those with stable or slightly declining eGFR has been reported. Sarcopenia, edema, and other indicators of clinical deterioration may be responsible for the increased risk of poor outcomes among subjects with improving eGFR. We aimed to assess the association between slopes of eGFR and time to cardiovascular events and all-cause mortality accounting for many factors potentially confounding this relationship.

Methods: We studied 3024 participants of the CRIC Study, a multi-center cohort of adults with CKD. We performed Cox Proportional Hazards models with time-varying covariates to investigate the association between slopes of eGFR and cardiovascular events and all-cause mortality. Slopes were estimated using linear mixed effects models and were updated whenever a new eGFR was assessed over a median of 9 years. Individuals were characterized according to three groups based on their slope at year 2: decliner (slope<=-2); stable (slope>-2 and <2); improver (slope>=2ml/min/1.73m2).

Results: In the CRIC Study, 327(11%) presented improvement of eGFR, 1045 (34%) were stable, and 1652 (55%) were decliners. Improvers were predominantly male (60%), had lower systolic blood pressure (mean: 118 mmHg), and lower proteinuria (median: 0.09 g/day). In models adjusted for demographics, diabetes, eGFR, proteinuria, systolic blood pressure, fat-free mass, ejection fraction, antihypertensive drugs and other laboratory markers, time-updated improvement of eGFR was associated with increased risk of death compared to stable slopes: HR 1.89 (95%CI: 1.63 -3.22). The risk of death for steep decliners was also significantly higher: HR 1.63 (95%CI: 1.25 - 2.14).

Conclusions: Slopes of eGFR higher than 2ml/min/1.73m2/year were associated with increased risk of death compared to subjects presenting stable slopes of eGFR. This association was not explained by markers of cardiovascular function, body composition, or by a time-updated approach.

Funding: NIDDK Support

SA-PO761

First-Year Estimated Glomerular Filtration Rate Variability After Pre-ESRD Program Enrollment and Adverse Outcomes of CKD

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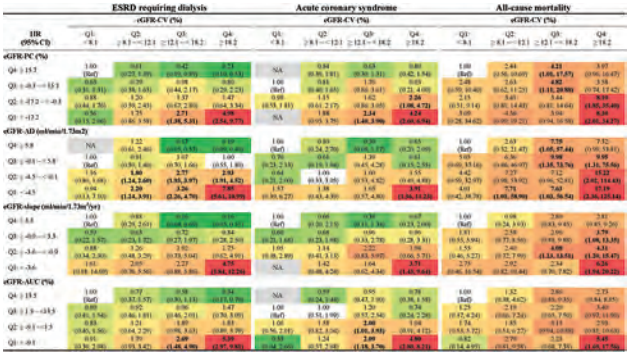
Background: Scarce evidence associates the first-year estimated glomerular filtration rate (eGFR) variability and longitudinal change scales concomitantly to the risk of developing end stage renal disease(ESRD), acute coronary syndrome(ACS), and death following pre-ESRD program enrollment in chronic kidney disease(CKD).

Methods: We conducted a prospective cohort study of 5,092 CKD patients receiving multidisciplinary care between 2003 and 2015 with careful ascertainment of ESRD, ACS, and death during the follow-up. First-year eGFR dynamics included coefficient of variation (eGFR-CV), percent change (eGFR-PC), absolute difference (eGFR-AD), slope (eGFR-slope), and area under curve (AUC).

Results: A total of 786 incident ESRD, 292 ACS, and 410 death events occurred during the follow-up. In the multiple Cox regression, the fully adjusted HRs for incident ESRD comparing the extreme with the reference quartiles of eGFR-CV, eGFR-PC, eGFR-AD, eGFR-slope, and eGFR-AUC were 2.67(95% CI, 2.11, 3.38), 8.34(6.33, 10.98), 19.08(11.89, 30.62), 13.08(8.32, 20.55), and 6.35(4.96, 8.13), respectively. Similar effects on the risk of developing ACS and mortality was observed. In the 2x2 risk matrices, patients with the highest quartile of eGFR-CV and concomitantly with the most severely declining quartiles of any other longitudinal eGFR change scale had the highest risk of all outcomes.

Conclusions: The dynamics of eGFR changes, both overall variability and longitudinal changes, over the first year following pre-ESRD program enrollment are crucial prognostic factors for the risk of progression to ESRD, ACS and deaths among patients with CKD. A risk matrix combining the first-year eGFR variability and longitudinal change scales following pre-ESRD enrollment is a novel approach for risk characterization in CKD care.



Risk matrices demonstrating the adjusted hazard ratios (aHRs) for ESRD requiring dialysis, ACS, and all-cause mortality by using eGFR-CV (in quartiles) and other scales of eGFR longitudinal change scales, namely eGFR-PC, AD, slope, and AUC.

SA-PO762

Estimating Short-Term Risk of Disease-Related Outcomes in ADPKD: A Prediction Model Based on Longitudinal Data from the OVERTURE Study

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Background: Models are available for predicting rapid decline in kidney function in autosomal dominant polycystic kidney disease (ADPKD), but there is a need for a clinical tool that estimates the short-term risk of other ADPKD-related complications. We analyzed observational data to identify patient baseline variables most useful for estimating risk of complications and to construct a patient risk calculator.

Methods: OVERTURE was a prospective study with follow-up at 6-month intervals to assess for 17 types of ADPKD-related manifestations that included hematuria, kidney pain, albuminuria, urinary tract infection (UTI) and nephrolithiasis. In our analysis, occurrence of each type of manifestations in a patient was assigned a score of 1, yielding a maximum ADPKD severity score of 17. Item response analysis[1] was used to determine the complications that contributed most to overall disease severity across the population, and multivariate logistic regression was performed to ascertain which patient baseline risk factors best predicted experiencing ≥1 of the identified complications in the follow-up 6–18 months.

Results: Among 1880 subjects with follow-up data over the analysis period, the manifestations that contributed most to overall ADPKD severity were hematuria, kidney pain, albuminuria, UTI, and nephrolithiasis. In the regression model, baseline risk factors most predictive of occurrence of ≥1 of these manifestations over 6–18 months were: age ≤35, male sex, non-Hispanic ethnicity, higher baseline total kidney volume growth rate, and higher risk class in the Mayo ADPKD classification system.[2] These predictive variables were incorporated into a simple nomogram for patient risk scoring.

Conclusions: Patient baseline risk factors can be used to estimate the risk of experiencing ≥1 of 5 important ADPKD-related manifestations over 6–18 months. A prediction nomogram that assigns point scores for each predictive variable enables rapid risk estimation in the clinic.

Funding: Commercial Support - Otuska Pharmaceutical Research and Development, Inc

SA-PO763

Predicting CKD in the CARRS Study: Strategies for Screening in the Indian Population

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Background: Chronic kidney disease (CKD) is a significant global health issue. Much of the rise in CKD-attributable deaths has occurred in low- and middle-income countries (LMICs). Population-wide screening for CKD is not cost-effective and likely untenable in resource-limited settings. Development of a tool that identifies at-risk persons and allows targeted screening is paramount to manage this growing problem.

Methods: Using data from the Centre for Cardiometabolic Risk Reduction in South Asia (CARRS) study, we fit a logistic regression model based on 30 variables easily measured during a home visit. Final predictors were selected through a step-down procedure. We defined presence of CKD as eGFR <60 ml/min/1.73m^2 by the CKD-EPI equation or urine albumin-to-creatinine ratio (UACR) ≥30 mg/g. Discrimination was assessed with the c-statistic and calibration with the calibration slope. Model predictive ability was compared across different probability cut-offs. We used bootstrap for internal validation.

Results: In our sample of 8,698 participants from Delhi and Chennai, CKD prevalence was 10.9%. Our final model consisted of 19 variables (**Figure 1**). Development and validated c-statistics were 0.79 and 0.78, respectively. Calibration slope was 0.97 after validation. Using a probability cut-off of 0.075, the model identified 3,489 people (40% of original sample) as needing confirmatory testing for CKD with serum creatinine or UACR, giving a sensitivity of 78% and specificity of 65%.

Conclusions: Our prediction model exhibited good sensitivity and discrimination for CKD, while narrowing the pool of people who necessitate confirmatory testing. We are the first to use large-scale population data to develop a tool that facilitates targeted screening for CKD in urban India. Future efforts include external validation on a separate Indian cohort.

Funding: NIDDK Support, Other NIH Support - Fogarty International Center

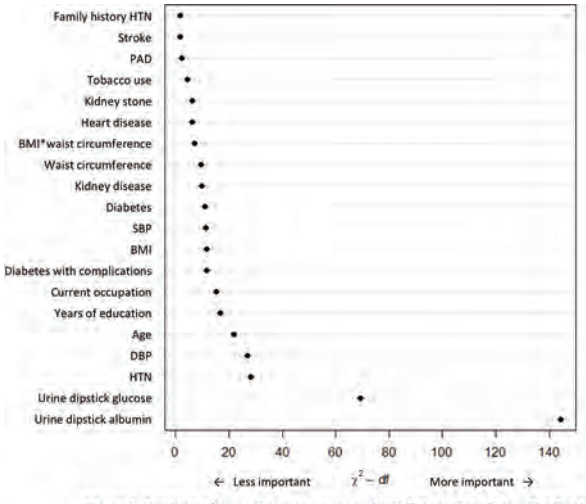

Figure 1. Ranking of apparent importance of predictors included in the final model
*Abbreviations: HTN, hypertension; PAD, peripheral arterial disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure

SA-PO764

CKD Without Significant Proteinuria—Is It Possible to Predict Faster Decline in eGFR?

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Background: CKD patients without significant proteinuria have been recognized that they tend to have slower eGFR decline than proteinuric CKD patients have. However substantial population of those patients eventually reach ESRF. The aim of this study is to elucidate risk factors for progressive decline in eGFR in patients without significant proteinuria.

Methods: A hospital-wide survey included a whole set of laboratory tests over 24 months. Patients with at least 3 measurements of eGFR over 365 days or more, with an averaged eGFR of less than 50mL/min/1.73m^2 were collected. An eGFR slope was calculated for each patient. For the assessment of proteinuria, a dipstick urine protein determination was considered to better represent the real-world clinics for all the subspecialities in the Hospital; numbers of 0, 0.5, 1, 2, 3 or 4 were applied to (-), (+-), (1+), (2+), (3+) or (4+) respectively, then the numbers were averaged during the study period (avUprot); an excellent relation between avUprot and averaged U-protein/U-creatinine ratio has been previously confirmed in a different cohort (Up/Ucr = -0.346 + 1.185*avUprot, n=1,379; p<0.0001). Patients with avUprot less than 1.0 comprised the final cohort for this study. All the laboratory values such as serum albumin were equally averaged during the study period for each patient.

Results: Among the total 40,797 patients with laboratory examination, the final cohort included 1,174 patients (M:F 581:593, age 32-95 (median 77)), with eGFR 5.8-49.9 (41.3) mL/min/1.73m^2 and avUprot 0.00-0.96 (0.14) g/g Cr. In a univariate analysis, the eGFR slope was associated with age, plasma ALT (alanine aminotransferase), serum Na and serum albumin. In a multivariate stepwise analysis, the eGFR slope was correlated with ALT, serum Na and serum albumin. In a 3x3 table where the cohort was divided into tertiles for ALT and serum albumin, patients with the lowest tertile of serum albumin (1.70-3.87 g/dL) combined with the highest tertile of ALT (22.0-265.4 IU/L) had the fastest eGFR decline (-4.07+-9.11 (median -2.44) mL/min/1.73m^2/yr) among the 9 divisions, with an OR 2.13 for the fastest-eGFR-slope tertile (-2.47 mL/min/1.73m^2/yr or below) against the sum of the remaining 8 divisions as a reference.

Conclusions: Combination of serum albumin and ALT might serve as a simple measure to predict progressive decline in eGFR in the CKD patients with minimal or no proteinuria.

SA-PO765

Can Rapidly Progressing CKD Patients Be Identified Using Billing Codes?

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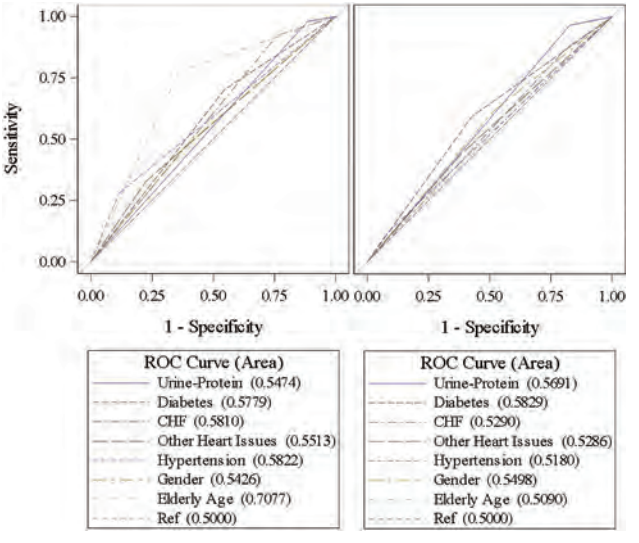
Background: The International Classification of Diseases (ICD) coding system is the industry standard diagnostic coding tool. However, ICD codes often do not reflect the clinical diagnosis, particularly among Chronic Kidney disease (CKD) patients. This study evaluates the diagnostic accuracy in identifying rapidly progressing CKD patients using CKD-related ICD codes in a large insurer database.

Methods: Serial observations from 2007 through 2014 were examined. 216,529 individuals had valid serum creatinine measurements. The progression of CKD using a longitudinal mixed-model was contrasted with that documented by ICD codes. Rapid progressors (yearly eGFR loss greater than 4 ml/min/1.73m^2) were identified. Clinical diagnosis according to the Kidney Disease Outcomes Quality Initiative (KDOQI) was compared to diagnosis using ICD codes.

Results: 323 rapid progressors were identified among the 10,927 CKD patients qualifying for inclusion in the clinical progression analysis. ICD codes identified 83 of these, for a sensitivity of 25.7% and specificity 95.09%. Of 28,762 laboratory-confirmed CKD patients, 9,249 had a qualifying ICD code, for a sensitivity of 16%. Of 187767 patients without laboratory-confirmed CKD, 182,359 did not have a qualifying ICD code, for a specificity of 97.12%.

Conclusions: This study leverages 7 years of serial observations, facilitating identification of disease progression, and depicts the novel finding that ICD-codes display poor capacity to identify rapidly progressing CKD patients when compared to gold standard KDOQI guidelines, and further demonstrates the limitations of coding in CKD diagnosis management. This study further defines the limitations of ICD codes in addressing diagnosis of disease severity or disease progression for clinical or epidemiological purposes.

Funding: Clinical Revenue Support



ROC Curves for Detecting CKD (Left) and Rapid Progressors (Right) for Comorbid Conditions

SA-PO766

Comparisons of Different Equations for Estimated Glomerular Filtration Rate in Chinese Han Patients with CKD in Real World

Huijuan Mao. *First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: The currently recognized and most accurate estimate of glomerular filtration rate(eGFR) formula is the creatinine- cystatin C joint formula(EPI_Cr_CysC) developed by the Chronic Kidney Disease Epidemiology Research Group. However,

cystatin C (CysC) can not be determined in many cases, so that the wide application of EPI_Cr_CysC formula is limited. The purpose of this study is to study the agreement, precision and accuracy between other eGFR formulas and EPI_Cr_CysC formulas, and to find the best alternative formula for EPI_Cr_CysC.

Methods: We conducted a cross-sectional study research of 1913 CKD patients. The eGFRs were calculated separately by creatinine clearance rate and Cockcroft-Gault equation corrected for standard body surface area (Ccr_BSA and eCcr_BSA), CKD-EPI_creatinine equation (EPI_Cr), CKD-EPI_cystatin C equation (EPI_CysC), EPI_Cr_CysC equation, Modification of Diet in Renal Disease equation with standardized serum creatinine (MDRD) and full-age-spectrum creatinine equation (FAS). And EPI_Cr_CysC equation was used as the reference.

Results: When compared with EPI_Cr_CysC equation, EPI_Cr equation achieved the highest agreement in eGFR estimates [Lin's concordance correlation coefficient (95%CI), 0.936(0.930, 0.941)]. And eCcr_BSA and EPI_Cr equation achieved the first and second highest percent agreement in accurate classification of the CKD stage [percent agreement, 72.55% VS 71.25%]. MDRD equation got the minimal bias and was closely followed by EPI_Cr equation [median difference (95% CI), -1.3(-2.0, -0.8) VS 2.5(1.7,3.3) mL/min/1.73m2]. EPI_CysC and EPI_Cr equations achieved the first and second highest precision [IQR of the difference (95% CI), 12.2(11.6,12.9) VS. 15.5(14.7,16.3) mL/min/1.73m2]. EPI_Cr and MDRD equations performed similarly and tied for first place in 30% accuracy [1-P30 (95% CI),18.6(16.9,20.4) % VS 18.6 (16.8, 20.3) %].

Conclusions: For assessment of renal function, EPI_Cr equation performed the best and remained an acceptable alternative to EPI_Cr_CysC equation in the absence of cystatin C.

Funding: Government Support - Non-U.S.

SA-PO767

Estimation of Glomerular Filtration Rate in Multi-centre Chinese Individuals: Comparison of 2017 New FAS (Full Age Spectrum) and 2012 CKD-EPI (CKD Epidemiology Collaboration) Equations

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Background: The recent guidelines recommend using the estimated glomerular filtration rate (eGFR) to evaluate renal function. There are two reported full-age-spectrum (FAS) equations in 2017, which based on serum cystatin C (Cys) concentrations with or without accompanying serum creatinine (Cr) level (FAS_{Combi} or FAS_{Cys}). We compared the performance and assessed the applicability of the new FAS formulae with the 2012 CKD-EPI ($CKD\text{-}EPI_{Cys}$ and $CKD\text{-}EPI_{Cr\text{-}Cys}$) equations in Chinese subjects.

Methods: A total of 1184 technetium-99m diethylene-triamine-penta-acetic acid (99mTc-DTPA) renal dynamic images from four different hospitals in China to measure GFR (mGFR) regarded as the referenced method. The bias, precision and accuracy of eGFR and mGFR calculated by four formulae were compared.

Results: The two CKD-EPI equations performed poor in elderly with moderately-severely injured GFR (the proportion of estimated GFR within 30% of referenced GFR, P30, <70%). FAS_{Combi} formula had less bias (median bias, -2.87), more precision (the inter-quartile range of difference, IQR, 19.01), and more accuracy (P30, 74.16%) in whole cohort, and the difference compared with other three equations was statistically significant. In the rGFR <60 ml/min/1.73m^2 subgroup, the FAS_{Combi} formula showed the best performance and the differences were statistically significant. In older subjects, compared with FAS_{Cys}, $CKD\text{-}EPI_{Cr\text{-}Cys}$ and $CKD\text{-}EPI_{Cys}$, the FAS_{Combi} formula had relatively less bias (median bias, -8.09 vs. -9.63, -7.52, -11.04, p<0.05), most precise (IQR, 15.18 vs. 16.32, 15.22, 16.63), and most accuracy, P30 was statistically different from the other equations, and achieved a ideal value >70%.

Conclusions: The performance of the FAS_{Combi} formula is better than that of the $CKD\text{-}EPI_{SCr\text{-}Cys}$ formula in the Chinese population, particularly in the elderly. Yet, further modification of FAS equations from a large-scale study could be more suitable for the Chinese population, particularly in older subjects.

SA-PO768

GFR Slopes – The Statistical Method Matters

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Background: The FDA is considering the use of eGFR decline and eGFR slope as surrogate endpoints in CKD research. Several statistical methods can be used to estimate GFR decline (Coresh 2014, Leffondre 2015, Asar 2015). We questioned if these methods differed with respect to the estimates of GFR slopes.

Methods: We used the MASTERPLAN (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse practitioners) dataset, which included 762 patients with an eGFR between 20 to 70 ml/min, a median follow-up of 4.8 yr (IQR 4.3-5.3) and 103 ESRD events. We estimated percentage and annual change in MDRD eGFR over a period of 2 years using 3 methods. For annual change: 1) last estimated GFR – first estimated GFR, 2) linear mixed model (LMM) using the first and last measured GFR, 3) LMM using all GFR measures in 2 years' time. For percentage change: 4) (last estimated GFR – first estimated GFR) / (first estimated GFR) * 100 and 5) LMM with log-transformed GFR using the first and last measured GFR, 6) LMM with log-transformed GFR using all GFR measures in 2 years' time.

Results: Overall data were available of 6275 visits and 91% of patients had at least 4 visits within 2 years. Both the distribution for annual and percentage change in eGFR varied greatly between the different statistical methods (Figure 1). Using the first-last eGFR method to estimate GFR slope resulted in a 5 fold wider distribution on the annual scale and 10 fold on the relative scale compared to using a LMM.

Conclusions: The statistical method that is used to estimate change in GFR has a great impact on the estimated GFR slopes. The current debate about the use of eGFR declines and eGFR slope as surrogate endpoints in CKD should also consider the statistical method how to estimate GFR decline.

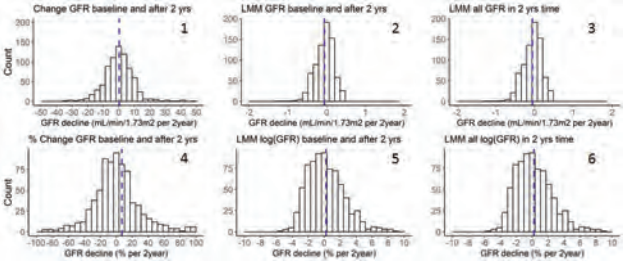

Figure1: Distribution of GFR slopes. The number in the figure corresponds to the statistical method described in the methods. The blue line is the average GFR slope.

SA-PO769

Optimal Follow-Up Intervals for Different Stages of CKD

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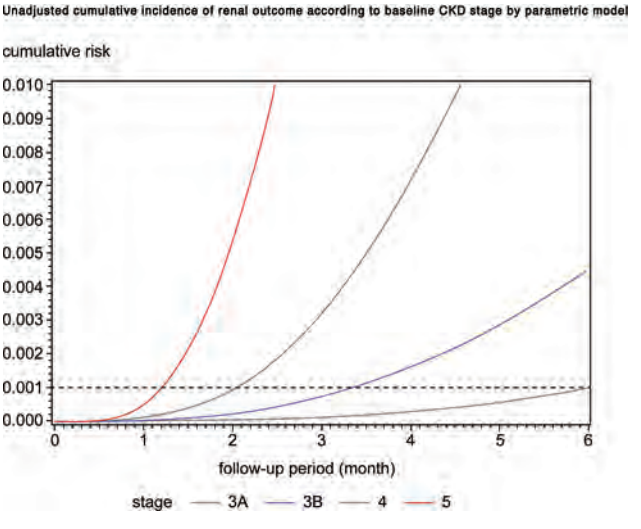
Background: Chronic kidney disease is a public health challenge. However, no evidence-based, optimal, follow-up intervals for patients with chronic kidney disease have been suggested. This study aimed to clarify appropriate follow-up intervals for different chronic kidney disease stages.

Methods: We studied 2682 patients with chronic kidney disease. Both of the numbers of patients experiencing a 50% increase in creatinine and those reaching end-stage renal failure were tabulated by their chronic kidney disease stage. The renal function-testing interval was defined as the estimated time for 0.1% of the patients with chronic kidney disease to have a composite renal outcome, when adjusted for clinical risk factors. Transitions from chronic kidney disease stage-based subgroups were analyzed using parametric cumulative incidence models. Other sensitivity analyses involved the estimation of the time to renal event occurrence for 1% of patients.

Results: Of the 913 patients (34%) who had a composite renal event, 29 patients had stage 3A (10.5%), 151 had stage 3B (16.3%), 429 had stage 4 (41.0%), and 304 had stage 5 chronic kidney disease (70.9%). The estimated renal function testing intervals were 6.0 months for chronic kidney disease stage 3A, 3.4 months for stage 3B, 2.0 months for stage 4, and 1.2 months for stage 5.

Conclusions: The optimal follow-up intervals were longer for patients with lower chronic kidney disease stages. These estimates are longer than those recommended by the relevant guidelines, and may serve as a reference to inform nephrologists in selecting follow-up intervals for their individual patients.



SA-PO770

Methods to Identify Novel, Repeatedly Measured Biomarkers of CKD Outcomes

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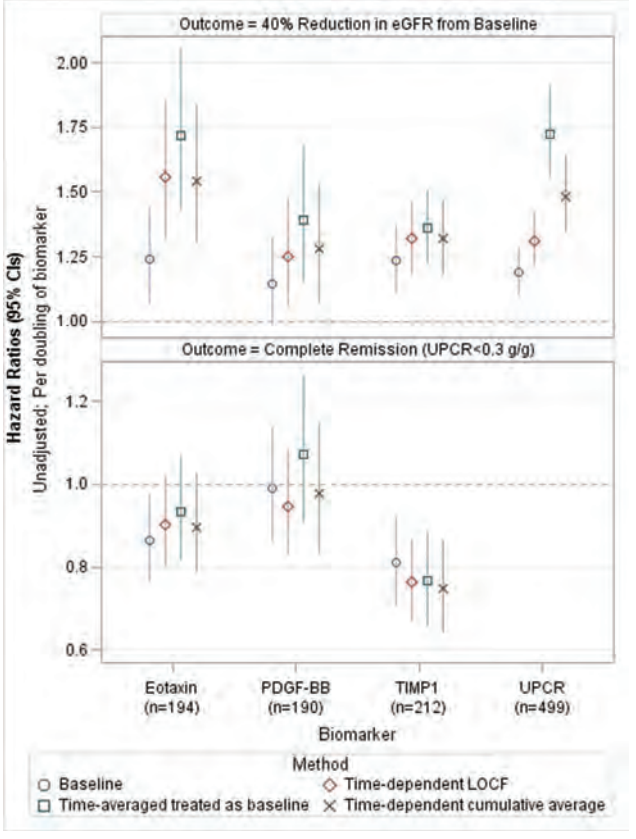
Background: Identifying novel biomarkers is critical to advancing diagnosis and treatment of CKD, but relies heavily on the statistical methods used. Inappropriate methods can lead to both false positive and false negative associations between biomarkers and outcomes. This study assessed accuracy of methods using computer simulations and compared biomarker effect estimates in NEPTUNE, a prospective cohort study of patients with glomerular disease.

Methods: We compared four methods for analyzing repeatedly measured biomarkers in Cox models: 1) baseline, that only uses the single baseline biomarker value, 2) time-dependent with last observation carried forward (LOCF), that assumes the biomarker is unchanged until the next value, 3) time-averaged, that averages the biomarker values over all follow up and uses that average as a baseline covariate, and 4) time-dependent cumulative average, that updates the average using biomarker values at or before each time point.

Results: Simulation results showed the time-averaged method often gave extremely biased, inaccurate results. In NEPTUNE, all assessed urinary biomarkers were positively associated with 40% reduction in eGFR. Compared to the LOCF method, the baseline method had 6-21% lower hazard ratios (HRs), and the time-averaged method had 3-32% higher HRs [figure]. For complete remission, Eotaxin and TIMP1 were negatively associated with the outcome, and PDGF-BB had little association. HRs from the time-averaged method were always higher (1-13%) than the LOCF method.

Conclusions: Different analytic methods resulted in markedly different results. Using inappropriate methods such as time-averaging can bias effect estimates, while other methods provide prognostic (baseline), additive (cumulative average), or instantaneous (LOCF) effects depending on the hypothesized underlying mechanism.

Funding: NIDDK Support



SA-PO771

GFR Decline Based on Albuminuria Status in Patients with DM, Hypertension, and eGFR≥60

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Background: In patients with GFR≥60, CKD is defined by presence of 2 albuminuria (UACR), obtained 3 months apart. Often, due to the clinical stability of these patients and limited clinic resources, most patients ended up with 1 UACR done annually with a potential delay in CKD diagnosis and treatment. We postulate that a single UACR reading in DM and hypertensive patients at high risk for the development of CKD, could have a significant impact in the progression of CKD. Our study aims to determine the eGFR decline in patients with only 1 UACR reading at baseline compared to those who meets the traditional criteria for CKD of 2 readings.

Methods: In this retrospective cohort study, we included patients with DM or hypertension, GFR≥60, from 9 primary care clinics between 2010 to 2014. UACR results were obtained for up to 2 years prior to study period, and patients were stratified into 3 groups (Gp) – Gp 1: normal UACR; Gp 2: 1 abnormal ACR; Gp 3: 2 abnormal UACR at least 90 days apart. The patients were followed up for 2 years and GFR decline were compared, and adjusted for age, ethnicity, HbA1c, blood pressure and ACEi use.

Results: Of 11,783 patients in the study, 85.4% have DM. Baseline parameters between groups were similar. Malay patients with DM was found to have a greater GFR decline (-1.0 [-1.6, -0.4], p<0.001), consistent with previous reports. Unadjusted GFR decline, when stratified by DM status, was greater for those with positive UACR (See table). GFR decline was similar between Gp 2 and 3, especially in DM patients. In the multivariate analysis with Gp 1 as reference, GFR decline was similar between Gp 2 and 3 in diabetic patients, but higher in Gp 3 in hypertensive patients.

Conclusions: In diabetic and hypertensive patients, albuminuria was associated with greater GFR decline. GFR decline was similar regardless of 1 or 2 UACR results, especially in patients with DM. This suggests that treatment should be considered with a single albuminuria result before a second reading is needed to meet the CKD definition.

	Unadjusted GFR Decline (DM)		Unadjusted GFR Decline (Non-DM)	
	GFR≥90	GFR 60-89	GFR≥90	GFR 60-89
Gp 1	-2.0±4.6	-0.9±5.7	-1.7±4.2	-1.1±5.5
Gp 2	-3.8±6.4	-3.0±7.1	-2.7±5.0	-2.2±6.2
Gp 3	-3.2±5.5	-3.0±7.0	-3.9±5.8	-3.5±5.7
	GFR Decline after Multivariate Analysis			
Gp 1	Reference			
Gp 2	-1.5 (-1.8 to -1.1) p<0.001	-1.8 (-2.2 to -1.5) p<0.001	-1.0 (-1.7 to -0.4) p=0.003	-1.1 (-1.8 to -0.3) p=0.008
Gp 3	-1.0 (-1.6 to -0.4) p<0.001	-1.8 (-2.4 to -1.3) p<0.001	-2.1 (-3.5 to -0.7) p=0.003	-2.8 (-4.2 to -0.7) p=0.006

SA-PO772

High Instead of Lower CKD-EPI-Based eGFR Values in Dutch Ethnic Minorities at Risk for CKD

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Background: According to the widely adopted KDIGO guidelines, classification of chronic kidney disease (CKD) and evaluation of prognosis is based on two components: estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR). This approach has, however, never been validated for various ethnic groups living in the Netherlands and might lead to uncertainty in CKD staging. We investigated to what extent ethnic differences in eGFR and ACR can be explained by differences in demographics and traditional cardiovascular risk factors.

Methods: Baseline data from the HELIUS study, a multi-ethnic cohort study conducted in the city of Amsterdam, were used. Analyses were conducted among 18,534 participants (aged 18-70 years) of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Moroccan and Turkish ethnic origin. We used multiple regression analyses to determine ethnic differences in eGFR (CKD-EPI formula) and ACR, with additional adjustments for age, sex, traditional cardiovascular and kidney risk factors, and educational level.

Results: Mean (SE) eGFR was higher in all ethnic minority groups as compared to those of Dutch origin (eGFR 94.9±0.3 mL/min/1.73m^2), ranging from 1.9±4.1 in subjects from South-Asian Surinamese origin to 15.0±0.39 in subjects from Moroccan origin. Also, ACR was higher among all ethnic minorities as compared to those of Dutch origin (ACR 0.6±0.2 mg/mmol), ranging from 0.5±0.2 in subjects from African Surinamese origin to 1.7±0.2 in subjects from South-Asian Surinamese origin. Adjustment for age, sex, traditional cardiovascular and kidney risk factors diminished the differences in both eGFR and ACR for most ethnic groups but these differences were still highly significant.

Conclusions: Our results show that eGFR is higher among ethnic minority groups as compared to those from Dutch origin. Regarding previously found higher CKD prevalence in ethnic minority groups of HELIUS, these findings underscore the need for ethnicity specific GFR estimations, as the currently recommended use of the CKD-EPI-based eGFR, which only distinguishes 2 ethnic groups, might lead to an underestimation of risk in multi-ethnic populations. Given the observed higher ACR values among minority groups, ACR might represent a more useful risk factor in multi-ethnic populations.

SA-PO773

Mortality Risk for Low Density Lipoprotein Cholesterol Across CKD Stages in 1.95 Million US Veterans

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Background: Prior studies have shown that higher low-density lipoprotein cholesterol (LDL) levels are associated with worse survival in the general population, yet this

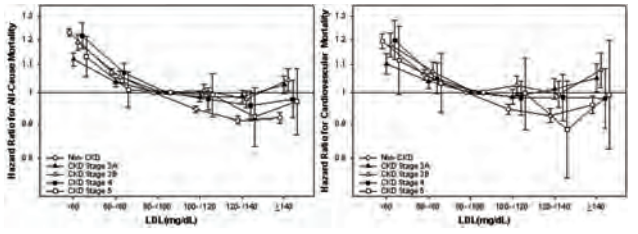
association is attenuated in chronic kidney disease (CKD) patients. However, the graded impact of kidney disease on the association of LDL with mortality is unclear.

Methods: We investigated a cohort of 1.95 million US veterans with baseline LDL and creatinine data from 2004-2006. Over a median[IQR] follow-up of 10.5[7,11] years, we examined the relationship of baseline LDL with all-cause and cardiovascular (CV) death risk across CKD stage in Cox proportional hazard models adjusted for demographics, comorbid conditions, smoking status, other lipids and prescription of statins and non-statins. CKD stage was determined according to estimated glomerular filtration rate (eGFR) at the time of LDL measurement.

Results: The cohort had a mean±SD age of 65±14 years, and included 5% females, 15% African-Americans, 22% diabetics, 32% statin-users and 44% current smokers. The median[IQR] of baseline LDL was 103[82,128] mg/dL and eGFR was 76[61,91] mL/min/1.73m^2. Patients with higher LDL were more likely to be younger, African-American, a current smoker, not on a statin, and have a higher eGFR. Patients with lower LDL (<60mg/dL) had a higher risk of all-cause and CV mortality across all stages of CKD, compared to LDL 80-<100 mg/dL. Higher LDL(≥140 mg/dL) was associated with higher all-cause and CV mortality risk in CKD3A and 3B, but these associations were attenuated for CKD4 and 5. Of note, in non-CKD veterans, higher LDL was protective for both CV and all-cause death risk. [Figure]

Conclusions: Elevated LDL ≥140 mg/dL is associated with higher all-cause and CV mortality risk among CKD 3A and 3B, but not among more advanced CKD stages. Future studies are needed to evaluate the impact of lipid lowering therapies and effect of time-updated LDL with mortality risk across CKD stages.

Funding: Veterans Affairs Support



SA-PO774

Associations of Cholesterol and Mortality Across eGFR Strata in the NHANES Cohort

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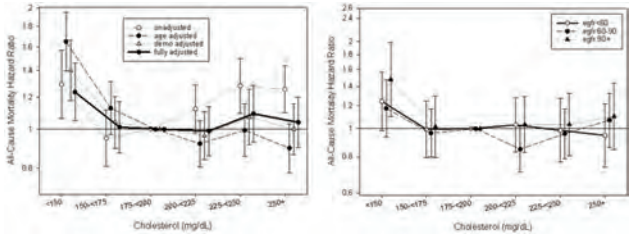
[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]University of California, Irvine, Orange, CA; [3]UC Irvine Medical Center, Bishop, CA; [4]University of Tennessee Health Science Center, Memphis, TN; [5]University of California Irvine, School of Medicine, Orange, CA.

Background: Prior studies in chronic kidney disease (CKD) patients have shown a paradoxical association where CKD patients with higher cholesterol did not have the higher risk of mortality, as observed in the general population. However, the cholesterol-mortality relationship has not been thoroughly examined in a single nationally representative cohort with the ability to assess the impact of CKD stage on this relationship.

Methods: Using data from the National Health and Nutrition Examination Surveys (NHANES), we identified 31,270 adults with available measurements on serum cholesterol and creatinine between 1999-2006. We examined the association of cholesterol with mortality in 6 groups of cholesterol, and stratified by 3 levels of estimated glomerular filtration rate (eGFR). Associations were examined with Cox models with multivariable adjustment for demographics, comorbidities, medication use, body mass index and albumin.

Results: The cohort mean age was 47±20 years and comprised of 52% females and 20% non-Hispanic black patients. Patients with higher cholesterol tended to be older, female, non-Hispanic white, but less likely to be diabetic, or take medications for high cholesterol. Over a median follow-up of 6[3, 9] years, 2,802 deaths occurred. Compared to cholesterol 175-<200 mg/dL, both low and high cholesterol was associated with higher death risk in unadjusted models, but associations for higher cholesterol was attenuated after age adjustment. In fully adjusted models, patients with lower cholesterol (<150 mg/dL) had or trended towards a higher risk of mortality across all strata of eGFR. Yet, higher cholesterol was not associated with higher mortality risk in any strata of eGFR. [Figure]

Conclusions: Among the nationally representative NHANES cohort, higher cholesterol is not associated higher mortality risk. Future studies evaluating the impact of kidney disease on the cholesterol-mortality association are needed.



SA-PO775

Patterns of Troponin Elevation in Patients with CKD and Long-Term Mortality Risk After Progression to ESRD

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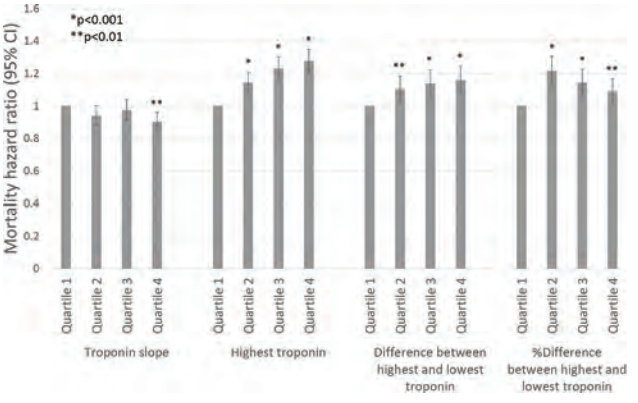
Background: Elevated troponin as a marker of myocardial infarction is associated with poor short and long term mortality. Chronic kidney disease is commonly associated with higher and sustained levels of troponin due to reduced clearance. It is not known if the pattern of troponin elevation in patients with advanced CKD confers higher mortality risk after starting dialysis.

Methods: We examined 16,563 US veterans who had troponin levels measured during the 3 years prior to start of dialysis. We examined associations of 24-hour slope of troponin elevation, maximum troponin level, and the absolute value and percentage of the difference between the maximum and minimum troponin levels with all-cause mortality in Cox models adjusted for demographics, comorbidities, smoking status, blood pressure, BMI and baseline eGFR.

Results: Patients were 66±10 years old, 97% male, 37% African-American, 77% diabetic, and 67%, 69% and 41% had histories of ischemic heart disease, congestive heart failure and cerebrovascular disease, respectively. 11,196 patients died (mortality rate: 243/1000 patient-years, 95%CI: 238-248) over a median follow-up of 2.43 years after starting dialysis. Steeper rise in troponin level over 24 hours was not associated with higher mortality (Figure). Higher levels of maximum troponin level were associated with significantly higher mortality, whereas a higher absolute and percentage difference between maximum and minimum troponin levels was less consistently associated with increased mortality (Figure).

Conclusions: Elevated troponin in patients with advanced stage CKD is associated with higher risk of mortality after initiation of dialysis. Higher levels of maximum troponin values show the most consistent association with higher mortality, whereas the rate of troponin rise over a 24-hour period is not associated with long term mortality.

Funding: NIDDK Support, Veterans Affairs Support



SA-PO776

Longitudinal Relationship of Left Ventricular Hypertrophy with Cardiovascular Events in CKD

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Background: We aimed to evaluate the relationship between left ventricular (LV) hypertrophy and adverse cardiovascular (CV) events among patients with chronic kidney disease (CKD).

Methods: Based on the Chinese Cohort Study of CKD (n=3499), 2000 participants with interpretable echocardiograms, complete relevant clinical data and without a baseline CV disease history were enrolled in the study. LV mass was calculated using the area-length method and indexed to height$^{2.7}$. CV events included incident acute myocardial infarction, unstable angina, hospitalization for congestive heart failure, cerebrovascular events and peripheral vascular diseases. The population was followed-up until occurrence of CV events or by June 30, 2017. Cox proportional hazards regression model was used to estimate the relationship between the exposure and outcomes.

Results: The mean age of the population was 47.2±13.7 years, with 56.4% of males. The mean level of estimated glomerular filtration rate (eGFR) was 52.9±31.3ml/min/1.73m^2. The proportions of CKD stages 1, 2, 3a, 3b and 4 were 16.8%, 17.5%, 14.9%, 23.3% and 27.7%, respectively. Mean level of LV mass/ height$^{2.7}$ was 39.7±12.7g/m$^{2.7}$, with

the proportion of LV hypertrophy (LV mass/height$^{2.7}$≥47g/m$^{2.7}$ in women and ≥50 g/m$^{2.7}$ in men) being 17.9%. After a median follow-up of 4.45(inter-quartile range: 3.76-5.05) years, 89 CV events occurred, with an incidence rate of 1.03 per 100 person-years among total patients with CKD, 2.23 per 100 person-years among those with LV hypertrophy and 0.78 per 100 person-years among those without LV hypertrophy (log-rank p-value<0.001). LV hypertrophy or a standard deviation increase in LV mass/ height$^{2.7}$ was significantly associated with increased risk of CV events after adjustment for traditional CV risk factors, albuminuria and eGFR. The hazard ratios and 95% confidence interval were 1.78(1.12-2.81) and 1.40(1.19-1.66), respectively. Sensitivity analysis among those with chronic glomerular nephritis or excluding congestive heart failure from the CV events showed consistent results.

Conclusions: LV hypertrophy is independently associated with increased risk of CV events among patients with CKD. Further studies are needed to evaluate the clinical effectiveness of screening high risk population among patients with CKD by using LV hypertrophy.

Funding: Government Support - Non-U.S.

SA-PO777

Association Between Polymorphism of rs11864909 and Serum Uromodulin Among CKD Was Modified by Kidney Function

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Background: The single nucleotide polymorphism (SNP) of rs11864909 is located close to uromodulin gene of *UMOD*. A genome-wide association study in east Asian populations detected a genome-wide significant association between the SNP and estimated glomerular filtration rate (eGFR). We aimed to test the association of the SNP with serum uromodulin among patients with chronic kidney disease (CKD) and test if the association was modified by eGFR.

Methods: Altogether, 1812 participants with complete relevant clinical and genotyping data in the Chinese Cohort Study of CKD (n=3499) was enrolled in the study. Genotyping for rs11864909 was conducted by TaqMan genotyping assay. Serum uromodulin was measured by a commercially available ELISA kit. Linear regression analysis was used to test the association between rs11864909 and serum uromodulin.

Results: The mean age of the population was 48.4±13.7 years, with 56.9% of males. The mean level of eGFR was 52.5±30.5ml/min/1.73m^2. The proportions of patients with CKD stage 1, 2, 3 and 4 were 15.3%, 16.8%, 41.2% and 26.7%, respectively. The mean level of serum uromodulin was 90.9±61.2 ng/mL. The CC, CT and TT genotype of the rs11864909 polymorphism accounted for 72.7%, 24.7% and 2.6% of the population (*P* for Hardy-Weinberg equilibrium>0.05). People with the CT&TT genotype had a significantly lower level of serum uromodulin than those with CC genotype (79.7 ng/mL vs. 95.1 ng/mL, *P*<0.001). After inclusion of the interaction term between rs11864909 and eGFR (*P* for interaction<0.001) in the multi-variable adjusted linear regression model, the regression coefficient (standard error) per 1 ml/min/1.73m^2 increase in eGFR increased from 1.4(0.039) to 1.5(0.045), while the effect of rs11864909 (CT&TT vs. CC) lost statistical significance (regression coefficient increased from -20.6[2.3] to -2.1[4.6]). Sensitivity analysis among those with CKD stages 3 and 4 and those from large central study sites got consistent results.

Conclusions: The common polymorphism of rs11864909 in the *UMOD* gene associated with the level of serum uromodulin among patients with CKD, but the relationship was influenced by kidney function. The results add further insights into the effect of *UMOD* gene among CKD.

Funding: Government Support - Non-U.S.

SA-PO778

Early Impairment of Kidney Function Is Associated with Changes in Cardiac Structure and Function – Findings from a Large Population-Based Cohort of Elderly Subjects

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Background: The pathophysiological association between heart and kidney diseases is often referred to as the cardiorenal syndrome. There are only few previous community-based studies reporting on the association between renal function and left ventricular (LV) function. In recent years also a minor reduction of glomerular filtration rate (GFR) has emerged as a risk marker for changes in cardiac structure. However, there is little knowledge about this in early renal impairment and echocardiographic functional parameters indicating diastolic dysfunction in community-based cohorts.

Methods: The study population consisted of 1504 individuals with no prior history of congestive heart failure or asymptomatic left ventricular ejection fraction ≥40% and an estimated glomerular filtration rate (eGFR) based on cystatinC >15 mL/min/1.73m^2. Participants were categorized according to eGFR; ≥90; 75-89; 60-74; 45-59; 30-44; and 15-29 mL/min/1.73m^2. We evaluated associations between eGFR and echocardiographic findings. Transmitral pulsed Doppler flow and tissue Doppler imaging (TDI) in the four-chamber view were used to measure LV diastolic function. Peak myocardial velocity of the basal LV wall in early (É) and late (Á) diastole in the lateral (lat) and septal (sept) walls and Doppler measurement of peak velocity of blood flow through the mitral valve in early (E) and late (A) diastole were measured.

Results: Associations between reduced eGFR and echocardiographic findings indicating early structural changes were found for; left atrium area/body surface area (p=0.013) and diastolic function; peak early mitral valve velocity (A) (p=0.003), peak late atrial mitral valve velocity/ peak systolic myocardial velocity at mitral annulus in lateral wall; (E/Élat) (p=0.002), mean of É mean of lateral and septal wall/ Á mean of lateral and septal wall (mean Ém/Ám) (p=0.027). Associations between E/Élat and meanÉm/Ám and eGFR were present already in mild-moderate kidney dysfunction (eGFR 45-60 mL/min/1,73m^2). These associations were only significant among men.

Conclusions: A significant association between early impairment of renal function and echocardiographic markers of cardiac structure and diastolic function was observed supporting the hypothesis that interaction between the kidney and heart exists even in the early stages of renal impairment.

SA-PO779

The Association of Markers of Mineral Bone Disease with CVEs in Early CKD

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Background: Markers of mineral bone disease (MBD), particularly FGF23 and serum phosphate, are associated with a higher risk of cardiovascular events (CVEs) in Chronic Kidney Disease (CKD). However, it is not clear if these associations exist in early CKD, when phosphate is normal and FGF23 only mildly elevated. We investigated biomarkers of MBD as risk factors for CVE in people with CKD stage 3 in primary care.

Methods: 1741 people with estimated GFR 59-30mL/min/1.73m^2 (eGFR) were recruited to the Renal Risk in Derby (RRID) study and assessed at baseline, year 1 and 5. Data on all hospital admissions with CVE (using ICD-10 coding) and cardiovascular deaths between 2008 to 2015 were obtained from NHS Digital. Cox regression analysis was performed on the whole cohort, those with heart failure (HF) or atherosclerotic events to identify risk factors for CVEs.

Results: 608 CVEs occurred during a mean period of 5.1±2.2 years, a rate of 6.8/100 participant years. The most frequent CVE was HF (345/608=57%). In the whole cohort age, male sex, HDL cholesterol, smoking, eGFR and urinary albumin to creatinine ratio were confirmed as independent risk factors for CVEs. Among the MBD biomarkers, phosphate and PTH predicted CVEs but FGF23 and vitamin D did not. There were differences in risk factors for HF versus atherosclerotic events (Table).

Conclusions: We identified HF as the commonest CVE in those with early CKD. In addition we identified phosphate and PTH as independent risk factors for CVEs even at early stages of CKD, when there is only minor perturbation of these variables. Our findings suggest trials of interventions to lower serum phosphate in early CKD are warranted.

Funding: Private Foundation Support

Comparative risk factors for CVE

	All CVEs n=608		HF groups=345		Atherosclerotic groups=263	
Risk factor at baseline	p value	HR	p value	HR	p value	HR
Male sex	0.001	1.424	0.005	1.458	0.003	1.58
Age (yrs)*	<.0001	1.385	<.0001	1.369	<.0001	1.503
HDL cholesterol (mmol/l)*	0.003	0.866	0.01	0.851	0.03	0.854
Smoking	0.02	1.24	NS	NS	0.006	1.47.2
UACR (mg/mmol)‡	0.001	1.168	0.01	1.17	0.005	1.224
eGFR CKDEPI (mL/min/1.73m2)*	0.04	0.897	0.01	0.841	NS	NS
Serum phosphate (mmol/l)*	0.003	1.143	0.01	1.162	0.03	1.167
PTH (pg/ml)*	0.002	1.158	0.001	1.228	NS	NS

*per Standard Deviation, ‡log transformed data, HR=Hazard Ratio, UACR= Urinary albumin to creatinine ratio, PTH=Parathyroid hormone, NS=Not significant

SA-PO780

Worsening of Renal Function Predicts Mortality in Patients with Cancer and CKD

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Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for death in cancer patients with CKD.

Methods: Among 397 outpatients with cancer referred to nephrology evaluation (2009-12), 202 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The Cox regression was used to examine the predictors of mortality.

Results: After a follow-up of 3.9±2 years, the mortality rate observed was 57%. The patients features are shown in Table1. In the Cox regression analyses, serum albumin (aHR=0.38; CI 0.28-0.54, p<0.001), ongoing chemotherapy [aHR=0.61; CI 0.38-0.97, p=0.038], and CKD progression [aHR: 2.54; CI 2.54-4.18, p<0.001), defined as a sustained decline in eGFR of more than 5ml/min/1.73m^2/yr, were the independent predictors of mortality in our population. Of note, worsening of renal function remained a independet risk factor for mortality even after adjustments for important cancer related factors (presence of metastasis) and Karnofsky index.

Conclusions: Patients with cancer and CKD have a poor prognosis. Serum albumin, ongoing chemotherapy, and CKD progression were independent factors associated to mortality.

Table 1. Baseline Features

	Death (n=116)	Surviving (n=86)
Age (yr)	67±12	65±12
Male (%)	76	64
Solid Tumors (%)	86	84
Metastasis (%)	34	18*
Ongoing Chemotherapy (%)	46	21*
Karnofsky index	84±14	92±12*
Obstructive uropathy (%)	21	10
Baseline eGFR (ml/min/1.73m2)	37±16	40±14
Albuminuria > 300 mg/g (%)	62	59
Serum Albumin (g/dL)	3.9±0.7	4.3±0.5*
Hemoglobin (g/dL)	11.1±2	12.1±2*
CKD progression (%)	32	9*

Results are expressed as mean±SD and percentage. * < 0.05 vs Death group.

SA-PO781

Association of eGFR and ACR with Cardiovascular Outcomes in the Elderly

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Background: Data on the effect of kidney function (eGFR) / kidney damage (ACR) on cardiovascular (CV) outcomes in the elderly remain scarce. We investigated the effect of eGFR on cardiovascular outcomes using data of the Berlin Initiative Study (BIS).

Methods: The BIS has followed 2069 older adults ≥70 yrs since 2009. eGFR/kidney damage were assessed by eGFR-BIS2(crea/cysC) and ACR, respectively. ICD-10-based outcomes were stroke or myocardial infarction (MI), combined or single, ischemic stroke, and death to all-cause. A Competing Risk Model was set up for CV events, a Cox proportional hazards model for all-cause mortality for hazard ratios(HR) and 95% confidence intervals (CI). Individuals with CV event before baseline were excluded. Models adjusted for age, sex, diabetes, smoking, waist-to-hip-ratio, antihypert. treatment, systolic BP, pulse pressure, c-reactive protein, total and high density cholesterol.

Results: Within a median f/up of 7.1 yrs, 276 CV events and 680 deaths occured. For eGFR<60mL/min/1.73m^2 highest HRs were seen for (ischemic) stroke (Table 2). Highest HR of 2.11 (1.36-3.29) was observed for ischemic stroke if eGFR was 45-59mL/min/1.73m^2. HRs were highest for the combination of eGFR <60mL/min/1.73m^2 and ACR >30mg/g for all outcomes. For stroke, isolated reduced eGFR revealed a similar HR of 1.85 (1.19-2.90) as reduced eGFR and increased ACR combined. For death, isolated increased ACR had a HR of 2.04 (1.43-2.90).

Conclusions: After adjusting, reduced eGFR was highly associated with hazard of stroke in older adults. As for the combination of eGFR and ACR, the distribution of HRs for the cardiovascular outcomes suggests an association of ischemic stroke risk only with eGFR and a strong independent association of ACR with all-cause mortality.

Funding: Private Foundation Support

Baseline characteristics

Group by eGFR (BIS2)	All individuals	eGFR ≥ 60mL/min/1.73m^2	eGFR < 60mL/min/1.73m^2
Individuals (% of total)	2069 (100.0)	810 (39.2)	1257 (60.8)
Age (mean±SD*), years	80.4 ± 6.7	76.5 ± 5.0	82.9 ± 6.4
Female (%)	1098 (52.6)	419 (51.7)	668 (53.1)
Prior stroke (%)	201 (9.7)	51 (6.3)	150 (11.9)
Prior myocardial infarction (MI) (%)	309 (14.9)	85 (10.5)	224 (17.8)
Prior stroke or MI (%)	460 (22.3)	126 (15.6)	334 (26.6)
Diabetes mellitus (%)	541 (26.2)	192 (23.7)	349 (27.8)
Systolic blood pressure (mean±SD*), mmHg	145.7 ± 21.8	146.8 ± 21.0	145.0 ± 22.3
Pulse pressure (mean±SD*), mmHg	64.2 ± 18.7	62.9 ± 17.8	65.0 ± 19.2
ACR (%) ≤ 30 mg/g	1523 (74.1)	663 (82.0)	858 (69.0)
> 30-300 mg/g	458 (22.3)	137 (16.9)	321 (25.8)
> 300 mg/g	74 (3.6)	9 (1.1)	65 (5.2)
missing	14 (0.7)	1 (0.1)	13 (1.0)

Table 2: Hazard Ratios (adjusted) for developing respective outcome A - E depending on eGFR by BIS2 and ACR

Reference*	category*	n*	A - incident stroke or MI: 1607 individuals, 276 events, 338 competing* — Hazard Ratio (95% CI)	B - incident stroke: 1607 individuals, 166 events, 448 competing* — Hazard Ratio (95% CI)	C - incident ischemic stroke: 1607 individuals, 144 events, 470 competing* — Hazard Ratio (95% CI)	D - incident MI: 1607 individuals, 113 events, 501 competing* — Hazard Ratio (95% CI)	E - death to all cause: 2067 individuals, 680 deaths* — n*	E - death to all cause — Hazard Ratio (95% CI)
eGFR by BIS2								
	< 60	923	1.63 (1.20 - 2.20)	1.90 (1.26 - 2.88)	1.97 (1.27 - 3.06)	1.32 (0.85 - 2.06)	1257	1.28 (1.04 - 1.57)
eGFR ≥ 60	45-59	591	1.67 (1.23 - 2.28)	2.03 (1.34 - 3.07)	2.11 (1.36 - 3.29)	1.25 (0.78 - 2.01)	771	1.18 (0.95 - 1.46)
	≥ 45	352	1.47 (1.00 - 2.15)	1.42 (0.83 - 2.42)	1.42 (0.81 - 2.49)	1.53 (0.90 - 2.61)	486	1.55 (1.21 - 1.97)
albumin-to-creatinine ratio								
ACR ≤ 30	≤30	389	1.14 (0.86 - 1.51)	0.98 (0.68 - 1.43)	0.99 (0.66 - 1.47)	1.38 (0.90 - 2.11)	532	1.92 (1.63 - 2.27)
	>30-300	340	1.09 (0.82 - 1.47)	0.92 (0.62 - 1.37)	0.90 (0.59 - 1.38)	1.38 (0.89 - 2.12)	458	1.90 (1.60 - 2.25)
	> 300	49	1.44 (0.81 - 2.55)	1.46 (0.68 - 3.11)	1.59 (0.74 - 3.44)	1.41 (0.59 - 3.35)	74	2.11 (1.52 - 2.93)
eGFR combined with ACR								
	eGFR / ACR							
eGFR ≥ 60 ACR ≤ 30	≥ 60 / > 30	122	1.09 (0.65 - 1.85)	0.88 (0.41 - 1.86)	0.89 (0.39 - 2.01)	1.32 (0.63 - 2.78)	146	2.04 (1.43 - 2.90)
	< 60 / ≤ 30	647	1.62 (1.16 - 2.26)	1.85 (1.19 - 2.90)	1.92 (1.19 - 3.10)	1.31 (0.80 - 2.15)	858	1.26 (0.98 - 1.61)
	< 60 / > 30	267	1.83 (1.22 - 2.76)	1.86 (1.07 - 3.23)	1.93 (1.07 - 3.49)	1.81 (0.98 - 3.34)	386	2.35 (1.81 - 3.07)

eGFR: estimated glomerular filtration rate (by BIS2), ACR: albumin-to-creatinine ratio, CI: confidence interval, MI: myocardial infarction
* total number of individuals and events for eGFR analysis, for ACR and combined exposure the numbers deviet slightly due to 14 missing urine assessments
† for eGFR in mL/min/1.73m², for ACR in mg/g
* total number of individuals in category

SA-PO782

Trends in Mortality Among Medicare Beneficiaries with and Without CKD

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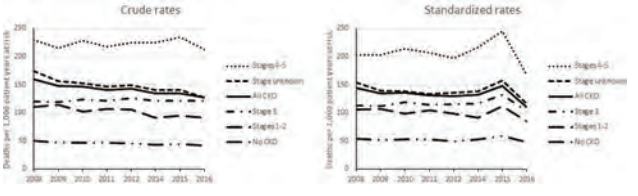
Background: Decreasing mortality rates have been observed for Medicare beneficiaries with claims-based diagnosis of CKD. It is unclear whether this is a true decline in CKD mortality or an artifact of increasing recognition of earlier stages of CKD. We sought to examine trends in mortality rate by stage of CKD.

Methods: Persons from 2008-16 Medicare 5% samples were required to be alive, aged >65 on Jan 1, without ESRD, and covered by Medicare Parts A and B but not C for all of the year. Years at risk were calculated from Jan 1 each year and censored at the start of ESRD, Dec 31, or disenrollment from Medicare. CKD claims-based diagnoses were searched from the year before, using ICD-9-CM and ICD-10-CM codes used to define CKD and its stages. The crude mortality rate each year was calculated as the number of deaths divided by the patient-years at risk. Cox regression, stratified by CKD stage, was used to estimate annual (hazard) rates standardized to the age-sex-race distribution of the Medicare 2011 population.

Results: Between 2008 and 2016, the percentage of people with diagnosed CKD stages 1-3 decreased. Persons without CKD had the lowest mortality rate each year, with unadjusted rate decreasing by 49.6 since 2008 to 41.9 in 2016. While the crude mortality rate decreased in CKD stages 1-2 and stage unknown by 17.6% and 27.5% respectively, the rates for stages 3-5 remained relatively unchanged. With standardization for age, sex, and race, we observed less change in mortality rates between 2008 and 2014, but sudden increases in 2015 and sudden decreases in 2016, especially in more advanced CKD stages. (See Figure)

Conclusions: The decline observed in the crude mortality rate among all CKD patients may be due to the changing distributions of age/sex/race/CKD stage, improved care of underlying risk factors, but not to greater recognition of early stage CKD. We acknowledge the limitations of claims-based diagnosis of CKD in this study. Furthermore, the sudden changes in standardized mortality rates between 2014 and 2016 remain unexplained and require further study.

Funding: NIDDK Support



SA-PO783

Albuminuria, Reduced Kidney Function, and the Risk of ST and Non-ST Elevation Myocardial Infarction

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Background: Myocardial infarctions (MIs) in patients with chronic kidney disease (CKD) are associated with high rates of mortality and complications. CKD is a recognized risk factor for cardiovascular disease, but whether the risk of ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) differs in the CKD population is unknown. We examined the association of CKD (defined by reduced estimated glomerular filtration rate (eGFR) or albuminuria) with risks of STEMI and NSTEMI.

Methods: Using administrative data from Ontario, Canada, we examined older individuals (≥66 years of age) with an outpatient eGFR and albuminuria measure for incident MI from 2002 to 2015. Multivariate Fine & Gray sub-distribution hazards (sHR), adjusted for demographics, comorbidities, health resource utilization and medications, accounting for the competing risk of death were used.

Results: In 248,438 patients with over 1.2 million person-years of follow-up, STEMI, NSTEMI and death occurred in 1,436 (0.58%), 4,431 (1.78%) and 30,015 (12.08%) patients, respectively. In adjusted models, both eGFR and urine albumin to creatinine ration (ACR) were associated with STEMI and NSTEMI (P<0.0001). The highest level of ACR (>30 mg/mmol) was associated with a two-fold higher adjusted risk of both STEMI and NSTEMI among patients with eGFR ≥60 ml/min/1.73m^2 compared to ACR <3 mg/mmol. The lowest level of eGFR (<30 ml/min/1.73m^2) with ACR < 3 mg/mmol was not associated with higher STEMI risk but a four-fold higher risk of NSTEMI compared to eGFR ≥60ml/min/1.73m^2. The lowest eGFR (<30 ml/min/1.73m^2) and highest ACR (>30 mg/mmol) was associated with a greater than four-fold higher risk of both STEMI and NSTEMI (sHR (95% CI) 4.53 (3.30-6.21) and 4.42 (3.67-5.32), respectively) compared to ACR <3 mg/mmol and eGFR ≥60 ml/min/1.73m^2.

Conclusions: Elevations in albuminuria are associated with a higher risk of both NSTEMI and STEMI, regardless of kidney function, whereas reduced kidney function with minimal albuminuria is associated with only a heightened NSTEMI risk.

SA-PO784

The Bidirectional Nature of the Cardio-Renal Link in Stable CKD Patients

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Background: In patients with heart disease, left ventricular (LV) dysfunction and heart failure are associated with reduced GFR and vice-versa, in CKD patients, LV hypertrophy and dysfunction go along with the CKD severity. Experimental models support the causal nature of these cardio-renal links. However, there is no clinical study investigating the bi-directionality of these links in stable non-dialysis CKD patients.

Methods: We tested the longitudinal relationship between the estimated GFR (eGFR) and the LV mass index (LVMI) and vice versa in a cohort of 206 stage G1-5 (non-dialysis) CKD patients. Overall, 498 simultaneous eGFR and LVMI measurements in 206 patients were available over a 3 year follow-up. Data analysis was performed by the mixed linear model. In this analysis each predictor (either the eGFR or LVMI) was paired with the subsequent measurement of the pertinent outcome measure (i.e. LVMI when the predictor was the eGFR and the eGFR when the predictor was the LVMI) and adjusting for both, the eGFR and the LVMI of the preceding visit.

Results: At baseline the eGFR (MDRD) was 54±29 ml/min/1.72 m^2 and LVMI was 70±24 $gr/m^{2.71}$. In the analysis testing the LVMI as a predictor of the evolution of the eGFR over time, an increase in LVMI of 10 $gr/m^{2.71}$ predicted a eGFR loss of 0.41±0.25 ml/min/1.72 m^2over follow up but such an effect failed to attain statistical significance (P=0.10). Vice versa, in the analysis testing the eGFR as a predictor of the evolution of the LVMI over time, a decrease in eGFR of 10 ml/min/1.73m^2predicted an increase in LVMI of 1.1±0.4 $g/m^{2.71}$ over follow up and this change was highly significant (P=0.001).

Conclusions: This longitudinal analysis in stable non-dialysis CKD patients shows that eGFR loss predicts a rise in LVMI over time. A similar trend exists for the opposite relationship, i.e. LVMI worsening predicts a subsequent eGFR loss but this relationship is much weaker than the previous one and does not achieve formal statistical significance. Overall, these observations suggest that the kidney disease-driven risk for cardiomyopathy progression is more consistent than the simultaneous heart-disease driven risk for CKD progression.

SA-PO785

Inflammatory Markers and Incidence of Hospitalization with Infection in CKD: The Chronic Renal Insufficiency Cohort Study

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Background: Low grade inflammation may be linked to the impaired immune response in CKD. Whether inflammatory markers are associated with risk of hospitalization with infection is unknown.

Methods: In 3,622 participants of the CRIC Study, we assessed the association between the baseline levels of four inflammatory markers (interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], interleukin-1 receptor antagonist [IL-1RA], and transforming growth factor-β [TGF-β]) and incidence of hospitalization with major infections (pneumonia, urinary tract infections, cellulitis and osteomyelitis, and bloodstream infections) using Cox models adjusted for potential confounders including eGFR and uACR to estimate hazard ratio (HR). The inflammatory markers were log-transformed and modeled as restricted cubic spline with the knots at 5th, 50th, and 95th percentile.

Results: During a median follow-up of 7.5 years, 36% (n=1,294) had a hospitalization with major infections. Higher levels of IL-6 and TNF-α, but not IL-1RA or TGF-β, were each monotonically associated with increased risk of hospitalization with infection (**Figure**) (HR at 95th vs. 5th percentile, 2.27 [95%CI, 1.81-2.85] for IL-6 and 1.96 [1.59-2.42] for TNF-α). The associations of IL-6 and TNF-α were independent of each other and consistent across types of infection or in demographic and clinical subgroups.

Conclusions: Higher levels of IL-6 and TNF-α, but not IL1RA or TGF-β, were independently associated with increased risk of hospitalization with infection. Future studies are needed to explore the underlying mechanisms of the discrepant patterns in the association with risk of infection across inflammatory markers.

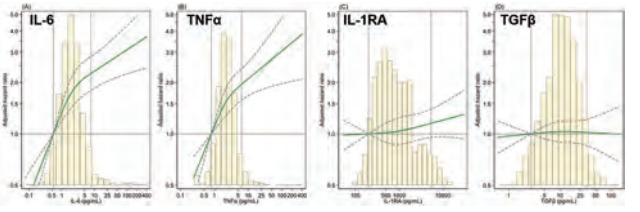

Figure: Histogram and HRs of hospitalization with infection for (A) IL-6, (B) TNF-α, (C) IL-1RA, and (D) TGF-β. Vertical lines indicate 5th (reference) and 95th percentiles.

SA-PO786

Infection-Related Hospitalizations Across Different Levels of Kidney Function: Data from the EXTEND45 Study

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Background: The risk of infection associated with differing levels of kidney function is unclear. We sought to determine the risk of infection-related hospitalization and mean hospital length of stay across different levels of kidney function in a community-based cohort study.

Methods: Based on data from the EXTEND45 Study (the 45 and Up Study linked to hospital and community pathology datasets by the Centre for Health Record Linkage [CHeReL]), we identified a population-based cohort (2006-2014) of 41,099 people aged ≥45 years who had a measure of kidney function (estimated glomerular filtration rate [eGFR]). The risk of infection-related hospitalization and mean hospital length of stay were assessed by eGFR categories (≥90, 60-89, 45-59, 30-44 and <30ml/min/1.73m^2) using multivariable Cox regression.

Results: Of 41,099 participants, 18.6% had an eGFR <60 ml/min/1.73m^2. Overall, 2,598 (6.3%) participants experienced ≥1 infection-related hospitalization over a mean follow-up of 5.8 years. After adjusting for age and sex, risk of infection increased with declining eGFR in a graded and linear fashion (HR 0.91 [95% CI: 0.79-1.04], 1.16 [0.99-1.37], 1.48 [1.22-1.78], and 1.83 [1.44-2.31] for eGFR ≥90, 60-89, 45-59, 30-44, and <30 ml/min/1.73 respectively). Pneumonia, urinary tract infections, and cellulitis were the most common infections across all eGFR categories. Mean hospital length of stay similarly increased with declining eGFR categories (4.9, 6.5, 7.5, 7.8 and 7.9 days, respectively).

Conclusions: The risk of serious infection increases as kidney function declines, independent of age and sex, suggesting that susceptibility is likely related to other factors (e.g. alterations in immune function) and begins in mild-moderate renal impairment.

Funding: Commercial Support - The EXTEND45 Study is funded through peer-reviewed (NSW Cardiovascular Research Network Collaborative Project Grant) and unrestricted industry (from MSD, Amgen and Eli Lilly) research grants., Government Support - Non-U.S.

SA-PO787

Predictors of CKD in the EXTEND45 Study: An Australian Population-Based Study

Amy Kang,[2] Louisa Sukkar,[1] Min Jun,[2] Celine Foote,[1,6] Roberto Pecoits-Filho,[3] Brendon L. Neuen,[1] Anish Scaria,[1] Jannah F. Baker,[1] Kris Rogers,[1] Alan Cass,[4] Carol A. Pollock,[5,7] Germaine Wong,[5] John Knight,[1] David Peiris,[1] Martin P. Gallagher,[2] Meg J. Jardine.[2] *[1]The George Institute for Global Health, Camperdown, NSW, Australia; [2]The George Institute for Global Health, UNSW Sydney, Newtown, NSW, Australia; [3]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [4]Menzies School of Health Research, Darwin, NT, Australia; [5]The University of Sydney, St. Leonards, NSW, Australia; [6]Department of Renal Medicine, Concord Repatriation General Hospital, Sydney, NSW, Australia; [7]Kolling Institute for Medical Research, Sydney, NSW, Australia.*

Background: The AUSDIAB study found an incidence rate of CKD (eGFR<60ml/min/1.73m^2) of 0.4 per 100 person-years in the adult Australian community aged ≥25 years. We aimed to assess: 1) the incidence and prevalence of chronic kidney disease (CKD), 2) risk factors for incident CKD in a contemporary Australian population-based cohort of adults aged 45 and older.

Methods: Based on data from the EXTEND45 study (the 45 and Up Study linked to [1]hospital and community pathology datasets by the Centre for Health Record Linkage[CHeReL] and [2]the Medicare Benefits Schedule[MBS] and Pharmaceutical Benefits Scheme[PBS] datasets provided by the Department of Human Services), we identified a population-based cohort (2006-2014) of 41,099 people aged ≥45 years who had ≥2 measures of kidney function. Prevalent CKD (defined as eGFR <60 ml/min/1.73m^2) was determined at study recruitment. The CKD incidence rate over the study period was determined using Poisson regression. Cox regression was used to determine associations between baseline sociodemographic factors, comorbidities and future incident CKD.

Results: Of 41,099 participants, 7,641(18.6%) had prevalent CKD and 5,481 developed incident CKD over a mean follow-up of 5.6 years. The incidence rate of CKD was 3.2(95% CI:3.1-3.3) per 100 person-years. Baseline characteristics: age (per year increase; HR: 1.08[1.07-1.08]), regional residence (inner regional vs city: 1.26[1.18-1.36]), diabetes (1.28[1.19-1.38]), hypertension (1.58[1.48-1.70]), heart disease (1.22[1.14-1.31]), stroke (1.16[1.03-1.29]), depression (1.25[1.15-1.35]) and higher BMI (obese vs normal: 1.38[1.27-1.49]) were predictive of incident CKD. Alcohol consumption (7-13 vs 0-6 drinks/week 0.89[0.82-0.97]) was associated with a lower risk of incident CKD.

Conclusions: Baseline depression and regional residence predicted future incident CKD in conjunction with established risk factors of age, diabetes, hypertension, high BMI and vascular disease.

Funding: Commercial Support - The EXTEND45 Study is funded through peer-reviewed (NSW Cardiovascular Research Network Collaborative Project Grant) and unrestricted industry (from MSD, Amgen and Eli Lilly) research grants.

SA-PO788

Burden of Metabolic Complications with Advancing CKD in the Irish Health System

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Background: The prevalence of Chronic Kidney Disease (CKD) exceeds 15% in the Irish health system and is associated with adverse clinical outcomes. The goal of this study was to describe the burden of common metabolic complications in CKD and assess the impact of deteriorating kidney function.

Methods: Utilising data from the National Kidney Disease Surveillance System, we conducted a cross sectional study of adult patients, age > 18 years, from the Midwest region in 2014 with data on serum creatinine measurements and metabolic indicators of anaemia, nutrition, metabolic bone disease and acidosis. Dialysis patients were excluded. The following definitions were used: anaemia: haemoglobin <13 g/dL in men and <12 g/dL in women; hyperkalaemia: K+ > 5.5 mmol/L; hypoalbuminaemia; serum albumin <35g/L, metabolic acidosis: bicarbonate < 22 mmol/L, and hyperphosphatemia: phosphate >1.5 mmol/L. Logistic regression models explored associations of estimated glomerular filtration rate (eGFR) with each metabolic complication expressed as adjusted odds ratio (OR) and 95% Confidence intervals.

Results: There were 133,558 adults with average age 54.3 (±17.7) years and eGFR 87.9(±21.1) ml/min/1.73m^2. The prevalence of metabolic complications were as follows: acidosis (28.9%), anaemia (13.6%), hyperkalaemic (13.1%), hypoalbuminaemia (9.9%), and hyperphosphatemia (2.3%). In multivariate models adjusting for age and sex only, each 5mL/min/1.73m^2 fall in eGFR was associated with higher odds of anaemia, [OR 1.08 (95% CI; 1.07-1.09)]; hyperkalaemia [OR 1.09 (95% CI; 1.08-1.10], hypoalbuminaemia, [OR 1.02 (1.01-1.03)], metabolic acidosis [OR 1.03 (95% CI; 1.02-1.04)], and hyperphosphatemia [OR 1.23 (95% CI; 1.21-1.26)].These findings were accentuated in the elderly (Table 1).

Conclusions: The burden of CKD-related metabolic complications is substantial within the Irish health system and increases with advancing CKD. Patients with low eGFR, especially the elderly, are at increased risk for several serious but treatable metabolic complications. Early identification and treatment of these disorders may lead to improved patient outcomes

Funding: Government Support - Non-U.S.

Table 1. AOR of metabolic complications for a 5mL/min/1.73m^2 decrease in eGFR stratified by Age group

Variable	<40	40-59	60-80	>80
Anaemia	0.86 (0.84-0.87)	1.00 (0.99-1.01)	1.18 (1.18-1.19)	1.13 (1.11-1.14)
Hyperkalaemia	1.10 (1.08-1.12)	1.09 (1.07-1.10)	1.09 (1.08-1.10)	1.12 (1.10-1.15)
Hyperphosphatemia	1.07 (1.02-1.12)	1.23 (1.19-1.26)	1.29 (1.25-1.33)	1.40 (1.28-1.53)
Metabolic Acidosis	0.94 (0.92-0.95)	1.00 (0.99-1.02)	1.08 (1.07-1.10)	1.14 (1.11-1.16)
Hypoalbuminemia	0.76 (0.74-0.77)	1.03 (1.01-1.05)	1.12 (1.11-1.13)	1.05 (1.03-1.06)

Model: Sex & eGFR adjusted. The likelihood of these complications were far greater in older patients with declining eGFR. (p values for the age X GFR interaction term: <0.001 for anaemia, acidosis, hyperphosphatemia, hypoalbuminaemia and p=0.016 for hyperkalaemia)

SA-PO789

Assessing the Risk and Severity of Hospitalisations According to Level of Kidney Function: An EXTEND45 Analysis

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Background: Contemporary assessments of the relationship between chronic kidney disease (CKD) and health services use in Australia by level of eGFR have been limited. Prior studies typically used diagnosis codes to identify CKD which have relatively low sensitivity for ascertaining earlier stages of CKD. We determined the risk and severity of all-cause and cardiovascular hospitalisations by eGFR in a community-based cohort study of adults aged ≥45 years in New South Wales, Australia.

Methods: Based on data from the EXTEND45 study (the 45 and Up Study linked to hospital and community pathology datasets by the Centre for Health Record and Linkage [CHeReL]), we identified a population-based cohort (2006-2014) of 41,099 people aged ≥45 who had a measure of kidney function (eGFR). The risk and severity of hospitalisations (defined by the hospitalisation length of stay [HLOS]) were assessed by eGFR category (≥90 [reference], 60-89, 45-59, 30-44 and <30ml/min/1.73m^2) using multivariable Cox regression.

Results: Of 41,099 participants, 80.2% experienced ≥1 hospitalisation event over a mean follow-up of 5.8 years. All-cause hospitalisation risk increased as eGFR declined (HR 0.99 [95% CI:0.97-1.03]; 1.05 [1.00-1.09]; 1.17 [1.10-1.24] and 1.57 [1.43-1.72] for eGFR 60-89, 45-59, 30-44, and <30ml/min/1.73m^2, respectively; p-trend<0.001) even after adjustment for age and sex. Cardiovascular events rose even more steeply than all-cause hospitalisations (HR 1.23 [1.08-1.39]; 1.49 [1.28-1.73]; 1.73 [1.45-2.07] and 2.24 [1.80-2.79], respectively). Mean HLOS also increased as eGFR declined (all-cause hospitalisation [2.3, 2.8, 3.9, 5.1 and 5.7 days, respectively]; cardiovascular hospitalisations [3.7, 3.8, 5.7, 5.9 and 8.3 days, respectively).

Conclusions: In contemporary NSW, declining kidney function is associated with higher illness burden, particularly cardiovascular burden. The increased mean HLOS suggests that discrete medical events are more severe as kidney function declines.

Funding: Commercial Support - The EXTEND45 Study is funded through peer-reviewed (NSW Cardiovascular Research Network Collaborative Project Grant) and unrestricted industry (from MSD, Amgen and Eli Lilly) research grants., Government Support - Non-U.S.

SA-PO790

Genome Wide Association Study Identifies Novel SNPs Associated with Albuminuria in Japanese General Population

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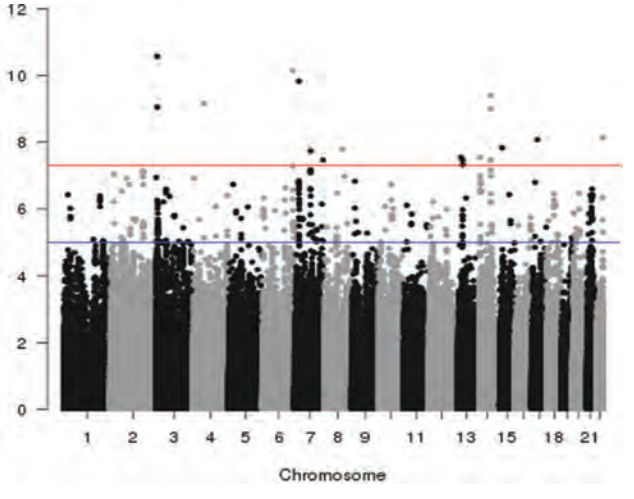
Background: Urinary albumin excretion (UAE) is a good biomarker for chronic kidney disease, cardiovascular disease, diabetes mellitus or obesity. We usually expect the individual amounts of UAE show large variations among similar conditioned patients. The variations could be contributed with many genetic factors. However, a few Genome-wide association analysis studies (GWAS) of UAE based in European population were reported and there was not in Japanese general population. Here we conducted GWAS using health-survey data collected by Tohoku Medical Megabank Organization (ToMMo) and listed up several candidates of single nucleotide polymorphisms (SNPs) on UAE.

Methods: GWAS of continuous variables of UAE as an outcome was performed using about 1 million SNPs genotypes (Illmina HumanOmniExpressExome) from 9966 participants (Miyagi; 4974, Iwate; 4992) collected by ToMMo in 2013. As quality control, SNPs with low call rates (<0.98), low Hardy–Weinberg equilibrium exact test P-values (<1×10^{-4}) or low minor allele frequencies (MAF; <0.01) were filtered out. As a covariate, age, sex, BMI, blood pressure, renal function (eGFR calculated by plasma cystatin C), HbA1c was used. Genotypic imputation was performed using a haplotype panel consisting of 2000 samples NGS data, further analysis was performed on the data, and each MAF and INFO value after imputing were adjusted.

Results: Analysis results were examined with p <5 × 10 - 8 as the significance level, and 18 candidates of novel SNPs related to UAE were identified. SNPs with particularly strong associations were observed on chromosome 14.

Conclusions: The 18 SNPs were identified associated with UAE and we are considering the mechanisms and the further verification necessarily.



SA-PO791

Downregulation of Renoprotective Factors Is Associated with Outcome in CKD

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Background: An imbalance of nephroprotective factors and renal damaging molecules contributes to development and progression of chronic kidney diseases. Molecules with renoprotective properties and capacity to induce renal repair might serve as biomarkers, drug targets as well as therapeutic options themselves. In this study we determined the

potential of renoprotective factors to predict disease progression in a set of chronic kidney disease (CKD) patients.

Methods: Gene expression profiles were determined for 197 previously published proteins with renoprotective properties in renal biopsies of 63 CKD patients with different disease diagnoses. The statistical analysis of microarray method was used to identify downregulated factors in the group of progressive patients as compared to those showing a stable course of disease with a false discovery rate < 5%. Progression was defined as reaching end-stage renal disease or doubling of serum creatinine. Significance of renoprotective factors to predict course of disease was in addition analysed in time-to-event analysis using Kaplan Meier curves and log-rank statistics. Cox regression models were used to adjust for the clinical parameters estimated glomerular filtration rate (eGFR) and diagnosis type.

Results: The six renoprotective factors dicarbonyl and L-xylulose reductase (DCXR), epidermal growth factor (EGF), glutathione S-transferase mu 1 (GSTM1), kininogen 1 (KNG1), nitric oxide synthase 3 (NOS3), and uromodulin (UMOD) were significantly downregulated in the group of progressive patients and were also significantly associated with outcome in time to event analysis. DCXR (p-val = 0.0277), EGF (p-val = 0.0264), GSTM1 (p-val = 0.0039), and KNG1 (p-val = 0.0372) remained significant after adjustment for eGFR and diagnosis in Cox regression analysis thus being independently associated with outcome. This is to our knowledge the first study describing the prognostic potential for DCXR in human CKD samples with literature evidence already being available for the other three markers showing significance in our cohort.

Conclusions: We identified a set of four renoprotective factors being downregulated in progressive CKD patients on the mRNA level and independently associated with disease outcome.

Funding: Government Support - Non-U.S.

SA-PO792

Association of Polygenic Risk Scores and CKD in the UK Biobank

Thi ha my Vy, Lili Chan, Kumardeep Chaudhary, Steven G. Coca, Ron Do, Girish N. Nadkarni. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Genome wide association studies (GWAS) have tested for associations between single nucleotide polymorphisms (SNPs) and chronic kidney disease (CKD). Polygenic risk scores (PRS) have shown significant promise for risk discrimination in complex disease but there are no studies on PRS in CKD.

Methods: We generated per-individual genome-wide additive polygenic risk scores (PRS) using published GWAS statistics and tested them for association with CKD in 8,432 cases and 400,529 controls of self-identified white British ancestry in the UK Biobank. We derived PRS using GWAS summary statistics from four different sets of SNP's; (1) 33 loci significantly associated with $eGFR_{creatinine}$; (2) 53 loci significantly associated with CKD; (3) >38,000 independent SNVs using a linkage disequilibrium (LD) pruning approach; and (4)~1,800,000 SNVs with re-assigned coefficients adjusted for linkage disequilibrium (LD) by LDpred.

Results: Among the four PRS, the area under the curve (AUC) was slightly higher for PRS score 4 using ~1,800,000 SNPs (AUC=0.703) compared to PRS score 1 (0.7); 2 (0.700) or 3 (0.701). The odds ratios (OR) for CKD prevalence increased significantly at higher quintiles of genome wide PRS score 4 compared to bottom quintile (Table 1). Individuals with highest decile of PRS score had two-fold odds of CKD vs. lowest decile (OR=2.0; 97.5% Confidence Interval 1.7-2.3; $p=2.28x10^{-24}$).

Conclusions: PRS incorporating higher number of SNPs had slightly higher discrimination compared to those incorporating only GWAS significant SNPs, indicating polygenic architecture of CKD. PRS may provide modest improvements in risk prediction, especially in the extremes of genetic risk distribution.

Prevalence of CKD in higher polygenic score bins in comparison with the bottom 20% of polygenic score distribution

PRS Quintile	Odds Ratio	2.5% CI	97.5% CI	P value
20-40%	1.3	1.1	1.4	2.12x10-4
40-60%	1.3	1.1	1.5	2.48x10-5
60-80%	1.5	1.3	1.6	4.06x10-10
>80%	1.8	1.6	2.0	8.70x10-22

SA-PO793

Using an IgA Genetic Risk Score to Estimate the Prevalence and Improve Diagnosis of IgA Nephropathy

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Background: IgA nephropathy(IgAN) is the commonest glomerulonephritis worldwide. It is difficult to assess true prevalence of IgAN, people with mild disease do not commonly receive a biopsy. Multiple single-nucleotide polymorphisms(SNPs) are associated with IgAN. We aimed to generate and validate an IgAN genetic risk score(GRS) and assess the excess IgAN genetic risk in people with haematuria, hypertension and microalbuminuria in UK Biobank(UKBB) to estimate the proportion of these phenotypes.

Methods: We calculated the IgAN GRS using 14 SNPs associated with IgAN in Caucasians using established methods. We generated the GRS in 464 biopsy proven IgAN from the UK Glomerulonephritis (UK GN) DNA Bank, and in 344,244 Caucasians from UKBB, using SNP array data. We accessed diagnostic codes from electronically linked healthcare records, questionnaire data and baseline albumin creatinine ratio from UKBB. We compared the IgAN GRS in UK GN cases with healthy individuals in UKBB. We assessed the proportion of hypertension and microalbuminuria by comparing IgA GRS using this formula: *Proportion=(phenotype - control)/(IgAN - control)*

Results: The IgA GRS was discriminative of IgAN v non-IgAN (Mean[95% confidence interval]) GRS 4.35 (4.26,4.41) v 3.98 (3.96,3.99); P <0.0001. UKBB participants with an ICD10 diagnosis of IgAN (N=116) GRS 4.19(4.01, 4.36) had a similar GRS to the IgA GN cohort; P=0.1 and combined score of 4.307 (4.24,4.38). The GRS was higher in phenotypes with possible undiagnosed IgAN compared to healthy subjects, haematuria (N=13,119) GRS 4.04(4.03, 4.06); P<0.0001, haematuria and proteinuria (N=1827) GRS 4.06(4.01,4.1); P=0.002, and haematuria, hypertension and microalbuminuria (N=1431) GRS 4.07(4.02,4.11); P=0.002. We calculated that IgA accounted for 19% (15-25) of haematuria, 22% (10-37) haematuria and microalbuminuria and 27% (13-40) haematuria, hypertension and microalbuminuria in UKBB.

Conclusions: We used a novel GRS approach to estimate the prevalence of IgAN contributing to common phenotypes that would not normally be biopsied. These data may allow a UK population estimate for the prevalence of undiagnosed IgAN. Further work is needed to assess if an IgAN GRS may be useful for individual diagnosis.

Funding: Other NIH Support - Fellowship funded by UK NIHR

SA-PO794

Significant Urinary Metabolites in the Progression of CKD

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Background: Despite the development of diagnostic techniques, methods for predicting changes in renal function or outcomes are still insufficient. Metabolomics is considered to be a breakthrough method to address the shortage of tools by analyzing the end metabolites, reflecting genetic and environmental factors. Herein, we would like to propose the metabolites which significantly associated with development and progression of chronic kidney disease (CKD).

Methods: We measured urinary metabolites from 1,274 urine samples at the time of renal biopsy and 147 urine samples from healthy subjects using nuclear magnetic resonance. The clinical outcome was defined as a decrease in estimated glomerular filtration ≥ 30%, doubling of serum creatinine, or development of end-stage renal disease.

Results: Initial partial components analysis and partial least squares-discriminant analysis score plots showed discriminated cluster between CKD and control, and according to the stage of CKD. A total of 41 metabolites confirmed to candidate marker associated with CKD. Six of metabolites (betaine, glycine, glycerol, trimethylamine-N-oxide, taurine, choline) showed increasing pattern, and 6 of metabolites (1-methylnicotinamide, formate, hypoxanthine, ethanolamine, citrate, 3-hydroxyisovalerate) showed decreasing trend to the stage of CKD. A total of 14 metabolites (phenylalanine, fumarate, betaine, glycine, glycerol, taurine, trimethylamine-N-oxide, betaine, choline, acetoacetate, acetone, acetate, isoleucine, leucine) had significantly increased hazard ratio to composite outcomes, and four metabolites (fumarate, betaine, taurine, choline) showed higher hazard ratio to outcome of creatinine doubling. In survival analysis using the median value of each metabolite, the cumulative incidence of clinical outcomes was significantly increased in 19 metabolites and decreased in 4 metabolites.

Conclusions: Metabolites which inform the disease progression or development can be a noble biomarker. In our study, betaine, choline, taurine, trimethylamine-N-oxide, glycine, and glycerol were shown to be a significant predictor in the progression of CKD. Although additional study for validation should be performed, we could find significant metabolites associate with CKD. And these results could be an instrumental keynote to moving ahead.

SA-PO795

Urinary Metabolites Associated with Non-Diabetic CKD Progression

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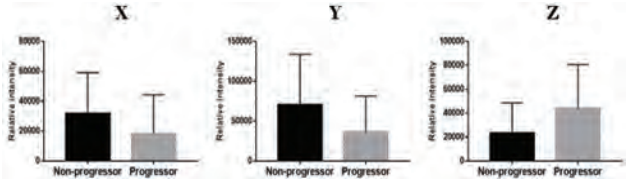
Background: Metabolome analyses have been on the rise recently for the discovery of biomarkers for chronic kidney disease. Urinary metabolome can be appropriate prognostic markers to predict CKD progression.

Methods: We conducted a case-control study comparing progressor (case) with non-progressor (control) in non-diabetic chronic kidney disease patients (polycystic kidney disease excluded). Urine samples and clinical data were taken from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD). These random urine samples were harvested at enrollment. Participants were followed-up for eGFR at 6- or 12-month interval for > 2 years. Subjects of the study were 100 individuals that are comprised of 50 progressors and 50 non-progressors with their age, gender and initial eGFR values matched. Progressor and non-progressor group were divided on the basis of estimated GFR slope, which revealed -0.91±0.75 and 1.43±1.23 ml/min/1.73m^2/yr, respectively. The urinary metabolite profiling was performed with an untargeted metabolomics approach using ultra-performance liquid chromatography time-of-flight mass spectrometry in conjugation with multivariate statistical analysis.

Results: A total of 9,345 compound ions were detected in positive ion mode, and 27 endogenous ions satisfied the false discovery rate adjusted p-value (Q-value). Among them, three candidate markers were discovered; X, Y and Z. These three metabolites showed statistically significant difference between CKD progressor and non-progressor group. X and Y had higher concentration in non-progressors unlike Z which were lower in concentration from non-progressors.

Conclusions: We identified three urinary metabolic markers associated with renal progression of non-diabetic chronic kidney disease. They can provide information to predict CKD progression as prognostic markers.

Funding: Government Support - Non-U.S.



SA-PO796

Concordance of Metabolite Correlations with Measured GFR in Children and Adults

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Background: Metabolites are strongly influenced by reduced GFR but it is unknown whether the associations are similar in adults and children.

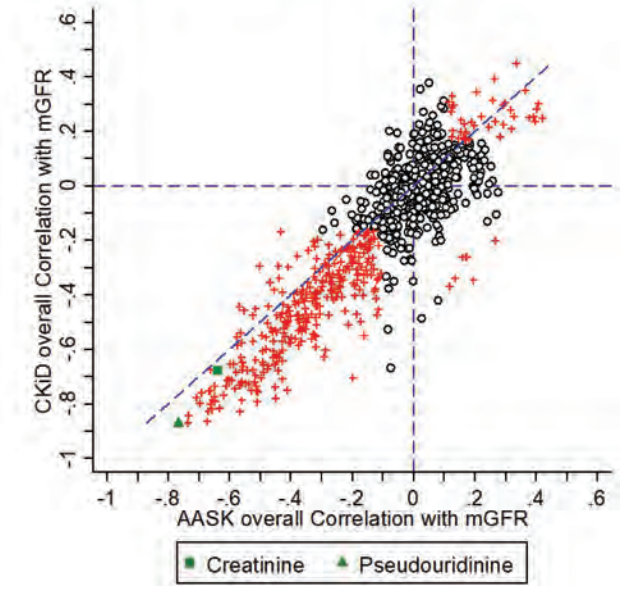
Methods: We evaluated an untargeted GC/MS2 and LC/MS2-based metabolomics quantification (Metabolon) of frozen serum from 962 African-American Study of Kidney Disease and Hypertension (AASK) and frozen plasma in 702 Chronic Kidney Disease in Children (CKiD) participants. Metabolites were standardized, log transformed and then correlated to measured GFR (mGFR). GFR was measured using urinary Iothalamate clearance in AASK and plasma Iohexol clearance in CKiD (median (5^{th}-95^{th} %ile) GFR of 48 (24-64) in AASK and 57 (23-114) in CKiD).

Results: There very high agreement between the correlation of the 871 metabolites with mGFR in AASK and the corresponding correlation in CKiD (Figure; correlation of the correlations 0.896). Both studies had an excess of negatively correlated metabolites with mGFR, 311 of them at p<0.001 (denoted with red pluses on the lower left quadrant). Creatinine is shown for reference and pseudouridine for being the most negatively correlated. Among these, the negative correlation with mGFR was stronger in CKiD than AASK (mean difference -0.10, p<0.001), likely due to the wider GFR range in CKiD. The first principal component explained 10% and 13% of the variance and had a correlation with mGFR of -0.71 and -0.86 in AASK and CKiD respectively.

Conclusions: GFR is strongly associated with a large proportion of the metabolome concordantly in children and adults with CKD. These findings hold promise for improvements in adjusting for confounding by GFR and developing equations to better estimate GFR that incorporate metabolite data.

Funding: NIDDK Support, Commercial Support - Metabolon funded assays in AASK as part of a collaboration agreement

Figure. Scatter plot of correlations of 871 metabolites with mGFR in CKiD vs. AASK (red plus denotes p<0.001)



SA-PO797

A Metabolomics Approach to CKD Prediction After RCC Nephrectomy

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Background: Patients with RCC who undergo nephrectomy can develop CKD as result of reduction in renal mass and given common risk factors between CKD and RCC it is likely that RCC patients already have parenchymal kidney disease. Thus it is imperative to obtain additional information in order to identify those at higher risk for CKD and/or its progression.

Methods: We hypothesized that there is a metabolomics signature for future renal functional decline in tumor-adjacent "normal" kidney tissue. We utilized a non-targeted metabolomics approach coupled with longitudinal patient data from post-operative visits to identify metabolites in non-malignant renal tissue linked to future eGFR decline. We used two statistical approaches: (1) univariate analysis adjusting for age, BMI, and nephrectomy type, and (2) cross-validated penalized regression (elastic net) methodology. Metabolomic analysis was performed by Metabolon (Durham, NC) using non-targeted metabolomic gas and liquid chromatography coupled to a mass spectrometry approach.

Results: We studied 138 samples from nephrectomies performed at MSKCC. 79 were radical (57.2 %), 100 subjects were male (72.5%), 122 were white (88.4%), average age was 61.9 years and 23 were diabetic (16.7 %). 476 metabolites were included in our analysis. Using univariate linear regression, we found that the most significant associations with eGFR slope were by the metabolites N6-trimethyl-lysine, guanosine and tyrosyl-leucine, as well as two unidentified metabolites, X13871 and X15168, with p<=0.012, although none reached significance when adjusted for multiple comparisons using FDR. We also created composite metabolite score utilizing all of the metabolites using elastic net modelling fitted on cross-validation samples. This score was univariately associated with the eGFR slope with p<0.001 and remained significant after adjusting for clinical variables. A similarly developed score based on tumor tissue metabolites was not significantly associated with the slope (p=0.18).

Conclusions: In this study we identified metabolites found in the adjacent non-malignant kidney tissue that are associated with eGFR decline post-nephrectomy. Prospective evaluation of surgical specimens using a targeted metabolomics approach to validate our findings will lead to a new paradigm by which RCC patients can be evaluated, and potentially treated, for unrecognized and incipient CKD.

Funding: NIDDK Support

SA-PO798

Blood Microbiome Profile Characteristics in Patients with CKD

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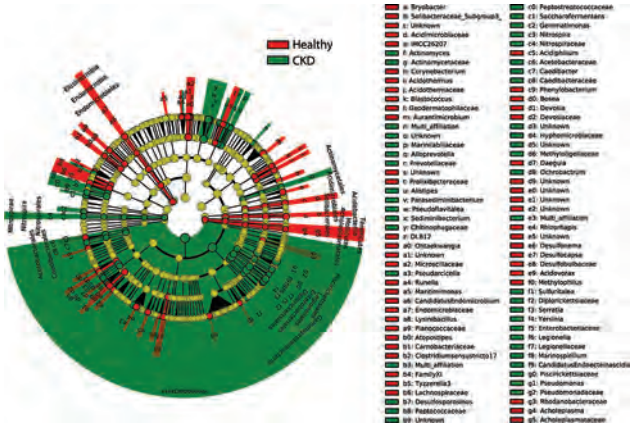
Background: Association between gut dysbiosis, increased intestinal permeability and endotoxemia mediated inflammation has been well established in Chronic Kidney Disease (CKD). Microbiome data in circulating blood is lacking. Our pilot study's aim was to compare blood microbiome 16S ribosomal DNA (rDNA) levels and metagenomic profiles between CKD patients and healthy controls.

Methods: A case control study of 20 non-diabetic CKD and age and sex matched 20 healthy controls was done. Blood bacterial DNA was studied in buffy coat samples both quantitatively by 16S PCR and qualitatively by 16S targeted metagenomic sequencing using a molecular pipeline specifically optimized for blood samples. Patients with inflammatory bowel disease, WBC>$11x10^9$/L or taking antibiotics at enrollment were excluded.

Results: Median 16S rDNA levels did not significantly differ between CKD and healthy groups (117 vs 122 copies/ng DNA, p=0.38). 16S Metagenomic sequencing revealed a significant decrease in alpha diversity (Chao1 index) in CKD group compared to healthy (p=0.0483). Linear discriminant analysis effect size (LEfSe, Fig 1) displays numerous bacterial taxa with proportions significantly modified in CKD group. There was significant increase in proteobacteria phylum, gammaproteobacterial class and enterobacteriacea, pseudomonadaceae and legionellaceae families in the CKD group compared to healthy group. At deeper taxonomic levels, there were other striking differences between bacterial profiles. No significant correlation was found between glomerular filtration rate and 16S rDNA levels (r= -0.002, p=0.98).

Conclusions: Our study demonstrates reduced alpha diversity and significant variations in blood microbial profile in CKD patients with numerous bacterial taxa impacted. Studying larger populations of CKD from various etiologies may help identify microbiome patterns as predictive and diagnostic biomarkers.



Taxonomic Cladogram using LEfSe analysis

SA-PO799

Bariatric Surgery Reduces Elevated Urinary Mitochondrial DNA Copy Number in Non-Diabetic Obese Patients

Haekyung Lee, Hyoungnae Kim, Moo Yong Park, Hyunjin Noh, Soon hyo Kwon. *Soonchunhyang University Hospital, Seoul, Republic of Korea.*

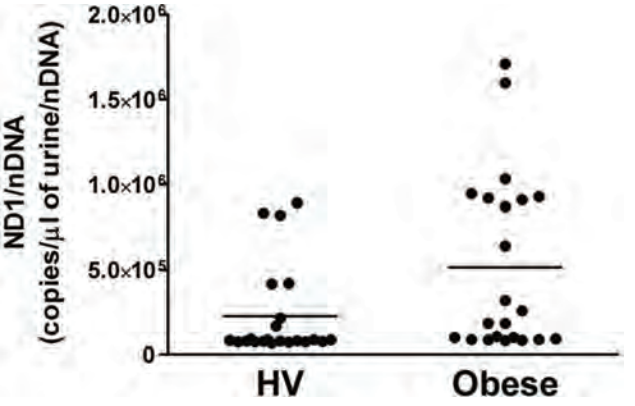
Background: Obesity is an independent risk factor for chronic kidney disease (CKD). However, the mechanisms responsible for renal injury have not been totally elucidated. Mitochondrial damage is considered to have implications for renal injury, and urinary mitochondrial DNA (mtDNA) is a marker of mitochondrial damage. We hypothesized that urinary mtDNA copy number in non-diabetic obese patients would be higher than in healthy volunteers, and bariatric surgery could reverse elevated urinary mtDNA copy number.

Methods: We prospectively recruited age-sex matched healthy controls and non-diabetic obese patients who were going to undergo bariatric surgery (n = 22 each; male=8, female=14) at a single center in Korea. We quantified the urinary absolute copy number of the mitochondrial nicotinamide adenine dinucleotide dehydrogenase subunit-1 (mtND-1) gene in healthy volunteers by quantitative polymerase chain reaction. In obese patients, mtND-1 copy number was measured before bariatric surgery and six months after bariatric surgery.

Results: Age (35.2 ± 9.6 years vs 32.2 ± 10.0 years) and eGFR (108.1 ± 11.7 mL/min vs 109.7 ± 24.0 mL/min) in both groups were not significantly different. 24 hour urinary albumin was higher in the obese group (2.7 ± 3.0 mg/day vs 52.9± 163.6 mg/day, *P*<0.001). In the obese group, BMI decreased from 41.0 ± 5.7 to 36.0 ± 7.2 *(P*=0.002) six months after bariatric surgery. Urinary mtND-1 copy number in the obese group was higher in healthy controls (*P*=0.001) (fig 1). In obese patients with high urinary mtND-1 copy number, bariatric surgery reduced urinary mtND-1 copy number (*P*=0.006).

Conclusions: Obesity is associated with elevated urinary mtND-1 copy number. Bariatric surgery reduces urinary mtDNA in obese patients with especially high mtDNA copy number. This suggests bariatric surgery would improve mitochondrial damage in kidney cells.

Funding: Government Support - Non-U.S.



Urinary ND-1/nDNA copy number in healthy volunteers and obese patients

SA-PO800

Kidney Ly6c- Macrophages Directly Promote Ischemia Induced Renal Fibrosis

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Background: Macrophages are a plastic and heterogeneous cell type in renal injury, repair and fibrosis in acute kidney injury (AKI) to chronic kidney disease (CKD) progression, but the function of different macrophage population is still elusive.

Methods: In our study, we focused on exploring the function of Ly6c- macrophages in AKI induced renal fibrosis, which are widely considered to be derived from derived from sac yolk. The AKI to CKD transition was induced by severe (30 min) ischemia reperfusion (I/R).

Results: We found CCR2 deficience alleviated acute kidney injury after I/R, which is consistent with previous reports, however, deteriorates renal fibrosis in CKD phase. Furthermore, we identified the cell type in $CCR2^{-/-}$ mice with I/R induced CKD, and it showed $Ly6C^-$ macrophages were predominantly infiltrated in $CCR2^{-/-}$ kidney during CKD phase after I/R, which suggested that $Ly6C^-$ macrophages play a critical role in AKI induced renal fibrosis. To further confirm the hypothesis, we used chlodronate liposome to deplete the renal $Ly6c^-$ macrophages in $CCR2^{-/-}$ mice during I/R induced CKD, and we found renal injury and fibrosis were both alleviated compared to $CCR2^{-/-}$ with PBS intervention. Similar results were identified in wild type mice by depletion of $Ly6C^-$ macrophages with chlodronate liposome. Furthermore, $Ly6C^-$ macrophages were extracted and adoptive transferred to severe immune deficient mice, which showed that renal injury and fibrosis were directly induced by $Ly6C^-$ macrophages. In vitro, we further confirmed that $Ly6C^-$ macrophages exerted their profibrotic function by promoting fibroblasts transdifferentiation into myofibroblasts.

Conclusions: In conclusion, kidney Ly6C- macrophages play an important role in directly promoting ischemia induced renal fibrosis, and this function is related to affecting fibroblast transdifferentiation.

Funding: Government Support - Non-U.S.

SA-PO801

iTRAQ-Based Renal Proteomic Analysis Exploring the Influence of Bone Marrow Derived MSCs on CKD Rats

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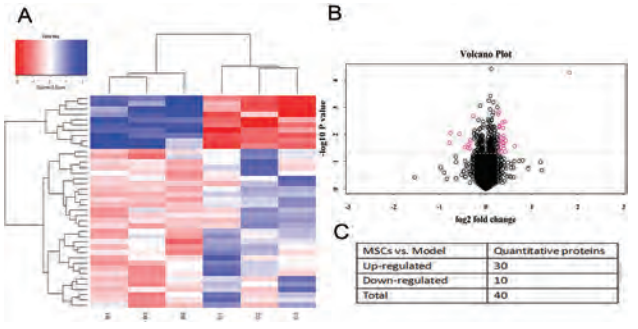
Background: The antifibrosis still represents the final target to treat chronic kidney disease (CKD). Mesenchymal stromal cells (MSCs) have been verified with significant improvement in the therapy of anti-fibrosis in the lastest 10 years. We attempted to clarify iTRAQ-based renal proteomic analysis exploring the new mechanism of MSCs on renal fibrosis.

Methods: Chronic kidney disease (CKD) models were established through combined with adriamycin and adenine in rats. A single intravenous MSCs injection was performed in the early period. Renal fibrosis was evaluated by sirius red staining and extracellular matrix components labeled by immunohistochemistry, respectively. Renal proteomic analysis was analyzed using iTRAQ-based mass spectrometry, and primarily differentially expressed proteins were further assessed by quantitative PCR and Western Blot.

Results: MSCs delivery decreased myofibroblast marker (α-SMA), extracellular matrix expression, and ameliorated the renal function in MSCs group compared to model group. 6,213 proteins were identified, and 40 proteins exhibited significant differences (30 up-regulated, 10 down-regulated) compared to model group. Bioinformatics analysis revealed that these proteins play important roles in biological process, cellular process, biological regulation, response to stimulus, metabolic process, organic substance metabolic process, single-organism process. Lgals3, Ifi47, Armc1 and Mgat3 may play important roles in the improvement of CKD fibrosis by MSCs. Lgals3 protein was down-regulated in MSCs group which has recently been deemed as a new biomarker of renal fibrosis.

Conclusions: We depicted the differently expressed proteins in the early period of MSCs delivery in adriamycin and adenine-induced CKD rat kidney by iTRAQ-based proteomic analysis which may provide valuable information to understand the molecular mechanisms involved in MSCs-based therapy for CKD fibrosis.

Funding: Private Foundation Support, Government Support - Non-U.S.



Global protein expression patterns in CKD rat kidneys in MSCs group compared to model group

SA-PO802

Macrophage-Derived miR-155-Containing Exosomes Promotes Angiotensin-II Induced Senescence and Oxidative Stress in Proximal Tubular Cells

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Background: The activation of the renin-angiotensin (Ang)-aldosterone system (RAAS) is a major hallmark in the development and progression of organ damage in chronic kidney disease (CKD). Here, we examined the role of macrophage-derived miR-155-containing exosomes in regulating oxidative stress and senescence in Ang-II induced PTCs both in vivo and in vitro.

Methods: CKD mice model: An osmotic minipump was implanted subcutaneously to infuse Ang-II for 4 weeks after a right uninephrectomy or sham operation in wild type or miR-155-deficient mice. Macrophage-derived miR-155-containing exosomes were infused in miR-155-deficient mice through tail injection. In vitro, primary cultured PTCs were treated with Ang-II (10^{-7}M) in the presence or absence of macrophage-derived miR-155-containing exosomes or miR-155 inhibitor. Finally, kidney samples and cultured PTCs in various groups as indicated above were analyzed for markers of senescence and oxidative stress.

Results: Our study revealed that miR-155 expression, the number of infiltrated macrophages, and oxidative stress and senescence were substantially increased in PTCs in Ang-II infused mice relative to the control group. Ang-II infused miR-155-deficient mice display attenuated senescence and mild oxidative stress compared that in wild type mice. Conversely, macrophage-derived miR-155-containing exosomes enhanced oxidative stress and senescence in Ang-II infused miR-155-deficient mice. Interestedly, pri-miR-155 was only expressed in macrophages, but not in PTCs, and macrophage-derived miR-155-containing exosomes can be transferred into PTCs. Hence, it is not strange that blocking exosome secretion with GW6849 attenuated oxidative stress and senescence in Ang-II infused wild type mice. Additionally, we found that miR-155 inhibitor abrogated oxidative stress and senescence in PTCs by directly down-regulating FoxO3a expression.

Conclusions: Taken together, our results demonstrated that infiltrated macrophages secreted miR-155-enriched exosomes and promoted oxidative stress and senescence by directly targeting FoxO3a in Ang-II infused PTCs injury.

Funding: Government Support - Non-U.S.

SA-PO803

Macrophage Chemoattractant Protein-1 (MCP-1) Promotes Renal Fibrosis in AKI-to-CKD Transition

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Background: Acute kidney injury (AKI) significantly increases the risk of developing progressive kidney fibrosis and chronic kidney disease (CKD). Macrophages play complex roles in AKI, with proinflammatory macrophages initially serving for clearance of apoptotic cells/debris after injury, followed by reparative macrophages promoting tubule repair. Using a CKD model of unilateral ischemia-reperfusion (U-IRI) in which the injured kidney undergoes fibrosis and atrophy rather than effective repair, we recently showed that macrophages downregulate reparative activation and transition to a profibrotic phenotype by day 14 after injury. In this study, we investigated the mechanism by which macrophages become profibrotic during the AKI-to-CKD transition.

Methods: Male wild-type or Ccr2-/- mice were subjected to warm U-IRI (27 min). Serum KIM1 level on day 1 after U-IRI was used to define the degree of initial injury. The injured kidney was removed on day 14 or 30 after U-IRI. Renal cells were flow sorted on day 14 to define the macrophage homing signals. Renal fibrosis was assessed on day 30 by Sirius red staining, qPCR and Western blotting for Col1a1, Col3a1 and Fn1. Macrophage accumulation was assessed by IHC for F4/80 and qPCR for Cd68. Interstitial inflammation was assessed by qPCR for Tnfa.

Results: Failure of kidney repair by day 14 after U-IRI led to sustained high expression of macrophage chemoattractant protein-1 (Mcp1) in the injured kidney compared to the contralateral control kidney (53-fold increase, n=10, $p<0.001$). CD45+F4/80+ macrophages and CD45+CD11c+F4/80- dendritic cells were the major cellular sources of this late, persistent Mcp1 expression (34- and 5-fold increase compared to renal cells and CD45+CD11c-F4/80- T cells/PMNs), while all bone marrow derived CD45+ cells expressed high levels of the Mcp1 receptor Ccr2. Injured kidneys from Ccr2-/- mice showed ~30% less profibrotic macrophage accumulation, interstitial fibrosis and inflammation in comparison to the wild-type control mice (n=5, $p<0.01$). Furthermore, administration of a CCR2 inhibitor (RS102895, 5 mg/kg, every 12 h) to wild-type mice for 7 days beginning 7 days after U-IRI replicated these results (n=8, $p<0.05$).

Conclusions: Our data showed that MCP-1 may serve as an autocrine and/or paracrine factor for profibrotic macrophage accumulation, leading to increased interstitial fibrosis during the AKI-to-CKD transition.

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SA-PO804

"Nephrogenic" Systemic Fibrosis Is Driven by C-C Chemokine Receptor 2-Dependent Myeloid- and Resident Tissue-Derived Fibrocyte Activation

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Background: Gadolinium-based contrast agents are now associated with multiple conditions, including 'nephrogenic' systemic fibrosis/gadolinium-associated systemic fibrosis (NSF) and symptoms attributed to gadolinium retention. Bone marrow-derived fibrocytes and the monocyte chemoattractant protein 1 (MCP1) inflammatory pathway have been implicated as mediators. *Mechanistic studies are scant.* We established a mouse model of NSF.

Methods: Marrow was transplanted to lethally-irradiated mice: 1) recipients with 5/6 nephrectomies received green fluorescent protein- (GFP-) expressing marrow, 2) C-C chemokine receptor 2- (CCR2-) deficient mice received GFP-expressing marrow, and 3) wild-type mice received CCR2-deficient marrow. After engraftment periods, recipients were randomized to untreated or gadolinium-based contrast agent treatment (Omniscan—96% gadodiamide—2.5 mmol/kg, 20 doses intraperitoneally over 4 weeks).

Results: Dermal cellularity was increased in contrast-treated GFP chimeric mice. Compared to control, skin GFP, fibronectin, and type I collagen were increased in the contrast-treated chimeric animals. Importantly, CD45RO—a fibrocyte marker—was abundant in the dermis of contrast-treated animals and expressed by the myeloid cells. Many of these cells expressed cytoplasmic α-smooth muscle cell actin, a marker of myofibroblast activation. Activated myofibroblasts and fibrosis colocalized with the myeloid marker in contrast-treated animals. MCP-1 and CCR-2 were increased in the tissues from contrast-treated mice. CCR2-deficient recipients of GFP-expressing marrow had a partial abrogation of gadolinium-induced pathology and displayed less GFP positivity in the skin. Wild-type animals that received CCR2-deficient marrow had a complete abrogation of dermal pathology.

Conclusions: Systemic fibrosis is induced by gadolinium contrast in mice. The abundance of myeloid cells in an involved organ, the skin, in tandem with a fibrocyte marker—CD45RO—supports the blood-borne circulating fibrocyte hypothesis of the disease. This is the first demonstration of fibrocyte trafficking ever demonstrated in mice. Similar to what is observed in a rat model, our data demonstrate that the monocyte chemoattractant protein 1/CCR2 axis plays a critical role in the pathogenesis of gadolinium-induced systemic fibrosis.

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SA-PO805

Bone Marrow Mesenchymal Stem Cells (BMSCs) Ameliorate Experimental Renal Interstitial Fibrosis via Promoting Tertiary Lymphoid Organ Neogenesis

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Background: Earlier studies indicate that bone marrow mesenchymal stem cells (BMSCs) is effective in protecting experimental renal interstitial fibrosis. However, the exact mechanism is not clear. We purpose that BMSCs may ameliorate renal interstitial fibrosis via promoting renal tertiary lymphoid organ (TLO) neogenesis.

Methods: We establish unilateral ureteral obstruction model using C57/BL6 male mice. BMSCs is given to animals 4 hours after surgery via tail vein, single time, 10^6 cells per mouse. Animals are sacrificed at the seventh day after surgery and kidney

tissues are harvested for histopathological assessment, immunoflurescence staining, immunohistochemistry staining and Western Blotting protein assay.

Results: BMSCs treatment significantly ameliorates renal tubulointerstitial fibrosis and reduce kidney injury score at the 7th day after UUO surgery. BMSCs treatment also reduces PDGFRβ+ fibroblast and α-SMA+ myofibroblast infiltration within the kidney, as well as suppresses the renal expression of extracellular matrix proteins collagen I, vimentin and fibronectin. BMSCs treatment also promotes the formation and neogenesis of tertiary lymphoid organ within the kidney, identified with markers PNAd, LYVE-1, and GL-7. Further more, BMSCs treatment significantly inhibits the renal infiltration of CD3e+ T lymphocytes, CD11b+ monocytes and Ly6C/Ly6G+ neutrophils. Our results indicate a possible role of tertiary lymphoid organ formation and leukocyte trafficking in BMSCs' ability to ameliorate kidney injury and interstitial fibrosis.

Conclusions: BMSCs protection from experimental renal tubulointerstitial fibrosis could at least partly be attributed to their promotion of tertiary lymphid organ neogenesis and leukocyte trafficking within the obstructed kidney.

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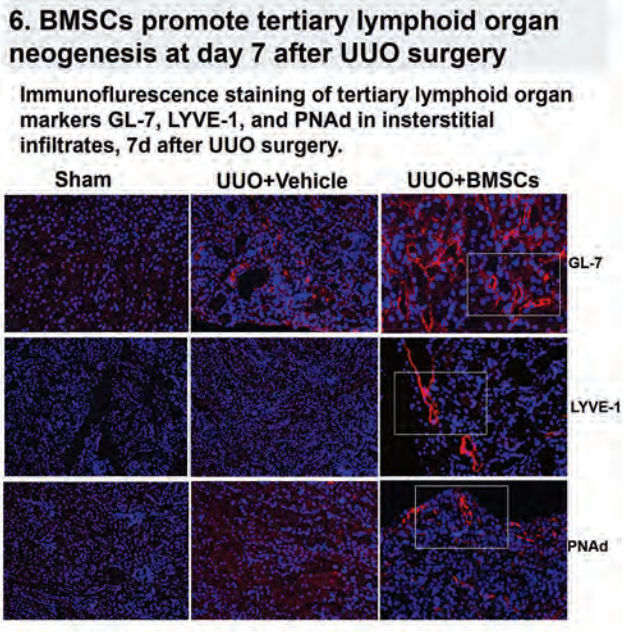

Figure 6. BMSCs promote neogenesis of tertiary lymphoid organ in UUO model, day 7.

SA-PO806

Twist1 in Kidney Epithelium but Not Macrophages Propagates Aristolochic Acid Nephropathy

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Background: Aristolochic acid, the causative agent in Chinese herbal and Balkan nephropathies, triggers persistent tubular injury and interstitial inflammation culminating in renal fibrosis. The transcription factor Twist1 induces pro-fibrotic gene expression programs in renal tubular cells (RTCs) but suppresses pro-fibrotic cytokines in macrophages. To discriminate these opposing, cell-specific actions of Twist1 in CKD, we subjected mice with RTC- or macrophage-specific Twist1 deficiency to chronic aristolochic acid nephropathy (AAN).

Methods: Mice with a floxed allele for the gene encoding Twist1 were backcrossed to the injury prone 129/SvEv strain and bred with 129/SvEv Ksp-Cre or LysM-Cre mice to yield Twist1 "KKO" or "MKO" mice with RTC- or macrophage-specific Twist1 deletion, respectively. AA (5mg/kg IP) was injected into Twist1 KKO, Twist1 MKO, and wild-type (WT) littermate control mice every other day for 12 days.

Results: 5 weeks after the last AA injection, Twist1 KKO mice compared to WTs had attenuated CKD as measured by BUN (41 ± 4 vs 52 ± 3 mg/dl; p = 0.035), blinded injury scores of PAS stains (2.0 ± 0.3 vs 2.9 ± 0.2; p = 0.038), and renal NGAL mRNA levels (0.6 ± 0.1 vs 1.0 ± 0.1; p = 0.036). Twist1 deletion in RTCs ameliorated kidney fibrosis as exhibited by reduced mRNA for Col-I (0.69 ± 0.05 vs 1.00 ± 0.09; p = 0.022) and TGF-β1 (0.81 ± 0.05 vs 1.00 ± 0.05; p = 0.019) and decreased protein levels of fibronectin (0.60 ± 0.03 vs 1.00 ± 0.07; p< 0.001) and α-SMA (0.55 ± 0.06 vs 1.00 ± 0.06; p<0.001). Twist1 in RTCs also secondarily regulated innate immune responses in the kidney as Twist1 KKO kidneys showed reduced mRNA expression for the macrophage chemokine CCL2 (0.72 ± 0.07 vs 1.00 ± 0.10; p = 0.046) and cytokine TNF-a (0.73 ± 0.08 vs 1.00 ± 0.08; p = 0.038). Accordingly, flow cytometric analysis after 5 weeks of AAN revealed reduced numbers of CD64+ (45906 ± 5279 vs 62986 ± 4822; p = 0.03) and F4/80+ (49949 ± 4441 vs 65581 ± 5005; p = 0.033) CD11b+Ly6G- macrophages in the Twist1 KKO kidneys versus WT controls. By contrast, robust deletion of Twist1 directly from myeloid cells in the Twist1 MKO cohort (>80%, p < 0.0001) had no impact at 5 weeks on renal tubular injury, interstitial fibrosis, or local inflammation.

Conclusions: Twist1 in RTCs rather than in myeloid cells regulates chronic inflammation and injury in the kidney during AAN.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO807

Genetic Depletion of Adenosine Kinase in Macrophage Aggravates Renal Fibrosis by Modulating M1/M2 Macrophage Polarization

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Background: Renal fibrosis is a common pathological manifestation of chronic renal diseases to end-stage renal failure, regardless of the cause. Accumulating evidence suggests a key role of macrophages in the pathogenesis of renal fibrosis. Adenosine (ADO) is an endogenous nucleotide involved in the energy metabolism and adenosine can be metabolized by adenosine kinase (ADK) or adenosine deaminase in cells. Adenosine can regulate the function of multiple immune cells. Therefore, we assume that the specific knockout of adenosine kinase gene can affect the function of macrophages and play a role in renal fibrosis.

Methods: 12 wild-type adult male mice and 12 ADK-deficient adult male mice undergo a sham operation or a unilateral ureteral occlusion operation.14 days after surgery, the kidney cortex was preserved to investigate renal pathological changes and renal fibrosis extent. F4/80 immunofluorescence staining and immunohistochemical staining was used to detect the degree of macrophage infiltration and M1 and M2 macrophages respectively. in vitro, we investigate the effrct of ADKI to RAW264.7 macrophages.

Results: ADK-/- UUO group had more severe interstitial fibrosis than that in WT UUO group. Infiltrated macrophages in the ADK-/- UUO group were increased than the WT UUO group (P<0.05) and M2 macrophages were predominate. ADKI promoted the RAW264.7 macrophages migration (P<0.05) and increased M2 macrophages biomarker expression along with inhibiting pron of -inflammatory cytokines release. ADKI increased the basic oxygen demand and maximal oxygen consumption of macrophages and reduced the extracellular acidification rate compared with Contol group (P<0.05). The numbers of M2 macrophages were negatively correlated with eGFR. The numbers of macrophages infiltrated in patients of Class III and IV DN was significantly higher than Class IIa or IIb stage(P < 0.05). patients with more severe renal tubular injury and interstitial fibrosis had more M2 macrophage.

Conclusions: Genetic depletion of adenosine kinase of macrophage exacerbates UUO-induced fibrotic lesions by mediating macrophage migration and promoting M2 macrophages transformation. Inhibition of ADK promote the conversion of macrophages to M2 type by inhibiting the glycolytic pathway. the more severe renal damage in patients with DKD, the more macrophages infiltrate.

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SA-PO808

Glycolytic Reprogramming and Development of Renal Fibrosis

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Background: Tubule dysfunction, myofibroblast differentiation and macrophage polarization are important in the development of renal fibrosis, which accompanies chronic kidney disease (CKD). Glycolytic reprogramming is critical for myofibroblast differentiation and fibrosis in the lung and the polarization of macrophages to an M1 phenotype. Although, dysregulation of cellular metabolism plays a role in the pathogenesis of several diseases, the role of glycolytic reprogramming in kidney fibrosis is unclear.

Methods: Glycolytic flux was measured by determination of extracellular acidification rates (ECAR) using Seahorse respirometry. An acute kidney injury (AKI)-CKD fibrotic model was performed by 31 min unilateral I/R, followed by uninephrectomy at day 8 and initiation of administration of the glycolysis inhibitor, PFK15 every 3 days until day 28. Human renal proximal tubule epithelial cells, mouse renal fibroblasts, and freshly isolated renal macrophages were used for in vitro studies.

Results: Transforming growth factor-β (TGF-β) is a master regulator of glycolytic reprogramming. TGF-β treatment led to increased glycolytic flux in both cultured renal epithelial cells and fibroblasts, as indicated by increased ECAR and ATP production. Glycolysis was reduced to basal levels with glycolytic inhibitors, PFK15 or 3-PO. TGF-β-induced glycolysis in fibroblasts was also confirmed by increased production of lactate. TGF-β-induced proliferation, differentiation (α-SMA), and matrix production (fibronectin) of renal fibroblasts was inhibited by PFK15. I/R injury for 2 days led to increased glycolysis in isolated CD11b+ renal macrophages, which was inhibited by PFK15. In the AKI/CKD fibrotic model, PFK15 markedly decreased renal interstitial fibrosis, indicated by less Sirius red and Masson's Trichrome staining. PFK15 also inhibited matrix and collagen deposition, α-SMA+ myofibroblasts, epithelial injury (e.g., KIM-1), and immune cell infiltration, including macrophages, CD3+ lymphocytes, and neutrophils.

Conclusions: These results suggest that glycolytic reprogramming is involved in renal tubular epithelial cell dysfunction, myofibroblast differentiation, and macrophage polarization in AKI, and inhibition of glycolytic flux may provide a new therapeutic target to prevent renal fibrosis when recovery from AKI is incomplete.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO809

The FDA-Approved MEK Inhibitor Trametinib Ameliorates Kidney Fibrosis by Suppressing ERK1/2 and mTORC1 Signalling

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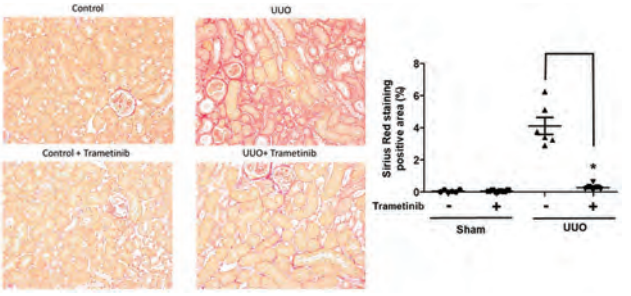
Background: The incidence of Chronic Kidney Disease (CKD) is reaching epidemic proportions with rising associated morbidity and mortality. Consequently, there is an urgent need for novel treatments. The ERK1/2 pathway is activated during kidney fibrosis, a hallmark and promoter of CKD irrespective of the underlying cause, and has been detrimentally implicated in the differentiation and expansion of kidney fibroblasts. Trametinib, an ERK1/2-pathway inhibitor has been recently approved for the treatment of melanoma. However, the efficacy of trametinib in the setting of renal fibrosis has not been explored.

Methods: Unilateral Ureteral Obstruction (UUO) was established in male C57BL/6J mice. Trametinib (3mg/Kg) was admisnistered, once daily, by oral gavage for 6 days. or. in a parallel study, 4 days after UUO once daily for six days. Human kidney fibroblasts were from Cambridge Bioscience. Immunoblot was conducted using the NuPAGE system (Invitrogen). Immunostaining was performed with the DISCOVERY XT (Ventana) instrument.

Results: Trametinib significantly attenuated collagen deposition and myofibroblast differentiation and expansion in the UUO model of kidney fibrosis. In addition to the ERK1/2 pathway trametinib also ameliorated mTORC1 activation, another key pro-fibrotic signalling pathway, in injured kidneys. Trametinib also supressed ERK1/2 and mTORC1 pathways activation in cultured primary human renal fibroblasts in response to TGF-β1. Additionally, trametinib reduced the expression of the myofibroblast marker αSMA and the proliferation of these cells.. Crucially, trametinib also significantly ameliorated renal fibrosis progression when administered to animals with established fibrotic injury.

Conclusions: Our work shows that trametinib could be beneficial for the treatment of chronic renal fibrotic diseases of diverse aetiologies.



Sirius red staining of kidney sections from UUO or contralateral control kidneys 7days afer surgery. Animals received trametinib (3mg/kg for 6days) or vehicle as indicated. N=6

SA-PO810

ATF6α and PPARα Cross-Talk Provides New Insights into Lipotoxicity-Induced Tubulointerstitial Fibrosis

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Background: Lipid accumulation in renal tubules is frequently observed in CKD patients with tubulointerstitial fibrosis (TIF). However, the molecular mechanisms modulating lipotoxicity-induced TIF remain obscure. ATF6α, a transcription factor of the unfolded protein response, is reported to be an upstream regulator of fatty acid metabolism. Fatty acids are the main energy source of proximal tubular cells (PTCs), resulting from their high energy demand. We therefore hypothesized that ATF6α regulates tubular fatty acid metabolism, and is thereby linked to lipotoxicity-induced TIF.

Methods: Human proximal tubular cells, HK-2, were transduced with Mock, dominant active ATF6α or dominant negative ATF6α lentivirus for various experiments. Kidney unilateral ischemia-reperfusion (uIRI) (27 mins) was used as a chronic kidney injury model and kidney injury was assessed on day 14 post-uIRI using WT and Atf6α-/- mice. Mitochondrial fatty acid β-oxidation, glycolysis and function were measured using a Seahorse flux analyzer.

Results: Overexpression of activated ATF6α transcriptionally downregulates PPARα, the master regulator of lipid metabolism, leading to reduced activity of fatty acid β-oxidation and cytosolic accumulation of lipid droplets in HK-2. Such ATF6α-induced lipotoxicity causes mitochondrial dysfunction, enhanced apoptosis and connective tissue growth factor (CTGF) expression, as well as reduced cell viability, suggesting the promotive effects of ATF6α in TIF. Atf6α-/- mice showed less tubular lipid accumulation in association with sustained PPARα expression after uIRI, resulting in the amelioration of apoptosis; reduced expression of CTGF, α-SMA and collagen I; and subsequent TIF. These findings indicate the pivotal role of ATF6α in lipotoxicity-mediated TIF. Administration of fenofibrate, a PPARα agonist, in uIRI-operated mice alleviated the tendency to lipid accumulation and TIF.

Conclusions: These findings indicate that under the pathogenic condition, maladaptive ATF6α activation deranges fatty acid metabolism in PTCs, which leads to lipotoxicity-mediated apoptosis and CTGF upregulation, both of which may accelerate TIF.

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SA-PO811

STAT3 Deletion from Stromal Cells Protects Mice from Folic Acid or Aristolochic Acid-Induced Kidney Fibrosis by Limiting Differentiation and Migration of Pericytes

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Background: STAT3 is a key transcription factor, which is phosphorylated in response to growth factors and cytokines. Upon phosphorylation, STAT3 regulates cell proliferation and migration. Here, we investigated the function of STAT3 signaling in the development of kidney fibrosis.

Methods: STAT3 activation was measured in 5 patient biopsy samples. Stromal cell-specific STAT3 deletion was performed by breeding STAT3 floxed mice with FoxD1 Cre mice. Kidney fibrosis was induced by administering 300 mg/kg folic acid (FA) or 5 mg/kg body weight aristolochic acid (AA). We developed STAT3 activated pericytes like 10T1/2 cells using two CRISPR based methods: i) Synergistic Activation Mediators (SAM) sgRNA, and ii) mutation of alanine 662 and asparagine 664 residues to cysteines. Additionally, using CRISPR, we mutated serine 727 to alanine of STAT3 in pericyte cell line. Cell migration was evaluated with wound scratch assays. RT-PCR, immunostaining and western blotting were performed to measure changes in STAT3-dependent genes and to quantitate pro-fibrotic cytokines.

Results: STAT3 phosphorylation was increased in tubular epithelial cells and interstitial cells of 5 human subjects with chronic kidney disease. Deletion of STAT3 from pericytes protects mice from FA or AA-induced kidney fibrosis at 7 and 14 days post-treatment. Fibrotic markers, including fibronectin, collagen1a1, and α-SMA, were reduced in STAT3 KO mice. STAT3 KO mice show similar acute injury and have less KIM-1 expression at 7 and 14 days. CRISPR-Cas9 mediated activation and inhibition studies *in vitro* confirmed that STAT3 is directly regulating profibrogenic signaling in pericytes. STAT3 phosphorylation increased migration and differentiation of pericytes. STAT3 is phosphorylated after treatment with TGF-β. Inhibition of TGF-β induced STAT3 phosphorylation significantly decreased the proliferation, production of profibrotic cytokines and differentiation of pericytes.

Conclusions: STAT3 leads to fibrosis by increasing proliferation, migration and differentiation of pericytes into myofibroblasts. STAT3 is a potential therapeutic target for kidney fibrosis.

Funding: NIDDK Support

SA-PO812

Renalase (RNLS) Attenuates Cisplatin (CP)-Induced CKD by diminishing Stress Kinases and Regulated Necrosis

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Background: CP is widely used as an effective chemotherapeutic agent for cancer yet it causes CKD upon repeated doses, which limits its use. We have induced CKD in mice using 2 doses of CP 2 weeks apart and have shown that CKD developes 2 weeks after the second dose. Previously we have shown that RNLS attenuates acute ischemic and cisplatin-induced AKI. We now report on the role of RNLS to prevent CP-induced CKD.

Methods: CKD was induced by 2 doses of CP 15 mg/kg ip 2 weeks apart in C57BL/6J mice. Mouse PT cells (TKPTS) were incubated with 25 ug/ml CP and studied 24 hours after treatment. A non-enzymatic peptide of RNLS (p81), 4mg/kg sc, that signals via a surface receptor was given to a separate group of mice 3 times a week beginning with the first dose of CP. Immunoblotting, immunoflourescence, cell viability, and serum creatinine was applied to evaluate the effect of RNLS on cell viability, expression of stress kinases and regulated necrosis mediators, and renal function.

Results: RNLS expression was reduced in CP-induced CKD by 60% at 4 weeks and almost completely at 9 weeks in the proximal tubules of CKD mice. CP reduced renalase expression in TKPTS cells treated with CP as well. RNLS peptide p81 reduced CP-induced CKD signifcantly(n=4, p<.05) and reduced Kim-1, RIPK1, and MAPK activation. Viability of TKPTS cells was increased and activation of caspase 3 (apoptosis), TLR2, RIPK 1 and 3, and MLKL (necroptosis) was supressed. RNLS knockout animals had a heightened stress kinase and necroptotic response to CP.

Conclusions: We conclude that RNLS attenuates CP-induced CKD by intervening in cell death pathways activated by CP. RNLS acts as a survival factor for proximal tubule cells as RNLS knockout provokes cell death by similar pathways. These data suggest that RNLS may be an effective therapeutic agent to prevent CKD in patients treated with repeated doses of cisplatin.

Funding: Other NIH Support - NIH/NCI STTR Phase I, R41CA189537-01

SA-PO813

Failed Repair, Not Fibrosis, Determines the Conversion of AKI to CKD in Cisplatin (CP)-Induced CKD

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Background: Repeated doses of CP leads to CKD in humans but its mechanism is unknown. Previously we reported on a model of CP-induced CKD in mice that fully recapitulates the human disease.

Methods: Mice received CP 15mg/kg (ip) 2 weeks apart and multiphoton microscopy, cDNA microarray, PCR, western blotting, and immunocytochemistry were applied 4 weeks after the first dose in the two-dose model, when CKD is fully developed, and compared in mice 2 and 4 weeks after a single dose, when recovery is completed. Statistically significant differences ($p<.05$) were determined after correction for multiple comparisons.

Results: A fixed decline in GFR occured at 4 weeks in the 2 dose group and was associated with a loss of the glomerular parietal epithelial cells, a lesion that develops in CP-CKD. No increase in collagen deposition, the invasion of macrophages, or the loss of endothelial cells accompanied these changes. The onset of CKD showed expression of genes underlying regulated necrosis including Toll-Like Receptors 2 and 4, the Receptor-Interacting Protein Kinases 1 and 3, the Mixed Lineage Kinase-Like, and Cyclophilin D, while apoptosis played a minor role in cell death. Expression of the damage molecules Kim-1 and Ngal persisted after the second dose as did the reactivation of the stress kinases JNK and ERK, indicating continued injury. Cell cycle activity was markedly reduced after the second dose of CP. Although levels of CXCL1, CCL2, and CCR2 that play a critical role in CP AKI were elevated,. knockout of these genes did not prevent the development of CKD. Prominent and prolonged expression of the p21 gene was observed, which underlies the progression of CKD after 5/6 nephrectomy, but p21 knockout animals still progressed to CKD in the model.

Conclusions: Epithelial cell loss and regulated necrosis is a primary event in the development of CKD induced by two doses of CP. Progression of CKD is independent of the accumulation of fibrous tissue, macrophages, the loss of endothelial cells, or the production of key cytokines activated in AKI. Rather, deficient repair and continued loss of proximal tubule cells is the primary event in the conversion of AKI to CKD after repeated doses of cisplatin. A focus on interceding in the mechanisms of regulated necrosis could be successful in preventing CKD

Funding: Other NIH Support - NIH/NCI STTR Phase I, R41CA189537-01

SA-PO814

DNA Methylation Suppresses HoxA5 for Jag1-Notch1 Signaling in Renal Interstitial Fibrosis

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Background: DNA methylation has been implicated in the regulation of renal interstitial fibrosis in kidney diseases, but the mechanism remains incompletely understood.

Methods: In this study, we analyzed genome-wide changes in DNA methylation during renal fibrosis in the mouse model of unilateral ureteral obstruction (UUO) by using the reduced representative bisulfite sequencing.

Results: UUO induced renal interstitial fibrosis, which was accompanied by an overall increase in DNA methylation in kidney tissues. 5-aza-2'-deoxycytidine (5-aza, DNA methylation inhibitor) blocked DNA methylation in UUO and suppressed renal fibrosis. Among the genes with altered DNA methylation in UUO, HoxA5 had seven hypermethylated CpG sites on its promoter that were further verified by pyrosequencing. Hypermethylation of HoxA5 was associated with decreased HoxA5 expression in UUO. 5-aza could partially prevent HoxA5 decrease in UUO, further confirming the regulation of HoxA5 by DNA methylation. Overexpression of HoxA5 suppressed renal fibrosis in UUO and attenuated TGF-β-induced fibrotic changes in renal tubular cells. Mechanistically, HoxA5 was shown to repress Jag1 via gene promoter binding, resulting in the suppression of the Jag1-Notch signaling pathway of renal fibrosis.

Conclusions: Together, these results suggest that DNA methylation may promote renal interstitial fibrosis by suppressing HoxA5 for the activation of Jag1-Notch1 signaling.

SA-PO815

Genetic Nrf2 Enhancement Increases Proteinuric Renal Injury

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Background: Proteinuric chronic kidney disease (CKD) is a major cause of progressive renal failure and has limited therapies. Nrf2 (nuclear factor erythroid 2 like 2) is a transcription factor that upregulates cytoprotective mechanisms including antioxidants and detoxifying genes. Keap1 (kelch-like ECH-associated protein 1) binds and inhibits Nrf2 under normal conditions to prevent activity. Under conditions of oxidative stress or chemical exposure, the Keap1 repressor releases Nrf2 which then initiates target gene transcription. While this might be expected to prevent disease, both preclinical and clinical data have suggested that Nrf2 could paradoxically aggravate proteinuria. We therefore hypothesized that Nrf2 activity accelerates progression of proteinuric CKD.

Methods: Keap1 hypomorphic mutant mice have reduced Keap1 expression and enhanced Nrf2 activity. Wild-type mice and Keap1 hypomorphs were subjected to a variety of proteinuric injuries including continuous angiotensin II infusion, adriamycin, and albumin overload models. Urinary albumin excretion was measured with ELISA, and glomerular damage assessed via assessment of foot process effacement, nephrin, and Wilms Tumor 1 (WT1). Systemic blood pressure was measured with radiotelemetry, and glomerular filtration rate (GFR) was determined with FITC-sinistrin. The synthetic triterpenoid, CDDO-Im, was used in the adriamycin model to upregulate Nrf2 activity.

Results: Compared to wild-type mice, Keap1 hypomorphs had significantly increased proteinuria in all disease models. This was associated with worsened podocyte foot process effacement and decreased nephrin and WT1, indicating increased glomerular injury. We did not detect any increase in GFR in the mutants to explain this difference. While there were mild elevations in the systolic, diastolic, and mean blood pressures in the Keap1 hypomorphs before and after angiotensin II infusion, the proteinuria was out of proportion to these differences. Treatment of wild-type mice with CDDO-Im enhanced Nrf2 activity but also increased mortality after adriamcyin exposure.

Conclusions: Genetic Nrf2 upregulation significantly promotes glomerular injury and lethality in proteinuric kidney injury models. This phenomenon is partly explained by higher blood pressure in hypomorphic mice but other mechanisms likely play a role.

Funding: NIDDK Support, Private Foundation Support

SA-PO816

Involvement of Endoplasmic Reticulum Stress and Autophagy on Homocysteine Induced Apoptosis of Human Glomerular Mesangial Cells

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Background: Homocysteine (Hcy) levels significantly increased in chronic renal failure (CRF). It has been reported that Hcy can induce proliferation and apoptosis of glomerular Mesangial cells. The purpose of this study was to investigate whether autophagy and endoplasmic reticulum stress were involved in the induction of glomerular Mesangial cells apoptosis by Hcy, and to provide evidence for further elucidation of the toxicity of Hcy on Mesangial cells.

Methods: Human Glomerular Mesangial cells (HMC) were incubated with different concentrations of Hcy (50~1000 μ mol/L) for 24h and Hcy 250 μmol/L for different hours (0~48h). Flow cytometry was used to detect the changes of apoptosis after different concentrations and times of Hcy treatment. Western blotting was used to detect the changes of related proteins after exposure to Hcy 250 μmol/L for 24h. Apoptosis as well as protein changes were separately detected by flow cytometry and Western blotting after treatment with endoplasmic reticulum inhibitor 4-PBA and Atg 5 siRNA respectively.

Results: The proliferation ability and cell viability of HMC gradually decreased. The proportion of Mesangial cell apoptosis increased with the increase of the concentration of Hcy and the prolongation of the incubation times in a time-and concentration-dependent manner. The expression of apoptosis-related protein Bax and cleavage caspase-3 were significantly increased, with the autophagy related proteins LC3-II/LC3-I, beclin1 and Atg5 were significantly increased and p62 decreased. The expression of ER stress-related proteins ATF4, CHOP, GRP78 and p-eIF2α all increased significantly. After the intervention of 4-PBA, the ER stress-related proteins and the proportion of apoptosis decreased with the expression of apoptosis-related protein improved. The expression of p62 increased and LC3-II/LC3-I, beclin1 and Atg5 decreased. At the same time, after intervened with Atg5 siRNA, the expression of Atg5 decreased, and the ratio of LC3-II/LC3-I decreased and the p62 degraded with cleavage caspase-3 and CHOP increased, but p-eIF2α did not change significantly.

Conclusions: Hcy induced glomerular mesangial cell apoptosis in a concentration- and time- dependent manner and may via an ER stress-triggered signaling pathway. Atg5-dependent autophagy plays a protective role in the process.

Funding: Government Support - Non-U.S.

SA-PO817

Regulation of Klotho by Proteinuria in CKD

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Background: Albuminuria, caused by lesions in the glomerular filtration barrier, promotes tubular inflammation, apoptosis and fibrosis in Chronic Kidney Disease (CKD). Previously, it was shown that albuminuria is associated with lower Klotho levels. Our aim is to further investigate how albuminuria regulates Klotho expression.

Methods: Transgenic mice with inducible podocyte apoptosis (POD-ATTAC) were used, as well as Alport mice, either wild type or deficient in albumin. For the *in vitro* experiments, HEK cells overexpressing the human transmembrane form of Klotho and HK-2 cells were used.

Results: *In vivo* in POD-ATTAC mice, 3 and 7 days after podocyte loss, both Klotho mRNA and protein levels were downregulated without modifications of ADAMs activities and expression. *In vitro*, upon BSA treatment, the total and membrane fractions of the Klotho protein were decreased while Klotho protein half-life was also significantly reduced. Cleaved Klotho as measured in the supernatant was decreased proportionally, arguing against enhanced cleavage. Likewise, a reduction of Klotho mRNA and protein levels was

observed in HK-2 cells. In the Alport mice, Klotho expression was decreased as measured by qPCR and Western blot. However, this was not the case in the Alport albumin deficient mice, implying some specificity of the regulation by albuminuria itself and not only by the primary renal disease. Similarly, there was no Klotho downregulation upon exposure to immunoglobulins *in vitro*. *In vivo* and *in vitro*, albuminuria induced some features of ER stress. Inhibition of ER stress increased Klotho protein levels *in vitro and in vivo*, suggesting that this mechanism may participate to the enhanced Klotho degradation by albuminuria.

Conclusions: In conclusion, albuminuria has a specific role on Klotho downregulation *in vitro* and *in vivo* that seems to depend on ER stress induction.

SA-PO818

Calcitriol Ameliorates Kidney Injury and Fibrosis by Activating Klotho and Inhibition of TGFβ1 Signaling Pathway

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Background: Active vitamin D3 (Calcitriol) can effectively remit the progression of chronic kidney disease, but its mechanism is not clear. Klotho as an anti-aging protein played a variety of physiologic roles in the kidney. The main purpose of this experiment is to explore whether Calcitriol could up-regulated expression of the Klotho in vitro and in vivo, and ameliorates kidney injury and fibrosis by targeted inhibition of TGFβ1 activation.

Methods: (1) Animal Experiment: The rats were divided into three groups: sham group, 5/6 nephrectomy group, 5/6 nephrectomy + calcitriol group. 1) Through serum biochemical tests, to detect the levels of BUN, Creatine in various groups and determine expression of Klotho, TGFβ1 in serum. 2) By HE, Masson staining of renal tussues, Observation of renal fibrosis and collagen deposition; 3) Detection expression of Klotho, TGFβ1, E-cadherin and α-SMA in renal tussues by Immunohistochemical staining. 4) Using PCR and Western-Bloting detect expression of Klotho, TGFβ1, E-cadherin and α-SMA in renal tussues; (2) In Vitro: Calcitriol, Klotho siRNA and TGFβ1 ware prepared and mouse renal tubular epithelial cells were cultured in vitro. Mouse renal tubular epithelial cells was treatment with various concentrations and time period of Calcitriol before TGFβ1 stimulation, and pretreatment or not with Klotho siRNA. Klotho, Snail1, PAI-1, E-cadherin and α-SMA were measured by real-time PCR and Western-blot.

Results: (1) Animal Experiment: 1) Calcitriol could effectively reduce the elevated creatinine, BUN in the 5/6 nephrectomy rats; 2) Calcitriol might ameliorate kidney injury and fibrosis by light microscopy; 3) In renal tissue, calcitriol may induce Klotho and E-cadherin expression and reduce TGFβ1 and α-SMA expression; (2) In Vitrio: Calcitriol in a dose and time dependent manner induce Klotho and E-cadherin expression and reduce Snail1, PAI-1 α-SMA expression by TGFβ1 stimulation. Klotho siRNA could mitigate effective role of Calcitriol.

Conclusions: Calcitriol could ameliorate kidney injury and mitigate TGFβ1 induced fibrosis by activating Klotho in vivo and in vitro.

Funding: Government Support - Non-U.S.

SA-PO819

PBI-4050 Signals via GPR40 to Decrease Adenine-Induced Tubulointerstitial Injury and ER Stress

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Background: PBI-4050, a novel first-in-class orally active compound currently in clinical phase III in IPF patients, exerts antifibrotic effects in several organs via a novel mechanism of action. In the kidney, PBI-4050 exerts its antifibrotic effects primarily through GPR40 activation. The aim of this study was to further examine the effects of PBI-4050 in both WT and GPR40$^{-/-}$ mice on adenine-induced tubulointerstitial fibrosis, inflammation and the unfolded protein response pathway, all of which contribute to CKD progression.

Methods: Adenine-induced CKD was achieved in eight-week old male C57BL/6 mice fed a diet supplemented with 0.25% adenine. After one week, PBI-4050 (50, 100, 200 mg.kg^{-1}day) or vehicle was administered daily by oral-gavage for three weeks. In parallel, eight-week old wild-type and GPR40$^{-/-}$ mice were also subjected to adenine-CKD, with or without a PBI-4050 (200 mg.kg^{-1} day) treatment.

Results: PBI-4050 treatment reduced adenine-induced polyuria and maintained urine osmolality. Plasma urea and creatinine were significantly increased four and two-fold respectively in vehicle treated mice, while PBI-4050 decreased these values. PBI-4050 treatment decreased adenine-mediated renal fibrotic lesions in a dose dependent manner. Accordingly, α-SMA and fibronectin expression were also reduced by PBI-4050 as well as several pro-inflammatory genes. Moreover, renal ER-stress and pro-apoptotic markers were significantly reduced by PBI-4050 in adenine fed mice. In parallel, GPR40$^{-/-}$ mice given adenine had increased tubulointerstitial injury, exacerbated renal function and ER-stress associated protein expression compared to WT mice. PBI-4050 treatment in adenine-fed GPR40$^{-/-}$ mice failed to reduce anemia, tubulointerstitial injury and ER-stress.

Conclusions: PBI-4050 treatment decreased the severity of several adenine-induced sequelae including tubular injury, tubulointerstitial fibrosis, anemia, apoptosis and ER-stress. The GPR40 receptor mediates PBI-4050's beneficial effects in this model. Taken together, these data reinforce PBI-4050's use as a renoprotective therapy and identify important pathways involved.

Funding: Commercial Support - Prometic Life Sciences Inc.

SA-PO820

Peroxiredoxin V (PrdxV) Negatively Regulates EGFR/Stat3-Mediated Fibrogenesis via Cys48-Dependent Interaction Between PrdxV and Stat3

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Background: Activation of epidermal growth factor receptor (EGFR)/signal transducer and activator of transcription 3 (Stat3) signaling pathway has been reported to be associated with renal fibrosis. In addition to the anti-inflammatory effect and the anti-oxidative effect of Peroxiredoxin V (PrdxV), recently it has been shown that PrdxV acts as an anti-fibrotic effector by inhibiting the activity of Stat3 in TGF-β-treated NRK49F cells. However, the relevance and the underlying mechanism of Prdx V to renal pathobiology remains poorly understood.

Methods: To investigate the role of PrdxV in renal fibrosis, we used a transgenic mouse model with PrdxV siRNA expression controlled by U6 promoter (C57BL/6J-Tg(U6-PrdxVsi)1Thlee/Krb; PrdxVsi mice). Both PrdxV^{wt} and PrdxV^{si} mice were subjected to unilateral ureteral obstruction (UUO) for 7 days (Control vs. UUO group, n = 8 per each group). To understand the molecular mechanism for anti-fibrotic effect of PrdxV, HA-tagged WT PrdxV and C48S PrdxV were transiently transfected into 209/MDCT cells and treated with TGF-β.

Results: We confirmed that the protein level of PrdxV was inversely related to the progression of UUO-induced renal fibrosis. Transgenic PrdxV^{si} mice exacerbated epithelial-to-mesenchymal transition as well as the increase of oxidative stress by UUO. In the fibrotic kidney of PrdxV^{si} mouse, knock-down of PrdxV increased Y1068-specific EGFR and Stat3 phosphorylation, whereas overexpression of WT PrdxV in 209/MDCT cells showed the opposite results. Immunoprecipitation revealed the specific interaction between WT PrdxV and Stat3 in the absence or presence of TGF-β stimulation, whereas no PrdxV-EGFR or C48S PrdxV-Stat3 interaction were detected under any conditions.

Conclusions: PrdxV is an anti-fibrotic effector that sustains renal physiology. Direction interaction through Cys48 between PrdxV and Stat3 is a major molecular mechanism.

Funding: Government Support - Non-U.S.

SA-PO821

cMet Agonistic Antibody Attenuates Renal Fibrosis in Obstructive Nephropathy

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Background: Hepatocyte growth factor (HGF) and its receptor, cMet, activate biological pathways necessary for repair and regeneration following kidney injury. The Met receptor is expressed in multiple cell types within the kidney, each of which is capable of regulating fibrotic responses. Since HGF is a quite unstable molecule in its biologically active form, we asked whether a monoclonal antibody (Ab) that displays receptor full agonist activity could protect kidney from fibrosis.

Methods: We tried to determine whether cMet agonistic Ab might reduce fibrosis, the final common pathway for chronic kidney diseases. We primary cultured human proximal tubular epithelial cells (PTECs) for in vitro study and a mouse model of renal fibrosis disease induced by unilateral ureteral obstruction (UUO) was introduced.

Results: In kidney biopsy specimens of CKD patients, cMet immunohistochemistry staining showed remarkable increase than patients with normal renal functions. cMet Ab treatment significantly increased phospho-cMet expression and abrogated protein expressions of fibrosis markers such as fibronectin, collagen IV, αSMA and also Bax2 which is a marker of apoptosis triggered by recombinant TGF-β1 in PTECs. In a wound healing scratch assay, PTECs treated with cMet Ab progressed into the wound area more rapidly inducing wound healing than untreated cells. Remarkably, injections of cMet Ab significantly prevented renal fibrosis in the obstructed kidneys quantified by Masson Trichrome staining. Consistently, cMet Ab decreased the expression of fibrosis markers such as, collagen 1 and αSMA, and E-cadherin which is a cell-to-cell adhesion molecule was recovered.

Conclusions: cMet-mediated signaling may have a considerable role in the renal fibrosis. And cMet agonistic Ab may thus be a valuable substitute for HGF, being more easily available in a biologically active, stabilized, and purified form.

SA-PO822

The Histone Demethylase Jumonji Domain-Containing Protein 3 Acts as an Epigenetic Suppressor of Renal Fibrosis

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Background: The histone demethylase Jumonji domain-containing protein 3 (JMJD3) is the enzyme that induces demethylation of histone H3 lysine 27 (H3K27) and its activation is involved in the tumor genesis. Although activation of H3K27 methyltransferase has been shown to be required for renal interstitial fibroblast activation and renal fibrogenesis, the role of JMJD3 in these processes remains elusive.

Methods: In this study, we examined the effect of pharmacological inhibition of JMJD3 on renal fibroblast activation and renal fibrosis development in a murine model of unilateral ureteral obstruction.

Results: Following unilateral ureteral obstruction, expression levels of JMJD3 and methylated H3K27 were increased in the kidney. Administration of GSKJ4, a specific inhibitor of JMJD3, aggravated renal fibrosis and increased expression of alpha-smooth muscle actin (alpha-SMA), a hallmark of myofibroblasts (active fibroblasts) and promoted deposition of collagen I, one of major extracellular matrix proteins. GSKJ4 inhibition also increased expression of transforming growth factor β1 (TGF-b1) and enhanced the phosphorylation of Smad3, a key molecule of TGF-β signaling. Moreover, GSKJ4 potentiated expression of Notch1 and Notch3 as well as phosphorylation of NF-κB and Stat3. Finally, treatment with GSKJ4 increased expression of alpha-SMA, collagen I and fibronectin in cultured renal epithelial cells.

Conclusions: Collectively, these data suggest that JMJD3 functions as a suppressor of renal fibroblasts and renal fibrosis in the kidney after ureteral obstruction.

Funding: NIDDK Support

SA-PO823

A Pilot Study to Explore Relationships of Mitochondrial DNA Copy Number in Blood and Kidney Tissue and Their Associations with Kidney Health

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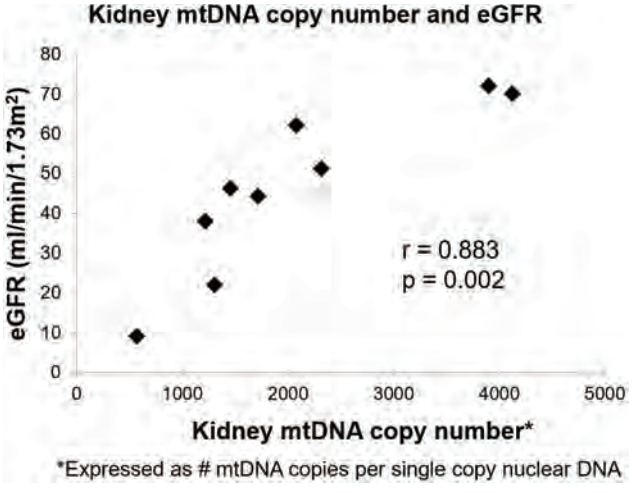
Background: Despite several animal studies linking mitochondrial damage to the development of acute and chronic kidney injury, human studies have been sparse due to our limited methods for assessment of mitochondrial health by stored specimens. A key question is whether peripheral mitochondrial measures adequately reflect mitochondrial health in kidney tissue. We conducted a pilot study to compare mitochondrial DNA (mtDNA) copy number in blood and kidney tissue and to evaluate their associations with renal function and pathology.

Methods: We measured mtDNA copy number in blood buffy coat and kidney specimens of 9 participants of the Brigham and Women's Hospital Nephrectomy Cohort who were selected to represent a broad range of age and kidney function. MtDNA copy number was determined by a real-time quantitative PCR assay that measures the ratio of the mtDNA-encoded *ND1* gene to the single-copy nuclear β2-Microglobulin gene. Kidney specimens were assessed by a pathologist using a standardized scoring protocol.

Results: The mean age was 64 ± 12 years and mean eGFR was 46 ± 21 ml/min/1.73m^2. Blood mtDNA copy number (r=0.739, p=0.023) and kidney mtDNA copy number (r=0.883, p=0.002; **Figure**) correlated strongly with eGFR and with each other (r=0.756, p=0.019). Compared to participants with severe tubulointerstitial fibrosis, participants with mild fibrosis had higher blood and kidney mtDNA copy numbers (p=0.03).

Conclusions: Higher mtDNA copy number, measured in blood or kidney, correlated positively with eGFR and negatively with tubulointerstitial fibrosis, suggesting that mitochondrial abundance is important for kidney health. Strong correlations between mtDNA copy number in blood and kidney tissue support the use of peripheral mitochondrial measures in future studies.

Funding: NIDDK Support



SA-PO824

Activation of FXR Regulates Kidney Autophagy for Suppressing Renal Fibrosis

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Background: Autophagy is an evolutionarily conserved catabolic process that removes damaged organelles and maintains cellular energy homeostasis. Acute regulation by nutrient-sensing of autophagy and long-term transcriptional regulation by nuclear hormone receptor farnesoid X receptor (FXR) is well known. Also, kidney autophagy regulates TGFβ expression and suppresses kidney fibrosis. However, the functional role of FXR on TGFβ-induced kidney autophagy is relatively unknown.

Methods: Expression levels of LC3 protein and autophagy related genes were measured on treatment with TGFβ and FXR agonists, GW4064, CDCA, and INT-747, in human proximal tubule cells (HK2 cells). Also, we tested expression levels of autophagy related proteins and genes in unilateral ureteral obstruction mice model. The LC3 Puncta formation was monitored by fluorescence microscopy. Expression levels of protein and autophagy related genes were measured on down-regulation of FXR by siRNA in HK2 cells or FXR knock-out mice.

Results: Treatment with TGFβ (5 ng/ml) in HK2 cells resulted in an increase in the level of LC3 protein and autophagy related genes, along with an increase in fibrosis markers. Activation of FXR by agonists in TGFβ-induced HK2 cells regulates LC3 I and II expression levels. Autophagy related genes were decreased in FXR agonists treated HK2 cells. Also, autophagic flux was further increased on co-treatment with GW4064 and TGFβ in HK2 cells. Autophagy related genes has no GW4064 effects on down-regulation of FXR by siRNA in HK2 cells. Protein levels of LC3 and fibrosis markers were increased in FXR-KO UUO mice model compared to those of WT UUO mice model.

Conclusions: These data reveal a functional role of FXR for kidney autophagy regulator in TGFβ-induced HK2 cells and suggest that FXR may play an important role in the suppression of renal fibrosis through kidney autophagy.

Funding: Government Support - Non-U.S.

SA-PO825

Rab27a Dependent Exosome Secretion from Tubular Epithelial Cell Promotes Albumin-Induced Tubulointerstitial Inflammation

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Background: Tubular epithelial cells (TECs) secrete increasing exosomes under with proteinuria toxicity. However, the mechanism through which exosomes are produced and the effect on tubular cell hemostasis and tubulointerstitial inflammation are unknown.

Methods: Proteinuric renal disease model was induced by adriamycin (ADR) administration through tail vein. Urinary albumin was determined at 0, 7, 14, 21 and 23 days after ADR injection. Histological changes were examined by PAS staining. For *in vitro* studies, TECs were treated with albumin. We found that the release of exosomes may result in TECs inflammation. Exosomes were isolated from isolated tubules of kidney and cell culture supernatant for characterization and functional study.

Results: Chronic kidney injury was induced by administration with ADR. Urinary albumin was significantly increased in ADR-treated mice 2 weeks after injection compared with controls. Histologically, the TEC injury and protein cast were observed in ADR-injected mice. Electron microscopy and western blotting analysis of exosome markers, CD9, CD81, Alix confirmed the typical characteristics of isolated exosomes from kidney. Exosome production was increased significantly in kidney of ADR mice and in TECs with albumin exposure. Interestingly, we showed increasing levels of Rab27a mRNA and protein both in the tubule of ADR-injected mice and in BSA-treated TECs in a dose dependent manner. And the increased exosome production was dependent on Rab27a up-regulation since silencing of Rab27a reversed the exosomes secretion. Importantly, the mRNA expression of inflammatory cytokines in TECs treated with BSA was reduced after inhibition of exosome secretion by Rab27a knocking down. To explore the effect of TEC exosome production under albumin exposure, TEC-exosomes were purified and added to naïve TEC. Up-regulation of inflammatory cytokines were found in receipt TECs.

Conclusions: These results provide a novel finding that TECs exosomes were produced increasingly through Rab27a dependent mechanism. And TEC exosome production exacerbated TECs injury by enhancing inflammatory response and may consequently lead to tubulointerstitial inflammation.

SA-PO826

Amelioration of Renal Fibrosis and Tubulointerstitial Damage in Fat-1 Transgenic CKD Mice by Compensation of Decreased Omega-3 Fatty Acids in the Kidney

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Background: Although recent advances have led to better understanding of the linkage between inflammatory diseases and lipid mediators, little has been reported on the changes of lipid profile of kidney tissue in chronic kidney disease (CKD). Lipidomics is a powerful

tool for the identification and the quantification of the lipid metabolites. In this study, we applied lipidomics to the kidney from the mice performed with subtotal nephrectomy, to identify specific lipid mediators as novel therapeutic targets in CKD.

Methods: Subtotal nephrectomy or oral administration of adenine was performed to C57BL/6J mice to establish CKD models. Kidney tissue samples from subtotal nephrectomy mice were analyzed with lipidomics to reveal lipid profile of CKD kidneys. We also analyzed the CKD models of *fat-1* transgenic mice expressing the *C. elegans fat-1* gene encoding an omega-3 fatty acid desaturase, leading to abundant omega-3 fatty acids in kidneys. To evaluate effects of lipid metabolites on fibrosis, we used cultured NRK-49F cells.

Results: Lipidomics analysis revealed that omega-3 fatty acids (EPA and DHA) and their downstream lipid metabolites were significantly decreased in CKD kidneys in comparison with sham control kidneys. Therefore, to investigate the effects of decreased omega-3 fatty acids on CKD kidneys, we examined two CKD models of *fat-1* transgenic mice, subtotal nephrectomy and adenine-induced nephropathy. Alpha-SMA (a marker of renal fibrosis) and NGAL (a marker of tubulointerstitial damage) were suppressed in *fat-1* transgenic CKD mice, suggesting that increased omega-3 fatty acids in kidney have beneficial effects on CKD. Some specific omega-3 fatty acid metabolites which were decreased in CKD kidneys attenuated fibroblast activation *in vitro*, indicating that they could be novel therapeutic lipid mediators for CKD treatment.

Conclusions: Lipidomics of the kidneys from subtotal-nephrectomy mice revealed reduction of omega-3 fatty acids and their down-stream lipid metabolites. Supplementation of omega-3 fatty acids and their downstream metabolites to kidneys might ameliorate tubulointerstitial damage and renal fibrosis in CKD.

SA-PO827

Renal Hemodynamic Effects of a sGC Stimulator vs Activator in Conscious Sprague-Dawley and Obese Diabetic ZSF1 Rats

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Background: Endothelial dysfunction and/or NO loss accelerate the progression of diabetic and non-diabetic chronic kidney disease (CKD). Therefore, soluble guanylate cyclase (sGC) stimulators and activators are being developed as potential novel therapeutic interventions in CKD. Stimulators sensitize sGC to low levels of bioavailable NO in the presence of reduced (ferrous) prosthetic heme, while sGC activators preferentially activate sGC when it is in an oxidized or heme free state. But their comparative renal hemodynamic effects have not been examined in conscious rat models.

Methods: Conscious chronically instrumented conscious Sprague-Dawley rats (body weight ~300g) and obese diabetic ZSF1 rats (body wt ~500g) underwent repeated simultaneous 1-2 hr BP (radiotelemetry) and RBF (Transonic) recordings over 3 wks (2-4 x wk) while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (BAY-543) or the stimulator (BAY-747) (3-4 days/wk with a ~3 day washout period). Effects on mean arterial pressure (MAP), RBF, renal vascular resistance (RVR) and the autoregulatory (AR) ability to buffer spontaneous BP fluctuations were assessed using a methodology recently developed in our lab.

Results: Table (mean ± SEM) While both the sGC stimulator and the sGC activator in the dosages used had similar BP effects in both SD and ZSF1 rats, the sGC activator tended to produce greater renal vasodilation with both doses in both strains but which was significant only in the ZSF1 rats. Despite the renal vasodilation, AR buffering of spontaneous BP fluctuations was not impaired by either agent in either strain.

Conclusions: The significantly greater renal vasodilatory effects of sGC activator in a renal disease model, the ZSF1 rat, may have relevance when considering therapy with sGC modulators in CKD states.

Funding: Commercial Support - Bayer Pharma AG

	SPRAGUE DAWLEY			ZSF-1		
	MAP (mmHg)	RBF (ml/min)	RVR (mmHg/ml.min)	MAP (mmHg)	RBF (ml/min)	RVR (mmHg/ml.min)
sGC Stimulator (BAY-747)						
Vehicle	103.0 ± 3.2	8.5 ± 0.6	12.9 ± 1.4	127.8 ± 3.1	8.8 ± 0.7	15.1 ± 0.8
0.3 mg/kg (Δ%)	−1.8 ± 2.1	+5.8 ± 8.2	−3.3 ± 7.0	−3.6 ± 2.4	+0.6 ± 5.7	−0.9 ± 4.9
1.0 mg/kg (Δ%)	−7.3 ± 1.5*	+12.3 ± 1.1	−13.7 ± 8.4*	−6.7 ± 1.7	+10.2 ± 6.2	−12.4 ± 5.9
sGC Activator (BAY-543)						
Vehicle	105.2 ± 3.5	7.9 ± 0.3	13.7 ± 0.9	129.4 ± 2.2	9.2 ± 0.8	15.2 ± 1.5
3 mg/kg (Δ%)	−1.7 ± 2.2	+11.9 ± 3.4	−11 ± 2.9	−5.4 ± 1.8	+19.2 ± 2.9#	−20.6 ± 2.7#
10 mg/kg (Δ%)	−9.0 ± 1.9#	+25.4 ± 9.2	−24.9 ± 6.4*	−12.4 ± 1.7*#	+45.7 ± 7.2*#	−38.9 ± 3.0*#

*p<0.05 maximum vs. lower dose; # 0.05 maximum vs. BAY-747 (n=9-11/group)

SA-PO828

High Salt Enhances ROS and Ang II Contractions of Glomerular Afferent Arterioles from Mice with Reduced Renal Mass

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Background: High salt intake, angiotensin II (Ang II), and reactive oxygen species (ROS) enhance progression of chronic kidney disease (CKD). We reported that myogenic contractions of renal afferent arterioles (RAAs) were enhanced by superoxide generated from $p47^{phox}$/NOX2 but inhibited by H_2O_2 generated from POLDIP2/NOX4. We tested the hypothesis that feeding a high salt diet to mice with the reduced renal mass (RRM) model of CKD generates specific ROS in their RAAs that enhances Ang II contractions.

Methods: C57BL/6 mice received surgical RRM or sham operations and 6% or 0.4% NaCl salt for 3 months. Ang II contractions were measured in RAAs perfused at 45 mmHg and superoxide and H_2O_2 by fluorescence microscopy.

Results: RRM enhanced the gene expression in RAAs for $p47^{phox}$ and NOX2 and high salt intake in mice with RRM enhanced the gene expression for AT1Rs, POLDIP2 and NOX4 and reduced the gene expression for catalase. Mice with RRM fed a normal salt diet had contractions to 10^{-6} M Ang II similar to sham (-56 ± 5 vs -52 ± 5 %; NS). However, RRM mice fed a high salt diet had an enhanced superoxide and H_2O_2 generation ($P<0.005$) with Ang II in RAAs and enhanced Ang II maximal contractions (-72 ± 2 vs -45 ± 2%; $P<0.005$) that were dependent on superoxide from NOX2 since they were prevented in $p47^{phox}$ -/- mice and on H_2O_2 from NOX4 since they were prevented in mice with transgenic smooth muscle cell expression of catalase ($tg^{CAT\text{-}SMC}$), and in POLDIP2 +/- mice. However, RAA contractions to lower concentrations of Ang II (10^{-8} to 10^{-11} M) were paradoxically enhanced in $tg^{CAT\text{-}SMC}$ vs Wt mice (-17 ± 2 vs -1 ± 1%; $P<0.01$) and in POLDIP2 +/- vs +/+ mice (-22 ± 3 vs -5 ± 3; $P<0.01$). Tempol normalized the ROS and Ang II contractions in RAAs from mice with RRM.

Conclusions: Both superoxide from $p47^{phox}$/NOX2 and H_2O_2 from NOX4/POLDIP2 enhance maximal Ang II contractions of RAAs from mice with RRM fed a high salt diet but H_2O_2 from NOX4/POLDIP2 reduces the sensitivity to lower concentrations of Ang II by >100-fold and tempol prevents all of these changes Thus, although a high salt intake reduces circulating Ang II, blockade of angiotensin receptors or ROS may prove beneficial for patients with CKD unable to restrict salt.

SA-PO829

Targeting Pathologic Gβγ-GRK2 Signaling in CKD

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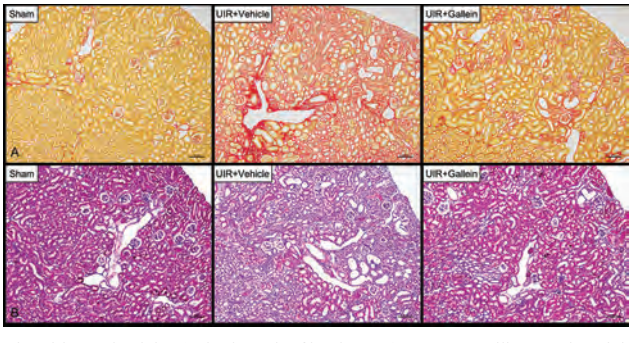
Background: Chronic kidney disease (CKD) is a progressive deterioration of renal function characterized by replacement of functional renal parenchyma with fibrotic tissue. Our group recently reported the beneficial effects of attenuating Gβγ-G-protein coupled receptor kinase 2 (GRK2) signaling in the ischemia/reperfusion murine model of acute kidney injury (AKI). In this study, we tested the hypothesis that inhibiting Gβγ-GRK2 signaling might bestow a renoprotective effect in animal models of chronic kidney injury.

Methods: Research animals (C57Bl/6 10 week old male mice) were subjected to unilateral ischemia-reperfusion (UIR, 30min) or sham surgery followed by 14 days of reperfusion. The Gβγ-GRK2 small molecule inhibitor, Gallein, or Vehicle (PBS) were given once daily i.p. beginning 7 days after the injury and continued until sacrifice. GRK2 expression was also evaluated in human kidney biopsies and whole murine kidney lysates by RT-qPCR and Western blot.

Results: We first identified a significant elevation of GRK2 mRNA (8 normal vs 10 dialysis, 1.9 fold increase, P=0.01) and protein (9 normal vs 10 dialysis, 20.6 fold increase, P=0.02) expression in biopsies obtained from dialysis patients vs normal human kidney biopsies. In the UIR model of CKD, GRK2 transcript expression positively correlated with Lipocalin 2 (NGAL) transcript, a clinically used renal injury marker (R squared=0.7488, P<0.0001). Small molecule inhibition of Gβγ-GRK2 significantly alleviated renal fibrosis as assessed by Picrosirius red staining (Sham, UIR+Vehicle, UIR+Gallein, n=8 per group, % fibrosis mean 1.422, 10.08, 4.665, respectively, P<0.0001), accompanied by a decline in NGAL gene expression.

Conclusions: Our results identify Gβγ-GRK2 signaling as a potential mediator of renal tubular injury and fibrosis and a promising target in CKD.

Funding: Other NIH Support - NIH 1R01HL133695-01 (BCB)



A: Pisrosirius Red staining (red color stains fibrotic areas); B: Hematoxilin & Eosin staining.

SA-PO830

WNK1 Regulates Skeletal Muscle Hypertrophy by Modulating Phosphorylation, Nuclear Localization, and Transcriptional Activity of FoxO4

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Background: With-no-lysine (K) (WNK) kinases, mutated in the inherited form of hypertension pseudohypoaldosteronism type II, are essential regulators of ion transporters. WNK kinases phosphorylate and activate SLC12A cation-chloride cotransporters via the intermediate kinases SPAK/OSR1. We previously showed that Na^+-K^+-$2Cl^-$ cotransporter 1, a member of SLC12A family, promotes mouse skeletal myogenesis and its inhibitor loop diuretics are associated with risk for sarcopenia in patients with chronic kidney disease (CKD). We further aimed to investigate the physiological role of WNK1 that is the major WNK isoform in mammalian skeletal muscle.

Methods: In C2C12 mouse skeletal muscle cells, differentiation was induced after transfection of *Wnk1*-targeted siRNA, and the diameter of differentiated myotubes was evaluated. In C57BL/6J mice, WNK1 protein abundance was evaluated after six weeks of voluntary wheel running or four weeks of 0.25% adenine-containing diet feeding (CKD model).

Results: In C2C12 cells, silencing of WNK1, but unexpectedly not SPAK/OSR1, induced myotube atrophy and remarkable increases in the mRNA expression of the muscle atrophy ubiquitin ligases MAFbx and MuRF1 called 'atrogenes'. These atrogenes are predominantly upregulated by transcription factors forkhead box protein O (FoxO)1/3/4 in CKD or other diseases causing sarcopenia. WNK1 silencing selectively increased FoxO4 nuclear localization, and co-transfection of *FoxO4*-targeted siRNA completely reversed the myotube atrophy and upregulation of atrogene transcription. Phos-tag SDS-PAGE revealed that WNK1 silencing decreased FoxO4 phosphorylation, which might be associated with nuclear localization and transcriptional activity of this protein. We further showed that WNK1 abundance in mouse skeletal muscle was increased by chronic exercise and decreased in adenine-induced CKD and sarcopenia. Moreover, to validate the role of WNK1 in muscle hypertrophy *in vivo*, a WNK kinase inhibitor WNK463 was administered by oral gavage (10 mg/kg), resulting in marked increase of atrogene expression in mouse skeletal muscle.

Conclusions: WNK1 physiologically regulates mammalian skeletal muscle hypertrophy via interactions with FoxO4. The WNK1-FoxO4 axis may be a novel therapeutic target in sarcopenia.

SA-PO831

Taurine Protects Against Urea-Induced Protein Carbamylation and Renal Fibrosis in an Oxalate Model of Kidney Injury

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Background: It has been long argued that the increased levels of urea in patients with chronic kidney disease (CKD) have negligible toxicity; However, there is growing evidence for the hypothesis that protein carbamylation modifications caused by high urea contributes to disease pathogenesis, vascular complications, uremic cardiomyopathy and mortality. Furthermore, it appears that amino acids can compete with proteins for carbamylation and effectively protect proteins from harmful carbamylation. Here we tested the hypothesis that concentrations of urea associated with chronic renal failure, exacerbate pre-existing renal disease and cardiomyopathy and that dietary taurine supplementation protects against this.

Methods: Mice were fed diets supplemented with sodium oxalate for 3 weeks to induce crystal nephropathy. Mice with mild/moderate oxalate crystal-induced nephropathy were then maintained on western-type diet and 50g/L urea with or without taurine 10g/L (as carbamylation scavenger) in their drinking water for 8 weeks. Control animals were similarly treated with oxalate but only fed western-type diet.

Results: Dietary urea induced hypercarbamylation of proteins in plasma, heart and kidneys in the CKD mice compared to the CKD control animals. Dietary urea exacerbated renal fibrosis and increased ROS levels in renal vessels as well as ANP expression in heart. The carbamylated albumin (C-Alb) and kidney homocitrulline/lysine were strongly correlated with the extent of interstitial fibrosis with a correlation coefficient of 0.84 and 0.86 respectively; (n=12, *P<0.001). Protein carbamylation and its associated pathologies were rescued with taurine supplements (Table below).

Conclusions: Urea-induced protein carbamylation contributes to renal fibrosis in the oxalate model of kidney injury and taurine may mitigate oxalate-induced renal injury, at least in part, by preventing excessive protein carbamylation.

Funding: Other NIH Support - NIH/NHLBI

Treatment Group	C-Alb (mmol/mol)	Heart homocitrulline/lysine (umol/mol)	Kidney homocitrulline/lysine (umol/mol)	Fibrosis Area (%)
Control	1.2±0.06	48.6±9.9	21.8±3.8	0.7±0.1
Oxalate diet followed by Western-type diet	0.9±0.06	35.3±1.3	22.5±4.0	2.3±0.6
Oxalate diet followed by Western-type diet + Urea	10.5±4.78*	406.8±190.4*	167.2±90.9*	10.0±1.6*
Oxalate diet followed by Western-type diet + Urea + Taurine	1.2±0.07	49.8±7.4	14.2±4.1	1.7±0.3

Mean±SEM, n=4/group, *P<0.01 versus all the other treatment groups; One-way ANOVA followed by Tukey's post hoc test.

SA-PO832

The Long Noncoding RNA Meg3 Mediates TLR4–Induced Renal Inflammation in Experimental Obstructive Nephropathy

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Background: Renal inflammation has been implicated in many types of kidney injury and is a potential therapeutic target for most chronic kidney diseases. Accumulating evidence shows that long noncoding RNAs function as critical regulators of inflammatory responses. This study aims at investigating the role of Toll-like receptor 4 (TLR4)-driven lncRNAs in regulating renal inflammation.

Methods: Tubule-specific TLR4 knockout mice were generated by crossing *TLR4* $^{flox/flox}$ and *Ksp-Cre* mice. Both *Ksp-Cre.TLR4* $^{flox/flox}$ (KO) and *TLR4* $^{flox/flox}$ (WT) mice were subjected to unilateral ureteral obstruction (UUO). Deep RNA sequencing was performed to identify dysregulated lncRNAs that are associated with tubular TLR4 expression. Candidate lncRNA was verified and its functional role in renal inflammation was investigated using cultured murine tubular epithelial cells.

Results: Loss of TLR4 in tubular cells resulted in less renal inflammation as compared to WT mice after 7 days of UUO. Expression of pro-inflammatory cytokines including CCL-2, CXCL-2 and TNF-α was reduced in the obstructed KO kidneys and accompanied by decreased NFκB signaling. Data from deep RNA sequencing showed that lncRNA maternally expressed gene 3 (Meg3) was upregulated in WT mice upon UUO, but its expression was down-regulated in KO mice. *In vitro*, LPS induced Meg3 expression in tubular epithelial cells. Knock down of Meg3 in tubular epithelial cells diminished inflammatory responses, as evidenced by reduced LPS-induced CCL-2 and CXCL-2 expression.

Conclusions: Our findings suggest that tubular TLR4 is important for mediating inflammatory responses in UUO model and lncRNA Meg3 may be a novel regulator in TLR4-driven renal inflammation. **Funding:** Research Grants Council of Hong Kong (Collaborative Research Fund, grant number C7018-16G).

SA-PO833

TSC1 Mediated Metabolic Switch to Glycolysis in Tubular Epithelial Cell Accelerates Renal Interstitial Fibrosis

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Background: Renal interstitial fibrosis is a key factor in the progression of chronic kidney disease (CKD). Energy reprogram to glycolysis is closely related to the development of CKD. As an important negative regulatory factor of mTORC1 signal,tuberous sclerosis complex 1 (Tsc1) is also the key regulatory point of glycolysis. In this study, we investigated whether Tsc1 could mediate the progress of renal interstitial fibrosis by regulating glycolysis in proximal tubular epithelial cells.

Methods: In vitro and in vivo models of renal interstitial fibrosis were established. The changes of Tsc1 in the progress of renal interstitial fibrosis and the relationship of glycolysis and Tsc1 were analyzed. The glycolysis level and degree of fibrosis in kidneys between proximal tubular epithelial cells-Tsc1 specific knockout mice($Tsc1^{ptKO}$ mice) and control mice were compared to explore the role Tsc1 in renal interstitial fibrosis.

Results: In TGF-β1 induced tubular epithelial cell phenotype transformation and UUO models, Tsc1 in tubular epithelial cells was reduced markedly. In $Tsc1^{ptKO}$ mice, mTORC1 signal was activated and showed the significant feature of renal interstitial fibrosis. Mitochondrial damage and enhanced glycolysis were observed in tubular epithelial cell phenotype transformation, UUO mice and $Tsc1^{ptKO}$ mice. Inhibiting glycolysis of proximal tubular cells induced by Tsc1 downregulation with 2-DG, the fibrotic phenotypic changes induced by Tsc1 decline were improved. The renal fibrotic degree was also alleviated by inhibiting the glycolysis of $Tsc1^{ptKO}$ mice with 2-DG.

Conclusions: Tsc1 could mediate the progress of renal interstitial fibrosis by regulating glycolysis in proximal tubular epithelial cells. It might be helpful to provide theoretical basis for design of new therapeutic strategies of CKD.

Funding: Government Support - Non-U.S.

SA-PO834

Knockdown of Cxcl10 Alleviates Renal Fibrosis in UUO Mice

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Background: Renal fibrosis is a common pathological manifestation of almost all renal diseases, including chronic kidney disease (CKD) and acute kidney injury (AKI), which can eventually lead to end-stage renal disease (ESRD). IFN-γ-inducible protein 10 (IP-10, CXCL10) has been widely demonstrated to be involved in chemotaxis, regulation of cell growth and angiogenesis inhibition. It has been reported that CXCL10 is involved in the pathogenesis of fibrosis in a variety of human tissues. However, the underlying mechanism of CXCL10 in renal fibrosis reminds unclear.

Methods: Wildtype ($CXCL10^{+/+}$) mice and CXCL10-deficient ($CXCL10^{-/-}$) mice were used to generate the unilateral ureteral obstruction (UUO) model and sacrificed at 3, 5, 7 and 14 days after surgery. The histological changes and collagen deposition levels in kidney tissue was examined by PAS, Masson and Sirius red staining. The expression of fibrosis related proteins were examined by Western blot. The macrophage infiltration was examined by immunofluorescence of F4/80. Furthermore, the effects of CXCL10 on transforming growth factor β1 (TGF-β1)-stimulated rat renal fibroblasts was investigated in vitro.

Results: A marked increase expression of Cxcl10 mRNA and protein were observed in whole kidney tissue in UUO model. The levels of serum creatinine and urea nitrogen were significantly lower in $Cxcl10^{-/-}$ mice than in $Cxcl10^{+/+}$ mice. Pathological staining results showed that the injury degree of renal tissue and the collagen deposition levels were lighter in $Cxcl10^{-/-}$ mice. Western blot results showed that the expression of α-SMA, FN and Col1 in $Cxcl10^{-/-}$ mice was significantly reduced compared with $Cxcl10^{+/+}$ mice. However, Interstitial F4/80-positive macrophages were unaffected by knockdown of Cxcl10. Furthermore, recombinant CXCL10 protein stimulation could obviously promote the expression of α-SMA, FN and collagen I in TGF-β1-treated NRK-49F cells.

Conclusions: Cxcl10 knockout could reduce renal injury, mitigate the deposition of collagen and inhibit renal fibrosis through promoting renal fibroblast activation in murine UUO model. These results may provide a novel insight into the mechanism and a potential therapy target of renal fibrosis.

SA-PO835

NF-κB Inhibition During Short-Term LNAME and Salt Overload Strongly Attenuates the Late Development of CKD

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Background: Brief NO inhibition by LNAME + high-salt diet (HS) results in marked hypertension (HT) and renal injury that abate upon treatment interruption but evolve to CKD along ensuing months. Activation of the NLRP3 and NF-κB pathways may participate in this process. Here we investigated whether NF-κB inhibition during LNAME+HS would prevent the acute and/or chronic effects of this treatment.

Methods: Male Munich-Wistar rats (N=11) received oral LNAME+HS. A second group (N=12) received in addition the NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC), 60 mg/kg/day vo. Control rats (C) received HS only (N=10). All treatments were ceased at 4 wks. Assessed at 4, 8 and 24 wks were: tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d), glomerulosclerosis (GS, %), interstitial collagen-1 (COLL, %), infiltration (cells/mm²) by macrophages (MΦ), lymphocytes (Ly), angiotensin 2+ (Ang2+) and NLRP3+ cells, and the renal abundance (x HS) of IL1β (pg/mg), nuclear p65 (NFκB), Casp1, TLR4, and IL-6.

Results: At 4 wks, HS+LNAME caused severe hypertension, ALB, GS, COLL, MΦ/Ly/Ang2+-cell infiltration and activation of the TLR4/NFκB/IL6 and NLRP3/Casp1/IL1β pathways, all of which were prevented or strongly attenuated by PDTC. Partial regression at 8wks was followed by progression to CKD at 28 wks, also largely prevented by early PDTC.

Conclusions: Early NF-κB activation is essential for subsequent autonomous activation of innate immunity and progression to CKD in this model, and may be the basis for future therapeutic strategies. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	4wks			8wks			28wks		
	C	HS+LNAME	HS+LNAME+PDTC	C	HS+LNAME	HS+LNAME+PDTC	C	HS+LNAME	HS+LNAME+PDTC
TCP	146±3	213±4*	192±5*#	146±3	164±4*	157±3	131±2	166±7*	158±4
ALB	8±2	151±24*	51±17*#	5±1	25±6*	7±2#	16±3	74±13*	42±12#
GS%	0.1±0.1	3±1*	2±1*	0.1±0.1	1±1*	1±1#	1±1	8±2*	3±1#
COLL	1±1	4±1*	1±1#	2±1	4±1*	2±1#	1±1	4±1*	1±1#
MΦ	29±4	255±27*	81±13*#	33±5	82±12*	80±10*	35±4	98±14*	49±6#
Ly	43±8	231±21*	34±7#	52±6	116±13*	29±6*#	39±6	138±13*	26±5#
Ang2	2±1	10±1*	4±1#	5±1	14±2*	5±1#	3±1	12±2*	3±1#
TLR4	1.0±0.1	3.1±0.5*	1.8±0.6#	1.0±0.1	3.2±0.5*	1.3±0.4#	1.0±0.1	2.0±0.4*	1.4±0.4#
NF-kB	1.0±0.2	4.4±0.7*	1.6±0.2#	1.0±0.1	2.6±0.4*	1.5±0.1*#	1.0±0.1	2.7±0.4*	0.4±0.1*#
IL-6	1.0±0.1	3.2±0.6*	2.1±0.2*	1.0±0.1	4.7±0.5*	1.9±0.3#	1.0±0.1	3.3±1.0*	1.1±0.3#
NLRP3	1.0±0.1	4.5±0.5*	0.6±0.2#	1.0±0.1	3.7±0.7*	1.1±0.4#	1.1±0.2	4.5±0.0*	0.8±0.2#
Casp1	1.0±0.2	4.1±0.7*	2.1±0.6#	1.0±0.1	2.4±0.5*	1.0±0.2#	1.0±0.1	2.5±0.8	1.4±0.5
IL-1β	2.2±0.3	4.1±0.6*	2.6±0.4	1.8±0.2	3.2±0.5*	2.6±0.4*	1.0±0.2	4.7±0.4*	2.6±0.8

Mean±SE; *p<0.05 vs HS; #p<0.05 vs HS+LNAME

SA-PO836

UCP2-Regulated HIF-1α Stabilization Promotes Reprogramming of Mitochondrial Metabolism and Induces Tubulointerstitial Fibrosis After Ischemic AKI

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Background: Acute kidney injury (AKI) is a global public health concern associated with hospitalizations and is especially common in critically ill patients. The transition of AKI to consequence chronic kidney disease (CKD) has major clinical significance. Tubular reabsorption is an energy consumption process relies mainly on mitochondrial metabolism, which is regulated by uncoupling protein 2 (UCP2). Whether UCP2 contributes to the progression of AKI-to-CKD is unknown.

Methods: We generated proximal tubular cells specific UCP2 knockout mice. AKI-to-CKD model was induced using ischemia-reperfusion injury (I/R). Mice kidney tissues were harvested six weeks after I/R. Alternations of mitochondrial morphology, metabolic products and critical enzymes that govern fatty acid oxidation and glycolysis were examined. Pimonidazole was used to evaluate hypoxia in kidney tissue.

Results: In I/R-induced AKI-to-CKD model, expression of UCP2 was markedly increased in fibrosis kidneys. Impairment of renal function and remarkable accumulation of extracellular matrix in the tubulointerstitial spaces were quite evident six weeks after I/R injury. Mitochondria reduction and swellings, as well as lipid droplets deposition suggested metabolic abnormalities of fatty acid. However, increased glycolytic enzyme expression and inhibitory phosphorylation of pyruvate dehydrogenase were exhibited indicating a switch to glycolysis. *Ucp2*-deficient mice suffered I/R injury experienced less tubulointerstitial fibrosis and metabolic disorders. Furthermore, tissue hypoxia was observed in I/R-induced fibrotic kidney and renal expression of hypoxia-inducible factor 1α (HIF-1α) was increased suggested hypoxia-induced stabilization of HIF-1α in fibrosis kidney. Nevertheless, knockout of UCP2 relieves the tissue hypoxia and reduces the stabilization of HIF-1α in the kidney.

Conclusions: UCP2 regulates tissue hypoxia-induced stabilization of HIF-1a, which promotes the reprogramming of mitochondrial metabolism from fatty acid oxidation to glycolysis and contribute to pathogenesis of AKI-to-CKD. UCP2 may provide a novel therapeutic target for prevention of chronic fibrosis caused by AKI.

Funding: Government Support - Non-U.S.

SA-PO837

Mitochondrial Dysfunction in FOXD1 Lineage Cells Is Associated with Renal Fibrogenesis and Anemia

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Background: Mitochondria play an important role in the pathophysiology of chronic kidney diseases (CKD), as mitochondrial uncoupling and dysfunction changes cellular metabolism impacting CKD pathogenesis and its progression. It is well established that renal function impairment correlates with the degree of tubulointerstitial fibrosis. Furthermore, fate-mapping studies have previously shown that the majority of collagen-producing renal myofibroblasts are derived from perivascular interstitial cells and pericytes. Despite the importance of these findings for renal fibrogenesis, the role of mitochondria and oxidative phosphorylation in renal interstitial cell function and myofibroblast transdifferentiation is only poorly understood.

Methods: To investigate mitochondrial function and the role of oxidative phosphorylation in renal interstitial cells, we have generated and analyzed mice with interstitial cell-specific inactivation of mitochondrial transcription factor A (TFAM) using *FoxD1-cre* transgenics. TFAM is required for mitochondrial gene transcription and DNA replication and thus essential for the maintenance of mitochondrial function and mass.

Results: We demonstrate that suppression of mitochondrial function in interstitial cells has a pivotal role in the pathogenesis of CKD, as inactivation of stromal TFAM resulted in progressive renal failure (BUN at 6-weeks of age: 76.0 ± 1.5 mg/dl vs. 27.8 ± 0.9 mg/dl in control; p<0.0001, n=4 each), which was associated with an increased number of α-SMA-expressing cells, the development of tubulointerstitial fibrosis and proteinuria at older age. Furthermore, interstitial cell-specific TFAM knockout mice developed anemia (Hct: 42.8 ± 1.5 % in control vs. 36.2 ± 1.0 % in mutants; p= 0.006, n=5 each) and were characterized by a reduction in their capacity to produce erythropoietin in response to hypoxic stimuli, a major pathologic feature of CKD.

Conclusions: Our data demonstrate that mitochondria play an important role in the maintenance of normal renal interstitial cell homeostasis and hypoxia responses. A detailed metabolic characterization of interstitial cell-specific TFAM knockout mice will be presented at the meeting.

Funding: NIDDK Support

SA-PO838

Dyslipidemia in Nephrotic Rats Associates with Increased Hepatic PCSK9 – Heparan Sulfate Interaction

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Background: Dyslipidemia characterized by higher levels of plasma lipids (triglyceride and cholesterol) increases the risk for cardiovascular disease in patients with Chronic Kidney Diseases (CKD). Here, our aim is to investigate the role of the LDL receptor (LDLR), heparan sulfate (HS) side chains of syndecan-1 and Proprotein convertase subtilisin/kexin type 9 (PCSK9) in CKD-related dyslipidemia using a dyslipidemic proteinuric rat model.

Methods: Eight male Wistar rats received 1.8 mg adriamycin/kg BW i.v. to induce proteinuria (ADR). Six control rats were injected with saline. Kidney function, proteinuria, and serum lipids were monitored weekly. Animals were sacrificed after 12 weeks. Tissues and plasma were collected. Expression of LDLR, syndecan-1, HS and PCSK9 were evaluated in the liver by immunofluorescence staining (IF), western blotting (WB) and qRT-PCR. Plasma PCSK9 was measured by ELISA. Mann Whitney test and Spearman Rank correlation were used for statistics.

Results: ADR showed increased proteinuria and serum lipids (all $p<0.001$) compared to controls without differences in protein and mRNA expression of LDLR. Interestingly, the localization of PCSK9 to the liver sinusoids was however significantly increased in ADR compared to controls ($p<0.001$, IF), without changes in gene expression. Serum triglyceride and cholesterol correlated with serum PCSK9 ($r=0.59$, $p=0.0035$; $r=0.71$, $p=0.006$) and with liver PCSK9 ($r=0.83$, $p=0.0004$; $r=0.80$, $p=0.001$ respectively). Moreover, PCSK9 protein was found to interact strongly with HS, and interaction was highly dependent on HS sulfation and chain length. Disaccharide profiling of HS revealed a remarkable increase in 6-O-sulfation of liver HS, which could be due to lower hepatic Sulf2 mRNA expression ($p=0.06$). Inverse association was found between serum triglyceride and cholesterol with Sulf2 mRNA levels ($r=-0.67$, $p=0.01$; $r=-0.64$, $p=0.02$).

Conclusions: Dyslipidemia in nephrotic rats is related to increased interaction of PCSK9 with hepatic syndecan-1/HS, which might hamper TRL clearance capacity.

Funding: Government Support - Non-U.S.

SA-PO839

The Role of CPT1α on Fatty Acid Metabolism and Development of Renal Fibrosis

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Background: Renal fibrosis is the common pathologic feature of chronic kidney disease (CKD). Proximal tubular epithelial cells (PTCs) prefer fatty acid as their energy source. Defective fatty acid oxidation plays a key role in kidney fibrosis development. CPT1α is the rate limiting enzyme that transport fatty acid into mitochondria. Moreover, CPT1α has a lysine succinyltransferase activity. In this study, we investigated the role of CPT1α in modulation of cellular fatty acid homeostasis in tubular epithelial cells during renal fibrosis.

Methods: Renal fibrosis was induced by folic acid (FA) injection. Relationship between renal fibrosis and expression of CPT1α was examined using renal biopsy samples from 30 patients and kidneys from FA mice. Mice with PTCs' specific ablation of CPT1α (KO) were generated and pharmacologic and genetic upregulation of CPT1α were used to investigate the role of CPT1α on renal fibrosis.

Results: Expression of CPT1α in proximal tubular epithelial cells was negatively correlated with the area of renal fibrosis in both human samples and FA model. Tubular $CPT1\alpha^{KO}$ mice experienced severe renal fibrosis and increased expressions of fibrotic markers, such as collagen I, fibronectin and vimentin than wild-type mice. While upregulation of CPT1α by administration of fenofibrate or transfection of CPT1α plasmid attenuated the accumulation of extracellular matrix and renal fibrosis in mice kidney. Moreover, upregulation of CPT1α increased the key enzymes of fatty acid metabolism, including ACAD, FASN, GPAT and GPD1. The decreased succinylation of the enzymes and regulators of fatty acid metabolism in fibrosis kidney were relieved by fenofibrate treatment.

Conclusions: These results demonstrate that CPT1α plays a major role in fatty acid metabolism disturbance in the tubular epithelial cells and contributes to renal fibrosis. Restoring the lysine succinyltransferase activity of CPT1α may provide novel therapeutic approach for kidney fibrosis.

Funding: Government Support - Non-U.S.

SA-PO840

Sodium Butyrate Alleviates Renal Failure (RF) in Animals by Mitigating Inflammation and Fibrosis

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Background: Renal failure (RF) is largely associated with inflammation and damage of kidney tissue. NFkB is a well-known marker for inflammation and for the regulation of fibrosis. Phosphorylated NFkB (pNFkB) is translocated into the nucleus and promotes transcription of various genes which play a role in inflammation and fibrosis. Treatment with sodium butyrate, a short-chain fatty acid (SCFA) and histone deacetylase (HDAC) inhibitor, has been shown to have anti-inflammatory effects in RF. We demonstrate that sodium-butyrate treatment can ameliorate RF at both the biochemical and histopathological level.

Methods: Five-sixth nephrectomized Sprague-Dawley rats were used as a model for RF. Animals were divided into three groups: Sham-operated control (SH), untreated nephrectomy (Nx), and nephrectomy with butyrate treatment (Nx+BU) 100 mg/kg/day sodium butyrate in drinking water. Kidney tissue cytosolic NFkB and nuclear pNFkB were measured by Western Blot analysis. Histological analysis was performed on the kidney tissues with both Periodic Acid-Schiff stain and Picro-Sirius Red stain to measure the extent of collagen networks in fibrosis. Renal biomarkers were measured by chemical assay.

Results: There was 3.5 fold increased translocation of pNFkB in the nucleus of Nx rats, which was significantly lowered in the Nx+BU group. There was no difference in cytosolic NFkB. Kidney tissue of the Nx animals had 35±4.4% segmental sclerosis, whereas Nx+BU animals had reduced to 24±5.6% ($p=0.003$). In Nx, 26% of the area was positively stained with sirius red compared to 1.7% in SH ($p<0.0001$), but was reduced by 50% in Nx+BU ($p<0.01$). The serum urea, urinary protein/creatinine ratio, and serum creatinine of Nx rats were significantly higher (3.6, 3, and 3.2-fold respectively) than SH. Nx+BU had significantly improved proteinuria and serum urea levels. Serum creatinine levels were reduced by 22% in Nx+BU ($p=0.05$).

Conclusions: Treatment with sodium butyrate has been shown to have beneficial effects on the translocation of NFkB, subsequent histological data on kidney fibrosis, and renal function in RF. Sodium butyrate, among other systemic and gut-related benefits, acts as an HDAC inhibitor and provides a possible mechanism for anti-inflammatory action in RF.

SA-PO841

Self-Assembled Polypeptide Gold Nanoparticles Selectively Target the Kidney for High-Efficiency Anti-Fibrosis Treatment

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Background: Many preclinical agents (e.g., cobalt chloride) have attracted great attentions because they can ameliorate chronic kidney fibrosis. However, many of these drugs are lack of kidney targeting ability or/and exhibit biological toxicity, which limits their clinical applications. Here we produced glutathione- and lipoic acid-modified Au nanoassemblies (GLAuNPs-Co) with good biocompatibility, high renal targeting capability and excellent anti-fibrosis efficacy through a Co^{2+}-induced coordination self-assembled strategy.

Methods: The LAuNPs and GLAuNPs were investigated using transmission electron microscopy (TEM), dynamic light scattering (DLS), fourier transform infrared (FTIR) spectra and thermogravimetric analysis (TGA). In vitro, Cell Counting Kit-8 (CCK-8) and Elisa Kits were used to evaluate the biocompatibility of GLAuNPs. Celluar uptake mechanism was explored by fluorescence microscopy and inductively coupled plasma-mass spectrometry (ICP-MS). Organs' distribution was examined using in- and ex-vivo fluorescence imaging software. The loading and release efficiency was evaluated by ICP-MS. The anti-fibrosis efficacy and mechanism were tested by pathological staining, western blot and real-time PCR in vivo using unilateral ureteral obstruction (UUO) mice.

Results: In aqueous solution, GLAuNPs-Co could self-assemble at neutral pH, and disassemble and release Co^{2+} when pH stwich to acid. Cytotoxicity and immunotoxicity assays and in vivo fluorescence imaging revealed that GLAuNPs had excellent biocompatibility, non-immunotoxicity and kidney-targeting ability. Pathological staining, western blot and real-time PCR analyses showed that GLAuNPs-Co had more excellent anti-fibrosis, anti-inflammatory, anti-oxidative stress, and anti-apoptosis efficacy than that of free $CoCl_2$ in UUO nephropathy mice.

Conclusions: With attractive characteristics of specific renal-targeting, controllable drug-release, non-toxicity and outstanding fibrosis therapeutic efficacy, the GLAuNPs-Co is hopeful to become a promising drug against renal fibrosis in clinic in the near future, which represents an innovative avenue of designing and developing therapy system for kidney diseases.

SA-PO842

Association Between Urine Output, Furosemide Stress Test, and Fibrosis in Kidney Biopsies

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Background: Interstitial fibrosis (IF) is one of the most potent risk factors for kidney disease progression. The Furosemide Stress Test (FST) is a validated tool that predicts the severity of acute kidney injury in critically ill patients. To our knowledge there is no data on the association between the functional tubular capacity by urine output (UO) and FST with IF on kidney biopsies. The aim of this study was to determine the correlation between UO, FST and the severity of IF in kidney biopsies

Methods: 84 patients that underwent kidney biopsy were included. Furosemde was administred at 1 mg/kg and UO was measured every h for 6 after confirmation of empty

bladder by US. Serum biochemical markers were measured and urine concentrations of furosemide at different times (2, 4 and 6 hours). IF was evaluated by subjective visualization by an experienced nephropathologist in addition to morphometry. We used the FEM equation to determine the Mass of Excretion of Furosemide (FEM: Furosemide Urine x Volume urinary)/furosemide administered dose). Values were expressed as mean, SD or % and Pearson Correlation

Results: Nephrotic syndrome and acute kidney graft dysfunction were the most frequent indications for biopsy. eGFR was inversely proportional to the degree of fibrosis. Subjects with grade 3 IF showed a significant decrease in urine volume at hour 1 when compared with grades I and II (155 mL ± 181 vs 316 mL ± 261 vs 328 mL ± 352 p=0.015 respectively). Likewise, the total urine volume and the excreted mass of Furosemide was progressively lower with higher degrees of IF, at 2 and 4 hours. An inversely proportional linear correlation between uresis and the degree of IF ($R^2$0.072) was observed

Conclusions: Our findings support that IF correlates with total UO and FEM. Both urine output and FST acould be a non invasive tool to predict IF.

Funding: Veterans Affairs Support

Table 1. Baseline Characteristics and Outcomes

Variable	Combined n= 84	IF Grade I n=45	IF Grade II n=27	IF Grade III n=12	p
Age, (years)	38.6 ± 15.1	39 ± 15.1	33.6 ± 11	48.7 ± 18.7	0.014
Gender, % male	37 (44)	20 (44.4)	11 (40.7)	6 (50)	0.883
Comorbidities					
Diabetes Mellitus	13 (15.5)	5 (11.1)	2 (7.4)	6 (50)	0.002
Hypertension	37 (44)	15 (33.3)	12 (44.4)	10 (83.3)	0.008
Baseline eGFR, mL/minute/1.73m^2	63.9 ± 41.6	82.2 ± 40.3	46.3 ± 34.2	35.1 ± 27.8	0.000
Uresis 2-hour (mL)	348 ± 255	362.1 ± 283.3	373.7 ± 233	240 ± 160	0.281
Uresis 4-hour (mL)	250 ± 212	291 ± 202	241 ± 243	125 ± 106	0.054
Uresis 6-hour (mL)	200 ± 179	195 ± 179	228 ± 182	155 ± 180	0.492
Total Uresis (mL)	1509 ± 779	1599 ± 790	1591 ± 816	995 ± 415	0.043
Albumin, g/dL	3.2 ± 0.90	3.0 ± 0.95	3.5 ± 0.84	3.2 ± 0.68	0.077
FEM-2 hour (%)	5.5 ± 6.5	6.8 ± 7.4	5.1 ± 5.7	1.6 ± 1.7	0.049
FEM-4 hour (%)	2.9 ± 4.0	4.0 ± 4.6	1.9 ± 2.9	0.8 ± 1.3	0.012

NSAIDS: Nonsteroidal anti-inflamatory drug, ARB-2: Angiotensin II receptor blocker, ACEI: Angiotensin –converting enzime inhibitors, eGFR: Estimated Glomerular Filtration Rate, AKI: Acute Kidney Injury, FEM: Furosemide Excreted Mass, IFI: Interstitial Fibrosis < 25%, IFII: Interstitial Fibrosis 26-50%, IFIII: Interstitial Fibrosis > 50%. *Data are presented as mean ± standard error unless otherwise indicated.

SA-PO843

Long-Noncoding RNA Atrolnc-1 Promotes Muscle Wasting in Mice with CKD

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Background: Chronic kidney disease (CKD) is commonly associated with cachexia, a condition that causes skeletal muscle wasting and an unfavorable prognosis. Although mechanisms leading to cachexia have been intensively studied, the advance of biological knowledges and technologies encourages us to make progress in understanding the pathogenesis of this disorder. Long non-coding RNAs (lncRNAs) are defined as >200 nucleotides RNAs but lack the protein-coding potential. LncRNAs are involved in the pathogenesis of many diseases, but whether they functionally involve in muscle protein loss has not been investigated.

Methods: We performed lncRNA array and identified an lncRNA, which we named Atrolnc-1, remarkably elevated in atrophying muscles from mice with cachexia. We examined how overexpression or knockdown of Atrolnc-1 could influence muscle protein synthesis and degradation. We also examined whether inhibition of Atrolnc-1 ameliorates muscle wasting in mice with CKD.

Results: We documented that Atrolnc-1 expression is continuously increased in muscles of mice with fasting, cancer or CKD. We found that depressed insulin signaling stimulates the transcription factor, C/EBP-α binding to the promoter of Atrolnc-1 and promotes the expression of Atrolnc-1. In cultured C2C12 myotubes, overexpression of Atrolnc-1 increases protein degradation; Atrolnc-1 knockdown significantly reduces the rate of protein degradation stimulated by serum depletion. Using mass spectrometry and a lncRNA pull-down assay, we identified that Atrolnc-1 interacts with A20 binding inhibitor of NF-κB-1(ABIN-1). The interaction impairs function, resulting in enhanced NF-κB activity plus MuRF-1 transcription. This response is counteracted by CRISPR/dCas9 mediated overexpression. In muscles from normal mice, overexpression of Atrolnc-1 stimulates MuRF-1 expression leading to myofibers atrophy. In contrast, Atrolnc-1 knockdown attenuates muscle wasting in mice with CKD via suppression of NF-κB activity and MuRF-1 expression.

Conclusions: Our findings provide evidence that lncRNAs initiates the pathophysiological process of muscle wasting. The interaction between Atrolnc-1 and NF-κB signaling modulates muscle mass and proteolysis in CKD and perhaps other catabolic conditions.

SA-PO844

Omega-3 Fatty Acid Modulates Molecules Associated with Sarcopenia in Muscle of 5/6 Nephrectomy Rats

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Background: Sarcopenia is common in dialysis patients and result in frail status. Myostatin, a member of TGF-β superfamily, inhibits myocyte differentiation and is increased in patients with chronic kidney disease. Myogenin is also important mediator for myogensis. Recent report showed that omega-3 fatty acid (FA) supplementation improved muscle volume in elderly. The present study aimed to investigate whether omega-3 FA effect on myostatin and myogenin related with sarcopenia in 5/6 subtotal nephrectomy (Nx) rats.

Methods: Male Sprague Dawley rats were divided into three groups and treated for 6 weeks: sham control (0.9% saline), 5/6 Nx control (0.9% saline) and 5/6 Nx treated with omega-3 FA (300 mg/kg/day by gastric gavage). The expression of muscular myostatin, myogenin, MyoD, Akt, phosphorylated(p) Akt, PI3K, p-PI3k, AMPK, p-AMPK, smad2/3/4, NF-κB, IL-6, mTOR, FoxO, MuRF1, MAFbx and USP14 were examined by western blot analysis. H & E staining of gastrocnemius muscle was performed.

Results: BUN and serum creatinine levels were significantly increased in 5/6 Nx groups compared to sham control and were not significantly different between 5/6 Nx group treated with omega-3 FA and 5/6 Nx control group. Compared with sham control, 5/6 Nx control significantly up-regulated myostatin and down-regulated myogenin and MyoD in skeletal muscle. Increased expression of myostatin and decreased expression of myogenin were significantly recovered by omega-3 FA supplementation. However, MyoD expression was not changed by omega-3 FA supplementation. The expression of p-Akt and mTOR was down-regulated in skeletal muscle of 5/6 Nx control compared to sham control and was recovered by omega-3 FA supplementation. The expression of smad2/3/4, NF-κB, IL-6, FoxO, MuRF1, MAFbx and USP14 was significantly up-regulated in skeletal muscle of 5/6 Nx control compared to sham control but were not changed by omega-3 FA supplementation. The thickness of myofiber was decreased in 5/6 Nx control compared to sham control and was recovered by omega-3 FA supplementation.

Conclusions: Omega-3 FA may prevent sarcopenia mainly by decreasing myostatin, increasing myogenin expression and partly affecting Akt-mTOR axis in skeletal muscle of 5/6 Nx rats.

SA-PO845

AMPK Deficiency Worsens Albuminuria Post Uninephrectomy (UNX)

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Background: Living donor (LD) kidney transplant offers the best prognosis for end-stage kidney disease patients. LDs have excellent outcomes, yet recent studies show that in the first year post-UNX there is an increased risk of hypertension that also drives microalbuminuria, a marker of kidney injury. Although hypertrophy contributes to a new steady-state in kidney function, it is unclear whether compensatory changes are beneficial long term for the LD. In several chronic kidney disease (CKD) models activity of the metabolic sensor AMP-activated kinase (AMPK) decreases compared to healthy kidneys. We hypothesize that low AMPK activity pre-UNX could worsen CKD post-UNX when combined with a high-Na+ diet. Our work aims to inform mechanisms that could lead to protective interventions for LDs with approved AMPK activators.

Methods: We used adult female mice with double-floxed AMPK alpha subunits (AMPKfl) and ± tamoxifen-driven(Tam) expression of CAG-Cre recombinase (Cre+ vs. Cre-AMPKfl). All mice underwent UNX 5 wks post-Tam and were placed on a high-Na+ (HNa) diet at that time (intervention). We measured GFR, urine albumin and plasma electrolytes at different time points. Explanted Kidneys (EK) were examined by immunoblot and qPCR.

Results: EK from Cre+AMPKfl have significant (>75%) AMPK knockdown (KD) compared to Cre-AMPKfl mice after Tam. No changes in kidney injury marker-1 gene expression were found in EK between the two groups. However, AMPK-KD (Cre+ mice) had a significant increase in albuminuria (overnight: 22.1±4 vs. 9.2±2 mg, Cre+ vs. Cre-, P<0.03) and anemia. UNX+HNa significantly increased albuminuria in Cre-AMPK (9.2 pre vs. 27.7 post, P<0.02), while in the AMPK-KD group this difference was more pronounced (22.1 pre vs 65.5 post, P<0.01). At two weeks after UNX+HNa there was a statistically significant increase in GFR and metabolic acidosis in both groups compared to pre-intervention. However, at that time there was no difference in GFR between Cre+ and Cre-AMPK mice.

Conclusions: Although female rodents have less severe kidney injury post-UNX than males, our studies show that AMPK KD in female mice worsens kidney injury (albuminuria) in a model of kidney donation and HNa diet. These findings implicate AMPK as an important target for potential pharmacologic interventions to prevent CKD in LDs.

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SA-PO846

Transcriptomic Profiling of Mitochondrial Dysfunction in Uremic Cardiomyopathy

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Background: Uremic cardiomyopathy is a life-limiting condition that occurs in chronic kidney disease (CKD). Emerging evidence suggests that mitochondrial dysfunction may be a cardinal event that occurs in the failing myocardium under uremic conditions. We previously reported mitochondrial structural deformity and reduction in its respiratory chain enzyme activity in septic rat hearts. These changes were mitigated by upregulation of the inducible molecular chaperone, Heat Shock Protein (HSP) 70. Whether HSP70 may induce cytoprotective effects in uremic cardiomyopathy is currently unknown. The goal of this study was to investigate mitochondrial changes and their association with the HSP70 system in uremic cardiomyopathy.

Methods: Human left ventricular tissues collected from CKD (n=23), CAD (n=11) and healthy donors (n=20) were subjected to RNA sequencing, *ex vivo*. We developed a digital cell sorting study model using deconvolution to enhance interpretation of heterogenous transcriptomic profiles inherent of mixed-cell type tissue. Primary human cardiomyocytes and cardiac-myofibroblasts were treated with calcification medium (CM) in time-course experiments (0-48 hours), *in vitro*.

Results: Cytoprotective mtHSP (HSPA9) and the HSP70 co-chaperone, Bcl2 associated Athanogene 1 (BAG1) were highly expressed in healthy control hearts compared to CKD and CAD. However, mitochondrial fusion regulation genes MFN1 and OPA1 were down-regulated in CKD hearts, together with down-regulation of downstream anti-apoptotic gene Bcl2 and up-regulation of pro-apoptotic genes cytochrome c, caspase 3, BAX and P53. The same pattern of changes were observed in cardiomyocytes and cardio-myofibroblasts treated with CM, *in vitro*. BAG1 was significantly increased at 6 hours prior to upregulation of Bcl2 at 12 hours after treatment. Furthermore, stress respondent genes, HSPA5 and DNAJB6 (HSP40) was significantly increased at 12 hours and 24 hours respectively in CM-treated primary cells.

Conclusions: The present study is the first to describe complex differential genomic changes involved in uremic cardiomyopathy. Mitochondrial dysfunction was associated with upregulation of apoptotic genes and reduced expression of cytoprotective HSP70 components. We postulate that induction of the HSP70 system may be a therapeutic target in uremic cardiomyopathy.

Funding: Private Foundation Support

SA-PO847

Tolvaptan Activates Nrf2/HO-1 Pathway Through PERK Phosphorylation

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Background: Tolvaptan slows the increase in total kidney volume (TKV) and the decline in kidney function in Autosomal Dominant Polycystic Kidney Disease (ADPKD). In addition, vasopressin type2 receptor (V2R) antagonists improve renal function in various rodent models of chronic kidney disease (CKD). However, the mechanism of tolvaptan improving renal function remains totally unclear. It has been reported that oxidative stress is associated with CKD progression, and the antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), is attracting the attention as therapeutic target. In fact, Nrf2 activator, bardoxolone methyl, improves renal function in patients with CKD. In this study, we examined the effects of tolvaptan on Nrf2.

Methods: The effect of tolvaptan was examined by mouse cortical collecting duct (mpkCCD) cells, H9C2 cells, and mice kidneys that endogenously express V2R.

Results: Tolvaptan led to Nrf2 nuclear translocation and induced mRNA and protein expression of heme oxygenase 1 (HO-1) in mpkCCD cells and H9C2 cells. Phosphorylation of unfolded protein kinase RNA-like endoplasmic reticulum(ER) kinase (PERK) by tolvaptan played an important role in activation of Nrf2/HO-1 pathway. Moreover, tolvaptan successfully activated Nrf2/HO-1 pathway in the outer medulla of mice kidneys.

Conclusions: This is the first report describing that tolvaptan activates Nrf2/HO-1 pathway through PERK phosphorylation. Tolvaptan may be a potential therapeutic target of CKD.

Funding: Government Support - Non-U.S.

SA-PO848

Tadalafil Treatment Attenuates Renal Dysfunction in Hypertensive Model Independent of Blood Pressure Lowering

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Background: Recently, phosphodiesterase 5 inhibitor (PDE5i) reportedly has renoprotective effects, which may be due to blood pressure (BP) lowering by PDE5i. Here, we assessed if the renopretective effect of tadalafil, a PDE5i, depends on its BP lowering using salt-sensitive hypertension rats.

Methods: Dahl salt-sensitive rats were divided into 4 groups (n=5-7): normal salt (NS), high salt (8 % NaCl included in diet; HS), low-dose (1 mg/kg/day, p.o; TL), and high-dose tadalafil treatment (10 mg/kg/day, p.o; TH). SCre, proteinuria, and BP were evaluated at 0 and 8 weeks. PAS staining and αSMA immunohistochemistry were performed. mRNA level of PAI1, which is reported to increase αSMA expression, was evaluated.

Results: In the HS, BP significantly increased at 8 weeks. The TH showed attenuated BP elevation. However, the TL showed BP elevation similar to the HS (Fig.1A). Proteinuria and SCre levels, which markedly increased in the HS at 8 weeks, were suppressed in the TH and TL (Fig.1B,C). PAS staining showed severe glomerulosclerosis in the HS and was prevented in the TH and TL (Fig. 2A). αSMA-positive area significantly increased in the HS and decreased in the TH and TL (Fig. 2B). PAI1 mRNA level was significantly upregurated in the HS. Tadalafil treatment dose-dependantly decreased PAI1 mRNA level.

Conclusions: Tadalafil treatment could prevent decline of the renal function independently of BP lowering. This effect might be associated with suppression of PAI1.

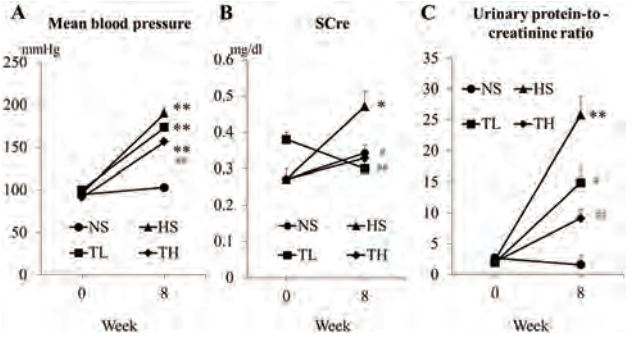

Fig.1 Variations of mean blood pressure (A), SCre (B), and Urinary protein (C) in each groups (n=5-7). *Turkey's* test. *P<0.05,**P<0.01 vs. NS, # P<0.05, ##P<0.01vs. HS.

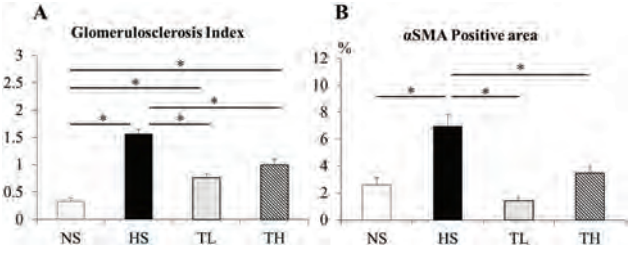

Fig.2 Histopathological assessment; glomerulosclerosis index (A) and αSMA positive area (B). (n=4-6). *Turkey's* test. *P<0.01

SA-PO849

TNF-α Blockade Attenuates Hypertension and Renal Expression of the Epithelial Sodium Channel A-Subunit in the Remnant Kidney CKD Model Using ATRAP Deficient Mice

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Background: We previously identified an angiotensin type 1 receptor (AT1R)-associated protein (ATRAP/Agtrap), which promotes AT1R internalization along with suppression of hyperactivation of tissue AT1R signaling. We hypothesized that dysregulation of renal ATRAP expression and subsequent AT1R hyperactivation plays a critical role in development of hypertension in remnant kidney chronic kidney disease (CKD) model.

Methods: First, we compared changes in endogenous ATRAP expression and blood pressure between 129/Sv and C57BL/6 mice using the remnant kidney model after 5/6

nephrectomy. Second, we examined the effect of ATRAP deficiency in C57BL/6 mice (with a hypertension-resistant strain background) on blood pressure regulation after 5/6 nephrectomy. Third, ATRAP-knockout (KO) mice were treated with the soluble TNF-α receptor, etanercept, or with vehicle after 5/6 nephrectomy.

Results: While 129/Sv mice that underwent 5/6 nephrectomy showed decreased renal ATRAP expression and developed hypertension, C57BL/6 mice exhibited increased renal ATRAP expression and resistance to progressive hypertension. Next, we performed 5/6 nephrectomy in ATRAP-KO mice on the hypertension-resistant C57BL/6 background. ATRAP-KO mice that underwent 5/6 nephrectomy showed hypertension with increased plasma volume. Moreover, in ATRAP-KO mice compared with wild-type C57BL/6 mice after 5/6 nephrectomy, renal expression of the epithelial sodium channel α-subunit (αENaC) and tumor necrosis factor-α (TNF-α) was significantly enhanced, concomitant with increased plasma membrane AT1R in the kidneys. TNF-α inhibition with etanercept significantly suppressed 5/6 nephrectomy-induced blood pressure elevation in ATRAP-KO mice. Furthermore, renal expression of αENaC protein was significantly decreased in ATRAP-KO mice treated with etanercept, compared with vehicle, at 4 weeks after 5/6 nephrectomy.

Conclusions: These results indicate that promotion of primary sodium reabsorption in the renal tubules of the remnant kidney via activation of the AT1R-TNF-α-αENaC axis is a plausible mechanism for the increased circulating plasma volume observed in ATRAP-KO mice after 5/6 nephrectomy.

SA-PO850

Functional Characterization of A1CF, a Novel eGFR Locus

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Background: A recent human genome-wide association study identified a common 5' UTR variant at the *A1CF* locus associated with eGFR. *A1CF* encodes an RNA binding protein (RBP) previously known to facilitate APOBEC1's editing of *APOB* mRNA in non-renal tissues to produce a shorter isoform. However, A1CF's role in modulating renal function remains unclear.

Methods: Leveraging human and rodent systems, we studied A1CF in a renal context with an integrated approach. We localized *A1CF* expression in human kidney organoids and mouse kidneys and assessed expression in human nephrectomy tissue and mouse models of renal fibrosis. Next we used RIP-seq to identify A1CF's RNA binding targets and their enriched pathways. To determine A1CF's renal effects *in vivo*, we measured markers of renal function and injury at baseline and after induction of stress conditions in *A1cf* knockout mice.

Results: Immunostaining of human kidney organoids and fluorescent RNA labeling of mouse kidneys demonstrate that *A1CF* expression is specific to the proximal tubule. Profiling of human nephrectomy tissue revealed that *A1CF* mRNA expression is decreased in CKD samples compared to healthy control (N=58, P=7.4 x 10^{-4}), correlates positively with eGFR (P= 9.5 x 10^{-5}), and correlates negatively with percent interstitial fibrosis (P=2.0 x 10^{-6}). This decreased expression was recapitulated in mice with folic acid (FA) nephropathy and unilateral ureteral obstruction (UUO) on the mRNA (P=2.7 x 10^{-7}; P=3.4 x 10^{-13}) and protein levels (P=6.4x10^{-4}; P=1.9x10^{-7}). To investigate how A1CF as an RBP might interact with injury pathways, we performed RIP-seq and identified 276 binding targets which were enriched in pathways for endoplasmic reticulum protein trafficking (P=6.6 x 10^{-5}) and peroxisomal function (P=3.6 x 10^{-4}), relevant to intracellular stress when perturbed. Although no baseline abnormalities were detected in *A1cf* ko mice, when subjected to stress of water deprivation or FA treatment we observed an increase in urinary albumin to creatinine ratio (N=16, P=0.03; N=16, P=8.0 x 10^{-3}). Furthermore, after FA treatment, *A1cf* ko mice exhibited higher *Bax/Bcl-2* ratios and higher *Acta2* expression in the kidney (N=7, P=0.01, P=4x10^{-3}).

Conclusions: Taken together, these findings suggest that A1CF plays a previously undiscovered role in modulating the intracellular stress response relevant to CKD.

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SA-PO851

Identification of β-Mannosidase (Manba) as a Key Gene for CKD

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Background: Chronic kidney disease (CKD) is a complex gene-environmental disease affecting close to 10% of the population worldwide. We integrated the CKD Genome-wide association studies (GWASs) and kidney expression quantitative trait loci (eQTL) analysis results and identified the lysosomal beta-mannosidase (Manba) as a candidate gene for CKD. We found that when compared to reference allele, expression of Manba was much lower in healthy human kidney tissue samples obtained from subjects with risk alleles. We used Manba knockout mouse model to explore the functional significance of lower Manba expression and precise pathomechanism of Manba in CKD.

Methods: Genotype and gene expression data by RNA sequencing for 121 healthy human kidney tissue samples of European descent were obtained and eQTL analysis was conducted. Single cell RNA-sequencing on healthy mouse kidneys was performed to define the expression of Manba. Manba$^{-/-}$ mice and age-matched WT mice were generated for experiment. CKD was studied in aging mice or following folic acid administration. Renal tubule epithelial cells (TECs) from WT and Manba$^{-/-}$ mice were primary cultured and treated with fed (F), starve (S) and starve+cholorquine (S+CQ) for in vitro study.

Results: Single cell RNA-sequencing analysis of healthy mouse kidneys indicated Manba is mainly expressed in proximal tubule (PT) and principal cell (PC) of collecting duct (CD). QPCR and Western blot showed the deletion of Manba and immunohistochemical staining in human kidney and mouse kidney confirmed the location of Manba. In aging mice, Manba$^{-/-}$ mice showed increased number of lysosome and increased number of vacuoles in tubule cells. In kidney fibrosis model, Manba$^{-/-}$ mice demonstrated worsened renal damage after folic acid (FA) injection. In vitro study, Treatment with CQ heightened the amounts of LC3B-II in nutrientdeprived WT TECs, whereas it did not change the already elevated levels of LC3B-II in nutrient-deprived Manba$^{-/-}$ cells.

Conclusions: This is the first study demonstrated the expression of Manba in mouse kidney and found that Manba deficiency induces kidney fibrosis development. Manba deficiency impair autophagy in CKD predominantly from a slower autophagosome clearance.

Funding: NIDDK Support

SA-PO852

LncRNA GAS5 Regulates TGF-β-Induced Renal Fibrosis via Smad3-Dependent Pathway

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Background: Increasing evidence shows that long noncoding RNAs (lncRNAs) play an important role in kidney disease. It is well known that some lncRNAs have been reported in renal fibrosis and renal inflammation, such as PVT1 is the first identified lncRNA-associated kidney disease. In our previous study, we found lncRNA- growth arrest-specific 5 (GAS5) was highly decreased in the fibrotic kidney of mouse unilateral ureteral obstructive nephropathy (UUO), however, the underlying mechanism of GAS5 in the pathogenesis of kidney disease remain largely unclear.

Methods: Firstly, we detected GAS5 expression in UUO kidney by using realtime-PCR and in situ hybridization(ISH). Then, we tested whether TGF-β1 had any effect on GAS5 expression in mouse tubule epithelial cell (mTEC), since TGF-β signaling is one of the major mediators of renal fibrosis. Finally, we aimed to investigate the biological role of GAS5 after over-expression or silencing its expression in mTEC.

Results: ISH staining showed that GAS5 was expressed by mTECs, interstitial fibroblasts in normal renal tissue, both in the nucleus and cytoplasm pattern. In vitro, GAS5 was down-regulated by TGF-b1 as dose-dependent. Over-expression of GAS5 blocked TGF-b1-induced collagen I, fibronectin and alpha-smooth muscle actin (a-SMA) expressions, however, silencing GAS5 promoted the expressions of these markers. Mechanistic studies revealed that Smad3, not Smad2, drove the expression of GAS5. TGF-b1 reduced GAS5 expression in both of the Smad3 and Smad2 wild-type MEFs, which was bΔlunted in Smad3 knock-out MEFs but still decreased in Smad2 knock-out MEFs. The addition of SIS3 recovered TGF-b1-induced expression of GAS5 in mTECs. Finally, we also found knockdown of GAS5 promoted TGF-β1-induced G2/M arrest, which might contribute to renal fibrosis via Smad3 pathway.

Conclusions: Taken together, our results have uncovered a GAS5-based mechanism that modulated TGF-β/Smad3 signaling by targeting extracellular matrix formation and cell cycle disruption.

SA-PO853

Newly Designed Recombinant Bone Morphogenetic Protein 7 Is a Potential Therapeutic in Renal Tubulointerstitial Fibrosis

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Background: Renal tubulointerstitial fibrosis, final common mechanism for all kidney diseases, is characterized by extracellular matrix (ECM) accumulation. In addition, transforming growth factor-β1 (TGF-β1) is known to plays a principal mediator in the accumulation of ECM. Bone morphogenetic protein-7 (BMP-7) is counteract of the profibrogenic role of TGF-β1. Recently, our group designed recombinant BMP-7 linked by protein transduction domain (PTD), which has capability to effectively deliver a large molecule protein in eukaryotic cells. In this study, we investigated the effect of PTD-mediated BMP-7 (tissue-regeneration polypeptide 2, TRP2) on renal tubulointerstitial fibrosis.

Methods: In vitro, inner medullary collecting duct cells (IMCDs) were cultured in DMEM/F12 media (Control) or TGF-β1 (5 ng/ml) with or without TRP2 (10 ng/ml) for 48 hours. *In vivo*, tubule-interstitial fibrosis were established by unilateral ureteral obstruction (UUO) in C57BL/6 mice, and TRP2 (1 μg) were directly injected intraureterally after UUO operation, and were sacrificed after 7 days. The protein expression of fibronectin, type I collagen (ColI), and α-smooth muscle actin (αSMA) were determined in cultured IMCDs and the kidneys by western blot analysis. Masson's trichrome staining and immunohistochemistry were also evaluated in the mouse kidneys.

Results: Xpress, reporter protein of TRP2, was expressed in TRP2-treated IMCDs after 2 hours in dose-dependent manner. Compared to control, the expression of fibronectin, ColI, and αSMA were significantly increased in TGF-β1-stimulated IMCDs. These changes in cultured IMCDs exposed to TGF-β1 were significantly abrogated by TRP2 treatment. A significant increase in ECM proteins expression was also observed in the kidney of UUO mice compared to the control group kidney. These changes were significantly ameliorated in TRP2-treated group.

Conclusions: These results suggest that TRP2 is directly suppressing the process of TGF-β1-induced ECM accumulation *in vitro* and *in vivo*. The effect of TRP2 can be

promising potential therapeutic for prevention of renal tubulointerstitial fibrosis in various kidney diseases.

SA-PO854

The Farnesoid X Receptor (FXR) Agonist EDP-305 Reduces Interstitial Renal Fibrosis in a Mouse Model of Unilateral Ureteral Obstruction

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Background: Farnesoid X receptor (FXR) is a nuclear receptor that has emerged as a key regulator in the maintenance of bile acid homeostasis. FXR agonists are currently under clinical investigation for the management of various clinical diseases such as primary biliary cholangitis and nonalcoholic steatohepatitis where they have been shown to reduce hepatic steatosis, inflammation, and fibrosis. However, the role of FXR in renal fibrosis remains to be established. Here, we investigate the effects of the FXR agonist EDP-305 in a mouse model of tubulointerstitial fibrosis via unilateral ureteral obstruction (UUO).

Methods: Male C57Bl/6 mice received a UUO on their left kidney. On postoperative day 4, mice received daily treatment by oral gavage with either vehicle control (0.5% methylcellulose) or 10 or 30 mg/kg EDP-305. All animals were sacrificed on postoperative day 12.

Results: EDP-305 dose-dependently decreased macrophage infiltration as measured by the F4/80 staining area with significant differences seen at the higher dose (4.5±0.46 vs. 1.4±0.49, $p<0.01$) which were associated with reduced pro-inflammatory cytokine gene expression (*Il-6* 208.3±59.46 vs. 32.53±3.28, $p<0.01$; *Tnf-α* 34.2±10.35 vs. 13.41±2.81, $p<0.05$). EDP-305 also dose-dependently reduced interstitial fibrosis as assessed by morphometric quantification of the collagen proportional area (CPA) and kidney hydroxyproline (HYP) levels with statistically significant differences observed at the higher dose (CPA 6.73±0.94 vs 2.58±0.39, $p<0.01$; and HYP 1504±140 vs. 1089±54, $p<0.05$). Finally, Yap activation, a major driver of fibrosis, increased after UUO injury and was diminished by EDP-305 treatment. Consistently, EDP-305 decreased TGF-β1-induced YAP nuclear localization in HK2 cells by increasing inhibitory YAP phosphorylation.

Conclusions: Our results suggest that Yap inhibition may be a novel anti-fibrotic mechanism of FXR agonism and that FXR agonists could be used to treat renal fibrosis in patients with chronic kidney disease.

Funding: Commercial Support - Enanta Pharmaceuticals

SA-PO855

Targeted Disruption of CD40 in Human Proximal Tubular Epithelial Cells Significantly Reduces Pro-Inflammatory and Pro-Fibrotic Signaling

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Background: We have demonstrated that levels of the TNF-α superfamily member CD40 predict progression of renal dysfunction in patients with ischemic and chronic kidney disease, and that CD40's soluble ligand (sCD40L) is significantly elevated in these settings. In the two-kidney one clip (2K1C) model of renal ischemia, CD40 expression is significantly elevated in the ischemic renal proximal tubule epithelium, and CD40 knockout (KO) rats show significantly reduced tubular interstitial fibrosis in the ischemic kidney and improved renal function verses controls. To test the hypothesis that activation of CD40 in the proximal tubule epithelium induces a significant pro-inflammatory and pro-fibrotic response contributing to ischemic renal injury we performed the following study.

Methods: Renal ischemia was induced via 2K1C in both Dahl-S wild type and Dahl-S CD40 KO male rats and kidneys were assessed for evidence of inflammation and fibrosis after 4 weeks. CRISPR/Cas9 was used for the creation of a CD40 KO human proximal tubular cell line (HK2/CD40KO) and confirmed by immunoblotting and gene expression. Parent HK2 cells and HK2/CD40KO cells were treated with sCD40L (100 ng/ml) or TNF-α (10 ng/ml) for 24h.

Results: Renal expression of the pro-fibrotic marker plasminogen activator inhibitor-1 (PAI-1) was elevated in Dahl-S rats after 2K1C renal ischemia and this was significantly attenuated in kidneys from Dahl-S CD40KO animals ($p<0.05$). In HK2 proximal tubular cells, sCD40L induced a significant increase in cytokine gene expression [CXCL2, CXCL5, IL23A, colony stimulating factor-1, and lymphotoxin beta (all > 5 fold increase)] as assessed by quantitative PCR. Importantly, sCD40L treatment also induced a significant increase in monocyte chemoattractant protein-1 (>20 fold increase) and PAI-1 (>2 fold increase) gene compared to TNF-α treatment. The responses to both sCD40L and TNF-α were substantially attenuated in the HK2/CD40KO cells ($p<0.05$).

Conclusions: Activation of CD40 in the proximal tubule epithelium induces a significant pro-inflammatory and pro-fibrotic response, and represents an attractive therapeutic target for treatment of ischemic renal disease.

SA-PO856

CD11c-Specific Ablation of SHP-1 Results in Renal Fibrosis with Age

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Background: Renal mononuclear phagocytes (rMoPh) which express traditional macrophage and dendritic cell marker, F4/80 and CD11c respectively, have attracted attention because of their immunoregulatory roles in healthy and diseased kidneys (JASN 23:194, 2012). We have previously generated CD11c-specific SHP-1 conditional knockout mice (SHP-1 CKO) which lack a protein tyrosine phosphatase, SHP-1, and reported that they spontaneously develop tubulointerstitial nephritis characterized by the marked accumulation of $CD11c^+F4/80^+$ double-positive rMoPh, (J Immunol 2012, ASN 2016). In the present study, we further analyzed the kidney of SHP-1 CKO to clarify the precise contribution of rMoPh to the development of the nephritis.

Methods: The kidneys obtained from SHP-1 CKO and its control mice (Ctrl) at the age of 40 weeks and were analyzed; in particular, the expressions of vimentin, a marker of mesenchymal cells, and α-smooth muscle actin (α-SMA), a marker of myofibroblasts, were evaluated by immunohistochemistry. Collagen-digested renal mononuclear cells from SHP-1 CKO and Ctrl were analyzed by flow cytometry (FCM).

Results: Masson's trichrome and Sirius Red staining showed that the area of renal fibrosis was significantly increased in SHP-1 CKO compared to Ctrl. The immunohistochemical analysis revealed marked expression of vimentin and moderate expression of α-SMA in tubulointerstitial area of SHP-1 CKO. Intracellular FCM staining revealed majority of vimentin as well as α-SMA positive-cells were $CD11c^+F4/80^+$ double-positive rMoPh in SHP-1 CKO. A small number of $CD45^-$, non-hematopoietic cells, were positive for vimentin or α-SMA, but not significantly different compared to Ctrl. To confirm the efficacy of depletion of SHP-1, we examined the SHP-1 expression in rMoPh by intracellular FCM staining. About 70% of $CD11c^+F4/80^+$ rMoPh did not express SHP-1. These results suggested that SHP-1 depletion in $CD11c^+F4/80^+$ rMoPh led to the upregulation of vimentin and α-SMA, and directly caused renal fibrosis.

Conclusions: Depletion of SHP-1 in $CD11c^+F4/80^+$ rMoPh induces renal tubulointerstitial nephritis and fibrosis with age. In addition, transformation of $CD11c^+F4/80^+$ rMoPh into myofibroblasts could be involved in underlying mechanisms of renal fibrosis.

SA-PO857

Endothelial Tie2 Deficiency Increases Capillary Rarefaction and Tubulointerstitial Fibrosis

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Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in aSMA+ fibroblasts, myofibroblasts, that produce collagen. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing, diabetic nephropathy, and the unilateral ureter obstruction (UUO) model. The tyrosine kinase receptor, Tie2, is expressed on endothelial cells and Angpt1 binding results in Tie2 signaling that is pro-survival and anti-inflammatory. Here, we test the hypothesis that loss of Tie2 signaling in endothelial cells results in capillary defects leading to an increased fibrotic response in kidney fibrosis.

Methods: Tie2 floxed mice were crossed with tamoxifen inducible endothelial specific Cadh5-Cre and a reporter line expressing TdTomato upon Cre-activation. This line enables both an endothelial specific KO of Tie2 and an endothelial lineage tracer. To study the role of Tie2 signaling in renal fibrosis we utilized the unilateral ureter obstruction (UUO) model of kidney fibrosis. An additional line (Pdgfra-H2b-GFP) was crossed into the above line, resulting in a reporter of myofibroblasts.

Results: Endothelial specific KO of Tie2 resulted in an increase in fibrosis as seen by increased expression of aSMA and vimentin compared to WT mice 3 days after UUO. At the same time, there was significant increase in Kim1 and tubular ferroptosis, suggesting a more severe injury in ecTie2KO. Electron micrographs of peritubular capillaries 3 days after UUO showed significantly more loss of fenestrations in ecTie2KO mice. Investigation of blood vessels before fibrotic onset 1 day after UUO, revealed less perfused capillary area and increased hypoxia in Tie2 KO mice. Ongoing work is designed to investigate blood vessel function in the early fibrotic process and to estimate the endothelial-mesenchymal contribution after UUO in controls and Tie2 knockout mice, utilizing the lineage tag of endothelial cells and myofibroblast reporter.

Conclusions: Our results suggest that loss of Tie2 signaling destabilizes the endothelial cell and increases tubulointerstitial fibrosis. The mechanisms we are investigating are an early loss of endothelial cells due to endothelial-mesenchymal transition and/or apoptosis, resulting in less functional peritubular capillaries and more fibrosis.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO858

Dose-Effect Response of Remote Ischemic Preconditioning for the Prevention of Hemodialysis-Induced Myocardial Stunning: Preliminary Results of a Randomized Controlled Trial

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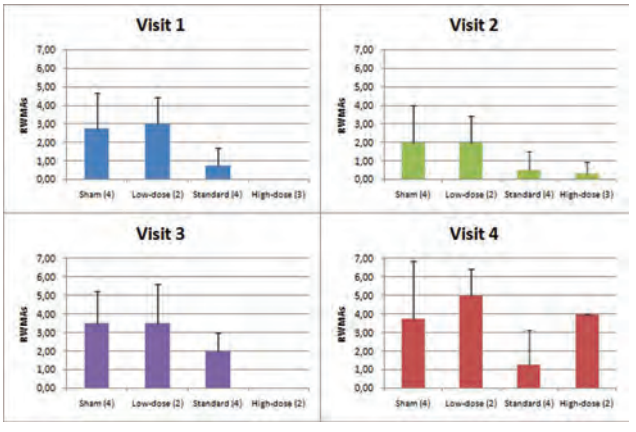
Background: Myocardial stunning is a common complication of standard hemodialysis and is implicated in the high cardiovascular mortality of end-stage kidney disease patients. This is an interim analysis of a randomized controlled trial aimed at testing the effects of different doses of remote ischemic preconditioning (RIPC) for the prevention of hemodialysis-induced myocardial stunning.

Methods: Study patients underwent speckle-tracking echocardiography predialysis and at peak stress (15 minutes before the end) at each visit. Images were analyzed for longitudinal systolic strain and the number of new regional wall motion abnormalities (RWMAs) (> 30% reduction in longitudinal systolic strain at peak stress) was recorded. Patients were screened for myocardial stunning (>/= 2 RWMAs) before enrolment: so far, 13 chronic hemodialysis patients showing evidence of hemodialysis-induced myocardial stunning were enrolled. Patients were followed-up for 4 weeks, once a week. They were randomized in a 1:1 ratio to receive either: predialysis Sham RIPC, Low-dose RIPC (2 RIPC cycles on visit 1), Standard RIPC (4 cycles on visit 1) or High-dose RIPC (4 cycles at each visit). Primary outcome was the reduction in RWMAs.

Results: See attached image.

Conclusions: These preliminary results show a trend towards a dose-effect response to RIPC: sham and low-dose RIPC failed at reducing hemodialysis-induced RWMAs, while standard and high-dose RIPC seem effective in preventing hemodialysis-induced myocardial stunning. These effects seem to last for at least 2 weeks after the delivery of the RIPC stimulus. We expect to confirm our hypotheses with further enrollments.

Funding: Government Support - Non-U.S.



Mean (+ Standard Deviation) RWMAs per group per visit. The RIPC stimulus was administered on visit 1 for the Sham, Low-dose and Standard groups and on visits 1 through 4 for the High-dose. Differences were not statistically significant.

SA-PO859

Prescribing Patterns of Anticoagulants in Dialysis Patients with Incident Atrial Fibrillation in the United States Between 2012 and 2014

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Background: Four direct acting oral anticoagulants are approved for stroke prevention in atrial fibrillation (AF) and offer advantages over warfarin. However, individuals with advanced kidney disease and dialysis were excluded from phase 3 trials and all agents are excreted by the kidney. Understanding longitudinal prescribing patterns of anticoagulation in dialysis patients is especially important as these agents become integrated into clinical care.

Methods: We used United States Data Renal System (USRDS) data to identify prevalent and incident dialysis patients with new onset atrial fibrillation occurring between Jan 1, 2012-December 31, 2014. Trends in use of apixaban, rivaroxaban, warfarin, or no anticoagulation were identified from Part D Medicare records. Subgroup analyses for demographics and comorbidities were also examined.

Results: Among 743,639 patients receiving maintenance dialysis (399,024 prevalent prior to Jan 1, 2012 and 344,615 incident patients from Jan 1, 2012 - Dec 31, 2014),85,032 had a new diagnosis of AF or flutter after Jan 1, 2012. Upon exclusion for non-continuous part A, B, and D Medicare coverage, death within 30 days of AF diagnosis, and or valvular disease, 27,202 individuals were included in the final analysis (25,372 on hemodialysis and 1,830 on peritoneal dialysis). Of these 6,717 (24.7%) were prescribed warfarin, 309 (1.1%) apixaban, 91 (0.3%) rivaroxaban, and 20,085 (73.8%) did not receive anticoagulation.

Conclusions: Results from this large observational study of 27,202 individuals on dialysis in the United States with AFshow that the majority did not receive anticoagulation (73.8%) between 2012-2014. Warfarin remains the most frequently prescribed anti-coagulant (24.7%). Use of direct acting oral anti-coagulants remains infrequent with the majority receiving apixaban.

Funding: Private Foundation Support

SA-PO860

Association Between Body Mass Index and the Incidence of Cardiovascular Disease in Patients Undergoing Hemodialysis: Ten-Years Outcome of the Q-Cohort Study

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Background: In hemodialysis (HD) patients, high body mass index (BMI) is paradoxically associated with better outcomes including a lower risk of cardiovascular and all-cause mortality (obesity paradox). However, the impact of BMI on the incidence of cardiovascular disease (CVD) [stroke, ischemic heart disease (IHD), or peripheral artery disease (PAD)] in patients undergoing hemodialysis remains unclear.

Methods: A total of 3,506 participants undergoing maintenance HD were followed up for 10 years. The primary outcome was the incidence of stroke, IHD, or PAD. The subjects were divided into 4 groups based on the quartile of the baseline BMI values (Q1, ≤19.1; Q2, 19.2–20.9; Q3, 21.0–22.6; Q4, ≥22.7 kg/m^2). The association between BMI and the incidence of each CVD was examined using Cox proportional hazards model.

Results: During the follow-up period, 526 (15%), 456 (13%), and 257 (7.3%) patients experienced stroke, IHD, and PAD, respectively. The 10-year incidence rate of stroke was significantly higher with lower BMI, whereas incidence rates of IHD and PAD were significantly lower with lower BMI. Compared with the highest quartile of BMI (Q4), the multivariable-adjusted hazard ratios (95% confidence interval) for stroke were 1.45 (1.13–1.85) in patients with Q1. Whereas, compared with the lowest quartile of BMI (Q1), the multivariable-adjusted hazard ratios (95% confidence intervals) for IHD and PAD were 2.04 (1.54–2.72) and 1.76 (1.21–2.55) in patients with Q4, respectively.

Conclusions: Low BMI was associated with high risk of stroke, whereas high BMI was associated with high risk of IHD and PAD in patients undergoing HD. Our results suggest that the influence of BMI on the incidence of CVD may be different depending on the type of cardiovascular events.

Funding: Government Support - Non-U.S.

SA-PO861

Long-Term Trends in Oral Anticoagulant (OAC) Use in US Patients with ESRD on Hemodialysis (HD) and Atrial Fibrillation (AF)

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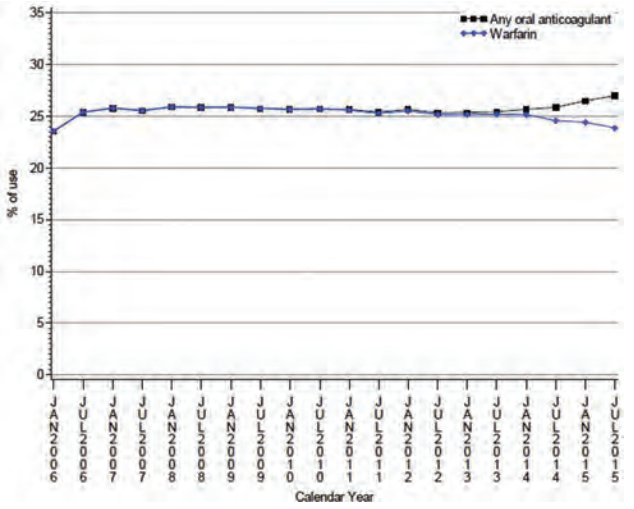
Background: OACs are recommended for most patients with AF to prevent thromboembolic complications. Low OAC use has been reported in patients with ESRD on HD and AF. We tested whether OAC practices in this population have changed during the decade, 2006-2015.

Methods: From the USRDS, 2006-2015, we selected subsequent 6-month interval cohorts of Medicare-insured HD patients diagnosed with AF in the current or preceding intervals. From Medicare Part D claims we identified any warfarin or direct-target OAC use in each interval. Study outcomes were the prevalence of any OAC use, or use of specific agents. We used repeated measures logistic regression and interrupted time series analysis to 1) determine whether OAC use increased during 2006-2015, and 2) whether this longer-term trend changed after the approval of a labeled dose for apixaban in ESRD in Jan 2014.

Results: While the number of period-prevalent HD patients with AF increased from 33,052 (Jan-Jun 2006) to 63,675 (Jul-Dec 2015), the proportion receiving any OAC remained remarkably stable during the decade, at ~25% (Figure). There was a slight increase starting in 2014, which was mostly attributable to increasing apixaban use, with >27% of patients receiving OAC in Jul-Dec 2015, and apixaban representing 13% of all OAC use. Compared with Jul-Dec 2006, adjusted odds ratios were near unity throughout time, with an aOR of 1.07 (CI, 1.04-1.09) for any OAC and 0.96 (CI, 0.93-0.98) for warfarin use for Jul-Dec 2015. Adjusted interrupted time series analyses failed to reject the null hypothesis of a zero slope over the decade and did not identify a significant difference in level or slope for 2014-15 vs. 2006-2013, either.

Conclusions: The proportion of HD patients with AF receiving any OAC remained remarkably stable over the decade, at ~25%, with increasing substitution of warfarin by apixaban after 2014.

Funding: NIDDK Support



SA-PO862

Peripheral Vascular Calcification Score Is Better Than Abdominal Aortic Calcification Score of Plain Radiographs in Predicting Cardiovascular Mortality in Hemodialysis Patients

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Background: Cardiovascular disease (CVD) is the major cause of death for dialysis patients. Vascular calcification (VC) serves as a key pathological factor resulting in the CVD. KDIGO advocates abdominal aortic calcification score (AACS) to evaluate VC. Meanwhile, some studies showed that the peripheral vascular calcification score (PVCS) could predict cardiovascular mortality. However, no studies compare two VC score systems in clinic. Thus, this study compared two VC score systems in predicting mortality of HD patients.

Methods: In this retrospective study with 243 HD patients, AACS and PVCS were measured from plain radiograph of lateral abdominal radiograph and pelvis and both hands radiographs, respectively.

Results: The prevalence of VC was 68.5% (167 patients), most patients showed AAC (63.7%). During the follow-up period of 24 (13,44) months, 65(26.6%) patients died. Among these died patients, 35 (53.8%) patients died of cardiovascular disease. The patients died showed higher AACS (5.0 (1.25,14.0) vs. 2.0 (0,6.75), *P*=0.001), PVCS (2.0(0,5) vs. 0(0,2.0),*P*=0.000), and overall VC score (5 (0,16) vs. 1 (0,6), *P*=0.001) compared to alive patients. When ROC curve was used to predict all-cause mortality, for PVCS, the area under ROC curve (AUROC) was 0.695 with 57.4% of specificity and 71.8% of sensitivity (*P*=0.000). As for AACS, the AUROC was 0.666 with 62.9% of specificity and 61.7% of sensitivity (*P*=0.001). The AUROC for PVCS was 0.668 with 68.0% of specificity and 62.5% of sensitivity (P=0.007), while the AUROC for AACS was 0.574 with 38.1% of specificity and 75.0% of sensitivity (P=0.239) when used to predict cardiovascular mortality. By the COX multivariate regression analysis (adjusted for age, gender, diabetes, period of dialysis, albumin, hypertension, cholesterol, phosphorus, calcium, intact-parathyroid and Kt/V), the PVCS was independently associated with all-cause mortality and cardiovascular mortality (HR, 1.287;95%CI, 1.140-1.453, and HR, 1.272;95%CI,1.079-1.499), respectively. However, AACS was only associated with all-cause mortality (HR, 1.069; 95%CI, 1.008-1.133) but not cardiovascular mortality.

Conclusions: VC score is independently associated with mortality. The PVCS is a better parameter in predicting cardiovascular mortality as compared with AACS.

SA-PO863

Predictors of Change in Left Ventricular Mass in a Randomized Trial of Extended Hours Dialysis

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Background: Extended hours dialysis was not associated with a significant reduction in LVMI in the ACTIVE Dialysis trial. Other factors, such as changes in fluid status and biochemical parameters, may predict regression of LV hypertrophy. We aimed to determine predictors of change in left ventricular mass index (LVMI) in the ACTIVE Dialysis study.

Methods: In the ACTIVE Dialysis study patients randomised to extended and standard dialysis, received median 24 and 12 haemodialysis hours per week respectively, predominantly delivered as three sessions per week. Ninety-five participants underwent cardiac magnetic resonance imaging (MRI) at baseline and 12 months. Predictors of change in LVMI were examined by multivariable linear regression in an observational analysis.

Results: In the overall MRI cohort, the change from baseline to 12 months in LVMI was -6.7g (95% confidence interval (CI) -11.2, -2.2; P=0.004) with non-significant reductions in mean normalised sessional ultrafiltration rate -1.0mL/kg/hr (95%CI -2.2, 0.24; P=0.114) and weekly total ultrafiltration -0.8L (95%CI -0.3, 2.0; P=0.165) and a significant reduction in systolic blood pressure (BP) -5.4mmHg (95%CI -8.8, -2.0; P=0.002). Baseline LVMI (P=0.003) was associated with improved LVMI in univariable analysis and this remained significant in the multivariable analysis (P=0.046). A non-significant improvement in LVMI was observed with longer dialysis vintage (P=0.137). There were no significant associations between changes in ultrafiltration rates and volumes, systolic and diastolic blood pressure, phosphate, and parathyroid hormone and change in LVMI.

Conclusions: Higher baseline LVMI, but not improvements in volume control, blood pressure or biochemical parameters, predicts regression of left ventricular hypertrophy over 12 months. Further study is warranted to identify predictors of change in this important treatment target.

Funding: Commercial Support - Baxter International, Government Support - Non-U.S.

SA-PO864

Association Between Bone-Derived Biomarkers and Aortic Arch Calcification in Maintenance Hemodialysis Patients

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Background: Aortic arch calcification (AoAC) is frequently detected in maintenance hemodialysis (MHD) patients and is associated with cardiovascular and all-cause mortality. We investigated the factors associated with AoAC and analyzed the relationship between bone-derived biomarkers and AoAC.

Methods: We enrolled 389 stable MHD patients. AoAC was assessed using chest-X ray examination. Demographic data was collected in addition to serum levels of biochemical and bone-derived biomarkers, including sclerostin and fibroblast growth factor 23 (FGF23).

Results: Two hundred sixteen patients (55.0%) had AoAC. Patients with AoAC score ≧ 4 were older, with a higher percentage being male, and exhibited lower serum levels of albumin and triglyceride. Serum FGF23 levels were inversely associated with AoAC severity, and FGF23was directly related to vascular calcification. Age, gender, and dialysis vintage were independent predictors of AoAC.

Conclusions: MHD patients have a high prevalence of AoAC. Levels of circulating FGF23 but not sclerostin were related to AoAC severity. Serum FGF23 levels were independently associated with AoAC.

SA-PO865

Lower Serum Magnesium (sMg) Is a Strong Predictor of Left Ventricular Hypertrophy (LVH) and Patterns of LV Remodeling in Patients with CKD Stage 5D

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Background: To evaluate the prognostic role of sMg on LVH and cardiac geometry in patients with stage 5D CKD

Methods: The study included 127 patients with stage 5D CKD (69 on hemodialysis and 58 on peritoneal dialysis) and a mean age of 62±15 years. Echocardiographic LVH was defined by LV mass index (LVMI) > 95 g/m^2 in women and > 115 g/m^2 in men. Based on LVMI and relative wall thickness (RWT), four LV geometric patterns were defined: normal (normal LVMI and RWT), concentric remodeling (normal LVMI and increased RWT>0.42), eccentric LVH (increased LVMI and normal RWT) and concentric LVH (increased LVMI and RWT). sMg and serum Ca (sCa) values were defined as the mean of all predialysis measurements available during the preceding 3 months.

Results: Patients (n=81) with LVH as compared to patients with no LVH (n=46) were older in age (p <0.001), had lower sMg (p<0.001) and higher sCa (p<0.05), malnutrition-inflammation score (p<0.05), body mass index (p<0.001), pulse pressure (p<0.01), prevalence of diabetes (p<0.05), coronary artery disease (p<0.05) and peripheral vascular disease) (p<0.01). In a multivariate logistic regression analysis adjusted for all factors mentioned above, each increase of sMg by 1 mg/dl was associated with 91% (OR= 0.09, 95% CI: 0.024-0.36; p <0.001) lower odds of having LVH. In a forward stepwise multivariate model (R^2= 0.271; p<0.001), sMg emerged a strong independent predictor of LVMI (p<0.01) explaining about 5.7% of its variance. The area under the ROC curve for predicting the development of LVH was 0.696 (p<0.001) and at an optimal sMg cutoff of 2.26 mg/dl the sensitivity and specificity of sMg in predicting the occurrence of LVH were 67.4 % and 66.7 %, respectively. Considering LV geometry, there was a progressive decrease in sMg from the normal group (2.38±0.38 mg/dl) to concentric remodeling group (2.37±0.40 mg/dl), eccentric (2.19±0.30 mg/dl) and then to concentric (2.08±0.36 mg/dl) group (p<0.01 for the trend).

Conclusions: A lower sMg is a major determinant of echocardiographic LVH. Prospective studies may determine whether therapeutic adjustments of sMg can prevent or reduce the risk of LVH in patients with stage 5D CKD

SA-PO866

Pre-Dialysis Serum Phosphorus and Intradialytic Hypotension

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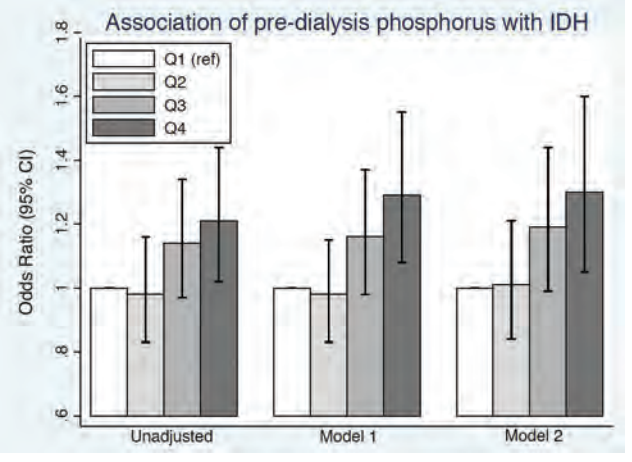
Background: Intradialytic hypotension (IDH) is a common complication of maintenance hemodialysis (HD) and is associated with excess morbidity and mortality. Higher serum phosphorus is associated with vascular calcification and adverse cardiovascular outcomes, however its association with the development of IDH is unclear. We hypothesized that higher pre-dialysis serum phosphorus is associated with a higher risk of IDH.

Methods: We performed a post-hoc analysis in 1825 participants (n=10,551 HD sessions) from the Hemodialysis (HEMO) Study, a multicenter randomized control trial examining standard or high dose dialysis and low-flux or high-flux membranes. Unadjusted and adjusted generalized linear models were fit to determine the association of pre-dialysis serum phosphorus with IDH (defined as any hypotensive event requiring an intervention). Serum phosphorus was examined as a continuous and categorical variable to assess for non-linear associations.

Results: Mean age of participants was 57.8 years (43.8% men, 37.4% white). Mean pre-dialysis serum phosphorus was 5.8 mg/dL; IDH occurred in 17.5% of HD sessions. In adjusted models (accounting for age, sex, race, comorbidities, flux group, Kt/V group, dialysis vintage, session length, ultrafiltration volume, access, pre-dialysis blood pressure, and pre-dialysis laboratory tests), higher pre-dialysis serum phosphorus (per 1 mg/dL) was associated with a higher risk of IDH (odds ratio (OR) 1.07; 95% confidence interval (CI) 1.03-1.12). Participants in the highest (≥ 6.9 mg/dL) vs. lowest (≤ 4.5 mg/dL) quartile of pre-dialysis serum phosphorus had a 30% greater risk (OR 1.30; 95% CI 1.05-1.60) of IDH (Figure 1).

Conclusions: Higher pre-dialysis serum phosphorus is independently associated with higher risk of IDH, even after adjustment for variables associated with 'compliance'. As HD may cause an acute decline in serum phosphorus, future studies to investigate the temporal association of changes in phosphorus and IDH should be performed.

Funding: Other NIH Support - T32DK007527-33



SA-PO867

U-EVE, a Method for Estimating the Extra-Cellular Fluid Volume with Serum Uric Acid Concentrations, Would Help to Find Latent Overhydration of Hemodialysis Patients

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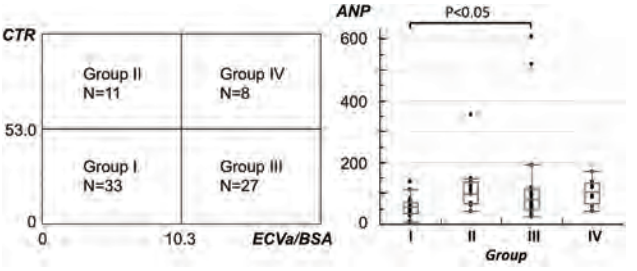
Background: We have developed a new method to estimate the extra-cellular fluid volume after HD (ECVa) with serum uric acid (UA) concentrations at pre- and post-hemodialysis (HD) sessions, which was named UA-assisted ECV Estimation (U-EVE). We studied the clinical value of U-EVE.

Methods: Among 108 Japanese outpatients undergoing HD in Kataguilli medical center, 79 patients maintaining stable blood flow and ultrafiltration rates on the day of blood sampling were studied. They had no cardiac events at least during the last twelve months. Plasma ANP concentrations and cardio-thorax ratios (CTR) of X-ray were measured after HD. ECVa was estimated by the U-EVE method as reported separately and was standardized by the body surface area (ECVa/BSA).

Results: ECVa/BSA values were significantly high in the patients with persistent atrial fibrillation. They, however, were unaffected by sex, diabetes, dialysis modality, and past events of myocardial infarction, pacemaker implantation, aortic valve replacement, percutaneous coronary intervention, and/or coronary artery bypass grafting. In univariate analysis, serum creatinine (Cr), ANP and Kt/V correlated with ECVa/BSA [R=-0.29133 (P=0.0092), R=0.2624 (P=0.0195), and R=-0.254 (P=0.0236), respectively]. Age, HD vintage, CTR, hemoglobin, and BNP at the pre-HD session were not significant. When the subjects were categorized into four groups, ANP concentrations of Group III were significantly higher than those of Group I (Figure). The increase of ECVa/BSA during the last twelve months correlated with age (R=0.280, P=0.0162), Cr (R=-0.386, P=0.0007), and Alb (R=-0.265, P=0.023), which suggested that the increase of ECVa/BSA might reflect the progression of sarcopenia.

Conclusions: U-EVE/BSA would help to find potentially overhydrated HD patients.

Funding: Clinical Revenue Support



The study subjects were categorized into 4 groups according to CTR and ECVa/BSA. Statistical comparison was done by Tukey-Kramer analysis. The cut-off values of CTR and ECVa/BSA were 53.0% and 10.3 L/m^2, respectively.

SA-PO868

A New Method to Estimate the Extra-Cellular Fluid Volume with Serum Uric Acid Concentrations at Pre- and Post-Hemodialysis

Takahito Ito,[1] Takahiro Shinzato,[2] Kazuhiko Shibata,[3] Shigeru Nakai,[4] Takeshi Aoki.[5] *[1]Kataguilli Medical Center, Shibata, Japan; [2]Daiko Medical Engineering Research Institute, Nagoya-shi, Japan; [3]Yokohama Minami Clinic, Yokohama, Japan; [4]Fujita Health University School of Health Scieneces, Toyoake, Aichi, Japan; [5]Nagoya Municipal Industrial Research Institute, Iwakura-shi, Aichi-ken, Japan.*

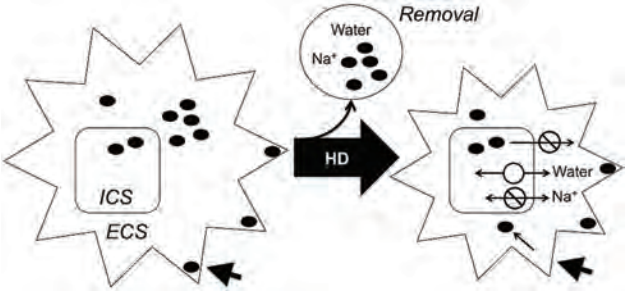
Background: Uric acid (UA) with a molecular weight of 168 Da is synthesized mainly in the liver and intestines as the end-product of purine metabolism, and is located throughout the body. We have found that we could approximate the extra-cellular fluid volume (ECV) with the amount of UA that was removed by hemodialysis (HD).

Methods: Our calculation is based on assumptions shown in the figure. The dialyzer mass transfer-area coefficient (KoA) and the physiologically-appropriate patient clearance time (tp) for UA were obtained in advance. In order to estimate ECV after HD (ECVa), clinical parameters required other than C_{UA} at pre- and post-HD were height, treatment time of HD, blood flow rate of HD, dialysate flow rate of HD, surface area of dialysis membranes, hematocrit at pre-HD, body weight values at pre- and post-HD, C_{UN} at pre- and post-HD, and C_{Na} at pre- and post-HD. The ECAa values estimated by our method were compared with those which were measured by multi-frequency bioimpedance analysis (BIA).

Results: We named our new method UA-assisted ECV Estimation (U-EVE) and assembled it as a Microsoft EXCEL® file for practice. ECVa values by U-EVE correlated with those by BIA: R=0.456 (P=0.0100, N=31, age 62.3±11.4, BIA was done by MLT555N), R=0.578 (P=0.0190, N=16, age 65.5±9.3, by InBody S10), and R=0.616 (P<0.0001, N=49, age 59.6±11.3, by MLT50) in three independent measurements. The formulas used in our program will be explained step by step.

Conclusions: U-EVE is innovative yet easy to estimate ECVa of HD patients without special devices. Clinical significances of U-EVE need to be further verified.

Funding: Clinical Revenue Support



Major assumptions about our method. (1) Removed UA molecules come only from ECS, (2) UA and Na^+ do not cross cell membrane during HD, (3) Water crosses cell membrane to maintain the ratio of C_{Na}^+ of ECS to that of ICS, (4) C_{UA} of ECS rebounds after HD simply due to redistribution of UA from hypo-perfused space of ECS (arrowhead). *ECS* and *ICS* stand for extra-cellular and intra-cellular spaces, respectively. Black dots represent UA molecules.

SA-PO869

Correlation of Intracellular Volume Calculated by Uric Acid Kinetic Modeling with Intracellular Volume Estimated by Bioimpedance Analysis

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Background: Previous studies indicate that uric acid is not transported through the cell membranes of erythrocytes during hemodialysis (HD). If uric acid is not transported through the cell membranes of not only erythrocytes, but also general body cells, the uric acid distribution volume is theoretically consistent with extracellular volume, and the difference between urea distribution volume and uric acid distribution volume is consistent with intracellular volume (ICV). We tentatively designated the difference between urea distribution volume and uric acid distribution volumeas kinetic modeling ICV (KM-ICV).

Methods: We calculated whole-body KM-ICV based on regular blood test results obtained at 49 occasions in 7 patients. Subsequently, we compared whole-body KM-ICVandbioimpedance analysis (BIA)-ICV, which were measured after HD on the day the regular blood tests were performed and examined their correlation. Moreover, we examined the correlation between KM-ICVnormalized to body surface area (normalized KM-ICV) andserum albumin level, and between normalizedKM-ICVandserum creatinine level.

Results: A significant difference was found between whole-bodyKM-ICV andBIA-ICV(17.30 ±4.30 ml/m^{2}and 15.88 ±2.43 ml/m^2[mean ±s.d.], respectively; p = 0.002). Moreover, a significant correlation was observed between whole-bodyKM-ICV(x) and BIA-ICV (y) (y = 0.402x + 8.931, r = 0.711, p = 0.0001). A significant correlation was found between normalizedKM-ICV(x) and serum albumin level(y) (y = 0.0324x + 3.072, r = 0.463, p = 0.0008). However, no correlation was found betweennormalizedKM-ICV and serum creatinine level.

Conclusions: NormalizedKM-ICV can be used as an alternative nutritional index.

SA-PO870

Inflammation Is an Amplifier of Lung Congestion by High LV Filling Pressure in Hemodialysis Patients: A Longitudinal Study

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Background: Lung congestion is exceedingly common in symptomatic and asymptomatic hemodialysis (HD) patients. Since inflammation alters vascular permeability, including vascular permeability in the lung, we hypothesized that it can be an amplifier of lung congestion in HD patients.

Methods: We investigated the effect modification by systemic inflammation as measured by serum C Reactive Protein (CRP) on the longitudinal relationship between a surrogate of the filling pressure of the LV [left atrial volume (LAV)] and lung water in a series of 273 patients participating into the LUng congeSTion in hemodialysis patients trial (LUST). Lung water was quantified by the number of ultrasound B lines (US-B) registered over the thorax. Paired lung-US and LAV (Echo-CG) recordings were performed at baseline, 6, 2 and 24 months. Overall, 407 simultaneous US-Echo-C estimates were obtained during follow up. Data analysis was made by the mixed Linear Model.

Results: Ninety-two patients had mild to moderate lung congestion (5-30 B lines) and 33 severe congestion (>30 B lines). The median LAV was 73 ml (Inter Quartile Range 53-105). The longitudinal series of US-B lines associated with simultaneous estimates of LAV in analyses adjusting for age, gender, dialysis vintage, SBP, diabetes, smoking, cholesterol, calcium (P=0.001). Effect modification analysis by CRP showed that this biomarker of inflammation was a strong modifier of the LAV- US B lines relationship both in unadjusted and adjusted analyses (P<0.001) so that at an identical increase in LAV the number of US-B lines was higher in more severely inflamed than in patients with less severe inflammation.

Conclusions: These data extend to the lung the detrimental effects of inflammation in HD patients and suggest that, at comparable LV filling pressure levels, patients with more severe degrees of inflammation are exposed to higher risk for pulmonary edema than those with no or mild systemic inflammation. ***Mallamaci F, Gargani L, Sicari R, Letachowicz K, Ekart R, Fliser D, Covic A, Siamopoulos K, Stavroulopoulos A, Massy ZA, Fiaccadori E, Caiazza A, Bachelet T, Slotki I, Martinez-Castelao A, Coudert-Krier MJ, Rossignol P, Gueler F, Hannedouche T, Wiecek A, Sarafidis P, Klinger M, Hojs R, Seiler-Mussler S, Lizzi F, Siriopol D, Balafa O, Shavit L, Loutradis C, Tripepi R, Tripepi G, Picano E, London GM, Zoccali C.**

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SA-PO871

Long-Term Course of Peri-Dialytic Blood Pressures in Hemodialysis and Online Post-Dilution Hemodiafiltration Patients

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Background: Data on the course of blood pressure (BP) changes over time in dialysis patients is scarce. We investigated the long-term course of the pre-dialytical and post-dialytical (peri-dialytical) systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and pulse pressure (PP), as well as the difference between these values (delta) in patients from 3 randomized controlled trials comparing conventional hemodialysis (HD) with online post-dilution hemodiafiltration (HDF).

Methods: Individual participant data (IPD) were pooled from the Estudio de Supervivencia de Hemodiafiltración (ESHOL, n=906), the Dutch Convective Transport Study (CONTRAST, n=714) and the French HDF study (Frenchie, n=391). Due to censoring only 1613 (80%) of the included 2011 patients had complete follow-up. After additional data were obtained, 2006 (99,8%) were available for the present IPD meta-analysis (Peters SAE et al. Nephrol Dial Transplant 2016 31 978). BP measurements were available every three months. Two-years changes were assessed with linear mixed models.

Results: Mean pre-dialytic SBP decreased by 0.09 mmHg/month (P<0.001) and post-dialytic SBP by 0.07 mmHg/month (P=0.005). Mean pre-dialytic DBP decreased by 0.12 mmHg/month (P<0.001) and post-dialytic DBP by 0.13 mmHg/month (P<0.001). Mean pre-dialytic MAP decreased by 0.11mmHg/month (P<0.001) and post-dialytic MAP by 0.11 mmHg (P<0.001). Mean pre-dialytic PP increased by 0.02 mmHg/month (P=0.064) and post-dialytic PP increased by 0.06 mmHg/month (P=0.004). The mean delta SBP, DBP, MAP and PP did not change significantly over time. None of the above mentioned parameters differed significantly between HD and HDF patients.

Conclusions: This is the first report comparing the longitudinal course of the peri-dialytical SBP, DBP, MAP and PP between HD and HDF patients. While both pre- and post-dialysis mean SBP, DBP and MAP decreased significantly over time and PP increased, differences between HD and HDF patients were not observed.

SA-PO872

The Course of Peri-Dialytic Blood Pressure over Time in Online Post-Dilution Hemodiafiltration Is Not Influenced by the Magnitude of the Convection Volume

Paul A. Rootjes,[1] Camiel L. de Roij van Zuijdewijn,[1] Peter J. Blankestijn,[2] Bernard J. Canaud,[3] Andrew Davenport,[4] Frans J. van Ittersum,[7] Muriel P. Grooteman,[1] Francisco Maduell,[5] Menso Nube.[6] on behalf of the HDF Pooling Project Investigators. *[1]VU University Medical Center, Amsterdam, Netherlands; [2]University Medical Center----, Utrecht, Netherlands; [3]FMC Deutschland GmbH, Bad Homburg, Germany; [4]Royal Free Hospital, London, United Kingdom; [5]Hospital Clinic Barcelona, Barcelona, Spain; [6]VU Medical Center, Bergen, Netherlands; [7]VU University Medical Center Amsterdam, Amsterdam, Netherlands*.

Background: Online post-dilution hemodiafiltration (HDF) is associated with a lower mortality rate than conventional hemodialysis (HD). The mechanism(s) behind this effect is (are) unknown. In a previous analysis on chronic HD and HDF patients we showed first, that pre- and post-dialytical (peri-dialytic) systolic blood pressure (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) declined over time, while pulse pressure (PP) increased. Second, differences between HD and HDF patients were not observed. Since the beneficial effect of HDF is highly dependent on the magnitude of the convection volume (CV), in the present analysis we investigated whether different CVs have a dissimilar influence on the course of peri-dialytic BP over time.

Methods: We used the pooled individual participant data (IPD) from the Spanish Estudio de Supervivencia de Hemodiafiltración (ESHOL, n=906), the Dutch Convective Transport Study (CONTRAST, n=714) and the French HDF study (Frenchie, n=391) (Peters SAE et al. Nephrol Dial Transplant 2016 31 978). The CV was divided in quartiles (<20L, 20-23L, 23-26L and >26L). Hereafter, we investigated whether the change in BP over time was different for these quartiles by using an interaction term (convection volume * time) in linear mixed models.

Results: The longitudinal courses of the pre- and post-dialysis SBP, DBP, MAP and PP were similar in the CV quartiles (P >0.05 for all interaction terms). The difference between pre- and post-dialysis values (delta) was also similar in all 4 categories.

Conclusions: The course of the peri-dialytical and delta SBP, DBP, MAP and PP over time in HDF patients is not related to the magnitude of the CV. Therefore, the lower mortality rate in HDF patients may not depend on a superior peri-dialytic BP regulation.

SA-PO873

Personalized Ultrafiltration Profile Design Using Crit-Line

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Background: Intradialytic hypotension (IDH) occurs in as many as 25%-50% of patients during fluid removal by ultrafiltration. We recently presented a novel approach for the design of personalized ultrafiltration rate (UFR) profiles. Our aim was to integrate this design with a parameter estimation algorithm for a patient's fluid volume dynamics during hemodialysis (HD) from Crit-Line hematocrit (HCT) measurements.

Methods: We used a validated fluid volume model during HD comprising intravascular and interstitial pools, microvascular refilling/filtration, and lymphatic flow. We used several 20-min segments of UFR and HCT (Fig. 2) data from an actual HD treatment (3.5L removed in 227 min) and advanced algorithms to estimate key model parameters: plasma volume, interstitial volume, red blood cell volume, and filtration coefficient. Based on the estimated parameter ranges (Fig. 1), a personalized UFR profile was designed to minimize max UFR level, maintain HCT below a critical HCT profile, and achieve same UF goal.

Results: The estimated model parameters in five segments of an HD treatment are consistent with expected physiological changes during HD (Fig. 1 left/bottom). These parameter ranges were used to design personalized UFR profile (right/top). Simulations of the fluid volume model with the designed UFR profile over the estimated range of model parameters confirmed expected outcomes: similar UF goal achieved with 17% lower max UFR and lower HCT increases (right/bottom).

Conclusions: The successful estimation of fluid volume model parameters during HD supports the design of personalized UFR profiles that could lead to reduction in the incidence of IDH events.

Funding: NIDDK Support

Segment	Plasma Volume (L)	Interstitial Volume (L)	Red-Blood Cell Volume(L)	Filtration Coefficient (L/min*mmHg)
1	3.15	15.09	1.44	0.0066
2	3.10	14.82	1.49	0.0064
3	3.00	14.00	1.59	0.0059
4	2.98	13.00	1.62	0.0058
5	2.96	11.87	1.64	0.0057

Fig. 1: Estimated model parameters

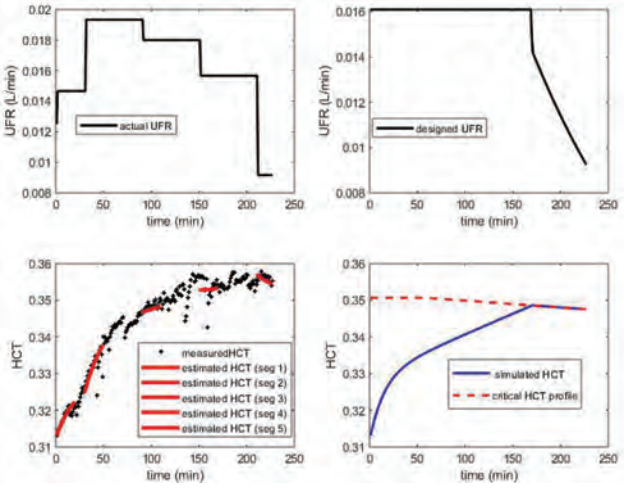

Fig. 2: Actual vs Designed UFR HCT dynamics

SA-PO874

Time-Integrated Fluid Load (TIFL) Predicts Left Ventricular Mass (LVM) reduction: Results from the Frequent Hemodialysis Network (FHN) Daily Trial

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Background: Serum sodium concentrations (SNa) less than 138 mEq/L act as effect modifiers to LVM reduction with increased hemodialysis (HD) frequency. Greater time-integrated fluid overload TIFL (incorporating interdialytic period length and increased fluid intake after Na-positive gradient HD) associates with LVM reduction (FHN Trial Group). We tested the interaction between the treatment effect of increased HD frequency on TIFL and change in LVM in the Daily Trial and evaluated, in the light of the "sick-cell" syndrome as a possible cause of low SNa, predictors of low SNa.

Methods: Treatment effects on LVM were analyzed in subgroups of subjects with a TIFL of ≤3 and >3 L*day. In a second step the interaction of the treatment effect with TIFL was tested using a mixed model. We measured CRP, Pentraxin, ICAM, IL-6 and -10, MCP-1, pre-albumin, TNF-Alpha, MPO at baseline of the FHN Daily Trial and compared between SNa greater or less than 138 mEq/L. Data presented as means and 95% CI.

Results: More frequent daily HD associated with a significant treatment effect on LVM when baseline TIFL was >3 L*day. The treatment effect on LVM showed a borderline significant interaction with TIFL [-5.8 (-15.0 to 3.5) g]. Significantly higher baseline CRP, IL-6, MPO, pre-albumin and pentraxin were found in the low SNa group, the intervention had no effect on inflammatory biomarkers.

Conclusions: Low SNa leads to increases in thirst and fluid intake, increasing TIFL and LVM. Decrease of TIFL by higher HD frequency, results in greater LVM reduction. A positive association between low SNa and inflammatory markers suggests inflammation to cause low SNa level and inflamed patients may benefit most from increased HD frequency.

Funding: NIDDK Support

LVM reduction [in g] as per TIFL

	Daily Trial (N=170)
TIFL ≤ 3 L*days	-5.6 (-21.5 to 10.44)
TIFL > 3 L*days	-26.0 (-39.4 to -12.6)

SA-PO875

Assessment of Plasma Refilling Rate in Dialysis Patients Using Plasma Body Weight Index Can Predict Intradialytic Hypotension

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Background: Intradialytic hypotension (IDH) is a major risk factor for mortality in hemodialysis (HD). IDH often occurs when plasma fluid removal outpaces plasma refilling rate (PRR) from the interstitial space. Increasing dry weight (DW) can easily increase PRR, but it can precipitate congestive heart failure (CHF). Plasma body weight index (PWI), calculated from plasma total protein (TP) concentration and body weight before and after HD, has been proposed as a convenient surrogate marker, which inversely correlates to PRR. Our aim was to determine if PWI can predict IDH, and if a combination with hANP can be used as a clinical index to determine relevant DW.

Methods: This study retrospectively examined records of 156 dialysis patients from December 30, 2015, to January 5, 2016 in Tachikawa Medical Hospital. IDH was defined by current KDOQI guidelines [a decrease in either systolic BP (SBP) ≥20 mmHg or mean arterial pressure≥10 mmHg as well as associated symptoms]. CHF was defined as patients with dyspnea and low SpO2 level (<96%). PWI was calcurated by using this formula: *PWI = [(post TP - pre TP)*100/post TP]/[(pre body weight - post body weight)*100/pre body weight].*

Results: IDH and CHF occurred in 28.2% and 7.7% of all patients, respectively. Patients with IDH had higher PWI levels than those without IDH (1.71±1.40 vs. 2.65±1.70, P = 0.007). PWI > 2.0 was predictive of high incidence of IDH (OR = 2.40, 95%CI, 1.12-5.12, P = 0.020), but was not associated with incidence of CHF (OR 1.00, 95%CI, 0.30-3.30, P = 1.000). On the other hand, hANP >100 pg/ml was predictive of high incidence of CHF (OR 3.52, 95%CI, 1.06- 11.71, P = 0.004), but not associated with incidence of IDH (OR 0.79, 95%CI, 0.37-1.71, P = 0.5504). Subdividing the patients into 4 groups by the two cut-off points of PWI and hANP revealed that in the cohort of PWI < 2.0/hANP < 100 pg/ml, there was no incidence of CHF and incidence of IDH was low (13.7%).

Conclusions: PWI is a useful marker to predict IDH. Evaluating hydration status by combining PWI and hANP ia a useful parameter to estimate DW.

Associations between PWI and IDH and CHF

	PWI ≥ 2.0 (n [%])	PWI < 2.0 (n [%])	OR (95% CI)	P Value
Intradialytic hypotension	32 (35.2)	12 (18.5)	2.40 (1.12-5.12)	0.0201
Congestive heart failure	7 (7.7)	5 (7.7)	1.00 (0.30-3.30)	1.0000

OR, odds ratio; 95% CI, 95% confidence interval.

SA-PO876

Agreement Between Spectra Hemoglobin and Crit-Line® Monitor Estimated Hemoglobin

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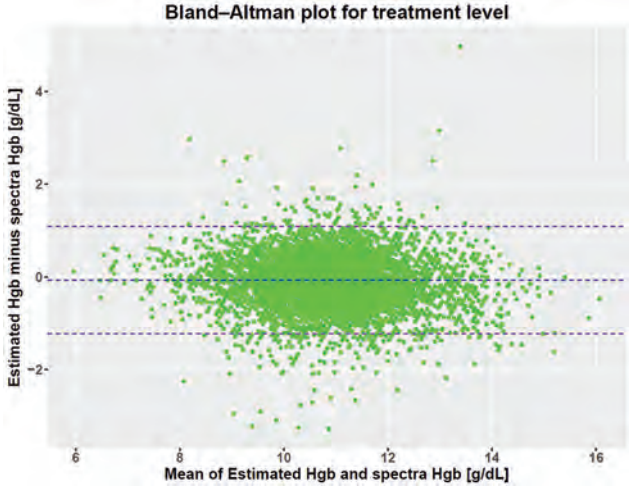
Background: Monitoring hemoglobin (Hgb) in hemodialysis is key in anemia management. Due to hemodilution, Hgb by Crit-Line® monitor ($Hgb_{CritLine}$) underestimates the pre-dialysis values measured by Spectra ($Hgb_{Spectra}$). An equation that considers blood volume, ultrafiltration rate, and saline dissipations can correct Hgb measured by Crit-Line ($Hgb^{CritLine}_{corrected}$). The aim of this study was to explore the concordance between the $Hgb_{Spectra}$ and $Hgb^{CritLine}_{corrected}$.

Methods: Pre-dialysis Hgb was measured by Spectra East, Inc. (Rockleigh, NJ, USA). ΔHgb ($Hgb_{Spectra}$ - $Hgb_{CritLine}$) and $Hgb^{CritLine}_{corrected}$ were estimated mathematically. The difference between $Hgb^{CritLine}_{corrected}$ and $Hgb_{Spectra}$ was denominated Hgb_{offset}. $Hgb_{CritLine}$ was determined by averaging the measurements between 0-2 minutes after the beginning of Crit-Line recording. Pre-dialysis blood volume was derived using anthropometric equations, then back-calculating the start of dialysis absolute blood volume based on the change in relative blood volume over the course of the treatment as measured by the Crit-Line® monitor and subtracting the saline infused (V_{saline} = 250ml). Saline's half-life was considered of 20min.

Results: 5731 hemodialysis treatments from 952 patients with $Hgb_{Spectra}$ and estimated $Hgb^{CritLine}_{corrected}$ measurements were analyzed. Hgb_{offset} average was –0.068g/dL, the standard deviation 0.59g/dL, and the bias -0.07g/dL. To asses the comparability between $Hgb^{CritLine}_{corrected}$ and $Hgb_{Spectra}$ measurements, the Hgb_{offset} was plotted against the mean of the two measurements in a Bland-Altman plot.

Conclusions: With Crit-Line Hgb correction for hemodilution, the $Hbg_{CritLine}$ values are on average identical to the $Hgb_{Spectra}$ and they share similar accuracy. This could be an opportunity in the future to replace Hgb laboratory measurements in the management of anemia.

Funding: Commercial Support - Fresenius Medical Care. Renal Research Institute



SA-PO877

Intradialytic Exercise Preconditioning: The Effect on Myocardial Stunning

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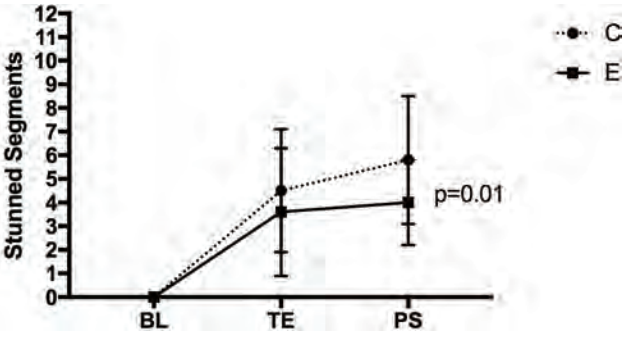
Background: Exercise preconditioning provides immediate protection against cardiac ischemia in clinical and pre-clinical studies. Intradialytic exercise (IDE) has been utilized to improve functional status in individuals receiving HD. The effect of intradialytic exercise on myocardial stunning is unknown.

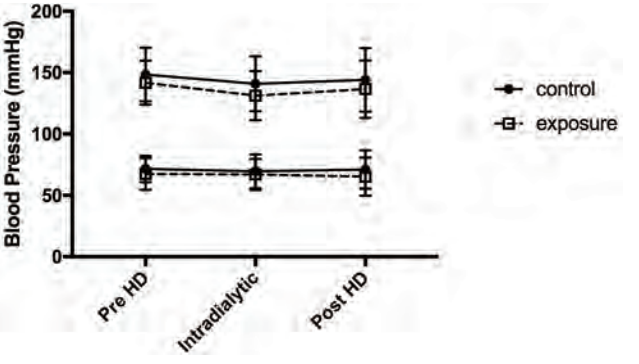
Methods: 19 adult patients participating in a clinical IDE program were evaluated over 2 HD sessions (control visit - no exercise, exposure visit - exercise). Echocardiography was performed, pre-HD, post exercise and at peak HD stress in each visit. Longitudinal strain (LS) for 12 left ventricular segments were generated using speckle-tracking software [EchoPac, GE], to assess the presence of HD-induced regional wall motion abnormalities (RWMA), indicative of myocardial stunning (>20% reduction in LS in two or more segments).

Results: Mean age was 59.2 and participants were 40% female with median dialysis vintage of 3.8 years. The number of stunned segments at usual exercise time was 4.5 (SD2.6) and 3.9 (SD2.8) in the control and exercise groups, respectively; p=0.168. The number of stunned segments at peak HD stress was 5.8 (SD2.7) and 4.0 (SD 1.8) in the control and exposed groups, respectively; p=0.012. Mean change in number of stunned segments post exercise between control and exposure sessions was -0.95 (SD 2.88). Mean change in number of stunned segments at peak HD was -1.8 (SD 2.8).

Conclusions: IDE significantly reduced HD-induced myocardial stunning at peak HD stress and was not associated with a reduction in intradialytic hypotension.



Number of RWMA at each echo timepoint(BL = baseline, TE = time of exercise, PS = peak stress)



Mean blood pressures

SA-PO878

The Effects of Intradialytic Exercise on the Improvement of Daily Physical Activity in Online Hemodiafiltration Patients

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Background: The mortality of hemodialysis (HD) patients treated with the novel online hemodiafiltration (OL-HDF) is better than conventional HD but is still higher than the healthy population. A low level of daily physical activity, associated with sarcopenia, uremic toxins, and functional impairment correlates with increased cardiovascular mortality. The effect of adding the intradialytic exercise program to improve daily physical activity and overall health status in patients particularly with online hemodiafiltration technique has yet to be explored.

Methods: Twelve OL-HDF treated patients (age 53.1±14.5 years, BMI 23.23 ± 5.5 kg/m^2) were randomly assigned to control or adding intradialytic exercise (IDX) group. The subjects in IDX group were trained with the customized exercise program to exercise, initiated by a multidisciplinary team, on a cycle ergometer (Figure 1) within the first hour of OL-HDF. Physical activity was measured in terms of the number of daily steps counted by a wrist-worn wearable triaxial accelerometer (Fitbit flex2®). The muscle mass and biochemical parameters were measured and compared at baseline and 6 months.

Results: The baseline physical activities measured by daily step count were 5,945±3715 and 6525±5389 steps (NS) in IDX and control groups, respectively. At 6 months, improvement of physical activity level in IDX group was greater than that in the control group (+1956.2 ± 2164.18 vs. -1302.92 ± 1956.03 steps, P = 0.021). The muscle mass changes were slightly higher, though non-significant, in IDX group [0.59 (IQR -0.58, 1.46) vs. -1.49 (-2.14, 0.28) kg., P=0.200]. Hemoglobin (+1.0 (-0.1,2.7) vs. -1.4 (-3.4,0.2) g/dL, P= 0.025) and albumin (+0.30(0.08, 0.50) vs. -0.15(-0.28, 0.05) g/dL, P=0.012) increased in IDX compared with the control group. The phosphate reduction was more favorable in IDX group (-1.95 (-2.80, -0.63) vs. -0.50 (-0.88,0.55), P=0.037).

Conclusions: Intradialytic exercise training as the add-on program for OL-HDF patients could improve daily physical activity as well as muscle mass and other metabolic controls. The regular intradialytic exercise program may contribute to reverse inactive behaviors and further improvement in the quality of life and cardiovascular mortality of dialysis patients.

Funding: Government Support - Non-U.S.

SA-PO879

Pedometers and Exercise in Dialysis

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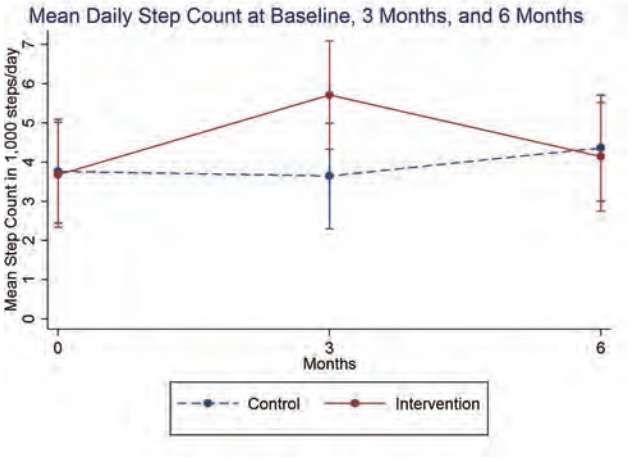
Background: Dialysis patients report very low levels of physical activity. We conducted a study using a pedometer based intervention to investigate whether it would result in increased physical activity and whether increasing activity could improve physical and endothelial function, heart rate variability (HRV), and symptom severity.

Methods: We conducted a randomized controlled trial of 60 patients receiving HD or PD. Patients were given a pedometer and instructed to record steps for one week. Patients were then randomized to either standard of care or a 12-week intervention program during which they were asked to record steps and given weekly activity goals. At baseline, 12 weeks, and 24 weeks (3 months after the intervention), we assessed physical function (SF-36 Physical Function scores, Short Physical Performance Battery), endothelial function (reactive hyperemia index with peripheral arterial tonometry), HRV, and symptoms (Dialysis Symptoms Index [DSI], KDQOL Vitality score).

Results: At 3 months, patients in the intervention increased average daily step count by 2,060 (95% CI 80; 4,060) compared to controls, though physical function, endothelial function, HRV, and symptoms did not change significantly. However, patients reverted to baseline levels of activity 3 months after the intervention. In post-hoc analyses increases in step count were associated with decreases in symptom burden (-0.38 symptoms on DSI per 1,000 steps), symptom severity (-1.34 points on DSI score per 1,000 steps), fatigue (2.33 points on KDQOL Vitality score per 1,000 steps), and increased HRV (2.29 ms SDNN per 1,000 steps).

Conclusions: Dialysis patients can effectively use pedometers to increase physical activity but may need continued counselling in order to maintain increases. We found preliminary evidence that increasing step counts may also lead to improvements in symptoms and heart rate variability.

Funding: NIDDK Support



SA-PO880

The Acute Effects of Intra-Dialytic Exercise on Arterial and Central Venous Oxygen Saturation and Oxygen Extraction Ratio

Diana Aguirre,[1] Daniel E. Ayala,[1] Armando Vazquez Avila,[1] Jesus Arellano,[1] Luis A. Mariscal,[2,1] Victor H. Gomez,[1] Israel Campos.[2,1] *[1]Hospital General "Dr. Miguel Silva", Morelia, Mexico; [2]NausLife Hemodialysis Clinics, Morelia, Michoacán, Mexico.*

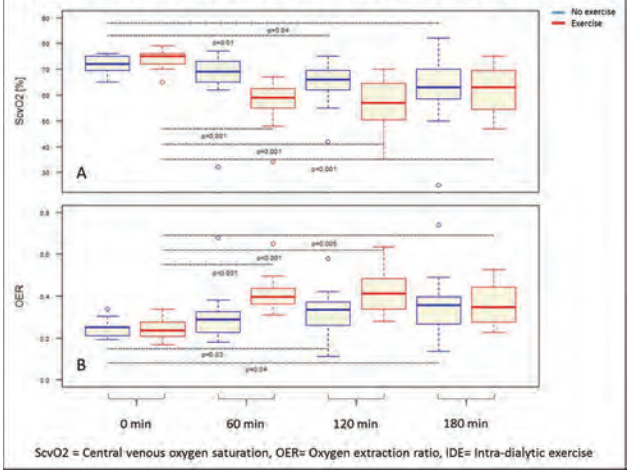
Background: Intra-dialytic exercise (IDE) improves cardiovascular function, physical function and quality of life. Arterial (SaO2) and central venous oxygen saturation (ScvO2) can be measured during hemodialysis (HD). The oxygen extraction ratio (OER) is the result from: SaO2-ScvO2/SaO2; its increment during HD has been associated with a higher mortality. The aim of this study was to explore the acute effects of IDE on SaO2, ScvO2 and OER.

Methods: Crossover study in maintenance adult HD patients. The ScvO2 by gas analyzer and SaO2 by pulse-oximetry were measured at 0, 60, 120 and 180 minutes during one HD treatment without IDE, same measurements were repeated in one HD treatment with IDE. The SaO2, ScvO2 and OER were compared at each time point and between treatments.

Results: 11 patients (22 HD treatments) were analyzed. The ScvO2 and OER trend during HD with and without IDE are reported (Figure 1). The ScvO2 median (P25, P75) with vs without IDE at 60 and 120 min were 59(55, 62.5) vs 69(65, 73) p=0.005; and 57(50.5, 64.5) vs 66(62, 69.5) p=0.04, respectively. OER median (P25, P75) with vs without IDE at 60 and 120 min were 0.39(0.36, 0.43) vs 0.28(0.22, 0.32) p=0.005, and 0.41(0.43, 0.48) vs 0.33(0.25, 0.37) p=0.05, respectively, no differences were found in SaO2.

Conclusions: The ScvO2 decreases during HD, this decline is deeper during IDE compare to non-exercise treatments. OER increases during HD and is higher during IDE compare to non-exercise treatments. Further studies are required to elucidate the oxygen dynamics during intra-dialytic exercise.

Figure 1. ScvO2 and OER trend across HD treatment with and without IDE



ScvO2 = Central venous oxygen saturation, OER= Oxygen extraction ratio, IDE= Intra-dialytic exercise

SA-PO881

Exercise During Dialysis Ameliorates the Decline in Plasma Volume by Ultrafiltration

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Background: Patients in hemodialysis (HD) remove the excess of water and Na+ by ultrafiltration (UF) that leads to an increase of hypotensive (Ht) episodes by a decline in circulating blood volumen (CBV). Exercise (EXE) leads an increase of CBV by mechanisms like redistribution of CBV and sympathetic activation. We evaluate the effects of acute moderate aerobic EXE in CBV during UF in comparison with sessions without EXE.

Methods: 19 CKD patients in regular HD (11 women, Age 40±6) were randomized for one HD session with EXE by bicycle pedaling without resistance in sitting position (P) during all the session or sedentary HD session (one in sitting P, in recumbent P or recumbent P with elastic socks). All patients received the four different sessions with BVM in line during all the session with exactly the same UF rate. Besides blood pressure and heart rate were registered.

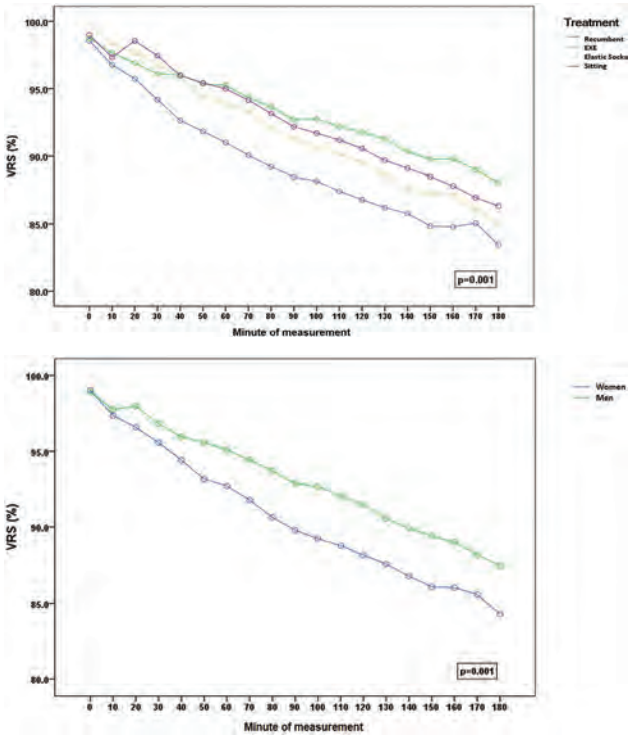
Results: We observed a lesser decline in CBV in the EXE HD session in comparison with sedentary HD. The difference were stadistically significant ($p<0.001$). In EXE HD we observed lesser Ht episodes (0 vs 13), and the fall in systolic and dyastolic pressure at the end of the session were lesser in EXE HD (-3 vs. 3.6 and -0.4 vs. 1.9 mmHg). Incidentally, it was observed that the effect of EXE during dialysis on the decline in CBV was clearer among males.

Conclusions: EXE during dialysis ameliorate the decline in plama volume by UF, especially in men.

Funding: Government Support - Non-U.S.

Clinical characteristics according to the intervention performed

	Sitting	Recumbent	Elastic socks	EXE	*P
Differential with dry weight	2.0 (0.93	2.2 (1.1)	2.0 (0.94)	2.1 (0.74)	0.90
KTV	1.47 (0.33)	1.45 (0.36)	1.46 (0.32)	1.49 (0.33)	0.98
Substitution (L)	19.5 (1.8)	19.7 (1.7)	19.4 (2.1)	19.3 (1.4)	0.93
Hypotension	36.8%	5.3%	26.3%	0	.007*



SA-PO882

Low BMI Is Associated with Higher Risk of Frequent Intradialytic Hypertension

Maurilo Leite,[1] Thays C. Pereira,[1] Renata M. Rodrigues,[1] Mahesh Krishnan.[2]
[1]DaVita-Brazil, Rio De Janeiro, Brazil; [2]DaVita, Inc, Denver, CO.

Background: Intradialytic hypertension (IDH) has been associated with high mortality and morbidity among hemodialysis (HD) patients. Factors such as fluid overload, dialysate sodium, clearance of anti-hypertensive drugs, and an endothelin effect have all been suggested to affect IDH. However, IDH has not been uniformly characterized: studies have defined IDH as a post-HD increase in systolic arterial pressure (SAP) occurring with differing monthly frequency. In this study we examined the associations between BMI and IDH ocurring with various monthly frequencies.

Methods: We followed 217 patients who were stable on HD for at least 90 days and evaluated the number of dialysis treatments affected by IDH (defined as pre- to post-HD increase in SAP of ≥ 10 mmHg, reaching values ≥ 140/90 mmHg) over 90 days. We assessed associations of IDH frequency (% of treatments affected) with patient gender, age, race, time on HD, as well as with hospitalizations and mortality over 6 months. Patients were stratified into 5 groups based on BMI (< 18.5, 18.5 to 24.9, 25 to 29.9, 30 to 35, and > 35 kg/m^2); numbers of patients experiencing IDH in at least 5% or at least 50% of treatments were assessed for each BMI group. Statistical tests applied were Chi-square and Pearson correlation.

Results: We found no significant correlation between IDH frequency and patient gender, age, or race. However, we found a positive correlation between IDH frequency and time on dialysis (r=0.17, *P*<0.01). No association of IDH frequency with hospitalization or mortality was observed. 78% of patients with BMI < 35 kg/m^{2}experienced IDH during at least 5% of treatments, compared with 100% of patients with BMI > 35 kg/m^2. In contrast, the proportion of patients who had 50% or more of treatments affected by IDH was strongly associated with BMI < 18.5 kg/m^2; RR: 3.2 (2.7-4.6).

Conclusions: Monthly frequency of IDH, observed over a period of 90 days in HD patients, was found to be slightly correlated with time on dialysis. Patients with BMI > 35 kg/m^2 experienced at least 1 episode of IDH during follow-up; patients with BMI < 18.5 kg/m^2 presented higher risk for IDH affecting ≥ 50% of HD sessions. Frequent IDH may contribute to high cardiovascular mortality and morbidity in HD patients with longer time on dialysis and lower BMI.

Funding: Commercial Support - DaVita Inc

SA-PO883

Continuous Intra-Access Pressure (IAP) Monitoring Helps Predict Intradialytic Hypotension (IDH)

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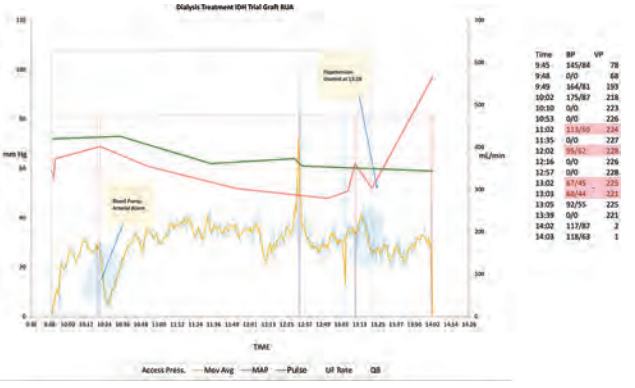
Background: IDH is a frequent hemodialysis (HD) complication associated with increased patient morbidity and mortality. Reliable IDH prediction that facilitates early intervention may reduce HD morbidity. We conducted a preliminary study exploring the hypothesis that that continuous IAP measurement using the Vasc-Alert™algorithm (Am J Kidney Dis. 2002;40(4):760-768)can predict IDH during hemodialysis (HD).

Methods: Fresenius™T2 dialysis machines (DM) were equipped with onboard computers and customized software to calculate IAP at 20-second intervals via Vasc-Alert. 24 DMs were monitored during routine use during 3 daily shifts 6 days weekly. Treatment and relative blood volume data, collected by the CLiC™ device, was digitally acquired and stored. IDH episodes and measures to resolve them including repositioning, saline administration, and ultrafiltration rate adjustmentwere charted, abstracted, and mergedwith the electronic medical records. IAP waveform was correlated with IDH. Duration and rate of decline of IAPs from a moving average of 10 readings were analyzed.

Results: 1,272,290 DM data points were collected from 2,290 HD treatments. A total of 139 IDH events (6%) were recorded and analyzed, yielding an equation demonstrating a linear correlation between IDH and IAP slope:*y*= –1986*x*+ 1136.5;RSqr= 0.69). An IAP drop ≥20 mm Hg over 15 seconds correlated with impending BP decrements. A representative example is shown (figure) where IDH at 11:02 correlated with a BP reduction from 145/84 mm Hg to 113/69 mm Hg. Subsequent IDH episodes at 12:02 and 13:02 were associated with abrupt, significant IAP slope declines.

Conclusions: The IAP slope and prolonged IAP declines of 20 mm Hg or more correlate with IDH during HD. Future analysis of relative blood volume may facilitate development of a more powerfully predictive model of IDH.

Funding: Clinical Revenue Support



SA-PO884

Intra-Dialytic Hypotension and Risk of Intra-Dialytic Cardiac Arrhythmia

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Background: Patients with end-stage renal disease receiving hemodialysis (HD) are at high risk of adverse cardiac events, including arrhythmia and sudden cardiac death. Intra-dialytic hypotension (IDH) is a common complication of HD and is associated with development of reduced myocardial perfusion, but its association with cardiac arrhythmia is unclear.

Methods: The Monitoring in Dialysis (MiD) study used implantable loop recorders to detect and continuously record all electrocardiographic data from maintenance HD patients (n=66 from the United States and India) over a six-month period. Negative binomial mixed effects regression models were fit to determine the association of IDH (decline in SBP >20 mmHg from pre-dialysis SBP) with the subsequent development of clinically significant arrhythmia (CSA) during the corresponding HD sessions.

Results: Average age was 56 years; 70% were male; and 65% were from the US. IDH occurred in 48% of 4,761 HD sessions, while 1.3% of total sessions were complicated by development of at least one intra-dialytic CSA. Participants who experienced IDH (vs. those with SBP decline ≤0mmHg) had a 9-fold greater rate of developing an intra-dialytic CSA (IRR 9.4; 95%CI 3.0-29.4).

Conclusions: IDH is common in maintenance HD patients and is associated with a greater risk of developing intra-dialytic CSA. Future studies investigating the effect of interventions to minimize IDH may wish to incorporate arrhythmia as a clinically relevant end-point.

Funding: NIDDK Support, Commercial Support - Medtronic

SA-PO885

Midodrine Is Effective in the Management of Intradialytic Hypotension Among Critically-Ill Patients with AKI (A Randomized Clinical Trial

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Background: Intradialytic hypotension commonly occurs among critically ill patients. Different tools were exploited to mitigate IDH. Midodrine showed promising results in small interventional studies. There was no randomized clinical trial to assess the efficacy

of midodrine. This study aims to evaluate the effectiveness of midodrine in a randomized placebo-controlled study among critically ill patients.

Methods: Eighty intensive care unit patients were eligible for this study. After IDH episode, they were randomized to either midodrine tablets or placebo. The count of IDH episodes, systolic blood pressure (SBP) and diastolic blood pressure (DBP) and lowest blood pressure were recorded. Mortality and adverse effects were recorded for both groups. The duration of the study was 30 days.

Results: eventy-five patients completed the study. Midodrine significantly decreased the count of IDH episodes. Both SBP and DBP were significantly higher among midodrine group. There was a reduction in mortality with midodrine therapy; the reduction was statistically insignificant (p = 0.43). The drug was tolerable with no adverse effects.

Conclusions: Oral midodrine therapy yielded beneficial results and was an adequate tool for management of IDH among critically-ill patients with the AKI.

SA-PO886

Midodrine in the Context of Intradialytic Hypotension: Association with Outcomes

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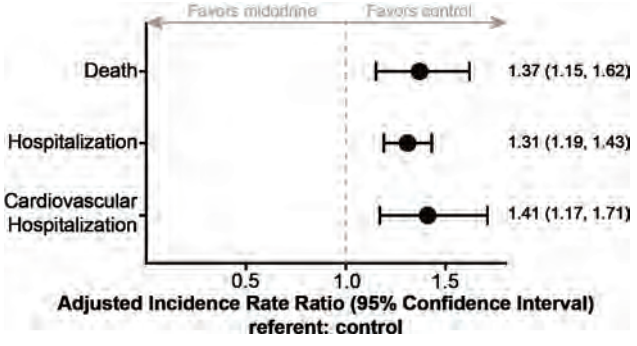
Background: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis, and is associated with significant morbidity and mortality. Off-label use of the alpha-1 andrenergic receptor agonist midodrine to reduce the frequency and severity of IDH is common. Small-scale clinical trial data support this practice; however, limited data exist with regard to real-world efficacy.

Methods: In this retrospective, observational study, clinical and hemodynamic outcomes were compared among patients who began midodrine (N=1046) and controls (N=2037) to whom they were matched on the basis of baseline pre-dialysis blood pressure, nadir intra-dialytic blood pressure and the frequency of intradialytic hypotension, all of whom were adults receiving in-center hemodialysis in the United States (July 2015-September 2016). All study data were derived from deidentified patient electronic health records. Outcomes were considered from the month following initiation of midodrine (or corresponding month for controls) until censoring for loss to follow-up or study end (30 September 2016). Outcomes were compared using adjusted Poisson or linear mixed models following intention-to-treat principles.

Results: Compared to non-use, midodrine use was associated with higher rates of death (adjusted incidence rate ratio 1.37, 95% confidence interval 1.15- 1.62), all-cause hospitalization (1.31, 1.19-1.43) and cardiovascular hospitalization (1.41, 1.17-1.71). With respect to hemodynamic outcomes, midodrine use tended to be associated with lower pre-dialysis systolic blood pressure (SBP), lower nadir SBP, greater fall in SBP during dialysis, and a greater proportion of treatments affected by IDH.

Conclusions: Although residual confounding may have influenced results, the observed associations are not consistent with a potent protective effect of midodrine with respect to either clinical or hemodynamic outcomes.

Funding: Commercial Support - This was a research project conducted by the DaVita Institute for Patient Safety and supported by DaVita Kidney Care



SA-PO887

Time-Specific Effects of Patient Factors on Intradialytic Systolic Blood Pressure Changes in Patients Receiving Maintenance Hemodialysis

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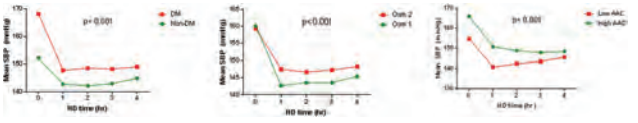
Background: Intradialytic systolic blood pressure (SBP) changes are affected by patient factors. However, the specific time point at which these factors predominantly affect blood pressure during a hemodialysis (HD) session is unknown.

Methods: Laboratory and HD data from previous 1 year were collected for 97 patients who were receiving maintenance HD. The subjects were classified into 2 groups according to diabetes mellitus (DM) status, abdominal aortic calcification (AAC) score, and the median values of serum hemoglobin (Hb), sodium (Na), albumin (Alb), and osmolality (Osm): DM vs. non-DM, high AAC (≥8) vs. low AAC (<8), Hb1 (≥10.17 g/dL) vs. Hb2(<10.17 g/dL), Na1(≥136.5 mEq/L) vs. Na2(<136.5 mEq/L), Alb1(≥3.93 g/dL) vs. Alb2(<3.93 g/dL), Osm1(≥312 mOsm/kg) vs. Osm2(<312 mOsm/kg). SBP measurements were standardized as SBP at 0 (SBP0), 1 (SBP1), 2 (SBP2), 3 (SBP3), and 4 (SBP4) hours. Intradialytic SBP changes were assessed on the basis of hourly SBP changes (ΔSBP_1: SBP0-SBP1, ΔSBP_2: SBP1-SBP2, ΔSBP_3: SBP2-SBP3, ΔSBP_4: SBP3-SBP4). Linear mixed regression analysis was used to identify patient factors associated with ΔSBP_1, ΔSBP_2, ΔSBP_3, and ΔSBP_4, respectively.

Results: The subject characteristics were as follows: number of females, 45; number of subjects with DM, 49; mean age, 59±15 years; HD duration, 69±64 months; AAC score, 8.0±7.7 (median, 6.0); and number of subjects with high AAC (≥8), 42. ΔSBP_1 was negatively associated with non-DM status (vs. DM) (β= -7.71, p=0.04), and positively associated with mean Hb level (β= 4.93, p=0.009). ΔSBP_2 was positively associated with high AAC (β= 5.22, p=0.001). ΔSBP_3 was positively associated with high AAC (β= 2.34, p=0.021), and negatively associated with mean albumin level (β= -4.19, p=0.044). ΔSBP_4 was positively associated with high AAC (β= 2.66, p=0.054), and negatively associated with mean Hb level (β= -2.90, p=0.008).

Conclusions: The effects of patient factors on intradialytic SBP changes during an HD session predominated at different time points and differed at an individual level.



SA-PO888

Intradialytic Hypotension in Hospitalized Patients: Does the Definition Matter?

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Background: Intradialytic hypotension (IDH) is a frequent, occurring from 15 to 50% of ambulatory sessions, and more frequent among hospitalized patients. Several complications can be associated with IDH: vascular access thrombosis, inadequate dialysis dose, fluid administration, early hemodialysis (HD) termination and mortality. Recently a large epidemiologic study, have shown that an absolute nadir systolic blood pressure (SBP)<90 mmHg was associated with mortality. However, several different definitions continue to be used in the literature and the clinical practice, preventing the appreciation of the effects of IDH and patient outcomes.

Methods: Patients from a prospective interventional study that included patients with albumin < 3 g/dl with AKI or ESRD who required fluid removal with HD were analyzed. Vital signs and ultrafiltration removal rate were recorded every 15 to 30 minutes during HD. The dialysis nurse recorded all symptoms associated with hypotension as well as interventions during the dialysis. We utilized 7 different classifications to determine hypotensive episodes.

Results: 65 patients completed 249 sessions; mean age was 58 (+/-12), 46 (70%) were male with a mean weight of 76 (+/-18) kg. Mean SBP and diastolic (DBP) at dialysis initiation were 126 (+/- 25) and 67.38 (+/-17), respectively. Presence of hypotension episode during a session varied from 12 (4.9%) to 111 (44%) according to the definition applied (Table). The HEMO definition, considering hypotension when an intervention results from an unspecific fall in BP, was more liberal, and occurred 50% more frequently than the KDOQI definition. Of the sessions with an absolute intradialytic nadir SBP<90 mmHg, only 30(56%) were followed by an intervention.

Conclusions: Intradialytic hypotension definitions that considered symptoms and interventions often miss episodes of hypotension that have been shown to be associated with increased mortality. Nadir based definitions of hypotension should trigger planned interventions and active questioning about symptoms, especially in hospitalized patients.

Funding: Commercial Support - Grifols

Intradialytic hypotension definition and frequency

Term	Definition	Sessions N(%)	Interventions N(%)
Nadir90	Min IHD SBP< 90 mmHg	53(21)	30(56)
KDOQI	Pre-HD SBP-min IHD ≥ 20 and symptoms of cramping, headache, lightheadedness, vomiting, or chest pain during HD	28(11)	18(64)
HEMO	Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration	42(17)	42(100)

SA-PO889

Intradialytic Hemodynamics and Autonomic Activity in Patients Without and with Blood Pressure Instability

Dvora Rubinger, Michal Dranitzki Elhalel, Dan Sapoznikov. *Hadassah Hebrew University Medical Center, Jerusalem, Israel.*

Background: The present study was undertaken to assess the intradialytic hemodynamics and autonomic activity in patients (pts.) without (*stable*) and with frequent hypotensive episodes (*unstable*).

Methods: Beat-to-beat systolic blood pressure (SBP) and interbeat intervals (IBI) were monitored using Finometer during a single constant blood flow hemodialysis (HD) session in 14 *unstable* and 18 age-matched *stable* chronic non-diabetic HD pts. Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were calculated using Modelflow simulation. LF/HF (the ratio of average IBI powers in the low (LF) and high (HF) frequency ranges) was considered to represent sympatho-vagal balance, whereas LF α (the ratio of IBI and SBP powers in the LF range) was considered to represent sympathetic activity. Positive correlation between IBI and SBP was considered representative of baroreflex

(*Baro)* activity. Repeated measures ANOVA was performed to assess time variations in both groups. Mixed design ANOVA was performed to assess differences in time variations between groups.

Results: During HD, SBP remained constant in both groups and there were no episodes of symptomatic hypotension. Comparable decreases in SV, CO and an increase in TPR were noted in all pts. LFα increased during HD in both *stable* and *unstable* groups. LF/HF increased in *unstable* and decreased in *stable* pts. *Baro* activity was predominant in the *stable* pts, in whom it consistently increased during HD, while in *unstable* pts. an increase in *Baro* activity was noted only at the beginning of dialysis (Figure 1).

Conclusions: Our data show that similar hemodynamic changes in *stable* and *unstable* pts are mediated by slightly different mechanisms. During HD, the sympatho-vagal balance is attenuated in *stable* and enhanced in *unstable* pts.SBP in *stable* seems to be predominantly controlled by *Baro*, while in *unstable* pts. SBP is controlled by both *Baro* and non-*Baro* mechanisms.

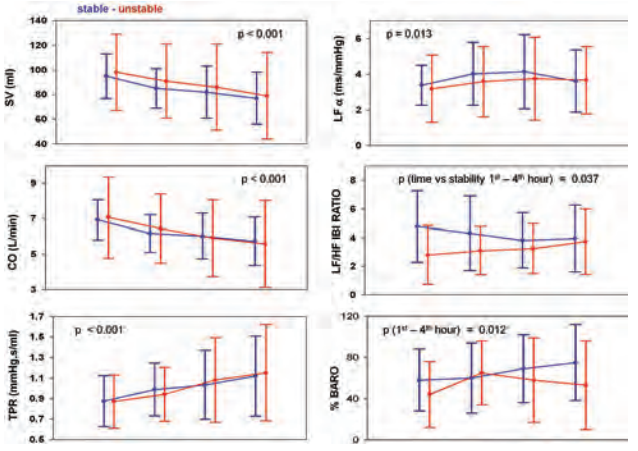

Figure 1.

SA-PO890

Blood Pressure Control and Days-in-Hospital Before and After Initiating Nocturnal In-Center Hemodialysis

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Background: Nocturnal dialysis (ND) can support longer sessions with lower ultrafiltration (UF) rates, compared to traditional in-center hemodialysis (HD). We compared UF rates, key blood pressure (BP) measures, and days hospitalized for ND patients before and after they initiated ND treatment.

Methods: We identified ND patients at a medium-sized dialysis organization to be those HD patients for whom ≥80% of dialysis sessions were ND sessions—starting at 6:30pm or later and lasted ≥5 hours—over the 3 months after their first ND session (≥20 sessions total) during 2010-16. Outpatient dialysis session and hospitalization dates were extracted for these patients within 12 months of ND transition (pre and post). BP measures included pre- and post-session sitting SBP and DBP, and minimum intradialytic SBP and DBP. Descriptive patient-month-level analyses of all outcomes were performed for all months with ≥7 sessions (i.e., still in care). We tested effects of ND care post-transition using generalized linear models with a Gaussian distribution and random intercepts and slopes; standard errors were clustered at the patient level.

Results: We identified 64 ND patients (4.7% of 1,357 eligible patients in care), with 354 pre-transition patient-months (3,974 sessions) and 496 post-transition patient-months (5,841 sessions). Post- vs pre-transition, we observed significant declines in UF rates (5.16 vs 9.34 mL/kg/hr, p<0.01), pre-SBP (154.1 vs 157.1 mmHg, p=0.05) and DBP (85.8 vs 88.0 mmHg, p=0.02), post-SBP (138.1 vs 142.6 mmHg, p<0.01) and DBP (77.0 vs 80.2 mmHg, p<0.01), and minimum intradialytic SBP (113.6 mmHg vs. 120.6 mmHg, p<0.01) and DBP (60.4 mmHg vs. 65.0 mmHg, p<0.01). We observed no change in hospitalized days per month (0.78 vs 0.82 days, p=0.80). Regression results accounting for patient-level clustering were similar, including a decline in UF rates (-3.57 mL/kg/hr, p<0.01) and no change in hospitalized days (-0.095 days, p=0.60) post-transition.

Conclusions: While patients experienced significant improvements in BP control both inter- and intradialytically after initiating ND treatment, we observed no change in their days hospitalized.

SA-PO891

Association Between Coronary Artery Calcification Density and Serum Magnesium Levels in Maintenance Hemodialysis (MHD) Patients

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Background: Coronary artery calcification score (CACS) is determined by the plaque area and density. In general population, calcified plaques with lower density are associated with higher risk of incident cardiovascular events, but report on calcification density in hemodialysis patients was scanty. This study aimed to analyze the association between coronary artery calcification density (CACD) and clinical parameters in MHD patients.

Methods: Methods: The subjects were 289 Japanese MHD patients. Total calcified area (area), CACD, CACS, laboratory parameters, and medication use were studied at baseline. The subjects were stratified into CACD level tertiles (T1–T3) and assessed by Kruskal-Wallis test. Regression analyses for CACD and CACS were examined, respectively. Independent variables were age, sex, diabetes, CVD, serum magnesium, phosphate, uric acid, C-reactive protein (CRP), low-density lipoprotein cholesterol (LDL-C) levels and use of proton pump inhibitors (PPI) or sevelamer hydrochloride. Spearman's correlations of the area and CACS or CACD were also analyzed, respectively.

Results: Among all patients, the mean age was 65±13 years, 37.2% were diabetics, and the median dialysis vintage was 72±99 months. The values of CACD of T1 (n=96), T2 (n=96), and T3 (n=97), were 3.61<, 3.62-3.89, and >3.90, respectively. The patients in T3 exhibited significantly higher serum magnesium, serum CRP and LDL-C levels (P<0.05). Multivariate regression analysis for CACD showed that age, diabetes, CVD [β 0.13, 95% confidence interval (CI) 0.00-0.12], and serum magnesium level [β 0.12, 95% CI (0.00-0.13)] were significantly related factors (P<0.05). While, multivariate regression analysis for CACS showed that age, diabetes, CVD [β 0.13, 95% CI 0.00-0.13], serum phosphate level [β 0.13, 95% CI (0.01-0.22)] were significantly related factors (P<0.05). CACS was correlated with total area (r = 013, P < 0.05), but the correlation between CACD and total area was not significant (r = 013, *P=0.07*).

Conclusions: CACD was significantly associated with serum magnesium levels, while CACS was significantly associated with serum phosphate levels in MHD patients. This may have a distinct clinical implication especially for coronary events.

SA-PO892

Pulmonary Artery Catheterization and Coronary Care Unit Location Predict Higher Incidence of Thrombocytopenia in Patients Receiving Continuous Veno-Venous Hemodialysis

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Background: Thrombocytopenia can occur in as much as 70% of patients receiving continuous renal replacement therapy (CRRT). The extent and temporal relation of thrombocytopenia is poorly understood. We recognized a high incidence of CRRT-related thrombocytopenia in the coronary care unit (CCU) at our institution. The purpose of our study was to compare the incidence of thrombocytopenia in patients receiving CRRT in the CCU and medical intensive care unit (MICU) and identify differences in risk factors for CRRT-related thrombocytopenia.

Methods: We performed a retrospective observational study of all patients admitted to the CCU and MICU of the Johns Hopkins Hospital who received CRRT for any reason between June 2010 to June 2017. Thrombocytopenia was defined as a decrease in platelet count of ≥ 50% within 72 hours of initiation of CRRT. The exclusion criteria included platelet count < 100 x 10^9 / liter prior to initiation of CRRT, decrease in platelet count of > 30% in the 48 hours prior to initiation of CRRT, duration of CRRT < 48 hours and death within 48 hours of CRRT initiation.

Results: We identified 795 patients who received CRRT in the CCU and MICU over a 7 year time period, 298 in the CCU and 497 in the MICU. 65 patients in the CCU and 67 patients in the MICU met inclusion criteria. The patients were well matched based on age, sex, race, comorbid illness and APACHE II score. There was a significant difference between the rates of those patients with a history of coronary artery disease (CAD) (55.8% vs 21.4%, P<0.001) and congestive heart failure (CHF) (84.9% vs 29.1%, P<0.001) in the CCU and MICU, respectively. Development of CRRT-related thrombocytopenia was seen in 22.5% of CCU patients compared to 13.9% of MICU patients. On adjusted MLoR, the odds ratio for development of thrombocytopenia-related CRRT based on CCU location was 2.5 (95% CI 1.4-4.5, P< 0.005). Patients with pulmonary artery catheterization were more likely to develop thrombocytopenia (OR 2.9; CI 1.1-7.9, P< 0.05).

Conclusions: The incidence of CRRT-related thrombocytopenia appears to be higher in the CCU as compared to the MICU. PA catheterization was significantly-associated with CRRT-related thrombocytopenia and requires further investigation.

Funding: Private Foundation Support

SA-PO893

Soluble Urokinase Plasminogen Activator Receptor Is Associated with Coronary Artery Calcification and Cardiovascular Disease in Patients Undergoing Hemodialysis

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Background: Cardiovascular disease (CVD) is an important cause of morbidity and mortality in hemodialysis patients. Vascular calcification is thought to play an important role in causing CVD. Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker strongly predictive of cardiovascular outcomes in the pathogenesis of diabetic patients with renal disease treated with hemodialysis. We investigated the relationship between suPAR and coronary artery calcification (CAC) in patients undergoing maintenance hemodialysis.

Methods: A total of 99 adult hemodialysis patients were enrolled in this study. Plasma samples were analyzed for suPAR with an enzyme-linked immunosorbent assay and the CAC score was determined with multidetector computed tomography. The occurrence of cardiovascular events and all-cause mortality during follow-up were recorded from January 1, 2010 to June 1, 2016.

Results: In 99 patients treated with maintenance hemodialysis, 91 (91.9%) had varying degrees of CAC, and suPAR correlated positively with the CAC score in a Spearman analysis. In a mean follow-up period of 33 months, 36 patients (36.4%) experienced at least one cardiovascular event. When the quartiles of suPAR concentrations were used as the cutoff points for a subgroup analysis, the incidence of CVD and all-cause mortality was much higher in the higher quartiles of suPAR. In a univariate Cox regression analysis, high suPAR was a risk factor for CVD and all-cause mortality.

Conclusions: suPAR is associated with the CAC score and is a risk factor for new-onset CVD in patients undergoing hemodialysis.

Funding: Government Support - Non-U.S.

SA-PO894

The Relationship Between Uric Acid and New-Onset Cardio-Cerebrovascular Disease in Maintenance Hemodialysis Patients

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Background: Serum uric acid (SUA) has been found to be a new marker of cardiovascular risk in patients with chronic kidney disease. In hemodialysis patients, the relevant studies are rare, and the conclusions were controversial. The aim of this study was to investigate the relationship between SUA and new-onset cardio-cerebrovascular disease in maintenance hemodialysis patients.

Methods: 96 maintenance hemodialysis patients who received hemodialysis more than 3 months were analyzed retrospectively between Aug. 2016 and Nov. 2017 in Beijing Tsinghua Changgung Hospital, including 66 males and 30 females. 44 (45.8%) patients had diabetes. The average age were 60.4±13.6 years (27 to 86 years old), and the average duration of dialysis was 3.0±3.5 years (6 months to 17 years). The basic characters of patients and new-onset cardio-cerebrovascular diseases during the period were recorded. Pre-dialysis laboratory tests were observed monthly. Patients were divided into two groups according to serum uric acid level as non-HUA group (155μmol/L<female≤357μmol/l or 208μmol/l<male≤428μmol/l), HUA group (>357μmol/l for female or >428μmol/L for male) respectively. SPSS 20.0 software was used to analyze the relationship between serum uric acid levels and new-onset cardio-cerebrovascular disease.

Results: 1. The mean pre-dialysis uric acid was 444.68±67.43umol/L, the prevalence of hyperuricemia was 68.75% (n=66). The prevalence of female (30, 100%) were significantly higher than male (36, 54.5%), $P<0.01$. 2. Multivariate logistic regression analysis showed that simultaneous hyperuricemia and diabetes were risk factors for new-onset cardio-cerebrovascular disease (OR=4.251, 95% CI 1.241-14.567, $P=0.021$). In diabetic patients, serum uric acid levels (OR=1.004, 95%CI 1.000-1.008, $P=0.040$) and ferritin (OR=1.022, 95% CI 1.004-1.041, $P=0.017$) were risk factor for new-onset cardio-cerebrovascular disease.

Conclusions: Higher serum uric acid was a risk factor for new-onset cardio-cerebrovascular disease in maintenance hemodialysis patients with diabetes.

SA-PO895

Mitral Annular Calcification (MAC) in Stage 5 CKD on Dialysis Therapy (CKD-5D)

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Background: MAC is a degenerative process involving the mitral valve and is a marker of advanced cardiovascular disease. Prevalence in the general population is upto 10% and increases in advanced age, females, systemic hypertension, hypercholesterolemia, diabetes mellitus (DM), atrial fibrillation, chronic kidney disease, end stage renal disease (upto 40%) and mitral valve prolapse. MAC has also been found in Egyptian mummies as a marker of atherosclerosis in the Horus study. The aims of this study were to assess the prevalence of MAC in CKD-5D patients and correlate with patients' characteristics.

Methods: Echocardiograms were obtained in 84 hemodialysis patients. Association of MAC with patient age, DM, Ischemic Heart Disease (IHD), duration of dialysis, smoking, dyslipidemia, serum calcium and phosphorus (PO4), Intact Parathyroid Hormone (iPTH) was studied. The individual highest values of serum PO4 and iPTH in the course of this study were used. Data was analysed using IBM SPSS v. 22.

Results: The mean age of the patients was 63.38 ± 12.3 years and 48(57%) were males. 36(43%) patients were females. 68 patients(81%) had DM and 79(94%) had hypertension. MAC was present in 37 out of 84(44%) patients. 64(72%) were diagnosed with IHD. The presence of MAC correlated significantly with IHD(Odds Ratio 6.42, p = 0.006). Mean follow up of the patients was 30.30 ±29.22 months and 37(44%) of the patients suffered mortality during this period. Patients who had been on dialysis for longer than 36 months were also found to be at elevated risk of developing MAC (OR=3.32, p=0.019). Among these findings we also saw that patients with the following risk factors: serum PO4 greater than 5.5 (OR=2.03), DM (OR=1.95), HTN (OR=3.35), Age >60 (OR=1.83), AFIB (OR=1.28); had an observable increase in incidence of MAC with time but they weren't statistically significant. There was no correlation between MAC and serum Calcium and iPTH.

Conclusions: MAC is common in hemodialysis patients and correlates significantly with IHD. Etiology of MAC in ESRD is multifactorial and needs to be analyzed further. Our findings support the recommendation by Kidney Disease Improving Global Outcomes (KDIGO) 2017 guidelines on Mineral and Bone Disease on the use of echocardiography for the detection of valvular calcification.

SA-PO896

Involvements of AGEs on Vascular Calcification in Hemodialysis Patients

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Background: Vascular calcification is one of the strong risk factors for cardiovascular events and mortality in chronic kidney disease (CKD) patients. Advanced glycation end products (AGEs) are known to be accumulated in diabetes and/ or CKD patients and contributing to the development of vascular complications such as the arteriosclerosis and vascular calcification. However, the mechanisms why and how AGEs are increased in patients with hemodialysis and its precise roles on the development of vascular calcification are remained to be elucidated.

Methods: To address this issue, we investigate the relationship among the serum levels of AGEs and metabolic factors in 37 chronic hemodialysis patients in our hospital. We also evaluated the relationship between AGEs levels and vascular calcification assessed by agaston score and abdominal aorta calcification score (ACI) in the abdominal CT.

Results: Serum AGEs levels are significantly associated with not only age, presence of diabetes and peripheral artery disease (PAD), geriatric nutritional risk index (GNRI), and inflammatory markers such as IL-6, TNF-alpha but also agaston score and ACI. Moreover, retrospective analysis reveals that annual increasing rates of vascular calcification score are tended to be associated with AGEs in addition to age, presence of diabetes, and TNF-alpha levels.

Conclusions: These observations strongly suggest that chronic inflammatory responses may be involved in AGEs formation in chronic hemodialysis patients and accumulated AGEs may contribute to the development of vascular calcification and cardiovascular disease such as PAD.

SA-PO897

Performance of Stroke Risk Scores in Dialysis Patients

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Background: Dialysis patients have an increased ischemic stroke risk. Stroke risk scores, including the CHADS2, ATRIA and CHA2DS2VASC, have been developed to identify patients with an increased stroke risk in patients with atrial fibrillation allowing for personalization of vitamin K antagonist prescription. In the original articles, CHADS2 (C-statistic 0.82), ATRIA (C-statistic 0.73) and CHA2DS2VASC (C-statistic 0.67) had reasonable predictive abilities. However, the predictive performances of these stroke risk scores have not been validated in dialysis patients. Therefore, the aim of this study was to validate existing stroke risk scores in dialysis patients.

Methods: A total of 755 incident dialysis patients from the NECOSAD study were prospectively followed for validated ischemic stroke within five years of dialysis. Hazard ratios with 95% confidence intervals (CIs) were calculated using Cox proportional hazards analyses for high and intermediate risk scores as compared with low risk scores for the CHADS2 (low risk= 0, intermediate risk=1-2 and high risk= ≥3), ATRIA (low risk= 0-5, intermediate risk=6 and high risk=≥7) and the CHA2DS2VASC (low risk= 0, intermediate risk=1 and high risk= ≥2). Furthermore, we evaluated the discriminative performance of these bleeding risk groups by calculating Harrell's C-statistics.

Results: During a median follow-up of 2.0 years (interquartile range 0.9-3.7), 58 (7.7% of all patients) first ischemic stroke events occurred. Of the 755 patients, 14% were classified as high risk by the CHADS2, 28% by the ATRIA and 72% by the CHA2DS2VASC. A high risk score as compared with a low risk score was associated with a 8.2-fold (95% CI 1.1-63.1) increased ischemic stroke risk for the CHADS2 and a 2.2-fold (95% CI 1.3-3.9)

increased ischemic stroke risk for the ATRIA. A high CHA2DS2VASC risk score as compared with an intermediate risk score was associated with a 8.7-fold (2.1-35.7) increased ischemic stroke (no stroke events in low risk group). The C-statistics were **0.59** for the CHADS2, **0.61** for the ATRIA and **0.62** for the CHA2DS2VASC.

Conclusions: In this prospective cohort with validated data on ischemic stroke, we showed that the CHADS2, ATRIA and CHA2DS2VASC had poor predictive abilities. Therefore, these stroke risk scores may not be useful for guiding individual decision-making in dialysis patients.

SA-PO898

DNA Methylation of Klotho Promotor Gene Is Associated with Cardiovascular Disease and Malnutrition in Patients Under Hemodialysis

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Background: Cardiovascular disease (CVD) and protein-energy wasting are common in patients under hemodialysis (HD). While multiple factors are associated with those comorbidities, we hypothesized that gene silencing, including alteration of epigenome might influence the comorbidities in HD patients. Thus, the aim of this ongoing study is to assess the prevalence of epigenetic modifications of Klotho, aging-related genes, and its association of comorbidities.

Methods: Whole blood samples were drawn in 131 prevalent HD patients and genomic DNA were purified from white blood cells. Epigenetic modifications of Klotho promotor gene were defined by methylation of CpG sites. Extracted DNA were modified by bisulfate treatment and then the methylated sequences were selectively amplified by methylation-specific PCR. The products were visualized by agarose gels and were quantified. Patient characteristics, complication and baseline laboratory data were recorded.

Results: Epigenetic analysis had performed in one hundred and twenty-five patients of 131. Of 125, 48 patients showed the DNA methylation of Klotho promotor gene. Patients with Klotho gene methylation had high prevalence rate of CVD such as acute coronary syndrome and myocardial infarction, and low levels of serum albumin and creatinine and geriatric nutritional risk index compared with those without Klotho gene methylation.

Conclusions: Epigenetic modifications of Klotho promotor gene may be associated with CVD complication and malnutrition in patients under HD.

SA-PO899

Blood Myostatin Levels Are Related with Abdominal Aortic Calcification in Dialysis Patients

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Background: Myostatin which is a member of the transforming growth factor-β superfamily, regulates synthesis and degradation of skeletal muscle protein and it is up-regulated in the skeletal muscle of chronic kidney disease (CKD) patients. There are few studies on relationship between myostatin levels and vascular calcification, important risk factors for cardiovascular disease in CKD. The aim of this study was to assess the association between serum myostatin levels and abdominal aortic calcification (AAC) in patients with dialysis.

Methods: In this cross-sectional study, 71 outpatients undergoing dialysis were included. We assessed AAC semiquantitatively from the lateral lumbar spine obtained using plain radiograph. Serum myostatin level was determined by commercially available enzyme-linked immunosorbent assay and divided by median for analysis.

Results: Our study included 37 hemodialysis patients and 34 peritoneal dialysis (PD) patients with a median age of 59.0 years and a median myostatin level of 4991.4 pg/mL. Patients with low myostatin level were older and had a higher proportion of men, PD, and AAC scores ≥ 5 than those with high myostatin level. The median myostatin level for patients with AAC scores ≥ 5 was 4073.5 pg/mL, whereas that for AAC scores <5 was 5838.6 pg/mL. Age and AAC scores showed a significantly negative correlation with myostatin levels. After adjustment for potential confounding factors, including age, gender, diabetes mellitus, dialysis vintage, dialysis modality, osteoprotegerin, and AAC score ≥ 5, the presence of AAC was significantly and negatively associated with serum myostatin levels.

Conclusions: Low serum myostatin levels were associated with elevated AAC scores in dialysis patients. Further studies are necessary to determine the significance of measuring serum myostatin level in patient with dialysis.

SA-PO900

A Global Study Assessing Albumin Levels on Expanded Hemodialysis

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Background: Expanded hemodialysis (expHD) utilises a new form of hemodialysis membranes which enable more effective removal of middle and large molecular weight uremic toxins. These medium cut-off (MCO) membranes have pores which are significantly larger and more uniform than conventional high flux dialysis membranes but have the potential to allow some albumin leak. The purpose of this study was to assess expHD's effect on patients' pre-dialysis serum albumin levels over 6 months.

Methods: Patients receiving expHD were identified from dialysis centres in North and South America, Europe and Australasia. Details of basic demographics, dialysis prescription, laboratory parameters and recombinant erythropoietin dose were captured retrospectively.

Results: Data was available for 56 patients from 5 centres in Brazil, Canada, France, Italy, New Zealand and the United Kingdom. Median age was 67 years (range 23-91), 69% were male, 41% were diabetic, average time on hemodialysis was 55 months (10-215); median dry weight was 76 kg (44-124). 55% received dialysis on the larger MCO membrane dialyzer (Theranova 500 ©). Average dialysis prescription was: 4 hours (range 4-5.5) with Qb 300 ml/min (250-400) delivering an average Kt/V of 1.4 (1-2.5). Pre-dialysis serum albumin levels over the study period are presented in the table. No significant changes in albumin levels at 3 or 6 months from baseline are observed, p=0.42 and 0.66 respectively. CRP and haemoglobin levels were 4 mg/L (1.5-16) and 11 g/dL (8.2-14.2) pre-MCO use and 6 (1.5-25) and 11.3 (8.1-13) at 6 months respectively. Recombinant erythropoeitin dose increased in 15%, remained the same in 35% and decreased in 50% of participants over the observation period.

Conclusions: ExpHD did not result in any significant change in pre-dialysis serum albumin concentrations over 6 months treatment. Over this observation period, inflammatory markers and haemoglobin levels were stable but of potential interest 50% of the population had a reduction in erythropoietin dose.

Serum albumin levels

	Serum albumin (g/dL)			
	Pre-MCO	1 month	3 months	6 months
Median	3.7	3.5	3.6	3.7
Min	2.8	2.8	2.9	2.8
Max	4.5	4.6	4.5	5.1

SA-PO901

Outcome of Open Heart Surgery in ESRD Patients: A Single Center Experience for 16 Years

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Background: Mortality risk for cardiovascular disease is extremely high in ESRD patients. Nevertheless, dialysis patients are often undertreated due to the higher risk of operation or intervention compared to the general population. However, there are few studies comparing postoperative mortality and morbidity between dialysis and non-dialysis patients in Korea.

Methods: A retrospective analysis of 2,432 patients who underwent open heart surgery from 2002 to 2017 was performed to determine the mortality and morbidity after cardiac surgery in dialysis patients. Of total patients, we obtained comorbidities, NYHA classification, laboratory data, surgical method and postoperative outcomes from the two groups; dialysis group consisting of 38 patients with ESRD undergoing maintenance dialysis and control group consisting of 78 age-, sex-, and status of diabetes- matched control with normal kidney function.

Results: Dialysis group showed significantly higher postoperative mortality rate compared to the control group (18.4% versus 2.6%, P= 0.005). Dialysis group presented with more comorbidities, worse functional class of heart failure than control group. Urgent operation was more frequent (68.4% vs 32.1%, P = 0.000) in dialysis group, but there were no differences in the type of procedure between both groups. The postoperative hospitalization and time in ventilator were significantly increased in dialysis group (OR 4.631, P = 0.034; OR 7.617, P= 0.002). However, there were no significant difference in complication rate including rate of pneumonia, sepsis, stroke, wound infection, arrhythmia, bleeding, heart failure, except pulmonary edema and postoperative CRRT.

Conclusions: Dialysis patients showed higher in-hospital mortality rate compared to the control patients. The duration of postoperative hospitalization and time in ventilator were significantly increased in dialysis group. In dialysis patients, various comorbidities as well as dialysis itself may have contributed to the increase in hospital mortality. However, postoperative complications related to surgery were not significantly different between the two groups.

SA-PO902

The Hemodialysis Outcome Assessment: Troponin I Measurement Study

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Background: The impact of hemodialysis (HD) on cardiac biomarkers is unclear. The objectives of this study were to 1) To evaluate the intradialytic variability of high sensitivity troponin I (hs-TnI), galectin 3 (gal3) and human fatty acid binding protein (hfabp) and 2) To determine the factors associated with these changes.

Methods: In this prospective cohort study, hs-TnI, gal3 and hfabp were measured pre and post-HD for one week every month for 6 months in 178 prevalent adult HD patients with at least 2 HD treatments per week from a tertiary HD unit in Hamilton, Canada. Multilevel linear regression with HD treatments clustered within patients was performed to determine independent predictors of post-dialysis hs-TnI, gal3 and hfabp.

Results: The median (interquartile range) difference in pre and post-HD hs-TnI was -1ng/L (-2ng/L to +1ng/L) and the mean (standard deviation) differences in gal3 and hfabp were -38.06ng/mL (16.97ng/mL) and -20.85ng/mL (11.40ng/mL) respectively. Increases in hs-TnI, gal3 and hfabp were associated with ultrafiltration with B coefficients of +0.991ng/L, +1.053ng/mL and +1.877ng/mL per liter of fluid removal respectively. A change in hs-TnI was not associated with the total blood processed per HD session while decreases in gal3 and hfabp were associated with the total blood processed with B coefficients of -0.139ng/mL and -0.072ng/mL per liter of blood processed respectively. Dialysis length was associated with a decrease in all three cardiac biomarkers with B coefficients of -0.025ng/L for hs-TnI, -0.020ng/mLfor gal3 and -0.011mg/mL for hfabp per minute of HD.

Conclusions: Gal3 and hfabp decrease during dialysis while hs-TnI does not change. Increases in hs-TnI, gal3 and hfabp during HD are associated with ultrafiltration. Decreases in gal3 and hfabp during HD are associated with the total blood processed per HD session while hs-TnI is not.

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Table: Post-dialysis cardiac biomarker multivariate linear regression models

	hs-TnI				galectin-3				hfabp			
	B	P value	95% CI		B	P value	95% CI		B	P value	95% CI	
Age (per year)	-0.005	0.799	-0.048	0.037	-0.022	0.257	-0.059	0.016	-0.022	0.306	-0.066	0.021
Gender (male)	**1.337**	**0.036**	**0.091**	**2.584**	**-1.226**	**0.031**	**-2.342**	**-0.110**	**-2.333**	**0.000**	**-3.608**	**-1.059**
Ethnicity (non-white)	-1.297	0.112	-2.899	0.304	-0.647	0.387	-2.111	0.818	**-1.879**	**0.026**	**-3.535**	**-0.223**
Diabetes	**1.650**	**0.012**	**0.356**	**2.945**	**2.096**	**0.000**	**0.934**	**3.257**	1.263	0.061	-0.060	2.587
Heart failure	-1.063	0.412	-3.603	1.478	-0.232	0.838	-2.463	1.998	-0.216	0.868	-2.765	2.333
Coronary artery disease	**-1.953**	**0.008**	**-3.400**	**-0.506**	0.247	0.708	-1.043	1.536	0.282	0.707	-1.189	1.754
Cerebrovascular disease	0.137	0.888	-1.763	2.036	0.829	0.329	-0.834	2.492	0.089	0.929	-1.861	2.038
Peripheral vascular disease	-1.169	0.199	-2.953	0.616	-0.093	0.909	-1.505	1.690	1.239	0.184	-0.590	3.067
Residual renal function	0.242	0.743	-1.202	1.685	**-1.768**	**0.008**	**-3.084**	**-0.452**	-0.727	0.344	-2.233	0.779
Dialysis frequency >3x weekly	-0.032	0.972	-1.831	1.767	0.993	0.216	-0.579	2.566	0.481	0.598	-1.307	2.269
Dialysis time (per minute)	**-0.025**	**0.025**	**-0.048**	**-0.003**	**-0.009**	**0.020**	**-0.017**	**-0.001**	**-0.011**	**0.039**	**-0.022**	**-0.001**
Exeltra	-0.955	0.271	-2.656	0.746	**-2.512**	**0.000**	**-3.659**	**-1.364**	**-4.905**	**0.000**	**-6.372**	**-3.439**
Toray	0.096	0.943	-2.523	2.715	-0.881	0.392	-2.899	1.136	-1.638	0.189	-4.082	0.806
Ultrafiltration (per L)	**0.991**	**0.000**	**0.528**	**1.453**	**1.053**	**0.000**	**0.887**	**1.220**	**1.877**	**0.000**	**1.647**	**2.106**
Total blood processed (per L)	0.017	0.490	-0.032	0.066	**-0.139**	**0.000**	**-0.156**	**-0.122**	**-0.072**	**0.000**	**-0.095**	**-0.049**
intradialytic hypotension (SBP<90mmHg)	-0.402	0.435	-1.411	0.607	-0.119	0.491	-0.459	0.220	**-0.522**	**0.031**	**-0.997**	**-0.047**
Pre-dialysis biomarker (per unit/volume)	**1.128**	**0.000**	**1.122**	**1.133**	**0.235**	**0.000**	**0.223**	**0.246**	**0.637**	**0.000**	**0.623**	**0.650**

Note: hs-TnI= high sensitivity troponin I, B = beta coefficient, CI = confidence interval, L=liter, SBP=systolic blood pressure

SA-PO903

Plasma Levels of Endocan in Patients with ESRD on Hemodialysis as Biomarker for Prediction of Cardiovascular Disease

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Background: Endocan, a proteoglycan which is a potential biomarker of endothelial dysfunction, has been shown to be associated with increased cardiovascular risk. We investigated plasma levels of endocan in patients with end-stage renal disease (ESRD) on hemodialysis to predict the risk of cardiovascular diseases.

Methods: A total of 400 adult patients with ESRD undergoing hemodialysis were prospectively enrolled in 4 tertiary hospitals of South Korea from June 2016 to May 2018. They were observed for development of the cardiovascular composite outcomes. We compared clinical characteristics and the plasma levels of endocan between 47 patients with cardiovascular composite outcomes and 353 control patients without cardiovascular composite outcomes, and developed the predictive markers of cardiovascular diseases using Cox proportional-hazard analysis.

Results: Previous histories of diabetes, acute coronary syndrome, arrhythmia and congestive heart failure were higher in ESRD patients with the cardiovascular composite outcomes than control patients. Patients with cardiovascular composite outcomes showed lower levels of hemoglobin, albumin, and high-density lipoproteins compared with control patients. Higher level of plasma endocan and white blood cells were associated with patients with cardiovascular composite outcomes. Cox proportional-hazard analysis showed that previous histories of diabetes and plasma level endocan were significantly associated with cardiovascular composite outcomes: hazard ratios were 2.1 (95% confidential interval (CI), 1.1 to 4.3) ($p = 0.03$) for diabetes and 15.4 (95% CI, 3.2 to 75.2) ($p < 0.001$) for endocan (log pg/mL). The patients with level of endocan > 2.96 log pg/mL showed significantly higher cumulative incidence of the cardiovascular composite outcomes in Kaplan-Meier curve ($p = 0.03$).

Conclusions: Plasma Endocan level can a useful biomarker for prediction of cardiovascular diseases in patients with ESRD on hemodialysis.

SA-PO904

Investigation of Concentration of Blood Solubilized CD40 Ligand (sCD40L) in Maintenance Dialysis Patients

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Background: The soluble CD40 ligand (sCD40L), one of the factors released from activated platelets, has been recently suggested to relate to the pathogenesis of atherothrombotic events for a possible biomarker predicting cardiovascular outcomes. Thus, we examined the sCD40L levels in patients on maintenance dialysis.

Methods: The 15 patients undergoing maintenance dialysis in our hospital were enrolled after informed consents. The sCD40L levels before hemodialysis, 1 hour and 4 hours after initiation of hemodialysis were measured by enzyme-linked immunosorbent assays.

Results: The mean concentration of sCD40L before dialysis was 221.3 pg/ml, higher than that 34.3 pg/ml in healthy controls (n=3). The sCD40L levels were positively correlated with platelet counts and appeared to be higher in patients with a long duration of hemodialysis. The kinetics of sCD40L during hemodialysis showed that the concentrations increased to 271.0 pg/ml after 1 hour and decreased to 160.2 pg/ml after 4 hours, suggesting 30% of removal by hemodialysis. The rate of an increase during the first one hour were greater in diabetic patients (n=7) than that in non-diabetic patients (n=8). The average removal rate was 27.6%, with no differences among various types of dialyzers.

Conclusions: The sCD40L levels in hemodialysis patients are higher, although partially removed by dialysis, as compared to healthy people, and might be associated with an increased risk of atherosclerosis possibly through the platelet activation.

SA-PO905

Diagnostic Performance of Lung Ultrasound and a Clinical Score for the Evaluation of Hydration Status in Hemodialysis Patients

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Background: Estimating the hydration status of the hemodialysis patients is a key point in their management. So far, there is no gold standard feasible in daily routine. We performed a prospective study in chronic hemodialysis patients to evaluate the diagnostic performance of lung ultrasound and clinical examination for the evaluation of fluid overload using transthoracic echocardiography (TTE) as gold standard.

Methods: 31 patients performing chronic hemodialysis for more than 3 months in a dialysis center were included. Patients with pulmonary fibrosis were not included. The hydration status was assessed weekly by: a clinical score (Major criteria: dyspnea NYHA> III, orthopnea, minor criteria: jugular turgor (JT), hepatic jugular reflux (HJR), pulmonary crackles, peripheral edema and pre-dialysis hypertension); a TTE score (inferior vena cava diameter, E / E' ratio and systolic pulmonary arterial pressures); and Echo-comet score by lung ultrasound (sum of anterior and lateral B-lines in 28 chest areas).

Results: 5 patients had a TTE fluid overload. Compared with TTE, the diagnostic performance of the clinical score was: a sensitivity (Se) of 100%, a specificity (Sp) of 81%, a positive predictive value (PPV) of 50% and a negative predictive value (NPV) of 100%. Only orthopnea ($p = 0.008$), JT ($p = 0.005$) and HJR ($p = 0.008$) were significantly associated with TTE fluid overload diagnosis. The diagnostic performance of Echo-comet score by lung ultrasound has a Se of 80%, a Sp of 59%, a PPV of 26% and a NPV of 94%. 10 patients (32.3%) had an increase of extravascular lung water without evidence fluid overload with TTE or clinical score.

Conclusions: This is the first study that defines a clinical score to assess fluid overload in hemodialysis patients. This clinical score has a satisfying diagnostic performance compared to TTE and would be easily used in daily clinical routine to adjust dry weight. Fluid overload evaluation using the echo-comet score by lung ultrasound seems poorly correlated with the fluid overload evaluated by TTE score. Noteworthy, asymptomatic pulmonary congestion was detected with lung ultrasound without fluid overload according the clinical and TTE score. This particular patient group need further investigation to determine a diagnostic and prognostic significance.

SA-PO906

Online Hemodiafiltration Inhibits Endothelial Dysfunction and Vascular Calcification of Uremic Patients Modulating miR-223 Expression in Plasma Extracellular Vesicles

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Background: Decreased inflammation and cardiovascular mortality is evident in patients with end stage chronic kidney disease (CKD) treated by on-line hemodiafiltration (OL-HDF). Extracellular vesicles (EV) are key mediators of cell-to-cell communication. This study investigated whether OL-HDF may modulate the concentration and the RNA content of plasma EV.

Methods: 30 bicarbonate hemodialysis (BHD) patients were randomized 1:1 to continue BHD or switch to OL-HDF. Concentration, size, and microRNA content of plasma EV were evaluated for 9 months; we also studied EV effects on inflammation, angiogenesis and apoptosis of human endothelial cells (EC), and on osteoblast mineralization of vascular smooth muscle cells (VSMC).

Results: OL-HDF reduced different inflammatory markers such as CRP, IL6 and NGAL. All hemodialysis patients showed higher plasma levels of endothelial derived EV than healthy subjects, with no differences between BHD and OL-HDF. However, BHD-derived EV had an increased expression of the pro-atherogenic miR-223 in respect to healthy subjects or OL-HDF. Compared to EV from healthy subjects, those from hemodialysis patients reduced angiogenesis, increased EC apoptosis and VSMC calcification; however, all these detrimental effects were reduced with OL-HDF in respect to BHD. Cell transfection with miR-223 mimic or antagomiR proved the role of this miRNA in EV-induced EC and VSMC dysfunction.

Conclusions: Switch from BHD to OL-HDF significantly reduced systemic inflammation and miR-223 expression in plasma-EV, thus improving EC angiogenesis and reducing VSMC calcification.

SA-PO907

The Relation Between Peri-Dialytic Blood Pressure Changes over Time and Mortality Is Similar in Hemodialysis and Online Post-Dilution Hemodiafiltration

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Background: Online post-dilution hemodiafiltration (HDF) is associated with a lower mortality rate than hemodialysis (HD). The mechanism(s) behind this effect, however, is (are) unknown. In the present study we evaluated whether long-term changes in pre-, post-dialytical and delta (peri-dialytic) systolic blood pressure (SBP), diastolic BP (DBP), mean arterial pressure (MAP) or pulse pressure (PP) may contribute to the beneficial effect of HDF on survival.

Methods: Individual Participant Data (IPD) from the Spanish Estudio de Supervivencia de Hemodiafiltración (ESHOL, n=906), the Dutch Convective Transport Study (CONTRAST, n=714) and the French HDF study (Frenchie, n=391) were pooled. The difference in peri-dialytic SBP, DBP, MAP and PP was calculated between baseline and 6 months and divided into tertiles: stable, decreasing and increasing peri-dialytic values. The stable tertile (which included a change of 0mmHg in 6 months) was used as reference group. All values were related to mortality for the entire study follow-up using Cox regression models using an intention-to-treat approach. Hereafter, models were adjusted for relevant confounders (age, sex, BMI, dialysis vintage, diabetes and history of cardiovascular disease).

Results: In 6 months, SBP, DBP, MAP and PP changed with a median of 0 (interquartile range [IQR] -18 to 18.25), 0 (IQR -10 to 10), 0.33 (IQR -11 to 11) and 0 (IQR -16 to 16) mmHg, respectively. While patients with a decreasing peri-dialytical SBP had a HR of 0.82 (95% CI 0.65-1.03), patients with an increasing peri-dialytical SBP had a HR of 1.01 (95% CI 0.81-1.26). For DBP, these HRs were 0.88 (95% CI 0.71-1.10) and 0.87 (95% CI 0.70-1.10), for MAP 0.79 (95% CI 0.62-0.99) and 1.09 (95% CI 0.88-1.35) and for PP 0.76 (95% CI 0.61-0.96) and 0.93 (95% CI 0.75-1.15). After correction for confounders, no significant relation was found.

Conclusions: Since the relation between the long-term peri-dialytical BP course (SBP, DBP, MAP or PP) and mortality was similar in HD and HDF patients and mortality is lower in HDF (Peters SAE et al. NDT 2016), other mechanisms, such as intradialytical BP stability, may more fundamentally affect survival. This hypothesis is currently under investigation.

SA-PO908

Individualizing Dialysate Sodium Concentrations to Improve Fluid Management in Chronic Dialysis Patients: A Prospective, Nonrandomized, Open-Label Trial

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Background: Excessive fluid is associated with increased morbidity and mortality in patients on chronic dialysis. Excessive fluid measured as excessive interdialytic weight gain (EIDWG)% and above target weight (ATW)% in our dialysis unit reached nearly 50% of our patients despite interventions such as dietary counseling. We thus conducted a nonrandomized, open-label trial of 73 patients undergoing hemodialysis to explore the benefit of an individualized Na prescription.

Methods: Patients in the individualized Na group (n=33) received lower dialysate Na (135-137mmol/L) if their serum Na level<138 mmol/L, predialysis systolic blood pressure (SBP) >120 mmHg, and EIDWG% and ATW% being higher than the goal levels. Forty patients who used the standard dialysate Na at 138 mmol/L were considered the control group. All the variables were collected before and 2 months after intervention. We used student *t* tests to compare continuous variables between two groups. Multivariate-adjusted linear regression models were performed to assess the differences in each continuous outcome between two groups with adjustment for age and sex. Multivariable logistic regression models were conducted by modeling IDWG decrease and ATW decrease as dependent variables, adjusting for age, sex, and EDW change. All p values will be two-tailed. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results: Overall, such a moderate reduction of dialysate Na concentration was well tolerated. The SBP in patient group with individualized dialysate Na did not change from before intervention. Elevation in serum Na in the individualized dialysate Na group was significantly higher than that in the control group by 3.54 mmol/L (95% CI, 2.02 to 5.05) (P<0.0001), which may indicate the improvement of volume status. Patients with individualized dialysate Na were 3.50 times more likely to have IDWG decrease. The significant association remained after adjustment for age, sex, and EDW changes (OR:3.63; 95% CI, 1.03-12.9).

Conclusions: Our preliminary results showed that individualized dialysate Na prescription in patients on chronic dialysis is safe and well-tolerated and may be effective in the fluid management in hemodialysis patients. Future randomized controlled trials are warranted.

SA-PO909

Pre- and Post-Kidney Transplantation Body Weights: Assessing Dry Weight Levels

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Background: The single most important variable in fluid management during hemodialysis (HD) is dry weight (DW). Incorrect DW values result in hypo- or hypervolemic patients at the end of HD treatments, conditions with serious morbidity and mortality consequences. There is lack of consensus about the definition and assessment of DW; however, consensus opinion is that the optimal DW (ODW) target should be near a patient's weight at euvolemic state. We investigated this hypothesis by comparing patient weights pre- and post-transplantation (Tx) in hemodialysis patients early post transplant with functional grafts. We assumed that patients with functioning allografts achieve euvolemia by week 2 post transplant.

Methods: DW before Tx, weights, demographics, and biomarkers, were retrospectively collected for 42 patients that underwent kidney transplantation at Massachusetts General Hospital during 2016-2017. A creatinine level Cr<1.5 mg/dL was assumed to indicate a functioning graft and a euvolemic state. The ODW target was defined as the weight at week 2 post transplant for patients with a functioning graft. Patients with DW within +1% and -3% of ODW were considered to have DW values "sufficiently close" to ODW (+0.5 to -1.5 kg in a 50kg patient). In patients with a functioning graft, we used Wilcoxon signed rank test to analyze the agreement between paired changes in weight and hemoglobin (Hb) between weeks 1 and 2 post-Tx.

Results: 73% (N=31) of the 42 patients were males; 40% (N=17) received transplants from living donors; 10 patients had a functioning graft at week 1 (all living donor type) and 10 additional patients achieved that at week 2 (8 cadaver donor type). In the group with a functioning graft by week 2 (N=20) 21% had too low DW values (i.e., 3% or more below ODW), and 47% had too high DW values. Weight changes in the group with a functioning graft were significantly correlated with Hb changes between weeks 1 and 2 post-Tx r=-0.7 (p<0.001).

Conclusions: A high number (68%) of HD patients may have incorrect DW values with 21% rendered hypovolemic and 47% hypervolemic. Weight reduction in group with a functioning graft at week 2 issignificantly correlated with fluid volume reduction. It is imperative that new dry-weight assessment methods be developed that could improve cardiovascular outcomes in hemodialysis.

Funding: NIDDK Support

SA-PO910

Metabolic and Volemic Evaluation in the Long Interdialytic Interval of Patients in Hemodialysis with and Without Residual Renal Function

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Background: It is unclear whether residual renal function (RRF) in dialysis patients can attenuate the metabolic impact of the long 68-hour interdialytic interval, in which volume, acid and electrolyte accumulation occurs. The aim of this study was to evaluate serum electrolyte levels, water balance and acid-base status in dialytic patients with and without RRF over the the long interdialytic interval (LII).

Methods: It was a unicentric, transversal and analytical study, which compared patients with and without RRF, defined by diuresis above 200 mL in 24 hours. Patients were weighed and subjected to the collection of serum samples for biochemical and gasometric analysis after the last hemodialysis (HD) of the week and before the first session of the subsequent week.

Results: We evaluated 24 and 27 patients with and without RRF, respectively. The mean urea and creatinine *clearance* was 3.6 ± 2.12 mL/min/1.73 m2 in the RRF group. Patients without RRF had a higher increase of serum potassium during the LII (2.67 x 1.14 mEq/L, p<0.001) reaching higher values at the end of the study (6.8 x 5.72 mEq/L,p< 0.001), as well as lower post-HD pH value (7.40 x 7.43, p=0.018) and tendency to lower pre-HD pH value (7.30 x 7.27, p=0.07) (table). In addition, at the end of the LII, they presented a higher proportion of patients with serum bicarbonate<18mEq/L (50 x 14.8%, p = 0.007), mixed acid-base disorder (57.7 x 29.2%,p=0.042), higher interdialytic weight gain (14.67 x 8.87 mL/kg/h,p<0.001) and lower natremia (137 x 139 mEq/L,p=0.02). Serum calcium and phosphorus levels, as well as blood pressure, were not different between groups.

Conclusions: Patients with RRF had better control of serum potassium, sodium, acid-base status, and volemia throughout the LII.

Variation of electrolytes and acid-base status over the LII acordding to RRF

Variable	With residual renal function N=27	Without residual renal function N=24	p †
Potassium (meq/L)	----	----	----
post- HD	4.48 ± 0.76	4.12 ± 0.67	0.08
Mean Variation	1.14 ± 1.26	2.67 ± 1.23	< 0.001*
pre –HD	5.72 ± 0.96	6.8 ± 0.67	< 0.001*
Sodium (mEq/L)	----	----	----
post- HD	139.03 ± 5.14	137.87 ±2.99	0.337
Mean Variation	0.00 ± 4.14	– 0.79 ± 5.05	0.542
pre –HD	139.03 ± 3.00	137.08± 2.78	0.020*
Phosphate (mg/dl)	----	----	----
post- HD	3.73 ± 0.84	4.43 ± 1.69	0.084
Mean variation	1.24 ± 1.61	1.12 ± 1.62	0.784
pre –HD	4.98 ± 1.54	5.55 ± 1.90	0.241
Calcium (mg/dL)	----	----	----
post- HD	10.79 ± 1.01	10.79 ± 1.01	0.927
Mean variation	-2.11 ± 0.95	-2.11 ± 0.95	0.683
pre –HD	8.68 ± 0.54	8.68 ± 0.54	0.640
pH	----	----	----
post- HD	7.43 ± 0.47	7.40 ± 0.04	0.018 *
Mean variation	-0.12 ± 0.05	-0.13 ± 0.08	0.940
pre-HD	7.30 ± 0.05	7.27 ± 0.06	0.073
Bicarbonate (mEq/L)	----	----	----
post- HD	26.62 ± 2.50	26.00 ± 2.40	0.372
Mean Variation	-6.71 ± 3.52	– 6.76 ± 3.48	0.959
pre-HD	19.91 ± 2.85	19.24 ± 2.84	0.403
pCO2	----	----	----
post- HD	39.80 ± 3.99	41.93 ± 5.47	0.116
Mean Variation	- 0.60 ±4.08	-0.88 ± 4.70	0.821
pre-HD	39.19 ± 6.24	41.04 ± 4.02	0.221

†= independent samples t-test,

* = p< 0,05

SA-PO911

Clinical Impact of CMS' Ultrafiltration Limit on Hemodialysis Patients

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Background: In January 2018, CMS instituted a reporting requirement: dialysis facilities must report the percentage of treatments during which patients removed less than 13 cc/kg/hr of fluid based on data demonstrating a relationship between higher ultrafiltration (UF) rates and adverse cardiac effects including myocardial stunning. Many dialysis patients demonstrate adverse effects from volume overload both acutely and chronically including hospitalizations for related complications and poorly controlled hypertension. We sought to evaluate the effect of the new CMS requirement on the clinical status of our maintenance hemodialysis (HD) patients.

Methods: As part of the QAPI program at The Rogosin Institute, we began monitoring the percentage of patients meeting CMS' UF requirement in January 2018. After three months living with this limit, we asked facilities to report on the proportion of patients demonstrating evidence of fluid overload and methods for managing patients not thriving in the face of the UF limit. We analyzed the data using descriptive statistics to look for relationships between the measured variables.

Results: More than 90% of the 1,197 patients dialyzed in our seven facilities met CMS' UF requirement each month. Problems living with the fluid restriction and problems reaching target weight with the UF requirement were reported by 283 (24%) and 143 (12%) of our patients, respectively. Despite 27 patients (2%) receiving more than three treatments weekly, 50 (4%) patients were hospitalized during a three month period for symptoms related to volume overload. In our population, 299 patients (25%) had inadequate blood pressure control and 262 (22%) required more than three medications to control blood pressure.

Conclusions: Despite the documented benefits of limiting UF rates for patients treated by maintenance HD, the restriction has adverse effects: more than 4% of our population was hospitalized during the first three months of the restriction and more than 25% of our population has inadeaquate blood pressure control despite standard interventions. We are developing best practices for managing fluid overload and attempting to improve the clinical outcomes for patients struggling to live with the new CMS UF limit.

SA-PO912

Global Trends of Stroke in Haemodialysis (2000-2012): A Retrospective Cohort Study of the Monitoring Dialysis Outcomes Initiative

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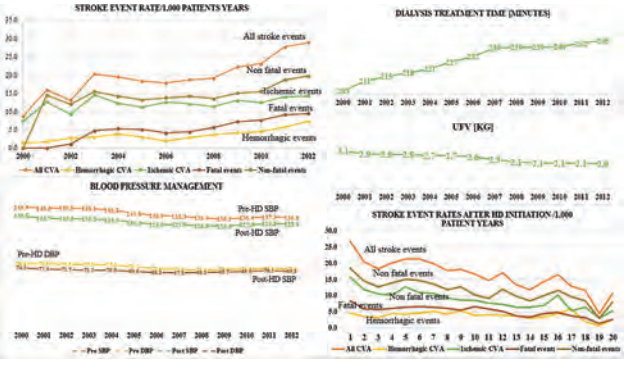
Background: Stroke remains a key cause of death&morbidity in HD patients(pts) that exhibit stroke rates 10-12x higher than the general population(GP). Primary&secondary prevention strategies have progressively reduced the burden of stroke in the GP but it is unclear if this trend has transposed to HD pts globally.

Methods: We studied 4,388 strokes in 150k pts. The MONDO Initiative consists of HD pts from 41 countries [von Gersdorff GD et al.]. All adult pts from the MONDO database [2000-2012] were studied with fatal&non-fatal hospitalized stroke defined by ICD-9&10 codes and excluded transient ischemic attack.

Results: The overall incidence of stroke rose from 8.7-28.7/1k pt yrs. This compares to static rates worldwide in the GP[2.5-2.6/1k pt yrs,1990-2010] with falling rates in high-income countries. A sharper rise in hemorrhagic stroke rate was seen compared to ischemic stroke in HD pts[Fig], reflecting trends seen in younger age groups worldwide. Despite falling stroke mortality worldwide[1.4-1.1/1k pt yrs,1990-2012], there was a progressive rise in HD populations [1.5-10.5/1k pt yrs, 2000-2012]. These stroke trends occurred despite increasing treatment time[203-245 mins], better BP control[mean pre-HD BP 150/80-137/72mmHg] and falling ultrafiltration rates. Stroke rates remained high 3 months after HD started and continued to fall for 2 yrs, driven by ischemic stroke incidence and with stable hemorrhagic stroke rates.

Conclusions: There is a progressive rise in stroke incidence and mortality over time in HD pts globally which starkly contrasts with global trends. This appears to be driven predominantly with rising rates of hemorrhagic stroke which carries a higher case-fatality rate. Stroke rates are at their highest within the first year of HD and there is a pressing need to reduce stroke risk in a particularly vulnerable pts at an early stage.



SA-PO913

Racial Disparities in Percutaneous Coronary Intervention in the ESKD Population

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Background: Racial disparities in invasive cardiac procedures such as percutaneous coronary intervention (PCI) in the general population are well documented. However, contemporary national-level data on such disparities in the end-stage kidney disease

(ESKD) population are lacking. Herein we assessed racial differences in the receipt of PCI between Blacks and Whites with ESKD, after the start of maintenance dialysis.

Methods: Using the US Renal Data System database, we abstracted Medicare inpatient procedure claims for PCI in a cohort of 269,984 Medicare primary patients who initiated on maintenance dialysis from 1 January 2009 through 1 June 2013, and followed until 31 December 2013. We conducted Cox regression analyses, adjusted for demographic characteristics, cause of ESKD, comorbidities, and socioeconomic factors (Medicare-Medicaid dual eligibility as a proxy measure of individual-level poverty, employment status, and ZIP code-level median household income obtained from the 2010 US Census). We also modeled death as a competing event in competing risk regression using the Fine and Gray method.

Results: The crude incidence rates of PCI among Whites were 32.9 per 1000 patient-years (PY) vs. Blacks 20.4 per 1000 PY, respectively [Figure 1]. Cox regression analyses demonstrated that Blacks were significantly less likely to undergo PCI compared to Whites (adjusted hazard ratio [aHR] 0.64, 95% CI 0.55-0.74, p<0.001). The aHR was similar in non-Hispanic Blacks vs. non-Hispanic Whites (aHR 0.62, 95% CI 0.53-0.73, p<0.001). In the competing risk model, the racial gap for PCI among Blacks and Whites narrowed but remained significant (subdistribution HR 0.73, 95% CI 0.62-0.88, p<0.001).

Conclusions: There exists a racial gap among incident dialysis patients undergoing PCI despite having comprehensive coverage with Medicare. These findings persisted despite accounting for demographic, clinical, socioeconomic factors and death as a competing risk.

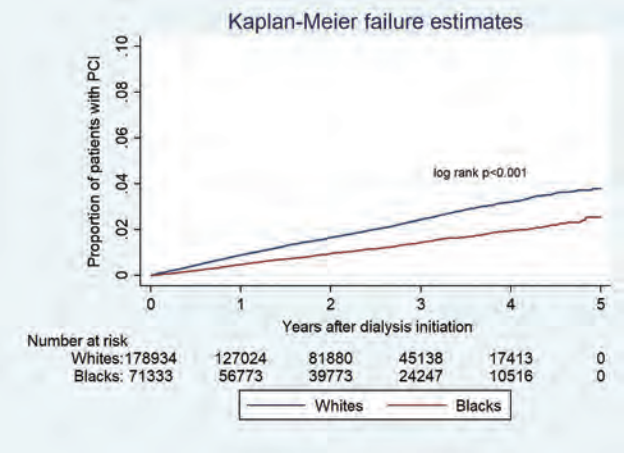

Figure 1

SA-PO914

Survey of Patient Awareness of and Attitudes Towards Home Dialysis in New York City

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Background: Since 2008, CMS regulations have obligated dialysis practitioners to inform in-unit hemodialysis(HD) patients about alternatives to in-unit HD, including home dialysis modalities. Despite this mandate, home dialysis remains underutilized nationwide with just 8.6% of prevalent patients performing any home modality. Home modalities are even more disproportionately underutilized in New York City (NYC), with only 3.6% of patients using a home modality. Because of the unique challenges faced by patients living an intensely urban setting such as NYC, we attempted to understand the factors that might be responsible for that underutilization.

Methods: The PRIMARY CARES (Primary Care Attitudes and Renal Replacement Selection) survey was performed in 7 HD units in the NYC area representing a diverse population of ethnicities, languages, and socioeconomic categories with the objective of assessing factors influencing the utilization of home dialysis.

Results: 832 in-unit HD patients were approached and 511 completed the survey. Of these, 469 (92%) indicated they received education regarding any renal replacement modality. Of those, only 180 (35%) reported having been educated about home hemodialysis (HHD) and only 142 (28%) reported having been educated about peritoneal dialysis (PD). Of the 180 patients educated about HHD, 39 (21.7%) seriously considered the modality after receiving education. Only 5 (12.8%) of the 39 patients who seriously considered HHD came to the conclusion they "would never do HHD". Of the 142 patients educated about PD, 61 (43%) seriously considered the modality after receiving education. Only 11 (18%) of patients who seriously considered PD came to the conclusion they "would never do PD".

Conclusions: Patient awareness of home modalities remains poor despite mandated modalities education. A significant proportion of patients educated about home modalities seriously considered dialyzing at home, whereas only a small minority indicated they would never consider dialyzing at home after receiving that education. Our data suggests that there may be a large reservoir of home dialysis patients within the NYC in-unit HD population, and that current in-unit modalities education programs could be improved.

SA-PO915

The Impact of Frailty on Technique Failure and Mortality in Patients on Home Dialysis

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Background: Patients on home based dialysis therapies will experience technique failure, which is associated with morbidity and mortality. Reasons for technique failure are complex, and often related to functional decline in the patient or caregiver. Frailty is associated with an increased risk of adverse health outcomes. The aim of the study was to investigate the impact of frailty on technique failure and mortality in a prospective cohort of patients on home dialysis therapies.

Methods: We studied 109 prevalent patients from the Peritoneal Dialysis (PD) and Home Hemodialysis (HHD) programs at our institution between 2012 and 2016. We collected objective [Fried criteria and Short Physical Performance Battery (SPPB)], and subjective measures (physician and nurse impression) of frailty. Our primary outcome was a composite of technique failure, defined as a permanent transition (> 30 days in duration) to facility based hemodialysis or all cause death. The association between different frailty assessment tools and the primary composite outcome was evaluated using Cox proportional hazards models.

Results: Frail status, as determined by the Fried criteria and physician impression was associated with a greater than two-fold increase in risk of our composite outcome (HR: 2.10 [95% CI 1.09-3.99], 2.15 [95% CI: 1.15-4.00, respectively] in models adjusted for age, sex and comorbidity. Weakness and weight loss subdomains of the Fried criteria were both associated with an increased risk of technique failure or death in adjusted analyses (HR: 2.16 [95% CI: 1.23-3.78], 2.69 [95% CI 1.39-5.40], respectively).

Conclusions: Objective and subjective measures of frailty are associated with a more than two-fold higher risk of technique failure or death in patients undergoing home dialysis. Assessing frailty as part of the clinical evaluation for home dialysis therapies may be useful for prognostication and clinical management.

Funding: Government Support - Non-U.S.

SA-PO916

The Effect of Interim Assessment on Home Hemodialysis Patient Readiness

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Background: Studies have demonstrated the favorable clinical outcomes and better quality of life of home hemodialysis (HHD) compared with conventional hemodialysis. Teaching strategies to ensure the patients' ability to administer their own therapies safely without supervision at home is fundamental to the success of home hemodialysis. Several studies showed mid-training assessments followed by final assessment at completion of training improved learning outcomes. The purpose of this study is to determine the impact of interim assessments on the readiness of HHD before transitioning home.

Methods: This is a prospective feasibility study examining consecutive end stage renal disease (ESRD) patient and caregiver who were undergoing HHD training between September 1, 2017 to May 31, 2018. Every potential home hemodialysis candidate was observed for their hemodialysis performance skills and asked basic knowledge questions regarding hemodialysis by an independent HHD nurse after 16 sessions of HHD training and at the end of training. HHD candidates and training nurse were provided feedback for observed errors. The confidence in performing dialysis at home was assessed by global rating scale (GRS) in every HHD patient and their primary nurse before and after every interim assessment.

Results: Of 11 candidates; 9 candidates were ESRD patients, 2 candidates were ESRD patients' caregivers. Mean age was 47.3 ± 14.3 years, 63.6 % was male, 54% was Asian, 81.8% graduated from college or higher education, 54% used central venous catheter for vascular access. The confidence level scores in performing HHD in both candidates and primary nurses before the 2nd interim exam was significantly higher than the 1st interim exam (57.6 vs 64.4 (p 0.014); 53.1 vs 60.3 (p 0.026). The confidence level scores in performing HHD in both candidates and primary nurses before the 2nd interim exam was significantly higher than the 1st interim exam (57.6 vs 64.4 (p 0.014); 53.1 vs 60.3 (p 0.026).

Conclusions: Interim observed evaluation is a feasible strategy to enhance patients and nurses' ability to train a complex medical procedure. Prospective evaluation of the clinical impact of interim training evaluation on adverse outcomes warrant further evaluation.

SA-PO917

Home Hemodialysis Assisted by Personal Support Workers Among Eight Pilot Programs in Ontario

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Background: Increasing the uptake of home dialysis is a strategic priority of the Ontario Renal Network (ORN). Home hemodialysis (HHD) is associated with a higher

quality of life and improved symptom control. Barriers to the adoption of HHD can include patient inability to manage HHD independently, psychological barriers such as fear of catastrophic events, concerns about burdening family, or lack of appropriate support. This pilot project utilized Personal Support Workers (PSWs) to support patients who required additional assistance to dialyze at home.

Methods: The ORN funded 8 Regional Renal Programs (RRPs) to initiate PSW-assisted HHD. PSWs were trained in a manner consistent to that of independent HHD patients. Patient information was collected via the Ontario Renal Reporting System. Patients, PSWs, nurses and administrators were surveyed to gather feedback on patient experience and outcomes, model feasibility, training success, safety, and monitoring and support processes(e.g. including ongoing focus groups to obtain information about project progress).

Results: Between October 2015 and March 2018, approximately 65 patients participated in the PSW-assisted HHD project. As of March 2018, 35 prevalent patients were actively receiving PSW-assisted HHD. Rates of HHD increased by 0.1% to 2.2% across the 8 RRPs due to PSW-assisted HHD since the implementation of the project. The main challenge of the pilot was the PSW turnover rate (41%). Key survey measures include: 94.5% (n=35) of patients indicated that they switched to HHD due to the PSW support received. 91% (n=33) of patients indicated that are happier dialyzing at home than in an in-centre dialysis unit.

Conclusions: Successful implementation of a PSW-assisted HHD was achieved across 8 RRPs in Ontario. PSW-assisted HHD appears to be a promising model of care to increase uptake of HHD and was associated with high patient satisfaction scores. Further evaluations of the program are underway to inform the operational and financial sustainability of this model of care.

Funding: Government Support - Non-U.S.

SA-PO918

Nurse Assisted Home Hemodialysis (NAHHD) by Using NxStage Cycler for Home Bound, And Multi-Comorbid Hemodialysis Patients: One Year Experience

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Background: Home hemodialysis (HHD) is used to treat active, HD patients. The steady increase in the number of HD patients, with multi comorbidities, and bed bound, is creating a significant burden on the active hospital beds. We are presenting our one year experience of treating those highly comorbid HD patients, with (NAHHD), at home or in long term care facilities.

Methods: HD patients who were fulfilling criteria for HHD were accepted in the NAHHD program. NxStage System One is used to deliver HD therapy at home or at long term care, by an experienced HD nurse. Dialysate volume, length, and weekly number of the HD sessions, were calculated by a calculator given by NxStage Company, targeting weekly standardized KT/V≥ 2. Only patients who were at least for three months and those who completed one year in the (NAHHD) program were included in the study.

Results: Forty seven dialysis patients on NAHHD were included in this study. Eighteen males (38%), and 29 females (62%). Mean age 69.2±17.7 year. Mean duration on NAHHD was 12 months. Etiology of end stage renal disease was DM 35(74%), HTN 10 (21%), and others 2(5%). Average number of comorbidities 9.3±3(6–16). Indications of NAHHD were: bed bound 27 (57%), morbid obesity 9(19%), psychiatric disorders, mental retardation 7(15%), and others 4(9%). Vascular access: AVF 23 (49%), AVG 2(5%), and tunneled catheter 22 (46%). Average dialysate volume was 25 L. Number of weekly session was 4, and average duration of session 3.3 hours. All patients tolerated well their dialysis sessions. The average weekly standardized KT/V was 2. There were 7 line sepsis, with an incidence of 0.6 episode/ 1000 catheter days. There was 56 hospital admissions (1.2 admission/ patient/year), with average hospital stay of 7.4 days. The annual mortality rate of the total cohort was 17.7%. There was a positive impact of the NAHHD on the patients' quality of life, as measured by time of recovery of 21 minutes, average sleeping of 6.5 hours, good appetite in 81%, along with patients and families satisfaction of 80%.

Conclusions: The results of one year experience of NAHHD by using NxStage machine in bed, home bound, and multi comorbid, HD patients, confirmed its efficacy, good quality of care, and its safety. It has significant positive impact on the quality of life and satisfaction of both patients, and their families.

SA-PO919

An Audit of Compliance with Prescribed Dialysis Hours in a Home Hemodialysis Population

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Background: Increased weekly hemodialysis(HD) hours(hrs) completed is associated with improved quality and quantity of life. There are no studies examining compliance with prescribed dialysis hours(PDH) in home hemodialysis(HHD) populations who are not remotely monitored.

Methods: The number of hours each HD machine has run, as displayed on machines, was recorded on 2 occasions during routine home visits to all prevalent HHD patients of Princess Alexandra Hospital. With ethics approval, patients and staff were unaware this information was being collected. The number of HDhrs completed between the 2 readings was calculated, accounting for periods of HD away from home, set up and maintenance. This was compared with PDH documented in the medical record. Nurses and Nephrologists blindly rated compliance based upon clinical acumen. Descriptive statistics were performed to analyze trends and examined for predictors of %PDH completed.

Results: 54 HHD patients were included:Age:52±14years; 26% female; diabetic nephropathy:28%, duration HHD 4(2-8)years. Duration between the 2 readings was 11(7-17)weeks. %PDR dialysed:≥90%hrs: 52%, 70-89% hrs:30%, 50-69%hrs:11% and <50%hrs:7%. Average number of hrs/week performed was 16±7. 41% of patients dialysed <15hrs/week. 46% were prescribed but only 35% performed ≥18hrs/week. Compliance was accurately estimated by nurses in 48% and by nephrologists in 43% of cases. Nephrologists rated patient compliance as significantly worse than nurses. Out of 27 demographic, psychosocial, medical and laboratory parameters, only age(coefficient 0.64, 95% confidence interval (CI) 0.26-1.02, p=0.002) and diabetes mellitus (-14.8, 95% CI -26- -3.6, p=0.01) were significantly associated with compliance with PDH in multivariable regression analysis.

Conclusions: Recording the hours HD machines have run provides a useful estimate of the HDhrs completed at home. It is minimally intrusive on patient privacy, requires no special equipment and little staff time. It does not provide information on HD session frequency or duration being performed. Accuracy of clinicians' impressions of compliance is poor and common parameters used to monitor HHD patients are poorly predictive of compliance with PDH. Rates of poor compliance with PDH in HHD patients are significant and may contribute to the lack of consistent improvement in outcomes seen in clinical trials.

SA-PO920

Single Centre Experience of Vascular Access Related Infection Rates in Frequent HD

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Background: There are many benefits to Frequent Home HD (FHHD) but it only accounts for 0.4% of the dialysis population worldwide. One of the perceived barriers to FHHD relates to vascular acces srelated infections (VARI), as Infection is still the leading cause of morbidity and mortality in the dialysis population. Fear exists that frequent cannulation or use of vascular catheters (CVC) at home will increase this. Wessex Kidney Centre (WKC), Portsmouth, UK has a large HHD programme using NxStage. This retrospective study will review VARI and the strategies put in place to minimise them.

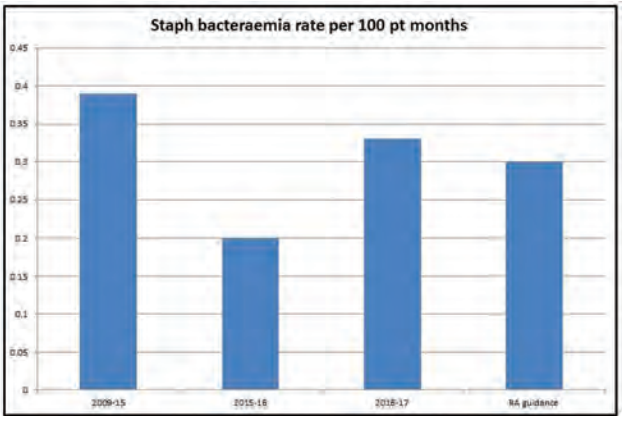
Methods: Data was collected on HHD patients between 2009- 2017. Demographic data, type of vascular access, proven bacteraemia via blood cultures and exit/cannulation site infections was collected. Rates of staph aureus bacteraemia were compared to UK Renal Association (UKRA) standards for HD. Monitoring methods in place were reviewed.

Results: Table 1 shows demographic data and number of VARI during this period. All patients received dialysis 5 or 6 times per week (20 patients received alternate night therapy). Figure 1 shows staph aureus related bacteraemia per 100 patient months compared to UKRA standard. The rate of all VARI were highest in the first 5 years and have since reduced despite increasing numbers on HHD. They are comparable to the UKRA standard. Monitoring strategies and educational material have been put in place, including a real time monitoring app alerting the HHD team to any concerns, aiming to treat any infections early.

Conclusions: In this large FFHD cohort an increase in VARI rates were not observed despite frequent cannulation or use of CVC at home. Careful monitoring and ongoing education is essential to reduce infection rates and ensure prompt treatment.

Table 1

Year	No of patients	Age	Sex	AVF / PTFE / CVC usage	Bactereamia	Exit/cannulation site infections
2009-15	89	50 (18-80)	60% Male	69 / 7 / 13	11	7
2015-16	94	53 (19-82)	65% Male	66 / 15 / 26	3	1
2016-17	107	53 (19-83)	66% Male	70 / 8 / 29	5	5



SA-PO921

European Experience of Nocturnal Home HD Using NxStage System One

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Background: More frequent HD is associated with increased survival, improved physical health, and reduced LVH. Studies have shown benefits with long, slow dialysis, with reduction in blood pressure, improved solute removal, anaemia, and quality of life. This study documents for the first time the outcome of a cohort treated with nocturnal home HD (NHHD) with low-volume dialysate in Europe.

Methods: A retrospective analysis of 20 patients at 4 European centres who received ≥12 months NHHD with the NxStage System One, a device that uses ≤60 L/session of lactate-buffered dialysate. Single-bolus low-molecular weight heparin was administered at the start of therapy. Fistulas were cannulated with double needle and button hole technique; needle strapping and moisture sensors were used. Data analysis included demographics, prescriptions, biochemical data, training and safety measures. Descriptive analysis was used to assess patient characteristics and prescriptions. Mean, standard deviation, and range of biochemical data at baseline, 6 and 12 months were calculated.

Results: Mean age was 44.4 years (range, 26-66). Most patients received 3.5 sessions per week, with 60 L/session of dialysate and ≥24.5 cumulative treatment hours. The table summarises biochemical outcomes, which met European standards. Reduced pill burden was also noted.

Conclusions: Data from this cohort supports the use of NHHD with low-volume dialysate, providing biochemical outcomes that meet European standards and reduced pill burden. Therapy was safe and effective, and extends a viable option for more patients to receive NHHD and its associated benefits.

Biochemical data

Biochemical parameter	Baseline Mean (SD)	6 Months Mean(SD)	12 Months Mean(SD)
Standardised Kt/V	2.1 (0.6)	2.4 (0.3)	2.5 (0.4)
Pre Phosphate mmol/L	1.7 (0.5)	1.6 (0.4)	1.6 (0.6)
Pre Calcium mmol/L	2.4 (0.1)	2.4 (0.2)	2.4 (0.2)
Pre Potassium mmol/L	5.0 (0.7)	4.6 (0.7)	5.0 (0.7)
Pre Bicarbonate mmol/L	24.6 (2.8)	25.9 (3.4)	25.7 (3.0)
Pre Hemoglobin g/dL	11.5 (1.6)	12.0 (2.1)	12.1 (1.5)
Pre Albumin g/L	35.6 (6.5)	37.7 (6.3)	37.5 (7.3)
No. phosphate binders	4.3 (5.0)	1.9 (2.8)	1.5 (2.3)
No. of BP meds	1.2 (1.3)	1.0 (1.1)	1.1 (1.2)

SA-PO922

Frequent Home Haemodialysis as "Palliative Dialysis": Time for a Paradigm Shift

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Introduction: Increasingly the profile of dialysis patients has changed from young and fit to older and multi-comorbid. Dialysing these patients is fraught with difficulties due to their comorbidities. Managing such complex patients requires a collaborative approach by Renal and Palliative physicians. A Palliative approach to dialysis embraces the transition from a conventional disease-oriented focus on dialysis as a rehabilitative treatment to an approach prioritizing comfort and alignment with patient goals. Palliative care affirms life, provides symptom relief by integrating medical, psychological and spiritual needs of a patient and considers dying as a normal process. Palliative dialysis as part of palliative medicine is not a well-recognized concept.

Case Description: We describe our experience with six individual patients on Home Haemodialysis (HHD) using NxStage system One, who have benefitted from a palliative approach to dialysis as part of their holistic treatment. Table 1 outlines the patients included. As outlined in the table, we had patients with variable age and comorbidities who underwent dialysis for symptom control on a palliative basis, either at home or at the hospice. All patients had significant symptom burden and co-existing illness, but wished to continue dialysis at home spending quality time with family. Dialysis was continued in the context of palliation, focusing on symptom control. This also offered flexibility and thereby improved the quality of the final month of life.

Discussion: Palliative care programs result in beneficial effects on symptoms, reduced hospital costs, increase likelihood of death at home, and improve patient and family satisfaction, compared to conventional care. Patients undergoing maintenance dialysis with associated significant comorbidities, a high mortality rate, and possibly co-existing terminal illness could be candidates for a palliative approach to dialysis. It is time to incorporate this as a part of the continuum of renal treatment, providing a patient centered holistic approach.

Table 1

Age at Death	Sex	Total time on dialysis (months)	Terminal Diagnosis	Time on HHD (Months)	Dialysis in hospice setting?	Place of Death
32	F	360	Frailty	30	Yes	Hospice
83	M	97	lymphoma	37	No	Home
76	M	31	Lung Cancer	7	No	Home
54	F	34	Ovarian cancer	24	No	Home
46	F	72	Myeloma	48	Yes	Hospice
68	M	106	Bladder Cancer	10	No	Home

SA-PO923

Human Factors Testing of the Quanta SC+ Hemodialysis System: An Innovative System for Home and Clinic Use

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Background: Compared to traditional in-centre hemodialysis, home hemodialysis (HHD) is a more cost-effective option, offering patients more autonomy, better quality of life, and improved health outcomes. However, uptake rates of HHD are the lowest among all other modality types. Therefore, there is a need to develop efficient HHD systems that are user-friendly and appealing to patients. The SC+ Hemodialysis System developed by Quanta Dialysis Technologies for home and clinic use, provides patients with a compact, safe, and easy-to-use HHD system that minimizes the burden of traditional dialysis treatments, whilst providing equivalent dialysis adequacy.

Methods: As part of the design validation of the SC+, Human Factors Testing (HFT) was performed with 15 Home Users (patients and caregivers) and 17 Healthcare Professionals (nephrology nurses and healthcare assistants), to assess safety, performance, and ease of usability. The HFT involved a training session with each participant at Smethwick Dialysis Centre in Birmingham, United Kingdom, which was subsequently followed by a test session where participants independently performed 38 subtasks on the SC+. A detailed study protocol was used to critically evaluate each participant in a standardized manner.

Results: In aggregate, 1,171 from the 1,216 subtasks attempted between the two user groups were completed successfully. Overall, the Healthcare Professionals performed with a higher degree of use safety, with a task-specific success rate of 97.4%, compared to 95.1% in the Home Users (patient and caregiver) group. Healthcare Professionals encountered use errors in 0.9% of sub-tasks attempted. In contrast, 0.2% of subtasks attempted by home users resulted in a close call (they initially encountered a use error, but were able to self-correct), and 3.9% resulted in use errors. Due to circumstances unrelated to the study itself, 1.7% of subtasks attempted by healthcare professionals, and 0.9% by home users, were unperformed. No errors resulted in adverse events.

Conclusions: The SC+ Hemodialysis System was found to have minimal issues related to ease of usability by patients, caregivers, and healthcare professionals. The data from this usability study indicates that in the real world, a high degree of use safety will likely be achieved, resulting in an optimal user experience.

Funding: Commercial Support - Quanta Dialysis Technologies Ltd.

SA-PO924

Effect of Dialysate Lactate Concentration During Daily Hemodialysis (DHD) on Serum Bicarbonate (BIC) Concentration After Transfer from In-Center Hemodialysis (ICHD)

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Background: Lactate is used as an alternative dialysate buffer to BIC during DHD, but the outcome of dialysate lactate concentration on acid-base balance is unclear. We examined the effect of the dialysate lactate concentration during DHD on serum BIC concentration after transfer from ICHD.

Methods: This post hoc analysis evaluated data from patients who transferred from ICHD to DHD during the FREEDOM Study (N=284). DHD was performed at low dialysate flow rates; treatment frequency per week and dialysate volume per session were 5.9±0.2 and 22.1±4.0 L, respectively. Dialysate lactate concentration during DHD was either 40 or 45 mM. Serum BIC was the average concentration from the last 3 months of ICHD or the first 3 months of DHD.

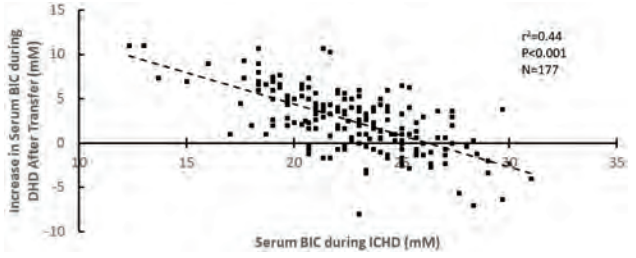
Results: Mean±SD serum BIC values are tabulated. Overall, a larger increase in serum BIC after transfer from ICHD to DHD was associated with higher dialysate lactate concentration during DHD ($P<0.001$) and lower serum BIC during ICHD ($P<0.001$), the latter is illustrated for dialysate lactate concentration of 45 mM in the figure.

Conclusions: Transfer from ICHD to DHD using lactate as the dialysate buffer may be accompanied by changes in serum BIC. This study provides guidance for choosing dialysate lactate concentrations for DHD at low dialysate flow rates.

Funding: Commercial Support - NxStage Medical

Dialysate BIC during ICHD (mM)	Dialysate Lactate during DHD (mM)	N	Serum BIC during ICHD (mM)	Serum BIC during DHD (mM)
≤35	40	37	22.8±2.4	22.5±2.7
	45	83	22.1±2.9	25.6±3.0*
>35 & ≤38	40	33	23.7±3.1	23.2±2.4
	45	41	23.8±2.9	24.8±2.5
>38	40	37	23.7±2.4	21.5±2.5*
	45	53	22.6±3.9	24.9±2.7*

*Different from value during ICHD (P<0.001) by paired Student's t-test.



SA-PO925

Associations of Treatment Frequency and Dialysate Volume with Conversion from Home Hemodialysis to Another Dialytic Modality

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Background: Home hemodialysis (HHD) readily permits increased treatment frequency, which reduces left ventricular mass, blood pressure, and serum phosphorus and improves physical health-related quality of life. However, conversion from HHD to another dialytic modality (*e.g.*, in-center hemodialysis) is common, particularly during the first year of HHD. There is little literature about clinical predictors of conversion. We assessed associations of treatment frequency and dialysate volume with conversion in a contemporary cohort of HHD patients.

Methods: We identified patients who initiated HHD training with the NxStage System One between January 1, 2013, and December 31, 2017, in a large dialysis organization. We retained patients who completed HHD training and were initially prescribed 4-6 sessions/week and ≥90 L/week of dialysate. We followed patients from the first treatment at home until the earliest of conversion to another dialytic modality, death, kidney transplant, or January 31, 2018. We used Cox regression to estimate the hazard of conversion to another dialytic modality, as a dynamic function of treatment frequency and cumulative dialysate volume per week, with adjustment for age, race, sex, body mass index, and vascular access type.

Results: We identified 5545 patients who completed HHD training. Mean age was 54.6 years, 69% of patients were white, 65% were male, and 71% used a fistula. Patients accumulated 6645 patient-years of follow-up. Prescriptions of 4, 5, and 6 sessions/week constituted 28%, 59%, and 14% of follow-up time, respectively, and prescriptions of 90-119, 120-149, 150-179, 180-209, and ≥210 L/week of dialysate constituted 8%, 23%, 34%, 21%, and 14% of follow-up time, respectively. There were 1727 conversions from HHD to another dialytic modality, 685 deaths, and 467 kidney transplants. The adjusted hazard ratio of conversion from HHD to another dialytic modality was 1.06 (95% confidence interval, 0.95-1.18; $p = 0.31$) for 4 vs. 5 sessions/week and 0.99 (0.85-1.44; $p = 0.86$) for 6 vs. 5 sessions/week. The corresponding hazard ratio for each 30-L/week increment in dialysate was 1.00 (0.96-1.04; $p = 0.96$).

Conclusions: Among patients on frequent HHD with low-volume dialysate, neither HD frequency nor dialysate volume per week were associated with conversion to another dialytic modality.

Funding: Commercial Support - NxStage Medical, Inc.

SA-PO926

Home Dialysis Utilization by African-Americans Is Influenced by Psychosocial Factors

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Background: Racial disparities have been reported in utilization of home dialysis modalities. While psychosocial factors are assumed to play a role, there is a paucity of definitive data. The aim of this study was to examine the relationship between psychosocial factors and the utilization of home dialysis among prevalent African-American dialysis patients.

Methods: Data were extracted from the initial comprehensive assessment performed by social workers for patients starting dialysis treatment between 2010- 2016. Our exposures were social worker-assessed psychosocial factors; depression/anxiety, substance abuse, marital status, employment status, and level of independence (daily social support, no ambulatory assistance, and community-dwelling). Our outcome was dialysis modality assignment: in-center hemodialysis (ICH), peritoneal dialysis (PD), or home hemodialysis (HHD). Statistical analysis was performed using ANOVA, *t* test, and Pearson's chi-square.

Results: Of 1338 patients, 85 were on PD, and 18 on HHD. Our population is predominantly AA with 91% of ICH, 69% of PD, and 77% of HHD patients being AA. Compared to ICH patients, PD and HHD patients were younger, less likely to have history of substance abuse, and more likely to be employed and independent (Table 1). There was no difference in depression/anxiety across modalities. When just the AA sample (n=1094) was analyzed, history of substance abuse, employment status, and independence similarly varied between modalities.

Conclusions: Our results suggest that African-American ESRD patients who utilize home dialysis are more likely to be employed, live independently, and less likely to have substance abuse history. Comparisons of outcomes of home vs. in-center modalities should take these psychosocial factors into account. Further investigation of other factors which could inform targeted interventions to improve utilization of home dialysis is warranted.

Table 1. Baseline demographic and psychosocial data for all dialysis patients by modality (ICH: N = 1338, PD: N = 85, HHD: N = 18)

Characteristics	ICH (% or mean ± SD)	PD (% or mean ± SD)	HHD (% or mean ± SD)	P-Value
Mean age/SD	56.59 ± 14.99	53.01 ± 14.98	46.67 ± 12.79	0.0051
Patients with depression/anxiety	15.35	15.38	16.67	0.988
Patients with a history of substance abuse	13.36	4.94	0.00	0.023
Married, Partner	31.27	45.78	41.18	0.075
Employed	8.76	24.10	12.50	<0.001
Lives alone	20.00	18.07	0.00	0.098
Has daily social support	72.80	56.25	50.00	0.001
No ambulatory assistance	58.02	77.38	88.89	<0.001
Lives in a community dwelling	88.61	98.73	94.44	0.015

SA-PO927

The Mechanism of Intestinal Mucosal Dysfunction Induced by Long-Term Peritoneal Dialysis - Activating the P38MPAK Signaling Pathway

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Background: During long-term PD treatment, the abdominal cavity is always in a high pressure, high glucose environment, resulting in peritoneal and intestinal injury. The peritoneal and intestinal injury lead to a series of complications including endogenous peritonitis, abdominal infection, malnutrition, gastrointestinal disorders inadequate dialysis. Unfortunately, the underlying mechanisms of long-term PD induced intestinal mucosal dysfunction remain unclear The present study was designed to investigate the potential molecular mechanisms of intestinal mucosal dysfunction induced by long-term peritoneal dialysis (PD) treatment.

Methods: Modified peritoneal dialysis rat model and lipopolysaccharide induced IEC-6 cell were used to observe. We examined the intestinal mucosal architecture injury induced by long-term PD by HE staining. Intestinal mucosal permeability was determined by measuring the intestinal clearance of fluorescein-isothiocyanate dextran (FD4), the transepithelial electrical resistance (TER) and the serum levels of D-lactate, Diamine oxidase (DAO) and endotoxin. the potential molecular mechanisms were explored by detecting the mRNA expression of ICAM-1, IL-1β, iNOS and TNF-α via real-time qPCR and the protein expression levels of P-p38MAPK, occludin, ZO-1 and DUSP1 via western blot.

Results: Long-term PD could increase the intestinal mucosal permeability by decreasing the level of TER and increasing the intestinal clearance of FD4, resulting in the serum levels of D-lactate, DAO and endotoxin significantly increased. Co-treatment with Fushen granule could decrease the intestinal mucosal permeability. In vivo and vitro studies, long-term PD markedly decreased the mRNA expression of ICAM-1, IL-1β, iNOS and TNF-α, and further activated the p38MPAK signaling pathway via up-regulating the protein expression of P-p38MPAK and down-regulating the protein expression of occludin, ZO-1 and DUSP1. Co-treatment with Fushen granule could markedly increase the mRNA expression of ICAM-1, IL-1β, iNOS and TNF-α and inhibit the activation of p38MPAK signaling pathway.

Conclusions: The present study is the first to demonstrate that long-term PD induces intestinal mucosal dysfunction by activating the p38MAPK signaling pathway.

SA-PO928

High Salt Intake Increases Baseline Peritoneal Transport Rate Through Local TonEBP Activation in Subtotal Nephrectomized Mice

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Background: Baseline peritoneal solute transport rate (PSTR) measured by peritoneal equilibration test (PET) within 6 months after PD commencement varies between patients independently of PD therapy. Previously, we have reported a positive association between baseline D/P Cr and the number of peritoneal blood vessels, macrophages and IL-6-positive cells (2011,NDT). Besides, our recent work has shown that high salt intake promotes tissue inflammation in uremic mice (2017, Lab Invest). The present study aims to probe whether high salt intake causes pre-dialysis intraperitoneal inflammation and leads to high PSTR in subtotal nephrectomized mice.

Methods: Sham-operated (Sham) and subtotal nephrectomized (Nx) mice were randomly given tap water or 1% salt (NaCl)-containing water. After 8 weeks, 4.25% glucose-based PET was performed to evaluate peritoneal function. In another experiment,

overexpressed intraperitoneal IL-6 was functionally blocked by MR16-1 to examine the role of IL-6 in this process. Human mesothelial cell line Met5A was used for in vitro studies.

Results: A significant elevation of D/P Cr and a decrease of D/D0 glucose were observed in Nx+salt group. There was also enhanced angiogenesis and macrophage infiltration in the peritoneum of Nx+salt mice, along with elevated VEGF-A and MCP-1 concentration in the dialysate. Compared to Nx+water group, the increased concentration of effluent but not serum IL-6 suggested a strong local production in Nx+salt group. Blockade of IL-6 signaling by MR16-1 alleviated angiogenesis and macrophage infiltration in Nx+salt mice and rescued peritoneal transport function. In cultured human mesothelial cells, 40mM additional NaCl in the medium could significantly upregulate the expression of IL-6, as well as VEGF-A and -C, companied by an increased expression and nuclear translocation of TonEBP, an osmolality-sensing transcription factor. Knockdown of TonEBP by siRNA could lower such overexpression caused by high tonicity. Notably, peritoneal expression of TonEBP in Nx+salt group also showed an upregulation, indicating a key role of it in higher peritoneal transport status.

Conclusions: These findings suggest that high salt intake under uremic status could increase peritoneal transport rate via local TonEBP activation.

Funding: Commercial Support - CHUGAI PHARMACEUTICAL CO.,LTD., Government Support - Non-U.S.

SA-PO929

Attenuation of Glucose-Induced Inflammatory Reaction by Blocking of TonEBP in Primary Cultured Human Peritoneal Mesothelial Cells

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Background: Long-term exposure to high-glucose concentration in peritoneal dialysate can cause peritoneal damage by inflammatory reaction and fibrosis in the peritoneum, which finally leads to withdrawal from peritoneal dialysis. Recently, it is known that tonicity induced transcriptional activator, TonE binding protein (TonEBP), is involved in the pathogenesis of diabetic complications such as retinopathy and nephropathy (*Cardiovasc Diabetol. 2016 Jan 29;15:18, J Am Soc Nephrol. 2018 Feb;29(2):492-504*).

Methods: Here, we examined the role of TonEBP in glucose induced inflammation using primary cultured human peritoneal mesothelial cells (HPMCs). HPMCs were isolated from peritoneal effluents of patients on peritoneal dialysis. Isolation and characterization of HPMCs were verified by cobblestone like characteristic morphology and the expression of the standard mesothelial markers.

Results: First, we observed that both high concentration of NaCl and 2% glucose induced increase in TonEBP mRNA expression and activation of TonEBP by nuclear translocation in cultured HPMCs. Aldose reductase (AR) mRNA expression, a target gene of TonEBP, was increased by high NaCl and glucose as expected. The treatment of NaCl and glucose increased in abundance of p65, NF-κB protein, but did not induce nuclear translocation of it. The gene expression of inflammatory markers such as IL-6, IL-8, MCP-1 and IκB was increased in culture HPMCs by high glucose treatment. High glucose also increased cytokine levels of IL-6, IL-8 and MCP-1 in supernatant of HPMCs. Next, we examined the role of TonEBP in those inflammatory reactions by blocking of TonEBP using TonEBP disrupted MEF cells and TonEBP siRNA in HPMCs. IL-6 and IL-8 mRNA expression was decreased in both TonEBP disrupted MEF cells and TonEBP si-RNA treated HPMCs. However, there was discrepancy in the effect of high glucose on MCP-1 and IκB expression by TonEBP blocking between TonEBP disrupted MEF cells and TonEBP si-RNA in HPMCs.

Conclusions: Our findings suggest that TonEBP is involved in high-glucose induced inflammatory changes in the peritoneum of peritoneal dialysis patients, which could be prevented by blocking TonEBP action.

SA-PO930

Transcriptomic Analysis of PCK Rat Peritoneum After Long -Term Infusion of Dialysate with Mono or Dual Therapy of a JAK1/2 Inhibitor and/or Losartan

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Background: Peritoneal dialysis (PD) is limited by reduced efficacy over time. Peritoneal membrane (PM) injury is characterized by inflammation, hypervascularity, and fibrosis. JAK/STAT signaling mediates inflammatory pathways, including angiotensin signaling. Our previous work showed in rats with polycystic kidneys (PCK) chronically infused with 4.25% Dianeal x 16 wks, treatments with JAK1/2 inhibitor (JAK1/2i), losartan, or both preserved PM structure; JAK1/2i conferred better structural preservation vs losartan. Monotherapy with either JAK1/2i or losartan failed to consistently preserve PM function; dual infusion consistently preserved PM function. In order to elucidate mechanism at the transcriptomic level, we performed RNAseq analysis on PCK rat peritoneum.

Methods: PCK rats received dialysate infusions BID via an implanted subcutaneous port in the neck tunneled to the intraperitoneal cavity for 16 wks in the following groups: **(1)** 4.25% Dianeal; **(2)** 4.25% Dianeal + JAK1/2i (5mg/kg BID); **(3)** 4.25% Dianeal + Losartan (5mg/kg BID); and **(4)** 4.25% Dianeal + Losartan +JAK1/2i (5mg/kg BID each). PM with muscle was sampled for RNAseq. Total RNA was used, cDNA libraries were single-end sequenced (50bp) on an Illumina HiSeq 3000. Differentially expressed genes are defined as at least 2-fold change and $p<0.05$.

Results: Compared to PCK rats receiving Dianeal only, concomitant infusion of Dianeal and JAK1/2i or losartan up- or downregulated expression of 88 genes in 132 canonical pathways and 36 genes in 55 pathways respectively. Combination treatment with JAK1/2i and losartan caused differential expression of 29 genes in 65 pathways. When comparing PCK rats that received JAK1/2i to losartan, 38 genes in 98 pathways were differentially expressed. 12 genes were regulated by either JAK1/2i or losartan with a similar pattern, of which, only three were similarly regulated when both JAK1/2i and losartan were infused.

Conclusions: The differentially expressed gene pattern may explain superior morphologic protection in the JAK1/2i group and the functional preservation in the dual therapy group that we previously showed in our study. The transcriptomic analysis in this study provides gene differential expression profiles of JAK1/2i and losartan that helps explain different treatment effects.

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SA-PO931

Trehalose Ameliorates Peritoneal Fibrosis Through the Suppression of Fibroblast Proliferation and Extracellular Matrix Production in Fibroblasts

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Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies to treat and/or prevent for it. Trehalose is a non-reducing disaccharide and can be an osmolyte of peritoneal dialysis solution. We have previously revealed that trehalose ameliorated peritoneal fibrosis through the induction of autophagy and the downregulation of Snail protein in peritoneal mesothelial cells. In this study, we examined if trehalose also has anti-fibrotic effects on fibroblasts in the peritoneum.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chlorhexidine gluconate (CG). 5% trehalose or vehicle (normal saline) was administered by intraperitoneal injection to mice every other day.

Results: Trehalose attenuated CG-induced increases in peritoneal thickness, type I pro-collagen mRNA expression and hydroxyproline content (n=4-9). In addition, CG challenges induced a marked peritoneal accumulation of α smooth muscle actin $(\alpha SMA)^+$ fibroblasts that was significantly reduced by trehalose. We next examined fibroblast proliferation induced by CG challenges in $ColI\alpha_2$-enhanced green fluorescent protein (GFP) transgenic mice. In order to specifically identify proliferating fibroblasts, we double-stained peritoneal sections with anti-PCNA antibody and anti-GFP antibody. The number of PCNA and GFP dual positive proliferating fibroblasts in the peritoneal tissue after CG challenges was significantly increased in the vehicle group as compared to the trehalose group, as was the percentage of proliferating fibroblasts among total fibroblasts. We also performed an in vitro study to confirm the effects of trehalose on the proliferation of fibroblasts. TGF-β_1 induced fibroblast proliferation; however, trehalose suppressed the fibroblast proliferation in a dose-dependent manner. In addition, trehalose attenuated αSMA, $ColI\alpha_1$, $Col3\alpha_1$ and fibronectin mRNA expression induced by TGF-β_1.

Conclusions: Our results suggest that trehalose might be a novel therapeutic reagent for peritoneal fibrosis through the suppression of fibroblasts proliferation and extracellular matrix production in fibroblasts.

SA-PO932

Novel Role of Nuclear Factor of Activated T-Cells 5 (NFAT5) as a Mediator of EMT of Peritoneal Mesothelial Cells (MCs) via Modulation of Nod-Like Receptor-3 (NLRP3) Inflammasome

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Background: Epithelial-to-mesenchymal Transition (EMT) of MCs is known as an early mechanism of peritoneal fibrosis in PD. NLRP3 inflammasome is comprised of the NLRP3, ASC and procaspase-1, which leads to the maturation of IL-1β and IL-18. NFAT5 is an essential transcription factor regulating cellular homeostasis to hypertonicity-induced osmotic stress, and recently reported as a pro-inflammatory mediator. We investigated whether NFAT5 plays a role in peritoneal EMT via a modulation of NLRP3 inflammasome in MCs.

Methods: The expressions of NFAT5, components of NLRP3 inflammasome, nuclear translocation of NFAT5, β-catenin and snail were evaluated by western blotting. EMT was evaluated by the changes in morphology and markers of epithelial and mesenchymal cells. E-cadherin promoter activity was confirmed by luciferase assay. Effect of gene silencing of NFAT5, NLRP3 and ASC on EMT was examined using siRNA. Animal model of peritoneal fibrosis was established by intraperitoneal injection of adenoviral vector of TGFβ in BL6 mouse.

Results: TGFβ increased NFAT5 expression and its nuclear translocation in MC. TGFβ-induced EMT was associated with an up-regulation of NLRP3, ASC, procaspase-1 and an increased production of IL-1β/IL-18. In adenoviral TGFβ-injected mice, EMT of MC with submesothelial fibrosis was observed with an increased expression of NFAT5 and NLRP3. siNFAT5 ameliorated TGFβ-induced EMT with an increase in E-cadherin

promotor activity as well as a decrease in snail expression and nuclear translocation of β-catenin. siNLRP3, siASC and neutralizing antibodies of IL-1β and IL-18 alleviated TGFβ1-induced EMT. siNFAT5 also alleviated TGFβ1-induced activation of NLRP3 inflammasome. Neither MAPK inhibitors (PD98059, SB203580) nor antioxidants (NAC, Apocynin, Mitotempo) altered TGFβ1-induced up-regulation of NFAT5 of MC.

Conclusions: This data suggest NFAT5 plays a key role in peritoneal EMT via tonicity-independent mechanism by either an inhibition of E-cadherin transcription and activation of NLRP3 inflammasome. Modulation of NFAT5 and NLRP3 inflammasome in MCs could be a novel approach to protect the peritoneum from the development of EMT and peritoneal fibrosis in PD patients.

SA-PO933

Intra-Nuclear Binding of NFAT5/TonEBP to ß-Catenin Is a Key Process of Hypertonicity-Induced Phenotype Transition of Peritoneal Mesothelial Cells (MCs)

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Background: Epithelial-to-mesenchymal transition (EMT) of MCs is an early mechanism of peritoneal fibrosis in peritoneal dialysis. Nuclear Factor of Activated T Cells-5 (NFAT5), also known as TonEBP, is a transcriptional factor that enables cellular adaptation to hypertonic osmotic stress. Recent data demonstrated the role of NFAT5/TonEBP in phenotype transition of cancer cells. The aim of this study is to investigate whether NFAT5/TonEBP is involved in hypertonicity-induced EMT of MCs and to identify the potential mechanisms of NFAT5/TonEBP-mediated peritoneal EMT.

Methods: The expressions of NFAT5/TonEBP, other osmotic stress-related genes including sodium-myoinositol cotransporter (SMIT), betaine/γ-aminobutyric acid transporter (BGT1) and aldose reductase (AR) and nuclear translocation of β-catenin were evaluated by real-time PCR and western blotting. EMT was evaluated by morphological changes of MCs and the expressions of E-cadherin and α-SMA after stimulation of high glucose (HG, 30-120 mM) and mannitol (30-120 mM). E-cadherin promoter activity was confirmed by luciferase assay. The interaction between TonEBP and β-catenin was analyzed by immunoprecipitation.

Results: Both HG or Mannitol enhanced the expression of NFAT5/TonEBP as well as SMIT, BGT1 and AR at transcriptional and translational levels from the concentration of 30 mM. HG induced EMT of MCs, however mannitol did not show the evidence of EMT even at the concentration of 120 mM. HG (>30 mM) induced nuclear translocation of NFAT5/TonEBP which was associated with an enhanced binding to β-catenin. Mannitol also promoted nuclear translocation of NFAT5/TonEBP only at the highest concentration we tested (120 mM), however it was not associated with intra-nuclear binding of NFAT5/TonEBP to β-catenin. In contrast to persistent increase in intra-nuclear β-catenin in HG-exposed MCs, there was only a transient increase in β-catenin with 120 mM of mannitol at 1 hour. HG decreased E-cadherin promoter activity whereas mannitol did not alter the transcription of E-cadherin.

Conclusions: The role of NFAT5/TonEBP as a mediator of peritoneal EMT is demonstrated in this study for the first time. Not the increased expression of NFAT5/TonEBP per se but intra-nuclear translocation with binding to β-catenin is a key mechanism by which NFAT5/TonEBP induced EMT of MCs.

SA-PO934

The Expression of Glucose Transporters (GLUTs) and Sodium-Glucose Co-Transporters (SGLTs) in Peritoneal Mesothelial Cell (MC) and Its Role in Phenotype Transition of MC

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Background: Phenotype transition of MCs such as epithelial-to-mesenchymal transition (EMT) by glucose or proinflammatory cytokines is known as an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). Given the consideration of high glucose concentration in peritoneal dialysate, the expressions of GLUTs and SGLTs in MC may play a role in peritoneal EMT. However, there are few data on the expression and regulation of GLUTs and SGLTs in MCs. We investigated the expression of each isoform of GLUTs and SGLTs, and their role in EMT of peritoneal MCs.

Methods: MCs were also isolated from overnight dwell dialysate effluents from clinically stable PD patients (MCs-DE) as well as omentum (MCs-OT) to assess the expression of GLUTs and SGLTs. The expressions of GLUT-1, -2, -3, SGLT-1, and -2 were investigated by real-time PCR and Western botting. EMT was evaluated by the changes in cell morphology and expression of epithelial and mesenchymal cell markers. To investigate the role of SGLTs in peritoneal EMT, the effects of Dapagliflozin (SGLT2 inhibitor, 500nM) and Empagliflozin (SGLT 1/2 inhibitor, 500nM) were evaluated.

Results: GLUT-1, -2, -3, SGLT-1 and -2 were constitutively expressed in MC, and up-regulated by the stimulation with high glucose (HG, 60 mM) both at mRNA and protein levels. GLUT-1 and -3 were quantitatively major transporters in MCs, however HG-induced upregulation was more prominent in SGLT-1 and -2. The expression of GLUT-1, -2, SGLT-1 and -2 were higher in MCs-DE compared to MCs-OT which have never been exposed to dialysate. TGFβ also increased the expression of GLUT-1, -2, -3, SGLT-1 and -2. High glucose- and TGFβ-induced EMT in MCs-OT were ameliorated by pre-treatment with Dapagliflozin or Empagliflozin.

Conclusions: Modulation of the activity and expression of glucose transporters in MCs by specific inhibitors or glucose-sparing prescription of peritoneal dialysis could be a novel therapeutic approach to protect the peritoneum from the development of EMT and peritoneal fibrosis in PD patients.

SA-PO935

Astragalus Inhibits Epithelial-to-Mesenchymal Transition of Peritoneal Mesothelial Cells by Down-regulating β-Catenin

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Background: The epithelial-to-mesenchymal transition (EMT) of peritoneal mesothelial cells (PMCs) is a crucial event in the induction of peritoneal fibrosis (PF), in which canonical Wnt/β-catenin signaling participates. Smads signaling is reported to interact with β-catenin and synergistically regulates EMT. Astragalus is the traditional Chinese herbal which has an effect to restrain the ROS, anti-inflammatory, anti-fibrosis, etc. This study was aimed to reveal the effect of Astragalus on β-catenin in EMT of PMCs.

Methods: The HMrSV5 cell line and gene transfection rats were treated with Astragalus. EMT markers or signaling pathway-related indicators were detected by western blotting, immunofluorescence, immunohistochemistry, immunoprecipitation and real-time PCR.

Results: HMrSV5 EMT model was established by TGF-β1, and the peritoneal fibrosis rat model was established by 4.25% glucose peritoneal dialysis solution. Astragalus inhibited EMT of PMCs including increased E-cadherin and decreased α-SMA and Vimentin, as well as attenuated peritoneal thickening and fibrosis in rats. During the process of PMCs EMT, Astragalus could inhibit β-catenin expression. Astragalus down-regulated β-catenin by stabilizing the GSK-3β/β-catenin complex and further inhibited the nuclear translocation of β-catenin. Meanwhile, Akt is the upstream protein of GSK-3β/β-catenin, which could regulate the degradation of β-catenin. On the other hand, Astragalus down-regulated β-catenin by enhancing Smad7 expression. Silencing Smad7 in HMrSV5 and rats antagonized the EMT-inhibitory effect of Astragalus.

Conclusions: Astragalus inhibits EMT of PMCs by down-regulating β-catenin. The modulation of β-catenin in peritoneum can be a novel tool to prevent PF.

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SA-PO936

Connective Tissue Growth Factor Is Correlated with Peritoneal Lymphangiogenesis

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Background: Lymphatic absorption in peritoneal cavity may contribute to ultrafiltration failure in peritoneal dialysis (PD). Lymphatic vessels develop during PD-related peritoneal fibrosis. Connective tissue growth factor (CTGF, also known as CCN2) is an important determinant of fibrotic tissue remodeling, but little is known about its possible involvement in lymphangiogenesis. We studied the relationship between CTGF and lymphangiogenesis in association with PD.

Methods: Protein levels of CTGF and vascular endothelial growth factor-C (VEGF-C), a major lymphangiogenic factor, were measured in 77 human PD effluents. Messenger RNA (mRNA) expression of CTGF, lymphatic markers (lymphatic endothelial hyaluronan receptor-1 [LYVE-1] and podoplanin), and VEGF-C was analyzed in 56 human peritoneal biopsies. CTGF and VEGF-C mRNA were assessed in cultured human peritoneal mesothelial cells (HPMC) (N=21) treated with transforming growth factor-β1 (TGF-β1). CTGF involvement in diaphragamatic lymphangiogenesis was explored in a rat peritoneal fibrosis model induced by chlorhexidine gluconate (CG). Finally, the role of CTGF inhibition in peritoneal lymphangiogenesis was evaluated in the CG model using CTGF knockout mice.

Results: A positive correlation was observed between CTGF and VEGF-C concentration in human PD effluents ($R=0.428$, $p<0.001$). CTGF mRNA positively correlated with VEGF-C ($R=0.67$, $p<0.001$), LYVE-1 ($R=0.638$, $p<0.001$), and podoplanin ($R=0.592$, $p<0.001$) mRNA in human peritoneal biopsies. There was a positive relationship between CTGF and VEGF-C mRNA fold-increase in HPMC at 12 hours after TGF-β1 treatment ($R=0.722$, $p<0.001$). Immunohistochemstry and in situ hybridization showed that CTGF, VEGF-C, and LYVE-1-positive lymphatic vessels were increased in the rat diaphragm of CG model compared with controls. CTGF expression positively correlated with VEGF-C expression ($p<0.001$) and lymphatics ($p<0.05$) in the rat diaphragm of CG model. Finally, CTGF gene deletion significantly reduced VEGF-C expression and suppressed lymphangiogenesis in the mouse peritoneum of CG model.

Conclusions: Our results suggest a close relationship between CTGF and PD-associated lymphangiogenesis.

SA-PO937

The Role of Suppression of Tumorigenicity-2 (ST2) in the Peritoneal Fibrosis and Peritoneal Dialysis (PD) Outcomes

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Background: Peritoneal fibrosis (PF) is an intractable complication which leads to peritoneal membrane failure in PD. The aim of this study is to investigate the role of ST2 involved in PF.

Methods: Samples of dialysate and clinical data were prospectively collected from 54 patients at Seoul National University Hospital between 2010 and 2016. Dialysate soluble ST2 (sST2) levels were measured after 1 month of PD initiation (baseline) using the ELISA technique. Fibrosis induced by TGFβ and high concentration of glucose in primary cultured human peritoneal mesothelial cells (HPMCs) were evaluated with ST2, fibronectin, β-galactosidase, snail and E-cadherin protein expressions. Anti-ST2 monoclonal antibody (mAb) was treated to evaluate the neutralizing effect of ST2 on PF. Immunohistochemistry (IHC) stain of ST2 was performed in peritoneum tissue samples of chlorhexidine gluconate (CG)-induced PF mice and control.

Results: Baseline dialysate sST2 (sST2-b) levels were 2063.4 ± 2457.8 pg/mL and mean duration of follow-up periods was 53.4 ± 18.8 months. We observed that patients who changed dialysis modality to hemodialysis due to PD failure had high sST2-b levels in peritoneal effluent compared with others (1576.2 ± 199.9 vs 4143.1 ± 1107.3, P = 0.03). High sST2-b was associated with a hazard ratio (HR) for PD failure of 7.72 (95% CI 1.10-54.3, P = 0.04) in a fully adjusted model. sST2-b showed a good performance of predicting PD failure; the area under the ROC curve was 0.784 (P = 0.001). We found that in primary cultured HPMCs, TGFβ treatment increased protein expressions of ST2, fibronectin, β-galactosidase, snail and decreased expression of E-cadherin in a dose-dependent manner. Protein expression of ST2 and fibronectin were decreased after anti-ST2 Ab administration. High concentration of glucose (100mmol/L) also induced fibrosis in HPMCs and fibrosis was ameliorated after treating anti-ST2 Ab. ST2 was found in fibroblasts and mesothelial cells within the underlying submesothelial zones of CG-induced PF mice.

Conclusions: Elevated dialysate levels of sST2 is associated with PD failure. Thus, an elevated dialysate levels of ST2 appears to play a role in fibrosis and inflammation during peritoneal injury. And ST2 blockade is a potential therapeutic target for renal preservation.

SA-PO938

Longitudinal Changes of NF-kB Downstream Mediators and Peritoneal Transport Characteristics in New Peritoneal Dialysis Patients

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Background: The success of peritoneal dialysis (PD) depends on the semi-permeable peritoneal membrane. The regulation of peritoneal transport remained to be fully elucidated, but intra-peritoneal cytokines, notably interleukin-6 (IL-6), cyclo-oxygenase-2 (COX-2), and hepatocyte growth factor (HGF), probably play important roles. We investigate the relation between longitudinal changes in PD effluent cytokine levels and the corresponding alterations in peritoneal transport parameters over 1 year.

Methods: We studied 46 new PD patients who had peritoneal equilibration test performed at baseline and then one year later. Dialysate-to-plasma creatinine level at 4 hours (D/P4), mass transfer area coefficient of creatinine (MTAC), and ultrafiltration (UF) volume were taken as peritoneal transport parameters. Concomitant PD effluent levels of IL-6, COX-2 and HGF were measured and compared.

Results: There were significant correlations between baseline as well as one-year PD effluent IL-6 and COX-2 levels with the corresponding D/P4 and MTAC. The change in PD effluent IL-6 and COX-2 levels from baseline to one year also correlated with the change in D/P4 and MTAC during the same time. In contrast, PD effluent HGF did not showed any significant correlation with the corresponding D/P4 and MTAC, both at baseline and one year later. After one year, patients who had peritonitis had higher PD effluent IL-6 (26.6 ± 17.4 vs 15.1 ± 12.3 pg/ml, p = 0.037) and COX-2 levels (4.97 ± 6.25 vs 1.60 ± 1.53 ng/ml, p = 0.007) than those without peritonitis, and the number of peritonitis episode during follow up period significantly correlated with the PD effluent IL-6 and COX-2 levels after one year. No significant difference in PD effluent HGF level after 1 year of dialysis are noted between patient with and without peritonitis. There was no significant difference in any cytokine level between patients who received conventional and low glucose degradation product PD solutions.

Conclusions: PD effluent IL-6 and COX-2 levels significantly correlate with the peritoneal transport characteristics. Patients who had peritonitis during the follow up period had higher PD effluent IL-6 and COX-2 levels after one year than patients without peritonitis. Our result suggests that intra-peritoneal IL-6 and COX-2 play important roles in the short-term regulation of peritoneal transport.

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SA-PO939

Inhibition of mPGES-1 Blocks High Glucose-Induced Mesothelial-to-Mesenchymal Transition of Peritoneal Mesothelial Cells

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Background: Peritoneal mesangial cells (PMC) undergoing mesothelial-to-mesenchymal transition (MMT) induced by chronic sterile inflammation promotes peritoneal fibrosis. Microsomal prostaglandin E2 synthase-1 (mPGES-1)-derived PGE2 plays an important role in inflammatory disease. Previous studies have shown that the secretion of PGE2 increased significantly in PMC under the circumstance of high glucose. This study aimed to investigate the role of mPGES-1 in phenotype transition of PMC.

Methods: The expression of mPGES-1 in human peritoneum tissue was evaluated by immunohistochemical. Human mesothelial cells were incubated with 138mmol/L glucose for various periods of time. After transfection of shRNA plasmid targeting mPGES-1, human mesothelial cells were incubated with 138mmol/L glucose and harvested for further analysis.

Results: Immunohistochemical analysis displayed mPGES-1 was expressed in the outermost layer of the peritoneal membrane and upregulated in peritoneal tissue of patients with peritoneal ultrafiltration failure. In cultured human mesothelial cells, high glucose time-dependently increased the expression of mPGES-1. Western blots confirmed that mPGES-1 was increased more than threefold by high glucose. Besides, application of mPGES-1 shRNA plasmid significantly reduced protein and mRNA expressions of mPGES-1 in human mesothelial cells. Moreover, inhibition of mPGES-1 in human mesothelial cells dramatically reversed levels of E-cadherin and decreased the synthesis of MMT-related proteins, such as fibronectin and vimentin.

Conclusions: The findings suggest that mPGES-1 could be activated by high glucose and could contribute to MMT of PMC.

SA-PO940

Hyaluronan Generated During Peritoneal Dialysis Does Not Drive Fibrosis, but Regulates Inflammatory Cell Recruitment Through Differential Hyaluronan Synthase (HAS) Expression

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Background: Peritoneal membrane dysfunction is a key determinant of Peritoneal Dialysis (PD) failure, and is associated with repeated episodes of peritonitis and exposure to bio-incompatible dialysis solutions. TGF-β1-driven transdifferentiation of mesothelial cells to myofibroblasts through mesothelial to mesenchymal transition (MMT) underlies peritoneal membrane dysfunction and ultimately peritoneal fibrosis. In solid organ fibrosis (kidneys & lungs), pro-fibrotic cell differentiation is driven by changes in synthesis and macromolecular organisation of the matrix polysaccharide hyaluronan (HA). In this work, we determine whether factors that regulate HA synthesis in the peritoneum have a the role in driving peritoneal inflammation and in the prevention/reversal of fibrosis

Methods: *In-vitro* studies were performed on human peritoneal mesothelial cells and *ex-vivo* PD effluent from patients with peritonitis. Genetic and histological analysis of peritoneal membranes from a murine model of peritoneal inflammation (live attenuated *staphylococcus epidermidis* induced peritonitis) were utilised *in-vivo*

Results: Patients with PD peritonitis had significantly increased HA concentrations day-1 after developing acute bacterial peritonitis compared to non-infected patients. TGF-β1-driven MMT in primary human mesothelial cells significantly increased extracellular HA generation, predominantly driven by Hyaluronan Synthase-1 (HAS1) isoenzyme expression. In contrast to kidney and lung fibrosis this increased HA was not causally involved in driving MMT. Instead, HAS1 in peritoneal tissues and mesothelial cells was associated with enhanced leukocyte recruitment and activation in the peritoneum. Blockade of HAS1 driven HA synthesis in mice led to delayed neutrophil clearance and monocyte recruitment indicating a delayed inflammatory response

Conclusions: In contrast to solid-organ fibrosis where HA seems to have an important role in driving fibrosis through a HAS2 dependent phenotype, TGF-β1 driven MMT in mesothelial cells generates HA that is not involved in peritoneal fibrosis. HAS1 generated by mesothelial cells appears to be involved in regulating the acute inflammatory response and may be involved in reparative processes that limit fibrosis in the peritoneum

SA-PO941

Protein Kinase C-Beta Deficiency and Inhibition Exacerbate High Glucose-Induced Peritoneal Damage via M1/M2 Macrophage Polarization

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Background: Macrophage (MØ)-driven inflammation is a key hallmark of glucose-mediated damage to the peritoneal membrane (PM) during peritoneal dialysis. We have recently shown that in mesothelium PKCα is a major mediator of PM damage, whereas PKCβ deficiency results in increased glucose-mediated PM damage. PKCβ is expressed most abundantly in MØ. We hypothesized that within a high glucose milieu PKCβ plays an important role in controlling MØ activation and function.

Methods: Combining qPCR, ELISA, Western blot, and flow cytometry we investigated primary murine peritoneal MØ of *PKCβ*$^{-/-}$ and wild type (WT) mice, murine bone marrow-derived MØ of WT mice, and primary human peripheral blood monocyte-derived MØ

during normal (10mM) and high glucose (120mM) conditions. Some experiments involved LPS stimulation and pharmacological PKCβ inhibition using ruboxistaurin. *In vivo* PM damage was evaluated in a chronic peritoneal dialysis mouse model in *PKCβ*$^{-/-}$ and WT mice using flow cytometry and immunofluorescence.

Results: *In vitro* murine MØ, in comparison to PKCα, abundantly (>50-fold) expressed PKCβ mRNA at normal glucose conditions. A high glucose milieu induced PKCβ and suppressed PKCα mRNA and protein expression. High glucose conditions facilitated murine and human MØ polarization towards M2. Both genetic deficiency and pharmacological inhibition of PKCβ increased high glucose+LPS-mediated IL-6, TNFα, and MCP-1 production and decreased IL-10 release compared to a state of genetic or functional presence of PKCβ. *In vivo* catheter-delivered treatment with high glucose peritoneal dialysis fluid for 5 weeks induced PKCβ up-regulation in omentum rich of MØ in WT mice and resulted in an inflammatory response and PM damage characterized by fibrosis and neo-angiogenesis. In comparison to WT mice, destructive changes were strongly aggravated in *PKCβ*$^{-/-}$ animals. Finally, flow cytometry and immunofluorescence demonstrated a substantial M1 polarization of peritoneal MØ in *PKCβ*$^{-/-}$ mice, while WT mice predominantly mounted an M2 response.

Conclusions: PKCβ is the dominant PKC isoform in peritoneal macrophages. It is up-regulated and exerts peritoneal anti-inflammatory effects in a high glucose milieu both *in vitro* and in an *in vivo* mouse model of chronic peritoneal dialysis via M1/M2 macrophage polarization.

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SA-PO942

The Global DNA Methylation Profile of Human Peritoneal Fibrosis

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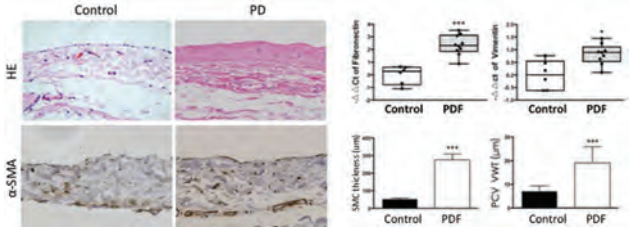
Background: Long-term exposure to biocompatible peritoneal dialysate induced peritoneum fibrosis, exacerbating peritoneal dialysis (PD) efficiency.

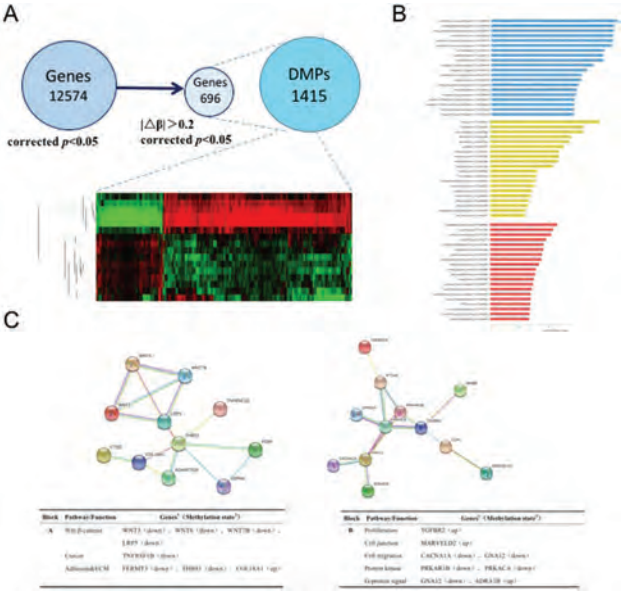
Methods: Peritoneal tissues of PD patients were obtained during kidney transplantation (PD group, n=10), along with Control group from normal individuals (n=6). Histological staining and qRT-PCR were applied to evaluate the peritoneal fibrosis level, while Infinium® HumanMethylation EPIC was used to analyze differentially methylated probes (DMPs), which formed the gene clusters (corrected p<0.05, |Δβ|>0.2). Functional network analysis was applied to extract the key regions within the interaction.

Results: Structural remodeling was found in Peritoneum from PD patients, including SMC significant thickening, vascular wall of peritoneal postcapillary venules thickening (p<0.001). The number of α-SMA positive cells in PD peritoneum increased, with up-regulation of Fibronectin and Vimentin mRNA (p<0.05). The global DNA methylation level decreased in PD peritoneum, with 9,948 up-regulated DMPs and 39,109 down-regulated DMPs, which covered all euchromosome and were enriched in function or pathway terms such as cell morphology, cell migration, and ECM buildup; functional analysis of the CpG-rich regions revealed THBS1 and PRKACA are two key functional blocks related to cell proliferation/migration, which involved Wnt/β-catenin signaling pathway and PKA signaling pathway, respectively.

Conclusions: Fibrotic structural remodeling was presented in the peritoneum of PD patients, with a hypomethylated reprogramming of the global DNA methylation profile.

Funding: Government Support - Non-U.S.





SA-PO943

Direct Interaction of Mesothelial Cells with Macrophages via Stalked Fractalkine Promotes Dialysate Induced Peritoneal Fibrosis

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Background: Fibrosis limits the use of peritoneal dialysis (PD) as renal replacement therapy. PD solution induces mesothelial cell activation and macrophage accumulation in the peritoneal wall. Macrophages highly express chemokine receptor CX3CR1. Its ligand fractalkine (CX3CL1) exists in a stalked surface-bound and a soluble form. This study addressed their role in peritoneal fibrosis.

Methods: Wildtype and CX3CR1 deficient mice received dialysis solution for human use via a peritoneal catheter for six weeks and tissues were analyzed by histology. Murine and human primary cells were investigated using a combination of qPCR, ELISA, flow cytometry and confocal microscopy.

Results: Human and murine peritoneal mesothelial cells expressed surface-bound and secreted fractalkine/CX3CL1. During experimental PD treatment in mice, CX3CL1 increased on the peritoneal membrane. Cytokines TNFα, IL-1β and TGFβ markedly induced CX3CL1 expression by mesothelial cells in vitro. In addition, direct co-culture with CX3CR1-competent macrophages induced CX3CL1 and also TGFβ, a main promoter of fibrosis. The increase of CX3CL1 and TGFβ in direct macrophage-mesothelial coculture was no longer observed in transwell co-cultures and also disappeared in direct coculture with CX3CR1 deficient macrophages, indicating a role for cellular CX3CR1-CX3CL1 interaction. TGFβ increased macrophage CX3CR1 expression and Increased CX3CR1 was observed during PD treatment. Wildtype mice developed significantly more peritoneal fibrosis than CX3CR1 deficient animals. Peritoneal dialysis solution directly induced macrophage IL-1β, one of the mesothelial CX3CL1-promoting cytokines, thus providing a mechanism of initiation for this pro-fibrotic interaction loop. Peritoneal dialysis patients' peritoneum expressed more CX3CL1 than untreated tissue and CX3CR1 was higher in serum of patients that recently started PD than in controls, providing evidence of relevance in the human situation.

Conclusions: PD solution initiates a pro-fibrotic loop of mesothelial CX3CL1 binding to macrophage CX3CR1 that promote peritoneal fibrosis in vivo. Similar observations in human cells suggest that CX3CR1-CX3CL1 interaction should be investigated further as a new therapeutic angle in peritoneal fibrosis.

SA-PO944

Early Peritoneal Dialysis Ameliorates Acute Lung Injury Induced by Blast Injury in Rats

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Background: Blast injury frequently occurs in wars and disasters. Blast lung injury is the most common type of blast injury with a remarkable lack of effective treatment. Blast lung injury manifested as pulmonary hemorrhage, edema and secondary systemic inflammation. This study aimed to investigate the therapeutic efficacy and mechanism of peritoneal dialysis in rats with blast lung injury.

Methods: 75 SD rats were randomly divided into five groups: control group, sham group, glucocorticoid (GC) group, peritoneal dialysis (PD) group, PD+GC (PDGC) group. All rats were injured by bio-shock tube (BST-I) apparatus. PD group was treated with continuous peritoneal dialysis for 6 hours. GC group were injected with a small dose of

methylprednisolone. Lung function, pathological changes and pneumonedema in rats were detected after 24h treatment. Inflammatory cytokine levels in serum were determined by the technology of Milliplex.

Results: 37 rats (49.3%) survived at 24 hours after blast injury. There was no significant difference in the mortality rate between the groups. Lung water content of rats in PD and PDGC groups were significantly lower than that of the control group. Pathological staining showed that the degree of pulmonary interstitial edema in PD and PDGC rats was significantly lower than that in the control group. Pulmonary function (FVC, functional residual capacity, oxygen saturation, arterial oxygen pressure, oxygenation index, and maximal mid expiratory flow) in PD and PDGC groups was significantly higher than that of the control group. The serum levels of IL-1β, IL-6, MCP-1 and TNFα in the PD and PDGC rats were significantly lower than those in the control group. The levels of IL-1β and TNFα in the serum of GC rats were significantly lower than those of the control group.

Conclusions: Early peritoneal dialysis improves acute lung injury and systemic inflammation induced by blast injury.

Funding: Government Support - Non-U.S.

SA-PO945

Is Abdominal Muscle the Right Parietal Peritoneal Tissue for Gene Expression Analysis?

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Background: Recently there has been increased interest in studying peritoneal membrane pathophysiology at a transcriptomic level in animal models. Standard tissue sampling includes abdominal wall muscle. Some consider muscle as part of the peritoneal barrier. However the massive muscle mass overwhelms signals from the mesothelium and sub mesothelial compact zone where much of the peritoneal ultrafiltration occurs. To address this, we performed RNAseq in microdissected parietal peritoneum without muscle compared to the samples with muscle in rats with polycystic kidneys (PCK) chronically infused with 4.25% Dianeal, with or without JAK1/2 inhibitor (JAK1/2i) or losartan for 16 wks.

Methods: PCK rats received dialysate infusions BID for 16 wks in the following groups: Control-no infusion; 4.25% Dianeal; 4.25% Dianeal + JAK1/2i (5mg/kg BID); 4.25% Dianeal + Losartan (5mg/kg BID). Parietal peritoneum was sampled either with microdissection under anesthesia without muscle or standardly with muscle. Total RNA was used, cDNA libraries were single-end sequenced (50bp) on an Illumina HiSeq 3000. Differentially expressed (DE) genes are defined as at least 2-fold change and $p<0.05$. Comprehensive pathway analysis was performed using Ingenuity's Pathway Analysis (IPA).

Results: As shown (Table), there are significant differences in DE genes or pathways when using different samples with the same intervention. The peritoneum without muscle shows significantly more DE genes with more pathways involved. When comparing samples ± muscle, only a few shared gene transcript changes were observed.

Conclusions: Microdisseted parietal peritoneum samples showed more DE genes and pathways than samples with muscle. Our study suggests more precise tissue sampling should be considered to better reflect peritoneal signals in transcriptomic analysis studies.

Funding: Commercial Support - Renal research Institute

Groups	Samples	DE Genes	Canonical Pathways	Overlapped Genes	Top 3 pathways	Top 5 Upregulated Genes	Top 5 Downregulated Genes
Control vs Dianeal	Peritoneum with muscle	56	186	Cpz, Gbp1, Gdf11, Gltpd2, Mmp8, Pygl, S100a8, S100a9	Role of IL-17A in Psoriasis; HIF1α Signaling; Atherosclerosis Signaling	Sectm1b, Gdf11, Snai3, Cd3, Fam131c	Tgfbr1, Mmp8, S100a9, S100a8, Klk1c9
	Peritoneum without muscle	597	376	Cpz, Gbp1, Gdf11, Gltpd2, Mmp8, Pygl, S100a8, S100a9	G-Protein Coupled Receptor Signaling; Hepatic Fibrosis / Hepatic Stellate Cell Activation; Axonal Guidance Signaling	Cdc129, Ptprv, S100a4, Cd109, Gdf11	Crocr2b, Grifin, Cldn2, Pck1, Mmp8
Dianeal vs Dianeal +JAK1/2i	Peritoneum with muscle	88	132	Ankrd1, Bdh1, Efhd1, Nr4a3, Ostn	Toll-like Receptor Signaling; Complement System; NGF Signaling	Ankrd1, C3, Cdh11, Cd209f, Rab15	Ostn, Nr4a3, Susd4, Rgs14, Il2rb
	Peritoneum without muscle	123	221	Ankrd1, Bdh1, Efhd1, Nr4a3, Ostn	IL-4 Signaling; Antigen Presentation Pathway; Netrin Signaling	Ankrd1, Adamts8, Ltbp2, Crlf1, Tagln	Lep, Slc7a10, Pck1, Tmem179, Natβ
Dianeal vs Dianeal +Losartan	Peritoneum with muscle	96	55	Fgf10, Hmgcs2, Rrad, Sectm1b, Snai3	FXR/RXR Activation; Gα12/13 Signaling; Ketogenesis	Cdh11, C3, Hmgcs2, Cpz, Lrat	Nr4a3, Sectm1b, Rrad, Snai3, Il2rb
	Peritoneum without muscle	1572	405	Fgf10, Hmgcs2, Rrad, Sectm1b, Snai3	Mitochondrial Dysfunction; Calcium Signaling; TCA Cycle II (Eukaryotic)	Lrp2, Galnt14, Slc51a, Muc16, Tagln	Pex19, Dusp13, Xirp1, Myh8, Myh3

SA-PO946

Vascular Access Practices in Japan

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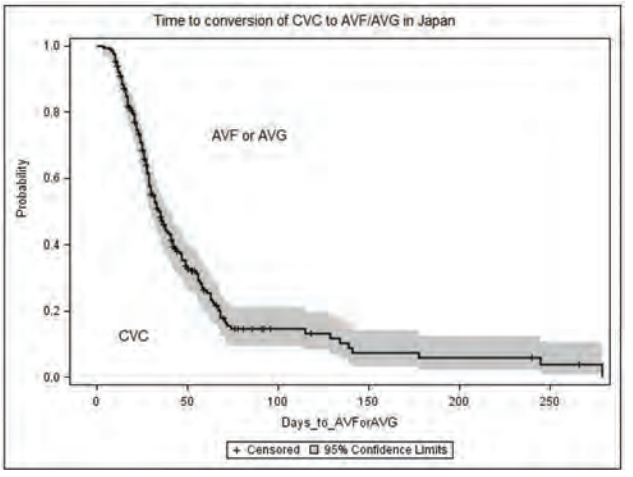
Background: Increasing fistulas (AVF) and grafts (AVG) and decreasing catheters (CVC) is a priority for all hemodialysis (HD) patients. DOPPS data indicate that Japanese patients have superior vascular access outcomes, so we examined vascular access practices for new HD patients in Japan.

Methods: Chart review identified patients presenting to two Japanese hospitals (an academic medical center in Okinawa and a private referral hospital in Ibaraki prefecture) for new kidney failure with no vascular access, from 2013-2017. Demographic and clinical data were collected, as well as the timing of vascular access surgery, hospital discharge/transfer, and cannulation of any new AVF or AVG. Time data are shown as median (interquartile range). Patients were censored upon transfer from facility or death.

Results: Among 222 patients (103 from Okinawa and 119 from Ibaraki), 36.9% were female, age was 70 (60, 79) years, and weight 54.6 (46.7, 61.3) kg. AVF/G were successful during 164/222 (73.9%) of hospitalizations. 58 patients left hospital with CVC, of whom 4 had unsuccessful surgery. Time from admit to surgery was 14 (7,26) days. There were 9 AVG, 9 upper arm AVF, and the remainder were Cimino or snuffbox AVF. AVF/G were cannulated with 17 gauge needles at a median of 13 (8,16) days after surgery. Hospital length of stay was 30 (20, 49) days, so cannulation usually occurred prior to hospital discharge. A Kaplan-Meier curve shows time to conversion from CVC to AVF or AVG in days. Treatments were 240 (240,240) min; blood pump rates were 150 (120,180) mL/min at first use and increased to 200 mL/min over time.

Conclusions: Initial hospitalization of a new Japanese HD patient frequently includes creation and first use of AVF/AVG; hospital length of stay is longer than in many other countries. Early construction and early use of native fistulas in the forearm and wrist is associated with very low usage of CVC in Japan, which may be facilitated by low blood pump speeds and longer treatments.



SA-PO947

Octogenarians in Pre-Dialysis Phase Do Not Have Worse Results of Radio Cephalic Arteriovenous Fistula Compared to Younger Patients

Raffaella Mauro, Mohammad Abualhin, Rodolfo Pini, Anna Laura Croci Chiocchini, Gabriele Donati, Alessia Pini, Gianluca Faggioli, Gaetano La Manna, Andrea Stella, Mauro Gargiulo. *Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.*

Background: KDOQI guidelines recommend radiocephalic arteriovenous fistula (RCAVF) as a first choice access for hemodialytic treatment, but there is no clear indication in octogenarians. The study aim was to compare the results of RCAVF in octogenarians and younger patients.

Methods: All patients treated by RCAVF from Jan-2013 to Dec-2017 were included in a retrospective study. The population was divided according to age: <80 years (Group-A: mean age 61 years ±15; 80.9% males) and ≥80 years (Group-B: mean age 83 years ±3; 91.8% males). Patient demographics, comorbidities, and dialytic treatment were collected prospectively. The endpoints were technical success, defined as AVF presenting vascular murmur and thrill at the end of operation, primary patency defined as patency of vascular access with no significant arterial/venous stenosis, and assisted patency defined as patency of vascular access following a salvage procedure (PTA or surgical).

Results: Within the study period, 366 RCAVF were performed. 72(19.6%) patients were lost to follow-up. A total of 294 RCAVF were analyzed: 249(83.3%) RCAVF were performed in Group-A and 49(16.7%) in Group-B. Technical success was obtained in 95.9% of cases with no differences between the two groups (P=0.70). The mean follow up was 25 months. Primary and assisted patency rates were significantly higher in Group A (P=0.002 and P=0.023, respectively). Primary patency rates at 12,24 and 36 months were respectively 77.5%,73.9% and 73.9% in Group-A and 66.0%,49.8% and 46.0% in Group-B. Assisted patency rates at 12,24 and 36 months were respectively 79.6%,76.5% and 75.8% in Group-A and 70.2%,62.4% and 54.8% in Group-B. At univariate analysis pre-dialytic phase was an independent positive predictor for patency in Group-B (P=0,013) but not in global population (P=0.66). Considering all patients in pre-dialytic phase, there was no significant difference in primary patency rates between Group-A and B (P=0.59). Considering the octogenarians, 81.6% RCAVF became functional within the first 3 months.

Conclusions: According to the study results, RCAVF is associated with good results in octogenarians in pre-dialytic phase with suitable anatomical features and could be indicated as a first choice treatment.

SA-PO948

Influence of Arteriovenous Fistula on Daily Living Behaviors Involving the Upper Limbs in Hemodialysis Patients: A Questionnaire Study

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Background: Arteriovenous fistulae can restrict daily living behaviors involving the upper limbs in hemodialysis patients, but no studies have investigated the detailed effects

of an arteriovenous fistula on routine life activities. Accordingly, many medical caregivers are unable to explain the effects of an arteriovenous fistula on daily life, particularly during non-dialysis periods, because they cannot observe them directly.

Methods: Thirty outpatients undergoing hemodialysis at 2 facilities scored the difficulty due to an arteriovenous fistula in performing 48 living behaviors during non-dialysis and 10 behaviors during dialysis into 5 grades in a comprehensive questionnaire survey. These behaviors were selected based on an open-answer pre-questionnaire administered to the 30 patients beforehand. The scores were also compared between dominant arm and non-dominant arm arteriovenous fistula groups.

Results: During non-dialysis, the difficulty scores of behaviors restricted out of concern for arteriovenous fistula obstruction (wear a wristwatch, hang a bag on the arm, carry a baby or a dog in the arms, wear a short-sleeved shirt, etc.) increased. The difficulties of "wear a wristwatch" and "hang a bag on the arm" were significantly higher in the nondominant arm arteriovenous fistula group (both P<0.05). In contrast, scores related to motor function (write, eat or drink, scratch an itch, etc.) increased remarkably during dialysis because of connection of the arteriovenous fistula to the dialysis machine. The difficulties of "write" and "eat or drink" were significantly higher in the dominant arm arteriovenous fistula group (both P<0.05)

Conclusions: Several key daily living behaviors restricted by an arteriovenous fistula were identified in this questionnaire survey. These results will be useful for preoperative explanation of arteriovenous fistula surgery and arm selection in end-stage renal disease patients.

SA-PO949

Gender Disparities in Vascular Access Surgical Outcomes Among Elderly Hemodialysis Patients

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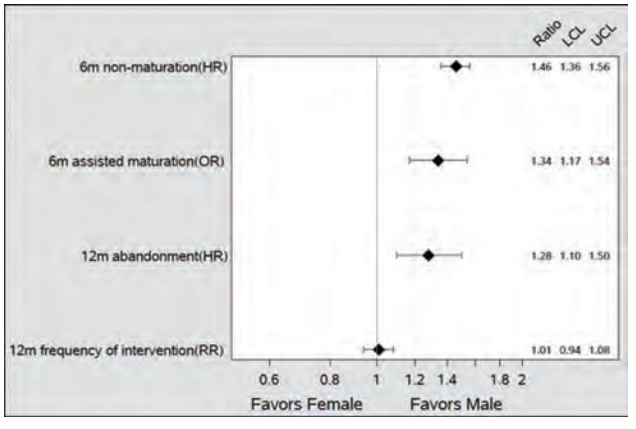
Background: Despite national vascular access guidelines promoting use of arteriovenous fistulas (AVF) over arteriovenous grafts (AVG) for dialysis, AVF use is substantially lower in females. The objective of this study was to assess clinically relevant AVF and AVG surgical outcomes in elderly male and female patients initiating hemodialysis with a central venous catheter (CVC).

Methods: Using the United States Renal Data System standard analytic files linked with Medicare claims, we assessed incident hemodialysis patients in the United States, 9,458 elderly patients (≥67 years) (4,927 males and 4,531 females) initiating hemodialysis from July 2010 to June 2011 with a catheter, and received an AVF or AVG placed within 6 months. We evaluated vascular access placement, maturation (successful use for diaysis), assisted maturation (requiring an intervention before maturation), abandonment after maturation, and rate of interventions after maturation.

Results: Females were less likely than males to receive an AVF (adjusted likelihood 0.57, 95% confidence interval [CI] 0.52-0.63). Among patients receiving an AVF (Fig. 1), females had higher adjusted likelihoods of AVF non-maturation (HR 1.46, 95% CI 1.36-1.56), assisted AVF maturation (OR 1.34, 95% CI 1.17-1.54), and AVF abandonment (HR 1.28, 95% CI 1.10-1.50), but similar relative rate of AVF interventions after maturation (RR 1.01, 95% CI 0.94-1.08). Among patients receiving an AVG, females had a lower likelihood of AVG non-maturation (HR 0.83, 95% CI 0.73-0.94), similar rates of assisted AVG maturation (OR 1.05, 95% CI 0.78-1.40) and AVG abandonment, and greater relative rate of interventions after AVG maturation (RR 1.16, 95% CI, 1.01-1.33).

Conclusions: In elderly patients initiating hemodialysis with a catheter, clinical AVF surgical outcomes are uniformly worse in females. AVGs may be a viable alternative, notwithstanding current national recommendations.

Funding: NIDDK Support, Veterans Affairs Support



SA-PO950

A Novel Prospective in Maturation of Native Arteriovenous Fistula (AVF): Preliminary Data from a Single Center

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Background: Our objective was to quantitatively evaluate time alterations of parameters, predictive of hemodynamic maturation of the newly created AVF, in the immediate and late postoperative period (60 days).

Methods: Observational prospective cohort study of 80 incident hemodialysis (HD) and non-dialysis dependent end-stage renal disease (ESRD) patients, who were referred to for AVF creation. Measured parameters predictive of AVF hemodynamic maturation were; lumen diameter of feeding artery (brachial artery, dBA), efferent vein lumen diameter (dEV) and wall thickness (tEV), access volume flow rate (VF) and brachial artery resistive index (RI). Measurements were conducted daily from postoperative day 1 to 7, days 14, 21, 28 and day 60 from AVF creation (day 0). Daily average alteration value of each parameter was assessed and comparison of average observed values followed.

Results: A total of 80 patients, 63 males and 17 females aged 62±15 years, 48 on HD and 32 with non-dialysis dependent ESRD, were enrolled. Fistulae of 4 patients failed during the study period (5% primary failure rate). In total, 43 distal and 33 proximal AVF were successfully created and studied upon completion of follow-up. A daily increase of 0.71% in dBA and 0.70% in dEV from day 1 to 7 was observed. Daily increment rate of dBA a nd dEV, from day 8 to 28, was calculated at 0.07% and 0.06%, respectively, whereas from day 29 to 60 dBA was daily increased by 0.01% and dEV by 0.01%. Regarding tEV, a daily increase by 2.75% from day 1 to 7, 0.08% (days 8 to 28) and 0.01% daily from day 29 to 60 was observed. Resistive Index RI was decreased by 1.33% (days 1 to 7), 0.10% from day 8 to 28, while from day 29 to 60 it was increased by 0.03%. Lastly, VF was increased daily by 1.79% (day 1 to 7), while increase rate was calculated at 0.01% (day 8 to 28) and 0.004% from day 29 to 60.

Conclusions: Hemodynamic maturation of a newly created AVF is thought to be concluded in the first postoperative week. These findings may offer a new perspective to determine the optimal time to assess the hemodynamic and clinical maturation of AVF but most importantly contribute on decisions making about time of interventions to assist maturation. However, future research is considered mandatory for establishment of firm conclusions.

SA-PO951

Surgeon Variation in Dialysis Vascular Access Outcomes in the United States

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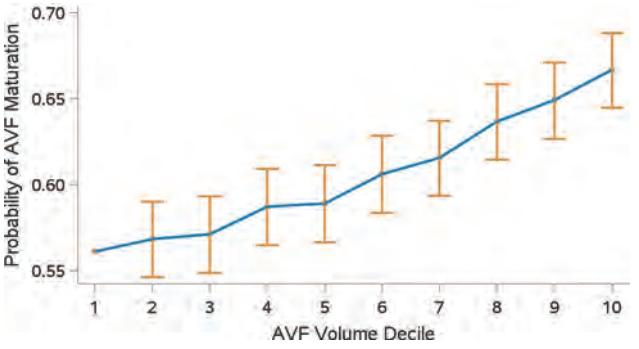
Background: An arteriovenous fistula (AVF) is the access of choice for most patients on chronic hemodialysis. Operating surgeon characteristics have been proposed as contributors to successful AVF creation and AVF survival, but previous studies have been limited by small sample size. We examined surgeon-related vascular access outcomes at the national level.

Methods: From the United States Renal Data System, we used Medicare claims and web-based data submitted by dialysis facilities to examine the primary outcome: % of AVFs with successful use within 6 months of placement, i.e. 'maturation', over the period 2013-2014. A multilevel logistic regression model was used to examine the association of surgeon characteristics (year of graduation, type of surgical specialty, volume, ie number of AVF placements per year) with the outcome, adjusted for patient characteristics (age, sex, race, comorbidities, dialysis vintage, prior access placement) and dialysis facility effects.

Results: Over the study period, 2,770 surgeons were identified as placing at least 5 AVFs, with a total of 49,826 AVF placements. The median AVF maturation rate was 59% (interquartile range 44% to 71%). In the model, more recent year of medical school graduation, but not surgical specialty (general surgery, transplant surgery, vascular surgery) was associated with higher odds of AVF maturation. In addition, increasing historical volume of AVF placement was associated with higher odds of successful AVF maturation: odds ratio 1.46 (95%CI 1.37-1.57) for highest (>84 AVF placements in 2 years) vs lowest (<14) volume quintile. Expressed as AVF maturation probability, outcomes varied from 56.8% to 66.6% from lowest to highest volume decile (Figure).

Conclusions: We observed wide surgeon level variation and a strong surgeon volume-outcome relationship for the outcome of AVF maturation.

Funding: NIDDK Support



SA-PO952

Risk Factors Associated with Distal Hypoperfusion Ischemic Syndrome in Patients with an Arteriovenous Access

Muhammad Sohaib Karim,[1] Ali I. Gardezi,[1] Kyla M. Bennett,[3] Brad C. Astor,[1,2] Micah R. Chan.[1] *[1]Division of Nephrology, University of Wisconsin School of Medicine and Public Health, Madison, WI; [2]Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI; [3]University of Wisconsin, Madison, WI.*

Background: Steal syndrome, or distal hypoperfusion ischemic syndrome (DHIS), is a complication in up to 20% of patients using an arteriovenous access such as a fistula or synthetic graft for chronic hemodialysis. The purpose of this study was to determine the risk factors associated with the development of DHIS.

Methods: Thirty-nine (39) patients with a diagnosis of DHIS were identified and compared to thirty-nine (39) randomly selected patients with arteriovenous access without DHIS (control group) from December 2008 to September 2017. Univariate and multivariate analysis were done to assess the relationship between development of DHIS and risk factors such as age, gender, race, distal versus proximal location of vascular access, peripheral vascular disease, diabetes and congestive heart failure.

Results: Risk of DHIS did not differ significantly by age, race, diabetes mellitus, coronary artery disease or peripheral vascular disease (Table 1). Proximal versus distal placement of access (odds ratio= 5.98, 95 % CI: 1.35, 26.42) as well as female gender (odds ratio= 4.15, 95 % CI: 1.35, 12.76) were associated with a higher incidence of DHIS.

Conclusions: Age, race, congestive heart failure, diabetes and peripheral vascular disease did not appear to be risk factors associated with the development of distal hypoperfusion ischemic syndrome. Female gender and proximal location of vascular access were associated with significantly higher risk of DHIS. Further studies are required to investigate these findings.

Results

Distal hypoperfusion ischemic syndrome	Odds ratio	95 % CI	Standard Error	P Value
Age per Decade	1.07	0.69 to 1.66	0.240	0.752
Female	4.15	1.35 to 12.76	2.37	0.013
African American	2.71	0.67 to 10.95	1.93	0.161
Diabetes Mellitus	0.91	0.29 to 2.85	0.53	0.877
CHF	1.43	0.45 to 4.45	0.82	0.536
PVD	2.68	0.66 to 10.83	1.91	0.166
Proximal versus distal location of access	5.98	1.35 to 26.42	4.53	0.018

SA-PO953

Using Machine Learning to Predict Optimal Renal Replacement Therapy Starts in Patients with Advanced Renal Function Loss

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Background: Building on our previous work using machine learning techniques to identify patients at risk of progression to End Stage Renal Disease (ESRD), we focused this model more precisely on identifying patients with advanced kidney function loss who should plan for optimal renal replacement therapy. The most recent USRDS data indicates that more than 80% of patients begin hemodialysis with a catheter and only 2.5% receive preemptive renal transplants.

Methods: Using longitudinal patient data of 109,028 patients from The Rogosin Institute, we identified a cohort of patients with advanced kidney function loss, defined as an eGFR <20, and built a machine learning model to predict which patients would need to begin renal replacement therapy in the next six months, based on progression to an eGFR <10. Information in the model included patient demographics, vital signs, comorbidities, laboratory values, and medications. We used an algorithm to remove measurements taken during an AKI episode. We evaluated whether the model could identify the need for renal replacement therapy prior to clinical need.

Results: Between 2014 and 2016, only 17 of 214 patients who progressed within a six month period received an AV fistula prior to their decline to an eGFR <10. The model identified 181 patients as the top quintile of risk who would benefit from preparation for renal replacement therapy. Our model has an AUC of 0.93, a sensitivity of 0.81 and a specificity of 0.89 at the top quintile.

Conclusions: We demonstrate improved ability to identify patients who will need renal replacement therapy using an advanced machine learning model incorporating longitudinal data commonly available in EHRs. We plan to augment clinical decision making with machine learning tools.

Funding: Commercial Support - pulseData

Numbers for 2014-2016

Total patient cohort	109,028
Patients in dataset who progress to an eGFR <20	2,416
Patients who continue on to an eGFR <10	241
Patients who received an AV fistula in the six months prior to their decline to an eGFR <10	17
Patients identified by the model (at the top risk quintile) in the six months prior to a decline to an eGFR <10	181

SA-PO954

A Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plastic Cannula Compared with Metal Needle in Incident Hemodialysis Patients

Sung gyun Kim, Narae Joo, Jwa-kyung Kim. *Hallym University, Anyang, Republic of Korea.*

Background: Successful cannulation of arteriovenous fistula (AVF) is an important issue especially in patients who start hemodialysis. Metal needles have been used for decades, but more recently, the usefulness of plastic cannula has been introduced. In this study, a

Methods: This was a single-center, prospective, randomized, open-label study with incident hemodialysis patients. Eligible patients were randomized into 2 groups in a 1:1 ratio (n=20 in each group). Maturation of AVF was confirmed using Doppler US, and well-trained two nursing staffs implemented AVF cannulation. Primary endpoint was the rate of early successful cannulation, defined as the successful completion of three consecutive dialysis sessions with adequate blood flow rates. Secondary outcomes were incidence of vessel injuries (bruising, swelling, erythema, and hematoma), degree of pain, difficulties during cannulation, and urea clearance. Devices examined were metal needle (JMS, 16G, Singapore), and plastic cannula (Supercath Clampcath®, 17G, Togo Medikit, Japan).

Results: Among the 40 patients, radiocephalic AVFs were 47.5 % (n=19) and mean duration from AVF creation to first cannulation was 51.7 ± 26.5 days. No significant difference was found between groups with respect to patient age, sex, prevalence of diabetes, or types of AVF. Failure of early successful cannulation was observed in 9 patients, and the failure risks tended to be higher in metal group (2 cases in plastic group, but 7 cases in metal group, p=0.060). In addition, the risk of vessel injury was significantly higher in metal group than in plastic group (44.4% vs 11.1%, p=0.030). However, the degrees of pain that patients feel was slightly higher in plastic group than in metal group (4.5 vs. 2.9, p=0.066). The difficulties during cannulation felt by nursing staffs or urea clearance were similar in both groups.

Conclusions: Use of plastic cannulas provided less vascular injury and may increase the rate of successful cannulation especially in early period of dialysis. It could be a new and innovative tool for improve dialysis quality.

SA-PO955

Lower Access Flow After Banding Reduces Frequency of Interventions and Increases Access Patency

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Background: Patency of brachial-cephalic autogenous accesses is mainly limited by cephalic arch stenosis (CAS). Shear stress is one factor believed to contribute to recurrence and high flow may be associated with less favorable shear stress. Angioplasty (PTA) is effective in the short term but complicated by high recurrence rates and stent grafts have been used to prolong patency. We report the long-term outcome after CAS PTA and stent graft placement in relation to access flow reduction.

Methods: The Brigham Health Interventional Nephrology dataset was reviewed for all patients with angioplasty and stent graft placement in patients with brachial-cephalic fistula 2008-2018, including only those patients with CAS interventions prior to the banding procedure. We used this dataset to compare the frequency of patients requiring cephalic arch angioplasty or stenting in a subset without banding procedure (control), and those with a banding procedure (exposure) to reduce the inflow segment to 3-5 mm diameter. We compared the frequency of interventions using Wilcoxon matched pair signed rank test given the non-parametric distribution of frequency of interventions.

Results: 22 patients meeting inclusion criteria were included in the study. We observed a flow reduction from 1807 ± 477 pre- to 1300 ± 454 post- banding; p<0.001. Along with the flow reduction we observed an increased intervention free period from 229 (IQR: 129-320) pre- to 432 (IQR: 232-717) post-banding; p=0.02. We did not appreciate an association between the absolute flow value and number of days per procedure.

Conclusions: High blood flow is common in brachial-cephalic autogenous accesses and banding significantly decreases access flows. This access flow reduction increases the days between procedures for CAS suggesting a protective role for the development of restenosis.

SA-PO956

Arteriovenous Shunt for Hemodialysis – A Viable and Cost-Effective Vascular Access Option in Hemodialysis Patients

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Background: In India, the most common vascular access for HD(95%) is Arteriovenous fistula (AVF). Primary AVF is the most preferred permanent vascular access - which can be created by radiocephalic or brachiocephalic anastomosis. Ageing population and diabetic patients presenting with sub-optimal veins, along with the issue of late referral makes timely AVF creation an unmet goal. Managing associated complications is an indispensable part of patient care but is also responsible for drain of fiscal resources.

Methods: We started hemodialysis programme in the Dept. of Nephrology, Sir Ganga Ram Hospital in 1981. Due to late referral and immediate need of dialysis, AV shunts were created. In patient with AKI, this shunt could be removed after recovery. In ESRD patients, the same shunt could be converted into AV fistula. Thus, a fistula created after maturation of veins following shunt placement could be used as early as 1-2 weeks. Since its inception, at our centre, vascular access creation has been in the domain of nephrologists.

Results: We have created 2640 AV Shunts till 2014 with infection rates <5% and 3-month shunt blockage <10%. In view of logistic reasons, due to non-availability of shunt material, the programme suffered a setback. We continued to re-use shunts after sterilization, but, they are no longer available now. We have created 7920 AV Fistulas since 1981 till December 2017–achieving a primary patency rate of 95% and incidence of infection of <5%. From 1981-2010, the standard practice was to convert AV Shunt into AV Fistula after 4-6weeks or primary AVF was created asvascular access. Due to non-availability of AV Shunts, now we use Internal-jugular (IJ) catheter for acute dialysis. We have placed over 300 IJ catheters/year since 2014. However, the incidence of IJ catheter related blood stream infection is very high (around 90%) requiring catheter removal usually within 1 month of placement. We have put permcath in 10 patients last year, with average life of 1 year; with permcath thrombosis rates of 20% within 6 months.

Conclusions: To conclude, AV Shunt is still a viable, cost effective and preferred mode of vascular access in patients requiring hemodialysis and should be reintroduced in our practice.

SA-PO957

Likelihood of Failed Thrombectomy (LOFT)

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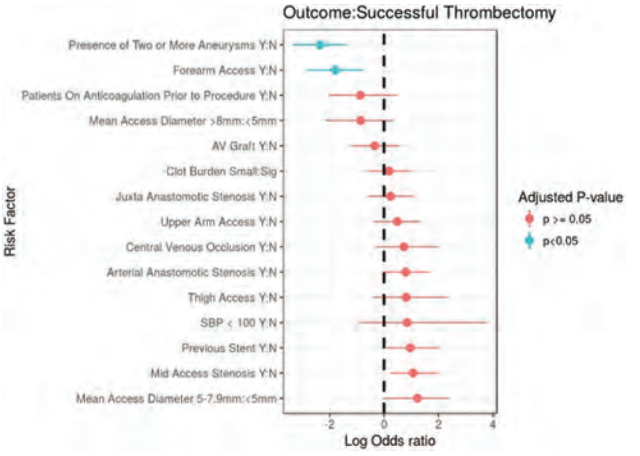
Background: Currently percutaneous thrombectomy (PCT) is widely used for clot removal, however if unsuccessful, the patient is referred for open surgical thrombectomy. The current literature suggests that the success rates for thrombolysis of thrombosed fistulas ranges from 76-96%. To date it is unknown what risk factors and or access characteristics result in PCT failure.

Methods: Retrospective single center study including 212 hemodialysis patients, with 179 successful and 33 failed dialysis access thrombectomies. The following characteristics were evaluated for each patient: age, sex, diabetes, clot burden, central venous stenosis, presence of ≥ 2 aneurysms, previous stent placement, on outpatient anticoagulation, SBP<100mmHg, type and location of access, venous outflow stenosis, juxta-anastomotic stenosis, feeding artery diameter, arterial anastomotic stenosis, mid access stenosis, use of TPA or teratola, time of procedure, and presence of venous outflow stenosis. To assess the impacts of several risk factors, we constructed various models of success as a function of age group, sex, diabetes, and one of the other risk factors. The Holm-bonferroni step down method was used to adjust the p-values to deal with familywise error rates for multiple hypothesis tests.

Results: Risk factors for failed thrombectomies included the presence of ≥ 2 aneurysms and or patients with a forearm access. Patients with AV grafts and or venous outflow stenosis had significantly longer procedure times, and the use of teratola or TPA in patients with AV grafts did not affect PCT outcomes.

Conclusions: Our data illustrates that two indepednent risk factors for PCT failure include patients with a forearm access and or the presence of ≥ 2 aneurysms. A patient with both of these independent risk factors is perhaps better off being sent directly for open surgical thrombectomy. Moving forward, larger trials and a larger sample size are needed in order to prove the aforementioned results.



Plot Confidence Intervals

SA-PO958

Predictors of Complications During Outpatient Dialysis Access Procedures

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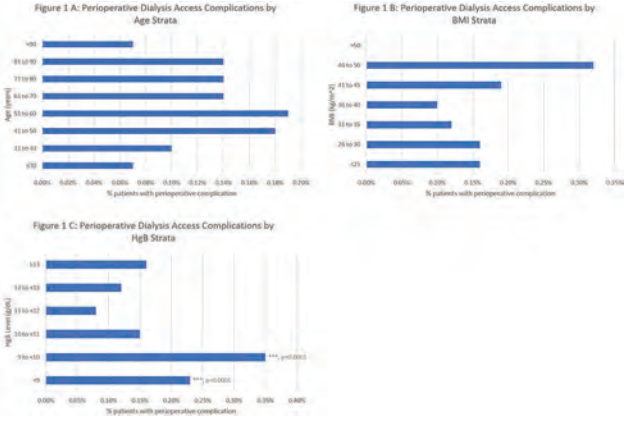
Background: It is unknown if patient specific factors contribute to complications during dialysis vascular access (VA) interventions. We detailed the characteristics of dialysis patients who underwent a VA procedure and investigated risk factors for perioperative complications.

Methods: We analyzed data from patients treated at a large dialysis provider who had ≥1 VA procedure at an affiliated freestanding outpatient access center during 2016 and 2017. The distribution of perioperative complications (e.g. adverse drug reactions, falls, post-operative infections, required interoperative airway management, medication/fluids, and/or additional surgery/procedure) was assessed across strata for age (≤30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, >90 years), body mass index (BMI) (≤25, 26-30, 31-35, 36-40, 41-45, 46-50, >50 kg/m^2), and hemoglobin (HgB) levels (<9, 9-<10, 10-<11, 11-<12, 12-<13, ≥13 g/dL). Chi-square tests were used to compare the percent (%) of complications within strata.

Results: We analyzed data from 29,322 unique dialysis patients who underwent a total of 100,070 VA procedures. The % of perioperative complications were evenly distributed for age (p=0.54) and BMI (p=0.09) strata (Figure 1 A & B). However, the % of perioperative complications was observed to be elevated for those with a HgB level <10 g/dL versus ≥10 g/dL (Figure 1 C; p<0.0001).

Conclusions: This research indicates that patients with low HgB levels may be at a higher risk for perioperative complications as compared to those with higher HgB levels; however, patients with low HgB levels are also at a higher risk of all-cause hospital admissions and mortality.

Funding: Commercial Support - Fresenius Medical Care North America



SA-PO959

A Hybrid Technique in Recanalization of Multiple Central Venous Occlusions in Hemodialysis Patients: A Cohort Study

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Background: The management to multiple central venous occlusions (CVO) in hemodialysis patients remains difficult. This present study aims to assess the feasibility and safety of a hybrid technique in recanalizing multiple CVO in hemodialysis population.

Methods: From January 2014 to November 2017, hemodialysis patients with multiple CVO were enrolled. Under DSA guidance, patients received a hybrid technique combining direct puncture, sharp transversal, and balloon dilation of the SVC, followed by tunneled cuffed catheter implantation (figure). The demographic information and clinical outcomes were recorded.

Results: A total of 16 patients were involved in this study. The procedure was successfully performed in 15 cases and failed in 1 patient due to full-length obstruction of the SVC. 1 patient presented with transient cardiac arrest. 2 patients suffered mild pericardial tamponade, both stabilized afterwards. All 14 patients with successful catheter implantation had satisfactory patency after the procedure.

Conclusions: This hybrid technique could be performed effectively in selected hemodialysis patients with multiple CVO. It could be a viable alternative for hemodialysis catheterization in the setting of an exhausted central venous system with multiple CVO.

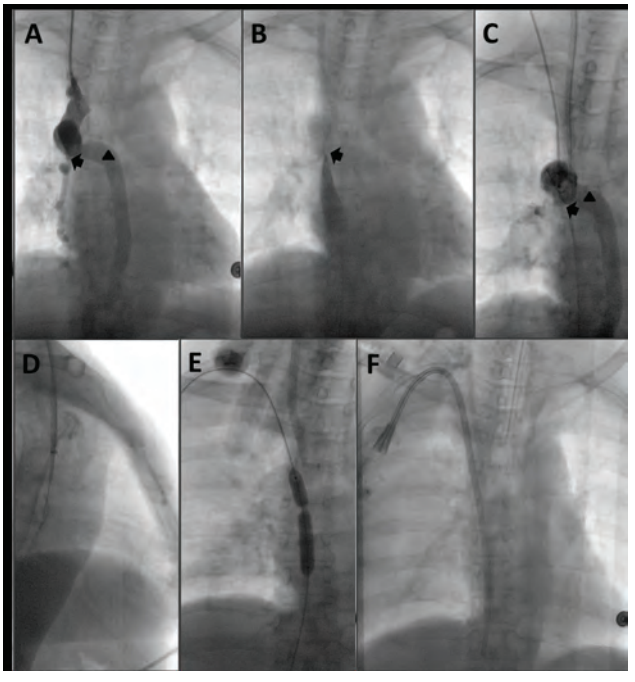

Figure: the procedure of the hybrid technique(Under DSA guidance, patients with SVC occlusion (arrow head) with dilated azygos vein (triangle) were identified (figure A, B). The distal part of SVC was directly punctured (figure C), as verified by contrast. Under guidance in anterior-posterior view and lateral view of DSA, we penetrated the occlusive SVC segment and then advance guide wire through the SVC into the IVC (figure D). The occlusive lesion was dilated with balloon (figure E), which enabled successful tunneled cuffed catheter implantation (figure F).)

SA-PO960

Reasons for Dialysis Catheter Insertion at a National Level – Real Time Data from the REDUCCTION Project

Sradha S. Kotwal,[1,2] Girish S. Talaulikar,[4] Nicholas A. Gray,[5] Kevan Polkinghorne,[6] Stephen P. McDonald,[7] Alan Cass,[8] Martin P. Gallagher.[1,3] REDUCCTION Project Investigators *[1]The George Institute for Global Health, Sydney, NSW, Australia; [2]Nephrology, Prince of Wales Hospital, Sydney, NSW, Australia; [3]Concord Clinical School, Sydney, NSW, Australia; [4]The Canberra Hospital, Garran, ACT, Australia; [5]Sunshine Coast University Hospital, Birtinya, QLD, Australia; [6]Monash Medical Centre and Monash University, Melbourne, VIC, Australia; [7]Royal Adelaide Hospital, Adelaide, SA, Australia; [8]Menzies School of Health Research, Darwin, NT, Australia.*

Background: Dialysis catheters are inserted for reasons which are not well measured or understood. Understanding reasons for catheter insertion on a real-time basis allows units to measure practice and catheter use in a national context. We aimed to understand the reasons for dialysis catheter insertion in patients of Australian renal units participating in a prospective national project (Reducing the burden of dialysis catheter complications - REDUCCTION).

Methods: Data was collected using a web-based data collection tool on all patients who had a dialysis catheter inserted between 20/12/2016 and 23/03/2018 (censored) at any of the 37 units participating in the REDUCCTION project. The reasons for insertions were grouped into Acute Kidney Injury (AKI), commencement of maintenance dialysis, arteriovenous fistula/graft (AVF/AVG) dysfunction, transition from Peritoneal Dialysis (PD) without permanent vascular access and other as reported by study site. Study data collection continues.

Results: Data on 3572 (2522 patients) dialysis catheters were captured so far, representing 316,039 catheter days. Of these, 1176 (32.5%; 60% Tunnelled) catheters were inserted for AKI, 1047 (29.4%; 85.8% tunnelled) for commencement of maintenance dialysis, 464 (13%) for AVF/AVG dysfunction, 401 (11.3%) for transition from PD and 481 catheters (13.5%) for other reasons. Twenty-nine catheters were inserted in 27 patients for failing renal transplants. A total of 1075 catheters remained in situ at the censor date while 2497 catheters were removed after a median of 18 days (IQR 6-71 days). The median duration for tunnelled catheters was 75 days (IQR 26-170) and non-tunnelled catheters was 6 (IQR 3-9) days.

Conclusions: This prospective national data highlights the reasons for dialysis catheter exposure, most notably the high burden arising from AKI. Understanding the outcomes, such as catheter-related bacteraemia (the primary outcome of REDUCCTION), for these different patient groups may aid in reducing complications.

Funding: Government Support - Non-U.S.

SA-PO961

Surveillance of Catheter Conversion (CC) and Future Vascular Access (VA)

Jeffrey J. Sands,[1,3] Lalathaksha Murthy Kumbar,[2] Kim Hirschman,[1] Stanley Frinak,[2] Gerard Zasuwa,[2] John B. Kennedy.[1] *[1]Vasc-Alert LLC, Evanston, IL; [2]Henry Ford Health System, Troy, MI; [3]Renal Systems Consulting LLC, Orlando, FL.*

Background: We evaluated the impact of AV access (AVF or AVG) conversion (CC) to a central venous catheter (CVC) on patients future VA. Recent efforts focus primarily on AVF placement and maturation. VA outcomes including the extent of CVC use post access complications are less appreciated.

Methods: We identified CC from downloaded treatment (Tx) records utilized for Vasc-Alert™ VA surveillance from 1/1/14—6/30/17 in patients (pts) using a single AV access from 10/2013-12/2013. CC was defined as a recorded change to a CVC for ≥4 Tx within 30 days. Missed treatments were identified from Tx records gaps.

Results: Data included 1,598,680 Tx from 4923 pts (76.1% AVF; 23.9% AVG); mean age 61.1±14.5 yrs (60.6±14.6 AVF; 62.8±14.3 AVG), mean vintage 4.1±3.8 yrs (3.8±3.5 AVF; 5.0±4.6 AVG) in 137 facilities (10 dialysis providers). CC occurred in 16.7% (820/4923) of pts (13.1% AVF, 28.1% AVG; P<0.001); CC rate: 8.2/100 pt-yrs (6.2 AVF; 15.5 AVG). At 1 yr, mean CVC exposure was 168.1 days/pt-yr (162.8 AVF; 176.6 AVG). Vasc-Alert™ provided an alert prior to CC in 57.2% (52.9% AVF; 63.6% AVG). Missed Tx (%) were greater in AVG (P<0.001) and similar in non-CC (4.8% Tx; 4.6% AVF; 5.5% AVG) and pre-CC pts (4.7%; 4.5% AVF, 5.1% AVG)(P=NS). Missed Tx then increased post-CC (6.4%; 5.7% AVF; 7.3% AVG)(P<0.001). Post CC, 52.9% were CVC dependent at 3 months, 33.9% at 6 months and 21.3% at 1 year. Only 23.9%, 27.7% and 30.1% returned to their original VA at 3, 6 and 12 months respectively and 44.3% had a new AV access at 1 yr.

Conclusions: CC results in prolonged CVC use in a high percentage of HD patients. Only ~30% of patients returned to their original access and >44% had a new AV access at 1 year. CC was more frequent in AVG, led to significantly more missed Tx and catheter exposure of >168 days/pt-yr. These data emphasize the importance of access surveillance and preventing terminal access failure to decrease CVC prevalence.

Funding: Commercial Support - Vasc-Alert LLC

Access in Use Post CC

Pre-CC VA	AVF			AVG			Total		
Post CC VA	3 m	6 m	12 m	3 m	6 m	12 m	3 m	6 m	12 m
N	448	412	349	304	284	242	752	696	591
Original AV Access (%)	24.8	28.9	30.1	22.7	26.1	30.2	23.9	27.7	30.1
New AV Access (%)	20.8	35.4	47.0	18.1	33.8	40.5	19.7	34.8	44.3
CVC (%)	51.6	32.8	18.9	54.9	35.6	24.8	52.9	33.9	21.3
Mean CVC days/ patient	69 ± 26	109 ± 63	162 ± 127	69 ± 27	112 ± 65	175 ± 135	69 ± 27	110 ± 63	167 ± 130

SA-PO962

Utilizing a Multidisciplinary Approach to Lower the Central Venous Catheter Rate Among Chronic Hemodialysis Patients: A Quality Improvement Project

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Background: United States Renal Data System (USRDS) evidence shows that the number of Central Venous Catheter (CVC) dependent patients is 20% and 12% after 1 and 2 years of hemodialysis (HD) initiation respectively. At our hospital, the CVC dependence among chronic hemodialysis patients remains very high. Therefore, we sought to determine if a multi-disciplinary approach, involving the Nephrologists, Interventional Radiologists, and the Vascular Surgeons could reduce CVC use in long-term HD patients.

Methods: From August 2016 to July 2017, we identified 26 CVC-dependent long-term HD patients, 73% of who had a history of at least one failed Arterio-Venous (AV)

access. The Interventional Nephrologist reviewed their records including comorbidities, access failure and complications history and venograms or fistulograms. This data was then presented at monthly multi-disciplinary meetings, also attended by Interventional Radiologists and Vascular Surgeons, during which, potential AV access options including arteriovenous fistulas (AVF) and arteriovenous grafts (AVG) were discussed in detail. A viable AV access option was then identified and placed after discussion with the patient.

Results: 27% (7/26) patients developed a functional AV access. Of these 57% (4/7) were AVGs, 29% (2/7) were AVFs and 14% (1/7) were HeRO (Hemodialysis Reliable Outflow) grafts. 46% (12/26) patients were not able to receive an AV access due to severe peripheral vascular disease or poor overall prognosis while 27% (7/26) patients died through the course of the year.

Conclusions: Monthly multi-disciplinary vascular access meetings with an individualized approach led to an increase in the prevalence of AV accesses among chronic HD patients. We impress that AVG and HeRO graft creation should be considered in patients who are poor candidates for an AVF, as any functional AV access leads to a reduction in CVC dependence and its related complications.

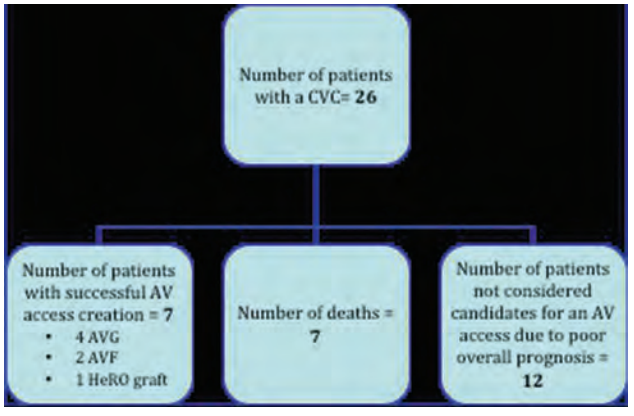


Fig.1 Outcomes

SA-PO963

Minimizing Complications During Renal Replacement Therapy with Tunneled Dialysis Catheters in Patients with AKI

Lumen A. Mendez Castaner,[2] Marco A. LadinoAvellaneda,[1] Antonio A. Armstrong,[2] Emilian A. Cristea,[2] Lorena Cuebas-Rosado,[3] Daniel J. Soberon,[3] Vasuki N. Venkat.[3] *[1]Miami VA Medical Center/University of Miami/ Jackson Memorial Hospital, Plantation, FL; [2]Jackson Memorial Hospital, Miami, FL; [3]Miami VA Hospital, Miami, FL.*

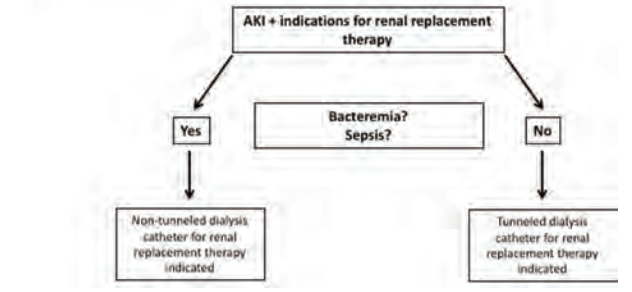
Background: Patients with acute kidney injury that need renal replacement therapy have an increased morbidity and mortality. Bacteremia and poor renal replacement therapy delivery are complications that are present with the use of non-tunneled dialysis catheter. There is not enough data to support which option is the best vascular access to start renal replacement therapy in patients with acute kidney injury. We report our protocol using tunneled dialysis catheters for renal replacement therapy based on our 5-year experience.

Methods: This is a retrospective study of 62 patients with AKI that had indications to start renal replacement therapy. The vascular access for renal replacement therapy was a tunneled dialysis catheter. Patients did not have bacteremia or sepsis prior to catheter placement.

Results: All 62 patients had a tunneled dialysis catheter placed. 14 patients were started on continuous replacement therapy (CRT), 48 patients were started on intermittent hemodialysis (IHD). No infections (bacteremia, exit site infection, tunnelitis) in the first 14 days after tunneled catheter placement were reported. A good clearance was obtained in the patients on CRT with a median duration of the dialyzer (No need for exchange) of 3 days. Appropriate clearance was also obtained in the patients on IHD. Blood flows were appropriate in both modalities.

Conclusions: TDCs should be the vascular access of choice for patients (Figure 1) with AKI in need for dialysis if no contraindications are present (bacteremia, sepsis, hemodynamic instability). Patients didn't have catheter related infections. Dialysis delivery was always appropriate without complications. The use of TDCs decreases length of stay in the hospital, costs and complications from non-tunneled catheters.

Figure 1. Dialysis catheter options for patient with AKI that need renal replacement therapy



SA-PO964

Clinical Outcome in the Use of Biopatch in Preventing CRBSI Among Hemodialysis Patients via Hemodialysis Catheters in a Private Tertiary Hospital

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Background: According to CDC, CLABSI result in thousands of deaths each year. Biopatch is a novel catheter dressing impregnated with chlorhexidine gluconate, used in conjunction with the standard catheter dressing to prevent CRBSI.

Methods: This is a retrospective cohort study design with target population of in hospitalized and outpatients who had HD via HD catheters exclusively in St. Luke's Medical Center–QC, a private tertiary hospital from January 2013 to December 2017.

Results: A total of 427 HD patients via HD catheters (IJ,Femoral,Permanent Catheter) met the inclusion criteria. Of which, 255 HD patients on biopatch and 172 without biopatch.117 in the biopatch group developed CRBSI and 72 patients in those without biopatch. The incidence rate of CRBSI with biopatch was 6.47/1000 catheter days (6 cases of CRBSI/1000 Catheter days) and was higher than those without biopatch, 3.4/1000 catheter days (3 cases of CRBSI/1000 Catheter days) and was statistically significant (P=0.002;HR, 1.614 times among those with biopatch as compared to those without biopatch). Those with significant association with CRBSI among those with biopatch were aged 18 to 60 y/o (P=0.001;HR, 2.841), male patients (P=0.034;HR, 1.57), female patients (P=0.025;HR, 1.717), those with ESRD secondary to DKD (HR, 1.67), other causes of ESRD from solitary kidney, CTIN (P=0.013;HR, 6.564), those with other causes of AKI (P=0.000) and PVD (P=0.000) as compared to those without biopatch. Of the organisms isolated, Klebsiella pneumonia was common among those with biopatch and Pseudomonas aeruginosa among those without biopatch. The risk of CRBSI using permanent catheter with biopatch was 2.853 (P=0.000).

Conclusions: The use of Biopatch had a higher incidence rate of CRBSI among HD patients with biopatch compared to those without biopatch. There was significant association with CRBSI and those with biopatch </=60 y/o, male and female, those with ESRD due to DKD, other causes of ESRD, other causes of AKI and PVD. Majority of organisms isolated were gram positive bacteria, Staphylococcus epidermidis, both in HD patients with and without biopatch. Among CRBSI patients who had Klebsiella pneumonia, the use of biopatch may not be preventive in the development of CRBSI. However, among CRBSI patients with Pseudomonas aeruginosa, biopatch may decrease the risk of CRBSI.

SA-PO965

A New Initiative to Measure the Provincial Rate of Catheter-Related Bacteremia in Ontario

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Background: The use of a Central Venous Catheter (CVC) is associated with high morbidity and mortality, in part due to increased risk of catheter-related bacteremia (CRB). Patients using a CVC have a greater risk of infection and sepsis compared to patients dialyzing using an arteriovenous access. In 2016, the Ontario Renal Network (which funds dialysis in Ontario) launched a provincial quality improvement (QI) initiative with the aim to shift from local monitoring of CRB rates to a province-wide standardized tracking system. The initiative was launched with the objectives of: 1) Defining a provincial average rate of CRB, and an individualized rate for each of the Regional Renal Programs (RRP); and 2) sharing provincial data and developing program-level QI plans to help minimize CRB risk.

Methods: All 26 RRPs in Ontario collected and reported data from May 2016 – December 2017 using a tracking tool incorporating indicator methodology developed by an expert panel. Reported CRB events formed the numerator for the rate calculation, while the denominator was derived from the Ontario Renal Reporting System database (ORRS) to calculate person-time with a hemodialysis catheter. The CRB rate is expressed as infections

per 1000 patient days, combining patient-time from all in-centre chronic dialysis patients at each RRP.

Results: Over a period of 20 months (May 2016 to December 2017), 696 unique CRB cases were reported over a total of 3,096,046 patient days (approximately 8482 annualized patients). Program-level CRB rates ranged from 0.09 – 0.56 and the provincial average was 0.22 episodes/1000 catheter-days. Quarterly reports were shared with the programs for data validation, comparison and monitoring purposes. The initiative enabled consistent measurement and reporting of CRB, allowed programs to benchmark themselves against their peers, and design local plans for improvement.

Conclusions: The risk of CRB is deemed to be relatively low in Ontario. This initiative has produced a sustainable system of data collection for monitoring the risk of CRB. This initiative is part of a larger strategy to ensure that all patients receiving dialysis therapy experience as few complications regardless of the type of access they have.

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SA-PO966

Differential Impact of Central Venous Catheters versus Arteriovenous Fistulas on Quality of Life Among Irish Haemodialysis Patients

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Background: The arteriovenous fistula (AVF) is associated with superior clinical outcomes than central venous catheters (CVC) in haemodialysis (HD). Recent studies have questioned the relative benefits in survival and quality of life using an AVF strategy over a CVC strategy. We compared the attitudes and opinions of HD patients using an AVF versus a CVC in an Irish cohort.

Methods: A cross-sectional study was conducted in maintenance HD patients (n=119) at a centre-based HD programme in 2018. A validated Vascular Access Questionnaire wasused to measure and compare quality of life across key domains. Patient satisfaction between AVF and CVC was compared in physical functioning, social functioning and dialysis complications using Likert scale with a p-value of <0.05 indicating statistical significance. Comparisons between groups were conducted using student t test and multivariable logistic regression expressed as odds ratio and (95% Confidence intervals).

Results: Average age was 66.1 years, 52.1% were using AVF with 47.9% a CVC. Patients with an AVF experienced higher overall satisfaction scores than a CVC (6.2 vs 4.9, P<0.01), however AVF patients reported more problems with bleeding, swelling and bruising than CVC patients [2.9 (2.2) vs 1.6(1.4), 2.9 (2.1) vs 1.7 (1.5), and 3.6 (2.2 vs 1.8) respectively, all p<0.005]. In contrast CVC patients reported greater difficulties in bathing and showering than AVF (4.5 (2.3) vs 2.1 (1.8), p <0.001). In multivariable analysis, adjusting for demographic and clinical factors, dialysing with a CVC (vs AVF) was associated with less difficulties in physical functioning OR, 0.35 (0.13-0.96), P=0.04, and higher odds of dialysis complications OR, 2.14 (0.78-5.89), P=0.1.

Conclusions: Compared to AVF, CVC use is associated with less physical complaints from bleeding and bruising but greater negative impact on social activities including bathing and showering. Minimising the impact of these on QOL should be considered in any long term vascular access strategy.

Funding: Government Support - Non-U.S.

Table 1. Association between Access type (Catheter vs Fistula) and Upper Quartile QOL score for each domain

Variable	AOR (95 %CI)	P-value
Physical Functioning		
Unadjusted	0.36 (0.15-0.85)	0.02
Model1	0.38 (0.16-0.93)	0.03
Model2	0.35 (0.13-0.96)	0.04
Social Functioning		
Unadjusted	1.28 (0.56-2.94)	0.56
Model1	1.28 (0.54-3.05)	0.57
Model2	1.28 (0.47-3.45)	0.63
Dialysis Complications		
Unadjusted	1.58 (0.67-3.74)	0.30
Model1	1.74 (0.70-4.30)	0.23
Model2	2.14 (0.78-5.88)	0.14

Note: Model 1; adjusted for age & sex ; Model 2; adjusted for age, sex &comorbidities

SA-PO967

Interim Analysis of Randomized Trial Comparing VectorFlow and Palindrome Tunneled Dialysis Catheters

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Background: Tunneled dialysis catheters (TDC) remain an important bridge to permanent hemodialysis (HD) access, a critical transition to new access creation when surgical access fails, and the only source of HD access when venous anatomy is exhausted for surgical access. Selection of an HD catheter capable of providing efficient HD with high primary patency is of utmost importance to improving outcomes in ESRD patients. The purpose of this trial is to compare a widely used symmetrical tip TDC, Palindrome (P), to a recently FDA-approved symmetrical design with helical flow at the tip to reduce blood cell shear stress, VectorFlow (VF).

Methods: The target recruitment of the study was 100 subjects enrolled at two centers with 1:1 randomization. Exclusion criteria included uncorrectable coagulopathy or thrombocytopenia; neutropenia, bacteremia, or infected surgical HD access within 7 days prior to enrollment; central venous stenosis or occlusion preventing jugular catheter insertion. The primary endpoint was primary patency at 90 days. Secondary endpoints include dialysis adequacy with Kt/V and URR monthly for 3 months, catheter flow (Qb) and lumen pressures at initial HD and monthly for 3 months.

Results: At present, the trial has enrolled 78 subjects and is anticipated to complete enrollment by the fall of 2018. Interim analysis showed 90-day primary patency of 74% in the VF group compared to 71% in the Palindrome group (P=0.81). Mean Kt/V at 30, 60 and 90 days was higher with the VF than P (30 d ay, 1.48 vs. 1.40; 60 days, 1.48 vs. 1.37; 90 days, 1.51 vs. 1.35); mean Kt/V averaged across all time points was significantly higher among subjects receiving the VF catheter compared to P (1.48 vs. 1.38, P=0.020). No significant differences were seen with URR (69 vs. 69) or Qb. Additional study data are pending final subject enrollment.

Conclusions: The ongoing trial comparing VectorFlow tunneled dialysis catheter to Palindrome tunneled dialysis catheter is the first US randomized trial comparing different HD catheter tip designs in nearly two decades, and the first to address dialysis adequacy. The results of this trial may elucidate which catheter design provides optimal HD adequacy and catheter patency.

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SA-PO968

Relationship Between Central Venous Catheter Protein Adsorption and Water Infused Surface Protection Mechanisms

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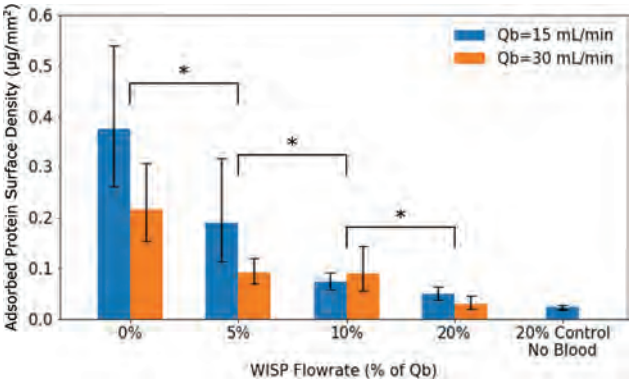
Background: Many dialysis patients are implanted with central venous catheters (CVCs) despite increased patient risk due to thrombosis and biofilm formation. These complications are caused by fibrin sheath formation, which is initiated by blood protein adsorption upon exposure. Current solutions to prevent thrombotic occlusion and biofilm formation remain ineffective at preventing these failure modes and remediation treatment options are limited and often harmful. We propose an active method to reduce protein adsorption and effectively disrupt adherent protein sheaths, water infused surface protection (WISP).

Methods: Experiments were performed *in vitro* using a modeled CVC that simulated the WISP mechanism. A hollow fiber membrane (HFM), representing the CVC lumen, was mounted in a concentric chamber. The WISP was achieved by pressurizing the concentric chamber with saline while blood flowed through the HFM, causing a continuous saline infusion across the HFM wall. The resulting water boundary layer at the lumen surface limited the blood contact with the HFM wall resulting in decreased protein adsorption.

Results: Analytic lubrication models matched our experimental pressure measurements suggesting the WISP created a blood-free boundary layer on the HFM surface. Figure 1 shows the WISP boundary layer reduced the average density of adsorbed protein on the model CVC with increasing WISP flowrates, up to 96.4% over the 0% WISP condition (* denotes P≤0.016, 2-way ANOVA). Additionally, the WISP CVC displayed the ability to reduce previously-adsorbed protein films, and deliver chemical agents, such as heparin, within the WISP flow.

Conclusions: The proposed WISP technology has functionality that could reduce failure incidence to improve clinical outcomes. WISP shows the ability to significantly reduce protein adsorption, as well as presents a new methodology to treat major CVC complications; removing pre-adsorbed material or treating a resulting infection by more effectively delivering drugs to the point of adhesion.

Funding: Commercial Support - The Charles Stark Draper Laboratory



SA-PO969

Gaining Central Venous Access Safely and Quickly in Patients with Occlusion of the Upper Central Veins with a Novel Device Using an Inside-Out Approach

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Background: Left-sided and subclavian central accesses cause the highest rate of central venous thromboses and occlusions. Exhaustion of vascular access options caused by thoracic central venous occlusion (TCVO) adds to dialysis-related morbidity and mortality. We report the first case series of a novel device, the Surfacer, for repeated right-sided central venous access in patients with TCVO.

Methods: The Surfacer consists of a metal pole with a sharp wire inside attached to a handle. The procedure is performed on an outpatient basis using local anesthesia under fluoroscopy as follows: A 10F sheath is introduced up to the TCVO over a standard guidewire from the right femoral vein. After removal of this wire, the 7F metal pole of the Surfacer is introduced through the sheath to the TCVO and pushed through until its tip has passed the clavicle. The sharp wire is then released using a plunger at the handle from the tip of the Surfacer piercing the skin inside out in the right supraclavicular region. This now serves as a guidewire for a central venous access. We analyzed success rate, duration of procedure and complications of all Surfacer cases performed at the Department of Nephrology, Medical University of Vienna between July 2016 and April 2018.

Results: The Surfacer procedure was considered in 37 cases. Following CT angiography, four patients did not qualify because of complete occlusion of either right external iliac vein or inferior or superior vena cava. The majority of patients had a TCVO type 3 with occlusion of both brachiocephalic veins but a patent azygous vein. The procedure had a 97% success rate (32 out of 33; one patient had a massive scoliosis which blocked the passage of the device). The mean intervention time was 14 min. There were no Surfacer related complications defined as early infections, bleeding, hematoma or pericardial effusions. In five patients the procedure was repeated due to infection or dysfunction > 3 months after initial placement.

Conclusions: This is the first case series of a novel device for inside-out placement of central venous access in patients with TCVO requiring dialysis. The procedure is highly successful, safe and repeatable allowing for an "always right, never subclavian" approach.

SA-PO970

Catheter-Related Right Atrial Thrombus on Hemodialysis Patients: Results of a Cohort Study

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Background: Catheter-induced right atrial thrombus (CRAT) is a serious complication in hemodialysis (HD) patients and optimal treatment is not well defined. We reviewed clinical characteristics, treatments options, and outcomes of CRAT in HD patients

Methods: Single-center retrospective cohort study of CRAT confirmed by echocardiogram (2008-2018).

Results: We identified 23 CRAT cases in HD. Thrombus was visualized initially by transthoracic echocardiogram in 74% (17/23); all but one had transesophageal echocardiogram. The largest thrombus dimension was 52x23 mm. Factors related to CRAT were long catheter vintage (7 [IQR 4-13] months) and catheter misplacement in 65% (15/23). All cases received anticoagulation as initial treatment. The most relevant clinical data for subsequent treatment decision was suspicion of catheter-related bloodstream infection (CRBSI). Patients were divided in those that had early catheter removal due CRBSI (39%, 9/23) and those who had non-urgent indication of catheter removal (61%,14/23) [Table]. Early removal group had worse outcomes:100% had catheter removal before therapeutic anticoagulation was achieved, 44% had embolic complications after catheter removal, 78% required surgical definitive treatment, and 44% (4/9) died. Non-urgent catheter removal group received total anticoagulation for 22 [IQR 13-28] weeks, dissolution of thrombus occurred in 64% (9/14), thrombus shrinking in 14% and 42% required delayed catheter removal without major adverse events.

Conclusions: To our knowledge, this is the first large cohort of CRAT on HD. Total anticoagulation is essential after CRAT diagnosis and may be sufficient to dissolve or shrink thrombus <52 mm in asymptomatic or stable febrile HD patients without an urgent indication for catheter removal. Infection related to CRAT had a high risk of adverse outcomes, including mortality.

Characteristics of the HD cohort and clinical outcomes.

	All CRAT(n=23)	Urgent catheter removal (n=9)	Non-urgent catheter removal (n=14)	p value
Age (years) Female (n)	41±16 16 (67%)	45±19 8 (89%)	38±13 8 (57%)	0.26 0.12
Fever Dialysis vintage, mo	14 (61%) 16 [7-39]	9 (100%) 9 [4-36]	5 (36%) 19 [12-47]	0.002 0.37
Median maximum thrombus diameter, mm	23 [16-29]	25 [23-40]	19 [15-27]	0.096
Successful thrombus dissolution or shrinking with OACs	11 (47%)	0 (0%)	11 (78%)	<.001
Embolic complications Cardiac surgery as final treatment	5 (22%) 7(30%)	5 (36%) 7 (50%)	0 (0%) 0 (0%)	0.0037 ≤.001
Deaths, n	5 (22%)	4 (29%)	1 (11%)*	0.056

*Death not directly related to CRAT event

SA-PO971

Anxiety and Pain with Tunneled Dialysis Catheter Insertion in Patients with ESRD

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Background: About 50% of hemodialysis patients require tunneled catheters for hemoaccess because a fistula is not feasible. Tunneled catheters are typically inserted with local anesthetic (LA) alone. However, conscious sedation (CS) is sometimes used and may be associated with slightly increased cardiorespiratory risk, or require several hours of post-procedure observation in hospital. Given limited access to recovery beds, patients receiving CS are usually bridged with a non-tunneled catheter until conversion to a tunneled catheter can be booked. As there is no consensus on the benefit of CS in this setting, clinical practice varies widely and patient preferences regarding this choice are unknown. Our objectives are to assess: 1) pain and anxiety experienced by patients during tunneled catheter procedures; 2) patient preferences with respect to the time vs. discomfort trade-off inherent in the choice of using or not using CS.

Methods: We mailed a 10-item questionnaire to all patients >18y who had tunneled catheter procedures in Manitoba, Canada between Apr-16 and Oct -17; as well as to incident patients from Nov-17 until present. Participants rated their experience of pain and anxiety from their most recent procedure on a Likert scale from '0' to '10'. Patients were also asked which procedure they would prefer in the future.

Results: A total of 148 of 651 questionnaires were returned (22.7%); where 80 patients had LA only and 37 had CS. Pain (median = 2) and anxiety (median = 4) during the procedure were low in both groups. Patients undergoing CS experienced a higher level of pain post-procedure (median of 2.5 vs. 1; p = 0.02) and anxiety during procedure (median of 5.5 vs 3; p=0.01). The majority of respondents preferred one procedure with LA only to two procedures (non-tunneled insertion, then CS for tunneled catheter) (68% vs. 32%), or to waiting for a CS procedure at a later date (76% vs. 24%). Limitations: retrospective survey. Response rate was low.

Conclusions: Low levels of pain and anxiety were experienced regardless of procedure type. When faced with a trade-off, patients preferred a procedure that took less time even if more discomfort was involved. We conclude that LA alone can be used without significant additional distress in most patients.

SA-PO972

Nitric Oxide (NO) Releasing Tunneled Dialysis Catheters (TDC) Reduce Catheter Related Blood Stream Infection (CRBSI) and Dysfunction

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Background: Tunneled dialysis catheter complications, due to infection, thrombosis and central vein stenosis are responsible for a very significant morbidity, mortality and economic cost. Nitric oxide (NO) is an important biological mediator, which has potent anti-microbial, anti-platelet and anti-smooth muscle cell activities. We have previously developed a novel and innovative technology that results in a prolonged polymer based (silicone rubber, polyurethanes, etc.) release of NO. The goal of this study, therefore, was to assess the impact of NO releasing TDCs on infection, thrombosis and central vein stenosis, using a validated pig model of TDC complications

Methods: 9 Yorkshire cross pigs were used in this study. 4 non-treated commercial catheters and 5 NO-releasing catheters were placed using a percutanous jugular approach. Catheters were accessed twice a week in a sterile fashion, in order to mimic the dialysis procedure and to score TDC dysfunction using a semi-quantitative scale. Study animals were monitored daily for signs and symptoms of infection. Catheter and tissue samples were collected in a standardized fashion at the time of sacrifice or at 28 days, and analyzed using standard histological and scanning electron microscopy(SEM) techniques

Results: NO-releasing catheters had a significantly delayed time to onset of infection (19.4±8.6d vs 8±3.36d; p = 0.03) and also a delayed (but not significant), onset of catheter dysfunction (12.4±9.9d vs 6.7±3.4d). Despite this significant clinical benefit, a compact fibrin sheath was detected in both the control and treated arms, together with a significant degree of central stenosis. SEM imaging revealed the presence of biofilm formation in both groups.

Conclusions: Our data demonstrate for the first time, an important clinical benefit of NO releasing TDCs on infection and dysfunction. Interestingly, this clinical benefit seemed to occur independently of the presence of a fibrin sheath, venous wall thickening and biofilm formation. We believe that a prolonged release of NO using our innovative polymer technology could result in a very significant reduction of the morbidity, mortality and economic cost currently associated with TDC complications.

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SA-PO973

Echocardiographic Measurements Before Different AVF Types Created Before and After Hemodialysis Initiation and the Contribution to Pulmonary Hypertension

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Background: Pulmonary hypertension (PH; PAP of 25 mmHg at rest or higher than 30 mmHg with exercise) is common in end-stage renal disease patients, which has been associated with uremic toxins, volume status, and hemodynamic changes that occur with vascular access creation. Little is known about the effects that different vascular access techniques, performed before or after initiation of dialysis, have on echocardiographic measurements.

Methods: A retrospective study was performed at the University of Miami Hospital/ Jackson Memorial Health System from 2009 to 2014, evaluating patients who underwent an arteriovenous fistula (AVF) creation for hemodialysis. Patients who had a 2-D echocardiogram done before and after surgical AVF creation were analyzed. A total of 125 patients were included. From these, 22 patients had the AVF created before the need for dialysis, while 103 patients had already initiated hemodialysis (HD) using a dialysis catheter. The 2-D echo measurements analyzed were ejection fraction EF (%), right ventricular systolic pressure (RVSP; mmHg), and right ventricular end diastole (RVDd; cm).

Results: The mean age at the time of AVF creation was 50 ± 12 years in patients with AVFs created before HD initiation, and 51 ± 13 in the after HD subgroup. 55 and 62% of patients were men, and essential hypertension was present in 100% of participants in both cohorts. The prevalence of diabetes mellitus was 68% and 59% in patients with AVF created before and after HD initiation, respectively. The AVF inflow was brachial-based in 50% and radial-based in 50% of the accesses in the pre-dialysis group, compared to 58% brachial vs. 42% radial in AVFs created after HD initiation. No statistical differences were found in RVSP or RVDd comparing brachial-based vs. radial-based inflow AVFs in patients with access created before or after HD initiation. However, EF (%) was higher in patients with radial-based vs. brachial-based AVFs when the access was created after HD initiation (53.8 ± 11 vs. 57.8 ± 6, p=0.04).

Conclusions: With these results, we can conclude that timing of AVF creation or type of arterial inflow has no correlation with PH in end-stage renal disease patients. The differences in EF in the after HD subgroup need to be further investigated.

SA-PO974

The First-in-Man Trial of the av-Guardian Vascular Access System

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Background: The ability to successfully cannulate the AVF reliably is a critical step in the delivery of hemodialysis therapy. The av-Guardian vascular access system (avGD; Advent Access, Singapore) is designed to overcome the technical barrier to establishing reliable blunt needle access in patients with mature AVF. avGD is a single component titanium device (15mm x 5mm x 3 mm) with a palpable entry point that is subcutaneously implanted between the skin and the AVF to allow repeated cannulation through a single puncture site.

Methods: This was a first-in-man, prospective, non-randomized trial performed to assess the safety and feasibility of avGD in facilitating blunt needle access in patients with matured AVF. The primary end points of the study included rate of successful hemodialysis sessions via avGD cannulation over 3 months and changes in AVF flow rates after implantation

Results: Six patients were enrolled in the study, of which 5 had AVFs that were difficult to cannulate. A pair of avGD was implanted each at the arterial and venous cannulation sites under local anaesthesia as shown in figure 1. Cannulation via the avGD commenced 14 days post-implantation. Overall, the rate of successful cannulation through the avGD over 3 months in 216 hemodialysis session was 98.1%(424/432) at the arterial site and 94.4% (408/432) at the venous site. Significantly, 85.5% and 90% of the cannulations at the A and V site respectively were successful at first attempt. Blood flow rates within the AVF were unaffected by the devices. The patients were transited to blunt needle cannulation after a median of 15.5 and 18.5 sessions at the A and V site respectively.

Conclusions: The results of this first in man trial demonstrated the safety and feasibility of a subcutaneously implanted, extravascular device to facilitate blunt needle access in matured AVF. The device did not adversely affect flows within the AVF after implantation and successful cannulation through the devices can be achieved > 94% of the time

Funding: Commercial Support - Access Advent

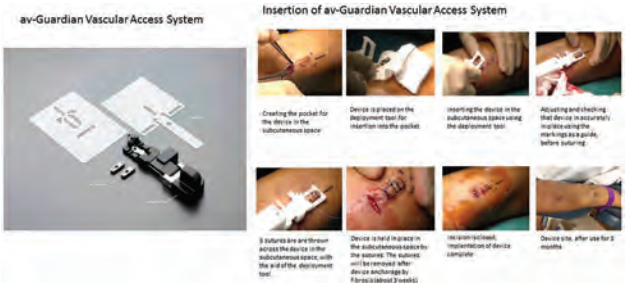

Figure 1: The av-Guardian vascular access system and implantation process

SA-PO975

Extracellular Matrix Stiffness Mediates Human Aortic Smooth Muscle Cell Phenotype via Rho-Kinase

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Background: Chronic Kidney Disease (CKD) is associated with increased vascular stiffness and accelerated atherosclerosis. However, the mechanisms by which stiffness accelerates the development of atherosclerosis is not known. Rho-kinase (ROCK), a key mechanosensor, influences the phenotype of vascular smooth muscle cells. A synthetic phenotype characterized by increased migration and proliferation of vascular smooth muscle cells is associated with atherosclerosis. We hypothesized that matrix stiffness upregulates ROCK activity to affect vascular smooth muscle cell phenotype.

Methods: Human aortic smooth cells (HASMC) were plated on regular tissue culture plates or polyacrylamide gels engineered to varying stiffness (2kPa – 50kPa). Proliferation of cells was measured by a formazan-based assay. ROCK activity was measured using an ELISA based detection of substrate phosphorylation, and ROCK transcription was assayed by PCR.

Results: Proliferation of HASMC increased with increasing stiffness of the matrix (Fig 1A). Stiffness increased ROCK activity in these cells (Fig 1B). In addition, PCR showed that stiffness increases ROCK1 mRNA but not ROCK2. Inhibition of ROCK with Fasudil abolished the stiffness induced increase in proliferation.

Conclusions: Our results suggest that stiffness increases proliferation of HASMC via Rho-kinase. Thus, ROCK pathways might be a target to prevent vascular complications of kidney disease.

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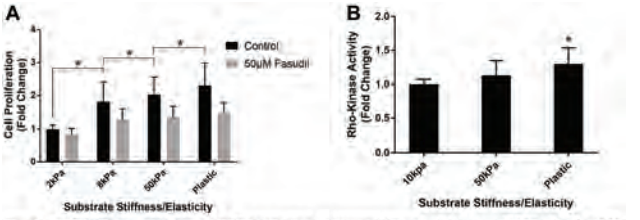

Figure 1. (A) ECM stiffness causes increased HASMC proliferations. (B) Increased stiffness leads to increased ROCK activity. * p < 0.05.

SA-PO976

Iron Stimulation Induced Calcification in Human Aortic Vascular Smooth Muscle Cells Through Interleukin-24 (IL-24)

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Background: In CKD patients, atherosclerosis is one of important life-limitting factors. The feature of the atherosclerosis in CKD patients was called as Moenckeberg's arteriosclerosis which was seen in vascular media, but the relationship between iron and calcification in vascular smooth muscle cell remained unclear. To reveal the relationship between calcification in vascular media and iron stimulation using cultured vascular smooth muscle cells.

Methods: The aorta smooth muscle cells were cultured for three weeks. At day 0, we changed the usual culture medium to calcification medium, and TNF-alpha and iron were added to the calcification medium. Calcification in each condition was confirmed by Alizarin staining. And to reveal early mechanism to enhance the calcification by iron and TNF-alpha stimulation, we compared the gene expression profile between each condition in day 1 and day 3 using microarray analyses. We confirmed gene expression of IL-24 which had increased in microarray analysis by mRNA level (real-time PCR) and by protein level (ELISA) in time course. Calcification induced by recombinant IL-2 instead of iron was also evaluated.

Results: Both iron and TNF-alpha stimulation enhanced calcification by Alizarin Staining. Moreover, both iron and TNF-alpha stimulation at the same time enhanced

calcification more strongly than single stimulation. We picked up IL-24 which had increased with both iron and TNF-alpha stimulation. We confirmed IL-24 expression by real-time PCR. Gene expression was increased at day1 by stimulation of iron(5.8±3.0 fold change vs control), TNF-alpha (7.8±1.9 fold change vs control), and both stimulation(53.1±27.1fold change vs control), synergistically(shown below). At day 3, gene expression showed as same increase as at day 1. The time course of IL-24 was confirmed in mRNA level by real time PCR and in protein level by ELISA. Calcification was induced in human vascular smooth muscle cells by IL-24 instead of iron, and quantification of calcification also confirmed the result.

Conclusions: Iron stimulation enhanced calcification in vascular smooth muscle cells along with TNF-alpha stimulation. Iron stimulation along with inflammatory might induce calcification in human vascular smooth muscle cells through IL-24.

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SA-PO977

Indoxyl Sulfate Aggravates Vascular Calcification via Suppress the Matrix Gla Protein by the the ROS/NF-κB Signaling Pathway

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Background: Vascular calcification (VC) is the major complication and contributes to the cardiovascular mortality in chronic kidney diseases (CKD). Indoxyl sulfate (IS) has been recognized as the major uremic toxin involved in the vascular calcification in CKD due to its high oxidative stress, but the underlying mechanisms remain largely unknown. Matrix Gla protein (MGP) plays roles in vascular calcification as an important inhibitor of calcification. Here, we investigated whether MGP is involved in IS-induced vascular calcification.

Methods: In vitro, radial arteries from CKD patients were used for histological examination. In vitro, HASMCs were cultured with IS to induce vascular calcification, which was detected by Alizarin red S staining. Gene expression and protein levels of MGP and osteogenic differentiation markers were determined by qRT-PCR and western blotting, respectively. ROS were detected using probes with a fluorescence detector. The phosphorylation of Ikkβ, NF-κB and IκB degradation were detected by western blotting, and the role of ROS/NF-κB was further confirmed by using the inhibitor of DPI and PDTC.

Results: We observed the average level of MGP expression was decreased in the calcified vessels in CKD patients. Simultaneously, IS also decreased MGP expression accompanied by the calcification of HASMCs. osteogenic differentiation was confirmed by the increased expression of BMP2 and Cbfa1 and decreased expression of the α-SMA, which was accompanied by the increased level of ROS. The phosphorylation of Ikkβ, NF-κB and IκB degradation increased by IS but reversed by an ROS inhibitor of DPI. In contrast, suppression of MGP and calcification of HASMCs calcification were attenuated by pretreatment with PDTC, an NF-κB inhibitor.

Conclusions: These observations provide evidence that inhibition of MGP expression may contribute to the pathogenesis of IS-induced vascular calcification in CKD.

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SA-PO978

CDK9-Cyclin T1 Complex Mediates Medial Calcification Through the Induction of CHOP

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Background: Our recent studies indicate that activation of the Activating transcription factor 4 (ATF4) pathway through the ER stress response induced by saturated fatty acids (SFAs) plays a causative role in vascular calcification in chronic kidney disease (CKD). we 1) studied a pro-apoptotic CHOP transcription factor that contributes to CKD-dependent medial calcification and 2) identified a novel regulator of ER stress-mediated CHOP expression

Methods: 1) To study the smooth muscle cells (SMC)-specific role of CHOP in regulating medial calcification, we generated SMC-specific CHOP conditional transgenic mice and analyzed aortic region of control and SMC-specific CHOP TG mice under CKD (5/6 nephrectomy). 2) To explore a signaling pathway that blocks SFA-induced CHOP expression, we screened a kinase inhibitor library containing >140 compounds by treating human vascular smooth muscle cells with a saturated fatty acid.

Results: SMC-specific CHOP transgenic mice developed severe vascular apoptosis and medial calcification under CKD. Protein kinase inhibitor library screening identified 16 compounds, including 7 cyclin-dependent kinase (CDK) inhibitors, that significantly suppressed the induction of CHOP through ER stress. In addition, selective inhibitors against CDK9 and CDK9-specific inhibition through a gene-editing technique blocked SFA-mediated induction of CHOP, while other CDK isoform inhibitors did not affect CHOP expression. Knockout of cyclin T1 inhibited SFA-mediated induction of CHOP and mineralization, whereas deletion of cyclin T2 and cyclin K promoted CHOP expression levels and mineralization. The CDK9-cyclin T1 complex directly phosphorylated and activated ATF4.

Conclusions: These results demonstrate that 1) the CDK9-cyclin T1 and CDK9-cyclin T2/K complexes have opposing roles in CHOP expression and vascular calcification and 2) the CDK9-cyclin T1 complex mediates vascular calcification due to CHOP induction through phosphorylation-mediated ATF4 activation.

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SA-PO979

Mechanisms Linking CKD and Atherosclerosis: CD34+ Cell in the Atherosclerosis Plaque

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Background: Chronic kidney disease (CKD) is associated with a higher incidence of atherosclerotic vascular disease (ASVD) but its pathogenic mechanism is not well known. CKD is associated with lower circulating $CD34^+$ Endothelial Progenitor Cells (EPCs) and atherosclerotic lesions have a focal distribution suggesting an impaired vascular repair mechanism. The aim of this study was to localize stems and $CD34^+$ EPCs in the vascular wall from humans and in a mouse model of atherosclerosis.

Methods: We assessed CD34 + hematopoietic stem cells in the atherosclerotic plaque by IHQ in the abdominal aorta obtained from 10 human necropsies (5 patients with CKD). CD34 levels were quantified by qPCR. Furthermore, we analyzed CD34+ by IHQ in 10 $APOE^{-/-}$ mice with a CD40 blockade using a specific siRNA (siCD40) and in 10 $APOE^{-/-}$ controls (5 mice treated with scrambled siRNA (SC) and 5 mice treated with vehicle (veh)) at 24 weeks.

Results: We included 18 samples (9 atherosclerotic plaques and 9 samples from normal abdominal aorta without injury) from 9 patients (5 patients with CKD). Atherosclerotic plaque was associated with increased inflammation in the intima (14 ± 15% in the sample without injury, n=9 vs 54 ± 25% in the plaque, n=8, p=0.004). $CD34^+$ cells were increased in the atherosclerotic plaque (-4.7 ± 0.76 cycles, n=6 in normal aorta vs -3.2±1 cycles, n=4 in plaque, p=0.028). Furthermore, we have identified niches of $CD34^+$ cells in the neointima and in the adventitia of human arteries. Then, we analyzed mRNA levels of CD34+ patients in normal vascular walls with CKD and we observed a trend to display lower number of CD34 cells (-4.5±0.7 cycles in non-CKD patients, n=4, -5.3±0.75 cycles in CKD patients, n=2; p=0.3). Finally CD34+ cells were identified especially in the perivascular adipose tissue (PVAT) of mice treated with siCD40 (9±1% in 5 mice treated with veh, 3±2% in 5 mice treated with SC, vs 13±6% in 10 mice treated with siCD40, p<0.0001).

Conclusions: Atherosclerotic plaque is associated with increased inflammation and an increase number of cells hematopoietic stem cells (HSCs)/endothelial progenitor cells (EPCs) $CD34^+$cells. HSCs/EPCs could participate in vascular remodeling (regeneration), but also in the neovascularization that may contribute to plaque growth and its destabilization.

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SA-PO980

Exosomes from Activated Kidney Fibroblast Stimulate Transcription of PlGF on Endothelial Cells

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Background: Exosomes are small membrane vesicles that contain host cell's proteins, mRNAs, and microRNAs. The body of evidence revealed that these contents were biologically active and had roles in intracellular communication. On the other hand, it is well known that CKD patients are at risk of cardiovascular diseases, but the mechanism of this distant organ crosstalk is not fully understood. Recently, placental growth factor (PlGF) received attention in pathogenesis of cardio-renal syndrome (CRS). Under the hypothesis that exosomes are involved in pathophysiology of CRS, the aim of this study is to explore the role of exosomes from kidney fibroblasts, which actively proliferate in diseased kidney, on vascular endothelial cells.

Methods: Clinical samples; HUVECs were stimulated by serum exosomes from stage G5 CKD patients and healthy donor. Exosomes tracking; Activated kidney fibroblasts were isolated from unilateral ureteral obstruction (UUO) mice kidney. These exosomes were labeled by microRNA of C. elegance (Cel-miR-39), then labeled Exosomes were injected to the mice through tail vein. Effects of exosomes on endothelial cells; We purified exosomes from culture media of TGF-b stimulated kidney fibroblasts cell line (NRK-49f), and then primary culture of vascular endothelial cells (RAOEC) was stimulated using these exosomes. By qPCR, we evaluated the expression of PlGF genes.

Results: (1) Not only the serum but also exosomes from CKD stage G5 patients stimulated PlGF expression on HUVECs. (2) Injected labeled exosomes from activated kidney fibroblast distributed mainly in lung, liver, and aorta. (3) RAOEC stimulated with exosomes form TGF-b activated rat kidney fibroblast (RAOEC-T) showed higher expression of PlGF than control (RAOEC-C).

Conclusions: So far, CRS is considered to be caused by uremic factor, RAS system, chronic inflammation, and so on. From this study, both serum and exosomes from CKD patients stimulated PlGF transcription on endothelial cells. Exosomes from activated kidney fibloblast had same tendency. We speculated that exosomes from diseased kidney have some roles in atherosclerotic change by modulating the expression of PlGF on endothelial cells. Farther studies are needed to elucidate the degree of contribution to CRS.

SA-PO981

Senescent MVs from IS-Treated Endothelial Cells Induce Vascular Calcification

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Background: Vascular calcification (VC) is a premature event of cardiovascular inflammatory diseases (CVD) in patients with chronic kidney disease (CKD). But identifying patients at risk of developing VC is complex, and it is necessary to expand the knowledge of the initial events that allow the progression of this pathology. Recently, we reported that senescent endothelial cells produce microvesicles (MV) which can act triggering the development of VC. As induction of premature endothelial senescence is a physiopathological mechanism in CVD associated with CKD, the objective of this study is to investigate whether MVs from endothelial cells that undergo premature senescence induced by the uremic toxin indoxyl sulfate (IS) can also modify vascular smooth muscle cells by making them susceptible to bone transformation. Besides, we study the mechanism(s) involved in VC promotion.

Methods: Endothelial cells (HUVEC) were treated with IS (250 μM; 4 days) and senescence was quantified with the β-galactosidase kit. The MV produced by these senescent HUVECs were isolated and subsequently characterized by flow cytometry and used for the treatment of vascular smooth muscle cells (HASMC). In HASMC, the calcium deposits were evaluated by alizarin red. At 30 days, the calcium content was quantified by the phenolsulfonephthalein kit. Expression of pro-calcifying genes was determined in HASMC by quantitative PCR. Western blot established the expression of a specific HASMC marker.

Results: IS-treated induced early senescence in HUVEC (control: 7.07±2.87% vs. IS: 72.90±13.09%, p <0.0001) and an increase in the production of MV was observed (control: 1.68±1.00 vs. IS: 9.92±4.29 MV/cell, p <0.005). Senescent MVs from IS-treated endothelial cells induced calcification in HASMC associated with deregulation in the expression of procalcifying genes (Runx2, BMP2). Also, the MV generated in HUVEC treated with IS produce a dedifferentiation process of the HASMC (SM22α expression).

Conclusions: MV produced by endothelial cells which develop early senescence as a consequence of the stress generated by the uremic toxins promote the development of VC. These results may be useful to develop biomarkers and therapeutic tools to prevent or treated patients with CVD and/or CKD at risk of developing VC.

SA-PO982

The Circadian Clock Provides Beneficial Effects Against the Endothelial Dysfunction to Promote Atherogenesis by Regulating PDGF Generation and iNOS Expression

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Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence growth factors, such as platelet-derived growth factor (PDGF) or inducible nitric oxide synthase (iNOS) which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of PDGF and iNOS expression in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in PDGF and iNOS expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include PDGF and iNOS, which are significantly elevated in Bmal1 KO mice. We also confirmed that PDGF levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating PDGF generation and iNOS expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

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SA-PO983

Endothelial-Specific Krüppel-Like Factor 2 Inactivation Promotes Endothelial Dysfunction in the Setting of Uremia

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Background: Uremic solutes that accumulate in end-stage renal disease(ESRD) may contribute to endothelial dysfunction and subsequent cardiovascular disease and vascular access dysfunction in ESRD patients. However, the mechanisms which mediate uremia-induced endothelial dysfunction in ESRD are not understood. Kruppel-like factors(KLFs) are key regulators of endothelial homeostasis which may be affected by the uremic milieu. In this study we examined the role of endothelial KLF2 in mediating endothelial dysfunction in the setting of uremia

Methods: We used serum from a porcine model of chronic renal failure to assess the impact of uremia on endothelial KLF2 expression in vitro. Human umbilical vein endothelial cells (HUVECs) were treated with increasing concentrations of uremic or non-uremic porcine serum and analyzed for KLF2 expression. Similarly, cells were treated with individual protein-bound toxins at average uremic concentrations. Reactive oxygen species (ROS) production and monocyte adhesion were then assessed in treated cells with and without KLF2 overexpression. To assess if the loss of KLF2 impairs endothelial function in vivo, we quantified flow-mediated dilation (FMD) of the femoral artery in endothelial-specific KLF2 conditional knockout (cKO) mice after 5 minutes of hindlimb ischemia

Results: KLF2 expression was dose-dependently decreased in HUVECs with uremic serum versus normal serum. Carboxymethyl-lysine(CML) modified albumin, a uremic advanced glycation end-product(AGE), also inhibited KLF2 expression. KLF2 suppression also promoted endothelial dysfunction in vitro, as adenoviral overexpression of KLF2 inhibited reactive oxygen species production and leukocyte adhesion in HUVECs treated with uremic serum or CML-AGE. Assessment of FMD in KLF2cKO mice demonstrated a 50%reduction in vasodilation compared to controls. The lack of femoral artery vasodilation in KLF2cKO mice was also accompanied by an attenuated return of wall shear stress to baseline independent of blood velocity

Conclusions: Collectively, these observations implicate loss of endothelial KLF2 as a mediator of endothelial dysfunction in the setting of uremia, and suggest that elevating KLF2 expression may be a novel strategy for prevention and treatment of vascular access dysfunction and cardiovascular disease in ESRD

SA-PO984

The Role of Autophagy in Neutrophil Extracellular Trap (NET) Formation in CKD

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Background: Increased neutrophil extracellular trap (NET) formation could be an endogenous stimulus of chronic vascular inflammation despite its bacterial killing effect. However, researches about the degree of NET formation in chronic uremic conditions and its relationship with vascular complications have been limited. We assessed the relationship between NETs and vascular endothelial dysfunction in maintenance hemodialysis (MHD) patients, and evaluated the role of autophagy in NET formation in uremia

Methods: To quantify extracellular DNA level, serum cell-free nucleosome was measured between MHD patients (n=60) and healthy volunteer (HV, n=20). Then, neutrophils were isolated and stimulated with phorbol 12-myristate 13-acetate (PMA). The NET formation was visualized with confocal microscopy and the activity of neutrophil elastase (NE) were directly measured to confirm the amount of NETs in both groups. Endothelial dysfunction was measured by flow-mediated dilatation (FMD) of brachial artery using an automated device. The autophagic status were evaluated, and the effect of autophagy inhibition on NET formation was further investigated.

Results: The median basal levels of serum cell-free nucleosome were prominently increased in MHD patients than HV (p<0.001). Also, neutrophils isolated from MHD patients showed an increased NE activity as well as higher NET formation than controls both at basal and activated state, suggesting neutrophil priming in MHD group. The increased extracellular DNA level as well as NE activities were strongly associated with FMD (%) even after adjustments for traditional cardiovascular risk factors and uremic toxin levels (nucleosome: β=-0.429 p=0.001, NE β=-0.429 p=0.001). Moreover, neutrophils isolated from MHD patients showed an increase in autophagy function, especially autophagy induction. Interestingly, after treatment of 3-MA or ammonium chloride, inhibitors of autophagy pathways at early and late stages respectively, the levels of NET formation were markedly augmented, suggesting the protective role of autophagy in uremia.

Conclusions: Increased NETs formation may be one of important contributing factors of vascular endothelial dysfunction in hemodialysis patients. Increased autophagy induction in uremia could be an adaptive response as a protective manner to remove uremic toxins, and the inhibition of autophagy may induce excessive NET formation.

SA-PO985

Macrophage and T-Cell Infiltration in a Rat Model of Limb Ischemia: Effect of Impaired Kidney Function on the Pattern of Post-Ischemic Cell Infiltration

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Background: The outcome of limb ischemia is worse in rats with chronic kidney disease (CKD) as was previously shown by others and us. We hypothesized that a different pattern of T-lymphocyte and macrophage infiltration into the ischemic muscle in rats with CKD may underlie the deficient repair and angiogenesis processes.

Methods: CKD rats (N=10) underwent 5/6 nephrectomy; controls (N=8) sham operation. After 8 weeks, ischemia of the right limb was induced by ligation and resection of the femoral artery. Rats were sacrificed 3 days later. Cross sections of musculus soleus of the ischemic and non-ischemic limbs were stained for macrophage markers ED-1 and CD163 as well as lymphocyte markers CD3, CD4 and CD8a. Positive cells were counted in 20 high-power fields. The expression of a panel of cytokines (including CCL2, CCL5, CCL7, osteopontin, IL-6 and TNFα) in muscle tissue was measured by RT-PCR.

Results: All investigated cell types were increased in ischemic versus non-ischemic limbs. There was a trend towards a higher increase of ED-1 macrophages in ischemic limbs of CKD (15±3-fold versus 10±3-fold in controls, p=0.492) but there was no significant difference. Absolute numbers of ED-1 and CD163 positive cells as well as the ratio between ED-1 and CD163 (M2 macrophages) did not differ between CKD and control. The number of CD3 T-cells in ischemic limbs was not different between CKD (5.4±0.7 cells/view) and controls (4.9±0.5, p=0.897). However, the number of CD8a cells in ischemic limbs was higher in CKD (1.8±0.2) than in controls (1.0±0.1, p=0.006). The ratio of CD8a to CD4 cells was significantly elevated in CKD rat ischemic limbs, as was the ratio of CD8a to CD3 cells. All investigated cytokines increased in ischemic limbs but there was no consistent difference between CKD and controls. In ischemic limbs, CD8a cells correlated tightly with the expression of CCL5 (r=0.722, p=0.001) but not with other cytokines.

Conclusions: Our results point to a higher infiltration of CD8a cytotoxic T-cells into ischemic limbs in CKD rats which may contribute to a worse outcome. In contrast, we did not find an altered pattern of M1/M2 macrophages.

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SA-PO986

Soluble Klotho Acts as a Co-Receptor for FGF23 That Interferes with FGF23's Action on the Heart

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Background: Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via klotho and FGF receptor (FGFR) 1. Klotho also exists in a soluble form that is released from the kidney. In patients with chronic kidney disease (CKD), changes in FGF23 and circulating sKL levels are associated with the development of cardiovascular disease and mortality. We have reported that FGF23 can contribute to cardiac hypertrophy by directly targeting cardiac myocytes via FGFR4 and inducing phospholipase Cg (PLCg) signaling. Experimental studies have shown that sKL has pleiotropic functions, including cardio-protective actions. Since a recent structural study has shown sKL acts as a scaffold to mediate FGF23-FGFR1 binding, we tested whether sKL interferes with FGF23-FGFR4 complex formation and effects in cardiac myocytes.

Methods: We purified recombinant sKL from stably transfected HEK293 cells, and determined its ability to bind recombinant FGF23 coated to a 96-well plate in the presence or absence of different FGFR isoforms. Furthermore, we co-treated neonatal rat ventricular myocytes (NRVM) with FGF23 and sKL and analyzed the activation of downstream signaling events by immunoblotting and hypertrophy via ^{3}H-phenylalanine incorporation.

Results: sKL binds FGF23 in the absence of FGFRs and exponentially increases the affinity of FGF23 for multiple FGFR isoforms. In NRVM, co-treatment with sKL blocks FGF23-mediated PLCγ activation and stimulates Ras/MAPK signaling. Furthermore, sKL inhibits FGF23-induced hypertrophic growth of NRVM, but has no effect on FGF2-mediated hypertrophy.

Conclusions: The binding of sKL to FGF23 does not require FGFRs and might therefore act as the initial event in the formation of FGF23/sKL/FGFR signaling complexes. Similar to membrane-associated klotho, sKL increases the affinity of FGF23 for FGFR binding, and thereby causes FGF23 responsiveness of cells that express FGFRs but lack klotho. The sKL-mediated interaction between FGF23 and FGFRs appears to be more promiscuous than previously reported by not only involving FGFR1, which might explain the pleiotropic actions of sKL on various cells types. By inducing a switch in downstream signaling, sKL blocks FGF23-induced hypertrophy in cardiac myocytes and might serve as a cardio-protective therapy in CKD.

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SA-PO987

Cardiac-Specific FGF23 Knockout Leads to Increased Cardiovascular Risk

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Background: Patients with CKD have an higher risk for cardiovascular disease (CVD) and mortality associated with increased levels of FGF23. Recent studies indicate that FGF23 is expressed by cardiac myocytes and activates the calcineurin/NFAT pathway via activation of FGFR4 in the heart and may contribute to the development of LVH. We hypothesized that cardiac FGF23 is a modifier of CVD risk in mice.

Methods: To this aim we generated a mouse model with a cardiac myocyte-specific FGF23 knockout (FGF23-KO) in the C57BL/6 background using the Cre/loxP system. we evaluated the impact of cardiac FGF23 on the heart. Cardiovascular outcome in FGF23-KO receiving a standard diet was compared to wild-type littermates (WT) during an observational period of up-to 6-months. In addition, we compared pressure overload-induced cardiac hypertrophy induced by transverse aortic constriction (TAC) in 8-weeks old FGF23-KO and WT mice.

Results: Body weight, heart weight, tibia length and parameter of mineral metabolism including FGF23 synthesis in bone and plasma intact FGF23 levels did not differ between FGF23-KO mice and WT group. FGF23-KO mice showed significantly increased mortality compared to WT associated with enhanced end-diastolic LV volume and stroke volume examined by cardiac magnetic resonance imaging (cMRI). On molecular level, pro-hypertrophic and pro-fibrotic markers ANP, BNP, collagen 1, TGF-β and CTGF were enhanced in heart tissue of FGF23-KO mice and local cardiac renin-angiotensin-aldosterone system was activated compared to WT mice. As expected, heart function was impaired in WT mice 2 weeks after TAC compared with Sham along with increased relative heart weight, cardiac myocyte size and the induction of pro-hypertrophic genes and bone and cardiac FGF23 synthesis. Interestingly, FGF23-KO mice after TAC showed the same heart phenotype like WT TAC with exception of cardiac FGF23 synthesis. Moreover, cMRI revealted increased end-systolic LV volume and systolic LV diameter in FGF23-KO TAC compared to WT TAC mice.

Conclusions: In conclusion, cardiac myocyte-specific FGF23 knockout leads to impaired heart function and increased mortality in mice and results in increased CVD in the high pressure-induced hypertrophic mouse model. Thus our data suggest a physiological role of cardiac FGF23 in heart function and adaption to pressure overload.

SA-PO988

Cardiac-Specific Overexpression of FGF23 Fails to Induce Cardiac Hypertrophy in Mice Without CKD

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Background: High circulating and cardiac FGF23 levels are associated with increased risk of cardiovascular events and all cause mortality in CKD patients. We showed on molecular level that FGF23 stimulates hypertrophic growth of isolated cardiac myocytes in the absence of klotho via activation of FGFR4/calcineurin/NFAT pathway leading to left ventricular hypertrophy (LVH). It is still a matter of debate if elevated FGF23 results in LVH under healthy conditions, e.g. in the absence of CKD.

Methods: By generating a mouse model with cardiac specific overexpression of FGF23 using cardiovascular gene transfer with an adeno-associated virus expressing FGF23 (AAV-FGF23) under the control of the cardiac troponin T promotor, we investigated the pro-hypertrophic properties of cardiac FGF23 in C57BL/6N wild-type mice.

Results: The detection of AAV expression within various organs verified the specific accumulation of AAV-FGF23 in the heart. Cardiac *Fgf23* mRNA expression was 2,000-fold increased in AAV-FGF23-treated mice compared to controls and immunoblot analysis point out that the cardiac FGF23 protein was full-length biologically active. This was further confirmed by enhanced cardiac and plasma intact FGF23 levels in AAV-FGF23 mice. Parameters of mineral metabolism and renal expression of klotho did not differ between AAV-FGF23 and controls, whereas *NaPi2a* and *NaPi2c* mRNA levels were significantly reduced. Although, AAV-FGF23-treated mice showed a moderate induction of cardiac *Fgfr4* mRNA expression, relative heart weight and cardiac myocyte size did not differ between both groups and pro-hypertrophic NFAT target genes *Rcan1*, *Trpc6*, *b-MHC*, and *ANP* remained unchanged. Moreover, *BNP* levels were even significantly reduced in AAV-FGF23 mice compared to controls. Cardiac MRI analysis demonstrated no impairment of heart function in AAV-FGF23 mice but echocardiography studies showed significant increased stroke volume and cardiac output, which might be due to increased cardiac preload and/or enhanced contractility.

Conclusions: In conclusion, AAV-FGF23 induces the expression of full-length biological active FGF23 in the heart but fails to induce LVH under healthy conditions, suggesting that additional factors associated with CKD, e.g. klotho deficiency or high phosphate load, are necessary for FGF23 to tackle the heart.

SA-PO989

FGF23 Contributes to Cardiac Fibrosis in CKD

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Background: The risk for cardiovascular diseases is enormously increased in patients with chronic kidney disease (CKD). Over 90% of patients with end-stage renal disease develop pathologic cardiac remodeling, including hypertrophy and fibrosis that can lead to heart failure. Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via FGF receptor (FGFR) 1 and klotho. In early stages of CKD, serum FGF23 levels increase to compensate the rise in serum phosphate concentrations. High FGF23 concentrations are associated with the development of cardiovascular disease and a strong predictor for mortality in CKD. Our previous studies in rodents have shown that FGF23 can directly target the heart and contribute to cardiac hypertrophy. FGF23 binds to FGFR4 on cardiac myocytes in a klotho-independent manner, leading to the activation of a pro-hypertrophic signaling cascade, including phospholipase Cγ (PLCγ) and calcineurin. Since in animal models with elevated serum FGF23 levels cardiac hypertrophy is accompanied by fibrosis, we wanted to test if FGF23 can also directly target cardiac fibroblasts, using isolated primary cell culture models.

Methods: We have established primary cardiac fibroblast cultures from newborn rats, as well as adult mice and rats, and we analyze expression levels of different FGFR isoforms and klotho by qPCR. We treat cells with increasing FGF23 concentrations and investigate the activation of FGFRs, downstream signal mediators and pro-fibrotic gene programs by qPCR, immunoblotting and enzymatic assays. Furthermore, we study cell proliferation, migration and survival. We determine if co-treatment with inhibitors against FGFRs, PLCγ or calcineurin blocks FGF23-mediated effects on fibroblasts.

Results: Cardiac fibroblasts isolated from mice and rats express high levels of FGFR1 and to a lower extent also FGFR4. FGF23 promotes proliferation, migration and activation of fibroblasts when compared to vehicle-treated control cells.

Conclusions: We postulate that FGF23 contributes to pathologic cardiac remodeling by directly targeting different cell types in the myocardium, i.e. cardiac myocytes via FGFR4 and cardiac fibroblasts via FGFR1. Pharmacological blockade of FGFRs might serve as novel cardio-protective therapy in CKD.

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SA-PO990

Cytoskeletal Dysregulation in Uremic Cardiomyopathy

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Background: Ventricular remodeling involving left ventricular (LV) hypertrophy, dilatation and fibrosis in uremic cardiomyopathy contribute to the high rate of premature cardiovascular death in chronic kidney disease (CKD). Alterations in the cytoskeleton are well described in hypertrophied and failing myocardium and appear to be an important regulator of pro-fibrotic pathways in CKD. The mechanisms of cytoskeletal dysregulation in uremic cardiomyopathy remain largely unknown. Herein, we performed a comprehensive investigation of cytoskeletal adaptations in uremic cardiomyopathy.

Methods: We conducted a cross-sectional analysis of explanted human LV tissues from advanced CKD donors (n=23; hemodialysis (HD; n=20); peritoneal dialysis (PD; n=3)) compared to CAD (coronary artery disease; n=11) and healthy (n=20) controls. Primary human cardiomyocytes and cardiac-myofibroblasts were treated with calcification medium (CM) in time-course experiments (0-48 hours), *in vitro*. We developed a novel digital cell sorting study model using deconvolution to accurately assess hetereogenous transcriptomic profiles inherent of mixed-cell type tissues from RNA sequencing. qPCR and western blotting was used to confirm expression of target genes.

Results: Cross-sectional analysis revealed that the major cytoskeletal proteins β-tubulin and type III intermediate filament Vimentin, were significantly down-regulated in both CAD and CKD hearts compared to controls ($p<0.01$). However, major anchor protein Vinculin was upregulated in both CAD and CKD hearts compared to controls ($p<0.05$). Interestingly, β-actin, a critical component of the microfilament system was down-regulated in CAD hearts, but further down-regulated in CKD hearts compared to CAD and controls ($p<0.01$). Furthermore, on subanalysis HD patients had significantly lower β-actin expression compared to PD patients ($p<0.01$). Analysis of primary human cardiomyocytes and cardiac-myofibroblasts treated with CM revealed the same pattern of changes, *in vitro.*

Conclusions: We show for the first time severely reduced β-actin expression in human CKD hearts compared to CAD and controls. These findings may contribute to accelerated cardiac remodeling in uremic conditions and may be affected by dialysis modality. Upregulation of Vinculin may be involved in reduced contractile function of cardiomyocytes in uremia.

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Cardiac structure in Patients with Mild to Moderate CKD – an MRI Study

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Background: Abnormal cardiac structure, in particular left ventricular hypertrophy (LVH), is common in patients with advanced chronic kidney disease (CKD), and predisposes to heart failure and sudden cardiac death. The prevalence, patterns and determinants of abnormal cardiac structure in patients with mild to moderate CKD has not been studied with magnetic resonance imaging (MRI).

Methods: We examined cardiac structure by MRI in 290 patients with mild to moderate CKD (median eGFR 50 ml/min), and explored associations with clinical and hemodynamic parameters (Mobil-O-Graph®, IEM, Germany), hydration status (bioimpedance spectroscopy), endothelial function (flow-mediated vasodilation), inflammation (high sensitive C-reactive protein, interleukin-6, tumor necrosis factor(TNF)-α, soluble TNF-receptors I and II) and CKD-mineral bone disease (MBD) markers (calcium, phosphate, 1,25-OH Vitamin D, intact parathyroid hormone, α-klotho, intact fibroblast growth factor (FGF)-23, C-terminal FGF-23). Linear regression analyses were used to identify variables independently associated with cardiac structure.

Results: Normal geometry was found in 56%, dilation in 4%, concentric remodeling in 10%, and LVH in 29% of patients. Abnormal cardiac structure was more prevalent in women than in men with CKD (P=0.06). Greater left ventricular mass (LVM) was independently associated with the variables male gender, greater BMI and higher 24h-systolic blood pressure (24h-SBP). Concentric remodeling was independently associated with male gender, higher 24h-SBP and greater hemoglobin levels. Neither endothelial function, nor hydration status or any of the inflammatory or CKD-MBD parameters contributed to the models.

Conclusions: Using state-of-the art MRI, abnormal cardiac structure was found in almost half of all patients with mild to moderate CKD. Targeting the modifiable factors 24h-SBP, BMI (for LVM) and avoiding high hemoglobin concentrations (for concentric remodeling) may prevent the development of adverse cardiac structure in patients with mild to moderate CKD.

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Renal Functional Reserve Mirrors the Sympathetic Overdrive Influence on the Heart

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Background: Renal functional reserve (RFR) refers to the capacity of the kidney to increase the Glomerular Filtration Rate (GFR) under the influence of certain stimuli. It is a promising diagnostic tool for assessing the risk of Acute Kidney Injury and of Chronic Kidney disease development in specific populations. The aim of our study was to assess the relation of RFR with diverse clinical parameters in normotensive patients with eGFR>60ml/min/1.73m^{2}and without any evidence of kidney damage (proteinuria, anatomic lesion etc).

Methods: 15 normotensive subjects (mean age=52 years, BMI= 26 kg/m^2, office systolic/diastolic BP =138/88 mmHg, ABPM 120/76mmHg) were included. All subjects underwent the exercise treadmill stress test, 24hour ABPM, office BP measurements, kidney ultrasound and ACR test. All subjects were fasted for 8 hours and then baseline hydration status was recorded using bioimpedance analysis. Basal GFR was measured after hydration and stress GFR was achieved after ingestion of oral protein 1g/kg as cooked meal. Basal and Stress GFR were determined by Creatinine Clearance = Urine Creatinine/Serum Creatinine x Urine Volume/time× 1.73/BSA). RFR was calculated as Stress GFR – Basal GFR. Patients having adequate renal reserves considered as having values of RFR greater than 30ml/min/1.73m^2

Results: There was no correlation of RFR values with respect to family history of hypertension, smoking, age, BMI or office BP. In contrast, patients with higher RFR values, achieved lower maximum systolic BP during the treadmill test ($p<0.05$) (175.7 ± 9.75 mmHg vs 176.2±22.48mmHg). Additionally, a statistically significant positive correlation was found between RFR values and maximum heart rate (HR) during treadmill test ($r=0.517$, $p=0.048$).

Conclusions: RFR is related to treadmill exercise maximum systolic BP in normotensive patients and appears to correlate with maximum HR. These findings underlie the pleiotropic effects of sympathetic nervous system in kidneys and their long term influences in kidney function. Treadmill test could be used to identify normotensive patients with normal eGFR who may have susceptibility to renal injury.

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Chronic, Isolated Renal Venous Pressure Increase Induces Extensive Renal Venous Collateral Formation and Exacerbates Renal and Cardiovascular Dysfunction in Rats

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Background: Coexisting cardiac/renal dysfunction may be perpetuated by increased renal venous pressure (RVP). We previously showed that acute RVP elevation depresses renal blood flow (RBF), GFR and induces renal vasoconstriction in the absence of changes in blood pressure. Since physiological consequence of long-term, isolated RVP elevation are unknown, we tested whether chronic RVP elevation would impair baseline renal perfusion, exacerbating renal dysfunction and cardiovascular instability in response to superimposed acute RVP increase. **Objectives:** (1) Develop and characterize chronic, isolated RVP model (2) Evaluate baseline cardiovascular and renal response to chronic RVP elevation and superimposed acute increases in RVP.

Methods: Male rats were subjected to partial, graded occlusion of the left renal vein to induce chronic RVP elevation (20-25mmHg) and allowed to recover for either 1 (n=5) or 3 weeks (n=6). Rats were subsequently anesthetized and blood pressure, RVP, RBF and GFR were measured at baseline and during further RVP increase for 120 min.

Results: Chronic RVP elevation induced extensive renal venous collateral formation, evident within 1 week. This adaptation reduced RVP from 20-25 mmHg to 3.6±0.2 (1 wk) and 1.3±0.5 mmHg (3wk). Baseline blood pressure was unchanged by chronic RVP elevation (1 wk: 102±25; 3wk: 91±5 mmHg); however RBF and GFR were severely reduced at 1wk (RBF: 3.6±0.5 mL/min; GFR: 0.7±0.2 ml/min) and 3 wks (RBF: 3.1±1.2 mL/min). GFR was too low at 3 weeks to be reliably measured. Upon further RVP increase, blood pressure dropped in both 1 wk (-37±10 mmHg, $p<0.05$) and 3 wk groups (-19±1 mmHg, $p<0.05$). RBF also fell (1 wk: -2.3±0.7; 3wk: -1.3±0.6 mL/min, $p<0.05$), with reductions in renal vascular conductance (1 wk: -0.020±0.006; 3 wk: -0.010±0.007 mL/min.mmHg^{-1}) and GFR (1wk: -0.56±0.14 mL/min).

Conclusions: Chronic RVP elevation elicits extensive renal venous collateral formation which alleviates venous congestion; however baseline renal function is suppressed. RVP-induced renal and cardiovascular dysfunction is exacerbated compared to our previous report of acute increase in RVP alone, thus long-term RVP elevation impairs critical mechanisms required to stabilize hemodynamics.

SA-PO994

Lysyl Oxidase Insufficiency Exacerbates the Cardiovascular Phenotype Seen in a Mouse Model of Cutis Laxa

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Background: Mutations in the elastogenic extracellular matrix protein Fibulin-4 (*FBLN4*) have been identified in humans with cutis laxa (ARCL 1B). Mice carrying the E57K mutation in *Fbln4* recapitulate the cardiovascular phenotype observed in humans, including ascending aortic aneurysms and arterial tortuosity. Mutations in lysyl oxidase (LOX), the enzyme that crosslinks elastin, have recently been identified in patients with familial thoracic aortic aneurysms and dissection. The phenotypic similarities between mutant and knock-out mouse models of *Fbln4* and *Lox*, in addition to *in vitro* data showing that FBLN4 promotes binding of pro-LOX to tropoelastin have led to the currently accepted hypothesis that FBLN4 facilitates elastin's crosslinking by LOX. Whether this occurs *in vivo* is unclear however.

Methods: To determine whether FBLN4 interacts with LOX in the process of elastic fiber formation and arterial development, we bred recently characterized $Fbln4^{E57K}$ mice to *Lox* hemizygous mice ($Lox^{+/-}$) and assessed the structural and functional effects of LOX insufficiency on the cardiovascular system of $Fbln4^{E57K}$ mice.

Results: By 3-4 months of age $Fbln4^{E57K}$;$Lox^{+/-}$ mice were similar in size to $Fbln4^{E57K}$ mice and littermates. Ascending aortic aneurysms, which were incompletely penetrant and confined to the ascending aorta in $Fbln4^{E57K}$ mice were significantly worsened by LOX insufficiency as they were fully penetrant and extended from the aortic root through the aortic arch in $Fbln4^{E57K}$;$Lox^{+/-}$ mice. Additionally, arterial tortuosity and elastic fiber fragmentation of large conduit arteries were exacerbated by LOX insufficiency. Interestingly, muscular arteries remained intact. $Fbln4^{E57K}$;$Lox^{+/-}$ mice had significant cardiac hypertrophy and widening of the pulse pressure that was due to lower diastolic blood compared to $Fbln4^{E57K}$ mice.

Conclusions: In summary, LOX insufficiency exacerbated the vascular phenotype seen in mice with mutant FBLN4 suggesting that there is a functional interaction between the two molecules. Interestingly, elastic fiber formation was unaffected in muscular arteries raising the possibility that the process of elastic fiber assembly, previously thought to be the same in all elastic tissues, may differ between vascular beds. Further studies are underway to determine whether a direct interaction between FBLN4 and LOX occurs in the process of elastic fiber formation.

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SA-PO995

Effect of Omega-3 Fatty Acid on AKT-mTOR and FoxO in Heart of 5/6 Nephrectomy Rat Model

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Background: Cardiac hypertrophy is common and results in mortality in patients with chronic kidney disease (CKD). Akt-mammalian target of rapamycin (mTOR) axis is related with cardiac hypertrophy. Forkhead box class O (FoxO) family is related with autophagy and apoptosis, but there is no report in the heart of CKD. The present study aimed to investigate whether omega-3 fatty acid (ω-3 FA) effect on Akt-mTOR axis and FoxO in heart of 5/6 subtotal nephrectomy (Nx) rat model.

Methods: Male Sprague Dawley rats were divided into three groups and treated for 6 weeks: sham control (0.9% saline), 5/6 Nx control (0.9% saline) and 5/6 Nx treated with ω-3 FA (300 mg/kg/day by gastric gavage). The expression of cardiac Akt, phosphorylated(p) Akt, mTOR, FoxO, PI3K, p-PI3k, AMPK, p-AMPK, smad2/3, NF-κB, cleaved caspase 3/7, LC3, muscle-specific ring finger protein-1 (MuRF1), and muscle atrophy F-box protein (MAFbx) were examined by western blot analysis. Hematoxylin and eosin staining of heart was performed.

Results: Serum creatinine level was significantly increased in 5/6 Nx group compared to control group and were not significantly different between 5/6 Nx group treated with ω-3 FA and 5/6 Nx group. Compared with control group, cardiac hypertrophy of 5/6 Nx group was found in gross and microscopic findings. No definite cardiac hypertrophy was found in 5/6 Nx group treated with ω-3 FA. P-Akt and mTOR were significantly up-regulated in heart of 5/6 Nx group compared to control group and were recovered by ω-3 FA. Compared with control group, 5/6 Nx group significantly up-regulated FoxO1 and FoxO3a expression of heart, which were significantly recovered by ω-3 FA. However, the expression of MuRF1 and MAFbx was not different among three groups. The expression of smad2/3, NF-κB, cleaved caspase 3/7, LC3 was up-regulated in the heart of 5/6 Nx group compared to control group and was recovered by ω-3 FA. The expression of p-AMPK was down-regulated in the heart of 5/6 Nx group compared to control group and was recovered by ω-3 FA.

Conclusions: ω-3 FA may prevent cardiac hypertrophy not only by decreasing p-Akt, mTOR and FoxO expression but also by reducing molecules of inflammation, autophagy and apoptosis.

SA-PO996

Subsequent Impaction on Renal Tissue After Myocardial Infarction in Animal Models

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Background: The interaction between kidney and heart has been an important entity for decades. Investigation of pathogenesis may optimize therapeutic strategies and modalities, which potentially leads patients with cardiac and renal impairments to better outcomes. The major goal for this research is to investigate the biological functions of the latent transforming growth factor-beta-binding proteins (LTBPs) and identify pathophysiological role in renal impairment after myocardial infarction.

Methods: We created myocardial infarction with ligation over left anterior descending artery in mice. Echocardiogarphy and picrosirius red/fast green-stained histology studies were used to demonstrate the cardiac dysfunction after myocardial infarction. Gene and protein expression have been studied one week, two weeks, and four weeks after the surgery.

Results: Echocardiography successfully demonstrated cardiac wall motion abnormalities after myocardial infarction and cardiac fibrosis had been shown in histology studies. Ltbp4, pSMAD2 and pERK had been up-regulated in cardiac tissue obviously two weeks after myocardial infarction. On the other hand, one week after myocardial infarction, interleukin 6 (IL- 6) and monocyte chemoattractant protein -1(MCP-1) in renal tissues had been up-regulated significantly ($p<0.001$). It is interesting that increasing expression of kidney injury molecule-1 (KIM-1), ltbp4 and transforming growth factor beta (TGF-β) in renal tissue had been detected until two weeks after the surgery. Moreover, renal platelet-derived growth factor receptor beta (Pdgfrb) was detected increasing steadily. In addition, increased ltbp4 expression in renal after kidney injury had been found as an essential regulatory factor in TGF-β pathways.

Conclusions: Cardiac fibrosis can enhance renal inflammation early and induce KIM-1 and Pdgfrb expression in renal tissue. Inflammation served as a prelude before the expression of fibrotic factors. Ltbp4 is an essential regulatory in TGF-β signaling and is one of the significant factors to manipulate the progress of renal injury and the crosstalk between kidney and heart, the cardiorenal syndrome.

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SA-PO997

The Role of the Adipocyte Na/K-ATPase Oxidant Amplification Loop in Uremic Cardiomyopathy

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Background: Chronic kidney disease upregulates oxidative stress, increasing morbidity and mortality of cardiovascular disease. We demonstrated that administration of pNaKtide, a peptide mimicking control of Src activation via plasmalemmal Na/K-ATPase, halts development and reverses experimental uremic cardiomyopathy. Adipocyte contribution to systemic disease is an important topic; we investigated the expression of adipocyte production of NaKtide, a component of pNaKtide lacking the cell-permeant sequence derived from TAT, to observe the affects on the development of uremic cardiomyopathy. We examined high fat diet (HFD) on the development of cardiomyopathy in the model involving partial nephrectomy (PNx).

Methods: C57Bl6 mice, 10 weeks old male, subjected to 2-part sham or PNx surgical procedure and injected with lentivirus+adiponectin+NaKtide. Then randomly divided into 4 groups: (1) Sham, (2) Sham+NaKtide, (3) PNx (4) PNx+NaKtide. Metabolic function was assessed via oxygen consumption cages, blood pressure readings, glucose tolerance tests, and echocardiography. Following four weeks of treatment, the animals were sacrificed, tissues and fluid samples were collected.

Results: Plasma creatinine levels significantly increased with PNx compared to Naktide treatment ($p \leq 0.05$). Histological analysis of cardiac tissue shows increased fibrosis with PNx and decreased with NaKtide treatment ($p \leq 0.05$). Mice developed cardiomyopathy with diastolic dysfunction and left ventricular hypertrophy 4 weeks after PNx. Concomitant administration of HFD worsened changes and caused decreased ejection fraction and fractional shortening (both $p<0.01$). Transfection with adiponectin promoting lentivirus for NaKtide expression normalized cardiac abnormalities in PNx and PNx + HFD. Normal hematocrit values, IL6 and TNFa were seen with NaKtide transfection as opposed PNx and PNx + HFD (both $p<0.01$). Transfection with empty vector or NaKtide with myoD promoter did not affect any measurements.

Conclusions: Our study demonstrates that adipocytes contribute to oxidant stress associated with uremic cardiomyopathy. These data suggest that the adipocyte Na/K-ATPase oxidant amplification loop may be a viable clinical target for the prevention or treatment of uremic cardiomyopathy.

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SA-PO998

Plasma Lipidomic Analysis Reveals Differential Mitochondrial Fatty Acid Metabolism in Diabetic and Non-Diabetic CKD-Associated Heart Failure

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Background: Cardiac myocytes utilize fatty acids predominantly for mitochondrial energy metabolism. Diabetic cardiomyopathy is characterized by increased β-oxidation due to elevated free fatty acids (FFA). Alterations in energy metabolism in diabetic and non-diabetic heart failure (HF) with chronic kidney disease (CKD) is less clear. This study investigated lipid metabolism by comparing the FFAs, acylcarnitines (ACs, a metric of β-oxidation), and complex lipids in diabetic and non-diabetic CKD patients with and without HF.

Methods: From the Clinical Phenotyping Resource and Biobank Core (CPROBE) 214 patients at various stages of CKD were selected for plasma lipidomic analysis. Of the 89 patients with diabetes, 10 had HF; in 125 subjects without diabetes 21 had HF. Plasma lipids and ACs were measured using mass spectrometry based untargeted and targeted lipidomic platforms, respectively.

Results: The mean age was 60 years (standard deviation=16). One hundred ten patients were males (51.4%), 64 were African-Americans (29.9%), and 150 were Caucasians (70.1%). In patients without diabetes median (interquartile range) of ACs in patients with HF were significantly higher than the patients without HF (Table, $P<0.05$ for all). In patients with diabetes the ACs were not different in patients with and without HF. Mixed linear model showed decreased abundance of saturated FFAs with lower carbon numbers in non-diabetic patients with HF, but an increased abundance of these metabolites in diabetic patients with HF as compared to no HF ($p=0.002$). In non-diabetic patients with HF, linear regression showed an inverse association between abundance of saturated FFAs with intermediate-chain ACs ($p=0.025$) and a direct association with long-chain ACs ($p=0.044$), a relationship which disappeared in diabetic patients with HF.

Conclusions: In non-diabetic HF, increased ACs at the cost of depletion of saturated FFAs is noted, while in diabetic HF saturated FFA increases without change in AC. Differential energy metabolism in HF with and without diabetes in CKD highlights the need for differential targeted therapies by etiology to optimize heart function and outcome in CKD.

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Table 1: Increased level of acylcarnitines (mmol/L) in heart failure compared to no heart failure in patients without diabetes

ACs:		C6:0	C8:0	C10:0	C12:1	C12:0	C14:1	C14:0	C16:1	C18:2	C18:1	C20:1
No HF	Median	0.5	0.9	1.3	0.3	0.2	0.5	0.3	0.4	1.7	2.7	0.1
	IQR	0.7 - 1	1.4-1.9	1.9-2.8	0.4-0.7	0.4-0.7	0.7-1.5	0.4-0.7	0.6-1	2.6-3.5	4-5.8	0.1-0.2
HF	Median	0.8	1.4	2.2	0.6	0.6	1.1	0.5	0.7	2.6	4.3	0.1
	IQR	1.4-1.8	2.8-4.1	3.5-5.6	0.9-1.3	0.8-0.9	1.8-2.7	0.8-1.1	1.2-1.5	3.7-6.4	6.5-10.5	0.2-0.3

Table 1

SA-PO999

Hyperreactivity of Aldosterone to Renin Contributes to Pathogenesis of Malignant Hypertension and Renovascular Hypertension

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Background: Malignant hypertension (MH) and renovascular hypertension (RVH) are known as diseases exhibiting high renin hypertension. By comparing the two groups, we examine how renin-angiotensin aldosterone system (RAAS) participates not only in the onset of hypertension but also in the onset of nephropathy.

Methods: A total of 33 patients who were diagnosed as MH(n=19) and RVH (n=14) at Toranomon Hospital from 1986 to 2017 were evaluated retrospectively.

Results: There was no significant difference in plasma renin concentration (PRC) between MH group and RVH group. While, age was younger in MH group than in RVH group with median [interquartile range]; 40 years [32-48 years] vs. 65 years [62-76 years], $P=0.0001$). Blood pressure (median; 230/130 vs 164/98 mmHg), UN (median;53.0 vs 28.8 mg/dl), Cre (median; 6.0 vs 2.0 mg/dl), plasma aldosterone concentration (PAC) (mrdian;49.7 vs 32.0 ng/dl)and aldosterone -renin-ratio (ARR)(1.10 VS 0.64)were significantly higher in MH group than in RVH group. Serum K (median; 3.7 vs 4.3 mEq/L) was significantly lower in MH group than in RVH group. The majority of MH group showed intimal edematous thickening (onion skin lesion) of small arteries including arteriole by renal biopsy. While four patients out of patients with RVH showed focal glomerular sclerosis on non-narrowed kidney by renal biopsy, but did not show onion skin lesion of small arteries.

Conclusions: Hyperreninemia was similar on both groups, but aldosterone value and APR were significantly higher in MH group. This indicates that hyperreactivity of aldosterone to renin might contribute not only to the formation of MH with onion-skin lesion via higher blood pressure, and result in also to hypokalemia, though renal function was higher on MH group. Whenever hyperreactivity of aldosterone to renin exists on MH group remains unknown. These results suggest that the mechanism by which renin stimulation leads to overproduction of aldosterone may be thought to be involved in MH and the progression of nephropathy.

SA-PO1000

Critical Role of Histone Deacetylase 3 in the Pathogenesis of Hypertensive Kidney Disease

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Background: Hypertension is a major cause of chronic kidney disease, which is characterized byinflammation and fibrosis. However, the underlying molecular mechanisms are not fully understood. In this study, we examined the function role of histone deacetylase 3 (HDAC3) in renal inflammation and fibrosis in a mouse model of angiotensin II-induced hypertension.

Methods: Myeloid HDAC3 knockout mice were generated by crossing $HDAC3^{f/f}$mice with Lyz-Cre mice. Both Lyz-$Cre^{-/-}HDAC3^{f/f}$mice and Lyz-$Cre^{+/+}HDAC3^{f/f}$mice were infused with angiotensin II at 1.5ug/kg/min or vehicle for 28 days. Blood pressure was monitored by tail-cuff method. Renal function was assessed by measuring blood urea nitrogen (BUN). Kidney sections were prepared and stained for histological and immunological analysis. Western blot analysis was performed to detect the levels of fibronectin and a-SMA. Quantitative RT-PCR was performed to examine mRNA levels of proinflammatory cytokines. Cultured macrophages were used to study the role of HDAC3 in proinflammatory molecule expression in vitro.

Results: There is no significant difference in blood pressure at baseline. Blood pressure increased after angiotensin II treatment in both Lyz-$Cre^{-/-}HDAC3^{f/f}$ and Lyz-$Cre^{+/+}HDAC3^{f/f}$ mice that are similar between the two treatment groups. Compared with Lyz-$Cre^{-/-}HDAC3^{f/f}$ mice, mice with myeloid HDAC3 deficiency were protected from angiotensin II-induced renal injury with lower BUN. Furthermore, mice with HDAC3 deficiency in myeloid cells accumulated significantly fewer macrophages, T cells, and myeloid fibroblasts. HDAC3 deficiency in myeloid cells significantly reduced the mRNA expression of pro-inflammatory molecules the kidney after angiotensin II treatment. HDAC3 deficiency in myeloid cells significantly attenuated the protein levels of fibronectin and a-SMA and markedly inhibited collagen deposition in the kidney following angiotensin II treatment. In cultured macrophages, knockdown of HDAC3 with shRNA suppressed pro-inflammatory molecule expression. Furthermore, knockdown of HDAC3 inhibited NF-kB p65 binding to IL-6 promoter.

Conclusions: Our study identifies a critical role of HDAC3 in the regulation of hypertension-induced renal inflammation and fibrosis. Therefore, targeting HDAC3 may represent a novel therapeutic strategy for hypertensive kidney disease.

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SA-PO1001

Prevalence of Angiotensin II Type 1 Receptor Antibodies (AT1RAbs) in Persons with Hypertension and Relation to Blood Pressure and Kidney Outcomes

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Background: AT1RAbs are associated with vascular hypertension and allograft dysfunction after kidney transplantation. We aimed to determine the prevalence of AT1RAb in a non-transplanted hypertensive population and the relationship to blood pressure (BP) control and kidney outcomes.

Methods: We used data on 1006 Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study participants with hypertension, and treated with angiotensin receptor blockers (ARB), angiotensin converting enzyme inhibitors (ACEi) or other anti-hypertensive medications. AT1RAb detection was performed by ELISA (One Lambda) and levels ≥ 17 units/ml were considered positive. BP, uncontrolled BP (systolic BP ≥140 or diastolic ≥90 mmHg), albuminuria [urine albumin-to-creatinine ratio (ACR) ≥30mg/g] and rapid kidney function decline (loss of eGFR >3ml/min per 1.73m^2 per year over a median of 5 years) were compared for AT1RAb positive (+) versus negative (-) participants using descriptive statistics and multivariable regression models.

Results: Overall, 132 (13%) participants were AT1RAb+. Compared to AT1RAb-, AT1RAb+ persons were more likely to be Caucasian (47% versus 37%) and non-smokers (44% versus 30%). In models adjusting for age, sex and race, AT1RAb+ persons had 2.6 mmHg higher diastolic BP than AT1RAb- persons (p=0.01). The adjusted odds ratio (aOR) for uncontrolled BP was 1.33 (95% CI 0.9, 2.0) comparing AT1RAb+ to AT1RAb- persons. In adjusted models, AT1RAb+ persons treated with either ARB or ACEi had 12.3 mmHg higher systolic and 5.4 mmHg higher diastolic BP compared to AT1RAb+ persons using other BP medications (p=0.003 and 0.03); aOR for uncontrolled BP was 1.48 (95% CI 0.68-3.21). BP did not differ for AT1RAb- participants regardless of medication. The prevalence of albuminuria was similar between AT1RAb+ (19.1%) and AT1RAb- (19.5%) groups. Rapid kidney function decline occured in 18.1% of AT1RAb+ and 15.5% of AT1RAb- persons (p=0.5). There was no statistically significant association between AT1RAb status and rapid kidney function decline (aOR 1.23; 95% CI 0.74-2.05).

Conclusions: AT1RAbs were associated with higher diastolic BP in this hypertensive population, and use of ARB or ACEi was associated with higher BP among AT1RAb+ persons compared to use of other medications.

Funding: Private Foundation Support

SA-PO1002

Proximal Tubule Angiotensin II Type 1 Receptor-Associated Protein Does Not Influence Angiotensin-Dependent Hypertension

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Background: The activation of renal angiotensin II (Ang II) type 1 receptor (AT1R) can evoke excessive sodium retention, resulting in hypertension when inappropriately stimulated. The AT1R-associated protein (ATRAP) has been identified as the specific binding protein of the C-terminal domain of AT1R, and functions as an endogenous inhibitor that suppresses AT1R hyper-activation at local tissue sites. We previously reported that systemic ATRAP-knockout mice (ATRAP-KO) exhibited an exacerbation of Ang II-induced hypertension, concomitant with an increase in sodium retention, compared wild-type mice (WT). We here report a functional role of proximal tubule ATRAP in angiotensin-dependent hypertension using proximal tubule-specific ATRAP-knockout (PT-KO) mice.

Methods: In the present study, we generated PT-KO mice for the first time by the Cre/loxP system using *Pepck*-Cre. We next compared blood pressure in response to Ang II (1000ng/kg/min) treatment in wild-type littermate control (LC) and PT-KO mice. Since cardiac hypertrophy is closely associated with the blood pressure elevation, we further examined heart weight/body weight ratio in PT-KO and LC mice.

Results: The ATRAP mRNA expression in the proximal tubules of the PT-KO mice was decreased by approximately 80% compared with LC mice, estimated by laser capture microdissection method. Ang II infusion for 2 weeks significantly and similarly increased systolic blood pressure in both PT-KO and LC mice. Ang II infusion for 2 weeks significantly increased heart weight/body weight ratio in both PT-KO and LC mice to the same extent.

Conclusions: These results indicate that ATRAP deficiency in proximal nephron does not influence angiotensin-dependent hypertension *in vivo*.

SA-PO1003

Global Coagulation Assay Changes in Hemodialysis Patients

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Background: Chronic kidney disease (CKD), and hemodialysis in particular, is thought to be a hypercoagulable state, which may contribute to increased cardiovascular risks. Given the limitations of current available coagulation testing in assessing thrombotic risks, we aim to evaluate the changes of global coagulation assays in patients with CKD undergoing haemodialysis.

Methods: This prospective observational study recruited patients undergoing hemodialysis. Fasting blood samples were collected prior to starting hemodialysis for baseline investigations such as full blood evaluation, coagulation studies and lipid studies, in addition to experimental testing via thromboelastography (TEG® 5000S) utilising citrated whole blood. Additional samples were double-centrifuged to obtain platelet-poor plasma for later assessment with calibrated automated thrombogram (CAT) and overall haemostasis potential (OHP).

Results: Twenty-six patients were recruited and the results were compared to age-matched normal controls previously collected. Hemodialysis patients had lower platelet count with increased fibrinogen, VWF antigen and factor VIII levels (p<0.01). They also had more hypercoagulable TEG® profile when compared to normal controls, with increased maximal amplitude (69.6 vs 60.0 mm, p<0.001) and reduced clot lysis (0.0% vs 0.4%, p=0.001). Interestingly, there was no significant difference in the thrombin generation parameters. In addition, D-dimer was markedly increased in hemodialysis patients independent of age (860 vs 189 ng/mL, p<0.001) but this did not correlate with fibrin generation parameters.

Conclusions: Hemodialysis patients appear to have a more hypercoagulable state characterised by increased fibrinogen, VWF antigen and factor VIII levels, as well as TEG parameters. D-dimer was markedly increased, which brings into question the clinical usefulness of D-dimer in predicting venous thromboembolism in haemodialysis patients. The lack of correlation with fibrinolytic potential may signify reduced renal clearance of D-dimer.

	Control (n=41)	Haemodialysis (n=26)	p-value
Haemoglobin (g/dL)	143.2 ± 11.7	110.0 ± 9.2	**p<0.001**
Platelet (x10^9/L)	238 (± 49)	192 (± 56)	**p=0.014**
Fibrinogen (g/L)	3.2 (± 0.6)	4.1 (± 0.9)	**p<0.001**
vWF Antigen (%)	118 (86 – 168)	155 (120 – 187)	**p=0.006**
Factor VIII (%)	121 (± 35)	161 (± 45)	**p=0.002**
TEG parameters			
R time (min)	6.3 (5.4 – 7.5)	8.2 (8.0 – 8.9)	**p<0.001**
Alpha-angle (°)	62.7 (± 7.2)	54.5 (± 7.6)	**p<0.001**
Maximum amplitude (mm)	60.0 (± 5.7)	69.6 (± 6.9)	**p<0.001**
Lysis 30 (%)	0.4 (0.1-1.1)	0.0 (0.0-0.4)	**p=0.001**
CAT parameters			
Endogenous thrombin potential	1363 (± 216)	1282 (± 239)	p=0.170
Peak thrombin	227 (± 61)	206 (± 41)	p=0.269
OCP parameters			
Overall coagulation potential	67.2 (± 8)	65.6 (± 17)	p=0.611
Overall haemostatic potential	32.9 (28 – 38)	34.7 (25 – 43)	p=0.439
Overall fibrinolytic potential	51.1 (48 – 55)	46.5 (45 – 57)	p=0.081
D-dimer	189 (149 – 310)	860 (565 – 1300)	**p<0.001**

SA-PO1004

Characterization of the Effects of a Vacuolar H+-ATPase (V-ATPase) Mutation Linked to Distal Renal Tubular Acidosis (dRTA)

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Background: Distal renal tubular acidosis (dRTA) Type I is a disease affecting the kidney's ability to secrete non-volatile acid. This disease can lead to severe kidney and systemic sequelae. Improper functioning of collecting duct (CD) intercalated cells (ICs) due to autoimmune or infectious conditions can lead to dRTA. More recently, single point mutations in transport proteins in ICs have been found to result Type I dRTA. One such mutation is the 1231G>T in ATP6V0A4, the a4 isoform of the V_0domain of the V-ATPase. This mutation results in a D411Y (Aspartate to Tyrosine) variant. Carriers of this mutation are seemingly healthy and therefore this mutation likely acts in an autosomal recessive fashion. We identified a 26 year-old man with refractory dRTA that was homozygous for this mutation by a NextGen dRTA sequencing panel. One of his half-siblings has presented with metabolic acidosis and hypokalemia, consistent with dRTA. Published reports from Brazil and Mexico identify this mutation as causative for dRTA. However, the exact effects of this mutation on the expression and activity of the V-ATPase has yet to be determined. We hypothesized that this mutation in a reportedly non-transmembrane region of the a4 subunit would have effects on the subcellular localization of the subunit as the underlying mechanism for decreased V-ATPase membrane function.

Methods: We performed transfections of FLAG-Tagged wild-type (WT) vs. D411Y pTracer plasmids into HEK and Clone C cells (of IC origin), followed by immunoblot and immunofluorescent labeling and confocal imaging.

Results: Our results demonstrate low expression of both WT- and D411Y ATP6V0A4 in Clone-C cells, although an anti-FLAG antibody detected a band at ~100 kDa by immunoblot in transfected Clone-C lysates. By immunolabeling and confocal microscopy we detected the WT subunit at the apical domain of transfected Clone-C polarized

monolayers on transwell filters. In contrast, the D411Y mutant subunits were detected in a cytosolic distribution.

Conclusions: Our preliminary findings indicate that the D411Y mutation interferes with normal accumulation of the V-ATPase at the apical membrane of ICs, thus offering a potential mechanism for defective V-ATPase function and dRTA patients with this mutation.

Funding: Private Foundation Support

SA-PO1005

A Novel I551F Mutant of Na+/HCO3- Cotransporter NBCe1 Has Cytosolic Retention and Diminishes Transport Activity

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Background: Homozygous mutations in SLC4A4 encoding the electrogenic Na^+/HCO_3^- cotransporter cause proximal renal tubular acidosis associated with ocular abnormalities. Although up to 14 SLC4A4 mutations have been identified, the mechanism of NBCe1 inactivation due to the individual mutations has not been completely clarified.

Methods: In the present study we investigated the impact of SNP (Single Nucleotide Polymorphism) mutations on NBCe1 function. We identified 14 mutations in NBCe1A, resulting in the single amino acid substitutions, A425T, F461L, A465S, L494F, N503H, A518T, A518G, I523V, V533D, Y535H, I551F, Y554H, M753V, and L785I.

Results: Immunohistological analysis with confocal microscopy revealed that almost all of SNP mutants except I551F were predominantly expressed in the plasma membrane of HEK293 cells and MDCK cells. On the other hand, I551F mutant was expressed only in the cytoplasm of HEK 293 cells and MDCK cells. Functional analysis using *Xenopus* oocytes revealed that I551F mutant had a significantly reduced activity corresponding to 52% of that of wild-type ($p<0.01$). Western blotting in HEK293 cells confirmed that the surface expression of I551F mutant was significantly reduced and showed immaure band. To examine the role of I551 in more details, we also examined the properties of artificial mutants I551A, I551P, I551K, I551R, I551D and I551E in HEK293 cells. Artificial mutants were properly expressed in the plasma membrane. By contrast, only I551F mutant was predominantly expressed in cytoplasmic regions.

Conclusions: These results indicate that I551F mutation inactivates the NBCe1 function with cytoplasmic retention. Because NBCe1 plays a major role in renal proximal sodium and bicarbonate reabsorption, I551F SNP may be associated with the disturbance in systemic acid-base balance or the changes in blood pressure.

SA-PO1006

NFAT5 Regulates Endothelin Gene Expression: Possible Common Pathway in Skin and Kidney Responses to High Na+ Intake

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Background: High Na^+ intake stimulates collecting duct endothelin-1 (ET-1) production which in turn promotes a natriuresis. High Na^+ intake induced ET-1 involves several factors, however increasing extracellular osmolality, as occurs in the renal medulla during Na^+loading, stimulates ET-1 by inner medullary collecting duct (IMCD3 cells) more potently than any other known stimulus. In addition, following a Na^+ load, the skin stores Na^+ leading to increased local osmolality; release of skin Na^+ into the circulation (facilitating renal elimination) partly depends upon ET-1. The current studies were undertaken to determine how osmolality augments ET-1 in IMCD and skin.

Methods: Cultured IMCD3 and dermal microvascular endothelial cells (DMVEC) were studied. Osmolality was increased for 2-4 hr using 50 mOsm/L mannitol. ET-1/GAPDH mRNA were measured. ET-1 promoter/reporter constructs were transfected into cells and secreted luciferase/alkaline phosphatase assayed. NFAT content and subcellular distribution were analyzed by western analysis.

Results: Increasing osmolality increased IMCD3 ET-1 mRNA associated with an increase in nuclear fraction NFAT5 protein content. Osmolality-stimulated ET-1 was markedly reduced by NFAT5 siRNA. Transfection of 1, 2 or 3 kb (5' to transcription start site) ET-1 promoter/reporter constructs revealed maximal osmolality induced activity in the 1 kb fragment. This region contains two NFAT5 consensus binding sites; mutation of both sites (TGGAAA to TCACGA) completely prevented hyperosmolality induced promoter activity. Increasing osmolality also increased DMVEC ET-1 mRNA content; initial studies suggest this is also NFAT5 dependent.

Conclusions: These studies identify for the first time that NFAT5 directly regulates ET-1 promoter activity. Both the skin and IMCD NFAT5/ET-1 may be involved in the Na^+ homeostatic response to high Na^+ intake. Thus, there may be a remarkably common system used by the skin and the kidney to regulate body Na^+content.

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SA-PO1007

Large-Scale Meta-Analysis in European Ancestry Identifies 114 Independent Signals for Serum Urate

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Background: High serum urate levels are a cause of gout, an excruciating disease with suboptimal treatment affecting ~4% of the adult population in many developed countries. Patients with kidney disease have higher risk for gout. Genome-wide association studies (GWAS) of serum urate in European ancestries have identified 28 loci. Together the index SNPs at these loci explain <10% of the phenotypic variance, suggesting that additional loci remain to be identified.

Methods: We performed meta-analyses of serum urate GWAS among 288,649 individuals of European ancestry from 60 studies and of gout among 753,884 individuals of European ancestry from 17 studies using fixed-effect inverse variance weighting. To reveal independent signals of serum urate, we used GCTA model selection to identify independent variants ($r2<0.01$) in genome-wide significant urate loci ($p<5x10^{-8}$). To prioritize significant urate-associated variants, we conducted finemapping by calculating posterior probabilities in each independent region based on the Wakefield Bayes factor and constructed credible sets with 99% probability of containing driver variants.

Results: Meta-analyses identified 123 genome-wide significant 1-Mb intervals associated with serum urate (genomic control factor: 1.04). Of these, 87 were not annotated to known serum urate loci, and 98% were associated with gout in the same direction. GCTA model selection identified 114 independent signals of urate in 99 genomic regions, which were merged from the 123 intervals when index SNPs in adjacent intervals were correlated ($r2 > 0.2$). Of these 114 independent signals, half of the 99% credible sets had <17 variants, and 25% had only one variant.

Conclusions: We identified 114 independent signals associated with serum urate among European ancestry individuals. The concordance in effect direction of urate index variants for gout are consistent with established causal role of urate in gout pathophysiology. Following up on these GWAS findings with functional studies will generate novel insight in serum urate regulation and potential treatment targets for lowering urate levels for the prevention of gout.

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SA-PO1008

Calcium-Dependent Contraction of Renal Tubules

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Background: Over several years, we have observed, that perfused renal tubules show "odd movements" when exposed to extracellular ATP. Whether this observation was merely an artefact or a relevant biological observation remained elusive. It is well known that renal tubules express a contractile machinery localized closely to the apical membrane. The functionality of this structure is enigmatic. Plate grown kidney cells show a pattern on their apical membrane consistent with active contraction of the luminal membrane domain. Here we test if isolated perfused renal tubules can contract.

Methods: We measured the effect on tubular diameter in isolated murine thick ascending limbs (TAL), when inducing a cytosolic $[Ca^{2+}]$ ($[Ca^{2+}]_i$) increase with uncaging ATP/stimulation of the apical P2Y2 receptors.

Results: Uncaging luminal ATP elicited a marked increase of $[Ca^{2+}]_i$, which could be fully blocked by intracellular Ca^{2+} chelation following BAPTA-AM loading. Remarkably, within 40 seconds following apical P2Y2 receptor stimulation, both the inner and outer diameter of the perfused TAL were significantly reduced. The inner and outer diameter decreased by 0.236μm (SEM ±0.041, n=5) and 0.170 μm (SEM ±0.022, n=5), respectively. This reduction could be largely prevented either blocking the $[Ca^{2+}]_i$ increase with BAPTA or by hindering actin-myosin interaction with highly specific antagonists.

Conclusions: We report the remarkable observation that renal tubules in a $[Ca^{2+}]_i$ -dependent manner can contract. This suggests that the diameter of renal tubules is a subject to active and acute regulation.

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SA-PO1009

MR Modulator AZD9977 Causes Reduced Plasma Potassium Elevation Compared to Eplerenone After Potassium Challenge in CKD Model

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Background: Hyperkalemia is a potential side effect of mineralocorticoid receptor (MR) antagonists since they cause renal Na^+ excretion and K^+ retention. MR antagonist dependent renal Na^+ excretion can be studied acutely in rodents and translates well to man. However, rodents are largely refractory to plasma K^+ elevations and hence the potential reduced liability of novel MR modulators to cause hyperkalemia is difficult to explore in rodent models.

Methods: Acute effects on 7 hours urine electrolyte excretion were studied after single dose administration of 30, 100 or 200 mg/kg eplerenone or AZD9977 to mice fed a low

salt (0.02%) diet for 3 days prior to dosing. Effects on plasma K^+ elevations were studied in 5/6 nephrectomised mice with developed chronic kidney disease (CKD) treated for 5 days with 100 mg/kg bid eplerenone or AZD9977 followed by a KCl load over night before measuring plasma K^+.

Results: 100 and 200 mg/kg eplerenone treatment caused an increased urinary Na^+/K^+ ratio (0.57±0.11, p=0.0022 and 0.68±0.08, p<0.0001, respectively) compared to vehicle (0.06±0.09). AZD9977 exposure did not alter urinary Na^+/K^+ ratio. Subchronic treatment with eplerenone or AZD9977 in CKD at exposures 14x above in vitro IC_{50} did not alter plasma K^+ levels. Eplerenone vs vehicle treatment followed by K^+ challenge led to a robust elevation of plasma K^+ (6.5±0.2 vs 5.4±0.2 mM, p<0.001). The plasma K^+ elevation after AZD9977 treatment and K+ challenge (5.9±0.2 mM, p=0.042 vs vehicle) was significantly lower compared to eplerenone (p=0.0045).

Conclusions: AZD9977 is a novel MR modulator developed to yield maximal efficacy on organ protection and minimal effects on plasma K^+. AZD9977 did not cause the typical acute urinary Na^+ excretion in mice observed with MR antagonists. Lack of effect on urinary electrolytes translated to a reduced plasma K^+ elevation in a mouse CKD model after potassium challenge. Whether the reduced effect on plasma K^+ observed with AZD9977 vs eplerenone will translate into a clinically meaningful differentiation will be explored in clinical studies.

Funding: Commercial Support - AstraZeneca

SA-PO1010

Dietary K-Induced Temporal Changes in mRNA Encoding Proteins Associated with Renal K Secretion in Mouse

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Background: Flow-induced K secretion in the cortical collecting duct (CCD) of the distal nephron is mediated by Ca^{2+}/stretch-activated BK channels, which also contribute to the renal adaptation to a high K diet (HKD). We reported that CCDs from rabbits fed a HKD for 10 d exhibit an increase in steady-state abundance of BK channel subunit-specific mRNAs and expression of immunodetectable BKα and L-WNK1 expression in the apical membrane of β-type intercalated cells (ICs). Overexpression of L-WNK1 increases BKα whole cell abundance and functional channel expression in HEK cells suggesting that an increase in L-WNK1 in ICs may mediate enhanced BK channel expression and K secretion in K-adapted CCDs. We sought to examine the temporal changes in mRNA abundance of BK channel subunits and L-WNK1 as well as other major CCD transport and regulatory proteins in mouse kidney following initiation of HKD or low K diet (LKD).

Methods: C57BL/6 mice on a control K diet were switched to either a HKD or LKD for up to 11 days. On the day of sacrifice, spot blood and urine samples were collected for measurement of [Na] and [K] by flame photometry. qPCR primers and probes specific for BKα, β1, β4, and γ subunits and for regulatory kinases L-WNK1, KS-WNK1, and WNK4 were used to assess message abundance in renal cortical homogenates.

Results: Steady state expression of BKα mRNA increased >3-fold by day 7 of HKD (n=4, p<0.05) but did not significantly change during LKD. No significant changes were observed for message encoding BK β1, β4, γ subunits or L-WNK1, KS-WNK1, and WNK4 during either diet. Plasma [Na] and [K] remained unchanged under HKD and LKD, while urine [K] increased during HKD and decreased during LDK.

Conclusions: HKD increased steady state abundance of message encoding BKα. The failure to detect an increase in message encoding WNK1, a regulatory protein known to increase BK channel expression during HKD, may reflect post-translational modification.

Funding: NIDDK Support

SA-PO1011

Sexual Dimorphic Responses of Renal Transporters to High Salt Diet Favor More Diuresis in Females

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Background: Previous studies have shown that there are distinct sexual dimorphic patterns of transporters along the nephron. Compared to males (M), female (F) rats and mice at baseline have less proximal tubule sodium transporters (NHE3, NaPi2) and more activated distal NCC and collecting duct epithelial sodium channels (ENaC). Also, F are reported to have a have more robust pressure natriuretic response than M. This study aimed to test the hypothesis that, in F vs. M C57Bl/6 mice, high salt diet regulates renal Na^+ transporters, claudins (Cld) and the regulatory kinase (SPAK) in a pattern that facilitates more natriuresis in females.

Methods: For 2 wk, mice (n=7/group) received a normal salt diet (0.26% NaCl, NSD) or a high salt diet (4.0% NaCl, HSD). Urine Na^+ and K^+ were measured by flame photometry and osmolality with an osmometer. Renal transporter and channel abundance was determined by quantitative immunoblot, and subcellular distribution by confocal immunohistochemistry.

Results: At baseline, F exhibit lower urinary volume (UV), Na^+ (UNaV), K^+ (UKV), and osmoles (UosmV); F also had lower abundance of the PT NHE3, NHE3p and Cld2 and higher DCT NCC and SPAK compared to M. In response to HSD, F vs. M exhibit greater fold increases in UV (5- vs. 1.6-fold), UNaV (25- vs. 8-fold), UKV (2.3-fold vs. no increase) and UosmV (6 vs. 2-fold) and no change in plasma [Na^+] or [K^+]. During HSD NHE3p, a marker for less activity, increased in M but not F. During HSD, abundance of NKCCp, NCCp, and cleaved ENaC alpha decreased in both sexes, evidence of less activity of these transporters from loop through collecting duct. SPAK and Cld7 were unchanged. At baseline, NHE3 and NHE3p were located in the villi in M and at the base of the villi in F; with HSD NHE3, NHE3p redistributed to the villar base in M and were unchanged in F. NCCp remained localized to the apical membranes in both sexes.

Conclusions: The renal responses to a high salt diet are sex dependent: redistribution of NHE3 and NHE3p in males, and reduced NKCC2p, NCC, NCCp and α ENaC cleavage in both sexes contribute to natriuresis. Females exhibit more robust natriuresis and diuresis during HSD which we hypothesize is due, at least in part, to the lower baseline PT NHE3 and Cld2.

Funding: NIDDK Support

SA-PO1012

Notch Signaling and Adam10 in Lithium-Induced Collecting Duct Remodeling in Mouse Kidney

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Background: The cell biology of lithium (Li) induced collecting duct (CD) remodeling, whereby the percent of AQP2-positive principal cells (PC) is decreased with a proportionate increase in [H^+]-ATPase-positive intercalated cells (IC), is not well defined. It has been reported that genetic suppression of Notch signaling or Adam10 interferes with the development of CD resulting in off-spring with very low percentage of PC in the kidney. Hence, here we evaluated whether these two play a similar role in Li-induced CD remodeling in adult mice.

Methods: Groups of mice (B6D2; N = 5/group) were fed either a regular or LiCl-containing chow for 30 days and humanely euthanized. Using confocal immunofluorescence microscopy and double labeling, kidney sections were examined for the percent of AQP2 or [H^+]-ATPase positive cells. cDNA prepared from the medulla was subjected to Notch signaling PCR Array, and expression of selected genes was further confirmed by real-time PCR on all samples.

Results: Li treatment caused significant polyuria associated with a significant decrease in percentage of PC in the medulla (88.2 ± 3.4 vs. 69.2 ± 0.8, $P < 0.05$), and a proportionate increase in the percentage of IC (11.3 ± 3.4 vs. 30.0 ± 0.8, $P < 0.05$). Several genes were under or over expressed in Li-treated mice (Table).

Conclusions: Similar to its role during embryonic life, Notch signaling plays a role in Li-induced CD remodeling. However, our results do not support a role for Adam10 in Li-induced CD remodeling in adult mice. The roles of Nr4a2, Neurla1A and Figf in CD remodeling need to be further defined.

Funding: NIDDK Support, Veterans Affairs Support

Expression of Genes in Li-treated Mice

Gene	Name	Change*
Notch1	Notch gene homolog 1	19
Notch 2	Notch gene homolog 2	28
Notch 3	Notch gene homolog 3	16
Notch4	Notch gene homolog 4	15
Jag2	Jagged 2	23
Dll1	Delta-like 1	34
Runx1	Runt related transcription factor 1	27
cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)	29
Nr4a2	Nuclear receptor subfamily 4, group A, member 2	619
Neurla1A	Neuralized homolog 1A	839
Figf	C-fos induced growth factor	1119
Adam10	A disintegrin and metallopeptidase domain 10	500

*Percent of the mean values in the control diet-fed group

SA-PO1013

Metformin Has Natriuretic Effects Through Reduction of the Sodium-Chloride Cotransporter Phosphorylation

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Background: Metformin is an antidiabetic drug that is widely used to treat patients with type 2 diabetes mellitus. Recent studies have reported that treatment with metformin not only improved blood glucose levels but also reduced blood pressure. However, it remains unclear how metformin reduces blood pressure. We hypothesized that metformin affects sodium reabsorption in the kidneys.

Methods: We firstly examined urinary sodium excretion and expression of renal sodium transporters in 8-week-old male C57BL/6 mice with acute and chronic treatment of metformin. In addition, we examined metformin effects using *ex vivo* preparations of mice kidney slices. We also performed experiments using the spontaneously hypertensive rat (SHR).

Results: In this study, we demonstrated that metformin increased urinary sodium excretion by reducing phosphorylation of the thiazide-sensitive Na-Cl cotransporter (NCC) in acute and chronic metformin administration. We also confirmed reduction of phosphorylated NCC in an *ex vivo* study. Expression levels of other renal sodium transporters, such as NKCC2, ENaC, and NHE3 did not show significant changes. WNK-OSR1/SPAK kinase signal was not involved in this effect of metformin on NCC. We finally performed experiments using SHR, whose blood pressure is well known to be decreased by metformin. We observed decreased phosphorylated NCC in SHR by metformin treatment,

suggesting that this decreased NCC phosphorylation is involved in the mechanisms of metformin-induced blood pressure reduction.

Conclusions: Metformin increased urinary sodium excretion by reducing phosphorylation of NCC. Considering that metformin could have natriuresis effect, metformin could be an ideal drug for excessive salt intake, in addition to excessive calorie intake.

Funding: Government Support - Non-U.S.

SA-PO1014

Urinary Exosomes Quantitation of Renal Transporter Abundance Correlates with Function

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Background: Urinary exosomes have the potential to provide considerable insight into renal tubular function. However, estimates of urinary exosomes been qualitative or semi-qualitative using Western blotting. Therefore, we sought develop approaches to measure several relevant sodium and calcium transporters simultaneously in the urine from humans and then correlate them to function in humans.

Methods: 4 healthy males were studied in a CRC setting. Fasting and fed urine and blood samples were collected hourly. Serum ultrafiltrate and urine calcium, magnesium, sodium, potassium, creatinine, and urine volume were measured. Lithium was measured in deproteinated serum and urine by atomic emission spectroscopy. Urinary exosomes were isolated via ultracentrifugation. NHE3, SLC26A6, NKCC2, NCC, TRPV5 and prostasin abundance were measured via ELISA at each collection point in triplicate and these values were compared with metabolic parameters of tubule function at each time point.

Results: The presence of enriched amounts of ALIX, CD63, and TSG-101 protein in the exosomal fraction compared to the various wash fractions was verified via Western blotting. NHE3, SLC26A6, NKCC2, NCC, TRPV5 and prostasin abundance were measured. NHE3 and fractional excretion of lithium are significantly correlated, indicating that proximal tubule function is related to the exosomal abundance of NHE3 (-0.66, p=0.001). Fully corrected for multiple comparisons, significant inverse correlations between the fractional excretion of distally delievered Ca and TRPV5 (-0.76, p=0.001) and FEDNa and prostasin (-0.78, p=0.001) were demonstated.

Conclusions: Our findings represent reliable and precise methods for quantitation of urinary exosomal abundance of the transport proteins NHE3, SLC26A6, NKCC2, NCC, TRPV5, and prostasin. The quantitation of urinary exosome renal transporter protein abundance allows for greater insight into human renal transport, allowing for direct measurements of markers of molecular solute transport. In this way, this system has the potential to further our understanding of molecular electrolyte physiology and disease in humans by confirming previous theories and finding new connections.

Funding: NIDDK Support

SA-PO1015

Urinary Exosomes as a Novel Tool to Study the NaCl Cotransporter in Hypertension

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Background: The NaCl cotransporter (NCC) is located at the apical membrane of epithelial cells lining the distal convoluted tubule of the kidney, and plays an instrumental role in blood pressure regulation by fine-tuning renal sodium excretion. Renal salt transporters such as NCC are excreted in urinary exosomes (uEs) after internalization into multivesicular bodies. The aims of this study were to investigate the effect of thiazides on the abundance of NCC in uEs of patients with hypertension, and to assess whether NCC abundance in exosomes can predict the blood pressure response to thiazides.

Methods: The NCC abundance was compared in uEs both before and after treatment in patients with hypertension (n=41) who did or did not respond to thiazides. Responders to treatment were defined as patients with a significant anti-hypertensive response to thiazides (≥5 mmHg, n=24), while non-responders had a minimal or no response (<5 mmHg in blood pressure, n=17). To analyze whether normalization by urinary creatinine resulted in a similar number of uEs loaded on a gel, the abundance of the exosomal-marker CD9 was measured.

Results: Despite the inhibitory action of thiazide on NCC, immunoblot analysis of exosomes showed increased abundance of NCC (>2.5-fold, $P<0.05$). The increase in NCC abundance in uEs after thiazide treatment correlated with the blood pressure response and change in plasma potassium levels ($R^2=0.22$, $P<0.05$; $R^2=0.19$, $P<0.05$, respectively). The abundance of NCC in uEs before treatment was significantly higher in responders compared to non-responders (>6-fold,$P<0.05$). Moreover, after thiazide treatment, the increase in abundance of NCC in uEs and decrease in plasma potassium levels was stronger in responders compared to non-responders ($P<0.05$). No significant differences in CD9 abundance were observed between the two experimental groups, suggesting comparable urinary exosomal numbers.

Conclusions: Our studies highlight that NCC is upregulated by thiazides and this increase correlates with the blood pressure response to thiazides and the change in plasma potassium levels. Additionally, we show that higher abundance of NCC prior to treatment with thiazides predicts the blood pressure response to thiazides. This implies that assessment of NCC in uEs could represent novel method to guide anti-hypertensive therapy in hypertensive patients.

SA-PO1016

Parathyroid Hormone (PTH) Increases Paracellular Permeability to Na and Ca in the Cortical Thick Ascending Limb (CTAL)

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Background: Ca absorption in the CTAL is passive along the paracellular pathway and requires the expression of claudin-16 at tight junction that increases the paracellular permeability to Ca (PCa). In vivo, Na is passively secreted along the paracellular pathway due to the transepithelial Na gradient, and to the permeability to Na of the tight junction that requires the expression of claudin-10b. In the CTAL, the lumen-positive transepithelial voltage (Vte) gradient that depends on claudin-10b expression and back diffusion of Na is critical for driving passive Ca reabsorption. PTH increases Ca transport across the CTAL but the mechanisms involved are imprecise. We aim to elucidate if claudin-16, which determines PCa, and claudin-10b, which determines Vte and PNa, are involved in the effects of PTH on the CTAL and to identify the underlying mechanisms.

Methods: Murine CTAL were microperfused *in vitro* to measure transepithelial Ca and Na absorption under symmetrical conditions and ionic paracellular permeabilities under asymmetrical conditions with 0.1 mM furosemide in the lumen. All measures were made under control and experimental conditions. The ratio of permeabilities PNa/PCl was calculated according to the Goldman-Hodgkin-Katz equation.

Results: PTH (10^{-10}M) significantly increased Ca reabsorption in CTAL from claudin $16^{+/+}$(+44 %) and claudin $16^{-/-}$(+60 %) mice; Vte did not change, indicating that PTH increased PCa. PTH increased Na reabsorption (+15 %) and PNa/PCl (+22 %) in CTAL from wild type mice. Dibutyryl cAMP (5.10^{-4}M), ionomycin (10^{-7}M), thapsigargin (10^{-6}M), but not phorbol 12-Myristate 13-Acetate (10^{-6}M), significantly increased PNa/PCl. Dibutyryl cAMP and ionomycin had additive effects on PNa/PCl. H-89 (PKA inhibitor, 10^{-5}M) partly inhibited the effect of PTH on PNa/PCl.

Conclusions: We conclude that, in the mouse CTAL, PTH - increases PCa independently of the presence of claudin-16 - increases PNa via cAMP- and cytosolic calcium-dependent signaling pathways. Our results show that properties of intercellular tight junctions can be directly and rapidly controlled by intracellular signaling pathways in intact tissue.

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SA-PO1017

Systems-Level Identification of PKA-Independent Vasopressin Signaling in Renal Epithelial Cells

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Background: Vasopressin signaling in the renal collecting duct is believed to be mediated predominantly by the activation of protein kinase A (PKA). The recent generation of mouse cell lines ("PKA dKO" cells), derived from mpkCCD cells, in which both PKA catalytic subunit genes have been deleted via CRISPR-Cas9 affords us an opportunity to identify PKA-independent signaling.

Methods: We used protein mass spectrometry to profile proteome-wide phosphorylation changes in response to vasopressin (dDAVP, 0.1 nM, 30 min) in PKA dKO cells and in control mpkCCD cells. dDAVP-treated and vehicle-treated cells were metabolically labeled using the SILAC method to allow quantification of dDAVP-induced changes in tryptic phospho-peptide abundances in an Orbitrap Fusion Lumos Tribrid mass spectrometer. Experiments were done in triplicate.

Results: Overall, >13,000 unique phosphopeptides were quantified in both PKA dKO and control cells. In control cells, 691 distinct phosphopeptides were altered in abundance in response to dDAVP. In contrast, in PKA dKO cells, only 73 phosphopeptides were altered in abundance, indicating that a large component of the vasopressin response is PKA dependent. However, altered phosphorylation in response to dDAVP in PKA dKO cells is indicative of substantial PKA-independent signaling. Notably, phosphorylation of Ser256 of AQP2 (thought to be a PKA site) increased in response to dDAVP in PKA dKO cells, indicating that other kinases can phosphorylate this site. The upregulated phosphorylation sites in PKA dKO cells mapped to an X-R-(A/S/T)-X-S*-X motif, consistent with activation of other basophilic kinases such as SGK, PKG, CAMK2B or PAK2. Interestingly, cAMP measurements showed that baseline cAMP levels in PKA dKO cells, were ~10-fold higher than in control mpkCCD cells, although both PKA dKO and control cells showed significant increases in response to dDAVP. This indicates that there is likely to be a PKA-dependent feedback on some component of the Avpr2-G_{α}s-Adcy6 signaling pathway responsible for cAMP generation.

Conclusions: In cultured mouse principal cells: (1) the signaling response to vasopressin is largely PKA-dependent; (2) a smaller component of the vasopressin response is PKA-independent; (3) Ser256 of AQP2 can be phosphorylated by kinases other than PKA; (4) PKA is responsible for a feedback inhibition of cAMP generation.

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SA-PO1018

Ticagrelor Reduces Urinary Concentration and Arginine Vasopressin (AVP) Levels: Potential Use in AVP Excess States

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Background: Previously we showed that blockade of $P2Y_{12}$ receptor by thienopyridine anti-thrombotic drugs (clopidogrel or prasugrel) increases urinary concentration and AVP levels. However, it is not clear whether non-thienopyridine drugs, such as ticagrelor, have similar effects on urine concentration and AVP levels.

Methods: Groups of B6D2 mice (N = 5/group) were fed regular chow containing different concentrations of ticagrelor (0.15, 0.20 and 0.25%) for 14 or 21 days and euthanized. Urine output, osmolality and AVP levels were determined prior to and at the end of treatment. Terminal plasma ticagrelor levels were assayed by LC-MS/MS. The effect of ticagrelor (0.5, 2 or 10 μM) added in vitro on dDAVP (synthetic analog of AVP; 20 nM)-induced AQP2 and AQP3 mRNA expression in primary cultures of rat inner medullary collecting duct (IMCD) cells was assessed.

Results: Administration of ticagrelor to mice caused increased urine output associated with decreased urine osmolality and AVP levels. (see Table). There was significant negative correlation between the plasma ticagrelor and urinary AVP ($P < 0.04$). But, blockade of $P2Y_{12}$ receptor in cultured IMCD cells by ticagrelor caused dose dependent enhancement of AQP2 and APQ3 mRNA expression.

Conclusions: The observed decrease in urinary AVP excretion appears to be due to an unexpected off-target effect on hypothalamic AVP production/secretion. However, the in vitro effect on IMCD cells was an expected one based on our previous studies on $P2Y_{12}$ receptor blockade. Hence, it appears that the *off-target* effect of ticagrelor on AVP production in vivo has apparently overridden its *targeted* effect on IMCD cells. Thus, our results suggest that the off-target effect of ticagrelor may find potential use in conditions associated with AVP excess, such as ADPKD, congestive heart failure, cirrhosis of liver, diabetic ketoacidosis, and cardiorenal syndrome, among others.

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Terminal Plasma and Urine Data (mean ± SE)

Ticagrelor in Chow (%, w/w)*	0.15	0.20	0.25
Plasma Ticagrelor (μM)	1.30 ± 0.15	2.49 ± 0.21	5.30 ± 0.90
Urine Output per day**	164 ± 35	169 ± 62	203 ± 75
Urine Osmolality**	75 ± 9	69 ± 11#	44 ± 13#
Urine AVP per day**	79 ± 8	76 ± 19	33 ± 6#

*after 21 days of treatment; **as percent of respective day 0 values (14 days of treatment); #signficantly different from the respective day 0 values

SA-PO1019

Decreased Release of Aquaporin-2 in Urinary Extracellular Vesicles in Rats Subjected to Allogenic Kidney Transplantation

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Background: Diuresis has been observed within a week following renal transplantation. Aquaporin-2 (AQP2) plays an important role in the regulation of urinary concentration. Recently, AQP2 has been shown to be predominantly localized to urinary extracellular vesicles (uEVs). However, the release pattern of AQP2-bearing uEVs (uEV-AQP2) in an early phase after renal transplantation is largely unknown. In this study, we examined the release pattern of uEV-AQP2 in the recipient animals after allogenic kidney transplantation.

Methods: All animal studies were approved by the committee on the Care and Use of Laboratory Animals at the University of Miyazaki. Male SD rats were used as recipients and male Wistar rats were used as donors. The donor right kidney was transplanted into the recipient whose right kidney had been removed, and thereafter the remaining left kidney was removed (Tpx group). For the control group, a simple left kidney nephrectomy was performed. Urine and renal samples were collected at 5 days after the surgery. uEVs were isolated by differential centrifugation.

Results: Urine output was increased and urine osmolality was decreased in Tpx group in comparison with the control group. The level of renal AQP2 expression was significantly decreased in Tpx group. The release of uEV-AQP2 was significantly lower in Tpx group. Correlation analysis showed that the release of uEV-AQP2 was related to urine osmolality. When we examined marker proteins for uEVs, such as TSG101 and Alix, the release of both proteins in uEVs increased in Tpx group.

Conclusions: These data indicate that the release of uEV-AQP2 was associated with its renal expression. Furthermore, uEV-AQP2 might be an indicator for urinary concentration ability in the case of renal transplantation.

SA-PO1020

Contribution of Collecting Duct NOS1 in the Regulation of Urine Flow in Hydrated and Dehydrated States

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Background: We previously determined that collecting duct (CD) nitric oxide synthase-1 (NOS1) was critical for maintaining fluid-electrolyte balance during high Na^+ intake. Mice with genetic deletion of all NOS1 splice variants from the principal cells of the CD (CDNOS1KO), have reduced urine flow after a single high Na^+ meal compared to control mice even though food and water intake was similar. This suggests that CD NOS1 may regulate CD water permeability during high Na^+ challenges. The purpose of this study was to determine if CD NOS1 is a regulator of water permeability during chronic hydration or water deprivation.

Methods: Male and female (n=6 per sex/genotype/treatment) CDNOS1KO and littermate $NOS1^{flox/flox}$(control) mice were randomly assigned to the hydration or 24 h dehydration protocols. All mice were placed on 5% sucrose water to encourage hydration. After 3 days, half of the mice were switched to water deprivation. Urine was collected diurnally matching the 12 h light schedule of the room.

Results: In male mice, both genotypes drank similar amounts while hydrated, and produced similar amounts of urine. With water deprivation, CDNOS1KO male mice produced significantly more urine than controls during their active period (182±0.04 vs 40±0.03 μl/12 h, $p = 0.02$), and urine from CDNOS1KO male mice was very concentrated (UOsm= 4632±193 mOsm/kg H_2O). Plasma osmolality rose similarly in both control (300±3 vs 315±2 mOsm/kg H_2O) and CDNOS1KO (301±2 vs 314±3 mOsm/kg, $P_{genotype}$=0.53 $P_{hydration}$<0.01, P_{gxh}= 0.3) during dehydration. In the females, fluid intake was significantly reduced in the CDNOS1KO mice during their active period compared to controls (7.2±1.6 vs 15.2±2.6 ml/day, p=0.01), and likewise there was a reduction in urine volume (3.1±1.2 vs 8.2±2.0 ml/day, p= 0.03). With dehydration, female control and CDNOS1KO mice both produced very little urine and concentrated urine (125±0.05 and 105±0.04 μl/12h, $p = 0.99$). Plasma osmolality following dehydration was increased in the controls (from 300±3 to 308±2 mOsm/kg H_2O) and further exacerbated in CDNOS1KO (from 309±4 to 319±6 mOsm/kg, $P_{genotype}$=0.02 $P_{hydration}$ = 0.03, P_{gxh} = 0.8).

Conclusions: In conclusion, CD NOS1 does contribute to the urine concentrating mechanisms of the kidney in both sexes, although it is a minor component. Interestingly, CD NOS1 is crucial in female mice to properly regulate plasma osmolality.

Funding: NIDDK Support

SA-PO1021

Effects of TGF-β1 on the Activity of NFAT5, an Osmoprotective Transcription Factor

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Background: NFAT5 (nuclear factor of activated T-cells 5, or TonEBP) is a transcription factor that stimulates the expression of osmoprotective genes in response to extracellular hypertonicity, resulting in cell survival even in extremely hypertonic conditions. Activated NFAT5 is translocated from the cytoplasm to nucleus, and then binds to the osmotic response element (ORE) to induce transcription. Not only hypertonicity but also hypoxia, oxidative stress, and toll-like receptor signaling, which promote fibrogenesis in the kidney, have been suggested to increase the NFAT5 activity. Transforming growth factor-β1 (TGF-β1) is an important factor that stimulates fibrogenesis, but little is known about the interaction between TGF-β and NFAT5. We evaluated the effects of TGF-β1 on the NFAT5 activity.

Methods: For *in vivo* experiments, mice were subjected to unilateral ureteral obstruction (UUO). After 14 days, the expression of NFAT5 and TGF-β1 in the kidney was examined by real-time PCR. For *in vitro* experiments, we used human embryonic kidney 293 (HEK 293) ORE-X cells which stably express the ORE-X-luciferase reporter gene. Cells were incubated in 300 mOsm/kg or 500 mOsm/kg (NaCl added) for 24 hrs, and then the luciferase activity was measured to evaluate the NFAT5 transcriptional activity. Protein expression of NFAT5 was examined by Western blotting. To examine the effect of TGF-β on nuclear translocation of NFAT5, whole cell lysate was fractionated to nucleus and cytoplasm.

Results: The expression of NFAT5 and TGF-β1 mRNAs was 2.5 and 12 times greater in the kidney in UUO mice than that in sham-operated mice, respectively. TGF-β1 suppressed tonicity-induced NFAT5 transcriptional activity and protein expression in HEK293 cells. Nuclear translocation of NFAT5 was inhibited by TGF-β1. These results suggest that TGF-β1 directly inhibits the activation and expression of NFAT5.

Conclusions: TGF-β1 inhibits NFAT5 in the kidney, which might exacerbate renal fibrogenesis during fibrotic renal disorders.

Funding: Government Support - Non-U.S.

SA-PO1022

Dog and Human Zip10 (SLC39A10) Localization Is More Than Proximal Tubule, Helping to Explain Role in Nephrolithiasis

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Background: In the past several years, we and others have implicated zinc (Zn^{2+}) and Zn^{2+} transporters, e.g., SLC39A10 / ZIP10, to have a role in dog and human nephrolithiasis using a *Drosophila* model. As for other ions and solutes, Zn^{2+} is moved into and out of cells by specific membrane transporters: ZnT, ZIP, and NRAMP/DMT proteins. In rodents, ZIP10 has been localized at the apical membrane of renal proximal tubules (PT), where it is believed to play a role in Zn^{2+} import.

Methods: Our group has used *Drosophila* as a model of calcium oxalate kidney stones We expressed ZIP10 from dog, human, and *Drosophila* (*CG10006*), tested clones for Zn^{2+} uptake, electrogenicity (voltage clamp) and ability to change intracellular pH (pH_i) in *Xenopus* oocytes. Finally using immunofluorescence, we localized the ZIP10 protein in mouse, dog, human and fly renal structures.

Results: *CG10006*, rather than *foi* (fear-of-intimacy, *CG6817*) is the primary ZIP10 homolog found in *Drosophila* Malpighian tubules. All of these ZIP10-proteins were found to transport $^{63}Zn^{2+}$ (PET isotope) in oocytes; however, we were unable to elicit membrane currents or pH_i changes with addition of Zn^{2+}. The ZIP10 antibody recognizes recombinant and native rodent, dog, human and *Drosophila* ZIP10 proteins. Immunohistochemistry reveals that Zip10 in higher mammals is found not only in the PT but also in AQP2-positive tubules (collecting duct, CD).

Conclusions: 1) CG10006 is the likely ortholog of ZIP10; 2) ZIP10 transport is not electrogenic; 3) ZIP10 transport is not HCO_3^- coupled; 4) ZIP10 in dogs and humans has both PT and CD localization. Together these studies reveal ZIP10 has multiple roles in renal Zn^{2+} transport and may provide additional insights to the role of Zn^{2+} in calcium oxalate nephrolithiasis.

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SA-PO1023

Acetazolamide Inhibits Ammoniagenesis and Prevents the Correction of Metabolic Acidosis in Rat

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Background: Acetazolamide (ACTZ), a potent inhibitor of carbonic anhydrases (CA), increases renal bicarbonate wasting and causes metabolic acidosis. Intracellular acidic pH, *per se*, upregulates the glutamine transporter SNAT3 and the ammoniagenic enzymes (glutaminase or GA and glutamate dehydrogenase or GDH). CAII binds to the basolateral Na^+:HCO_3^- cotransporter (NBCe1) and facilitates HCO_3^- reabsorption across the proximal tubule. However, whether ACTZ alters NBCe1 activity and interferes with the ammoniagenesis pathway during the onset of ACTZ-induced metabolic acidosis remains elusive.

Methods: We compared male Sprague Dawley rats treated with ACTZ or its vehicle (control) to those subjected to NH_4Cl loading inthe drinking water. The animals were housed in metabolic cages for daily measurements of urine volume, Na^+ excretion, NH_4^+ excretion and urine pH. The animals were sacrificed after 6 days or 2 weeks. Blood composition was analyzed and the protein abundance of SNAT3, GA and GDH in the kidney cortex was examined.

Results: ACTZ-treated rats exhibited a significant increase in urine flow, natriuresis and bicarbonaturia (urine pH = 8.1 vs. 6.8 in controls). NH_4Cl-loaded rats showed a significant decrease in urine pH (5.6 vs. 6.7 in controls) with no change in Na^+ excretion or urine flow. ACTZ caused a significant and sustained metabolic acidosis for up to 2 weeks (serum $[HCO_3^-]$ = 20 and 21 mM for 6 days and 2 weeks, respectively, vs. 30mM in controls). Whereas in NH_4Cl loaded rats, metabolic acidosis was developed in 6 days but was fully corrected after 2 weeks of treatment (serum $[HCO_3^-]$ = 20 and 28 mM for 6 days and 2 weeks, respectively, vs. 29 mM in controls). NH_4^+ excretion increased by 4-fold in NH_4Cl-loaded rats but only slightly (0.6-flod) in ACTZ-treated rats for 6 days despite similar degree of metabolic acidosis. Immunoblotting studies showed that the protein abundance of GA (4-fold), GDH (06-fold) and SN1 (8-fold) increased significantly in NH_4Cl-loaded rats, but remained unchanged in ACTZ-treated animals.

Conclusions: 1- We propose that ACTZ binds to CAII and inactivates NBCe1. This alkalinizes proximal tubule cells and therefore suppresses the ammoniagenesis pathway despite systemic metabolic acidosis. 2- Metabolic acidosis of ACTZ is generated by renal HCO_3^- wasting and maintained by the inhibition of ammoniagenesis pathway in the proximal tubule.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO1024

Co-Localization of NKCC2 with AQP2 in the Collecting Duct Principal Cells Contributes to the Acute Diuretic Effects of Furosemide and Overall Water Handling by the Kidney

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Background: The activity of $Na^+/K^+/2Cl^-$ cotransporter (NKCC2) in the thick ascending limb (TAL) plays an important role in the process of urinary concentrating mechanism and the control of water balance by the kidney. Acute furosemide (NKCC2 inhibitor) administration to both human and animals is associated with a rapid (minutes) diuresis, natriuresis, diluted and acidified urine. This raises the question as to whether NKCC2 is co-localized with AQP2 in the collecting duct (CD) principal cells.

Methods: Male rats housed in metabolic cages were injected with furosemide (FURO, 5mg/kg BW) and urine was collected every hour for 2 hours and after 7 days of daily treatment. Urine of vehicle-injected rats (control) was collected over a 3-hour period and after 7 days. Urine volume, urine osmolality, Na^+ excretion and urine pH were measured. Rat and human kidney tissues were used to examine the localization of NKCC2 and AQP2 and ENaC by immunofluorescence labeling technique.

Results: Compared to control group, furosemide-treated rats exhibited an increase in urine output and Na+ excretion by 9- and 33-fold, respectively, during the first hour of treatment. Urine osmolality decreased to 439 mosm/kg H2O during the first hour and remained low (450~ mosm/kg H2O) after 7 days vs. 1373 (3 hours) or 1635 (7 days) mosm/kg in control group. Urine pH decreased significantly (from 6.56 to 6.04, $P<0.04$) during the second hour of furosemide treatment. The later effect is inhibited in the presence of low dose of amiloride (ENaC inhibitor). Merged images of double immunofluorescence labeling of rat and human kidney tissues with AQP2 and NKCC2 or with AQP2 and ENaC showed NKCC2 expression in the apical membrane of both AQP-free (TAL), as well as AQP2 expressing cells; whereas ENaC is exclusively co-expressed with AQP2 in the CD principal cells of both rat and human kidneys.

Conclusions: We demobnstarte for the first time that NKCC2, ENaC and AQP2 are co-expressed in the apical membrane of principal cells in the cortical and outer medullary CD of both rat and human kidneys. The co-localization of NKCC2 with AQP2 contributes to the acute diuretic and natriuretic effects of furosemide, and the co-localization of NKCC2 with ENaC in the CD is responsible for furosemide-induced urinary acidification.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO1025

Urinary Uromodulin Is Increased in Magnesium Deficiency and Stimulates Tubular Magnesium Absorption via TRPM6

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Background: Uromodulin (UMOD) is the most abundant urinary protein in humans. We describe a novel role for Uromodulin in renal magnesium homeostasis. Mild to moderate chronic hypomagnesemia occurs in up to 15% of the population and is associated with type 2 diabetes mellitus, hypertension, and chronic kidney disease.

Methods: Whole-animal experiments for urinary excretion of magnesium and UMOD, and response to furosemide were performed in nine months-old wild-type (WT) and Uromodulin knockout (*Umod*$^{-/-}$) mice. Kidneys from both strains were studied for qRT-PCR studies and immunofluorescent TRPM6 expression. Whole-cell patch-clamp recording and biotinylation assays were performed in HEK293 cells to determine TRPM6 whole-cell current density and cell surface abundance.

Results: *Umod*$^{-/-}$ mice, compared to WT, excreted more urinary magnesium (WT 18 ± 3 μmol/24h vs. *Umod*$^{-/-}$ 34 ± 5 μmol/24h; $p<0.05$) and displayed upregulation of genes promoting renal magnesium absorption, confirming magnesium deficiency in *Umod*$^{-/-}$ mice. The thick ascending limb in both strains responded the same to furosemide, indicating appropriate function. Fine-tuning of magnesium absorption occurs in the distal convoluted tubule (DCT) via the apical magnesium channel TRPM6. We found decreased apical TRPM6 staining in the DCT of *Umod*$^{-/-}$ mice. Applying *in vitro* biotinylation assays and whole-cell patch-clamp recording we found that UMOD enhanced TRPM6 cell surface abundance and current density from the extracellular space (42 ± 6 vs 196 ± 10 *p*A/*p*F for control vs UMOD; $p<0.0001$). Co-immunoprecipitation studies showed that UMOD physically interacted with TRPM6, and thereby impaired dynamin-dependent TRPM6 endocytosis. UMOD depended on the urinary lectin galectin-1 to form a lattice together with a novel extracellular TRPM6 N-glycan to increase TRPM6 current density. To examine if a low magnesium state could modify urinary UMOD secretion we fed WT mice with a low magnesium diet and detected almost two-fold increased urinary UMOD excretion compared to the same mice on a regular diet.

Conclusions: Our data suggest that increased urinary UMOD secretion in low magnesium states defends against further urinary magnesium losses through upregulation of TRPM6 cell surface abundance by impairing TRPM6 endocytosis.

Funding: NIDDK Support

SA-PO1026

Molecular Mechanism of High-Potassium Induced Na-Cl Cotransporter Dephosphorylation

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Background: Sodium-chloride cotransporter (NCC), expressed in distal convoluted tubules (DCT), is a key molecule in the regulation of urinary potassium (K^+) excretion. We previously reported that tacrolimus (a calcineurin inhibitor) and W7 (a calmodulin inhibitor) inhibited the K^+-induced NCC dephosphorylation and the increase in urinary K^+ excretion in mouse kidneys. These results suggest that calmodulin and calcineurin (CaN) were activated by calcium (Ca^{2+}) signal in response to the increase in extracellular K^+ concentration ($[K^+]_{ex}$) in DCT. However, the precise mechanism of K^+-induced CaN activation in DCT cells remains unknown.

Methods: Flp-in NCC HEK293 cells were transfected with constitutively active CaN-A (CA-CaN-A), CaN-A, and -B plasmids to determine the role of CaN in NCC dephosphorylation. Intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) were analyzed by live cell imaging using fluo-4 AM. SEA0400 (an NCX reverse-mode inhibitor) and ω-agatoxin (a P/Q type Ca^{2+} channel inhibitor) were injected to C57BL/6 mice 1 hour before K^+ oral gavage.

Results: We confirmed that CA-CaN-A over-expression clearly dephosphorylated NCC in HEK293 cells. In the following experiments, we used HEK293 cells in which both CaN-A and CaN-B were transiently overexpressed. In these cells, K^+-induced NCC dephosphorylation was inhibited by tacrolimus and EGTA treatment. The rapid increase in $[Ca^{2+}]_i$ after high K^+ stimulation was not observed with EGTA treatment, suggesting that the increase in $[Ca^{2+}]_i$ after K^+ stimulation was caused by Ca^{2+} influx. To determine the influx pathway, we treated the cells with several Ca^{2+} transporter inhibitors, and identified that SEA0400 and ω-agatoxin inhibited the K^+-induced $[Ca^{2+}]_i$ increase and NCC dephosphorylation. Furthermore, we found that both SEA0400 and ω-agatoxin inhibited K^+-induced NCC dephosphorylation in mouse kidneys.

Conclusions: This study showed that the K^+-induced NCC dephosphorylation by CaN was mediated by high-$[K^+]_{ex}$-induced influx of Ca^{2+} through reverse-mode NCX and/or P/Q type Ca^{2+} channel.

SA-PO1027

Involvement of CaSR, Claudin-14, and 16 in the Development of Hypermagnesiuria Associated with Tubulo-Interstitial Nephropathy

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Background: Hypermagnesiuria is well known clinical feature of tubulo-interstitial nephropathy (TIN), and would be a diagnostic tool for TIN. We studied the changes in the expression of renal magnesium transporting molecules with the development of TIN in rats with unilateral ureter obstruction (UUO).

Methods: Left ureter of male SD rats was ligated, and the left kidney was sampled at day-0 (control), day-1 (early phase) and day-7 (late phase). Just before sampling, urine from the ureter-ligated kidney was collected by catheter insertion into the ureter. Immunohistochemistry, immunoblotting and RT-PCR were applied to this study.

Results: Fractional Mg excretion was significantly increased in the late phase but not in the early phase (FEMg: 3.13±0.81 at day-0, 4.72±0.54 at day-1, 10.7±0.81% at day-7). Immunohistochemistry and RT-PCR for fibrosis related gene indicated that TIN was developed in the late phase but not in the early phase. Expression of claudin-16, Mg reabsorption pathway in the thick ascending limb, was significantly decreased in the late phase but not in the early phase (100.2±2.9% at day-0, 90.3±6.3% at day-1, 36.4±1.6% at day-7). The results were confirmed by immunohistochemistry and immunoblotting. However, mRNA expression of TRPM6, Mg pathway of distal tubule, was significantly down-regulated even in the early phase (0.94±0.14% at day-0, 0.50±0.06% at day-1, 0.05±0.01% at day-7). Claudin-14 which is known to be an inhibitory regulator of claudin-16 was remarkably up-regulated. Because calcium sensing receptor (CaSR) signal is reported to function as an inhibitory regulator of claudin-14, we finally studied the expression of CaSR. CaSR mRNA was significantly down-regulated in the late phase (100.5±4.7 at day-0, 42.5±13.0 at day-1, 7.5±1.8% at day-7), and immunohistochemistry showed remarkable reduction of CaSR signal in the late phase.

Conclusions: Our findings may indicate that the characteristic hypermagnesiuria in TIN is principally caused by a dysfunction of magnesium reabsorption in the thick ascending limb of Henle resulting from a significant decrease in the claudin-16 expression. The down-regulation may be closely related to the development of TIN through CaSR-claudin-14-claudin-16 regulatory network.

SA-PO1028

MAGE-D2 Regulated Na-Cl Cotransporter Through Chaperon-Dependent ERAD

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Background: Mutations in MAGE-D2 gene, encoded in X-chromosome, was reported to associate with transient antenatal Batter's syndrome with severe polyhydramnios. Reduced Na-K-2Cl cotransporter 2 (NKCC2) and Na-Cl cotransporter (NCC) was observed in the renal tubules of affected male patients.

Methods: To explore the role of mutant MAGE-D2 in the kidney, we created mutant Mage-d2 knock-in (KI) mice and examined the possible molecular mechanisms in vitro.

Results: Three strains of disease-mutant Mage-d2 (c274dupA, Y346X and A495G) KI mice were generated and only female A495G/+ mice could be produced from chimera mouse. By sonography, some embryos with polyhydramnios were found in A495G/+ female mice at E15.5D. Compared with the WT embryos, more amniotic fluid amount in male A495G/+ embryos but not female A495G/+ embryos was observed. The osmolarity of the amniotic fluid was not significant between female or male WT and A495G/+ embryos. When the different types of Mage-d2 cDNA [WT, c274dupA (truncated protein), Y346X (truncated protein) and A495G (missense full-length protein)] was transfected into the HEK293 cells, Y346X and A495G Mage-d2 showed interruption of the cell cycles in the G2/M phase and reduction of the abundance of NCC. Immunoprecipitation study revealed NCC could interact with WT and A495G Mage-D2 instead of truncated c274dupA and Y346X Mage-D2 proteins. Y346X and A495G Mage-d2 also reduce the expression of HSP40, HSP90 and CHIP. These chaperon proteins were reported to form a complex and play a role in the ER-associated degradation (ERAD) of the NCC.

Conclusions: These results suggested that Mage-D2 might affect the cell cycles of renal tubular cells and the NCC expression through regulating ERAD chaperon proteins.

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SA-PO1029

SLC41A1 Mediates Magnesium Reabsorption in the Kidney

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Background: Solute carrier family 41 member A1 (SLC41A1) has been suggested to mediate magnesium (Mg^{2+}) transport and to maintain Mg^{2+} homeostasis in humans. However, the function of SLC41A1 in the kidney, the main organ maintaining Mg^{2+} homeostasis, remains to be elucidated.

Methods: In this study, cellular Mg^{2+} transport assays combined with zebrafish *slc41a1* knockdown experiments were performed to disclose SLC41A1 function in the kidney.

Results: The gene *slc41a1* is ubiquitously expressed in zebrafish tissues and is regulated by water and dietary Mg^{2+} availability. Knockdown of *slc41a1* resulted in renal Mg^{2+} wasting in zebrafish larvae and elicited compensatory mechanisms to cope with the renal Mg^{2+} leakage induced. These compensatory mechanisms were illustrated by an up-regulation of the gene expression of the zebrafish orthologs of human magnesiotropic genes expressed in the distal convoluted tubule (*TRPM6*, *SLC12A3*, *SLC41A3* and *CNNM2*). Importantly, the renal Mg^{2+} wasting phenotype is rescued when mouse SLC41A1 is expressed in *slc41a1*-knockdown zebrafish. This proved the specificity of the knockdown approach used, as well as the functional equivalence of zebrafish Slc41a1 with the mammalian SLC41A1. Conversely, expression of mammalian SLC41A1-p.Asp262Ala, harbouring a mutation in the ion-conducting SLC41A1 pore, did not reverse the renal Mg^{2+} wasting observed in *slc41a1*-knockdown zebrafish. $^{25}Mg^{2+}$ transport assays in human embryonic kidney 293 (HEK293) cells overexpressing SLC41A1 demonstrated that SLC41A1 mediates cellular Mg^{2+} extrusion independently of sodium (Na^+). In contrast, SLC41A1-p.Asp262Ala expressing HEK293 cells displayed similar Mg^{2+} extrusion activities than control (mock) cells. In polarized Madin-Darby Canine Kidney cells, SLC41A1 localized to the basolateral cell membrane.

Conclusions: Our results demonstrate that SLC41A1 facilitates renal Mg^{2+} reabsorption in the zebrafish model. Furthermore, our data suggest that SLC41A1 extrudes Mg^{2+} across the basolateral membrane by a mechanism that is independent of Na^+. Based on the SLC41A1 function disclosed, patients with hereditary hypomagnesemia should be screened for *SLC41A1* mutations.

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SA-PO1030

Disruption of a C-Terminal Di-Leucine Motif Directs NKCC1 to the Apical Membrane and Lysosomes in Polarized Epithelia

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Background: Delivery of NKCC1 cotransporter to the basolateral membranes play in crucial rule in ions homeostasis in epithelia. We recently reported the first known SLC12A2 (NKCC1) mutation that causes epithelial dysfunction in an undiagnosed clinical case. The 11 bp deletion resulted in a *non-functional* transporter with a shorter cytosolic COOH-terminal tail. NKCC1-DFX maintains its ability to interact with wild-type NKCC1, leads to increase dimerization of the cotransporter, and causes mis-tafficking of the NKCC1-DFX mutant and wild-type transporters to the apical/subapical region of polarized epithelia.

Methods: In this study, we used sequential truncation and site-directed mutagenesis within NKCC1 COOH domain and immunofluorescence to examine the trafficking of wild-type and mutants NKCC1 cotransporters in polarized MDCK cells.

Results: Our results show that truncation of NKCC1 COOH domain uncouple the co-transporter from the lateral membrane. We also targeted a di-leucine motif ($DxxxLL^{1193-1194}$) part of a previously described tetrad in the extreme C-terminus of NKCC1 as well as a di-leucine motif ($DxxxLL^{1036-1037}$) located upstream. Disruption of the $DxxxLL^{1036-1037}$ motif led to some increase localization in the cytoplasm, although most the cotransporter remained at the plasma membrane. In contrast, mutation of the terminal $DxxxLL^{1193-1194}$ motif led to cotransporter accumulation in the cytoplasm and mis-trafficking to the apical/sub-apical region of polarized epithelial; recapitulating the phenotype observed in NKCC1-DFX mutant. This observation indicates that the $DxxxLL^{1193-1194}$ motif is important for trafficking and maintenance of NKCC1 to the basolateral membrane. Truncation deletion and LL substitution mutants are trafficked out of the Trans-Golgi network and ER but accumulates in early endosomes and late endosomes where they are degraded. Whether they reach the endosomes by trafficking transiently through the plasma membrane is currently under investigation.

Conclusions: Our data demonstrate that NKCC1 basolateral trafficking is regulated by a conserved di-leucine motif in its C-terminal domain. Loss of $DxxxLL^{1193-1194}$ leads to mis-trafficking of NKCC1 to the apical membrane and accumulation in late endosomes in the subapical region of the polarized epithelia.

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SA-PO1031

The Inhibitory Role of ERK1 Signaling in Renal Sodium Handling and Blood Pressure Through Affecting Sodium Chloride Co-Transporter

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Background: Sodium chloride cotransporter (NCC) plays a key role in regulating blood pressure and electrolyte homeostasis. Our previous study showed that WNK4 inhibits NCC by activating ERK1/2 signaling. Although ERK1 and ERK2 share 80% amino acid sequences, roles of ERK1 and ERK2 were reported to be different. Our preliminary studies showed that NCC was decreased in the inducible renal tubular specific ERK2 knockout (KO) mice, suggesting that the ERK1 and ERK2 pathways modulate NCC differently. Thus, we hypothesized that ERK1 signaling pathway plays an inhibitory role in regulating renal sodium excretion and blood pressure through NCC.

Methods: ERK1 global KO mice, western blot analysis, cell culture, siRNA knock-down, metabolic cage study, and tail-cuff blood pressure (BP) measurement were used in this study.

Results: To determine whether ERK1 involves in NCC regulation *in vivo*, we first did western blot experiments. We found that NCC abundance was increased in ERK1 KO mice. To investigate whether ERK1 affects NCC protein expression *in vitro*, we did ERK1 siRNA knock-down experiments in Cos-7 cells cotransfected with NCC and siRNA ERK1. We found that ERK1 knockdown increased NCC protein expression. To explore whether ERK1 signaling pathway involves in sodium excretion**,** we collected 24-h urine using metabolic cage. We found that 24-h urinary sodium excretion / body weight was significantly lower in ERK1 KO mice compared to WT control mice (0.0088 ± 0.0009 vs 0.0107± 0.0014 mmol/g, n=6, $p < 0.05$). To further investigate the role of ERK1 signaling on NCC function, we did metabolic cage study in ERK1 KO mice administrated with either control vehicle or hydrochlorothiazide (HCTZ), a specific NCC inhibitor. We found that ERK 1 mice have more exaggerated response to HCTZ treatment (25mg/kg wt, i.p.) compared to WT mice in urinary sodium excretion (0.49 ± 0.10 vs 0.28 ± 0.14 mmol, $p < 0.05$, n=3), indicating a higher NCC activity in ERK 1 KO mice. Furthermore, we found that systolic BP was higher in ERK1 KO mice than that in WT mice (127.2 ± 4.7 vs 112.9 ± 9.8, n= 4, $p < 0.05$) by tail-cuff method.

Conclusions: Taken all above data together, we concluded that ERK1 signaling pathway plays an inhibitory role in NCC function and NCC protein expression, which affects renal sodium handling and blood pressure.

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SA-PO1032

Cyclosporin A Aggravates Hypomagnesemia and Hypercalciuria in Claudin 16-Deficient Mice

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Background: Calcineurin inhibitors are instrumental for immunosuppression in patients after organ transplantation but renal side effects such as hypomagnesemia and hypercalciuria often limit their therapeutic benefits. The tight junctions protein claudin 16 (Cldn16) is essential for paracellular reabsorption of calcium and magnesium along the cortical thick ascending limb (cTAL). In this study we treated wild-type (WT) and Cldn16-deficient (Cldn16-/-) mice with a calcineurin inhibitor cyclosporin A (CsA) to identify the role of Cldn16 in calcineurin inhibitor-induced abnormalities of renal divalent cation handling.

Methods: Kidney performance was evaluated in metabolic cages. Key paracellular and transcellular distal calcium and magnesium transport proteins were assessed by quantitative PCR, immunoblotting and immunofluorescence.

Results: Labeling of Cldn16 produced strong signal in cTAL tight junctions of WT but not of Cldn16-/- kidneys. Physiological analysis showed baseline hypomagnesaemia and hypercalciuria in Cln16-/- mice compared to controls. CsA administration (25 mg/kg i.p. for 7 days) induced hypomagnesaemia and hypercalciuria in WT and aggravated calcium and magnesium wasting in Cldn16-/- mice. Analysis of Cldn10, Cldn14, Cldn16, and Cldn19 isoforms did not reveal any CsA-dependent changes of their expression or protein abundance. In contrast, expression and abundance levels of relevant transcellular divalent cation transporters including the transient receptor potential channel TRPM6, calbindin, parvalbumin, and divalent metal cation transporter CNNM2 were significantly reduced upon CsA in both genotypes with stronger decreases in Cldn16-/- mice.

Conclusions: In summary, our data suggest that calcineurin inhibitors cause renal calcium and magnesium loss via suppression of transcellular reabsorption pathways, rather than via inhibition of the Cldn16-mediated paracellular transport.

SA-PO1033

Intracellular Chloride Depletion Promotes WNK4-RRXS Phosphorylation by a PKC/PKA Dependent Mechanism

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Background: Mutations in *WNK4* gene cause Familial Hyperkalemic Hypertension (FHHt) due to increased salt reabsorption by the Na^+:Cl^- cotransporter (NCC). While WNK4 activity is inhibited by chloride, this kinase can be activated by angiotensin II or CaSR-induced PKC or PKA-mediated phosphorylation in different WNK4-RRXS motifs. This is essential for full activation of WNK4. NCC activity is inversely proportional to plasma K^+ concentration and evidence suggests that modulation of WNK4 by chloride underlies this phenomenon. Here we analyzed if WNK4 phosphorylation in its RRXS motifs is also modulated by intracellular chloride concentration ($[Cl^-]_i$).

Methods: We used a mouse model of hypokalemia generated by feeding WT mice with low K^+ diet for 7 days. WNK4-RRXS phosphorylation was analyzed by Western Blot and immunofluorescence in hypokalemic mice and in WNK4-transfected HEK293 cells incubated with different media and pharmacological inhibitors. ELISA was used to determine PKC activity.

Results: WNK4 phosphorylation at RRXS motifs S64 and S1196 increased in mice fed with low K^+ diet compared to controls. Interestingly, this was only observed in NCC positive tubules. Incubation of transfected HEK293 cells with low K^+ medium also resulted in WNK4-RRXS phosphorylation. Furthermore, two different maneuvers that decrease $[Cl^-]_i$ (low chloride hypotonic stress or NEM-incubation) in HEK293 cells also caused an increase in WNK4-RRXS phosphorylation. This was prevented by PKC inhibitor BIM and PKA inhibitor H89, as well as by intracellular Ca^{2+} chelation by BAPTA-AM. Accordingly, we found that PKC activity was increased upon $[Cl^-]_i$ depletion. Given that WNKs are the only kinases known to be regulated by $[Cl^-]_i$, we hypothesized that WNK activity was involved in the PKC/A-induced WNK4-RRXS phosphorylation. However, the specific WNK inhibitor WNK463 did not ablate low K^+-induced WNK4-RRXS phosphorylation. Instead, WNK463 increased WNK4-RRXS phosphorylation, probably due to the expected $[Cl^-]_i$ decrease.

Conclusions: WNK4 is phosphorylated in its RRXS motifs during reduction of $[Cl^-]_i$ by a mechanism that involves PKC or PKA activation. This process seems to be independent of WNK activity and was also observed *in vivo* since low potassium diet resulted in WNK4-RRXS phosphorylation in mouse DCT.

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SA-PO1034

High Chloride Silences Aldosterone Signaling in the Distal Nephron

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Background: The adrenal steroid hormone aldosterone plays a primary role in maintaining normal body electrolyte homeostasis. Physiologically, aldosterone secretion from the adrenal glands is under the control of angiotensin II and plasma $[K^+]$. Surprisingly, high aldosterone levels due to high K^+ intake are normally not associated with renal salt retention and disturbances of systemic Na^+ and Cl^- homeostasis. K^+ supplementation consistently enhances renal Na^+ excretion in animals as well as in humans particularly during NaCl loading when Na^+ delivery to the distal nephron is high. We therefore questioned whether a further mechanism may exist which in the context of a high NaCl and high K^+ intake attenuates the aldosterone-MR-ENaC pathway.

Methods: We analyzed the effects of a normal or high K^+ diet on Na^+ excretion, MR localization, ENaC mRNA and protein expression, and ENaC activity in salt replete mice. The effects of high extracellular chloride concentration $[Cl^-]$ on MR localization and ENaC expression was also determined in mCCD cells, a cellular model of principal cells in the collecting duct.

Results: The canonical cellular responses to aldosterone, encompassing translocation of the mineralocorticoid receptor (MR), transcription and activation of epithelial sodium channel ENaC, and ENaC-dependent Na^+ reabsorption, were undetectable in mice receiving a high K^+ /high NaCl diet in spite of increased plasma aldosterone concentrations. Elevating extracellular chloride concentration [Cl^-] was sufficient to suppress the aldosterone-induced MR translocation and ENaC protein expression in vitro and in vivo. Functionally and biochemically, the aldosterone response was rescued in vivo when the extracellular [Cl^-] increase was prevented during the high K^+ diet.

Conclusions: These findings show that aldosterone signaling in the kidney is silenced by increased extracellular [Cl^-] and provide an explanation for the natriuretic effect of a high K^+ intake in the presence of a high NaCl consumption characteristic for the Western diet.

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SA-PO1035

SCAMP4, a New Player in the Regulation of NKCC2 Surface Expression

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Background: The apically located Na-K-2l cotransporter is the pacemaker of NaCl reabsorption in the thick ascending limb (TAL) of the loop of Henle. We have previously shown that secretory carrier membrane protein 2 (SCAMP2) regulates exocytic insertion of NKCC2 into the cell membrane. The aim of the present study was to investigate the effect of SCAMP4, a member of the SCAMPs family that lacks the highly conserved N-terminal NPF repeats, on NKCC2 surface expression.

Methods: To examine the expression of SCAMP4 in TAL, we checked for the presence of its transcript in native TAL cells using real-time RT-PCR. Protein-protein interaction was assessed by co-immunopreciptation assay. NKCC2 surface expression was monitored in transiently transfected OKP and HEK cells, using protein biotinylation, immunoblot and confocal imaging.

Results: Real time PCR on renal microdissected tubules demonstrated the expression of SCAMP4 in TAL. Co-immunoprecipitation experiments showed robust interaction between SCAMP4 and the complex-glycosalyed form of NKCC2 in cultured renal cells, suggesting that the interaction takes a place at the post-Golgi level. Consistent with this notion, co-immunolocalization experiments revealed that similar to SCAMP2, SCAMP4 co-localizes with NKCC2 in recycling endosomes. However, in contrast to SCAMP2, SCAMP4 co-expression promoted NKCC2 surface expression, whereas SCAMP4 knock-down had the opposite effect. Interestingly, deleting the deleting N-terminal NPF repeats from SCAMP2, abolished its negative effect on NKCC2 surface expression, suggesting that this highly conserved domain plays a crucial in the differential regulation of NKCC2 surface expression by SCAMP2 and SCAMP4.

Conclusions: We identified SCAMP4 as a novel NKCC2 binding partner that plays a key role in the modulation of NKCC2 surface expression. Most importantly, our results are consistent with SCAMP2 and SCAMP4 having differential and antagonistic effects with regard to NKCC2 transit through recycling endosomes, thereby revealing a new regulatory mechanism governing the co-transporter intracellular trafficking.

Funding: Government Support - Non-U.S.

SA-PO1036

Dietary Mg2+ Restriction Downregulates NCC Through a SPAK-Independent Pathway

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Background: Hypomagnesemia is often observed in critically ill patients and is associated with lower kidney function and life-threatening complications. The distal convoluted tubule (DCT) is the major site of active Mg^{2+} reabsorption, determining the final urinary Mg^{2+} excretion. The Na^+-Cl^- cotransporter (NCC), expressed along the DCT, plays a key role in ion homeostasis. Dietary interventions have a strong effect on NCC.

Methods: We studied the effect of dietary Mg^{2+} manipulation on NCC in C57BL/6J mice by assessing levels of total NCC (tNCC), phospho-NCC (pNCC) and other relevant proteins with blood electrolyte analysis.

Results: We observed that abundances of tNCC and pNCC, a surrogate for NCC activity, were lower following acute (3 days) and chronic dietary Mg^{2+} (14 days) restriction, compared with normal and high Mg^{2+} diets. However, pNCC:tNCC was unchanged, suggesting the primary effect is on tNCC abundance. It is well-established that low blood [K^+] induces NCC phosphorylation. We observed that while tNCC was still downregulated by combined K^+ and Mg^{2+} restriction, pNCC abundance was strongly increased compared with normal and Mg^{2+} deficient diets. These data suggest that distinct signaling pathways mediate the effects of dietary Mg^{2+} and K^+ restriction on NCC. STE20 (Sterile 20)/SPS-1 related proline/alanine-rich kinase (SPAK) directly phosphorylates NCC, and SPAK knockout (KO) mice have ~90% lower tNCC abundance compared with wild type mice. Dietary Mg^{2+} restriction of SPAK KO mice further decreased tNCC, suggesting a strong effect of dietary Mg^{2+} restriction on tNCC abundance, and showing that SPAK was not involved in mediating the effect of dietary Mg^{2+} restriction. The E3 ubiquitin-protein ligase neural precursor cell expressed developmentally downregulated gene 4-like (Nedd4-2) induces tNCC degradation on a high Na^+ diet, but targets the epithelial sodium channel (ENaC) during K^+ restriction. As activated Nedd4-2 promotes self-degradation, its abundance reflects its activity. We found that Nedd4-2 abundance was lower on Mg^{2+} deficient diet compared with normal diet, suggesting activation of Nedd4-2 by Mg^{2+} restriction. However, abundances of ENaC subunits were unaffected.

Conclusions: Overall, our data suggest that dietary Mg^{2+} deficiency may alter NCC function by downregulating total abundance of NCC by activating Nedd4-2 selectively along the DCT.

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SA-PO1037

Association Between Estimated Dietary Acid Load and Albuminuria in Japanese Adults

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Background: Acid-base imbalance might promote the progression of chronic kidney disease (CKD). Albuminuria is a risk factor for cardiovascular disease and mortality even in the high normoalbuminuric range and is also one of the diagnostic markers for CKD. However, the exact relationship between dietary acid load and albuminuria is unclear. In this study, we assessed the association of dietary acid load with albuminuria in Japanese adults.

Methods: Subjects were a Japanese cohort comprising 3,202 men and 3,429 women (age range 40-97 years); subjects with a urine albumin-to-creatinine ratio (UACR) ≥ 300 mg/g or eGFR < 15 mL/min/1.73 m^2 were excluded. We performed a cross-sectional analysis of net endogenous acid production (NEAP) score and the presence of low-grade albuminuria. NEAP score was derived from nutrient intake based on food frequency questionnaire assessment. Low-grade albuminuria, evaluated using UACR from spot urine samples, was defined as high normoalbuminuria (UACR: 10-29 mg/g) or microalbuminuria (UACR: 30-299 mg/g).

Results: Median NEAP was 43.3 (interquartile range: 34.2, 53.4) mEq/d in men and 35.1 (27.7, 43.7) mEq/d in women. Median UACR and eGFR were 9.6 (5.0, 22.0) mg/g and 73.8 (64.1, 84.3) mL/min/1.73 m^2 in men and 13.0 (7.2, 25.0) mg/g and 73.7 (64.7, 83.7) mL/min/1.73 m^2 in women, respectively. High normoalbuminuria and microalbuminuria were found in 976 and 616 men and 1,449 and 703 women, respectively. After adjusting for potential confounders, such as diabetes mellitus, the odds ratio of the highest versus lowest NEAP quartile for the presence of high normoalbuminuria and microalbuminuria was 1.28 (95% CI: 1.04–1.58) in men and 1.34 (95% CI: 1.08–1.65) in women. Among the subjects without microalbuminuria, the odds ratio of the highest versus lowest NEAP quartile for the presence of high normoalbuminuria was 1.21 (95% CI: 0.96–1.53) in men and 1.30 (95% CI: 1.04–1.63) in women.

Conclusions: NEAP score was associated with the presence of low-grade albuminuria in a Japanese adult population. Further studies are needed to confirm whether dietary acid load influences the development and progression of albuminuria.

SA-PO1038

A Diet Rich in Vegetables and Fruits and Incident CKD: Community-Based Prospective Cohort Study

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Background: A diet rich in vegetables and fruits can lower blood pressure (BP) and reduce cardiovascular risk. However, it is unknown on the association between this diet and incident chronic kidney disease (CKD) in general population.

Methods: Using the database from the Korean Genome and Epidemiology Study, we analyzed 9487 subjects with normal renal function. Habitual diet survey was performed using a validated food frequency questionnaire at baseline. The study subjects were classified into tertiles according to the consumption of raw and fermented vegetables, and fruits. The primary outcome was incident CKD defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The secondary endpoint was incident proteinuria determined by dipstick test ≥ 1+.

Results: At baseline, BP, C-reactive protein levels and estimated net endogenous acid production were significantly lower in the highest tertile of raw vegetable intake. During a mean follow-up of 8.2 years, 1741 (18.4%) subjects had incident CKD. Compared to the lowest tertile of raw vegetable intake (19.3%), CKD occurred less in the middle (18.8%) and the highest (16.9%) tertile groups (P<0.001). Incidence rate of proteinuria was also lower in the latter two groups. In multivariable Cox analysis, the highest tertile of raw vegetable intake was associated with a 14% lower risk of CKD development compared to the lowest tertile (P < 0.001). The highest tertile also conferred a 28% lower risk of proteinuria development than the lowest tertile (P < 0.001). There were no associations between fermented vegetable and fruit intake and CKD development. However, both highest tertiles of fermented vegetable and fruit intake were associated with 14% and 45% lower risk of incident proteinuria compared to the lowest tertiles, respectively (P < 0.001 for both).

Conclusions: This study suggests that a diet rich in vegetables and fruits may have beneficial effects on the prevention of kidney disease.

SA-PO1039

Comparison of Mixed-Based vs Animal-Based Low Phosphorus Diet on Hyperphosphatemia in Dialysis Patients: Randomized Clinical Trial

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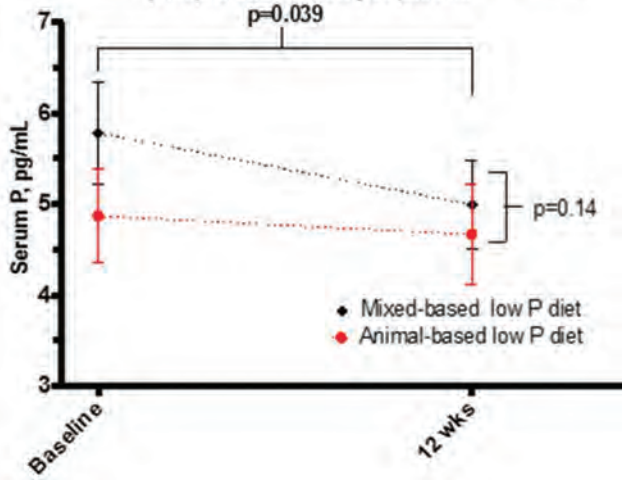
Background: Dietary P restriction is major component of hyperphosphatemia treatment in dialysis. Bioavailability of vegetable and animal P sources is not taken in consideration. KDIGO recommends to conduct clinical trials with different sources of dietary P. Aim:assess the effect on serum P of 2 low-Pdiets(<1000mg/day;Animal Vs.vegetal+animal) in dialysis patients.

Methods: Randomized, multicenter, open-label clinical trial. Subjects on dialysis for>6 mo and P>4.5mg/dL were randomized into a mixed-based(3oz equivalent animal protein+3oz equivalent legumes)vs.animal-based(6oz equivalent animal protein) low P diet with equivalent nutrients (protein=1.3 g/kg/d). Primary outcome was the change in serum P after 12 wks. We excluded patients who modified their dialysis dose, phosphate binder or vitamin D prescription during trial.

Results: 56 subjects(38HD,18PD) were randomized. Age, sex, phosphate-binders use and other baseline characteristics were similar between groups. Baseline P values were 5.6±1.6 and 4.9±1.2 in mixed-based and animal-based groups respectively(p=0.06). Mixed-based group had a significant decrease in P after 12 wks of intervention(5.6±1.6 to 5.0±1.3, p=0.04). Animal-based group did not change P significantly(4.9±1.2 to 4.7±1.4, p=0.46). Serum P in the mixed-based and animal-based declined by -0.66(95%CI:-1.39 to -0.04)mg/dL and -0.21(95%IC:-0.81 to 0.38) respectively(p=0.14, Fig). There were no differences between groups in the change of other biochemical parameters.

Conclusions: Dietary P restriction with animal or mixed-based P sources had a similar efficacy to achieve and maintain P concentration in dialysis. Mixed-based group had a non-statistically significant trend to achieve a higher decrease in serum P.

Figure. Serum P changes after *mixed-based* Vs. *animal-based* low phosphorus diet in dialysis patients



SA-PO1040

Effect of Low-Protein Rice on Progression of CKD

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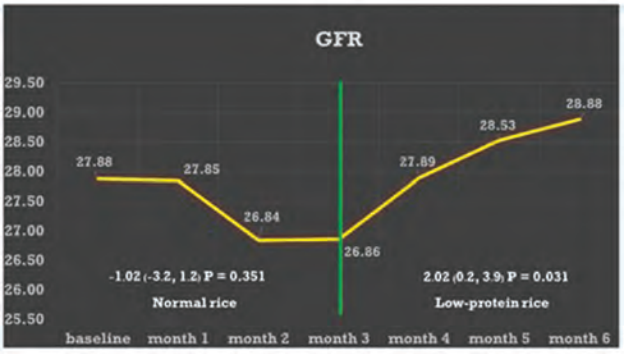
Background: CKD is a worldwide public health problem. Protein restriction is effective in slowing the progression of kidney disease. Rice is the main staple foods in Thailand. However, besides carbohydrates, rice also consists of low biological value proteins. Since it is not easy to control dietary protein intake in patients who eat normal-protein rice(protein content 8g/rice100g), low protein rice(protein content 1.6g/rice100g) has been developed to counter these problems. As it is, the data on low-protein rice's effect on CKD progression is limited. This pilot study was done to determine the impact of low-protein rice on CKD progression.

Methods: This involved a controlled before-and-after study in patients with stage 3-4 CKD who had protein intake of> 0.8 g/kg/day. The study covered a total duration of 6 months: the first 3 months when patients ate normal-protein riceand the second 3 months when they ate low protein-rice. All patients received multidisciplinary team care and were advised to have 0.6-0.8 gram/kg/day of protein intake along the study.

Results: 32 patients were included in this study. Majority of patients were male (56.3%): 62.5% have diabetes and 81.3%have CKD stage 4. Mean age of patients is 55.9 years. After eating low-protein rice for 3 months, we noted that the GFR increased from baseline by 2.0 ± 3.1 ml/min/1.73m^2(P=0.031). The nPNA reduced from baseline by 0.1 g/kg (95%CI: -0.2, 0.1, P = 0.04). In addition, eating low-protein rice significantly decreased waist circumference.

Conclusions: Low protein-rice has an impact on improving kidney function. It is also helping patients controlling dietary protein intake and improved there's body composition. Further studies are required before applied to all CKD patients who eating rice as a main cultural cuisine.



SA-PO1041

Dietary Pattern Modifies the Association of APOL1 Variants with CKD: The Jackson Heart Study

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Background: Apolipoprotein L1 (*APOL1*) variants are associated with increased risk of chronic kidney disease (CKD), however, not everyone with high risk *APOL1* genotypes develops overt kidney disease. We evaluated the modifying effects of dietary pattern on the association between *APOL1* risk variants and prevalent CKD among African Americans (AAs).

Methods: We conducted a cross-sectional analysis of 2,841 AAs from the Jackson Heart Study (JHS) with genotyped *APOL1* variant data. Three dietary patterns, designated "southern", "fast food" and "prudent" were derived from a validated regional specific food frequency questionnaire (Deep South) using factor analysis. The factor scores for each pattern were divided into tertiles labelled low, moderate and high levels, respectively. CKD was defined at baseline as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. First, we assessed the association between *APOL1* Variants and prevalent CKD using multivariate logistic regression model, controlling for demographic, clinical factors to and population stratification. We then added diet and *APOL1* x diet interaction terms to assses the effect modification of each diet pattern.

Results: The mean (± standard deviation) age of included participants was 55±13 years, 62% were female, 5.5 % had CKD. Of the total participants studied, 13% had two *APOL1* risk variants. We observed that the models accounting for *APOL1*× diet interactions fitted the data significantly (P<0.001) better than the main effects model. In multivariable adjusted main effects model, two *APOL1* risk variants were significantly associated (Odds Ratios, OR [95% confidence Interval, CI]; p-value) with prevalent CKD 1.87 (1.16-2.96); p=0.0102. In individuals consuming high levels of fast food diet, 2 *APOL1* risk variants were significantly associated (OR, 95% CI) with greater odds, 3.66 (1.43, 9.39), p=0.007 of prevalent CKD compared to low and moderate levels of fast food diet (Figure 1). Similarly, in individuals consuming high levels of southern diet, the OR were 2.92 (1.16, 2.96); p=0.02.

Conclusions: In a large community-based study of AAs, all dietary patterns studied modified the association between *APOL1* two-risk alleles and increased CKD prevalence.

Funding: Other NIH Support - NHLBI

SA-PO1042

Dietary Protein Intake, Protein Energy Wasting, and Progression of CKD

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Background: There have been a paucity of literatures regarding on the effect of dietary protein intake (DPI) on the progression of chronic kidney disease (CKD), in conjunction with the potential hazard of protein-energy wasting (PEW).

Methods: The database of a large-scaled multicenter prospective study in Korea of 2238 patients enrolled from 2011–2016 was reviewed. After excluding 319 with missing data to define DPI and PEW, and 347 with collecting 24-hour urine incompletely, the study included 1572 non-dialysis CKD patients. CKD progression was defined by a >50%

estimated glomerular filtration rate (eGFR) decline, serum creatinine doubling, or dialysis initiation.

Results: During mean 41.6 months' follow-up period, 296 CKD patients (18.8%) progressed. Cross-sectionally, increased DPI was significantly associated with increased eGFR. Similarly, increased DPI tertile was significantly associated with increased renal survival in Kaplan-Meier curve analysis (Log-rank P <0.001). In multivariate Cox proportional hazard regression analysis, the hazard ratio (95% confidence interval) of the third vs. first tertile was 0.685 (0.495-0.948, P = 0.022). However, the statistical significance of DPI tertile group on CKD progression was lost when variables related to PEW were added as covariates. In penalized spline curve analysis, the adjusted odds ratio of PEW was significantly increased as DPI increased.

Conclusions: DPI per se was not a major determinant of CKD progression. Instead, intimate association between reduced DPI and PEW may be more important than DPI per se to predict CKD progression.

Funding: Government Support - Non-U.S.

SA-PO1043

Prevalence and Impact of Food Insecurity in Children with ESRD

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Background: Food insecurity (FI) affects 1 in 6 children in America. Children with kidney disease, especially those with End-Stage Renal Disease (ESRD) may be at higher risk, due to their complex care needs, medication burden, and dietary restrictions. Adults with kidney disease and FI progress more quickly to ESRD. The prevalence and impact of FI in pediatric ESRD patients is largely unknown. We sought to determine the prevalence of FI among children with ESRD receiving dialysis and to examine the relationship between FI and clinical factors, healthcare utilization, and quality of life.

Methods: We assessed food insecurity among families of dialysis patients age <21 years seen for ESRD at an academic pediatric center. The primary predictor was household FI status, determined using the Hunger Vital sign, a validated 2 question-screening tool. We compared demographic features, clinical factors, and outcomes including health care utilization between families identified as FI versus those not. We defined unplanned healthcare utilization as unscheduled admission to the hospital, Emergency Department visit, or dialysis related infection.

Results: A total of 43 families were enrolled in this study; 24 (55%) were on peritoneal dialysis (PD) and 19 (45%) were on hemodialysis (HD). 27 of 43 (65%) of children with ESRD lived in food insecure households, with a larger percentage of children on HD reporting FI compared to those on PD (73.7 vs. 54.2%). Food insecure children were more likely to have an unplanned healthcare utilization event (96.3 vs. 75.0%, p = 0.035), including hospitalization (p=0.008) and intensive care unit admissions (p=0.03). Children with FI had a trend towards more dialysis related infections (48.1 vs. 25.0%). Clinically, children with FI were less likely to have adequate Kt/V for the last 3 months (63.0 vs. 93.4%, p=0.03). Both child and parent proxy quality of life scores tended to be lower in those with FI on all subscales, particularly the worry subscale.

Conclusions: FI is common among children on dialysis therapy and negatively impacts clinical care, healthcare utilization, and quality of life. Further exploration into how FI and other social determinants of health influence management of and impact outcomes for children with ESRD is warranted as are interventions to decrease rates of FI.

Funding: NIDDK Support

SA-PO1044

Association Between Estimated Protein Intake and Single-Nephron Glomerular Filtration Rate in Healthy Adults

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Background: High protein intake can increase renal plasma flow and glomerular filtration rate (GFR) in response to excretory overload, which may exacerbate kidney disease progression. Glomerular hypertrophy has been shown to be closely associated with sclerosis at the level of a single nephron in experimental models. However, the mechanisms by which an excessive protein diet causes glomerular hyperfiltration and increases single-nephron GFR (SNGFR) have not been fully elucidated in humans. The present study aimed to calculate SNGFR by estimating the number of nephrons in living kidney donors and to evaluate the clinicopathological findings associated with SNGFR.

Methods: We identified 33 living kidney donors with a normotensive status who underwent enhanced computed tomography (CT) and kidney biopsy at donation in the Jikei University School of Medicine Hospital from 2007 to 2017. The number of nephron was calculated according to the cortical volumes of both kidneys as assessed on CT and the 1-hour post-transplant renal biopsy-determined glomerular density. Effective renal plasma flow (ERPF) was assessed as ^{99m}Tc-MAG3 clearance, and SNGFR was calculated as the 24-hour creatinine clearance (24hCCr) divided by the total number of non-sclerosed glomeruli. The sodium intake and protein intake of the donors were estimated through a 24-hour urine collection test.

Results: Among the 33 subjects, 13 (39.3%) were males, and the mean age was 53.7 ± 8.7 years. Additionally, the mean arterial pressure (MAP) was 84.4 ± 9.2 mmHg, and the mean 24hCCr was 112.8 ± 25.5 ml/min/1.73 m^2. Urinalysis findings were normal. The estimated total nephron number was 698,308 ± 218,740/kidney, and the mean SNGFR was 90.3 ± 33.7 nl/min/1.73 m^2. SNGFR was strongly and directly associated with the estimated sodium and protein intake (EPI) (P = 0.0365 and 0.0048, respectively) but was not associated with the donor age, BMI, MAP, ERPF, glomerulosclerosis index, or tubular injury level. Interestingly, SNGFR was only associated with EPI as assessed by multivariate analysis.

Conclusions: In healthy adults, we noted a strong positive correlation between SNGFR and EPI. Our study findings indicate that high protein intake might increase SNGFR and cause glomerular hyperfiltration.

SA-PO1045

Dietary Phosphorus and Protein Intake in a Diverse Cohort of Hemodialysis Patients

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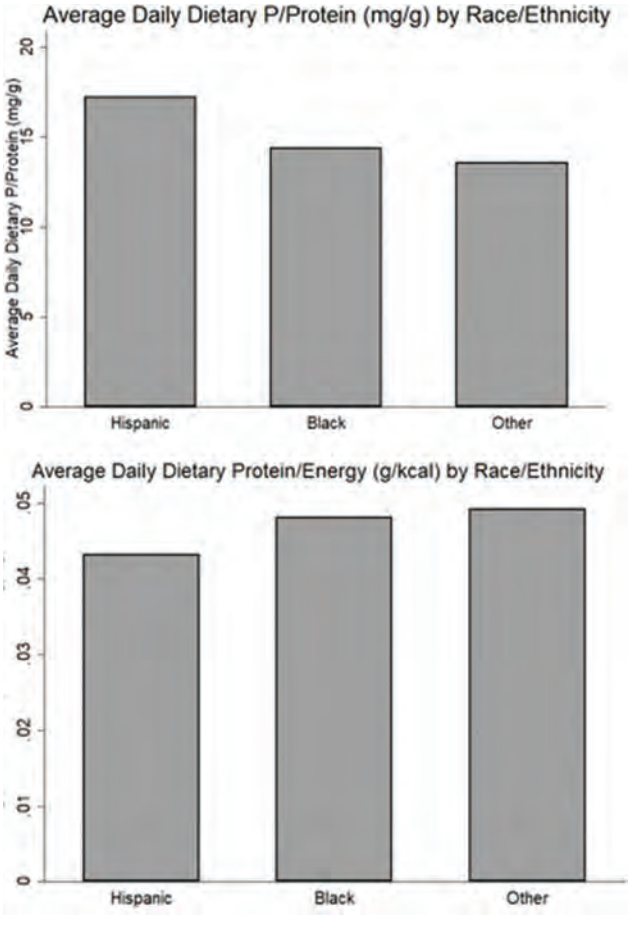
Background: We sought to determine whether dietary phosphorus (P) and protein intake in hemodialysis (HD) patients varies across race/ethnicity.

Methods: We identified 407 patients from the "Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease" (MADRAD) study, a racially/ethnically diverse prospective hemodialysis cohort who underwent food frequency questionnaire assessment. We compared baseline daily dietary intake of P, protein, and ratios of P/protein, P/kcal, as well as protein/kcal across racial/ethnic groups using one-way ANOVA and Bonferroni post hoc analyses.

Results: Blacks had the highest average daily intake of dietary P (882.7±765.7mg) and protein (62.8±54.5g), while patients of other race/ethnicities had the highest ratio of protein/kcal (0.049±0.01g/kcal). The differences in P/protein intake across racial/ethnic groups were significant, such that Hispanics had significantly higher ratios than Blacks and others: 17.2±5.3, 14.4±2.7, and 13.6±2.9mg/g, respectively; p<0.01. Hispanics also had the highest ratio of P/kcal (0.71±0.16mg/kcal). The differences in dietary protein/kcal ratios across racial/ethnic groups were also significant, such that Hispanics had significantly lower intake than Blacks and those of other race/ethnicity: 0.043±0.01, 0.048±0.01, 0.049±0.01, respectively; p<0.01.

Conclusions: These data suggest that, compared to other racial/ethnic groups, Hispanic HD patients' dietary P intake relative to protein intake is higher, whereas their dietary protein intake relative to their total caloric intake is lower. Further studies are needed to determine the specific dietary sources of P among HD patients of varying race/ethnicity, and whether these variations may have a differential impact on their health and survival.

Funding: NIDDK Support



SA-PO1046

Safety and Impact of Low Protein Diet and Ketosteril Before ESRD

Chih-Hsiang Chang. *Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

Background: Low protein diet with ketoacid analogue supplement (LPD-KA) remained under employed in patients with chronic kidney disease (CKD) because of safety issue and low compliance. This study aims to evaluate the sepsis and cardiovascular outcome in patient who received LPD-KA before end stage kidney disease (ESKD).

Methods: The study analyzed encrypted datasets from Taiwan's National Health Insurance Research Database. The exposure group was the patients received LPD and ketoacid analogue over 6 months before ESKD and the comparison group was patients who did not received LPD. Outcomes included mortality cardiovascular event, sepsis and in follow up.

Results: The data of 2607 patients in the LPD group and 10428 propensity score matched patients without LPD between January 1, 2001 and December 31, 2013 were analyzed. Patients on LPD-KA had lower mortality (23.1% vs. 27.6%; hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.70-0.84), lower composite cardiovascular events (19.2% vs. 21.5%; HR 0.86, 95% CI 0.78-0.94), and sepsis death (6.6% vs. 8.5%; HR 0.74, 95% CI 0.63-0.87).

Conclusions: LPD might be a safe therapy for patient of CKD. Overall mortality, cardiovascular event and sepsis death are less in LPD-KA group.

SA-PO1047

Diet and Renal Function in the ELSA-Brasil Cohort: A Mediation Analysis

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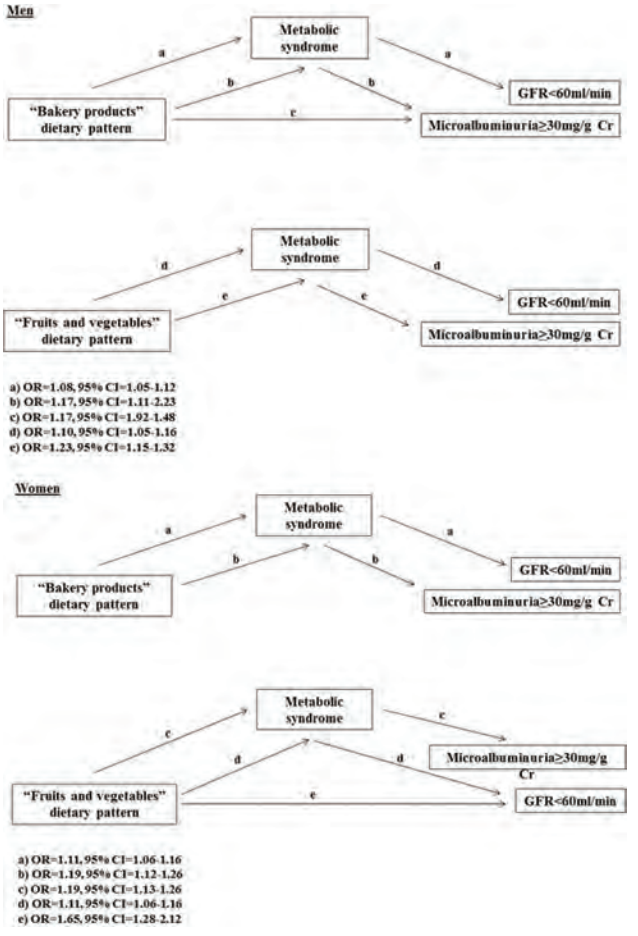
Background: Previous studies suggest the influence of diet on renal function. The aim of this study was to investigate the associations between diet and renal function among adults in Brazil.

Methods: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is the largest cohort study in Latin America, with 15,105 participants from 6 cities in Brazil. We have identified 4 dietary patterns in this cohort: 1) Traditional Brazilian, 2) Low sugar/low fat, 3) Fruits and vegetables, and 4) Bakery. Renal function was based on microalbuminuria and glomerular filtration rate (GFR) estimated through CKD-EPI formula. Association between dietary patterns and renal function was investigated through mediation analysis.

Results: Participants mean age was 52±9 years, with 54% female. Dietary patterns found were: traditional (45.7%), fruits/vegetables (25.5%), bakery (24.4%), low sugar/low fat (4.3%). For men, the patterns "bakery" and "fruits and vegetables" had significant effects on GFR and microalbuminuria. The "fruits and vegetables" pattern had only indirect effect on both GFR and microalbuminuria. For women, the "bakery products" pattern presented total effect on GFR and microalbuminuria. The "fruits and vegetables" pattern had the same effect, except for also presenting direct effect on GFR without adjustment (Figure 1).

Conclusions: There is association between dietary patterns and renal function. The "bakery" diet seem to have negative effect on renal function. The "fruits and vegetables" pattern have association with renal function possible due to epidemiological reverse causality effect.

Funding: Government Support - Non-U.S.



SA-PO1048

Nutritional Assessment in Dialysis Patients: Are We Missing Something from Subjective Assessment?

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Background: Malnutrition is very common in dialysis patients and is associated with increased mortality and morbidity. It is not clear whether subjective assessment can accurately identify malnourished dialysis patients. Also, handgrip strength and body composition analysis are not incorporated in nutritional assessment scoring system.

Methods: Nutritional assessment was carried out by subjective and objective parameters on subjects undergoing thrice a week maintenance hemodialysis. Subjective assessment was done using Subjective Global Assessment (SGA) and Dialysis Malnutrition Score (DMS). Objective assessment was done using handgrip strength and body composition analysis. Subjects with albumin less than 3.5 g/dl were considered as malnourished. Handgrip strength analysis was performed by handgrip dynamometer (CAMRY, model EH101) while body composition analysis was performed by Body Composition Monitor (BCM) (Fresenius Medical Care).

Results: Nutritional assessment was conducted on 81 subjects (46 males and 35 females) undergoing thrice a week hemodialysis. The average age was 54.8 ± 12.7 years and average BMI was 24.8 ± 4.3. The average serum albumin was 3.2 ± 0.3 g/dl. Malnutrition was observed in 76.5% subjects by albumin <3.5 g/dl criteria. On subjective assessment, 55 % and 69.3% subjects were found to be malnourished by SGA and DMS scores respectively. Handgrip strength and BCM (objective assessment), categorized 89% subjects as malnourished.

Conclusions: Subjective assessment is not accurate in identifying malnourished dialysis patients. Simple, bedside tools like handgrip strength and body composition monitor may help to better characterize nutritional assessment and early intervention in dialysis patients.

SA-PO1049

Use of Medical Nutrition Therapy Is Low Among US Veterans with Stage 3-5 Non-Dialysis Dependent CKD

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Background: Once chronic kidney disease (CKD) is established, dietary modifications such as decreasing intake of animal protein and salt and increasing intake of fresh fruits and vegetables may slow CKD progression. However, dietary modifications require patient education and close monitoring due to risks of malnutrition and hyperkalemia. Medical Nutrition Therapy (MNT), the individualized nutrition assessment, care planning and dietary education provided by a registered dietitian nutritionist remains an effective intervention for slowing CKD progression and delaying end-stage renal disease (ESRD). We examined MNT utilization among U.S. Veterans with established non-dialysis dependent stage 3-5 chronic kidney disease (CKD-ND) during calendar year 2015. We hypothesized that utilization of MNT may be low and requires more attention.

Methods: We used data from the VA Corporate Data Warehouse which includes demographics, inpatient and outpatient encounter diagnosis and procedure codes and Current Procedural Terminology (CPT) codes] and patient labs. Since a percentage of Veterans receive their care from non-VA sources, we linked data from the Center for Medicare & Medicaid Services Medicare administrative databases to capture non-VA health care use. CKD status was based on presence of at least two estimated glomerular filtration rate (eGFR) values < 60 ml/min/1.73 m^2 in outpatient laboratory data spaced 90+ days apart.

Results: There were 242,865 Veterans age ≧50 years with at least two eGFR <60 ml/min/1.73 m^2 spaced 90+ days apart during calendar year 2014 with no history of dialysis or transplantation. Mean age was 76.4 years (standard deviation 9.6) and 96.7% were male and most were white with 14.9% reporting black race. During calendar year 2015, only 9.6% of Veterans with stage 3-5 CKD-ND saw a VA dietician and 0.1% saw a Medicare reimbursed dietician. MNT utilization overall was significantly higher among black vs. whites (13.9% vs. 9.0%, p<0.001). Only 1.7% of Veterans with stage 3-5 CKD-ND were enrolled in the VA MOVE! program designed to increase exercise.

Conclusions: Utilization of MNT is very low in U.S. Veterans with stage 3-5 CKD-ND. Increasing utilization of MNT for patients with CKD-ND should be a priority for health systems in order to delay ESRD.

Funding: Veterans Affairs Support

SA-PO1050

Temporal Changes in Nutritional Markers and Their Association with Mortality in Non-Dialysis Dependent CKD

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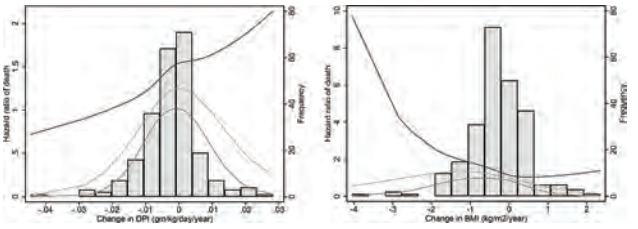
Background: The pathophysiology of protein-energy wasting (PEW) involves both decreased nutrient intake and increased catabolism. The temporal changes of different PEW components and their association with mortality in CKD are not well characterized.

Methods: We examined 234 US veterans with CKD stages 3-5. We assessed serially body weight (BW)/body mass index (BMI), and spot urine urea nitrogen creatinine ratio to estimate 24-hour urine urea nitrogen excretion and daily protein intake (DPI) using the Maroni formula. We estimated the slopes of DPI, BMI and eGFR vs. time in mixed effects models. The association of the slopes of DPI and BMI with all-cause mortality was examined in Cox models adjusted for age, gender, race, diabetes, eGFR and baseline DPI and BMI, respectively.

Results: Patients were 68.6±9.5 years old, 97% male, 38% African-American and 41% diabetic. Mean baseline eGFR, DPI and BMI were 33.1±12.1 ml/min/1.73m^2, 0.41±0.15 g/kgBW/day and 30.3±7.1 kg/m^2, respectively. Patients had a median (25th-75th percentile) of 5 (3-8) measurements over a median follow-up time of 3.2 years, and 64 patients died (mortality rate 93/1000 patient-years, 95%CI: 73-119). Patients experienced modest but statistically significant decreases in eGFR and BMI over time, but no significant average change in DPI (Table). The slope of DPI was not associated with multivariable adjusted mortality risk (p=0.3), while increase in BMI was associated with a trend towards lower mortality (p=0.1, Figure).

Conclusions: Patients with moderately advanced CKD and relatively stable kidney function experienced small changes in BMI and stable protein intake over time. These modest changes in nutritional markers showed no association with all-cause mortality. Larger studies with longer follow-up are needed to better assess the effects of declining kidney function on different PEW components, and the effects of these changes on survival.

	Slope (95%CI)
eGFR (ml/min/1.73m2/year)	-2.09 (-2.84, -1.34), p<0.001
DPI (gm/kgBW/day/year)	-0.0024 (-0.0096, 0.0048), p=0.5
BMI (kg/m2/year)	-0.28 (-0.45, -0.11), p=0.001



SA-PO1051

Efficacy of Segmental Bioelectrical Impedance Analysis in Regular Nutritional Assessment in Autosomal Dominant Polycystic Kidney Disease

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Background: Increased risk of malnutrition in autosomal dominant polycystic kidney disease (ADPKD) are found in patients with declined renal function and/or large abdominal cystic organ volume. Therefore regular nutritional assessment are important in ADPKD patients. Increased ratio of extracellular water to total body water (ECW/TBW) and decreased phase angle (PhA) are known malnutrition marker of bioelectrical impedance analysis (BIA). In this study, we analyzed the efficacy of BIA in the nutritional assessment follow-up compared to modified subjective global assessment (SGA) in ADPKD patients.

Methods: This is a prospective cohort study undertaken at a tertiary university hospital. Nutritional status were assessed with SGA and segmental BIA (Inbody S10) at the two visits of outpatient clinic between Dec. 2013 and Mar 2018. Height adjusted total kidney volume (htTKV) were calculated using ellipsoid method from CT scans of two visits.

Results: Total 135 patients were analyzed and 46.7% were female. At the initial visit, the mean age was 48.1±10.2 years and the mean eGFR was 62.8±21.7 mL/min/1.73m^2. The median values of htTKV were 801 mL/m (IQR 495–1185 mL/m). Interval between two visits were 28.5±4.4 month. Between two visits, eGFR decreased (62.8±21.7→56.4±23.5 mL/min/1.73m^2, p<0.001) and htTKV increased (927.4±627.8→1235.8±868.0 mL/m, p<0.001). However there were no statistical difference in SGA score (6.7±0.6→6.6±0.7), weight, body mass index, serum albumin, and cholesterol level during follow-up. Among the segmental BIA parameters, ECW/TBW of whole body (0.384±0.007→0.386±0.007, p<0.001), trunk (0.383±0.007→0.386±0.008, p<0.001) and lower extremity (0.387±0.008→0.388±0.008 p=0.015) increased significantly. The lean mass of whole body (48.4±10.67→47.8±10.6 p<0.001), upper extremity (2.7±0.8→2.6±0.8 p=0.007) and trunk (22.1±4.8→21.8±4.9 p=0.001) and PhA of upper extremity (5.3±0.6→5.1±0.7 p<0.001), trunk (9.0±1.4→7.8±1.2 p<0.001) and lower extremity (5.3±0.8→5.2±0.8, p<0.001) decreased significantly during the follow up.

Conclusions: Increased ECW/TBW level and decreased lean mass and PhA were found in ADPKD patients during follow up. Using quantitative parameters of segmental BIA, clinician were able to monitor nutritional status of ADPKD patients more sensitively, in addition to laboratory data and SGA.

SA-PO1052

Diet Dependent Systemic Acid Load (AL) Impacts Decline in Kidney Function Through Serum Albumin (SA)

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Background: Inflammation may be present with CKD and diet composition may affect inflammation thereby impacting kidney health. Higher intakes of proteins and fats yielding a higher AL have been linked with worsening of kidney function and inflammation may play a role. We investigated whether AL estimated from urine measures is associated with kidney function decline and whether the effect of AL on an inflammatory marker, SA, is a pathway to this association.

Methods: We studied 188 post-menopausal women in a clinical trial of potassium bicarbonate treatment for up to 36 months. 24-hr urine and arterialized blood collections were done at baseline and at subsequent 3 month follow-up visits. AL was estimated from the urine potential renal acid load (UPRAL), calculated using measures of chloride, phosphate, sodium, potassium, calcium, and magnesium. Mixed effects (ME) model with random-intercept and slope was used to estimate subjects' annual decline rate in creatinine clearance (CrCl) and eGFR. We used the ME model to estimate the association between (1) UPRAL and SA, and (2) SA and CrCl, adjusting for age, body mass index, systolic BP, and glucose. A Cox proportional regression model was used to study the relative hazard for decline in CrCl with UPRAL, adjusting for potential covariates and baseline CrCl. Our models were repeated with eGFR decline as the outcome.

Results: A 25 mEq/day increase in UPRAL was inversely associated with SA (95% CI:–0.01[–0.09;-0.0001; p=0.05]). SA was inversely associated with CrCl (p<0.05). During 28 months mean follow-up, 45 women (23.9%) had a rapid decline in kidney function (loss ≥5 ml CrCl/yr). For each 25 mEq/day increase in UPRAL, the risk of a rapid decline in CrCl increased by 17% (95% CI:1.06-1.28). Adjusting for potential confounders, the

risk attenuated to 5% (1.02-1.14). Mediation analysis indicated that of the total effect of the association between UPRAL and CrCl, the proportion mediated by SA was 0.32 (i.e. 32%). Using eGFR, the proportion mediated by SA increased to 0.41.

Conclusions: Higher UPRAL was associated with lower SA as well as reduced kidney function in post-menopausal women. Our findings suggest inflammatory response may exert a modulatory effect on the association of UPRAL and kidney function and might be a potential pathway to explain the effects of systemic AL on kidney function decline.

Funding: Commercial Support - Arm and Hammer

SA-PO1053

Dietary Acid Load and the Risk of Metabolic Acidosis in Prevalent Hemodialysis Patients

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Background: Metabolic acidosis is associated with protein energy wasting, bone disease, and higher mortality in end-stage renal disease (ESRD). Although higher dietary acid load can exacerbate metabolic acidosis, there is a lack of data evaluating their relationship in ESRD patients. Therefore, we investigated the association between dietary acid load and metabolic acidosis in ESRD patients undergoing hemodialysis (HD).

Methods: One hundred and eleven prevalent HD patients were included from the ESRD-Clinical Research Center (ESRD-CRC) cohort in South Korea. Dietary intake data were obtained from a self-reported food frequency questionnaire and a 7-day food diary. Dietary acid load was estimated using the equation for potential renal acid load (PRAL). Metabolic acidosis was defined as serum bicarbonate <22 mEq/L.

Results: The median value of PRAL was 9.97 (interquartile range, 4.45-14.06) mEq/day. Metabolic acidosis was observed in 47 patients (42.3%). The independent association of PRAL with metabolic acidosis was analyzed by binary logistic regression analysis. Multivariable analysis indicated that higher PRAL was significantly associated with risk of metabolic acidosis after adjusting confounding factors (per 1 standard deviation increase, odds ratio=3.258, 95% confidence interval [CI]=1.106-9.599, P=0.03). Subsequent linear regression analysis was performed to find dietary behavior factors affecting PRAL. Higher intake of processed meat including ham, sausage, or bacon, was significantly associated with increased PRAL (per 1 intake/week increase, β=0.244, 95% CI for B=0.704-9.164, P=0.02).

Conclusions: PRAL was the independent risk factor for metabolic acidosis in prevalent HD patients, suggesting deleterious effect of higher dietary acid load. Therefore, dietary counseling or intervention to reduce processed meat intake may be helpful for management of metabolic acidosis in these patients.

SA-PO1055

Comparison of Three Technology-Supported Behavioral Interventions for Phosphorus Management in Hemodialysis Patients

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Background: Behavioral methods enhance the effectiveness of lifestyle interventions, but are often resource intensive. Although mobile health (mHealth) technology can help create lower input interventions, their feasibility, acceptability and efficacy have not been adequately evaluated in hemodialysis (HD) patients.

Methods: Maintenance HD patients with persistent hyperphosphatemia (n=40) were randomized to receive: (1) educational (Edu) videos (EDU), (2) Edu + mobile self-monitoring (SM) with MyNetDiary® (MON), or (3) Edu + SM + social cognitive theory (SCT)-based behavioral counseling videos (SCT) over a 12-week period with videos for each group delivered using iPads. Serum phosphorus concentrations (sPO_4) were measured at baseline, 12 and 24 weeks, and a 5-point Likert scale survey on the mHealth technology was completed at 24-weeks. Two participants in the EDU group with no follow-up sPO_4 measurements were excluded; missing sPO_4 measurements at 12- and 24-weeks were imputed by carrying forward the most recent sPO_4 values.

Results: At the end of the intervention phase (12-weeks), there was a non-significant trend towards greater decreases in sPO_4 in the MON (-0.5±1.6 mg/dL, p=0.32) and SCT (-0.3±2.1 mg/dL, p=0.56) groups compared to the EDU group (+0.2±1.4 mg/dL), but these differences had mostly disappeared by the end of the monitoring phase (24-weeks) (EDU +0.1±1.2 mg/dL, MON -0.1±1.9 mg/dL, SCT -0.1±2.1 mg/dL). Most participants agreed or strongly agreed that the iPads were convenient (64%), and SM helped them stay motivated (68%), take binders (61%), and limit phosphorus intake (68%). Relatively few participants reported that they agreed or strongly agreed that they sometimes "got lost" maneuvering the iPad programs (24%), felt that SM wasn't worthwhile (16%), or would have preferred face-to-face meetings offsite (4%).

Conclusions: Many HD patients are willing, able and report benefits of engaging in technology-supported behavioral interventions involving SM and SCT. Although these programs are easy to disseminate with limited resources once developed, any benefits for phosphorus management in HD patients may last only as long as the intervention is active.

Funding: NIDDK Support

SA-PO1056

Association Between Healthy Diet Score and Kidney Function: A Population-Based Survey

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Background: While it is recognised that a healthy diet can reduce the risk of cardiovascular disease, dietary risk factors for chronic kidney disease remain relatively undetermined. This study aimed to assess the association between the American Heart Association's (AHA) healthy diet score and estimated glomerular filtration rate (eGFR).

Methods: The present study is a survey of random adults between 40 and 69 years-old. Diet was assessed using the NIH Diet History Questionnaire II. We determined the association between eGFR (CKD-EPI equation) and the overall AHA diet score (based on five components: fruits and vegetables, fish, fiber, sodium and sugar-sweetened beverages), using linear regression models adjusted for important confounders, including age, sex, income, education, caloric intake, smoking, physical activity, body mass index, hypertension, dyslipidemia, diabetes and cardiovascular disease. We also studied the association between eGFR and protein intake.

Results: The Diet History Questionnaire was completed by 8,128 participants. Mean age was 55.3 ± 7.7 years and mean eGFR was 86.9 ± 14.6mL/min/1.73m². Overall AHA healthy diet score was positively associated with eGFR (p<0.001), after adjusting for potential confounders (listed above). Upon analyzing individual food components, the intake of fruits and vegetables, fish and fiber were associated with improved eGFR, after adjustment for age and sex (cf. table). After further adjustment for confounders, fruits and vegetables consumption and dietary fiber intake remained significantly associated with a higher eGFR, while fish consumption was no longer significant (cf. table). Protein intake was not significantly associated with eGFR.

Conclusions: Among the five dietary components of the AHA healthy diet score, fiber, and to a lesser extent fruits and vegetables, are significantly associated with a higher eGFR in this population-based survey.

Funding: Government Support - Non-U.S.

eGFR and dietary components

	Adjusted for age & sex		Adjusted for all covariates	
	β coefficient*	P-value	β coefficient*	P-value
Fruits & vegetables	0.75	0.04	0.88	0.05
Fish	0.88	0.04	0.95	0.06
Fiber	1.42	<.001	1.32	0.002
Sodium	-0.22	0.6	-0.12	0.8
Sugar-sweetened beverages	0.30	0.5	0.74	0.13
Protein	0.003	0.6	0.006	0.6

* ml/min/1.73m2

SA-PO1057

Nutrition Information: What Resources Are Used by Patients?

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Background: It can be challenging for CKD pts to choose safe and healthy foods, partly because of complex dietary recommendations. There are many potential sources of dietary information, including physicians, other pts, dieticians, paper handouts, and the internet. Patients who are empowered and educated about food choices may be more adherent to a prescribed diet. This study surveys patient use of paper and electronic resources to learn about diet, focusing on potassium.

Methods: CKD pts were enrolled during outpatient clinic visits, given a survey assessing knowledge of potassium in foods, and preferences for dietary information sources. Pts were then provided with one handout with written information, and one handout with three investigator curated dietary websites. A second survey was administered several weeks later, reassessing pt knowledge about high potassium foods and pt preference for sources of information.

Results: N=110 responses were analyzed. Mean age was 58.8 yrs, with median 59.5 yrs, and range 28-83 yrs. The sample was 46% female, and 43% diabetic. Distribution of kidney stages were 2: 5%, 3: 50%, 4: 22%, 5: 22%. Pt percentages that were not sure, somewhat sure, and very sure that they could choose low potassium foods were 40%, 40%, and 20%, respectively. 66% of pts knew orange juice has more potassium than apple juice, 5% thought apple juice has more potassium than orange juice, and 29% were unsure. 24% knew whole wheat bread has more potassium than white bread, 38% thought white bread has more potassium than whole wheat bread, and 38% were unsure. 49% preferred paper handouts, 75% preferred internet videos or websites (answers not mutually exclusive). Preference for use of websites decreased with older age. For every 10yr increase in age, the odds of preferring websites decreased by 27% (OR 0.23, 95% CI 0.54, 0.98).

Conclusions: This sample shows variation in knowledge about high potassium foods, and variation in patient-perceived ability to choose low potassium foods. Although it was not surprising that older patients preferred paper handouts over the internet, the percentage of patients who used the internet as an information source for diet was quite high. These initial results suggest areas for improved pt nutrition education, and indicate a need for readily available and accurate paper and internet resources.

SA-PO1058

Salt-Related Knowledge, Attitudes, and Compliance in CKD on Dialysis and Heart Failure

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Background: Evidence of the adverse effect of high dietary sodium on the kidney and heart is growing. The WHO, CDC and AHA recommend consumption of <2, <2.3 and <1.5 g/day, respectively. Despite efforts, general and high-risk patient(HF and ESRD) compliance remains low. The primary aim of our study is to evaluate Na intake in HF and ESRD and correlate it with label-reading ability.

Methods: This cross-sectional study recruited patients with ESRD and HF inpatient at Staten Island University Hospital from September 2017-March 2018. A Block Sodium Screener © estimated daily Na intake and a questionnaire asked about shopping habits and label-reading proficiency with Likert scale conversion to a score(6-30). Subjects were grouped based on score, daily Na intake: <1500 mg/day or ≥1500 mg/day. Characteristics were analyzed using Student's t-test, nonparametric Mann-Whitney U test, or $\chi 2$ test then linear regression to evaluate the relationship between Na intake and score.

Results: We recruited 61 patients: 34 ESRD, 14 HF and 13 both. We found a negative correlation between Na intake and score(R= -0.49, p<0.0001, Figure 1). There was no difference in age, BMI and gender among the 2 groups. Compliant patients had less years since diagnosis(2.70 +/-1.16 vs. 5.05 +/-5.75; p=0.0205). Other variables did not show any association with Na intake(Table 1).

Conclusions: This study showed that more knowledge about salt content and better shopping habits are associated with a lower daily Na intake in high risk populations(ESRD and HF). A larger sample is needed to evaluate for patient demographic and medical characteristics associated with non-compliance to low Na diet.

Table 1: Patient characteristics

	<1500 mg/day	>= 1500 mg/day	p value
Age			
BMI			
Years since diagnosis			
Gender			
Male	67.64 (+/-11.48)	61.66 (+/-17.57)	
Female	27.36 (+/- 5.71)	28.10 (+/-7.66)	
Ethnicity	2.70 (+/-1.16)	5.05 (+/-5.75)	
White	7 (20)	35 (80)	
Black	4 (16)	21 (84)	
Hispanic	8 (19.51)	33 (80.49)	
other	1 (9.09)	10 (90.91)	
Diagnosis	2 (33.33)	4 (66.67)	
ESRD	0 (0)	3 (100)	0.2869
HF	7 (20.59)	27 (79.41)	0.7631
both	0 (0)	14 (100)	0.0205
Nursing home	4 (30.77)	9 (69.23)	0.7486
Assistance	0 (0)	2 (100)	1
Education level	2 (28.57)	5 (71.43)	0.6271
No schooling	1 (100)	0 (0)	0.0682
8th grade	0 (0)	1 (100)	1
Some high school, no diploma	1 (20)	4 (80)	0.6017
High school graduate	5 (22.73)	17 (77.27)	0.6211
Some college credit, no degree	2 (11.11)	16 (88.89)	0.0674
Trade/technical/vocational training	0 (0)	1 (100)	0.0674
Associate degree	0 (0)	1 (100)	n/a
Bachelor's degree	2 (25)	6 (75)	1
Master's degree or higher	0 (0)	3 (100)	0.6757
Marital status	6 (19.35)	25 (80.65)	1
Married	0 (0)	14 (100)	1
Single	3 (42.86)	4 (57.14)	0.3334
Widowed	1 (14.29)	6 (85.71)	0.5077
Separated/Divorced	1 (50)	1 (50)	1
In a relationship	0 (0)	7 (100)	1
Smoker	0 (0)	0 (0)	1
Drug use	0 (0)	3 (100)	0.0511
Alcohol use	3 (25)	9 (75)	n/a
Atrial Fibrillation	1 (12.50)	7 (87.50)	0.2988
Cancer	4 (17.39)	19 (82.61)	0.7383
CHF	6 (24.00)	19 (76.00)	0.1481
CAD	4 (13.33)	26 (86.67)	1
DM	4 (17.39)	19 (82.61)	1
DL	0 (0)	1 (100)	1
Depression	0 (0)	3 (100)	0.5803
Kidney transplant	11 (23.91)	35 (76.09)	1
HTN	0 (0)	0 (0)	1
Liver cirrhosis	2 (9.09)	20 (90.91)	0.717
Other PMH	5 (20.83)	19 (79.27)	0.5587
BP meds	1 (5.26)	18 (94.74)	0.4789
CCB	0 (0)	2 (100)	n/a
Loop diuretics	7 (19.44)	29 (80.56)	1
Non-loop diuretics	1 (11.11)	8 (88.89)	0.1803
Beta-blockers	0 (0)	6 (100)	0.3322
ACE inhibitor	0 (0)	2 (100)	0.5587
ARB	2 (15.38)	11 (84.62)	0.4811
Neprilsyn inhibitor/ARB	4 (22.22)	17 (77.78)	0.6269
Other	1 (25)	3 (75)	
Etiology of ESRD	5 (25)	15 (75)	
Diabetes	0 (0)	0 (0)	
Glomerulonephritis	0 (0)	2 (100)	
HTN	1 (100)	0 (0)	
Obstructive	0 (0)	7 (100)	
Systemic diseases	1 (25)	3 (75)	
Polycystic kidney disease	2 (11.11)	16(88.89)	
Other	2 (25)	6 (75)	
Unknown			
Type of CHF			
Ischemic			
Non-ischemic			

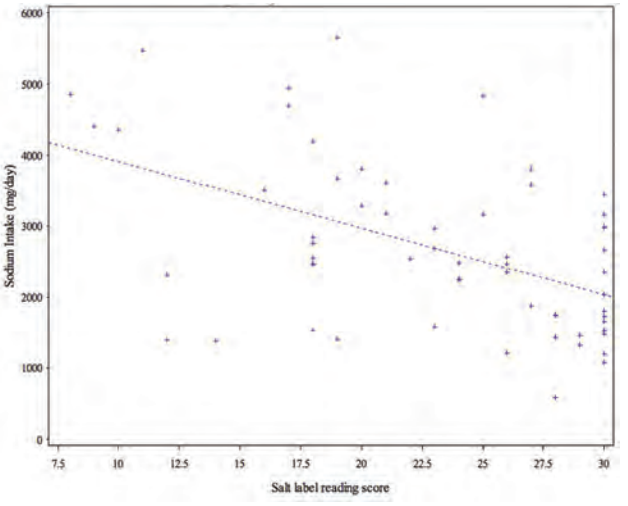

Figure 1: Relationship of Na intake and label-reading score

SA-PO1059

Long Chain Omega-3 Polyunsaturated Fatty Acids and Patient Important Outcomes in CKD: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Long-chain omega-3 polyunsaturated fatty acid (n-3 PUFA) has recognised vascular benefits in the general population, but knowledge of supplementation among patients with CKD is largely restricted to vascular access outcomes.We aimed to assess the benefits and harms of n-3 PUFA therapy in patients with chronic kidney disease (CKD).

Methods: MEDLINE, Embase, CENTRAL and reference lists were searched up to January date, 2018. We included randomised controlled trials evaluating n-3 PUFA supplementation compared with placebo or standard care on cardiovascular and all-cause mortality, progression to end stage kidney disease (ESKD), acute transplant rejection, and graft loss. Risks of bias and evidence certainty were assessed using Cochrane and Grading of Recommendations Assessment, Development and Evaluation processes, respectively.

Results: Sixty studies (n=4129), median sample size of 41 participants (interquartile range 30 to74) and median follow-up duration of 6 months (3 to 12), were included. N-3 PUFA reduced cardiovascular death (n=1,045; relative risk [95% confidence interval], 0.45 [0.23, 0.89]; moderate evidence certainty) in dialysis patients, and progression to ESKD (n=170; 0.30 [0.09, 0.98]; very low evidence certainty) in patients with moderate to advanced stage CKD. Effects on all-cause mortality (n=1876; 1.05 [0.83, 1.33]; low evidence certainty); acute transplant rejection (n=543; 0.98 [0.80, 1.21]; low evidence certainty) and graft loss (n=434; 0.98 [0.54, 1.81]; very low evidence certainty) were uncertain. Risks of bleeding (n=770; 1.40 [0.78, 2.49]) and gastrointestinal side-effects (n=1455; 1.14 [0.79, 1.67]) were uncertain.

Conclusions: N-3 PUFA supplementation may protect patients on dialysis against cardiovascular mortality. It appeared to prevent ESKD in patients with moderate to advanced stage CKD but the evidence certainty was very limited.

SA-PO1060

Impact of Dialysis Treatment Shift on Malnutrition Indicators

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Background: Malnutrition is strongly associated with morbidity and mortality among hemodialysis patients. It has been a long-term clinical concern that patients on afternoon shifts (AS) are more prone to malnutrition than those on morning shifts (MS), as their dialysis scheme and post-dialysis symptoms interfere with their meal intake. Thus, we evaluate the role of dialysis shifts on malnutrition indicators.

Methods: We conducted a retrospective study among 9.963 incident hemodialysis NephroCare patients using 2011-2016 European Clinical Database data. Linear mixed models were used to compare the course of Body Composition Monitor assessed lean and fat tissue index (LTI, FTI) between MS and AS patients over 2 years. These models included fixed effects (age, sex, vascular access, diabetes mellitus) and random effects (country, patient). Secondary malnutrition indicators were body mass index, albumin, creatinine and normalized protein catabolic rate.

Results: Patients had a mean age of 63.6 years, 41.8% were female and 29.9% were diabetic. Mean baseline LTI and FTI levels were comparable between MS (LTI: 12.5±2.9kg/m^2; FTI: 13.7±6.0kg/m^2) and AS (LTI: 12.4±2.9kg/m^2; FTI: 13.2±6.1kg/m^2) patients. During follow-up LTI slightly decreased and FTI constantly increased in both groups with a mean absolute change (baseline-24months) of -0.3 kg/m^2 for LTI and +1.0 kg/m^2 for FTI (**Figure 1**). The course of these malnutrition indicators did not differ between dialysis shift groups (*Treatment x time* interaction p-values ≥0.10). We did not observe substantial differences between groups when descriptively evaluating secondary malnutrition indicators.

Conclusions: Dialysis shift does not seem to impact long-term nutritional status of dialysis patients and may not represent a modifiable risk factor.

Funding: Commercial Support - Fresenius Medical Care

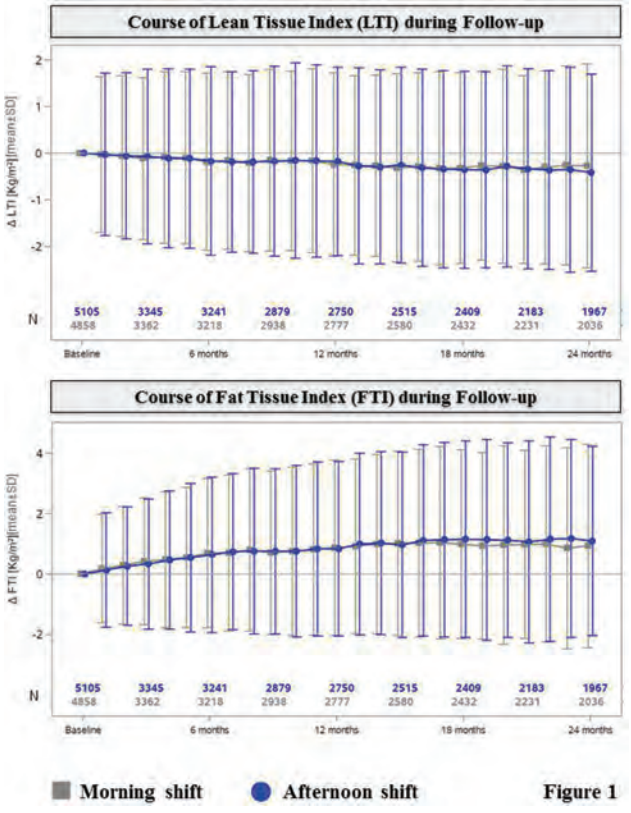

Figure 1

Table 1

	EPA treatment (+)			EPA treatment (-)		
	Baseline	End of the study (5-year)	P	Baseline	End of the study (5-year)	P
EPA (μg/ml)	65.6±30.5	250.0±66.2	<.05	65.9±25.8	62.1±24.6	N.S.
EPA/AA	0.38±0.15	1.47±0.46	<.05	0.38±0.15	0.36±0.15	N.S.
TG (mg/dl)	215.2±104.1	137.0±45.1	<.05	187.9±67.2	202.6±98.7	N.S.
Right baPWV (cm/s)	1724.3±291.5	1596.5±203.7	<.05	1705.3±218.4	1762.3±145.0	N.S.
Left baPWV (cm/s)	1762.8±338.5	1613.4±218.9	<.05	1704.8±196.2	1775.9±124.1	N.S.
Right max IMT (mm)	0.96±0.27	0.77±0.11	<.05	0.96±0.15	0.99±0.16	N.S.
Left max IMT (mm)	0.92±0.23	0.78±0.10	<.05	0.96±0.16	0.98±0.15	N.S.
eGFR (ml/min/1.73m2)	41.1±10.3	43.9±12.6	N.S.	42.9±9.1	39.9±10.0	<.05

SA-PO1061

Eicosapentaenoic Acid (EPA) Powerfully Prevents the Progression for Both Renal Dysfunction and Atherosclerosis in CKD Patients Due to Benign Nephrosclerosis

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Background: Effect of EPA for CKD patients is not fully known. We studied the efficacy of EPA to prevent the progression of both renal impairment and atherosclerosis in CKD stage 3-4 patients due to benign nephrosclerosis (BNS).

Methods: 28 CKD stage 3-4 patients due to BNS with dyslipidemia were followed for 5years after the start of EPA treatment (EPA (+): n=20) or treatment without EPA (EPA (-): n=8). The dosage of 1800 mg/day of EPA was newly prescribed in EPA treatment group. T-cho, LDL-cho, Triglycerides (TG), eGFR, the amount of proteinuria, EPA, arachidonic acid (AA), Dihomo-gamma-linolenic acid (DGLA) and docosa hexaenoic acid (DHA) were examined. Both right and left (RL) brachial-ankle pulse wave velocity (baPWV), RL maximum carotid intima-media thickness (max IMT), RL maximum carotid plaque thickness and RL ankle-brachial index (ABI) were evaluated at before treatment (baseline), after every year and at the end of the study (5-year).

Results: EPA, EPA/AA ratio, TG. RL baPWV, and RL max IMT showed significant improvement and eGFR did not decrease at 5-year in EPA treatment group (table 1). Furthermore, both EPA and DHA levels were significantly low in eGFR exacerbation patients group (n=7) compared with the improvement group (n=13) at both baseline and 5-year in EPA treatment group. EPA treatment patients showing the highest EPA levels at baseline (EPA: 107.5±15.2μg/ml, n=5) showed significant improvement in both eGFR and baPWV compared with those with the lowest EPA levels (31.0±9.2 μg/ml, n=5). There was no difference on both plaque thickness and ABI between baseline and 5-year.

Conclusions: EPA powerfully prevents the progression of both renal dysfunction and the atherosclerotic change in CKD stage 3-4 patients due to BNS.

SA-PO1062

Effect of Intra-Dialysis Nutrients Admixture vs Conventional Intra-Dialysis Parenteral Nutrition on Nutrition Status and Inflammation in Malnourished Hemodialysis Patients

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Background: Protein/caloric malnutrition and inflammation is a major problem in long-term hemodialysis patients. Total nutrients admixture containing 80% olive oil-base intravenous lipid emulsions and low proportion of polyunsaturated fatty acids may offer several advantages such as a reduction of oxidative and inflammatory effects in end stage renal disease (ESRD).

Methods: The study was a randomized controlled trial; patients with malnourished ESRD on hemodialysis were randomly assigned into an admixture-IDPN group (n=13) and a conventional-IDPN group (n=13). Nutritional assessment, and inflammatory markers including high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were measured at baseline and 4 weeks following intervention.

Results: At the end of 4-week, nutritional parameters including serum albumin (0.41±0.18 vs 0.16±0.22, P=0.004), pre-albumin (7.88±4.6 vs. 2.01±2.63. P=0.001) and urea reduction ratio (2.92±0.76 vs 0.92±2.78, P=0.026) in the admixture-IDPN group have a significantly greater improvement than the conventional-IDPN group. The decline in serum IL-6 levels was -13.9 pg/mL larger among admixture-IDPN vs conventional-IDPN group (95% CI -20.41 to -7.4 pg/mL). The admixture-IDPN group had also higher absolute lymphocyte counts and lower hs-CRP levels after treatment, but there were no significant changes in the conventional-IDPN group. There were no statistically significant differences between the two groups in the risk of electrolytes abnormalities and adverse events.

Conclusions: Malnourished ESRD patients on dialysis receiving olive oil-base lipid emulsions and low polyunsaturated fatty acids IDPN resulted in modest improvements in nutritional status and inflammatory cytokines.

SA-PO1063

1500-Day All-Cause Mortality and Carnitine Profile in Hemodialysis Patients

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Background: Patients on dialysis are in a chronic carnitine-deficient state. This condition may be associated with abnormalities of the fatty acid and organic acid metabolisms. Carnitine is required for β-oxidation of the long-chain fatty acids; therefore, carnitine deficiency decreases the efficiency of ATP synthesis and may incur death. However, the details of this association remain unknown. We examined the relationship between β-oxidation efficiency represented by the carnitine profile and 1500-day all-cause mortality in hemodialysis patients.

Methods: The carnitine profiles of 122 hemodialysis patients were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The associations between 1500-day all-cause mortality and carnitine profile as well as the clinical backgrounds of the patients were investigated. A survival analysis was conducted by the Kaplan-Meier survival method and multivariate Cox proportional hazard analysis. The bootstrap method was performed to confirm the stability and robustness of our model.

Results: Of the 122 subjects analyzed, 111 were selected and 24 died during the observation period. Stepwise multivariate Cox regression demonstrated that diabetes state [$p < 0.001$, $\exp(\beta) = 4.981$], age [$p = 0.006$, $\exp(\beta) = 1.052$], and the acetylcarnitine/(palmitoylcarnitine+octadecenoylcarnitine)[C2/(C16+C18:1)]ratio[$p<0.001$,$\exp(\beta)=0.937$] were independent significant factors of 1500-day all-cause mortality. The bootstrap method confirmed the significance of these three factors.

Conclusions: The 1500-day all-cause mortality negatively correlated with the C2/(C16+C18:1) ratio. Improvement of the impaired β-oxidation state after L-carnitine administration may ameliorate prognosis.

SA-PO1064

Ketosteril Prolongs Predialytic Diabetic Nephropathy Patients' Survival: A Nationwide Population-Based Study

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Background: Metabolic changes in chronic kidney disease contribute to poor survival. Accumulated evidences indicate that dietary supplementation with branched-chain amino acids exerts a variety of beneficial effects in diabetic animals and humans. The aim of this study was to find out possible impact of Ketosteril supplement on survival of diabetic patients under predialysis status.

Methods: We analyzed a nationwide cohort from Taiwan's National Health Insurance Research Database, to study the long-term impact of Ketosteril supplement in predialytic diabetic nephropathy patients. We enrolled 14257 out of 1,000,000 random subjects with diabetic nephropathy and predialysis status between January 1, 2004, and December 31, 2007. Patients who ever received Ketosteril therapy after confirmation of predialysis status were defined as Ketosteril users. All patients were followed-up for 5 years after entering predialysis status. The study endpoints were all-cause mortality and occurrence of stroke, congestive heart failure, and chronic dialysis.

Results: The prevalence of Keosteril usage in diabetic nephropathy patients with predialysis status was 2.72%. The 5 yrs all-cause mortality of Ketosteril users was significantly lower than that of non-users (33.7% vs 46.5%, $p < 0.001$). After adjustment for known risk factors, the Ketosteril users had significantly lower risk for mortality (hazard ratio:0.61, 95% confidence interval: 0.50-0.75, $p < 0.001$). When further stratified according to age, hazard ratios of mortality were 0.73 and 0.49 among patients who younger and older than 70 years, respectively.

Conclusions: Predialytic diabetic nephropathy patients who received Ketosteril supplement had a significantly prolonged survival. This study suggests Ketosteril might be a therapeutic choice to prolong the survival of predialytic patients.

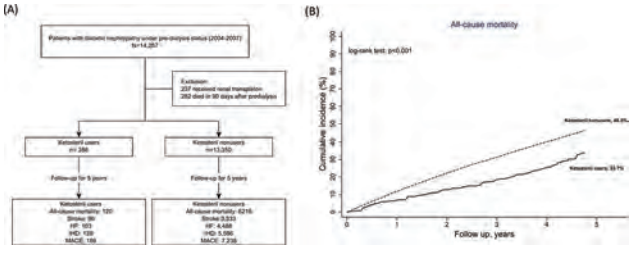

Figure 1. Ketosteril prolongs the survival of predialytic diabetic nephropathy patients. A. Taiwan's National Health Insurance Research Database study flow chart. B. 5 yrs all-cause mortality.

SA-PO1065

Adequate Protein Supplementation for Hospitalized Dialysis Patients

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Background: A high protein diet (1.2 gm/kg/day) is recommended for dialysis patients[1]. It is important for hospitalized dialysis patients to receive a high protein diet since inadequate protein intake worsens outcomes in hospitalized dialysis patients[2,3]. However, chronic kidney disease (CKD) patients who are not on dialysis may benefit from a protein restricted 'renal diet'[4]. Hospitalized dialysis patients could inadvertently receive a protein-restricted diet if placed on a 'renal diet' intended for CKD patients.

Methods: At the University of Utah Hospital, patients with CKD, including dialysis patients, were commonly placed on a 'Renal diet' that consisted of a 60 gm per day protein-restriction. The University of Utah uses EPIC software that has a template for 'Renal diet'. In order to provide dialysis patients with adequate protein, we approached the Nutrition Care Services Department with recommendations to modify this template, to allow for the option of either increasing protein supplementation for dialysis patients, or restricting protein to 60 g/day for patients with CKD but not on dialysis.

Results: In collaboration with the EPIC software team at the University of Utah Hospital, the 'Renal diet' template was modified. When placing this diet order, providers still choose a 'Renal diet' but now are required to select a modifier of either 'Dialysis' or 'Non-Dialysis'. Choosing the 'Dialysis' option provides the patient with a higher protein diet. In the 12 months preceding this template modification, providers ordered a 'Renal diet' 1594 times at our hospital. In the week following the modification, half of the 'Renal diet' orders (13 out of 26) had the 'Dialysis' modifier resulting in an appropriate higher protein diet given to dialysis patients. Modifying the EPIC template for 'Renal diet' has helped the dialysis patients admitted to our facility receive an appropriate higher protein diet.

Conclusions: We recommend that all acute care hospitals around the country examine their 'Renal diet' order templates; and modify renal diet templates, when necessary, to ensure an adequate protein diet for hospitalized dialysis patients.

SA-PO1066

Impact of Patient Awareness and Age on Serum Albumin in Chronic Hemodialysis Patients

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Background: Hypoalbuminemia is associated with cardiovascular death in patients on maintenance hemodialysis (HD) and is a marker of malnutrition–inflammation complex syndrome. In addition to dialysis adequacy, serum albumin is influenced by socioeconomic status and level of education and awareness regarding dietary requirements. The aim of our study was to identify potential factors determining hypoalbuminemia in population of prevalent HD patients in Saudi Arabia.

Methods: The study included 372 prevalent patients receiving maintenance HD at DaVita-KSA (215 female, 157 male). Mean age was 54.4 ± 17.2 years. The study population was divided into two groups based on serum albumin recorded in Feb 2018 (G1: ≤3.5 g/dL, G2: >3.5 g/dL) and parameters of socioeconomic status, food preparation/intake, and dialysis adequacy were assessed. We performed multiple logistic regression analysis to identify parameters that were independently associated with serum albumin level.

Results: There were 160 patients in G1 and 212 in G2 with no significant difference between males and females. In univariate analysis, factors found to be associated with hypoalbuminemia were: old age, low level of education, diabetes, short ESRD duration and lack of diet awareness. Patients in G2 had higher levels of serum creatinine, potassium, phosphorus, nPCR, and hemoglobin, and greater gain in dry weight. There were no significant differences between groups with respect to other socioeconomic factors or food intake. Multivariate analysis revealed that old age (RR: 1.032/year; 95% CI [1.017-1.047]) and diet awareness (RR: 1.2; 95% CI [1.0.2-1.36]), were independent predictors of hypoalbuminemia.

Conclusions: In our study, hypoalbuminemia correlated with age and level of diet compliance, which itself is determined by the education level of HD patients. Lower serum albumin is also associated with weight loss without correlation with monthly income or other socioeconomic factors.

Funding: Commercial Support - DaVita

SA-PO1067

Clinician Attitudes Toward Lowering Sodium Intake

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Background: Lowering dietary sodium (Na) intake is of utmost importance for patients with hypertension (HTN), kidney, liver, and heart disease particularly when there is evidence for fluid retention, but patient adherence to low Na diets is suboptimal. Primary care practitioner (PCP) attitudes and prescription of low Na diets can impact adherence. To understand PCP attitudes, prescription and follow up of low Na diets, we administered a brief survey.

Methods: An email 8-question survey was sent to all 234 PCPs at the Salem VA Medical Center (Salem VAMC) and at Carilion Roanoke Memorial Hospital (CRMH) clinics. Questions asked PCP attitudes towards recommending Na restriction for medical conditions including HTN, kidney disease (KD), and lower extremity edema. Survey also queried PCP processes to determine dietary adherence.

Results: We received 57 responses (41 MD/DO, 16 PA/NP) with a 45% response rate at Salem VAMC and 40% at CRMH. PCPs self-reported varied diet instruction practices (Fig 1). 54% of respondents recommend patients with KD follow a low Na diet and 45% personally instruct patients on following a low Na diet. 13% of respondents gave KD patients dietitian referrals for low Na diet instruction. PCPs mostly checked adherence by asking hypertensive patients if they follow a low Na diet (Fig 2).

Conclusions: Of PCP respondents, 46% never discuss or prescribe a low Na diet to patients that can benefit from it. Of those that discuss or prescribe a low Na diet, <20% made a nutrition referral. There is also limited effort with dietary adherence follow up. Given significant variability in PCP practices and attitudes towards low Na diet prescription, suboptimal low Na diet adherence in patients is expected. Improving low Na diet instruction at PCP level can impact key patient risks factors for renal and cardiovascular morbidity.

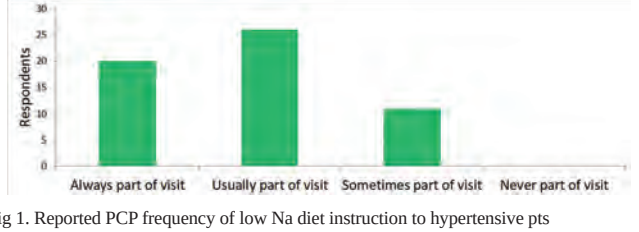


Fig 1. Reported PCP frequency of low Na diet instruction to hypertensive pts

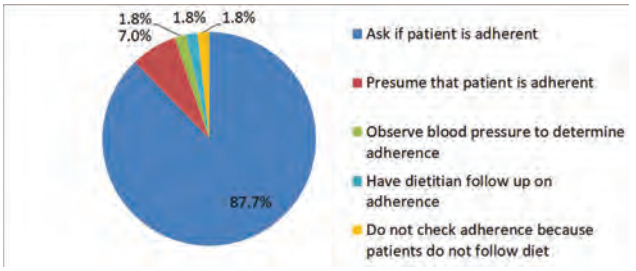


Fig 2. Self-reported methods of determining adherence to low Na diet

SA-PO1068

The Impact of Pre-ESRD Testosterone Level upon Post-ESRD Mortality Among US Male Veterans: A Transition of Care in CKD Study

Jui-Ting Hsiung,[2] Elani Streja,[3] Amy S. You,[2] Praveen Kumar Potukuchi,[4] Melissa Soohoo,[5] Danh V. Nguyen,[2] Alpesh Amin,[6] John J. Sim,[8] Csaba P. Kovesdy,[4] Kamyar Kalantar-Zadeh,[7] Connie Rhee.[1] *[1]University of California Irvine, Huntington Beach, CA; [2]University of California, Irvine, Orange, CA; [3]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN; [5]University of California at Irvine, Orange, CA; [6]UC Irvine, Orange, CA; [7]University of California Irvine, School of Medicine, Orange, CA; [8]Kaiser Permanente Southern California, Los Angeles, CA.*

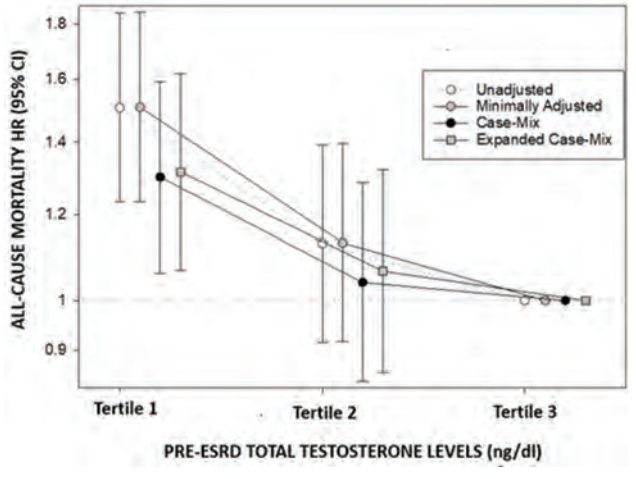
Background: Testosterone deficiency is a common endocrine complication in the elderly male population, with a disproportionately high prevalence observed in those with chronic kidney disease (CKD). While lower circulating levels of testosterone have been linked with higher risk of cardiovascular disease and death in the general population, little is known about the impact of testosterone deficiency upon the health and survival of non-dialysis dependent (NDD) CKD patients transitioning to end-stage renal disease (ESRD).

Methods: Among a national cohort of male US veterans with NDD-CKD transitioning to ESRD over 2007-15, we examined the association of total testosterone levels averaged over the two-year pre-ESRD prelude period with post-ESRD mortality risk using Cox models adjusted for sociodemographics, cause of ESRD, Charlson comorbidity score, and comorbidities.

Results: Among 1219 veterans who underwent one or more total testosterone measurements in the two-year prelude period, those in the lowest testosterone tertile had higher mortality risk in expanded case-mix models (ref: highest tertile): adjusted HR (aHR) (95%CI) 1.31 (1.07-1.62) (Figure). A similar relationship between the lowest total testosterone tertile and higher death risk was observed when measurements were examined over six-month and one-year prelude periods: aHRs (95%CI): 1.70 (1.16-2.49) and 1.46 (1.11-1.93), respectively.

Conclusions: In male US veterans transitioning to dialysis, lower total testosterone levels in the pre-ESRD prelude period were associated with higher post-ESRD mortality risk. Further studies are needed to determine the specific underlying pathways between testosterone deficiency and mortality in this population, and whether administration of testosterone replacement therapy in the pre-ESRD prelude period can improve post-ESRD outcomes.

Funding: NIDDK Support



SA-PO1069

Association Between Pre-ESRD Phosphodiesterase Type 5 Inhibitors Use and Post-ESRD Mortality

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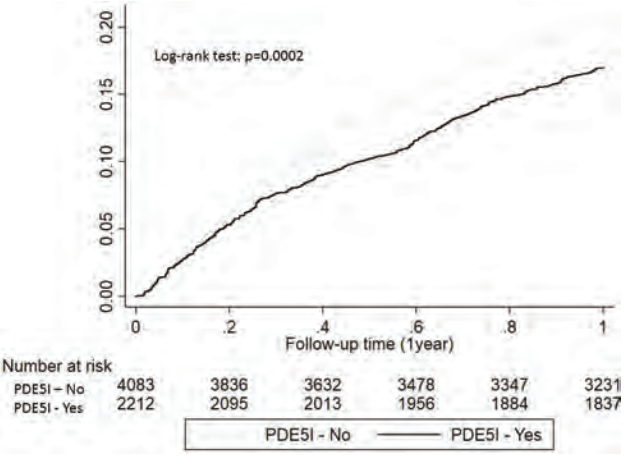
Background: Phosphodiesterase 5 inhibitors (PDE5i) are widely used to treat erectile dysfunction. Due to their vasodilatory properties, PDE5i may have systemic benefits, but information about the association between PDE5i and mortality in end-stage renal disease is lacking.

Methods: In a contemporary national cohort of 6,299 male US veterans with incident ESRD, we compared patients who received PDE5i treatment within 1 year prior to dialysis initiation to patients with a diagnosis of erectile dysfunction who did not receive PDE5i therapy. The association between PDE5i use (compared to non-use) and 1-year all-cause mortality after transition to ESRD were assessed using Cox proportional hazards models adjusted for sociodemographics, comorbidities, baseline vital parameters, and medication use.

Results: The mean age of the cohort was 65±10 years, 51% were white, 46% were African Americans, and 78% were diabetic. 2,212 (35%) patients received PDE5i treatment. PDE5i users displayed lower mortality than the non-users [Figure, unadjusted hazard ratio (95%CI): 0.80 (0.71-0.90, p<0.001)], but the survival advantage was attenuated after multivariable adjustments [0.93 (0.76-1.08, p=0.31)].

Conclusions: Pre-ESRD phosphodiesterase type 5 inhibitor use for erectile dysfunction was not associated with post-ESRD mortality. Further clinical studies are needed to study the effects of PDE5i use to determine its potential benefits in patients with ESRD.

Funding: NIDDK Support, Veterans Affairs Support



SA-PO1070

Clinical Predictors for the Incidence of Severe Acute Pyelonephritis During Antepartum Based on National Health Examination Data

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Background: Acute pyelonephritis is common during pregnancy, and increases the risk of maternal and fetal outcome. However, it has not been clearly revealed yet which demographic and clinical characteristics are associated with the incidence of acute pyelonephritis during pregnancy

Methods: Study data were collected from the Korea National Health Insurance Claims Database of the Health Insurance Review and Assessment Service. Women who had delivery between 2010 and 2014 in Korea and received health examination prior within one year of pregnancy were enrolled. A model of multivariate logistic regression analysis was performed to evaluate the risk of acute pyelonephritis during pregnancy.

Results: The mean±SD age of the overall cohort of 370,248 women was 31±4 years. The incidence of acute pyelonephritis (APN) treated under hospitalization was 2,526 patients (0.7%). In multivariate logistic regression analysis, younger age (OR 0.93 for every 5 years increase, 95% CI, 0.88-0.98), previous history of APN within one year of pregnancy (OR 9.37, 95% CI, 8.26-10.64), and abnormal results of health examination such as high fasting glucose without history of diabetes (>100mg/dL, OR 2.06, 95% CI, 1.41-2.99) and proteinuria (OR 1.81, 95% CI, 1.16-2.83) were associated with increasing risk of acute pyelonephritis during pregnancy.

Conclusions: Certain maternal demographic and clinical characteristics were associated with the incidence of acute pyelonephritis during pregnancy, and they should be monitored closely during antenatal care.

SA-PO1071

The Effects of Restricted Protein Diet Supplemented with Keto-Analogue on Renal Function, Nutritional Status, and CKD-Mineral and Bone Disorder in CKD Patients: A Meta-Analysis

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Background: The prevalence of CKD and its complications are incessantly increasing. The important strategies are how to delay the progression of CKD and postpone renal replacement therapy. Dietary protein restriction(low or very low protein diet) with or without KA supplement might slow down the rate of renal function declination without increasing the risk of malnutrition. We aimed to evaluate the efficacy and side effects of restricted protein diet supplemented with KA on the treatment of CKD.

Methods: A literature search was performed via PubMed, Scopus, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov from January 1960 to May 2018 to identify randomized controlled trials(RCTs) which explored the effects of restricted protein diet with KA on slowing progression of CKD, nutritional status, and CKD-MBD. Random-effect model was used to compute the weighted mean difference (WMD) for continuous variables.

Results: Seventeen RCTs with 1,475 participants were included in our meta-analysis. Restricted protein diet with KA supplementation significantly improved estimated GFR (WMD = 3.14 mL/min/1.73m^2 (0.68, 5.61), P=0.013), reduced proteinuria (WMD=-0.86g/d(-1.71,-0.02),P=0.046),serumphosphate(WMD=-0.68mg/dl(-1.02,-0.33), P < 0.001), parathyroid hormone level (WMD = -73.70 pg/mL(-132.79, -14.61), P = 0.015), systolic blood pressure (WMD = -4.96 mmHg (-8.03, -1.90), P = 0.002), diastolic blood pressure (WMD = -2.39 mmHg (-3.84, -0.95), P = 0.001), and serum cholesterol (WMD = -17.66 mg/dL (-33.19, -2.14, P = 0.03). Of interest, the treatment could raise serum albumin (WMD = 0.12g/dl (0.01, 0.22), P= 0.04) and serum calcium (WMD =0.50 mg/dL (0.21, 0.80), P=0.001).

Conclusions: Restricted protein diet supplemented with KA could effectively improve kidney endpoints, CKD-MBD parameters and blood pressure parameters without causing malnutrition. However, the significant increased serum calcium should be monitored.

SA-PO1072

Effects of Oral Nutritional Supplements on Clinical Outcomes and Nutritional Markers in Hemodialysis Patients Qualifying with Serum Albumin 3.6 or 3.7 g/dL

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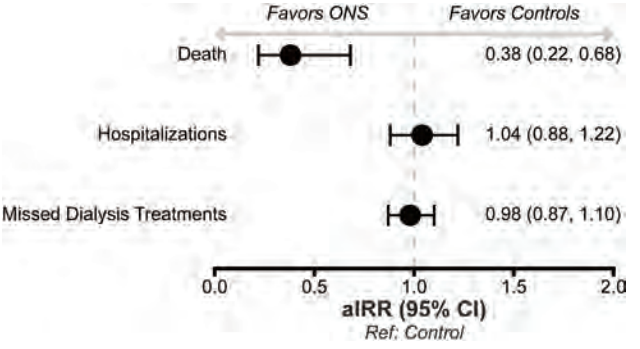
Background: Use of oral nutritional supplements (ONS) has been shown to improve clinical outcomes in dialysis patients with serum albumin ≤ 3.5 g/dL. However, there is evidence indicating patients with albumin < 3.8 g/dL are also at increased risk for death. Here, we evaluated the effects of providing ONS to dialysis patients with serum albumin 3.6 or 3.7 g/dL on clinical outcomes and nutritional markers.

Methods: This was a retrospective evaluation of a pilot program (May-Aug 2017) to provide ONS to in-center hemodialysis patients with a qualifying serum albumin measurement of 3.6 or 3.7 g/dL. ONS was provided to the patient at the time of dialysis treatment. ONS patients were matched to control patients from non-pilot facilities who had the same qualifying albumin (3.6 or 3.7 g/dL) and preceding albumin (n = 2902 per group). Clinical outcomes (death, hospitalization, missed dialysis treatments) and nutritional markers (albumin, normalized protein catabolic rate [nPCR], creatinine) were assessed over 180 days using longitudinal generalized linear models.

Results: There was a significantly lower death rate among ONS patients relative to controls (0.07 vs 0.12 per patient-year [PPY]; adjusted incidence rate ratio [aIRR] = 0.38; 95% confidence interval [CI] = 0.22-0.68). No significant differences were observed in hospitalizations (1.37 vs 1.16 PPY; aIRR = 1.04; 95% CI = 0.88-1.12), missed dialysis treatments (11.2 vs 11.4 PPY; aIRR = 0.98; 95% CI = 0.87-1.10), or nutritional markers.

Conclusions: These finding indicate that provision of ONS to dialysis patients with albumin > 3.5 g/dL could be beneficial in reducing mortality. Dialysis providers should consider expanding ONS programs to include patients with albumin <3.8 g/dL.

Funding: Commercial Support - This was a research project conducted by the DaVita Institute for Patient Safety and supported by DaVita Kidney Care



SA-PO1073

New Nutritional Risk Index on the Basis of Protein Energy Wasting for Japanese Hemodialysis Patients

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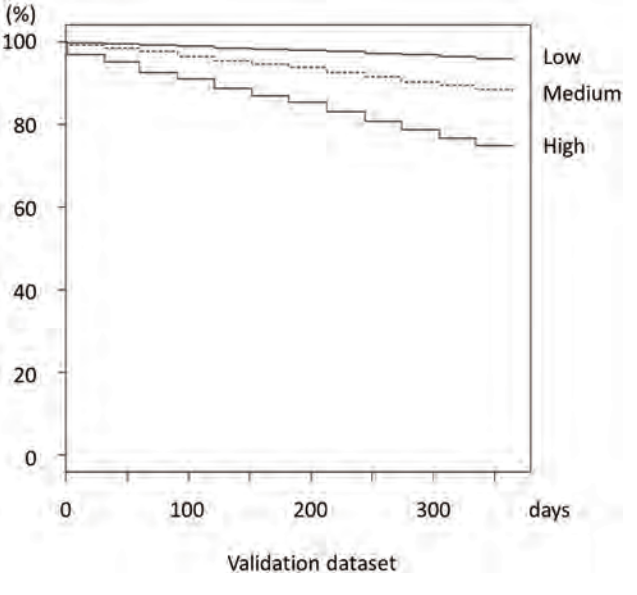
Background: Because the criteria for protein energy wasting (PEW), which is a risk factor for death, are not necessarily appropriate for Asian hemodialysis patients, we developed a new nutritional risk index for one-year all-cause death of Japanese maintenance hemodialysis patients on the basis of the concept of PEW, and evaluated their prognosis.

Methods: We analyzed data from a nation-wide prospective cohort study of the Japanese Society for Dialysis Therapy Renal Data Registry to develop and validate a nutritional risk index (n=48349, 48349, respectively). The association of nutritional factors with one-year death was tested using Cox proportional hazards models. Their cutoff levels were determined from the hazard ratios or receiver operating characteristic curves. Then, risk index was developed using scoring models.

Results: Male was 61.5 %; average age, 65.7±12.2 years; and diabetes mellitus, 32.7 %. Four clinical factors were retained in the final model: low BMI (<20kg/m2), yes=3, no=0; low serum albumin level (young <3.5g/dL; old <3.7g/dL), yes=4, no=0; abnormal serum total cholesterol level, low (<130mg/dL)=1, high (220≥mg/dL)=2, no=0; low serum creatinine level (young female, <9.7mg/dL; old female, <8.0mg/dL; young male, <11.6mg/dL; old male, <9.7mg/dL), yes=4, no=0. In the validation dataset (n=48349), medium- and high-risk groups (total score 8 to 10; 11 or more) showed a higher risk of all-cause death than the low-risk group (0 to 7): medium-risk group (10.5%), hazard ratio adjusted for baseline characteristics 1.96 (95% confidence interval 1.77, 2.16); high-risk group (8.2%), 3.91 (3.57, 4.29) (Figure 1). The medium- and high-risk groups also showed a higher risk of cardiovascular disease- and infection-caused deaths than the low-risk group.

Conclusions: We developed a new nutritional risk index for hemodialysis patients, which may be useful for identifying patients with PEW at an increased risk of death for early treatment.



SA-PO1074

Segmentation Outperforms Classification to Enumerate Glomeruli in Whole Slide Renal Biopsy Images Using Deep Learning

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Background: Accurate detection and counting of glomeruli in renal biopsies is used to assess biopsy adequacy, and for diagnosis (for example, the percentage of sclerotic glomeruli). Rosenberg et al. recently showed that standard, manual histopathology methods can under-count glomeruli by ~50% compared to more labor-intensive annotation methods. Deep learning has significantly advanced image analysis with previously impractical technologies, such as facial recognition, now possible. We have applied these advances to classification and segmentation of glomeruli. *Classification* separates small, overlapping *image tiles* into two classes [glomerulus vs. no glomerulus]. *Segmentation* separates *individual pixels* in an image into two classes [inside glomerulus vs outside glomerulus]. Segmentation is similar to masking or finding the border of a glomerulus.

Methods: Fifteen biopsy H&E stained sections were digitized with whole slide scanners (Aperio and Hamamatsu) for training and validation of the model. The outline of each glomerulus was annotated by two people using a custom application we developed. A network with 3 convolutional layers was used for classification and a 7 layer U-Net structure used for the harder problem of segmentation.

Results: The number of glomeruli per biopsy ranged from 1 to 72. Human annotators showed good agreement in the number and area of glomeruli (R^2 = 0.75 and 0.66, respectively). Classification reached an overall machine-human accuracy in cross-validation of 94% on a dataset with an equal number of positive and negative examples. However, classification on full biopsies (with more negative than positive areas) had a low precision (45%) with an overall F1 score (harmonic mean of precision and recall) of 51%. In contrast to classification, segmentation applied to entire biopsies identified glomeruli with zero false positives and an overall F1 score of 99%. Neither model's performance was altered by changes in stain intensity or the scanner used for imaging.

Conclusions: Glomeruli can be detected with high accuracy in renal biopsies using deep learning techniques; image segmentation worked better than image classification. These computational models can be leveraged to improve and automate enumeration of glomeruli, and can be adapted for classification of glomerular morphology.

Funding: NIDDK Support

SA-PO1075

Artificial Intelligence Can Classify Human Kidney Biopsy Images

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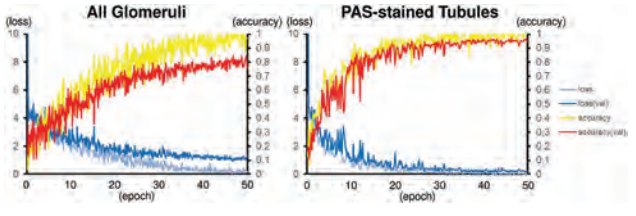
Background: Diagnosis based on kidney biopsy is a complicated decision process that includes some elements of uncertainty. Therefore, appropriate diagnoses require trained pathologists. If artificial intelligence could classify kidney biopsy images, it would be beneficial for appropriate and objective diagnosis for kidney diseases.

Methods: We obtained micrographs of PAS, PAM, or Elastica-Masson (EM)-stained human kidney biopsy samples using virtual slide system. Squared 13,017 images were manually cut out from the micrographs and then labelled into 87 (29 disease x 3 staining) categories based on diagnoses made by at least two nephrologists. We also obtained 7,177 squared tubulointerstitial images form PAS stained sections. Validation datasets were generated from the dataset by random selection. GoogLeNet, a convolutional neural network, was used to classify these images.

Results: GoogLeNet was well trained to classify glomerular images. The accuracy and loss of validation dataset were 0.7948 and 1.1301, respectively. To confirm that GoogLeNet really learned glomerular images, we prepared augmented dataset of 52,068 glomeruli which was prepared from original 13,017 squared glomerular images by 90°, 180°, and 270° rotations. We labelled these images according to disease categories and rotations. Learning of this negative control dataset yielded only 0.36866 of accuracy and 1.47506 of loss. We also examined whether GoogLeNet can classify glomerular diseases from tubulointerstitial images. Learning of PAS-stained tubular images yielded 0.9475 of accuracy and 0.2495 of loss.

Conclusions: GoogLeNet can classify glomerular diseases not only by glomerular images but also by tubulointerstitial images.



Light blue, deep blue, yellow, and red lines indicate loss of training data, loss of validation data, accuracy of training data, and accuracy of validation data, respectively.

SA-PO1076

Deep Learning for Segmentation of Glomeruli, Interstitial Fibrosis, and Tubular Atrophy in Renal Biopsies

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Background: Evaluation of the renal biopsy typically involves assessment of the renal cortical compartments, which consist of glomeruli, tubules, interstitium, and vessels. Of particular importance is the degree of what has been considered "chronic" or irreversible injury in the form of glomerulosclerosis, interstitial fibrosis and tubular atrophy (IFTA). These features are the main indicators for renal prognosis, irrespective of the etiology of renal disease. However, evaluation for such features can be imprecise and variable between experts, especially for IFTA. We have tested a deep convolutional neural network (CNN) segmentation of IFTA and glomeruli from whole slide images (WSIs) in a limited dataset of diabetic nephropathy (DN) biopsies.

Methods: Seven biopsies of patients diagnosed with DN were used. One WSI from each patient was completely annotated for IFTA and glomeruli. A Python interface was designed to accept WSI annotations from Aperio ImageScope, train a deep CNN, and perform subsequent WSI predictions. The network selected was Deeplab V2, implemented in Tensorflow.

Results: In this first study, training and testing was performed on the same 7 biopsies, due to data limitations. The deep CNN achieved significant performance on 3 out of the 7 biopsies tested, for both IFTA and glomeruli. For these cases the network achieved specificity for segmenting both IFTA and glomeruli (see Fig. 1).

Conclusions: For the first time we have shown computational segmentation of IFTA and glomeruli from renal biopsies. The Deeplab V2 system demonstrates the capability for high performance in addition to generalization to other histological compartments with an increase in dataset size. Future work will increase the training cases and implement a validation set.

Funding: NIDDK Support

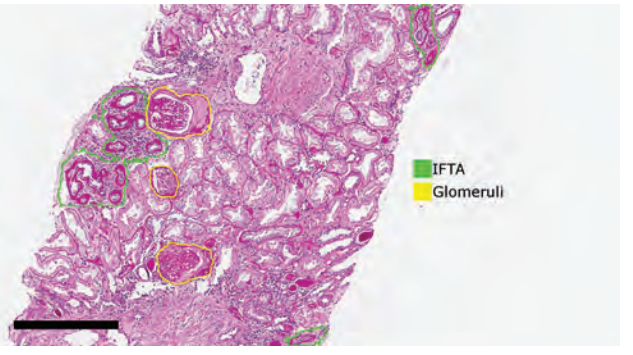

Figure 1. Segmentation of IFTA and glomeruli by deep CNN. Green outlines regions of IFTA, yellow outlines glomeruli. Scalebar is 300μm.

SA-PO1077

A Proposal of Modified Berden's Classification of ANCA-Associated Glomerulonephritis Focusing on a Proportion of Active Crescents for an Appropriate Treatment

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Background: In 2010, Berden et al. proposed the histological classification of ANCA-associated glomerulonephritis and categorized sclerotic(S), focal(F), crescentic(C), and mixed (M) classes. The validation studies confirmed the best renal prognosis for F and the worst for S. However, the results of C and M were inconsistent. Therefore, we modified the Berden's classification by focusing on a pure proportion of active crescents in each C and M from a view point of a further choice of therapy and analyzed the correlation between these subclasses and renal prognosis.

Methods: The 35 patients with MPO-ANCA-associated glomerulonephritis (male 57%, 68±7.8 yrs), who were followed more than 5 years, were analyzed. E-GFR at entry was 23.7±21.7ml/min per 1.73m^2. In the modified classification, at the first step. S, F and C or M were categorized according to the Berden's original classification. At the second step, in the category of C or M, New Crescent class (NC) was categorized by active crescents with more than 50% after eliminating global sclerosis and the rest were categorized as New Mixed class (NM), because the global sclerosis in the category of C or M did not respond to the immunosuppressive therapy. In each category, cumulative risk of ESRD (0-5 yrs) and ΔeGFR or ΔCr (serum creatinine) (0-5 yrs) were evaluated

Results: F: C: M: S were 13:5:9:8 respectively, whereas F: NC: NM: S were 13:7:7:8 respectively. Cumulative risk of ESRD (0-5 yrs) showed that F and S revealed best and worst prognosis, respectively (log rank $p<0.05$). C and M were in the middle, and the prognoses of C and M were not significantly different. However, NC and NM showed significant difference for ΔeGFR (0-5 yrs) and ΔCr (0-5 yrs). A significant cut off point of

a percent of active crescent for ΔeGFR (0-5 yrs) was 50% but not 25% or 75%. Therefore, NC showed a significant better eGFR-improvement than that of NM ($p<0.05$) indicating a better response to immunosuppressive therapy.

Conclusions: A modified Berden's classification showed clear discrimination between NC and NM and can propose an appropriate rationale for a further choice of immunosuppressive therapy.

SA-PO1078

Utility of the Modified Berden's Histological Classification of ANCA Vasculitis for a Choice of Immunosuppressive Therapy

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Background: For a rationale of the therapeutic choice for ANCA vasculitis, a quantitative assessment of the active crescents (AC) is indispensable. Since a newly proposed modified Berden's classification (Ogawa Y et al. 2018) focusses a ratio of remaining active crescents, we evaluated a utility of this classification for a choice of therapy by evaluating a correlation between this classification and the clinical profile.

Methods: The 35 patients (pts) with MPO-ANCA-associated glomerulonephritis (male 57%, 68.6 +-7.8 years old), who were followed more than 5 years were analyzed in the present retrospective study. All pts were treated according to the Japanese guideline (JSN 2011). In the modified classification, after classifying Sclerotic (S) Focal (F) and crescent (C) or mixed (M) classes with a cut-off point of 50%, New Crescent class (NC) was categorized by active crescents with more than 50% after eliminating global sclerosis and the rest was categorized as New Mixed class (NM) in the category of C or M. Clinical information including serum creatinine (sCr), eGFR and grade of hematuria (GH) at onset as well as at 5-years (yrs) after renal biopsy, and amelioration of sCr per day (ΔCr/day) were retrieved.

Results: Percent of AC correlated positively with GH ($r=0.337$, $p<0.05$), sCr ($r=0.474$,$p<0.01$), and negatively with eGFR at admission($r=-0.488$, $p<0.01$)and ΔCr/day($r=-0.420$, $p<0.05$). Moreover, 8 mL/min of eGFR was a cut off point for 5 year's renal prognosis, because 50% of the pts with eGFR more than 8 mL/min in the S showed ESRD, whereas no pts with eGFR more than 8mL/min developed ESRD in F, NC, and NM. On the other hand, 100%, 100%, 80%, and 50% of the pts with eGFR less than 8 mL/min developed ESRD in S, NM, NC, and F, respectively. ΔCr/day of the pts with NC(0.41 mg/dL/day) revealed significantly greater than that of pts with NM(0.05mg/dL/day). Cut off of the ΔCr to predict NC was ≧0.16 mg/dL/day.

Conclusions: A newly proposed modified Berden's classification together with 8 mL/min of eGFR and 0.16 mg/dL/day of ΔCr as cut-off points were useful to predict the renal outcome and a response of immunosuppressive therapy.

Funding: Private Foundation Support

SA-PO1079

Differences in Renal Histopathology Between PR3-ANCA-Associated Vasculitis and MPO-ANCA-Associated Vasculitis

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Background: Clinical and experimental data suggest a pathogenic role for antineutrophil cytoplasmic antibodies (ANCA) in ANCA-associated glomerulonephritis (AAGN), with possible differences between anti-myeloperoxidase (MPO)- and anti-proteinase 3 (PR3)-ANCA. The aim of this study was to investigate differences in histopathological profile between MPO- AAGN and PR3-AAGN. Additionally, the effect of ANCA serotype on long-term renal outcome was examined.

Methods: 135 patients from 10 centers worldwide (Europe, North-America, Asia) with AAGN who underwent a diagnostic renal biopsy between 1991 and 2011 were included. Biopsies were scored on a secured website. Data on demographics, renal outcome and diagnostic delay were collected retrospectively.

Results: 50 patients were positive for PR3-ANCA and 73 for MPO-ANCA; 12 patients were either double-positive or negative. At diagnosis, patients with MPO-AAGN were significantly older (64.5±12.0 years) than those with PR3-AAGN (57.4±12.8 years). Mean diagnostic delay did not differ between groups. MPO-ANCA-positive patients showed less focal class and more mixed class than PR3-ANCA-positive patients (P=0.04). MPO-AAGN biopsies showed significantly more interstitial fibrosis and tubular atrophy (IFTA) than PR3-AAGN biopsies (P=0.04). On immunofluorescence, MPO-AAGN showed less C3-positive staining than PR3-AAGN (P=0.02). We found no association between ANCA serotype and death, renal relapse or development of end-stage renal disease.

Conclusions: In this large, international, multicenter cohort, we found a different histopathological profile in MPO-AAGN compared to PR3-AAGN, characterized by a lower percentage of focal and higher percentage of mixed histopathological class, more IFTA and less C3 in MPO-AAGN. These findings could not be explained by differences in diagnostic delay between groups and therefore support a difference in pathogenesis between MPO- and PR3-AAGN.

SA-PO1080

Effect of Autoantibodies to Erythropoietin Receptor in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: To examine the effect of autoantibodies to the erythropoietin receptor (EPOR) in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: Sixty-three Japanese patients with AAV were enrolled in this study and followed for a median of 31 months. Sera from these patients were screened for anti-EPOR antibodies using enzyme-linked immunosorbent assays.

Results: The patients comprised 26 men and 37 women aged 67±14 years. Fifteen patients had developed end-stage renal disease (ESRD) during follow-up period. Anti-EPOR antibodies were detected in 7 patients (11%). Anti-EPOR antibodies were associated with increased Birmingham vasculitis activity score (BVAS), especially systemic and skin scores. In addition, anti-EPOR antibodies were positively correlated with systemic and skin scores of BVAS. Cox regression analysis revealed that male gender, proteinuria and estimated glomerular filtration rate at disease onset were significant risk factors for ESRD. Among 6 patients who were positive for the antibodies at baseline and had follow-up examination of their sera, the antibodies disappeared in 4 patients by 2 months after immunosuppressive treatment, while remained positive in the other 2, and one of these developed ESRD.

Conclusions: Anti-EPOR antibodies were associated with disease activity, especially systemic manifestations and skin lesions in patients with AAV.

SA-PO1081

Impact of Infiltrating Neutrophils' Phenotype on Disease Activity in Various Glomerulonephritis

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Background: Activated neutrophils release neutrophil extracellular traps (NETs), resulting in cell death called NETosis. NETs formation has been reported to be involved in the onset of systemic lupus erythematosus and ANCA-related vasculitis (AAV). However, the precise mechanism remains unclear. Citrullination of histones is an essential step for NETs formation, and the presence of citrullinated histones in neutrophils may be involved in disease induction and activity. We investigated the association between infiltrating neutrophils with/without citrullinated histone and disease activity in various glomerulonephritis (GN).

Methods: We selected kidney biopsy samples of AAV, lupus nephritis (LN), Henoch schonlein purpura nephritis (HSPN), and acute post-streptococcal GN (APSGN)(n = 5, each), which presented proliferative GN with neutrophil infiltration in glomeruli and interstitium. To identify infiltrating neutrophils and citrullinated histones, we performed immunostaining for myeloperoxidase (MPO) and citrullinated histone H3 (CitH3), and assessed the frequency of citrullinated histone positive neutrophils in glomeruli and interstitium.

Results: Number of MPO+ neutrophils in glomeruli tends to be higher in APSGN, LN and HSPN than in AAV. In APSGN and HSPN, however, CitH3+ neutrophils were very few in their endocapillary proliferative lesions in glomeruli. In addition, a few MPO+ neutrophils and CitH3+ neutrophils infiltrated the interstitium. In LN and AAV, CitH3+ neutrophils were observed in necrotizing lesion and wire-loop lesion along glomerular capillaries. Moreover, in AAV, the frequency of CitH3+ neutrophils in both glomeruli and interstitium was significantly higher than the others and correlated with crescent formation.

Conclusions: CitH3 immunostaining was useful tool for identifying activated neutrophils. In addition, it was suggested that there was correlation disease activity of GN with the frequency of activated neutrophils.

SA-PO1082

Histopathologic Spectrum of Kidney Biopsies in Patients with Eosinophilia

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Background: Eosinophilia has been linked to diseases including interstitial nephritis (IN) and other autoimmune diseases in many case reports. However, no kidney biopsy series has examined the predictive role of peripheral eosinophilia and tissue eosinophilia within kidney biopsies in patient's with established kidney disease. This study evaluated a large series of kidney biopsies with known eosinophilia to better define the spectrum of kidney disease in this patient population.

Methods: A retrospective review of native and allotransplant kidney biopsies obtained from 1996 to 2018 identified 58 patients with eosinophilia (serum as a percentage of circulating leukocytes >4% on hematology). Patient characteristics, clinical and laboratory data were obtained. Standard processing of all biopsy specimens included light microscopy, immunofluorescence, and electron microscopy, focusing on the number of inflammatory markers including tissue eosinophils, number per high field (hpf), was performed.

Results: While IN was the most common primary diagnosis, other diagnoses include FSGS (17%), ANCA (14%), hypertensive arteriosclerosis (9%) (Table 1). Of the 58 patients, the most common indication for kidney biopsy was acute (51%), acute on chronic kidney failure (41%) and subnephrotic protrinuria (53%). In IN, mean eosinophilia was 13% and mean kidney tissue eosinophil number was 12 per hpf. In FSGS, mean eosinophilia was 14% and mean kidney tissue eosinophil number was higher at 18 per hpf. Outcomes show 17% of IN and 5% of FSGS patients progressed to ESRD.

Conclusions: Eosinophilia is seen in a spectrum of kidney diseases other than IN, such as FSGS and hypertensive arteriosclerosis. The role of eosinophilia in predicting major adverse kidney events requires further investigation.

Primary kidney biopsy findings in patients with peripheral Eosinophilia

Diagnosis	(n/N)
Interstitial nephritis (acute and chronic)	29/58
FSGS	10/58
ANCA	8/58
Hypertensive/arteriosclerosis	5/58
Diabetic nephropathy	4/58
Membranous glomerulopathy	2/58
IgG4 disease	1/58
Minimal change disease	1/58
AA amyloid	1/58
Thrombotic microangiopathy	1/58

SA-PO1083

Glomerular Staining and Serum Antibodies of THSD7A in Malignancy-Associated Membranous Nephropathy

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Background: Thrombospondin type 1 domain-containing 7A (THSD7A) is recently identified as the target antigen in patients with membranous nephropathy (MN). A notable phenomenon is the high rate of cancer (reported to be as high as 20%) in patients with THSD7A-associated MN. The prevalence of THSD7A in patients with malignancy-associated MN deserves further clarification.

Methods: Glomerular expression of THSD7A was examined by immunohistochemistry in 36 patients with malignancy-associated MN. Immunofluorescence assay was performed to investigate anti-THSD7A antibodies. Anti-PLA2R antibodies and glomerular PLA2R expression was also screened. THSD7A expression of cancer tissues was tested in 9 among the 36 patients.

Results: Among the 36 patients with malignancy-associated MN, 3 (8.3%) patients were identified as glomerular THSD7A staining positive: one patient was THSD7A positive alone, which accounted for 6.3% (one of 16) of PLA2R negative patients; two patients were dual-positive for both THSD7A and PLA2R staining. No anti-THSD7A antibody was detected among the 36 patients, whereas 18 of 36 (50%) had anti-PLA2R antibodies. Among the 9 patients who were available for cancer THSD7A staining, five (56%) patients showed enhanced expression of THSD7A localized in cancer tissue: one patient also had enhanced expression of THSD7A in glomeruli.

Conclusions: We found that positive glomerular THSD7A staining was uncommon in patiens with malignancy-associated MN.

SA-PO1084

The Size of Urinary Podocyte in Focal Segmental Glomerulosclerosis

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Background: Previous reports indicated that the number of urinary podocytes is higher in FSGS with nephrotic range of proteinuria than those in FSGS in remission and minimal change nephrotic syndrome (MCNS) in relapse. To date, the size of urinary podocyte has not been evaluated. In the present study, we examined the size of urinary podocyte in various glomerular diseases including FSGS in children.

Methods: Eight patients with FSGS (primary, n=6; genetic, n=2), 7 patients with MCNS in relapse and 10 patients with glomerulonephritis (GN) were included in the study. GN included IgAN (n=3), IgA vasculitis (n=4), ANCA-associated GN (n=1), lupus GN (n=1), and infection related GN (n=1). Patients with eGFR <60 ml/min/1.73m^2 were not included. Fresh urine samples of 10ml voided in the morning were obtained and urinary podocyte was detected by immunofluorescence using anti-human podocalyxin monoclonal antibody with a DAPI positive nucleus. The number of urinary podocytes was calculated per 10ml sample. Images of podocalyxin-positive cells were taken under an immunofluorescence microscope with 400-fold magnification and were quantified by image analysis. The size of urinary podocyte was defined as mean area of the podocytes in a field (pixel/cell). Statistical analyses were performed with Wilcoxon tests. Data are expressed as median (IQR). A *P* value of <0.05 was accepted as statistically significant.

Results: Urinary protein/creatinine ratios (UP/UC) were not significantly different among FSGS, MCNS and GN. The number of urinary podocytes (/10ml) in GN (200 (154.5-200)/10ml) was significantly higher than those in FSGS (81.5 (42.8-140.3)/10ml) and MCNS (68 (35-98)/10ml) (*P*=0.0225), while there was not a significant difference between FSGS and MCNS. Of note, the size of podocyte in FSGS (2947.9 (2571.4-3400.0) pixel/cell) was significantly larger than those in MCNS (1242.3 (756.0-2214.5) pixel/cell) and GN (859.4 (753.2-1079.3) pixel/cell) (*P*=0.0034).

Conclusions: This preliminary study suggested that the size of urinary podocyte may be a specific marker of FSGS.

SA-PO1085

Anticoagulants and the Kidney: 10 Years Later After Discovery of Warfarin Related Nephropathy

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Background: Ten years ago we associated acute kidney injury (AKI) and occlusive red blood cell (RBC) tubular casts with high international normalized ratio (INR) in a patient on warfarin therapy. We named this condition warfarin related nephropathy (WRN). Later, we and others demonstrated that WRN is a part of the broader syndrome, anticoagulant related nephropathy (ARN). Herein we provide our 9-year experience with ARN based on a single-center renal pathology laboratory data.

Methods: The renal pathology database at the Ohio State University Wexner Medical Center (OSUWMC) was searched for native kidney biopsies performed between January 1st 2009 and December 31st 2017 using keywords "kidney biopsy", "warfarin", "anticoagulant", "nephropathy". All identified cases were reviewed and those with kidney biopsy findings suggestive of ARN were included into this study.

Results: Among 8636 native kidney biopsies, there were 47 (0.54 %) patients in whom deterioration in the kidney function could not be explained by kidney biopsy findings alone if anticoagulation was not taken into the equation. There were 32 (68%) males and 15 (32%) females, 90% of the patients were Caucasian. The average age was 61.7 +/- 14 years. Thirty five (74%) were on warfarin therapy, five (11%) were on anti-platelet medications, six (13%) did not have records of anticoagulation therapy, but they had acute coagulopathy at the time of deterioration of kidney function and their biopsy findings suggested of ARN. In addition to acute tubular necrosis and RBC casts, these patients had underlying glomerular changes, but the severity of that glomerular disease was out of proportion to the number of RBC casts and/or hematuria in these patients. The most common was mild glomerular immune complex deposits without significant proliferative lesions (23 cases, 49%), followed by mild focal pauci-immune crescentic glomerulonephritis (7 cases, 15%), diabetic glomerulosclerosis (5 cases, 11%) and focal segmental glomerular sclerosis (FSGS, 5 cases, 11%).

Conclusions: ARN is an uncommon diagnosis in renal pathology practice, but it should be considered when there is a disproportion between the severity of glomerular changes and the number of RBC casts and/or hematuria in a kidney biopsy in patients on anticoagulant therapy or who presented with acute coagulopathy.

SA-PO1086

Congo Red Positive Fibrillary Glomerulonephritis

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Background: Fibrillary glomerulonephritis (FGN) is characterized by the glomerular deposition of Congo red-negative fibrillary material with fibers that are larger in diameter than amyloid fibrils. With recent identification of DnaJ homolog subfamily B member 9 (DNAJB9) as a sensitive and specific marker for FGN, we sought to examine the specificity of these traditional diagnostic criteria used to distinguish FGN and amyloidosis.

Methods: The study population consisted of renal biopsies accessioned at the University of Washington, Seattle, USA from 01/01/2014 to 05/15/2018. We performed a database search of pathology reports for terms "fibrillary" and "atypical amyloid". Cases were included if all of the following: 1) glomerular and/or extra glomerular fibrillary deposits were present 2) Congo red stain was performed 3) FGN was diagnosed by conventional criteria and/or DNAJB9 was demonstrated in the deposits by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and/or immunofluorescence.

Results: During the study period, 49 patients were diagnosed with FGN, of which 4 patients' biopsies had positive Congo red staining. The most prominent light microscopic findings were necrotizing and crescentic lesions (2 cases) and mesangial expansion with glomerular basement membrane thickening (2 cases). Immunofluorescence showed polytypic IgG staining in all 4 cases. The average fibrillary diameter ranged from 8.8-14.2 nm with two cases below the 12 nm diagnostic cut-off (figure).

Conclusions: Congo red positive staining and fibril diameter less than 12 nm should not be used as exclusion criteria for the diagnosis of FGN. The diagnosis of FGN should be considered in Congo red positive biopsies with findings that are atypical or inconclusive for amyloidosis, and LC-MS/MS and/or DNAJB9 immunostaining should be performed to confirm or exclude the diagnosis of FGN.

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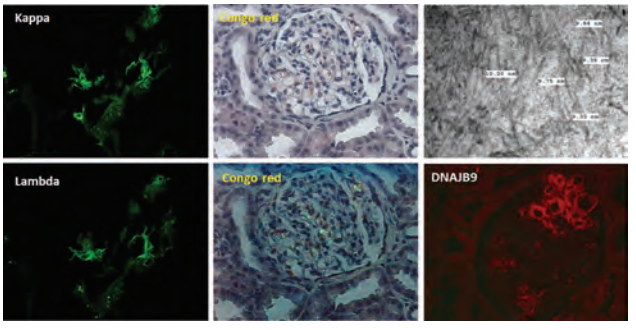

The Congo red and immunofluorescence (light chains and DNAJB9) staining and the fibrillary organization of the deposits in one of the cases. LC-MS/MS of the Congo red positive glomerular deposits showed DNAJB9 but no amyloidogenic peptides.

SA-PO1087

Acute Transient Arteriopathy Mimicking Vascular Rejection in Allograft Kidneys

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Background: Early dysfunction of renal allografts raises the specter of acute rejection processes that require medical intervention vs. self-limiting peri-operative conditions for which conservative management is indicated. We sought to determine the clinical course in patients who present with delayed graft function and demonstrate a unique pattern of vascular injury that mimics rejection in their biopsy.

Methods: The study population consisted of renal allograft biopsies accessioned at the University of Washington, Seattle, USA from 1/1/2000 to 12/31/2017. We performed a database search of pathology reports for "transplant" and "arteriopathy" within one year following transplantation. Included cases showed a distinct arterial vasculopathy, characterized by endothelial cell swelling, lifting, and intimal edema in the absence of endotheliitis or rejection (Banff IA or higher). We also determined the clinical course of these patients on followup.

Results: We have identified 30 patients with arteriopathy but without rejection in the first year post-transplant. Of these, we have collected follow up on 14 patients to date (*remainder in process*). These patients (10 male, 4 female) were compliant with their immunosuppression and presented with delayed graft function soon after transplantation (median=13 days, range 7-139). Interlobular-sized arteries were most frequently affected. 11/14 patients received no intervention, while 3/14 received anti-thymocyte globulin (ATG), plasmapheresis or intravenous immunoglobulin (IVIg). 30 days post-transplantation, 11 patients were off dialysis and had a median serum creatinine of 1.85 mg/dL. 90 days after transplantation 13 patients were off dialysis with a median creatinine of 1.67 mg/dL (one patient lost the allograft due to suspected early infarction, indeterminate for vascular rejection).

Conclusions: Acute transient transplant arteriopathy is a rare vascular lesion that is associated with early graft dysfunction in the absence of rejection. Recognition of this lesion and distinguishing it from vascular rejection is important to prevent over-treatment since most patients appear to recover function rapidly without specific interventions.

Funding: Clinical Revenue Support

SA-PO1088

An Epidemic of Serum Amyloid A Protein Amyloidosis Fueled by Injection Heroin Use Associated Infections in the Pacific Northwest

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Background: Renal amyloidosis is an uncommon but problematic cause of proteinuria and nephrotic syndrome, which has very limited treatment options and usually leads to ESRD requiring renal replacement therapy. In this study, we assessed the incidence of different subtypes of amyloidosis over time in our patient population to better understand the etiology of renal amyloidosis.

Methods: We reviewed our kidney biopsy database from 1984 through 2017 to define the incidence of renal amyloidosis and the subtypes of amyloid contributing to this disease. Amyloidosis subtype was correlated with clinical data.

Results: We observed a dramatic increase in serum amyloid A (AA) protein-type amyloidosis (Fig. 1), beginning in 2000 and becoming in 2015 the most common renal amyloidosis subtype in our patient population. AA-type amyloidosis was associated with heroin injection associated infections (skin and deep muscle abscess, cellulitis and osteomyelitis) in over 90% of the cases. In a subset of patients (n=8) with extensive clinical data, renal biopsy was preceded by Initial documentation of injection drug use associated infections (4.0 -18 years) and proteinuria (1.0 -14 years), and renal failure or death occurred 0.45 – 2.7 years after biopsy.

Conclusions: Since 2000, there has been a dramatic increase in the incidence AA-type amyloidosis, which is attributed to injection drug use and its associated infectious complications. Longitudinal data suggest repeated injection drug use associted infections and asymptomatic proteinuria precede clinical presentation prompting biopsy by several years.

Funding: Clinical Revenue Support

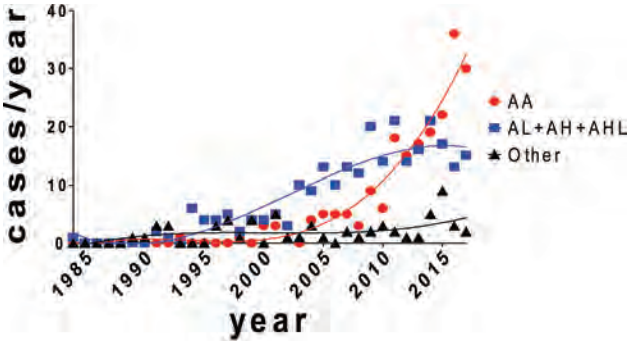

Figure 1. A surge in AA-type amyloidosis diagnosed in renal biopsies after 2000 in our institution. Shown are the number of cases diagnosed per year of AA-type (red), immunoglobulin-type (AL+AH+AHL, blue) and other type (undetermined, ALECT2, APOA4, ALys) amyloidosis. The lines represents represent non-linear third order polynomial fits to the data (r-squared values: AA = 0.94, AL+AH+AHL = 0..88, Other = 0.28).

SA-PO1089

Normal Serum Free Kappa-Lambda Light Chain Ratios in AL Amyloidosis - A Single Center Experience

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Background: Quantification of serum free light chains (FLC) is reported to be highly sensitive for diagnosis of primary systemic amyloidosis, with reported sensitivities of 90-100%. Although tissue diagnosis remains the gold standard for establishing definitive diagnosis, normal FLC ratios are often interpreted clinically as effectively ruling out amyloidosis. The aim of this study is to examine if our experience is different from the reported literature.

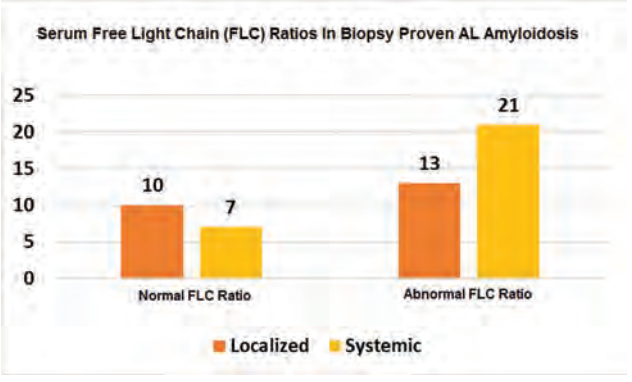
Methods: All patients who had serum FLC quantification and bone marrow biopsy at Loyola University Medical Center between the years 2007-2017 were analyzed in a retrospective chart review. A total of 1,270 patients were identified and 51 had a confirmed diagnosis of AL-amyloidosis. A FLC ratio of 0.26-1.65 was considered normal, consistent with past studies. Reported p-values were determined using a chi-squared test.

Results: Of the 51 patients with tissue diagnosis of AL amyloidosis, 45% had localized disease (confined to one organ) while 55% had systemic disease (more than one organ involvement). Serum FLC ratios were normal in 33% of the cases (17/51). 43% with

localized disease had normal FLC ratios compared to 25% of patients with systemic disease (p=0.14) (Figure 1). 23 patients (45%) had renal involvement and 5 of the 23 had normal FLC ratios at presentation. Overall, 28/51 (55%) patients had a concomitant plasma cell dyscrasia confirmed on bone marrow biopsy. Patients with plasma cell dyscrasia were significantly less likely (14%) than those without a plasma cell dyscrasia (57%) to have a normal free light chain ratios (p=0.001) at presentation. Although patients with systemic disease were more likely to have an underlying plasma cell dyscrasia than those with localized disease, this result did not reach statistical significance (p=0.14).

Conclusions: When amyloidosis is clinically suspected, serum FLC quantification may be insufficient to rule out the diagnosis, leaving biopsy of affected organ(s) as the prevailing gold standard.

Funding: Clinical Revenue Support



SA-PO1090

Importance of Adjusting the Normal Range of the k/L Free Light Chain Ratio According to the CKD Stage in Myeloma Patients

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Background: The development of an effective laboratory test to quantify the concentration of free light chains (FLC) has optimized the diagnosis of multiple myeloma (MM). However, the metabolism of FLC depends to a large extent on renal function, which can lead to a misinterpretation of the results. The objective of this study was to determine the concentration of serum FLC in a group of MM patients and a group of healthy patients, and to establish the variation of the FLC ratio normal range and its diagnostic performance for MM in relation to the CKD stage.

Methods: The FLC ratio κ/λ in serum and GFR was analyzed retrospectively by CKD-EPI in 1469 consecutive patients between December 2014 and December 2017. Two groups were chosen: 1) healthyand complete remission MM patients,(n=174); 2) patients with a diagnosis of active MM (n=416). The reported normal range of the FLC ratio is 0.26-1.65. We excluded patients with a diagnosis of MGUS or other hematological diseases. ROC analysis were made for these groups depending on the GFR and the Sensitivity/Specificity value obtained for each subgroup was compared. The optimal cut-off was established based on the maximum value of Sensitivity/Specificity.

Results: A MM diagnosis based on the initial FLC normal range has a specificity of 96% in the group with GFR>90 (n=244) 79% in GFR 30-60 ml/min (n=87) and 43% in GFR<30 ml/min (N=45). The sensitivity and specificity of the FLC κ/λ ratio is maximum when we divide the patients in two groups (GFR < or > 55 ml/min) and apply an adjusted renal range (0.82 - 2.75):-for MM Kappa patients with GFR<55 ml/min, the initial Specificity/Sensibility of 87.7%/56.5% changed to 80.7%/95.6% while for MM Lambda patients with GFR<55 ml/min, the initialSpecificity/Sensitivity of 73.3%/100% changed to 96.7%/100%.

Conclusions: The FLC k/L ratio is a safe method for the study of selective proteinuria in MM in patients with normal renal function but, if we do not correct the FLC ratio as the GFR decreases, its specificity is reduced. The need for this correction is most likely due to the different clearance rates of the kappa and lambda FLC and how they change with GFR levels. Thus, it is necessary to take into account the GFR for its interpretation and validate this new renal range for CKD stage 4 and 5, in future studies.

SA-PO1091

Clinical and Pathological Analysis of Renal Light Chain Deposition Disease With or Without Cast Nephropathy

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Background: To investigate the clinicopathological features of renal light chain deposition disease (LCDD) with or without cast nephropathy (LCDD & LCN).

Methods: The clinical features of the 55 cases of LCDD diagnosed by renal biopsy from January 2000 to March 2018 were retrospectively analyzed. The pathological sections were re-read and divided into two groups: isolated LCDD group (I-LCDD, 36 cases) and LCDD coexisted with cast nephropathy group (LCDD & LCN, 19 cases). The semi-quantitative evaluation of the main features of renal pathology include the degree of glomerular mesangial expansion, acute tubular injury, tubulointerstitial inflammatory cell infiltration, tubular atrophy with interstitial fibrosis, and renal arteriosclerosis.

Results: all LCDD patients (55 cases) had a mean age of 53.6 years with a male to female ratio of 2.7:1, and the average duration of the disease was 10.3 months. The multiple myeloma (MM) accounted for 31.58% in LCDD patients. The type of light chain is predominantly κ (κ: λ, 2.6:1). The incidence of hypertension, anemia, renal dysfunction, urine protein (≥3.5 g/24h) and microscopic hematuria in patients with LCDD were 43.6%, 80.4%, 82.1%, 54.5%, and 76.4%, respectively. The percentage of LCDD & LCN was 34.6% (19/55 cases). Compared with the I-LCDD group, the LCDD&LCN group had an acute onset (P=0.04), higher serum creatinine (P=0.000), lower hemoglobulin level (p=0.027). The composition of urine protein was mainly small-molecule protein in LCDD&LCN and albumin dominant urinary protien in I-LCDD respectively (P = 0.007, P = 0.021). The type of light chain was λ dominant (λ:κ=7:3) in LCDD&LCN (vs I-LCDD, λ:κ=3:11, p=0.035). The glomerulopathy varied from mild mesangial expansion to typical mesangial nodular sclerosis, and crescents were existed in 27.3% of LCDD patients. The frequency of typical mesangial nodular sclerosis was significant lower in LCDD&LCN patients (15.8% vs 58.2% in I-LCDD, p=0.01). There was no significant difference in tubulointerstitial lesions between the two groups.

Conclusions: One third of LCDD coexisted with cast nephropathy. The dominant λ light chain and less mesangial nodular sclerosis was the prominent features of LCDD&LCN compared with isolated LCDD, which suggested LCDD&LCN has a distinct pathogenesis from that of I-LCDD.

SA-PO1092

Paraneoplastic Cast Nephropathy Associated with Secretary Pancreatic Carcinoma

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Introduction: We report the case of a patient with pancreatic mixed acinar-neuroendocrine carcinoma who presented with irreversible acute kidney injury (AKI) due to myeloma-like cast nephropathy. We performed proteomic and immunohistochemical studies which revealed that the AKI was triggered by tubular obstruction by acinar cell carcinoma-secreted proteins. A novel pathomechanism for carcinoma-associated nephropathy is being described.

Case Description: A 64-year old male was found with a large abdominal mass after workup for unintentional 35 pound weight loss over 6 month period. Biopsy of the mass showed pancreatic mixed acinar-neuroendocrine carcinoma. He developped AKI after the diagnosis. Urinalysis showed 1 + protein but no hematuria. Serologies were negative. Serum protein electrophoresis with immunofixation did not show monoclonal protein and serum free kappa/lambda ratio was normal. Kidney biopsy showed myeloma-like cast nephropathy. He was initiated on hemodialysis and received rescue plasmapheresis without success in renal recovery. He received gemcitabine and Abraxane with no improvement in his condition. He remained on dialysis, had a decline in his clinical condition, developed severe refractory septic shock and died 4 months after cancer diagnosis.

Discussion: Kidney biopsy showed acute cast nephropathy with many distal tubular PAS-negative and trichrome-polychromatic casts, associated with mononuclear and giant cell reaction, acute tubular injury, and mild interstitial inflammation and fibrosis. Ultrastructurally, the casts were electron dense and some were admixed with fibrillar uromodulin casts. The casts did not stain for kappa or lambda on immunofluorescence. Analysis by laser microdissection/mass spectrometry and by immunohistochemistry detected large amounts of two acinar-cell specific proteins, REG 1α and CPA1, in the renal casts and the patient's pancreatic carcinoma cells. Thus, the acute kidney injury in this patient is likely due to distal tubular obstruction by aggregates of filtered carcinoma-secreted proteins and uromodulin, with subsequent tubular injury, interstitial inflammation and fibrosis, as has been proposed in myeloma cast nephropathy. This case describe a new mechanism for paraneoplastic cast nephropathy in the absence of multiple myeloma.

SA-PO1093

Beyond Morse: How Do Kidney Biopsy Registries Code Renal Disease? On Behalf of the Kidney Biopsy Codes (KBC) for Pathologists Project

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Background: Data collected from kidney biopsy registries are used for quality control, research, teaching and health policy decisions. For analysis and comparison, unified pathology codes are a prerequisite. The KBC for pathologists project aims to provide a complete, structured set of terms and codes applicable to non-neoplastic kidney biopsies for use by nephropathologists or kidney biopsy registries. The first step is an inventory of existing coding practice.

Methods: A structured 10-question questionnaire was sent out to 12 national and regional kidney biopsy registries. Additional information was collected by a pubmed search, through web pages of registries and personal communication.

Results: The questionaire was returned by 11/12 registries; 7/10 use self-made codes, 2/10 ERA-EDTA codes and 1/10 an updated SNOMED version based on SNOMED II. One registry does not code, only lists diagnosis. Codes are compatible with SNOMED-CT

in 3/11 registries. Mean user satisfaction was 3.4 on a scale from 0 to 5. Self-made coding systems represented classifications with hierarchical structures and meaningful, easy to understand code numbers. Problems were: coding difficulties with clinically-based coding systems, problematic mapping of systems to one another, updates and maintenance lacking, difficulties in coding multiple diagnoses and missing codes, e.g. documentation of applied technology or diagnostic certainty.

Conclusions: The inventory phase of the KBC project has identified multiple challenges in coding kidney disease. Considering the current coding practice and future needs, a common system should be easy to understand, apply, maintain and update. It should contain specific pathology codes. Mapping to a reference terminology would be necessary for interoperability.

SA-PO1094

Accuracy of Nephrologist in Identifying Kidney Disorders Prior to Kidney Biopsy

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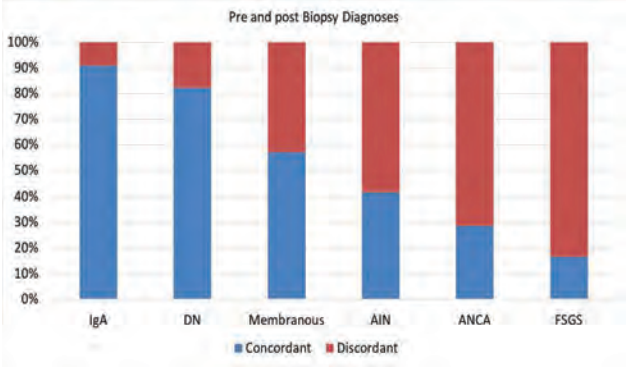
Background: New biomarkers have been developed for identification of kidney diseases; however the kidney biopsies remain the gold standard in diagnosis and management. Our aim was to determine the ability of nephrologist to accurately identify etiology of kidney dysfunction prior to a biopsy.

Methods: This is a retrospective cohort study of 251 patients who underwent a native kidney biopsy at Mount Sinai Hospital (MSH) and Albany Medical Center (AMC) from 2013 - 2017. Clinical indication and nephrologist diagnosis was determined by review of pre-biopsy provider notes while final diagnoses were determined by review of biopsy pathology reports.

Results: There were 251 patients who underwent kidney biopsy; mean age was 51 ± 16 years, 52% were male, 50% were inpatient, and 60% were done under ultrasound guidance. The most frequent indication for biopsy was non-nephrotic range proteinuria, 83 (33.2%) and acute kidney injury, 79 (32%). We were able to identify the nephrologist pre-biopsy diagnosis in only 93 patients. The most frequent diagnoses were diabetic nephropathy (20%), ANCA vasculitis (12%), and membranous nephropathy (8%). The post-biopsy diagnosis matched 45% of the time; the highest concordance was seen in diabetic nephropathy (32/39) and IgA nephropathy (10/11) while the lowest concordance seen in ANCA (6/21), FSGS (2/12), and minimal change (2/7). There was no consistent alternative diagnosis in the lowest concordance groups; patients who were biopsied with a presumptive diagnosis of ANCA were found to have diabetic nephropathy, HSP, and MPGN among others on pathology.

Conclusions: Nephrologists were able to accurately identify underlying etiologies nearly half the time in patients who were referred for biopsy. Given the relative safety of kidney biopsies, we should have a low threshold to refer patients for kidney biopsies.

Funding: NIDDK Support



SA-PO1095

Pre-Biopsy Lab Work and Decision Making

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Background: Labwork is often ordered prior to obtaining a kidney biopsy, to assess risk of bleeding and less often ordered afterwards. We sought to determine which factors influenced the decision to monitor hemoglobin (Hb) levels after biopsy.

Methods: All kidney biopsies performed on adult patients by the Nephrology service at the University of Chicago between September 2009-October 2015 were retrospectively assessed. Pre-biopsy Hb, INR, platelet count, and platelet function assays (PFA) were collected, and the nadir Hb level over the next 14 days was assessed, when available. Median values compared with Wilcoxon test, with P<0.01 due to multiple comparisons. A multinomial regression model was used to calculate odds ratios (OR) for post-biopsy outcomes of: a) Significant drop in Hb (defined as >1.5 grams), b) Lack of post-biopsy labwork, compared to a reference outcome of available post-biopsy Hb with no significant drop. Models adjusted for age, sex, and allograft vs. native organ, with single imputation of median values for missing pre-biopsy data.

Results: Among 905 kidney biopsies, 43.8% were native and 56.2% were allografts, 49.2% were women and the mean age was 47.5±15.2 years. Hb drop > 1.5 gm occurred in 11.7%, and post-Hb data was missing for 44.6%. Labwork by outcome and OR for each post-Hb outcome are shown in the tables. Female sex, higher pre-biopsy Hb and INR were positively associated with significant Hb drop, as were lower eGFR and platelet count. Omission of the post biopsy Hb was associated with increased age, female sex, higher pre-biopsy Hb, and negatively associated with higher INR. PFA did not contribute significantly for either outcome.

Conclusions: Post biopsy Hb was more likely to be checked for allograft biopsies and patients with elevated INR, but not for several other factors that had significant associations to the risk of bleeding. Platelet function assays did not appear to contribute to decision making or blood loss. Utilization of labwork before and after kidney biopsies deserves further study.

Pre Biopsy Labwork, by Post-biopsy Hemoglobin

	No Hb	<=1.5 GM	>1.5 GM
	n=404	n=106	n=396
eGFR, ml/min/1.73 m²	32 (20, 48) †	24 (14, 37)	13 (8, 22)†
INR	1.0 (1.0, 1.1)†	1.1 (1.0, 1.2)	1.1 (1.0, 1.3)†
Hemoglobin, g/dL	11.5 (10.3, 13.0)†	10.1 (8.6,11.7)	10.1 (9.1, 11.1)
Platelet count,10³/ µL	220 (182, 255)	214 (165, 268)	183 (135, 239)†
PFA (ADP), seconds	83 (70, 97)†	88 (74, 106)	101 (19, 115)
PFA (epinephrine), seconds	114 (95, 144)	114 (98, 153)	123 (91, 191)

† P<0.01 vs <=1.5 g, using Wilcoxon test

	Multinomial Regression: modeled outcome			
	Hb Drop		Missing Hb	
	OR (95% CI)	P	OR (95% CI)	P
Age (per 10 years)	1.01(0.87, 1.18)	0.9	1.37 (1.23, 1.52)	<0.001
Female sex	2.42 (1.50, 3.93)	<0.001	1.52 (1.10, 2.12)	0.01
Allograft	0.82 (0.51, 1.33)	0.4	0.53 (0.39, 0.73)	<0.001
eGFR (per 10 ml/min/1.73 m²)	0.65 (0.54, 0.78)	<0.001	1.07 (0.99, 1.16)	0.1
Platelets (per 25,000/µL)	0.87 (0.80, 0.94)	0.001	0.98 (0.93, 1.03)	0.4
Hemoglobin (per 1 g/dL)	1.29 (1.20, 1.38)	<0.001	1.36 (1.29, 1.43)	<0.001
INR (per 0.1)	1.19 (1.05, 1.35)	0.005	0.75 (0.65, 0.86)	<0.001

SA-PO1096

Kidney Injury Molecule-1 (KIM-1) Identifies Antemortem Injury in Fetal Postmortem Kidney

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Background: KIM-1, a type I transmembranous protein, is a specific and stable protein marker for identifying injury in proximal tubules during acute kidney injury. There is currently no technique to unambiguously diagnose antemortem kidney injury on postmortem examination since postmortem tissue damage and autolysis are common. We hypothesized that KIM-1 could be very useful for detecting antemortem proximal tubular injury in autolyzed kidneys upon postmortem examination.

Methods: A total of 52 fetal/neonatal autopsy kidneys, from 30 stillborns and 22 liveborns, were assessed for KIM-1 staining. Kidney autolysis was evaluated by light microscopy and disappearance of CD133 expression. The autolysis was graded from 0 (no autolysis) to 3+ (entire loss of chromatin staining). Correlation between KIM-1 and autolysis scores was evaluated by linear regression analysis. Given that serum creatinine is unreliable in neonates, we assessed pre-terminal hypoxia in fetuses by the presence of squames in pulmonary alveoli and/or the need for intubation.

Results: The expression of KIM-1 was seen in a majority of the fetal and neonatal autopsy kidneys (77%, 40/52) as early as 16 weeks of gestation, even in the presence of autolysis. There was no significant correlation between KIM-1 scores and autolysis scores ($r = 0.201$ and $p = 0.1521$). There was a high correlation between KIM-1 expression and these clinical indices of hypoxia, either presence of aspirated amniotic fluid contents in stillborn or need for intubation in liveborn.

Conclusions: Our data suggest that KIM-1 is a specific and stable marker of antemortem tubular injury in fetuses, despite postmortem autolysis. A high correlation between KIM-1 expression and these clinical indices of hypoxia implies that KIM-1 may be a reliable marker to indicate the hypoxic state in pediatric autopsies.

Funding: Other U.S. Government Support

SA-PO1097

Extensive Tubular Ectasia Indicating Occult Urological Obstruction in Renal Allografts

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Background: Urological obstructive complications (UOC) affect up to 10 % of kidney transplantation (KTX) cases. The majority of the cases may be excluded by routine ultrasound (US), however its accuracy may be limited in the early transplant setting. Renal allograft biopsy (BX) may be valuable, but histological features indicating UOC are ill defined. Experimental data suggest that extensive tubular ectasia (TE) may be indicative

of OUC. In our center, occult UOC is suspected when tubular ectasia (TE) occurs together with one or more of the following distinct features: acute tubular injury, tubular protein casts and tubular vacuolization. In this study we aimed to assess their accuracy for UOC.

Methods: We included 976 of 1537 consecutive KTX with an early indication BX. Relevant hydronephrosis (HN) was excluded by routine US. The bioptical finding of TE suspicious of UOC by the renal pathologist was compared to clinical endpoints as delayed graft function (DGF) and occurrence of UOC. Thereafter, all biopsies initially classified as suspicious for UOC were reevaluated by a single pathologist (H.R.) in order to increase accuracy of histomorphology suggestive of UOC.

Results: Fifty eight (5.9%) presented with TE indicative of UOC which was associated with a higher rate of DGF (40% vs. 29%; p=0.08) and was not related to long-term graft loss. Out of these, 23 (39.7%) had UOC, (most frequently ureteral stenosis) close to BX. To assess the relevance of TE as a marker of UOC without relevant HN, cases with TE were then subsequently compared to matched controls. Solely TE was significantly associated with an increased risk for UOC [OR 2.69 (IQR: 1.19 – 6.09); p = 0.018]. For histopathological reevaluation of the 58 cases, we defined extensive TE (>20% of the renal cortex). Subsequently, a score including additional histological criteria (tubular injury, tubular protein casts and tubular vacuolization) was developed: AUC 0.705, p=0.012. Using a threshold of 1.5, we observed 91% sensitivity, 37% specificity and a 84% negative predictive value.

Conclusions: Occult UOC may be identified in up to 40% of the cases by subtle histopathology including extensive TE together with additional signs of tubular injury. This phenotype should trigger more detailed evaluation for UOC when there is no evidence of relevant HN in the ultrasound.

SA-PO1098

Non-Lupus Immune-Complex Glomerulonephropathy (ICGN) After Kidney Transplantation: A Report of 9 Cases

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Background: ICGN with positive immunofluorescence (IF) for IgG, IgA, IgG, C3, and C1q has been termed "non-lupus full-house nephropathy (FHN)" in the absence of clinical or serologic features of systemic lupus erythematosus (SLE). We describe characteristics and outcomes of ICGN with IgG, C3, and C1q +/- IgM/IgA deposits in the kidney allograft.

Methods: We retrospectively reviewed a single-institution pathology database from 2007-2017 to identify cases of allograft ICGN with IgG, C3 and C1q in the absence of SLE. Clinicopathologic and outcome data were derived from patient records.

Results: Of 9 patients, most were non-white (89%), male (89%), and pediatric-adolescent (66%). None had ICGN as cause of ESRD. Median time from transplant to ICGN was 1.6 (range 0.5-5.2) years and 5/9 (56%) were identified on surveillance biopsy. Two of 7 patients had a positive donor-specific antibodies. By light microscopy, 7 cases had mesangial hypercellularity, and two had FSGS. At last follow-up (median 3.9 years, range 0.5-13.8), 7 of 9 patients (78%) had a stable serum creatinine with minimal proteinuria in 6. The remaining 2 patients had persistent allograft dysfunction. Four patients had subsequent biopsies with immunofluorescence: 3 (75%) showed persistent ICGN while 1 (25%) had resolution of immune complexes.

Conclusions: Post-transplant ICGN with IgG, C3 and C1q may be clinically silent and/or resolve spontaneously and in most cases appears to follow an indolent clinical course. Whether immune complex formation results from an auto- or allo-immune response remains to be elucidated.

Pt #	Age	Sex	Race	Native Disease (Bx, Y/N)	Years Post-Tx	Indication	Light Microscopy Findings	Therapy Change	Years Post-Bx	Follow-Up
1	73	M	Other	Diabetic (N)	5.2	sCr 1.5, uPCR 2.9	FSGS, MICD-HY	None	3.9	Death, sCr 0.8
2	20	M	Pacific Islander	FSGS (N)	1.6	Surv	MICD-HY	None	2.5	sCr 1.6
3	19	M	White	Alport (N)	1.3	Surv	MICD-HY	Steroid Pulse, increase MMF	9.3	sCr 0.7, uPCR 2.0
4	16	M	Pacific Islander	Unknown (N)	2.9	sCr 1.5, uPCR 1.1	MICD-HY	Increase MMF	13.8	sCr 3.1, uPCR 7.0
5	12	M	Unknown	Methylmalonic Acidemia (N)	0.5	Surv	MICD-HY	Add Steroid	0.9	sCr 0.6
6	4	M	Black	Denys-Drash (N)	1.1	Surv	MICD-HY	None	5.0	sCr 0.8
7	19	F	Other	FSGS (Y)	2.3	sCr 1.3	MICD	None	4.1	sCr 0.9, uPCR 0.12
8	32	M	Asian	IgA (Y)	1.0	Surv	MICD-HY	None	0.6	sCr 1.2, uPCR 0.29
9	60	M	Unknown	Hypertension (N)	1.6	sCr 1.9, uPCR 1.1	FSGS, MICD	Steroid Pulse	0.5	sCr 1.9

Tx = Transplant; Bx = biopsy; FSGS = Focal Segmental Glomerulosclerosis; HY = hypercellularity; sCr = serum creatinine, mg/dL; uPCR = urine protein-creatinine ratio, g/g; surv = surveillance; MICD = mesangial immune complex deposition; MMF = mycophenolate mofetil

SA-PO1099

Human Chorionic Gonadotropin (hCG) in Dialysis Patients

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Background: The FDA mandates pregnancy testing before and 8 days after initiation of therapy with MMF/MPA because its use in pregnancy is associated with an increased risk of miscarriage and congenital defects. However, a few case reports showed hCG to be elevated in transplant candidates resulting in refusal of transplantation.

Methods: We examined hCG serum concentrations in female dialysis patients, 18-50 years of age, and defined fertility status according to STRAW criteria. We classified hCG positive above a cut-off at 5 mIU/l. For an enhanced index test we classified hCG positive above a cut-off at 5 mIU/l for fertile patients and 14 mIU/l for non-fertile patients to calculate diagnostic test accuracy. We estimated the ideal cut-off for hCG using Liu's method with bootstrapped 95% CIs. We report estimates for hCG as a diagnostic test and predictors for elevated hCG using multivariable linear regression.

Results: Among 71 women two (2.8 %) were pregnant presenting with elevated hCG serum concentrations. We observed hCG concentrations greater than 5 mIU/ml, potentially indicating pregnancy, in 10 further patients. A hCG serum concentration > 5 mIU/ml had a sensitivity of 100% (95% CI: 100 to 100), a specificity of 86% (95% CI: 77 to 94), a positive predictive value (PPV) of 17% (95% CI: 8 to 25) and a negative predictive value (NPV) of 100% (95% CI: 100 to 100) for the diagnosis of pregnancy. Using a hCG cut-off of > 14 mIU/ml for non-fertile patients sensitivity and NPV did not change, the specificity increased to 93% (95% CI: 87 to 99) and the PPV was 29% (95% CI: 18 to 39). Excluding 23 non-fertile patients resulted in a specificity of 98% (95% CI: 94 to 100) and a PPV of 67% (95% CI: 53 to 80) whereas sensitivity and NPV did not change. The ideal hCG cut-off was 25.0 mIU/ml (95% CI: 17 to 33). Pregnancy (coefficient: 8.7; 95% CI: 6.6 to 10.7; p<0.001) and fertility (coefficient: -2.7; 95% CI: -3.5 to -1.8; p<0.001), but not age (coefficient -0.03; 95% CI: -0.08 to 0.01; p=0.13) were independent predictors of log transformed hCG.

Conclusions: hCG is elevated > 5 mIU/ml in 14,5% of non-pregnant dialysis patients of child-bearing age. In fertile women this cut-off can be used to exclude pregnancy. For our population the ideal hCG cut-off was 25 mIU/ml.

SA-PO1100

Post-Translational Modifications of Albumin Causes a Decreased Binding Capacity of Hydrophobic Metabolites

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Background: Since post-translational modifications of proteins may have an impact on the pathogenesis of diseases like atherosclerosis or chronic kidney disease (CKD), post-translational modifications are currently gaining increasing interest. In this study, a comprehensive method for analysis ofpost-translational modifications is established for the clinical diagnostic routine.

Methods: Here, we analysed albumin isolated from CKD patients and healthy controls by chromatographic steps and identified by mass-spectrometry. Post-translational modifications of albumin were identified after digestion by analysing mass-signal shifts of albumin peptides using pertinent mass-databases.

Results: Albumin isolated from plasma of CKD patients but not from healthy control subjects was specifically post-translationally modified by guanidylation of lysines at positions 249, 468, 548, 565 and 588. After identification of guanidylations as post-translational modifications of albumin isolated from CKD patients, these modifications were quantified by mass-spectrometry demonstrating a significant increase in the corresponding mass-signal intensities in CKD patients compared to healthy controls. The relative amount of guanidylation of lysine at position 468 in CKD patients was determined as 63 ± 32 % (N=3). *In-vitro* guanidylation of albumin from healthy control subjects caused a decreased binding capacity of albumin in a time-dependent manner. Binding of indoxyl sulfate (protein bound fraction) decreased from 82 ± 1 % of non post-translationally modified albumin to 56 ± 1 % after *in-vitro* guanidylation ($p < 0.01$) whereas the binding of tryptophan decreased from 20 to 4%. These results are in accordance with the binding of indoxyl sulfate to albumin from healthy control subjects and CKD patients (88 ± 3 vs. 74 ± 10, $p < 0.01$). Thus, *in-vitro* post-translational guanidylation of albumin had a direct effect on the binding capacity of hydrophobic metabolites like indoxyl sulfate and tryptophan.

Conclusions: We used a mass spectrometry-based method for the characterisation of post-translational modification and demonstrated the pathophysiological impact of a representative post-translational modification of plasma albumin. The data described in this study may help to elucidate the pathophysiological role of protein modifications.

SA-PO1101

Validation of a Modified Serum Ammonia Assay to Quantify Urine Ammonium in CKD

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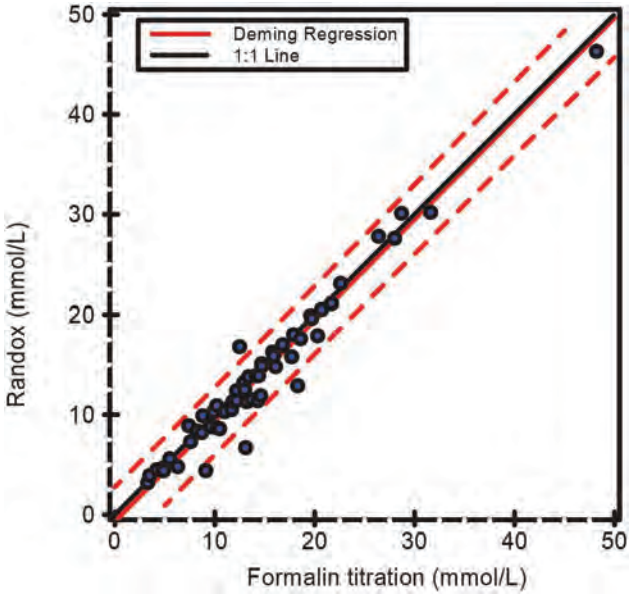
Background: Low urine (u) NH_4^+ excretion is associated with higher risk of GFR decline in CKD. Few clinical laboratories measure uNH_4^+ limiting clinical application, and urine anion and osmolar gaps poorly estimate uNH_4^+ in CKD. We determined whether a clinically-approved serum NH_3 assay reliably quantifies uNH_4^+ in CKD.

Methods: uNH_4^+ was measured using the Randox (Ireland; glutamate dehydrogenase method) serum NH_3 assay on the Architect *ci*8200 chemistry analyzer. Preliminary studies found that 1:40 dilution of urine with Architect on-board diluent quantified uNH_4^+ within limits of the assay (20–1180 µmol/L). Precision studies were performed using synthetic urines with known [NH_4^+] (2.5, 15.6, and 29.5 mmol/L) over 20 days (n=80 measurements per synthetic urine). We then compared [uNH_4^+] obtained by the Randox assay and by formalin-titration in 22 CKD patients (n=58 samples) using Deming regression.

Results: Randox serum NH_3 assay total imprecision (%CV) with 1:40 dilution was 17.7%, 5.1%, and 2.2% in the 2.5, 15.6 and 29.5 mmol/L uNH_4^+ synthetic urines, respectively. In all 58 patient samples, 1:40 dilution quantified uNH_4^+ within the range of the Randox NH_3 assay. After accounting for the pH of formalin, the correlation between uNH_4^+ by formalin-titration and the modified Randox assay was 0.9778 with a regression slope of 1.01 and intercept of 0.70 mmol/L (Figure).

Conclusions: After 1:40 urine dilution, precision of the Randox serum NH_3 assay to quantify uNH_4^+ was better with higher uNH_4^+. Nevertheless, agreement between uNH_4^+ by this approach and by formalin-titration was excellent across a wide range of values in CKD. uNH_4^+ can be reliably quantified in CKD after 1:40 dilution using a standard plasma NH_3 assay and an automated chemistry analyzer.

Funding: Veterans Affairs Support



Comparison of uNH_4^+ by the modified Randox serum NH_3 assay and formalin-titration

SA-PO1102

Validation of the Novel SOMAscan-Based Proteomic Platform in ESRD

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Background: End stage renal disease (ESRD) is characterized by complex metabolic abnormalities. The clinical relevance of many abnormalities in ESRD remains unclear due to the lack of clinically applicable and reproducible diagnostic tests to measure the full spectrum of abnormal proteins and metabolites seen in these patients. The development of multiplex diagnostic platforms is creating opportunities to develop novel diagnostic and therapeutic approaches in patients with ESRD. SOMAscan is a novel multiplex proteomic platform which can measure >1,300 circulating proteins, which, however, has not yet been validated in patients with ESRD. In the present study, we aimed to explore the reliability of SOMAscan for ESRD biomarker measurement.

Methods: We obtained plasma samples from 21 maintenance hemodialysis patients and applied the commercially available SOMAScan proteomic assay to simultaneously measure the concentrations of 1,372 proteins. We employed quality control assessments to remove the SOMAscan assay and sample bias and used Student's t tests to identify differentially expressed SOMAmer reagents. We compared concentrations of SOMAScan-measured prostate specific antigen (PSA) between males and females to test for the presence of biologically expected differences. We validated the SOMAScan concentrations of fibroblast growth factor 23 (FGF23), FGF receptor 1 (FGFR1), and FGFR4 using ELISA. We used Pearson correlation coefficients for correlation analysis and we performed principal component analysis.

Results: Patients were 57±14 years old, 52% were males and 48% were African American. All 21 samples passed the quality control assessments of SOMAscan assay. The mean (± standard deviation) SOMAScan PSA concentration was 4205.6 ± 2799.3 relative fluorescence units (RFU) in males vs. 1060.8 ± 1102.5 RFU in females ($p<0.01$), suggesting biological plausibility. Concentrations measured by SOMAscan correlated well with the ELISA results for FGF23 (R=0.970) and FGFR4 (R=0.507). No significant correlation was found between the FGFR1 SOMAscan and ELISA measurements (R=0.055).

Conclusions: There is a good albeit not perfect correlation between the SOMAscan assay and standard immunoassays. The SOMAscan technology may be useful for the measurement of circulating plasma proteins in ESRD.

SA-PO1103

A Vicious Cycle of Steroid Therapy, Hyperlipidemia, and Macrophage Activation in the Progression of Chronic Renal Lesions

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Background: We have previously reported that increasing numbers of LDL-scavenger receptor $(SR)^+$ macrophages (MQ) is a feature of refractory nephrotic syndrome (RNS) in hyperlipidemic patients treated with high-dose glucocorticoids. To investigate potential pathogenic mechanisms, we examined how glucocorticoids and hyperlipidemia alter the function of human MQ.

Methods: Normal human monocyte-derived MQ (huMQ) were incubated with dexamethasone (Dex), or oxidized LDL (oxLDL) or both, for 48 hours and then analysed by DNA microarray.

Results: Dex and/or ox-LDL stimulation induced up-regulation of scavenger receptors characteristic of M2-type MQ (CD163, CD204 and CD36). Dex and/or ox-LDL also induced up-regulation of cytokines and growth factors associated with inflammation and fibrosis (CCL2, CXCL13, NOS2, TGF-β1, FGF-1, FGF-2 and VEGF-D). In addition, a change in MQ metabolism is suggested altered expression of glucokinase regulator, aldose reductase and acetyl-CoA carboxylase. Immunohistochemistry revealed significant expression of FGF1 in biopsies from RNS patients with RNS which co-localized with $CD204^+$ MQ in areas of fibrosis.

Conclusions: Our data suggest that a vicious cycle of steroid therapy, hyperlipidemia, and M2-type MQ activation promote the progression of renal chronic lesions and treatment resistance.

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SA-PO1104

Effects of Kidney Diseases on Platelet Activation

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Background: Platelet activation can lead to intravascular thrombosis formation. Immature platelets comprise the youngest component of circulating platelet pool and actively participate in thrombosis formation. Although patients with kidney diseases are at increased risk of altered coagulation of both thrombotic and bleeding, little data on the presence of immature platelets in kidney diseases are available. We investigated the relationship between renal function and immature platelets count (IPC) and evaluated effects of endothelial dysfunction, inflammation and thrombopoietin on IPC in patients with kidney diseases.

Methods: First, we measured IPC in patients with 235 chronic kidney diseases, 32 patients with acute kidney injury (AKI), and 75 patients with hemodialysis (HD). Immature platelets were measured with an automated hematoanalyzer that uses fluorescent dyes containing polymethine and oxazine. Second, we analyzed serum interleukin-6, thrombopoietin, and thrombomodulin in HD patients and evaluated the correlation between IPC and them.

Results: In patients with CKD, IPC had a tendency to decrease with the deterioration of renal function, but was not significantly correlated with eGFR (G1+2: n=69, 0.71±0.33, G3: n=83, 0.66±0.35, G4+5: n=83, 0.62±0.38×10^4 /µL). Patients with HD showed significantly lower IPC than patients with CKD (0.47±0.33×10^4 /µL, $p < 0.05$). On the other hand, patients with AKI showed significantly higher IPC than other groups at the peak of serum creatinine (0.99±0.76×10^4 /µL, $p < 0.05$). Among HD patients, patients with catheters showed significantly increased IPC compared to patients with fistulas (0.69 vs. 0.38×10^4 /µL, $p < 0.05$). Second, IPC was not correlated with thrombopoietin (r=-0.159) and IL-6 (r=0.223), but significantly related with thrombomodulin (r=0.359, P< 0.01) in HD patients.

Conclusions: HD patients showed decreased platelet activation compared to non-HD patients, suggesting that uremia might decrease the activation of platelets. In AKI patients, there was a transient platelet activation in the course of AKI. Microvascular endothelial dysfunction might cause platelet activation and intravascular thrombus formation.

SA-PO1105

Removal of sFLT-1 and PlGF with Plasmapheresis in Pregnancy

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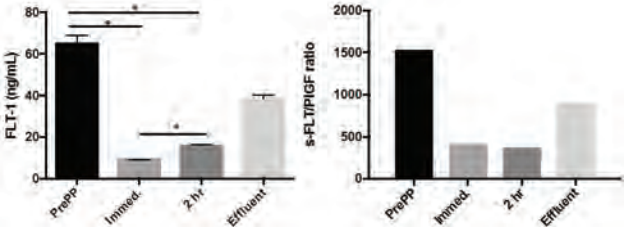
Background: Preeclampsia is characterized by HTN and proteinuria >20 weeks of gestation with glomerular endotheliosis thought to be due to an imbalance of angiogenesis (placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFLT-1)). sFLT-1 levels are higher near the end of normal pregnancies; however, sFLT-1 levels increase earlier and to higher concentrations and inhibit PlGF in preeclampsia. Removal of sFLT-1 using selective apheresis in early preeclampsia prolongs time to delivery. The effect of membrane-based plasma exchange (mTPE) on sFLT-1 and PlGF levels are not known.

Methods: A 33 y/o 35 week pregnant patient presented with a concern for HELLP vs. TTP. Empiric daily mTPE sessions with FFP replacement were initiated until her ADAMTS13 returned at 42%. Her clinical status gradually improved after delivery of the placenta and a viable baby. Serum samples were obtained before, immediately following, and two hours after one mTPE session. We examined sFLT-1 and PlGF concentration of these samples as well as in the effluent in duplicate.

Results: sFLT-1 was immediately reduced by 86% with mTPE (64.94 ng/ml to 9.17 ng/mL, p=0.03) and rebounded to 15.88 ng/mL two hours after (p=0.02), 4 times less than pre-mTPE values. Effluent sFLT-1 was 38.46 ng/mL. PlGF was immediately reduced by 48% (42.40 pg/ml to 21.89 pg/ml, p=0.13) and rebounded to pre-mTPE values two hours after (42.7 pg/mL, p=0.07). Effluent PlGF level was 42.4 pg/ml. The reduction in the sFLT-1/PLGF ratio was 1.53 to 0.42 (73% reduction) (p<0.01) (Fig 1).

Conclusions: mTPE removed sFLT-1 from the serum at nearly a 4:1 ratio compared to PlGF in pregnancy, and PlGF rebounded to pre-mTPE values within two hours. This ratio reduction is theoretically favorable to improve the angiogenic imbalance in preeclampsia and suggests that mTPE may have a role as therapy for preeclampsia in the future.



Removal of sFLT-1 and sFLT-1/PlGF ratio in pregnancy with mTPE. *p<0.05

SA-PO1106

Sterile Pyuria Is Common in CKD and Differential Counting of Urinary Leukocytes Could Be Helpful for Predicting Urinary Tract Infection

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Background: Pyuria is a helpful marker for urinary tract infection (UTI) in general population. Meanwhile, pyuria is not infrequent in advanced chronic kidney disease (CKD) patients. There has been assumption that sterile pyuria can be seen in CKD due to chronic renal parenchymal inflammation. However, there are limited data on whether CKD increases the rate of pyuria or how we should interpret pyuria of CKD. Here, we aimed to investigate the prevalence and characteristics of pyruia of CKD.

Methods: This was a cross-sectional study of a single center. Urine analysis (UA) was performed in all the stable hemodialysis (HD) and non-dialysis CKD (eGFR < 60ml/min/1.73m^2) patients of the outpatient clinic during 3 month. Patients with urinary symptom or recent history of antibiotics were excluded. Pyuria was defined as white blood cell (WBC) ≥ 5/high power filed by microscopy. WBC differential counting was done in case UA showed pyuria. Culture-positive pyuria was defined as UTI.

Results: UA was examined in 70 HD patients who voids at least once every day and 228 non-dialysis CKD patients. The prevalence of pyuria was 51.4% (male (M) 36.1%, female (F) 67.6%) in HD and 22.4% (M 12.5%, F 39.3%) in CKD population, and were much higher compared to that of the age-matched general population (overall 7.3%, M 1.6%, F 19.1%) which was obtained from health examination in the same hospital (n=4897). Of the 86 patients with pyuria, only 22.1% were proven to be UTI (11.1% of HD and 30.0% of CKD). Female gender, lower stages of CKD, more leukocytes in urine, and positive nitrite-response were associated with true UTI in pyuric patients. As for differential counting, the majority of urinary leukocytes were still neutrophils even in sterile pyuria. However, the percentage of neutrophil was significantly lower (69.1% vs 92.5%), and the percentages of lymphocyte and monocyte were higher (18.5% vs 4.9% and 9.9% vs 2.1%, respectively) in sterile pyuria compared with UTI. In multivariate logistic regression analysis, the degree of pyuria, nitrite response, and the percentage of neutrophil remained independently associated with UTI in pyuric patients.

Conclusions: Pyuria is more common in CKD than in the general population. Differential cell counting of urinary leukocytes could be helpful for predicting UTI in asymptomatic CKD patients with pyuria.

SA-PO1107

New Urine Biomarkers for Site-Unique Injuries in the Kidney

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Background: In kidney diseases, various sites, such as glomerulus and other sites are injured to appear functional impairments and symptoms varied according to the injured sites and its degree. We aimed to develop urine examination to obtain the kidney site-unique injuries by proteomic biomarker discovery. To select kidney site-unique proteins as candidates of urine biomarkers for these site injuries, various parts of the kidney sections were analyzed by proteomics. To validate usefulness of the biomarker candidates, we established antibody-based assays for measurement of these biomarker candidates in urine and examined relationship between the urine excretion and the degree of kidney injuries. Finally we could select several urine biomarkers for injuries at various parts such as the glomerulus, proximal tubule and interstitium.

Methods: Sections of human kidney parts (glomerulus, proximal tubule, distal tubule, collecting duct etc) were laser micro-dissected from formalin-fixed paraffin-embedded kidney sections and peptides were collected from these sections of kidney parts by the on-site direct digestion method for mass spectrometry (Orbitrap Fusion, Thermo Scientific). The proteomes of these kidney parts were compared each other and also with those of plasma and urine proteomes to select proteins, which were uniquely excreted from each site or part of the kidney. We established immunoassay system by using a surface plasmon resonance (SPR) device (ProteOn, Bio-Rad). Several site-unique urine proteins selected by proteomics: PRA2R1 and GPRC5C for glomerulus-, NPR1 for proximal tubule- and GGT5 for interstitium-injury) were quantitatively measured in urine samples from CKD patients (IgA nephropathy and diabetic nephropathy) by SPR for validation.

Results: Concentrations of the proteins increased significantly in urine with the stage of CKD: PRA2R1 and GPRC5C excretion in urine presumed to reflect the degree of glomerular injury, NPR1 to predict the proximal tubule reactions and GGT5 the interstitial expansion, indicating that these new urine biomarkers are useful for evaluation of kidney injuries more precisely as or more than the kidney biopsies or evaluation of kidney injuries more precisely.

Conclusions: Non-invasive urine tests for the new biomarkers may be beneficial for clinical quantitative evaluation of kidney site-unique injuries for precision medicine in the near future.

Funding: Commercial Support - Tosoh compary

SA-PO1108

Comparison of Urine and Plasma Biomarker Levels Measured by Aptamer-Based versus Immunoassay Methods in Cardiac Surgery Patients

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Background: Protein-detection assays are invaluable tools in biomarker discovery. However, only immunoassays are widely used, measuring 10-20 analytes per biosample. The novel aptamer-based assay uses nucleotide aptamer technology to measure over 1,300 analytes per biosample. We sought to compare the aptamer-based platform versus traditional immunoassay approaches to quantify analytes in paired samples before and after cardiac surgery.

Methods: In a sub-study of the TRIBE-AKI cohort, 54 individuals with acute kidney injury (AKI) after cardiac surgery were identified. The group included AKI progressors and AKI non-progressors. The levels of preoperative and postoperative plasma and urine biomarkers which had been previously evaluated via immunoassays were compared to the levels detected by an aptamer-based assay using Spearman correlations.

Results: Spearman correlations were estimated when at least 50% of biomarker values were within detectable ranges (plasma: preoperative 26/33, postoperative 31/33; urine: preoperative 13/16, postoperative 16/16). Twenty seven percent of reportable plasma preoperative biomarkers displayed correlations ≥0.75 between immunoassay and aptamer measurements, 23% displayed correlations of 0.50-0.75, and 50% displayed correlations <0.50. In urine these values were 15%, 39%, and 46%, respectively. Forty two percent of reportable plasma postoperative biomarkers displayed correlations ≥0.75, 16% displayed correlations 0.50-0.75, and 42% displayed correlations <0.50. In urine these values were 19%, 25%, and 56%, respectively.

Conclusions: The aptamer-based assay detects proteins with moderate to strong correlation to current immunoassay methods. The correlations in urine are weaker compared to plasma. Aptamer-based assay technology should be further validated in multiple settings as a high-throughput screening tool for biomarker discovery.

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Table 1. Spearman Correlation between Aptamer-Based Platform and Immunoassays in Plasma and Urine by Collection Time Around Surgery

	Low Correlation (<0.50)		Medium Correlation (0.50-0.75)		High Correlation (≥0.75)	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Plasma	IL-6 MCP-1 TNF-alpha bFGF IFNg Gal 3 IL-18 IL-13 Tie 2 VEGF-C IL-12 KIM-1 VEGF	bFGF IFNg Gal 3 IL-18 IL-13 IL-2 IL-4 CK-MB Tie 2 VEGF-C IL-12 TNNI2 KIM-1	IL-8 HFABP YKL-40 TNTHS BNP-3 CK-MB	VEGF-D TNF-alpha TNTHS IL-1b BNP-3	IL1R1 TNF-R2 Cystatin C NT-proBNP TNF-R1 VEGF-D NGAL	IL1R1 IL-8 TNF-R2 IL-6 Cystatin C NT-proBNP TNF-R1 TNNI3 MCP-1 NGAL HFABP YKL-40 IL-10
Urine	Cystatin C IL-1b IL-13 IL-4 IFNg IL-2	Albumin IL-1b IL-13 IL-4 TNF-alpha IFNg IL-12 IL-10 IL-2	NGAL IL-6 IL-18 KIM-1 Albumin	LFABP IL-18 KIM-1 Cystatin C	IL-8 LFABP	NGAL IL-8 IL-6

Table 1

SA-PO1109

GFR Adjusted Uric Acid Levels Are a Superior Cardiovascular Outcome and Mortality Predictor Than Uric Acid Levels Alone

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Background: Hyperuricemia is associated with increased cardiovascular risk and mortality. Chronic renal failure increases uric acid (UA) levels due to decreased filtration. A formula calculating GFR adjusted UA levels (estimated UA, eUA) has been developed by our group. The aim of this study was to evaluate the potential of eUA levels in predicting cardiovascular outcome and mortality in a cardiovascular risk cohort of patients.

Methods: The relation of GFR and UA levels was investigated with the eUA-formula in the LURIC cohort. LURIC was a prospective cohort study to identify genetic and metabolic risk factors in coronary heart disease. Patients were excluded with GFR levels <10ml/min and >100ml/min because of eUA-formula reasons. Subgroup analysis was performed (eUA < UA as risk group and eUA > UA as control group). Mortality, chronic heart failure (CHF) and cardiac events (CE) were documented outcome parameters. Binary univariate and multivariate logistic regression analysis were performed to study prediction of outcome variables by eUA or UA.

Results: 3316 patients were included in the LURIC cohort. Due to GFR, 652 patients were excluded. Of 2654 patients (1774 male) at an age of 64.71 ± 9.21 the GFR was 75.78 ± 16.98 ml/min. UA levels were measured with 5.24 ± 1.75 mg/dl. 686 patients (25.8%) died of all-cause mortality during the follow up period of the study. Mean UA levels in the subgroups did not differ. GFR was significantly lower in the risk group vs. the control group. Mortality and CHF NYHA > 1 were significantly higher in the risk group than in the control group (OR 1.35 and 1.65), while no differences were noted for CE. Univariate analysis revealed a significant benefit of using the eUA model compared to the classic UA model in predicting mortality (OR 1.8 vs. 1.23; -2LL 2874.32 vs. 2962.33) and CE (OR 1.54 vs. 1.16; -2LL 3231.37 vs. 3301.27). Multivariate regression analysis showed a significant better prediction of the outcome variables mortality (OR 6.06 vs. 1.25; -2LL 2187.17 vs. 2264.13), CHF (OR 2.96 vs. 1.65; -2LL 3160.43 vs. 3170.40) and CE (OR 2.35 vs. 1.48; -2LL 2445.85 vs. 2474.54) in the adjusted eUA-model compared to the UA-model group.

Conclusions: GFR adjusted uric acid (eUA) levels predict cardiovascular outcome significantly better in a cardiovascular risk cohort than uric acid levels alone.

SA-PO1110

The Automated Urinalysis in Proliferative Glomerulonephritis

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Background: Since the introduction of automated urine analyzers, manual examination of the urine sediment has rapidly fallen out of favor. Limited data are available on the test performance characteristics of the modern automated urinalysis (UA).

Methods: We studied whether features on an automated UA distinguish proliferative glomerulonephritis (PGN) from other forms of kidney disease using a prospective observational cohort of adult patients undergoing native kidney biopsies at 3 tertiary care hospitals in Boston, MA. We included individuals who had an automated UA within 30 days of kidney biopsy along with an adjudicated clinicopathologic diagnosis. We excluded individuals who were on immunosuppression at the time of the biopsy.

Results: 134 of 512 patients had PGN. The mean age was 53.9±15.9 years, 46.3% were female, and 68.6% were white. The mean estimated glomerular filtration rate was 53±34 mL/min/1.73m^2 and median proteinuria was 2.0 (interquartile range 0.63-4.97) g/g creatinine. **Table 1** shows the sensitivity and specificity of automated urine RBC counts for diagnosis of PGN at different levels of dipstick proteinuria. The automated urine RBC count identified PGN with an area under the receiver operating characteristic curve of 0.75. At a threshold of >2 RBCs per high-power field (HPF), the positive predictive value was 38% and the negative predictive value was 91% for PGN. Among those with ≤1+ proteinuria, the negative predictive value rose to 97%. RBC casts and dysmorphic RBCs were rarely reported (1 and 3 cases of PGN, respectively).

Conclusions: Hematuria and proteinuria from the automated UA had modest ability to differentiate PGN from other kidney diseases. The diagnostic performance characteristics of the manual sediment exam should be investigated and compared directly to those of the automated UA.

Funding: NIDDK Support

Table 1. Sensitivity and specificity of automated UA RBC counts and dipstick protein for diagnosis of PGN.

	RBCs ≥0/HPF (sensitivity/specificity)	RBCs >2/HPF (sensitivity/specificity)	RBCs >5/HPF (sensitivity/specificity)	RBCs >10/HPF (sensitivity/specificity)	RBCs >15/HPF (sensitivity/specificity)
Dipstick protein ≥ 0	100% / 0.0%	86.2% / 51.0%	77.1% / 61.9%	61.5% / 75.0%	51.4% / 80.8%
Dipstick protein ≥ Trace	94.7% / 14.7%	82.6% / 57.3%	73.4% / 68.0%	58.7% / 78.0%	48.6% / 82.9%
Dipstick protein ≥ 1+	85.7% / 24.3%	74.3% / 59.2%	67.0% / 69.3% %	52.3% / 78.6%	43.1% / 83.5%
Dipstick protein ≥ 2+	73.7% / 36.0%	64.2% / 65.1%	57.8% / 73.8%	45.0% / 82.2%	36.7% / 86.7%
Dipstick protein ≥ 3+	39.1% / 61.3%	35.8% / 77.4%	33.0% / 83.2%	25.7% / 89.0%	18.4% / 91.9%

RBC, red blood cell; HPF, high-power field; UA, urinalysis.

SA-PO1111

Comparison of Different Methods of Urinary Protein Excretion Measurement–Is the King Really Dead?

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Background: Assessing proteinuria is one of the most important diagnostic tests for a clinical nephrologist. When treating patients, it is often indispensable to accurately quantify the amount of protein lost, hence cumbersome timed urine collections (the gold standard or "king" of methods– 24h protein excretion rate- PER) are often replaced by spot urinary protein to creatinine ratio (PCR). The aim of the study was to determine whether the latter can reliably compare to the gold standard and whether "timing" of a spot urine sample is essential (as there is a diurnal and postural effect on protein excretion).

Methods: 143 adult patients hospitalized in the I Department of Nephrology with proteinuria (both primary and secondary glomerular diseases) were examined (a total of 187 cases). Subjects with an active infection or tumors of the urinary tract were excluded. Each patient was instructed how to perform a 24-hour urine collection and on the same day three consecutive urine samples were also collected (starting with the first morning void). Concentration of protein and creatinine in spot urine samples and the timed urine collection were measured.

Results: PCR from all three spot samples moderately correlated with 24h PER (0.76, 0.79 and 0.82 respectively). Log transformation of examined variables slightly improved observed association (0.80, 0.84 and 0.86). The sensitivity and specificity for proteinuria above 1.0 g/day were 0.79 and 0.73 for sample 1, 0.82 and 0.68 for sample 2 and 0.82 and 0.67 for sample 3. For nephrotic proteinuria it was respectively 0.62 and 0.94, 0.62 and 0.93, 0.66 and 0.92. Sex, age, weight and serum albumin concentration were significantly associated with 24h PER and were used for development of prediction equation yielding adjusted $R^2$of 0.78, 0.83 and 0.86. Bland-Altman analysis revealed an increasing difference between 24h PER and PCR with increasing proteinuria irrespectively of sampling time.

Conclusions: In patients with primary and secondary glomerular diseases spot urine protein to creatinine ratio only modestly correlates with daily proteinuria whether it's morning or random urine sample. It seems, while searching for new markers, nephrologists can just say: "long live the king".

SA-PO1112

Quantitation of Urinary Sediment Podocalyxin (u-sed-PCX) Predicts Urinary Podocyte Numbers

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Background: Immunostaining of urine sediments shows a small number of podocytes and numerous cell debris resulting from the destruction of podocytes due to cell death, therefore, to know the exact number of urinary podocytes it needs to add a portion of cell debris to the number of podocytes evaluated as whole cells. In the present study we developed a procedure to count the exact podocyte numbers (podocytes + cell debris) in the sediments.

Methods: 1) Urinary sediment PCX was quantified by ELISA (Diabetologia 55:2913, 2012) in normal control and various glomerular diseases. 2) The idea to obtain the exact number of urine podocytes is based on the calculation of urine sediment PCX (reflecting whole podocytes + cell debris from destructed podocytes) divided by PCX content belonging to single podocyte. We named this number as estimated urine podocyte number (eUPN). 3) To obtain the PCX content belonging to single podocyte we caluculated from 3 models;

model 1 (assuming that it takes 150 years until complete podocyte loss from glomeruli in normal control), model 2 (evaluating podocyte loss during the interval in serial performed renal biopsies from our own patient with IgA nephropathy) and model 3 (evaluating podocyte loss from the published data in diabetic kidney disease (Diabetes 51;3083-3089, 2002). The mean value from 3 models was used in this study. 4) Several assumptive figures for normal control were used such as; urine volume:1000ml/day, Creatinine excretion:1 g/day, nephron number:$1.5x10^6$, podocyte number/glomerulus:500 cells.

Results: 1) Single podocyte PCX content was calculated as 141.6, 153.2 and 100.0 pg/podocyte by model 1, 2 and 3, respectively. The mean value (131.6 pg/podocyte) was taken for determining eUPN in this study. 2) U-sed-PCX and (eUPN) in normal control, DKD, IgAGN, Nephrotic syndrome, Lupus nephritis, membranous nephropathy, ANCA related GN, and others were1.9 ng/mg creatinine (14.7 podocytes/mg creatinine), 3.6 (27.3), 2.0 (15.0), 11.5 (87.0), 7.1 (54.3), 5.2 (39.1), 1.7 (13.1), and 1.8 (13.3), respectively. 3) U-sed-PCX and (eUPN) in diabetic kidney diseases (normoalbuminuric, microalbuminuric and macroalbuminuric) was 1.6 (11.8), 3.7 (27.9) and 8.8 (66.7), respectively.

Conclusions: Quantitation of u-sed-PCX predicts more exact urinary podocyte number (eUPN), indicating this might be a better podometric biomarker in clinical nephrology.

SA-PO1113

Genotyping Apolipoprotein L1 (ApoL1) from Dry Plasma with Proteomics

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Background: ApoL1 has two genetic risk variants (G1 & G2) associated with increased risk of nondiabetic CKD and kidney transplant failure. As these risk variants occur almost exclusively in African Americans, genetic testing may improve both monitoring and outcomes of CKD as well as allocation of donor organs in this population. To this end, we developed a bottom-up proteomic assay to identify genetic variants of ApoL1 from both liquid plasma samples collected by venipuncture as well as from dry plasma samples produced on a blood plasma separation device that can be collected in-home via a finger prick.

Methods: Both 20 μL of plasma or ~95 mm^2 punch of dried plasma were processed using a common workflow. Samples were denatured in DTT and deoxycholate for 30min at 56°C, then digested with 800μg of trypsin for 30min at 37°C (pH 8) after addition of labeled internal standards. Digestion was quenched and the deoxycholate precipitated by the addition of formic acid and the clarified supernatant analyzed by liquid chromatography coupled with tandem mass spectrometry. The three ApoL1 protein variants (WT, G1, G2) were uniquely detected by monitoring for the specific surrogate peptides containing the point mutations, which were produced by the trypsin digestion. Two surrogate peptides common among all protein variants were also monitored for quality control of sample processing.

Results: Reproducibility of the proteomic assay was demonstrated over 20 assay runs by analysis of dry and liquid specimens from 3 heterozygous individuals (WT/G1, WT/G2, and G1/G2). Dry plasma from the same heterozygous genotypes were observed to be stable for up to 4 weeks stored at ambient (22°C) and elevated temperature (37°C). Finally, perfect agreement with a Sanger Sequencing assay was observed in matched liquid and dry plasma specimens in a cohort of 209 African American donors, which consisted of 82 WT/WT, 64 WT/G1, 38 WT/G2, 10 G1/G1, 10 G1/G2, and 5 G2/G2 individuals.

Conclusions: This proteomic assay provides the feasibility for ApoL1 genotyping using dry plasma which can be collected in-home via finger prick using blood plasma separation devices. Such testing should allow for more widespread and cost-effective genotyping of this high risk population.

SA-PO1114

Macrophages as a Marker for Endocapillary Hypercellularity in Lupus Nephritis

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Background: Lupus Nephritis (LN) is a manifestation of Systemic Lupus Erythematosus (SLE) which occurs in up to 60% of patients suffering from SLE. LN is strongly related to mortality and morbidity in SLE, especially class III and IV LN. The interobserver agreement of endocapillary hypercellularity which determines whether a biopsy is classified as class III or IV in LN, has been found to be moderate. In IgAN, the presence of glomerular macrophages was put forward as a surrogate marker for endocapillary hypercellularity. We investigated whether in LN, the presence of glomerular macrophages could serve as a surrogate marker for endocapillary hypercellularity as well.

Methods: 99 lupus nephritis biopsies were scored for the number of endo- and extracapillary macrophages per glomerulus using CD68 staining, as well as the overall presence of endocapillary hypercellularity (categorical variable *E0/E1*) and percentage of glomeruli with endocapillary hypercellularity (continuous variable *E-continuous*) per biopsy using a silver staining. Overall presence of endocapillary hypercellularity and percentage of glomeruli with endocapillary hypercellularity were both correlated with endo- and extracapillary macrophage count using a Mann-Whitney U test and a Spearman correlation test.

Results: A strong correlation was found between the quantity of glomerular macrophages and the presence of hypercelullarity, as well as between the percentage of glomeruli with endocapillary hypercellularity and number of glomerular macrophages. The correlation was stronger using only endocapillary macrophages in our analysis compared to extracapillary macrophages.

Conclusions: In lupus nephritis, the presence of glomerular macrophages is an excellent surrogate marker for endocapillary hypercellularity. This marker could be a useful tool towards a more effective and reproducible usage of the LN classification.

	E1/E0	E continuous	
	p	p	rho
Total glomerular Macrophages	<,001	<,001	0,780
Endocapillary Macrophages	<,001	<,001	0,764
Extracapillary Macrophages	<,001	<,001	0,566

SA-PO1115

The Japanese Histological Grade Classification and the Oxford Classification of IgA Nephropathy Show the Same Prediction Performance on Renal Functional Decline in 905 Japanese Patients

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Background: The Japanese Histological Grade Classification (JHGC) (Gr1-Gr4) was established as a lumped system corresponding to <25%, 25-49%, 50-74% and ≥75% of total glomeruli exhibiting active crescents (C), global sclerosis (G), segmental sclerosis (S), or fibrous crescents. In contrast, the Oxford classification is a split system constituting of dichotomized M, E, S, T1, T2, C1, and C2. The purpose was to compare the 2 classifications systems focusing on their ability to predict renal functional decline.

Methods: The 905 Japanese patients (pts) with IgA nephropathy (male : 49%, median age: 38 yrs) were prospectively followed for a median of 48 months. The average amount of proteinuria (PU) was 1.07 g/day. Mean eGFR and median rate of decline in eGFR were 77.0 ml/min/1.73m^2 and -0.95 ml/min/1.73m^2/y, respectively. The prediction performance was compared using the Harrell's C statistic (HCS). The clinical and therapeutic variables were additionally collected including initial PU, initial square root eGFR (SReGFR), initial mean arterial pressure, steroid therapy (ST), RAS blockade (RASB) and tonsillectomy (TON).

Results: 66 %, 54% and 42% of the patients were treated by ST, RASB, and TON, respectively. In stepwise Cox regression analysis for the full model, Gr4, Gr3, Gr2, PU, SReGFR, TON and ST for 1.5 time's increase of serum creatinine (sCr) were selected as independent predictors, whose HR were 28, 7, 4, 2, 1, 1 and 0, respectively. HCS was 0.87. In Oxford, T2, T1, M, RASB, C1, PU, TON, SReGFR, ST and E were selected, whose HR were 4, 3, 2, 2, 2, 2, 1, 1, and 0, respectively, HCS was 0.86, which was statistically not different from that of JHGC. For the limited model without clinical and therapeutic parameters, Gr4, Gr3, and Gr2 were selected, whose HR was 79, 14, and 5, respectively. HCS was 0.82. In Oxford, T2, T1, M, and E but not S, C1, and C2 were selected, whose HR were 20, 5, 3, and 1, respectively. HCS was 0.81.

Conclusions: Both the lumped system of JHGC and the split system of Oxford showed the same high prediction performance on renal functional decline in full and limited model. However, a flexibility in a lumped approach of JHGC as opposed to a split system of Oxford may be more robust when being applied to diverse cohorts.

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PUB001

Renal Transplant Function After Coronary Angiography with Iodinated Contrast

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Background: There is perceived risk to renal transplant function in administering iodinated contrast agents. There may be reluctance to perform coronary angiography in kidney transplant patients, despite an increased risk of cardiovascular disease compared with the general population. We sought to determine if renal transplant function was adversely affected within 30 days of coronary angiography.

Methods: Prevalent renal transplant patients undergoing coronary angiography in a single centre (01/2006 – 02/2018) were identified. Biochemical and demographic data were extracted from the electronic patient record. The most recent serum creatinine (SCr) prior to angiography (or average value over 3 months) was considered the baseline. Highest SCr within 7 days and within 30 days (or next available) of coronary angiography were extracted. Rise in creatinine >26 micromol /l was considered significant (equivalent to Acute Kidney Injury (AKI) Network criteria stage 1 AKI).

Results: There were 127 coronary angiographies conducted in 89 patients: 67.4% were male and mean age was 58.0 ± 10.1 years. Median time since transplant was 6.2 years (IQR 2.5 – 16.1); median time since start of first renal replacement therapy was 13.4 years (IQR 6.8 – 25.0). Median baseline SCr was 155 micromol/l (IQR 110-220, range 56-738). The most common indications for coronary angiography were angina (27.6%) and non-ST

elevation myocardial infarction (23.6%). Diagnostic angiography was conducted in 59.1%; balloon angioplasty or stenting in 40.9%. There was a significant rise in SCr within 7 days in 24.5% cases (n=24/98; median rise 52, range 28-163 micromol /l). SCr returned to baseline within 7 days or there was an alternative explanation for rise in SCr in 20/24 cases. In 4 cases with a clinically significant rise in SCr, there was known severe and progressive renal transplant dysfunction. Of those with no available SCr within 7 days (n=29/127), none had a persistent rise in SCr (7-30 days/next available). In the absence of critical illness at time of coronary angiography, no patient required dialysis or extended hospital stay for contrast-associated AKI.

Conclusions: In this cohort of renal transplant recipients undergoing coronary angiography, there was a clinically significant rise in SCr in a minority of cases. Renal transplant should not be regarded as a contra-indication to coronary angiography.

Funding: Private Foundation Support

PUB002

Community Acquired AKI in Mansoura Nephrology Dialysis Unit, One Year Prospective Observational Study

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Background: Acute kidney injury (AKI) is a major health problem with poor patient prognosis. We evaluated the clinical characteristics, risk factors, associated comorbidities and outcomes of AKI patients

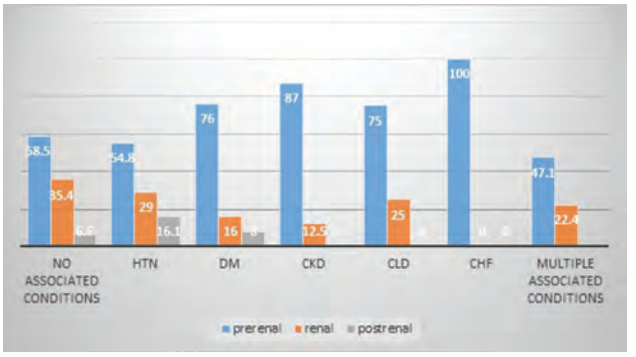
Methods: A single center prospective observational study. The patients were admitted in Nephrology and Dialysis Unit in Mansoura University Hospitals over one year from January, 2016 to December, 2016. These patients were diagnosed to have AKI or AKI on top of CKD according to the KDIGO 2013 criteria. All patients were subjected to complete history taking, physical examination and full laboratory investigations

Results: We evaluated 199 (96 males plus 103 females) aged between 18 to 88 years old. Dehydration was the commonest precipitating factor for AKI in our patients (68.8%) and Oliguria was the commonest symptom present in 47.7 % of patients. 65.8 % of patients received intravenous fluids, 22.6 % of patients received diuretics and 33.7 % received renal replacement therapy in the form of intermittent haemodialysis while twenty five patients (13.16%) died and 44 patients showed no recovery

Conclusions: community acquired AKI (secondary mainly to dehydration and infections) is a major health problem with high morbidity and mortality

Description of clinical criteria of the patients

Factor	Patient N(%) Total Number=199 patients
Contributing factors	
Dehydration	137(68.8%)
NSAIDs	51 (25.6%)
Infection	83 (41.7%)
Sepsis	35 (17.6%)
ACEIs	32 (16.1%)
AGN	20 (10.1%)
Obstruction	12(6%)
Presentation	
Oliguria	95(47.7%)
Infection symptoms	44(22.1%)
Dysuria	38(19.1%)
Hypotension	35(17.6%)
Management	
Fluids	131(65.8%)
Diuretics	45 (22.6%)
RRT	67(33.7%)
Outcome of 190 patients N(%)	
Mortality n %= 25 (13.16%)	
No recovery n %= 69 (36.3%)	
Recovery according to hospital stay	Recovery Rate
Recovery in 66 patients with hospital stay <1-week n(%)	48(72.7%)
Recovery in 42 patients with hospital stay (1-2) weeks n(%)	19 (45.2%)
Recovery in 13 patients with hospital stay >2weeks n(%)	7(54%)



PUB003

Urinary Urea Excretion as an Early Biomarker of AKI

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Background: Acute kidney injury (AKI) increases intensive care unit (ICU) morbidity and mortality, the diagnosis being based on urine output (UO) and serum creatinine (sCr), neither of which provides reliable, timely information. Most of the known AKI biomarkers are costly to determine and not widely used. Urinary concentration is impaired early in chronic kidney disease, and higher excretion of urea may be a marker of renal recovery for hemodialysis weaning. We hypothesized that low fractional excretion of urea (FeU) would be a timely biomarker of AKI.

Methods: We evaluated adult ICU patients at high risk for AKI according to a clinical score. We excluded patients with a basal estimated glomerular filtration rate (eGFR) <45ml/min/1.73m^2, history of AKI or kidney transplantation, or body mass index <19kg/m^2. On a daily basis, we evaluated urinary urea (UU), 6h-excreted urinary urea volume (UUv), FeU, and the UU/urinary creatinine (UU/Ucr) ratio. AKI was diagnosed on the basis of the KDIGO criteria (i.e., sCr or UO). Results are mean±SD.

Results: At baseline, the 17 patients included were 54±15 years of age, with a SAPS3 of 50.6±11.9, sCr of 0.72±0.30mg/dl, and eGFR of 106±30ml/min/1.73m^2. One day before AKI diagnosis (D–1), FeU was lower in the patients with AKI (n=5) than in those without (Table 1), with an area under the receiver operating characteristic curve of 0.88 (Figure 1). An FeU cut-off ≤22.75 had 80% sensitivity and 81.8% specificity for next-day AKI development.

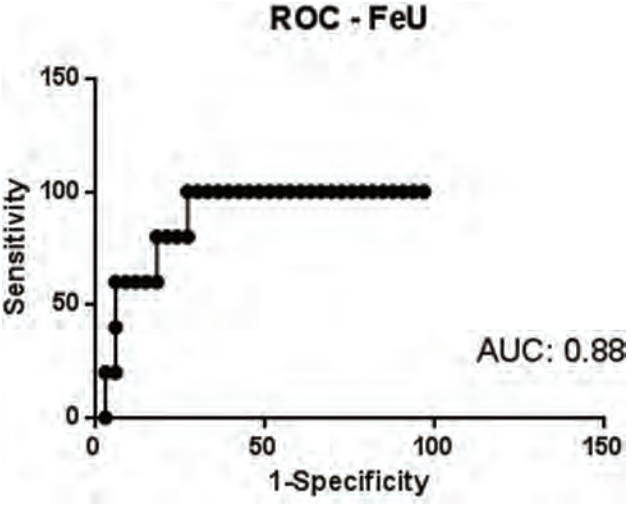
Conclusions: FeU may be a feasible, accessible early biomarker of AKI. Supported by FAPESP.

Funding: Government Support - Non-U.S.

	No-AKI (n=33)	AKI D–2 (n=3)	AKI D–1 (n=5)	AKI D0 (n=4)
UU (g/L)	15.9±8.6	10.2±10.5	12.7±9.0	18.7±9.0
UUv (g)	7.1±5.8	6.3±4.3	4.4±3.5	6.3±5.4
UU/Ucr	14.0±6.2#	24.8±15.2	11.2±3.5#	15.1±7.3
FeU (%)	35.7±13.3	41.5±12.4	20.3±4.8*	25.4±14.0

# p<0.05 vs AKI D-2

* p<0.05 vs No-AKI



PUB004

Risk Factors of Postoperative AKI in Patients with CKD

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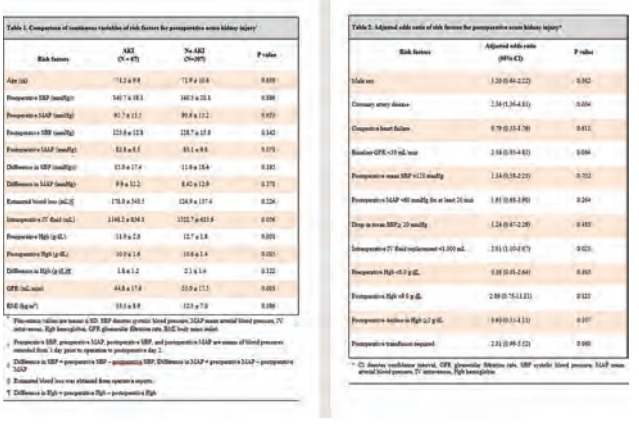
Background: Postoperative acute kidney injury is associated with increased mortality and cost in major inpatient surgeries. Patients with chronic kidney disease are at high risk of postoperative acute kidney injury and associated complications.

Methods: We retrospectively collected perioperative data of 399 patients with chronic kidney disease who underwent common inpatient orthopedic or general surgeries (appendectomy, colectomy, cholecystectomy, total hip replacement, total knee replacement) at 5 hospitals in Washington State between January of 2015 and October of 2017. Total of 374 patients were included for data analysis. Multivariate logistic regression analysis was used to identify statistical significance of each risk factor.

Results: 67 out of 374 patients (17.9%) developed acute kidney injury. Between the acute kidney injury group and the no acute kidney injury group, there were significant differences in preoperative hemoglobin (mean±SD 11.9±2.0 vs. 12.7±1.8 g/dL, P=0.001), postoperative hemoglobin (10.0±1.6 vs. 10.6±1.4 g/dL, P=0.005), and baseline glomerular filtration rate (44.8±17.6 vs. 53.0±17.5 mL/min, P=0.001). Coronary artery disease (29.8% vs. 12.6%, P <0.001), postoperative mean arterial blood pressure less than 60 mmHg for at least 20 minutes (29.8% vs. 16.2%, P=0.023), and postoperative transfusion (38.1% vs. 15.3%, P<0.001) were more common in the acute kidney injury group. In the multivariate logistic regression analysis, history of coronary artery disease (adjusted odd ratio [OR] = 2.56, Confidence Interval [CI] = 1.36 - 4.81) and intraoperative intravenous fluid replacement less than 1,000 mL (OR = 2.01, CI = 1.10 – 3.67) were associated with increased risk of postoperative acute kidney injury.

Conclusions: History of coronary artery disease and intraoperative intravenous fluid replacement less than 1,000 mL were associated with postoperative acute kidney injury in patients with chronic kidney disease.



PUB005

Arterial Stiffness in CABG - A Pilot Study

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Background: AKI following coronary artery bypass graft (CABG) affects 20% of patients and is potentially preventable but there is currently no widely accepted risk stratification method to identify those at risk. This was a pilot study to assess the hypothesis that vascular stiffness may be a predictor of AKI post CABG surgery.

Methods: 43 patients (18-80 years) undergoing isolated elective CABG were recruited. Anthropometric variables, renal function and pulse wave velocity (PWV) were measured pre-operatively and renal function post-operatively for 5 days. Aortic tissue samples obtained intra-operatively were histologically analysed. AKI staging was based on the KDIGO definition. Statistical analysis was obtained using SPSS 25.

Results: Baseline characteristics are as shown in table 1. There was no statistically significant differences between AKI and non-AKI patients. Three patients (7%) developed AKI stage 1 following surgery. PWV in patients who developed AKI tended to be higher but not statistically significant (11.7 ± 3.1 vs 10.1 ± 2.5 m/s; p=0.306). PWV increased with age (Pearson correlation 0.568; p=0.000), diabetes (12.4 ± 2.0 vs 9.5 ± 2.3 m/s; p=0.001). PWV was also high with high systolic BP, <140mmHg vs >140mmHg, (9.3 ± 2.4 vs 11.7 ±2.2 m/s; p=0.002). Histological comparison of aortic samples of an AKI patient with high PWV compared to a non- AKI patient with low PWV (Figure 1) shows differences in calcification and elastin.

Conclusions: The PWV was higher in CABG patients with diabetes, older age and sBP. Patients with AKI following CABG trend towards high PWV but further study will be needed with more patients to establish a link.

Variable	Study population (n=43)	Patients who did not develop AKI (n=40)	Patients who developed AKI (n=3)
Age, years	68 (16.5)	68 (19.25)	66 (11)
Male	37 (86%)	34 (85%)	3 (100%)
Caucasian	34 (79%)	32 (80%)	2 (67%)
Non-smoker	15 (35%)	13 (33%)	2 (68%)
Diabetic	11 (26%)	9 (23%)	2 (67%)
Hypertension	29 (67%)	27 (68%)	2 (67%)
Dyslipidaemia	38 (88%)	35 (88%)	3 (100%)
Previous MI	7 (16%)	6 (15%)	1 (33%)
Coronary stent	10 (23%)	7 (18%)	3 (100%)
Past stroke/TIA	2 (5%)	2 (5%)	0 (0%)
sBP	136 ± 22	137 ± 22	137 ± 20
dBP	74 ± 10	75 ± 10	70 ± 3
PWV	10.3 ± 1.4	10.1 ± 2.5	11.7 ± 3.1

Table 1 | Patient baseline characteristics and PWV measurements. Results are expressed as mean ± standard deviation, median (IQR) or number and percentage (%) where indicated.

Baseline clinical characteristics and PWV

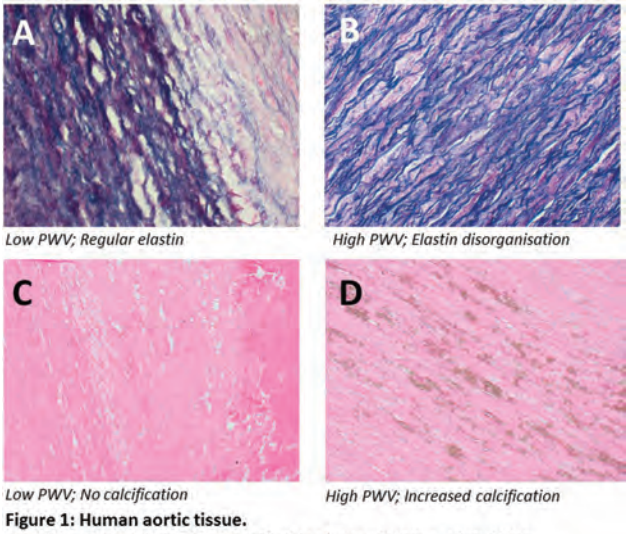

Figure 1: Human aortic tissue.
A and B - EVG stain (x200 magnification); Low PWV vs. High PWV
C and D - Van Kossa stain (x100 magnification); Low PWV vs. High PWV

Histopathology of aortic tissue in patients with/without AKI

PUB006

Two Cases of AKI Caused by Asymptomatic Unilateral Ureteral Tract Obstruction in Patients with Underlying Kidney Disease

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Introduction: Postrenal kidney injury is one of the causes of acute and chronic kidney injury. Nephrologists and urologists should not miss or delay the diagnosis of postrenal kidney injury as renal function can be easily recovered with appropriate treatment.

Case Description: Case-1 A 79-year-old man was admitted to our hospital due to the acute exacerbation of kidney function (serum creatinine 1.30 mg/dl to 2.89 mg/dl). The patient was diagnosed with IgA nephropathy by renal biopsy when he was 58 years old. After being diagnosed with IgA nephropathy he had a tonsillectomy and steroid therapy followed by oral prednisolone for one year and achieved complete remission of IgA nephropathy (defined as proteinuria less than 0.30 mg/gCr and macrohematuria less than 5/High Power Field). For six months prior to admission, the patient had been aware of general fatigue and pretibial edema. However, he felt no symptoms related to renal stones

such as back pain or pyuria. On admission, his urinary protein was 3+ (2.07 g/gCr), and occult urinary blood was ±. First, we considered the worsening of his renal function as a relapse of his IgA nephropathy because he had no newly prescribed medication, symptoms such as back pain, or fever. In addition, he had a history of worsening proteinuria up to nephrotic range, which recovered upon conservative therapy. However, routine abdominal ultrasound examination revealed right kidney hydronephrosis caused by a ureter stone. After inserting a W-J stent, serum creatinine improved to 1.41 mg/dl, and his urinary protein decreased. Case-2 Similarly, a 54-year-old woman with CKD due to nephrosclerosis was admitted to our hospital due to worsening renal function, with her eGFR decreasing from 13.5 ml/min to 5.9 ml/min during the previous three months without symptoms. Although we decided to start her on dialysis, routine abdominal ultrasonography revealed right ureter dilation and hydronephrosis caused by an abdominal aortic aneurysm operation scar from two years previously. After appropriate procedures, she avoided starting hemodialysis.

Discussion: Routine abdominal ultrasonography is an essential examination when we meet worsening of renal function even if patients have no back pain, fever, and pyuria.

PUB007

The Need for Dialysis Treatment Among Hospitalized Patients with AKI: A Single Centre Experience

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Background: Acute Kidney Injury (AKI) is a serious complication in hospitalized patients, with single-center studies reporting a rising incidence over the past two decades and case fatality rates exceeding 50% among those who require dialysis treatment. Our aim was to assess the risk for dialysis among hospitalized patients with AKI and previously normal renal function. Secondarily we assessed the effect of comorbidities such as arterial hypertension (HTN), diabetes mellitus (DM) and coronary artery disease (CAD) on dialysis risk.

Methods: The study was conducted prospectively for 24 months recording all consenting hospitalized patients in a single general hospital in Piraeus, Greece. Patients were included if they had previously normal renal function and AKI at the time of their admission at the hospital. Parameters recorded and analyzed were: demographics, full blood and biochemistry tests, history for HTN, DM and CAD and the need for dialysis treatment. The statistical analysis was carried out by single-factorial and multivariate regression analyses.

Results: 212 patients were studied, (115 men and 97 women), average age of 75 ± 12 years. 10.8% (23/212) of the patients with AKI (95% CI 7.1; 16.0) underwent dialysis. The effect of comorbidities was not statistically significant. Statistically important factors associated with the need for dialysis in single-factorial analysis were admission values of serum creatinine (SCr) > 3.3 mg / dL (p = 0.03), age >80 years (p = 0.001) and male gender (p = 0.045). In the multifactorial analysis the only independent dialysis factor was SCr> 3.3 mg / dL (p = 0.045).

Conclusions: The percent of hospitalized patients with AKI needing dialysis in our hospital was relatively low. Comorbidities did not aggravate the need for dialysis.The only parameter significantly affecting the risk for dialysis was the SCr value at the time of admission.

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PUB008

qSOFA as a Predictor of AKI in Patients with Sepsis: A Single-Center, Retrospective, Chart Review

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Background: According to the new surviving sepsis campaign (sepsis-3), the application of a new scoring system to gauge severity of infection is needed as the initial theorized continuum of the Systemic Inflammatory Response Syndrome (SIRS) criteria was too broad and did not effectively risk stratify patients. A proposed algorithm called the Sequential Organ Failure Assessment (SOFA) was introduced. However, the feasibility of incorporating all the required data in a timely fashion led to the development of an initial "quick" screening tool entitled the qSOFA. We propose that qSOFA is a more specific predictor of development of AKI.

Methods: The study was designed by the first two and last author as a single-center retrospective chart review. Data were abstracted from the electronic medical records at Staten Island University Hospital using the search terms "sepsis", "septic shock", and "severe sepsis". Charts were analyzed for number of SIRS criteria obtained as well as the number of qSOFA criteria obtained. Serum creatinine on admission as well as within 48 hours after admission were documented to assess for acute kidney injury both at admission and at 48 hours.

Results: The preliminary data analysis of 219 patients show that the odds ratio (OR) for qSOFA to predict AKI was 2.79 (CI 1.11 – 6.96, p =0.04), whereas the OR for SIRS to predict AKI was 0.57 (CI 0.33 - 0.98, p = 0.052). The AUROC for qSOFA to predict AKI was 0.547 (CI 0.503 – 0.590) compared to SIRS, which was 0.569 (CI 0.503 – 0.636). The results also showed that the OR of qSOFA to predict ICU admission was 7.26 (CI 2.78 - 18.9, p = <0.0001) compared to SIRS, which was 0.825 (CI 0.45 – 1.51, p = 0.54). The AUROC for predicting ICU admission for qSOFA was 0.605 (CI 0.546 – 0.663) compared to SIRS, which was 0.524 (CI 0.449 – 0.599). Both mortality at 48 hours and total mortality did not show statistically significant results for both SIRS and qSOFA.

Conclusions: In this preliminary analysis the authors found that when compared to SIRS, qSOFA was a marginally stronger predictor of AKI. However, when predicting ICU admission qSOFA was a stronger prognostic indicator than SIRS.

PUB009

Relation of Kidney Function Decline and NT-ProBNP with Outcomes in ADHF

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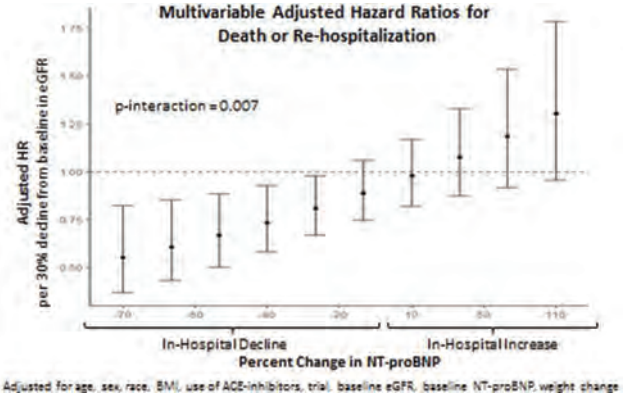
Background: Approximately 30% of patients admitted for acute decompensated heart failure (ADHF) experience an in-hospital decline in estimated glomerular filtration rate (eGFR). The association between this decline and clinical outcomes has been inconsistent. Understanding the circumstances in which a decline in kidney function is associated with either improved or adverse outcomes may influence clinical care. We hypothesized that adequate decongestion, as measured by a decrease in levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), may modify the relationship between decline in eGFR and clinical outcomes.

Methods: We performed a retrospective analysis of a limited dataset from the NHLBI of the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome Study (CARRESS) and Diuretic Optimization Strategies Evaluation (DOSE) trials, in which patients with ADHF were randomized to various modalities of decongestion with serial measures of kidney function and NT-proBNP. Multivariable Cox proportional hazards regression models were used to evaluate the association of decline in eGFR with a composite outcome of mortality and re-hospitalization. We evaluated for an interaction between decline in eGFR and change in NT-proBNP with this same outcome.

Results: A total of 496 patients were included in this analysis, with median follow-up of 59 days. Median (IQR) baseline eGFR was 40.5 ml/min/1.73m^2 (IQR 29.4, 60.1). In-hospital eGFR decline was not associated with risk for composite outcome of death or re-hospitalization (HR of 0.85 per every 2-fold decline in eGFR, 95% CI 0.60, 1.21). However, there was a significant interaction (p-value=0.007) between decline in eGFR and change in NT-proBNP such that decline in eGFR is associated with better outcomes with a decline in NT-proBNP but worse outcomes with an increase in NT-proBNP (Figure).

Conclusions: Incorporation of changes in markers of congestion may provide additional data to help decision making in cases of eGFR declines in ADHF.

Funding: Other NIH Support - T32 grant: 1T32DK07777



Adjusted for age, sex, race, BMI, use of ACE-inhibitors, trial, baseline eGFR, baseline NT-proBNP, weight change

PUB010

Comparison of Renal Prognosis Between Renal AKI and Prerenal AKI: A Single Center Study

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Background: Acute kidney injury (AKI) is a relatively new disease concept that represents a sharp decline in kidney function in several days. AKI is divided into renal, prerenal and postrenal. There is much debate about the difference in prognosis between renal AKI and prerenal AKI. Here, we estimated the difference of renal prognosis between renal AKI and prerenal AKI in the Japanese population.

Methods: Inpatients and outpatients aged 18-80 years were retrospectively enrolled. AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, using SCr levels. Patients who received infusion and who recovered within 7 days after the onset of AKI were defined as prerenal AKI and patients requiring more than 8 days as renal AKI. Survival time analysis was performed by defining the recovery date as zero hour, the 30% decrease in eGFR as an event, and the time to event occurrence as survival time, and the Kaplan - Meier (KM) curve and the Cox proportional hazard ratio were obtained.

Results: We analyzed data from 76,160 Japanese patients. The number of renal AKI patients and prerenal AKI patients were 563 and 760, respectively. In the KM curve, results showing that the prerenal AKI is significantly longer than the renal AKI has been obtained. Compared with non-AKI control, the hazard ratio of the 30% decrease in eGFR in renal

AKI and prerenal AKI were 5.10 and 3.42, respectively. the hazard ratio in renal AKI was significantly higher than that in prerenal AKI.

Conclusions: For long-term prognosis after recovery from AKI, prerenal AKI has better renal prognosis than renal AKI but worse than non-AKI. We suggest that prerenal AKI is not a favorable prognosis condition.

PUB011

Renal Injury Caused by Cocaine and Polysubstance Abuse: A Case Report

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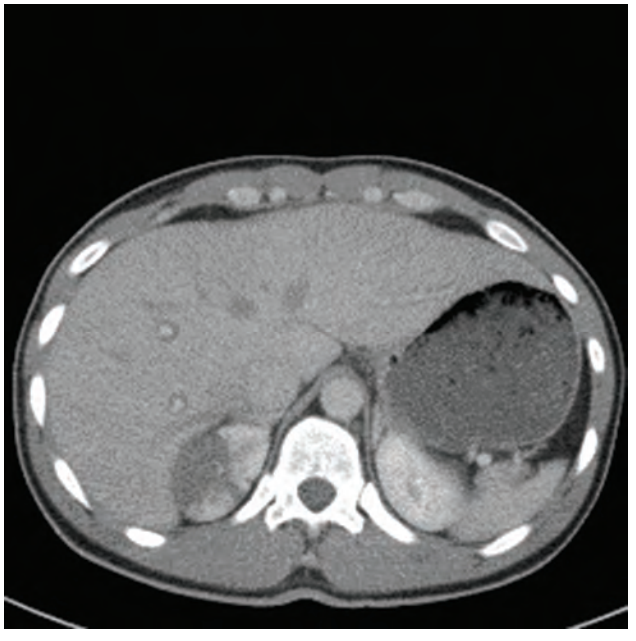
Introduction: Drug abuse involves life time exposure of 46% of US population. Recreational substances like alcohol, opioids, cocaine, cannabis, nicotine etc. can cause both acute and chronic renal injury.

Case Description: A 46 years old male with no significant past medical history, came to ER for sudden onset right flank pain. His vitals were stable except blood pressure was elevated to 150/90 mmHg. He had right costovertebral angle tenderness. Basic metabolic panel, LDH, complete blood count and urine dipstick were unremarkable except creatinine of 1.3mg/dl. Computed tomography showed diffusely reduced blood flow on right renal parenchyma involving 80 % of cortex suggestive of renal infarction. Renal doppler ultrasound showed vasospasm of right single renal artery. Urine was positive for cocaine, amphetamine and marijuana. Patient was treated with heparin infusion and intravenous normal saline. His hypercoagulability work up and vasculitis panel were negative. Patient's renal function improved to 0,6mg/dl after 24 hours of conservative care. He was discharged home with lisinopril and aspirin.

Discussion: Here renal injury is caused by ischemia due to a renal artery vasospasm. Pathophysiology of cocaine nephrotoxicity is multifactorial including changes in renal hemodynamics, glomerular matrix synthesis, toxic metabolites degradation, oxidative stress, and induction of renal atherogenesis. We need more epidemiological studies and translational researches on the mechanism of multiorgan damages or failures due to chronic polysubstance abuse which can causes acute organ injuries like renal infarction as well as promotes sub clinical renal hypoperfusion. Early diagnosis, prompt withdrawal of recreational drugs, aggressive supportive measures, as well as prophylactic treatments with aspirin, RAAS blockade, anti-cholesterol medications etc. may improve long term renal outcome.



PUB012

Kidney and Blood Pressure Outcomes from 6 to 11 Years After Pediatric Intensive Care Admission

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Background: Acute kidney injury (AKI) during pediatric intensive care unit (PICU) admission may be a risk factor for chronic kidney disease (CKD) and hypertension development. We determined 1)CKD and elevated BP (eBP) prevalence 11years(y) after PICU admission; 2)If PICU-AKI is associated with worsening CKD and BP from 6-11y post-PICU.

Methods: Follow-up study (≥9.5y post-PICU) of children previously studied at 6y post-PICU. Protocol: Children were contacted for a study visit 11±1.5y post-PICU admission; blood (serum creatinine) and urine (albumin/creatinine[ACR]) were collected and height/weight/BP measured. Exposure: AKI during PICU (KDIGO definition). Outcomes: CKD [estimated glomerular filtration rate (eGFR) <90ml/min/1.73m^2 or ACR ≥3mg/mmol]; eBP: BP ≥90th percentile or ≥120/80mmHg in adults. 6 *vs.* 11y outcome prevalences and AKI *vs.* non-AKI change in eGFR, ACR and BP percentile were compared (univariate tests).

Results: Data were available for n=71(4.5±5.3y old at PICU; 55% male). Prevalences of low eGFR, high ACR, CKD and eBP remained high at 11y post-PICU, similar to 6y post-PICU (Table). There was a statistically significant decrease in eGFR and diastolic BP from 6y to 11y follow-up ($p<0.05$), but no significant change in ACR or systolic BP (Table). AKI during PICU was not significantly associated with change in eGFR, ACR or BP percentile from 6y to 11y follow-up (Table, all $p>0.05$).

Conclusions: High prevalence of CKD and eBP persists at 11y after PICU admission. We did not find that PICU-AKI impacts on CKD or eBP progression over time. Interventions are needed to reduce long-term cardiovascular risk in PICU patients. Risk factors for persistent or progressive CKD and eBP must be elucidated.

Funding: Government Support - Non-U.S.

Table. Kidney and blood pressure outcomes at 6 and 11-year after PICU admission and change in outcomes by AKI status.
Continuous variables: Mean ± SD; Categorical variables: column percent

6 and 11 year post-PICU kidney and blood pressure outcomes *Data available in up to 71 subjects*		
	6 year post-PICU follow-up	11-year post-PICU follow-up
% low eGFR	2.9%	9.0%
% high ACR	12.7%	8.5%
%CKD	15.7%	17.7%
Any BP ≥90th percentile	18.6%	22.5%
eGFR (ml/min/1.73m^2)	139.9 ± 29.4	122.3 ± 25.4*
ACR (mg/mmol)	2.4 ± 7.2	1.4 ± 1.8
Systolic BP percentile	59 ± 25	56 ± 28
Diastolic BP percentile	52 ± 22	46 ± 21*
AKI *vs.* non-AKI change in eGFR, ACR and blood pressure from 6 to 11y follow-up *A negative number = decrease from 6 to 11 years follow-up*		
	AKI *n=13*	No AKI *n=58*
eGFR change (ml/min/1.73m^2)	-16.5 ± 19.5	-17.8 ± 20.5
ACR change (mg/mmol)	-0.1 ± 0.9	-1.2 ± 8.0
Systolic BP percentile change	3.8 ± 29.9	-4.5 ± 33.5
Diastolic BP percentile change	-12.0 ± 14.9	-7.4 ± 25.0

* = p<0.05 for comparison of 6 year versus 11 year follow-up.
t-tests used to compare means between groups (paired t-tests for 6 versus 11 year; student's t-test for AKI versus non-AKI); Chi-square tests used to compare categorical outcomes between groups.

PUB013

Prevalence of AKI in an ICU Department in Chihuahua, Mexico

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Background: The impact and prognosis of acute kidney injury (AKI) vary considerably depending on the severity, clinical setting, comorbid factors, and also geographical location. AKI is associated with higher mortality, hospital length of stay, re-admission, costs and CKD development. The aim of our study was to report the prevalence of AKI in an intensive care unit (ICU) from northern Mexico in a private hospital.

Methods: A retrospective observational study was carried out from May 2014 – May 2017. Data from 1436 patients that were admitted to the intensive care unit in this period were analyzed, only 1158 patients had enough data to screen for AKI, AKI was diagnosed by serum creatinine criteria from KDIGO guidelines.

Results: Baseline characteristics of the patients, ICU department of admission and AKI severity are summarized in Table 1.

Conclusions: The prevalence of AKI in our ICU was similar to previous reports. This is the first epidemiological study for AKI of northern Mexico in an ICU and in our hospital, currently there is not a single nephrologist in our hospital in charge of AKI consultations, this study highlights the importance of this entity. The lack of recognition of AKI in our hospital should encourage the creation of an AKI clinic / Nephrology rapid response team.

Table 1. Baseline characteristics, ICU department and AKI severity.

	All	AKI	Without AKI	
n (%)	n=1158 (100)	n=265 (22.9)	n=893 (77.1)	p
Female	582 (50.3)	121 (45.7)	461 (51.6)	0.08
Age (years)	66 (49-76)	68 (52-75)	65 (49-76)	0.49
Pediatric (<16 years)	30 (2.6)	8 (3)	22 (2.5)	0.61
Diagnostics				
Major surgery	94 (8.1)	23 (8.7)	71 (8)	
Neuro ICU	213 (18.4)	41 (15.6)	172 (19.3)	
Trauma and orthopedics	63 (5.5)	12 (4.6)	51 (5.7)	
Sepsis	93 (8.1)	26 (9.9)	67 (7.5)	0.61
Cardiology ICU	380 (32.9)	86 (32.7)	294 (33)	
Oncology	26 (2.3)	8 (3)	18 (2)	
Medical ICU	257 (22.3)	63 (24)	194 (21.7)	
Obstetric	16 (1.4)	2 (0.8)	14 (1.6)	
Other non-specified	13 (1.1)	2 (0.8)	11 (1.2)	
KDIGO 1	228 (19.7)	228 (86)	-	
KIDIGO 2	29 (2.5)	29 (11)	-	
KDIGO 3	8 (0.7)	8 (3)	-	

Values presented as median (IQR) and frequency (%).
Abbreviations: ICU, intensive care unit; AKI, acute kidney injury.

vomiting associated with sharp left flank pain. Examination revealed tenderness on right upper quadrant palpitation. Laboratory findings were notable for creatinine of 80umol/L, bland urine analysis, negative urine culture and Lactate dehydrogenase of 1,282U/L. She received oral analgesia along with IV fluids. CT imaging with IV contrast showed a wedged shape reduced enhancement on right kidney. On second day with migrating pain to left, a second CT scan revealed evolving wedged shape defect on left kidney [Figure1]. Patient was started on anticoagulation with heparin and warfarin. Furthermore, patient underwent a transesophageal echocardiogram for embolic disease, holter monitor, antibody screen for vasculitis and antiphospholipid syndrome, flowcytometry for PNH, and hemophilia screen that were all normal. Patient was started on Topiremate, and has been off zolmitriptan with no recurrence of disease on 3 months follow up.

Discussion: Renal infarction should be considered in severe flank pain with negative work up for kidney stone and pyelonephritis. Although zolmitriptan is an effective drug to treat maigraine headaches, it can potentially cause renal artery vasospasm leading to acute renal infarction.

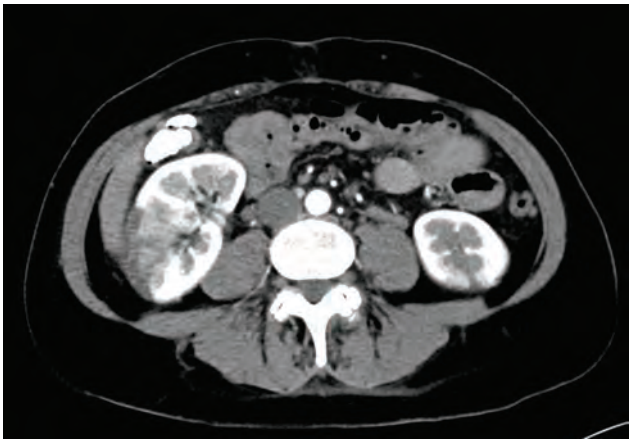

Figure 1. Bilateral Wedge shaped filling defect suggestive of renal infarction

PUB014

Early Persistent AKI Is Associated with Death and Renal Recovery in Cardiac Surgery

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Background: Early recovery of acute kidney injury (AKI) is associated with better prognosis in critically ill patients. It remains to be known which type of cardiac surgery-associated AKI (CSA-AKI) impacts prognosis. This study investigated the association between type of CSA-AKI and prognosis.

Methods: We analyzed the data on 2,060 non-CKD, post-cardiac surgery patients admitted to ICUs in 18 hospitals in the Tokushukai Medical Database between 2012 and 2014 who had No-AKI (n = 1,530), transient AKI (<3 days of ICU admission; n = 300), persistent AKI (≥3 days of ICU admission; n = 91), and late-onset AKI (occurred after ICU discharge; n = 139). The primary outcome was in-hospital death or renal recovery at hospital discharge, and the secondary outcome, eGFR decline > 50% during 3-year follow-up.

Results: There were more, older male patients in AKI groups. There were no differences in the type of surgery or use of cardiopulmonary bypass. Transient and persistent AKI were prognostic factors for in-hospital mortality (odds ratio [OR], 24.2 [8.7-85.9] and 195.6 [65.0-743.6], respectively). Persistent AKI was associated with a significantly lower OR for renal recovery (0.13 [0.07-0.26]). Most of patients with persistent AKI met the secondary outcome within 1 year of discharge (hazard ratio [HR], 8.13 [4.75-13.9]; *P*<0.001). It took two years or more for half of patients with transient and late-onset AKI to achieve the outcome (HR, 3.04 [2.08-4.43] and 2.58 [1.60-4.16]; *P*<0.001).

Conclusions: Persistent AKI was a notable prognostic factor for mortality and non-recovery and associated with fast eGFR decline, while transient and late-onset AKI were associated with moderate eGFR decline.

PUB015

Bilateral Renal Infarction During the Use of Zolmitriptan

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Introduction: Zolmitriptan is a 5-HT_{1B} agonist that leads to vasocontriction of blood vessels and used for the treatment of migraine headaches. Triptans have been associated with myocardial infarction and bowel ischemia, but there are only 5 reports associating them with renal infarction. Here we report a case of bilateral renal infarction following treatment with Zolmitriptan.

Case Description: This is a 58 year old lady history of chronic migraine presented to emergency department with flank pain and vomiting. Patient has been on zolmitriptan 2.5mg as needed for migraine headache which she reports taking frequently in past month, with last dose 3 days prior to presentation. Patient experienced sudden onset nausea and

PUB016

Prediction Scale for the Development of AKI in a Hispanic Population

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Background: Acute kidney injury (AKI) affects 10 million people annually in the world. Is an independent risk factor for mortality. The impact of this entity is more significant in developing countries where there are limited resources, and patients struggle to obtain renal replacement therapy. There is a worldwide need to recognize, detect and early approach of AKI and provide a better prognosis of renal recovery. The objective of the study is to evaluate the capacity of a practical risk scale for the detection of patients at risk of developing AKI

Methods: Prospective analytical cross-sectional study. 83 patients were registered from May to October in the 2018. Patients were evaluated from admission to hospitals in northeastern Mexico recording the most prevalent risk factors in our population and were followed until discharge, recording those who developed AKI based on the current KDIGO classification and degree severity. The primary analysis was performed with multiple logistic regression, the calculation of sensitivity, specificity was performed through ROC curve

Results: Mean age was 61 years, 52 patients (62%) developed AKI, 55% KDIGO stage I, 25% stage II, 19% stage III. Identifying statistical significance in the proposed model (p =< 0.001), each variable was converted into a score coded by its OR (anemia 3 points, IV contrast and cirrhosis 1 pt, CKD 9 pts, sepsis 2 pt, nephrotoxic drugs 1 pt each). With these values the calculation of the total score of each patient with AKI was made (OR= 2.6, p =<0.001). The best performance of the diagnostic test through a ROC curve was a score of 4 points with a sensitivity of 84% and a specificity of 73%

Conclusions: In AKI, early recognition and protective measures are essential to obtain a higher rate of renal recovery and positively impacting the survival and quality of life of patients. Access to new biomarkers of early kidney injury is limited in our setting and the proposed screening scale prompts detection of kidney damage. We obtained a quick and practical prediction scale with a sensitivity level of 84%, being an adequate screening tool to detect patients at risk of developing AKI allowing the establishment of appropriate nephroprotective measures to reduce the incidence and/or severity of AKI. Nevertheless, in future this predictive model together with AKI biomarkers could be an interesting tool to predict AKI

PUB017

An Interesting Case of Renal Infarction and Spontaneous Adrenal Haemorrhage in a Patient on Thrombopoietin (TPO) Receptor Agonist Therapy and Vitamin K Antagonist

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Introduction: Eltrombopag is the first TPO-receptor agonist and is widely used for the treatment of Idiopathic thrombotic purpura (ITP). Though the British National Formulary (BNF) cautions against use of Eltrombopag in patients with risk factors for venous thromboembolisms (VTEs), there is a paucity of guidance of its concomittant use with anticoagulant therapy.

Case Description: A 61 year old lady presented with two day history of abdominal pain and vomiting 10 days after starting Eltrombopag for ITP. She has a background of discoid lupus, antiphospholipid syndrome, hypothyroidsim and haemolytic anaemia. She had previosly been treated for deep venous thrombosis, pulmonary embolism and ischaemic stroke with haemorrhagic transformation. She was on warfarin for prevention of VTEs secondary to her antiphospholipid syndrome. She had a tender right upper quadrant of her abdomen, with normal bowel sound and no organomegaly. Her chest was clear and with normal heart sounds. She was afebrile, haemodynamically stable and a urine dipstick was negative for any sediments. Admission bloods revealed an increase in her platelet count from 32,000/mL to 1,84,000/mL within days of starting Eltrombopag. She also had acute kidney injury stage 2 (eGFR 31 from 87 ml/min/1.732 m2) and International normalised ratio of 2.5 on admission. Her eGFR dropped to 9 ml/min/1.732 m2 and she required haemodialysis secondary to deteriorating renal function and fluid overload. A computeriseed tomography of her abdomen showed evidence of organised left adrenal haematoma. She was seen by the haematology and rheumatology teams who agreed that in all likelihood the patient had an intrarenal thrombus with sencondary haemorrhagic tranformation. Her Eltrombopag was stopped and she was managed with unfractioned heparin and bridged to warfarin with an INR target of 3.5. for Her kidney function improved few weeks after the treament and she is now dialysis independent with gradual improvement in her kidney function.

Discussion: After this expeience we advice cautionary use of Eltromobag in patients with previous episodes or high risk for VTE on or off anticoagulation. There should also be guidelines to dictate the rate of increase in platelt count to avoid thrombotic complications related to a sudden increase in platelet count.

PUB018

Urinary Cystatin C (UCysC) as an Early Biomarker of AKI in Critically Ill Patients

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Background: AKI is common in critically ill patients. Despite all advancements prognosis of AKI continues to be bad. Early diagnosis results in better outcome. Serum creatinine is an insensitive marker in early stages of AKI. A marker which can predict AKI or identify AKI early is a great need. Cystatin C is a cysteine protease inhibitor, synthesized by all nucleated cells in the body, freely filtered by the glomerulus, fully reabsorbed and not secreted by the tubule, making serum cystatin a better marker for estimation of GFR than creatinine. The urinary excretion of Cystatin C indicates acute tubular injury. Urinary Cystatin C is a marker of renal tubular injury which precedes the elevation of serum creatinine or serum cystatin C. **Aim:** To evaluate UCysC as early biomarker of AKI.

Methods: A prospective observational study. Consecutive critically ill subjects admitted to ICU during Jan 2017 to Oct 2017 were taken for the study. **Exclusion:** Age <18 years & over 80 years; Hematuria, and polycythemia; Preexisting renal failure; Not expected to survive 72 hrs; **Methods:** Serum creatinine (daily), UCysC, sodium, electrolytes and haemoglobin levels were measured using standard protocols. Glomerular filtration rate was calculated using the standard MDRD formula. RIFLE classification system was used to define AKI. The patients were divided in to two groups based on development of AKI. Finally, the statistical analyses were performed between the groups to see if urinary cystatin C levels could be a reliable diagnostic marker for AKI.

Results: Total 83. Male 57; Female 26. 36 (43%) developed AKI. Sepsis was the common cause. Out of day 1 investigations UCysC was the one which was significantly indicative of development of AKI.

Conclusions: 1. UCysC was significantly elevated in critically ill patients who developed AKI than in those who did not. 2. UCysC on the first day was significantly elevated than serum creatinine in those who developed AKI. 2. UCysC is an ideal early biomarker for AKI.

Characteristics	Non-AKI (N=47) Mean ± SD	AKI (N=36) Mean ± SD	p- Value
TC	13572.1 ± 5195.7	14980 ± 4672.8	0.198
Sodium (mmol/l)	135.5 ± 4.13	134.3 ± 5.9	0.3
Potassium (mmol/l)	4.1 ± 0.89	3.9 ± 0.58	0.267
Calcium Carbonate (mg/dl)	103.2 ± 4.1	105.1 ± 8.69	0.237
Bicarbonate (mmol/l)	23.6 ± 3.7	32.0 ± 28.3	0.083
HB (g/dl)	11.0 ± 2.5	32.06 ± 28.3	0.519
Creatinine day 1 (mg/dl)	0.8 ± 0.2	1.0 ± 0.17	0.080
Creatinine day 3 (mg/dl)	0.7 ± 0.31	1.73 ± 0.36	0.001
Cystatin C (ng/µl)	61.0 ± 20.6	150.4 ± 42.0	0.001

p-Value; t-test p-Value

Comparison of parameters - AKI vs Non AKI

PUB019

AKI of Nephrotic Syndrome in Children

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Background: Nephrotic syndrome is the most common kidney disease in children. Acute kidney injury (AKI) is one of the common complications of nephrotic syndrome, and its incidence is reported from 1% to 50.9% in various studies worldwide. Well known risk factors of acute kidney injury are intravascular volume depletion, infection, edema and steroid resistance. Detailed report about incidence and risk factors of pediatric nephrotic syndrome in Korea is lacking, therefore we studied incidence, causes, risk factors of acute kidney injury of nephrotic syndrome in children in this study.

Methods: We conducted a retrospective review of the electronic medical records of pediatric patients who were admitted to Seoul National University Children's Hospital for occurrence or recurrence of idiopathic nephrotic syndrome, from January 1st, 2015 to July 31th, 2017. Patients with chronic kidney disease or congenital nephrotic syndrome were excluded.

Results: During the study period, 90 cases (Male:Female 44(67.7%):21(32.3%)) were admitted for management of nephrotic syndrome. Among them, total 47 cases met the KDIGO criteria of AKI (52.2%, Male:Female 2(66.7%):1(33.3%), median age 7). AKI developed in association with infection (24), aggravation of nephrotic syndrome (17), methyl prednisolone pulse therapy (4), and dehydration (2). Those with AKI were not statistically different from those without AKI in regard of sex, age, pathological diagnosis, age of nephrotic syndrome onset, number of relapse during the previous year, or trough level of calcineurin inhibitors (CNI) if they were taking CNIs. On the other hand, AKI occurred more commonly when the patients were taking cyclosporine (67.5% with cyclosporine, p=0.011, odds ratio=3.115). The median recovery time of serum creatinine level was 7 days and most patients had AKI at the time of admission. While most of the AKI episodes had resolved without long-term complication, duration of hospitalization was longer in the AKI group than the non-AKI group.

Conclusions: Complication of AKI occurred in more than half of the hospitalization of pediatric nephrotic syndrome. Cyclosporine increased the risk of AKI. Therefore in managing children with nephrotic syndrome, we need to consider AKI especially for those taking cyclosporine.

PUB020

Biomarkers N-Gal and Kim-1 for AKI Post Major Elective Non-Vascular Abdominal Surgeries

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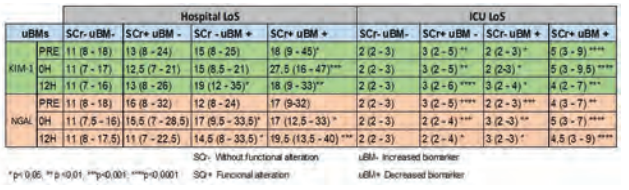
Background: The role of renal injury urinary biomarkers (uBMs)for predicting AKI in surgical patients (pts) remains undetermined. The aim of this study was to compare the efficacy of urinary biomarkers, NGAL and KIM-1, in patients submitted to major elective non-vascular abdominal surgeries (MENVAS) admitted to ICU.

Methods: Two hundred and twenty five pts were prospectively evaluated, peri-operatively, from the ICU admission until day 7. Serum creatinine (SCr mg/dl) was measured before surgery and once a day until day 7 or ICU discharge. AKI was diagnosed using either SCr or urinary output (UO) according to KDIGO definition. Two uBMs were assessed: NGAL and KIM-1 by Luminex x-MAP method. Urine sample was collected 1 day before surgery (baseline); upon arrival in ICU and 12 h after ICU admission. The value of the fifth quintile was considered positive for uBMs. Data are presented as mean S SD, median (first and fourth quartiles) or frequencies. Statistical significance was $p<0.05$.

Results: A total of 225 pts were analysed, 126 (56%) developed AKI. Most frequent types of surgery were: hepatectomy, sleeve gastroplasty, gastrectomy, hepatectomy + cholecystectomy, gastroduodenopancreatectomy and adrenalectomy. AKI pts were older 57.6 ± 1,2 vs. 50.8 ± 1,6 (p = 0.0007). Mortality in the AKI group was 10.2% vs. 2.0 % in Non-AKI (p=0.0149). The following table (image) shows the efficacy of the biomarkers NGAL and KIM-1 in the outcomes hospital length of stay (LoS) and ICU LoS. Among the non-survivor (15 pts), 4 had higher biomarkers (uBM +) without functional alteration (SCr-) and 4 had functional deterioration (SCr+) with no uBM increase (uBM -). After 12h from ICU admission, 4 pts had higher biomarkers (uBM +) without functional alteration (SCr -) and 4 had functional deterioration (SCr+) with no uBM increase (uBM -). On the other hand, six pts with both functional alteration (SCr +) and uBM increase (uBM+) all died.

Conclusions: Surgical patients with higher urinary biomarkers N-GAL and KIM-1 even without functional deterioration (SCr increase) presented longer hospital and ICU LoS and higher mortality.

Funding: Government Support - Non-U.S.



uBMs		Hospital LoS				ICU LoS			
		SCr- uBM-	SCr+ uBM -	SCr - uBM +	SCr+ uBM +	SCr- uBM-	SCr+ uBM -	SCr- uBM +	SCr+ uBM +
KIM-1	PRE	11 (8 - 18)	13 (8 - 24)	15 (8 - 25)	18 (9 - 45)*	2 (2 - 3)	3 (2 - 5) **	2 (2 - 3) *	5 (3 - 9) ****
	0H	11 (7 - 17)	12,5 (7 - 21)	15 (8,5 - 21)	27,5 (16 - 47)****	2 (2 - 3)	3 (2 - 5) **	2 (2-3) *	5 (3 - 9,5) ****
	12H	11 (7 - 16)	13 (8 - 26)	19 (12 - 35)*	18 (9 - 33)**	2 (2 - 3)	3 (2 - 6) ****	3 (2 - 4) *	4 (2 - 7) **
NGAL	PRE	11 (8 - 18)	16 (8 - 32)	12 (8 - 24)	17 (9-32)	2 (2 - 3)	3 (2 - 5) ****	2 (2 - 3) ***	4 (3 - 7) **
	0H	11 (7,5 - 16)	15,5 (7 - 28,5)	17 (9,5 - 33,5)*	17 (12,5 - 33) *	2 (2 - 3)	2 (2 - 4) ***	3 (2 -3) **	5 (3 - 7) ****
	12H	11 (8 - 17,5)	11 (7 - 22,5)	14,5 (8 - 33,5) *	19,5 (13,5 - 40) ***	2 (2 - 3)	2 (2 - 4) *	3 (2 -3) *	4,5 (3 - 9) ****

SCr- Without functional alteration uBM- Increased biomarker

* p< 0.05, ** p <0.01, ***p<0.001, ****p<0.0001 SCr+ Funcional alteration uBM+ Decreased biomarker

PUB021

High Serum Sodium Levels at the Time of Nephrology Consultation and Adverse Outcomes in Burn Patients with AKI

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Background: Acute kidney injury (AKI) is a common complication after severe burn injuries and is associated with high mortality. Dysnatremias have been found to be associated with mortality in many populations, but its role in burn patients with AKI is not fully understood.

Methods: We retrospectively evaluated data on burn patients with acute kidney injury in the ICU of a tertiary hospital using logistic regression to evaluate the association of serum sodium levels with adverse outcomes.

Results: 109 patients were included in the analysis. At the time of the nephrology consultation, the median age was 42.5 years, 70% were males, the baseline GFR was 101 mL/min/1.73m^2, the median total body surface area (%TBSA) burned was 34.5%, and the median serum creatinine was 2.31 mg/dL. Median serum sodium was 143 mEq/L (IQR 139-149 mEq/L), 44 subjects had serum sodium above the upper limit of the normal range (> 145 mEq/L). On univariate analysis, serum sodium levels above 145 mEq/L were associated with higher odds of the composite outcome of RRT requirement or in-hospital death (OR=3.27, 95% CI: 1.10–12.10, p=0.048) but this association did not persist in multivariate analysis (OR=1.79, 95% CI: 0.63–5.38, p=0.282). In this population, sepsis, baseline GFR, fluid balance, and the requirement of mechanical ventilation were also associated with the composite outcome in univariate analysis. Sepsis and baseline GFR remained associated with an increased risk of the composite outcome (OR=28.18, 95% CI 3.47-371.40, p=0.004 and OR=0.96, 95% CI 0.94-0.99, p=0.003, respectively) on the final multivariate model that also included sodium level, %TBSA burned, mechanical ventilation, and SOFA score.

Conclusions: Hypernatremia at the time of nephrology consultation might predict the composite outcome of RRT and death. Larger studies are warranted to confirm or dispute these findings.

PUB022

Gender and Age Differences in AKI During Hospitalization for Left Ventricular Assist Device Implantation: National Estimates

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Background: Left ventricular assist device (LVAD) placement is associated with high incidence of AKI, and AKI post-LVAD is associated with increased mortality. Outcomes are gender-dependent, with females having higher risk for thrombosis, right heart failure and mortality. Gender differences in renal disease have been described in trauma, cardiopulmonary bypass, chemotherapy toxicity and rates of delayed graft function after kidney transplant. Rodent models of ischemia/reperfusion and other AKI have demonstrated protective effects of the female hormonal milieu and deleterious effects of male hormones. We therefore investigated relationships of sex and age with AKI diagnosis during hospitalizations for implantable LVAD placement.

Methods: We performed a retrospective, observational cohort study using the National Inpatient Sample (2006-2015) to estimate diagnoses of AKI in females versus males among patients ≥ 18 years of age who received LVAD. ICD-9 codes were used for identification of LVAD placement, presence of AKI without and with RRT (AKI-D), and comorbidities. We used appropriate survey methods to obtain national estimates. We used logistic regression models (adjusted for demographics, comorbidities, year of implantation) and predictive margins to assess relationships of age, sex, and AKI.

Results: An estimated 5,681 female (mean age 53) and 18,702 male (mean age 57) patients received LVADs, with men having higher prevalence of hypertension (43% versus 36%) but not diabetes. 50% of females carried AKI diagnosis, versus 57% of males. The adjusted risk of AKI in females age less than 60 was 47% (CI 0.44-0.51) versus 56% (CI 0.53-0.59) for males. No difference was found in AKI of males versus females greater than age 60, or in AKI-D between males and females, regardless of age. Mortality was higher in females with AKI (OR 1.53, CI 1.13-1.92).

Conclusions: Women had lower risk of AKI in this population of LVAD patients; this protective effect was lost in postmenopausal women. However, women with AKI had higher mortality. Given that female gender has demonstrated reno-protective effects in animal and human models, it would be judicious to consider the effects of gender, hormone status and supplementation, and sex-directed therapeutics in the design of future studies of ischemia/reperfusion injury, transplant and AKI.

PUB023

Prevalence of AKI in PD-1 Inhibitors: A Single Center Experience

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Background: Programmed cell death protein 1 (PD-1) inhibitors, i.e. nivolumab and pembrolizumab, are being increasingly used and the incidence of acute kidney injury (AKI) has been reported to be 2.2% by a recent meta-analysis of clinical trials.

Methods: The major objective of this study is to determine the AKI rates of all patients that have received a PD-1 inhibitor at Mayo Clinic Rochester over a span of 3 years. We performed a retrospective chart review of all patients that had a PD-1 inhibitor until April 1, 2017. We included patients that had a baseline creatinine value within 30 days of drug initiation. We searched for AKI episodes as defined by AKIN criteria as increase in creatinine of ≥0.3 mg/dl form baseline at 3 different time points – Day 1-14, day 80-100 and day 300-400 from the time of initiation of the drug.

Results: Out of the 495 unique patients that received either nivolumab or pembrolizumab, only 134 patients fit our inclusion criteria. We found 53% (33/62) in nivolumab and 43% (31/72) in pembrolizumab group had AKI episodes. Out of those that clinically significant AKI (AKIN stage 2 and greater), in nivolumab 2 of 3 patients and in pembrolizumab 5 of 8 patients had likely drug related AKI. Only 2 of these patients had a kidney biopsy showing nephritis. A large proportion of these patients were closer to the 1 year time point 38% (24/62) in nivolumab and 22.2% (16/72) in pembrolizumab group.

Conclusions: Our study reinforces the ongoing concern among nephrologists that AKI episodes are being missed. We also found that consistent with the current literature the AKI appears to be of a delayed onset. Only a handful of these patients were seen by nephrology and fewer had kidney biopsies. With the increasing use of these drugs in cancer therapy there is a need for more definitive guideline for nephrologists in the management of these AKI patients.

AKI by AKIN stages

	Nivolumab (33)	Pembrolizumab (31)
AKIN stage 1	30	23
AKIN stage 2	1	8
AKIN stage 3	2	0

PUB024

Obesity Linked to AKI and Mortality in Acute Distress Respiratory Syndrome

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Background: One of the most important organ to organ cross-talk in critically ill patients is the one taking place between the lung and kidney, especially in patients under mechanical ventilation. Barotrauma, volutrauma, atelectrauma and biotrauma have been the mechanisms described as responsible for damage in both organs. Acute distress respiratory syndrome (ADRS)is characterized by a global reaction of the lung parenchyma which leads to fluid extravasation and edema. One of the most common comorbidities found in ARDS patients is obesity. It has been linked to increase in both, mortality and incidence of acute kidney injury (AKI)

Methods: This is a retrospective analysis of 30 records of patients admitted to the intensive care unit (ICU) with ARDS during the Influenza season 2016-2017. Demographic, laboratory, and clinical data were obtained. We measured weight and height of each patient at admission and used the body mass index (BMI) formula (weight in kg/(height in m)^2 to obtain each patient's BMI. We classified patients into two groups, obese (BMI ≥30 kg/m^2) (group A) and not obese (BMI <30 kg/m^2) (group B). We compared both groups.

Results: Mean age in our cohort was 46.4yrs, 66.6% were male and 46.6% were obese. Global mortality among obese patients was 57.9%, compared with a 42% in non-obese patients (p=0.11). AKI was diagnosed in 20 patients (66.6%) with 16.6%, 10% and 36.6% of KDIGO stages 1-3 respectively. RRT was initiated in 10 (50%) of AKI patients. Among groups A and B AKI was diagnosed in 55% and 45% of patients respectively (p=0.2). ICU mortality was 60% among the whole cohort, 61.1% of obese patients died during the ICU stay compared with 38.9% of non-obese patients (p: 0.72)

Conclusions: In our cohort of ARDS patients, obesity with BMI ≥30kg/m^2 was linked to an increase in the incidence of AKI and increase global mortality as well as ICU mortality. With these findings, we can strongly recommend special attention in obese patients with ARDS because of the greater susceptibility to complications and mortality. More studies with bigger cohorts are needed to obtain statistical significance and clearly demonstrate these associations.

PUB025

Acute Interstitial Nephritis in Patients with Hepatitis C Virus Infection and CKD Treated with Direct Acting Antiviral Agents: A Case Series

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Background: Hepatitis C virus (HCV) infection has been shown to have an adverse impact on clinical outcomes in patients with chronic kidney disease (CKD) and end stage renal disease (ESRD), including an accelerated rate of loss of kidney function and an increased mortality. Patients achieving a sustained viral response at 12 weeks post treatment completion (SVR12) are considered to be cured. Clinical trials using the direct-acting antiviral agents (DAAs) uniformly achieve SVR12 rates of >90% in the general population as well as in patients with CKD/ESRD. Both sofosbuvir and its metabolite are renally excreted and its use has been associated with worsening kidney function. In the HCV-TARGET study, patients with eGFR <30 ml/min/1.73m2 at start of sofosbuvir-based therapy had higher rates of deterioration of kidney function compared to patients with higher eGFR. Current recommendations are to avoid sofosbuvir in patients with eGFR <30 ml/min

Methods: The current report describes 8 HCV-infected patients who developed acute kidney injury with biopsy-proven acute interstitial nephritis (AIN) associated with the use of DAAs.

Results: Mean age of the group was 61.3 (±6 years) with 100% men and 5 (62.5%) African Americans. The most common genotype (GT) was 1a (n=7) with 1 GT 4. The DAA formulations were sofosbuvir/ledipasvir (n=5), elbasvir/grazoprevir (n=2) and sofosbuvir/simeprevir (n=1). All patients achieved SVR12. The mean creatinine at start of DAA treatment was 1.6 mg/dl (±0.6) and increased to 2.0 mg/dl (±0.8) at the conclusion of therapy (p=0.03). All patients received a course of high dose steroids after the diagnosis of AIN was confirmed. Serum creatinine at 3 and 6 months post steroids was 3.0 (±1.2) and 3.2 mg/dl (±1.4), respectively. Three patients had progression of the CKD and developed ESRD

Conclusions: These results are consistent with earlier studies demonstrating the efficacy of DAAs in HCV-infected CKD patients. Biopsy-proven AIN may explain the AKI events reported with the use of DAAs in CKD patients. Our results show that AIN can occur with use of different DAAs, although particular caution must be used prescribing sofosbuvir to patients with eGFR <30 ml/min1.73m2 as it is the only DAA renally cleared.

PUB026

Postoperative AKI: A Prospective Randomized Controlled Trial of the Impact of Two Different Intraoperative Systolic Blood Pressure Levels on Renal Outcomes

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Background: Postoperative acute kidney injury (PO-AKI) is a significant contributor to hospital acquired AKI. It is unclear what the optimal intraoperative blood pressure is for preserved renal health. Evidence that controlled hypotension has advantages like shortened surgery time, reduced blood loss and less blood transfusions but without renal consequences were based on studies of younger patients with preserved kidney function. There is accruing evidence that more severe and longer periods of IOH in older patients with later stage CKD could indeed result in catastrophic renal failure. We had raised concerns about IOH as a neglected risk factor for PO-AKI in the Mayo Clinic Health System. The most common definition of IOH are SBP <80 mm Hg, MAP <55-60 mm Hg, and/or decreased SBP or MAP of 25% from baseline. For intraoperative MAP <60 mm Hg, the adjusted odds ratio for AKI was 1.84 (1.11–3.06) for 11–20-min exposure (Sun; 2015). From our experience and from the published literature, we hypothesize that the comparison of renal outcomes while keeping SBP >105 mm Hg versus SBP >85 mm Hg in the operating room would enable a scientifically robust study of this question. We therefore plan to carry out a pilot study of this RCT in orthopedic surgery (joint replacement) and in CV (non-bypass) surgery, respectively.

Methods: A prospective randomized controlled trial (pilot study) of PO-AKI in two subsets of patients undergoing noncardiac (orthopaedic) surgery and cardaic (non-bypass) surgery, with target intraoperative SBP >105 mm Hg vs >85 mm Hg in each category and we aim to have at least 20-30 patients randomized to each of the two arms of each substudy.

Results: The primary outcome is PO-AKI as defined by the AKIN criteria as a 50% relative or 0.3 mg/dL absolute increase in serum creatinine over the preoperative value during the first two post-operative days.

Conclusions: We hope to confirm our hypothesis that during anesthesia/controlled hypotension, the maintenance of SBP >105 mm Hg vs SBP >85 mm Hg reduced PO-AKI, patient morbidity and mortality, length of stay, the need for RRT and resulted in significant reductions in cost of care. Subsequently, we intend to use this pilot study preliminary data to apply for an NIH-funded study that would enable a larger national multi-center randomized controlled study.

PUB027

Enteric Fever Causing Hemolytic Uremic Syndrome

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Introduction: Hemolytic uremic syndrome presents with a classic triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. It is usually caused by toxigenic strains of Escherichia coli and Shigella dysenteriae. It can also be caused by Streptococcus pneumoniae and complement disorders. Typhoid fever causing hemolytic uremic syndrome is quite rare.

Case Description: A fifty four year ol male with no known comorbids presented with a seven day history of diarrhea. He had been started on ciprofloxacin after a stool for salmonella antigen was found to be positive. He presented after seven days with worsening of diarrhea and one day history of vomiting. Examination revealed mild dehydration with normal vital signs and tenderness in the right and left iliac fossa regions. His laboratory investigations showed an elevated urea and creatinine with a low potassium. Blood cultures done on the day of admission grew Salmonella typhi which was sensitive to ciprofloxacin. The platelets and hemoglobin dropped on the second and third day after admission. The lactate dehydrogenase was markedly elevated and a peripheral blood film showed schistocytes. He was started on hemodialysis, intravenous antibiotics and potassium supplementation. After three sessions of dialysis his kidney function started improving and had complete recovery of his renal function.

Discussion: Typical hemolytic uremic syndrome occurs secondary to infection by shiga-toxin producing E.coli and less frequently due to S.dysenteriae. It can also be caused by Streptococcus pneumoniae. Salmonella typhi is not a common cause of hemolytic uremic syndrome and there a few case reports in the literature of salmonella induced HUS. The inciting toxin in HUS due to Salmonella has not been identified. The treatment is mainly supportive comprising appropriate antibiotics, correcting fluid and electrolyte imbalances and timely dialysis. Most cases of acute kidney secondary to typical HUS are self limiting like in our case.

PUB028

Effect of Renin-Angiotensin-Aldosterone System Blockade on Long-Term Outcomes in Post AKI Patients with Hypertension

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Background: Post-acute kidney injury (AKI) patients are at risks for various complications. However, evidence regarding effective therapies to improve patient outcomes is lacking. We hypothesized that RAAS blockade is effective in improving renal outcomes in post-AKI patients who have hypertension.

Methods: From 2000 to 2013, we identified 12,084 AKI patients with hypertension in the nationwide database. All these patients experienced an AKI episode which required temporary hemodialysis therapy.

Results: In a median follow-up of 3.6 years, 2,637 patients (21.8%) required long-term dialysis and 5,094 (42.2%) died before progression to ESRD. Compared to post-AKI patients without using ACEI/ARB, ACEI/ARB users are less likely to suffer from future ESRD (adjusted HR, 0.90; 95% CI 0.83-0.99, $p = 0.022$) and all-cause mortality (adjusted HR, 0.92; 95% CI 0.86-0.97, $p = 0.003$). The renal benefit of ACEI/ARB use in post-AKI survivors was consistent across patient subgroups with different post-AKI renal function status, including those who fully recovered [non-chronic kidney disease (CKD)] and those who complicated with subsequent CKD stages 1-4.

Conclusions: For patients who experienced AKI and had hypertension, RAAS inhibitors should be the drug of choice to treat their hypertension.

Funding: Government Support - Non-U.S.

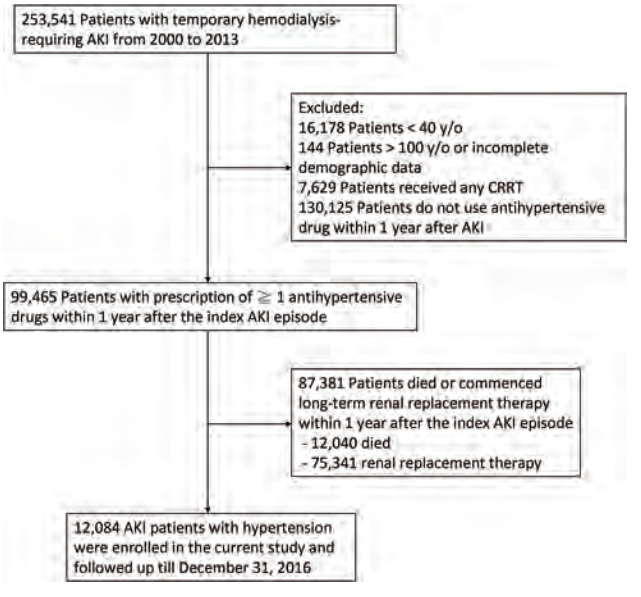

Figure 1. Flow diagram for the study.

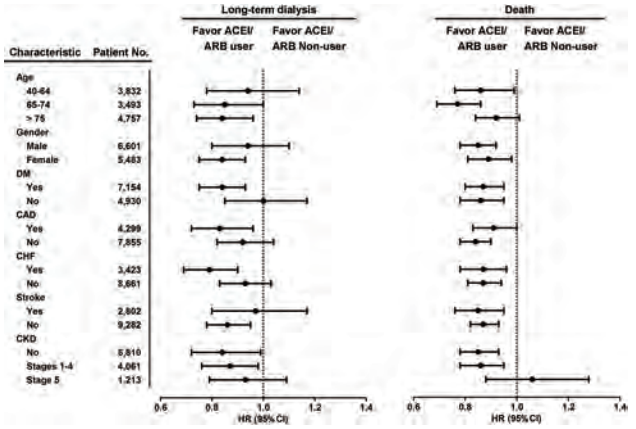

Figure 2. Forest plots of long-term risks of chronic dialysis and all-cause mortality.

PUB029

The Role of Extracellular Histones in Patients with Lung-Kidney Cross-Talk: A Prospect Study

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Background: Extracellular histones have potential to affect distant organs when released from tissue injury. In this prospect study, we aim to investigate the impact of extracellular histones on the community-acquired pneumonia (CAP) patients with acute kidney injury (AKI), acute lung injury (ALI) or the combination of both.

Methods: Blood samples were obtained from 83 patients within 24h after admission at the hospital who were diagnosed with CAP. According to the discharge diagnosis, the patients were divided into 4 groups (AKI+CAP, ALI+CAP, AKI+ALI+CAP, and CAP). Then the subjects were split into 2 groups (histones <30 μg/ml and histones ≥30 μg/ml).

Results: Compared with the CAP group, the logarithms of the concentrations of the extracellular histones in AKI+CAP, ALI+CAP, and AKI+ALI+CAP groups were higher (P = 0.004, P = 0.029, and P < 0.001, respectively). The incidences of AKI and ALI were 39.8% and 28.9% in CAP patients. In CAP patients, Log_2 Histones (P = 0.002) and chronic kidney diseases (P = 0.039) were predictors of AKI, Log_2 Histones (P = 0.006) and surgery (P = 0.019) were risk factors of ALI. Compared with the histones <30 μg/ml group, patients in the histones ≥30 μg/ml more likely to admit to ICU (65.6% *vs* 33.3%, P = 0.004), to need mechanical ventilation (62.5% *vs* 31.4%, P = 0.005), and had longer duration of mechanical ventilation (6.9±9.5 *vs* 1.3±2.8, P = 0.002), longer ICU length of stay (6.1±7.9 *vs* 1.9±3.5, P = 0.007), and longer length of in-hospital stay (18.4±8.7 *vs* 12.7±5.9, P = 0.002).

Conclusions: Elevated extracellular histones were observed in CAP patients with AKI, ALI, and the combination of both. Our data supported that extracellular histones were a higher risk of developing AKI or ALI in CAP patients and a predictor of worse short-term outcomes.

PUB030

Effect of Hypertonic Saline and Furosemide on Urinary Markers of Kidney Injury

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Background: Chloride is speculated to have nephrotoxic properties. In healthy subjects we tested the hypothesis that and acute chloride load with hypertonic saline would induce kidney injury, which could be prevented with the loop-diuretic furosemide.

Methods: The study was designed as a randomized, placebo-controlled, crossover study. Subjects were given hypertonic saline accompanied by either placebo or furosemide. Before, during and after infusion of hypertonic saline we measured glomerular filtration rate (GFR), fractional excretion of sodium (FENa), urinary chloride excretion (u-Cl), neutrophil gelatinase-associated lipocalin (u-NGAL) and kidney injury molecule-1 (u-KIM-1) as marker of kidney injury. Four days prior to each of the two examinations subject were given a standardized diet and fluid intake.

Results: U-NGAL and KIM-1 excretion increased slightly during hypertonic saline infusion. The increase in NGAL was absent when furosemide was given simultaneously, the responses in u-NGAL were not significantly different from placebo control (p = 0.214) with a general linear model (GLM)). Furosemide changed responses in KIM-1, where a delayed increase was observed. (p < 0.001 with GLM) GFR was increased by hypertonic saline, but decreased when furosemide accompanied the infusion. U-Na, FENa, u-Cl, and u-osmolality increased in response to saline and the increase was markedly pronounced when furosemide was added (p<0.001 with GLM for all variables)

Conclusions: This study shows minor increases in markers of kidney injury after hypertonic saline. Furosemide only changed response to KIM-1 and further investigations need to clarify if this is a protective renal response.

Funding: Government Support - Non-U.S.

PUB031

Multiple Myeloma: An Uncommon Presentation of a Common Neurological Complication

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Introduction: Multiple myeloma is a neoplastic proliferation of abnormal plasma cells. The clinical features of multiple myeloma depends on either direct proliferation of plasma cells resulting in extensive bony destructive lesions or indirectly related to paraprotein production mainly monoclonal immunoglobulins resulting in renal damage e.g. proteinuria, renal impairment (acute kidney injury), electrolyte disturbances and amyloid deposits. Multiple myeloma can also present with signs of spinal cord compression resulting in paraesthesia and paraplegia which can be missed and lead to delay in diagnosis and treatment.

Case Description: A 73 years old patient with past medical history of; asthma, atrial fibrillation on warfarin, bilateral knee replacements; presented to the emergency department, following recurrent mechanical falls. The patient had suffered prepatellar lacerations which was treated with suturing and discharged home. The patient further attended the emergency department with right knee pain and an inability to walk. The working diagnosis was right knee haematoma due to raised international normalised ratio (INR) since she was on warfarin. She required knee washouts and multiple blood transfusions due to anaemia and was subsequently discharged. The patient was re-admitted with recurrent falls. Further physiotherapy was arranged and plans made for discharge. During a weekend on call; the patient's husband asked the oncall consultant to review his wife as he was worried about her general decline and no one seemed to have listened so far. . The consultant listened to the husband and revisited patient's history. Upon examination; the patient appeared to have had significant neurological symptoms of spinal cord compression. A myeloma screen was requested due to anaemia. The patient underwent an urgent MRI scan and was transferred urgently to a neurosurgical centre for surgical decompression on the same day.

Discussion: Spinal cord compression from multiple myeloma, should be suspected in patients presenting with severe back pain along with weakness or paraesthesia, bladder or bowel dysfunction or incontinence, including unexplained anaemia (requiring blood transfusions). It is important to listen to patients and family when they warn us that their "loved ones" are not feeling right. Listening to patients and concentrating on their problems gives one more realistic ideas and insight into their problems

PUB032

Long-Term Outcomes After Leptospirosis: A Population Cohort Study

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Background: Acute kidney injury (AKI) is a common complication of leptospirosis infection. However, the long-term outcomes following leptospirosis infection is not fully clarified. The aim of this study is to elucidate the long-term outcomes of adult patients who survived after leptospirosis.

Methods: The study analyzed datasets from Taiwan's National Health Insurance Research Database. The data of 2145 patients who survived after leptospirosis between January 1, 2003, and December 31, 2013, were analyzed. Characteristics and outcomes were compared according to the AKI or not to evaluate the impact of AKI on long-term mortality and major adverse kidney events.

Results: Of the 2145 patients, 26.0% had AKI and 3.5% received renal replacement therapy (RRT). Compared between the non-AKI, AKI and AKI-RRT, those with RRT had highest rates of all-cause mortality (22% vs 12.6% vs. 7.0%) and, advanced chronic kidney disease (0% vs. 1.09% vs 6.49%) respectively, demonstrating a significant trend (P < 0.001).

Conclusions: Patients who has leptospirosis related AKI, compared to those without AKI, have an increased risk of long-term mortality and major adverse kidney events.

PUB033

CRRT with Oxiris®: An Option for Multidisciplinary Treatment of AKI in Sepsis?

Nicoletta Pertica,[1] Alessia Corvo,[1] Paolo Ria,[2] Lorenzo Signorini,[1] Gianluigi Zaza.[3] [1]*Nephrology, AOUI - Borgo Trento, Verona, Italy;* [2]*Nephrology, Ospedale - V. Fazzi, Lecce, Italy;* [3]*University of Verona, Verona, Italy.*

Background: Septic shock is a serious cause of morbidity/mortality in ICU. MODS and AKI are common sepsis complications, burden by high mortality rates. CRRT, carried out by filters adsorbing sepsis mediators, can improve the outcome. The actual guidelines on sepsis highlights the importance of a timely start of CRRT.

Methods: We selected 27 consecutive patients with AKI in septic shock and treated through CVV-HDF with Prismaflex® and Oxiris®. We considered different laboratory parameters at regular time lapses after the CRRT start. As control group, we enlisted 20 patients from a historical cohort matched for diagnosis, treated with filter ST-150.

Results: We observed a statistically significant improvement for those treated by Oxiris®, particularly over kidney function recovery at 6 days (p =0.021) and reduction of inflammatory parameters (PCR p=0.006; PCT p=0.005). Over mortality, no difference emerged between infections caused by Gram + or Gram–, even if a better outcome was noted for Gram + related sepsis (G+ 83%vsG- 53%)

Conclusions: The use of specific filters for the treatment of sepsis with timely start of CRRT might help to improve the outcome of septic patients with AKI, not in terms of

absolute mortality, but reducing the indices of inflammation and shortening the functional recovery time.

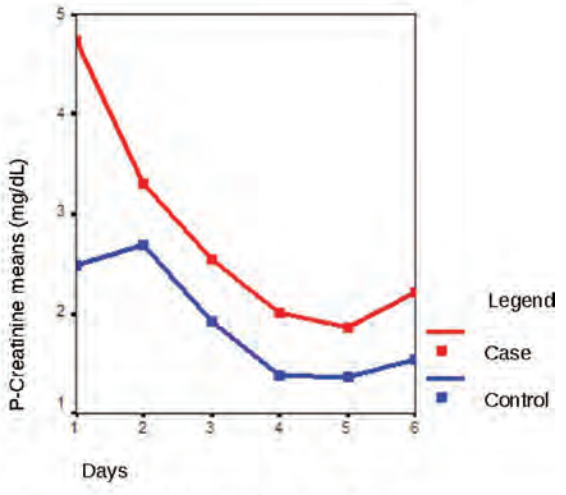

Fig.1 p-Creatinine curves in time (day 1 – day 6)

p-creatinine curves in the two groups of patients

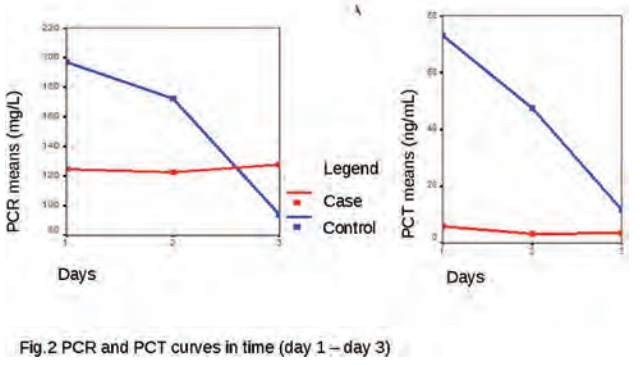

Fig.2 PCR and PCT curves in time (day 1 – day 3)

PCR and PCT curves in the two groups of patients

PUB034

The Anticoagulation Is the Single Most Important Factor Leading to Prolonged Filter Time on CRRT

Muhammad O. Saleem,[1] Colleen S. Boyle,[1] Azeem Mohammed,[1] N. Stanley Nahman.[1,2] Nephrons@AU *[1]Medical College of Georgia, Augusta University, Augusta, GA; [2]Norwood VAMC, Augusta, GA.*

Background: When providing continuous renal replacement therapy (CRRT) to the critically ill, circuit clotting is a key impediment to effective dialysis. Filter clotting may result from dysfunctional vascular access, inadequate anticoagulation, and/or selection of dialysis parameters that may promote clotting. To investigate the effect of these variables on filter life we performed a retrospective, performance improvement, analysis of the records of 33 CRRT patients treated in the intensive care units at Augusta University

Methods: A chart review was conducted and patients were sorted into two groups based on the presence or absence of anticoagulation. On each patient, we documented the indication for CRRT, vascular access specifications, dialysis modality, and prescription, which included therapy fluid rates, blood flow rates, and filtration fraction. The clinical characteristics of patients were also compared. Students t-test was used to compare the groups.

Results: Of the 33 patients 15 were anticoagulated with heparin, 18 received no anticoagulation. No patients received regional citrate anticoagulation in this study. The mean filter life in the first 24 hours for all patients was 16.03±11.9 hours. Patients treated with heparin had a significantly longer filter life in the first 24 hours (23.3±13.5 vs 9.9±6.8 hours for heparin vs no heparin, respectively, $p < 0.005$) The majority of patients (85%) received CVVH with the pre-filter administration of replacement fluid. The mean filtration fraction of all prescriptions was 19.40±4.03%. There was no difference in site, size, or diameter of dialysis catheters between the two groups.

Conclusions: Anticoagulation with heparin prolongs filter half life when compared to no anticoagulation. The use of heparin and prolonged filter life must be balanced with the risks of bleeding, however, substantially more dialysis can be given without interruption in heparinized patients. The role of regional citrate anticoagulation vs heparin or no therapy remains to be studied. The results support the use of heparin, when possible, to help maintain filter half life in CRRT.

PUB035

Infection in Community Acquired AKI

James Tollitt,[1] Nicola Bennett,[2] Smeeta Sinha,[1] James Ritchie,[1] Emma Flanagan,[3] Denise Darby,[1] Philip A. Kalra,[1] Dimitrios J. Poulikakos.[1] *[1]Salford Royal NHS Foundation Trust, Salford, United Kingdom; [2]University of Manchester, Manchester, United Kingdom; [3]Salford Care Organisation, Salford, United Kingdom.*

Background: The majority of acute kidney injury (AKI) is community acquired (CA). The interaction between community acquired (CA-I) and CA-AKI is incompletely understood. Recent sepsis guidance has included assessment of AKI for risk stratification to guide treatment. The aim of this study was to evaluate characteristics of CA-I and CA-AKI and their impact upon patient outcomes in general population and a care home population.

Methods: Adult, non-elective patient attendances to a single centre were analysed retrospectively. CA-AKI (AKI within 48 hrs of hospital attendance) and/or CA-I (antibiotic within 48 hrs of attendance) were recorded. Outcomes were 30-day all-cause mortality (30 DM), intensive care unit (ICU) admission and length of stay (LOS) dichotomised at median. Binary logistic regression models were created to predict the probability of the outcome variables in both patient groups.

Results: Of 61,471 attendances 4.2% were from a care home. In the total cohort 28.1% suffered CA-I and 5.7% suffered CA-AKI (3.8% AKI1, 1.1% AKI2, 0.8% AKI3). 3.4% suffered CA-I and CA-AKI. CAI-I was present in 58.9% of CA-AKI cases. 30 DM showed a stepwise increase in patients with CA-I (8.1%), with CA-AKI (11.8%) and with combination of CA-I and CA-AKI (26.2%). In the care home population 30 DM for the group with both CA-I and CA-AKI was 43.4%. In non-care home group those with both CA-I and CA-AKI had the highest rate of ICU admission (24%), followed by CA-I alone (7.2%) and CA-AKI alone (7.1%). Odds ratios (OR) for all outcome variables in non-care home population demonstrated an escalating association for poor outcomes (CA-AKI and CAI>CA-AKI alone>CAI alone) (Figure1).

Conclusions: CA-I is present in the majority of CA-AKI and their coexistence is associated with increased risk of poor outcomes.

Model for 30 Day Mortality in non care home patients

	OR	CI
Male	1.24	1.15-1.33*
Age	1.06	1.06-1.06*
CA-I	3.01	2.78-3.28*
CA-AKI1	2.90	2.36-3.58*
CA-AKI2	6.19	4.42-8.67*
CA-AKI3	3.16	1.93-5.17*
CA-I and CA-AKI1	6.77	5.85-7.82*
CA-I and CA-AKI2	14.05	11.39-17.32*
CA-I and CA-AKI3	11.02	8.42-14.41*

* Significant

PUB036

Transcatheter Repair of Tricuspid Regurgitation with the MitraClip Device and the Observed Rate of Post Procedure AKI

Ramy M. Hanna, James Wilson. *UCLA Health, Rolling Hills Estates, CA.*

Background: The MitraClip device was approved for transcatheter repair of significant mitral valve insufficiency instead of surgical repair. The device is now being used for non-surgical candidates with severe tricuspid regurgitation. As IV contrast dye is often not necessary for placement of the device in this subset of patients, we have sought to evaluate the risk of renal failure in patients who received the Clip in the tricuspid position.

Methods: At the University of California Los Angeles, the MitraClip is being used off-label in patients with significant tricuspid regurgitation who are not surgical candidates. We report our experience with the first five patients who have had this procedure completed at UCLA. We examine the rates of acute kidney injury post procedure in these five patients.

Results: Of the five patients, one had normal kidney function, three had underlying CKD and were not on dialysis, and one had ESRD and was on dialysis. Acute kidney injury, defined as a rise in serum creatinine by 0.5mg/dL was observed in two of four patients (50%) who underwent this procedure and were not on dialysis. The one patient without CKD did not suffer acute kidney injury but had a mild rise in serum creatinine. The one dialysis patient who underwent this procedure had no discernible change in renal function. These procedures were done without iodinated contrast

Conclusions: We examine the rate of AKI post off label tricuspid valve repair with MitraClip, further data should be sought out as this procedure is increasingly implemented.

Table 1: Clinical cases involving percuatenous tricuspid valve repair (TriClip) procedure

Patient #	Age	Gender	Race	Other valvular disease	CAD	DM2	Contrast used	Etiology of TR	ESRD	AKI	RRT
1	75	M	Hispanic	N	LAD	Y	0 ml	functional	N	N	N
2	68	F	Caucasian	N	N	N	0 ml	constrictive physiology	N	N	N
3	23	M	Hispanic	N	N	N	0 ml	malcoaptation	Y	N	chronic
4	77	M	Middle Eastern	AV, MV	N	N	0 ml	rheumatic fever	N	Y	acute
5	71	F	Hispanic	N	N	Y	0 ml	malcoaptation	N	Y	N

Table 1 Figure legend: AKI=Acute kidney injury, AV= aortic valve, CAD=coronary artery disease, ESRD=end stage renal disease, F=Female, LAD= corornary disease in left anterior descending coronary artery, M=Male, ml=milliiter, MV=mitral valve, N=No, RRT=renal replacement therapy, TR=tricuspid regurgitation, Y= yes

PUB037

Renal Prognosis Is Related with Delta Neutrophil Index in Patients with Alcoholic Ketoacidosis

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Background: Alcoholic ketoacidosis is metabolic abnormalities often diagnosed in malnourished patients chronically abuse alcohol and have a history of alcoholic binge. Delta neutrophil index (DNI), representing an elevated fraction of circulating immature granulocytes in acute infection, has been reported as a useful predictable marker for mortality in patients with sepsis. We make an attempt to reveal clinical charateristics and found prognostic factor including DNI associated with alcoholic ketoacidosis in this study.

Methods: We investigated patients diagnosed with AKA who visited the emergency department fo Wonju Severance Christian hospital from October 2009 to March 2014 retrospectively. Patients have history of alcohol abuse and recent episode of binge drinking with metabolic acidosis in ABGA and increased serum anion gap in serum chemistry were included. We categorized according to KDIGO Acute kidney injury criteria and compared groups about prognostic factors

Results: In a total of AKA cases, 95 (80.5%) were diagnosed with AKI by KDIGO criteria: 27 cases (22.9%) were classified as AKI stage 1, 15 cases (12.7%) as AKI stage 2, 53 cases (44.9%) as AKI stage 3. Mortality was reported in 38 cases (32.2%), and the mean time from admission to mortality was 6.4 ± 12.1 days. Major causes of death included uncontrolled metabolic acidosis (n=25, 21.2%), septic shock (n=10, 8.5%), and gastrointestinal tract bleeding (n=1, 0.8%). There were significant differences in pH, PCO_2, lactate, Hb, platelets, PT, PTT, Cr, albumin, AST, GGT, Total bilirubin, P, Ammonia, T3, fT4, and DNI (P<0.001) between survivors and non-survivors. DNI was higher value in AKI stage III compared with AKI 0 to 2 stage significantly (p<0.001)

Conclusions: Delta neutrophil index have a significant value in predicting alcoholic ketoacidosis with poor renal outcome and mortality.

PUB038

Obstructive Uropathy with Uremia Due to Advanced Cervical-Uterine Cancer

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Background: Cervical-uterine cancer (CUC) is a worldwide public health problem. Advanced CUC affects nearby regional structures causing obstruction. Rarely, obstructive uropathy can cause acute kidney injury (AKI), which leads to uremic syndrome. In extreme situations, urgent treatment such as ureteral stent placement, nephrostomies and hemodialysis, as saving life modalities, are required.

Methods: We retrospectively analyzed the characteristics of AKI patients due to obstructive uropathy caused by advanced CUC presenting to the emergency department in a teaching hospital, located in Mexico, during may 2013 to may 2018.

Results: 28 patients were analyzed, 45 years as mean age. The main identified comorbidities were Diabetes Mellitus, identified on 5 (17%) of the patients, and Hypertension identified on 5 patients also. The mean evolution of CUC period was 22 years. 60% of the patients had metastatic CUC. The mean Eastern Cooperative Oncology Group score was 2.3. The most common presenting symptom was malaise and weight loss on 57% and 46%, respectively. The mean Blood Urea Nitrogen and Creatinine was 86 ±60 mg/dL and 6.9 ± 6.5mg/dL, respectively. 46.4% of the patients underwent JJ stent placement, and 39% required nephrostomies. 96% had bilateral hydronephrosis. The mean hospitalization period was 6.7 days. 10 patients (36%) died, with a mean survival of 6 ±6 months. Survival analysis showed no difference in mortality when comparing both treatment arms (long-rank test: 0.95).

Conclusions: Advanced CUC, in our country, is a public health issue and a considerable cause of uremia and AKI. Those patients had a mean survival of 6 months irrespective of the palliative treatment modality.

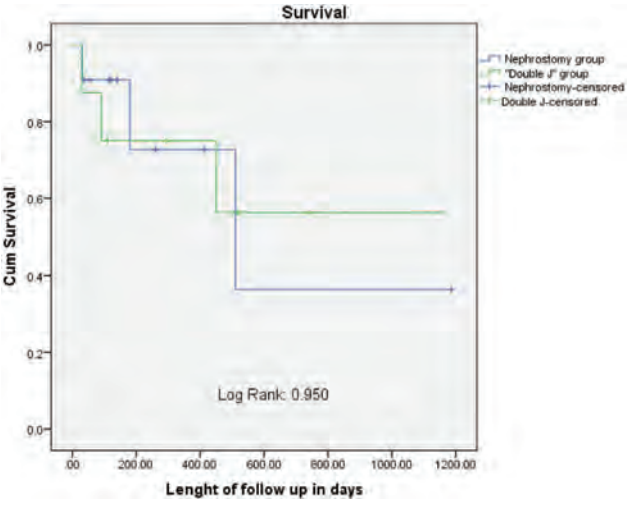

Fig 1. Survival Analysis.

PUB039

From Heparin to Citrate Anticoagulation in CRRT: Efficiency and Expense Evaluation

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Background: CRRT is used as a therapy for acute kidney injury in intensive care units. Heparin has long been used as an anticoagulant during CRRT (efficacy-low cost) but, starting from the KDIGO 2012 guidelines, citrate has become first-choice anticoagulant.

Methods: From 2011 to 2017 we performed 11,109 CRRT treatments (1 treatment = 24 h CRRT) with an increasing percentage of citrate anticoagulation, from 2.9 to 73%. We performed a retrospective analysis starting from the quantity and cost of materials (Kits+solutions) and evaluated efficiency and expense.

Results: a) reduction in the number of filters used for every 72 hours of treatment, from 2.4 to 1.5; b) increase in the administered dialysis dose, from 25.7 to 37.5 ml/kg/h; c) reduction in the difference between prescribed and administered dialysis dose, from 22 to 7%; d) slight increase in the total cost for 24 hours' CRRT, from €161.03 to €184.54; e) reduction in the total cost for each 35ml of solution administered, from € 0.13 to € 0.10 (e.g. 134960000 ml solution used in 2017).

Conclusions: The limits of the study are its retrospective nature and data collection not regarding single treatments but starting from the total quantity of materials used and thus ruling out statistical analysis of significance. With citrate we observed a slight increase in the total cost but also a reduction in the cost per unit of administered dialysis dose. Furthermore, we obtained an increase in the average life of the filter and an increase in the efficiency of the treatment (prescribed dialysis dose *versus* administered dose).

Year	2011	2012	2013	2014	2015	2016	2017
Number of treatments*	1479	1087	1309	1735	1706	1637	2156
Percentage of citrate anticoagulation (%)	2.9	5.7	21.4	37.1	49.5	72	73
n. filters/72h	2.4	2.3	1.9	1.7	1.6	1.5	1.5
Administered dialysis dose (ml/Kg/h)	25.7	25.5	30.1	36.5	37.2	37.5	37.5
Cost for 24 hours' CRRT (€)	161.30	141.65	163.31	178.20	187.17	185.32	184.54
Cost for each 35 ml solution administered (€)	0.13	0.13	0.11	0.10	0.10	0.09	0.10

* 1 treatment = 24 h CRRT

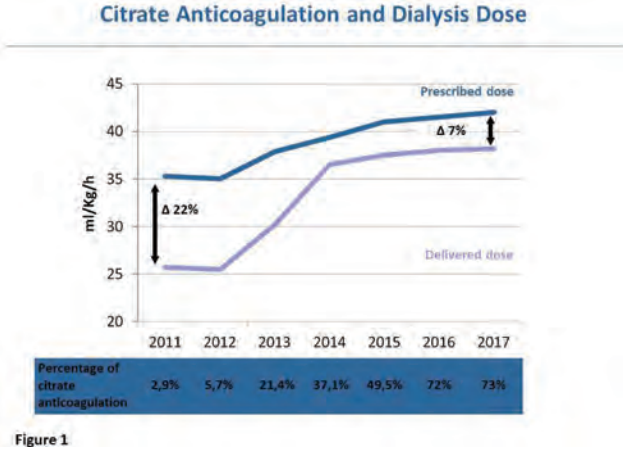

Figure 1

PUB040

An Update on the Use of Novel Biomarkers for AKI in Drug Development

Carolina Panico, Aliza M. Thompson. *U.S. Food and Drug Administration, Silver Spring, MD.*

Background: In 2008, FDA qualified 7 urinary biomarkers to be used, in conjunction with serum creatinine, BUN and histopathology, as additional evidence to identify early signals of kidney injury in the rat. Since then, there has been increased use of these biomarkers in drug development programs. The objective of this study is to characterize the data that can be leveraged on the performance of these biomarkers and use to inform decision making in drug development programs.

Methods: The FDA document archiving, reporting and regulatory tracking system was used to retrieve biomarker information contained in Investigational New Drug applications (INDs), using KIM-1 (kidney injury molecule-1) as the search term. The following information was collected: urinary biomarkers assessed, pre-analytical information, such as collection method, storage and processing of samples, information on assays, and status of the drug development program, including stage of clinical development and whether studies were still being pursued under the IND.

Results: A total of 143 INDs referenced the use of KIM-1 between 2005 and 2016. Of these, 51 INDs contained summary or patient-level data on KIM-1; 41 also contained information on other novel urinary biomarkers. In 45 INDs, the biomarkers were used in safety assessments, whereas in 6 INDs the biomarkers were used in efficacy evaluations. Among the 51 INDs, 45 reported the use of the biomarkers in preclinical studies and 11 in clinical studies (8 phase I and 3 phase II studies). 15 of 51 applications contained pre-analytical and assay information, though the granularity of that information varied greatly across the 15 INDs. Of the applications in which the biomarkers were used to assess drug-induced kidney injury, 33 were still active. In contrast, only two of 6 INDs identified as using the biomarkers for efficacy assessments were still active at the end of 2016. Based on the submitted data, it is unclear to what extent the biomarker data influenced the decision to pursue further investigation of the drug.

Conclusions: Although novel renal biomarkers are being used in drug development, most INDs do not appear to contain granular information on pre-analytical variables and assay(s) or data sets, which may limit the ability to leverage data that are currently available to FDA to learn about the performance of the biomarkers as drug development tools.

PUB041

Reduction of Inpatient Length of Stay, Readmissions, and Associated Healthcare Costs Through Early Detection of AKI Using a Urinary Biomarker: Results of an Economic Model

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Background: [TIMP-2/IGFBP-7] NephroCheck® (NC) is a novel biomarker-based, FDA-cleared urine test to aid in assessing risk for moderate or severe acute kidney injury (AKI) in ICU patients. NC measures the levels of two urinary biomarkers indicating higher risk of AKI, and is thus able to identify AKI earlier than the existing standard of care (SOC). We evaluated via an economic model if early identification of AKI, by using NC, could reduce the severity of AKI, thereby improving patient outcomes, such as length-of-stay, readmissions and healthcare costs.

Methods: An Excel-based economic model (2017 USD) using peer-reviewed data was developed from the perspective of a hypothetical hospital system. The model estimated the impact of testing patients for AKI using SOC versus a combination of SOC plus NC over a 1-year period. Outcomes considered included lengths of ICU and non-ICU inpatient stays, 30-day readmissions, and net impact on hospital budget. Model inputs included literature-based estimates for diagnostic efficacy of NC plus SOC and for patient healthcare resource utilization associated with levels of AKI severity, as well as data on file for costs associated with NC test meters and cartridges.

Results: Assuming 500 hypothetical at-risk patients were tested, improved diagnostic efficacy using NC in addition to SOC would result in 283 fewer non-ICU inpatient days (0.6 days per tested patient [PTP]), 152 fewer ICU days (0.3 days PTP), and 5 fewer 30-day readmissions. The incremental cost of using NC is more than offset by these reductions, resulting in annual net savings of $799,479 ($1,599 PTP) or 10.1% to the overall hospital budget. Deterministic and probabilistic sensitivity analyses support improved patient outcomes and associated savings in over 99% of scenarios.

Conclusions: This model demonstrates that the addition of NC to SOC for the earlier identification of AKI is likely to result in moderate reductions in inpatient non-ICU and ICU lengths of stay, 30-day readmissions and total healthcare costs. Further studies are needed to confirm these findings in a real-world setting.

Funding: Commercial Support - bioMérieux Inc.

PUB042

AKI Mortality Across KDIGO Classification Strata: Does Previous CKD Matter?

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Background: Few works compare in-hospital mortality in individuals with previous normal (ARF) and impaired (Acute on CKD) renal function who suffer AKI, and fewer compare mortality between strata inside KDIGO stages. We hypothesize that AoCKD individuals perform distinctly across the classification.

Methods: Retrospective study of ARF and AoCKD patients classified by KDIGO guidelines. We analyzed epidemiological variables, compared the clinical outcome in-hospital mortality, and analyzed the distribution through KDIGO stages of all cohort and subanalyzed dead patients.

Results: 1269 individuals were included. Table 1 summarizes clinical characteristics and results of both groups. Compared with ARF individulals, AoCKD patients are older, have a higher Charlson's Index, are more frequently classified in Stage 1 (both criteria), lesser in Stage 2, and equal in Stage 3. Global mortality is not significantly different between groups, we checked every KDIGO Stage and mortality was significantly higher in Stage 1 (for both criteria), lower in Stage 2 and equal in Stage 3. When evaluating every component of Stage 3 we found that 29% of AoCKD individuals (vs 67% ARF) reached a 3x SCr increment, 65% (vs 42% ARF) reached a SCr ≥4.0 mg/dl (21 patients had already a basal SCr ≥4.0 mg/dl), and no difference in initiation of renal replacement therapy (RRT).

Conclusions: Although in-hospital mortality is not significantly different between groups, when analyzing KDIGO strata we found excess mortality for the AoCKD individuals in Stage 1 and 3. The smaller proportion of SCr x 3.0, and the excess in SCr ≥4.0 mg/dl may be due to diminished renal reserve and higher basal SCr. The facts that the same proportion of patients in both groups initiate RRT, and that in Stage 2 a smaller proportion of AoCKD patients died, deserves further investigation.

Characteristic	ARF (491)	AoCKD (778)	P Value
Age - years	68 ± 14	75± 12	<0.001*
Sex (male)	339 (69)	544 (70)	0.75§
Charlson´s I.	3.9 ± 2.5	4.9 ± 2.2	<0.001*
Results			
Initiation RRT	62 (26)	105 (28)	0.64§
Mortality	100 (20)	179 (23)	0.30§
KDIGO-2012 AKI Stage			
1 (global)	165 (33)	327 (42)	0.003§
≥ 0.3 mg/dl	42 (9)	190 (24)	<0.001§
SCr 1.5-1.9x	126 (26)	239 (31)	0.06§
2 (SCr x 2.0-2.9x)	91 (19)	76 (10)	<0.001§
3 (global)	235 (48)	372 (48)	1.00§
SCr ≥3.0x	230 (98)	129 (34)	<0.001§
SCr ≥4.0 mg/dl	151 (64)	354 (95)	<0.001§
Initiation RRT	62 (26)	105 (28)	0.64§
In-Hospital Mortality	**ARF (100)**	**AoCKD (179)**	**P Value**
KDIGO-2012 AKI Stage			
1	10 (10)	43 (24)	0.04§
≥ 0.3 mg/dl	2 (2)	22 (12)	0.003§
SCr 1.5-1.9x	9 (9)	50 (28)	<0.001§
2	21 (21)	12 (7)	0.001§
3 (global)	69 (69)	123 (69)	1.00§
SCr x 3.0	67 (67)	52 (29)	<0.001§
SCr >4.0 mg/dl	42 (42)	117 (65)	<0.001§
Initiation RRT	24 (24)	39 (22)	0.77§

PUB043

Incidence of AKI in a Large Retrospective Cancer Cohort Using Checkpoint Inhibitors

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Background: With the advent of the era of immunotherapy there has been marked increased survival in several cancers such as advanced melanoma, renal cell carcinoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, and head and neck cancers. Although the incidence of renal toxicity is reported 3.8%, we believe that it is much higher. In this study we sought to retrospectively review a 10 year experience at MD Anderson Cancer Center of patients with cancer and treated with CPI and evaluate incidence of AKI, CKD, and overall survival.

Methods: We performed a retrospective chart review from 2008-2018 and extracted all patients treated with Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, and Avelumab. We identified 6412 unique patients and extracted all avaliable creatinine and GFR. We have defined AKI based on KDIGO guidelines excluding urine output. We also are also interested in evaluating the overall renal outcomes looking at CKD as persistent GFR over three month period at end of the study. Variables to be studied basic demographics, type of cancer, type of CPI, number of doses, dosages, and CKD stage at beginning of the study period. We have three primary endpoints: incidence of AKI, stage of CKD, and overall survival. We will perform Cox proportional hazards regression models to estimate unadjusted and adjusted cause-specific hazards ratios (HR) of risk factors for all three endpoints.

Results: We have identified 6412 patients with diagnosis melanoma, sarcoma, lung cancer, renal cell cancer, and hematological malignancies. The patients have been categorized as either single agent CPI or combinations. Based on our preliminary data and further verification is underway the incidence of AKI is higher than reported in the literature and estimated at >25%. Since patients with Renal cell cancer maybe predisposed to having AKI and CKD in setting of solitary kidneys we will be perform a subpopulation analysis.

Conclusions: With such a large population of patients treated with CPI we would be able to understand the variables associated with renal toxicities, such as type of CPI, combinations, or dosage and help create more accurate guidlines. This would impact renal survival which would impact ultimately patients overall survival.

PUB044

AKI in the Setting of Coronarography Procedures: A Monocentric Analysis

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Background: Acute Kidney injury (AKI) is a common complication of coronarography, PTCA and TAVI, with a literature reported incidence ranging from 7 to 12%. This study investigates incidence, risk factors and outcomes of AKI in patient who undergo to coronarography procedures with intraarterial administration of contrast medium.

Methods: We retrospectively reviewed data from all the adults who underwent to diagnostic or therapeutic coronarography procedures at the Cardiology Department of Brotzu Hospital in 2016 and had least one creatinine value 7 days before and 72 hours after the procedure. Patients who were on dialysis at the time of the procedure and those who underwent to cardiac catheterization were excluded from the analysis.

Results: 375 patients were included in our analysis. Among them a total of 57 (15.2%) developed AKI (according KDIGO definition): 30 patients (8%) developed CI-AKI. 49 patients reached stage 1 AKI (according KDIGO definition), 2 and 6 developed stage 2 and stage 3 AKI respectively. Diagnosis of AKI was associated with older age (73.6 vs 65.7), lower eGFR before procedure (53 ml/min vs 81.5 ml/min), preexisting CKD (OR 5.3), hypertension (OR 1.86), CHF (OR 2.20) and higher Mehran score (8.47 vs 5.01). AKI required begin of renal replacement treatment in 3 patients. The mean contrast medium dose was not significantly different between patient who developed AKI and those who did not, while radial access was associated with a lower incidence of AKI. At 12 months follow-up 7 patients of AKI group were on dialysis, while only 1 patient from non-AKI group needed RRT (12.3% vs 0.03% OR 44.4); risk of mortality was significantly higher in patients who developed AKI (17.5% vs 3.7% OR 5.42). No significative difference were found between who developed CI-AKI and those who developed AKI but did not meet criteria for CI-AKI.

Conclusions: Our analysis describes risk factors who should evaluated in patients who should undergo to coronarography procedures: older age, previous CKD, hypertension, CHF. Since criteria for CI-AKI were met in 52% of AKI cases, 48% of patients developed a kidney damage with no clear correlation with contrast medium: hemodynamic factors, renal atheroembolism and drug nephrotoxicity should, therefore, be considered as further kidney injury cause in these patients

PUB045

The Location of the Short Term Catheter for Continuous Renal Replacement Therapy Does Not Affect the Patient's Short Term Outcome

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Background: Many severe acute kidney injury (AKI) patients in the intensive care unit(ICU) has received renal replacement therapy and the patients with hemodynamic instability receive the continuous renal replacement therapy (CRRT). The vascular access for CRRT is usually performed using a short term catheter. In KDIGO guidline., When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences.: 1st choice: right jugular vein (RJV); 2nd choice: femoral vein(FV); 3rd choice: left jugular vein(LJV); Last choice: subclavian vein(subV). But, There are many patients who have access to the FV more than the Internal JV in the clinical setting, The aim of this study was to investigate the relationship between catheter location and patient prognosis and norepinephrine(NE) dose changes.

Methods: We retrospectively studied on patients who received CRRT in the ICU on our hospital from January 5, 2016 through December 31, 2016. Among these patients, We excluded patients under 18 years, End stage renal disease, without central venous catheterization, not using NE, using NE and other additional vasopressors and using Extracorporeal membrane oxygenation. They were divided two groups based on the double lumen catheter insertion site. Femoral vein insertion was assigned to group 1 and the other site was assigned to group 2. The 28-day mortality and NE dose changes were compared between the two groups. We calculated the difference by measuring the amount of NE injection at the start of CRRT and the amount of NE injection after 6 hours.

Results: All patients who received CRRT in the ICU on our hospital was initially screened.(n=186). We excluded 124 patients according to exclusion criteria. A total of 62 patients were included in the analyses. The median age of patients is 68(21-90) year-old and men were 67.7% (n=42). 28-day mortality rate was 56.5% and the septic shock was the main cause of CRRT (n=46, 74.2%). The 28-day mortality rate was not different between the two groups. [48.4%(n=15) vs.64.5% (n=20), P=0.2]. And NE dose changes were also not different between the two groups. [-1.3699(-44.99 – 128.74) vs. 0.0000(-66.67 – 97.86) ug/kg/hr, P=0.767.].

Conclusions: The insertion site of the catheter in patients with CRRT does not affect the patient's short term out coming.

PUB046

A Novel Hemodialysis System, Deployed in an Acute Setting, Provides Volume Management at Lower Cost Than CRRT

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Background: There is an increasing prevalence of AKI requiring renal replacement therapy. Care of this patient population is challenging to health care systems (HCS) both in costs and logistics. HCS increasingly face nursing shortages and flat reimbursement rates for care of this patient population, straining abilities to provide effective dialysis.

Methods: As part of a QAPI project, we first examined the number of dialytic therapies, grouped by modality, conducted in intensive care settings at the Cleveland Clinic between 2013 and 2016. Secondly, we piloted the use of novel, simple to use hemodialysis system (Tablo) as a transitional modality, in 80 patients ready to transition off CRRT, but that remained clinically volume overloaded. This is a cost-effectiveness analysis of our PIRRT experience using Tablo compared to existing options.

Results: During 4 years of study, the number of intermittent dialysis treatments in the ICU stayed stable, however the number of continuous dialysis treatment days increased (Table 1). 80 patients were dialyzed using Tablo, for 6-8 hour treatments at QB of 200-300 ml/min and QD of 300 ml/hr. The cost of PIRRT using Tablo is presented in Table 2.

Conclusions: Treating this critically ill cohort at the Cleveland Clinic, we demonstrate that Tablo can enable transitional hemodialysis while markedly reducing staffing costs. These data suggest that Tablo can provide increased functionality and flexibility to cost and staff constrained ICUs.

Funding: Commercial Support - Outset Medical

Treatment Type		2016	2015	2014	2013
Intermittent (# treatments)	ICU	3396	3322	3173	3229
	RNF	4689	4003	3641	3187
	Total	8085	7325	6814	6416
Continuous (R Days)		5952	5697	4828	4664

Table 1

Costs Associated with the Different RRT modalities.

	PIRRT (IHD)	PIRRT (CRRT)	PIRRT (Tablo)
Supply Costs: Tubing/Filters	35	185	85
Solutions*	5	192	5
Staff Costs	170**	38	38
Cost Per Day	210	415	128
Cost Per Week	1470	2905	896

*6L/hour for 8 hours (pharmacist cost not included for CRRT)
** One nurse supervising 2 machines

Table 2

PUB047

Clinical Study and Outcome of Patients with AKI Following Exposure to Various Poisons with Special Emphasis on Paraquat Poisoning

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Background: Exposure to compounds like pesticides, herbicides and insecticides have hazardous effects. ARDS, AKI, multiorgan failure are the frequent causes of mortality. Paraquat is a weedicide used commonly for suicide in southern Maharashtra. It is always fatal as there is no specific antidote. Current study highlights the occurence of Acute kidney injury and its outcome after exposure to various poisons amongst patients admitted to RCSM GMC and CPR Hospital, a tertiary care centre in Kolhapur, Maharashtra.

Methods: We carried out a retrospective observational study where data was collected from case records of patients admitted from May 2015 to April 2018 and their outcome was noted. The aim was to study the morbidity and mortality rates of different poisons with special focus on Paraquat compound. Almost all patients included required hemodialysis, especially with Paraquat poisoning and associated mortality was compared with other poisons combined. Adequate statistical test was used and a p-value <0.05 was considered statistically significant

Results: During the study period we found 347 patients of poisoning who developed AKI requiring dialysis. The largest group was from Paraphenyline diamine (PPD) of 94 patients followed by Organophosphorus compound (73), Paraquat (66), Copper sulphate (42) Methanol (20) and other poisons (52). The outcome of ingestion of these poisons is summarized in Table 1. Mortality associated with Paraquat was 86.36% (N=57) whereas it was 43.82% (N=78) among other poisons combined. This difference was statistically significant ($x^2 = 69.70$, $p < 0.0001$)

Conclusions: It is important to report all the poisonous substances. causing nephrotoxicity to increase awareness among general population and health care providers. Of all registered herbicides, Paraquat is the most fatal and despite early hemodialysis, the mortality rates remained high. Newer treatment options like early hemoperfusion may help to reduce the mortality in future.

Outcome in different groups (N=347)

Outcome	Paraquat (N=66)	PPD(N =94)	OP(N=73)	CUSO4(N=42)	Methanol (N=20)	Others (N=52)
Complete recovery	7	77	34	20	14	33
Partial recovery & lost follow up	2	4	0	7	3	5
Left against advice during acute phase	0	3	0	0	0	3
Died	57	10	39	15	3	11

PUB048

AKI and Complete Heart Block in Hepatitis E Infection

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Introduction: Hepatitis E is a benign, usually self-limiting viral infection with primary symptoms of fever, myalgia, fatigue, nausea and vomiting. Acute kidney injury is uncommon in hepatitis E infection and hence not frequently anticipated. We present a patient with type II diabetes mellitus (DM) with two episodes of syncope. Investigation revealed AKI, hyperkalemia and complete heart block, all secondary to Hepatitis E infection.

Case Description: A 71 year male, presented with two episodes of syncope and fall, decreased urine output and complete heart block. Temporary pacemaker implantation was done. On detailed evaluation, he gave history of fever, vomiting, fatigue and loss of appetite for the last 1 week. Examination revealed bradycardia, right hypochondrial tenderness and decreased breath sounds in bilateral intrascapular regions. Initial investigations revealed grossly elevated cardiac enzymes, leukocytosis, hyperglycemia, hyperkalemia (Serum potassium - 6.4 mEq/L) and markedly deranged renal, liver and coagulation profiles. Measures to counter hyperkalemia, broad spectrum antibiotics and insulin therapy were initiated. Ultrasound was suggestive of ascites and bilateral pleural effusion; and possible underlying chronic kidney disease. 2D Echocardiography showed hypokinesia of the basal inferior and infero-lateral walls with ejection fraction of 50%. He was hemodialysed in view of the decreased urine output and hyperkalemia. Investigations done to rule out the cause of acute liver injury revealed serology positive for hepatitis E infection. After clinical and symptomatic improvement, the pacemaker support was withdrawn and there was reversion to sinus rhythm. The patient was discharged in a stable condition after over a fortnight in the hospital. He was followed up in OPD where he was asymptomatic and had a normal renal profile.

Discussion: Acute Kidney Injury is an uncommon manifestation of Hepatitis E infection. Complete heart block due hyperkalemia secondary to AKI (with a serum potassium of 6.4 mEq/l) is unlikely and may occur due to myocarditis or an underlying coronary artery disease. The clinician should be aware of the extra hepatic manifestations of hepatitis E infection including AKI and arrhythmias, which, if identified in time could be treated promptly with good outcomes.

PUB049

Nonagenarians in Northern Jordan Are at Risk for AKI: A Retrospective Case-Control Study

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Background: Improvements in healthcare systems worldwide have had notable effects on the life expectancy of older individuals. As a result, nonagenarians are emerging as a separate age group with distinct healthcare needs. We evaluated the incidence and outcome of acute kidney injury (AKI) in nonagenarians who were admitted to one regional city hospital in Jordan

Methods: In our retrospective chart review, we included all patients 90 years of age and above who were admitted to the floor at our University hospital, between January 2010 and December 2013. Patients with Stage I, II or III chronic kidney disease (CKD) were included in the analysis. Our exclusion criteria included those patients with Stage IV and V CKD. The incidence of AKI was determined by using data from the Acute Kidney Injury Network Classification (AKIN). Primary outcome variables included length of in-hospital stay and mortality rates.

Results: Of the total 283 patients who were evaluated during the study period, 48 patients with end stage renal disease (ESRD) were excluded. In the 253 patients who were included, the mean age was 91.5 years, 61 of the patients developed AKI (25.9%), and 41 patients were in Stage 1 AKI (66.1%) according to AKIN criteria. A total of 57 patients died during the study period and 33 of these patients (57.9%) had AKI. Hospital stay was longer in patients with AKI with a mean length of stay of 8.1 days. Congestive heart failure, cancer, and use of non-steroidal anti-inflammatory drugs were the main risk factors for AKI in our patients.

Conclusions: AKI is common in nonagenarians with increased risk for mortality and increased hospital stays.

Baseline characteristics

variable	N (%)
Male	123(52.3%)
DM	34(14.5%)
HTN	41(17.5%)
CAD	44(18.7%)
CHF	20(8.5%)
CVA	25(10.6%)
PVD	53(22.6%)
Cancer	14(5.9%)
ACEI	80(34%)
ARB	38(16.2%)
NSAID	8(3.4%)
Baseline Creatinine	134.9 (SD 105.3)

PUB050

The Kinetics of Fluid Overload Are Associated with Outcomes in Critically Ill Patients

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Background: Recent data indicate fluid accumulation in critically ill patients, termed fluid overload (FO), is associated with poor outcome. There is little discussion of how timing and rate of fluid accumulation associate with morbidity. We hypothesized how fluid accumulates is associated with patient morbidity.

Methods: We performed a post-hoc analysis of a prospective observational study of patients requiring mechanical ventilation admitted to a pediatric intensive care unit (PICU). Fluid accumulation was studied using three definitions. Absolute FO was calculated as a percentage (%FO). Delta FO was the defined as the change in %FO on consecutive days (e.g., %FO Day 2 - % FO Day 1). Fold FO was defined as the fold difference in %FO between days (e.g., % FO Day 2 / % FO Day 1). The maximum value identified in the first seven days of ICU was used and FO were definitions separated into strata. The primary outcome of interest was mechanical ventilation (MV) duration. Other outcomes of interest included length of stay (LOS), renal replacement therapy (RRT) use, and mortality. All outcomes were assessed at 28-days.

Results: 124 patients (64 male) aged 8.6 ± 6.5 years were studied (Figure 1). While there was no difference in MV duration for patients based on Absolute %FO (f-ratio=0.22, p=0.79), MV duration steadily increased between the Delta FO strata and also in the Fold FO strata (f-ratio=1.99, p=0.13 and f-ratio=2.55, p=0.08, respectively). Absolute %FO was not associated with ICU LOS (f-ratio=0.7, p=0.49), but there was a significant LOS difference with both escalating Delta FO and Fold FO (f-ratio=3.2, p=0.04 and f-ratio 3.3, p=0.04, respectively). RRT utilization and mortality were not associated with absolute % FO, delta % FO, or % fold FO.

Conclusions: Our data suggests how fluid accumulates in critically ill patients affects morbidity. Rapid accrual fluid through ICU course, even after initial resuscitation, demonstrates a greater association with poor outcome than absolute maximum fluid overload. Expanded study of our initial findings is warranted.

Index	N (%)	MV Duration (Days)	ICU LOS (Days)	RRT Use N (%)	Mortality N (%)
All	124 (100%)	5.5 ± 5.1	10.0 ± 8.2	6 (5)	12 (10)
Absolute % FO					
< 10	38	5.4 ± 5.2	10.5 ± 10.8	3 (8)	5 (13)
10 – 20	50	5.3 ± 4.8	8.9 ± 5.9	0	1 (2)
> 20	36	6.0 ± 5.9	10.9 ± 7.6	3 (5)	6(17)
Delta % FO					
< 5	49	4.4 ± 4.7	7.8 ± 7.7	0 (0)	3 (6)
5 – 10	46	6.3 ± 4.9	10.9 ± 8.6	3 (7)	7 (15)
> 10	29	6.2 ± 5.8	12.2 + 7.4	3 (11)	2 (7)
Fold % FO					
< 1.5 x	34	4.2 ± 4.9	7.1 + 6.3	0 (0)	4 (12)
1.5x – 2x	27	4.9 ± 3.8	10.1 + 8.7	1 (4)	1 (4)
> 2x	63	6.5 ± 5.5	11.5 + 8.5	5 (8)	7 (11)

Figure 1

PUB051

Functional Investigation of miR-17-5p Inhibition in Kidney Ischemia-Reperfusion Injury in Mice

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Background: One of the most common causes of acute kidney injury (AKI) is ischemia-reperfusion (IR), which increases the risk of renal fibrosis and chronic kidney disease. Our group has previously described the activation of the pro-proliferative and anti-apoptotic miR-17-5p in IR induced AKI. Our aim was to investigate the function of miR-17-5p in IR-induced renal fibrosis in mice.

Methods: AKI was induced in the left kidneys of C57BL / 6N mice with 20-minute ischemia, without the removal of the right intact kidney. One day before the IR operation, mice were given miR-17-5p silencing (17-LNA-IR group, N = 10) or scrambled sequence (SCR-

IR group, N = 10) locked nucleic acid (LNA) modified antisense oligonucleotides[EO1] (30 mg / kg, ip). On the 7th reperfusion day, the efficacy of the miR-17-5p inhibition was evaluated in the injured and control kidneys (qPCR). In addition, we investigated the extent of tubular damage in histological sections (PAS, HE), the miR-17-5p-target p21 mRNA expression, the tubular damage (KIM1 mRNA), fibrosis (FN1 mRNA), inflammation (TNFα mRNA), the oxidative stress response (NRF2 mRNA), and the proliferation (PCNA mRNA) with real-time PCR.

Results: At the 7th reperfusion day, specific LNA inhibition prevented the increase in miR-17-5p expression (1.62x, p <0.01, SCR-IR vs. non-IR) in the damaged kidneys (0.49x, p < 0.0001; 17-LNA-IR vs. SCR-IR). The inhibition of miR-17-5p following IR had no[EO1] significant effect either on the histological damage, or on increased KIM1 (83.2x, p <0.0001), FN1 (8.6x, p <0.0001), TNFα (5.8x, p < 0.0001), NRF2 (1.4x, p <0.01), PCNA (1.3x, p <0.05), and p21 (3.8x, p <0.0001) mRNA levels.

Conclusions: While miR-17-5p could have renoprotective effects, our findings suggest that miR-17-5p inhibition has no significant effects on the IR-induced AKI outcome. New National Excellence Program (Immuno Pathophysiology) OTKA (114619), Kispál Gyula Program 30021

Funding: Government Support - Non-U.S.

PUB052

Intestinal Apoptosis, but Not Tight Junctions, Contributes to the Translocation of Bacteria/Endotoxin in a Rat Model of Non-Ischemic AKI

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Background: To investigate whether translocation of bacteria and endotoxin develops in acute kidney injury (AKI), and, if so, what are the mechanisms behind it.

Methods: Sprague–Dawley (SD) rats were subjected to bilateral nephrectomy (BNx) or sham-operation (n=5/group) and observed for 24h. The pathology of ileum was scored. Apoptosis in ileum was detected by TUNEL staining and DNA fragmentation ELISA. Gut mucosal permeability was evaluated in vivo and ex vivo. Serum endotoxin levels were measured by LAL method. Bacterial load in liver was measured by 16srDNA analysis. The expression of tight junctions(TJs) in ileum, including zonula occluden-1, Occludin and Cludin-1 was measured by Western blot. Transmission electron microscopy was used to detect the alterations of cell-cell junction.

Results: Compared with the sham rats, the BNx rats showed elevated intestinal damage scores (Fig.A-B), accelerated apoptosis in ileum (Fig.C-D), increased serum levels of D-lactate (FigE) and promoted intestinal clearance of FITC-dextran (Fig.F). Serum levels of endotoxin and bacterial load in liver increased significantly after 24h nephrectomy (Fig.G-H). BNx did not reduce the expression of the selected epithelial TJ proteins(Fig.I), but resulted in the disruption of cell-cell junction(Fig.J).

Conclusions: Our study shows that non-ischemic AKI causes impairment of intestinal functions and histology, which in turn promotes the translocation of gut-derived bacteria and endotoxin. Accelerated intestinal mucosal apoptosis and the disruption of cell-cell junction are the most likely mechanisms for the translocation of bacteria and endotoxin.

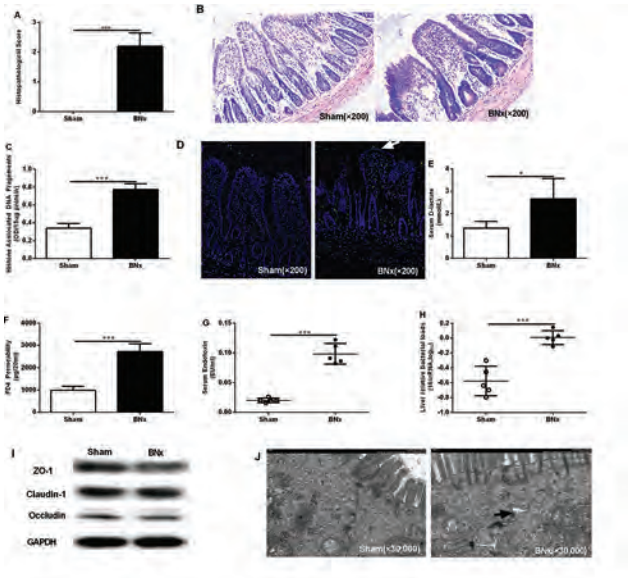

Figure A-I, The intestinal consequences of non-ischemic-AKI. Mean ± SD, n=5/group. ***P<0.001,**P<0.01,*P<0.05
White arrow: apoptosis in epithelial cells; Black arrow: a disrupted cell-cell junction .

PUB053

Insulin-Dependent Diabetes Mellitus Aggravates the Systemic Inflammatory Response

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Background: Acute Kidney Injury significantly worsens the prognosis of hospitalized patients. Diabetes mellitus (DM) affects a growing number of individuals in the western world. DM subjects are at higher risk for aquiring AKI during the stay at the hospital, in addition the long-term prognosis of kidney function is particularly poor in subjects suffering from this metabolic condition. The most frequent cause of AKI, renal ischemia typically induces tubulopathy, microvasculopathy, and interstitial inflammation. The latter has extensively been investigated in recent years. The current study intended to quantifiy serum levels of certain immunomodulatory cytokines in diabetic mice suffering from AKI.

Methods: DM was induced in male C57/Bl6N mice by repeated systemic injections of beta cell-toxic streptozotocine. Animals underwent bilateral renal ischemia (45 minutes) 6 weeks later. Mice were either injected with native or preconditioned (zVAD or MD132 - autophagy inducers) syngeneic murine proangiogenic cells (PACs). Two days after surgery, mice were harvested and analyzed. Beside kidney function and morphology, serum levels of numerous (n=18) immunomodulatory cytokines were quantified.

Results: Post-ischemic diabetic mice showed significantly different serum concentrations of the majority of all analytes as compared to untreated controls and to non-diabetic (post-ischemic) animals. Cell therapy did not modulate cytokine patterns in a consistent manner.

Conclusions: Together, our data suggest significant DM-associated immunoactivation in AKI. One may suppose that inadequate stimulation of the humoral / cellular immune response potentially contributes to the higher ischemia-susceptibility of the organ in DM.

PUB054

Antioxidative and Antiapoptotic Effects of (+)-Clausenamide on Acetaminophen-Induced Nephrotoxicity in Mice

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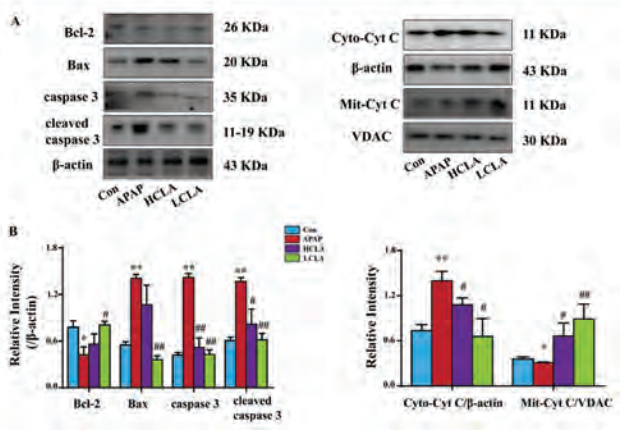
Background: Renal insufficiency occurs in nearly 1–2% of patients with APAP overdoses. We assumed that oxidative damage caused by reactive oxygen species (ROS) might be involved in APAP-induced renal injury, and available antioxidative agents, clausenamide (CLA) might be able to reduce the adverse effects. The aim of the study was to evaluate the protective effect of (+)-CLA against APAP-induced nephrotoxicity and to elucidate the mechanisms of the protective effect of (+)-CLA

Methods: Mice were divided into control, APAP, high-dose (+)-CLA, and low-dose (+)-CLA groups. Then, mice were preadministered (+)-CLA (50 and 100 mg/kg) for 5 consecutive days. After the last treatment, the animals received a single intraperitoneal injection of APAP (600 mg/kg). Renal histopathology was evaluated by staining with hematoxylin and eosin. The levels of MDA and GSH and the activities of CAT and SOD were determined using corresponding kits. Western blotting was used to analyze the expression of apoptosis-related proteins in renal tissue.

Results: Administration of APAP increased Scr and BUN levels in comparison with the control group. Renal MDA level increased, GSH, CAT and SOD activities reduced in renal tissue. The expressions of Bax and caspase-3, cleavage of caspase-3, and cytoplasm cytochrome c (Cyt c) levels were up-regulated in renal tissue, whereas Bcl-2 expression and mitochondrial Cyt c levels were down-regulated in the APAP group. The histopathology of kidney tissue supported these biochemical mechanisms. (+)-CLA can reverse changes in most of the abovementioned parameters and nearly restore the normal structure of the kidney.

Conclusions: Oxidative stress and apoptosis are considered to be the mechanisms underlying APAP-induced nephrotoxicity. (+)-CLA could be a promising antidote for APAP-induced AKI owing to its antioxidative and antiapoptotic effects.

Funding: Government Support - Non-U.S.



Effects of (+)-CLA on Bcl-2, Bax, Caspase3, Cleaved Caspase3 and Cytochrome c protein expression.

PUB055

A Case Imitating Thrombotic Microangiopathy

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Introduction: The combined finding of hemolytic anemia, thrombocytopenia and organ injury, in particular AKI, are the hallmark signs of thrombotic microangiopathies (TMA). The differential is broad, presentations are diverse and most cases severe and life threatening. Risks associated with therapy must be calculated accordingly.

Case Description: A 44 year old female presented with fatigue and body aches 1 week after a motor vehicle accident. Hemoglobin 7.6 g/dl and platelets 16K. Prior to accident she had left knee pain, nausea, poor oral intake and weight loss for 2-3 weeks. No major trauma or injuries resulting from the accident. Only past medical history was a neck plaque like rash 9 months prior that was treated with antibiotics. Later she reported dysuria, fever and chills. Social history positive for prior cocaine use and current marijuana. Initially afebrile, then developed a temp 37.9 BP 115/92 HR 108. Exam was notable for suprapubic/costovertebral tenderness, left knee erythema, warmth and pain and a macular erythematous rash. WBC 6.4K, BUN 107 mg/dl Cr 4.59 mg/dl Albumin 1.6 g/dl UA: 182 WBC 112 RBC, Urine Protein/Cr ratio 3.7 gm Blood cultures and Urine cultures positive for E coli. Orthopedic evaluation ruled out septic joint. She was treated with antibiotics, fluids and platelet transfusion. Central venous catheter was placed for plasmapheresis. Blood smear revealed that schistocytes present, however haptoglobin values were high and bilirubin was normal. Therefore patient was managed medically and plasmapheresis was not implemented. Cr gradually improved to 1.82 mg/dl, on day 4 platelets>50K. ADAMTS13 levels were within normal range and serologies were negative: ANA, ANCA, HBV, HCV, HIV.

Discussion: The differential for the presentation of thrombocytopenia, hemolytic anemia and organ dysfunction is broad including TMAs such as TTP, HUS (shiga toxin or complement mediated) but also include other etiologies that augment complement activation such as sepsis, auto-immune disorders, malignancy, malignant hypertension and pregnancy. Treatment options such as plasmapheresis for TTP or complement cycle immune modulators such as eculizumab for aHUS are available however risks must be calculated based on clinical judgement. In this case the findings were due to E. Coli sepsis due to pyelonephritis rather than TTP or HUS and patient improved with sepsis treatment.

PUB056

The Effect of L-Carnitine in Contrast-Induced Nephropathy in Diabetic Rats

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Background: Contrast-induced nephropathy (CIN) has been defined as an abrupt reduction in renal function, resulting from iodinated contrast (IC) use. Studies show that Diabetes Mellitus is an important predisposing factor for CIN. It is known that L-carnitine is a lipidic metabolism compound and antioxidant effect is one of its major mechanisms. The aim of this study was evaluated the L-carnitine effect on CIN in diabetic rats.

Methods: Adult male Wistar rats was sorted into four groups: Citrate (control), Diabetes Mellitus (DM), Diabetes + iodinated contrast (DM+IC) and DM + IC+L-Car. Renal function (Inulin clearance); hemodynamics (renal blood flow; renal vascular resistance) and oxidative profile (urinary peroxides, urinary TBARS, thiols in renal tissue and urinary nitric oxide- NO) were evaluated.

Results: Diabetes was associated with significant decrease in inulin clearance that was additionaly reduced after the infusion of IC. DM+IC group also showed a significant increase in the urinary peroxides, TBARS and NO, a reduction in the thiols levels. Considering the renal hemodynamics parameters, this group showed a reduction in renal blood flow and increase in renal vascular resistance when compared with DM group. These parameters were significantly changed by L-carnitine in diabetic rats and those that received IC. Supplementation with L-carnitine resulted in an antioxidant protection in this IC model.

Conclusions: Our data reinforced that DM is an important risk factor for contrast-induced nephropathy. Supplementation with L-Carnitine showed a renoprotective effect in diabetic animals submitted to CIN, sugesting a possibility of a novel role of L-carnitine promoting anti-oxidant responses in the CIN.

Funding: Government Support - Non-U.S.

Table 1. Renal function, renal hemodynamic and oxidative profile

Group (n)	Inulin clearance (ml/min/100g)	Renal blood flow (ml/min)	Renal vascular resistance (mmHg/ml/min)	Urinary peroxides (nmol/g urinary creatinine)	TBARS (nmol/g urinary creatinine)	Renal tissue thiols (nmol/mg total protein)	Urinary nitric oxide (nmol/g urinary creatinine)
Citrate (n=7)	0.89±0.23	7.39±1.64	15.18±3.36	2.0±0.9	0.25±0.15	33.8±6.1	37.68±10.10
DM (n=7)	0.52±0.12α	4.33±1.65α	25.20±7.85α	13.5±5.7α	12.91±3.02α	17.2±2.9α	70.86±14.13
DM+IC (n=7)	0.16±0.04αβ	3.13±1.16α	37.85±11.27αβ	21.3±9.8αβ	22.55±5.20αβ	10.6±2.1αβ	142.87±33.27αβ
DM+IC+L-carnitine (n=7)	0.51±0.21αδ	6.26±0.71βδ	18.30±2.99δ	4.5±2.4βδ	0.64±0.12βδ	36.0±13.9βδ	130.21±38.42αβ

Data a shown as mean±SD. αp<0,05 vs Citrate; βp<0,05 vs DM; δp<0,05 vs DM+IC.

TBARS: tiobarbituric acid reactive substances, DM: Diabetes Mellitus, IC: iodinated contrast.

PUB057

Deficiency of IKKα in Kidney Tubular Epithelial Cells Alleviates TGFβ1-Induced Kidney Fibrosis via Wnt/β-Catenin

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Background: Nuclear transcriptional factor NF-κB plays an important role in inflammation, and the activation of NF-κB is mediated by IκB kinase (IKK) which is consisting of two subunits IKKα and IKKβ. Previously, we found that IκB kinase α (IKKα) protects against kidney ischemia/reperfusion(IR) injury.

Methods: However, its regulation and role in the pathogenesis of CKD remain poorly defined. To study this, we initially treated HK-2 cells with TGFβ1 and found that TGFβ1 activated IKKα and Wnt/β-catenin signaling in cultured cells. Blocked with IKKα small interfering RNAs (siRNA) markedly inhibited TGFβ1-induced vimentin and α-smooth muscle actin(α-SMA).

Results: Ensuing western blotting or immunostaining results showed that IKKα and Wnt/β-catenin signaling was activated in kidney tubular epithelial cells (TECs) in mice kidney ischemia/reperfusion(IR) injury. We found that IKKα in mouse model with TECs deletion was reduced. Compared with control group, the kidneys of IKKα knockout mice developed less interstitial extracellular matrix deposition and inflammatory cell infiltration at 2 weeks after-ischemia/reperfusion injury.

Conclusions: Our study suggests that IKKα activation mediated TGFβ1-induced kidney fibrosis and up-regulated Wnt/β-catenin signaling. In addition, IKKα contributes to the development of kidney fibrosis. This may provide a therapeutic target for chronic kidney diseases.

PUB058

The Association Between Urinary Markers of Fibrosis and Tubular Injury and Recovery of Kidney Function After Moderate to Severe AKI

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Background: Acute kidney injury (AKI) is a risk factor for chronic kidney disease (CKD). Tubulointerstitial fibrosis is strongly associated with urine collagen type III amino-terminal propeptide (PIIINP) in patients with CKD. We examined if urine collagen fragments, or other markers of kidney injury, were associated with renal recovery post-AKI.

Methods: The VALID study is a prospective study of critically ill adults. Among the first 1732 patients enrolled with available biosamples, we identified 147 with stage 2/3 AKI and urine available <48 hours of peak serum creatinine and at least 1 serum creatinine available between peak SCr and 9 months. We excluded patients with ESRD, no creatinine before enrollment, and stage 1/no AKI. We measured PIIINP, alpha-1 microglobulin, IL-18, MCP1, YKL-40, NGAL, and KIM-1 using multiplex panels, except for PIIINP (radioimmunoassay). Biomarkers were indexed to urine creatinine. 118 patients had complete measurements available, 26 with dialysis-requiring AKI and 92 patients without dialysis-requiring AKI. Renal recovery was defined as a return to <20% of baseline creatinine within 9 months. Relaxed Lasso logistic regression models were used to examine the association between biomarkers levels and renal function recovery.

Results: Among the 92 individuals not requiring dialysis, median age was 56(47,71), baseline creatinine 0.96 (0.72, 1.23), and peak creatinine of 2.5 (1.9,3.6) mg/dL. Fifty-seven (62%) recovered kidney function. Statistical modeling did not reveal any relationships between biomarker levels and odds of renal recovery in univariate or multivariable analyses adjusted for age, gender, race, baseline creatinine, peak creatinine, presence of sepsis and APACHE score. Biomarker information did not contribute to predictive ability for renal recovery beyond baseline creatine. Among the 26 dialysis, twenty-one (81%) were able to discontinue dialysis. None of the biomarkers were associated with dialysis discontinuation. There was also no association of biomarker levels with death.

Conclusions: Among a broad panel of biomarkers of kidney injury and fibrosis, we did not observe an association or predictive ability between biomarker measurements at the time of peak injury and renal recovery.

Funding: NIDDK Support

PUB059

AKI and Hemolytic and Uremic Syndrome (HUS) After Bothrops Envenomation - Interest of Renal Biopsy: About an Observation

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Introduction: The snakebite by a Bothrops (Viperidae, Crotalinae, Botrops) is responsible for severe complications, and especially AKI whose origin is multifactorial. We report an observation of AKI following a bite by a Bothrops in which a renal biopsy could be performed to assert the mechanism of renal damage.

Case Description: 42-year-old patient was hospitalized 4 days after a bite by Bothrops Atrox, during which time she was treated only with traditional decoctions (no administration of antivenom). At the entrance, the patient was anuric, serum creatinine was 1077 µmol / l (SOFA score: 8). She had haemolytic anemia (Hg 6.8 g / dl, 25% schizocytes), haemostasis disorders (TP 71%, hypofibrinogen), thrombocytopenia, rhabdomyolysis. In front of this viperian envenomation complicated by HUS and anuria, without hypovolemic

shock, plasmapheresis sessions (4 liters plasma exchanges replaced by diluted albumin and fresh frozen plasma) associated with sessions hemodialysis were performed to control the HUS, correct hemostasis disorders. Resumption of diuresis was observed on D8 and the patient came out of resuscitation unit at D16. The evolution was made towards the recovery of the renal function, the disappearance of the hemolytic syndrome. A renal biopsy puncture was performed at day 30.

Discussion: The sample concerned 35 glomeruli all permeable. No image of thrombotic microangiopathy or inflammatory infiltrate was noted. Marinozzi and PAS stains showed only a thickening of Bowman's capsule and on one glomerulus a flocculo capsular synechiae draft. The tubes were lined with a flattened, regenerative epithelium showing sequelae of tubular necrosis. The immunofluorescence study was negative. In total, the renal biopsy was in favor of tubular necrosis associated with a discrete interstitial inflammatory reaction. There were no glomerulopathy lesions apart from discrete podocytosis lesions and no evidence of thrombotic microangiopathy. The clinical history of this patient was initially in favor of renal impairment secondary to intra-renal thrombotic microangiopathy in the context of HUS and described after Viperidae envenomation. The kidney renal biopsy allowed to rule out this hypothesis showing only tubular necrosis lesions secondary to a direct toxic attack of Bothrops' venom.

PUB060

Primary Cilium Length and Urine Primary Cilia Can Be Indicative of Cisplatin-Induced AKI

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Background: The primary cilium protrudes to kidney epithelial cell surface and is associated with the pathogenesis of many kidney diseases including acute kidney injury (AKI). During cell cycle, the length of primary cilium dynamically alters; when cell proliferates cilium is shortened by retraction into the cell body, whereas when cell is matured cilium is lengthened. In addition, during the progression of diseases, the length of primary cilium is changed; shortened or elongated, indicating that primary cilium length reflects cell and tissue conditions. Cisplatin nephrotoxicity limits its administration and is associated with increased oxidative stress. Here, we investigated whether cisplatin nephrotoxicity is associated with primary cilium and the alteration of primary cilium length can be indicative kidney injury.

Methods: Cisplatin was injected with the presence or absence of (2-(2,2,6,6-Tetramethylpiperidin-1-oxyl-4-ylamino)-2-oxoethyl) triphenylphosphonium chloride monohydrate (Mito-TEMPO, a mitochondria-specific antioxidant).

Results: Cisplatin increases kidney tubular injury in dose-dependent manner, shortening of primary cilia, and shedding of primary cilia fragments into the urine together with increased ROS production/oxidative stress. Cisplatin did not induce the cell proliferation when evaluated by BrdU incorporation assay. In addition, cisplatin did not induce significant changes in p21 and proliferation cell nuclear antigen (PCNA) expression in the kidney. Cisplatin-induced those changes were prevented by Mito-TEMPO, a mitochondria-targeted antioxidant, treatment.

Conclusions: Taken together, these results indicate that cisplatin nephrotoxicity is associated with primary cilia and cisplatin-induced shortening of primary cilia is due to disruption of primary cilia via increasing oxidative stress, suggesting that cisplatin nephrotoxicity is related with the alterations of renal primary cilia length and urine primary cilia protein can be a useful indicative of kidney injury.

PUB061

Kidney Injury Molecule-1 Staining Reflecting Proximal Tubule Injury Is a Common Finding in Pediatric and Adult Kidney Diseases

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Background: Proximal tubules (PT) are known to be vulnerable to ischemic and toxic injury due to their high metabolic activity. The PT is also sensitive to hypoxic injury due to reduced post-glomerular blood supply. Kidney injury molecule-1 (KIM-1) is an injury marker specific for the PT. The purpose of this study was to determine whether KIM-1 expression was observed in human renal biopsies in a variety of kidney diseases where PT injury may be secondary to a primary disease process.

Methods: We randomly selected 184 renal biopsies from patients with various forms of kidney diseases and excluded cases with severe interstitial fibrosis. Biopsies were divided into three groups: 63 pediatric patients (< 20 years of age), 64 adults < 65 yr and 57 senior patients (> 65 yrs of age). All biopsies were stained using immunochemical techniques for KIM-1 (AKG7 monoclonal antibody) and examined by light microscopy. The intensity scores of KIM-1 in non-atrophic PT, ranging from 0 to 3+, were correlated with serum creatinine (sCr) levels.

Results: The patients' ages ranged from 2 to 82 years old. Regardless of primary etiology of injury (vascular or glomerular), positive staining of KIM-1 was seen in the majority of biopsies (80% to 91% in each age group). In all three groups, the KIM-1 staining scores were significantly positively associated with levels of sCr ($p < 0.05$). Compared to adult renal biopsies, there was a high KIM-1/sCr ratio in pediatric renal biopsies.

Conclusions: Our data indicate that acute damage in PT, determined by enhanced KIM-1 expression in non-atrophic proximal tubules, is a common finding in wide variety of pediatric and adult intrinsic kidney diseases. A high KIM-1/sCr ratio could be a potential repair and regenerative predictor in the early phase of acute kidney injury (AKI), reflecting active synthetic function of the PT cells with potential for PT recovery after injury. Thus, KIM-1 can serve as a sensitive and reliable biomarker for identification of acute tubular injury in non-atrophic PT of pediatric and adult renal biopsies.

Funding: Clinical Revenue Support

PUB062

Inhibition of Rac1-GTPase Attenuates Renal Ischemia/Reperfusion-Induced Injury by Suppressing Macrophage Infiltration

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Background: Migration of inflammatory cells is a pivotal for numbers of diseases including ischemia/reperfusion (I/R) injury. Rac1, a member of the Rho-family of small GTPase, plays a critical role for activation of NADPH oxidase, a major ROS producing enzyme. Rac1 also regulates the cell migration. However, the role of Rac1 on the macrophage migration after renal ischemia remains to be defined. Here, we investigated the role of Rac1 in the kidney ischemia/reperfusion injury and its mechanism focusing on macrophage migration.

Methods: Mice were intraperitoneally injected with either a single dose of NSC23766, an inhibitor of Rac1, or vehicle for 3 days before surgery and subjected to either ischemia or sham operation.

Results: Thirty-minutes bilateral renal ischemia in the kidney induced renal functional and morphological impairments along with the increase of Rac1 expression in the kidney. After ischemia, Rac1 was strongly expressed in the interstitial cells rather than renal tubular epithelial cells. Rac1-positive interstitial cells were mostly F4/80, a marker of macrophage, -positive. The treatment of NSC23766, an inhibitor of Rac1 activity, significantly inhibited the increase of F4/80-positive cell number after I/R together with reduced renal morphological and functional impairments. NSC23766 hindered the migration of RAW264.7 cell, a mouse monocyte/macrophage cell line cell, after treatment of MCP-1, a chemoattractant cytokine. Furthermore, Rac1 inhibition by NSC23766 also suppressed MCP-1-induced lamellipodia and filopodia of RAW264.7 cells.

Conclusions: These results indicate that I/R increases Rac1 expression, enhancing migration of monocytes/macrophages into the injured site. This suggests that Rac1 represents a potential therapeutic target protein for the treatment of acute kidney injury.

PUB063

Is It Possible to Prevent Contrast Induced Nephropathy with Dexpanthenol?

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Background: To demonstrate the effect of dexpanthenol, known to be antioxidant, in contrast-induced nephropathy(CIN) rat model.

Methods: Sprague Dawley rats, 12 weeks old, were kept without water for 3 days to produce contrast nephropathy. Thereafter L-NAME (10mg / kg), tenoxicam (0.5mg / kg) and sodium amidotrizoate (10ml / kg) were administered via the tail vein. Rats were euthanized after 48 hours (CIN group). Dexpanthenol (Dxp) was administered intraperitoneally at a dose of 500 mg/kg for 3 days, as the day prior, on the day and next day of contrast administration. The rats in this group were also euthanized at the 48th hour after the contrast administration (CIN + Dxp group). While Dxp was administered intraperitoneally for 5 days at equal doses to the Dxp group, control rats were administered saline solution. All rats were observed for 5 days and euthanized on the 6thday after blood draw.

Results: The comparison of contrast+dexpanthenol group and the contrast-only group showed that dxp provided significant decline at acute tubular injury and necrosis histopathologically (Figure 1). Serum creatinine levels were found similar amongst the groups, whereas cystatin C level was the highest in the CIN group (Figure 2). There was no statistically significant difference between the groups in total oxidant and antioxidant level evaluations.

Conclusions: Dexpanthenol, which has been demonstrated as a significant inhibitor on renal ischemia reperfusion model, did not show any significant effect on biochemicemistry on this CIN model. However, it has ameliorated histopathological findings of CIN.

Funding: Private Foundation Support

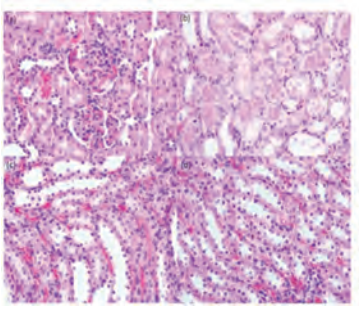

Figure 1: Light microscopic changes in kidney parenchyma of 4 different groups, H&E X 400: (a) Control group; light microcopy is unremarkable (b) Contrast group; prominent tubular necrosis is present (c) DEXP-1 group; mild medullary congestion is present (d) Contrast + DEXP-1 group; mild medullary congestion is present. (Note that light microscopic features of DEXP-1 and Contrast+DEXP-1 groups are similar)

PUB064

Severe Renal Failure After Immunoglobulin Transfusions Requiring Dialysis as a Life Saving Measure

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Introduction: We are presenting a rare cause of renal failure developed after Intravenous Immunoglobulin (IVIg) infusions given for acute exacerbation of Myasthenia gravis requiring dialysis

Case Description: 72 year-old-lady with h/o of Myasthenia gravis admitted with 5 days of progressive dysphagia, dysphonia, fatigue and bilateral ptosis. Diagnosed Myasthenia gravis exacerbation and treated with 5 days of IVIg infusions. Home medications were pyridostigmine and prednisone. Vitals on admission were blood pressure 159/61, temperature 98, heart rate 81, respiratory rate 16, saturating 97% on room air. Physical examination was with in normal limits. Laboratory results on admission were sodium 145, potassium 3.5, chloride 104, bicarbonate 26, bun 30, creatinine is 1.0 mg/dl, calcium 9.3, phosphorus 3.1, wbc 6, Hemoglobin is 13 .3 g/dl and platelets 212 x 10^3. After finishing 5-day course, bulbar symptoms were improved, but she developed severe anemia, Jaundice and Renal failure. Further labs include hemoglobin dropped 6.5, platelets 186 x 10^3, reticulocyte count 4.4%, wbc 11.8, LDH 2148, CPK 230, haptoglobin <10, direct coombs test negative, bicarbonate 11, creatinine 9.50 mg/dl, BUN 204 mg/dl, total bilirubin 5.1, direct bilirubin 0.40, total protein 11.5 g/dl, albumin 2.7 g/dl, ratio of kappa/lambda ratio 1.56, C3 135, C4 7, negative for MPO and PR3 antibodies, p-ANCA <1:20, c-ANCA 1:80, peripheral blood smear showed rouleaux and no significant schistocytes, serum IFE and SPEP showed no monoclonal proteins, urinalysis revealed cloudy red colored urine, numerous WBC's, 30-40 RBC, 3+ blood, 1+ protein, 1+ leukocyte esterase, negative for bilirubin, urine eosinophils and nitrite. Hospital course was complicated with atrial fibrillation with rapid ventricular rate and pulmonary edema requiring intubation. Emergent dialysis was started for refractory metabolic acidosis, fluid overload and 4 units of PRBC was transfused. Patient was stabilized hemodynamically and discharged with intermittent dialysis follow up and renal function tests

Discussion: Our case strongly suspects any undetected passive antibodies might have trigger acute hemolytic reaction causing renal failure. It's a rare complication of IVIG that is estimated to occur less than 1 % of infusions. Anecdotal reports showed elderly age, preexisting renal disease, and non-O blood group recipients have high risk

PUB065

Female Spontaneous Hypertensive Rats (SHR) Have Better Recovery in Response to Renal Ischemia Reperfusion (IR) Injury Than Males

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Background: Experimental and clinical evidence suggests that normotensive males are more susceptible to acute kidney injury (AKI) vs females. Hypertension is a known risk factor for AKI, however if hypertensive males and females respond comparably to AKI is unknown. Present study tested hypothesis that hypertensive males have worse renal outcomes than females following renal IR

Methods: 13wk old male and female Sprague Dawley (SD) and SHR were subjected to sham or 25min warm bilateral IR (n=6). Blood and urine were collected at 1 and 7 days; kidneys were isolated at 7 days for histological analysis

Results: IR increased plasma creatinine (Pcr) and BUN in all groups compared to respective sham at 24 hrs, although increases in Pcr and BUN were greater in male vs female (SHR-Pcr: $P_{Sex}*_{IR}$=0.03; BUN: P<0.05; SD-Pcr: $P_{Sex}*_{IR}$<0.05; BUN: P<0.05). At 7 days Pcr and BUN remained elevated in male SHR compared sham (Pcr P_{IR}=0.03; BUN P_{Sex}<0.05); Pcr and BUN returned to baseline levels in all other groups. Histological examination of SHR kidneys following 7 days of reperfusion showed significant increase in vascular congestion ($P_{Sex}*_{IR}$=0.002), damaged tubules ($P_{Sex}*_{IR=}$0.001) and tubular cell apoptosis ($P_{Sex}*_{IR}$=0.001) compared to sham only in males. Since IR induced vascular congestion has been implicated in loss of renal function, additional male and female SHR were pretreated with heparin (1500U/kg) prior to IR. Pretreatment with heparin reduced IR induced vascular congestion and improved renal function in male SHR at 7 days (Pcr-$_{IR}*_{Hep}$<0.05; BUN: P=0.02).

Conclusions: Our data suggest that persistent vascular congestion in hypertensive male SHR results in delayed recovery following IR

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Animal Treatment	Pcr (mg/dL) at 24hrs	BUN (mg/dL) at 24hrs	Pcr (mg/dL) at 7 days	BUN (mg/dL) at 7 days
Male SHR Sham	0.25±0.05	20.3±1	0.22±0.06	20.3±2
Male SHR IR	0.55±0.2	51.2±8	0.46±0.2	36.6±8
Female SHR Sham	0.25±0.06	18.3±1	0.25±0.06	18.7±1
Female SHR IR	0.44±0.06	35.2±6	0.27±0.06	21.9±2
Male SHR Sham + Heparin	0.27±0.05	20.6±2	0.27±0.03	23.3±3
Male SHR IR + Heparin	0.46±0.1	32.1±1	0.39±0.1	24.3±2
Female SHR Sham + Heparin	0.3±0.06	17.2±4	0.25±0.06	20.7±5
Female SHR IR + Heparin	0.36±0.1	21.2±1	0.26±0.01	19.4±5
Male SD Sham	0.33±0.03	28.7±4	0.34±0.04	25.6±2
Male SD IR	0.63±0.12	61.3±13	0.41±0.14	26.9±4
Female SD Sham	0.32±0.02	27.9±4.2	0.35±0.08	25.3±2
Female SD IR	0.52±0.09	43.8±6.3	0.37±0.012	25.9±3

PUB066

Diverse Gene Expression Patterns of Renal Transporters in AKI

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Background: Restoration of tubular function may be a prerequisite for recovery of GFR and overall kidney function after acute kidney injury (AKI). We performed RNA sequencing (RNA-seq) to gain more insights on the expression pattern of tubular transporters in a murine model of AKI.

Methods: We induced ischemia/reperfusion (IR) injury by bilateral clamping of the renal arteries for 10 or 15 minutes (min) vs sham in C57BL/6J males. On days 1, 3 and weeks (wks) 2 and 14 after reperfusion, we assayed glomerular filtration rate (GFR) (by FITC-sinistrin plasma elimination kinetics in awake mice, n= 4-5/group) and harvested kidneys for RNA-seq analysis (n= 3-5/group).

Results: GFR in the 10 min IR group did not change while the 15 min IR group showed a sharp decrease on day 1 with partial recovery at 14 wks. The mRNA expression pattern seen in most tubular transporters was an ischemia time-dependent decrease on day 1 followed by subsequent gradual normalization with close to sham levels by 14 wks. This included Na transporters such as Nhe3, Nkcc2, Ncc, Enac, and Na-K-Atpase. An initial reduction on day 1 was also observed for Sglt2, Sglt1 and Glut2, which together mediate transcellular glucose reabsorption in proximal tubules. In contrast, Glut1, which in tubular epithelial cells can mediate the basolateral uptake of glucose used for glycolysis, showed an initial ischemia time-dependent increase in expression followed by eventual normalization. The phosphorous (Pi) transporters Pit1 and Pit2 showed a similar pattern to Glut1.

Conclusions: The mRNA expression of the main renal Na transporters and GFR are both reduced on day 1 after 15 min IR, and partially or fully recovered by 14 wks. Initial tubular cell loss and eventual restoration, and the kidneys' need to conserve energy during AKI may contribute to this pattern. In contrast, Glut1 is upregulated initially, potentially as part of the shift from fatty acid oxidation to glycolysis in early AKI. Upregulation of Pit1 and Pit2 may serve to conserve intracellular Pi availability including the uptake of extracellular Pi derived from cell lysis.

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PUB067

Double-Negative αβ T Cells in Murine Cisplatin-Induced AKI

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Background: Cisplatin treatment for malignancies is limited by nephrotoxicity. Though T cells have been implicated in cisplatin induced acute kidney injury (AKI), the role for $CD4^-CD8^-$ (double-negative, DN) T cells is unknown.

Methods: 8-week-old C57BL/6 male mice (n=8) were administered 30 mg/kg cisplatin and followed for 72 h. Serum creatinine (SCr) and histologic examination were assessed to confirm AKI. Kidney mononuclear cells (KMNCs) and splenocytes from cisplatin-treated mice were analyzed for DN T cell proliferation (Ki67, BrdU), immune cell trafficking/activation (CD69, CD62L), apoptosis (Annexin v) and differentiation (NK1.1, PD1) by flow cytometry.

Results: Cisplatin administration led to significant (p<0.0001) increase in SCr at 72 h (2.1 ± 0.4 mg/dl). DN T cell frequency increased at 24 h (52.6 ± 3.0%, p<0.001) after cisplatin treatment and subsequently decreased at 72 h (30.0 ± 3.0%, p<0.001) compared to 72 h vehicle treated mice (33.2 ± 3.2%) as well as the absolute number (vehicle: 1295.0 ± 194.1 versus 24 h: 2602.4 ± 295.7 versus 72 h 488.2 ± 118.4)(vehicle versus 24 h, p<0.001; 24 h versus 72 h, p<0.001). Kidney $CD4^+$ T cells were activated after cisplatin treatment (p<0.05), but not DN T cells. DN T cell proliferation decreased at 24 h (p<0.05) but increased (p<0.05) at 72 h. In contrast to ischemic AKI which showed expansion of the $PD1^+$ DN T cell subset, cisplatin-induced AKI increased both $NK1.1^+$ and $PD1^+$ DN T cell subsets (p<0.05).

Conclusions: Kidney DN T cells respond rapidly to cisplatin induced AKI, but in distinct ways compared to CD4 and CD8 T cells. Furthermore, there are key differences between DN T cell responses to nephrotoxin versus ischemia, including differentiation characteristics. Ongoing studies are investigating the role of DN T cells during early injury and recovery from cisplatin-induced AKI.

PUB068

The Use of Renal Doppler Ultrasonography in Critically Ill Patients with AKI

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Background: Acute kidney injury is one of the major organic dysfunctions that occur in critically ill patients. Ultrasonography of the kidneys and urinary tract is always a tool used by nephrologists as a way of evaluating this pathology. Despite this practice, its clinical utility in determining the cause of acute kidney injury is poorly established.

Methods: Retrospective cohort study of critically ill patients that underwent renal ultrasound for acute kidney injury over a 5-year period at Hospital Portugues da Bahia. Renal Resisitive Index was determined by the doppler sonography.

Results: Over the 5-year period, 350 renal ultrasounds were performed for evaluation of acute kidney injury. Renal ultrasound was normal in 76% of patients. Hydronephrosis was detected in only 6% of studies and in only 2% of the cases was obstructive uropathy considered the cause of acute kidney injury.. Less than 1% of patients had urinary tract obstruction on ultrasound without a suggestive medical history. Median renal RIs were 0.68 (0.62-0.75) in patients with sepsis related AKI and 0.74 (0.72-0.80) in patients with non sepsis related AKI (P = 0.001). RIs were 0.72 (0.70-0.79) in transient AKI and 0.76 (0.70-0.80) in persistent AKI (P = 0.64).

Conclusions: The role of renal ultrasonography in every critically ill patients with acute renal injury still needs to be determined In patients with history suggestive of urinary tract obstruction renal ultrasound for evaluation of acute kidney injury should be indicated. The use o renal resisitive index could to be a tool to reflect vasomotor tone in patients with AKI related to sepsis.

PUB069

Effects of Properdin Associated with EPOR/βcR on Repair Post Renal Ischaemia-Reperfusion Injury

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Background: Ischaemia-reperfusion injury (IRI)-induced acute kidney injury is common with high mortality. Properdin is an only positive regulator of the alternative pathway of complement activation, while it could also act as a pattern recognition molecule. Our previous study has demonstrated more severe damage in properdin deficient (P^{ko}) mice than wild type (WT) mice upon IRI. However, its mechanisms, especially its association with tissue protective EPO receptor/β common receptor (EPOR/βcR) in kidney repair post IRI are not clear.

Methods: The bilateral occlusion of renal pedicles for 30 min (n=7-9) and sham control (n=4-5), was performed in WT and P^{ko} male C57BL/6 mice, followed by 72-h reperfusion. EPOR/βcR protein in kidneys was detected, together with mitosis, apoptosis and inflammation markers. Moreover, apoptosis and phagocytosis were measured in proximal tubular epithelial cells (PTECs) isolated from both WT and P^{ko} mice and stimulated with H_2O_2.

Results: The expression of EPOR/βcR was significantly increased by IRI in both WT and P^{ko} mice compared with that in the sham controls. Interestingly, renal EPOR/βcR was further increased in P^{ko} mice after IRI in comparison with WT mice. EPOR/βcR was positively correlated with, proliferating cell nuclear antigen (PCNA) and mitosis, active caspase-3, apoptosis, $F4/80^+$ cells, tubulointerstitial damage (TID) and renal function. Moreover, apoptotic cells in tubular lumens of the IRI kidney were significantly increased by P^{ko}. Apoptotic cells were higher in P^{ko}-PTECs subjected to H_2O_2 stimulation compared with that in WT-PTECs. The phagocytic ability of PTECs to engulf apoptotic cells was compromised by P^{ko}. Both apoptosis and phagocytosis were not affected by additional WT or P^{ko}-serum.

Conclusions: Properdin might be associated with EPOR/βcR to facilitate the clearance of apoptotic cells by the phagocytosis of PTECs and initiate repair and remodeling of the kidney post 72-h IRI. The precise role and mechanism of properdin and EPOR/βcR in IRI and repair are worthy to be further studied.

PUB070

Contrast-Induced Acute Renal Oxalosis with Sustained AKI in Enteric Hyperoxaluria

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Introduction: Intratubular deposition of calcium oxalate crystals induces chronic renal disease in settings of primary hyperoxaluria (chronic renal oxalosis). Acute oxalosis is reported with extreme oxalate or Vitamin C intake and renal transplant settings.

Case Description: A 65-year-old W/M w creatinine 4.62 on chemotherapy screening (CS). Creatinine 1.3 six weeks prior to screening (PTS). CT scan w contrast 4 weeks PTS. **PMH**. adenocarcinoma of caecum (2013) treated w cytoreduction, HIPEC, right hemicolectomy + resection 2 feet terminal ileum. Chemo-Rx last 6 months was capecitabine-bevacizumab. **ROS**: No oliguria, flank pain, hematuria, dysuria, fever. Reports 2-4 loose stools/day since 2013 surgery. Serum HCO3 normal, urine SG ≥ 1.020 x 12 months. **Med:** lisinopril, loperamide, citalopram, ferrous sulfate. Recently took amoxicillin\clavulanic acid x 7 days for "toe infection." No NSAIDS **PE**: BP 130/80 no orthostasis, no edema; H/L/A normal. **Lab and imaging**: BUN 43, creatinine 4.33, bicarbonate 20, uric acid 10.4. Lytes, Ca, Mg, LFTs, CBC normal. Noncontrast CT: normal-sized kidneys, no hydro. U/A: pH 5.5, SG 1.009, P/B/leuk. negative. Sediment: no casts, cells or crystals. UNa 64, Ucreat 82. **Renal biopsy**: Acute tubular injury with intratubular calcium oxalate deposits DCT c/w oxalate nephropathy. **Treatment**: 3 L fluid intake, low oxalate diet, Calcium + citrate supplements. **Subsequent course**: 14 d after peak Creat and prior to therapy, Creat ↓to 3.08, 24 hr U oxalate elevated (58 mg), U citrate undetectable. Plasma oxalate undetectable.

Discussion: Proposed mechanisms: PRE-EXISTING CONDITIONS: 1) ***Enteric mechanisms***;↑ Ox permeability, ↓Ox secretion (intact ileum, proximal colon are net oxalate secretors), ↑ Ox availability (Ca binding to FFA). 2) *chronic diarrhea*; ↑U osm, ↓U citrate. CONTRAST INDUCED CONDITIONS: 1) ***Acute supersaturation:*** a) subclinical tubular injury → systemic Ox accumulation → acute ↑ filtered Ox. b) early osmotic diuresis ↓washout/tubular stasis. 2) Contrast binding to Tamm-Horsfall protein→↓***inhibitor crystallization***. OTHER: eradication of oxalate degrading gut flora (***Oxalobacter formigenes***) by antibiotics. **Teaching point:** Contrast loads in patients with Enteric hyperoxaluria and diarrhea following bowel resection may induce acute secondary oxalosis with sustained AKI. Appropriate screening, prophylaxis, imaging alternatives are advised.

PUB071

Cannabidiol-Induced Regulation of Innate Lymphoid Cells in AKI

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Background: Cannabidiol, a non-psychoactive cannabinoid, is increasingly believed to be of therapeutic potential for several conditions including those accompanied with inflammation. Intense immune and inflammatory responses are pivotal to the pathogenesis and manifestation of acute kidney injury (AKI). We recently showed renoprotective effects of cannabidiol in the murine model of AKI prompting us to explore cannabidiol-induced regulation of immune and inflammatory responses in this condition. Innate lymphoid cells (ILCs) have emerged as a new class of lymphocytes capable of regulating and amplifying the immune response through a variety of effector functions that parallel those of the T lymphocytes. Based on expression of signature molecular markers and cytokine expression, ILCs are classified into three groups: ILC1s, ILC2s and ILC3s. While ILC1s and ILC3s are linked to pro-inflammatory effects, ILC2s exert counter-inflammatory roles. Thus, we tested the hypotheses that AKI is associated with significant changes in frequency of each subset of ILCs and b) cannabidiol treatment restores frequencies of ILCs subsets to normal levels.

Methods: male mice were subjected to either bilateral renal ischemia (20 min)-reperfusion (24 hrs.) injury (IRI), a model of AKI, or sham operation; sham-operated mice and those subjected to IRI were further subdivided to receive either cannabidiol (10 mg/Kg; i.p.) or the vehicle (DMSO) 10 min before restoration of renal blood flow. Thereafter, kidney cells were prepared for subsequent flow cytometry analyses of subsets of ILCs.

Results: Induction of IRI markedly increased frequencies of ILC1s and ILC3s but significantly reduced ILC2s. Cannabidiol treatment of sham-operated animals did not affect frequency of each ILCs subsets. However, cannabidiol treatment of animals subjected to IRI resulted in restoration of frequencies ILCs subsets to levels of sham-operated animals although a differential persisted for ILC1s.

Conclusions: Collectively, our observations indicate that cannabidiol-induced regulation of ILCs contributes importantly to its renoprotective effect in AKI.

PUB072

Hypoxia-Induced Long Non-coding RNA Malat1 Is Dispensable for Renal Ischemia/Reperfusion-Injury

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Background: Renal ischemia/reperfusion (I/R) injury represents a major socioeconomic health problem. Non-coding RNA are crucially involved in pathophysiology. Long non-coding RNA *Malat1* (Metastasis Associated Lung Adenocarcinoma Transcript 1) was upregulated in renal I/R injury. We elucidated the functional role of *Malat1 in vitro* and its potential contribution to kidney injury *in vivo*.

Methods: *In patients*, kidney biopsies and plasma samples were collected. *In vivo*, *Malat1* knockout- (KO) and wild-type (WT) mice were subjected to unilateral and bilateral I/R. Histopathology-, gene expression-, kidney function- and survival studies were performed. *In vitro*, *Malat1* was silenced by antisense oligonucleotides in endothelial cells (EC) and tubular epithelial cells (TEC) subjected to hypoxia/reoxygenation. Transcriptional activation- and functional studies were implemented. Genome-wide RNA analysis was performed.

Results: *Malat1* was upregulated in human kidney biopsies and plasma and in murine kidney tissue, EC and TEC and mainly nuclear-chromatin associated. *In vitro*, *Malat1* inhibition reduced EC in the S-phase of the cell cycle. Proliferation decreased. Less EC were apoptotic after *Malat1* silencing. TEC were not functionally altered. *Malat1* was transcriptionally activated in EC and TEC by Hypoxia-inducible factor 1-alpha. *In vivo*, *Malat1* KO- and WT mice showed similar degrees of tubular epithelial injuries and proliferating cells. Capillary rarefaction was not affected. Kidneys of *Malat1* KO- and WT mice expressed more pro-inflammatory (IL-1beta, IL-6, MIP2a, MCP-1) and pro-fibrotic (Col1a2, Col III, TGF-beta) genes. Similar amounts of macrophage-, T-cell infiltration and tubulointerstitial collagen were detected. mRNA- and smallRNA expressions showed only minor differences. The reduced kidney function was not altered by *Malat1* KO. *Malat1* KO mice showed no survival benefit.

Conclusions: *Malat1* plays a pivotal role in hypoxia/reoxygenation induced endothelial cell pathology. Even though previous studies have suggested a prominent role of *Malat1* in

the induction of disease, we did not confirm an effect of *Malat1* loss on the progression of renal I/R-inury.

PUB073

Detection of Erythropoietin (Epo) Protein Expression by Western Blot

Hiroshi Nonoguchi,[1] Yukiko Yasuoka,[2] Yuichiro Izumi,[6] Takanori Nagai,[7] Yushi Nakayama,[5] Hideki Inoue,[10] Masayoshi Nanami,[3] Tomomi Oshima,[9] Takeshi Nakanishi,[4] Masashi Mukoyama,[5] Yuichi Sato,[2] Katsumasa Kawahara.[8] *[1]Kitasato University Medical Center, Kitamoto, Japan; [2]Kitasato University, Sagamihara, Japan; [3]Internal Medicine, Division of Kidney and Dialysis, Nishinomiya, Japan; [4]Hyogo College of Mediicne, Nishinomiya, Japan; [5]Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [6]Kumamoto University, Kumamoto, Japan; [7]Internal Medicine, Nagai Clinic, Nishinomiya, Japan; [8]Dept of Physiol, Kitasato Univ School of Med, Sagamihara, Japan; [9]Kitasato University, School of Medicine, Sagamihara-shi, Japan; [10]Kumamoto University School of Medicine, Kumamoto, Japan.*

Background: It has been believed that erythropoietin is secreted into plasma soon after the production by the erythropoietin producing cells in the kidney probably because of the difficulty of immunohistochemistry and Western blot analysis. We investigated the expression of Epo protein by Western blot analysis using the monoclonal and polyclonal antibodies against Epo.

Methods: Both the polyclonal and monoclonal antibodies against Epo were used for the detection of Epo protein by Western blot analysis. Antigen-peptide absorption tests using recombinant rat Epo and the antibodies were used to check the specificity of the band. Since Epo is known to be a glycoprotein, deglycosylation of the recombinant rat Epo and produced Epo using N-glycosidase F was performed.

Results: Both the polyclonal and monoclonal antibodies against Epo showed recombinant Epo as a broad band at 34-43 kDa. The kidney and liver from control rat showed a broad but faint band at 36-40 kDa and a narrow band at 42 kDa. The polyclonal antibody was used for immunohistochemistry and the monoclonal antibody was used for Western blot analysis. Severe hypoxia increased an expression of a broad band at 36-40 kDa in the kidney but reduced a band at 42 kDa in the liver. Antigen-peptide absorption test using recombinant rat Epo largely decreased the expression of the bands of recombinant Epo and kidney/liver Epo. Deglycosylation of recombinant Epo and hypoxia-induced kidney sample showed a shift of the bands to 22 kDa, which is identical to the size of Epo by LC/MS analysis. These data clearly show that the bands at 36-40 and 42 kDa correspond to Epo protein.

Conclusions: In conclusion, Epo protein can be detected at 36-40 and 42 kDa by Western blot analysis using the monoclonal antibody.

Funding: Government Support - Non-U.S.

PUB074

The Effect of Ferric Citrate (Auryxia) on Hemoglobin, Iron Levels, As Well As, Phosphorus Management in Dialysis Patients

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Background: Hyperphosphatemia in end stage renal disease is associated with increased morbidity and mortality. Ferric Citrate (FC) is indicated for hyperphosphatemia in patients with CKD on dialysis and in the treatment of iron deficiency anemia in adult patients with CKD III and IV. We present real-world serum phosphorus, hemoglobin and other iron-related data from patients treated with FC in one dialysis center compared to second group of patients from the same center on other phosphorus binders.

Methods: Retrospective chart review in one dialysis center of two study groups, each with 19 patients. One group was prescribed FC for hyperphosphatemia for an average of 9.89 months. The second group was prescribed other phosphorous binders for one year. FC and control group treatment data collected: Treatment Duration, Average Daily Prescribed Pill Count, Average Monthly Intravenous (IV) Iron Dose, Start and End for the following parameters: Serum Phosphorus, Iron Saturation (ISAT), Serum Ferritin and Hemoglobin (Hgb).

Results: We compared 19 patients who were prescribed FC as a phosphorus binder to 19 patients prescribed other phosphorus binders. Both groups had similar characteristics: Gender (26.3% F/ 73.6% M vs 42.1% F/57.8% M), Age (52 vs 60.5), Diabetic Status (63.1% vs 68.4%), BMI (27.5 vs 33.1). The mean daily prescribed pill burden was FC 5.1 vs Control 6.9. There was net reduction of serum phosphorus by more than 1 mg/dL reaching the goal of 5.5 mg/dL compared to the control group where there is an increase in phosphorus by ~1 mg/dL reaching 5.72 mg/dL. The patients taking FC showed an increase in HgB of 1 gm/dL FC group vs decrease HgB ~0.4gm/dL, ISAT of 14% FC group vs no significant change in control group, Average IV venofer need per month 110.8 mg in FC group vs. average IV venofer need per month 145.2 mg in control group.

Conclusions: The use of Ferric Citrate as a phosphorous binder for patients on Hemodialysis showed a decrease of total monthly IV iron requirements by 25% with an average increase in the HgB by 1 gm/dL, and an increase in ISAT by 13.4%. In addition, FC Group reached the target phosphorus level of 5.5mg/dL. The Control Group showed no significant changes in either HgB or ISAT and an increase in phosphorus levels.

Funding: Private Foundation Support

PUB075

Efficacy of Intravenous Ferumoxytol Compared to Sodium Ferric Gluconate for Anemia Management in Outpatient Hemodialysis Population

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Background: Intravenous iron is one of the main therapies for anemia management in hemodialysis dependent patients. Data comparing the efficacy of ferumoxytol versus other parenteral iron supplements are scarce. The objective of the study was to compare the efficacy and safety of ferumoxytol as compared to sodium ferric gluconate in hemodialysis patients

Methods: A prospective observational study was conducted on hemodialysis outpatients who received ferumoxytol 510 mg once or twice quarterly compared to sodium ferric gluconate 125 mg weekly in a single center southwestern Ontario community hospital between Oct 2013 and June 2014. Patient demographics, iron indices, hemoglobin levels, iron doses, and erythropoiesis stimulating agent (ESA) doses were collected

Results: The study sample consisted of 291 observations from 173 patients. Generalized estimating equations of multiple linear regression modeling was conducted to compare the outcomes while adjusting for baseline scores. About 25% of the study participants received ferumoxytol while 75% received sodium ferric gluconate. Males (58.4%), mean age was 68.73 (SD ± 13.03) years. Both groups did not show significant difference in their hemoglobin levels (*Wald* $z = 0.54$; $p = 0.46$), ESA utilization at 3 months (*Wald* $z = 0.20$; $p = 0.65$) and TSAT levels (*Wald* $z = 3.45$; $p = 0.06$). However, the iron levels (*Wald* $z = 4.24$; $p = 0.04$) and ferritin levels (*Wald* $z = 5.14$; $p = 0.02$) were higher in the ferric gluconate group (*Wald* $z = 58.78$; $p \leq 0.001$) and patients who received ferumoxytol received more blood transfusion as compared to those who received sodium ferric gluconate ($\chi^2 = 16.71$; $p \leq 0.001$)

Conclusions: Both iron products maintained hemoglobin levels with those receiving ferumoxytol had lower iron indices and received more blood transfusions compared to sodium ferric gluconate

PUB076

Effect of the Paricalcitol on the Hemoglobin Variability and Anisocytosis Degree in Hemodialysis Patients

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Background: Hemoglobin variability(Hb-V) and higher red cell distribution width (RDW- a marker to describe the amount of anisocytosis-) are two factors associated with higher mortality in dialysis patients. A potential benefit of the selective vitamin D receptor activator (paricalcitol) lowering ESA doses was described; however its effect on Hb-V and RDW is unknown. **Objective:** To describe the influence of the paricalcitol on Hb-V and RDW in hemodialysis patients.

Methods: This is cross-sectional study. Patients with paricalcitol(N=56) and without paricalcitol (N=41) were compared. Prevalent hemodialysis patients with the following inclusion criteria were included: Hb ≥ 9g/dl, transferrin saturation(TSAT) ≥20% and/or plasma ferritin levels ≥200pg/ml. Hb stability range was defined as Hb within 10-12g/dl. Higher RDW values >15%. Hemoglobin and RDW relationship was evaluated by regression analysis.

Results: Median parathyroid hormone was higher in group A in comparison with group B (234 pg/ml versus 154 pg/ml, P>0.001). Hb, RDW, TSAT, ferritin, albumin, cholesterol, iron supplements and ESA doses showed no differences between groups. The percentage of patients with diabetes, hypertension, were similar between groups. As a whole, a quadratic regression model explained the relationship between Hb and RDW (R^2:0.09, P=0.01). No association between the percentage of patients treated with paricalcitol and Hb stability, or higher RDW was observed. However, a negative relationship between Hb and RDW (r: -0.28; P=0.03) was observed in those with paricalcitol, while it was positive in those without paricalcitol (r:0.41; P=0.006). Those patients with PRC and higher RDW showed lower Hb levels than those with lower RDW (mean difference: 1,20g/dl, P = 0.01); while in those without PRC patients with higher RDW, no differences in Hb values respect to those with lower RDW values were observed (mean difference: -0.88 g/dl, P=0.07).

Conclusions: The use of the paricalcitol in patients with Hb stability was associated with a decrease in the anisocytosis, while in those without paricalcitol an opposite association was observed. These data suggest a direct effect of the paricalcitol on the hematopoiesis process.

PUB077

Effect of Ferric Citrate on Iron Parameters in ESRD Patients with Elevated Ferritin: Interim Report of a Pilot Pragmatic Clinical Trial

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Background: Iron deficiency is prevalent in ESRD patients. Patients with elevated Ferritin (>1000 mcg/dL) are poorly responsive to IV Iron & may be at risk of infection. We investigated the efficacy of oral Ferric Citrate on Iron parameters in ESRD patients with

low transferrin saturation (TSAT) but elevated ferritin in a pragmatic pilot clinical trial at a single dialysis center in the US.

Methods: This is an un-blinded, open label study to determine the effect of Ferric Citrate on iron parameters in ESRD patients with elevated ferritin & low TSAT. All ESRD patients on hemodialysis for at least 3 months at the US Renal Care Baylor Scott Street Dialysis unit were eligible to participate. Patients were included in the trial if they satisfied the following criteria: 1) Mean Serum Ferritin >1000mcg/dL on 2 consecutive samples 3 months apart 2) TSAT <30% on 2 consecutive samples 3 months apart 3) Able to tolerate phosphate binders We collected the following information pre-enrollment into the trial: Ferritin, TSAT, hemoglobin, ESA dose, Calcium, Phosphorus, and PTH. Subjects were given Ferric Citrate 210 mg 2 tabs with meals (minimum 6/day) for 3 months. Clinicians could change the dose as clinically indicated. Management of IV Iron & ESA was per the standard clinic anemia management protocol. Labs were monitored monthly This is an interim report after completion of 9 patients in the trial.

Results: Mean serum Ferritin & TSAT at enrollment were 1246 ng/ml & 23.7 %. After completion of 90 days of Ferric Citrate the mean ferritin and TSAT increased to 1303 ng.ml (4% increase) and 38.29% (38% increase) respectively. ESA use decreased from 38 units/week of Darbepoetin to 15 units/week (60% reduction) after 90 days.

Conclusions: Oral Ferric Citrate appears to be an effective iron supplement that increases iron stores in ESRD patients with high Ferritin & low TSAT. Further studies with larger numbers of patients are needed to investigate its impact on ESA use in ESRD patients.

Funding: Commercial Support - Keryx Biopharmaceuticals

Anemia parameters

Parameter (mean)	Baseline	Visit 3
Hemoglobin (g/dL)	10.2	10.5
TSAT (%)	23.74	38.29
Ferritin (ng/ml)	1246	1303
Iron (mcg/dL)	59.3	85.4
ESA (dose units/week)	38.3	15

PUB078

Effect of Ferric Citrate on KDQOL-36 Scores in ESRD Patients with Elevated Ferritin: Interim Report of a Pilot Pragmatic Clinical Trial

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Background: Iron deficiency is prevalent in ESRD patients. Patients with elevated Ferritin (>1000 mcg/dL) are poorly responsive to IV Iron and have higher risk of infection. We investigated the efficacy of oral Ferric Citrate on KDQOL-36 scores in ESRD patients that have low TSAT but high Ferritins in a pragmatic pilot clinical trial at a single dialysis center in the US

Methods: This is an unblinded, open label study to determine the effect of Ferric Citrate on anemia management in ESRD patients with elevated Ferritin and low TSAT. Primary end point was change in weekly ESA use. Secondary end points were changes in TSAT and KDQOL scores. All ESRD patients on hemodialysis for at least 3 months at the US Renal Care Baylor Scott Street Dialysis unit were eligible to participate. Patients were included if they satisfied the following criteria: Serum Ferritin >1000 on 2 consecutive samples 3 months apart, TSAT <30% on 2 consecutive samples 3 months apart, and able to tolerate phosphate binders. Subjects were given Ferric Citrate 210 mg 2 tabs with meals (minimum 6/day) for 3 months. Treating clinicians were allowed to change the dose of Ferric Citrate as clinically indicated. Anemia management was per the standard clinic protocol. KDQOL 36 scores were collected upon enrollment and again at 90 days at the end of trial. This is an interim report after completion of 9 patients in the trial.

Results: Mean Physical Health Composite and Mental Health Composite at enrollment were 37.98 and 44.72. After completion of 90 days of Ferric Citrate, the mean Physical Health Composite and Mental Health Composite increased to 48 and 50.86 respectively. Notably 2 of the 9 patients had self-reported low compliance with Ferric Citrate (18% and 14%) and had worsening of KDQOL scores.

Conclusions: Ferric Citrate appears to be a safe and effective phosphate binder in ESRD patients with high Ferritin and low TSAT. Further large scale studies are need to be conducted to study its impact on Quality of Life in ESRD patients.

Funding: Commercial Support - Keryx Biopharmaceuticals

KDQOL-36 subscale scores

Subscale	Mean scores (baseline)	Mean scores (90 day follow up)	Standard Deviation
Physical Health Component	37.98	48	13.58
Mental Health Component	44.72	50.86	10.87
Burden of Kidney Disease	61.49	59.38	23.48
Symptoms of Kidney Disease	81.25	80.89	19.43
Effect of Kidney Disease on Daily Life	69.79	67.19	23.48

PUB079

Association Between Renal Function, Serum Levels of Interleukin-6 and Stroke in Nondialysis CKD Outpatients

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Background: Cardiovascular disease is the leading cause of mortality and stroke is a frequent complication inchronic kidney disease (CKD) patients. Inflammation is associated with cardiovascular disease. To assess if serum renal function and inflammatory cytokines are associated with stroke in nondialysis CKD outpatients.

Methods: We retrospectively analyzed a database with 100 nondialysis CKD outpatients and identified 20 patients with stroke up to 96 months after enrolment in nephrology office. Demographic data, eGFR, blood count, ACEi, erythropoiesis-stimulating agents (ESAs) use, serum sFas, and inflammatory cytokines levels from baseline were recorded. We performed comparisons between stroke group (n=20) and non-stroke group (n=80). Binary logistic regression was used to determine the impact of factors on stroke.

Results: The primary cause of CKD was diabetes followed by hypertension. Stroke occurred after 37±8 months. Transient ischemic attack-9, ischemic-7 and hemorrhagic stroke-4 patients. We observed lower eGFR (37.8±20.8, 25.5±8.7 mL/min; p=0.01), Hb (12.4±2.1, 11.2±2.4 pg/mL; p=0.04) and platelets [(227±56, 200±50)x10^3; p=0.04)] in stroke group. We found higher levels of serum sFas levels (4007±1668, 2985±940 pg/mL; p=0.001) and serum IL-6 levels (10.1±5.8, 5.6±4.2 pg/mL; p=0.002) in stroke group. We did not observed difference in smokers, diabetes and hypertension, ACEi and ESA use. Serum IL-6 (b = 1.133, 95%CI 1.002-1.131; p=0.04) and GFR (b = 0.911, 95%CI 0.844-0.983; p=0.01) were independently associated with stroke.

Conclusions: In this study lower GFR and higher serum IL-6 were predictors of stroke in nondialysis CKD outpatients within 96 months.

PUB080

Nephrology and Biodesign: Using the Needs Finding Process for Nephrology Innovation

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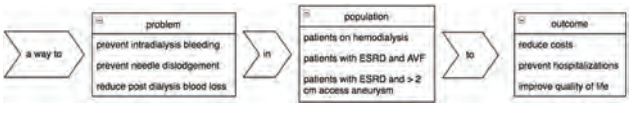
Background: There is renewed demand to accelerate innovation in nephrology and both public and private sectors are creating programs to support its growth. The Stanford biodesign innovation process, first developed in 2000, provides a roadmap for health technology innovation. The program includes three phases: identify, invent, and implement. There is insufficient published guidance on the application of this process in the generation of novel devices to address nephrology clinical needs. We present our process of needs identification in a hemodialysis unit, using the biodesign innovation process.

Methods: We applied the identify phase of the biodesign innovation process in two stages: 1. needs finding and 2. needs screening. We performed a qualitative retrospective review of observations within a hemodialysis unit, generated needs statements, actively tested those needs, and validated them. The needs finding stage includes background research, direct clinical observations, interviews, documenting those observations, and development of multiple needs statements. The needs screening stage includes a deeper review of the disease state, an analysis of stakeholders and market, and ranking of needs statements.

Results: A dozen retrospective observations were reviewed to create needs statements. One of the twelve observations were utilized to generate multiple related needs statements. The figure is based on observations of a cannulated hemodialysis access within a hemodialysis unit.

Conclusions: We conclude that the needs finding and needs screening stages of the biodesign innovation process can be used to identify meaningful unmet clinical needs in nephrology and foster new device inventions.



Need statement scoping (actively testing and refining need statement) with multiple problems, populations, and outcomes

PUB081

Vascular Calcifications in Animal Models: Can They Be Compared to Those in Humans?

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Background: Rat models of vascular calcification are an important tool to evaluate safety and efficacy of compounds aimed at reducing vascular calcifications in humans. Calcifications in rats can be detected using μCT imaging of the aorta, bulk calcium analysis and/or Von Kossa (VK) staining of vessels. In renal failure patients, calcifications are generally detected using the CAC score which has been shown to be associated with cardiovascular morbidity/mortality in these patients. An important question in translational

studies on vascular calcification is the extent to which CAC scores, and thus vascular calcification, in humans can be correlated to calcifications observed in animal models.

Methods: Vascular calcifications were induced in 15 male Wistar rats using the adenine-low protein model. After 4 weeks, all animals underwent both in-vivo and post-mortem μCT imaging of the aorta, using a Skyscan 1076 μCT, with a 35μm voxel size. Scans were also made of 12 human blood vessels, obtained during transplant surgery. Additionally, VK staining and bulk Ca analyses were performed in all rat and human samples.

Results: Seven animals showed clear calcification (bulk Ca > 10 mg/g). A good correlation (R=0.885, p<0.05) was found between the in-vivo and post-mortem scans. Both bulk Ca levels (16.32 ± 5.74 mg/g) and VK positive area (10.96 ± 4.43 %) correlated well with the in vivo scan (R=0.829, p<0.01 and R=0.813, p<0.001). Six out of the 12 human samples showed detectable calcifications using μCT. Four of these had bulk Ca levels > 10 mg/g. In the human samples, a good correlation was also found between the μCT scan and both bulk Ca levels (56.5 ± 40.3 μg/g) and VK positive Area (7.2 ± 4.83%) (R=0.991, p<0.001 and R=0.932, p<0.001). Both bulk Ca levels and VK positive area were similar in the human and animal samples (p > 0.05).

Conclusions: In summary, we found a good correlation between μCT, bulk Ca and VK staining in both animal and human samples. Furthermore, bulk Ca levels and VK staining in human and rat samples were similar. In order to evaluate whether CAC scores in humans correlate with the various parameters of vascular calcification, sample collection of patients with known CAC scores is currently ongoing.

Funding: Commercial Support - Sanifit (Spain)

PUB082

Osteoblastic Differentiation of Bone Marrow-Derived Mesenchymal Stem Cells in Uremic Rats with Secondary Hyperparathyroidism

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Background: Although severe secondary hyperparathyroidism (SHPT) represents a high turnover bone disease, osteitis fibrosa, but the pathogenesis of osteitis fibrosa is not fully clarified. We examined the characteristics of bone marrow-derived mesenchymal stem cells (BMSCs) differentiation into osteoblasts in uremic rats with SHPT.

Methods: We bred 5/6 nephrectomized (Nx) rats with a high phosphorus (P) diet (containing 1.2 % phosphate) to progress SHPT (Nx+high P diet (HP) group, n=10), or Nx (Nx+normal P diet (NP:containing 0.6 % phosphate) group, n=6) and normal rats (Normal+NP group, n=5) with a standard diet. After 8 weeks all rats were sacrificed and BMSCs (obtained from femur), tibia, and serum were analyzed. BMSCs were confirmed by flow cytometry for the expression patterns of the cell surface marker (CD90+, CD29+, CD45-, and CD31-). Osteoblastic differentiation was induced by an osteogenic medium containing 10mM β- glycerophosphate, 50 μg/mL ascorbic acid and 10 nM dexamethasone in minimal essential medium α (MEMα). The osteoblastic differentiation was assessed by ALP mRNA expression and alizarin red staining.

Results: Serum creatinine (Cre) levels were significantly elevated in the Nx+NP rats compared with the Normal+NP rats. The Cre levels in the Nx+HP rats showed levels similar to those in the Nx+NP rats. Serum P and PTH levels were significantly elevated in the Nx+HP rats compared with the Nx+NP rats (P level: 11.1±2.4 vs 7.3±1.3 mg/dL, PTH level: 1820.6±665.1 vs 197.8±151.9 pg/mL). Bone morphometrical analysis showed an increase in both osteoid volume and eroded surface in the Nx+HP but not in the Nx+NP rats. The population of harvested BMSCs were similar in all three groups. The ALP mRNA expression in the BMSCs from the Nx+HP rats was significantly suppressed compared with that in the other rats. Alizarin red staining showed a tendency similar to the ALP mRNA expression.

Conclusions: These results suggested that the BMSCs differentiation into osteoblasts was disturbed in the SHPT rat. The discrepancy between the high osteoblastic activity in the bone and impaired differentiation of the progenitor cells were found. P load might contribute to this differentiation impairment.

Funding: Government Support - Non-U.S.

PUB083

Bone Morphogenetic Protein-7 Upregulates Collagen I, Sp7, and IBSP Genes in Human Mesenchymal Stem Cells

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Background: Bone morphogenetic proteins are reported to be associated with proliferation and differentiation of various types of cells. This study was performed to evaluate the effects of short-term application of bone morphogenetic protein-7 on human mesenchymal stem cells with next-generation sequencing.

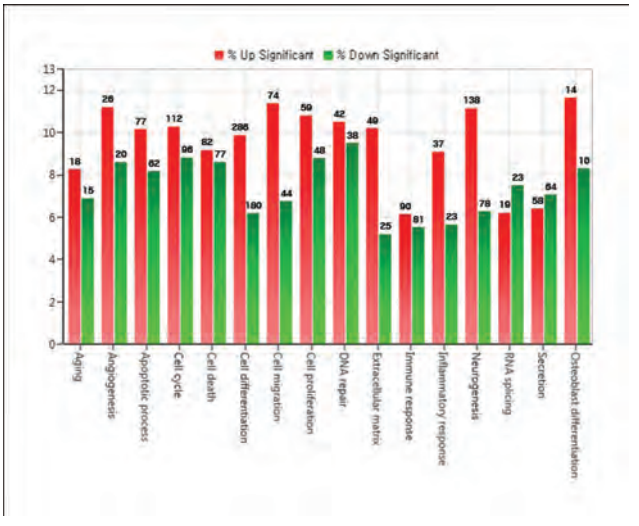
Methods: Stem cells were treated with a final concentration of 100 ng/ml bone morphogenetic protein-7. Sequencing of mRNA and analysis of data were performed. Gene ontology and pathway analysis were done. Quantitative real-time polymerase chain reaction of mRNA of ColI, Sp7, IBSP and Western blot analysis of collagen I, osterix and bone sialoprotein and β-actin were performed.

Results: A total of 25,737 mRNAs were differentially expressed and up and down-regulated mRNAs were documented based on the related pathway. Expression of collagen I, Sp7 and IBSP were increased with the application of BMP-7 at 3 hours and this was confirmed with Western blot analysis.

Conclusions: The short-term application of BMP-7 produced increased expression of collagen I, Sp7 and IBSP and this was related with target genes chosen for osteoblast differentiation. This study provided new insights into role of bone morphogenetic protein-7 using mRNA sequencing.

Funding: Government Support - Non-U.S.

Gene ontology analysis by categorization of the importance



Gene ontology analysis by up- and down regulation

PUB084

Study of Fibroblast Growth Factor 23 in Patients with CKD in Indian Population

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Background: Historically there are four main 'Players' in CKD-MBD, namely calcium, phosphate, parathyroid hormone (PTH) and vitamin D endocrine system. The treatment strategies are designed to keep all four parameters within defined ranges in an attempt to maintain bone and vascular health in a patient with CKD. FGF-23 is pivotal as a marker of progression of CKD as well as a therapeutic target for assessing response to treatment.

Methods: Total 64 patients were enrolled over a period of 18 months after obtaining consent. The blood samples were collected for serum calcium, phosphorous, PTH, Vitamin

D and haemoglobin. The statistical significance in the difference in the outcome variables between the groups was assessed using Kruskal -Wallis for FGF-23. Data was analysed using STATA 13 software.

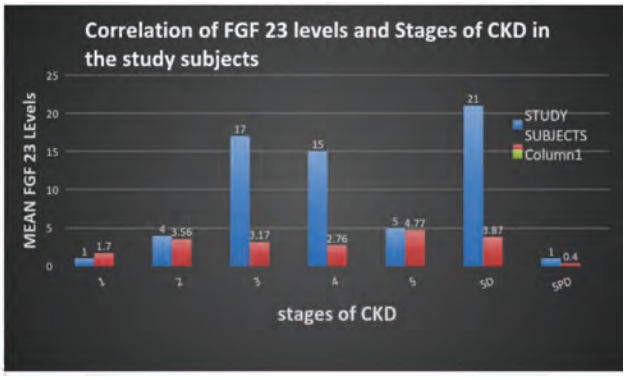
Results: The mean value for FGF 23 was found to be highest in CKD stage 5 (4.77) followed by stage 5D (3.87) and stage 2 (3.56). This was not statistically significant. FGF-23 was compared with existing markers of CKD MBD and except for marginal significance for phosphorus (P value 0.09); there was no statistically significant correlation. The drop in haemoglobin level with CKD progression was correlated negatively with FGF 23 level. (p=0.01)

Conclusions: The FGF-23 levels do not correlate with present markers of CKD-MBD. FGF-23 values were observed to be lower in low turnover disease and higher in high turnover bone disease. But estimating CKD-MBD severity by utilising FGF-23 as a marker may not be helpful as majority CKD population has low PTH in our study.

FGF-23 correlation with existing markers

Variables	FGF-23	P-Value
Calcium	-0.03	0.79
Phosphorus	0.22	0.07
Vitamin D	0.11	0.37
PTH	-0.01	0.58
Calcium x phosphorus	0.2	0.09

There is no statistical significance between FGF-23 and existing markers of CKD-MBD.



Levels of FGF 23 among different stages of CKD

PUB085

Correlation of Vitamin D and Islet β Cell Function Among Calcium Kidney Stone Formers

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Background: Existing evidence suggest that low vitamin D store affects normal release of insulin from β-islet cells after glucose intake, hence could play a role in the pathogenesis of glucose intolerance and type 2 diabetes mellitus. However, the interaction between 25(OH)-vitamin D (25D) with β cell function has not been studied in calcium kidney stone formers, a unique population whose 1,25(OH) vitamin D (1,25-D) action seems to be hyperactive.

Methods: Prevalent non-diabetic calcium kidney stone formers from 2015 to 2018 were enrolled in this study. We assessed the association between serum 25D and β cell function measured by HOMA- β [(360 × fasting insulin (μU/L)/(fasting glucose (mg/dl)–63)] using univariate analysis and multivariate regression model adjusting for demographics and important clinical covariates. P values less than 0.05 were considered significant.

Results: A total of 94 non-diabetic calcium kidney stone formers were enrolled in this study. Among them, 51% were male, 86% were Caucasian, 38% had history of hypertension and 29% had history of dyslipidemia. Mean age was 54 years, mean creatinine clearance (CrCl) was 131 ml/min, mean body mass index (BMI) was 31.3 kg/m^2, mean serum 25D was 28 ng/ml, mean serum 1,25D was 52 pg/ml, and mean serum parathyroid hormone level was 66 pg/ml. As a measure of islet β-cell function, mean HOMA β was calculated to be 270. In univariate analysis, CrCl, BMI and history of hypertension and dyslipidemia, associated significantly with HOMA- β ($p<0.05$), but 25D did not have a significant association ($p=0.2$). After adjusting for demographics, 25D associated significantly with HOMA- β ($p=0.02$). Likewise CrCl, BMI, history of hypertension and dyslipidemia continued to carry significant associations with HOMA- β ($p<0.05$). After adjusting for demographics, histories of hypertension and dyslipidemia, CrCl, BMI and serum uric acid, the association between 25D and HOMA- β remains significant ($p=0.01$). Unlike 25D, serum 1,25D levels have no association with HOMA- β in univariate and multivariate analyses.

Conclusions: Like the general population, low serum 25D levels, not 1,25D levels, associate strongly with islet β cell function measured by HOMA- β in calcium kidney stone formers.

Funding: Private Foundation Support, Clinical Revenue Support

PUB086

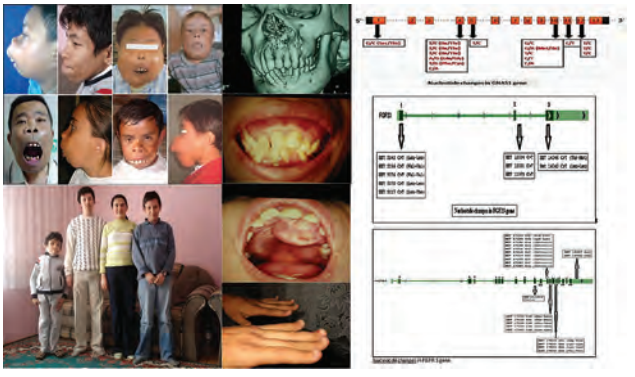
Multiple GNAS1, FGF23, FGFR3 Genes' Striking Mismutations in CKD with SH: Brand New Bone Dysplasia and Uglifying Human Face Appearances - Sagliker Syndrome (SS)

Yahya Sagliker. *Sagliker Hypertension Unit, Adana, Turkey.*

Introduction: SS so far, seems to be related to chronic kidney disease (CKD) and consequent secondary hyperparathyroidism (SH). SS starts and develops particularly before puberty, while CKD reaches stage III level with overt SH. Since it occurs only in some patients (%1), it is plausible to think SS is genetically predisposed. Genes' mismutations on the genesis of SS is unclear and no data are available so far.

Case Description: We conducted clinical studies and screening for mismutations in GNAS1 gene in 23, FGF23 and FGFR3 genes in 17 patients. DNA isolations performed from blood samples and mismutation regions were amplified by PCR. In 73.9% (17/23) patients, 17 different abnormalities in GNAS1 were detected.58.3% (7/12) nucleotide alterations comprised novel mismutations in different manners. There were 6 heterozygous tranversion polymorphism in exons.6 were introngenic mismutations found in introns 65626, 70387, 70817. We found 10 different mismutations in FGF23 gene. 8 were novel mismutations defined first in our study. 3 were in intronic region near exon 2. In FGFR3 gene we found 22 different mismutations. 16 were novel mismutations defined first in our study. 12 mismutations were found in exons. 8 were found in introngenic region near exon 11. 2 were found in non-coding exonic regions of exon 18.1 was in the exon-exon junction region between exon 11 and 12. 3 were nonsense Therefore mismutations might be preventing splicing of introns.

Discussion: There are plenty mismutations on 3 genes consistent with an insufficiency of genes playing a role in clinical phenotype of loss of function mutations with functional alleles having predominant roles in preventing hormonal resistance. Since incidence of CKD stage 3 is around 8% in world but the incidence of SS is around 1% and although our patients were not resembling any of them, but they could be in between and SS might be a combination-compulsion of Genetical Bone displasias such as McCune-Albright syndrome, Achondroplasias etc and SH and CKD.



PUB087

Warfarin Based Anticoagulation Is a Major Risk Factor for Calciphylaxis

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Background: To assess clinical risk factors, altered laboratory parameters, epidemiology and survival rates of patients suffering from calciphylaxis, we conducted a retrospective study of patients with biopsy-proven calcific uremic arteriolopathy (CUA).

Methods: In an eight year period from 2008-2016 we included 15 patients in a single center retrospective study for final analyses. Only patients with both, strong clinical suspicion of calciphylaxis and confirmative histological patterns such as intimal hyperplasia, micro thrombi or van Kossa stain positive media calcification, were included. Patients with clinical suspicion but lacking dermatohistological evidence were excluded.

Results: The mean age of patients was 64.8 years. 9 patients (60%) were female; 12 (80%) were obese with a Body-Mass-Index above 30 kg/m2; 3 (20%) did not have chronic kidney disease (CKD); 12 (80%) had stage 4 or 5 CKD and 10 (66.7%) were on dialysis (CKD 5D). One-year mortality in the entire cohort was 73.3%. With respect to medication history, the majority of patients (n=13 (86.7%)) received Vitamin-K-Antagonists (VKA); 10 (66.7%) weretreated with Vitamin D; 6 (40%) were supplemented with oral calcium; 5 (33.3%) had been treated with corticosteroids; 12 (80%) were on protonpump inhibitors. 13 (86.7%) patients showed hyperparathyroidism. The serum-phosphate level was elevated in 9 (60%) patients and the serum-calcium level was reduced in 7 (46.7%) patients. Ten (66.7%) patients presented with hypoalbuminemia at diagnosis.

Conclusions: Calciphylaxis is a rare disease with high mortality associated with female sex, obesity, severe chronic kidney disease and hyperparathyroidism. Especially treatment with VKAs and liverdysfunction are important risk factors for the development of calciphylaxis.

PUB088

Rationale, Design, and Characteristics of EPISODE Trial

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Background: In dialysis patients, mortality risk due to cardiovascular diseases is remarkably high and prognosis is poor; coronary artery calcification is considered one of the major contributing factors. It is known that hyperphosphatemia is associated with coronary artery calcification. Therefore, controlling serum phosphate levels and thereby mitigating vascular calcification could improve the poor prognosis of dialysis patients. However, the optimal phosphate range in dialysis patients remains unknown; hence, this study was planned to compare the effects of two types of non-calcium-based phosphate binders, and examine the effect of strict control of phosphate on coronary artery calcification.

Methods: EPISODE is a randomized, open-label, multi-center, interventional trial with a two-by-two factorial design. We enrolled 160 hemodialysis patients (men 109, women 51, diabetes 59, hypertension 116) with a pre-dialysis serum phosphate level of at least 5.0 mg/dL or at least 6.1 mg/dL, respectively, in those taking or not taking a phosphate binder, as measured during the observation period. Registered patients were randomized to the sucroferric oxyhydroxide or lanthanum carbonate arm in order to reduce serum phosphate to two target ranges (3.5 - 4.5 mg/dL in strict arm and 5.0 - 6.0 mg/dL in standard arm) for 12 months. The primary endpoint will be percent change in coronary artery calcification score (CACS), and the secondary endpoints will include change in serum phosphate and calcium levels, change in renal anemia-related factors, etc.

Results: At baseline, the median CACS was 840 (IQR; 270-2705).

Conclusions: This study may show the optimal phosphate range in dialysis patients.

PUB089

Calciphylaxis: What Are These Patients Dying from? A Single Centre Study

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Background: Calciphylaxis is a rare metabolic entity most commonly associated to chronic kidney disease, with a mortality rate over 80% in the first year after diagnosis. The optimal treatment for calciphylaxis continues to be discussed. There is not one healing treatment that works in every case, although there is many that can be useful for avoiding the progression of the lesions and in some cases even lead to curation (ulcer debridement, Paracalcitrol, sodium thiosulfate, biphosfonates and paratiroidectomy are some of them.) We present a series of 23 patients diagnosed of calciphylaxis in our center and review the treatment regimen and survival in each case.

Methods: From January 2002 to october 2017 our Nephrology department attended 2131 patients with chronic kidney disease, 23 of them (1%) developed calciphylaxis: 11 men/12 women with a mean age of 58 years (range 32 to 87 years). At the time of diagnosis, 13 patients were receiving treatment with hemodialysis, 7 were on peritoneal dialysis and 3 had a functioning transplant. The mean risk factors identified in these patients were: severe hyperparathyroidism in 11 cases (PTH>600), oral anticoagulants in 10 patients., steroid treatment in 8 patients, active-D-vitamin supplements in 4 patients, severe hyperphosphatemia in 6 patients (P> 6 mg/dl). In 11 patients calciphylaxis occurred coincidental with a decompensation of another illness. All of them were treated by trained nurses who performed ulcer debridement and applied antiseptic and healing bandages. Other treatments were Paracalcitrol (n=12), parathyroidectomy (n=4), Biphosphonates (n=3), Sodium thiosulfate (n=3).

Results: During the follow-up 13 patients died, 2 were lost and 8 are alive. 3 patients died as a result of calciphylaxis (13%), improving the skin lesions in the remaining 20. However, in the first year after diagnosis, another 9 patients died due to pathology not related to calciphylaxis (5 cardiac, 1 lung transplant rejection, 1 gastrointestinal hemorrhage, 1 pneumonia, 1 HD withdrawal), thus total mortality was 52%.

Conclusions: Secondary hyperparathyroidism and oral anticoagulants were the most prevalent risk factor in our series. Although calciphylaxis is associated to a very high mortality rate, the main cause of death was the decompensation of unrelated illnesses.

PUB090

Early Detection of Mineral Abnormalities in Patients with CKD Stage 3-4

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Background: Mineral and Bone Disorders (MBD) are highly prevalent in all stages of chronic kidney disease (CKD). Secondary hyperparathyroidism (SHPT) and hyperphosphatemia (HP) are the most prominent mineral abnormalities. Progression of CKD has been associated with increased iPTH, phosphorus (P) and Calcium x Phosphate product (CaxP) and with decreased calcium (Ca) and 1,25 dihydroxyvitamin D levels. Our aim was to determine the prevalence of mineral disorders in our outpatient CKD stage 3-4 patients.

Methods: We studied 336 CKD stage 3-4 patients (190 men, 56.5% and 146 women 43.5%, mean age 65±14 years). Patients were not receiving Ca supplements, phosphate binders, or vitamin D. Mean eGFR was 34±9.5 ml/min/1.73m2. The parameters determined and analyzed were: Ca, P, iPTH and CaxP.

Results: The percentage of patients with Ca, P, iPTH and CaxP within the recommended targets are presented in the Table. 58% of our patients had iPTH>110 pg/ml (95%CI ∑49.8-65.2), 34.2% had P>4.6mg/dl (95%CI 25.8-40.4), 86.3% had CaXP>55mg2/dl2 (95%CI 79.9-90.9) and 22.3% had Ca<8.4mg/dl (95%CI 15.6-28.5). P correlated positively with iPTH and CaxP (r=0.25 p=0.001 and r=0.41 p=<0.001 respectively), and negatively with Ca (r=0.85 p<0.001). (Table)

Conclusions: In patients with CKD stages 3-4, out-of target mineral parameters are highly prevalent. Early detection of mineral abnormalities is critical for timely and effective treatment of SHPT in pre-dialysis patients and could delay the progression of CKD-MBD.

Funding: Government Support - Non-U.S.

Biochemical Parameter	Target Value	% of patients within target	95% CI
P	2.7 - 4.6 mg/dl	61%	(52.2 - 67.5)
Ca	8.4 - 9.4 mg/dl	38.7%	(30.2 - 45.3)
iPTH	50 - 110 pg/ml	32.7%	(24.7 - 39.2)
Ca X P	<55 mg2/dl2	14.3%	(9.0 - 20.0)

PUB091

Relationship Between Young Adult Mean and Vascular Calcification in Patients with CKD on Maintenance Hemodialysis

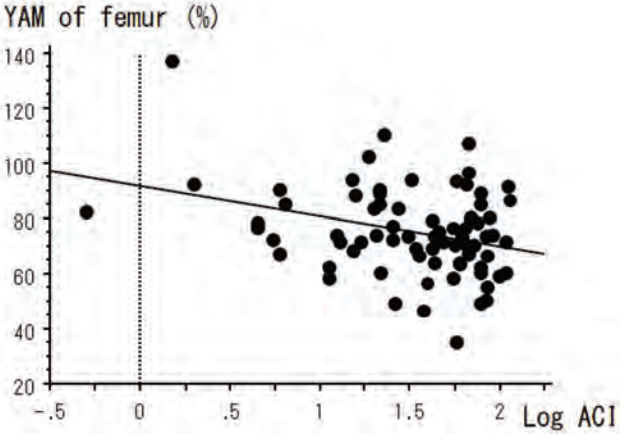
Wataru Fukao,[1,2] Yukiko Hasuike,[1] Tomoko Kimura,[1] Kosuke Mizusaki,[1] Yasuyuki Nagasawa,[1] Takahiro Kuragano.[1] *[1]Hyogo College of Medicine, Nishinomiya, Japan; [2]Takarazuka City Hospital, Takarazuka, Japan.*

Background: Patients with chronic kidney disease (CKD) often have osteoporosis and a high risk of bone fracture. Mineral bone disorder in CKD is associated with cardiovascular disease, although the mechanism remains unclear. The purpose of this study was to clarify the relationship between lower bone mineral density (BMD) and vascular calcification in patients with CKD on maintenance hemodialysis (MHD).

Methods: A total of 78 MHD patients were examined. BMD at the lumbar vertebral spine and femur were measured via dual-energy X-ray absorbsiometry by young adult mean (YAM). Factors related to bone marker (tartrate-resistance acid phosphatase 5b [TRACP 5b], bone specific alkaline phosphatase [BAP]), Ca, P, intact parathyroid hormone and 25-hydroxycalciferol [25(OH)D] were measured. Aortic calcification index (ACI) were measured by computed tomography, as previously reported.

Results: The patients' mean age ± SD was 66.1±11.1 years, and mean dialysis vintage was 7.4 years. YAM of femur was significantly lower than YAM of vertebra (YAM of femur [74.9±14.9%]; YAM of vertebra [91.3±18.0%], p<0.0001). YAM levels positively correlated with body weight, Ca, creatinine, albumin and 25(OH)D, and negatively correlated with TRACP 5b, BAP and ACI (r=-0.319, P=0.0044).

Conclusions: Lower BMD correlated with ACI in patients with CKD on MHD. These findings suggest that BMD is related ectopic calcification.



PUB092

Improving Control of Mineral Bone Disease in Peritoneal Dialysis Patients

Ryan Marinovich,[1] Robin Wigen,[2] Han Wang,[2] Nancy I. Woodcock,[4] Arsh Jain,[3] Elena Qirjazi.[2,3] *[1]Schulich School of Medicine, London, ON, Canada; [2]Schulich School of Medicine and Dentistry, London, ON, Canada; [3]London Health Sciences Center, London, ON, Canada; [4]London Health Sciences Centre, London, ON, Canada.*

Background: Peritoneal dialysis (PD) patients often have difficulty regulating their calcium (Ca), phosphate (PO4) and parathyroid hormone (PTH) levels, placing them at risk for mineral bone disease (MBD). Following Ca/PO4/PTH trends is key in evaluating the effectiveness of different treatments. However, out-patient laboratory blood work and physician shared-practice models in PD units make following these trends challenging. We

aim to increase the number of PD patients at our centre who meet targets for Ca/PO4/PTH levels by 15% within 9-12 months using quality improvement methods.

Methods: We developed a simple tracking tool which includes: a) the trend of individual patients' Ca/PO4/PTH values and subsequent interventions, and b) a treatment guide for MBD. The latter was generated from a combination of National Kidney Foundation KDOQI guidelines and local expert opinion. This tracking tool was rolled out at our PD Unit in October 2017. The primary outcome was the change in the proportion of patients (at clinic) who meet all three targets, before and after implementation of our tool. Baseline data was collected from a 12-week look-back window and an opinion survey of the stakeholders at our PD Unit. Post-implementation, we tracked uptake of our tool and elicited specific feedback from care-givers. We used Plan-Do-Study-Act (PDSA) quality improvement methodologies to continuously adjust the tool and its implementation.

Results: The opinion survey was completed by 16 health care professionals. 87.5% of respondents felt MBD management is poorly defined and 56% believed patient adherence is the biggest barrier. Baseline data indicated that 34.5% of our patients met targets for Ca/PO4/PTH. During PDSA cycle#1, 69.8% of charts utilized our tool and 37.2% of patients met targets (p=0.62). For PDSA cycle#2, the dietitian was recruited to champion our tool and uptake increased to 90.7%. The proportion of patients meeting targets rose to 44.2% (p<0.05, compared to baseline).

Conclusions: We achieved a 9.7% increase in the PD patients meeting Ca/PO4/PTH targets within 6 months by adjusting care-givers' behaviors, rather than patient factors. We will continue using PDSA methodologies to achieve our objective within 9-12 months.

PUB093

Change of Bone and Mineral Metabolism in Kidney Donors After Uninephrectomy: Prospective Observational Study

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Background: The aim of this study is to investigate whether uninephrectomy for kidney donation cause change of bone and mineral metabolism and also investigate factors associated with it in prospective kidney donors after uninephrectomy.

Methods: Serum and urine creatinine, calcium, phosphorus, and serum intact parathyroid hormone (iPTH), 25(OH) vitamin D values were obtained pre-donation and postoperatively in 32 donors. Renal fraction excretion rate of phosphate (FEpi) was calculated with 24-hour urine collection. Pre- and post-donation GFR was measured by DTPA scan in all donors. We defined post-donation chronic kidney disease-mineral bone disorder (CKD-MBD) as higher serum iPTH level than median (59.7 pg/ml) of all donors at post-transplant, and investigate factors associated with the development of CKD-MBD.

Results: After donor nephrectomy, MDRD eGFR declined (93.1 to 61.2 ml/min/1.73m^2) and remnant kidney's GFR measured by DTPA scan increased (53.9 to 63.8 ml/min), significantly. (both p<0.001) Post-donation serum iPTH increment was marked (56.8 Vs 47.4 pg/ml, p=0.055), and 25(OH) vitamin D level also rose (27.0 to 30.2 ng/ml, p=0.364). After donation, serum Ca was changed from 9.19 to 9.26 (p=0.181), serum phosphate changed from 3.4 to 3.3 (p=0.434). Renal fraction excretion rate of phosphate (FEpi) was increased after donation. (14.4 to 21.4, p<0.01) Compared with no-CKD group, CKD group showed higher increment of GFR by DTPA scan (15.1 Vs 8.6 ml/min/1.73m^2, p=0.069), higher increase of serum P level (+0.12 Vs -0.19, p=0.044), and higher change in serum Ca X P (1.4 Vs -1.7, p=0.04) In logistic regression analysis, after adjusting sex, age, BMI, pre-donation eGFR, the predictors of development of CKD-MBD was pre-donation FEpi. (OR 0.811, 95% CI 0.658-0.998, p=0.048)

Conclusions: Donor nephrectomy caused a significant change in bone and mineral metabolism in prospective kidney donors and pre-donation FEpi couble be a good predictive marker for early expecting development of CKD-MBD.

Funding: Government Support - Non-U.S.

PUB094

Serum Osteoprotegerin Is Associated with an Increased All-Cause Mortality in CKD Patients

Marek Stopinski,[1] Joanna Kaminska,[1] Krzysztof Mucha,[2,3] Anna Jedrzejczak,[2] Marta P. Soboniak,[2] Rafal Staros,[2] Monika A. Niewczas,[4,5] Leszek Paczek,[2] Bartosz Foroncewicz.[2] *[1]Department of Internal Diseases and Dialysis Unit, West Hospital of Saint Paul II, Grodzisk Mazowiecki, Poland; [2]Department of Immunology, Transplantology and Internal Diseases, Warsaw Medical Univeristy, Warsaw, Poland; [3]Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland; [4]Joslin Diabetes Center, Boston, MA; [5]Department of Medicine, Harvard Medical School, Boston, MA.*

Background: Bone related cytokines were reported to be linked to cardiovascular risk in chronic kidney disease (CKD) patients. The aim of this study was to assess the usefulness of osteopontin (OPN), osteocalcin (OC), osteoprotegerin (OPG) and fibroblast growth factor 23 (FGF23) as predictors of 5-year mortality in patients with different CKD stages.

Methods: The following study groups were enrolled: end stage renal disease (ESRD, n=38), stage 3 and 4 CKD (CKD3-4, n=19) and healthy controls (n=19). Blood samples were obtained at baseline to measure OPN, OC, OPG and FGF23 (ELISA or Luminex platform). 64-row computed tomography was performed to assess the calcium score. Patients were prospectively followed for 5 years to evaluate their all-cause mortality.

Results: All bone related cytokines concentrations significantly correlated positively with each other and had an inverse correlation to eGFR. Moreover, OPN and OPG were significantly correlated positively to calcium score, whereas OPG was associated with an increased risk of death in subjects with CKD3-4 or ESRD. The univariate logistic and Cox proportional hazard models analysis of incident all-cause mortality revealed odds and hazard ratios >4,4. whereas death hazard ratio in multivariate Cox analysis was 2,1 (Table).

Conclusions: We found that OPG correlated with declining eGFR, calcium score, other bone related cytokines and was associated with increased risk of all-cause mortality in patients with CKD3-4 or ESRD. Previous studies, mostly carried out in diabetic patients, suggested that OPG could be a biomarker for CKD progression. Our findings from the mixed population of diabetic and non-diabetic subjects at different CKD stages, provided new arguments to use OPG as a mortality predicting factor in CKD patients.

Logistic analysis and Cox proportional hazard models of incident all-cause mortality in subjects with CKD3-4 or ESRD at baseline (* p<0,05).

Biomarker	Univariate logistic analysis (CKD3-4 + ESRD)			Univariate Cox analysis (CKD3-4 + ESRD)			Univariate Cox analysis (ESRD only)		
	OR	95%CI	p value	HR	95%CI	p value	HR	95%CI	p value
Osteopontin	2,17 *	1,05 - 4,45	0,0355	1,74	0,95 - 3,18	0,0749	1,42	0,74 - 2,7	0,2904
Osteocalcin	0,96	0,5 - 1,85	0,9035	0,64	0,34 - 1,22	0,1727	0,61	0,32 - 1,19	0,1508
Osteoprotegerin	4,44 *	1,79 - 11,01	0,0013	5,81 *	2,17 - 15,56	0,0005	4,87 *	1,74 - 13,56	0,0026
FGF23	1,535	0,78 - 3,03	0,2172	1,23	0,59 - 2,59	0,5809	1,24	0,58 - 2,64	0,5814
				Multivariate Cox analysis					
Osteoprotegerin				2,16	0,68 - 6,86	0,1901			

PUB095

Medial Arterial Calcification: A Predictive Survival After Kidney Transplantation

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Background: Calcification detected from mammogram (MG) is exclusively medical arterial calcification (MAC) which is associated with morbidity and mortality in ESRD patients. The predictive value of MAC in kidney transplant recipients is unknown.

Methods: A retrospective cohort study of 305 kidney transplant recipients from 2012 to 2015 was reviewed and 51 female patients with ≥1 MG during pre-transplant period were included in this study. MAC is determined by linear calcified breast arteries detected in MG. The association between MAC and mortality was tested by using binary logistic regression analysis.

Results: Mean age±SEM is 57.08±1.47 years and mean duration of follow-up was 3.84±0.18 years. Of 51 patients, 20 patients had MAC prior to kidney transplantation. All laboratory related to mineral and bone metabolism were not different between MAC and non-MAC groups. Six patients died during study period with an incidence rate of 0.0306 person-years [Figure 1]. Five patients in MAC and 1 patient in non-MAC groups died. Patients in MAC group had 10 times higher the odd of death compared to non-MAC group (OR 10.000; 95%CI 1.070 to 93.437, p 0.043). After adjusted for presence or absence of diabetes, MAC group remains having higher mortality (OR 10.148; 95%CI 1.043 to 98.738, p 0.046).

Conclusions: Similar to non-transplant patients, kidney transplant recipients with MAC have significant higher mortality compared to those without MAC. Although kidney transplantation can reverse metabolic disarrangement, this may not be the main factors contributing to survival benefit of successful kidney transplantation.

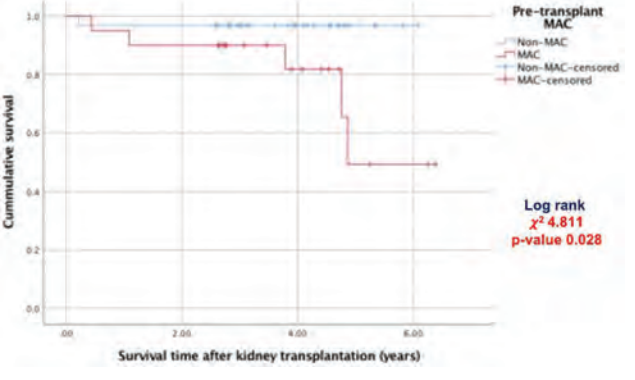

Figure 1: Kaplan-Meier curve demonstrates a significant higher mortality after kidney transplantation in patients with pre-transplant breast MAC compared to those without pre-transplant MAC.*MAC, medical arterial calcification*

PUB096

Arterial Stiffness Evaluated by Cardio-Ankle Vascular Index (CAVI) in Type 2 Diabetes Patients

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Background: Identification of early involvement of cardiovascular (CVD) and renal disease in type 2 diabetic patients (T2DM)is challenging. Cardio-Ankle Vascular Index (CAVI), a measurement of arterial stiffness with minimal operator dependence, could help recognize early vascular damage and the resultant CKD. We evaluated CAVI in T2DM patients who had no evidence of macrovascular diseaseand/orrenal insufficiency (estimated Glomerular Filtration Rate or eGFR≥60 ml/min/1.73m2).

Methods: CAVI was measured by VaSera1500 (Fukuda Denshi Co.) in 174 non old (≤ 60 years) T2DM patients (M/F = 100/74) diagnosed since <10 years and never on insulin therapy, and with CKD-EPI estimated GFR ≥60 mL/min /1.73 m2.

Results: Patients were 55.4±4.8 y.o., had a disease duration of 5.2±3.7 y, HbA1c of 6.4±0.9 % and eGFR of 93.5±10.8 ml/min /1.73 m2. None hadeGFR>125ml/min. Systolic blood pressure (SBP) was143,4±19,6 and diastolic (DBP) 87,6±8,7 mmHg. ACR averaged 21.9±58.3 mg/gr with pathologic values (≥30 mg/gr, indicative of CKD) in 11%. CAVI averaged normal values (7.9 ± 0.9) and was pathologic (higher than reference values for age) in 18%. Univariate analysis showed that CAVI correlated positively with age (p=.450; p<.001), Pulse wave velocity (r=.830; p <.001), Hb1Ac (r=.164; p<.05), and DBP (r=240; p<.01). Multivariate analysis confirmed age (p=7.41e-07) and DBP (P=0.014), and selected ACR (p=0.004) but not diabetes duration nor HbA1c as most predictive factors of CAVI.

Conclusions: In our population, age, ACR, and DBP are most relevant factors of arterial stiffness as measured by CAVI. Better than glycemic control and disease duration, CAVI could be a potential marker of early vascular damage indicating poor BPcontrol, endothelial dysfunction and/or CKD (as reflected by ACR).

PUB097

Identifying Patient Centered Strategies for Improving Cinacalcet Adherence

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Background: Cinacalcet is an effective pharmacological means of treating secondary hyperparathyroidism in patients with ESRD. However, high rates of non-adherence (50% to 85%) and discontinuation (67%) have been reported, limiting the potential benefits. We sought to investigate the underlying reasons for non-adherence and elicit patient directed interventions for improved adherence.

Methods: A sample of 25 patients from in an urban in-center hemodialysis unit who were prescribed Cinacalet for at least a month were administered a 16-item questionnaire during dialysis. These items addressed patient's self-reported adherence, barriers and potential targets for improving adherence. Demographic and laboratory data were extracted from medical records.

Results: All 25 patients were African American. Fifty-six percent were females and the mean age was 63 years. Despite 85% of patients reporting moderate to good adherence, only 5 (20%) had iPTH <600pg/ml. 20 patients (80%) were aware of the prescription, of these 17(85%) were able to identify the pill. Five patients (20%) were unaware of the medication and were unable to identify the pill. Medication refills was not a barrier for any patient. However, 6 (24%) were unable to afford medication due to high copay. Only 1 patient reported non-adherence due to diarrhea. Five patients (25%) identified medication administration during dialysis and 1 patient suggested more education as potential strategies to improve adherence. The majority of the patients did not think that additional education, pill-box management, medication reconciliation, or nursing reminders would achieve better adherence.

Conclusions: The majority of patients reported good to moderate adherence, yet very few had an iPTH at goal. Although 1/3rd of the patients were either unaware of the medication or were unable to identify it, they did not believe further education will be helpful. Unaffordability contributed to non-adherence in 25% patients. The common intervention suggested by the patients was administration during dialysis. As uncontrolled hyperparathyroidism has significant morbidity, we believe that administration of calcimimetics during dialysis and lower cost may hold the key to improved outcomes.

PUB098

Quantitative Systems Pharmacology Approach to Pharmacologic Management of Metabolic Bone Disorder in CKD

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Background: Metabolic Bone Disorder (MBD) is a frequent comorbidity and a risk factor in Chronic Kidney Disease (CKD). Achieving established goals for MBD-CKD treatment is challenging. We show a proof-of-concept feedback controller for pharmacologic management of MBD-CKD and test its feasibility *in sillico* across late stages of CKD.

Methods: In the management of MBD-CKD, the three therapeutic goals are serum concentrations of Calcium (Ca), Phosphorus (PO4), and Parathyroid Hormone (PTH). Here we focus on targeting PTH using a calcimimetic and a vitamin D analog. Based on a Quantitative Systems Pharmacology (QSP) model of Ca-PO4-PTH metabolism in a healthy human (GFR = 100), we developed a Model Predictive Control (MPC) algorithm for determining therapeutic concentrations of Cinacalcet and Calcitriol. We tested the feasibility of the algorithm at CKD stage IV-V (GFR = 30,20,10) targeting PTH concentration ≤ 100 pg/mL.

Results: The MPC algorithm successfully achieved target PTH concentration for all simulated CKD stages. Therapeutic concentrations of Cinacalcet and Calcitriol and the equivalent daily Cinacalcet doses are shown in the table below. An example of simulated of Ca, PTH, Cinacalcet and Calcitriol trajectories over time is shown in the figure. Concurrent dosing of Cinacalcet and Calcitriol results in a dose reduction of the calcimimetic.

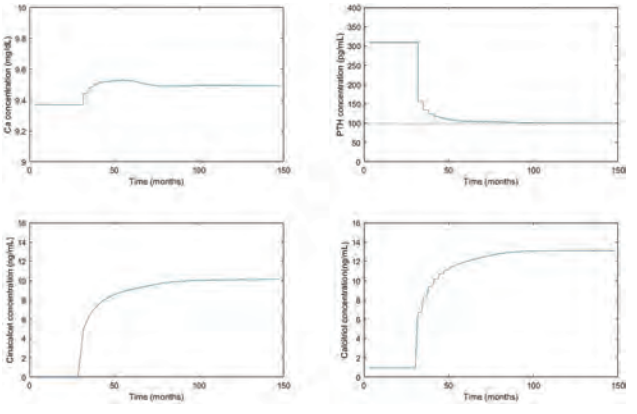
Conclusions: We developed a control algorithm for supporting pharmacologic management of PTH levels in MBD-CKD. *In silico* simulations at late stages of CKD demonstrate the algorithm feasibility. Our results also show the synergy between the calcimimetic and vitamin D.

Funding: Veterans Affairs Support

Therapeutic concentrations of Cinacalcet and Calcitriol as determined by the MPC algorithm

	Cinacalcet		Cinacalcet + Calcitriol	
GFR	Cinacalcet (dose)	Calcitriol	Cinacalcet (dose)	Calcitriol
30	5.0 (30)	22.8	2.0 (15)	25.7
20	9.7 (60)	12.4	6.3 (30)	21.2
10	13.8 (90)	0.9	10.1 (60)	13.1

concentration in ng/mL, dose in mg/day



Example of Cinacalcet and Calcitriol control at GFR of 10.

PUB099

Effect of Secondary Hyperparathyroidism on Bone Turnover Markers in ESRD

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Background: To investigate the effect of secondary hyperparathyroidism (SHPTH) with higher parathyroid hormone (iPTH) on the markers of bone turnover in maintenance dialysis patients.

Methods: The bone turnover markers in 38 patients with maintenance dialysis patients combined with secondary hyperparathyroidism were investigated. Twenty men and eighteen women, aged 28-72 years (median 50.61y), including 22 cases with hemodialysis, 16 cases with peritoneal dialysis, dialysis time 36~125 months (median 84.89). 38 cases with parathyroid nodule or adenoma, 15 cases (39.47%) were diagnosed of bone osteoporosis by X ray. 26 cases (68.4%) accompanied by arterial vessels, and or heart valves calcification, soft tissue calcification.

Results: Serum calcium was 2.32 ±0.16(range 1.87n2.64) mmol/L, and serum phosphorus was 2.17±0.51 (range 1.23~3.11) mmol/L. The level of serum iPTH was 1712.60±635.51(range 1009.00~3864.40)pg/ml, The iPTH of hemodialysis patients (1997.60±147.73 pg/ml) was significantly higher than that of peritoneal dialysis patients (1320.90 ±50.79pg / ml) (P < 0.01). Osteoclast biomarkers: β-CTX degradation products 5486.80 ±849.96 (range 3248.00 ~6025.00) pg/ml. Type I collagen amino terminal propeptide was 1135.90 ±173.34 (range 590.80~1223.00)ug/L. Osteocalcin N-terminal molecular fragment 267.30 ±56.81(range 104.80 ~ 326.00) ng/ml. Serum alkaline phosphatase 277.42 ±211.71(range 84.00~976.00)U/L. Alkaline phosphatase (ALP) in hemodialysis patients (349.18 ±252.97 U / L)was significantly higher than that in peritoneal dialysis patients (178.75±55.09U/L)(P<0.01). 1 month after Parathyroidectomy and autologous forearm transplantation in 3 patients, serum PTH:6.7~2.9pg/ml, β-collagen degradation product: 729.8~800.1pg/ml, Type I collagen amino terminal prepeptide: 138~789.3 ug/L, osteocalcin N-terminal molecular fragment: 17. 38~280.9 ng / ml.

Conclusions: The markers of osteoclasts and osteoblasts were significantly increased, suggesting that the increase of parathyroid hormone level in secondary hyperparathyroidism

significantly promoted bone turnover and made the patients in a state of high transport bone metabolism. The increase of parathyroid hormone and the excess of osteolysis may be an important cause of CKD-MBD osteoporosis in dialysis patients. The monitoring of bone turnover markers can provide a convenient method for dynamic assessment of bone transport status in dialysis patients.

Funding: Government Support - Non-U.S.

PUB100

Total Parathyroidectomy Combined with Autotransplantation Under Tracheotomy for the Fatal Uremic Leontiasis Ossea (ULO): A Rare Case Report

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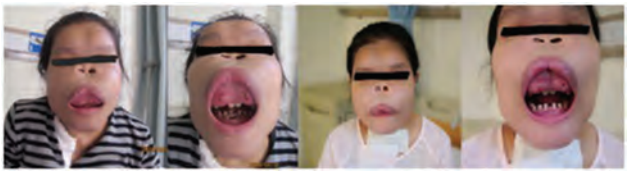
Introduction: ULO is a rare medical condition, which is characterized by overgrowth of the facial and cranial bones. The severe airway and esophageal deformities can lead to respiratory depression and eating difficulties. Here we report a rare case of parathyroidotomy with complications of ULO.

Case Description: A 25.Y.O Asian woman with ESRD due to glomerulonephritis had undergoing regular hemodialysis for 6 years. She has uncontrolled SHPT with developed severe ULO for 2 years. The level of serum iPTH was 3724pg/ml, serum calcium, phosphate and alkali phosphatase were 2.32mmol/L, 2.53mmol//L and 1155u/L, respectively. The ultrasonography showed four hyperplastic parathyroid glands. Facial deformity of patient was progressing and experienced difficulties with speaking, breathing, swallowing and chewing. Maintenance of the airway during procedural sedation is quite a challenging task for the anesthesiologist. Total parathyroidectomy was successfully carried out with the general anesthesia by tracheostomy. PTH values 24 hours after surgery was 11.9pg/ml, serum calcium 1.7mmol/L, phosphate was 1.11mmol/L, Patient bone pain disappeared and nasal airway improved right away after surgery. The tracheal tube was removed after 15 days intensive care for complications of tracheostomy. Patient has been discharged with improvement of facial deformation and will be close followed up.

Discussion: ULO of this condition is rare, the patientdeveloped numerous comorbid conditions including airway obstruction. Surgical intervention has been the only option. Because of the lack of cases published so far in the literature, proper surgical management is not developed. This is a unique case to show total parathyroidectomy can be successfully carried out under tracheotomy support for severe ULO.



Preoperative and postoperative comparison of frontal and lateral view of the 25-year-old woman with leontiasis ossea.

The state and parathyroid tissue after general anesthesia under endotracheal intubation.

PUB101

The Value Contribution of an Innovative Remote Monitoring of Longitudinal Estimated Glomerular Filtration Rate Trajectories in CKD Patients

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Background: CKD affects over 20 million Americans. Existing CKD prediction models are not generally applicable. Most CKD patients remain stable over the years; therefore repeated provider office visits represent expensive unnecessary care. CKD prediction is an inexact science. Current CKD prediction models are cumbersome and generally untested. Individual eGFR trajectories have increasingly become recognized as underutilized diagnostic/prognostic tools. The general consensus is that eGFR trajectories remain mostly linear. A new IT product, The CKD Express ©, developed in a 2012 University of Wisconsin Consortium MBA Class by a team including this author enables remote tracking of serum creatinine/eGFR trajectories. A retrospective study of eGFR trajectories in a patient database will demonstrate the practicality of this innovative CKD Care approach. This system would monitor CKD status of subjects in real-time, determine lab testing frequency using established algorithms and initiate appropriate referrals, as needed, for a population cohort that could involve thousands of subjects. Vermont with a mostly rural-based population, and given the Vermont State-UVMC ACO model of care, would benefit maximally from this efficient, effective, cost-effective yet affordable and very convenient, patient-centered and patient-friendly CKD Care paradigm.

Methods: A retrospective analysis of EMR-based patient records at the University of Vermont Medical Center, January 2008 - December 2017, of CKD III patients. Standard demographics including co-morbidities will be extracted. All serum creatinine/eGFR values will be recorded.

Results: Smoothed linear regression-based eGFR trajectories with spline models evaluated by Bayesian approach would be completed for every patient and correlated with observed renal outcomes: stable, progressive and need for RRT. Our hypothesis of accurate CKD prediction would be confirmed. This would be followed by the development of the new Software prototype, The CKD Express ©, utilizing intrinsic algorithms derived from the eGFR trajectories' analysis, decision support systems (DSS) tools, and artificial intelligence (AI).

Conclusions: The result would be a new innovative approach to CKD Care that is convenient, efficient, effective, affordable, patient-centered, patient-friendly, integrated and cost-saving.

PUB102

Albuminuria Is a Risk Factor for White Matter Hyperintensities on Brain MRI in Elderly Japanese: The Hisayama Study

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Background: Albuminuria and kidney dysfunction, which are determinants of chronic kidney disease, are acknowledged as independent risk factors for stroke. Similarly, white matter hyperintensities (WMH), which are often seen in cerebral magnetic resonance imaging (MRI) among the elderly, are reported to be associated with an increased risk of symptomatic stroke. The aim of the present study was to investigate the association of albuminuria and kidney dysfunction with WMH volume in a general Japanese elderly population.

Methods: A total of 1,214 community-dwelling Japanese subjects aged ≥65 years underwent brain MRI scans and a comprehensive health examination in 2012. Urine albumin-creatinine ratio (UACR) was categorized as normoalbuminuria (<30 mg/g) and albuminuria (≥30 mg/g). Subjects with normoalbuminuria were further divided into the following tertile categories: low-normal (≤7.3 mg/g), medium-normal (7.4-12.8 mg/g), and high-normal (12.9-29.9 mg/g). Kidney dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2. The severity of WMH was evaluated with the ratio of WMH volume to intracranial volume (WMHV/ICV). The association of UACR levels or kidney dysfunction with WMHV/ICV ratio was estimated using the analysis of covariance.

Results: The age- and sex-adjusted geometric mean value of the WMHV/ICV ratio increased significantly with higher UACR levels (low-normal: 0.18%, medium-normal: 0.21%, high-normal: 0.25%, albuminuria: 0.27%; P for trend <0.001). This association remained significant after additional adjustment for hypertension, diabetes mellitus, total cholesterol, body mass index, eGFR, electrocardiogram abnormalities, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI (P for trend =0.001). In contrast, there is no evidence of a clear association between kidney dysfunction and WMHV/ICV ratio.

Conclusions: Our data suggest that albuminuria, even within the normal range, is a significant risk factor for larger WMH volume in a general Japanese elderly population.

PUB103

Cardiometabolic Risk Factors Associated with Renal Function in Apparently Healthy Young: Cross Sectional Study

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Background: The Presence throughout life of hypertension, hypertriglyceridemia, diabetes mellitus, BMI ≥ 30, hyperuricemia and proteinuria, increase risk up to 7 times for the development and progression of CKD. The objective was to identify the prevalence and strength of association between cardiometabolic risk factors and kidney function in young adults (18-25 years of age).

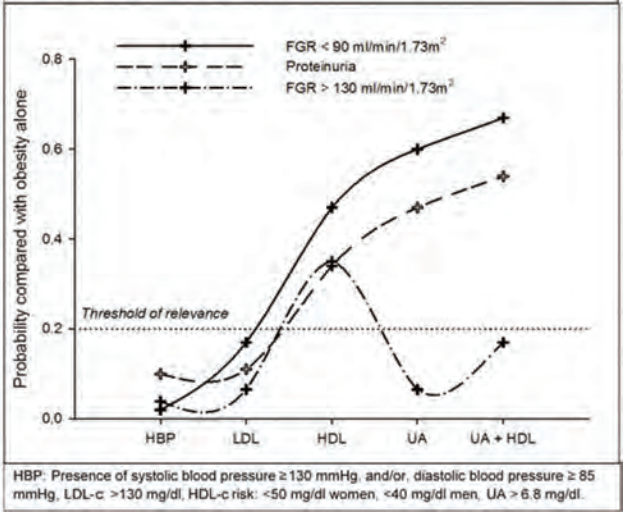
Methods: We included 5,531 apparently healthy young adults, with measurements of waist circumference, overweight and obesity (Ow/OB) by BMI, blood pressure risk systolic and diastolic (≥130/85 mmHg); hyperglycemia (≥100 mg/dl); hypertriglyceridemia (≥150mg/dl), HDL of risk (<40 mg/dl men, <50 mg/dl women), LDL of risk (> 130 mg/dl), hyperuricemia (> 6.8 mg/dl), insulin resistance (HOMA-IR,> 2.9 M,> 2.3 W),

and glomerular filtration rate (GFR) by CKD-EPI. Logistic regression was performed for adjusted OR (95%CI, p <0.05).

Results: The mean age was 19.3±1.6 years old; 76% (4130) presented at least 1 cardiometabolic risk factor for the development of CKD. Out of them 33% (1705) had GFR ≥130 ml/min/1.73m^{2}sc, 3% (157) GFR <90 ml/min/1.73 m^2, and 3% (170) proteinuria. Factors associated with GFR ≥130 were Ow/OB ORa 1.3 (95%IC 1.14-1.47), hyperuricemia ORa 0.2 (95%IC 0.15-0.26), HDL ORa 1.4 (95%IC 1.2-1.6) and IR ORa1.3 (95%IC 1.05-1.7). While hyperuricemia ORa 1.8 (95%IC 1.3-2.6), LDL ORa 1.66 (95%IC 1.05-2.6) and proteinuria ORa 3.4 (95%IC 2.07-5.7) were associated with GFR <90. Proteinuria was associated with hyperuricemia ORa 1.59 (95%IC 1.01-2.5) and LDL ORa 1.8 (95%IC 1.031-3.18). The coexistence of hyperuricemia, Ow/Ob and HDL of risk predict up to 70% the present of GFR> 90 or proteinuria. Fig 1

Conclusions: The coexistence of hyperuricemia, Ow/Ob and HDL of risk predicts the presence of renal failure in young adults. Early detection of cardiometabolic risk factors associated with CKD and the implementation of public health programs that favor its modification will contribute to the reduction of the risk of progression and development of CKD.

Figure 1. Probability of presenting alterations in renal function according to the presence of cardiometabolic risk factors



HBP: Presence of systolic blood pressure ≥ 130 mmHg, and/or, diastolic blood pressure ≥ 85 mmHg, LDL-c >130 mg/dl, HDL-c risk: <50 mg/dl women, <40 mg/dl men, UA > 6.8 mg/dl.

PUB104

Triglycerides and Cardiovascular Disease in Patients with CKD: Results from the SHARP Trial

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Background: Triglycerides (TG) may contribute to the high cardiovascular disease (CVD) risk of patients with chronic kidney disease (CKD). This study evaluated associations of TGs and other lipids with CVD in patients with CKD.

Methods: Analyses were conducted in 9,270 participants with CKD in the Study of Heart and Renal Protection (SHARP) including 3,023 participants on dialysis. Cox regression methods were used to evaluate the association of selected lipids and lipoproteins with incident atherosclerotic (AVE) and non-atherosclerotic vascular events (NAVE).

Results: Median TG concentrations were 1.9 mmol/L (168 mg/dl). During a median follow up of 4.9 years, 1406 participants experienced at least one AVE. Higher baseline TGs were modestly associated with AVE (hazard ratio (HR) per 1.5x higher concentration 1.07; 95% CI 1.00-1.13) with no evidence of effect modification by kidney function (p=0.95). The TG to high-density lipoprotein cholesterol ratio (TG/HDL) was significantly associated with AVE (HR per 1.9x higher TG/HDL 1.10; 95% CI, 1.03-1.18). Significant inverse associations with NAVEs were found for TG (HR per 1.5x higher concentration 0.86, 0.81-0.92) and TG/HDL (HR per 1.9x higher ratio 0.88, 0.82-0.94).

Conclusions: High TG concentrations and TG/HDL ratio were independently associated with AVE. The observed inverse associations with NAVE may reflect non-causal associations. Future studies should determine if treatments targeting TG and TG-rich lipoproteins decrease atherosclerotic cardiovascular risk in patients with CKD.

PUB105

Effect of Diabetes Mellitus on Incidence and Progression of CKD in General Japanese

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Background: To study the effects of diabetes mellitus on incidence and progression of chronic kidney disease (CKD) in general population of Japanese.

Methods: This is a retrospective cohort study using health checkup data in Iki City, Nagasaki Prefecture, Japan. The participants of the study included 5,554 residents aged 40 years or older who attended health checkups twice or more over 8 years. This study consists of 2 sets of analyses: (1) the effects of diabetes mellitus on new-onset CKD (defined by an estimated glomerular filtration rate (eGFR) less than 60 mL/min or positive urinary protein) among 4,571 subjects who did not have CKD at the initial health checkup, and (2) the effect of diabetes mellitus on progression of CKD (defined as exacerbation of the GFR category or the proteinuria category) in 983 subjects with CKD at the initial health checkup.

Results: Over a mean follow-up period of 4.6 years, 746 patients with new-onset CKD and 189 patients with CKD progression were confirmed. The incidence of CKD (per 1,000 person-years) in individuals with diabetes mellitus was 55.1%, which was higher than those without diabetes mellitus (33.9%). This correlation was significant (multivariate adjustment [hazard ratio (HR)] 1.44, 95% confidence interval [CI] 1.13-1.84) even after adjusting for the effects of other risk factors. The population attributable fraction was 3%. Similarly, the risk of CKD progression was also significantly higher in individuals with diabetes mellitus than in those without (HR 2.24, CI 1.57-3.19), and the population attributable fraction was 13%.

Conclusions: Diabetes mellitus is a significant risk factor for both new-onset CKD and CKD progression in general population of Japanese. Approximately one-sixth of CKD progression was likely to be attributable to diabetes mellitus.

PUB106

Renal Function Is Preserved During Ketoanalogue Supplementation but Declines After Supplementation Is Withdrawn - A Follow-Up of Randomized Clinical Trial

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Background: We reported preservation of renal function and nutritional status in patients who were noncompliant to vLPD supplemented by ketoanalogues. The aim of the study was to evaluate i) if very low protein diet (vLPD) given along with ketoanalogue in CKD patients retards progression of CKD based on GFR. and ii) is the renal function maintained after withdrawing ketoanalogue supplementation.

Methods: 40 CKD patients were randomized into two groups: Group 1 (Intervention) patients were supplemented with 6 tablets of ketoanalogue for 10 months. Patients were advised very low protein diet 0.4 g/kg/day. Group 2 (Control) patients were given conservative treatment with 0.6 g/kg/d protein restriction. Dietary assessment was done at visit 1 and at visit 2 (10 months), Nutritional Assessment was evaliated with SGA score. GFR and serum albumin were evaluated at baseline and at 10 months. After 10 months ketoanalogue supplementation was stopped. and patients were followed up for two years.

Results: At baseline, the GFR was higher in controls (51.14±15.1 ml/minute). compared to intervention group (47.79±13.2 ml/minute). GFR declined in the control group from 51.14 ml/min at baseline to 35.5±7.94 ml/minute after 10 months. In intervention group the GFR remained stable at 47.79±13.2 ml/minute. The serum albumin level decreased from 3.8±0.90 g/dL to 3.09±0.38 g d/l in control group, while the levels were maintained at 4.11±0.43 in intervention group. In ketoanalogue group decline in GFR was 3.5 ml/min in 10 months while in the control group decline in GFR was 16 ml/minute in 10 months. In ketoanalogue group patients did not comply to low protein diet, in stead they consumed normal protein diet 0.62±0.24 g/kg/d. After 10 months ketoanalogue supplementation was stopped and patients were followed up for two years. Gradual decline in GFR from 47.79±13.2 ml/minute to 28.0 ml/minute and in serum albumin (declined) from 4.11±0.43 to 3.6 g/dL was observed. Serum creatinine decreased from 1.61±0.52 to 1.40±0.52 during ketoanalogue supplementation and increased to 2.2 mg% after stopping ketoanalgue within 2 years. There was no change in the dietary pattern.

Conclusions: Ketoanalogue supplementation is an effective way of preserving renal function and nutritional status. without adherence to vLPD.

PUB107

The Approach of Non-Nephrologist Medical Practitioners to Abnormal Urinalysis and Kidney Function Test

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Background: Chronic kidney disease (CKD) is a devastating medical condition with a negative impact on the individual patient and the whole community. Primary screening for the high-risk group of patients is a crucial issue for early intervention and mitigation the progression of disease or at least minimization its complications. The aim of our study to evaluate the knowledge, attitude, and practice for non-nephrologist medical practitioners to abnormal renal function test.

Methods: A cross-sectional, KAP study conducted among the medical practitioners who are working in Najran city. A structured, self- administered questionnaire which consists of 20 items has been distributed to the targeted population.

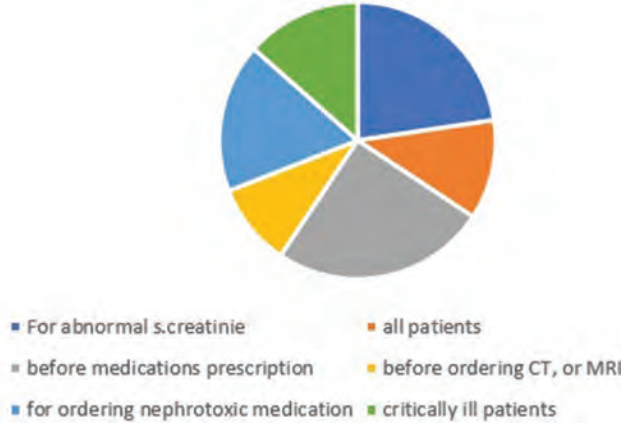
Results: The total number of responders is193. Around 80% of them routinely screen the high-risk patients for CKD. Regarding the approach to abnormal active urine sediments, a 25% of responders are preferred to consult the nephrologist, while the remaining are either prefer to repeat the test or to do further investigations. Regarding high serum creatinine, a 38% of them used to directly referred such patient to nephrologist while the others either they used to repeat the test or doing further investigations including imaging. Surprisingly, only 26% of the responder only used to calculate glomerular filtration rate (GFR) and most of them are not aware of the new equations for eGFR.

Conclusions: Most of the non-nephrologist medical practitioners are aware of CKD diagnosis, most of them they are aware when and whom to refer to a nephrologist. They need more orientation for interpretation of abnormal urinalysis and the proper way for calculation of eGFR.

Approach to abnormal urinalysis

	Repeat urinalysis immediately	Repeat with proper collection	Check Renal function	Check urine protein	Consult nephrologist	Take others opinion (non-nephrologist)	No action	urine culture	start treatment
Urine RBCs	9.1%	20%	28%	8.6%	25.7%	8.6%			
Urine WBCs	7.7%	23%	23%	6.6%	23.5%	11.5	1.1%	2.2%	1.6%
Urine casts	8.2%	10.3%	29.3%	2.7%	40.8	8.2%			0.5%
Proteinuria	8.2%	13.2%	30.8	7.1%	34.6%	5.5%			0.5%

RBCs = red blood cells, WBCs = white blood cells



PUB108

The Importance of a Multifaceted Care Approach for CKD

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Background: It is well known that chronic kidney disease (CKD) patients have several comorbidities such as anemia, hypertension, hyperuricemia, and CKD-MBD. To prevent the progression of CKD or adverse events in these patients, multifaceted care approaches by nephrologists are needed. In this study, we evaluated the effect of a multifaceted care approach by nephrologists on the progression of CKD.

Methods: The study was an observational study in a single center for a period of 3 years. In 88 patients with various stages of CKD (not HD) who were treated by nephrologists, blood levels of Hb, ferritin, iron, total iron-binding capacity (TIBC), and albumin were measured every 3 months, and high sensitive C reactive protein (hsCRP), β2microglbulin (MG), and intact-parathyroid hormone (iPTH), in addition to urinary sodium, potassium, calcium, phosphorus protein, and β2MG levels, were measured every 6 months. All patients were treated according to the clinical practice guideline for CKD (Japanese Society of Nephrology 2013).

Results: (Progression of renal dysfunction) In multiple regression analysis, baseline blood level of Hb (β=0.5, P<0.001), int-PTH (β=-0.33, P=0.001), vitamin D 125 (β=0.26, P=0.006), urinary phosphorus (β=0.33, P=0.001), urinary β2MG (β=-0.23, P=0.03) and urinary protein (β=0.28, P=0.02) were selected as predictors of estimated glomerular filtration rate (eGFR) or 1/ creatinine(Cr) at the end of the study. (Progression of renal anemia) Although there was no significant correlation among Hb level, serum ferritin and TSAT, serum phosphorus level (β=-0.24, P=0.03) and urinary logβ2MG (β=0.25, P=0.02) were selected as predictors of future Hb levels. (Risk factors for the initiation of RRT and adverse events) In the Cox hazard model, low calcium (HR: 0.37, P=0.03), high phosphate (HR:5.90, P<0.001), low 125 vitamin D (HR: 0.94, P=0.01), high int-PTH (HR:1.02, P<0.001) level, use of a phosphate binder (HR: 4.95, P=0.01), and use of vitamin D (HR:3.75, P=0.01) are selected as risks for initiation of RRT.

Conclusions: In this study, we found that although phosphate binder or vitamin D was administered appropriately, CKD-MBD factors (phosphate, calcium, vitamin D, int-PTH) were related with anemia progression, renal dysfunction and RRT initiation. With the multifaceted care approach for CKD, the focus on CKD-MBD related factors appeared to reduce the risk of CKD progression or RRT initiation.

PUB109

Relationship Between Sleep Duration and Kidney Function in General Adults: A Systematic Review and Meta-Analysis

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Background: The possible relationship between the duration of sleep and chronic kidney disease related disease are not clear. This study aimed to determine the relationship in general adult populatiion.

Methods: We searched MEDLINE, EMBASE, Cochrane Library from database inception to November 20, 2017. The studies related to sleep duration and chronic kidney disease in general adult population were included. Sleep duration was grouped into 3 categories, short sleep (< 6h), reference (≥ 6h %<8h), long sleep (≥ 8h). We included studies which reported odds ratio (OR) comparing the risks of chronic kidney disease, proteinuria and renal hyperfiltration. Pooled OR and 95% confidence intervals (CI) were calculated using the random-effect model with Stata 12.0 software.

Results: A total of 12 studies divided into 17 substudies were analyzed in this meta-analysis, covering 682,449 patients. Sleep duration had no significant risk of chronic kidney disease. There was a higher risk of proteinuria (OR = 1.38, 95% CI = 1.13 – 1.67) in short sleep group, while renal hyperfiltration (OR = 1.04,95% CI = 0.93 – 1.18) not. Long duration sleep had a higher risk of proteinuria (OR = 1.35, 95% CI = 1.17 – 1.54) and renal hyperfiltration (OR = 1.08, 95% CI = 1.01 – 1.15).

Conclusions: Though there was no significant association between sleep duration and chronic kidney disease, we suggested a potential association of proteinuria in both long and short sleep duration group, while not being with renal hyperfiltration. Objective sleep measurements and more cohort studies should be considered in future epidemiological studies.

PUB110

Validation of Self-Reported Race in a Provincial Renal Administrative Database

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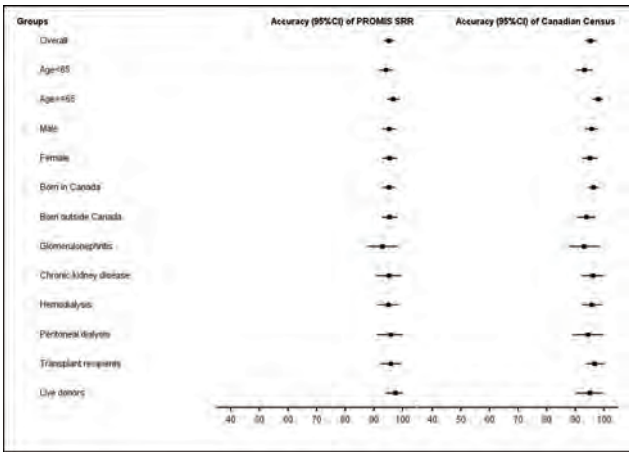
Background: Administrative data is commonly used to study clinical outcomes in renal disease. Race is an important determinant of renal outcomes but is not validated in most administrative data, and the correlation with census-based definitions of race is unknown. We validated self-reported race (SRR) in a Canadian provincial renal administrative database (PROMIS) from British Columbia using a prospective patient survey and compared it to the Canadian census categories of race.

Methods: This is a cross sectional telephone survey of a random sample of all adults in PROMIS conducted from 02/2016 to 11/2016. Responders selected a race category from PROMIS and from the Canadian census. Sensitivity (Sn) and specificity (Sp) were calculated with 95% confidence intervals (CI).

Results: 21,039 patients met inclusion criteria, 1,677 were selected for the survey and 637 participated (38% response rate). There were no differences between the PROMIS, sampled and responder populations. PROMIS SRR had an accuracy of 95.3% (CI 94.2-97.0%) when validated against the survey SRR with Sn and Sp ≥90% in all race groups except in Aboriginals (Sn 87.5%). The positive and negative predictive values were ≥95%, except in very low and high prevalence groups, respectively. The Canadian census had an accuracy of 95.7% (CI 94.4-97.6%) when validated against PROMIS SRR with Sn and Sp ≥90%. The results did not differ in subgroups based on age, sex, birth outside Canada, or renal group (glomerulonephritis, chronic kidney disease, hemodialysis, peritoneal dialysis, transplant recipients or live donors).

Conclusions: We have shown high accuracy of PROMIS SRR that validates its use in the secondary analysis of administrative data for research. There is high correlation between PROMIS and census race categories which allows linkage with other data sources that use census-based definitions of race.



Accuracy of PROMIS SRR and census race categories with 95%CI, overall and for individual subgroups

PUB111

CKD Monitoring in Routine Clinical Practice: An Analysis of a National Laboratory Database

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Background: Published guidelines for chronic kidney disease (CKD) have existed for many years, but guideline implementation remains inconsistent in clinical practice. We evaluated the frequency of guideline-based CKD monitoring for patients with laboratory evidence of CKD in a data set from a national laboratory.

Methods: We identified all patients who had at least 2 eGFR results below 60 ml/min/1.73m2 at least 3 months apart based on serum creatinine testing performed at a LabCorp facility between November 2011 and April 2018. We then analyzed whether certain guideline-recommended tests (urine albumin/creatinine ratio (UACR), serum phosphorus (P), plasma parathyroid hormone (PTH), and LDL cholesterol (LDL-C)) were performed a) within 1 year of or b) at any time after the first qualifying eGFR result.

Results: Among the 4,909,840 patients who met criteria for the study, 58.2% were women. Mean age was 71.2 ± 12.0 years. Median follow-up was 25.7 (IQR=12.2 – 45.8) months. The percentage of patients in stage 3a, 3b, 4, and 5 based on the initial eGFR result were 70.3%, 21.9%, 6.3%, and 1.5%, respectively. At 1 year, rates of testing for UACR, PTH, and P were 24.4%, 11.8%, and 16.9%, respectively. Any time testing rates were only slightly higher: 35.4% (UACR), 20.5% (PTH), and 25.3% (P). However, rates of LDL-C testing at 1 year (75.5%) and any time (84.4%) were much higher, indicating that other routine testing was being performed on these patients.

Conclusions: Despite guideline recommendations, routine laboratory testing for CKD and its comorbidities remains low in US clinical practices. This data highlights the need for further strategies to improve CKD evaluation and management.

PUB112

Predicting the Progression of CKD to Kidney Failure in a Southeastern US Population

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Background: There are >100,000 adults transitioning from chronic kidney disease (CKD) and end stage renal disease (ESRD) with a geographic disparity of ESRD incidence in the Southeastern U.S. We aimed to determine the risk factors associated with progressing from CKD to ESRD in a Southeastern population.

Methods: Adult (18<age<100) CKD Stage 3-5 patients of a large, Southeastern integrated healthcare system (2010-2017) were included in the cohort. CKD and ESRD were defined using diagnosis codes. Risk factors were collected at the time of CKD diagnosis. Descriptive statistics and Cox proportional hazard models were completed to determine the association and predictive power of the risk factors.

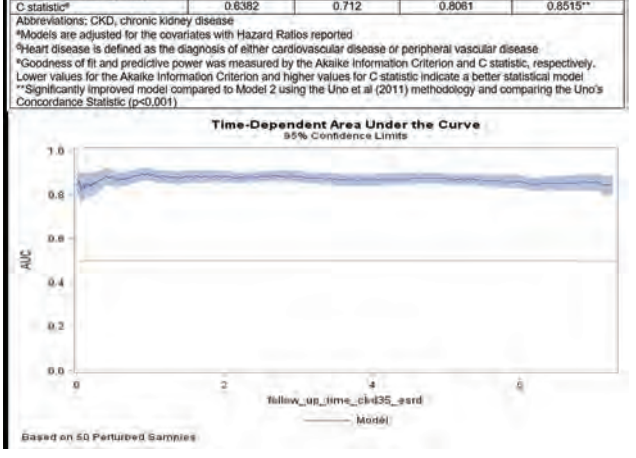
Results: Among 3,399 patients, 442 (13%) started dialysis with average age was 58, 60.4% were male, 71% Black, and the average estimated glomerular filtration rate was 31.0 per 5 mL/min/1.73m². Among those with ESRD, the average time between CKD and ESRD was 1.6 years, with Blacks having a significantly longer time (2.4±2.1) vs Whites (1.8±1.5) (p=0.01). In the fully adjusted model 4, Blacks (vs White), and patients with hypertension were 2.3 (HR=2.3; 95% CI 1.8, 3.0), and 2.5 (HR=2.5; 95% CI 1.2, 5.3) times more likely to transition to ESRD, respectively. Model adjustment improved predictive power and Goodness of Fit, with model 4 (c-statistic=0.8515). The area under the curve for the fully adjusted model remained stable around c=0.85 during follow-up time 0-6 years.

Conclusions: A predictive model using clinically routine variables can predict CKD progression to ESRD. Healthcare systems should consider integrating predictive analytics in their routine clinical visits to help alert them to a patient's increased risk for ESRD to enable timely intervention.

Figure 1. Hazard ratios, Goodness of Fit, and Predictive Power of survival models predicting the risk factors associated with CKD progression to dialysis, and time-dependent area under the curve for the final adjusted model (Model 4)

	Models[a]			
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Risk Factors at time of CKD diagnosis				
Age	0.98 (0.97, 0.98)	0.96 (0.95, 0.97)	0.98 (0.97, 0.99)	0.97 (0.97, 0.98)
Gender (ref=Female)	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)	1.7 (1.4, 2.0)	1.6 (1.3, 1.9)
Race (ref=White)				
Black	1.9 (1.5, 2.4)	1.7 (1.3, 2.2)	2.5 (2.0, 3.2)	2.3 (1.8, 3.0)
Other	1.7 (1.1, 2.9)	1.7 (1.0, 2.8)	1.3 (0.8, 2.1)	1.3 (0.8, 2.2)
Unknown	2.3 (1.5, 3.7)	2.1 (1.3, 3.3)	2.2 (1.4, 3.5)	2.1 (1.3, 3.3)
Systolic Blood Pressure		1.01 (1.01, 1.02)		1.00 (1.00, 1.01)
Diastolic Blood Pressure		1.00 (1.00, 1.01)		1.01 (1.00, 1.01)
Diabetes		1.7 (1.4, 2.1)		1.6 (1.3, 2.0)
Hypertension		3.0 (1.4, 6.5)		2.5 (1.2, 5.3)
Heart disease[d]		2.1 (1.7, 2.6)		1.4 (1.1, 1.7)
Estimated Glomerular Filtration Rate per 5mL/min/1.73 m²			0.93 (0.92, 0.94)	0.93 (0.92, 0.94)
Serum Calcium per mg/dL			0.81 (0.69, 0.95)	0.85 (0.72, 1.01)
Serum Albumin, per 0.5 g/dL			0.43 (0.36, 0.50)	0.45 (0.38, 0.53)
Serum Phosphate per 1.0 mg/dL			1.2 (1.1, 1.4)	1.2 (1.1, 1.4)
Model Performance Measures				
Akaike Information Criterion[a]	6591.7	6425.4	5830.4	5784.8
C statistic[a]	0.6382	0.712	0.8081	0.8515**

Abbreviations: CKD, chronic kidney disease
[a]Models are adjusted for the covariates with Hazard Ratios reported
[d]Heart disease is defined as the diagnosis of either cardiovascular disease or peripheral vascular disease
[a]Goodness of fit and predictive power was measured by the Akaike Information Criterion and C statistic, respectively. Lower values for the Akaike Information Criterion and higher values for C statistic indicate a better statistical model
**Significantly improved model compared to Model 2 using the Uno et al (2011) methodology and comparing the Uno's Concordance Statistic (p<0.001)



PUB113

Retrospective Observation of the Prevalence of Proteinuria in a Newly-Diagnosed HCV Population

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Background: In response to a growing Hepatitis C (HCV) epidemic, many states are mandating screening programs for high risk populations to facilitate HCV treatment. Despite the well-recognized risk of chronic kidney disease (CKD) in patients with HCV, currently there are no guidelines for CKD screening. Given Pennsylvania's new mandate for HCV screening and CKD risk, we assessed the prevalence of dipstick positive proteinuria in newly-diagnosed HCV positive patients without history of CKD. The goal of this study was to explore the potential for early-detection of CKD in this high risk population.

Methods: A cross-sectional retrospective analysis was performed using data collected from electronic medical records of patients who were screened, diagnosed, and/or treated for HCV at Temple University Hospital, an urban tertiary care center in North Philadelphia in 2017. For identification of possible early-stage CKD, this analysis reviewed the availability and results of urine protein assessment after HCV diagnosis in patients with eGFR>60 ml/min. Data collection included demographics, comorbidities, eGFR, and urinalysis. Overt proteinuria was defined as urine dipstick with protein >1+. Positive proteinuria findings were excluded in samples with diagnosis of UTI, hematuria, or glycosuria.

Results: Of the 637 patients identified as HCV-positive, 498 had eGFR > 60 ml/min. The mean age was 52.4 ± 13.1 and 67.7% were male. Urinalysis was obtained in 199 patients (39.9%). Eighteen urine samples were excluded from qualitative analysis. Overall, 34 of 181 patients (18.8%) had overt proteinuria. Of these 34 patients, one was evaluated for proteinuria by a nephrologist within the Temple Health System.

Conclusions: Proteinuria is an early marker of CKD and its detection within high-risk populations may be beneficial. Our findings indicate a minority of HCV positive patients had urine evaluation after HCV diagnosis. The prevalence of overt proteinuria in our study was higher than reported in the general US population in NHANES (18.8% vs 1.3% respectively). Nephrology referral was infrequent. Although there are some limitations, these preliminary findings highlight the need for further investigation of CKD screening

in various high risk populations. Further prospective studies are needed to validate these results and outcomes of early detection.

PUB114

The Effect of CKD Risk Factor Scorecard Intervention Among Patients with Non-Dialysis CKD

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Background: Long-term management of chronic kidney disease (CKD) requires high-level patient involvement. Mayo Clinic developed a scorecard that contains 12 items of CKD risk factors to improve self-management skills for the purpose of reducing risk factors and slowing the progression of CKD. In this study we aim to compare the prognosis of patients of CKD3 with and without CKD Risk Factor intervention.

Methods: A single-center retrospective cohort study was performed using electronic medical records (EMR). Cases were included when patients (≥18 years) were followed up for at least 1 year or progressed to end-stage renal disease (ESRD) within 1 year from January 2009 to December 2017. Time-to-event analyses were performed with Kaplan–Meier method, and the time progressing to the ESRD in two groups was compared using log-rank test.

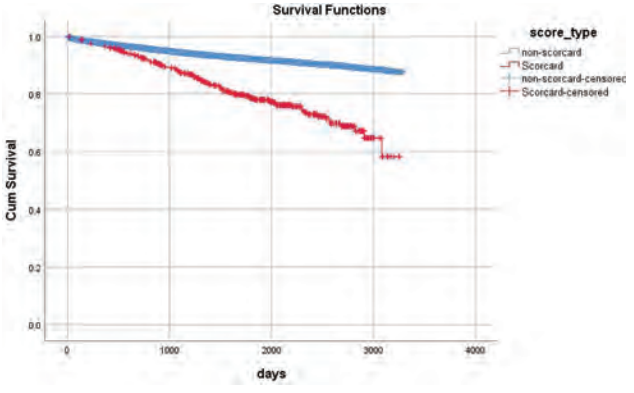
Results: We analyzed data of 19,973 patients (553 in scorecard group). The mean age was 73.03±12.71 years, 54.2% were male and 2.9% were African American. Kaplan-Meier analysis showed that renal survival was significantly lower in scorecard group compared with non-scorecard group (Log-rank test, p= .000).

Conclusions: The CKD Scorecard intervention isn't associated with progression reduction of kidney disease. Further studies are needed to explore the method of evaluating self-efficacy and the potential role of risk factors in the progression of CKD.

Funding: Government Support - Non-U.S.

CKD Risk Factor Scorecard

BP control is at goal (goal is < 130/80 mm/Hg)	Y-(1) N-(0)
Microalbumin is < or = to last visit	Y-(1) N-(0)
LDL (goal is < 100 mg/dl)	Y-(1) N-(0)
Alcohol ≤ previous use (goal is less than 1 drink for women and 2 drinks for men/day)	Y-(1) N-(0)
Weight < or = previous, or is at ideal weight	Y-(1) N-(0)
Hemoglobin is at goal (goal is 9-11 g/dL)	Y-(1) N-(0)
Calcium and phosphorus are normal	Y-(1) N-(0)
Anticoagulant use	Y-(1) N-(0)
Tobacco use	N-(1) Y-(0)
Dietary effort (low salt, low fat, or diabetic diet)	Y-(1) N-(0)
Cardiovascular exercise (3-5 x week for 30 minutes)	Y-(1) N-(0)
Hemoglobin A1c is at goal (goal is ≤ to 7.0%)	Y-(1) N-(0)



PUB115

Affective Status, Disease Knowledge, and Treatment Adherence in CKD Mexican Patients

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Background: CKD is a public health concern and low adherence to treatment has been associated with poor health outcomes. Low adherence to treatment varies between 20%-70%. Multidisciplinary care (MDC) could improve management and outcomes of patients with CKD. We evaluated the prevalence of the affective status, depression, disease knowledge, and treatment adherence in CKD patients attending our MDC clinic.

Methods: A cross-sectional study in a convenience, non-probabilistic sample of pre-dialysis CKD patients, stage 3-5. Individuals were interviewed by psychologist with no time limitation. Measures: KiKS and PSS, Spanish versions; Adherence Scale for Chronic Patient Based on Explicit Behaviors; PANAS; Personality Inventory for DSM-5 (PID-5)-Adult, Depression and Anxiety Subscales.

Results: Table 1, Fig 1

Conclusions: Our results showed that a coordinated MDC can improve management and quality of care in patients with CKD, as demonstrated by the high levels of positive affect, disease knowledge, self-efficacy, and treatment adherence found in our study. Further research is needed to evaluate the program component effectiveness in CKD progression and management.

Results

	n=17
Age (y)	53.41 ± 15.87
Male (%)	10 (58.8)
Married	9 (52.9)
Illiterate Primary school Junior High-School Other	2 (11.8) 2 (11.8) 7 (41.25) 8(35.6)
Housewife Self-employed	6 (35.3) 5 (29.4)
DM (%)	7 (41.25)
Scr (mg/dL)	2.75 ± 0.99
eGFR (ml/min/1.73 m2)	27.73 ± 14.49
Time known to have CKD (y)	4 (1-9)
Disease Knowledge	0.77 ± 0.063 (High)
Positive Affect - Medium Positive Affect (%) - High Positive Affect (%)	3.20 ± 0.57 (High) 5 (29.4) 12 (70.6)
Negative Affect - Low negative affect (%) - Medium Negative Affect (%) - High Negative Affect (%)	2.31 ± 0.86 (Low) 9 (52.9) 7 (41.2) 1 (5.9)
Anxiety Level - Low (%) - Moderate (%) - High (%)	1.40 ± 0.71 (Moderate) 5 (29.4) 7 (41.2) 5 (29.4)
Depression Level - Low (%) - Moderate (%) - High (%)	0.53 ± 0.74 (Low) 13 (76.5) 2 (11.8) 2 (11.8)
Stress level - Without perceived stress (%) - Very low - Moderate (%) - High (%)	1.40 ± 0.74 (Low) 5 (29.4) 8 (47.1) 3 (17.6) 1 (5.9)
Treatment adherence - Adherence to medications and food - Behavioral medical persuit - Self-efficacy - Adherence to medications	94.0 ± 4.31 (High) 88.48 ± 7.75 (High) 98.31 ± 2.21 (High) 95.21 ± 5.99 (High) 89.60 ± 10.4 (High)

Spearman Correlation of study variables

	Behavioral Medical Persuit	Adherence to medication	Positive Affect
Self-Efficacy	r= 0.573 p < 0.05	r= 0.797 p < = 0.05	
Age	r= 0.795 p < 0.01		
Negative Affect		r=0.524 p >0.05	
Time with CKD (y)			r= 491 p < =.05

PUB116

Risk Factors for CKD Progression to ESRD: Experience on 15 Years Follow-up in the Multidisciplinary CKD Clinic

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Background: Chronic kidney disease (CKD) is a significantly worldwide health problem. Risk of CKD progression under holistic approach in developing countries are scarcely studies. Our aim was to investigate risk factors for chronic kidney disease progression to end-stage renal disease (ESRD) with dialysis in the multidisciplinary CKD clinic.

Methods: The retrospective cohort study was conducted in the CKD clinic at Srinagarind, A University Hospital in Thailand during January 1, 2000, to December 31, 2015. Our CKD clinic has been established for 15 years with multidisciplinary and holistic cares that include a nephrologist, nurse educator, dietician, pharmacist and physical therapist. The adult CKD patients who followed up at least 6 months were recruited. The medical and laboratories data every 6 months were recorded.

Results: Of 506 CKD patients were recruited, the mean age was 65.2 ± 13.5 years and mean follow up time was 41.5 ± 34.8 months. The majority CKD stage that physician refer to the specialist was CKD stage 4. The incidence rate of dialysis was 5/1000 patient-months. The overall renal survival rate in CKD clinic at 50 and 100 months were 75, 50 %, respectively. The overall mean slope of the estimated glomerular filtration rate decline

was -2.67 mL/min/1.73m² in the first year of follow-up. The results of multivariate Cox regression model showed that age > 55 year (hazard ratio[HR] 0.46, 95% confidence interval[CI] 0.30-0.72), diabetes (HR 1.56, 95%CI 1.04-2.33), hypertension (HR, 4.00, 95%CI 1.44-11.0), renal cancer (HR 2.67, 95%CI 1.13-6.30), CKD stage 4 (HR 15.95, 95% CI 2.17-117.2), and CKD stage 5 (HR 93.67, 95%CI 12.5-700.1) were independent association risk factors for ESRD with dialysis.

Conclusions: This study demonstrated that diabetes, hypertension, and referral to nephrologist with advanced CKD stage are independent predictors of dialysis-dependent ESRD.

PUB117

Culinary Techniques to Improve Education in Legume and Vegetable Consumption in CKD Patients

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Background: Good nutrition is relevant in for CKD pts. Legumes and vegetables by P & K content are restricted in CKD pts. Guidelines on Nutrition do not include recommendations on culinary techniques. The aim was to assess the influence of culinary techniques on removal P and K in legumes and vegetables and to assess the nutrients in manufactured as well.

Methods: Legumes (lentils, beans, chickpeas) obtained at supermarket and dried packaged in 1000 g packs. Likewise, legumes are obtained in glass jars that are cooked and conservate with water enriched with salt. Collard greens and chards (rawl and frozen) were obtained as well. Determination of humidity and ashes were performed accordance to method 934.01 AOAC (2012) (George and Latimer, 2012). Mineral assessments were performed by Optical Emission Spectrometer with Coupled Plasma (ICP-OES Optima 4000 DV by Perkin Elmer. The ashes of each samples were dissolved in 4 mL of a solution of 3 M HCl + 21 mL distilled water for the analysis of Zn, Fe, Ca, P, Mg, Na and K. Legumes were analized in raw, after soaking (12 hrs) and after soaking followed by boiling. Vegetables were included in 4 groups to analyze: the fresh product, after to be subjected to direct cooking, after being subjected to boil previous blanch and after being frozen with a prevoius blanching and then applying a boiled. Elements Na, K, Ca, Mg, Fe, Zn were measured after each and compared with fresh.

Results: Legumes: all techniques reduced P & K content respect to raw, being 12 hrs soaking plus boiling more efficient reducing up to 76.2%, keeping levels < 100 mg/100 mg fresh sample, and manufactured as well. Vegetables: all techniques reduced K content respect to raw. The more favourable techniques were blanching+boiling (82%), frozen (81%) and frozen manufactured (82%). All of them showed a K level <10 mg/ 100 mg fresh sample.

Conclusions: Industrial legumes; combining 12-hours-soaking and boiling reduced up to 70% of P & K content. Vegetables reduced K content in both in industrial frozen and fresh managed with all culinary techniques. Healthy culinary techniques should be included in the nutritional education programs for CKD pts. Legumes & vegetables provide fiber, vitamins of group B and are a good source of protein of vegetable origin.

Funding: Other NIH Support - University of Santiago de Compostela. Departamento de Dietetica y Nutrición Humana

PUB118

CKD of Non-Traditional Etiology in the United States, 2000-2015: Incidence Rates Using Administrative and Electronic Health Records

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Background: Chronic kidney disease of non-traditional etiology (CKDnt) affects populations without traditional risk factors for chronic kidney disease (CKD). In Central America CKDnt affects primarily young working men, reaching epidemic proportions. Incidence in the United States has not been characterized.

Methods: We conducted a retrospective analysis of claims and electronic health record (EHR) data from the OptumLabs® Data Warehouse which includes de-identified claims data for privately insured and Medicare Advantage enrollees in a large, private, U.S. health plan, and de-identified EHR data from a nationwide network of provider groups. Our case definition of CKDnt was CKD with no prior documented diagnosis of 22 conditions known to cause CKD (e.g., nephropathies, diabetes, heart disease, autoimmune disease and malignancies). By definition, traditional CKD cases had prior diagnoses of these conditions. CKD cases with prior diagnosis of hypertension (a cause and consequence of kidney disease) were excluded from analyses. We used nonparametric regression to estimate annual incidence of CKD and CKDnt in claims data, examining differences by sex, age, race/ethnicity and geographic region. We examined new cases in EHR data, and differences by the same risk factors and insurance type.

Results: Seven percent of CKD cases with a year of continuous enrollment in claims were CKDnt. Incidence rates of CKD and CKDnt in claims data increased from 2000-2015 in all age groups with the exception of <18 years. CKD rates increased with age category, although were equal among the age 18-39 and 40-59 groups. In contrast, CKDnt rates were significantly higher in the 40-59 age group compared with all other age groups. This difference was driven by male cases. Compared to traditional CKD, CKDnt cases <60 years were 29% more likely to have advanced disease at initial diagnosis (RR=1.29; 95% CI 1.23-1.35). New CKD and CKDnt cases in EHR were more likely to be male and have Medicare compared to all other types of insurance.

Conclusions: Our results are the first to characterize increasing CKD incidence rates by age in the US, highlighting that CKD with no known risk factors may disproportionately affect men of younger ages.

Funding: Private Foundation Support

PUB119

Racial Disparities in the Effect of Inflammation on the Prediction of Albuminuria in Patients with the Metabolic Syndrome Using Machine Learning

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Background: C-reactive protein (CRP), an inflammatory marker, is associated with the metabolic syndrome (MetS) and chronic kidney disease. We previously showed that CRP mediated the association between microalbuminuria (MA) and MetS components by race/ethnicity. However, little is known about the effect of CRP on the predictive value of albuminuria in MetS patients, by race. In this study, we used a machine learning (ML) strategy to determine the extent to which the addition of CRP impacts the performance of predictive models among racial/ethnic groups.

Methods: We analyzed National Health and Nutrition Examination Surveys data (1999-2010) for adults (aged ≥20 years) with the MetS (N=5700). We created ML models using a comprehensive cloud-based platform (Microsoft Azure), which allowed us to build a variety of ML applications for testing and prototyping different models as well as integrating R, a programming language for statistical computing for data preprocessing and feature engineering. We created a boosted tree regression and performed random sweep parameter optimization. Regression models were created for each of the racial/ethnic subgroups both including and excluding CRP as a parameter, and the change in coefficient of determination (R^2) was calculated, which represents the total proportion of variance accounted for by the predictive model.

Results: The coefficient of determination (R^2) was 0.081, 0.154 and 0.113 in African Americans (AAs) Hispanics and Whites, respectively. The R^2 was most highly increased in AAs (0.119, 47%) followed by Hispanics (0.163, 5%) and Whites (0.119, 5%) with the addition of CRP to the models.

Conclusions: The data shows that the effectiveness of CRP to predict albumin concentration is greatest for AAs compared to Hispanics and or whites. This suggests that targeting CRP may be a feasible strategy to manage albuminuria in AAs. ML is a useful tool to support epidemiologic research and clinical management decisions.

Funding: Other NIH Support - NIMHD

PUB120

Exercise Counseling for People with CKD: An International Survey of Nephrologists' Practice Patterns and Research Perspectives

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Background: People with chronic kidney disease (CKD) have identified the impact of lifestyle interventions such as exercise as a research priority. We investigated nephrologists' practice patterns and research perspectives with respect to exercise in CKD patients.

Methods: A 19-item electronic survey regarding exercise-related practice patterns and resources was administered to practicing nephrologists with publicly available email addresses in Canada (n=354), practicing nephrologists in Australia and New Zealand and to the members of the Australian and New Zealand Society of Nephrology (n=598).

Results: 198 nephrologists (21% response) completed the survey; 63% were 35 to 50 years old, 57% practiced in Canada, and 67% were men. Overall, 60% thought that exercise counseling was within a nephrologist's role. The most frequently reported barrier for exercise programs was lack of funding. On average, 96% agreed that regular exercise provides "health benefits" for all CKD stages and 71% reported "frequently" or "always" counseling patients on exercise. 38% respondents agreed that sufficient evidence exists to support regular exercise prescription for CKD patients. In a multivariate model, agreement with a sufficient evidence base for exercise in CKD and personal physical activity were not associated with exercise counseling practices. Female respondents (OR 2.31; 95% CI 1.16-4.58) and older respondents (OR 1.94; 95% CI 1.15-3.26) were more likely to offer exercise counseling. Exercise impact on patient-reported outcomes (quality of life [QoL] [28%],

symptoms [26%], and mental health [25%]) followed by cardiovascular parameters (18%) and CKD progression (16%) were identified as important outcomes for future research.

Conclusions: Most nephrologists consider exercise counseling as a component of their practice and consider that exercise offers patients improved health. Lack of funding for exercise programs is perceived as the principal barrier to implementation. Nephrologists identify core patient-centred outcomes as central to the future research agenda.

Funding: Clinical Revenue Support

PUB121

Socioeconomic Status and Geographic Factors May Be Related to Lower Renal Biopsy Rate and Higher ESKD Events: A Retrospective Study in Chiba Prefecture, Japan

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Background: It is important to grasp the prevalence of kidney disease when we discuss about health policies in living area. Previous studies have reported that there are regional variations in the incidence of biopsy-proven kidney disease and end stage kidney disease even in small region. However, it is unclear whether those variations are associated with socioeconomic status or geographic factors. The aim of this study is to examine the relationships between regional backgrounds and incidence of kidney diseases at Chiba prefecture in Japan, with a population of six million.

Methods: We collected clinical data on renal biopsies performed between Apr.2014 and Mar.2016 at seven main hospitals in Chiba prefecture. We divided the prefecture into nine medical areas, and calculated biopsy rates in each area using regional statistical data from government's open data site. The biopsy rates were age-adjusted by using data from Japan Renal Biopsy Registry. Spearman's rank correlation coefficient was used to estimate associations between biopsy rate and regional backgrounds.

Results: A total of 910 cases were enrolled. The patients were mean age of 57 years and 56% of patients were male. There were different renal biopsy rates (19.9 ± 10.6 /100000 population) and disease variations in nine different area. No association was found between the number of nephrologist or health check-up participation rates and renal biopsy rates. But average incomes and numbers of hospitals in districts have correlations. (ρ=-0.87; p= 0.005, ρ=0.92; p=0.001)

Conclusions: Low-income regions had more renal biopsy than high income-regions, and the number of hospitals in areas was related to renal biopsy rates. It suggests that there may be some relationships between standard of living and onset of diseases, and that medical environment may affect chance to receive accurate diagnosis. Further studies are needed to verify those actual associations with regional backgrounds and incidence of kidney diseases.

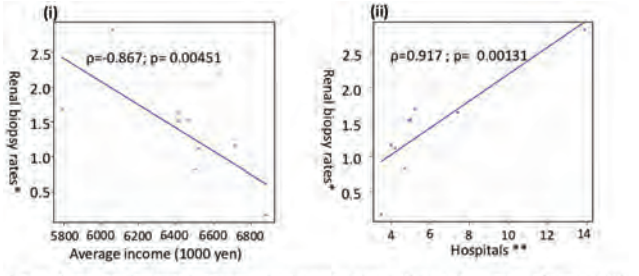

Figure: Association between biopsy rates and average income (i), and the number of hospitals (ii). Each dots indicates the medical areas.
* Compared overall prefecture as 1 , age-adjusted ** per 100000 population

PUB122

Individuals with Unrecognized CKD Can Be Identified and Referred into Care by a Workplace Wellness Program

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Background: Of the 30 million Americans who have chronic kidney disease (CKD), 85 percent are unaware of their disease. Once recognized, lifestyle changes and medical therapy can slow CKD progression. A workplace wellness program was modified with the aim of improving the recognition of CKD and referral into physician care. We asked whether this modified program improved management of individuals with previously unrecognized CKD.

Methods: An ongoing workplace wellness screening program provides annual estimated glomerular filtration rate (eGFR) results. Those individuals (n=402) who had an eGFR <60 mL/min/1.73 m^2 in 2016 were invited to participate in the CKD program. All 402 received a confirmatory eGFR test during the 2017 wellness screening program. Those who agreed to participate in the CKD program also received a urine albumin test and were offered a telephone consultation with a program physician to discuss their test results and referral into physician care. Using a limited data set of health plan claims, we compared the proportion of physician visits between participants and non-participants using a logistic regression model that adjusted for age, sex and education level.

Results: Of the individuals eligible for the CKD program, 51 percent (205/402) agreed to participate. CKD was confirmed in 51 percent (105/205) of the participants, either by repeat eGFR <60 mL/min/1.73 m^2 or by urine albumin to creatinine ratio (ACR) ≥30 mg/g. The comparison group consisted of the 88 of the 402 individuals who had not accepted the invitation to participate and who had an eGFR result <60 mL/min/1.73 m^2 in the 2017 screening program. In the 3 months following confirmatory CKD testing, 2 participants visited a nephrologist, but no non-participants did. Because of the program, one participant with low eGFR levels (eGFR=10 mL/min/1.73 m^2 in 2016; eGFR=3 mL/min/1.73 m^2 in 2017) initiated kidney dialysis. The proportion of participants who visited a physician was about 2-fold greater than non-participants (21% vs. 10%): OR 2.3, 95% CI 1.0-5.4, p=0.047; this difference was not appreciably changed after adjustment for age, sex, and education level.

Conclusions: A workplace CKD outreach program can identify individuals who will benefit from a timely referral into physician care.

Funding: Commercial Support - Quest diagnostics: the CKD program was a part of the work-place wellness screening offered by Quest Diagnostics to it's employees at no cost

PUB123

Evaluation and Intervention of Barriers to Behavioral Modification in Avoiding NSAID Use for Pain Among Underserved Patients with CKD

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Background: The negative consequences of non-steroidal anti-inflammatory drugs (NSAIDs) use in patients with Chronic Kidney Disease have been long established in medicine and the American Society of Nephrology urges providers to encourage patients with kidney disease to avoid NSAIDs. Multiple studies have shown that use of NSAIDs progressively worsens renal function in patients with CKD. A large cohort study has demonstrated that this is still an aspect that requires further intervention and that disease awareness has not been associated directly with the proportion of patients using NSAIDs. Even recovery from acute kidney injury seems to be insignificant in affecting decision to avoid NSAIDs in patients who are vulnerable to developing CKD and patient-physician rapport plays an important role in reducing use of NSAIDs. The patient-physician relationship appears to have an important role in facilitating replacement of NSAIDs with other renally-friendly medications. It is not solely recognition and awareness of CKD that drives healthy behaviors and a better understanding of barriers to adaptation of healthy actions is necessary to identify the significant targets for intervention.

Methods: We select underserved patients who receive their care at the resident-led Internal Medicine Clinic in Greenville, SC with various stages of CKD and survey patient knowledge regarding pain as well as their perceptions and attitudes toward selecting medications, specifically NSAIDs to address pain. Patients are then provided with individualized interventional counseling targeting their original motifs for NSAID use and barriers to avoiding NSAIDs. Following intervention, patients are given a post-survey with the same attitude and perception questions to evaluate for change in understanding and behavior in use of NSAIDs.

Results: Per preliminary and observational evaluation, NSAID use among underserved patients with CKD appears to be driven by ease of access of these medications and a symptom-centered rather than co-morbidity vigilant approach to addressing pain. This study is currently accumulating further data and post-survey results following interventional interviewing is not yet available.

Conclusions: Identifying factors that drive individual behavior of using NSAIDs is significant in developing appropriate intervention to affect patient behavior.

PUB124

Annual Estimated GFR Decline in Japanese Patients with CKD G3b-5: A Result from a Japanese Nationwide Cohort Study for Patients with Advanced CKD: The Reach-J Study

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Background: CKD progression in Japanese patients with advanced chronic kidney disease (CKD)—an estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2—has remained largely unexamined.

Methods: We conducted a nationwide cohort study of Japanese patients with advanced CKD. We recruited 2,249 advanced CKD patients (eGFR<45/ml/min/1.73m^2) receiving nephrologist care from a national sample of 31 facilities throughout Japan, randomly selected with stratification by region and facility size, aligned with the international CKD Outcomes and Practice Patterns Study (CKDopps). From baseline data, we calculated annual eGFR declines by CKD stage and causes of CKD over 4 years before enrollment.

Results: Of 1903 eligible patients with eGFR data before enrollment, their mean(±SD) median (IQR) annual eGFR declines were -2.49±4.20 and -2.00 (-3.96, -0.40) ml/min/1.73m^2. The reported causes of CKD were 474 had diabetic nephropathy(DN), 269 had CGN, 507 had nephrosclerosis, 110 had PKD, and 543 had other renal diseases. Their median (IQR) annual eGFR decline were: DN, -2.73(-5.46, -0.68); CGN, -2.07(-3.75, -0.53); nephrosclerosis, -1.57(-3.23, -0.12); PKD, -2.75(-4.35, -1.70); and others, -1.62 (-3.65, -0.24) ml/min/1.73m^2, respectively. For all causes of CKD, eGFR decline was faster with more advanced CKD. In addition, in CKDG5, eGFR declines of DM (-4.11 (-6.82, -2.02)) and PKD (-3.90 (-5.60, -2.19) ml/min/1.73m^2) were significantly faster than those of other groups (CGN, -2.84 (-4.85, -1.33); nephrosclerosis, -2.51 (-3.83, -1.56); others -2.08 (-4.20, -0.84) ml/min/1.73m^2).

Conclusions: Our study clarifies annual rates of eGFR decline by CKD stage and cause of CKD in a national sample of advanced CKD patients receiving nephrologist care.

Prospective data collection is ongoing to facilitate study of international practice variation in advanced CKD and with focus on the transition to ESKD.

Funding: Government Support - Non-U.S.

PUB125

Clinical Features of Patients with Multiple Myeloma with Renal Injury

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Background: To understand the clinical features of patients with multiple myeloma (MM) patients **with renal injury (**defined as proteinuria or/and eGFR is less than 60ml/min**) for** reduceing missed diagnosis and misdiagnosis.

Methods: A retrospective analysis of patients with multiple myeloma diagnosed in this hospital for the past 5 years in the database was performed. According to the presence or absence of renal injury **(**defined as proteinuria or/and eGFR is less than 60ml/min**),** divided into no kidney injury group and kidney injury group, comparing the two groups in gender, age, serum calcium, hematuria light chain and hypercalcemia. At the same time, compared with patients with IgA nephropathy and SLE from the database in the recent 5 years. Use spss software analysis.

Results: A total of 559 patients with multiple myeloma were enrolled, including 290 males and 269 females. Of these, 343 were associated with renal impairment (defined as proteinuria or/and eGFR is less than 60ml/min). There was no significant difference in age and gender between the two groups with renal injury and no kidney injury. There were no significant differences in the blood globulin. The expression of M-band in renal damage was lower than that in the group without renal damage, but the incidence of hypercalcemia was higher in renal damage than that in the group without renal damage. The hemoglobin in the renal damage group was significantly lower than that in the no kidney damage group. There was no significant difference in the total blood kappa, lamda and kappa/lamda ratio between the two groups, but there were significant differences in the urinary kappa, lamda and kappa/lamda ratio between the two groups. Compared with SLE and IgA non-plasma cell nephropathy, the albumin ratio of urinary protein electrophoresis was less than 30% in MM patients with renal injury.

Conclusions: 1 There were significant differences in the urinary kappa, lamda and kappa/lamda ratio between renal damage and without renal damage group; Compared with MM without renal injury, Kidney injury group has higher incidence of high calcium and lower hemoglobin. The electrophoresis M band rate was lower in Kidney injury group. 2 Compared with patients with SLE and IgA, less than 30% of the albumin ratio in urine protein electrophoresis, and abnormal blood kappa/lamda ratio greater than 4:1 or less than 1:4 is an important feature of MM associated with kidney damage.

PUB126

Assessing Hyperkalemia Risk and Its Associated Clinical Sequelae: A Novel Risk Tool

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Background: Patients with chronic kidney disease (CKD) and heart failure (HF) are at greater risk of hyperkalaemia (HK). HK is associated with increased risk of death, major adverse cardiovascular events (MACE), hospitalisation, and discontinuation of renin-angiotensin-aldosterone system inhibitors (RAASi). This study aimed to develop an interactive tool to synthesise current evidence relating patient characteristics and serum potassium (K^+) concentrations to clinical outcomes.

Methods: A review of studies published 1/11/2002–1/11/2017 was conducted to identify risk equations quantifying risk of HK and related clinical outcomes in patients with CKD or HF, and with or without diabetes or RAASi usage. Patient population, clinical outcomes and risk prediction methods were extracted from all eligible studies. The HK Risk Awareness and Impact Tool (RAIT) was developed in Microsoft Excel to characterise associations between patient characteristics and the incidence of HK and related clinical outcomes in CKD or HF patients.

Results: A total of 91 studies were identified, allowing for risk of HK, death, MACE, hospitalization and RAASi discontinuation to be characterized within the RAIT. For example, the RAIT shows how risk of HK increases in CKD patients with age, severity of renal impairment, diabetes or cardiovascular comorbidity, and RAASi use. For a 75-year old male CKD patient, not on RAASi and with eGFR 45mL/min/1.73m^2, a 15mL/min/1.73m^2 decrease in eGFR is associated with a 65.1% increase in 1-year HK risk; RAASi use is associated with a further 37.5% increase in risk. Additionally, the RAIT quantifies elevated risk of adverse outcomes associated with HK. For the same CKD patient receiving RAASi, estimated 1-year risks of death, MACE, hospitalization, and RAASi discontinuation were 3.3%, 7.5%, 13.6% and 10.4%, respectively, with HK (K^+=5.5mmol/L) versus 2.1%, 6.9%, 11.2% and 6.8% with normokalaemia (K^+=4.5mmol/L); relative increases of 57.1%, 8.7%, 21.4% and 52.9%, respectively.

Conclusions: HK imposes a significant burden to patients and healthcare providers/payers; particularly in CKD and HF populations. The RAIT provides a basis for synthesising contemporary evidence to quantify the association between patient characteristics, HK and its clinical sequelae. Further validation of the risk scores in a RCT setting is warranted.

Funding: Commercial Support - AstraZeneca

PUB127

An New Glomerular Filtration Rate Estimating Model Using Mini-Deep Neural Network

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Background: Accurate estimating glomerular flirtation rate (GFR) is crucial in clinical practice. The performance of GFR estimating equations has remained unimproved since the famous Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was presented on NEJM in 2012.

Methods: We hypothesized that a deep neural network (DNN) may achieve better GFR estimating performance for its capacity in modeling complicated non-linear correlation.

Results: Here a cohort of 937 chronic kidney disease patients were assigned as the development dataset and additional 377 patients were enrolled as the external validation data set. GFR was measured by ^{99m}Tc-DTPA renal dynamic imaging and then recalibrated to a dual plasma sample ^{99m}Tc-DTPA GFR. New models of mini-deep fully connected forward neural network (mini-DNN) and revised CKD-EPI-like equations with 4 variables (age, sex, serum creatinine and Cystatin C) and 3 variables (sex, age and serum creatinine) were developed in the same time. In the external validation dataset, bias and accuracy of the proposed mini-DNNs were better than revised equations, especially in the case of 4 variables mini-DNN achieved superior bias, precision, and accuracy than the 4 variables revised equation. This work provides insights into the advantage of representative machine learning strategy DNN in GFR estimating, and finally the 4-variable mini-DNN was deployed through a exe file. We also discussed the challenges of accurately estimating individuals' GFR and potential solutions were suggested.

Conclusions: The DNN was expected to perform further better when derived from a larger development data set.

Funding: Government Support - Non-U.S.

Performance of the derived GFR estimating models in the external validation data set

	Bias	Precision	P30	RMSE
Revised-equation-4	4.55(2.46,6.43)	21.02(18.25,23.48)	80.10(75.86,83.81)	47.37(16.75,109.60)
Mini-DNN-4 model	1.05(-0.60,2.65)	20.43(17.91,23.34)	83.28(79.04,87.00)	16.55(15.34,18.09)
Revised-equation-3	3.20(2.23,4.73)	20.32(16.71,23.72)	79.57(74.80,83.28)	17.16(15.80,19.15)
Mini-DNN-3 model	0.50(-1.62,2.33)	20.64(17.66,24.26)	83.82(79.57,87.00)	17.22(15.99,18.78)

PUB128

Association Between Malnutrition Risk and Drug-Related Adverse Reactions in Patients with CKD from the Hospital Civil De Guadalajara "Dr. Juan I. Menchaca" and Clinica 46 del IMSS

Jorge Andrade-Sierra,[1,2] Diana M. Hernandez corona,[5] Erika Cardona reynozo,[5] Leonardo Pazarin-Villaseñor,[3,2] Tonatiuh Gonzalez-Heredia,[4] Lydia A. Mercado,[4] Jorge fernando Topete reyes,[4] Francisco G. Yanowsky-Escatell.[6] *[1]Universidad de Guadalajara, Cucs, Guadalajara, Jalisco Mexico, Mexico; [2]Internal Medicine, Opd-Civil Hospital "Dr Juan I Menchaca", Guadalajara, Mexico; [3]I.M.S.S., Guadalajara, Mexico; [4]Universidad de Guadalajara, Guadalajara, Mexico; [5]Universidad de Guadalajara, Tonalá, Mexico; [6]Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Mexico.*

Background: Patients with chronic kidney disease (CKD) manifest a high prevalence of malnutrition risk and constitute a high-risk population to drug related adverse reactions. The selection and appropriate dosage of the drug are vital to avoid adverse effects in this population. **OBJECTIVE:** To associate malnutrition risk and the presence of drug related adverse reactions in patients with CKD.

Methods: Descriptive cross-sectional study in which 89 patients with CKD were evaluated as outpatients in the Nephrology service of two hospitals from September-December 2017. Malnutrition risk was measured using the Subjective Global Assessment (SGA) form and the adverse reactions were identified through a survey. The association between malnutrition risk and adverse events was analyzed by bivariate correlation and was considered significant at $p < 0.05$.

Results: Sixty-five (73%) of the patients were men and twenty-four (27%) were women, with an average age of 47.3 ± 18.4 years, BMI of 25.3 ± 5.8. According to the CKD stages it was found that: 7 patients (7.9%) were stage 3, 14 (15.7%) stage 4, and 64 (71.9%) were stage 5. According to the SGA, 54 (60.1%) patients had malnutrition risk. It was found that 43 (67.2%) patients had stage 5 and malnutrition risk. The reported adverse reactions corresponded to anorexia 13 (14.6%), nausea 8 (9%), vomit 6 (6.7%), diarrhea 9 (11.1%), constipation 20 (22.5%), dizziness 17 (19.1%) and 28 (31.5%) with reduced muscle strength. An association between the malnutrition risk and anorexia was found: 3 (3.4%); $p<0.001$, likewise malnutrition risk and reduced muscle strength 10 (11.2%); $p<0.05$.

Conclusions: The adverse events related to mild-moderate malnutrition, by SGA, are anorexia and reduced muscle strength, and the more advanced the renal disease stage is, the greater the malnutrition.

PUB129

Recurrence of Hyperkalemia in the United States

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Background: The objective of this study was to describe the frequency of recurrent hyperkalemia (HK) in patients with a documented case of HK in the United States (US) adult population

Methods: Adult patients with HK, defined as having at least two lab results with serum potassium>5.0 mEq/L (positive potassium lab), or one diagnosis code of HK (ICD-9: 276.7), or one prescription for sodium polystyrene sulfonate (SPS), were identified from a large US commercial claims database (1/1/2010-12/31/2014). Patients were required to have continuous enrollment for at least 6 months before (baseline period) and 12 months after (study period, 1-year cohort) the date HK was first identified (index date), and to have at least two potassium lab tests during the study period. HK events, defined as a positive potassium lab or diagnosis code for HK or SPS prescription, during the study period were analyzed. Time from the index date to the next HK event was analyzed using Kaplan-Meier analysis. Additional analyses were conducted on patients during a 36-month study period (3-year cohort) and for the subgroup of patients with chronic kidney disease and/or heart failure (CKD/HF) at baseline. Sensitivity analyses were conducted using a cutoff of 5.5 mEq/L to define a positive potassium lab result.

Results: A total of 11,990 patients with an HK event were included in the 1-year cohort. Mean age was 60.8 years and 53.4% were men. Most patients (58.9%) had a subsequent HK event during the 1-year study period, and 44.0% had a subsequent HK event within the first 6 months following the index date. The median time from the index date to the subsequent HK event was 7.9 months. Among the CKD/HF subgroup (N=4,798), 67.1% had an HK event during the study period and the median time to subsequent HK event was 5.3 months. In the 3-year cohort of CKD/HF patients (N=1,198), 78.4% had a subsequent HK event. In a sensitivity analysis, 46.7% of patients overall - and 53.7% of CKD/HF patients - had at least one subsequent HK event during the 1-year study period using the alternate 5.5 mEq/L cutoff for positive potassium lab results.

Conclusions: The majority of patients with documented hyperkalemia went on to have another hyperkalemia event within 12 months, indicating that hyperkalemia is often a recurrent condition, and the rate of recurrence is even higher in patients with chronic kidney disease and/or heart failure.

Funding: Commercial Support - AstraZeneca

PUB130

A Cross Sectional Analysis of Retinal Layer Thinning and Renal Function in a Clinical Population

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Background: Reduced thickness of the neuronal tissue of the retina and the vascular choroid have been linked to vascular damage and diabetes. Retinal thinning may offer utility as a biomarker of accumulated damage in chronic kidney disease (CKD). We aimed to assess associations between retinal and choroidal thickness and reduced renal function in a population with a high burden of comorbidity.

Methods: A cross-sectional analysis of participants attending nuclear cardiology or renal medicine clinics was carried out. Retinal thickness and choroidal measures were obtained using spectral domain optical coherence tomography. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration creatinine equation (CKD-EPI). CKD stage 3-5 status was based upon a single measure of eGFR <60 ml/min/1.73m^2.

Results: 241 participants with a mean age of 65 years (standard deviation [SD] 9.48) had a mean eGFR of 66.91 ml/min/1.73m^2 (SD 24.75) with 27% of the population using diuretics. In the present sample, 39% had diabetes. In unadjusted analyses, lower inner retinal thickness was associated with lower eGFR and CKD stage 3-5, a pattern similar to that reported in diabetes. In adjusted analyses, significant associations were found bilaterally (i.e. in both eyes) between lower thickness of the temporal and superior segments of the inner nuclear layer (INL) and the foveal area of the outer nuclear area (ONL) of the retina with lower eGFR. In the outer temporal segment of the nerve fibre layer (NFL), greater thickness was significantly associated with lower eGFR. There were no significant associations between choroidal measures and eGFR or CKD stages 3-5 after adjustment.

Conclusions: INL and NFL thickness were associated with renal function in a minority of retinal segments. Given the large number of associations tested, these findings do not indicate reliable independent associations between retinal thickness and renal function. INL and NFL thickness were associated with renal function in a minority of retinal segments. Given the large number of associations tested, these findings do not indicate reliable independent associations between retinal thickness and renal function.

Funding: Government Support - Non-U.S.

PUB131

Factors Associated with the Non-Inclusion of a Kidney Transplant Protocol: Results of a Mexican Cross-Sectional Study

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Background: Kidney transplantation is the best option for patients with ESRD. Some clinical situations could contraindicate a kidney transplant. In our setting there is scarce information regarding that factors. ***Objetive:*** To determine the factors that are associated with non-inclusion to kidney transplant protocol (KTP).

Methods: Cross-sectional Study, performed in Hospital General Regional 110. A survey was applied to patients with chronic kidney disease stage 5 *K-DOQI*, with age ≥16 years old, any gender were included. Further Clinical/biochemical data were obtained from medical chart: age, gender, body mass index, systolic and diastolic blood pressure, The comorbidity index was calculated (Charlson) **Statistical Analysis:** Comparisons were done with t-student, Mann-Whitney-U, Wilcoxon of test. Logistic regression analysis was used to evaluate associated factors with not including to KTP

Results: 355 patients were included, age 48±17 years, 57 % men, 106 (30%) patients were included to KTP; of them 65% were on the waiting list. Clinical and biochemical comparisons between patients included and not including in a KTP are shown in table. The factors associated with not including to KTP were: Charlson index (*OR,1.25;IC:0.97-1.6 p=0.84),* evolution time of CKD (*OR,0.98; IC:0.97-0.99 p=0.008,* dialysis time *(OR,1.01;IC:1.0-1.03 p=0.05),*cholesterol *(OR, 1.01;IC:1.01-1.03 p=0.02),* serum albumin *(OR,0.47; IC:0.23-0.95 p=0.03)* and Diabetes *(OR,4.87; IC:1.82-13.02 p=0.002)*.

Conclusions: It is necessary to shorten the waiting list and replacement therapy times to avoid more comorbidities.

Variable	KTP	Non KTP	p-value
Age (years)	37±14	53±16	<.001
Diabetes, N (%)	17 (10)	145 (90)	<.001
Hypertension, N (%)	106 (30)	249 (70)	0.04
Time in dialysis (months)	50±40	34±42	0.001
waiting list time (months)	38±34		
Systolic blood pressure (mmHg)	145±25	141±27	0.20
Diastolic blood pressure (mmHg)	82±16	79±14	0.02
Cholesterol (mg/dL)	145±33	163±43	0.004
Triglycerides (mg/dL)	121±72	161±92	0.001
Albumin (g/dL)	4±0.5	3.7±0.7	0.05

PUB132

Psychosocial Stress Is Associated with Incident CKD Development in Subjects with Normal Renal Function

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Background: Recent investigations have shown that psychosocial stress could be related with the development of several diseases including metabolic syndrome and cardiovascular diseases. Nonetheless, the impact of psychosocial stress on renal function has not been fully elucidated yet. Therefore, this study was conducted to examine the association between psychosocial stress and the development of incident chronic kidney disease (CKD).

Methods: Data from the Korean Genome and Epidemiology Study (KoGES), a prospective observational cohort, were used for the analysis. A total of 7,625 subjects with normal renal function were included in the final analysis. Psychosocial stress was measured by psychosocial wellbeing index-short form (PWI-SF) through self-administered questionnaires. The mean PWI-SF score during the study duration for each individual was considered as the amount of psychosocial stress inflicted. The subjects were classified into low stressed and high stressed groups based on the mean amount of psychosocial stress. Incident CKD was defined as estimated glomerular filtration rate (eGFR) < 60mL/min/1.73 m^2.

Results: The mean age of the subjects was 51.9 ± 8.7 years and 47.8% were male. Low stressed and high stressed groups were composed of 6,411 (84.1%) and 1,214 (15.9%) subjects, respectively. The baseline eGFR (94.1 ± 14.1 vs 94.2 ± 13.8 ml/min/1.73m^2, P =0.946) was comparable between the groups. Subjects with hypertension (14.0% vs 18.2%, P<0.001) and diabetes mellitus (5.8% vs 9.5%, P<0.001) was more prevalent in the high stressed group compared to the low stressed group. During a mean follow-up duration of 118.9 ± 36.7 months, incident CKD development was observed in 1,361 (21.2%) and 331 (27.3%) subjects in the low stressed and high stressed group, respectively. Multivariate Cox proportional hazard analysis revealed that subjects in the high stressed group were at a higher risk of developing CKD [hazard ratio (HR), 1.187; 95% CI, 1.051 – 1.342; $P = 0.006$] even after adjustments were made for confounding factors including hypertension and diabetes status.

Conclusions: Exposure to higher amounts of psychosocial stress was significantly associated with incident CKD development in normal renal function subjects. Managing psychosocial stress issues may have a role in preventing CKD development.

PUB133

Changes in Estimated Glomerular Filtration Rate (eGFR) Are Significantly Associated with Serum Uric Acid Levels in a Population-Based Screening: The Aragon Workers' Health Study (AWHS)

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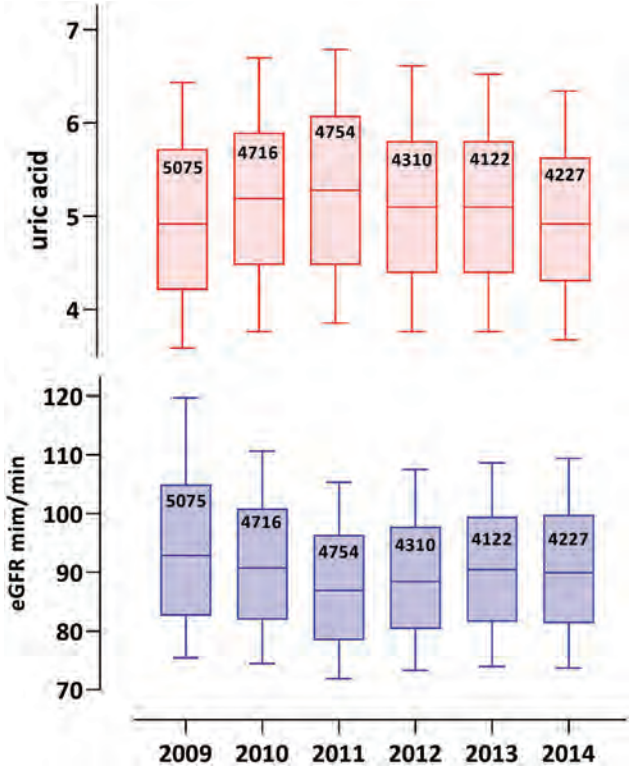
Background: Serum uric acid (SUA) is associated with hypertension, metabolic syndrome, diabetes and heart failure in the general population. There is mixed evidence suggesting that SUA levels may play a role in the development and progression of CKD. The aim of present study was to determine the association between SUA and eGFR in a population-based screening of Spanish middle-aged adults.

Methods: This longitudinal follow-up study of Aragon Workers' Health Study(AWHS) included 5075 subjects (median age 50 years, 94%male, 7%diabetes, 38%dyslipidaemia, 30%hypertension) with anthropometric and biochemical data. The recruitment started in 2009 and participants were followed annually for 6 years. Blood pressure, BMI, HDL, triglycerides, and SUA were available at each visit. The longitudinal association between uric acid and eGFR was evaluated by logistic regression mixed models.

Results: At baseline, there were associations between eGFR and SUA (rho= -0.22 p<0.001), total cholesterol(rho= -0.14 p<0.001), glucose(rho= -0.13 p<0.001), ASAT(rho= -0.21 p<0.001), ALAT(rho= -0.13 p<0.001), hsCRP(rho= -0.01 p=0.55) and BMI (rho= -0.15 p<0.001). In a multivariable-adjusted linear mixed model, changes in eGFR were significantly associated with diabetes 1.31(0.26), hypertension -0.23(0.22), dyslipidaemia -0.92(0.21), and longitudinal changes BMI -0.18(0.03) and SUA -2.87(0.08).

Conclusions: SUA was negatively associated with variation of eGFR in a cohort of community-dwelling middle-aged men, supporting the notion that SUA may be a risk factor or marker of CKD progression.

Funding: Government Support - Non-U.S.



Box plot of SUA (mg/dl) and eGFR (ml/min), median (10-90 percentiles).

PUB134

The Association Between Serum Uric Acid with Inflammation, Body Fat, and Renal Function

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Background: Hyperuricemia has been related to metabolic syndrome, cardiovascular disease, and renal disease. Uric acid is associates with the presence of atherosclerosis in recent studies and adiposity and inflammation lead to atherosclerosis. It is unclear whether serum uric acid could be a predictive marker to determine adiposity, inflammation, and renal progression in longitudinal study.

Methods: Among the 56,367 adult participants who underwent health check-ups during 2004-2017, we included 16,695 participants with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m^2 and repeated measurements of uric acid and eGFR. We divided participants into sex-specific quartile groups according to the baseline serum uric acid level. The decline of renal function aggravation was defined by the decrease in eGFR by more than 30%. Body fat and muscle were evaluated by bioimpedance analysis.

Results: The average age of the participants was 46.7±12.5 years and 52.5% were male. Baseline serum uric acid is positively associated with body mass index, serum C-reactive protein (CRP), monocyte count, and body fat at baseline and follow up examination (P<0.05) after the adjustment of multiple factors. In addition, serum uric acid is negatively related to body muscle (P<0.05). The highest quartile of uric acid was associated with the development of metabolic syndrome (RR, 1.608; 95% CI, 1.068-2.423) during 54.3± 37.5 months of follow up period. The risks of decline in renal function were significantly higher in the third (RR, 3.015; 95% CI 1.455-6.247) and highest quartile (RR, 4.848; 95% CI 2.379-9.878) compared than the lowest quartile. The participants with highest quartile showed 2.329-fold risk elevation of CKD development (95% CI 1.482-3.659).

Conclusions: Serum uric acid is associated with adiposity and inflammation at baseline and follow-up study. Hyperuricemia is associated with development of metabolic syndrome, renal function decline, and chronic kidney disease.

PUB135

Correlation Between Home, Clinic, and Ambulatory Blood Pressure Monitoring Among CKD Patients

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Background: There are various options for BP monitoring like home blood pressure (HBP), office(clinic) (CBPM) and twenty four hour Ambulatory BP monitoring (ABPM). HBP could provide an appropriate alternative to ABPM in terms of diagnosis, particularly in primary care where it might not be immediately available or deemed too costly or when patients find it inconvenient or uncomfortable. By early detection of hypertension (HTN) in CKD patients, life threatening adverse outcomes can be prevented and management can be modified accordingly. Hence, the study was conducted to detect masked hypertension in CKD patients and to investigate whether home HBP monitoring provides feasible and reliable alternative to ABPM and repeated CBPM in detection of HTN and differentiating true from white-coat HTN.

Methods: Total 75 patients, >18 yrs of age and having CKD stage1-4 (pre-dialysis) were enrolled and those having heart disease, acute infection and pregnancy were excluded. HTN was defined as per JNC-7 and British hypertension society as CBP:≥140/90mmHg, mean HBP:>135/85mmHg, mean ABPM daytime:>135/85mmHg, mean ABPM nighttime:>120/70 mmHg. Patient details were incorporated in proforma along with CBP measurement on two different occasions and ABPM once during time period of 7 days of HBP measurement.

Results: Majority of patients were males (61%) with age of 58.3±6.31 years. More than half were CKD stage 3. Around 69%, 61% and 40% were hypertensive when detected by ABPM, HBP and CBP respectively. Among hypertensive, 38.7% were masked HTN, 9.33% observed with white coat HTN, 30% were sustained HTN and 21% were normotensive. Prevalence of normotension showed concordance between ABPM and HBP when it compared by all three methods. Similarly ABPM and HBP showed concordance in 88.46% hypertensive. HBP achieved a specificity of 100% and a sensitivity of 88.45% for the detection of hypertension when using ABPM as gold standard. For accuracy and precision of HBP and CBP in predicting ABPM, HBP was superior to CBP.

Conclusions: ABPM was the gold standard for detecting of hypertension. HBP was no more far behind to ABPM in terms of detecting white coat and masked HTN. The present data may serve as a starting point for more elaborate cost-effectiveness studies and reimbursement of BP monitoring devices.

PUB136

Assessing the Rate of Progression of CKD of Unknown Etiology in Sri Lanka

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Background: Chronic kidney disease of unknown etiology (CKDu) is a global epidemic, identified in the lowland, arid agricultural regions of many countries including Sri Lanka. The primary research objective thus far has been to identify individual causal factors. The research presented in this paper shifts the focus to understand risk factors for kidney disease progression in established cases.

Methods: Working with a Ministry of Health screening operation in the Wilgamuwa Division of the CKDu endemic Central Province, 296 individuals with CKDu were identified using a clinical case definition. They were consented, and administered a detailed survey covering exposure, behavioral and clinical factors with micro-environmental assessment of water and soil agrochemical contamination at the household level. A follow-up clinical exam was conducted at the Wilgamuwa kidney clinic. Serum creatinine was repeated to confirm the diagnosis of CKDu. Thereafter participants undergo quarterly clinical exams and serum creatinine assessments.

Results: The recruited participants are between 30-65 (mean 54 [SD 8.2]) years. Consistent with the reported sex distribution of CKDu, 76.6% are men. The mean education is to the 6th standard; 75% live in nuclear families. Baseline CKD-EPI eGFR was 40.7 (SD=13.7) ml/min/1.73m^2, with a range from 17 to 80. eGFR mean change from baseline to first quarterly follow-up was 2.97 (SD=8.0) ml/min/1.73m^2, with a range of-32.3 to +54.6. 81 (41.5%) participants showed a decline in eGFR of more than 5 ml/min/1.73m^2; 114 (58.5%) showed no change or an increase in eGFR.

Conclusions: Our initial results indicate that there is a range of variation in progression of the disease, enabling us to explore the environmental, behavioral and clinical factors associated with progression. There is currently little available for primary and secondary prevention; it is our hope that by identifying the contributing factors this research can provide guidelines for slowing progression.

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PUB137

Heat Stress as the Main Cause of CKD in Agricultural Communities - Seven Arguments Against the Hypothesis

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Background: There are two main hypotheses suggested as causative of the global epidemics of chronic interstitial nephritis of agricultural communities (CINAC). The toxic hypothesis implicates an environmental/occupational toxin while the heat stress/dehydration hypothesis (HSDH) attributes the disease to recurrent acute kidney injury (AKI) caused by heat stress. Our aim is to demonstrate that heat stress is unlikely to be the main cause for this epidemic.

Methods: The following data sets are used to refute the HSDH as the driving force of CINAC: 1.Geographil, 2. Climatologic, 3. Ecologic, 4. Epidemiologic, 5. Physiopathologic, 6. Biochemical and 7. Agrarian.

Results: Absence of CINAC in many hot agricultural regions of the world is a stronger anti-correlation than the correlation assumed by presence of CINAC in a few such regions. The mosaic pattern of case distribution in Sri Lanka contradicts the HSDH. It is doubtful that the small temperature increases in the latter twentieth century caused significant renal effects. CINAC is seen in people not exposed to hot working conditions, while it is not seen in many occupations with higher temperature exposure. Individuals who drink spring water are not affected in contrast to those who drink from shallow wells in nearby communities. It is doubtful that field studies in agricultural workers show significant AKI, and that this degree of community-acquired recurrent pre-renal injury is adequate to cause CINAC. Biochemical changes postulated to perpetuate CKD have not been proven. In Sri Lanka, mechanization of paddy farming has reduced farmers' heat exposure.

Conclusions: It is unlikely that heat stress is the main cause for the CINAC epidemic.

PUB138

To Assess the Association Between Obesity and CKD in New York City Population

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Background: The increasing prevalence of obesity in the United States is a major public health concern. Obesity is known to be associated with several conditions that can compromise renal function, such as diabetes and hypertension. It is unclear, however, if obesity is an independent risk factor for chronic kidney disease. Currently, there is limited, conflicting research concerning obesity and chronic kidney diseases at the population level. This study was performed to better understand the association of obesity and chronic kidney disease in the population of New York City.

Methods: A cross sectional study was performed to identify the association between obesity and CKD using the 2013-2014 New York City Health and Nutrition Examination Survey. Obesity status, determined by BMI, was the exposure, and the outcome was chronic kidney disease defined using a survey question about the presence of kidney disease. Chi-Square and univariate tests were used to test for bivariate association between obesity and covariates of interests: age, gender, marital status, physical activity level, diabetes, and hypertension. Logistic regression was performed to find association between obesity and chronic kidney disease adjusted for age, gender, physical activity, diabetes, hypertension, and marital status.

Results: This study includes study population of 6,008,489. A statistically significant association was found between obesity and chronic kidney disease at p-value: 0.03 (Chi-square test). After adjusting for confounders, however, there was no statistically significant association between obesity (BMI > 30) and CKD (p-vale: 0.2811, OR: 1.90, 95% CI (0.589, 6.171).

Conclusions: In this population-based, cross sectional study, a statistically significant association was found between obesity and chronic kidney disease. However, after adjusting for known risk factors, this association was no longer significant, indicating that obesity may not be an independent risk factor for chronic kidney disease. This study was limited by the use of a survey question to determine the presence of renal disease, rather than objective laboratory data. However, this study adds to the currently available evidence and encourages further research regarding the association between obesity and chronic kidney disease.

PUB139

Gender Difference About Clinical Outcomes in CKD Patient over 55 Years of Age

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Background: Gender differences in chronic kidney disease (CKD) are reported in previous researches. For example, graft survival time is reduced in recipients of kidneys from female donors as compared with recipients of male donor kidneys. However, few studies compared with male and female in CKD patients, because sex were previously treated as a kind of co-factor on outcomes.The aim of this study is to examine the characteristics of CKD patients over 55 years old and the factors contributing to death and cardiovascular disease (CVD) events.

Methods: Setting : Multicenter Prospective cohort study. The subject of this study was 1392 CKD patients over 55 years old. they were observed 5 years (till 2013). Male were 55.0% of them. We surveyed patient characteristics, laboratory findings (Hb, sCr, eGFR etc…), medication. Outcome:All-cause mortality, CVD events.

Results: In CKD patients of over 55 years old, there was gender difference in the risk of mortality and ESKD but not in that of CVD events. Lower systolic blood pressure, lower serum albumin, lower eGFR, past CVD, and lack of angiotensin receptor blocker were related with all cause mortality in male. On the controther hand, lower hemoglobin, proteinuria, needs of iron, diuretics, and vitamin D were significant with mortality in female. CVD risk was not shown statistically significant difference between gender. Past CVD was most important risk for both gender. Lack of RASI, positive proteinuria, and need of beta blocker were significant in male. Need of erythropoiesis stimulating agent was significant in female.

Conclusions: As a result, characteristics and risk factors differed even between male and female CKD patients of age after menopause. Blood pressure effected the prognosis in male and anemia controlled that in female. We should consider the different risk factors in CKD between gender even elderly.

Funding: Commercial Support - Astellas Pharma INC.

PUB140

Cardio-Renal Risk Factors Are Highly Prevalent in Rural Population - Findings from Multi-site Screening Programs in Bangladesh

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Background: Population of urban and rural areas have difference in life style, environment and livelihood. Rural population are generally less investigated. The aim was to investigate the dirtribution pattern of diabetes (DM), hypertension (HTN), dyslipidemia and proteinuria as cardio-renal risk factors in rural and urban population.

Methods: Multiple screening programs in different urban and rural areas of Bangladesh were conducted by Kidney Disease Research Group (KDRG). An 'open to all' invitation was announced in selected areas for interested adult population to attend on a specified date in early morning preferably fasting. On screening day attending participants were interviewed by research physicians. Socio-demographic information, blood pressure (BP) recording and anthropometric measurements were done. Spot urine was collected and blood sample was drawn for blood sugar, lipid profile and serum creatinine (non-enzymatic) measurements. Estimated GFR (eGFR) was calculated by MDRD equation.

Results: In 2000 subjects 51% was male, age between 18-40 years in 61%; 69% had school level of education; 59% belonged to low income group and 18% were tobacco user. Parental DM was present in 16% and HTN in 23%. At screening pre-diagnosed HTN was present in 13%, DM 10% and nephropathy <1% subjects. After screening hypertension was detected in 23% (18% systolic and 19% diastolic). Blood sugar was >7.0 mmol/l in 22 % (of which 7% had > 11.1). The lipid profile showed raised TG (>150mg %) in 58%, low HDL (<40 mg %) in 58% and high LDL (>130 mg %) in 24%. Proteinuria was detected in 4.4 % subjects. The eGFR < 60ml/min was found in 18.6% subjects. Comparison of urban versus rural population showed diastolic HTN 16% vs. 23% (p<0.002); blood sugar <5.5 mmol/l in 64% vs. 53% (p<0.001); HDL <40mg% in 47% vs. 65% (p<0.001); TG> 150 mg % in 53% vs. 60% (p<0.01) and eGFR < 60ml/min in 16% vs. 19% (p<0.001).

Conclusions: The prevalence of hypertension, altered blood sugar, dyslipidemia and renal dysfunction is higher in rural population than the urban. This indicates a probable paradigm shift in diseases in an unaware underprivileged larger cardio-renal risk group needing urgent attention.

PUB141

Pre-Renal Biopsy (PRB) Bleeding Prophylaxis with Desmopressin (DDAVP)

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Background: DDAVP is a synthetic vasopressin analog. Its use to reduce bleeding risk pre PRB is arguable due to side effects, like reduced coronary flow and hyponatremia.

Methods: Analyze DDAVP complications when administered pre PRB from January 2013 until December 2017 in our centre.

Results: Of 482 PRB's, 65 (13,5%) received a single intravenous DDAVP dose (0,3 mcgr/kg) to enhance platelet function (table 1). DDAVP indications: altered PFA100 (72,5%), 15,5% uremia (GFR <25 ml/min), 9% antiplatelet drugs and 3% thrombocytopenia. 71% did not take any antiplatelet agents previously, 15% used anticoagulation that was either suspended 8-12 days pre PRB or replaced by low molecular weight heparin (not given one day pre procedure). PRB complications: 30,4% minor asymptomatic complications detected by routine ultrasound and 4,6% had major complications (surgical or radiological intervention and/or blood products requirement). Risk factors: pre PRB hemoglobin levels <10 g/dL and diastolic blood pressure >90 mmHg were significant risk factors. Abnormal PFA 100 wasn't statistically significant. DDAVP complications: Mean sodium decline was 0,9±3,4 mEq/L. 2 patients had hyponatremia without neurological symptoms: one dropped from 128 to 124 mEq/L and another one had a sodium decrease of 12 mEq in 24 hours. None of the patients had a cardiovascular event after dosage (up to one month).

Conclusions: Single dose DDAVP pre PRB is safe and can be used in patients with higher risk of hemorrhagic complications, such as uremia.

Table 1

		Range
Age	55 ± 13,3	30-84
Gender	43 males (66%) 22 females (34%)	
Kidney type	36 native (55,4%)	
Glomeruli	Mean 10,74 Median 10	0-41
Passes	1 = 22 (34%) 2 = 36 (55%) 3 = 7 (11%)	
Needle	14G = 11 (17%) 16G = 54 (83%)	
Platelet (/mm3)	201049,23 ± 71110,142	75,3 - 413 x103
Hb pre (g/dL)	11 ± 2,2	8,1-17
Hb post (g/dL)	10,5 ± 2,2	2,5-16,1
GFR (ml/min MDRD)	27,25 ± 22,28	2,1-102
BPs pre (mmHg)	143,66 ± 32,8	100-212
BPd pre (mmHg)	81,80 ± 9,5	60-99
Sodium pre (mEq/L)	138,12 ± 3,69	128-145
Sodium post (mEq/L)	136,62 ± 3,98	124-144

Hb: hemoglobin; BPs: systolic blood pressure; BPd: diastolic blood pressure.

PUB142

A Pilot Study of Wearable Devices to Detect Sepsis

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Background: Infection is an important cause of morbidity and mortality among patients with kidney disease, and early identification and treatment reduces mortality. Diagnosis remains a challenge, but fever is a relatively reliable sign. Health monitoring devices are popular, accepted and purchased by many patients. We assessed the feasibility of a watch device to detect infection.

Methods: We conducted a single-center prospective cross-sectional pilot study of inpatients to demonstrate proof of concept. Patients admitted under the nephrology unit between August 2017 and April 2018 were consented to wear a monitoring device. Participants wore a clinical grade device that measured peripheral temperature at the wrist (Empatica E4) along with other physiological variables, and we report early analysis of temperature *(t)* alone. We classified patients as having sepsis, no sepsis and/or treated sepsis and examined how well *t* correlated with the presence of sepsis.

Results: 104 patients underwent data recording and 82 patients had complete data. 58 patients had no sepsis, 15 patients had sepsis and 9 patients had treated sepsis. None of the 41 patients who had at least 84% of readings <35°C had active sepsis. Of the 41 patients with greater than 16% of readings ≥35°C, 15 had sepsis (PPV=21%, NPV=100%). 9 out of 10 patients who had >0.5% of readings ≥37°C had sepsis (PPV=52%, NPV=92%). 1 false positive was admitted with limb ischaemia after occlusion of a vascular graft.

Conclusions: Peripheral temperature measurement may add value to sepsis detection. Further data analysis is underway to refine the detection algorithm. We hope to be able to incorporate such algorithms into a consumer device that can continuously monitor and signal the user of impending infection.

PUB143

Clinical Feature of Tuberculosis in Japanese CKD Patients

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Background: The chronic kidney disease (CKD)-related immunodeficiency would suggest that early stage CKD could also be a risk factor for Tuberculosis (TB). Immunodeficiency associated with CKD appears to be multifactorial in etiology. Changes in immunity begin as early as stage 3b CKD (defined as a glomerular filtration rate <45ml/min per 1.73 m2) and worsen in later stages as kidney function deteriorates and waste products accumulate. Active TB is an infectious complication that may develop and result from progression of *Mycobacterium tuberculosis* infection after recent exposure or reactivation of latent tuberculosis infection (LTBI) from a distant exposure, often years before the disease develops.

Methods: Retrospective cohort study was performed in CKD patients who were diagnosed as TB during recent 11 years (from January, 2006 to December, 2017). The end point is all cause of death.

Results: Twenty hundred thirty-seven CKD patients who was diagnosed as TB were admitted to and followed up 11 years. Mean age of the patients was 76.0±11.8 years. One hundred sixty-three (68.8%) patients were male and 74 (31.2%) were female. Sixty-five patients were died (mortality rate: 27.4%). CKD was stratified by eGFR into 4 groups of G3b (eGFR 30-45 ml/min. per1.73m2 n=65;27.4%), G4 (eGFR 15-30 ml min. per1.73m2 n=48;20.3%), G5 (eGFR <15 ml/min. per1.73m2 n=33;13.9%), G5D (hemodialysis n=91;38.4%). Moreover, the mortality rate increased with progress of stage as G3b: 23.1, G4: 35.4, G5: 42.4, G5D: 20.9 (%), respectively, while the mortality rate tended to decrease with dialysis.

Conclusions: The mortality rate of TB patients with CKD was enhanced, compared without CKD patients. The mortality rate was gradually enhanced with CKD stage-depending. The mortality rate of TB in G5D was significantly decreased in that in G5 patients. Comparing G5 with G5D, the frequency of use of Levofloxacin among anti-tuberculous drugs is more common in G5 than G5D (24%: 8%). The treatment with anti-TB drugs were started in the patients with dialysis. From now on, it is considered that study of tuberculosis treatment for each CKD stage is necessary by further investigation. In the future study, we clarified the efficacies of TB treatment for each stages of CKD patients.

PUB144

Renal Embolization Therapy in Nephrological Patients: A Retrospective Analysis

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Background: Renal embolization (RE) is an invasive procedure used in Nephrology for the treatment of some pathologies such as renal bleeding (ReB), angiomiolypoma (AML), post renal biopsy vascular complications (arteriovenous fistulae (AVF) and pseudoaneurysm) complicated cysts or renal graft intolerance. There are few studies with small sample sizes. Our objective was to analyze the data and adverse events of ReB.

Methods: We retrospectively reviewed the RE performed in our unit for 22 years (1995-2017), including both complete and super selective RE. Data were obtained from hospital database and patient's clinical records.

Results: Thirty-eight embolization, 24 males/14 females (mean age 58.35+/-13 years). Seventeen patients were already on dialysis (45%). Super selective embolization was performed in 24 cases (63%) and complete kidney embolization in 14 cases (37%); 16 on native kidneys and 22 on kidney grafts. The main indication was ReB (32%), most spontaneous or after renal biopsy. Second indication was complicated AVF secondary to renal biopsy (37%) that caused hemodynamic instability or bleeding. Post-embolization syndrome occurred in 6 patients (16%), acute anemia requiring blood products in 10 (26%), hypotension in 3 and major hematuria in 1. Mild-moderate hyponatremia (126-135 mEq/l) appeared in 45% and mild hyperkalemia (5.5-5.9 mEq/l) in 2 cases who had it previously. In the non-dialysis group (n=21), there was a non-significant mean increase in creatinine of 0.6+/-1.89 mg/dl at 48 hours (p = 0.1); 0.3+/-1.6 mg/dl at 10 days (p = 0.63) and 0.4+/-1.9 mg / dl at 6 months (p = 0.9). Embolization triggered the onset of dialysis in 8 cases (21%). Two patients died during the first month (respiratory infection and hypovolemic shock). A second embolization was performed in 5 patients and nephrectomy in 3.

Conclusions: In our experience, post-biopsy complications are the most frequent cause of kidney embolization. Embolization can trigger the onset of dialysis in a significant percentage of patients mainly in patients with previous CKD. Mild-moderate asymptomatic and unexplained hyponatremia was frequent, that may be secondary to a transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

PUB145

Clinico-Pathological Characteristics and Outcome of Patients with Biopsy-Proven Oxalate Nephropathy

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Background: To investigate the etiology, clinicopathological features, treatment and prognosis of oxalate nephropathy.

Methods: A retrospective analysis of patients diagnosed as oxalate nephropathy by renal biopsy from January 2013 to April 2018 in Jinling Hospital was performed. The etiology and clinicopathological characteristics of the patients were analyzed.

Results: A total of 52 cases of OxN were collected, including 39 males and 13 females with a mean age of 49yr. Two cases were primary hyperoxaluria and 50 cases were secondary OxN. The most common cause was medication, including infusion of Vitamin C (16 cases), glycine (5), tiopronin (1), xylitol (1). Ingestion of foods rich in oxalate was in 4 cases, and dimethyl oxalate poisoning was in 1 case. The most frequent chief complains were oliguria/anuria (50.0%), followed by, edema (30.8%), lumbodynia (30.8%). Thirty-nine cases were diagnosed as AKI, 10 cases were AKI on CKD (ACKD), and 3 cases were allograft kidney. The highest serum creatinine during hospitalization was 8.86(range 1.73-20.03) mg/dl. There were 38.5% cases with hypoalbuminemia, and 40.4% with anemia. Urine test showed that elevated of retinol-binding protein (RBP), NGAL, lysozyme in 92.3%, 77.5%, and 59.2% cases, respectively. Kidney biopsy showed extensive calcium

oxalate crystal deposition with acute tubulointerstitial nephritis. Ten of them were in the background of glomerulonephritis or hypertensive nephrosclerosis. Percentage of acute tubular injury, interstitial cells infiltration were 46(10-70)%, 39(5-90)%, respectively. Twenty-seven patients (51.9%) received continuous renal replacement therapy. At the end of follow-up of 12.1 (0.2-57.2) months, 2 patients reached ESRD. In 33 of 41 patients who followed up for >3 months, renal function returned to normal in 56 (14-165) days. Compared with those of renal function non-recovery, the renal function recovery patients had lower ACKD rate, higher serum albumin and hemoglobin, lower urinary RBP and lysozyme, and less renal interstitial cells infiltration.

Conclusions: The oxalate nephropathy is associated with a cluster of etiologies and manifestations as AKI or ACKD. Half of the patients required renal replacement therapy. Most of the patients had renal function recovery.

PUB146

Development and Validation of a Cognition Questionnaire for Patients with CKD

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Background: To date, there is no a validated questionnaire which is used to know chronic kidney disease(CKD) patients' level of cognition for their disease. Being as the basis for Knowledge-Attitude-Practice Model, the level of cognition is essential if we need to conduct medical behaviors in a targeted manner. Therefore, the aim of the present study is to develop and validate a cognition questionnaire for CKD patients.

Methods: A cross-sectional study was conducted among CKD patients using the self-developing questionnaire in Guangdong Provincial Hospital of Traditional Chinese Medicine. Additionally, we conducted statistic analysis to know whether this questionnaire was appropriate.

Results: 110 questionnaires were distributed and 100 of which were qualified ones. After the item analysis, 2 items were excluded. Therefore, 18 items were retained to compose the final set of the questionnaire. For validity analysis, 4 components could explain cumulative 72.046% extraction sums of squared loadings; For reliability analysis, Guttman Split-Half coefficient was 0.918.

Conclusions: This cognition questionnaire reveals favorable validity and reliability. It seems to be an impactful method for the evaluation and measurement of levels of disease-related cognition among the CKD patients.

	Know nothing	Know a bit	Know the basis	Know most of it	Know clearly
1.Do you know what the symptoms will occur when your condition get worse?					
2.Do you know what will aggravate your kidney disease?					
3.Do you know the long-term prognosis of your disease?					
4.Do you know the most appropriate range of your blood pressure?					
5.Do you know the name and the usage of the medicine you are taking?					
6.Do you know the effectiveness of the medicine you are taking?					
7.Do you know which medicine may impair your kidney functions?					
8.Do you know what the unhealthy eating habits are?					
9.Do you know what foods contain high-quality protein?					
10.Do you know what foods should be avoided?					
11.Do you know the maximum of salt for each day?					
12.Do you know what exercise are recommended each day?					
13.Do you know what laboratory examination you should review regularly?					
14.Do you know how to leave the specimen of urine?					
15.Do you know how to read the laboratory examination reports?					
16.Do you know how to judge the curative effect?					
17.Do you know what health education activities are organized regularly in our clinic?					
18.Do you know how to contact our medical staffs when you have problems?					

The final questionnaire

PUB147

Strong Association Between Endothelial Dysfunction and Arterial Stiffness in Pre-Dialysis Patients with Stage 3-5 CKD

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Background: Cardiovascular disease (CVD) is the most common cause of mortality in chronic kidney disease (CKD) patients. Arterial stiffness is a major risk factor for cardiovascular and all-cause mortality in CKD patients. Endothelial function is impaired in CKD patients and contributes to a high risk of cardiovascular morbidity and mortality in this population. The aim of study was to investigate the association between endothelial function and arterial stiffness in pre-dialysis patients with stage 3-5 CKD.

Methods: In this cross-sectional study, hospitalized pre-dialysis patients who were diagnosed of stage 3-5 CKD in a single center from November 2016 to February 2018 were enrolled. On enrollment, demographic and clinical data collected included age, sex, height, weight, diabetic status and etiology of CKD. Ultrasound evaluation was conducted on brachial artery to estimate endothelial-dependent flow-mediated dilation (FMD). Automatice pulse wave velocity (PWV) measuring system was applied to examine the carotid-femoral PWV. Blood pressure and biochemical parameters were detected. Pearson's correlation and Stepwise multiple regression analysis were performed to explore relationship between FMD and PWV.

Results: We enrolled 206 patients in our center into this study. PWV was significantly higher in patients with diabetes as compared to those without diabetes (12.37 ± 2.15 m/s vs 10.50 ± 1.97 m/s; $P < 0.001$). PWV did not differ significantly between male and female patients. PWV was correlated with age ($r = 0.39$, $P < 0.01$), SBP ($r = 0.38$, $P < 0.001$), 24-hour proteinuria ($r = 0.18$, $P < 0.01$), uric acid ($r = 0.16$, $P < 0.05$), and CRP ($r = 0.15$, $P < 0.05$). Also, PWV correlated negatively with FMD ($r = -0.21$, $P < 0.01$) and estimated glomerular filtration rate ($r = -0.23$, $P < 0.01$). In multivariate regression analysis, FMD, age, SBP, DM, estimated glomerular filtration rate were each independently associated with PWV after adjustment.

Conclusions: Endothelial dysfunction is associated with greater arterial stiffness in pre-dialysis patients with Stage 3-5 CKD. This result suggests that increased CVD due to increased arterial stiffness is mediated by endothelium dysfunction in pre-dialysis patients with Stage 3-5 CKD.

PUB148

Validating Cardiac Troponin T in Predicting Cardiovascular and Mortality Risk in Kidney Transplant Candidates

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Background: We evaluate cardiac troponin T (cTnT) as a predictor of cardiovascular (CV) and mortality risk in a racially diverse cohort with high morbidity presenting for KTx evaluation.

Methods: 484 patients presenting for KTx evaluation from 2011-2013 at Mayo Clinic Arizona were evaluated. CV event was defined as coronary artery disease (CAD) or heart failure, and/or vascular event (stroke or peripheral vascular disease (PVD)). Normal cTnT <0.01ng/ml. The outcome of interest was combined CV event and/or mortality after KTx evaluation.

Results: Mean age 53.7±14 years; 58.5% male; 70.9% white, 23% Hispanic, 11.0% African American (AA), and 8.3% Native American; 42.1% diabetic; 30.2% CV event; 41.4% on statins; 32.8% on antiplatelet therapy; 57.2% on dialysis and mean time on dialysis 20.1±25 months; mean body mass index (BMI) 29±5.9kg/m^2; mean follow-up after KTx evaluation 44±19 months; 53.8% had cTnT≥0.01ng/ml. 61% had a KTx. 23.6% had a composite event (3.7% cardiac, 3.1% vascular, 19% died) with 79.8% occurring prior to KTx. ROC analysis identified cTnT≥0.036ng/ml to be best predictive of composite outcome (sensitivity 60%, specificity 71.4%). cTnT differed racially; more AA (55.6% vs 44.4%) and fewer whites (32.4% vs 67.6%) had cTnT≥0.036ng/ml. Predictors of increased cTnT included: male sex, older age, higher BMI, hypertension, diabetes, dialysis, CV events, and use of statins and antiplatelet therapy. On multivariable analysis of predictors of composite events, cTnT≥0.036ng/ml, older age and cardiac disease were independent predictors of composite outcome [Table 1].

Conclusions: We confirm that cTnT≥0.036ng/ml was the most powerful predictor of the composite outcome independent of other clinical variables in a racially diverse cohort with significant CV burden at the time of KTx evaluation.

Table 1. Multivariable analysis of predictors of composite outcome.

Variable	HR (95% CI)	P value
cTnT≥0.036ng/ml	2.58 (1.68-3.97)	p < 0.001
Age (years)	1.02 (1.00-1.03)	0.035
BMI (kg/m2)	1.00 (0.97-1.03)	0.923
Sex (Female)	0.75 (0.50-1.13)	0.164
Dialysis	1.12 (0.73-1.73)	0.609
Hypertension	0.59 (0.30-1.14)	0.114
History of CAD	1.82 (1.19-2.78)	0.006
History of PVD	1.78 (0.98-3.26)	0.060

PUB149

Training Peer Mentors for Patients with CKD and Their Caregivers: A Qualitative Study

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Background: Peer mentoring may improve patient-centered outcomes such as quality of life and engagement in care among patients with chronic kidney disease (CKD). However, training programs for peer mentoring and the mentors' experiences are not well-studied. Our study consisted of a structured 16-hour program to train peer mentors (PMs) for face-to-face and online mentoring of patients with CKD and their caregivers. This qualitative analysis examines perceptions of PMs regarding their training and the overall mentoring experience.

Methods: PMs were recruited to participate in training. Six months following training and serving in this role, 17 PMs participated in 3 focus group discussions. Discussions followed a guide, which identified how PMs felt about their training, their experiences with mentees, and their perception of how the program changed mentees' attitudes. Discussions were audio-recorded and transcribed. Thematic analysis was performed by 2 researchers (MA; NG), assisted with use of NVivo11.0 software.

Results: Analysis revealed an overall positive perception of the training. PMs commented that training provided appropriate information, improved their understanding of the disease and clarified their role as mentor. Suggestions for improvement included incorporation of more interactive sessions such as role play. The PMs used strategies learned during training to foster mentees' engagement in their own care by encouraging them to ask questions of their care team and by empowering them to request lay language in discussions. PMs perceived that their mentoring improved mentees' adjustment to modality of treatment and to treatment failure. PMs felt valued and appreciated the relationship based on shared experience. They perceived the mentoring experience to have increased their knowledge of treatment modalities. The main perceived challenge was the mentees' inadequate understanding of purpose of the mentoring program and the PMs' role. PMs suggested educating mentees about the program and the PMs' role.

Conclusions: A structured training program for peer mentoring is associated with satisfaction and perception of effectiveness by PMs. Peer mentoring provides benefits to PMs, including emotional satisfaction and perceived improvement in knowledge about their disease. **Funding: PCORI**

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PUB150

Short-Term Prognosis of Emergently Hospitalized Dialysis-Independent CKD Patients: A Nationwide Retrospective Cohort Study in Japan

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Background: In patients with chronic kidney disease (CKD), low body mass index (BMI) is associated with high mortality. This relationship in emergently hospitalized CKD patients is unknown. We investigated short-term protective effects of obesity in emergently admitted dialysis-independent CKD (DI-CKD) patients with and without inflammation.

Methods: This retrospective cohort study examined Diagnosis Procedure Combination data of 19822 emergently hospitalized DI-CKD patients. Patients were divided into 8 groups according to their BMI and the presence of inflammation. The primary outcome was in-hospital death within 100 days.

Results: Cox proportional hazards models adjusted for baseline characteristics showed that low BMI was associated with the outcome both in inflamed and in noninflamed patients (referred to as noninflamed and medium BMI [24–26 kg/m^2] group): inflamed and the lowest BMI (≤20 kg/m^2) group, hazard ratio (HR) 3.46 (95% confidence interval 2.80, 4.26); noninflamed and the lowest BMI group, 1.86 (1.48, 2.33). When patients were stratified according to presence of diabetes mellitus (DM), patients with DM showed that low BMI was associated with the outcome both in inflamed and in noninflamed patients, whereas in non-DM patients, this relationship was not observed in the noninflamed group.

Conclusions: For emergently hospitalized CKD patients with inflammation, high BMI was associated with lower mortality irrespective of the DM status. For noninflamed patients, the protective effects of obesity for in-hospital mortality were modified by the DM status.

Model	BMI quartile	Inflammation Present			Inflammation Absent		
		HR (95% CI)		P	HR (95% CI)		P
I	Q1 (≤20 kg/m^2)	3.46	(2.80, 4.26)	<0.001	1.86	(1.48, 2.33)	<0.001
	Q2 (21–23 kg/m^2)	2.79	(2.23, 3.48)	<0.001	1.35	(1.07, 1.71)	0.011
	Q3 (24–26 kg/m^2)	2.33	(1.82, 2.97)	<0.001	1	Ref	
	Q4 (≥27 kg/m^2)	1.64	(1.26, 2.14)	<0.001	0.79	(0.61, 1.02)	0.075
II	Q1 (≤20 kg/m^2)	2.64	(2.13, 3.27)	<0.001	1.62	(1.29, 2.04)	<0.001
	Q2 (21–23 kg/m^2)	2.26	(1.81, 2.84)	<0.001	1.28	(1.02, 1.62)	0.037
	Q3 (24–26 kg/m^2)	2.03	(1.59, 2.59)	<0.001	1	Ref	
	Q4 (≥27 kg/m^2)	1.63	(1.25, 2.13)	<0.001	0.92	(0.71, 1.20)	0.547

Model I: non-adjusted. Model II: adjusted for demographics and medical history: age, sex, history of DM, hypertension, anemia, CAD and CKD stage 5.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; Ref, reference

All-cause mortality by BMI and inflammation in DI-CKD patients without DM; Cox proportional hazards analysis.

PUB151

Aging and Renal Arterio-Arteriosclerosis in Relatively Younger Patients with CKD

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Background: Aging is well known risk factor for renal areterio-arteriolosclerosis. However, effect of relatively younger age on the renal areterio-arteriolosclerosis is unknown in patients with chronic kidney disease (CKD).

Methods: A total of 174 consecutive patients who underwent renal biopsy at our department between 2010 and 2013 were considered for the study. We excluded patients with vasculitis and those who were receiving calcineurin inhibitors leaving us with 139 patients. Arteriolar hyalinosis (Hy) and small arterial intimal thickening (IT) was semiquantitatively assessed via grading system. Arterial stiffness and endothelial function was assessed by brachial-ankle pulse wave velocity (ba-PWV) and % flow-mediated dilatation(%FMD) of brachial artery.

Results: The mean for age, BP, estimated glomerular filtration rate (eGFR), and urine protein were as follows: 46 years, 124/72 mmHg, and 72 ml/min/1.73 m^2, respectively. Even in the teens, Hy and IT were observed some patients, and their prevalence and the severity were linearly elevating as age group advancing. Similarly, the severity of ba-PWV was linearly elevating from the twenties. While, decreased %FMD was prevalent from the forties. Multivariate logistic analysis for the presence of Hy or IT were conducted adjusted with sex, systolic blood pressure, HbA1c, total cholesterol, uric acid and Brinkman index. The twenties was significantly associated with the presence of Hy (OR 9.8, 95% CI 1.2-76.7, p=0.03) and (OR 7.1, 95% CI 1.1-46.0, p=0.04), respectively compared with the teens. Additional adjustment with ba-PWV disappeared the significance of the twenties.

Conclusions: Aging may be associated with renal arterio-arteriolosclerosis even in relatively younger age group. Age-related arterial stiffness may be responsible for this association.

PUB152

Does Peripheral Vascular Disease Affect Loss of Glomerular Filtration Rate?

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Background: Ankle-brachial index (ABI) is a non-invasive diagnostic marker for the diagnosis of atherosclerotic peripheral vascular disease(PVD) and is frequently used in subclinical PVD. In our study, we aimed to investigate the effect of peripheral artery disease on GFR loss in patients wih stage 3-4 chronic kidney disease(CKD).

Methods: Totally 82 patients with stage 3-4 CKD who applied to our hospital between November-December 2015 were included in the study. Demographic characteristics, laboratory findings and comorbidities of all patients were recorded. Those with ABI<0.9 were considered as PVD. Progression in CKD was accepted as at least 25% loss of GFR or development of ESRD.

Results: The mean age of the patients was 65.5 years (23-78), 30(36.6%) were female. The most common comorbities were hypertension (85%), diabetes mellitus (45%) and ischemic heart disease (32.9%), respectively. Four patients were died and six patients had progression in CKD during follow-up. PVD was observed in 25% of patients. The baseline and 24-month follow-up laboratory values of patients are shown in Table 1. There was no statistically significant relationship between PVD and renal deterioration (p=0.213), but when deaths were accepted as renal progression, a trend towards significance is found (p=0.09). Baseline higher proteinuria and higher uric acid levels were corralated with CKD progression in patients with non-PVD patients (p=0.02 and p=0.004, respectively), but this effect was not observed in patients with PVD.

Conclusions: Our study did not reveal any relationship between PVD and renal survival during a 24-month follow-up in patients with CKD 3-4. However, proteinuria and uric acid levels in patients with non-PVD, stage 3-4 CKD may be good markers for CKD progression.

Figure 1. Proteinuria and uric acid levels in patients with non-PVD, stage 3-4 CKD

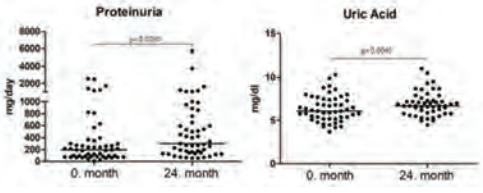

Table 1. Baseline and 24th month laboratory parameters

	Baseline (Mean ± SD)	24th Month (Mean ± SD)
GFR	39 ± 12	42 ± 16
Proteinuria (mg/day)	212 ± 816	308 ± 1715
Creatinine (mg/dl)	1,67 ± 0,66	1,55 ± 1,06
Uric Acid (mg/dl)	6,5 ± 1,3	6,9 ± 1,4
Albumin (g/dl)	4,2 ± 0,26	4,1 ± 0,29
C-Reactive Protein (mg/L)	4 ± 7	5 ± 10
Phosphorus (mg/dl)	3,4 ± 0,6	3,4 ± 0,6
PTH (pg/ml)	75 ± 69	97 ± 122

PUB153

Light Chain Amyloidosis in a Kidney Donor

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Introduction: Light chain amyloidosis is a relatively rare plasma cell dyscrasia characterized by the formation of amyloid from immunoglobulin (Ig) light chains that leads to the deposition of Ig light chain Kappa and lambda in different organs, most importantly in kidney and heart. The clinical presentation depends on the organs involved, and the degree of involvement and includes proteinuria, decreased renal function and cardiomegaly with heart failure. The condition has been reported in kidney transplant recipients in the past, but not in kidney donors. The response to treatment depends on various factors, most important of them being the degree of proteinuria and glomerular filtration rate (GFR) at the baseline.

Case Description: Our case was a 51-year-oldfemale who had donated her kidney to her brother (suffering from ESRD as a result of IgA nephropathy). The donor's past medical history before donation included benign bilateral breast masses, and anxiety. Pre-donation imaging showed a non-significant punctate non-obstructing lesion in the left kidney. Past surgical history included laminectomy and appendectomy. She underwent an uncomplicated laparoscopic donor left nephrectomy. Two years post-donation, the patient was diagnosed with proteinuria as much as 4.8 gram and creatinine of 1.2 from baseline of 0.9 (Post-donation creatinine were 1.2, 1.3 and 0.9 at 6, 12and 24 months post-donation, respectively), and was referred for further follow-up. She underwent a kidney biopsy that showed global mesangial kappa restriction and apple-green birefringence in Congo-red stain, compatible with Ig light chain deposition disease. The treatment started with daratumumab which led to significant drop in kappa light chains (from 28.2 to 2.23 mg/L, shown in table 1) and improvements in the proteinuria and GFR.

Discussion: Ig light chain deposition disease is relatively rare, and involves kidney and heart the most. The response to treatment is highly depends on the initial proteinuria and GFR. Our patient had a good response to treatment, with decrease in proteinuria and increased GFR. The fact that the patient was post-nephrectomy and single kidney did not affect her prognosis.

Light chain levels pre and post donation

	Kappa(0.33-1.94)	Lambda(0.57-2.63)	Kappa/Lambda Ratio(0.26-1.65)
At time of diagnosis	28.2	1.46	19.36
After treatment	2.23	1.36	1.64

PUB154

CKD with Multisystem Nocardia Infection

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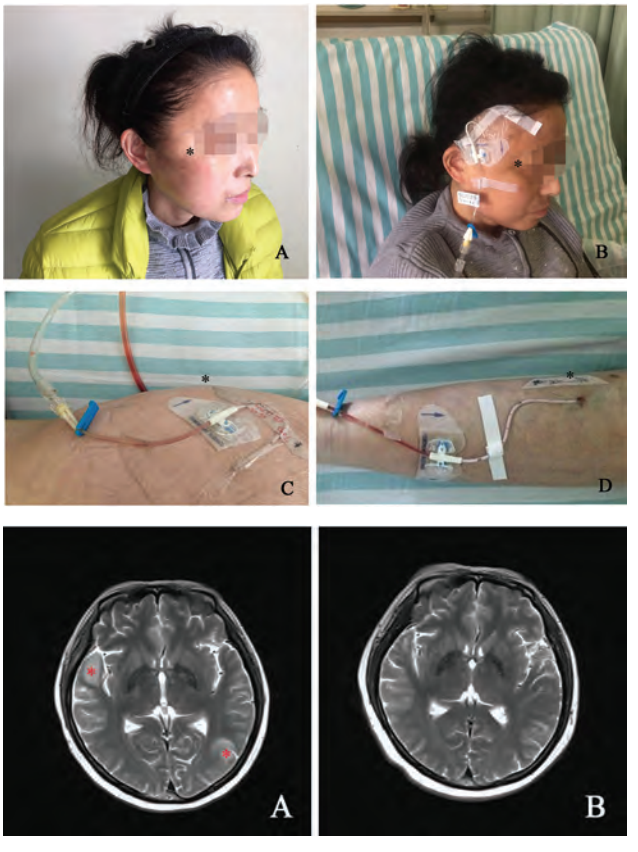
Introduction: Here is a case of 42-year-old female with membranous nephropathy, chronic kidney disease (CKD G1A1), type 2 diabetes. She suffered multisystem nocardia infection (pulmonary and soft tissue infection, multiple brain abscesses) which is rare in clinic.

Case Description: She was diagnosed as pulmonary infection with cough and expectoration. In other hospitals, she was successively treated with multiple antibiotics and voriconazole after stopping Cyclosporin. Cystic masses were found on right temporal, buttocks and popliteal fossa, accompanied by pain and normothermia (Fig1). Chest CT and head MRI showed right lung infection and multiple brain abscesses. Routine culture of blood and soft tissue puncture fluid were all negative, while nocardia was positive. We reduced dose of Medrol and gave Smzco+ Linezolid+ Imipenem and cilastatin sodium+ Minocycline. Cardiopulmonary arrested and epilepsy took place suddenly and she was saved. Her renal function and urine protein was normal through the six-month follow up. Imaging examinations showed infection was controlled(Fig2).

Discussion: Nocardia is Gram-positive and conditional pathogenic bacteria. Lung is involved mostly often through hematogenous spread. Due to atypical manifestation and slow growth of nocardia, nocardiosis is easy to escape diagnosis. It's reported that the mortality rate is as high as 100% when combined with brain abscess. This case has susceptible factors of infection such as CKD, diabetes, long-term use of Medrol and immunosuppressive agents. Sensitive antimicrobial treatment should be continued for 6 to 12 months.



PUB155

Food Consumption, Eating Behaviors, and Nutritional Status in Poor CKD Mexican Patients

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Background: CKD patients must consume food according to dietary recommendations and modify their eating behaviors to retard disease progression, maintain adequate nutrition, and reduce complications. We evaluated food consumption (FC), eating behaviors (EB), and nutritional status (NS) in pre-dialysis CKD patients.

Methods: Cross-sectional study in 40 CKD patients stages 3-4. A semiquantitative food frequency questionnaire was used to determine nutrient and FC; a behavioral questionnaire was applied to identify EB. NS was assessed by anthropometry.

Results: The median age was 52 y; 90% had deficient energy intake and 25% had inadequate protein intake. Most patients had deficient intake of lipids, carbohydrates and almost all vitamins and minerals, with the exception of vitamin B12, C and iron; 42.5% were overweight and 22.5% were obese; 15% had decreased muscle mass. The consumption of oils and fats, sugars with fat and sugary drinks were positively associated with BW, BMI, % body fat and waist circumference (Fig 1). The EB of "choice of foods by visual appeal", "the preparation of their food is in charge of another person" and "avoid consuming some type of food because it makes them feel bad" were associated with a minor muscle mass and body fat.

Conclusions: Eating behaviors and dietary factors were associated with nutritional status in patients with CKD. In addition, regardless of stage, FC was deficient in quality and quantity, together with a high prevalence of overweight and obesity. It is suggested the need to implement nutritional interventions with a multidisciplinary approach to improve the nutrition of CKD patients, to meet nutritional requirements, and to avoid disease progression to terminal stages and complications.

Results

	All n=40	Stage 3 n=15	Stage 4 n=25	p
Age (y)	52.0 (25.1-63.6)[1]	52.5 (33.8-62.3)	52.0 (24.8-64.0)	0.90
Male (%)	21 (52.5)	9 (60)	12 (48)	0.46
Illiterate (%)	9 (22.5)	4 (26.7)	5 (20)	0.62
DM (%)	19 (47.5)	7 (40)	12 (48)	0.93
Hgb (g/dL)	12 (10.7-14.3)	12.6 (10.0-16.1)	11.9 (10.6-13.3)	0.20
SCr (mg/d)	2.5 (1.7-3.7)[1]	1.7 (1.5-2.2)	3.0 (2.4-4.0)	**<0.01**
eGFR (ml/min/1.73 m²)	26.1 (17.0-41.2)[1]	40.4 (31.6-47.2)	18.0 (16.0-26.8)	**<0.01**
S Albumin (mg/dL)	4.1 (3.3-4.4)[1]	4.0 (3.2-4.3)	4.00 (3.3-4.9)	0.70
S Ca (mg/dL)	9.2 (8.7-9.7)	9.2 (8.8-9.5)	9.1 (8.1-9.9)	0.57
S PO4 (g/dL)	3.8 (2.6-4.3)[1]	3.4 (2.4-4.0)	4.1 (3.2-4.6)	**<0.01**
S K (mEq/L)	4.7 (3.8-5.3)1	4.6 (3.9-5.3)	4.9 (3.7-5.9)	0.56
Weight (kg)	74.5±19.3	73.6±19.3	75.0±19.7	0.82
BMI (kg/m²)	27.1 (20.3-34.3)[1]	27.7 (19.7-33.6)	26.9 (20.0-35.4)	0.96
≤18.49	4 (10)	2 (13.3)	2 (8)	
18.5-24.9	10 (25)	2 (13.3)	8 (32)	0.80
25-29.9	17 (42.5)	8 (53.4)	9 (36)	
≥30	9 (22.5)	3 (20)	6 (24)	
AMA (cm²)	47.6 (34.6-66.9)[1]	44.8 (32.9-78.1)	48.2 (34.0-67.9)	0.79
Dietary intake *				
Energy (kcal/kg/day)	18.6 (14.6-29.1)	18.6 (14.4-30.0)	18.5 (14.3-25.3)	0.60
< 90% (%)	36 (90)	14 (93.3)	22 (88)	
90-110 % (%)	2 (5)	0 (0)	2 (8)	0.62
>110 % (%)	2 (5)	1 (6.7)	1 (4)	
Protein (g/kg/day)	0.73±0.36	0.77±0.46	0.70±0.29	0.72
< 90% (%)	10 (25)	4 (26.7)	6 (24)	
90-110 % (%)	22 (55)	7 (46.7)	15 (60)	0.73
> 110 % (%)	8 (20)	4 (26.7)	4 (16)	
Fat (% energy)	29.2 (23.9-39.7)	30.3 (22.9-41.9)	29.0 (24.2-38.0)	0.62
< 90% (%)	36 (90)	13 (86.7)	23 (92)	
90-110 % (%)	2 (5)	2 (13.3)	0 (0)	0.90
>110 % (%)	2 (5)	0 (0)	2 (8)	
Carbohydrate (% energy)	57.4±7.8	56.5 (49.1-67.4)	59.5 (49.9-66.5)	0.89
< 90% (%)	36 (90)	14 (93.3)	22 (88)	
90-110 % (%)	3 (7.5)	1 (6.7)	2 (8)	0.83
>110 % (%)	1 (2.5)	0 (0)	1 (4)	

Abbreviations;*RDA; DM diabetes mellitus; BMI, body mass index; AMA, arm muscle area. [1]In case of non-parametric distribution: median percentiles 15th and 85th are presented

Fig 1.

PUB156

Renal Artery Revascularization in the Era of Negative Clinical Trials: Pattern of Practice and Outcomes of a Single Center

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Background: Renal artery stenosis is not an uncommon finding in atherosclerotic old patients. However, certain subgroups of patients appear to benefit from revascularization therapy. With concerns regarding patient selection in clinical trials comparing medical therapy to the revascularization, clinical equipoise still exists. We describe our center experience in renal revascularization therapy.

Methods: Study cohort consisted of all consecutive patients undergoing renal angioplasty for atherosclerotic renal stenosis, through referral by renal team in Royal Preston Hospital from January 2016 to January 2018. Data on demographics, comorbidities, and indications for angioplasty were collected retrospectively. Studied outcomes were change in eGFR, mean difference in the number of anti-hypertension medications at 6 months post intervention and the proportion of patient with. Data analysed using SAS 9.4

Results: Thirteen patients were included, of whom 6 were females. Mean age at the time of intervention was 64.2 (±11.8) years old. All were hypertensive, (23% had Diabetes, 30.7% had heart failure, 84% had CKD and peripheral vascular disease was prevalent on 53.8%. Indications for revascularization (not mutually exclusive) were; pulmonary edema (23.8%), worsening renal function (46.1%) and refractory HTN (69.23%). Six (46.1%) patients had only one indication, while 4 patients (30.7%) had 2 indications and 3 patients (23%) had 3 indications. Mean number of anti-hypertensive medications at baseline was 3.6 ±1.6 and in six month it dropped to 2.5 ±1 (P = 0.02). Furthermore, the proportion of those with controlled blood pressure has increased significantly from 8 % to 83% (P= 0.004). Mean eGFR at the time of intervention was 37.0 ±27 ml/min.1.73m². This improved to 45.5 ± 28 ml/min.1.73m², but the difference did not reach statistical significance (P= 0.14).

Conclusions: Outcomes for patients selected for renal revascularitaion in Royal Preston Hospital were excellent. Despite the negative trials, renal angioplasty for atherosclerotic renal disease still has a positive role that is achieved through careful patient selection with a clinical indication in addition significant renal artery stenosis. Larger scope studies with meticulous patient selection of high risk are warranted.

PUB157

Relationship Between Renal Function and Development of Remission in Patients with Chronic Refractory Gout Treated with Pegloticase

Naomi Schlesinger,[1] N. L. Edwards,[2] Richard J. Johnson,[3] Anthony Yeo,[4] Peter E. Lipsky.[5] *[1]Rutgers, The State University of New Jersey, New Brunswick, NJ; [2]University of Florida College of Medicine, Gainesville, FL; [3]University of Colorado Denver, Aurora, CO; [4]Horizon Pharma, Lake Forest, IL; [5]AMPEL BioSolutions, Charlottesville, VA.*

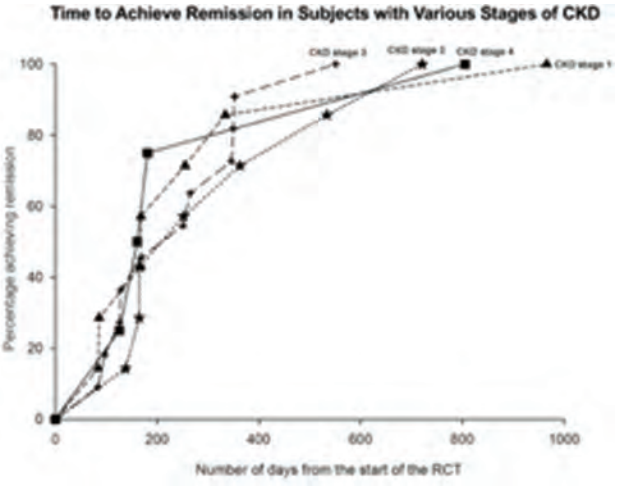
Background: Criteria for remission in gout have been reported[1] and they include: serum urate <6 mg/dL, no flares in last 12 months, no tophi, pain <2, and patient global assessment of disease activity <2, each on a 10-point scale. Impaired kidney function is a recognized comorbidity of gout, but it is not known whether chronic kidney disease (CKD) impairs the response to gout treatment.

Methods: This analysis used results from two 6-month randomized controlled trials of pegloticase in patients with chronic refractory gout to address this issue. The analysis included 34 patients who responded to pegloticase administered at a dose of 8 mg every 2 weeks (q2w) with sustained serum urate reductions (<6 mg/dL) over 6 months.

Results: Overall, 29/34 (85.3%) of these patients met the proposed criteria for remission. eGFR was determined at baseline and patients were divided into CKD categories. CKD category had no significant effect on the percentage of patients achieving remission nor on the time required to develop a remission. Notably, no significant change in eGFR was noted in these patients.

Conclusions: These results suggest that renal dysfunction estimated by eGFR does not influence remission or time to reach remission in pegloticase-treated patients with chronic refractory gout, thus maintaining persistent urate lowering. Reference [1] de Lautour H, et al. *Arthritis Care Res*(Hoboken). 2016;68:667.

Funding: Commercial Support - Horizon Pharma



PUB158

Addressing Metabolic Acidosis in CKD Patients with Liver Cirrhosis - No Good Deed

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Background: Uncorrected metabolic acidosis(MA) is detrimental in chronic kidney disease (CKD)with evidence of mortality benefit in correcting acidosis to bicarbonate(HCO3) levels of around 22 mmol/l. However, impact of correcting MA in liver failure with cirrhosis(LF-c)) is unclear. LF-c is a physiologically alkalotic state, with compensatory low HCO3. Correcting acidic milieu may provide overall benefit, however this commonly requires using sodium salts. This may be detrimental to LF-c patients' due to

sodium load resulting in increased interventions like paracentesis. We hypothesized that if there is evidence of MA as measured by blood gases(ABG/VBG), we can target a moderate correction of acidosis within the recommended sodium restriction.

Methods: We conducted a retrospective chart review to study outcomes in adults over 18 with MA and LF-calculated MELD score 0-39.

Results: Inpatient charts reviewed between 2015-17 had 14 patients with LF-c and CKD with MA proven by ABG/VBG. Of these, 3 were on oral NaHCO3 targeting near normal serum HCO3 level.

Conclusions: KDIGO recommends HCO3 level to 22 mmol/L to prevent CKD progression. However, it is unclear if we can imply the same to population with LF-c and CKD as such studies are unavailable. Our preliminary data shows no improved outcomes. We opine that we may target lower HCO3 levels to account for respiratory compensation and to prevent sodium overload. Our study is limited by sample size and observational data.

Patient Characteristics

AGE	SEX	AVERAGE BICARB	ON BICARB SUPPLEMENTS	CKD STAGE	NO OF PARACENTESIS	NO OF DEATHS
49	M	19	NO	III	2	
58	M	23	NO	III	0	
68	F	20	YES	IV	11	
54	F	19	YES	IV	1	1
40	F	22	NO	II	8	
39	M	20	NO	III	7	1
55	F	17	NO	IV	0	
58	M	18	NO	III	2	
58	F	25	YES	II	4	
61	F	19	NO	III	1	
63	F	25	NO	III	0	1
55	M	16	NO	IV	11	
43	M	15	NO	III	1	

PUB159

Effectiveness of PCSK9 Inhibitors in Dementia Patients with Chronic Renal Insufficiency

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Background: Based on 2017 data from Centers for Disease Control and Prevention, 15% of US population suffered from chronic kidney disease (CKD) and over 80% of end-stage renal disease patients were receiving long-term hemodialysis. In CKD patients, dementia is a common association and plays as an important factor that increases morbidity and mortality. PCSK9, the protein convertase enzyme, involves in degradation of low-density lipoprotein (LDL) receptors in the liver. PCSK9 inhibitors are proven to reduce LDL level in the blood by increasing available LDL receptors on the hepatocytes. Low plasma LDL subsequently reduces the risk of atherosclerosis, including the cerebral circulation. There is no report of the effect of PCSK9 inhibitors on dementia in CKD patients. Our study might be an initiation to this area.

Methods: This study was a non-randomized clinical trial study design. A total of 79 participants (39 males and 40 females; average age, 62) having chronic renal insufficiency with hypercholesterolemia and a certain degree of memory impairment was injected with PCSK9 inhibitor (Repatha 420 mg subcutaneous injection monthly) for 3 months. The severity of dementia was assessed and recorded at the start of the trial using Functional Assessment Staging Test according to Dementia Care Central. Patients were followed up biweekly to reassess the dementia stage and monitor any unwanted side effect of the drug. The targeted primary outcome was changes in the dementia stages and concurrent reduction of LDL levels.

Results: At the first follow-up visit, patients and their family members reported having increased energy and subjective improvement of memory. This effect has continued and the dementia stages gradually declined up to two stages below the initial stage at the end of the 3-month period. The LDL fell down from initial level of 185 mg/dl to 35 mg/dl after 3 months. No side effect was reported. The study is still ongoing.

Conclusions: The results clearly shows that PCSK9 inhibitor is effective in improving memory loss in those CKD patients. The hypothesis is that PCSK9 inhibitor improved cerebral circulation by halting or even reversing the process of atherosclerosis leading to the recovery of vulnerable brain areas with insufficient blood supply. However, more scientific approaches and researches in the larger study population are necessary to prove this hypothesis.

PUB160

A New Glomerular Filtration Rate Estimating Model for CKD Patients Using Ensemble Learning

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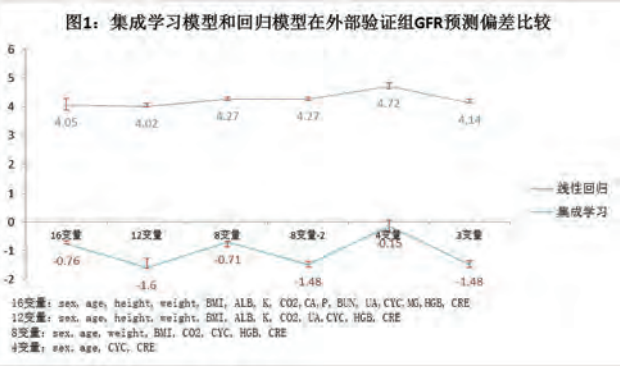
Background: Accurate estimating GFR is very important for clinical settings. However, since the CKD_EPI equation published in the NEJM on 2012, the performance of GFR estimating equation did not improved.

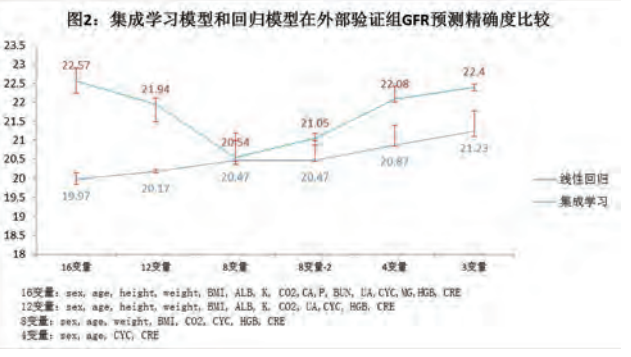
Methods: CKD patients in China from May 2011 to June 2015 were used as the development dataset and from July 2015 to June 2016 as the exteranl vailation dataset. sGFRs were measured by the DTPA kidnye scan callibrated to the 2 plasma sample DTPA serum clearance method.

Results: In the external validation dataset, eGFR by emsemble leaning improved bias and accuracy than the revised regression equatinos. The 30% accuracy of the 8 variables emsemble learning is 88%. Detailed imformation is showed in the figured attached

Conclusions: The emsemble leaning models achieved better performance than the revised equation models in GFR estimates.

Funding: Government Support - Non-U.S.





PUB161

Probiotic Supplements Prevented Oxonic Acid-Induced Hyperuricemia and Renal Damage

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Background: In chronic kidney disease, HU is extremely common, and uric acid (UA) excretion heavily relies on gut uricolysis by gut microbiotaMoreover, HU contributes to CKD physiopathology. Current therapy for lowering serum UA includes drugs that may produce undesired secondary effects. Therefore, this pilot study was designed to evaluate the potential of two probiotic supplements to reduce systemic uric acid concentrations and to evaluate whether hyperuricemic renal damage was prevented.

Methods: Groups of 6 rats each were followed by 5 weeks and allocated in C= Control; ND= Oxonic acid-induced hyperuricemia (HU) +regular diet; P= HU+placebo; F1= HU+ probiotics formula 1 and F2= HU+ probiotics formula 2. At the end of the study, systolic blood pressure measurement as well as blood samples and 16 h urine collections were taken. Then rats were sacrificed and kidneys were washed by perfusion, fixed and analyzed for arteriolar wall area using alpha-smooth muscle actin to mark the arteriolar vessels.

Results: Results are showed in Table 1

Conclusions: In conclusion, we demonstrated for the first time the ability of probiotics containing uricolytic bacteria to lower serum uric acid in hyperuricemic animals with beneficial consequences on blood pressure and renal disease. As probiotics supplements are innocuous for the human health, this might represent a safe therapeutic approach to treat HU.

Funding: Commercial Support - Kibow Biotech

Table 1

Group	Plasma UA, *mg/dL*	SBP, *mmHg*	CrCl, *ml/min*	U_{NAG}, *mmol PNP/16 h*	Arteriolar wall área, *μm^2*	U_{TBARS}, *μM MDA/16 h*
C	0.93±0.04	126±7	1.2±0.06	0.3±0.2	237±19	0.52±0.03
ND	4.5±0.11	135±7	$0.7±0.07^{1}$	$4.5±0.14^{1}$	$340±26^{1}$	$2.9±0.24^{1}$
P	4.5±0.14	138±4	$0.8±0.06^{1}$	$3.9±0.45^{1,2}$	$296±20^{1,2}$	$2.8±0.22^{1}$
F1	1.7±0.18	$118±8^{2,3}$	$0.9±0.19^{1,2}$	$1.1±0.10^{1,2,3}$	$270±17^{2}$	$1.6±0.16^{1,2,3}$
F2	1.5±0.19	$121±6^{3}$	$1.1±0.22^{2,3,4}$	$0.9±0.02^{1,2,3}$	$251±29^{2,3}$	$1.5±0.09^{1,2,3}$

Data presented as mean±SD. Multiple comparisons: 1=p<0.05 vs NC; 2=p<0.05 vs HU-ND; 3=p<0.05 vs HU-P

PUB162

The Transregional Collaborative Research Center SFB/TRR219: Mechanisms of Cardiovascular Complications in CKD

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Background: A new Research Center of the German Research Foundation (DFG) seeks understanding of the renal and cardiovascular interactions that underlie enhanced cardiovascular risk in patients with CKD, with the ultimate aim to trigger the development of novel treatment strategies to reduce cardiovascular morbidity and mortality in these patients.

Methods: Reducing the increased cardiovascular mortality in CKD patients through novel therapeutic strategies first requires the identification and understanding of the pathological mechanisms adversely affecting the cardiovascular system specifically in CKD. With exactly this goal two German universities, the RWTH University of Aachen and Saarland University, have initiated the Research Center to analyse in experimental and clinical studies the multi-factorial aspects of CKD-related cardiovascular morbidity and mortality.

Results: Some relevant mediators that affect renal, myocardial and vascular pathology have already been identified. However, their functions regarding the complex interactions between kidney, heart and vessel are still poorly understood. The consortium will characterize known and newly identified mediators relevant in CKD and seek understanding of the mechanisms underlying their effect on heart and vessels causing CKD-related CVD. The main mechanisms that will be investigated to underlie increased cardiovascular risk in CKD include calcification, inflammation, oxidative stress and fibrosis, in addition to alterations in thrombosis and neurohumoral activity. Secondly, SFB/TRR219 consortium will strive to identify novel mediators relevant in CKD with a strong impact on CVD. Also, the consortium will study the translational aspects by investigating novel mediators as potential biomarkers of CKD-related CVD, by analyzing the effect of novel interventions on CKD-related cardiovascular pathology, and by extending previously developed diagnostic tests for cardiovascular pathology to the context of CKD to aid its application into clinical practice.

Conclusions: In summary, the SFB/TRR219 is a German research consortium that seeks understanding of the renal and cardiovascular interactions that underlie enhanced CV risk in patients with CKD, with the ultimate aim to trigger the development of novel treatment strategies to reduce cardiovascular morbidity and mortality in these patients.

Funding: Government Support - Non-U.S.

PUB163

A Novel Model of Renal Vascular Disease in the C57BL/ 6 Mouse Strain

Julius E. Kieswich,[1] Jianmin Chen,[3] Samira Alliouachene,[2] Paul W. Caton,[6] Kieran Mccafferty,[5] Christoph Thiemermann,[3] Muhammad M. Yaqoob.[4] *[1]Centre for Translational Medicine and Therapeutics, LONDON, United Kingdom; [2]Queen Mary University, London, United Kingdom; [3]Queen Mary University of London, London, United Kingdom; [4]William Harvey Research Institute, London, United Kingdom; [5]NHS, LONDON, United Kingdom; [6]King's College London, LONDON, United Kingdom.*

Background: Vascular disease is prevalent in the chronic kidney disease (CKD) population having a 20 fold higher incidence of cardiovascular mortality compared to the population as a whole. Reno- cardiac syndrome (RCS), described as cardiovascular disease initiated by renal failure, is a growing world health problem thus necessitating the need for continued improvement of therapeutic strategies to combat it. Murine in vivo models contribute greatly to such research allowing for specific genetic modification and therefore reduced miscellany, however there is currently no reliable model of CKD in the most common genetically modified mouse strain, the C57BL/6. In this study we have manipulated an established model of CKD using adenine infused diet and prolonged the course of its pathology in order to achieve CKD and subsequent vascular disease in the C57BL/6 mouse strain.

Methods: 9 week old C57BL/6 male mice were administered a 0.15% adenine diet or control diet for 20 weeks.

Results: Administration of 0.15% adenine diet caused progressive renal failure resulting in renal vascular disease. The mice tolerated the diet well, weights being maintained with no mortality. At endpoint uraemia was confirmed by blood biochemistry which in the adenine fed mice showed significant increases in serum creatinine and urea, ($P<0.0001$) and a significantly reduced glomerular filtration rate as indicated by creatinine clearance ($P<0.05$). Immunoblotting of aortic tissues demonstrated classic features of vascular disease, that is increased apoptosis (caspase 3) and fibrosis (α-SMA) and increased levels of total Akt suggested a mechanistic pathway for this pathology. Haematoxylin and eosin staining illustrated the inflammatory state of the vasculature and immunohistochemistry for α-SMA further confirmed fibrosis.

Conclusions: We present a novel regimen of adenine diet which induces both CKD and reno-vascular disease in the C57/BL6 mouse strain. The non-surgical nature of this model makes it highly reproducible compared to other models currently available.

Funding: Private Foundation Support

PUB164

YAP/TAZ Upregulation During Kidney Injury Links Altered Metabolism to Fibrotic Response

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Background: Recent studies including ours link Hippo-YAP/TAZ pathway deregulation in kidney disease. YAP/TAZ upregulation during renal injury promotes maladaptive repair and transduces TGF-beta1 and mechanical signaling. Here we test the hypothesis that renal YAP/TAZ activation promotes metabolic reprograming associated with chronic kidney disease progression.

Methods: We investigated the potential relationship among YAP/TAZ, aerobic glycolysis and fibrosis using both in vitro and in vivo mouse models of renal injury.

Results: YAP and TAZ expression are persistently upregulated in the tubulointerstitium during obstructive nephropathy. Stable transduction of YAP or TAZ in renal epithelial cells promoted fibrotic factor induction (e.g., CTGF, fibronectin), dedifferentiation and G2/M cell cycle arrest relative to empty vector-expressing controls. Epithelial YAP/TAZ activation leads to SMAD3 activation and TEAD upregulation which are necessary for fibrotic response. YAP/TAZ overexpression also stimulated robust expression of hexokinase-1, phosphofructokinase and pyruvate kinase M2, three enzymes that catalyze irreversible steps of glycolysis. Pre-incubation with the YAP/TAZ inhibitor, verteporfin attenuated glycolytic reprogramming in YAP/TAZ expressing cultures. Concurrent induction of the glycolytic enzymes and YAP/TAZ is also evident in the ligated (UUO) mouse kidney compared to contralateral controls. Intraperitoneal administration of verteporfin not only attenuated fibrogenesis but decreased glycolytic enzyme expression in the obstructed kidneys compared to vehicle treated UUO controls.

Conclusions: Renal YAP and TAZ upregulation promotes glycolytic reprogramming and fibrotic epithelial dysfunction. Pharmacological inhibition of YAP/TAZ activation, conversely, attenuated aerobic glycolysis and renal fibrosis in mice, establishing novel pathological links between Hippo-YAP/TAZ deregulation and metabolic alterations in progressive CKD.

Funding: Other NIH Support - NIH GM057242 and a Capital Region Medical Research Institute Grants

PUB165

Study on the Correlation Between Serum NGAL Level and Clinical Progressive Risk Factors of Primary IgA Nephropathy

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Background: To investigate the correlation between serum neutrophil gelatinase-associated apolipoprotein levels(sNGAL) and the risk factors of primary IgA nephropathy and evaluate the early predictive value of sNAGL on the progression of IgA nephropathy.

Methods: Retrospectively analyzed 70 cases of primary IgA nephropathy, that diagnosed in the nephrology department of Ningxia People's hospital from April 2016 to August 2017. One-way ANOVA, bivariate Spearman correlation analysis and multivariate linear regression analysis were used to investigate the effect of sNGAL Correlation of serum levels with risk factors for the clinical progression of primary IgA nephropathy.

Results: The serum levels of sNGAL were positively correlated with blood pressure ($r=0.33$, $P=0.005$), urinary protein excretion ($r=0.371$, $P=0.002$), eGFR Correlation analysis showed statistically significant differences ($P<0.05$). The differences of sNGAL in 24h urine protein ($P=0.003$) and CKD staging ($P=0.000$) were statistically significant ($P<0.05$). Multivariate regression analysis showed that eGFR ($\beta= -0.509$, $P=0.000$) was an independent factor of sNGAL level.

Conclusions: sNGAL is closely related to renal dysfunction and proteinuria. Early detection of sNGAL can be used to assess renal function and predict the progression of the disease. tor of sNGAL level.

Funding: Government Support - Non-U.S.

PUB166

Alterations of the Lipid Profile in the Aging Kidney Identified by MALDI Imaging Mass Spectrometry

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Background: During aging, kidney experiences functional and physiological changes which are closely related with chronic kidney disease (CKD). There is increasing evidence supporting the role of lipid changes in the etiology of CKD.

Methods: To understand the role of lipids mediating various metabolic processes during aging, we conducted MALDI imaging mass spectrometry (MALDI IMS) analysis in kidneys harvested from young mice (2 months old, n=3) and old mice (24 months old, n=3).

Results: MALDI IMS analysis showed an increase in ceramide levels and a decrease in sphingomyelins (SMs) and phosphatidylcholines (PCs) levels in kidneys of old mice. Immunohistochemistry (IHC) confirmed elevation of PLA2 and Smase in kidneys of old mice.

Conclusions: Our MALDI IMS data showed the altered distribution of lipids on aged kidney as indicative for functional changes of the kidney with aging. Combined analysis of MALDI IMS and IHC confirmed lipidomic changes and expression levels of responsible enzymes as well as morphological changes.

PUB167

The Significance of NAD+ Metabolites and Sirtuins in CKD

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Background: Renal tissue fibrosis is a final common pathway toward the end-stage renal disease and the change in nicotinamide adenine dinucleotide (NAD+) metabolism contributes to the pathogenesis of renal dysfunction including fibrotic renal disease. The substrates of NAD+ synthesis such as nicotinamide (NAM) and nicotinamide mononucleotide (NMN) have become an emerging therapeutic target for kidney diseases by the activation of sirtuins. In this study, we examined the alteration of NAD+ metabolites in the unilateral ureter obstruction (UUO) model mice and CKD patients.

Methods: We measured NAD+ metabolite levels in the kidneys of UUO and sham-operated mice. In CKD patients, we recruited more than 25 subjects in each CKD stages and measured NAD+ metabolite levels in the serum.

Results: In the kidneys of UUO mice, renal NAM, NMN and NAD+ levels were significantly lower than in sham-operated mice. In contrast, the downstream products of NAD+ metabolites, N-methyl-2-pyridone-5-carboxamide (2-PY) and 4PY were accumulated in the kidneys of UUO mice. Sirtuin activity is regulated by NAD+ levels and Sirt1, Sirt3, and Sirt7 mRNA expression were significantly decreased in accordance with the increased fibrosis genes in the kidneys of UUO mice. In the CKD patients, across increasing CKD stages, gradual decreases in serum levels of NAM were found ($p<0.01$, for trend). On the other hand, the serum levels of 2PY and 4PY significantly increased respectively ($p<0.01$ for the trend test). In single regression analyses, NAM was significantly positively correlated with eGFR. 2PY and 4PY were negatively correlated with eGFR. Multiple regression analyses showed that eGFR was an independent explanatory variable for NAD+ metabolites after adjusting them with other factors such as age, BMI and HbA1c.

Conclusions: Substrates of NAD+ synthesis such as NMN and NAM decreased in both kidney and serum in chronic renal injury, which could contribute to the inhibition of sirtuin activity and the fibrosis in CKD. In CKD patients, NAD+ metabolites were strongly associated with renal dysfunction.

Funding: Commercial Support - Shionogi & Co., Ltd.

PUB168

Varying Nephrectomy Delay Time After Unilateral Ischemic Injury Allows Development of an Animal Model with a Controllable Degree of Renal Dysfunction

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Background: An important feature of the clinical course of CKD is the graded decline in renal function, divided into 5 stages (CKD1 to CKD5). Extrapolating data from animal studies to the clinical situation requires a good functional correlate between the target population and the experimental model. Based on the fact that an acutely injured kidney persistently loses renal mass in the presence of its healthy counterpart and an early nephrectomy (Nx) of the healthy kidney rescues the decay of the injured kidney, we hypothesized that a sufficiently delayed Nx would not allow efficient renal recovery of the injured kidney and that by varying the Nx delay time, one would be able to predefine the eventual degree of remnant renal function correlating with the clinically relevant CKD stages.

Methods: AKI was induced in male Wister rats by left ischemia/reperfusion (UIRI) for 60 min after which contralateral Nx was performed 3, 10 or 20 days later. Renal function was assessed by serum/urine creatinine and transcutaneous measurement of GFR 24 and 72 hours after Nx and weekly thereafter. Rats were euthanized 11 weeks after Nx. Kidneys were weighed and histology was evaluated by PAS stain.

Results: In all groups, 24h after Nx renal function was impaired. Early Nx (day 3) induced full recovery of renal function by week 11 starting from week 3. Late Nx (day 10, 20) led to a functional loss between 40% at week 3 and 20% at week 11 ($p<0.05$). There was no significant difference in renal function between groups of day 10 and 20. Nx induced compensatory hypertrophy/recovery in all groups as shown by an increased renal mass-to-body weight ratio from 2.9 mg/g (sham) to 4.6 mg/g (day 3) and 4.8 mg/g (day 10). Hypertrophy/repair was less pronounced when Nx was performed at day 20 (4.0 mg/g, $p<0.05$). Histological analysis confirmed hypertrophy and showed more cortico-medullary atrophy at day 10 and 20 as compared to day 3.

Conclusions: Early Nx rescues renal function, whereas sufficient delayed Nx does not allow a full functional recovery of the injured kidney, currently mimicking CKD2. Varying Nx delay time after UIRI thus can provide an experimental method to induce renal dysfunction of different but controllable severity.

PUB169

Uremic Toxins Activates Na/K-ATPase Oxidant Amplification Loop in Mouse Pre-Adipocytes Causing Phenotypic Change in Adipocyte and Oxidative Stress

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Background: Experimental CKD leads to accumulation of uremic toxins(UT) in the circulation resulting in increased ROS production which, in turn, is known to activate Na/K-ATPase signaling. Studies in mouse model of obesity has shown that increased oxidative stress in plasma is due to increased ROS and cytokines production from dysfunctional adipocytes. We hypothesize that adipocytes exposed to UTs will activate Na/K-ATPase signaling causing redox imbalance in adipocytes. We will also demonstrate that Na/K-ATPase antagonist, pNaKtide, will attenuate these pathophysiological consequences. We will employ our lentivirus construct, lenti-adiponectin-NaKtide, to specifically target adipocytes.

Methods: 3T3-L1 cells were treated with varying concentrations of UTs, indoxyl sulfate (25, 50 and 100 μM) and p-cresol (100, 200 and 250 μM), with or without pNaKtide (1 μM) for 5 days in adipogenic media. Cells were treated as follows: vehicle IS alone, p-cresol alone, NaKtide alone, IS+NaKtide, p-cresol+NaKtide, pNaKtide alone, IS+pNaKtide, and p-cresol+pNaKtide. RT-PCR and Western blotting was used to evaluate changes in RNA and protein expression, respectively, of adipogenic markers (PPARγ, C/EBPα, aP2, FAS, Mest), oxidative stress markers (ROS, TBARS), apoptotic markers (Bcl2, Bad, Caspase 3 and 9) and inflammation markers (TNF-α, IL-6, MCP-1).

Results: Our results demonstrated that 3T3-L1 adipocyte cells treated with uremic toxins induced oxidative stress, apoptosis and inflammation through activation of Na/K-ATPase signaling ($p<0.01$). However, pNaKtide treatment ameliorated adipocytes dysfunction and restored cellular redox, further attenuating the pathophysiological consequences.

Conclusions: This study suggests that the Na/K-ATPase signaling activated by elevated levels of uremic toxins induce redox imbalance in adipocytes and causes apoptosis and inflammation. Our results support that transfection of 3T3-L1 adipocytes cell with pNaKtide transformed the phenotype of these dysfunctional adipocytes to that of healthy adipocytes. Our study demonstrates that Na/K-ATPase-Src feed-forward oxidant-amplification loop and/or adipocytes are potential targets for CKD intervention and presents a novel treatment for the pathophysiological condition.

PUB170

Sensing-Failure to Detect Energy Depletion Is a Novel Therapeutic Target for CKD

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Background: Although it is known that the energy-status sensor 5-adenosine monophosphate (AMP)-activated protein kinase (AMPK) is inactivated in chronic kidney disease (CKD) status, to date, the mechanism of AMPK dysregulation in CKD remains unknown, and no study have shown the effects of AMPK activators on chronic stage of kidney injury, in which uremic condition has been substantially established. In this study, we hypothesized AMPK dysregulation in kidneys from subtotal nephrectomy (5/6 Nx) mice is caused by systemic factors, such as uremic metabolites.

Methods: Using capillary electrophoresis-time-of-flight mass spectrometry (CE-TOFMS), we specified several metabolites accumulated in kidney, muscle and heart in the CKD mice (n=4) compared to sham control mice (n=4). In HK-2 cells, murine skeletal myoblast cells (C2C12) and embryonic rat cardiomyocytes (H9C2), effects of uremic metabolites and AMPK activators on AMPK phosphorylation were assessed. Effects of selected uremic metabolites and AMPK activators on kidneys were assessed by immunoblotting, quantitative RT-PCR and histologic analysis.

Results: Principal component analysis (PCA) revealed remarkable differences of metabolome profiles in the 5/6 Nx kidney between sham-control mice and 5/6 Nx mice. Using metabolome analyses, we demonstrated that, in CKD kidneys, AMPK could not sense defective energy metabolism because of multiple uremic factors such as indoxyl 3-sulfate (IS). In consintent with this, AMP mimetics, 5-aminoimidazole-4-carboxamide-1-b-4ribofuranoside (AICAR), did not increase AMPK phosphorylation at Thr 172 and did not change profibrotic marker in 5/6 Nx mice kidney, despite the increased AMPK phosphorylation in kidneys from control sham mice. Direct AMPK activator A-769662, which bypasses the AMP sensing mechanism, ameliorated fibrogenic effects and energy status of the kidneys in a mouse model of CKD.

Conclusions: These results confirmed that AMP sensing failure caused by uremic metabolites is the key mechanism underlying the vicious cycle of energy depletion and CKD progression and can be a novel therapeutic target for CKD.

PUB171

NUAK1 Is a Novel Inhibitor of Fibroblast Hippo Activity and Driver of Kidney Fibrosis

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Background: Kidney fibrosis represents a final common damage pathway that is activated by nearly all forms of chronic kidney injury. Historically, studies have focused on TGF-beta as an important driver of fibrosis. Unfortunately, attempts to block TGF-beta have largely failed, in part due to the many non-fibrotic functions of this pleiotropic molecule. Recent work from our lab and others has shown that the Hippo pathway, a series of kinases that ultimately inhibit the transcription co-factors YAP and TAZ, is a critical inhibitor of fibrosis. Interestingly, the Hippo pathway is emerging as a central regulator of fibrosis, inhibiting fibrosis via both TGF-beta-dependent and -independent mechanisms. While AMP kinase (AMPK) is a well recognized regulator of the Hippo pathway, NUAK1 is a related kinase from the same serine/threonine kinase family that we recently have shown to be expressed by kidney fibroblasts.

Methods: The role of NUAK1 in the regulation of Hippo pathway activity and fibroblast activation was studied both genetically (NUAK1 silencing) or pharmacologically (using the NUAK inhibitor WZ4003) in NRK49F rat kidney fibroblasts both basally and in the context of TGF-beta stimulation. We generated tamoxifen-inducible fibroblast-specific NUAK1 knockout mice (Col1a2 Cre-NUAK1$^{f/f}$), and subjected them to unilateral ureteral obstruction (UUO).

Results: Both deletion and inhibition of NUAK1 resulted in increased Hippo pathway activity, as evidenced by increased YAP/TAZ phosphorylation, nuclear YAP/TAZ exclusion, and reduced expression of YAP/TAZ-inducible genes. NUAK1 inhibition also blocked basal and TGF-beta-induced fibroblast activation and expression of extracellular matrix genes. *In vivo*, fibroblast-specific NUAK1 deficiency protected against UUO-induced kidney fibrosis.

Conclusions: NUAK1 is a previously unrecognized fibroblast activator in the kidney, working at least in part through regulation of the Hippo pathway. Future efforts to inhibit NUAK1 may represent a novel anti-fibrotic strategy.

Funding: Government Support - Non-U.S.

PUB172

RON Inhibition by Egr-1 siRNA Attenuates Epithelial Mesenchymal Transition and Fibrosis via Suppressing Smad and MAPK in Human Proximal Tubular Epithelial Cells

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Background: Receptor tyrosine kinases play important roles in the pathogenic processes of renal fibrosis. Egr-1 is a transcription factor that regulates genes that modulate fibrosis, and role as common transcription factor of receptor tyrosine kinase. This study investigated the anti-fibrosis effect by inhibition of Egr-1, an important transcription factor for receptor tyrosine kinase activation in RON overexpressed-HK-2 cells.

Methods: Stable cell lines for RON overexpression and the transfected cells of Egr-1 siRNA for RON inhibition were developed to examine the renal fibrosis and molecular mechanisms by RON in human renal proximal tubular epithelial (HK-2) cells. The protein expression of epithelial-mesenchymal transition (EMT)-related proteins N-cadherin, E-cadherin, vimentin and fibrosis-related proteins TGF-β, α-smooth muscle actin (αSMA), fibronectin as well as Smad family and MAPK signal pathway was determined by semiquantitative immunoblotting. Staining of receptor tyrosine kinase family was evaluated using confocal laser microscopy.

Results: RON overexpression increased the protein expression of EMT- and fibrosis-related proteins such as N-cadherin, E-cadherin, vimentin, TGF-β, αSMA, and fibronectin in HK-2 cells. Moreover, overexpression of RON increased phophorylation of Smad2/3 and smad-4, and Erk1/2, p38, and Jnk MAPK pathways. In contrast, RON inhibition by Egr-1 siRNA attenuated expression of EMT- and fibrosis-related proteins and decreased phosphorylation of Smad family and MAPK pathway. In addition, the Egr-1 siRNA silencing attenuated expression of IGFR, VEGFR, and PDGFR.

Conclusions: Inhibition of Egr-1 may exert anti-fibrotic effect by suppression of EMT via controlling Smad and MAPK signal pathways in HK-2 cells.

Funding: Government Support - Non-U.S.

PUB173

Phosphorylation of PKM2 in Tubular Epithelial Cells Regulates Metabolic Reprogramming and Tubulointerstitial Fibrosis

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Background: Chronic kidney disease (CKD) is becoming the world's public health concern with high morbidity and mortality. Tubulointerstitial fibrosis is an inevitable pathologic outcomes of nearly all kinds of CKD no matter what the initial insult is. Structural and functional changes of tubular epithelial cells (TECs) during the pathogenesis contribute to the progression of fibrosis. Maintenance of the structure and function TECs is energy consuming and depends mainly on oxidative phosphrylation (OXPHOS). However, metabolic reprogramming from OXPHOS to glycolysis are defining features of injured TECs. Moreover, reprogramming toward glycolysis promotes TECs plasticity and extracellular matrix (ECM) accumulation, which is a newly discovered mechanism in renal fibrosis. Pyruvate kinase isozyme 2 (PKM2) is one of the key enzymes in glycolysis, whose dimerization after been phosphrylated critically determines the glycolytic reprogramming. In this study, we investigated the role of PKM2 in tubulointerstitial fibrosis.

Methods: Tubulointerstitial fibrosis was induced by unilateral urethral obstruction (UUO) and analyzed by morphologic staining and western blot. We generated proximal tubular cells specific PKM2 heterozygous mice to investigate its role on renal fibrosis. Shikonin, an inhibitor of PKM2 was given at the dose of 5mg/kg body weight.

Results: Phosphrylation of PKM2 in TECs was markedly increased accompanied with metabolic reprogramming towards glycolysis in obstructed kidney. *Pkm2*-deficient mice suffered UUO experienced less severe tubulointerstitial fibrosis and accumulation of ECM than wild-type (WT) mice. Shikonin inhibits the phosphrylation and activation of PKM2 and therefore attenuated the expression and accumulation of ECM in obstructed kidney. In primary TECs incubated with TGF-β1, shikonin treatment blocked the glycolysis and relieved the expression of fibronectin and collagen I, suggests that prevention of the phosphrylation and activation of PKM2 could mitigate metabolic reprogramming and reduce the production of ECM by TECs.

Conclusions: Phosphrylation and activation of PKM2 regulates the metabolism of TECs and is essential for prompting the expression of ECM and inducing renal fibrosis. Blocking the phosphrylation of PKM2 using shikonin might provide novel therapeutic strategy for CKD.

Funding: Government Support - Non-U.S.

PUB174

Hepatocyte Nuclear Factors as Possible Mediators of Inflammation and Pathogenesis of Coronary Heart Disease in CKD

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Background: The molecular background of CKD-related inflammatory state and renal fibrosis is rather obscure, though the most potent inflammatory biomarkers like CRP (C-reactive protein), MCP-1 (monocyte chemoattractant protein 1) and ICAM-1 (intracellular adhesion molecule 1) are linked with the pathogenesis of many CKD-related disorders, including cardiovascular diseases. Moreover, some data suggest that MCP-1 is involved in renal fibrosis. Recently, we have found that hepatocyte nuclear factors (HNFs) involved in the transcriptional regulation of several genes, were up-regulated in liver of CRF (chronic renal failure) rats. In this work, we analyzed the interplay between HNFs, MCP-1and ICAM-1 mRNA levels in liver of experimental CRF.

Methods: Rats with experimentally induced CRF (5/6 nephrectomy), pair-feds and controls (sham-operated) were used in the study. HepG2 cells were transfected with siRNA targeting *HNF-1α*. MCP-1, ICAM-1 HNF1α and HNF4α mRNA levels in liver and in HepG2 cells were determined using real-time RT-PCR.

Results: We found a significant coordinate up-regulation of *Mcp-1, Icam-1, Hnf1α* and *Hnf4α* expression in liver of CRF rats, when compared with pair-fed and control animals. These results suggest that HNFs may regulate expression of genes encoding MCP-1 and ICAM-1. To verify this we assessed the effect of *HNF1α* deregulation in hepatocellular model (HepG2 cells) by silencing its endogenous expression using small interfering RNA (siRNA) on MCP-1 and ICAM-1 mRNA levels. We found that the decrease in HNF1α mRNA by two different siRNA was associated with the decrease in MCP-1 and ICAM-1 mRNA level.

Conclusions: Obtained data allow us to recognize that HNFs may play an important role in the up-regulation of, *Mcp-1, Icam-1* genes in liver of CRF rats, and presumably in CKD patient. HNFs may be an essential element of molecular background of CKD-related inflammatory state and coronary heart disease.

PUB175

TSSC3 Overexpression Suppress Anoikis Resistance and Pro-Fibrotic Ability via Inhibiting PI3K-Akt Pathway in Myofibroblast

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Background: Myofibroblast activation is the key event of renal interstitial fibrosis (RIF). Anoikis resistance is the hallmarker of active Myofibroblasts conferred by the continuous activation of the PI3K-AKT pathway. Our previous study found that TSSC3 enhanced the sensitivity of cancer cells to anoikis via Src-dependent PI3K/Akt pathway. We hypothesize that Myofibroblast anoikis induction by TSSC3 may suppress RIF by inhibiting the PI3K-AKT pathway.

Methods: Anoikis was induced by exogenous addition of RGD-containing peptides or placing cells in suspension. Myofibroblasts were established by stimulating HK-2 cells by TGF-β. We transfected TSSC3 overexpression adenovirus in HK-2, then experimented with Annexin V-FITC and CCK8 assay. We detected the expressions of molecules related to PI3K/AKT-mediated apoptosis signaling and fibrosis by qRT-PCR and WB analysis.

Results: TGF-β significantly increased α-SMA and decreased Villin expression in a time-dependent manner, suggesting that TGF-β facilitates the phenotypic activation of HK-2 toward myofibroblasts, and significantly fewer myofibroblasts than HK-2 underwent anoikis, demonstrating that TGF-β, simultaneous with the induction of myofibroblast differentiation, confers significant protection from anoikis. We observed that phospho-PY20 PI3K-P85 and phospho-Ser473 AKT expressions were significantly increased, but cleaved-caspase3 expression was significantly decreased in the myofibroblasts as compared with HK-2. Myofibroblasts displayed a stronger ability to resist anoikis, than HK-2, as evidenced by higher rates of proliferation and lower rates of apoptosis, which were partly reversed by LY294002 treatment, a pharmacologic inhibitor of PI3K-AKT pathway. TSSC3

overexpression obviously impaired growth and anoikis resistance of myofibroblasts, as well as reduced phospho-PY20 PI3K-P85, phospho-Ser473 AKT expressions and increased cleaved-caspase3 expression of myofibroblasts in suspension culture. Moreover, TSSC3 upregulation significantly inhibited mRNA and protein expressions of collagens type I, collagens type III, fibronectin, PAI-1, MMP-2 and MMP-9 in myofibroblasts.

Conclusions: These data suggest that TSSC3 attenuates anoikis resistance and profibrogenic ability of TGF-β induced myofibroblasts by mediating PI3K-Akt pathway, and may provide an effective way of targeting myofibroblasts by TSSC3 in RIF treatment.

PUB176

Chronic Interstitial Nephritis in Agricultural Communities (CINAC): A Toxin-induced Proximal Lysosomal Tubulopathy Involving Calcineurin Inhibition

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Background: Almost 30 years after the detection of a chronic interstitial nephritis in agricultural communities (CINAC), there is no consensus on its etiology. Heat stress/dehydration and toxic agrochemical exposure are the two most likely etiologies. Also, there are no diagnostic criteria that can directly identify CINAC patients.

Methods: Thirthy-seven renal biopsies (24 Sri Lanka, 11 El Salvador, 1 India, 1 France) of patients with a diagnosis of CINAC (CKD 1-3A, 3B) were examined by light microscopy (LM) and electron microscopy (EM) in comparison to renal biopsies of patients with calcineurin inhibitor (CNI) toxicity (n=17), proteinuric nephropathies (n=15) and reduced renal function of various causes (n=39). A rat study was conducted comparing the histopathology of heat stress/dehydration with cyclosporine nephrotoxicity.

Results: In addition to previously described histopathological changes, CINAC patients demonstrated varying numbers of fine to coarse proximal tubular (PT) granules in preserved and atrophic tubules, showing silver positivity on Jones staining and autofluorescence. Immunofluorescence identified these granules as lysosomes. On EM, lysosomes were enlarged and had a unique dysmorphic morphology with medium electron dense matrix containing non-membrane bound dispersed electron dense aggregates and infrequently focal coarsely granular electron dense material. Identical lesions were only observed in patients on calcineurin inhibitor (CNI) therapy, in a subset of patients with light chain disease and in a patient with Lomustine nephrotoxicity. Some myeloma cells as well as Lomustine have reported CNI activity. Rats treated with cyclosporine for 4 weeks developed similar tubular cell lysosomal alterations, which were absent in the dehydration group.

Conclusions: A specific PT lysosomal lesion was detected associated with CINAC and CNI nephrotoxicity, suggesting CINAC patients are experiencing a tubulotoxic mechanism involving lysosomes and calcineurin inhibition, the latter being a known effect of pesticides.

PUB177

Bardoxolone Methyl Increases Nrf2 Activity, Reduces Inflammation, and Improves Mitochondrial Function in Autosomal Dominant Polycystic Kidney Disease Cells

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Background: Bardoxolone methyl is currently in clinical trials for the treatment of rare chronic kidney diseases, including autosomal dominanant polycystic kidney disease (ADPKD; PHOENIX, Phase 2, NCT03366337) and Alport syndrome (CARDINAL, Phase 2/3, NCT03019185). Common features of chronic kidney diseases include inflammation, remodeling, and fibrosis. Bardoxolone methyl potently activates Nrf2, a transcription factor that counteracts these features by restoring redox balance, improving mitochondrial function, and inhibiting the production of pro-inflammatory mediators. Consistent with a broad effect on kidney function, in clinical trials bardoxolone methyl has been shown to improve estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes and chronic kidney disease and in patients with Alport syndrome. In this study, we assessed whether bardoxolone methyl increases Nrf2 activity and inhibits inflammation in cells derived from renal cysts in patients with ADPKD.

Methods: We used two immortalized ADPKD cell lines, WT 9-7 and WT 9-12, and a normal human proximal tubule cell line, HK-2, to evaluate the effects of bardoxolone methyl.

Results: We found that bardoxolone methyl increased Nrf2 activity in all cell lines tested. Bardoxolone methyl also dose-dependently improved parameters of mitochondrial function, including spare respiratory capacity and maximal respiration, in the ADPKD cell lines. Consistent with the important role of inflammation in ADPKD, we observed higher basal levels of pro-inflammatory mediators in the ADPKD cell lines than in the HK-2 control cell line. Treatment with bardoxolone methyl significantly reduced the levels of C-C Motif Chemokine Ligand 2 (CCL2), also known as monocyte chemoattractant protein-1 (MCP-1).

Conclusions: In summary, bardoxolone methyl increased Nrf2 activity, improved mitochondrial function, and reduced inflammation in renal cell lines derived from patients with ADPKD. These results suggest that activation of Nrf2 by bardoxolone methyl may have the potential to improve the underlying molecular features of ADPKD.

Funding: Commercial Support - Reata Pharmaceuticals

PUB178

Human Mesenchymal Stem Cells and Canine CKD

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Background: Chronic kidney disease (CKD) is common in dogs, and conservative treatment is the best option even in advanced CKD. Here, we used human umbilical cord mesenchymal stem cells MSCs (huMSCs) to treat canine CKD, with the aim of slowing its progression.

Methods: We evaluated huMSC phenotypes and tested cells for multilineage differentiation. At baseline (T0), dogs with stage 2 or 3 CKD were randomized to i.v. injection of placebo (CKD2-p, n=5; CKD3-p, n=6) or 10^6 huMSC/kg (CKD2-msc, n=3; CKD3-msc, n=7). We measured serum creatinine (sCr) and the urinary protein:creatinine (UPC) ratio monthly until month 12 (T12). Urinary albumin was determined by urine exosomes on Western blots. Fibroblast growth factor 23 (FGF23) was quantified initially in normal dogs, then at T0 and T6 in dogs with CKD.

Results: Survival at T12 was similar among the groups. Although renal disease was more severe in CKD3-msc dogs than in CKD3-p dogs at T0, both groups showed similar sCr at T12 (Figure 1). The delta UPC ratio (T12 vs. T0) was lower in treated dogs than in untreated dogs, as was urinary albumin (Table 1). For FGF23 in normal and CKD dogs, the area under the receiver operating characteristic (ROC) curve (AUC) was 0.8, and the delta FGF23 (T6 vs. T0) was smaller in treated dogs than in untreated dogs (Table 1).

Conclusions: As a treatment for CKD, huMSCs show promise. Supported by FAPESP.

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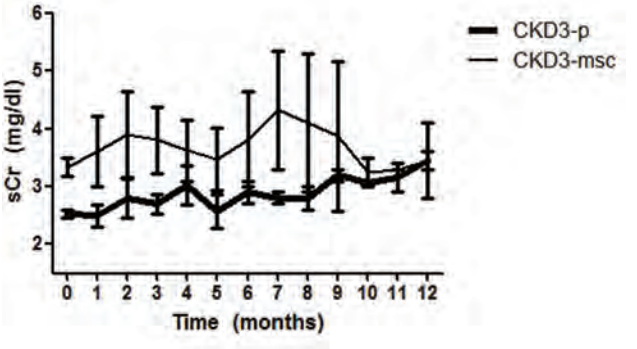
	CKD2-p (n=6)	CKD3-p (n=3)	CKD2-msc (n=6)	CKD3-msc (n=7)
Delta UPC ratio (g/g): T12 vs. T0	0.15±0.25	0.01±0.24	0.45±0.86	0.20±1.12
Delta Urinary albumin (%): T12 vs. T0	-13.77±26.96	-22.44±63.59	5.86±6.67	-49.78±90.34
Delta FGF23 (pg/ml): T6 vs. T0	31.98±94.65	-169.70±243.60	7457±10752	3515±4722



PUB179

TFP5 Specifically Inhibits Deregulated Activity of Cdk5 Protects Pancreatic Cells from High Glucose Toxicity and Recovers the Secretion of Insulin

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Background: Cdk5 may play an important role in the pathology of diabetes mellitus. We previously demonstrated that viral-infected CIP, a 126-residue truncated fragment of p35, effectively and specifically inhibited Cdk5/p25 hyperactivity, restored insulin secretion and rescued Min6 cells from apoptosis induced by high glucose. Because of its large size, however, the CIP molecule is unlikely to be a successful therapy in vivo. We identified a smaller peptide, TFP5, spanning CIP residues Lys^{245}–Ala^{277} (24 amino acid) which is a more effective inhibitor of hyperactive Cdk5.

Methods: We used Mouse pancreatic beta cells Min6 cells and the db/db mice as the in vitro and In vivo models to do the research experiments. TFP5 and scrambled peptide (SCB) peptide were commercially synthesized by Peptide 2.0 (Chantilly, VA, USA). Cells were treated with TFP5 or SCB (500nM). Animals were divided into 4 groups (C57/B6 + SCB, C57/B6 + TFP5, db/db + SCB, and db/db + TFP5). All cells and pancreases samples were prepared for further experiments by using immunohistochemical studies and biochemical analysis. One-way ANOVA was used for the data analysis.

Results: First, the in vitro experiments showed that TFP5 derived from p35, effectively inhibits Cdk5 hyperactivity in Min6 cells and inhibits Cdk5 overactivation induced by high glucose stimulation and recovers insulin secretion in Min6 cells. Secondary, The study found that TFP5 protects both Min6 cells and db/db mice pancreatic cells from high glucose induced apoptosis, and reduce hyperactivation of Cdk5 and recover insulin secretion in

both Min6 cells and pancreases of db/db mice. Furthermore, the study also found that TFP5 reduced inflammation in pancreatic islets by significantly reducing expression of TGFβ1,TNFαand IL1β.

Conclusions: We demonstrated that TFP5 protects or rescues Min6 cells from apoptosis induced by chronic high glucose stress, and rescued db/db mice from diabetes pathology. These data suggest future studies of TFP5 should provide insight as to the mechanism of drug action as a means of further insight into the etiology of diabetes.

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PUB180

Spontaneously Diabetic Rhesus Monkeys Develop Albuminuria and Glomerulopathy Resembling Human Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) remains a leading cause of end-stage renal disease, despite the availability of current treatment options. Over the past two decades, a number of new pathways and drug targets have emerged from rodent models. However, limited success has been achieved with the development of novel treatments for DN. Lack of translation from rodent models to clinical practice is the main challenge. In an attempt to develop a translatable animal model, we systematically characterized metabolic phenotypes in rhesus monkeys and assessed the renal function and structure.

Methods: A colony of 161 rhesus monkeys was longitudinally phenotyped for 6 years using intravenous glucose tolerance testing and DEXA scan for their spontaneous development of metabolic diseases. Among these monkeys, 42, 95, and 24 were identified as healthy, dysmetabolic, and diabetic subjects, respectively. We selected 17 healthy, 14 dysmetabolic, and 23 diabetic monkeys for albuminuria assessment by urine albumin/creatinine ratio (ACR) and glomerular filtration rate (GFR) evaluation by iohexol clearance. We also examined kidney samples at necropsy from 5 diabetic monkeys for histopathological changes.

Results: The metabolic characteristics of diabetic monkeys are aligned with clinical manifestations of type II diabetic patients as exemplified by insulin resistance, reduced β cell response, and hyperglycemia. Approximately 50% of the diabetic monkeys exhibited albuminuria (ACR: 142.9 ± 18.4 vs. 4.5 ± 1.2 μg/mg in healthy group) and hyperfiltration (GFR: 1.58 ± 1.11 vs. 1.32 ± 0.05 ml/min/kg in healthy group). Kidney histopathology from 3 out of 5 diabetic monkeys showed minimal to mild mesangium and Bowman's capsule thickening, tubular epithelium degeneration, and interstitium fibrosis.

Conclusions: Our data demonstrate that spontaneously diabetic rhesus monkeys develop albuminuria and glomerulopathy resembling human DN. Follow-up studies examining disease progression and response to current standard of care therapy in the DN monkey model is warranted.

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PUB181

Glomerular Thrombomodulin Expression Is Decreased in Patients with Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is characterized by endothelial dysfunction. Thrombomodulin is a key regulator of coagulation and inflammation on endothelial cells. Previously, it was demonstrated that thrombomodulin-mediated protein C activation inhibits apoptosis and inflammation in DN in vivo (Nat Med, 2007). Additionally, a complement-inhibitory role of thrombomodulin was described in DN in vivo (Thromb Haem, 2012). Collectively, these studies suggest that thrombomodulin could be involved in the development of DN. However, the role of thrombomodulin in human kidneys with DN remains elusive. Hence, we here investigate thrombomodulin expression in glomeruli of patients with and without DN.

Methods: We investigated the presence of glomerular thrombomodulin expression in 94 autopsy cases with diabetes and DN, 57 with diabetes without DN and 38 controls without diabetes and without renal disease. Sections of the kidneys were stained with thrombomodulin and scored semi-quantitatively. Researchers were blinded to the clinical data of the patients. Additionally, thrombomodulin mRNA expression was measured in microdissected glomeruli from renal biopsies of patients with DN (n=28) and controls (n=10).

Results: Thrombomodulin expression was 1.7 times lower in patients with diabetes, compared to non-diabetic controls (p=0.004). No difference in thrombomodulin expression was observed between diabetic patients with and without DN. Thrombomodulin mRNA levels of DN cases were not significantly different compared to those of control cases.

Conclusions: Thrombomodulin expression is decreased in glomeruli of patients with diabetes. Since glomerular mRNA levels for thrombomodulin are not changed, our data suggest that this loss is a result of increased thrombomodulin degradation. We hypothesize that decreased thrombomodulin expression plays a role in inflammation and complement activation in DN. Restoration of thrombomodulin levels could be a therapeutic goal to prevent the development in DN.

PUB182

Pathogenesis of the Insulin-Resistant Diabetes Induced by Deleting the Gene Encoding Canonical Transient Receptor Potential 1 (TRPC1) Channel: Role of Gene Dosage, Epigenetics, Adiponectin, and Leptin

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Background: Null mice raised by mating -/- ♂ with -/- ♀ showed sustained hyperglycemia & persistent hyperinsulinemia during glucose tolerance test (GTT) vs wild type (wt) raised by mating wt ♂ with wt ♀. Insulin resistance by HOMA was increased 8 fold, but HOMA beta cell function was normal. As null mice ate & weighed more, & as caloric restriction abolished these differences, our data support the role of hyperphagia, possibly due to hypothalamic neuron leptin resistance without TRPC1 channels.

Methods: We studied adipokines, environmental & genetic factors, including gene dosage, in this diabetic phenotype while minimizing epigenetics & hyperphagia in breeders & dams, using only ♂ littermates born to +/- breeders.

Results: 9-week-old null ♂ born to -/- breeders & nursed by -/- dams had severe random hyperglycemia (171 vs. 98 mg %) vs wt born to +/+ breeders & raised by +/+ dams. In contrast, null mice born to +/- breeders & nursed by +/- dams had minimal hyperglycemia (119 vs 171 mg %), implying anti-diabetic effects by a single maternal wt allele. Conversely, wt born to +/- breeders & nursed by +/- dams were hyperglycemic vs wt born to +/+ breeders & nursed by +/+ dams (118 vs 98 mg %), reflecting pro-diabetic effects of maternal haploid deficiency. These wt were as hyperglycemic as null littermates born to the same +/- breeders & nursed by the same +/- dams (118 vs 119 mg %). These data support the role of non-genetic parental influences. From 5th to 30th week, null but not +/- mice were obese vs wt. At 29 weeks, during GTT, both null & +/- mice were equally diabetic, with glucose (in mg %), respectively of 230 & 234 vs. 183 in wt at 20 min, 219 & 229 vs. 155 in wt at 60 min, & 179 & 188 vs 134 in wt at 90 min. These data support the role of both alleles in glucose homeostasis. In null mice, adiponectin was down (5.7) vs. wt (6.4) & +/- (6.2 μg/ml), but leptin up (2.3 vs. 1.3 in wt & 1.8 ng/ml in +/-).

Conclusions: We conclude: 1. Diploid TRPC1 gene deletion produces hyperphagia & obesity. 2. Haploid deficiency suffices to produce diabetes, associated with reduced adiponectin & increased leptin. 3. Non-genetic parental factors, via epigenetics & hyperphagia, markedly alter glucose homeostasis independent of genotypes.

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PUB183

Benefits of Exercise Training in Obesity-Induced CKD Mice Model: Involvement of AMPK Signalling and Autophagy

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Background: Obesity is a major contributor of progressive renal disease and is largely due to a combination of sedentary lifestyle and a high energy intake. Excessive caloric intake is associated to lipid accumulation in adipose tissue but also in non-adipose tissues, leading to deleterious cellular responses. In a previous work, we identified the role of AMPK in ectopic lipid depositions in proximal tubular cells in mice fed a high-fat diet (HFD). Moreover, lysosomal dysfunction and stagnant autophagy flux were highlighted. Here, the effect of exercise training (ET) in obese mice on renal lipotoxicity and autophagy pathway was investigated.

Methods: C57BL/6J male mice were randomized to a low-fat diet (LFD - 10% calories from fat) or a HFD (60% calories from fat) during 20 weeks. After 12 weeks on diet, mice were subjected to an endurance ET protocol on a treadmill for 8 weeks or no ET.

Results: Mice fed a HFD exhibited a significant increase in body weight combined to increases in plasma levels of NEFA and cholesterol. Moreover, they also developed insulin resistance. ET showed body weight stabilization and beneficial effects on plasma lipid profiles in HFD mice. In addition, hyperglycemia and insulin resistance were also clearly improved by ET. Regarding the renal function, ET improved albuminuria and proteinuria induced by obesity. We also demonstrated a decrease in ectopic lipid accumulation in proximal tubular cells in trained groups. This result was correlated to the inhibition of Acetyl-CoA carboxylase by phosphorylation mediated by AMPK activity. Interestingly, we showed a stagnation of autophagy flux in the kidney of obese mice that was restored in ET group by the regulation of autophagy-related proteins.

Conclusions: These results suggest that ET leads to beneficial effects on obesity-related metabolic disorders and regarding the kidney function and structure in mice fed a HFD. Particularly, we demonstrated the activation of AMPK and the improvement of autophagy flux by ET.

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PUB184

Interleukin-15, a Myokine for Preserving Podocyte Mitochondrial Function During Diabetic Nephropathy

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Background: Exercises can improve the prognosis of diabetic nephropathy (DN), however, the underlying mechanism remains unclear. Here, we further explore how exercise ameliorates DN via muscle-kidney communication.

Methods: To explore the mechanism, PGC-1α was overexpressed in mouse muscle (mPGC-1α) to mimic persistent exercises and crossed with db/m mice or STZ injection to generate mPGC-1α mice with diabetes. In vitro, we isolated podocytes and used cultured podocyte cells to evaluate mitochondrial function.

Results: we found that glomerulosclerosis and podocyte mitochondrial damage induced by diabetes were limited in mice with mPGC-1α. What is more, plasma from mPGC-1α mice prevented podocyte cells and its mitochondria injury in high glucose. Then we found out Interleukin-15 (IL-15), one of myokines upregulated by mPGC-1α, exhibited the similar protective effects on the cultured podocytes. Besides, we discovered that the IL-15-mediated protection were produced by enhancing OPA1 to improve podocyte mitochondrial dynamics.

Conclusions: These findings provided insights into the new role of IL-15 in mediating muscle-kidney crosstalk to ameliorate the progress of DN by maintaining podocytes mitochondrial homeostasis via OPA1.

Funding: Government Support - Non-U.S.

PUB185

Increased Urinary Prorenin and Soluble Prorenin Receptor Excretion in Early Type 1 Diabetes

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Background: Activation of the intra-renal, rather than systemic renin angiotensin system (RAS) has been suggested to play a role in the development of diabetic kidney disease. In this study, we examined plasma and urinary prorenin/renin levels and urinary soluble prorenin receptor (sPRR) levels in a murine model of Type 1 diabetes.

Methods: Male C57BL/6 mice were injected with streptozotocin (STZ) 50mg/kg at 3 months of age and metabolic balance studies conducted at 10 weeks post-injection. In a separate experiment, renal medullary renin and prorenin receptor mRNA was quantified using RT-PCR in 10 week old male Akita mice.

Results: STZ injected mice developed hyperglycemia within 4 weeks of injection (STZ: 335 ± 35 vs control: 145 ± 22 mg/dL) and remained hyperglycemic at 10 weeks. At 10 weeks post-injection, STZ injected mice had significant polyuria (STZ: 20.9 ± 5.9 vs controls 1.8 ± 0.4 ml/day), increased water intake (STZ: 26.2 ± 5.9 vs controls: 6.2 ± 0.9 ml/day) and lower body weight (STZ: 28.3 ± 1.3 vs controls: 23.6 ± 1.4 grams) despite similar food intake. Compared to controls, urinary angiotensinogen, total prorenin/renin and sPRR levels were increased in STZ injected mice; these increases were proportionally greater than the trend in increased urinary microalbumin excretion (Table 1). In particular, urinary sPRR excretion was markedly increased in STZ injected mice compared to controls. In contrast, plasma renin concentration and sPRR were similar between the controls and STZ injected mice. Similalry, 10 week old male Akita mice bearing a mutated *Ins2*gene, demonstrated a 4.8 fold increase in renal medullary renin mRNA expression and a 1.5-fold increase in renal medullary PRR expression.

Conclusions: Taken together, these results demonstrate early activation of the intra-renal RAS in Type 1 diabetes. These changes occur independent of the systemic RAS.

Funding: Private Foundation Support

Tale 1. Plasma and urine RAS components in early Type 1 diabetes

	Control (N=6)	STZ injected (N=5)	P value
Plasma renin concentration (ng/ml/hr)	134.6 ± 36.7	75.6 ± 12.6	0.09
Plasma sPRR (ng/ml)	24.8 ± 3.7	23.7 ± 4.9	0.43
Urine albumin (µg/day)	32.7 ± 7.3	69.5 ± 26.1	0.07
Urine angiotensinogen (ng/day)	133.6 ± 9.8	556.2 ± 160	0.005
Urine total prorenin/renin (ng/day)	5.7 ± 2.2	19.0 ± 4.8	<.001
Urine sPRR (µg/day)	ND	67.1 ± 22.3	<.001

PUB186

Role of the Inducible Calbindin-D28k Protein in Advanced Glycation End Products-Associated Renal Proximal Tubule Cell Injury

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Background: Diabetic nephropathy is a common diabetic complication associated to calcium dyshomeostasis. Previous studies suggested that diabetes-associated advanced glycation end products (AGEs) are associated with the increase of extracellular matrix proteins synthesis and renal fibrosis induction. Protein expression of calbindin-D28k, which plays a role in the calcium reabsorption in the renal distal convoluted tubules, has been shown to be increased in diabetic kidney. However, the role of calbindin-D28k induction in diabetic kidney is still unknown.

Methods: Human renal proximal tubule cell (HK-2) were transfected with/without calbindin-D28k siRNA and then treated with AGEs for 48hours. THe expression of several critical proteins were determined by Western blotting. Cell viabilit was evaluated by MTT assay. The expression of calbindin-D28k in renal tissue of db/db mice were detected by immunohistochemistry.

Results: We found that calbindin-D28k could be induced in the proximal tubules of the db/db diabetic mouse kidney. The increase of AGEs and extracellular matrix (ECM) proteins were also observed in the db/db diabetic mouse kidney. We further explored the role of calbindin-D28k in AGEs-induced human renal proximal tubule cell (HK2) injury and fibrotic changes. AGEs significantly induced the expression of calbindin-D28k in HK2 cells, but not in mesangial cells. AGEs also significantly induced the expressions of fibrotic molecules, ECM proteins, epithelial-mesenchymal transition (EMT) markers, and endoplasmic reticulum (ER) stress-related molecules in HK2 cells. Calbindin-D28k-siRNA transfection significantly reduced the cell viability and markedly enhanced the protein expressions of fibrotic factors, EMT markers, ER stress-related molecules, phosphorylated smad 2/3, and phosphorylated p38 in AGEs-treated HK2 cells. Treatment with 4-phenylbutyric acid, a chemical chaperone, significantly counteracted the AGEs-induced ER stress and EMT markers expressions in HK2 cells.

Conclusions: These findings suggest that the inducible calbindin-D28k plays a protective role against AGEs-induced ER stress and EMT induction and cell injury in renal proximal tubule cells. Calbindin-D28k may serve as a predicted marker for proximal tubule injury/fibrosis or a therapeutic target for diabetic nephropathy.

PUB187

Phosphorylation and Nuclear Translocation of PKM2 in Renal Tubule Regulates the Activation of NLRP3 Inflammasome in Diabetes

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Background: Diabetic kidney disease (DKD) is one of the major causes of renal failure. Activation of NLRP3 inflammasome in tubular cells contributes to the progression of DKD. However the underlying mechanisms that regulate NLRP3 inflammasome remain poorly understood.

Methods: In this study, streptozotocin (STZ) was injected intraperitoneally at the dose of 40mg/kg/day for 5 consecutive days to induce diabetic mouse model. Random blood glucose level greater than 16.7mmol/L tested 2 weeks later was considered as diabetes. Diabetic mice were sacrificed at 1, 2 and 4 weeks after confirmation of diabetes. *In vivo*, primary tubular cells (PTCs) were treated with 30mmol/L of glucose for indicated time points.

Results: NLRP3 inflammasome were markedly activated in both diabetic kidneys and in high glucose-treated PTCs as demonstrated by increased expression of NLRP3, ASC, cleaved caspase-1, cleaved IL-1β and cleaved IL-18. Phosphorylation of PKM2 was observed in diabetic kidneys and PTCs under high glucose condition. Moreover, western blot and immunohistochemistry staining showed nuclear translocation of PKM2 in tubular epithelial cells. Treatment with shikonin, an inhibitor of PKM2 activity, attenuated PKM2 phosphorylation and nuclear translocation. Furthermore, shikonin blocked the high glucose-induced activation of NLRP3 inflammasome in PTCs.

Conclusions: Our study suggests that phosphorylation and nuclear translocation of PKM2 promotes the activation of NLRP3 inflammasome and contributes to inflammation in diabetes. Pharmacological inhibitors targeting the activation of PKM2 may be a novel therapeutic strategy for DKD.

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PUB188

Quantitative Proteomics Identifies Interaction Proteins for Decoy Receptor DcR2 in Diabetic Nephropathy

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Background: Decoy receptor 2 (DcR2), a transmembrane receptor of tumor necrosis factor-related apoptosis inducing ligand (TRAIL), is a cellular senescent marker. DcR2 plays a crucial role in the progression of diabetic nephropathy (DN), but the interaction proteins for DcR2 not clear.

Methods: 139 DN patients which diagnosed by renal biopsy were enrolled. Renal DcR2 expression was detected immunohistochemically. Associations between renal DcR2 and renal functional parameters and pathological damage scores were evaluated. Double staining was undertaken for DcR2 with its ligand TRAIL, and antagonistic receptor DR4 in renal tissue. Co-immunoprecipitation (Co-IP) were analyzed for the DcR2 with TRAIL and DR4 in high glucose (HG) induced-primary tubular epithelial cells (PTECs). Co-IP combining with LC-MS/MS were screened the interaction proteins for DcR2.

Results: DcR2 was primarily expressed in renal proximal tubules. The percentage of renal DcR2 were higher in DN than control, correlated with renal functional parameters and scores of renal tissue damage. DcR2 was not co-expressed with TRAIL, DR4 in DN, and not binding to TRAIL, DR4 in vitro. Quantitative proteomics identified 59 differentially expressed proteins (DEPs) in HG, while 52 DEPs were detected specifically in HG. These DEPs are involved in endothelial cell migration, negative regulation of extrinsic apoptosis, ion homeostasis, regulation of keratinocyte differentiation, removal of superoxide radicals, hydrogen peroxide catabolic process, skeletal muscle tissue regeneration.

Conclusions: We explored the interaction proteins for DcR2 in high glucose-induced PTECs with quantitative proteomics, which will help to elucidate the mechanisms of DcR2 in renal tubular cells in DN.

Funding: Government Support - Non-U.S.

PUB189

Dipeptidyl Peptidase Inhibitor Linagliptin Induced Effects on Cardiac miRNA Expression in GLP-1 Receptor Knock-out Mice with 5/6 Nephrectomy

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Background: Chronic kidney disease (CKD) is a growing health problem with diabetes mellitus and hypertension being main drivers to its development and progression. Additionally, CKD is associated with an increased risk for the development of cardiovascular disease. Growing pre-clinical evidence indicates that the dipeptidyl peptidase (DPP)-4 inhibitor linagliptin (LIN) exerts beneficial renal and cardioprotective effects. However, clinical outcome data are still missing and also the exact molecular mechanisms remain unclear. Experimental studies suggest the involvement of the GLP-1/GLP-1 receptor (GLP-1r) pathway as a potential mechanism underlying the beneficial effects of DPP-4 inhibition in CKD.

Methods: Here we investigated regulation of microRNAs (miRNAs) in cardiac tissue (using the Nanostring nCounter technology) of 5/6 nephrectomized mice after LIN treatment (12 weeks, ~3-5 mg/kg/d in chow) in wildtype and GLP-1r knock-out mice. miRNAs are short non-coding RNA species which are important post-transcriptional regulators of gene expression and are implicated in the pathogenesis of diabetic nephropathy.

Results: Analysis of variance (ANOVA) ($p<0.05$) resulted in a deregulation (up or down) of 15 miRNA species between sham and 5/6 nephrectomized animals. Most of the deregulated miRNA species are involved in cardiac fibrosis, cardiomyopathy and cardiac hypertrophy processes, such as miR-1, miR-133b, miR-30d, miR27b, miR-690 and miR-142-3p. In particular, the ameliorative effects on the expression of the cardiomyocyte protective miR-142-3p were observed in 5/6 nephrectomy plus LIN treated animals. Deregulation of miRNAs in GLP-1r knock-out mice were consistent but effects of LIN were less prominent.

Conclusions: The data suggest cardioprotective effects of LIN via upregulation of miR-142-3p in a model of 5/6 nephrectomy induced uremic cardiomyopathy.

PUB190

Antioxidant Improves Diabetic Nephropathy and Cardiac Function in Diabetes Induced Renocardiac Syndrome

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Background: Diabetes mellitus(DM) is strongly associated with renocardiac syndrome (RCS) in a nationally representative population. RCS is characterized by primary renal failure that progressively leads to cardiac dysfunction. Pathophysiological mechanisms underlying initiation and maintenance of this interaction are complex and poorly understood. Furthermore, because of the development of resistance to standard therapies, targeting renocardiac remodelling process to develop novel therapies is essential. Evidence suggest oxidative stress play a major role in kidney-heart pathophysiological cross talk. The purpose of this study was to investigate wheather there is oxidative stress in this experimental model of RCS & if antioxidant treatment attenuate renocardiac injury

Methods: DM was induced in rats by streptozotocin(STZ)-induced pancreatic injury causing renal injury similar to human diabetic nephropathy. Animals were randomly divided into 3 groups, CONT+Carvediol(CARV), DM and DM+CARV. CARV was adminstered orally for 8 wks. At 8 wks animals underwent echocardiography to measure LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), left ventricular ejection fraction (LVEF), and left ventricular fraction shortening (LVEF). After sacrificing the animals, Kidneys and hearts were examined by Hematoxylin Eosin (HE) staining and periodic acid Schiff base(PAS). Kidney and heart antioxidant enzymes, and lipid peroxidation were determined

Results: In STZ-induced diabetics rats increase in renal and myocardial lipid peroxidation and decrease in antioxidants enzymes were associated with vacuolar degeneration of tubules; PAS positivity staining intensity in glomeruland basement membrane and thickening as well as significant prolongation of isovolumic relaxation time (IVRT) (38 ± 8 vs. 25 ± 6 ms, $p < 0.0001$), elevation of LV end-diastolic pressure (8 ± 6 vs. 2 ± 1 mm Hg, $p = 0.05$) and increased chamber stiffness. CARV improved kidney histopathological altereations and cardiac dysfunction that was associated with increase in antioxidant defense in the kidney and the heart and decrease lipid peroxidation

Conclusions: Our results suggest that in this model of renocardiac syndrome oxidative stress play a role in mediation of Kidney-Heart pathological cross talk and carvideolol with its significant antioxidant properties attenuate diabetic nephropathy and diabetic cardiomyopathy.

PUB191

Effects of Soluble Guanylyl Cyclase Stimulation or Activation on Blood Pressure and Renal Hemodynamics in Diabetic Rats

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Background: The second messenger, cGMP, influences blood pressure (BP) and renal hemodynamics. It is locally formed by soluble guanylyl cyclase (sGC). The activity of sGC can be enhanced by sGC "stimulators" or "activators", which target the enzyme in two different redox states, the nitric oxide (NO)-sensitive reduced enzyme and the NO-insensitive oxidized enzyme, respectively. Little is known about the relative effects of these agents on BP versus renal hemodynamics in diabetes mellitus (DM).

Methods: Acute effects of sGC stimulator BR9902 and sGC activator BR9904 were determined on mean arterial BP (MAP) and renal hemodynamics under terminal barbiturate anesthesia in 3 groups of rats: non-diabetic Wistar Froemter (WF) rats (CON); streptozotocin-diabetic WF rats, a model of type 1 DM (T1DM); and Goto-Kakizaki rats (GK), a non-obese model of type 2 DM (T2DM). Increasing doses of each compound were tested in individual animals in consecutive 20 min periods, and compared with vehicle. MAP was measured via femoral artery catheter; GFR and RBF by renal FITC-sinistrin clearance and perivascular ultrasonic transit time flow probe, respectively. n=6-8/group.

Results: BR9902 and BR9904 induced similar dose-dependent reductions in MAP among the 3 groups. The highest dose of either drug (1 mg kg^{-1} $30min^{-1}$) lowered MAP by 20-30%. Basal GFR and RBF were higher in T1DM and GK versus CON. Qualitative effects of BR9902 and BR9904 on RBF and GFR are shown in a table.

Conclusions: Systemic infusion of BR9902 or BR9904 lowers MAP, which challenges the kidney to autoregulate. Overall hemodynamic autoregulation is more efficient in WF rats (CON or T1DM) than in GK rats, and is more efficient during BR9902 than BR9904. From the latter we infer the existence of drug effects on sGC within the kidney that differ between BR9902 and BR9904, and therefore potentially between stimulators and activators of sGC. When dosed to lower blood pressure by 20-30%, both agents reduced glomerular hyperfiltration in GK-T2DM but not in WF-T1DM.

Funding: NIDDK Support, Veterans Affairs Support, Commercial Support - Bayer Pharma AG

	BR9902		BR9904	
	RBF	GFR	RBF	GFR
WF-CON	Stable	Stable	Decrease	Decrease
WF-T1DM	Stable	Stable	Decrease	Stable
GK-T2DM	Decrease	Decrease	Stable	Decrease

PUB192

Determinants of Renal Outcomes of Type 2 Diabetic Patients with Biopsy Proven Kidney Disease

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Background: We aimed to look at renal outcomes of patients with Type 2 diabetes mellitus (T2DM) who were biopsied and determine the risk factors associated with progressive CKD.

Methods: We retrospectively analyzed patients with T2DM with estimated glomerular filtration rate (eGFR) (MDRD) >30ml/min/m^2 who underwent kidney biopsy from 2007 to 2015 in our tertiary hospital with at least 1 year of follow-up. Outcomes of interest were progressive CKD defined by doubling of serum creatinine or ESRD. Survival curve was obtained using Kaplan-Meier analysis. Clinically relevant risk factors in univariate analyses were adjusted using Cox proportional hazards model.

Results: The cohort included 70 patients, median age 55.2 (IQR: 49.0, 61.4) years and duration of T2DM 102.0 (45.0, 183.0) months. The predominant ethnic group was Chinese (82.9%) with a median follow-up of 42.5 months (27.0, 71.3). Ninety percent of patients received renin-angiotensin-aldosterone-system blockade prior to biopsy and nephrotic range proteinuria was the most common indication for biopsy (77.1%). Forty-three patients had isolated DKD (Group 1) and 27 patients had isolated NDKD (Group 2). Four patients with mixed DKD and NDKD were excluded from analysis in view of small numbers. In Group 1, the median eGFR (MDRD) was 54.3 ml/min/m^2 (42.9, 72.8) and Group 2 was 72.2 ml/min/m^2 (43.8, 90.6). Sixteen patients (59.3%) from Group 2 received immunosuppression or disease specific therapy. Twenty-two patients (51.2%) from Group 1 and 8 patients (29.6%) from Group 2 had progressive CKD. ESRD occurred in 17 patients (39.5%) from Group 1 and 4 patients (14.8%) from Group 2, at median interval of 53.0 (38.6, 67.4) months from biopsy but median time to ESRD was not reached in patients from Group 2. Nine patients, all from Group 1, had died. Kaplan-Meier analysis showed that time interval to progressive CKD was significantly longer in Group 2 patients compared to patients in Group 1 ($p=0.026$). The independent risk factors to progressive CKD were DKD, baseline systolic blood pressure and baseline urine protein/creatinine ratio by Cox's proportional hazards model.

Conclusions: T2DM patients with DKD have significantly worse renal outcomes compared to patients with NDKD. Early biopsy to differentiate NDKD should be considered as disease-specific treatment can be given to achieve better renal survival.

PUB193

Association of Plasma Soluble CD146 with Arteriosclerosis and Cardiovascular Events in Patients with Diabetic Nephropathy

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Background: Diabetic nephropathy is an independent risk factor for arteriosclerosis. Patients with both DN and arteriosclerosis have poor prognosis due to the lack of early symptoms and specific markers. Endothelial cell injury plays a crucial role in arteriosclerosis. CD146, an endothelial marker, was used to reflect the severity of endothelial dysfunction. We aim to find out if CD146 can evaluate the severity of arteriosclerosis and predict cardiovascular events in patients with DN at early stages.

Methods: A total of 105 DN patients at CKD stage 1-3 were enrolled and another 94 diabetic patients without DN entered the control group. Plasma soluble CD146 (sCD146) was measured. Doppler ultrasounds of carotid and lower extremity artery were performed. All DN patients were retrospectively followed up for a medium duration of 28 months. The association between sCD146 and arteriosclerosis was assessed in DN patients. Kaplan-Meier curve was used to evaluate the predictive value of sCD146 in cardiovascular events.

Results: Plasma sCD146 was upregulated in DN patients compared with control group. sCD146 level was shown to be correlated with the intima-medium thickness of both carotid and lower extremity arteries. High level of sCD146 was proved to be an independent risk factor for the prevalence of carotid plaques and the instability of plaques in both carotid and lower extremity arteries. Survival analysis showed that patients with higher level of plasma sCD146 were more likely to have cardiovascular events.

Conclusions: Plasma sCD146 is associated with arteriosclerosis in patients with early stages of DN and can also predict their cardiovascular events.

Funding: Government Support - Non-U.S.

PUB194

Kidney Biopsy in Type 2 Diabetes Patients with CKD

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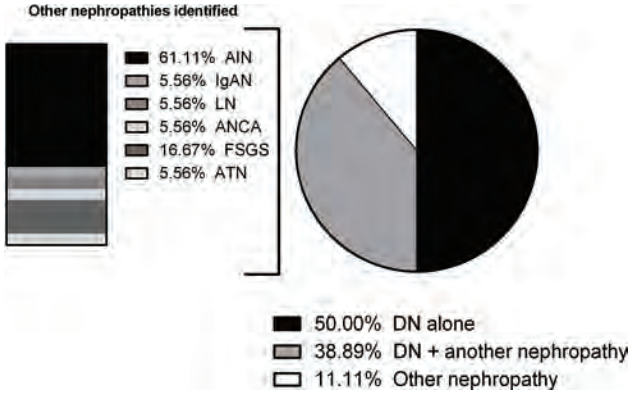
Background: T2D represent the most frequent cause of CKD worldwide. Reduced GFR and albuminuria are considered hallmark for the diagnosis of diabetic nephropathy (DN), but recently, there are growing concerns of the sensibility of these markers to identify DN from other nephropathies. Our objective was to describe the prevalence of biopsy proven DN and other nephropathies in patients with T2D.

Methods: During March 2017 to February 2018, we prospectively biopsied 35 with diagnosis of T2D and CKD and had no contraindications for the kidney biopsy. All histological results were read by a nephropathologist.

Results: The mean age was 52 ± 11.9 years, and 17 (77.2%) were female. The average BMI was 27.5 ± 5.1 kg/m^2, 31 (86.1%) had HTN, and baseline GFR was 56 ml/min (IQR 39.4-74.9). The mean time with T2D was 13 ± 7.5 years, and 21 (58.3%) had history of diabetic retinopathy. The sCr at the time of the kidney biopsy was 1.9 mg/dL (IQR 1.1-3.4), the main indications for the kidney biopsy were nephrotic syndrome in 17 (47.2%), nephrotic range proteinuria in six (16.7%), rapid progression of CKD in six (16.7%), AKI in two (5.6%), rapid progressive glomerulonephritis in one (2.8%), and two with subnephrotic proteinuria (5.6%). The histologic findings were isolated DN in eighteen (50%) patients, fourteen (38.9%) had DN + other glomerulopathy, and four (11.1%) had a non-DN glomerulopathy (Figure 1). None of the clinical or biochemical analysis was associated with the histological diagnosis or predicted the severity of the glomerular sclerosis in patients with DN.

Conclusions: The kidney biopsy is a useful tool to stablished a correct diagnosis and severity of the CKD in patients with T2D. Reduce GFR and albuminuria are not useful to differentiate DN from other glomerulopathies, nor stablish severity of the histological appearance.



Kidney bipsy results of T2D patientsAIN, acute intersticial nephritis; LN, lupus nephritis; FSGS, focal segmental glomerulosclerosis; ATN, acute tubular necrosis.

PUB195

Validation of the 2007 Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for the Diagnosis of Diabetic Nephropathy and Nondiabetic Renal Disease in Chinese Patients

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Background: Diabeties mellitus has overtaken infection and immunological factors as the most common cause of chronic kidney disease and end-stage renal disease. Pathological results of DM patients with CKD could be diabetic nephropathy (DN) and nondiabetic renal disease (NDRD), the prognosis and treatment of which are different. The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline (2007) is a widely accepted guideline for the clinical diagnosis of DN and NDRD. Our study sought to verify its diagnostic ability in the Chinese population.

Methods: We included 773 DM patients who underwent a renal biopsy at the Chinese PLA General Hospital from 2007 to 2016. All the patients were divided into three groups according to their renal biopsy: isolated DN, isolated NDRD, and isolated DN combined with NDRD. The calculation were performed under two conditions:isolated DN vs. isolated NDRD and isolated DN vs. non-DN [NDRD with and without DN].

Results: Good sensitivity and poor specificity were found for the prediction of NDRD in the Chinese population. Rapidly decreasing estimated glomerular filtration rate, systemic disease, refractory hypertension, and the existence of "grey area" patients may have contributed to the poor diagnostic ability.

Conclusions: The diagnostic ability of the KDOQI guideline (2007) for DN and NDRD was unsatisfactory. The high sensitivity and low specificity of the guideline made it more suitable as screening criteria rather than diagnostic criteria.

Funding: Government Support - Non-U.S.

Prediction of non-diabetic renal disease

	Isolated DN vs. Isolated NDRD	Isolated DN vs. non-DN
Sensitivity	96.14%	93.92%
Specificity	40.63%	40.63%
PPV	75.77%	75.82%
NPV	85.85%	77.12%
Kappa Statistic	0.286; P<0.001	0.268; P<0.001

PUB196

Comparison of the Risks of Cardiovascular Disease for Patients with Diabetic Kidney Disease Between Those Treated by Diabetologists and Nephrologists

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Background: Patients with diabetic kidney disease are managed by not only diabetologists, but also nephrologists. In this study, we examined the risk of cardiovascular disease for patients with diabetes mellites between those treated by diabetologists and nephrologists.

Methods: We randomly selected 200 and 30 outpatients with diabetes mellites managed by diabetologists and nephrologists, respectively. All of patients showed microalbuminuria during the four months from May to August, 2017. We analyzed sex, age, estimation glomerular filtration rate (eGFR), albuminuria, hemoglobin, HbA1c, and blood pressure correlation with past history of the cardiovascular diseases.

Results: Both age and microalbuminuria levels were significantly higher in the diabetes patientstreated by diabetologists with cardiovascular disease than those without cardiovascular disease. In contrast, a significant difference was not found in the age and the microalbuminuria levels of the diabetes patients treated by nephrologists with cardiovascular disease and those without cardiovascular disease. In outpatients with diabetes mellites managed by diabetologists, CKD stage 2 (eGFR 60-90ml/min) was the most stage (51.8%). In outpatients with diabetes mellites managed by nephrologists, CKD stage 3 (eGFR 30-60ml/min) was the most stage (40.0%). In multivariate analysis, age (cutoff levels : 68 years old), eGFR (cut off levels : 81.7 ml/min) and albuminuria (cut off levels : 197 mg/gCr) were independently associated factors of the cardiovascular diseases in outpatients by diabetologists. In outpatients by nephrologists, eGFR (cut off levels : 59.0 ml/min) was only independently associated factor of the cardiovascular diseases. In comparison with the severity classification of chronic renal failure, age, eGFR and albuminuria were independently risk factors for cardiovascular disease in CKD stage G1-2 group, but in CKD stage G3-5 group, both were not related factors.

Conclusions: Outpatient with diabetic kidney disease managed by nephrologist were in an advanced phase more than those managed by diabetologists. And this study suggested that the eGFR was more risk factor on cardiovascular disease than age and albuminuria in outpatients managed by nephrologists.

PUB197

Echocardiographic Findings in Type 1 Diabetics with End-Stage CKD

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Background: Diabetes mellitus(DM) and chronic kidney disease(CKD) are independent risk factors for the development of cardiovascular(CV) disease. They have been associated with changes of cardiac structure, function, and an excess risk of coronary artery disease(CAD). The aim of this study was to evaluate the echocardiographic findingsin patients with DM type1 and end-stage CKD.

Methods: 48 consecutive patients undergoing stress echocardiography prior to renal +/- pancreatic transplantation between December2008 and December2014 at a single center, were evaluated. At baseline, a complete comprehensive 2D and Doppler exam was performed, including evaluation of global longitudinal strain(GLS).

Results: Mean age was 42.3±7.1years-old, mean DM duration was 24.4± 6.0 years and mean HbA1c was 8.7 ±1.7%. The prevalence of other major atherosclerotic risk factors was: hypertension 69.4%, dyslipidemia 44,4% and smoking 36.1%. 4 patients had history of CAD with previous coronary angioplasty. At baseline, 38.5% were on hemodialysis(HD) and 25.6% on peritoneal dialysis(PD); 7.7% had previous renal transplant and 28.2% patients weren't on renal replacement therapy(RRT). 63.6% had left ventricular(LV) hypertrophy(LVMI>115g/m^2 for men, >95g/m^2 for women) and 45.3% had left atrial enlargement (LAE>34ml/m^2). Although LV ejection fraction was preserved in 72.9%, LV dysfunction as assessed by abnormal GLS(> -18%) was observed in 72,9%. 5 patients had neither LV dysfunction nor hypertrophy. 34.4% had rest elevated LV filling pressure(E/e' >13). No differences between HD, PD and no RRT groups. 6 patients (12,5%) had ischaemic response, 5 of whom underwent coronary interventions. During follow-up (5.6, 4.2-6.9 years), 14.3% had hospitalizations of any cause and 3 were hospitalized for CV causes. These 3 patients had both LV dysfunction and hypertrophy and 1 had ischaemic response. At the end of follow-up 50% of patients had transplant (mostly kidney-pancreas). No patient died.

Conclusions: Cardiac abnormalities are frequent in relatively young patients with DM type 1 and end-stage CKD. Most of them have LV hypertrophy and preserved ejection fraction, despite LV dysfunction. CAD is also frequently present and can be demonstrated by stress echocardiography, allowing for coronary intervention before renal transplantation.

PUB198

Stakeholder Perspectives on Implementing Personalized Medicine in Diabetic Kidney Disease

Michelle Pena,[1] Nienke Idzerda,[1] Gert J. Mayer,[2] Friedrich Schulze,[5] Jeannette Soderberg,[6] Dennis L. Andress,[4] Maria F. Gomez,[3] Hiddo J. Lambers Heerspink,[1] Dick de Zeeuw,[1] Peter G. Mol.[1] for Work Package 6 of the BEAt-DKD Consortium *[1]University Medical Center Groningen, Groningen, Netherlands; [2]Medical University Innsbruck, Innsbruck, Austria; [3]Lund University, Malmö, Sweden; [4]AbbVie, North Chicago, IL; [5]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [6]JDRF, Paris, France*.

Background: The Innovative Medicine Initiative BEAt-DKD consortium aims to discover and implement novel biomarkers for personalized medicine in diabetic kidney disease (DKD). Gaining stakeholder opinions and perspectives are important in this process. We describe here the opinions and perspectives of stakeholders obtained during focus group meetings.

Methods: Stakeholder focus groups were held with members of European regulatory agencies, health technology assessors, physician groups, and patient organizations. BEAt-DKD consortium partners included academia, pharmaceutical industry, and patient advocacy. General and stakeholder specific topic lists were developed by BEAt-DKD members. A background presentation on personalized medicine in DKD was given, and then an open discussion was held, moderated by an academia BEAt-DKD member. Themes discussed included: 1) determining whether there is a need for personalized medicine in DKD, 2) what additional evidence is needed, 3) identification of the pros and cons within each stakeholder environment, 4) identification of hurdles for implementation, and 5) engagement with other stakeholders.

Results: Attendees of the focus groups included representatives from European regulatory agencies (n=7), health technology assessors (n=4), physicians (n=5), and patients (n=4). BEAt-DKD partners included academia (n=6), pharmaceutical industry (n=3), and patient advocacy (n=1). Main points that came out of the stakeholder focus groups are presented in the table.

Conclusions: Implementing personalized medicine in DKD is complex, and early engagement of stakeholders in the developmental process is important. Different stakeholders have different priorities, and achieving the goal of implementing personalized medicine in DKD will only happen if we can align stakeholder goals.

Funding: Commercial Support - The BEAt-DKD project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115974. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA., Government Support - Non-U.S.

Stakeholder	Perspective on personalized medicine in DKD
European regulatory agencies	Need for prospective clinical trial evidence before regulatory qualification of a novel methodology.
Health technology assessors	Assessment of budget impact and cost effectiveness for new biomarkers is necessary but financial priorities vary from country to country.
Physicians	Better risk stratification and more precise options for treatment need to be developed and included in clinical practice guidelines.
Patients	Extra time for medical procedures and shared medical decision making should be considered. Benefit to quality of life is a higher priority than clinical endpoints.

PUB199

Pattern of Non-Diabetic Renal Diseases (NDRD) in Patients with Diabetes Mellitus at State Run Tertiary Care Center

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Background: Introduction A wide spectrum of non-diabetic nephropathy, including both glomerular and tubulo-interstitial lesions are reported in patients with Diabetes mellitus. Their precise diagnosis requires histological examination of kidney tissue. **Aim** We carried out this study to find the clinical, laboratory, and pathological features of non diabetic renal disease (NDRD) in diabetes mellitus(DM) patients. We also examined if any significant differences in clinical profile between the NDRD and diabetic nephropathy(DMN) groups

Methods: The demographic, clinical, and biochemical data of patients with DM (defined by ADA) who underwent renal biopsy in this institute for a duration of from 2012 august to october 2017 were analyzed prospectively. 220 patients were included in the study. Data were collected from inpatient file, monitor sheets, histopathological reports.

Results: Materials & methods: The demographic, clinical, and biochemical data of patients with DM (defined by ADA) who underwent renal biopsy in this institute for a duration of from 2012 august to october 2017 were analyzed prospectively. 220 patients were included in the study. Data were collected from inpatient file, monitor sheets, histopathological reports.

Methods: The demographic, clinical, and biochemical data of patients with DM (defined by ADA) who underwent renal biopsy in this institute for a duration of from 2012 august to october 2017 were analyzed prospectively. 220 patients were included in the study. Data were collected from inpatient file, monitor sheets, histopathological reports.

Conclusion: In this study, incidence of NDRD was 38%, DMN 42% AND combined was 20%. Chronic kidney disease (CKD),nephrotic syndrome(NS) and acute kidney injury(AKI) were the most frequent clinical presentation. Acute interstitial nephritis(AIN),post infectious glomerulonephritis(PIGN) and chronic tubulointerstitial disorder (CTID) were commonest NDRD. These results suggest that prevalence of different category of biopsy-proven renal disease in diabetic patients depends on the usual prevalence of renal disease in the total population, according to the geographical area and ethnic characteristics and NDRD is merely a coincidental in DM. 58% of patients in the study had NDRD [either isolated or combined]. This study showed isolated NDRD in 38%, this result is similar to that reported in India and other regions with incidence of isolated NDRD were less than 50%.

PUB200

Novel Biomarkers for Detecting Endothelial Dysfunction and High Cardiovascular Risk in Patients with Early Diabetic Kidney Disease

Ane karoline Medina neri,[1] Gdayllon Cavalcante meneses,[2] Renan Lima alencar,[1] Marina De paulo sousa fontenele nunes,[1] Mariane Souza rodrigues,[1] Igor Pinho saraiva,[1] Elizabeth De francesco daher,[2] Ricardo Pereira silva,[2] Geraldo B. Silva Junior.[1] *[1]University of Fortaleza, Fortaleza, Brazil; [2]Federal University of Ceara, Fortaleza, Brazil*.

Background: Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) worldwide, and the main cause of death is cardiovascular disease. We identified endothelial dysfunction and high cardiovascular risk among patients with early DKD using novel biomarkers.

Methods: A total of 128 patients with type 2 diabetes mellitus were enrolled in this study. They were all followed in a primary care facility in Fortaleza, Brazil, and had no previous history of cardiovascular or kidney disease. Blood samples were collected for lipid and glycemic profiles, FGF-23, Syndecan-1 and VCAM-1. We assessed cardiovascular risk (CVR) through the scores: Framingham lipids category (lipids FRE) and body mass index (BMI FRE), Brazilian Cardiology Society (SBC) score and UKPDS risk engine.

Results: Patients aged 56±10 years, and 68.8% of whom were women, with a mean diabetes diagnosis time of 7±6 years. The CVR stratification showed higher rates of high risk by lipids ERF (68.8%), BMI (78.1%) and SBD/SBC/SBEM score (98.4%). There were higher levels of VCAM-1 among patients with high CVR (lipids FRE), higher levels of VCAM-1, Syndecan-1, FGF-23 and microalbuminuria, and lower GFR among patients with high CVR (UKPDS) (Table 1).

Conclusions: DKD is associated with high CVR since its early stages. Novel biomarkers (VCAM-1, Syndecan-1, FGF-23) are useful for early detection of high risk patients. A longitudinal evaluation of these patients is required to assess the outcomes and the role of these novel biomarkers as predictors of prognosis.

Table 1. Association of novel biomarkers with cardiovascular risk (CVR) among patients with early stage diabetic kidney disease.

Biomarker	High CVR	Low CVR	p
Lipids FRE score			
VCAM-1 (ng/mL)	1155±254	964±336	0.02
Microalbuminuria (mg/24h)	41±75	21±53	0.01
UKPDS score			
VCAM-1 (ng/dL)	1273±280	1119±249	0.01
Syndecan-1 (ng/mL)	33±11	29±13	0.04
FGF-23 (pg/mL)	3121±5689	1077±2108	0.03
GFR (mL/mn/1.73m2)	83±14	95±16	0.002

PUB201

Retinopathy Predicts Rapid Decline in Renal Function in Ethnic Minorities with Diabetic Nephropathy

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Background: Retinopathy is seen in 66% of adult patients with type II diabetes (T2DM) and diabetic nephropathy and indicates advanced microvascular disease. However, association of retinopathy with progression of diabetic kidney disease is unknown. In our clinical practice, we have observed that certain patients with T2DM have a rapid decline in renal function, but it is unclear if any clinical parameters are associated with this presentation.

Methods: We retrospectively examined the Stroger Hospital kidney biopsy database from 2010 to 2017 and identified 57 cases of biopsy proven diabetic nephropathy. Indications for biopsy were either rapid decline in eGFR [defined as eGFR loss > 5ml/min/1.73m^2/ yr, KDIGO, Kidney Int. (suppl) 2013] or presence of a competing diagnosis. 29 of these cases had proliferative or non-proliferative retinopathy confirmed by an Ophthalmologist.

Results: In patients with more than 12 months of follow up (n=37), mean annual decline in eGFR was –15.9 (-11.2 to -20.1) ml/min/1.73m^2. The rate of decline in eGFR was significantly associated with presence of retinopathy (p=0.018) and hypoalbuminemia (serum albumin < 3.5 g/dL, p=0.002). There was a trend suggesting decline in eGFR correlated with severity of proteinuria (p=0.08). eGFR decline was not associated with hematuria ethnicity or gender (p ≥ 0.17).

Conclusions: In African-American and Hispanic patients with Diabetic nephropathy, presence of diabetic retinopathy correlated with rapid decline in eGFR and lower serum albumin despite RAAS blocker therapy.

Baseline demographic and clinical parameters (number, %)

Age: 54.3 ± 11.6 years	Male: Female 29:28	African American: 25 (44%), Hispanic: 26 (46%), Caucasian 3 (5%), Others: 3 (5%)
Proteinuria: 6.0 ± 4.7 g/g Cr Serum Albumin: 3.2 ± 0.6 g/dl Microscopic hematuria: 20 (35%)	Retinopathy: 29 (51%) No retinopathy: 19 (33%) No information: 9 (16%)	eGFR at biopsy: 35 ± 24 ml/min RAAS blockers use: 51 (89%)

PUB202

Potential Effectiveness and Mechanisms of Chinese Herbal Medicine for Diabetic Kidney Disease: Survival and Pharmacology Network Analysis on a Population-Based Clinical Database

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Background: Diabetic kidney disease (DKD) causes a great healthcare burden. In addition to western medicine (WM), Chinese herbal medicine (CHM) is attracting attention in the eastern culture societies. This study aims at exploring the mortality of CHM users and the potential mechanisms of CHM.

Methods: From 2004 to 2012, WM cohort (WM only, n=207,277) and CHM cohort (CHM with or without WM, n=26,522) were selected from all incident DKD patients in Taiwan's National Health Insurance Research Database. Risk of mortality was the study endpoint. To explore the potential mechanisms, pharmacology network analysis with pathway over-presentation tests were used.

Results: To the end of 2012, the cumulative incidence of mortality was 47.9% in WM cohort and 30.5% in CHM cohort (hazard ratio: 0.48 (99%CI: 0.45-0.51, p<0.001). The top 5 most prevalent CHM considerably covered the same target proteins as WMs used for DKD, and for WM uncovered proteins, cell cycle-related pathways were found most extensively.

Conclusions: CHM may be beneficial for DKD. Further studies are still needed for the clinical practicability.

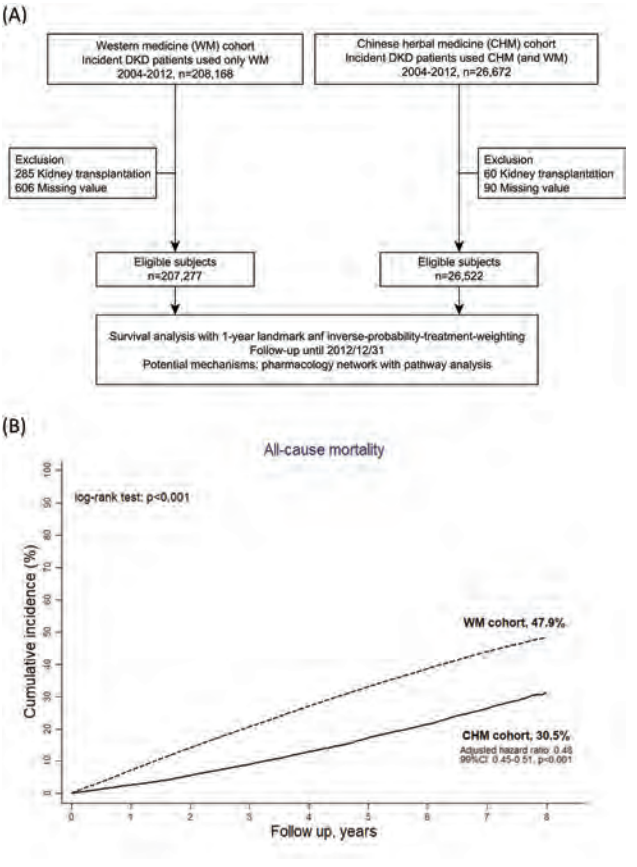

Fig1.(A) Flow diagram**(B)**Survival analysis

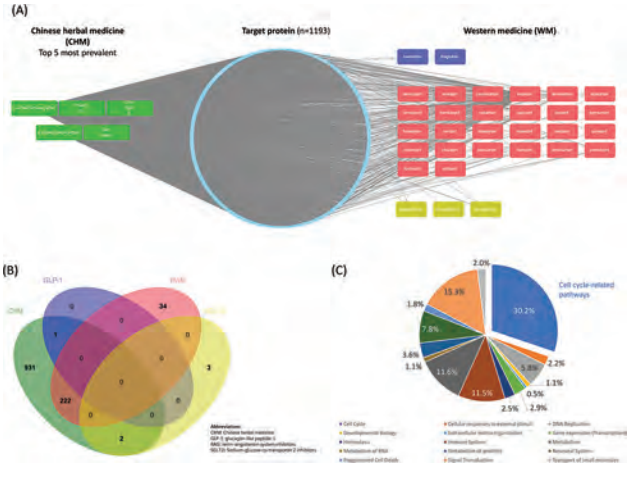

Fig2. Pathway analysis of the top 5 most prevalent CHM and WM**(A)**Drug-target protein interactions**(B)**Target protein comparisons**(C)**Pathways not covered by WM.

PUB203

Efficacy and Safety of Valsartan Combined with Huangkui Capsule for Diabetic Kidney Disease: A Meta-Analysis

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Background: Diabetic kidney disease (DKD) has been a global public health problem and a huge economic burden to developing countries. Currently, as for DKD populations, medication options limited in angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. Huangkui capsule, a Chinese patent medicine, has showed renal protective potential in experiments and retrospective studies. This meta-analysis will

systematically review the efficacy and safety of Valsartan combined with Huangkui Capsule for DKD patients.

Methods: We searched CENTRAL, MEDLINE, PubMed, Embase and Chinese databases including China National Knowledge Infrastructure, China Biology Medicine disc and Wanfang database from inception to August, 2017, to collect randomized clinical trials in adult patients (aged ≥18 years). According to the inclusion and exclusion criteria, two reviewers screened literature and extracted data separately and in parallel. The main outcomes were urinary albumin excretion rate (UAER), serum creatinine (SCr), 24-hour urinary protein (24h-UTP) and blood urea nitrogen (BUN) assessed by random-effects meta-analyses with RevMan 5.3. The quality of included studies was evaluated by the diagram of risks and bias provided by Cochrane collaboration.

Results: Nine RCTs from China were included with a total of 652 population. The analyses showed that combined therapy of Chinese and routine medicine was superior to routine medicine in decreasing UAER [MD=-9.70 ug/min, 95%CI(-13.1, -5.69), *P*[[FF1C;0.00001, low quality] and SCr [MD=-2.84 umol/L, 95%CI(-4.66, -1.03), *P*=0.002, low quality], the results had significant differences (*P*<0.05). However, the outcomes of 24h-UTP [MD=-0.31g/24h, 95%CI(-0.63, 0.00), *P*=0.05] and BUN [MD=-0.22 mmol/L, 95%CI(-0.47, 0.04), *P*=0.10] were similar between groups. The findings were robust to subgroup and sensitivity analyses. Six included studies mentioned adverse effects, summarized as gastrointestinal symptoms without detailed data.

Conclusions: Valsartan combined with Huangkui capsule could have a better clinical effect than using Valsartan alone in decreasing UAER and SCr but not 24h-UTP or BUN for DKD patients. However, the safety profile is unclear, and the quality of evidence is poor according to the grading of recommendations assessment, development, and evaluation approach, calling for high quality randomized, controlled RCTs.

Funding: Government Support - Non-U.S.

PUB204

Unexpected Etiology of ESRD in a Young Man with Unknown Past Medical History

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Introduction: Patients without access to the US health care system may have unidentified and untreated common medical conditions that may lead to severe and irreversible kidney disease. This case illustrates the consequences of lack of access to primary healthcare and the role of kidney biopsy in elucidating etiology of severe kidney disease in the context of paucity of prior clinical data

Case Description: A 32 year old Hispanic man was seen in a public hospital emergency department with one week history of progressive left visual loss and periorbital headache. BP was 186/116mmHg and systemic exam was unremarkable except for left eye depigmented vitreous hemorrhage suggestive of "hypertensive" retinopathy. Laboratory data showed non-fasting glucose -110mg/dl, serum creatinine -5.0mg/dl (eGFR 13ml/min), urine protein-8.75g/gCr and A1C -6%. All serological tests were negative and urine microscopy was unrevealing. Ultrasound showed normal size but echogenic kidneys. BP was 132/72 after two days on Nifedipine 30mg daily. Kidney biopsy done (Figure 1) showed "diabetic glomerulosclerosis with advanced global scarring (17 of 22 glomeruli) and severe interstitial fibrosis and tubular atrophy involving 90% of the cortex"

Discussion: Kidney biopsy was done in this patient because of his young age, normal size kidneys and uncertainty about the etiology and reversibility. The finding of "hypertensive" retinopathy and presumed hypertensive nephrosclerosis was not consistent with the nephrotic range proteinuria and the ease of BP control with monotherapy. Although up to 42% of US adults with undiagnosed diabetes may have CKD, it is very unusual for ESRD to lead to the diagnosis of "burnt-out diabetes". It is likely that access to basic primary care would have identified diabetes mellitus sooner and adequate treatment would have delayed or prevented this unfortunate outcome.

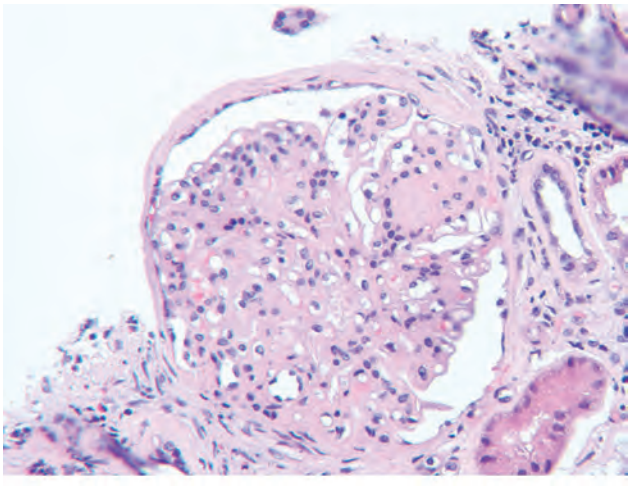

Figure 1

PUB205

Improving Inpatient Diabetic Management in Haemodialysis Patients: A Quality Improvement Project

Dhaarica Jeyanesan, Oscar Swift. *Renal Medicine, East and North Hertfordshire NHS Trust, Stevenage, United Kingdom.*

Background: The prevalence of diabetes is set to increase to 4.4% from 2.8% by 2030[1]. Some of the most vulnerable and severely affected patients are those with end-stage renal failure (ESRF) requiring haemodialysis. Until recently, sufficient UK national guidance to support healthcare professionals with the management of this particular population was lacking. In 2016, the Joint British Diabetes Society and Renal Association produced guidelines[2] covering the extensive and distinct needs of a diabetic patient with end stage renal failure on haemodialysis. Ongoing concern over the impact of hypoglycaemia on both cerebral function and risk of stroke mandates the need to optimise glycaemic control in this patient cohort.

Methods: Using this guidance as a framework, we have reviewed our own management of inpatient diabetic haemodialysis patients at Lister Hospital, Stevenage, a tertiary nephrology unit in the UK. We have applied quality improvement methodology using a "plan, do, study, act" model to the guidance to improve inpatient care.

Results: Initial results following baseline data collection over a two week period identified 12 haemodialysis inpatients with diabetes. 50% of these patients suffered a hypoglycaemic event, and 100% of this subgroup had a pre-dialysis capillary blood glucose (CBG) measurement of less than 7mmol/litre. No patients received bespoke insulin regimens to include reduced insulin dosage on dialysis days. Further investigation revealed issues with communication of hypoglycaemic episodes between nurses and doctors; acute dialysis staff using separate paperwork to document pre- and post-dialysis CBG measurements and discrepancies of management of pre-dialysis CBGs of less than 7mmol/litre, as well as poor inspection rates for diabetic foot ulcers (33%).

Conclusions: Primary interventions included notification and education of the relevant teams to ensure CBG measurements pre and post- dialysis were recorded on inpatient drug charts, which are easily accessible for all clinical staff, ensuring adequate pre-dialysis carbohydrate supplementation as per guidelines if pre-dialysis CBG measurements are less than 7mmol/litre and improved notification of hypoglycaemic events. Further quality improvement cycles are ongoing and will hopefully demonstrate an improvement in the management of diabetic haemodialysis patients in the areas described.

PUB206

Cost-Saving and High Efficiency of a Semi-Quantitative Screening Method for Detecting Microalbuminuria in Patients with Diabetes

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Background: Microalbuminuria is an important biomarker for diabetic nephropathy and cardiovascular complications. While quantitative measurement using turbidimetric immunoassay is the standard method for detecting microalbuminuria, it requires high cost and specialized laboratory equipment. In this study, we aimed to assess the diagnostic accuracy and verify the cost-saving effect of semi-quantitative urinary albumin-creatinine ratio (uACR) test as a screening tool for microalbuminuria in diabetic patients.

Methods: A total of 1,881 urine samples from patients with diabetes were analyzed between June 2017 and January 2018. Patients with low estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m^2, or abnormal urinary dipstick test were excluded. After investigating precision and reproducibility of the semi-quantitative method using URiSCAN® 2ACR, a cost-saving analysis was performed. To measure the economic burden of false negative results, probabilities of clinical outcomes were calculated using systematic literature review and subsequent meta-analyses. Information on annual medical costs was obtained from Korea healthy insurance review and assessment service. Statistical information of population and mortality rate according to age was extracted from Korean statistical information service.

Results: The coefficients of variation (CV) in within-run precision for albumin and creatinine were less than 5% in both. Between-run CVs for albumin and creatinine ranged up to 8% and 5% in positive result samples. Compared with the quantitative method, URiSCAN® 2ACR showed a sensitivity of 93.5% and 81.3% and specificity of 61.4% and 63.1% in patients with diabetes and diabetic patients with normal eGFR and normal dipstick result, respectively. False positive and false negative rate were 30.5% and 3.2%, respectively. After adjusting medical costs including the risk of disease progression, URiSCAN® 2ACR could save 9.86 USD per person for a year.

Conclusions: A semi-quantitative uACR test showed eligibility as a screening test for microalbuminuria in diabetic patients. This method would minimize the time required and inconvenience and enormously reduce the national health costs as well.

PUB207

Dialysis Induced Diffuse EEG slowing – A Diagnostic Dilemma

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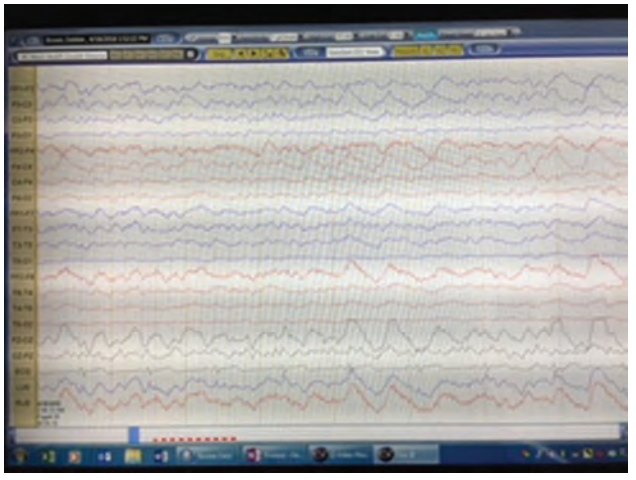
Introduction: Patient undergoing dialysis in ESRD have multiple cardio-cerebrovascular complications and it is very difficult to tease out those complications as some which are yet to be defined. We present a unique case where a patient has frequent syncopal episodes without major identifiable cause.

Case Description: This is a 60 year old African American female with history of DM2, HTN, CVA and ESRD on IHD for 4 years. Her EDW is 68.5 kg and most of the times she is without significant Intradialytic weight gain. Over last 6 months, she has been having recurrent passing out episodes during dialysis, without any clinical and biochemical evidence of fluid or electrolyte shifts or infections. At various stages of her single dialysis treatment, she slowly goes into drowsiness and then goes into an unresponsive episode. In spite of EDW adjustment and the minimal UF rate she persistently has been having these episodes. Following this, she underwent extensive cardiovascular and cerebrovascular work-up, which were unremarkable. Her echocardiogram showed EF was 40-50%, normal stress test. CT of the brain and carotid anatomy were unremarkable. Her MRI and MRA of the brain were remarkable for old minor strokes. She then underwent EEG which was also unremarkable. Lastly, she underwent video EEG during dialysis, at which point it showed diffuse slowing of electrical activity which wasn't present when she wasn't on dialysis.

Discussion: ESRD patients are at risk for sleep disorders as insomnia, restless leg syndrome, sleep-disordered breathing and excessive daytime sleepiness. Abnormal EEG changes have been shown in patients with chronic uremia and dialysis disequilibrium syndrome only. We present a case who has been on a IHD with intradialytic altered mental status for 6 months, depicting intradialytic EEG changes. The video EEG showed diffuse slowing of electrical activity (as shown in the Images) without any definitive diagnosis.



PUB208

Rituximab Therapy After ESRD in Lupus Patients Is Used for Thrombocytopenia

Vipawee S. Chat,[1] Jennifer L. Waller,[1] Rhonda E. Colombo,[1] Stephanie L. Baer,[2] Erin vanessa S. Spearman,[1] Lufei Young,[1] Mufaddal Kheda,[1] Leighton R. James,[1] N. Stanley Nahman.[1,2] *[1]Augusta University, Augusta, GA; [2]Augusta VA Medical Center, Augusta, GA.*

Background: Lupus nephritis (LN) is a serious complication of SLE that may lead to dialysis. Rituximab (RTX) is used in refractory LN prior to dialysis, and in acute cases, used after starting dialysis in an attempt to induce remission. In a pilot study, we queried the USRDS for patients with ESRD from lupus and found 68 who received RTX, however the mean time of administration of the drug was > than 1 year after starting dialysis, suggesting indications other than LN. To assess indications for RTX therapy in lupus patients with ESRD we re-queried the dataset for diagnostic indications for using the drug in this setting.

Methods: Incident dialysis cases in the USRDS from 2006-2010 were queried for ESRD from SLE using the code 7100 from CMS Form-2728. The indications for RTX in ESRD lupus patients were assessed using ICD-9 diagnosis coding found in the hospital, detailed, and physician-supplier claims files.

Results: There were 3,307 ESRD patients identified with ESRD secondary to SLE with a mean±SD age of 41±15 years, 82% female, 53% black and 40% white. RTX infusion was documented in 68 (2.1%) patients. RTX(+) patients were younger (37±15yrs) but otherwise did not differ from the SLE group. 36 patients had a diagnosis associated with the RTX infusion, including lupus (41.7%); thrombocytopenia (28%); cancer (17%); rheumatoid arthritis (8.3%); and miscellaneous causes (14%). The data shows that in these ESRD patients, RTX is given most commonly for unspecified lupus indications and thrombocytopenia (TCP). The lack of specific indications for RTX infusion in 32 of the 68 patients is unclear, however, in the 36 patients with a clear diagnosis, the administration of RTX for TCP was evident, and suggests that clinicians are encountering and treating autoimmune TCP in lupus patients on dialysis.

Conclusions: These data indicate that among patients with ESRD from lupus who were treated with RTX, ongoing SLE activity is the most common indication. The second most common indication was TCP, presumably of an autoimmune nature. We would speculate that extra-renal immune activity may remain high in some SLE patients on dialysis, in particular presenting as TCP. The high rate of TCP in dialysis patients in general, and perhaps SLE patients in particular, suggests consideration of active lupus as a cause.

PUB209

Dieulafoy's Ulcer on Hemodialysis Therapy: A Report of Two Cases

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Introduction: Dieulafoy's ulcer accounts for approximately 5% of all gastrointestinal hemorrhages. These ulcers are characterized by a ruptured artery that runs in the submucosal layer, and may be attributed to various abnormalities including dilation, micro-aneurysm, angiodysplasia and so on. Prior studies have established chronic kidney disease (CKD) as a risk factor for gastrointestinal hemorrhage, as angiodysplastic lesions are often seen in patients with CKD. Here we present a report of two cases of Dieulafoy's ulcer in the stomach and rectal colon.

Case Description: Case 1: A 76-year-old man with a past medical history of longstanding diabetic nephropathy presented to our hospital's Accident and Emergency department and underwent emergency hemodialysis. The patient suffered a bout of hemoptysis on post admission day 7, requiring emergency esophagogastroduodenoscopy (EGD). Endoscopic findings showed an ulcer on the lesser curvature of the stomach with pulsatile bleeding. The bleeding was successfully stopped via gripping with a hemostat. A second EGD done the following day showed no residual active bleeding. Case 2: A 69-year-old woman with end stage renal disease on hemodialysis therapy since 2008 presented to our hospital with sepsis. Antibiotics were started And on post admission day 7, bloody bowel discharge was observed twice, along with low blood pressure and anemia. An urgent colonoscopy examination performed showed an ulcer in the rectal Rs region with pulsatile bleeding. We cauterized the ulcer with forceps to confirm hemostasis. A second colonoscopy examination done the following day showed no active residual bleeding.

Discussion: Dieulafoy's ulcer is an important cause of gastrointestinal bleeding and is often diagnosed late. It has a tendency to cause severe, life-threatening, recurrent gastrointestinal bleeding but is amenable to life-saving endoscopic therapy. In addition, hemodialysis has been associated with gastrointestinal hemorrhage due to the use of heparin with hemodialysis therapy and uremia-induced platelet dysfunction. Fortunately, we were able to stop the bleeding in both cases. However, it is not always be easy to achieve hemostasis in bleeding ulcers and may even be fatal especially in patients on dialysis therapy. As such, gastrointestinal bleeding such as Dieulafoy's ulcer in dialysis patients is associated with a higher risk of mortality.

PUB210

Regional Differences in the Epidemiology of Incident ESRD in Arkansas: Developing an Understanding of Disparities

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Background: End-stage renal disease (ESRD) Network 13 that includes Arkansas, Louisiana and Oklahoma has the third highest adjusted incidence rate of ESRD in the nation. Furthermore, epidemiology of ESRD and pre-ESRD nephrology care for the state is unclear.

Methods: Using ESRD Network 13 data for incident ESRD cases from January through December 2016, we describe regional differences in the epidemiology and pre-ESRD nephrology care within the five regions of Arkansas [central, northwest, northeast, southwest and southeast].

Results: For the year 2016, 0.9% (n=1,212) of the total U.S. incident ESRD patients were Arkansans. 14% of them were <45 years of age, 21% ≥75 and 47% female-proportions similar to the national demographics. Patients ≥85 years comprised around 5% of the total incident cases in the central (metropolitan) and the southeast (rural) regions of Arkansas compared to <1% in the other regions. 33% of incident cases were African Americans compared to 26% in the U.S. There was no difference in the proportion of Arkansans choosing hemodialysis compared to the U.S. (89% vs. 88%). 87% of them started hemodialysis using a central venous catheter at the first ESRD service date- with the highest rate (93%) in the southeast region (the most rural region of the state). Within the regions, no one started peritoneal dialysis in the southwest region of Arkansas. Pre-ESRD nephrologist and renal-dietician care was received by 56% (n=605) and 4.8% (n=52) Arkansans compared to the national average of 64% (n=76,052) and 7.8% (n=9,274), respectively.

Conclusions: Using the Renal Network-13 data rather than the USRDS annual data report, we were able to gather data for Arkansas that are more recent and region-specific. We observed that a higher proportion of African American and Arkansans ≥85 years started dialysis. Dismal access to- and dramatic regional differences in pre-ESRD care may be contributing to the disproportionate burden of incident ESRD patients in Arkansas. These data can be basis for region-specific efforts to improve nephrology care that is urgently needed in order to develop a CKD action plan for the state of Arkansas.

PUB211

Risks of Cardiovascular Death(CVD) in Maintenance Hemodialysis Patients with Diabetic Nephropathy

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Background: Prevention of the development of CVD, which is the major cause of death, is key to improving prognosis. We had investigated factors associated with CVD mortality risk in maintenance dialysis patients. In this study, an additional analysis was performed on data in hemodialysis patients with diabetic nephropathy compared with those having other underlying diseases. And furthermore, we investigated factors that influence CVD mortality risk in hemodialysis patients with diabetic nephropathy.

Methods: This retrospective study was conducted with 201 outpatients with hemodialysis at our Blood Purification Therapy Center and our other related hemodialysis facilities (57 diabetic nephropathy and 144 others). Logistic regression analysis was conducted with outcome- measured as CVD death. Hemoglobin levels and blood pressure values before and after dialysis were summed up at 3, 6, and 12 months (Σ). A curve was obtained by changes in blood pressure per month and the area under the blood pressure curve (AUC) was calculated.

Results: Diabetic nephropathy was the highest mortality risk among underlying disease groups. A comparison with other underlying diseases revealed that significant differences were found for the variables older age (p<0.001) and a shorter history of hemodialysis (p<0.001) in patients with diabetic nephropathy. There was no significant difference in anemia control between two groups. Poor blood pressure control and higher dose of erythropoietin were found in patients with diabetic nephropathy. The multivariate analysis of risk factors for mortality in patients with diabetic nephropathy showed that smoking (odds ratio(OR): 4.71 [95%CI: 1.97~11.26, p<0.001], history of ischemic heart disease (OR: 2.56 [95%CI: 0.95~6.85, p=0.061], age (OR: 1.07 [95%CI: 1.03~1.13, p=0.002], and a history of dialysis therapy (OR: 0.78 [95%CI: 0.69~0.87, p<0.001] were risk factors.

Conclusions: Introduction to hemodialysis for patients with diabetic nephropathy, given higher CVD mortality risk, it is important to actively prevent the development of CVD shortly after hemodialysis. Furthermore, higher smoking rates with higher CVD mortality risk associated with smoking among patients with diabetic nephropathy suggested that smoking cessation is important for patients with diabetic nephropathy to improve their prognosis.

PUB212

Relationship Between Malnutrition and Hypervolemia in Peritoneal Dialysis and Hemodialysis

Guilherme P. Santa Catharina, Erica A. Guimarães, Lilian Cordeiro, Benedito J. Pereira, Hugo Abensur, Rosilene M. Elias, Bruno C. Silva. *University of São Paulo, São Paulo, Brazil.*

Background: Malnutrition and volume overload increase morbidity and mortality rates in patients on peritoneal dialysis (PD) and hemodialysis (HD). Bioelectrical impedance analysis (BIA) can assess both nutritional and tissue hydration status in these patients.

Methods: BIA was performed prior to dialysis in a cross-sectional, unicentric study that included 71 patients on PD and 109 on HD. Data provided from BIA were: extracellular water/total body water ratio (ECW/TBW), fat free mass (FFM), fat percentage (FP) and phase angle (PA), which is an objective measure of nutritional status.

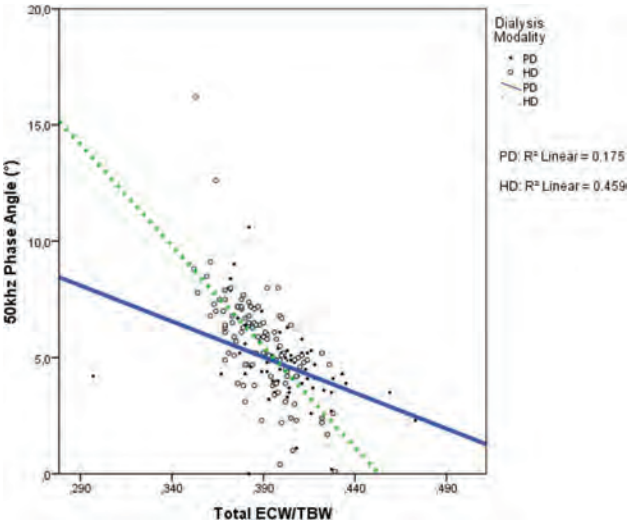
Results: Median PA was 4.5° (4.0; 5.2) and 5.8° (4.4; 6.8) in PD and HD respectively, p=0.0001. Median ECW/TBW was 0.403 (0.39; 0.41) and 0.39 (0.38; 0.4) in PD and HD respectively, p=0.0001. A negative correlation between ECW/TBW and PA was found in HD (r=-0.680, p=<0.0001) and PD (r=-0.665, p<0.001), with a statistically different slope of the curves (p<0.001). FFM and FP were similar between groups.

Conclusions: Patients on HD presented better nutritional status and lower volume overload in comparison to PD. Patients with poor nutrition status (lower PA) presented higher volume overload (higher ECW/TBW) in both HD and PD groups. The correlation is greater in HD patients.

Patients characteristics

	PD (n=71)	HD (n=109)	p
Gender (% male)	46	50	0.65
Age (years)	54 (38;65)	49 (32;60.5)	0.09
Weight (Kg)	60.9 (55.8;69)	65.4 (56.4;77.4)	0.04
BMI (Kg/m2)	23.7 (21;26.4)	24.8 (21.7;28.3)	0.05
ECW/TBW	0.403 (0.39;0.41)	0.390 (0.38;0.4)	0.00
FFM (Kg)	47.1 ± 10.8	49.3 ± 11.6	0.21
Fat (%)	24.2 ± 12.1	25.7 ± 11.9	0.42
PA 50Hz(°)	4.5 (4.0; 5.2)	5.8 (4.4; 6.8)	0.000

BMI, body mass index; ECW, extracellular water; TBW, total body water; FFM, fat free mass; PA, phase angle.



Correlation ECW/TBW and phase angle.

PUB213

Characterization of N-Terminal Pro B-Type Natriuretic Peptide and its Predictive Value for Longer-Term (7-Year) Survival in Maintenance Dialysis Patients

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Background: In a non-end-stage kidney disease (ESKD) population, NT-proBNP levels are significantly higher in women, the elderly, and those with lighter body weight; however, these characteristics have not been clarified in dialysis patients. In addition, NT-proBNP levels are predictive of 2-year survival in dialysis patients (Kawagoe C et al. Renal Failure 2018).

Methods: Differences in NT-proBNP levels were determined according to sex, age, and dry weight. The association between baseline NT-proBNP levels and mortality (total deaths, non-malignancy-related deaths, and malignancy-related deaths) was analyzed.

Results: A total of 875 dialysis patients (43.1% women, mean age 67.8 years old, median dialysis vintage 77 months) without atrial fibrillation were followed for up to 7 years. Baseline mean (SD) of log NT-proBNP; men vs. women was 3.67 (0.51) vs. 3.74 (0.51) pg/mL, p=0.04. Therefore, the findings showed borderline significance according to sex. A sex difference was not observed in younger patients (29-69 years old), but was prominent in elderly patients. As in those without ESKD, NT-proBNP levels increased with age, and the relationship between NT-proBNP and dry weight showed a significant negative correlation. During 7 years of follow-up, 34.1% died (30.6% due to non-malignancy-related death; 3.4% due to malignancy-related death). The Kaplan-Meier survival estimate showed a clear survival difference for total and non-malignancy-related deaths between quartiles of log NT-proBNP, but not for non-malignancy-related deaths. In univariable and multivariable analysis, the log NT-proBNP was strongly associated with total and non-malignancy-related deaths. This association was also observed when patients were divided according to sex, quartile of age, and quartile of log NT-proBNP, but was not seen in association with dry weight quartiles in women (Q2 and Q3).

Conclusions: In dialysis patients, NT-proBNP levels showed differences according to sex (men<women), however, this difference was not observed in younger patients. NT-proBNP levels are strongly associated with longer-term survival. However, NT-proBNP levels might have different significance in midsize women. Additional study is needed to clarify these findings in dialysis patients.

PUB214

Restless Legs Syndrome Effectively Treated with Constant-Pressure Predilution On-line Hemodiafiltration, A Case Report

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Introduction: We encountered a case of unstable predilution on-line HDF due to elevated transmembrane pressure (TMP) when performing constant-speed predilution on-line hemodiafiltration (HDF) as treatment for restless legs syndrome (RLS) in a dialysis patient, necessitating frequent adjustments of console settings such as the amount of dialysate and TMP. Here, we report the effectiveness of incorporating a newly developed constant-pressure predilution on-line HDF system as a preventive measure against unstable on-line HDF and frequent adjustment of settings when treating dialysis patients with RLS.

Case Description: A 55-year-old man who had suffered from RLS and been undergoing constant-speed on-line HDF with 45-L target predilution and an ABH-21P hemodiafilter. The symptoms of RLS rated 10 on the International Restless Legs Syndrome Rating Scale (IRLS). The α_1-microglobulin (α_1-MG) removal rate was only 27.8%, so the hemodiafilter was subsequently replaced with a PEPA hemodiafilter. However, episodes of elevated TMP exceeding 250 mmHg occurred after the replacement and were managed by reducing dialysate flow rate. This resulted in the replacement of 40.7±4.50 L, with removal of 30.4% of α_1-MG. The total amount of albumin (Alb) leakage in dialysate waste was 5.3 g. Therefore, we incorporated a newly developed fully automated console GC-110N (JMS Ltd, Japan) with a built-in automated dialysate infusion system to establish a constant-pressure predilution on-line HDF that maintains TMP below 200 mmHg. The amount of replacement was maintained at approximately 43.5±6.98 L and the α_1-MG removal rate was 39.5%, with no need to manually reduce the flow rate. The Alb leakage in dialysate waste was 7.9 g. The patient has maintained an IRLS rating of 0 with no RLS symptoms for the past 4 years.

Discussion: Using the constant-pressure mode enabled achieved the clinical endpoint, namely, resolution of RLS with no need to manually reduce the flow rate. The GC-110N console enables predilution on-line HDF at constant pressure or speed and also has a postdilution mode. Further study is needed to investigate the appropriate use of each mode, but the availability of this console is beneficial for dialysis patients by offering more treatment options.

PUB215

Demographic and Clinical Characteristics Are Associated with Physical Function Among Patients Receiving In-Center Hemodialysis

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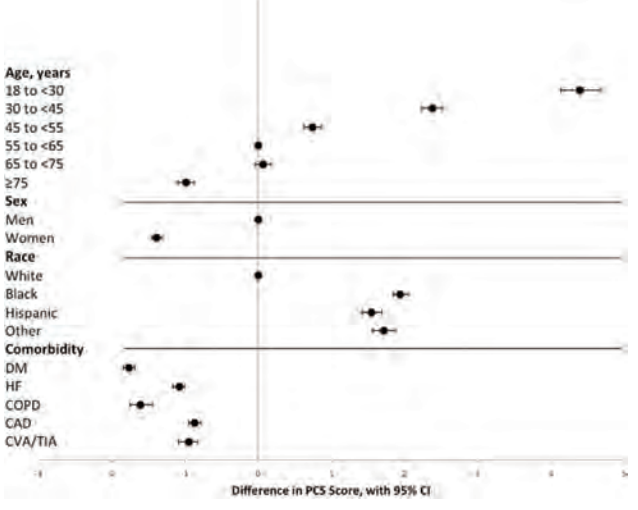
Background: Poor physical functioning is a pervasive disturbance among patients receiving maintenance hemodialysis, ranked by patients as of high importance and associated with higher mortality. However, few studies have examined demographic and clinical characteristics associated with physical functioning and change over time.

Methods: We collected longitudinal data from the Kidney Disease Quality of Life (KDQOL) survey administered as part of clinical care to 243,792 patients receiving in-center HD between Jan. 1, 2010 and Dec. 31, 2016. We used multivariable linear mixed modeling to examine changes in the Physical Component Summary (PCS) score over time and associations between patients' demographic and clinical characteristics and PCS.

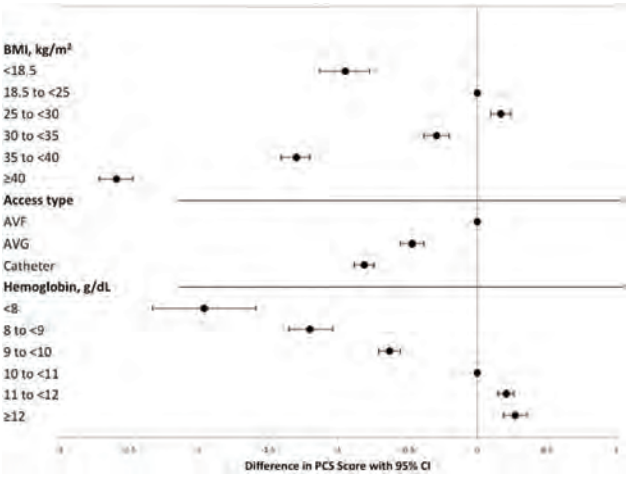
Results: Median age was 62 years, dialysis vintage 2 years; 57% were men, 48% white, 31% black, and 14% Hispanic. PCS declined by 0.16 points per year (95% CI 0.11,0.20). Older, female, and white patients had lower PCS, as did those with comorbid conditions and at both extremes of BMI (Figures). Low hemoglobin and catheter use were also associated with lower PCS.

Conclusions: Potentially modifiable factors, such as low hemoglobin, catheter use, and high BMI, were associated with lower physical functioning.

Funding: Commercial Support - Fresenius Medical Care North America



Association of demographic characteristics and comorbidity with PCS score



Association of modifiable factors with PCS score

PUB216

Efficient Removal of Large Solutes by Pre-Dilution On-line Hemodiafiltration Improves the Quality of Life of Dialysis Patients

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Background: Efficient removal of middle and large solutes is crucial for treating complications in dialysis patients. Here, we switched HD to pre-dilution on-line HDF (preHDF) in stable dialysis patients and observed changes in their health-related quality of life (QOL) for 6 months to assess the clinical effects of preHDF. Although the Medical Outcomes Study 36-Item Short-Form Health Survey is internationally used to assess health-related QOL, we used its shortened version SF-8.

Methods: We included 19 patients on maintenance HD (M/F, 13/6; age, 52.7±11.8 yrs), all of whom switched from HD to preHDF. HD was performed with a super high-flux dialyzer (blood flow rate [Qb], 253.2±24.5 mL/min; dialysate flow rate [Qd], 500 mL/min). After switching, preHDF was performed with a high-spec hemodiafilter (Qb, 260.0±20 mL/min; total Qd, 600 mL/min; Vs, 45.5 L/session). Both HD and preHDF were performed for 4 h/session, 3 times/wk. The removal efficiency was assessed in terms of Kt/V for urea, reduction rates of b_2-microglobulin (MG, 11.8 kDa) and a_1-MG (33 kDa). Changes in QOL were assessed with SF-8.

Results: Kt/V was 1.53±0.23 for HD, showing no significant change during the observation period. Compared with the b_2-MG reduction rate for HD, the rates were significantly higher at the time of switching to preHDF (74.0±4.4→81.7±3.0%) and 1, 3, and 6 months later. Compared with the a_1-MG reduction rate for HD, the rates were significantly higher at the time of switching to HDF (31.8±7.6→39.2±7.2%) and 1 and 6 months later. The SF-8 scores on all subscales increased after switching to preHDF. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (calculated from 8 subscale scores) increased after switching to preHDF. The MCS scores were significantly higher for preHDF than HD. Moreover, the patients presented markedly fewer unidentified complaints and appeared more active.

Conclusions: After switching to highly efficient preHDF, b_2-MG and a_1-MG reduction rates significantly increased, despite no changes in Kt/V. The SF-8 scores on each subscale and PCS and MCS scores also increased. These results indicate that enhanced removal of solutes in the LMWP range is beneficial for the internal environment of patients, consequently, their health-related QOL is improved.

Funding: Private Foundation Support

PUB217

Trend of Serum Albumin Among the Japanese Dialysis Population

Norio Hanafusa, Ken Tsuchiya, Kosaku Nitta. *Tokyo Women's Medical University, Shinjuku-ku, Japan.*

Background: Serum albumin (Alb) is one marker of protein-energy wasting (PEW) related to poor survival. Hypoalbuminemia is associated with both inflammation and malnutrition. Therefore, maintaining appropriate Alb levels requires appropriate protein intake and management against inflammation. This study investigated the trend of serum Alb, C-reactive protein (CRP), and normalized protein catabolic rate (nPCR) among the Japanese dialysis population.

Methods: We used summary table data of the Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry for 2001–2015. Numbers of patients and averages and standard deviations of the values were provided by age groups with width of 15 years. We investigated the trend of mean values of Alb, CRP, and nPCR for patients of 45 years or older using Joinpoint analysis. The proportions of the patients with low Alb, low nPCR, and high CRP were also investigated with different cut-off values. For each analysis, numbers of joinpoints and the annual percent change (APC) were evaluated.

Results: APCs of mean Alb values were negative during the entire period (Figure). However, APCs of mean nPCR values were negative, whereas those of CRP values were not significant. These results indicate that Alb and nPCR values have been declining, although CRP values were stable. The proportions of patients with hypoalbuminemia, low nPCR, and high CRP exhibited similar trends. All age groups showed similar trends.

Conclusions: Serum Alb in Japanese dialysis population seems to be decreasing overall, which might have some association with the decline in protein intake rather than the increase in inflammation, irrespective of the patient age. It might be necessary to increase the protein intake against PEW. Future studies might be required investigate the Alb trend with protein intake increased.

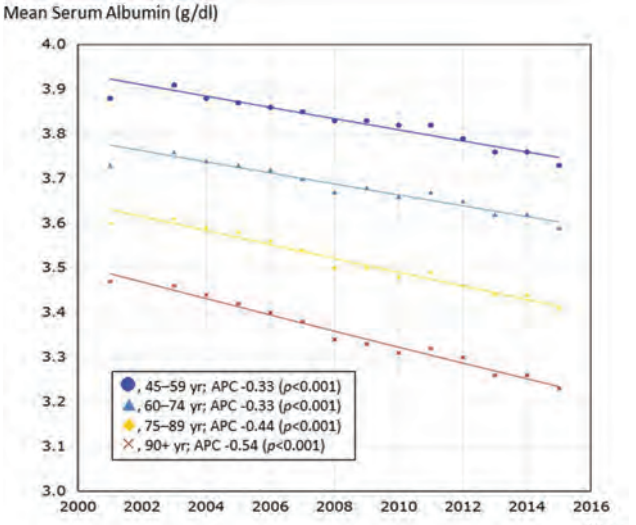

Figure. Trend of Mean Serum Albumin by Age Group
APC, annual percent change.

PUB218

The First Cambodian Dialysis Registry: The Facts of ESRD Therapy in Cambodia

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[1]Cambodian Association of Nephrology, Phnom Penh, Cambodia; [2]Eijin Clinic and Cambodian Association of Nephrology, Hiratsuka, Japan; [3]Cambodian Association of Nephrology, Phnom Penh, Cambodia; [4]Cambodian association of nephrology, Phnom penh, Cambodia.

Background: The number of hemodialysis (HD) patients keeps increasing, yet statistical data is still inexplicit in Cambodia. CAN has started the dialysis registry since 2017.

Methods: This is a cross-sectional study which was conducted on patients (n=407) who received HD in August 2017, from 5 hemodialysis centers in Phnom Penh capital city, Cambodia. Retrospective data such as age, gender, demographic, underlying diseases, HD frequency per month, and each HD session duration are deliberately collected and analyzed using SPSS.

Results: New patients make up 9.3%. Number of female patients is slightly lower than male (42.8% and 57.2%, respectively). Mean age is 52 years old (±SD15). Adult age group (25-64 years old) accounts for the highest number of patients (73.5%). Hypertensions, coexistence of hypertension and diabetes mellitus and kidney diseases are the common underlying diseases (46.7%, 31%, 13.9% accordingly). However, diabetes mellitus alone is responsible for 8.1%. The mean of HD frequency per month is 7.5 times (±SD2.3). HD session is 4-hour long.

Conclusions: The present condition of hemodialysis in Cambodia is gradually progressing forward, but it is still insufficient. Poor adherence to HD treatment needs to be tackled. Primary and secondary preventions of hypertension and diabetes mellitus are crucial.

PUB219

Risk Factors for Infectious Diseases in Patients with End-Stage Kidney Disease Undergoing Hemodialysis

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Background: In the recent years, increased hospitalization rate for infectious diseases in patients undergoing hemodialysis (HD) has become a problem. Herein, we examined the risk factors of infectious diseases in patients undergoing HD.

Methods: Based on the Carlson comorbidity index (CCI), age, sex, primary cause of end-stage kidney disease (ESKD), dialysis vintage, body mass index (BMI), serum calcium, phosphorus, magnesium, albumin, hemoglobin, alkaline phosphatase (ALP), and parathyroid hormone values in patients with ESKD who underwent HD three times a week at three dialysis centers in 2009, risk factors for emergency hospitalization due to infectious diseases from January 2010 to December 2014 were evaluated.

Results: Among the 708 patients undergoing HD, 142 had emergency hospitalizations for infectious disease (ID group: 90 men [63%]; mean age, 67.6 years; mean dialysis vintage, 8.5 years) during the study period, whereas 566 did not have emergency hospitalizations for infectious disease (control group: 340 men [60%]; mean age, 66.0 years; mean dialysis vintage, 8.4 years). The proportion of nephrosclerosis (as primary cause of ESKD) (7.7%, P=0.01) and ALP levels (298 U/I, P=0.03) were significantly higher and BMI (21.2 kg/m^2, P = 0.046) was significantly lower in the ID group than those in the control group (3.2%; 267 U/I; 21.8 kg/m^2). Moreover, CCI (5.01) was higher in the ID group than that in the control group (4.75), but the difference was not significant (P = 0.1). In the Cox proportional hazard model, CCI (hazard ratio [HR], 1.095; 95% confidence interval [CI], 1.001-1.193), nephrosclerosis (HR, 1.539; CI, 1.085-2.076), and ALP levels (HR, 1.002; CI, 1.001-1.003) were significant predictors of emergency hospitalization for infectious diseases.

Conclusions: This study evaluated the risk factors of emergency hospitalization for infectious diseases in patients undergoing HD; however, further investigation is required.

PUB220

Measurement of Body Composition in Hemodialysis Patients During One-Year Frequent Dialysis

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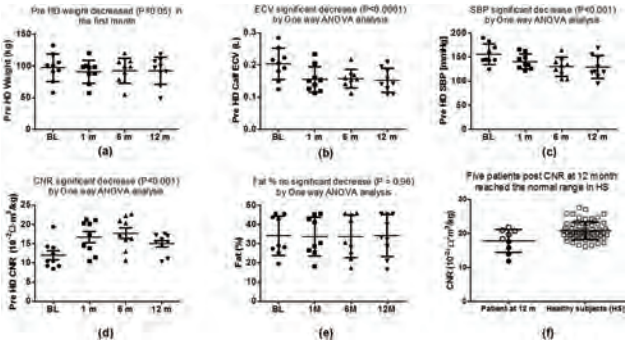
Background: The primary aim of this study was to evaluate the effect of increased frequency of dialysis (FHD) on changes in extracellular volume (ECV), systolic blood pressure (SBP), calf normalized resistivity (CNR) and fat percentage. Since ECV is not a useful target for denoting dry weight, we explored CNR as an alternative measure.

Methods: In 12 stable HD patient's treatment frequency was changed from 3times/week to 6 times/week HD (FHD). SBP, body weight and body mass index (BMI) were measured pre and post HD. Calf resistance at 5 kHz (R_5) was measured using a bioimpedance device (Hydra 4200). The data collected was used to calculate calf resistivity (Rho=R_5*area/length), normalized resistivity (CNR=Rho/BMI) and calf extracellular volume (cECV). Body fat percentage (Fat%) was measured by Futrex body composition analyzers (Futrex 6100, Futrex Tech, Inc.). All measurements were performed at baseline (BL) and thereafter monthly for up to one year.

Results: Nine patients completed one year of FHD. Data were presented at BL, and at first, six and twelve months. Compared to BL, body weight, cECV and SBP decreased significantly (Fig.1 a, b and c). CNR increased significantly by the first month but did not change thereafter (Fig. 1 d). Fat % did not change significantly (Fig.1 e). Antihypertensive drug dosing decreased significantly from baseline by month six and remained stable thereafter. The post HD CNR in five of nine patients reached the range of normal (>18.5 10^{-2}*Ohm*m^3/kg for males and >19.1 10^{-2} *Ohm*m^3/kg for females) after one year FHD (Fig.1 f).

Conclusions: Increasing the frequency of dialytic treatment, results in a reduction in ECV and increase in CNR, accompanied by a reduction in SPB. As a consequence, anti hypertensive medication was reduced. Body composition did not change except reduction of fluid status. Based on this small study which needs to be confirmed in a larger group of patients, increase in CNR was associated with decrease in fluid status which provides a goal for HD treatment.



PUB221

Conscious Survey of Japanese Physicians and Actual Trends in Proton Pump Inhibitor Prescription for Hemodialysis Patients

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Background: Proton pump inhibitors (PPIs) are widely prescribed but less is known about prescription in hemodialysis (HD) patients. We conducted 1) a conscious survey directed to Japanese physicians about PPI prescription to HD patients and 2) gathered clinical data on all HD patients from 3 clinics to elucidate factors related to PPI prescription.

Methods: 1) A conscious survey was conducted through email to physicians dedicated to HD practice. In addition, 2) patient characteristics and blood test data were retrieved from every HD patient in 3 in-center clinics who have been on HD for more than a year.

Results: 1) 200 physicians replied the survey and 60% would continue PPIs after 8 weeks prescription for gastric ulcer (GU) or gastroesophageal reflux disease (GERD) concerning relapse. The major reason for stopping PPIs was concern of adverse effects such as chronic diarrhea. 58% woulld choose to keep prescribing patients already on PPIs with unclear indications. 86% considered HD patients to be a high risk group for peptic ulcers (PUs). 2) Data from 374 HD patients were retrieved. Average age was 72 years, 63% male, and average HD vintage was 5.5 years. The cohort consisted of 41% diabetic kidney disease, 22% cardiovascular disease (CVD), 16% peripheral artery disease (PAD), 19% cerebral artery disease (CAD), 49% took anti-platelets, and 66% took PPIs. Those prescribed PPIs had higher ratio of CVDs (28% vs 12%), PADs (21% vs 5%), CADs (24% vs 5%), and anti-platelets (56% vs 37%). Further, though Hb were similar (11.2mg/dl), those on PPIs had higher ratio of iron prescribed (76% vs 71%), lower TSAT (26% vs 27%), and lower serum ferritin (78ng/ml vs 96ng/ml).

Conclusions: Japanese physicians frequently prescribed PPIs to HD patients and regarded them as a high risk group for PUs. More than half of the physicians would choose to keep HD patients on PPIs prescribed for unclear indications. Those with artherosclerotic diseases and anti-platelet medication had higher predisposition on PPIs.

Funding: Private Foundation Support

PUB222

The Current Prevalence and Prognosis of Frailty in Japanese Patients with Hemodialysis

Hidemi Takeuchi,[1,2] Haruhito A. Uchida,[1] Nozomu Otaka,[1] Yuki Kakio,[1] Yuka Okuyama,[1] Ryoko Umebayashi,[1] Hitoshi Sugiyama,[1] Hidetoshi Kanai,[2] Jun Wada.[1] *[1]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [2]Kokura Memorial Hospital, Kitakyushu, Japan.*

Background: The problematic expression of patients with hemodialysis is the frailty. Patients with hemodialysis easily fall into frailty due to the potential pathophysiological factors, such as physical deconditioning, chronic inflammation, and decreased anabolic hormones. Frailty is associated with severe mortality in several countries. However, the prevalence and prognosis of the frailty in Japanese patients with hemodialysis remain unknown. The purpose of this study is to identify the current status of Japanese hemodialysis patients with frailty.

Methods: This study is a multicenter investigation, which was conducted at 6 institutions. The subjects were all hemodialysis patients. To evaluate the frailty status, we used the modified Fried's frailty phenotype model, adjusted for the Japanese. In addition, we prospectively investigated the patients' survival, hospitalization and developed complications.

Results: Of the 542 patients, 385 patients including 82 patients with frailty (21.3 %), 203 with pre-frailty (52.7 %) and 100 without frailty (26.0 %), were enrolled in this study. At baseline, participants were 67.2 ± 11.9 years of age with more male gender (62.4 %) than female. With an average follow-up period of 17.1 months, a total of 41 patients died; 13.4% of patients with frailty, 11.8% with pre-frailty and 6.0% without frailty. The mean survival time of patients with frailty, pre-frailty and without frailty were 16.7, 17.1 and 17.6 months, respectively (Log-Rank P-value = 0.197). The mean hospitalization-free period of patients with frailty, pre-frailty and without frailty were 14.2, 16.0 and 16.7 months, respectively (Log-Rank P-value < 0.001), furthermore, significant differences were found among all groups in the post-hoc analysis. Similarly, significant differences were found in the analysis of the developed complications (Log-Rank P-value = 0.006).

Conclusions: The prevalence of frailty in Japanese patients with hemodialysis was relatively lower, and the frailty had less influence on the mortality, compared with the other countries. However, the frailty has the influence on healthy life expectancy, that is, higher rate of the hospitalization and complications were observed as the frailty status goes severe.

PUB223

A Simple Score to Identify the Potential Need for Intensive Hemodialysis Within a Facility

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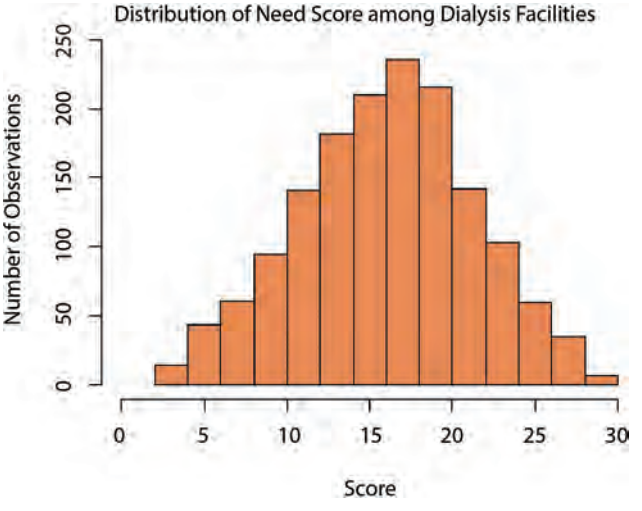
Background: Wider application of intensive hemodialysis (HD) requires reorganization of staff and patient scheduling and/or greater utilization of home HD. Tools that identify dialysis facilities with greater need for intensive HD may be useful. In a pilot study, we constructed a simple score that identifies potential need for intensive HD in a facility, insofar as need is reflected by plausible indications.

Methods: We used data from Dialysis Facility Compare, CROWNWeb, and Medicare claims to characterize facilities in a dialysis provider organization. For each facility, we calculated 3 metrics from data accumulated in 2013-2014: (1) the percentage of HD patient-months with ultrafiltration rate (UFR) >10 mL/hour/kg; (2) the percentage of HD patient-months with serum phosphorus >5.5 mg/dL; and (3) the heart failure (HF) hospitalization rate among HD patients with Medicare as primary payer. For each metric, we estimated deciles among facilities and transformed the metric to a scale from 1 (lowest decile) to 10 (highest decile). For each facility, we set the "need score" equal to the sum of metric scores.

Results: We identified 1546 facilities. Mean percentages of HD patients-months with UFR >10 mL/hour/kg and serum phosphorus >5.5 mg/dL were 32.6% and 35.5%, respectively, and the mean HF hospitalization rate was 15.6 admissions per 100 patient-years (PY). As displayed, the distribution of the need score was symmetric. There were 143 (10.8%) facilities with a score ≥24 points; these facilities had higher prevalence of high UFR, higher prevalence of hyperphosphatemia, and mean HF hospitalization rate of 24.7 admissions per 100 PY.

Conclusions: Facility scores that quantify plausible indications for intensive HD may be used to target therapy in local populations. Further study is needed to refine methodology, with consideration of hypertension and long post-dialysis recovery time.

Funding: Commercial Support - NxStage Medical, Inc.



PUB224

Infective Endocarditis in Hemodialysis Population - Experience from Center in India

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Background: Hemodialysis (HD) population is at increased risk for infective endocarditis (IE) due to impaired nutrition and vascular access, with its associated morbidity and mortality. Aim of present study is to present our data of patients with IE in HD population.

Methods: This was retrospective analysis from BLK Hospital, New Delhi, India. Data was collected from May 2015 to April 2018. All patient who underwent maintenance dialysis with a diagnosis of CKD were included. Patients diagnosed with Infective endocarditis based on clinical as well as echocardiographic (trans thoracic(TTE) or trans esophageal (TEE) criteria were identified. There demographic parameters, clinical presentation, and clinical outcome was recorded

Results: Out of 457 patients who underwent dialysis, 6 patient (1.31%, 4 male and 2 female) developed IE. Mean age was 41.3 years. 3 patients had temporary dialysis catheter, one had permacath and 2 had AVF as vascular access. Average duration on dialysis was 10.3 months. Duration of fever before diagnosis was 18.3 days (range 7 to 45 days). A pre-existing heart disease was present in 1/3rd of patients. Staph Auerus was identified in 2 and both were on dialysis catheter. Staph epidermiditis was identified in 1 patient and blood cultures were sterile in three. Only 1 patient was diagnosed with trans thoracic echocardiography while trans esophageal echocardiography was required in 5. Aortic valve was involved in 3, mitral valve in 2 and tricuspid valve was involved in one patient. One patient expired, one developed reactive arthritis as complication of IE. one developed red

man Syndrome and emboilc infarct to brain and one developed Steven Johnson Syndrome as drug related toxicity.

Conclusions: Infective endocarditis in not uncommon in Indian population and diagnosis is often delayed. Resulting in high morbidity and mortality. High Index of suspicion is required for early diagnosis. When suspected trans esophageal echocardiography should always be considered.

Clinical Feature of patients with Infective Endocarditis

Patient	Duration of fever (Days)	Organism isolated	Valve Affected	Duration of Treatment (Weeks)	Diagnosed with (TTE/TEE)	Complications	Outcome
1	12	Staph. Aureus	Aortic	4	TEE	Reactive Arthritis	Cured
2	14	Staph Aureus	Mitral	6	TEE	Stevens Johnson Syndrome	Cured
3	23	Sterile	Aortic	4	TEE	Red Man Syndrome, Embolic Infract	Cured
4	7	Staph. Epidermidis	Mitral	3	TTE	Expired	Expired
5	45	Sterile	Aortic	6	TEE	Nil	Cured
6	7	Sterile	Tricuspid	4	TEE	Nil	Cured

PUB225

Syndrome of Uremic Encephalopathy and Bilateral Basal Ganglia Lesions in Non-Diabetic Hemodialysis Patient

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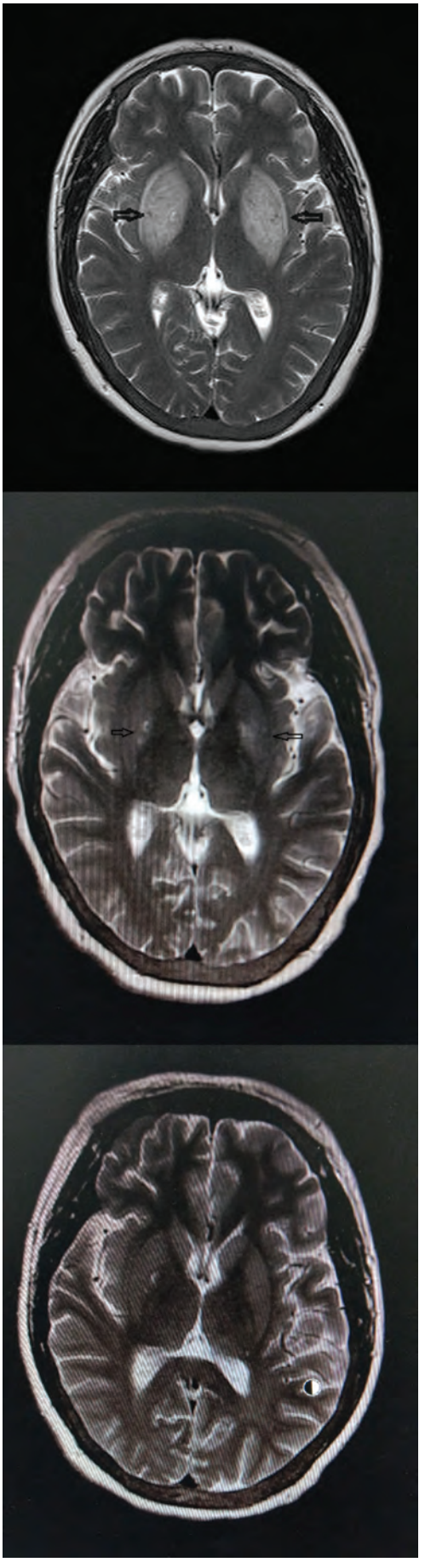
Introduction: Uremic encephalopathy (UE),the toxic metabolic encephalopathy, is an uncommon complication resulting from endogenous uremic toxins in patients with severe renal failure, and the syndrome of UE range from mild inattention to coma. The imaging findings of UE include cortical or subcortical involvement, basal ganglia involvement and white matter involvement. The basal ganglia type is uncommon, previous cases reported Asian patients with diabetes mellitus (DM) are usually affected by it

Case Description: A 32-year-old woman with history of non-diabetic hemodialysis for 3 years suffered from severe involuntary movement and Brain magnetic resonance image (MRI) showed symmetrical T2-weighted imaging (T2WI) and T2/fluid-attenuated inversion recovery (T2FLAIR) hyperintense nonhemorrhagic lesions in bilateral basal ganglia. She was diagnosed with UE as syndrome of bilateral basal ganglia lesions, due to a combined effect of uremic toxins and hyperthyroidism. After treatment with high frequency and high flux dialysis, hyperbaric oxygen therapy and declining parathyroid hormone, she was complete remission with normal body movement and discharged.

Discussion: UE is an unfamiliar toxic metabolic encephalopathy with typical CT/MR neuroimaging including bilateral vasogenic or cytotoxic edema at the cerebral cortex or basal ganglia region, producing a spectrum of brain abnormalities that range from mild inattention to coma. UE with basal ganglia involvement is uncommon and generally seen in Asian patients with DM. In our case, the patient had non-diabetic UE with typical bilateral basal ganglia lesions presented with involuntary movement. Recognizing this syndrome seems to be more and more important, especially considering its diagnostic and prognostic implications.



PUB226

Utilization of Sharesource Connect™ (SSC) Continuous Renal Replacement Therapy (CRRT) Data from Two Pediatric Centers: What Can We Learn?

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Background: Baxter SSC displays de-identified, downloadable, customizable CRRT data for each center, including filter life, dialysis dosing and fluid removal that facilitates center and inter-center data assessment relative to benchmark data from adult programs.

Methods: All de-identified data for SSC downloaded from Prismaflex machines at Loma Linda University Children's Hospital (LLUCH) + Rady Children's Hospital San Diego (RCHSD) from Jun - Dec 2017 was included for pooled and comparative analysis.

Results: 36 patients using 98 Prismaflex circuits (total 4823 treatment hrs) were included in the analysis. Mean delivered CRRT dose was 44 mL/kg/min despite mean circuit time loss of 14.5%. Mean hemofilter life: 43 hrs; 54.5% circuits reached desired end points of max filter life or treatment end. 10/98 filters were lost due to clotting. Inter-institutional differences are noted in Table. Overall outcomes were similar between LLUCH and RCHSD.

Conclusions: CRRT is a common treatment offered to critically ill pediatric patients with AKI. SSC provides a data-rich dashboard for CRRT programs, allowing real-time identification of CRRT parameters. Current study data is limited, but using pooled data from more comparable pediatric centers may assist in developing pediatric-specific CRRT metrics and quality benchmarks for pediatric CRRT programs. Due to data de-identification, SSC data allows easy data sharing between centers and could allow comparison with historical values from ppCRRT registry data. The de-identified data made it impossible to determine patient specific details and patient outcomes related to the CRRT dose or fluid removal. The display of pediatric data relative to adult norms without size standardization can be confusing. There is an opportunity 1) for more pediatric centers to share SSC data to identify better CRRT practices and develop quality metrics. 2) to obtain more granular, patient specific data 3) for Baxter to create a Pediatric/Adolescent versions of SSC.

	LLUCH	RCHSD	p-value
# Patients (average#/month)	19 (2.7)	17 (2.4)	0.38
Mean length of therapy per patient (d)	6.5 ± 3.7	4.8 ± 2.3	0.18
Dosing (mL/kg/hr)	36 ± 13.9	52.0 ± 6.9	0.01
Treatment time lost (%)	10.6 ± 4.2	18.3 ± 12.8	0.08
Monthly average filter life (hrs)	42.9 ± 20.4	43.8 ± 16.2	0.46
Hemofilters lost by clotting (%)	10.5 ± 17.1	2.1 ± 5.1	0.14

PUB227

Development and Implementation of a Training Program for Intravenous Administration of Calcimimetic

Becky Brosch, Brenda K. Shrader, Sharon Brandl, Nataliya Wilson, Parker Calbert, Carrie Chamblin, Jennifer E. Snyder, George R. Aronoff, Deborah A. Benner. *DaVita, Inc., Denver, CO.*

Background: The intravenous (IV) calcimimetic Parsabiv (etelcalcetide) was approved by the FDA for the treatment of secondary hyperparathyroidism in hemodialysis patients in February 2017. The package insert states that the medication requires refrigeration and is to be administered at the end of treatment during rinse back via IV push into the venous chamber or IV push after rinse back via the venous access followed by 10 mL normal saline. To prepare for use of Parsabiv at our organization, a pilot was conducted among select clinics to optimize clinical management and gain operational experience.

Methods: Here, we describe a Parsabiv administration training program for clinical staff that was developed over the course of the pilot.

Results: Initial training included aspects related to storage, handling and post-treatment administration. In the early phases of the pilot program, senior clinical staff conducted on-site visits to pilot clinics. During these visits and through direct observation, it was discovered that the standard practice of vial inversion and use of 1 inch needles made it more difficult to draw up the full prescribed dose. Through a troubleshooting process, clinicians identified that the full dose could be drawn up more effectively by tilting the vial 30-45 degrees (not inverting) and using a 1.5 inch needle. Based on this experience and in preparation for wider use through the organization, a training program was developed to educate nurses on this technique. The essential elements of this education program include mandatory online training modules with video demonstrating the appropriate draw techniques, check-lists, post-training evaluations, and quarterly clinic audits. Additionally, these experiences were shared with the drug manufacturer and their education materials were modified to include a description of this technique as a best practice.

Conclusions: This work demonstrates the value that pilot programs can provide, allowing issues to be identified and addressed prior to large-scale implementation of new clinical practices.

Funding: Commercial Support - DaVita Inc

PUB228

Achievement of KDIGO Hemodialysis Targets with Stepwise Increasing Comorbidity Burden: A European Multicenter Analysis

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Background: Hemodialysis (HD) patients often have multiple comorbidities that add to the complexity and burden of their clinical and subjective symptoms. Comorbidities and frailty also result in decreased life expectancy and high mortality rates.

Methods: We assessed 1,246 prevalent HD patients from 13 DaVita centers in Europe (Poland 8 centers, n=482; Portugal 5 centers, n=764) and analyzed achievement of KDIGO treatment targets that contribute to outcomes: adequacy (spKt/V > 1.2), anemia (Hb 10-12 g/dL on ESA, Ferritin 200-800 μg/L, TSAT 20-50%), CKD-MBD (phosphorus ≤ 5.5mg/dL, calcium ≤ 10.2 mg/dL, iPTH 150-600 pg/mL) and type of vascular access (AVF or CVC). We considered median Charlson comorbidity index (CCI) and added stepwise: median age (>70 yrs), median BMI (<25 kg/m^2), median albumin (<39 g/L) and diabetes (yes) in relation to the comorbidity burden.

Results: Mean (SD) age was 62 (14) years for patients with CCI ≤ 7 and 76 (10) for patients with CCI > 7 ($p<0.001$) with no differences in gender, dialysis vintage, treatment time per week, and ESA dose. The percentage of patients achieving KDIGO targets is shown (Table).

Conclusions: Comorbidities and frailty pose substantial challenges for the provision of optimal HD care. This large real-world retrospective study demonstrates that elderly, more-frail patients with comorbidities still had an AVF rate of ≥70% and achieve KDIGO targets as well as patients with lower CCI.

Funding: Commercial Support - DaVita, Inc

	n	% Patients Achieving KDIGO Target								
		spKt/V	Hb	Ferritin	TSAT	P	Ca	iPTH	AVF	CVC
CCI ≤ 7	687	97	68	61	73	74	98	58	79	16
CCI > 7	559	96	67	65	69	87***	99	65*	72**	23**
+ > 70 yrs	416	97	70	66	68	90***	99	67	72*	23**
+ BMI < 25 kg/m2	198	97	65	65	68	89***	99	63	70**	28***
+ Albumin < 39 g/L	141	97	66	63	68	91***	99	62	70*	28
+ Diabetes	60	97	72	70	68	92***	100	58	75	28*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs all patients with CCI ≤ 7

PUB229

Cancer Incidence and Characteristics in the Dialysis Patients: A Nationwide Cohort Study

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Background: As population of ESRD patients are increasing, detecting and managing cancer in the ESRD should be emphasized. It is known that CKD is associated with malignancy risk, as population of ESRD are increasing, detecting and managing cancer in the dialysis should be emphasized. However, it is still not recognized the incidence of cancer in ESRD, and the difference of primary cancer site is also unveiled. We investigated the incidence of cancer among the large numbers of dialysis patients using national health insurance data to inform cancer screening in dialysis clinic.

Methods: The data were obtained from Korean National Health Insurance Service (KNHIS) which contains reimbursement record from all medical facilities across the country. The dialysis cohort included patients who claimed any procedures or materials for both hemodialysis and peritoneal dialysis, based on the Korean electronic data interchange codes (O7020 for hemodialysis; O7061 for peritoneal dialysis). Cancers were defined by compatible ICD-10 codes of C00.0 to 99.9 as cancers. Proportional difference in independent variables between the ESRD cohort and control were analyzed using the Wald chi-square test.

Results: Total 45,312 patients and controls were observed for 17,1329.45 and 220,464.18 person years respectively. Incidence of cancer was 463.8 vs 244.8 per 10,000 person-year. Hazard ratio of cancer in ESRD is 2.008 ($p < 0.001$). The most common malignancy in the ESRD patients is liver cell carcinoma same as control. ESRD showed markedly higher incidence of oral cavity and neck area cancer (OR 9.28, $p < 0.0001$) which was second most common site in the dialysis patients. The kidney cancer were also higher (OR 5.81, $p < 0.0001$), but prostate and stomach were less than control (OR 0.78, $p < 0.0001$; 0.88, $p = 0.0305$, respectively). Cancer incidence was markedly incrased by patients' age. Patients older than 60 showed 7 times risk than younger patients below 20 years of age (OR 7.725 in 60-69; 6.877 in 70-79; 7.647 in > 80 years old; all $p < 0.0001$). There was no difference between dialysis modalities, and no difference with economic satus.

Conclusions: Patients on dialysis treatment should be considered the incidence of head and neck malignancy, and all patients should be screened to detect oral cavity and pharynx cancers as well as liver and common site of malignancies in the dialysis clinic.

PUB230

Lower-Extremity Muscle Strength and Survival in Hemodialysis Patients with Peripheral Artery Disease

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Background: Hemodialysis (HD) patients with peripheral artery disease (PAD) have an elevated mortality risk compared to those without PAD, and there is a need to identify factors that increase the mortality risk in these patients. Although lower-extremity muscle strength is one of the risk factors of mortality in HD patients, the association between lower-extremity muscle strength and mortality risk in HD patients with PAD is unclear. In this study, we investigated the prognostic significance of lower-extremity muscle strength in a cohort of HD patients with PAD.

Methods: A total of 148 outpatients (mean age, 67.9 ± 11.2 years, 42.6% male) undergoing maintenance HD therapy 3 times a week at an HD center and who were diagnosed with PAD with an ankle-brachial index of <1.00 or toe-brachial index of < 0.70 at baseline were monitored for 4 years. Clinical characteristics including age, sex, body mass index, time on HD, comorbid conditions, and blood biochemical data were obtained at baseline. In addition, maximum voluntary isokinetic knee extensor strength (leg strength), which reflects lower-extremity muscle strength, was measured using a handheld dynamometer (μTas F-1; Anima, Japan). Leg strength data were divided by dry weight and expressed as a percentage. Participants were categorized into two groups by a leg strength cutoff value of 40%. A Cox proportional hazards regression model was used to assess the contribution of leg strength to all-cause mortality.

Results: During a median follow-up of 38.0 months, 30 patients died. With a multivariate Cox model, the hazard ratio in the group with a leg strength <40% was 2.36 (95% confidence interval; 1.05–5.30) compared with that in the ≥40% group.

Conclusions: Decreased lower-extremity muscle strength was associated with survival in HD patients with PAD.

PUB231

The Multifactorial Key(s) to Deciding for the Timely Creation of Dialysis Access – An Exploratory Study

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Background: This study set out to understand how family members and renal care providers influence decisions around optimal initiation onto hemodialysis (access creation).

Methods: Indepth interviews were conducted with 69 participants including predialysis CKD 4 patients (n=31), newly initiated onto hemodialysis with (n=18) or without AVF/AVG (n=20). Data were inductively analysed using a thematic approach and deductively informed by the theory of relational autonomy.

Results: Patients' social relationships and vicarious experiences significantly shaped their behavioural activation regarding access creation. Unequal weightage to different relationships created boundaries around whom to include in the decision making process. Family had greatest influence, followed by friends then HCPs. Family involvement varied from active behaviours (verbalising preferences and sharing views), passive involvement (support with no explicit action to influence decision) to complete abstinence in the process. Patients who either chose not to involve others or had no input from others were least likely to prepare, or initiated HD without AVF/AVG. While most patients maintained that they have the final say indicating individualist autonomy in decision around modality and access, family considerations, vicarious experiences and hearsay were noted as being more important than clinical tests or information communicated by HCPs. Doctors' recommendations were described as influential only by those expressing trust in their clinician. Others expressed mistrust and apprehension to medical recommendations – these were closely linked to low symptomatic burden and lack of clarity and understanding of provided information. Patients perspectives on health care encounters were heterogeneous, fear of dialysis and exaggerated concerns related to access and dialysis (costs; lifestyle disruptions) were uniformly voiced – family and hearsay acted to either alleviate or intensify those concerns.

Conclusions: Social and relational factors influence how patients respond to dialysis counselling and preparation. The adequacy of pre-dialysis education as an individual approach needs review. Greater attention to relational forces and emotional concerns around dialysis is needed for effective decision making for optimal initiation onto dialysis.

Funding: Government Support - Non-U.S.

PUB232

Limited Options for the Measurement of Large Middle-Molecules in Routine Clinical Practice

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Background: Large middle molecules (MM) have recently been described as a group of 28 uremic toxins with molecular weights between 15 and 60 kiloDalton. This group of large non-protein bound toxins are involved in chronic inflammation, atherosclerosis, structural heart disease and secondary immunodeficiency. New medium cut-off hemodialysis membranes (Theranova) provide efficient removal of these molecules for chronic hemodialysis patients. The purpose of this study was to determine which of these molecules could be measured as part of clinical practice in dialysis units around the world.

Methods: Laboratories associated with dialysis units in Australia, Canada, Germany, Hong Kong, Italy, New Zealand and the United Kingdom were asked to identify which of the large MM could be measured in routine clinical practice; the cost; time to process the sample and method of analysis. The molecules include 5 cytokines, 4 adipokines, 4 growth factors, 8 immune mediated proteins and 6 other molecules.

Results: The number of large MM which could be measured as part of routine clinical practice varied greatly from dialysis unit to unit: from 1 to 23 large MM available to clinicians with a median of 9 molecules. Three molecules (FGF-2, Complement factor D and AGEs) could not be measured in any of these units. In contrast, kappa and lambda free light chains, myoglobin and prolactin were available for assessment in more than 80% of laboratories. The cost (in USD) for measuring these molecules varied by molecule and between dialysis units. The median cost was $39 (range $3.5 to $351). The lowest cost was to measure myoglobin in Germany, the most expensive FGF-23 in Canada. Ten molecules could be reported within 24 hours but 6 had average reporting periods of greater than 10 days. Luminex and ELISA based methods were the most common forms of assessment. Of the 28 large middle-molecules 8 would require specific transport requirements to the laboratory (e.g. cooling) limiting their utility in clinical practice.

Conclusions: While interest in the removal of large MM by new dialysis technologies grows the capacity to measure these uremic toxins in clinical practice is currently limited. Of the molecules free light chains (kappa + lambda), prolactin and myoglobin are the most accessible in terms of stability, availability, cost and reporting times.

PUB233

Estimating Absolute Blood Volume During Hemodialysis Using Crit-Line

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Background: Knowledge of absolute blood volume (ABV) can inform dry weight estimation and design of ultrafiltration rate profiles. Our aim was to compare ABV estimates obtained from a recently published 2-compartment blood water concentration (BWC) model during a dialysate dilution test with estimates obtained using a model modified for hematocrit (HCT) measurements.

Methods: Four dilution tests (150 mL) were performed within a single HD treatment in 4 patients. Changes in BWC and HCT were simultaneously measured using blood volume monitor (0.1 sec sampling time) and Crit-Line sensor (20 sec sampling time). The 2-compartment BWC model was adapted to estimate ABV using HCT measurements. Separate ABV estimates were obtained from the new HCT model and the BWC model. Bland-Altman (BA) analysis was used to analyze agreement between the estimates. Nested one-way ANOVA was used to compute intra-treatment variability of estimates.

Results: The HCT model successfully estimated HCT dynamics during the dilution test (Fig. 1). Intra-treatment standard deviation (SD) of estimates of BWC and HCT models were 0.12 L and 0.32 L, respectively. BA limits of agreement (Fig. 2) between the two estimates were 0.13±0.71 L (bias±2SD).

Conclusions: Means of ABV estimates based on the new HCT model are in agreement with estimates derived from a validated BWC model, however, slow HCT sampling times increased the estimates' SD which could be improved by reducing sampling time. A protocol for estimating ABV can be readily integrated into current HD machine technology and potentially enable the development of personalized fluid volume management protocols.

Funding: NIDDK Support

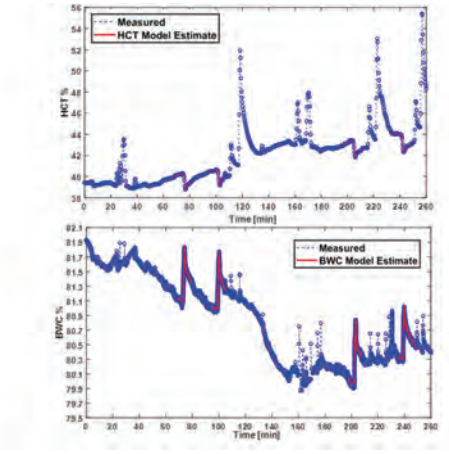

Fig 1. Sample model estimates

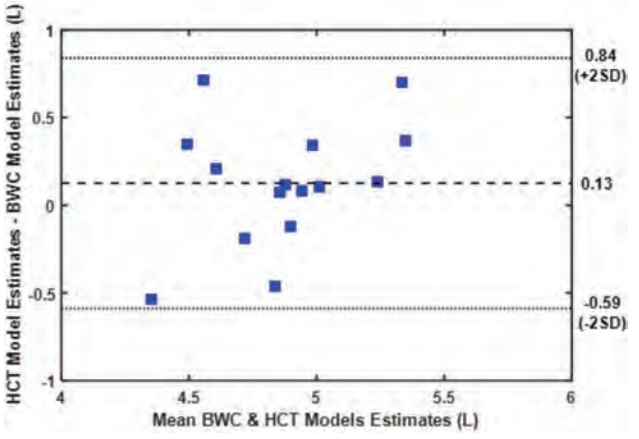

Fig 2. BA-analysis

PUB234

Using Standard Bicarbonate Bath for Hemodialysis of Critically Ill Patients with High Venous Oxygen Saturation (HVOS) Is Associated with Poor Outcomes

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Background: Management of critically ill patients with HVOS requiring Renal Replacement Therapy (RRT) is challenging. HVOS (>75%) is known to increase mortality in critically-ill patients by 20-30%. The role of modifying dialysate bicarbonate (Dia-HCO3) concentration to avoid metabolic alkalosis in critically ill patients with HVOS requiring RRT remains unknown. We present observational data on the effects of using 30mEq/l Vs 35mEq/l of Dia-HCO3 in critically-ill patients requiring RRT.

Methods: Over a six week period in April – May 2018, we identified 6 critically ill patients with renal failure requiring RRT who had HVOS in our ICU. The Dia-HCO3 was reduced to 30mEq/L in 3 patients while the other 3 patients underwent RRT with standard Dia-HCO3 of 35mEq/L. Complications during and after RRT and patient outcomes were documented, along with VOS & VBG before and after RRT.

Results: RRT was uneventful in 3 patients who received Dia-HCO3 of 30 mEq/l. By comparison, RRT was stopped within 2 hours in 2 of the 3 patients receiving Dia-HCO3 of 35 mEq/l due to the development of severe hypotension. Both patients had refractory shock leading to cardiac arrest in next 2-3 hours. An increase in the post HD venous oxygen saturation was observed in three of 6 patients, other three patients postHD VBG could not be done.

Conclusions: To our knowledge, the effect of using lower Dia-HCO3 in critically-ill patients requiring RRT has not been studied. HVOS in the critically ill is indicative of mitochondrial dysfunction and poor peripheral utilization of O2. High Dia-HCO3 shifts the hemoglobin-oxygen dissociation curve to the left thereby further worsening tissue oxygenation by decreased release of oxygen. This effect in addition to anemia and HVOS could explain the clinical worsening and high mortality in this patient population. Further studies are needed to determine the clinical benefit of using low-moderate Dia-HCO3 among critically-ill patients requiring RRT.

Clinical characteristics

Patient Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Pre HD VBG pH	6.78	7.36	7.30	7.32	7.28	7.41
Pre HD Venous SpO2 (%)	82.7	88.6	77.3	84.8	86.2	83.7
Post HD VBG pH	7.08		7.41	7.43		
Post HD Venous SpO2 (%)	86		83.4	89.6		
Dia-HCO3 concentration (mEq/L)	35	35	35	30	30	30
Post HD Survival	No	No	yes	yes	yes	yes

PUB235

Data Sonification: A Novel Way to Analyze "Big Data" from Kidney Patients

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Background: Electronic health records allow the collection of unparalleled rich data sets. For exploratory analysis, data is usually presented graphically. However, data visualization is challenging with high-dimensional data. We explored transforming data into auditory sensory inputs (sonification) as a novel means to represent data.

Methods: We used routinely collected data from 35,146 dialysis patients followed during their terminal 100 weeks before death (Usvyat, Kidney Int, 2013). Each parameter (interdialytic weight gain (IDWG), systolic blood pressure (SBP), albumin and C-reactive protein (CRP)) had an instrument assigned to it for sonification. We developed algorithms that used tonal ambiguity and variations in pitch, octave, dynamic, and texture to represent parameter dynamics, and a strong beat to represent the passage of time. We disassociated emotional reactions by avoiding the use of major/minor, consonance/dissonance, familiar harmonic progressions, and tonal center.

Results: In sonification #1 (https://youtu.be/IarHnxPmHeE) parameters are represented by flute (IDWG), cello (SBP), guitar (albumin), and trombone (CRP). We chose the whole tone scale because of its perfect symmetry, its lack of tonal center/absence of a leading tone, and its lack of emotional associations of other musical modes. Pitch represents the changing parameter levels. In sonification #2 (https://youtu.be/IE4-1S9pwGE) instrumentation was the same as in #1, except for albumin (drum). We used chord alternation with two chords that are a whole step apart, which have no associations with cadence or familiar harmonic progressions that would imply suspense and/or relief to the listener. We used pitch and texture (expressed by number of instruments and instruments being played on the off-beats) to represent changes in parameters.

Conclusions: Our results show, for the first time, that longitudinal data from kidney patients can be represented as auditory signals, complementing graphic data representation. We avoided musical modes and patterns that carry emotional associations, allowing listeners to approach the sonification without bias. Multi-sensory data representation will become particularly important when applied to high-dimensional, "big" data. Future research needs to address questions of optimal data representation.

Funding: Commercial Support - Fresenius Medical Care

PUB236

Trajectories of Health Markers in Dialysis Patients Before Death

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Background: We characterized trajectories of health markers before death and compared them to patients who did not die during the same period.

Methods: Data from patients treated at a large dialysis provider who died during 2010 to 2017 was compared to data from patients who survived 12 months from a randomly selected index date. Using data from 12 months prior to death (or index date for survivors), we computed slopes from monthly averages for laboratories and treatment parameters via linear regression. For each variable, we calculated the percentage (%) of patients with significant increases, decreases, and stable slopes.

Results: We analyzed data from 182,481 patients who died and 140,999 patients who survived. We found significant differences in slopes between those who died and survived for cardiovascular, inflammatory, and nutritional markers (Figure 1). We found 28% of patients who died had decreases in predialysis systolic blood pressure (pre-SBP); 15% of survivors had decreases. Patients who died had decreases of 4% in neutrophils and 13% in lymphocytes versus 7% and 6% in those who survived. More patients who died (28%) had decreases in albumin (Alb) versus those who survived (13%). We also revealed additional distinct findings in the % of patients with increases in parameters for those who died versus survived.

Conclusions: Patients appear to have distinct patterns of changes in health markers before death compared to patients who survived. For example, nearly twice as many patients who died exhibited decreases in pre-SBP and Alb during the 12 months before death compared to survivors. Identifying combinations of changes in different parameters could be useful for construction of artificial intelligence-based prediction models.

Funding: Commercial Support - Fresenius Medical Care North America

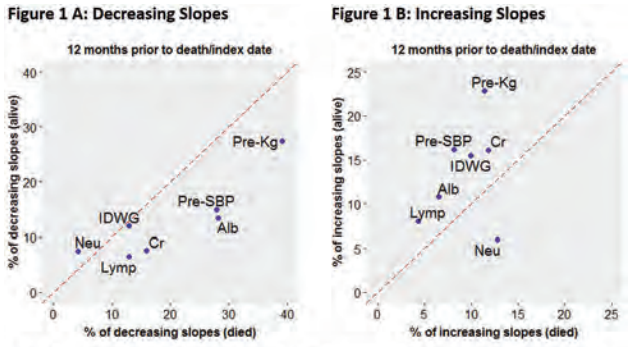

Figure 1. Percent of significant decreases (A) or increases (B) in slopes of health markers 12 months prior to the death on the x-axis, or the concurrent changes for those who survived on the y-axis for parameters related to: 1) cardiovascular diseases (Pre-SBP: predialysis SBP; IDWG: interdialytic weight gain; Pre-Kg: predialysis weight), 2) Inflammation (Lymp: lymphocytes; Neu: neutrophils), 3) nutrition (Alb: albumin; Cr: creatinine).

PUB237

Optimizing Fluid Management with Crit-Line® in HD

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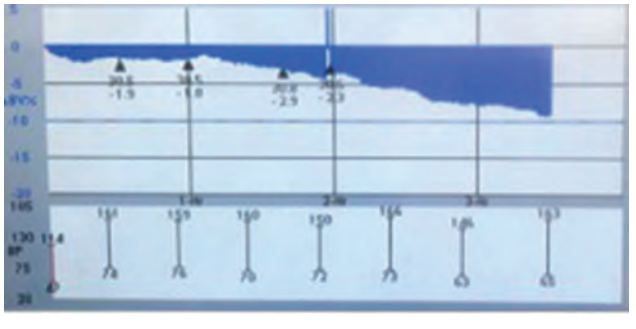
Introduction: Unigue patient cases presented here discuss use of Crit-Line technology in HD.

Case Description: Case 1: Case 1: A 72-yr-old female (dry weight/DW 51kg) has a predialysis weight (wt) of 52.6kg and initial ultrafiltration goal (UF) of 1.6L. During the first hr, the Crit-Line slope was initially slightly negative then trended upwards (relative change in blood volume/ΔBV% ≤ -3%/hr; A profile). UF goal was increased by 200mL at 0:35 and 1:45 and a saline bolus given at 1:55hrs (black triangles). At 3:30, her final ΔBV% was -9.3% (A profile), UF was 2175mL and she had no intradialytic events (IDEs). Although she achieved postdialysis wt (~50.7kg), profile suggested opportunity to remove more fluid and dry weight adjusted to 50.6kg for next session. Case 2: A 56-yr-old, hypotensive-prone male (DW: 110Kg) with a predialysis wt of 117.1kg was never able to achieve >4.5L UF due to IDEs prior to Crit-Line use. Systolic BPs in the 90s (mmHg) was clinically acceptable for this patient and initial UF goal was 6L. His ΔBV% decreased rapidly (-7.9% at 1:05; C profile). His UF goal was then decreased by 200 mL at 1:05, 2:40 (ΔBV% -16%) and 3:20 (ΔBV% -18.0%) with no IDEs. At 3:30, ΔBV% was -18.2% (C profile), his BP dropped to 79/44 and he had a mild hand cramp (yellow diamond). His UF goal was reduced by 200 mL and symptoms dissipated. His final ΔBV% was -16.9% with ~5.2L of UF and his postdialysis wt was 112.1kg. His DW was adjusted up to 111.5kg for later treatments.

Discussion: Cases show safe, effective, real-time use of Crit-Line technology, where clinicians can accurately assess and adjust fluid removal as needed, while reducing potential for IDEs and fluid overload.



PUB238

Environmental Sustainability of Dialysis Facilities

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Background: Haemodialysis is responsible for high resource consumption, resulting in a high economic burden and cost to the environment. Our aim was to assess the current environmental sustainability of haemodialysis facilities in regional Australia.

Methods: Nurse unit managers of all Tasmanian public dialysis facilities received an online survey, which asked 23 questions relevant to the environmental sustainability of dialysis services. The survey used was a modified version of the survey used to assess UK dialysis facilities.

Results: Responses were received from all dialysis units in Tasmania (n=6, 100%). Energy saving initiatives included the use of fluorescent lighting (n=6, 100%), motion sensor lights (n=1, 17%), thermostat controlled heating (n=6, 100%) and automatic hibernation settings of fax machines and computers (n=6, 100%). Five units (83%) were supplied with energy by Aurora and one unit (17%) from TasNetworks. Water saving initiatives included motion sensor taps (n=3, 50%) but no units harvested rainwater nor recycled reverse osmosis water. Recycling initiatives included waste segregation in all units and four recycled PVC plastic. Sustainable transport initiatives included active and public transport (n=3, 50%). Three units (50%) also provided bicycle parking with access to shower and changing facilities. None of the units used virgin paper and all had double-sided printing as an automatic setting. All units used a combination of paper and digital medical records. All units used paper towels and food sourcing was unknown. All units supported green initiatives, but no unit had an environmental sustainability policy nor had performed an audit of their environmental sustainability.

Conclusions: Sustainable initiatives were evident in all haemodialysis units, but significant opportunity exists to improve the environmental impact of dialysis in Australia.

PUB239

Life on the Bridge: A 40-Year Journey with Dialysis

Judy Weintraub. *Life On The Bridge, Los Angeles, CA.*

Introduction: Life On The Bridge is a 22-minute humanistic documentary by Judy Weintraub, that raises expectations about creating a good life while living with kidney dialysis. It raises awareness of the realities of kidney disease and the treatments available, highlighting what is possible. This theme is ultimately a universal one: though we may not control all the circumstances of our lives, we always have a choice in our attitudes

Case Description: As the story unfolds, Judy, after years of waiting, is called in for a third kidney transplant. She had previously received two transplants, both of which failed within a few short months. Judy had begun kidney dialysis treatments as a teenager and has been on some form of dialysis ever since. Over the decades, she did both in-center hemodialysis and more than a decade of peritoneal dialysis and nocturnal HHD. The documentary follows what happens from the first hopeful days and weeks to several months later, as Judy and her doctors fight to keep this new transplant. Throughout, we also hear the personal dstories and experiences of people of different ethnicities and backgrounds who are living with dialysis or transplantation. Family members share what it's like to be with loved ones who live with this disease. Professionals speak out - doctors, nurses, technicians, and social workers share their view of the field.

Discussion: Several themes arise from the film: Education of professionals, patients, family members and the general public as to the possibilites of living well with the various modalities of kidney dialysis; The role of physicians as champions in their patient's care; Maintenance of positive expectations in living life, especially with a chronic illness; The crucial role that encouragement plays in optimizing outcomes; The importance of ongoing evaluation and the willingness to think outside-the-box to individualize care. This film's ultimate mission is to help patients and the professionals who care for them move toward the optimal health outcomes that we know are achievable. Judy Weintrub M.S. Ed., holds degrees in Special Education from USC and Psychology from UCLA. She holds credentials in the areas of Education, Communication Handicapped and Early Intervention. She also served on the boards of *Nephrology News & Issues, the Southern California Renal Disease Patient Advisory Council (Network 18) and the Southern California Chapter of the National Kidney Foundation.*

PUB240

Inflammatory and Nutritional Markers Prior to Death in Chronic Hemodialysis Patients: Results from the Global MONDO Initiative

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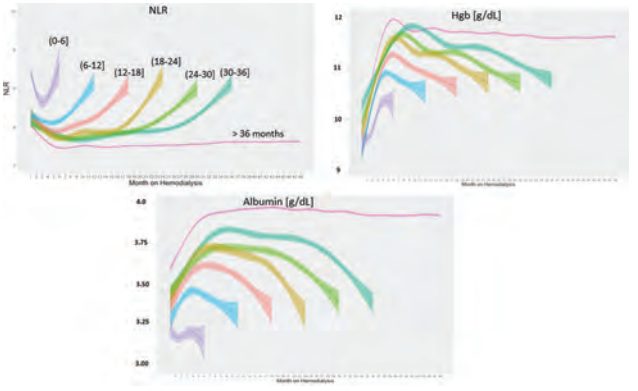
Background: Malnutrition, inflammation, and oxidative damage are highly prevalent in dialysis patients (pts) and each condition is associated with an increased risk of death. Hemodialysis pts with larger hemoglobin level fluctuations have higher mortality.

Methods: All the adult pts who died within the first 36 months (mos) of HD were stratified into 6 sub-groups, pts who died from month 0 to 6, 6 to 12, 12 to 18, 18 to 24,

24 to 30 and 30 to 36 mos after HD initiation. For those who survived 36+ mos on HD were served as the reference group. Monthly average NLR, Hgb, Pre-HD SBP and serum albumin were obtained, cubic spline function were applied to access the trends and rate of changes for each of the parameters of interest for up to 48 months after HD initiation. In addition, subgroup analysis was performed to study the regional differences.

Results: Totally, 18,276 incident HD pts were included, 2,068 were died within 6 mos, 1,231 died within 6 to 12 mos, 971 died within 12 to 18 mos, 792 died within 18 to 24 mos, 721 died within 24 to 30 mos, 648 died within 30 to 36 mos, and 12,295 survived more than 36 mos. For pts who died sooner after HD, NLR observed to be higher at the initiation of the dialysis, while Hgb and serum albumin were tended to be lower. In addition, NLR reached the nadir from 3 to 10 months after start of dialysis while serum Hgb and albumin seem to reach the maximum 3 to 10 mos after HD initiation, depends on the survival time.

Conclusions: Inflammation can interact with malnutrition, resulting in the excessively high mortality in the dialysis population. There are several readily available indicators reflecting catabolic, protein intake and oxidative stress that change prior to death in incident HD pts. The awareness of valuable index predicting worse outcomes is central therapeutic efforts, and interventions at the individual and regional levels.



PUB241

Patient Peer Mentoring in Hemodialysis: A Single Center Experience

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Background: Patients new to hemodialysis (HD) are educated by dialysis clinicians in order to improve their start to HD. Peer mentorship, from experienced dialysis patients, has been shown to enhance this transition increasing patient engagement and quality of life. The aim of this study was to measure the effect of a patient peer mentor program on self-efficacy, anxiety and depression.

Methods: Mixed methods study design. A patient to patient mentor program was introduced to one dialysis center consisting of: mentor identification, mentor training, mentor and mentee matching, and regular mentor/mentee meeting episodes over a 2-month period. The primary outcome was change in self-efficacy as measured by 6-Item Self-Efficacy for Managing Chronic Disease Scale. Secondary outcomes were change in anxiety and depression as measured by the 4 item Patient Health Questionnaire Scale (PHQ-4). Mentee and mentor evaluations through group interviews were performed.

Results: Thrirteen patients participated (7 mentors and 6 mentees) from a center of 100 patients. 100% of participants agreed that they would recommend other dialysis patients to talk with a mentor. 100% of pairs agreed to continue to meet after the study had completed. No statistically significant improvement in self-efficacy, anxiety and depression was found. A high level of engagement from key dialysis center champions including the social worker and the renal dietitian played a key role in the success of starting the mentor/mentee program.

Conclusions: A coordinated mentor program maintained by clinicians was identified by patient mentees and mentors as a positive strategy for dialysis centers. Commitment from the dialysis organization and center staff is pivotal to ensure the sustainability of mentor program. A larger randomized cluster study is required to demonstrate improvement in self-efficacy, anxiety and depression.

PUB242

Quality of Life Trends in Patients with ESRD Undergoing Hemodialysis

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Background: Health-related quality of life (HRQoL) has been the subject of a lot of recent studies involving many chronic diseases and conditions and guiding treatment modalities. In addition, HRQoL has been shown to be a strong predictor of morbidity and mortality in patients with end-stage renal disease (ESRD). We conducted this study to compare the quality of life score trends across the years for the patients and to look for the variables that affect these scores.

Methods: We recruited patients in an outpatient dialysis center on Staten Island, NY. KDQOL scores administered yearly were collected for each patient, along with demographic and lab data. each patient had at least 2 and up to 4 scores collected, and for each score, a set of lab data within a month from the score was noted. Our primary objective was to analyze the trend of the QOL scores along with the trend of the lab data for each patient. Data analysis was carried out in SAS software. We performed a mixed logistic regression to account for the repeated measures of the KDQOL scores. Least squared means were computed to identify inter- and intra-subject variability.

Results: 96 patients were recruited, with a mean age of 63.9 years; 69% were males and 54% were white. There was no observed difference between age and the various scores. On average, men had lower scores than women in all score subsets. There was also a significant difference among the ethnicities with scores in the black population having lower scores than other races. Ferritin had significantly a negative correlation with PCS score (p-value<0.045) as well as PTH levels that were positively correlated to the effect score. There was no significant correlation between the other laboratory markers and the QOL scores over time.

Conclusions: the difference found between genders and races cope with their disease burden may depend on how anxiety, depression, and loss of autonomy may vary between genders and cultures Laboratory tests that influenced the QOL scores were PTH and ferritin. This can be due to its effect on phosphorus and calcium, which links to acid-base disturbances and bone change related to kidney disease. Type of access could affect the score by limiting the patient's physical activity and association with infection and hospitalization which invariably have a negative correlation with KDQOL scores.

PUB243

Dialysis Disequilibrium Syndrome: Rare Serious Complication of Hemodialysis and Effective Management

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Introduction: Dialysis Disequilibrium syndrome (DDS) is an extremely rare central nervous system complication that occurs in patients receiving hemodialysis and can be potentially fatal. The prognosis is poor when this manifests as serious neurological manifestation like seizures, obtundation and evidence on effective management is sparse. We present the case of a patient who developed altered mental status during hemodialysis. Patient successfully recovered with administration of mannitol and 3% saline without any long-term neurologic squealae.

Case Description: A 72 year-old male who had not had any dialysis for 2 weeks because of peritoneal dialysis catheter malfunction was admitted with dyspnea and fluid overload. He was hyperkalemic, bradycardic and emergent hemodialysis was arranged. Labs showed severe azotemia with BUN 141mg/dl, Creatinine 9.8 mg/dl and Potassium 8.3 meq/L. Chest x-ray showed pulmonary edema. Patient developed twitching and became confused about 2 hours into dialysis. Dialysis was immediately terminated, patient was given mannitol 125 mg and 3% saline was started at 30 ml/hr. Post dialysis labs revealed BUN 64 mg/dl (urea reduction ratio 54.6%), Creatinine 5.2 mg/dl and Potassium 3.2 meq/L. He was dialyzed again the next day with low blood and dialysis flow rates. Mannitol and 3% saline were administered during dialysis. EEG revealed no epileptiform abnormality. Patient made full neurological recovery after 4 days.

Discussion: DDS usually occurs during or immediately after patients receive their first hemodialysis, but can rarely happen in patients already on dialysis. Prognosis of severe DDS is poor and prevention is ideal. It is important to identify the patients who are at high risk of developing DDS and use low efficiency dialysis with gradual urea reduction. Our patient was at risk for DDS considering severe azotemia that is a surrogate for uremic milieu. There is not much guidance in literature as far as management of DDS with severe neurologic manifestations is concerned. Our patient did well with administration of hypertonic agents that have not been used much in our current clinical practice. These agents may have a role to play in management of patients requiring emergent renal replacement therapy who develop DDS despite use of preventative measures such as low efficiency short hemodialysis sessions.

PUB244

Association of 3mTUG and All-Cause Mortality in Dialysis Patients

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Background: To evaluate the association between physical performance and all-causes mortality in maintenance dialysis patients,and identify whether physical activity could predict the mortality independendy.

Methods: In this study, we evaluated maintenance dialysis patients in Shanghai Tongji hospital from Dec 2014 to Mar 2018, collected clinical data and serum hemoglobin, albumin, calcium, phosphate and parathyroid hormone(PTH) levels. We measured physical activity including muscle strength and balance ability used by timed up and go (3mTUG).

Results: 121 patients were involved, average age (61.6 ± 13.0)years, 62 peritoneal dialysis patients and the other 59 hemodialysis, 76 men and 45 women, average dialysis duration 31.7(12.3, 69) months. During the median 36 months follow-up, 22 patients(17%) were died. Age, modality, DN, phosphates, PTH and 3mTUG were risk factors for all-cause mortality(P<0.05). After adjusting age, modality, DN, phosphates and PTH, 3mTUG was an independent risk factor of all-cause mortality(P<0.05).

Conclusions: 3mTUG can predict mortality of dialysis patients independently.

PUB245

Hypoglycemia in Hospitalized Patients Undergoing Hemodialysis

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Background: Approximately 40% of patients treated by hemodialysis (HD) have diabetes mellitus (DM). Hospitalized patients with DM have greater risk of hypoglycemic episodes; HD may further increase risk as it is an energy consuming procedure and patients may have decreased appetite, hypotension, nausea and dizziness. Malnutrition is an important contributor to poor outcomes among hospitalized patients so we began offering meal trays during HD but nursing staff reported a high rate of symptomatic hypoglycemia among patients receiving insulin dosed by standard hospital protocol.

Methods: With IRB approval, we retrospectively reviewed charts of patients undergoing HD between January and August 2016 who had point-of-care blood glucose (BG) testing during HD. In May, a Certified Diabetes Educator (EY) taught nursing colleagues to estimate the carbohydrate (CHO) content of meals. Patients who anticipated consuming at least 30g of CHO received full prandial insulin dose. For patients who anticipated consuming less than 30g, the nurse contacted the MD to consider reducing the insulin dose. The population was divided into pre- (January to May) and post- (June to August) education time periods. Charts were reviewed for co-morbid medical conditions, concurrent medications and BG levels for the 24 hours surrounding HD.

Results: Using the international definition for hospitalized patients (BG > 70 or < 100 with symptoms of hypoglycemia), 14/60 (23%) had hypoglycemia. After the education, there was no significant change in the occurrence of hypoglycemia during HD (20 vs 22.5%; p = 1.000). There were no significant differences among clinical factors between the two groups: age, race, sex, dialysis vintage, acute vs chronic kidney disease, co-morbid conditions, concurrent medications.

Conclusions: There is a high incidence of hypoglycemia among hospitalized patients with DM undergoing HD. The lack of change in the incidence of hypoglycemia after education may relate to stricter adherence to prescribed insulin dosing. We plan to develop a protocol for insulin for dosing during HD adjusting for the CHO content of the meal to be consumed and the anticipated energy utilization during HD. We will observe its effect on the frequency of hypoglycemic episodes during and six hours post-HD.

PUB246

Rapid Bedside Assessment of Diastolic Function in Hemodialysis Patients

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Background: The prevalence of diastolic dysfunction (DD) among hemodialysis (HD) patients is 75%. The presence of DD is often unknown to the treating nephrologist leading to complications from intradialytic hypotension due to high ultrafiltration rate. DD is traditionally assessed using spectral and tissue Doppler waveform analysis. These techniques are time consuming and may be beyond the training of many providers performing clinician-performed ultrasound (CPUS). We have previously demonstrated that physicians can identify DD using qualitative ultrasound findings. We aim to evaluate if 3 qualitative visual parameters obtained on real-time B-mode echocardiography can accurately detect DD in HD patients.

Methods: CPUS echocardiograms were prospectively obtained by residency and fellowship trained sonologists on a convenience sample of 49 HD patients presenting to the emergency department for any reason. Cases were deidentified and randomized with 11 cases of normal diastolic function to avoid potential spectrum bias due to case-mix. The images were reviewed by two fellowship-trained sonologists who scored the clips for presence or absence of DD based on three visual indicators: presence or absence of left atrial enlargement, impaired left ventricular relaxation, and impaired mitral valve descent. The images were then rated on the severity of DD on a 0 (absent) to 3 (severe) scale. The accuracy of these findings was evaluated against DD on final cardiologist interpretation of referral echocardiograms.

Results: 39 of the HD patients had a diagnostic echocardiogram with an assessment of diastolic dysfunction documented in the prior year. Combined with the 11 normal studies, this gave a total of 50 cardiac ultrasounds for review. The overall accuracy for determining presence or absence of DD was 95.0% (CI 88.7 – 98.3). The accuracy of assessing severity to within 1 category above or below the criterion standard was 92.0% (CI 84.8 – 96.4). Interobserver correlation measured by Cohen's kappa for assessment of presence or absence of DD was 0.75, and for specific diastolic grade was 0.54.

Conclusions: Qualitative visual echocardiographic parameters can be used by clinicians to determine DD accurately in HD patients. These techniques could be adapted for detection of DD at the point-of-care in the dialysis unit.

PUB247

Utilization of Emergency Department and Risk of Resuscitation Among Patients Receiving Maintenance Hemodialysis

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Background: The end-stage renal disease has to become a growing health problem globally with increased disease burden and high medical costs. The utilization of emergency department among dialyzed patients remains uncertained and risk factors of resuscitation at Emergency Department are deserved to explore.

Methods: This longitudinal cohort study was sampled from National Health Insurance Database in Taiwan. Patients aged 19 to 90 years old with maintenance hemodialysis between January 1 to December 31, 2010, were recruited. We matched non-dialytic individuals by age, sex and Charlson Comorbidity Index (CCI) as a control group from the same data source. The utilization of emergency department among enrolled individuals was identified in 2012. We used generalized estimating equations with multiple variables adjustment to explore risk factors associated with resuscitation in emergency department visits among all suffered patients.

Results: Between January 1 to December 31, 2012, 2,985 individuals with hemodialysis and 2,985 individuals without hemodialysis were enrolled. There were 4,803 patient-times emergency department visits in hemodialysis group and 1,744 patient-times emergency department visits in the non-dialysis group. The level of the visited hospital, diagnosis category, severity of triage, and the experience of resuscitation had a statistically significant difference between hemodialysis group and non-hemodialysis group (p<0.05) but no significant difference in death (p=0.76) between two groups. In an analysis of multivariable generalized estimating equations, individuals with maintenance hemodialysis had a higher risk of resuscitation in emergency department visits compared with individuals without hemodialysis (adjusted odds ratio [aOR], 1.30, 95% CI: 1.01 to 1.68). Other risk factors for resuscitation at emergency department included age between 55 and 69 years old (aOR 1.80, 95% CI: 1.25 to 2.59), age older than 70 years old, (aOR 2.30, 95% CI: 1.61 to 3.29), the experience of hospitalization prior in 1 year, (aOR 1.35, 95% CI: 1.09 to 1.65), and the first and second degree of triage (aOR 1.96, 95% CI: 1.60 to 2.41).

Conclusions: Patients with maintenance hemodialysis had increased utilization of emergency department and a higher risk of resuscitation at emergency department compared to patients without hemodialysis.

PUB248

Association Between Suicidal Phenomenon/Depression and Inflammatory Status in Patients with ESRD on Hemodialysis

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Background: Suicide is a worldwide public health problem and depression is the mental problem most closely related to suicide. Depression is highly prevalent in ESRD, inflammation is related to ESRD and to depression. Aim: To determine the presence and severity of depression and suicidal ideation in patients on HD and the association with inflammation.

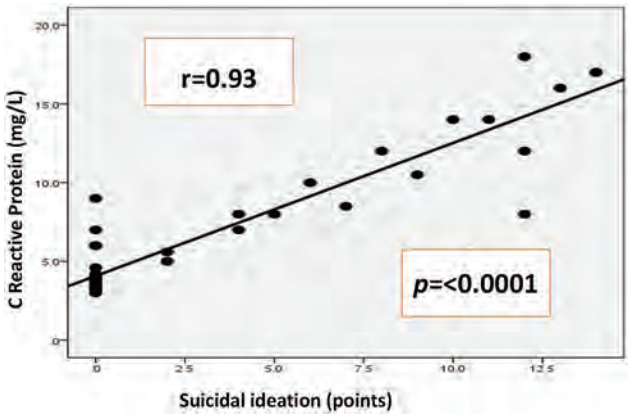
Methods: Cross sectional study, performed in 45 prevalent HD patients (June 2017-March 2018), Depression, suicidal ideation and hopeless were evaluated using Beck scales, performed by a single Psichiatrist blinded to biochemical data; inflammation was evaluated using CRP (High sensitivity), fibrinogen and globular sedimentation rate, age, time and acces type to dialysis and lipids. Subjects were infection free (3 previous months), with no current Psiquiatric therapy and/or medication, and no anti inflammatory therapy.

Results: Prevalence of depression is 88% and 33% had suicidal ideation. As higher was depression higher were CRP, fibrinogen globular sedimentation rate and suicidal ideation. In Graph is shown the correlation between suicidal ideation and CRP.

Conclusions: Inflammation measured by CRP, GSR and fibrinogen significantly correlates with depression and suicidal ideation. It is necesary to colaborate with multidisciplinary team to provide psicological and anti inflamatory therapy in ESRD.

Variable	No Symptoms	Depression mild	Depression moderate	Depression severe
PCR (mg/L)	3.40 ± 0.32	3.70 ± 0.62*	7.70 ± 1.4*	13.90 ± 3.20*
VSG (mm/H)	32.0 ± 1.2	34.0 ± 2.5	47.0 ± 7.2*	65.0 ± 8.5*
Fibrinogen (mg/dL)	338.0 ± 66.4	272.2 ± 88.4	329 ± 86.2	587.5 ± 24.1*
Suicidal ideation (pts)	0.0	0.10 ± 0.45	3.2 ± 2.8*	12.0 ± 3.0*

Student T tests; p≤0.05 vs no symptoms group.



Pearson Correlation between suicidal ideation and C Reactive Protein.

PUB249

The Total IV Iron Burden and Cognitive Impairment in Hemodialysis Patients

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Background: Hemodialysis (HD) patients routinely receive IV iron, which includes non-transferrin-bound iron that can accumulate in neurons and cause oxidative injury. Despite the established role of excess brain iron in dementia, the association between total accumulative IV iron dose and cognitive impairment, a highly prevalent condition in ESRD, has never been explored in HD patients.

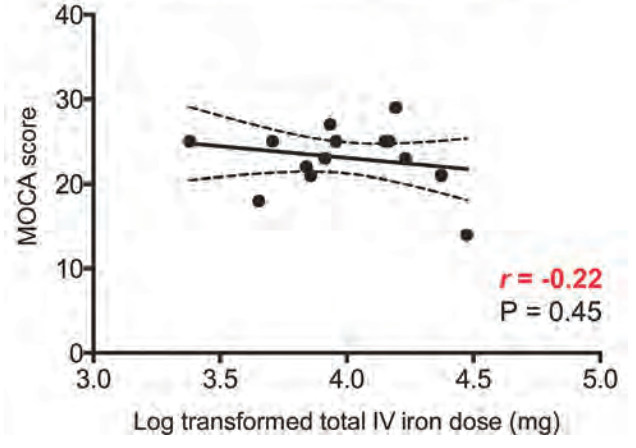
Methods: We performed an observational pilot study of prevalent HD patients at University of Utah (N=16). Patients with history of dementia, chronic hepatitis, steroid use, malignancy, hematologic disorders, hospitalization within one month of screening were excluded. Total accumulative dose of IV iron for the entire duration of dialysis was calculated for each participant. Montreal Cognitive Assessment (MoCA) test was used to screen for cognitive impairment. The total IV iron dose was log transformed to enable parametric analysis with Pearson correlation coefficient to evaluate its association with MoCA score.

Results: The study group was diverse (8 Hispanics, 4 Whites, 1 Asian, and 3 mixed), with 9 men and 7 women. Half of the group had diabetes. The mean±SD values for age, dialysis duration, systolic blood pressure, hemoglobin, and albumin were 52±14 years, 7.4±5.8 years, 142±28 mmHg, 10.6±1.9 g/dL, and 3.9±0.2 mg/dL, respectively. The median (IQR) transferrin saturation and ferritin were 28 (21, 39) % and 652 (300, 971) ng/mL. The median total IV iron dose was 10,825 mg (range of 2,400 to 29,748 mg). Two patients refused MoCA test. The mean±SD MoCA score was 23±4 (N=14). There was a trend for a negative correlation between the total IV iron dose and MoCA score (Figure 1).

Conclusions: This is the first study to evaluate the association between the accumulative IV iron burden and cognitive impairment. Larger studies are required to investigate if IV iron is associated with dementia risk in ESRD.

Funding: Private Foundation Support

Figure 1. The association between total IV iron dose and cognitive function



PUB250

How Accurate Is the Dry Weight?

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Background: Studies indicate volume overload in ESRD/CKD stage V patients are associated with worse outcomes. We observed in kidney transplant (tx) recipients usually diurese postoperatively & continues as outpatient, raising the question of the accuracy of estimated dry weight, since there is no accurate tool for ideal weight determination. We decided to investigate the weight difference on the day of tx, at 1-month & 3-months post-tx in kidney transplant recipients at Erie County Medical Center (ECMC).

Methods: Retrospective analysis of 244 kidney tx recipients at ECMC from 1/1/16-12/31/17. Demographics & clinical characteristics were collected. Exclusion criteria are age ≤18 years old, delayed graft function ≥ 1 month, & renal allograft failure within 3 months post-tx.

Results: There were 140 recipients on hemodialysis (HD) prior to tx, 48 patients on peritoneal dialysis (PD), 65 recipients received pre-emptive transplantation. Overall, age and gender and ethicity were not statatistically different among all three groups. Weight on the day of tx were statistically higher than weight at one-month & at three-months post-tx among all groups. The one-month & three-months post-tx weights were not statistically different among all groups.

Conclusions: Results showed there are weight losses after kidney transplantataion exceeding the volume administered peri-operatively. The weight loss (4-6 kg) post-transplantation mainly reflects volume loss. Fluid management poses challenging dilemma in dialysis patient since volume overload & too agressive volume removal can induce circulatory stress & multi-organ injury. Knowning that patient's ideal weight is actually 4-6 kg below their achievable dry weight on dialysis may help the clinicians to better manage patient's volume status on dialysis. Reducing dry weight even by relative small amonts has been showen to improve blood pressure & reduce left ventricular hypertrophy. Further studies are needed to better manage volume status in dialysis patients, with health, social, & economic implications.

Weight Changes Over Time (kg)

Type of Dialysis	Day of Tx Weight 1	1 Month Post-Tx Weight 2	3 Months Post-Tx Weight 2
Preemptive (N=56)	89.7±21.1	84.4±19.9	85.8±20.1
HD (N=140)	85.5±19.0	81.6±18.9	82.8±18.6
PD (N=48)	88.4±21.1	82.5±19.3	83.9±19.7
Total (N=244)	87.0±19.9	82.4±19.2	83.7±19.1

Different superscripts are statistically different from one another across time

PUB251

The Association of Gender with Avoidable Emergency Department Visits in Patients on Hemodialysis

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Background: In national samples drawn from the USRDS female patients and those younger than 44 years old utilize hospital ED and inpatients services at a higher rate than their counterparts. We set out to explore whether this association held with avoidable ED visits in a cohort of mostly minority patients in a single low socioeconomic burrough in New York City.

Methods: We use Montefiore's clinical database, "Looking Glass"™ To build a cohort of patients on hemodialysis with a first ED visit between 2013-2017 to any of 4 main EDs in the Bronx. All subsequent ED visits without a resultant admission for the duration of the observation period and the count of ED visits for 365 days prior to this index ED visit were recorded. We refer to these ED visits as avoidable because they did not result in an inpatient admission. We used bivariate analysis to test the association of demographic, socioeconomic and clinical variables with sex. We then built models using negative binomial regression adjusted for time in study, to test the association of gender with avoidable ED count alone, when adjusted for socioeconomic variables and clinical variables respectively.

Results: We identified 4,573 patients of which, 43.2% were female and 53.6% were black. The median avoidable ED visits were higher in females (4(25-75%IQR 2-9). Female patients were older, more commonly black, had lowere SES scores and were less commonly married than their male counterparts. Females less commonly had commercial insurance. Females a higher rate of avoidable ED visits when adjusting for clinical variables in the final model (1.07(95%CI:1.01-1.13)). Marital status and SES dichotomized at the NYS mean acted as confounders in the association between female gender and outcome.

Conclusions: Females had a higher rate of avoidable ED visits than males in a cohort of low SES, mostly minority patients on hemodialysis in the Bronx. Potential contributors to this association include marital status, SES and overall clinical status.

Association of gender and avoidable ED visits

Gender	Unadjusted IRR	95%CI	IRR adjusted for socio-economic variables	95%CI	IRR adjusted for clinic-anthropomorphic variables	95%CI	IRR adjusted for all variables	95% CI
Female	1.05	0.99-1.12	1.04	0.97-1.02	1.07	1.01-1.13	1.07	1.04-1.13

PUB252

Dry Weight and Intra-Dialytic Weight Gains Vary by Season, but Ultrafiltration Rates Remain Stable in Long-Term Hemodialysis Patients

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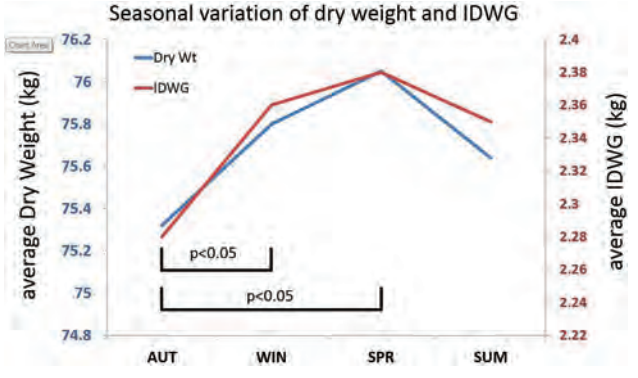
Background: In long-term hemodialysis (HD) patients, ultrafiltration (UF) rate is a function of intra-dialytic fluid weight gain (IDWG), dry weight (DW) and dialysis duration. IDWG and DW are known to vary according to the season of the year. UF rate, a measure that is being considered as a quality measure by regulators, may also vary seasonally; this may affect its appropriateness as a reportable measure.

Methods: We looked at a stable cohort of HD patients located in an urban area in a temporate climate zone, all of whom dialyzed for a 12 month period. We examined all post-HD weights (assumed to be DW), dialysis times, IDWGs and UF rates (mL/min/kg) for each subject. Seasons were defined as the month of the HD: Autumn=Sept-Oct-Nov; Winter=Dec-Jan-Feb; Spring=Mar-Apr-May; Summer=Jun-Jul-Aug. Differences in DW, IDWG and UF rate amongst seasons were analyzed by paired T-testing.

Results: 239 patients with complete HD treatment information for 2014-2015 were used in the analysis. Dry weight rose through the autumn and winter seasons, peaked in the spring, and decreased in the summer season. IDWGs followed a very similar pattern through the seasons, almost mirroring the change in DW (See Figure 1). DW and IDWG were both statistically different between the autumn and winter seasons, as well as between the autumn and spring seasons. UF rate, calculated as IDWG ÷ treatment time ÷ DW, was not statistically different across the 4 seasons, not surprising given that the DW and IDWG varied in the same direction and to a similar degree.

Conclusions: In stable HD patients, even though IDWG increased in certain seasons of the year, UF rate did not change because DW increased as well. We found that the seasonal variation of DW and IDWG followed a very similar pattern and magnitude of change. Therefore, UF rate remains fairly stable over the seasons of the year. As a quality measure, UF rate may not be significantly affected by the time of year when it is reported. These findings may differ in different climate zones.

Funding: Clinical Revenue Support



PUB253

Accuracy of Resting Metabolic Rate Prediction Equations in Persons on Maintenance Haemodialysis in Trinidad and Tobago

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Background: Establishing energy requirements is crucial in estimating nutritional needs and preventing malnutrition among persons with chronic kidney disease on haemodialysis. The study evaluated the accuracy of four commonly used resting metabolic rate (RMR) prediction equations among persons on maintenance haemodialysis (MHD).

Methods: Following informed consent and enrolment, participants had anthropometry and RMR measured using standard procedures. RMR predicted prediction equations were compared to that measured by indirect calorimetry using the Med Gem® device (microlife, USA). Anthropometry was measured using recomended procedures. Participation was voluntary. The study was approved by the Ethics Committee, The University of The West Indies..

Results: Sixty-five persons 50 to 65 years (females = 33; males = 32) participated in the study. Mean measured RMR was significantly higher in males than females (1373 ± 288 vs. 1222 ± 228; p = 0.02). RMR computed from predictive equations were significantly higher in males compared to females. There were no significant differences in RMR per kg of body weight or fat free mass between males and females. Overall, mean measured RMR was 20.1±5.0 per kg of body weight. The mean accuracy of predictive equation was significantly lower in males than females (39.1% ± 2.7% vs. 45.0% ± 4.3%; p <0.001). The level of RMR prediction equations underestimation (51.6% ± 2.7% vs. 39.4% ± 8.1%; p <0.001) and overestimation (16.7% ± 4.4 vs. 9.4% ± 2.2%; p <0.001) was higher in males than females.

Conclusions: RMR predictive equations had low level of accuracy with measured RMR. The level of accuracy was different for males and females. There is a need to develop sex-specific RMR prediction equations that improve the accuracy of estimating RMR among persons on MHD in this population.

PUB254

Lung Ultrasound in Maintenance Hemodialysis Patients Close to Dry Weight

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Background: Fluid overload is associated with adverse cardiovascular events in hemodialysis patients. Lung ultrasound has been validated in patients with excessive fluid overload, nevertheless in patients close to dry weight has not been validated. The aim of our study is to evaluate the utility of this method in this type of patients

Methods: Eighty hemodialysis sessions were examined, we divided the total population into two groups according to fluid overload estimated with a cut point of 1.5 liters, we realized a lung ultrasound (scanning for B-lines in 28 quadrants), NT-proBNP determination and multifrequency total body and thoracic bioimpedance extracellular water/body water ratio. Blood pressure, heart failure symptoms (dyspnea, orthopnea), hemoglobin delta and relative blood volume were measured by blood volume monitoring in BVM module of 5008 Fresenius

Results: 63% (17) of the patients corresponded to the female and the rest to male 37% (10). Mean age of the population was 42 ± 16 years. The vintage time of patients with hemodialysis was 3.6 ± 2.9 years. 30% (8) of the patients presented symptoms before the hemodialysis session. Up to 67% (18) of the patients b lines were observed before hemodialysis. In the setting of bioimpedance, the mean difference both total body to thoracic shows statistical significance as well as hemoglobin delta and blood volume circulating

Conclusions: B lines determination in patients close to dry weight they did not show statistical significance, nevertheless it iss important to highlight in the without fluid overload group, 4/20 patients with history of pulmonary hypertension had 9±3 B lines, we concluded that in later studies these patients could be excluded.

X±SD	Without fluid overload	Fluid overload	P-value
N	20	6	
B lines	2.1±3	2.91±3	0.73
NT pro-BNP PREHD (pg/mL)	6150±6464	7886±6561	0.31
NT pro-BNP PSTHD(pg/mL)	2875±5767	1985±1559	0.29
NT pro-BNP Delta PRE/PSTHD (pg/mL)	3275±3195	5901±5412	0.05
Hemoglobin (mg/dL)	10.6±4	10.3±2	0.63
Hemoglobin Delta PRE/PSTHD (mg/dL)	2.9±2	2.1±1	0.008
ECW/TBW total body	0.381±0.01	0.402±0.01	<.001
ECW/TBW thoracic	0.381±0.01	0.403±0.01	<.001
BVM min (%)	76±11	82±5	0.006
SBP (mmHg)	133±28	131±25	0.77
DBP (mmHg)	73±19	73±15	0.93

PUB255

Successful Pregnancy in an ESRD Patient Receiving Intensive Hemodialysis

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Introduction: In women with end stage renal disease (ESRD), the chances of both conception and pregnancy maintenance are low and associated with high rates of adverse maternal and neonatal outcomes. Past studies have highlighted residual renal function, early diagnosis of conception, and intensive hemodialysis for improved pregnancy outcomes. The literature still questions the optimum management of pregnant women with severe renal impairment as well as effective incremental dialysis dosing in this group. We report here a case of a stable hemodialysis patient with two live births two years apart, the latter being successful due to intensive hemodialysis.

Case Description: A 35-year-old woman (gravida 4, para 0) with ESRD on chronic in-center hemodialysis since 2015 was found to be pregnant in December 2016. Her 3 previous pregnancies had spontaneously aborted in the first trimester. Despite being recommended intensive hemodialysis 6 days a week, 6 hours per session, the patient did not follow these recommendations, and her son was born at 30 weeks with complications of prematurity and died at 4 months of age. In August 2017, the patient had positive blood and urine hCG levels and began intensive hemodialysis 6 days a week, 6 hours per day. In March 2018, an emergent C-section at 34 weeks produced a healthy 2200-g baby girl requiring only initial CPAP and encouragement to feed. The patient's hemoglobin level remained stable, blood pressure was well controlled without medication, and potassium level remained within normal range. The patient's phosphorus level declined and required supplementation. To date, the baby is 2 months old and healthy.

Discussion: Our case demonstrates a successful pregnancy in a patient of advanced maternal age and minimal residual renal function on intensive in-center hemodialysis. This case is unique due to the patient's older age involving two pregnancies with different outcomes, illustrating the importance of intensive hemodialysis in optimizing the maternal milieu early in pregnancy. We thus recommend that intensive hemodialysis be considered as a viable option for dialysis patients considering pregnancy.

PUB256

Is Central Venous Oxygen Saturation Decline During Hemodialysis Always Associated with Ultrafiltration?

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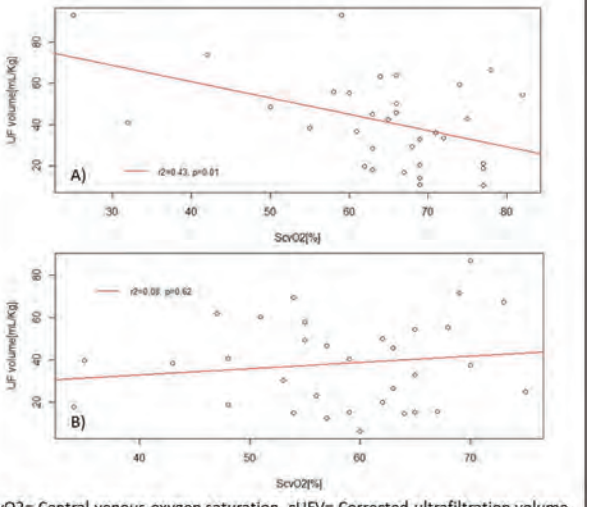
Background: Ultrafiltration volume inversely correlates with central venous oxygen saturation (ScvO2) during hemodialysis (HD). The effect of intra-dialytic exercise (IDE) on ScvO2 is unknown. The aim of this study was to explore the correlation between ScvO2 and corrected ultrafiltration volume (cUFV) during HD with and without intra-dialytic exercise.

Methods: Crossover study in maintenance adult HD patients. The cUFV (ultrafiltration volume/post dialysis body weight) reported in mL/Kg was computed through HD treatment at 60, 120 and 180 minutes, ScvO2 by gas analyzer was measured at the same time points, both were obtained during one HD treatment without IDE, then repeated in one HD treatment with IDE. The ScvO2 and cUFV correlation was estimated by Pearson's equation.

Results: 11 patients (22 HD treatments) were analyzed. The ScvO2 mean ±SD for all time points during HD treatment without and with IDE were 64 ±12.3% and 58.3 ±9.9%, p=0.04. The cUFV mean ±SD for all time points during HD treatment without and with IDE were 41.7 ±21.8 ml/kg and 38.2 ±20.6 ml/kg, p=0.57. Pearson's correlation moment between ScvO2 and cUFV during HD without and with IDE is reported in figure 1.

Conclusions: The mean value of ScvO2 during intra-dialytic exercise is lower compare to a non-exercise treatment. As expected, there is an inverse correlation between ScvO2 and corrected UF volume during a non-exercise HD treatment, this correlation is lost during intra-dialytic exercise. ScvO2 decline during intra-dialytic exercise is not associated with ultrafiltration volume.

Figure 1. ScvO2 and cUFV correlation during HD with and without intra-dialytic exercise.



ScvO2= Central venous oxygen saturation, cUFV= Corrected ultrafiltration volume
A) Without exercise, B) With exercise. Pearson´s correlation.

PUB257

Preoperative Systolic Blood Pressure Is an Independent Risk Factor for Aortic Valve Replacement in Hemodialysis Patients

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Background: Calcified aortic stenosis is a common complication in hemodialysis (HD) patients and the progression speed of stenosis in HD patients is faster than that in non-dialysis patients. Prognosis of HD patients with aortic stenosis is poor and the choice of surgical aortic valve replacement (AVR) is subject to debate. However, there are few studies regarding prognosis and its risk factor for AVR.

Methods: We had a single center retrospective study. Thirty HD patients with aortic stenosis were performed by AVR from January 2009 to September 2013 in our hospital. We investigated blood pressure, serum albumin, cardiac echo findings (EF, AV pressure gradient, AV area) before AVR and intra-operating findings (bleeding volume, in-out balance, transfusion volume, operation time, aortic cut-off time, cardiopulmonary bypass time).

Results: Age of 30 patients (male 19, female 11) was 71.6±6.3 years old. Average duration of HD was 156 months. Diabetes mellitus was 10/30. AV area, AV pressure gradient and EF were 0.75±0.20cm^2, 67.3±35.0mmHg, 54.0±12.8%, respectively. 30-day mortality was 16.7% (5/30) and the causes of death were sepsis, gastrointestinal bleeding, pneumonia and cardiac failure. In-hospital mortality was 33.3% (10/30) and 1 year survival rate was 60%. Risk factors of in-hospital death from AVR were systolic blood pressure, cardiopulmonary bypass time and bleeding volume in univariate analysis. However, multivariate regression analysis showed that systolic blood pressure was an independent risk factor (hazard ratio [HR], 0.94; 95% CI, 0.91 to 0.98; p=0.043).

Conclusions: Low blood pressure is an independent risk factor of AVR in HD patients with aortic stenosis. AVR should be considered while HD patients maintain blood pressure.

PUB258

Low Serum Albumin and Hospitalization Among ESRD Patients on Dialysis

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Background: Patients on hemodialysis (HD) have disproportionately high hospitalization and readmission rates. Although several factors contribute to this relatively high hospitalization rate, albumin has been consistently seen as a marker and we looked at this association at our HD center.

Methods: A retrospective cohort study was conducted at Saint Vincent Hospital, Nephrology dialysis center, from March 1, 2017 to Febraury 28, 2018. Our sample was comprised of 72 patients. The inclusion criteria were; A) ESRD patients aged > 18 years old. B) On dialysis treatment for > 12 months. Exclusion criteria were; A) Deceased ESRD patients before February 28, 2018. B) Those transfered to other dialysis center. C) Post renal transplant. Hypoalbuminemia was defined as albumin < 3.9 g/dL. Hospitalization was defined as hospital admission at least once during study period. The mean of serum albumin was calculated in two different ways. First; the average of albumin for 12 months for each subject and second; the average of quartiles (each quartile include four consecutive months). We evaluated the association between serum albumin, history of diabetes mellitus and hospital admission by using Chi-square test with a significant p-value level of <0.05.

Results: Out of 72, 59 dialysis patients met the inclusion criteria. The rate of hospitalization was 55.9 %. The mean of serum albumin level during the study period among hospitalized and non-hospitalized dialysis patients were 3.62g/dL and 3.96g/dL, respectively. Dialysis patients with mean of serum albumin (average of 12 months) < 3.9 g/dL had a higher percentage of hospital admissions (66.7 %) (P-value=0.006). The mean of serum albumin (average of four quartiles of the study duration) < 3.9 g/dL had a higher percentage of hospital admissions (66.6%) compared to dialysis patients with mean albumin level equal or more than 3.9 g/dL (33.4 %) (P-value=0.003). The dialysis patients with a history of diabetes mellitus had a higher percentage of hospital admissions (60.6%) compared to dialysis patients without diabetes (39.4 %) (P value=0.01).

Conclusions: There is a statistically significant association between mean serum albumin less than 3.9 g/dL, diabetes mellitus and hospitalization among dialysis patients. Further studies should be considered to evaluate the possible causal relationship of these factors

PUB259

Dialysis Nurse Driven Bedside Assessment of Peripheral Vascular Disease in Indian Dialysis Patients: A Quality Improvement Project

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Background: Peripheral vascular disease (PVD) is highly prevalent in dialysis patients and associated with increased mortality and morbidity. Early identification and intervention may help to decrease morbidity and amputation in prevalent dialysis patients.

Methods: Peripheral vascular disease was screened by bedside ankle brachial index (ABI) using handheld Doppler by trained dialysis nurse. The ABI was calculated by the ratio of ankle systolic BP divided by arm systolic BP. Subjects were divided into 3 categories according to their ABI values; low (ABI < 0.9), normal (ABI 0.9-1.3), incompressible (ABI >1.4). Systolic BP in upper extremity was measured on brachial artery of the arm contralateral to vascular access and in lower extremities on posterior tibialis artery.

Results: Of the 281 subjects, 62 % were males. The average age was 53.5± 13.4 years. The average dialysis vintage was 3.3± 2.5 years. 31% had diabetes, 66 % had hypertension and 30 % had history of ischemic heart disease. 12 % reported history of smoking or tobacco use. Low ABI (<0.9, suggestive of atherosclerosis) was found in 12.5% subjects, normal ABI was found in 67.1% and incompressible ABI (suggestive of calcified vessels) was found in 20.3% subjects.

Conclusions: Peripheral vascular disease is fairly common in dialysis patients. Among dialysis patients, 1-in-3 had either low ABI or incompressible ABI. This calls for quality improvement initiative in each dialysis unit to screen and monitor for PVD by dialysis nurses and facilitate early referral for timely intervention.

PUB260

Diuretics: To Use or Not to Use? A Survey of Hemodialysis Patients' Willingness to Use Diuretics

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Background: Chronic diuretics are empirically used to increase urine output (UO) in maintenance hemodialysis (HD) patients however conclusive evidence of benefit is lacking. Varied prescribing practices among nephrologists is evident from DOPPS data indicating that 0-84% of HD patients receive diuretics. DOPPS has reported a positive association

between residual renal function and diuretic use. Additionally, DOPPS showed improved survival in HD patients with greater daily urine output (UO) and lower interdialytic weight gain (IDWG).

Methods: An 8 item questionnaire was administered to HD patients at 3 dialysis centers in Philadelphia, PA. Demographic and patient characteristics collected included: age, gender, ethnicity, dialysis vintage, estimated daily UO, willingness to use diuretics and frequency. Data was analyzed using STATA v.13.

Results: Seventy four participants (42 male) were surveyed with mean age 59.4±12.6 years. Mean time on HD was 4±4.7 years with a mean UO of 196±288.6 cc daily. 65 were African Americans, 6 Hispanics, 2 Asians and 1 Caucasian. 15/74 (20%) surveyed were already receiving diuretics with a mean UO of 319±391.9 cc daily. The remaining 80% (59/74) not on diuretics had a mean UO of 164.5±250.7 cc daily. 31 patients surveyed, not on diuretics, reported a range UO of 0-60 cc daily. 9 patients on diuretics reported UO of 1L daily. A paired t test comparing UO among patients taking vs. not taking diuretics was statistically significant, $p<0.03$; if equal variance was assumed. Under an unequal variance assumption, the result was not statistically significant, $p<0.08$. See Table 1 for data on willingness of HD patients to take diuretics.

Conclusions: We discovered that the majority of HD patients surveyed are willing to use diuretics. We anticipate that patients with shorter dialysis vintage and residual renal function will benefit most from diuretic therapy. This survey is a pilot investigation for a large, prospective cohort study to determine the effects of loop diuretics on blood pressure, potassium, IDWG and quality of life in HD patients. We hope to define concrete parameters for predicting diuretic benefit in dialysis patients.

Table 1

	Willingness to use diuretics	Unwilling to use diuretics
n (%)	51 (69)	23 (31)
Female n (%)	20 (62.5)	12 (37.5)
Male n (%)	31 (73.8)	11 (26.3)

PUB261

7-Day iPTH Predicts Long-Term iPTH, Deserves as All-Cause Mortality Risk Factor in Secondary Hyperparathyroidism Patients After Parathyroidectomy

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Background: Parathyroidectomy(PTx) is an effective therapy to treat secondary hyperparathyroidism(SHPT). Though lots of studies have proved that PTx reduces mortality of SHPT patients, the effect of different postoperative PTH levels on long-term prognosis remains controversial. The aim of this research is to evaluate the appropriate PTH level after PTx and find out early predictors which can contribute to better prognosis.

Methods: We collected secondary hyperparathyroidism dialysis patients who underwent parathyroidectomy in Huashan Hospital in 2004-2017. Patients' data before and after PTx were collected including short-term (day 1 to day 7) and long-term (month 3, 6, 9 and 12) biochemical data. The primary endpoint is all-cause mortality and the secondary endpoint is surgery for recurrence.

Results: Ninety-one SHPT patients were enrolled in this research. Compared with preoperative parameters, serum calcium, phosphorous, iPTH and ALP of SHPT patients after PTx decreased significantly($P<0.001$). During follow-up vintage, 12 patients died and one patient had surgery because of recurrence. After PTx, postoperative iPTH rebounds within 3 months and then comes to a stable level. All patients were divided into three groups according to one-year average postoperative iPTH below 46 pg/ml or above 130 pg/ml. Of all parameters after PTx, all-cause mortality($P=0.046$) is significantly different among three groups. Kaplan-Meier curve shows that patients whose postoperative iPTH in the range of 46-130 pg/ml have the lowest all-cause mortality while those with postoperative iPTH<46 pg/ml have the highest mortality rate ($P=0.023$). Cox regression analysis also confirmed that low postoperative iPTH level is a risk factor of all-cause mortality in SHPT after PTx($P=0.036$, HR=0.086, 95%CI=0.009-0.848). In addition, patients in one-year iPTH<46pg/ml group have a lower 7-day iPTH levels comparing to those in one-year iPTH>46pg/ml group($P=0.001$). The ROC curve analysis results in 5 pg/ml of 7-day iPTH as a cut-off value (AUC=0.751, P=0.003).

Conclusions: SHPT patients with 7-day iPTH>5pg/ml have a higher rate to reach the proper iPTH level (one-year iPTH>46pg/ml). Low postoperative iPTH level is a risk factor of all-cause mortality in SHPT after PTx.

PUB262

Managing Severe Hypertension in a Patient on Hemodialysis – Combined Efforts of Physicians and Care Giver

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Introduction: Over 50% of CKD patients on hemodialysis have hypertension; more than half failing to achieve blood pressure goals. Despite optimum medications, patient may have uncontrolled hypertension. Non-pharmacologic methods and changes to dialytic approach may help in achieving the desired targets. The physician must remember four guiding principles: dietary sodium restriction, individualizing dialysate sodium, management of dry weight goals and adequate duration of dialysis. We present a chronic kidney disease patient on hemodialysis with severe uncontrolled hypertension. The combined efforts of the care-giver, treating physician and hypertension specialist resulted in better control of BP.

Case Description: A 68 year old male known hypertensive, diagnosed with ESRD, on hemodialysis for four years, presented with resistant hypertension and extreme intradialytic BP surges (SBP 240 mmHg). Various classes of antihypertensive medications at optimal doses had been tried, with dismal results. Many fruitful discussions took place among the care-giver, treating physician and hypertension specialist. Cumulative efforts led to changes in the treatment. The number of sessions of dialysis were increased from two to three per week; the duration of each dialysis increased from four hours to five hours. The dry weight goals were modified. Bio-electrical impedance analysis was used to detect over-hydration; daily fluid intake and ultrafiltration volume were modified. The dialysate sodium concentration was reduced from 135mEq/L to 134mEq/L. Anti-hypertensive medications were modified – intra-dialytic anti-hypertensive was switched from metoprolol to carvedilol(due to negligible intradialytic clearance of the latter); and pre-dialysis nifedipine was replaced with binedipine(a drug that shows prolonged depressor effect likely due to its high affinity for the dihydropyridine receptor). BP readings showed marked reduction and considerable drop in intradialytic surges.

Discussion: The case presents an insight into the perplexity of management of hypertension in patients with chronic kidney disease, more so in those on hemodialysis. Many such patients have resistant hypertension and are inadequately treated. A holistic approach, combining non-pharmacological means and inputs from the care giver, and treating physicians, may benefit such patients.

PUB263

Feasibility of Hemodilution Detection Following Extracorporeal Saline Bolus Injections Using Crit-Line® in a Clip (CLiC®)

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Background: Decreased cardiac output (CO) during hemodialysis increases the risk of sudden cardiac death, for this reason, CO monitoring is needed. The indicator dilution method used to measure CO with the Stewart-Hamilton equation is well established and currently in use. The aim of this pilot study is to demonstrate if CLiC® can detect a hemodilution signal induced by injections of saline boluses (SB) in the extracorporeal circuit. Data will support further exploration of the potential practical use of CLiC® to measure CO.

Methods: An ultrafiltration goal (UF) was prescribed, then, 120 mL were added to account for the SB. After a run-in period of 15 minutes, 3 SB in sequential volumes of 30 mL, 20 mL and 10 mL, each separated by 5 minutes, were infused into the arterial drip chamber, and 3 SB were infused in the same manner into the venous drip chamber. CLiC® data were recorded from the beginning of the session until 5 minutes after the last SB. Hemoglobin versus time data were plotted and further analyzed. Hemodilution curve was transferred into peak signal calculating the absolute change in hemoglobin with the baseline set to zero before the injection of saline.

Results: The above protocol was studied in 4 HD patients. CLiC ® was able to detect the hemodilution signal after SB injection and also the returning signal after cardiopulmonary recirculation. This was true for all three SB volumes studied.

Conclusions: The ability of the CLiC® to detect the hemodilution signal after the infusion of SB provides the opportunity to explore the applicability of this device in terms of attaining a more comprehensive hemodynamic monitoring during HD.

Funding: Commercial Support - Fresenius Medical Care. Renal Research Institute

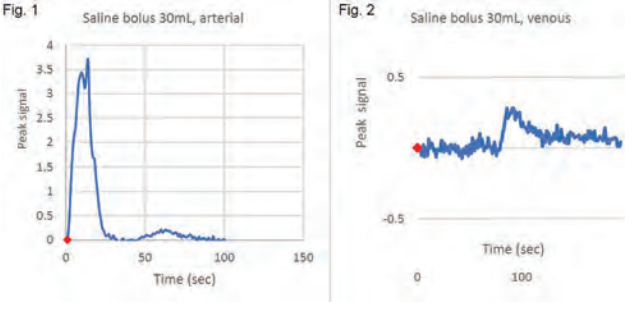

Fig. 1 Injection: arterial drip chamber. The first peak represents the hemodilution signal after the SB passes through the CLiC® for the first time, the second peak represents the return of the signal after cardiopulmonary recirculation.Fig. 2 Injection: venous drip chamber. The peak represents the hemodilution signal returning to the CLiC® after cardiopulmonary recirculation.

*Red marker indicates the time of injection of SB.

PUB264

Nephrologists' Opinion Regarding Rationing Strategies in Hemodialysis Facilities During a Supply Crisis in Brazil Caused by a Truck Drivers' Strike

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Background: Brazil has an internal transportation and supply system dependent on highways. Due to the rising price of diesel, a truck drivers' strike occurred in May 2018 affecting the entire country. Roadblocks occurred at more than 500 locations in 24 Brazilian states. With the interruption of distribution of healthcare supplies, a major concern emerged: how to avoid the lack of materials in dialysis facilities? Knowing that the discontinuation of dialysis would lead to the death of patients, dialysis facilities chose to adopt rationing strategies.

Methods: We conducted a survey with nephrologists in Brazil about their opinion regarding rationing strategies in dialysis facilities. First, we asked about their willingness to adopt rationing strategies and the timing of initiation of these strategies. Then, we asked which strategies would be first implemented and which would be the last strategy adopted.

Results: A total of 50 nephrologists answered our questionnaire. 44% of them were medical directors of dialysis facilities, and the majority (62%) were male. The mean age was 43.8 years (*SD* = 10.90). 50% would start rationing strategies immediately after the supply discontinuation, and 40% would adopt rationing strategies only when the internal inventory levels were considered low. No respondents disagreed about the need to adopt rationing strategies. Among the strategies to be adopted at the beginning, the reduction of the dialysate flow (chosen by 68% of respondents) and the reduction of the treatment time (chosen by 52%) were most common. The reduction of hemodialysis frequency from thrice- to twice-weekly was avoided and considered the last rationing strategy by 84% of nephrologists. Additional regression analyses revealed that female respondents adopted significantly fewer rationing strategies simultaneously than male (b = -.44, SE = 0.12, p < .01). This result is robust after controlling for respondent age and function.

Conclusions: All nephrologists considered adopting rationing strategies in the context of a supply crisis affecting the healthcare system. Among the strategies, the reduction of the dialysate flow and the reduction of the treatment time were the most common. Reduction of hemodialysis frequency was the last rationing strategy to be adopted.

PUB265

Relationship Between Ambulatory Blood Pressure Monitoring, Status Fluid, and Cardiac Function in Hemodialysis Patients

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Background: Hypertension is a cardiovascular risk factor common in hemodialysis (HD) patients, correlates with left ventricular hypertrophy. Volume overload is the main cause of hypertension in this patients. Aim: Determine the relationship between ambulatory blood pressure monitoring (ABPM), status fluid and cardiac function in HD patients.

Methods: In a cross-sectional study, 24 chronic HD underwent ABMP 44hours. To assess cardiac function, an echocardiogram was performed. The hydration status was evaluated by bioimpedance spectroscopy (BIS) and the brain natriuretic peptide (BNP). Hypertension was defined according to the recommendations of JNC 8, with values higher than 140/90 mmHg, which correspond to values of 135/85 mmhg in ABPM according to ESH/ESC guidelines.

Results: The mean age was 59.5 ± 17.6 years, 62.5%. The mean daytime BP of 134 ± 25/77 ± 11 mmHg, daytime pulse pressure (PP) 56 ± 17 mmHg, mean nighttime BP 132 ± 25/73 ± 13, night PP 57 ± 17 mmHg. 22.7% of patients had a dipper pattern. 13 patients received antihipertensive drugs, the mean of antihipertensive drugs was 1.25 ± 1.11. Patients with mean BPS (44 h), daytime> 135 mmg and nocturnal BPS> 120 mmhg had a higher predialysis BPS (147 ± 20 vs125 ± 18 mmhg, 147 ± 19vs125 ± 18 mmhg and 145 ± 18 vs122 ± 20mmHg p < 0.05). Mean BPD (44h)> 85mmhg and nocturnal BPD> 70mmhg had a lower TAPSE in echocardiogram (16.8 ± 0.17vs22.2 ± 3.9 and 17.9 ± 2.5vs23.7 ± 2.7 p <0.005), which is related to dysfunction of right ventricle. Average PP (44h), daytime and nighttime levels> 50mmHg had higher fluid overload, expressed as overhydration (liters) (2.1 ± 1.1vs.1 ± 2.2, 2.1 ± 1.1vs-0.1 ± 2.2 and 1.9 ± 1.3 vs -0.1 ± 2.5 p <0.05), as adjusted for extracellular water (12.1 ± 5.6vs0.7 ± 13.7, 12.1 ± 5.6vs0.7 ± 13.7 and 11.14 ± 6.5 ± 0.6 ± 15.3) and higher BNP (ng / L) (922 ± 836vs114 ± 122, 922 ± 835vs114 ± 122 and 824 ± 835vs129 ± 130, p <0.05). The patients who received antihypertensive drug were younger (51 ± 19 vs 69 ± 11 years) had a higher mean TAD (80 ± 10 vs 69 ± 11 mmHg, p <0.05) and higher daytime BPD (83 ± 9 vs 70 ± 11mmhg, p <0.05).

Conclusions: Elevated values of PAD correlate with right ventricular dysfunction. Overhydrated patients present higher pulse pressure. The dry weight adjustment can help control PP, which is a cardiovascular risk factor.

PUB266

Safety and Adequacy of NxStage® Home Dialysis Machine Providing Acute Dialysis in a Rural Hospital

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Background: The NxStage® home dialysis system is a simplified system designed for use by patients for home hemodialysis (HD). We evaluated the safety and adequacy of the NxStage® One S machine in a rural hospital. This hospital was unable to provide standard HD for patients in a low volume acute care setting, due to the cost of trained staff and the low volume of patients. By training registered nurses and technicians from the general care unit on the NxStage® machine, the hospital was able to continue to take care of dialysis patients rather than transfer them from their community.

Methods: In this observational, prospective study, patients who needed HD while hospitalized at Mid-Michigan Medical Center, Alpena, MI, were enrolled. Inclusion criteria: Patients with end stage renal disease (ESRD) or acute kidney injury (AKI) requiring dialysis. Exclusion criteria: Patients with drug overdose or poisoning. Data points collected included adverse events, dialysis flow sheets, hemoglobin, calcium, phosphorus, pre and post blood urea nitrogen, creatinine, and potassium. Prescribing guidelines were obtained from the dosing calculator NxStage.com. Adverse events (AE) were classified as mild or severe. Mild was defined as any intradialytic event that required intervention from the staff but did not require discontinuation of the treatment. Severe was defined as any intradialytic adverse event that required discontinuation of treatment.

Results: Twenty-seven patients were recruited and completed a total of 74 dialysis treatments over a 12-month period. The mean age was 66.2 years (STD +/- 15.7), 63 % were male, and 96 % Caucasian. Seventy three percent of patients had an AVF, 7 % AVG, and 10 % CVC. The average single treatment Kt/V achieved was 0.54 -1.07 per treatment. The average duration of treatment was 4.5 hrs. Admission diagnoses included: CHF, COPD, debility, hip fracture, ESRD, GI bleed, pneumonia, peritonitis, bacteremia, small bowel infarction. Mild AE's occurred in 18.5% of runs. There were no severe adverse events.

Conclusions: The NxStage® One S system provides safe and adequate acute dialysis. This system can be a viable alternative to a standard HD machine in a rural hospital.

PUB267

Characterization of Intradialytic and Interdialytic Cramping in Patients with ESRD

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Background: Muscle cramping is a common complication of hemodialysis that has been reported by 35-80% of End Stage Renal Disease (ESRD) patients as one of the leading reasons for interruption or early termination (approximately 18%). The cause of intradialytic cramping has not been established, but this painful complication often leads to interventions that may impact the adequacy of hemodialysis, such as reduction in ultrafiltration rate, administration of normal saline or hypertonic normal saline solution, use of pharmacologic agents, and premature termination of hemodialysis sessions. The incidence of cramping during dialysis and the interventions to treat these cramps are not commonly or consistently documented by treating centers. Because of this gap, there is a need to better understand the impact that this complication has on the quality of life for ESRD patients suffering from intra- and interdialytic cramps, and the correlation to hemodialysis session attendance and adequacy.

Methods: Flex Pharma is initiating an observational study at three hemodialysis centers in the USA to obtain information to characterize muscle cramping in adult ESRD patients. This study will document the overall patient cramping prevalence at these centers and capture the muscle cramping history prior to study start and during dialysis sessions in approximately 24 patients that have a history of intradialytic cramping. To obtain this information, questionnaires will be provided to the general patient population at these centers to determine cramping prevalence. Patients previously identified to have intradialytic cramping that enter the study will complete questionnaires before and during hemodialysis sessions for four consecutive weeks to capture cramping information and the impact to their quality of life. In addition, the adequacy of hemodialysis session goals will also be analyzed by comparing the planned goals and patient health status (target dry weight, planned ultrafiltration rate, and vital signs) against the success, deviations, or interventions responsible for whether these goals are met.

Results: The results of this study are expected by the end of the year.

Conclusions: The results of this study are expected by the end of the year.

Funding: Commercial Support - Flex Pharma

PUB268

Operationalizing Telemedicine for Home Dialysis Patients

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Background: Starting in 2019, CMS will reimburse 2 out of every 3 monthly visits performed by telemedicine (TM) for home dialysis (D) patients (pts). The aim is to explore steps required to operationalize TM for home D pts

Methods: We analyze the regulatory requirements for a comprehensive monthly visit conducted by TM & offer recommendations on operationalizing monthly visits for the pt, practitioner, & D facility

Results: The regulatory requirements are: -Providers may use & bill for TM encounters with ESRD pts from their home or a dialysis facility when using 2 way interactive video conferencing (VC) -D pts must receive in-person assessments monthly for the 1st 3 months of home D & at least once every 3 months thereafter -If home is the originating

site, the facility may not bill for a facility fee Operational considerations for TM include: **-Licensing**: Practitioners must be licensed in the state where the pt is located (originating site) **-Credentialing**: If the pt is originating from a health facility, the practitioner must be credentialed & have privileges for the health facility **-Risk management**: Practitioners should check with the state regulatory agencies where the pt is located & one's own insurance policy to ensure coverage for TM visits **-Technology adoption & utilization**: Acquire & deploy encrypted platforms to ensure HIPAA compliance. Ensure availability of equipment required for VC in the originating & distant sites. Acquire equipment to conduct a physical exam (stethoscope). **-Documentation requirements**: Items needed to document a monthly visit via TM encounter **-Reimbursement**: Be familiar with appropriate billing and location codes to indicate the encounter was conducted via TM -Additionally, A) develop a plan that facilitates pts obtaining monthly labs near their home & for the labs results be downloaded to CROWNWeb. B) Develop practice based policies & procedures for providing home TM to ESRD pts. C) Pending language from CMS regarding examining a home HD pt's vascular access

Conclusions: Home D pts may elect to have the monthly visits conducted by TM under the provisions of CMS guidelines. These virtual visits may improve compliance with appointment attendance & care plans. The implementation of TM involves new procedures & technologies as well as workflows for pts, practitioners & D facilities. A step wise approach to meeting all regulatory & operational requirements may improve opportunities for successful implementation.

PUB269

Seamless PD (sm)

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Background: A new program designed to facilitate and grow peritoneal dialysis for nephrology practices. Our integrated approach increases opportunity for patients to choose peritoneal dialysis. A multifaceted approach was used to allow patients who urgently needed to begin dialysis. These patients could not wait for a traditional peritoneal dialysis catheter to heal. Many of these patients were not candidates for "urgent start PD' as they are uncomfortable lying flat in the outpatient setting and wanted to begin training right away. In this new program, patients were given an integrated approach including education, nephrology, and specialized surgical services to facilitate rapid entry into a home program. Specific surgical technique was used to create immediate use peritoneal access. Patients were able to begin training within 24-48 hours of catheter placement.

Methods: 20 patients who presented with an urgent need to begin dialysis for newly diagnosed ESRD were assesed by nephrology. If the patient was interested in peritoneal dialysis, they were entered into the program and received an integrated approach by multiple providers. The patients received specialized surgical technique and a catheter which could be used immediately if necessary. The patient was admitted to a home dialysis program within 24-48 hours. Patients began training immediately in an upright seated position with full volume exchanges.

Results: Over a 14 month period, 20 patients received specialized education, speed to catheter placement and specialized surgical technique. Patients ranged in age from 31-79 years. Male to female ratio was 10:10 BMI ranged from 23-47. All patients began training within 24-48 hours of catheter placement. At 14 months, there have been zero episodes of catheter failure, zero peritonitis episodes, and zero exit site leaks. There was one hospitalization within 90 days of catheter placement. All patients were able to participate in their care and began training within 24-48 hours of catheter placement. 100% of these patients finished training in the outpatient setting. One of the patients changed modality.

Conclusions: We believe this program to be a safe and effective way for patients to enter peritoneal dialysis programs. SEAMLESS PD (sm) has clear benefits over "urgent start PD" both for the patient and the medical team. This program increases patients' options and allows home dialysis programs to grow while delivering high quality care at a lower overall cost.

PUB270

Potential Use of PhotoVoice for Assessing Peritoneal Dialysis Patients' House Environment

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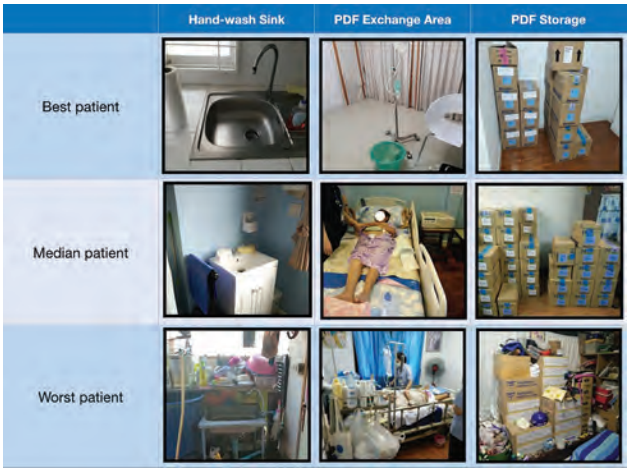
Background: PhotoVoice is a qualitative research technique, in which a picture is used as a tool for explaining a phenomenon of interest. As this technique can potentially be useful for assessing the house environment of peritoneal dialysis (PD) patients, this study aims to assess its potential use for differentiating the house environment of PD patients.

Methods: In January 2018, 15% of PD patients at King Chulalongkorn Memorial Hospital were randomly selected and sorted by the PD duration and number of peritonitis episodes then categorized into 3 ordinal groups: Best (long duration with no peritonitis), Median, and Worst (short duration with some peritonitis). One patient randomly selected from each group received home visit by our PD nurse. Pictures of various locations that might associate with PD outcome were taken. Cross-case analysis of the pictures was performed.

Results: Eight out of 51 PD patients were included and sorted. Best patient was a 45-year-old male underwent PD for 84 months, Median patient was a 78-year-old male on PD for 28 months, and Worst patient, a 67-year-old male had received PD for 22 months but already had 3 peritonitis episodes. Twenty, 25, and 18 pictures were taken from their house, respectively. The cross-case analysis revealed that the pictures of hand-wash sink, PD fluid storage area, and PD fluid exchanging area obviously vary across the three cases and, therefore, could be useful for differentiating house environment of PD patients.

Conclusions: PhotoVoice is a useful and simple tool for assessing PD patient's house environment. At least three house locations should be the main focus of any home visit.



PUB271

Peritoneal Dialysis: An Equal V in Calculating Kt/Vurea Underestimates the Dose for Women

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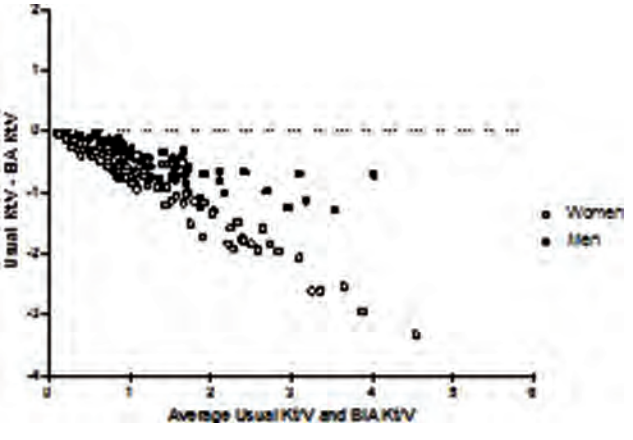
Background: Albeit PD technique and patient survival have been associated with residual renal function, the total amount of urea clearance (Kt/V) is recommended to be at least 1.7. The volume of distribution of urea (V) is based on total body water derived from anthropomorphic measurements, which certainly varies among patients.

Methods: To establish whether there is a difference in Kt/V, we compared V based on bioimpedance and V assuming 0.6 to all patients.

Results: A total of 170 Kt/V measurements were compared assuming V=0.6 x weight (usual Kt/V) and calculated using V obtained from the bioimpedance analysis (BIA Kt/V). We included incident patients on PD (50±18 years, 87 men); median diuresis was 440ml (from 100 to 1100ml). V from bioimpedance was 17.6±5.3 and 1.4±0.9L in women and men, respectively (p<0.0001), resulting in usual Kt/V and BIA Kt/V in the entire group of 0.93±0.62 and 1.63±1.12, respectively (p<0.0001). The usual Kt/V underestimated BIA Kt/V mainly in women, as shown in the Bland-Altman plot (Figure 1). We found no difference comparing BIA Kt/V between patients aging < or > 65 years old (p=0.736).

Conclusions: In PD patients, total body water calculated from bioimpedance allows a more reliable Kt/V calculation. Particularly for women, usual Kt/V underestimated the BIA Kt/V.



PUB272

Glycemic Control Before and After Starting Peritoneal Dialysis: A Single Center Case Series

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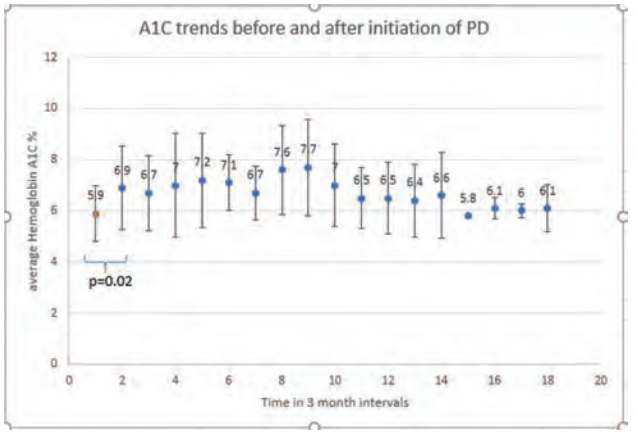
Background: Diabetes remains a leading cause of end stage renal disease in the US. Peritoneal dialysis because of glycemic load in the peritoneal dialysis fluid is often viewed as a potential risk factor for new onset or worsening diabetes. We present a case series

looking at hemoglobin A1c % pre and post initiation of peritoneal dialysis in our outpatient PD center and factors affecting it.

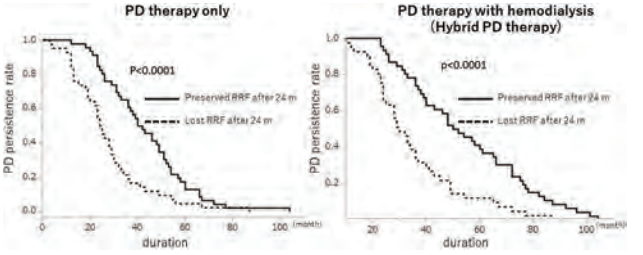
Methods: We collected data on nine PD patients, including demographics, medical history, BMI, pre-dialysis initation Hgb A1c and quarterly A1c levels after initiation of peritoneal dialysis. Average age was 51yrs, 7/9 patients were females. 3/9 patients had a diagnosis of T2DM before starting PD, 1 patient had a renal allograft failure as a cause of ESRD.

Results: There was a statistically significant difference in average pre-dialysis initiation Hgb A1c % vs post-dialysis Hgb A1c %, (5.9 +/- 1% vs. 6.8 +/- 1.5%, p = 0.02). The statistically significant increase in Hgb A1c level was noted only in the first quarter after which the Hgb A1c plateaued (figure 1). There was no statistically significant difference in BMI pre-dialysis initiation vs post-dialysis (29 +/- 10 vs. 30 +/- 9) or new diabetic medication use.

Conclusions: Our case series of 9 PD patients from a single outpatient PD center showed an initial increase in Hgb A1c after initation of PD, which plateaus immediately. Larger scale trials are required to look into the clinical and metabolic factors affecting glycemic control in peritoneal dialysis.



Hgb A1c % trends before and after initiation of peritoneal dialysis. Single center case series of nine patients. Orange circle represents average Hgb A1c% with SD vertical bars pre-dialysis. Blue circles represent average post-dialysis Hgb A1c% quarterly levels. Using Student's t-test there was a statistically significant difference in average pre-dialysis initiation Hgb A1c % vs post-dialysis Hgb A1c %, (5.9 +/- 1% vs. 6.8 +/- 1.5%, p = 0.02)



Persistence rate

Predictors of CVE using Cox proportional hazard model

Parameter	Univariate		Multivariate	
	HR(95%CI)	P	HR(95%CI)	P
Age(per 1years old)	1.056(1.024-1.109)	<0.001	1.023(0.940-1.138)	0.59
Male vs Female	0.726(0.168-2.213)	0.61		
DM	1.646(0.256-8.048)	0.51		
past CV event	**26.4(7.719-95.419)**	**<0.001**	**134.2(3.420-5272.5)**	**<0.001**
Systolic blood pressure(per 1mmHg)	0.973(0.941-1.001)	0.06		
Diastolic blood pressure(per 1mmHg)	0.936(0.889-0.982)	<0.01	1.026(0.824-1.276)	0.82
Mean blood pressure(per 1mmHg)	0.938(0.888-0.984)	<0.05	0.952(0.773-1.174)	0.65
Pulse blood pressure(per 1mmHg)	0.996(0.962-1.028)	0.82		
Body Surface Area (per m2)	0.641(0.001-215.2)	0.88		
Total Cor (per 1ml/min)	1.016(0.956-1.078)	0.66		
Total Kt/V	2.309(0.156-73.84)	0.6		
Labolatory parameters				
Hemoglobin(per 1g/dL)	1.099(0.736-1.645)	0.64		
Total Fe saturation: TSAT(per 1%)	1.016(1.002-1.026)	<0.05	0.635(0.004-114.3)	0.86
ferritin (per 1mg/dl)	**1.003(1.001-1.007)**	**<0.05**	**1.005(1.001-1.011)**	**<0.05**
Albumin(per 1g/dL)	1.034(0.370-3.026)	0.94		
β2mg(per 1mg/dL)	1.029(0.939-1.114)	0.51		
HANP(per 1pg/dL)	0.988(0.962-1.006)	0.22		
Creatinine (per 1mg/dL)	1.006(0.824-1.187)	0.94		
Int PTH(per 1pg/dL)	0.999(0.996-1.001)	0.46		
Urine Volume (per 1ml/day)	1.001(0.999-1.001)	0.21		
urinary protein (per 1g/gCr)	1.023(0.856-1.184)	0.78		
urinary protein (per 1g/day)	1.036(0.731-1.308)	0.81		
Echocardiographic data				
LVMI(per 1g/m2)	1.005(0.986-1.023)	0.576		
Residual renal function after 24 months	0.356(0.144-0.946)	<0.05	0.855(0.155-4.732)	0.86

CVE predictors

PUB273

Ferritin Is a Predictive Factor for New Cardiovascular Event with Regards to a Therapeutic Strategy for Peritoneal Dialysis and Combined Therapy (PD+HD Hybrid) Patients

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Background: Previous studies have reported that hypoalbuminemia showed definitely association with the degree of residual renal function (RRF) in peritoneal dialysis (PD) patients. The purpose of the present study was to analyze the predictive factors at the beginning of PD for a group that maintained RRF after 24 months, for PD persistence rate and cardio-vascular events (CVE).

Methods: The present study was retrospective and multicenter study with 132 PD patients. The predictive factors at the start of PD were analyzed between groups that maintained or lost RRF after 24 months. Furthermore, the predictive factors were also analyzed PD persistence rate and CVE.

Results: The group that lost RRF after 24 months had hypoalbuminemia and heavy proteinuria at the beginning of PD as compared to that of the group that maintained RRF. Patients with RRF had a better PD persistence rate when continuing not only PD therapy but also a combined HD with PD therapy than those without RRF (p<0.001) using a Kaplan-Meier method. The patients with past CVE (HR132.4, 95%CI3.420-5272.5) and high serum levels of ferritin (HR1.005,95%CI1.001-1.011) at the beginning of PD were independently associated with factors for new CVE after initiation of PD using a Cox regression analysis.

Conclusions: It is important to provide a strategy for PD indication in CKD patients with light proteinuria at the beginning of dialysis to maintain RRF and without past CVEs, low levels of ferritin to prevent CVEs after the initiation of PD.

PUB274

Peritoneal Ultrafiltration for Heart Failure - Experiences from a Randomised Controlled Trial

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Background: Peritoneal ultrafiltration (PuF) is sometimes employed for advanced heart failure (HF) with intractable fluid overload, but evidence for its benefit is lacking. The Peritoneal Dialysis for Heart Failure (PD-HF) study was a multi-centre RCT that aimed to address this. However, the trial was stopped early due to inadequate recruitment. This abstract describes trial activity and reasons for the study's failure with the aim of informing future trial design.

Methods: The trial aimed to recruit 130 participants from six UK centres, who had severe HF (NYHA class 3 and 4) and CKD stage 3 and 4 on optimal medical treatment for ≥4 weeks defined as being on ACE inhibitor or ARB, beta blockers and screened for cardiac revascularization and /or resynchronization if appropriate. Participants who were diuretic resistant were randomised to conventional HF treatment or one overnight exchange of Icodextrin. Primary outcome was change in six minute walk test (6MWT), between baseline and 28 weeks (end of trial). Secondary outcomes were changes in cardiomyopathy questionnaire (Kansas city) results, SF 36 health survey results, hospitalisation and mortality.

Results: Over a two year period approximately 290 patients were screened, 20 were eligible for the trial of which 10 were recruited. Baseline characteristics of the recruited patients were: mean age 70.1±8.4, all had NYHA class 3 HF, mean 6 MWT of 181.3±49.6 m (one patient declined 6MWT), mean eGFR was 28.6±5.4ml/min/1.73m^2. Of the 10 patients who were eligible but did not participate, some felt PD was too difficult to cope with, some died before agreeing to participate or before being approached whilst others were too unwell. The reasons for the high number of ineligible patients was eGFR out of range (usually too high), frailty and not being on optimal HF treatment. The investigators identified reluctance of patients to consider invasive therapy and lack of coordination between cardiology and renal services as the main contributors to poor recruitment.

Conclusions: Lessons learnt from the PD-HF trial can be used in the planning of future studies in this area. It is clear that any future trial should plan to use a much larger number of sites to achieve recruitment targets and that coordination of cardiology and renal care is essential.

PUB275

High Transport State and Reduced Sodium Sieving in Cirrhotic Patients on Peritoneal Dialysis

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Background: Peritoneal sodium sieving, an indirect measure of free water transport (FWT), is mainly the result of the osmotic conductance to glucose and the action of aquaporin channels. A high transport (HT) state and/or a plasma/ dialysate Na gradient > 5 mmol/lt, may counteract this sieving effect with sodium diffusion from plasma, and a diffusion correction applies. Upregulation of peritoneal aquaporins increases FWT in the kidney postransplant setting, related to steroid therapy (NDT 2011, vol 26) Cirrhotic pts are mostly HT with high UF and studies of FWT are not reported. **Objectives**: I) to evaluate results of sodium sieving (FWT) in 49 HT from 12/.2006 to 01/ 2017. Five patients are cirrhotic HT II) try to elucidate the possible causes of differences in sodium sieving between cirrhotics and other HTpts.

Methods: Patients : all consecutive high transport (HT) (4 hr D/P creat ≥0.81) pts in a single center since Dec.2006 till Jan.2017 (N =49 pts):.**Methods :** Minipets (lamilia2005) done yearly and when ultrafiltration changes.

Results: Results: GR1: HTcontrols: (N = 44): Gr 2: HTcirrhotic (N= 5). Table (1)

Conclusions: As compared to controls, NA sieving (FWT) is blunted and NA removal(NAR) is higher in cirrhotic patients. D0/D60min glucose is lower in cirrhotics P<0.006 pointing to a faster dissipation or more probably a dilution effect due to ascites generated " de novo".This effect could reduce the osmotic FWT. UF is higher in cirrhotics due to small pore water transport(UFSP)

Minipet results

	controls	cirrhotics	P
Group/ N	A: 44	B: 5	
Age	50,84 ± 14,59	58,22 ± 9,23	0.27
D/P creat 60 min	0,56 ± 0,11	0,61± 0,06	0,03
Plasma Na	139,61 ± 3,91	141,2 ± 2,86	0,38
D/P Na 3 min	0,94 ± 0,02	0,94 ± 0,04	0,689
D/P Na 60 min	0,88 ± 0,03	0,92 ± 0,02	0,0044
Na Dial 3 min	130,27 ± 2,73	132,80 ± 4,76	0,076
Na Dial 60 min	122,42 ± 4,21	129,78 ± 2,99	0,0004
DIP Na	-7,86 ± 3,72	-3,0 ± 3,8	0,0072
NAR (sodium removal mmol/l)	36,69 ± 19,12	76,47 ± 20,05	< 0,0001
UFSP ml	263,91 ± 139,26	539,60 ± 130,33	0,0001
% UFSP	56,57 ± 19,74	84,40 ± 6,50	0,0063
FWT ml	181,78 ± 86,13	96,40 ± 33,15	0,054
% FWT	43,43 ± 19,74	15,60 ± 6,50	0,0063
UF60min ml	445,68 ± 171,36	636 ± 132,21	0,02
D0/D60 Glucose	0,56 ± 0,10	0,43 ± 0,11	0,0064

PUB276

Need Finding in Peritoneal Dialysis with Mobile Eye Tracking

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Background: In the German Code of Social Law V in §5 (7), paragraph a, the text states: "Only patients may be treated with "dialysis in a center", who need this type of dialysis due to their clinical picture. However, the reality looks quite different. This drawback was the motivation for a need finding study to find approaches to lower the access limitation to the peritoneal dialysis (PD) therapy, the most common home dialysis modality. The need finding study was conducted using mobile eye tracking with experienced and novice dialysis patients.

Methods: The dialysis patients were visited at home and accompanied in all therapy handling steps to gain insights of the user experience of PD from a first-person view. The data analysis was not limited to the single central therapy steps but included also the preparation phase and the therapy handling steps as a whole.

Results: In total, eight possibilities could be identified which promise to facilitate the access to home dialysis like a waste handling and managing system or a novel PD furniture. The most promising was a controller for PD which increases the safety against use errors and the comfort for the patient.

Conclusions: For many patients, the use of an auto-connect device could increase safety and ease of use for patients. In addition, it could enhance standardization of the therapy process. Based on the eye tracking results, feasibility was proven with a functional prototype and a start-up was initiated for the further development and market readiness of such a device, with the public launch targeted early 2018.

Funding: Government Support - Non-U.S.

PUB277

Impact of Health Related Quality of Life Non-Renal Factors on the Life of Dialysis Patients: Should Mood Be the Focus?

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Background: Chronic kidney disease patients often have compromised health related quality of life (HRQOL) while on dialysis. Mostly factors, either demographic, renal and non-renal associated with it, are not valued as they should in the management of such individuals.

Methods: We conducted a cross-sectional study between July and September 2013, with 215 patients on hemodialysis (HD) and 58 on peritoneal dialysis (PD) in order to evaluate HRQOL using the Kidney Disease Quality of Life- Short Form Instrument 1.3 (KDQOL-SF), and to identify factors associated with it, emphasizing the non-renal ones: mood, sleep disorders and sexual dysfunction.

Results: Patients had a mean age of 51 years, mostly men (62%), with low educational (72%) and socioeconomic levels (95%). The prevalence of depression (29%), anxiety (30%), poor sleep quality (56%), excessive daytime sleepiness (43%) and male (48%) and female (76%) sexual dysfunction was high. Models by confirmatory factor analysis showed that anxiety (p <0.01), depression (p <0.01) and lower education (p 0.01) were factors independently associated with lower HRQOL. It showed a higher prevalence of anxiety in HD patients (32%) and depression on those on PD (36%).

Conclusions: Ssearching for better HRQOL is complex and challenging and no variable should be neglected, especially in the most vulnerable groups such as those with less schooling. It is necessary for dialysis professionals to have a higher level of attention to the presence of anxiety, especially in HD patients, and depression, on those in DP, as mood disorders have a strong negative impact on HRQOL. Longitudinal and intervention studies are needed to confirm our findings and to assess whether the treatment of mood disorders can affect HRQOL of patients.

Funding: Government Support - Non-U.S.

PUB278

PD PLUS Modeling with "Ideal" Dwell Times Predicts Adequate Kt/V and UF Without High Dextrose Solutions or Icodextrin

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Background: PD PLUS is an APD regimen with a mid- or late-day "PLUS" exchange with or without a last fill (LF). For high transporters, achieving UF goals can be challenging; for low transporters, achieving the Kt/V goal is a challenge. Using high dextrose (dex) or icodextrin dialysates can overcome this, but not without issues. This kinetic analysis modeled PD PLUS regimens that aimed to minimize total volume and dex exposure by utilizing a PLUS exchange (EX) with an "ideal" dwell time that targets max UF or Kt/V.

Methods: "Ideal" dwell times for maximum UF and Kt/V were determined for all PET transport categories with 1.5 and 2.5% dex dialysates using published data and algorithms derived from the PackPD® Program. Fifteen theoretical anuric patients were defined for modeling purposes by transport type (H, HA, A, LA, L) and patient size (S, M, L). The six modeled regimens (below) include overnight (ON) EXes with dwell times set at the predicted 1.5% UF Max time for each transport type with options for a dry day, LF, and PLUS EX. Dwell volumes for all EXes were set based on patient size; PLUS EX dwell times were set at "UF Max" or "Kt/V Max"; LF dwell time was set so total treatment time (TT) was 24 hrs. - 1.5% ON + 2.5% "UF Max" PLUS EX - 1.5% ON + 1.5% LF and 2.5% "UF Max" PLUS EX - 1.5% ON + 2.5% LF and 2.5% "UF Max" PLUS EX - 2.5% ON with dry day - 2.5% ON + 1.5% "Kt/V Max" PLUS EX - 2.5% ON + 1.5% LF and 1.5% "Kt/V Max" PLUS EX

Results: TTs for the overnight exchanges was 8-11 hrs, total volume was 6-18 L. At least 2 regimens for each patient achieved adequate clearance (weekly Kt/V ≥ 1.7) and UF (≥ 1 L/day). For some patients, a dry day was possible with 2.5% dex ON EX. Regimen 6 predicted adequate PD for all modeled patients.

Conclusions: This kinetic analysis demonstrates that adequate PD can be achieved without the use of high dextrose or icodextrin dialysates in most patients by using PD PLUS

in which the dwell time of the PLUS exchange is optimized for UF or Kt/V, as indicated. Data from clinical studies are needed to confirm the predictions of this modeling. Importantly, the accuracy of estimated ultrafiltration volumes using kinetic modeling is limited. Any PD prescription should be based on individual clinical needs and patient history.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

PUB279

Treatment of Infection in Tunneled Double Lumen Catheter for Hemodialysis with Pulses of Ethanol 70%

Sergio Sloboda. *Renalduc, Rio de Janeiro, Brazil.*

Background: Catheter Related Bloodstream Infection (CRBSI) contributes to increased mortality rate in hemodialysis patient. Thus we must develop strategies to eradicate the catheter colonization. Lock with high-concentration antibiotics is a common practice and its continuous use related to the emergence of multidrug-resistant bacteria. In ethanol use in long-stay polyurethane catheters, the time is relevant in the relationship between security and elimination of biofilm. Continuous use will damage its components, the toxicity causes high liver enzyme and embolization by catheter fragments. The purpose of our work was to implement an effective protocol for use of ethanol at 70% in eliminating the biofilm without the emergence of adverse events.

Methods: We started a treatment protocol with lock of ethanol at 70% solution associated with 20 mg of enoxiparin for 6 hours in three consecutive days to replace the use of antibiotics locks, in the six patients that used Tunneled Double Lumen Catheter (TDLC) in last 12 months. Used heparin locking between dialysis. Performed blood cultures (venous and arterial branch) every two weeks. Repeating the treatment in the positive. We analyze, pre and post Protocol, the number of episodes of CRBSI per 1000 catheter day, values of transaminases (ALT), bacteriological profile analysis of blood cultures and the occurrence of adverse events. In the statistical analysis was used Wilcoxon test and median as a measure of central tendency.

Results: The CRBSI occurred in rate 8 *vs.* 0 episodes, pre *vs.* post protocol, $p<0.05$. There was no statistical significance between the values of ALT in two periods, being 10 and 11, $p>0.05$. In two times we observed DLCT low blood flow in ethanol use, being reinstated using intraluminal Alteplase 1mg/ml. In the pre protocol 60% of the microorganism remained in following blood cultures, this not observed during the use of ethanol. Re-infection in the ethanol use occurred after 34 days, being for different pathogen

Conclusions: The absence of CRBSI without the emergence of adverse events and toxicity shows the efficacy of therapy with ethanol on elimination of intraluminal biofilm in TDLC. Reinfection warned about the need to increase surveillance and training for handling of TDLC by the team of professionals involved in assisting and patient. The bacteriological control became critical to the prevention of new episodes of CRBSI

PUB280

A Fractured Dialysis Catheter or Calcified Fibrin Sheath? A Radiological Dilemma

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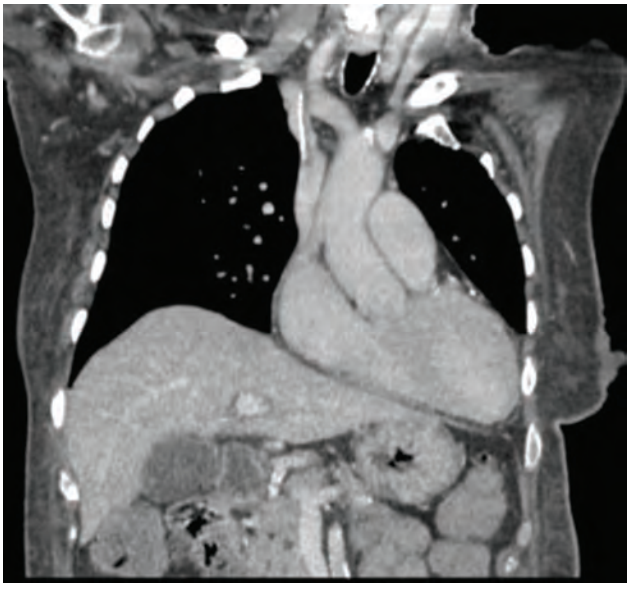
Introduction: Whilst a-v fistula is an ideal dialysis access, yet up to 80% patients are initiated on dialysis with tunneled dialysis catheters (TDC). Long term TDC, as vascular access is often unavoidable, despite the associated risk of infections, thrombosis, central vein stenosis, catheter dysfunction and fibrin sheath formation.

Case Description: A 75-year-old woman with ESRF was admitted with fever and chills during her dialysis session. Her dialysis access was a tunneled catheter inserted 5 years prior. In the interim she did not have any episode of catheter malfunction or previous catheter related blood stream infection. She refused arterio-venous fistula creation in the past. The catheter was removed due to catheter related blood stream infection. A routine non-contrasted CT scan of the chest was performed 3 days later for follow up of a left pulmonary nodule. The radiology report was consistent with a retained central venous catheter fragment. Subsequent examination of the catheter tip sent for microbiology was examined and was consistent with complete removal of catheter.

Discussion: Fibrin sheaths commonly form on long-term central venous catheters. The process involves endothelial damage, thrombus formation, collagen deposition and sometimes calcification. A sleeve may form over the distal tip of the catheter. During removal of catheters these sheaths remain in the vein. Calcified venous fibrin sheaths have been misdiagnosed as retained catheter fragments. Calcified fibrin sheaths can be differentiated from retained catheter fragment if attention is given on CT scan to their irregular morphology, discontinuous areas of calcification often contiguous with noncalcified portions. **Take away Message: A retained calcified fibrous venous sheath may mimic a retained catheter fragment. This may trigger unnecessary radiological intervention or surgical exploration.**



CT scan: Coronal

PUB281

Serum Phosphorous Is the Independent Risk Factor for Vascular Access Dysfunction in Maintenance Hemodialysis Patients

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Background: It is known that maintenance of function of arteriovenous fistula (AVF) is very important in the management of hemodialysis (HD) patients. Therefore, identifying a risk factor for decreased vascular access flow has a clinical relevance in real world practice. Although hyperphosphatemia plays a crucial role in the pathogenesis of vascular calcification, there is lack of studies evaluating the effect of hyperphosphatemia on AVF. This study investigated the impact of serum phosphorous (P) on vascular access flow in HD patients

Methods: Sixty-two maintenance HD patients who visited dialysis unit of Bundang CHA Medical Center from November 2016 to December 2017 were included in this study. Serum P levels were determined every month, and time-averaged serum P was calculated. All patients had left arm AVF (side to side anastomosis) and vascular access flow was assessed by Transonic HD 03. Decreased vascular access flow was defined as less than 600 mL/min.

Results: The mean age was 57.9 ± 12.1 years, 28 patients (50.9%) were men. The mean serum P levels were 5.1 ± 1.1 mg/dL and the vascular access flow was 1,071.4 ± 504.2 mL/min. Decreased vascular access flow was observed in 14 of 62 patients (22.6%). In univariate analysis, higher serum P was significantly associated with decreased vascular access flow (odds ratio [OR]=2.089, 95% confidence interval [CI]=1.159-3.766, P=0.014). But there was no significant association of dialysis blood flow rate, ejection fraction on echocardiography and serum calcium (Ca) levels with vascular access flow. Multivariable analysis indicated that higher serum P was independently associated with greater risk of decreased vascular access flow (OR=4.012, 95% CI=1.651-9.711, P=0.002). Old age, reduced EF, low dialysis blood flow rate and higher serum Ca was not associated with vascular access flow.

Conclusions: This study demonstrated that higher serum P was the independent risk factor for decreased vascular access flow in maintenance HD patients. Serial monitoring of serum P may be helpful to stratify the risk of vascular access dysfunction in these patients.

PUB282

Unused Mega Fistulas! A Case Series

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Introduction: A mega fistula forms due to aneurysmal dilatation of the whole outflow tract. It can lead to complications like high output cardiac failure and steal syndrome. We present a series of patients who developed mega fistulas due to lack of surveillance.

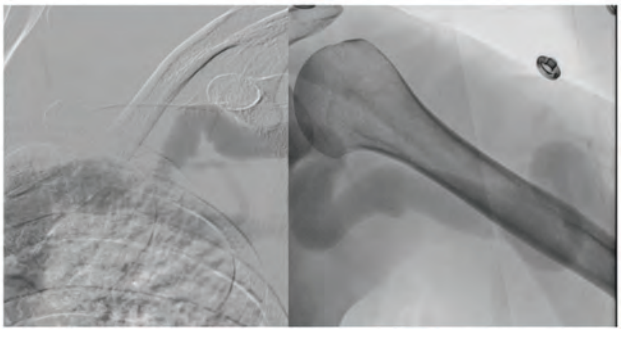
Case Description: Five post-transplant and one pre-dialysis patients were referred for evaluation of large aneurysmal fistulas. Angiogram was done in each case to define the anatomy. All the patients showed outflow stenosis. Details are shown in the table included.

Discussion: Undiagnosed venous outflow stenosis was the most likely reason of development of mega fistulas in this case series. Patients on dialysis undergo regular surveillance of their fistulas. Any abnormal sign usually prompts an evaluation in the form of angiogram with subsequent angioplasty of the outflow stenosis if found. Pre-dialysis

and post-transplant patients may not get surveillance of their fistulas which can cause a stenosis to go unrecognized. Outflow stenosis causes high pressure within the fistula which along with increased turbulence can lead to activation of pathophysiological mechanisms resulting in increased outward remodeling and overtime, increase in the size of the draining vein. Most of these mega fistulas require either ligation or surgical revision as the stenosis is usually chronic and difficult to intervene upon. Even if the stenosis is opened, it can lead to worsening of high output cardiac failure or steal syndrome. This case series highlights the importance of surveillance of the fistula even if it is not in use as it can prevent a complication like mega fistula by early diagnosis and treatment of outflow stenosis.

Findings and outcomes of patients with mega fistulas

Serial No.	Current Status of Renal Replacement Therapy	Type of AVF	Duration of Non Usage (Years)	Severity and Location of Stenosis	Outcomes
1	Post Transplant	Radiocephalic	12	100%, Cephalic vein at the elbow	Angioplasty not done. Referred for Ligation.
2	Post Transplant	Brachiocephalic	7	80%, Cephalic Arch-Subclavian vein junction	Stenosis resolved with successful angioplasty.
3	Post Transplant	Brachiocephalic	2	80% in Mid arm Cephalic vein. 70% at Cephalic arch	Angioplasty not done. Referred for Ligation
4	Post Transplant	Radiocephalic	14	100%, Cephalic vein at elbow	Angioplasty not done. Referred for Ligation.
5	Post Transplant	Radiocephalic	2	100%, Cephalic Arch-Subclavian vein junction	Angioplasty not done. Referred for Ligation.
6	Pre Dialysis	Brachiocephalic	4	100%, Cephalic Arch-Subclavian vein junction	Angioplasty unsuccessful. Referred for Ligation.



Mega Fistula with stenosis at the Cephalic arch-Subclavian vein junction.

PUB283

Pulmonary Embolism (PE) After Tunneled Catheter Removal in Dialysis Patients: An Underrated Complication?

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Introduction: Central venous catheters (CVC) cause complications and tunneled dialysis catheters (TDC) are associated with a higher mortality from infectious and cardiovascular causes. Asymptomatic catheter associated thrombosis has been described as frequent as in 25-40% of patients. Symptomatic thrombosis occurs in 1-5% of patient with CVC. The rate of PEs in patients with TDC is unknow. Removal of tunneled catheters is commonly perceived as low risk procedure and a PE as a complication has not been described. We want to present a dialysis patient with a PE after removal of his TDC.

Case Description: A 62 year-old man with ESRD on hemodialysis with a history of hypertension, diabetes mellitus, HCV, and bipolar disorder presented in the emergency department (ED) with chest pain and shortness of breath (SOB) one day after removal of right internal jugular vein TDC. The TCD was inserted to facilitate dialysis for a few weeks, while his left upper extremity autogenous access underwent surgical revision. The exit site appeared clean and intact without erythema. He had no signs of generalized infection and was hemodynamically stable with O2 saturation of 96%. Since the chest pain was localized over the exit site and his SOB was not severe, a chest X ray and a non-contrast chest CT were performed and were negative. The patient was discharged. Two days later, the patient reported continuing SOB with exertion and chest pain during inspiration while he was seen by his nephrologist on dialysis. He was sent to the ED, and ACS diagnostics as well as a CT-angiogram (CTA) were performed. CTA demonstrated a PE in the right upper lobe segmental artery. Echocardiogram showed no signs of right heart strain. The Patient was anticoaulated with warfarin with goal INR of 2-3 with heparin bridge. His symptoms improved and he was discharged home.

Discussion: Despite a reported high rate for catheter associated thrombosis, the rate of PE from line associated thrombus in patients with TDC is unknow. This case report demonstrates, that it is necessary to have a high rate of suspicion for PE in patients with indwelling dialysis catheters, especially if the TDC was manipulated. PE should be recognized as a possible complication of an otherwise low risk procedure as a TDC removal. Further studies are needed to clarify the amount of tunneled dialysis line associated PE.

PUB284

A Novel Collaborative Approach to Promote CKD Awareness in the State of Arkansas

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Background: Over 400,000 Arkansans have CKD, about 1200 start dialysis annually and there are about a 100 Department of Health (ADH) tele-health sites at outreach clinics. Despite one of the highest incident rates of ESRD and poor access to pre-ESRD nephrology care, there were no educational tools promoting CKD awareness across the rural state. University of Arkansas for medical sciences (UAMS) developed such tools but lacked the outreach. UAMS and ADH collaborated with stakeholders to form a CKD Advisory Committee to address CKD awareness in AR.

Methods: UAMS and ADH collaborated with stakeholders (major insurance companies, non-profit-organizations like Arkansas foundation for medical care, local nephrologists,CKD patients) to form the Arkansas CKD advisory committee (ARCKDAC), with the mission to increase CKD awareness, detection and education of Arkansans using community engagement activities. The committee has 4 arms: 1. Data assessment and innovation. 2. Finance and cost assessment. 3. Quality initiatives. 4. Education and CKD. ARCKDAC directed attention to following 6 items-1. Comparing and contrasting ESRD incident data provided by ESRD Network 13 by AHD regions 2. Explore development of a statewide CKD registry; 3. Compile financial analysis of current health-care expense of CKD and potential cost-savings from changes in patient and provider behaviors resulting from these initiatives;4. Design and implement campaign "Know-Your-Kidney-Number" to promote CKD awareness; 5. Engage local nephrologists; 6. Use the "CKD: What You Need to Know" tools and results from a prior pilot project to educate committee and raise awareness. This project also established that tele-education was non-inferior to traditional face to face education for CKD patients. Provider-education tools include learn-on-demand videos with CME credits, resident teaching, and a "10-point plan" for primary-care physicians to address CKD.

Results: Anticipated improved CKD awareness in AR

Conclusions: We hope to address the barriers to CKD awareness through committee efforts. Advisory Committee members have the expertise, resources and commitment needed to improve local outcomes and explore a broad range of solutions. This can lead to positive change for Arkansans with CKD and the health care system.

Funding: Commercial Support - Baxter

PUB285

Bedside Renal Ultrasonography: A Key Tool in the Nephrology Resuscitation Crash Cart

Abhilash Koratala, Maryam Sattari, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: Unstimulating nephrology elective experience during residency training has been identified as one of the reasons for the declining interest in nephrology as a career choice among internal medicine residents. Efforts have been made at redefining the scope of the specialty by incorporating novel educational approaches that not only enhance the learning experience but also portend salutary impact on patient care. Point-of-care ultrasonography (POCUS) is an inexpensive and relatively easy to learn tool that can be incorporated into day-to-day clinical practice and trainee curriculum.

Methods: We developed a focused renal POCUS curriculum for medicine residents at our institution. It is comprised of two 4-hour training sessions during the ambulatory rotation block. The first session includes an introductory lecture on ultrasound physics, instrumentation, and technique of performance of ultrasound, followed by hands-on training on normal subjects. The second session includes interpretation of various sonographic pathologies (using pre-defined images) and performance of renal ultrasound ± volume status assessment on pre-selected hospitalized patients. The images are saved and linked to electronic medical record of the patients, and are available for review as needed.

Results: Approximately 60 internal medicine residents with no prior renal ultrasound experience have completed the course over the past 12 months. By the end of the second session, all residents were able to adequately appraise the three most common sonographic pathologies namely, hydronephrosis, stone, and cyst. Moreover, they demonstrated better understanding of interpretation of renal size, cortical thickness and echogenicity in the clinical context. The feedback from the residents has been overwhelmingly positive leading to a constantly growing demand for participation.

Conclusions: Based on the success of the local process, we propose that more programs across US consider embracing this approach; POCUS has the potential to become an integral component of nephrology training after careful evaluation of resource utilization and cost benefit balance. In addition to helping generate more interest in nephrology as a career, it can have significant patient care implications and revive the declining rate of renal biopsy and hemodialysis catheter placement by nephrologists.

PUB286

Poor Awareness and Knowledge Among Internal Medicine House-Staff for Prescribing Cardiovascular Medications in Patients with CKD

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Background: Chronic Kidney Disease (CKD) alters pharmacokinetics of many cardiovascular medications resulting in increased risk of adverse drug events from their incorrect dose adjustment. The majority of cardiovascular medications in patients with

CKD are prescribed by primary care physicians. We study the awareness and knowledge of Internal Medicine (IM) house-staff for dose adjustment of commonly prescribed cardiovascular medications in patient with CKD.

Methods: We conducted a cross sectional survey among 341 IM house-staff. We studied the awareness whether a given medication needed dose adjustment ('medication dose needs adjustment' perception) and knowledge at what level of GFR a given medication needs to be adjusted ('medication dose adjustment at appropriate GFR level' perception) in CKD patients.

Results: Overall, there were high percentages for lack of awareness and knowledge in adjusting cardiovascular medications for CKD. Atenolol and Simvastatin had the highest percentages at 93.2% for incorrect 'medication dose needs adjustment' perceptions. Carvedilol and Amlodipine had the lowest percentages at 22.7% and 27.2% respectively for incorrect medication dose needs adjustment and incorrect medication dose adjustment at appropriate GFR level perceptions. PGY1 had greater odds for incorrect dose adjustment perception (OR: 5.56, 95% CI: 2.19, 14.12, p<0.001). Additional Nephrology exposure and training had lesser odds for incorrect dose adjustment perception (OR: 0.45, 95% CI: 0.21, 0.97, p<0.05).

Conclusions: IM house-staff have poor awareness and knowledge for cardiovascular medication dose adjustment in CKD patients. Medical schools and IM residency programs should place greater emphasis on Nephrology exposure and formal didactic Nephrology educational training. This can avoid incorrect dose prescribing and enhance patient safety.

PUB287

Principles and Strategies for Involving Patients and Caregivers in Research in CKD: Report of National Workshops

Talia M. Gutman,[4,1] Martin Howell,[4,1] Kathryn Dansie,[3] Carmel M. Hawley,[2,7] Jonathan C. Craig,[1,9] Allison Tong,[4,1] Shilpa Jesudason,[6,10] Jeremy R. Chapman,[5] David W. Johnson,[2,11] Lisa D. Murphy,[8] Donna M. Reidlinger,[7,11] Stephen P. McDonald.[6,10] Better Evidence and Translation - Chronic Kidney Disease (BEAT-CKD) *[1]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia; [2]Nephrology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [3]ANZDATA, Adelaide, SA, Australia; [4]School of Public Health, University of Sydney, Sydney, NSW, Australia; [5]Westmead Hospital, WESTMEAD, NSW, Australia; [6]CNARTS, Royal Adelaide Hospital, Adelaide, Adelaide, SA, Australia; [7]The University of Queensland, Woolloongabba, QLD, 4102, NSW, Australia; [8]Kidney Health Australia, South Melbourne, NSW, Australia; [9]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia; [10]Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia; [11]Australasian Kidney Trials Network, Brisbane, QLD, Australia.*

Background: Patient involvement in research is widely advocated to ensure that their priorities are reflected in all phases of the research process, from setting the agenda through to implementation. However, there is limited evidence on how patients want to be engaged and involved in research. This study aims to identify strategies for consumer engagement and involvement in research in chronic kidney disease.

Methods: 105 patients and caregivers and 43 clinicians and researchers participated in three workshops in Sydney, Adelaide and Brisbane (Australia). In facilitated breakout groups, participants discussed principles and strategies for patient and caregiver involvement in research. Transcripts were analyzed thematically

Results: We identified five themes: fostering a consumer-centered culture (facilitating knowledge exchange and translation, providing an opportunity to give back, empowering health ownership, allaying skepticism and suspicion, building a community); respecting consumer expertise and commitment (clarifying expectations and responsibilities, equipping for meaningful involvement, valuing unique and diverse experiential knowledge, keeping 'in the loop' with results and impact); attuning to individual context (a preference based multipronged approach to engagement, reducing the burden of involvement, being sensitive to the patient journey); harnessing existing relationships and infrastructure (partnering with trusted clinicians, increasing exposure in clinical settings, mentoring patient-to-patient, extending reach through established networks); and developing a coordinated approach (power in the collective and united voice, systematic approach for equitable inclusion, streamlining access to opportunities and trustworthy information).

Conclusions: Patients want to be involved in research to take ownership of their health, yet are unaware and uncertain about potential opportunities for involvement. Establishing a supportive, respectful research culture, responding to their individual context, coordinating existing infrastructure and centralizing the flow of information may facilitate patient involvement as active partners in research

Funding: Government Support - Non-U.S.

PUB288

Medication Adherence Analysis for CKD Patients

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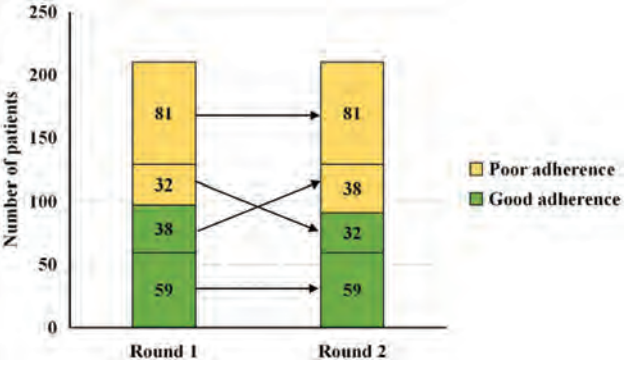
Background: According to the existing researches, the rate of medication adherence among chronic kidney disease patients was low. Improving patients'medication adherence might delay their disease progression.

Methods: Data were collected from CKD patients who had first visited the Chronic Disease Management Clinic at the Nephrology Department of the Guangdong Provincial Hospital of Chinese Medicine between March 2014 and April 2017. The collected data included the basic information of patients, the Morisky compliance scale, accompanying diseases, laboratory test results, what types of medication were being taken, and so on.

Results: 210 CKD patients were enrolled. Round 1: 97 patients were considered to have good adherence, 113 were considered to have poor adherence. Round 2: 91 patients were considered to have good adherence, 119 were considered to have poor adherence. 38 of the 97 good-adherence patients changed their medication adherence from good to poor, and 32 of the 113 poor-adherent patients changed their medication adherence from poor to good. Furthermore, Over 75% of the patients often forgot to take medication and or often did not pay attention to taking their medication. Additionally, the differences in the adherence between two groups were statistically significant including self-care or not, age, current residence and education level.

Conclusions: CKD patients had a high rate of poor medication adherence, accounting for 53.8% -56.7% of the total. Time had little impact on overall adherence, but had some effect on personal adherence. Younger age, higher education levels, living outside of Guangzhou city, and self-care or not, each led to worse medication compliance. Therefore, in actual clinical practice, we could improve patient compliance by taking corresponding measures.

Funding: Government Support - Non-U.S.



The trend map of medication adherence changes between two groups of patients within an interval of 1 year ± 3 months

PUB289

Predicting Success on Twitter: Nephrology Journals and Online Resources

Sarah Gleeson,[1] Swapnil Hiremath,[2] Silvi Shah,[3] Matthew A. Sparks,[4] Sinead Stoneman,[5] Joel M. Topf.[6] Nephrology Social Media Collective *[1]Nephrology, Auckland hospital, Auckland, New Zealand; [2]University of Ottawa, Ottawa, ON, Canada; [3]University of Cincinnati, Cincinnati, OH; [4]Duke University and Durham VA Medical Centers, Durham, NC; [5]University Hospital Waterford, Waterford, Ireland; [6]Oakland University William Beaumont School of Medicine, Rochester, MI.*

Background: Free open access medical education, often promoted and distributed through Twitter, is increasingly being used to supplement medical learning. An example is the Nephrology Twitter Journal Club (NephJC) which has hosted over 100 Twitter chats focusing on the medical literature impacting nephrology. Medical journals have also embraced Twitter with varying levels of enthusiasm. We hypothesise that on Twitter 1. Social media-based resources will have more followers than journals and 2 Amongst journals, those that commit to social media (through use of visual abstracts or social media editors) will have more followers

Methods: We evaluated the Twitter accounts of 18 nephrology journals and 4 nephrology social media-based resources for the number of followers and number of tweets to gauge their reach on Twitter. We report descriptive statistics, and comparisons between groups using non-parametric tests.

Results: Overall the median number of followers was 1947.5 (interquartile range, (IQR) 510.8-4179.3) and the median number of tweets was 966 (IQR 411.5-1730). We found little evidence that the subjects purchased 'fake followers' (< 5% of followers). The median number of tweets/day was 0.9 (IQR 0.4-1.8) and follower acquisition/day was 1.82 (IQR 1.1-3.3). Predictors of higher number of followers included Twitter vintage (p=0.005),

number of tweets (p=0.001), visual abstract usage (p=0.017) and journal impact factor (p=0.027). The social media-based accounts had more followers (median 3415, IQR 2031, 5172.8) than the journals (median 1579, IQR 510.8-3772.8)(p=0.27). They also had more tweets (Median 2396, IQR 783-7369.3) than the journals (median 872, IQR 411.5-327) (p=0.48).

Conclusions: This study shows that the number of followers a Twitter account has (and therefore its reach) is associated with both established (impact factor) and novel parameters (number of tweets, visual abstracts). Innovative social media centered initiatives such as NephJC had more followers than the journals, potentially due to their higher number of tweets and use of visual abstracts. The American Journal of Kidney Disease which has a social media editor and uses visual abstracts had the highest number of followers among the journals. Establishing a robust Twitter presence requires both consistent usage and adoption of new tools to disseminate information such as visual abstracts.

PUB290

Novel Technological Educational Tools for Patients with CKD

Geraldo B. Silva Junior,[1] Juliana G. Oliveira,[1] Marjan Askari,[2] Marilia Fahd,[1] Ronaldo A. Freitas filho,[1] Francisco aglalberto L. Silva,[1] José eurico Vasconcelos filho.[1] *[1]University of Fortaleza, Fortaleza, Brazil; [2]Erasmus University, Rotterdam, Netherlands.*

Background: Patients' adherence to treatment is far from ideal, and non-adherence impacts on outcomes. The aim of this study is to present novel technological educational tools to increase CKD patients adherence to treatment.

Methods: A multidisciplinary team (Health, Information Technology, Medical Informatics and Communication) discussed the technological possibilities based on CKD patients' needs. We have also interviewed patients in order to know their information needs and the main difficulties faced during treatment. We have them decided to create an application for smartphones, educational videos, a "smart medication box" and a shoe insole to monitor patients weight.

Results: The application was called "Renal Health", it included educational information for patients with CKD regarding the main aspects of the disease and its treatment, and provided tools for patients self-monitor their treatment, with alarms at the time of medications, dialysis, medical appointments etc. It also included information for the general population and for transplanted patients (mainly focused on immunosuppressants). The videos were intended to supply the necessities of illiterate patients who could not read the educational texts of the app. It was provided through a channel at youtube and would be incorporated in the application. The medication box was designed in a prototype version, in which a sensor is connected with the application. Whenever the patient open the box the app register the time and the name of the drug that was intended to be taken at that time. The shoe insole will be designed to monitor patients' weight, once interdialytic overweight is still a problem, which is associated with bad outcomes. Sensors will connect the information registered by the insole with the application, and alarms will be fired if a determined weight is overcome.

Conclusions: Patients' adherence to treatment is a challenge not only for CKD but for any disease. The Renal Health project evidence the countless possibilities that technology can provide to patients aiming to help them cope with a complex disease that requires a huge commitment to achieve good clinical outcomes, which is CKD. We intend to test these technologies in a large group of patients to assess its effects on clinical outcomes.

Funding: Government Support - Non-U.S.

PUB291

Establishment of a Telehealth Renal VA-ECHO Curriculum

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Background: Veterans Health Administration (VA) is the largest provider of health services in the nation for patients with chronic kidney disease (CKD). Many veterans with advanced CKD do not receive nephrology care before initiating dialysis. Veterans that do have access to this care do better. Reasons for this gap may include limited access due to geographical barriers, lack of local specialists and/or poor provider recognition of CKD. To bridge this access gap, the Seattle Renal VA-ECHO (Extension for Community Healthcare Outcomes) program developed a tele-mentoring program between nephrologists and underserved area primary care providers (PCPs). This program consists of didactic sessions with integrated case-based discussion via a Skype-meeting platform. To better facilitate learning, we developed a nationally delivered renal curriculum.

Methods: The goals of the curriculum are to: 1) Improve veteran access to renal specialty care; 2) Narrow PCP renal knowledge gaps; 3) Improve outcomes of veterans with kidney disease and other related complications. PCP knowledge gaps were identified via survey of VA PCPs and nephrologists and a review of electronic consultation (e-Consult) questions. A modular structure was chosen to develop common educational themes and allow for flexibility. Modules are logically sequenced to facilitate learning. Six modules with 3-16 didactic sessions were developed. Each session incorporates patient cases submitted by PCPs as e-consults. Learning objectives are integrated into each didactic topic. Nephrology and multidisciplinary content experts give didactics to create shared learning experiences. Curriculum development began in late 2016 and was in full use by 2017. Surveys were directed at frequent Renal VA-ECHO participants from 2016 and 2017 in an effort to capture learners pre and post-curriculum implementation.

Results: We surveyed 15 participants with a 47% response rate. The majority (57%) felt the curriculum was extremely helpful for learning focus, acquisition of knowledge, identification and filling of knowledge gaps and improvement in patient care. The remaining 43% found the curriculum to be quite helpful in these areas.

Conclusions: The development of a Telehealth Renal VA-ECHO Curriculum has helped to bridge knowledge gaps among rural PCPs and improve specialty care access and quality of care of veterans.

PUB292

A Kidney Biopsy Simulation Training Program: First Year's Results

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Background: Percutaneous kidney biopsy (PKB) is the most common procedure and should be adequately taught through simulation training according to ACGME requirements. We initiated a PKB simulation training program and we designed a two-year study to examine its effect on the confidence level, the procedural competence and the satisfaction with this training of Nephrology fellows compared to historical controls (fellows trained on PKBs before the initiation of the program).

Methods: All fellows were trained at UNM's simulation center (BATCAVE) with a PKB ultrasound training model (CAE Healthcare Blue Phantom™). Participants demographics and previous PKB experience was collected. Pre-assigned readings, online videos and hands-on practice on the simulation model were utilized. Performance of the trainee during each one-hour session was graded by the use of an evaluation form specifically designed for PKBs. Pre-and post-simulation surveys evaluated the participants' confidence level quantitatively (scale 0-5). All participants completed the satisfaction with PKB simulation experience scale (PKB-SSE).

Results: All three 1st and 2nd year current renal fellows completed the simulation training. The following table summarizes the basic information acquired from their training. Overall, the program enhanced the confidence level of fellows without previous experience on performing PKBs. All fellows expressed a high level of satisfaction (0-5) from their participation in this training.

Conclusions: PKB simulation training may improve trainees' confidence level especially for those without prior experience as well as their satisfaction with the training. The procedural competence of the trainees on PKBs will be evaluated during the second year of their fellowship and will be compared to the procedural competence of historical controls. Interventional Nephrology could re-foster interest in this subspecialty. Interventional Nephrology could re-foster interest in this subspecialty.

Funding: Clinical Revenue Support

Trainees	I	II	III
Year of Training	1st	1st	2nd
Previous experience	No	No	Yes
Number of sessions needed	1	3	1
Number of passes per session needed	5	6	3
Pre-training confidence level	4	3	5
Post-training confidence level	5	5	5
Satisfaction level	4	5	4

PUB293

Promoting Shared Decision Making Practice for CKD Patients Through Patient Decision Aids and Nephrology Staff Education

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Background: Shared decision making (SDM) process is integral for promoting patient centered care and patient and family engagement, leading to higher Quality of Life, patient satisfaction, and treatment outcome. However, practice of shared decision making is not fully implemented in routine healthcare practice in Japan. We aim to develop a program which promotes shared decision making through education and creating decision aid material.

Methods: We outline the development process of Japan Shared Decision Making Collaborative for Chronic Kidney Disease, an organization and a program to promote the practice of SDM. We also present its key educational elements. We describe issues associated with the implementation of the education program.

Results: Japan SDM Collaborative for Chronic Kidney Disease has been launched in October 2017 to promote education and practice of SDM for end stage kidney disease. After review of the literature, panel of members created sixteen pages patient decision aid booklet, aiming to accelerate patient-provider conversation, encourage patient and family engagement, and patients' understanding of treatment options. Decision aid booklet is approved by key nephrology organizations in Japan, including Japanese Society of Nephrology, the Japanese Society for Dialysis Therapy, the Japan Society for Transplantation, Japanese Society for Peritoneal Dialysis, and Japanese Society for Clinical Renal Transplantation. The booklet contains questionnaires for patient lifestyle, preferences, and values. It also provides key information about hemodialysis, peritoneal dialysis and kidney transplantation. Training seminars for nephrologists and nurses were held, which include key lecture and group work to share understanding of SDM and address issues to promote SDM. Group work consists of simulated healthcare provider and patient encounter, discussion about treatment options using decision aid. From April to May 2018, five educatinal seminars with 250 participants from 90 institutes were successfully held.

Conclusions: Japan SDM Collaborative for Chronic Kidney Disease has been launched to promote SDM practice for end stage kidney disease patients in Japan.

PUB294

Investigation and Management of Inpatient Hyponatremia in a Teaching Hospital

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Background: Hyponatremia is not a disease but a pathophysiologic process accounting for approximately 15% of general hospital admissions, and it is associated with significant morbidity and mortality. The objective of this study is to evaluate the investigation and management of hyponatremia in a teaching hospital.

Methods: Retrospective, observational study was conducted at a large teaching hospital for a year period (1st-June-2016 to 30th-June-2017). A retrospective chart review was performed on general internal medicine hospitalized patients with the diagnosis of hyponatremia including those who were admitted with serum sodium (sNa) ≤135 Meq/l and those who developed hyponatremia during the hospital stay.

Results: Six hundred and ninety five patients (321 male/374 female) with a Mean±SD age of 62±19 years and nadir sNa of 127.37 ± 6.22 Meq/l were included. Only 450/695 (65%) were admitted with sNa ≤130Meq/l, and the rest 245/695 (35%) developed hyponatremia while during their hospital stay. The severity was 45.46%, 45% and 0.09% for mild (sNa ≥130 Meq/l), moderate (sNa ≥120Meq/l to 129Meq/l) and severe (sNa <120 Meq/l) hyponatremia. The documentation of acuity and volume status assessment was missing for 83% and 62% of patients respectively. Only 20% patients had measurements of paired serum and urine osmolality and sodium, while 12% and 34% had an assessment of adrenal reserve and thyroid status respectively. The mean length of hospital stay was 5.11±4.03 days with an inpatient mortality rate of 1%. At hospital discharge, 14% patients had persistent hyponatremia. Overall, 22% patients didn't have any treatment recorded for hyponatremia. Among 532/695 (76.54%) patients with recorded treatment, the most common modality was isotonic saline (97%) followed by fluid restriction (29%). Expert opinion was sought in 28% of cases, with significant discrepancies noted in management. Offending drugs continued in 33% of patients.

Conclusions: This study highlights the need to improve clinical practice and educate residents. By accurate documentation, appropriate expert opinion, and highlighting inpatient hyponatremia electronic alerts can prompt optimal investigation and treatment, preventing associated morbidity and mortality.

PUB295

Epidemiology of Sodium and Potassium Electrolyte Imbalance in Ambulatory Care in United Arab Emirates: A Single Centre Study

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Background: Electrolyte imbalances are not common but important cause of morbidity, mortality and therapy outcome. The incidence of commonest Na^+ and K^+ abnormalities are ikely to rise due to increase in conditions like hypertension, diabetes mellitus, CKD & heart failure etc and due to drugs used for their management. There is lack of epidemiological data about these abnormalities in ambulatory care setup.. There was no study about Na^+ and K^+ imbalance in the arab world where the incidence of diabetes and cardiovascular disease is on rise in epidemic magnitude. It made us curious to assess about the incidence of these electrolyte abnormalities in ambulatory care setup.

Methods: Electronic record system of a Day Care Surgery Center serving all medical & surgical sub-specialities was acessed to retrieve retrospectively all the results of serum sodium and potassium tested during 1st January 2016 to 31st December 2017. The selection of center eliminated serious cases leading to a better presentation of ambulatory care patients. Age, sex, nationality, and value of electrolyte result but not the diseses were included in study. Excel 2016 was used for anlaysis.

Results: 73143 and 61480 patients utilized the facility in 2016 & 2017 respectively. 25872 & 17826 samples for K+, 24027 & 15090 samples for Na+ were analysed in 2016, 2017 respectively. 18272 patients in 2016 and 13520 patients were tested in 2016 & 2017 respectively. Age ranged from less than 1 year to 93 years in 2016 and 2 years to 89 years in 2017. The incidence of hyponatremia was 9.1% & 8.9% in 2016 & 2017 respectively while hyponatremia was les than 0.1%. incidence of Hypokalemia was 0.9 to 1% & hyperkalemia incidence was 0.32 to 0.35 %. Hypokalemia and hyponatremia was more common in younger age (no significant p) & among females (significant *p)* while hyperkalemia and hypernatremia was more common among males and older age (no significant p).

Conclusions: Incidence of Na+ & K+ abnormality in ambulatory care is low but its ablolute numbers may be significant. This is a single centre study with several limitations yet first of its kind in Arab world about epidemiology of sodium and potassium imbalance in ambulatory care setup A larger multicenter stuy ncluing relation to morbidity and drugs is to have better assessment of the problem is highly desirable and recommendable.

PUB296

Hypercarbia in a Patient with Acute Leukemia: Don't Be Tricked!

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Introduction: Nephrologists are frequently consulted to assist with the management of acid-base and electrolyte disorders in the intensive care unit (ICU). As such, it is important to recognize the spurious causes of laboratory abnormalities in this context.

Case Description: A 58-year-old man was admitted for multifocal pneumonia. Laboratory studies demonstrated severe leukocytosis with a WBC count of 123 thou/mm^3 (Ref: 4-10), with peripheral blood smear suggestive of Acute Promyelocytic Leukemia. He was admitted to the ICU for treatment of pneumonia and possible Leukapheresis. Soon after that, he developed hypotension and worsening respiratory status requiring endotracheal intubation. Arterial blood gas (ABG) analysis was significant for a pH of 6.9, PaCO2 of 98 mmHg, PaO2 67 mmHg, on Fio2 of 100%. Pulse oximetry reading at that time was 92%. Serum chemistries demonstrated a potassium of 8.5 mmol/L with creatinine ~1.2 mg/dL. Nephrology was consulted for possible dialysis in the setting of severe systemic acidosis and hyperkalemia. Further investigations revealed no EKG changes suggestive of hyperkalemia and a serum lactate of 18.6 mmol/L. We suspected spurious hyperkalemia from cell lysis, which was confirmed by whole blood potassium of 4.3 mmol/L. While renal replacement therapy is a reasonable strategy to correct systemic acidosis, we were faced with the question whether this is primarily metabolic (lactic) or respiratory acidosis. In hypercapnic acidosis, correction of pH above 7.2 is not typically recommended as it may adversely affect the overall outcomes. A repeat ABG revealed similar PaCO2 but interestingly, point-of-care (bedside) blood gas analysis at the same time demonstrated a PaCO2 of only 20 mmHg, which indicates that the original high value of PaCO2 was spurious.

Discussion: Spurious hypoxemia can occur in cases of extreme leukocytosis and thrombocytosis due to in vitro oxygen consumption by these metabolically active cells, even when there is a few-minute delay between sample collection and analysis. However, spurious hypercarbia is not expected to occur owing to considerably higher CO2 buffering capacity of blood. However, our case shows this can occur, especially when there is concurrent metabolic acidosis.

PUB297

Validity of Urine Osmolality Measurement in Healthy Adults

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Background: Hyponatremia, defined as a serum sodium level < 135 mEq/L, is the most common electrolyte disorder in clinical practice. Measurement of urine osmolality is critical part in the correct diagnose and management of patients with hyponatremia. The aim of this study is to quantify the changes in urine osmolality due to the presence of substances identified by urinalysis (UA), like glucosuria.

Methods: Albumin, ketones (e.g., acetoacetic acid and β-hydroxybutyrate), and glucose were added to the urine of healthy participants in amounts detected by dipstick urinalysis (Siemens multistix 10). For example, 0.2g of glucose per 10 mL of urine corresponded to 4+ glucose by dipstick. Urine osmolality was measured using freezing point depression (Model 2020, Advanced Instruments, Inc) at baseline and after adding fixed amounts of each substance. Change in urine osmolality was reported as median (range). Signed rank tests were performed to compare differences in osmolality from baseline; p-value < 0.05 considered statistically significant.

Results: The study population consisted of 10 participants (50% female, 40% African American, age ranging 27-62 years, and BMI ranging 25-34 kg/m2). Baseline urine osmolality ranged 74 – 874 mOsm/kg, and changes in urine osmolality were similar throughout the range of baseline values. Addition of acetoacidic acid at 160 mg/dL (e.g. 3+ketones by UA) raised the urine osmolality by 27.5 (20-29 mOsm/kg, p 0.004). β-hydroxybuterate at 160 mg/dL, which is not detected by urinalysis, raised the urine osmolality by 13.7 (3-20 mOsm/kg, p 0.016). Glucose at 2000 mg/dL (e.g., 4+ glucose by UA) raised the urine osmolality by 110 (97-116 mOsm/kg, p 0.004), and glucose at 500 mg/dL (e.g, 2+ glucose by UA) raised the urine osmolality by 24.7 (9-37 mOsm/kg, p 0.004). Albumin did not significantly change the urine osmolality with 4+ protein by urinalysis changing urine osmolality by -3 (-8-2 mOsm/kg, p 0.22).

Conclusions: The presence of ketones and glucose in the urine significantly increase urine osmolality measurements. When interpreting urine osmolality as an indicator of kidney water handling, one may need to correct for these substances, which can be detected by urinalysis. Importantly, the presence of albumin does not significantly alter urine osmolality.

Funding: NIDDK Support

PUB298

Acquired Renal Glucosuria in an Undifferentiated Connective Tissue Disease Patient with a SLC5A2 Heterozygous Mutation: An Unusual Case Report

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Introduction: Renal glucosuria is a renal tubular disorder characterized by persistent isolated glucosuria in the absence of hyperglycemia. The causes of renal glucosuria include a wide range of insults to proximal tubular cells including genetic conditions, drugs, and

poisons. Renal glucosuria caused by UCTD(undifferentiated connective tissue disease) is very rare.

Case Description: A 30-year-old woman was seen in the outpatient clinic for complaints of repeated frequency urination,odyuria. Laboratory tests showed urinary tract infection and renal glucosuria. After the antibiotic treatment, the UTI symptoms were relieved while renal glucosuria remained. Further laboratory test ruled out renal tubular acidosis, and immunologic tests showed a high antinuclear antibody titer (1:160), and elevated anti-Rho/SSA antibody. Schirmer's test, tear break-up time and lip biopsy were negative. The patient did not meet criteria for any known connective diseases. She was therefore diagnosed with UCTD. Genetic analysis showed SLC5A2 gene heterozygous mutation, and incubation of the patient's serum with normal mouse kidney tissue showed a pattern of SGLT2 in the epithelial tubules similar to that of incubation of normal mouse kidney tissue with the rabbit polyclonal anti-SGLT2 antibody. With the treatment of immune-suppression, the renal glucosuria doesn't exist.

Discussion: This case presents UCTD as a rare cause of renal glucosuria, and our findings suggest the presence of circulating autoantibodies to SGLT2.

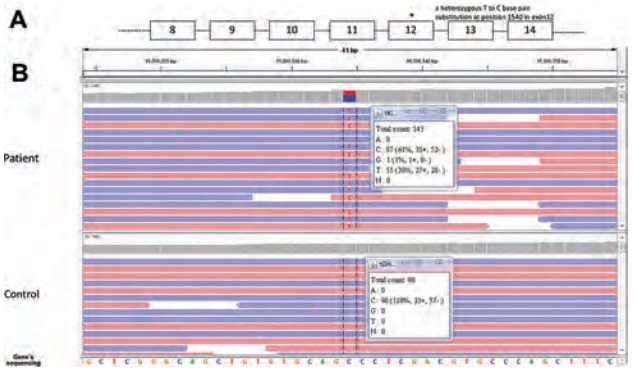

Fig1. Genome sequencing of all exon regions of SLC5A2

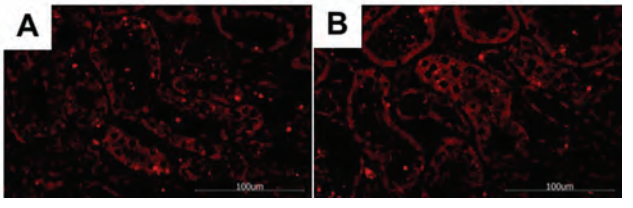

Fig2. Immunofluorescence staining of the frozen sections of normal mouse kidney with (A) the patient's serum and (B) rabbit polyclonal anti-SGLT2 antibody was performed.

PUB299

Changes in the Extracellular-to-Intracellular Water Ratio in a Sample of Japanese Adults Aged 15–88 Years Old: A Cross-Sectional Study to Develop a Formula for Quantifying Fluid Volume Overload

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Background: Fluid volume overload is common and is associated with adverse outcomes in patients with chronic kidney disease (CKD). However, accurate assessment of fluid volume status remains a concern. The fluid volume balance between intracellular water (ICW) and extracellular water (ECW) gradually changes with age, which may be associated with a reserve capacity for volume overload. This study was designed to estimate the physiological fluid volume changes with age for assessing volume overload.

Methods: We performed using sample data obtained from InBody Japan Inc. (Kameido, koto-ku, Tokyo, Japan). A total of 1,992 individuals (753 men and 1,239 women) aged ≥15 years included in this study had their body composition measurements performed at training gyms in 2014. We developed a regression formula to assess the association of age with the ratio of ECW to ICW in these subjects.

Results: The mean ages of male and female subjects were 51.2 ± 15.2 and 57.4 ± 15.2 years, and their mean body mass indices were 23.4 ± 3.3 and 21.1 ± 2.8 kg/m^2, respectively. The total fluid volumes of male and female subjects were 39.6 ± 4.9 and 27.7 ± 3.0 L, whereas the percent body fat mass/kg of body weight were 19% and 26%, respectively. The ECW/ICW ratio increased with age due to the steeper decrease in the ICW content than in the ECW content, especially after the age of 70 years. The regression formulas used for calculating the age-adjusted ECW/ICW ratio were as follows: $[0.5857 + 7.4334 \times 10^{-6} \times (\text{age})^2]$ in men and $[0.6062 + 5.5775 \times 10^{-6} \times (\text{age})^2]$ in women. The standard errors of the quadratic least square regression coefficient in male and female subjects were 0.2825×10^{-6} and 0.2516×10^{-6}, respectively. The standard errors of the y-intercept in the formulas for male and female subjects were 0.000989 and 0.000974, respectively.

Conclusions: Fluid volume balance is universally influenced by decreased cell volume driven by aging and muscle attenuation, which disturbs the standard ICW/ECW ratio of 62:38. Our proposed formula for calculating the age-adjusted ECW/ICW ratio may be a useful calculation tool for the normalized fluid volume balance, and it can be applicable to the quantitative analysis of volume overload in patients with CKD.

PUB300

Research on the Relationship Between Urolithiasis and Metabolic Disease

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Background: Calcium oxalate (CaOx) is the most common urolithiasis, metabolic disease such as obesity, diabetic mellitus, dyslipidemia, hyperuricemia, and hypertension can influence the incidence and recurrence of urolithiasis via many mechanisms. This study aim to explore the relationship between CaOx stone and metabolic disease in Chinese urolithiasis patients.

Methods: Patients treated by surgery in Beijing Tsinghua Changgung Hospital from Oct. 2015 to Aug. 2017 were retrospectively study. Demographic characteristic and stone composition were analyzed. Patients of CaOx stones and non-CaOx stones'data were compared, including clinical material and examination. The prevalence of metabolic disease in CaOx patients were analyzed and Logistic regression were used to analyze the influence factors related to hyperlipidemia among CaOx patients.

Results: 1. Among 707 patients, there are 446 (63.1%) males and 261 (36.9%) females. 573 (81.0%) cases are CaOx stones. 2. Compared with non-CaOx patients, CaOx patients had significantly higher BMI (25.40kg/m2 vs. 24.54kg/m2, P=0.024) and urine gravity (1.012 vs. 1.011, P=0.024), lower blood chlorine (105.6mmol/L vs. 106.4mmol/L, P=0.007) and lower proportion of urinary infection (62.4% vs. 78.4%, P=0.001). 3. Compared with general population, CaOx patients had higher proportion of metabolic disease. 4. CaOx patients with hyperlipidemia had significantly higher level of uric acid (364.3umol/L vs. 331.9umol/L, P<0.001), serum calcium (2.23mmol/L vs. 2.19mmol/L, P=0.009), total protein (67.6g/L vs. 65.7g/L, P=0.001) and albumin (39.8g/L vs. 38.2g/L, P<0.001). They had lower level of iPTH (43.17ng/L vs. 51.95ng/L, P=0.003) and urine pH (6.13 vs. 6.36, P<0.001). 4. Multivariate Logistic regression analysis showed that hyperlipidemia in CaOx patients are related with hyperuricemia (OR 1.609, 95%CI 1.018-2.543, P=0.042), blood calcium≥2.3mmol/L (OR 1.953, 95%CI 1.092-3.491, P=0.024), iPTH≤40ng/L (OR 1.576, 95%CI 1.013-2.453, P=0.044) and urine pH≤6 (OR 1.820, 95%CI 1.164-2.848, P=0.009).

Conclusions: 1. Compared with non-CaOx, CaOx urolithiasis patients have higher BMI and urine gravity, lower proportion of urinary infection and blood chlorine. 2. Metabolic disease is common in CaOx urolithiasis patients, dyslipidemia is the most common one. 3. Hyperlipidemia in CaOx urolithiasis patients is associated with hyperuricemia, hypercalcemia, the decrease of iPTH and urine pH≤6.

PUB301

Metabolic Acidosis and Clinical Outcomes in CKD Patients – Multicenter Large Cohort Study Using Instrumental Variable Analysis

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Background: Whether low serum total CO2 (TCO_2) concentrations, defined as metabolic acidosis, increase a risk for kidney function deterioration and mortality in chronic kidney disease (CKD) was controversial and not clear enough. Large-scale studies for the clinical impacts of metabolic acidosis in Asian CKD patients have been done, neither.

Methods: A multicenter cohort study of 42,270 adult nephrology outpatients, from 2001 to 2016, was conducted to investigate the association between serum TCO_2 concentrations measured at first outpatient visit and clinical outcomes. The patients diagnosed with end-stage renal disease (ESRD) from the first day of outpatient visit to 3 months were excluded. Instrumental variable was defined as the region divided to 4 groups based on the proportion of patients who have serum TCO_2 concentration lower than 22 mmol/L.

Results: The patients with initial TCO_2 < 22 mmol/L were 10.1%, hypertension and diabetes accounted for 29.3% and 20.9%, respectively. ESRD occurred at 8.5% patients and mortality rate was 12.2% during median 77.0 months follow-up period. Cox-proportional hazard regression model adjusted for initial estimated glomerular filtration rate demonstrated that low TCO_2 concentration increased a risk for progression to ESRD (hazard ratio [HR] 1.13; 95% confidence interval [95% CI] 1.04-1.23) and mortality (HR 1.47; 95% CI 1.37-1.59). Cox regression model using instrumental variable also verified a significant association between initial TCO_2 concentration and mortality (HR 0.58; 95% CI 0.51-0.66), however, there was no significant hazards of low TCO_2 concentration for progression to ESRD.

Conclusions: Metabolic acidosis was significantly associated with mortality, but not with progression to ESRD in this study using instrumental variable.

PUB302

Gitelman's Syndrome in a Patient with C1q Nephropathy: A Case Report

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Introduction: Coexistence of C1q Nephropathy (C1qN) and Bartter–Gitelman syndromes (BGS) is exceedingly rare.Few case reports of patients with BGS subsequently developing nephrotic range proteinuria secondary to C1qN or FSGS have been described. We present here a case diagnosed as C1qN who later developed electrolyte abnormalities consistent with Gitelman Syndrome.

Case Description: A 17 year-old male from a middle eastern country was being evaluated for nephrotic range proteinuria of 14gms/d. At age 3, he had a kidney biopsy performed showing FSGS. He was treated with steroids, cyclosporine, mycophenolate and cyclophosphamide in various combinations till age 10 and had attained complete remission. Repeat renal biopsy was performed. It showed 20 glomeruli, 1/20 sclerosed, 6 glomeruli showed increased mesangial matrix and hypercellularity. No significant IFTA. IF showed IgA2+, C1q3+, [IgG,IgM,C3, κ & λ chains – all 1+]. EM showed electron dense deposits in mesangial and paramesangial regions and focal foot processes effacement (40%). ANA, extractable nuclear antigen panel, C3 & C4 were unremarkable. Pt was started on MMF & prednisolone. Proteinuria gradually improved to less than 300mg/d and all immunosuppressants were stopped by end of 2 years. BP always remained normal and S. Crt was 0.6 mg/dl. One year later, he developed electrolyte abnormalities consistent with BGS. He had recurrent severe hypokalemia with Sr. K as low as 1.3. Patient had 3 hospitalizations for severe weakness and inability to stand when S. potassium dropped below 2.0. Hypomagnesaemia (Sr.Mg range 0.8-1.4 mg/dl), metabolic alkalosis (pH 7.50-7.65) with bicarb 32-37 mEq/L, hypochloremia (S.Cl 85-95 mEq/L), hyperuricemia and hypercalcemia were also noted. Patient denied any intake of thiazide diuretics or herbal medications. Pt declined genetic testing for BGS due to financial reasons. He is maintained on KCl supplementation 320mEq/d, magnesium orotate, aldactone and febuxostat.

Discussion: This case report decribes a unique case of C1qN subsequently developing electrolyte abnormalities consistent with BGS. It is unclear how immune complex related C1qN may predispose to development of renal tubulopathy like BGS or vice versa but the two are probably linked. Development of proteinuria in such patients should prompt clinicians to think about this rare but possible differential of co-existent C1qN/FSGS and renal tubulopathy-BGS.

PUB303

Is This Mutation Associated with Lactic Acidosis?

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Introduction: Herein, we report a case of recurrent symptomatic lactic acidosis in which genetic evaluation revealed a mutation associated with cardiac disease; but, hitherto, not lactic acidosis. Further studies to explore possible associations between this mutation and lactic acidosis are warranted.

Case Description: A 39 year old obese male with obstructive sleep apnea (OSA) & chronic hypoxia on oxygen presented with history of multiple hospitalizations (50 in two years) for lactic acidosis. All episodes were associated with muscle weakness, fatigue and lactic acid levels of 6-10 mmol/L in the face of hemodynamic stability and a normal liver profile. Genetic evaluation revealed a normal acyl carnitine profile and no pathogenic variants of the PDH or Mitochondrial Respiratory Chain Complex. However, a heterozygous mutation of **PRKAG2, a gene coding for subunit of AMP activated protein kinase (AMPK),** was discovered. Supportive treatment, with emphasis on controlling factors that exacerbated the lactic acidosis, was provided.

Discussion: This patient had a heterozygous variant of PRKAG2- a gene that encodes the gamma-2 subunit of a heterotrimeric protein- **AMP activated protein kinase (AMPK).** AMPK is present in many tissues and functions as a "energy sensor" within cells. "Excessive energy expenditure" resulting in ATP breakdown with consequent increase in intracellular AMP activates AMPK. AMPK, in turn, downregulates energy expending processes like fatty acid oxidation. AMPK gene mutations are associated with hypertrophic cardiomyopathy and cardiac arrhythmias (like WPW syndrome). Given the role of AMPK in energy metabolism, it is conceivable that abnormalities of AMPK be associated with lactic acidosis. However, to our knowledge, no such association has yet been reported. It is pertinent to note that Metformin, a drug that increases hepatic AMPK activity, can cause lactic acidosis. It is possible that alterations in AMPK activity affect the intracellular energy balance and/or metabolism of lactate. This patient had chronic hypoxia, OSA and excessive caloric intake, all of which predisposed him to lactic acidosis. Although unproven, it is likely that a combination of predisposing clinical features and a genetic mutation such as this one resulted in lactic acidosis in this patient. There is no known treatment. Circumstances that facilitate lactic acid production like hypoxia, volume depletion & excessive glucose consumption should be avoided.

PUB304

Death Due to Refeeding Syndrome (RFS) Described in 1507 by Antonio Benivieni, the Father of Pathology and Narrative Medicine

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Background: RFS, a disease presenting assevere electrolyte disturbance - low serum concentration of sodium, magnesium and phosphate-causing death due to cardiac arrhythmias, cardiac failure and pulmonary edema - was described in 1981by Roland L. Weinsier and Carlos L. Krumdieck,butit is rootedin a more distant past.

Methods: We aim to report heretofore unknown deathscaused by RFS described by Antonio Benivieni (1443-1502)in*The hidden and remarkable causes of diseases and recovery*(Florence, 1507).The book narrated 111 clinical histories. For the first time diagnoses were disclosed by autopsy. Thus Benivieni became the Father of Pathology and his book - recently - recognized as the first example of Narrative Medicine (DeSanto RM, 2018).

Results: Report no. LVII reads: "[In 1496] extensive famine affected nearly the whole Italy, that many died in the public roads and city streets. Many also through bad and injurious foods, were attacked by various disorders. I noticed too that very many of those who had, after long fasting, obtained more abundant food, enjoyed their fuller nourishment for a few days and then died, so harmful and dangerous is satiety preceded by a long period of abstinence. I also saw women who in this way did harm to the children at their breast, and so brought death upon their children and themselves. But very many who were reduced to the invalid state were, by the care and diligence of physicians, restored to their former health in the hospitals".

Conclusions: Data illustrate (i) Death due starvation; (ii) Death due to ingestion of deteriorated/toxic foods(inevitable in times of famine being healthy food scarcely available); (iii) Death caused by excessive food ingestion after long lasting abstinence from food; (iiii) Death of breast fed children and of their starved mothers; (v) Healing of many diseased persons receiving hospital care. Deaths are similar to those caused byunrestricted feeding after starvation in Nazi camps, Japanese prisoners of war, *Dutch Famine* (1944-45), and *Great Bengal Famine* (1943) described by Nobel economist and philosopher Amartya Sen. For 507 years Benivieni'sweighty description of RFS was ignored.

PUB305

Normal Fractional Excretion of Urate to Diagnose Reset Osmostat in Children

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Introduction: Reset osmostat (RO) is a subtype of syndrome of inappropriate anti-diuretic hormone secretion (SIADH) that is rare in child. RO is characterized by refractory hyponatremia despite variations in sodium and water intake with a retained ability to dilute urine in response to a water challege. It has been suggested that a normal fractional excretion of urate (FEUrate) (< 11%) can distinguish reset osmostat from the other subtypes of SIADH in adults, which have an elevated FEurate (>11%).

Case Description: Reported are three children with euvolemic hyponatremia that was refractory to fluid restriction and sodium supplementation (Table). Hypothyroidism and adrenal insufficiency were excluded. Patients 1 and 2 were profoundly developmentally delayed and with a seizure disorder treated with Depakote and Trileptal, respectively. Hyponatremia was of prolonged duration. Patient 3 had a rickettsial infection with transient hyponatremia that resolved with treatment of the infection. Traditional serum and urinary biochemistries varied widely between the patients, and not in keeping with classic SIADH (Table). Water loading tests were not performed due to the risk of worsening hyponatremia. FEUrates were normal at around 6% in all patients, helping to confirm a diagnosis of RO. A normal FEUrate is helpful in establishing a diagnosis of RO in children with SIADH.

Discussion: A normal FEUrate is helpful in establishing a diagnosis of RO is children with SIADH

Features if Reset Osmostat in Children

Patient	1	2	3
Age (yr)	16	10	13
Sex	M	F	M
PNa mEq/L (range)	126 - 133	130 - 135	126 - 133
PUrate mg/dl (range)	2.8 - 3.3	1.9 - 2.4	3.9 - 6.5
UNa mEq/L (range)	9 - 71	23 - 177	13 - 181
UOsm mOsm/kg (range)	351 - 930	252 - 770	121 - 806
FE Urate % (range)	5 - 8	6 - 7	5 - 6
FE Na % (range)	0 - 1.2	0.1 - 0.3	0.1 - 0.7
Duration	3 yrs	3 yrs	8 days
Treatment	3% NaCl	Oral NaCl tabs	0.9%-NaCl

PUB306

Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) Induced Just After Surgery for Non-Small Cell Lung Cancer

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Introduction: The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of impaired water excretion caused by the inability to suppress secretion of antidiuretic hormone (ADH). It has been commonly associated with small cell carcinoma. However, the case with SIADH developed after pneumonectomy is rare and has different pathogenesis with paraneoplastic syndrome. We present a unique case of SIADH induced just after left upper lobectomy with hilar lymph node resection for non-small cell lung cancer (NSCLC). This case reviews possible alternative mechanism of SIADH in patients with NSCLC.

Case Description: 71-year-old woman was hospitalized in order to have a surgery for lung adenocarcinoma. Before three months of admission, the levels of carcinoembryonic antigen (CEA) increased (6.5ng/ml). Clinical examination resulted in the diagnosis as lung cancer (T2aN3M0, stage IIIB). After 2 days of left upper lobectomy, she exhibited disorientation. Although preoperative examinations indicated no electrolyte abnormalities, laboratory examinations revealed reduced serum sodium levels of 121mEq/L, increased sodium excretion (140mEq/L) with plasma hypoosmolarity (244mOsm/kg/H_2O) and urine hyperosmolarity (427mOsm/kg/H_2O). The levels of ADH remained more than detectivity despite hyponatremia. These data suggest that the hyponatremia in this case was caused by SIADH. She was treated with hypertonic saline infusion (NaCl 2%). After 3 days of initial treatment, the serum sodium concentration increased to 133mEq/L, and her disorientation was improved. Finally, the levels of ADH decreased undetectable on 9 days after the onset of SIADH. Hyponatremia did not recur without any therapy.

Discussion: There are possible alternative mechanisms of SIADH in this case. The surgical stress and aging have been shown to be a risk factor for the induction of SIADH. Another possibility is that decrease of left atrial pressure in response to reduction of pulmonary vascular residence stimulates volume receptors in the cardiopulmonary circulation resulting in the release of ADH. This case indicates the importance of considering SIADH as a possible complication in older patients undergoing lobectomy.

PUB307

Pharmacodynamics and Safety of Sodium Zirconium Cyclosilicate in Healthy Chinese Subjects: Open-Label, Phase 1 Study

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Background: Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a selective potassium (K)-binder that exchanges Na and H for K. It has been shown to rapidly restore normokalemia in Caucasian patients with hyperkalemia. Here we report the effects of SZC on urine K and Na, serum K, and safety in healthy Chinese subjects.

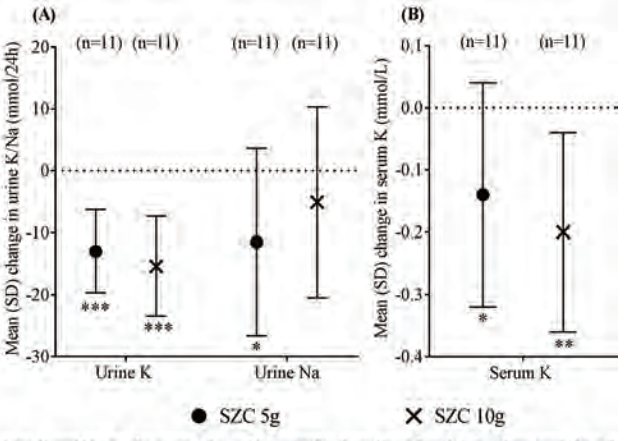
Methods: This open-label, phase 1 study randomized 22 healthy adults (18–55y) at a single center in Hong Kong. To control dietary Na and K intake, a standardized diet of 40 (±10%) mEq/d Na and 128(±10%) mEq/d K was given on Days 1–8. Oral SZC powder 5 or 10 g (n=11 each) was administered as a suspension in water once daily on Days 5–8. Urine K and Na was assessed from the mean of two 24-h samples at baseline (Days 3+4) and during SZC treatment (Days 7+8). Fasting serum K was measured daily. The primary endpoint was mean change from baseline in urine K; secondary endpoints included changes from baseline in urine Na, serum K, and other serum electrolytes, and adverse events (AEs).

Results: Subjects (59% male; mean age 33.5y) had a mean baseline serum K of 4.27 mmol/L. Urine and serum K significantly decreased from baseline with both SZC doses (Figure). Urine Na decreased; no clinically significant changes in other serum electrolytes, including Na, Ca, Mg, and PO_4, were reported. Overall, 16 subjects reported mild AEs during the study and 10 subjects reported mild AEs during SZC treatment. The most common AEs during the treatment period were gastrointestinal disorders but none were judged drug related. None developed hypokalemia or edema; no deaths, serious AEs, or discontinuation due to AEs were reported.

Conclusions: Oral SZC 5 and 10 g once daily significantly reduced urine and serum K in healthy Chinese subjects, and was well tolerated.

Funding: Commercial Support - AstraZeneca

Figure. Mean change from baseline in (A) urine K and Na, and (B) serum K in healthy Chinese subjects treated with SZC



Urine K and Na are the mean of two 24-h samples from Days 3 and 4 (baseline) and Days 7 and 8 (treatment); serum K values are the mean of values on Days 3–5 pre-dose (baseline), and Days 7 and 8 (treatment).
*P<0.05, **P<0.01, ***P<0.001 vs baseline.
K, potassium; Na, sodium; SD, standard deviation; SZC, sodium zirconium cyclosilicate.

PUB308

A Rare Case: Vitamin D Related Inappropriate ADH Syndrome

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Introduction: The most important renal activity of ADH is to increase the water permeability of the distal and the collecting tubule. This helps to protect from dehydration. Inappropriate ADH syndrome is an clinic syndrome which there is more ADH concentration versus any osmotic or volume stimulus that normally affects ADH secretion. Among etiologic causes small cell bronchogenic carcinoma, pancreas and duodenal adenocarcinoma, leukemia, lymphoma, thymoma, cerebral trauma and tumors, meningitis, encephalitis, pneumonia, tuberculosis, lung abscess are listed. Vitamin D deficiency is a rare, irrational but quit important cause. In this case, unusual to the treatment of SIADH, vitamin D replacement was sufficient and Tolvaptan was stopped and not needed anymore.

Case Description: A 52-year-old male patient was admitted to the ER department with nausea, weakness, and blurred consciousness. In his labrotory findings, there were not any pathologic finding except low serum sodium level (121 mEq/L). 3% NaCl treatment was started first because of his emergency situation. Due to lack of effective response, the treatment was switched to Tolvaptan. But his vitamin D level was low (25 OH-cholecalciferol = 10 nmol/L). On admission day, measured ADH level was 10 pg/mL (N: 1-5 pg/mL), so etiology for inappropriate ADH syndrome was evaluated. No pathology was detected in endoscopy, colonoscopy, abdominal ultrasound examination and MRI. However, enlarged, 33x22 mm sized lymphadenopathies were detected in paratracheal, subcarinal region by CT scan. Mediastinoscopic lymph node biopsy was performed due to the suspicion malignancy because of very intense FDG absorption (SUV max: 11.20) But ancotic lymph node containing reactive changes was stated on pathology report. So the Vitamin D treatment with 300,000 units per month orally was started and tolvaptan treatment was stopped. 1 month after discharge, serum 25 OH-cholecalciferol level was 20 nmol/L and serum sodium level was 134 meq/L.

Discussion: Vitamin D deficiency is associated with musculoskeletal, cardiovascular and immunological disorders, malignancy and even with diabetes and hypertension. However, when we updated latest knowledges about vitamin D relation with hyponatremia, we obtained very limited information. In addition, this treatment was more cost effective and accesible than Tolvaptan. For these reasons, we would like to remind the vitamin D deficiency to the clinicians in case of hyponatremia.

PUB309

Heart Transplant Patient Presenting with Rare Cause of Hyponatremia After Carboplatin-Based Chemotherapy

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Introduction: We are presenting a case of severe hyponatremia developed after carboplatin based chemotherapy requiring hypertonic saline and furosemide

Case Description: 81-year-old lady with h/o congenital heart disease s/p heart transplant 1995, hypertension, stage IV metastatic small cell cancer admitted for severe hyponatremia after 3rd day of first cycle of carboplatin etoposide. Home medications include cyclosporine, levothyroxine, pantoprazole, amlodipine, carvedilol, prednisone, lisinopril, and furosemide as needed basis only. She was complaining of new onset nausea, anorexia, mild abdominal discomfort, worsening fatigue and edema. Admission vitals were temperature of 97.7 f, blood pressure of 118/73 mm Hg, heart rate of 76 bpm, respiratory rate of 16 per minute and saturating 97 percent on room air. Examination shows tenderness at right quadrant and 2 + edema. Admission laboratory results showed serum sodium 119 meq/l, potassium 5.4 meq/l,

chloride 86 meq/l, bicarbonate 15, BUN 58 mg/dl, creatinine 1.71 mg/dl, ionized calcium 0.9 mmol/l, serum magnesium 1.4 mg/dl, white blood cells of 5.72 x 10^3 cells/ µL, Hemoglobin is 10.8 g/dl, Platelets 189 x 10^3 /L, total protein 5.3, albumin is 3.3 mgd/l. hyponatremia work up showed serum osmolarity 270 mosm/kg, TSH 6.9 IU/ml, random cortisol 4.5 µg/dL, serum uric acid 0.7 mg/dl, urine sodium <20 mmol/L, urine osmolarity 305 mosm/kg, random urine uric acid is 3 mg/dl, urine uric acid and creatinine ratio is 0.16 mg/mg, fractional excretion of Urea 26.7%, fractional excretion of uric acid is 16%. Antihypertensives were held and sodium polystyrene sulfonate was given on admission. Sodium was not improving after 1.4 liters of normal saline was given (119 > 120 > 119 meq/l). Immediately 2% hypertonic saline and furosemide was given. Within 36 hours, symptoms were resolved and patient was discharged in 4 days with sodium of 135 and creatinine of 1.1 mg/dl

Discussion: Literature was limited with carboplatin associated hyponatremia. Although multifactorial, two most important differentials to distinguish were SIADH and salt wasting nephropathy as treatment varies. Our case illustrates the difficulty of diagnosing salt wasting nephropathy from carboplatin, but treatable.

PUB310

Lymphocytic Hypophysitis: A Challenge to Diagnose Postpartum

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Introduction: Hypernatremia during pregnancy is not commonly encountered. Additionally, differentiating between transient diabetes insipidus of pregnancy from central or nephrogenic diabetes insipidus during pregnancy poses additional dilemma. Moreover, lymphocytic hypophysitis as an etiologic disorder contributing to the hypernatremia is rare. Here, we report a complex case of lymphocytic hypophysis diagnosed postpartum.

Case Description: A 32 year old, 37 weeks pregnant female underwent emergent cesarean section due to concerns for fetal compromise and acute fatty liver of pregnancy. Preoperative labs were notable for acute kidney injury (creatinine 3.3mg/dL), elevated liver enzymes (AST 259 U/L, ALT 536 U/L, TB 5.1 mg/dL), significant coagulopathy, and hypoglycemia. Her presenting sodium was 141 mmol/L which progressively increased and peaked to 156 mmol/L post operatively with 5 to 7L urine output daily. Per patient, for approximately 1.5 weeks prior to presentation, she had been experiencing significant polyuria and polydipsia. Urine osmolality was 137 mosm/kg. At first, her hypernatremia was attributed to transient gestational diabetes insipidus associated with pregnancy amplified by acute fatty liver of pregnancy, however further workup changed the diagnosis to central diabetes insipidus secondary to hypophysitis due to ACTH <5pg/mL, A.M. cortisol 0.8 ug/dL, FSH 0.3IU/L, LH <0.1IU/L, TSH 0.28uL/mL, and FT4 0.6ng/dL. Furthermore, MRI of the brain revealed absence of the normal pituitary bright spot, and thickened pituitary stalk. She was started on prednisone, ddavp, and levothyroxine and did well. Six months postpartum her MRI brain revealed resolution of the thickened pituitary stalk, reappearance of the pituitary bright spot, as well as a smaller pituitary gland. She still remains on oral desmopressin as well as levothyroxine supplementation.

Discussion: Diagnosing lymphocytic hypophysitis in the postpartum period can be a challenge. Although rare, most cases occur in late pregnancy or in the postpartum period and one must keep this in the differential when evaluating a pregnant or postpartum woman with hypernatremia. Multidisciplinary team approach and expertise involving the endocrinologist, nephrologist, and obstetrician is important for quick diagnosis and for prompt treatment to avoid life threatening complications that could ensue.

PUB311

The Use of Serum Sodium–Chloride Difference in the Evaluation of Metabolic Acidosis in Hospitalized Patients

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Background: Metabolic acidosis is generally defined by the presence of a low serum bicarbonate concentration. (It is hypothesized that metabolic acidosis would cause a compensatory decrease in the serum chloride (Cl) relative to sodium (Na) in order to preserve electroneutral balance.) Therefore, the purpose of our study was to investigate the use of Na-Cl difference or ratio as a bedside tool to evaluate the identifying metabolic acidosis in hospitalized patients as an alternative to measuring serum bicarbonate.

Methods: We retrospectively enrolled 17,320 adult patients who were admitted to the academic teaching hospital from January 2013 to December 2013. Serum Na, Cl, and bicarbonate were measured at admission and Na-Cl difference, Cl-Na ratio and corrected anion gap was calculated. Metabolic acidosis was defined as a bicarbonate below 23mEq/L.

Results: Metabolic acidosis occurred in 4488 (25.9%) of samples. Significant Spearman correlation coefficients were found between Na-Cl difference and corrected anion gap, and serum bicarbonate. Receiver operator characteristic curve showed that values revealing metabolic acidosis were less than 32.5 mEq/L for Na-Cl difference with sensitivities of 94.0% and specificity 90.0%. Additionaly, multivariate logistic regression analysis showed that Na-Cl difference levels at admission were independently associated with AKI and in-hospital mortality.

Conclusions: Na-Cl difference are simple and fast, and can be used as an alternative tool to identify metabolic acidosis in hospitalized patients.

PUB312

Edema Assessment of Dialysis Patients by Bioelectrical Impedance Analysis

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Background: Bioelectrical impedance analysis (BIA) is useful for assessment of body fluid status but it is rarely used in Chinese haemodialysis (HD) patients. So it is the first time to discuss the validity of BIA in Chinese HD patients. The aim of this study was to describe fluid status and volume overload in maintenance hemodialysis (MHD) patients with edema index (EI) by means of the bioelectrical impedance analysis (BIA) and to explore the associating factors of edema index (EI) in MHD patients.

Methods: Cross-sectional study design was used and 193 MHD patients in a hemodialysis center in China were enrolled. Body components were measured by using the body component analyzer MC-180 after dialysis. EI were calculated by using the ratio of extracellular water (ECW) to total body water (TBW). Age, urine volume, Kt/V, ultrafiltration volume, and nutritional biomarkers (albumin, feritin and creatinine) were collected. Descriptive statistics and multivariate logistic regression analysis were used to analyze the associating factors of the EI.

Results: There were 118 males and 75 females, with an average age of 50.22 ± 12.55 years and an average HD period of 60(3~216)months in this study. Sixty patients (69.77%) were indicated volume overload according to the standard of EI in neither diabetes nor hypoproteinemia group. Eighty-eight patients (92.63%) in diabetes or hypoproteinemia group and 12 patients (100%) in both diabetes and hypoproteinemia group were indicated volume overload respectively according to the EI in each group. Multivariable logistic regression analysis results were presented in figure 1.

Conclusions: The prevalence of volume overload is high in MHD patients especially in patients complicating with both diabetes and hypoproteinemia. Age, gender, dialysis age, Kt/v, muscle mass and body mass index are related with patients' fluid status. Edema index (EI) appears to be an easy and useful marker for the estimation of fluid status and volume overload in MHD patients with various clinical backgrounds.

Funding: Other NIH Support - This study was supported by a grant from Guangdong Science & Technology Department, China (No. 2017ZC0028).

Figure 1 Associating factors of the edema index (EI)

	OR	*95%CI*	*p*
Group 1			
Age	1.078	1.001～1.161	0.048
BMI	2.205	1.466～3.317	p<0.001
Female	0.007	0.001～0.217	0.005
Muscle mass	0.575	0.451～0.733	p<0.001
Group 2			
Female	0.001	0.0001～0.5240	0.030
Dialysis age	0.555	0.310～0.996	0.049
Kt/v	0.111	0.017～0.699	0.019
Muscle mass	0.685	0.483～0.973	0.035

*Group 1: neither diabetes nor hypoproteinemia group
Group 2: diabetes or hypoproteinemia group

PUB313

The Relationship Between Liver Cyst Volume and QOL in Japanese ADPKD Patients

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Background: To clear the relationship between the size of liver cysts and QOL in ADPKD patients, we started the prospective longitudinal study to clear the impact of liver cysts on QOL during 3 years.

Methods: This multi-institutional, prospective, observational study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, from the Ministry of Health, Labour and Welfare of Japan. We divided the included ADPKD patients into 4 groups (group A; control group < 25 %, group B; 25-49 %, group C; 50-75 %, group D; >75 %) according to liver cysts-parenchyma ratio (CPR). QOL was measured by FANLTC + FACT-Hep additional concerns for assessing general health-related QOL and liver-specific QOL, respectively. We compared QOL scores between groups during 3 years.

Results: We included 111 patients in this study. There are no significant differences between groups in eGFR ($p = 0.368$) and CKD stage ($p = 0.380$). At the time of enrollment, the FANLTC score ($p = 0.039$) and the FACT-Hep scores ($p < 0.001$) were significantly inversely correlated with liver CPR. With respect to the change of QOL score during study period 3 years, the larger liver CPR, the significantly decreased FANLTC score during 3 years ($p = 0.0011$, Figure 1). The trend test showed that FACT-Hep score also decreased significantly as the liver CPR became larger ($p = 0.0002$, Figure 2).

Conclusions: In this cross-sectional report, we could clear the long-term influence of the liver cyst volume on QOL in ADPKD patients.

Funding: Government Support - Non-U.S.

Figure 1

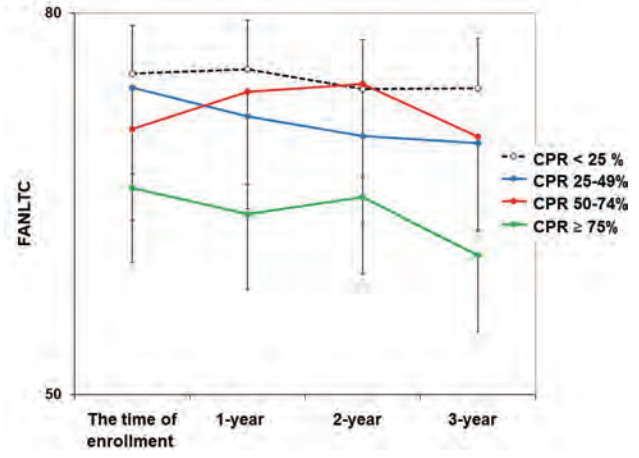
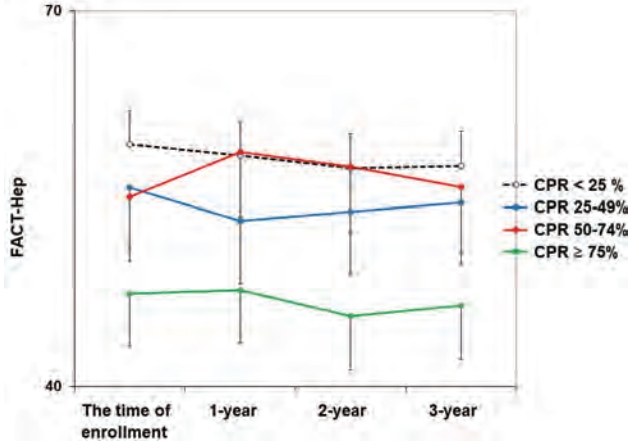


Figure 2



PUB314

Progression of Renal Function and Total Kidney Volume in Japanese ADPKD Patients: An Analysis of Data from Japanese Polycystic Kidney Disease Registry (J-PKD)

Satoru Muto,[1] Toshio Mochizuki,[2] Ken Tsuchiya,[3] Saori Nishio,[4] Kazushige Hanaoka,[9] Yoshifumi Ubara,[10] Kazuhiko Tsuruya,[5] Eiji Ishimura,[6] Tadashi Sofue,[8] Ichiei Narita,[11] Shoichi Maruyama,[7] Shigeo Horie.[1] *[1]Juntendo University, Tokyo, Japan; [2]Tokyo Woman's Medical University, Tokyo, Japan; [3]Tokyo Women's Medical University, Shinjuku-ku, Japan; [4]Hokkaido University, Sapporo, Japan; [5]Nara Medical University, Kashihara, Japan; [6]Meijibashi Hospital, Matsubara-shi, Japan; [7]Nagoya University Graduate School of Medicine, Nagoya, Japan; [8]Kagawa University, Kita-gun, Japan; [9]The Jikei Daisan Hospital, The Jikei University School of Medicine, Komae, Tokyo, Japan; [10]Toranomon Hospital, Tokyo, Japan; [11]Niigata University, Niigata, Japan.*

Background: The PKD Sectional Committee of a Grant-in-Aid for Progressive Renal Diseases Research, from the Ministry of Health, Labour and Welfare of Japan started the web-based, and prospective registry system, the Japan PKD Registry (J-PKD) in 2009, to record clinical, and laboratory data about PKD in Japan. Follow-up period of five years has been completed in all cases. We will report the final data of J-PKD registry.

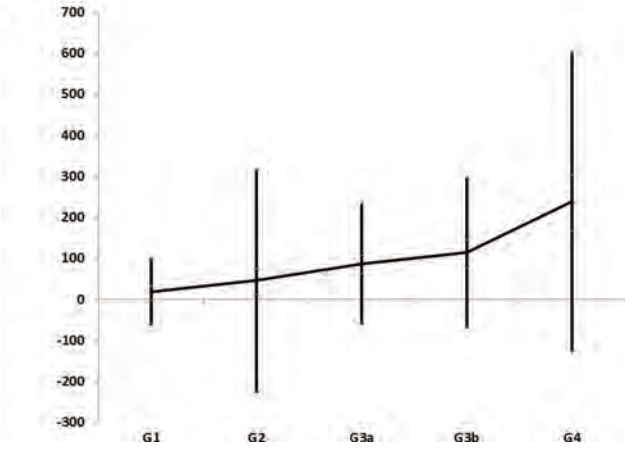
Methods: Patient data including age, gender, family history, complication, medical history, laboratory data, and clinical diagnoses were electronically recorded at each institution and registered on the J-KDR webpage via the Internet Data and Information Center for Medical Research system, which is part of the University Hospital Medical Information Network.

Results: We included 339 patients in this study (215 female and 124 male). Median age was 51.0 years. The mean eGFR was 50.4 ml/min/1.73m^2 at the time of enrollment. The mean annual amount of eGFR change (ΔeGFR/Y) was -3.1 ml/min/1.73m^2. There are no significant differences in ΔeGFR/Y between CKD stage (P = 0.3393). The mean total kidney volume (TKV) was 1683.6 ml at the time of enrollment. The mean annual amount of TKV change (ΔTKV/Y) was 92.1 ml. There are significant differences in ΔTKV/Y between CKD stage (P = 0.0041, Figure). ΔTKV/Y was significantly inversely correlated with ΔeGFR/Y (P < 0.001). In cases with TKV ≥ 750ml, the annual decline rate of eGFR in patients with the rate of TKV growth ≥ 5 % was significantly faster compared with the patients with the rate of TKV growth < 5 % (< 5 %: -3.21 ± 3.66 ml/min/1.73m^2/Y, ≥ 5 %: -4.53 ± 4.26 ml/min/1.73m^2/Y, p = 0.0383).

Conclusions: In this cohort study, we will clear the natural course of renal function and TKV in Japanese ADPKD patients.

Funding: Government Support - Non-U.S.

Figure



PUB315

Rapidly Progressive Kidney Dysfunction Due to Tubulointerstitial AL Amyloidosis with Concurrent Apolipoprotein A-I/A-IV Amyloidosis in a Case of Autosomal Dominant Polycystic Kidney Disease

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Introduction: AL or AHL amyloidosis usually cause paraprotein deposition mainly in glomerulus, whereas deposition of apolipoprotein A-I (ApoA1), and apolipoprotein A-IV (ApoA4) amyloidosis mainly occurs in renal tubulointerstitium (TI). Here, we describe a rare case of autosomal dominant polycystic kidney disease (ADPKD) who developed rapidly progressing non-proteinuric kidney disease which can be attributed to AL amyloidosis with concurrent apolipoprotein A-I/A-IV amyloidoses.

Case Description: A 54-year-old man was referred to our hospital for chronic kidney disease (CKD) with a serum creatinine (sCr) of 1.26 mg/dL. With multiple kidney cysts, and family history, we diagnosed as ADPKD. However, his kidney function declined too rapidly for ADPKD with sCr of 2.57 mg/dL in 1 year. Since his serum free kappa light chains were markedly elevated, with increased kappa-to-lambda light chain ratio, he underwent open renal biopsy, which revealed massive amorphous deposits confined to the TI, which stained positive for Congo red, sparing the glomeruli. Immunofluorescence showed dominant staining of the kappa light chain deposits. Electron microscopy revealed randomly arrayed straight 8- to 10-nm-thick fibrils. Bone marrow biopsy revealed amyloid deposits, and he was diagnosed as primary AL amyloidosis and underwent autologous hematopoietic stem cell transplantation. Unfortunately, he died of sepsis. Subsequently, mass spectrometry analysis revealed that extensive amount of ApoA1 and ApoA4 were also present in TI as well as kappa light chains. Hence, we conclude that our case was concurrent AL, ApoA1 and ApoA4 amyloidoses, with the latter being the main pathophysiology based on the mass spectrometry finding.

Discussion: Accurate diagnosis of amyloidosis is of paramount importance to avoid unnecessary treatment regimens. Even if renal biopsy suggests AL amyloidosis, mass spectrometry may unmask the complication of other type of amyloidosis, which can be useful to predict prognosis, and response to therapy. To our knowledge, this is the first report describing the case with ADPKD who suffered from several types of amyloidosis coexisting together.

PUB316

Continuously Evolving Phenotype of Fetal Presentation of HNF1B Gene Deletion

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Introduction: *HNF1B* mutations, consisting usually of heterozygous microdeletions (1.4-1.5KB) at 17q12 with variable penetrance dominant inheritance in 30-40%, are the most common genetic cause for fetal hyperechogenic kidneys(20-30% detection rate) and of isolated CAKUT(Congenital Anomalies of Kidneys and Urinary Tract)(5-30% mutation identification). The evolution of these renal abnormalities, their impact on renal function and appearance of extrarenal features is unpredictable.

Case Description: We present our center's experience with 5 cases with *HNF1B* mutation: Presentation consisted of fetal hyperechogenic normal-/ enlarged kidneys in2/5,

polycystic small/enlarged kidneys in 2/5 and hypomagnesemia during seizures 1/5. Molecular diagnosis with HNF1B mutation detection was performed at: 34GW(gestation week) on amniocentesis 1/5, 2yrs- for polycystic kidneys 1/5, 2yrs- during evaluation for global develoopmental delay in 2/5, at 5.5yrs –for hypomagnesemia and seizures(this patient also had had hyperechogenic kidneys on fetal ultrasound with complete normalization at the age of 2yrs). TOP(termination of preganancy) was performed on the fetus diagnosed at 34weeks on parental request. Complete normalization of kidneys' hyperechogenicity by the ages of 2-3yrs in 3/4 living patients and normal GFR at 3-7yrs(despite intial Scr↑ during first 1.5-3mo) was seen in 4/4(inlcuding the patient with polycystic enlarged kidneys). Enterococcus UTI at 3.8yrs in the patient with persistently polycystic kdineys triggerred diagnosis of bilateral grade 3-4 VUR(vesicoureteral reflux) and bladder diverticles necessitating surgical intervention. Family history: maternal seizures and autistic-spectrum-disorder- maternal aunt 1/5, MODY small-size normal functioning kidneys father 1/5.

Discussion: Spontaneous resolution of fetal hyperechogenic kidneys in patients with HNF1B mutation with complete normalization of initially slightly depressed renal function might occur. Persistent parenchymal cystic changes in patients with HNF1B mutations do not exclude normal renal function. HNF1B mutation- associated parenchymal cystic changes might coexist with urological malfomations exposing the patient to urinary infections with further kidney damage. Continuous pursuit for later-onset HNF1B-associated metabolic, neurodevelopmental abnormalities is recommended

PUB317

Preventive Strategy for ADPKD in the Southern Spain: Economic Evaluation

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the hereditary kidney disease most frequently causes renal failure. Dialysis and transplantation are the therapeutic currently used. These renal replacement therapies (RRT) entail high health expenditures. Nowadays, there is still no curative treatment for ADPKD. We aim to analyse the cost-effectiveness of preventive strategy to stop ADPKD transmission based on assisted human reproduction such as preimplantation genetic testing (PGT) that includes "in vitro" fecundation (IVF) and intracytoplasmic sperm injection (ICSI).

Methods: A comparative analysis of the costs of IVF+ICSI+PGT versus RRT cost was carried out. The RRT cost was obtained from the specialised literature. The cost of the preventive strategy was calculated by adding the costs of an assisted reproduction procedure in a public hospital and the market price of the PGT in Spain. The average cost of a standard patient during the natural course of the disease has been calculated with patients' records from the ADPKD registry of Granada (Spain).

Results: The average costs of transplantation (47,136 and 6,477 euros/year, first year and successive years respectively), haemodialysis (44,778 euros/year), and peritoneal dialysis (34,554 euros/year) are notably higher than costs of preventing the transmission of the disease (5,520-6,020 euros). An incremental cost-effectiveness ratio in favour of the preventative strategy was obtained in a scenario with three single embryo transfers.

Conclusions: From the perspective of the cost-effectiveness analysis, the preventive strategy proved to be a superior alternative to the RRTs currently applied. Thus, it would be advisable to promote the strategy of preventing transmission of this disease through assisted human reproduction and genetic testing. Despite the positive contribution of this strategy to the economic sustainability of the public health system, a decided health policy action in its favour is needed.

PUB318

What Happens in Early Stage of Autosomal Dominant Polycystic Kidney Disease? Study in an Adolescent Population

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a hereditary disease with progression to terminal Chronic Renal Disease, however the clinical findings begin in the 3rd decade of life: inability to concentrate urine, arterial hypertension and increased renal volume. There are few studies in children that analyze early markers of the disease. Objetive: to study and analyze the clinical characteristics in the initial phase of ADKPD in adolescents

Methods: -Adolescents of 12-22 years with a clinical or genetic diagnosis of ADPKD, followed in Nephrology or Pediatric consultations. -Analyzed variables: age, sex, mutation, glomerular filtration (CKD-EPI), urine osmolarity, proteinuria, hormones: Vasopressin, Aldosterone, Renin, Ambulatory blood pressure monitoring (ABPM):Dipper-No dipper pattern, kidney ultrasound:cysts and total renal volumen (TRV), health questionnaire

Results: -26 patients ADPKD: 43.5% men and 16.27±3.75 years. -46.2%PKD1, 15.4%PKD2, 38.5%without study -CKD-EPI 133,12±19,21 ml / min, Urinary osmolarity 650.8±278.08 -Cysts 12,58 ± 7,96 (0-28), TRV 343,47±129,46cc, TRV/height: 201,28±71,58 -Only 1 with previous HTA and 15.4% with low sodium diet. 61.5%Dipper Pattern. 1,42 ± 0,39 l/d of water -Dipper Pattern relationed with levels of Aldosterone (229.46±112.73 vs 97±11.31, p 0.001) and Renin (7.28±3.72 vs 3.05±1.03, p 0.036), without influencing of Vasopressin -CKD-EPI was related to: TRV (p 0.001) and TRV/height (p 0.009) -Vasopressin relationed with number of cysts (p 0.04), albuminuria (p = 0.004), proteinuria (p = 0.015) and Aldosterone (p 0.022). -In PKD1 the TRV is higher than in PKD2 (460.08±149.45 vs 228.18±14.59)

Conclusions: -Alterations urinary concentration, hypertension and deterioration of renal function are not early findings in this population. However, they have hyperfiltration, more cysts and TRV, and elevation of the renin-aldosterone, but normal vasopressin. -In patients with hyperfiltration there was an increase in TRV and Vasopressin in relation to cysts, proteinuria and aldosterone, so could be initial markers of progression. -PKD1 conditions higher TRV, but without alteration of the glomerular filtrate; so it would not be a bad prognostic factor in initial stages -We should explain to the patients general recommendations of drinking more water, low salt diet.

PUB319

CKD Patients with Autosomal Dominant Polycystic Kidney Disease or Other Inheritable Kidney Disease Have Distinct Characteristics and Higher Associated Healthcare Costs

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Background: Those with Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Inherited Kidney Disease (IKD) are an identifiable minority of chronic kidney disease (CKD) patients. Their health service utilisation (HSU) in Australia is not defined. We aimed to identify characteristics and HSU amongst patients with CKD due to ADPKD, non-ADPKD Inherited Kidney Disease (IKD) and all-CKD causes in Queensland.

Methods: Patients with ADPKD and IKD were identified from the CKD.QLD Registry (n=7,311) and a regionally matched Queensland Health CKD cohort (n=21,773) based upon ICD-10 coding. Characteristics and HSU related to hospital presentations were analysed for 5years retrospective from June 2016 with dialysis admissions/appointments and admissions for reasons other than dialysis analysed separately.

Results: 309 (1.06%) ADPKD and 277 (0.95%) IKD patients were identified from the combined cohort (n=29,084). The median age at first admission of PKD, IKD and All-CKD patients were 53.7, 47.9 and 65.7years respectfully with mean eGFR at CKD.QLD consent being 34.1, 36.5 and 40.8ml/min/1.73m^2. PKD and IKD compared to All-CKD had lower frequency of diabetes (17% vs 21% vs 48%) and cardiovascular disease (CVD; 34% vs 32% vs 46%), but similar frequency of hypertension (79%vs80%vs81%) and mean body mass index (29.8 vs 29.2 vs 31.2). PKD and IKD were also associated with a higher incidence of dialysis than the All-CKD group within that 5year period (34% vs 24% vs 9%). Median hospital admissions for reasons other than dialysis were higher in those with PKD and IKD compared to All-CKD (7 vs 8 vs 4) with similar average length of stay (3.2 vs 4.4 vs 3.6days) per admission. Median 5year healthcare costs, excluding dialysis admissions/costs, were also higher in those with PKD and IKD compared to All-CKD ($42,088 vs $45,929 vs $16,403).

Conclusions: Those with PKD and IKD are younger, with earlier stage CKD and lower prevalence of diabetes and CVD compared to other CKD patients. Despite this, they are more likely to require dialysis within 5years and have increased hospital costs.

PUB320

Can Trehalose Intake Affect the Progression of Polycystic Kidney Diseases? Insight from a Murine Experimental Study

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Background: Autophagy impairment has been recently proposed to play a central role in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). Trehalose is a natural, non-reducing disaccharide that has been shown to enhance autophagy *in vitro*. In this study, we explored whether trehalose treatment protects the kidney against cyst formation in a *Pkd1*-hypomorphic mouse model.

Methods: *Pkd1* miRNA transgenic (*Pkd1* miR TG) mice were given 2% trehalose for drinking from day 35 for eight weeks. The control groups were fed with 2% sucrose or pure water. We then compared the body weights, the relative weights of the the kidneys, the histological cystic indices, and the renal function of mice receiving different treatments. Autophagy activation was investigated by RT-PCR analysis for the expression of autophagy-related genes *atg5*, *atg12*, and *beclin1* in the whole-kidney lysates, and western blotting was performed for the detection of LC3-I to LC3-II conversion.

Results: The results showed that *Pkd1* miR TG mice have a lower mRNA expression of autophagy-related genes compared to wild-type control mice, but the differences were not reversed after trehalose treatment. Trehalose also did not significantly affect the kidney weights, cystic indices, fibrosis scores and proliferative indices. The serm levels of glucose, blood urea nitrogen, and cystatin C were not significantly different between treatment and control groups.

Conclusions: These findings suggest that trehalose treatment alone does not seem to have a significant impact on the progression of polycystic kidney disease.

Funding: Government Support - Non-U.S.

PUB321

Relationship Between Dietary Sodium and Protein Intake with Serum Copeptin in Autosomal Dominant Polycystic Kidney Disease

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Background: Elevated levels of arginine vasopressin (AVP) are hypothesised to worsen the renal progression of autosomal dominant polycystic kidney disease (ADPKD). In addition to fluid intake, dietary solute intake can also influence AVP release. However, this association has not been specifically investigated in ADPKD. This aim of this study was to determine the relationship between dietary sodium and protein intakes with serum copeptin (a marker of AVP) in patients with early-stage ADPKD.

Methods: Patients with ADPKD (18-65 years, eGFR≥30 mL/min/1.73m^2) underwent a structured diet history interview to assess usual intake over the past 3 months during the Baseline Visit of the PREVENT-ADPKD study. Sodium and urea excretion were measured from 24hr urine collections to validate diet history-reported sodium and protein intakes, respectively. Serum copeptin was measured by a sandwich immunoassay (B.R.A.H.M.S).

Results: Sixty-nine participants (37 male, age 43±11 yrs, serum creatinine 97±36 μmol/L; mean±SD) were analysed, with a subset of 29 undertaking dietary assessment. When compared to 24hr urine urea excretion, the diet history was a valid method for estimating dietary protein, as reported intakes demonstrated a strong correlation with urine-derived estimates (r=0.658; P<0.001), and there was no evidence of systematic bias by the Bland-Altman method. The median serum copeptin concentration was 5.01 (IQR: 8.41) pmol/L. Multivariate analyses (adjusted for age, gender, 24hr urine volume and serum creatinine) revealed that serum copeptin was positively correlated with 24hr urine sodium (B=0.444; P=0.010) (the gold-standard for dietary sodium intake), but not with 24hr urine urea (B=0.663, P=0.197). No association was found between serum copeptin and diet history-reported sodium or protein intake.

Conclusions: These cross-sectional, observational data support the hypothesis that higher dietary sodium (but not protein) intake stimulates AVP release in ADPKD. The ongoing PREVENT-ADPKD study will determine the combined long-term effects of adequate hydration with lowering dietary solute intake on serum copeptin and renal cyst growth in ADPKD.

Funding: Commercial Support - Danone Nutricia Research, Private Foundation Support, Government Support - Non-U.S.

PUB322

Current Patterns of Practice of Autosomal Dominant Polycystic Kidney Disease in BC

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Background: ADPKD is the most common inherited kidney disorder occurring in 1 of 400 to 1000 live births. Recently, novel biomarkers have shown promise in the literature for prediction of early disease progression such as total kidney volume (TKV). Landmark clinical trials have demonstrated the benefits of aggressive blood pressure (BP) control and specific medications such as Tolvaptan have been shown to slow disease progression. It is largely unknown if these recent breakthroughs have found their way into clinical practice. We sought to take a snapshot of 'real world' contemporary management of ADPKD, specifically assessing whether recent evidence is being incorporated into clinical practice.

Methods: This was a convenience sample of 54 patients under the care of 6 different nephrologists in 2 health authorities in British Columbia. For each patient, the dictated letter from the most recent out-patient clinical encounter was analyzed. All letters were assessed for the following quality indicators: documentation of date of renal imaging and plan for follow-up imaging, recording of TKV, consideration for Tolvaptan, BP, urine albumin:creatinine ratio (uACR), and frequency of follow-up visits.

Results: Mean (SD) age of the cohort was 51.2 (15.6) years and 48% were male. Median (IQR) eGFR was 66 (45-95) mL/min per 1.73m^2. The majority of patients (61%) had no documentation of renal imaging, and no patient had a measurement of TKV recorded. Two patients were receiving Tolvaptan and uACR was captured in 72% of cases. All patients had their medications listed and 65% were receiving antihypertensive therapy. The median BP was 123/80mmHg. The median follow-up time for patients with eGFR <60mL/min per 1.73m^2 was 6 months, compared to 11 months for patients with eGFR ≥60 mL/min per 1.73m^2.

Conclusions: Although these dictations were analyzed only at one point in time, the observed variability in care emphasizes the need for improved strategies to translate evidence-based interventions into clinical practice. This may include standardized care pathways for clinicians as well as strategies to maximize data capture such as an ADPKD registry.

PUB323

Empower PKD—What Do Patients Think?

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Background: The Establishing Meaningful Patient-centered Outcomes With Relevance for patients with Polycystic Kidney Disease (EMPOWER PKD) initiative aims to engage PKD stakeholders and patients to learn about health priorities, insurance issues, and patient engagement.

Methods: We developed and pre-tested a guide to conduct semi-structured focus groups. Participants discussed impact of PKD on daily living and identified and ranked outcomes in PKD using a nominal, multi-vote technique. Other focus group topics included insurability and factors that influence a patient's active engagement with PKD. We conducted thematic analyses using Grounded Theory.

Results: Of 57 participants, 82% were PKD patients and 13% were caregivers. Mean age was 53 (range 19-80) years with 52% female. Participants included 91% white, 4% African American, 4% American Indian, and 2% Latino. Six focus groups yielded 70 outcomes classified into six categories: kidney health, lifestyle, comorbidities, psychological impact, family and awareness, and mortality. The highest ranked outcome was slowing the progression/symptoms of PKD followed by keeping kidneys healthy, and diet. Qualitative analysis identified six over-arching themes for the impact of PKD including: decision-making, daily impact, psychological impact, testing dilemmas, healthcare related issues, and family. Variability in patient engagement and misconceptions about the disease were common. While psychological impacts were not ranked highly as target outcomes in clinical studies this was a leading theme of discussions during the focus groups.

Conclusions: Patients with PKD and their families are unique. While early diagnosis and detection is an important focus for research in kidney disease in general, the effects of "labelling" with PKD on insurability decision is a main factor that hinder patients' active participation in care and research. With a treatment now approved for use in the US, it is important to be aware that patients' views and values have pivotal effects on care. Additional exploration should consider psychological impacts of disease, expanded race/ethnicity representation and consideration of socioeconomic differences. Additionally, perspectives in the context of newly available treatments should be assessed with a focus on how to activate PKD patients who are otherwise not engaged in their care or research.

Funding: Other U.S. Government Support

PUB324

Reported Outcomes in ADPKD Studies: A Systematic Review

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Background: Studies for Autosomal Dominate Polycystic Kidney Disease (ADPKD) tend to have a wide variability in outcome measures. In this review we aim to identify different outcomes reported in ADPKD studies including composite outcomes.

Methods: We conducted a systematic review of published studies that included ADPKD patients as the main population or a main subgroup and measured renal outcomes. We searched the Cochrane Central Register (CENTRAL), OVID MEDLINE, EMBASE and Pubmed (from inception to December 2017). Our review included all studies regardless of design with ten or more participants. We excluded studies that only reported dialysis or transplant outcomes in ADPKD patients. We abstracted data in duplicate.

Results: We identified 391 records through database and grey literature searches. We included 146 records for full text screening and 87 published papers for data abstraction. Of these, we found 13 articles that reported composite outcomes. There is considerable inconsistency in the outcomes reported and how they are measured. We identified six different composite outcomes reported in these articles. These composite included: 1. 20% increase in Height adjusted Total Kidney Volume (HtTKV), Left ventricular mass index and Urinary albumin excretion, 2. time to 50% reduction of baseline estimated Glomerular Filtration Rate (GFR), end stage renal disease, or death, 3. Time to investigator-reported multiple ADPKD clinical progression events (e.g. onset or progression of hypertension, need for hypertensive treatment), severe kidney pain (requiring medical intervention), worsening albuminuria (by category), or 33% increase in serum creatinine (SCr), 4. onset/worsening of HTN, renal pain, proteinuria, 25% change from baseline renal function in reciprocal SCr levels, 5. doubling SCr, 50% reduction in GFR or need for renal replacement therapy, 6. 50% reduction in GFR, doubling of SCr, or initiation of dialysis, renal transplantation, or death.

Conclusions: There is a need to standardize outcomes in ADPKD studies. There is also a need for guidance about the appropriate components of composite outcomes in ADPKD studies. This will help comparison of results across studies especially if individual components are well defined.

PUB325

Epidemiology of Autosomal Dominant Polycystic Liver Disease (ADPLD) in Olmsted County

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Background: The incidence and prevalence of ADPLD are not known.

Methods: Mayo Clinic and Olmsted Medical Center (OMC) deliver most health care to Olmsted County residents. We searched diagnostic codes and the Mayo Clinic and OMC radiology databases to identify subjects and all medical records were reviewed to validate ADPKD diagnoses using the following criteria. A diagnosis of definite ADPLD was based on accepted radiographic findings plus a family history of ADPLD or genetic testing results; likely ADPLD, based on ≥20 liver cysts for any age; possible ADPLD, based on 5-19 liver cysts for any age; in all cases with no or only few kidney cysts. Incidence rates of ADPKD for the time period of 1980-2016 were calculated; point prevalences for the year 2010 were also calculated.

Results: We reviewed medical charts and abdominal images and/or radiology reports of 1,231 subjects with diagnostic codes of cystic liver during 1980-2016, and the medical charts and abdominal CT or MR scans of 2,765 subjects with multiple liver cysts from radiology databases during 1997-2016. In total, 134 patients with incident ADPLD (0 definite, 35 likely, 99 possible ADPLD) were identified during 1980-2016. Only 8 patients among 35 likely ADPLD and no patients with possible ADPLD had symptomatic hepatomegaly (total liver volume ≥ 2000 ml). Overall age- and sex-adjusted annual incidence rate of likely ADPLD was 1.01 (95%CI: 0.67 to 1.35) and that of likely or possible ADPLD was 4.01 per 100,000 person-years (3.32 to 4.69). The annual incidence rates of likely ADPLD increased gradually over time and those of possible ADPLD have increased markedly since 1997 when CT and MR scans became available electronically. Annual incidence rates of ADPLD were not different between females and males. On January 1, 2010, the overall age- and sex-adjusted prevalence of likely or possible ADPLD was 36.0 (25.3 to 46.6) and that for likely ADPLD alone was 9.5 (4.1 to 14.9) per 100,000 population.

Conclusions: The incidence rate of ADPLD with symptomatic hepatomegaly was very low. Incidence rates of likely or possible ADPLD have increased over time, possibly because milder cases of ADPLD have been increasingly detected with more frequent and better radiology imaging. Incidence and prevalence of ADPLD including mild cases of ADPLD may have been underestimated.

PUB326

Genetic Studies of Nephropathies with a Public Grant Funding in a Developing Country: A 3-Year Experience in an Academic Unit

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Background: Implementation of genetic tests has diverse ongoing challenges that are even greater in developing countries. Since the human genome was published, many genes have been discovered by Sanger sequencing (SS) in association with diseases. Actually, next-generation sequencing (NGS) technology is displacing SS, but although costs have decreased, they remain high for developing countries and any NGS derived-variant should be validated by SS. Here we describe the 3-yr experience in the Nephrology Unit at a Chilean university that received a US$140.000 as a public grant to perform genetic studies of particular nephropathies.

Methods: Tests were implemented for 17 genes by SS technology (PKD1, PKD2, PKHD1, NPHS2, NPHS1, WT1, INF2, ACTN4, TRPC6, APOL1, WNK4, KANK1, ARHGEF17, CTNS) or NGS technology (COL4A3, COL4A4, COL4A5), associated with autosomal dominant and recessive polycystic kidney disease (ADPKD/ARPKD), steroid-resistant nephrotic syndrome (SRNS), focal and segmental glomerulosclerosis (FSGS), Alport syndrome (AS), Wilms tumor (WT) and nephropathic cystinosis (NC). The study was approved by the local Ethics Committees of Health Service and university to be offered to 120 cases with one of the diseases with a proven clinical utility.

Results: Until date, a genetic defect has been identified in 20/41 ADPKD, 1/1 ARPKD, 21/56 SRNS-FSGS, 7/17 AS, 2/4 WT1 and 1/1 NC cases, reaching a 43% (52/120) detection rate. In 92% (48/52) of these cases, the defect was located in a causative gene, mainly PKD1 and NPHS2, and at least one clinical utility was proposed, in terms of diagnosis, prognosis, management, genetic counseling or transplantation. The major challenges were genetic heterogeneity (SRNS-FSGS), sporadic unavailability of long-range PCR reactives (ADPKD) and elevated costs of NGS technology (AS).

Conclusions: We consider this experience valuable to design an NGS strategy targeting the almost 50 genes associated with the diseases of interest and consider the genetically resolved/unresolved cases as a validation/discovery cohorts, respectively. Nephrologists in Chile are aware of the utility of genetic tests and more efforts need to be done in order to make NGS more accessible and affordable or to be able to establish local cost-effective genetic test algorithms, in benefit of the patients and their families.

Funding: Government Support - Non-U.S.

PUB327

Evaluation of Cost Drivers in the Management of Patients with Polycystic Kidney Disease Prior to the Development of ESKD in an Irish University Hospital

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Background: Economic evaluation of treatment in PCKD focuses on cost associated with ESKD. Considerable costs arise pre ESKD. We conducted the following retrospective study to define the clinical characteristics and main pre ESKD cost drivers of prevalent patients with ESKD as a result of PCKD at a single Irish University Hospital.

Methods: The medical record of all prevalent ESKD patients with PCKD was retrospectively reviewed to first referral. Prior ESKD followup was divided into 6 month bins and outpatient laboratory tests and clinical data closest to these was abstracted. eGFR was calculated using the MDRD formula.

Results: Of the 51 patients identified, 30 (59%) were female; the mean (sd) age was 56 (12) yrs. 33 (65%) had a reported family history of PCKD. Patients had first attended the renal outpatients a median (IQR) of 6 (3-11) yrs prior to developing ESKD and were treated for ESKD for a median (IQR) of 6 (3-12) yrs. 40 (78%) underwent renal transplantation, with a median (IQR) interval of 1 (0-3) yrs from the development of ESKD. During OPD follow up prior to commencing renal replacement therapy, the median (IQR) eGFR declined from 37.0 (26.5, 57.2) to 7.3 (5.1, 9.3) ml/min per 1.73m^2. The median (IQR) individualized rate of loss in eGFR pre ESKD was 4.7 (3.4, 6.0) ml/min per 1.73 m^2. 3 subjects had a rate of loss of eGFR of 10ml/min per 1.73m^2 per year or greater. The median (IQR) number of prescribed antihypertensive agents rose from 1 (0,2) to 2 (1,3) over per ESKD follow-up. At initial OPD visit the proportion of patients treated with an ACE inhibitor/ARB, Beta blocker or Calcium channel blocker were 30%, 20% and 24% respectively and pre dialysis was 61%, 31% and 55% respectively. At initial and end of pre ESKD OPD follow-up 28% and 23% reported persistent renal pain. 31 patients (61%) were treated with erythropoietin prior to developing ESKD, 20 for 1 year or less, 3 for 2 years and 8 for 3 or more years. 13 (26%) were treated pre ESKD with calcium free phosphate binder. Over follow-up 10 (20%)required a nephrectomy.

Conclusions: Patients with PCKD have substantial utilization of costly treatments pre-ESKD (erythopoetin, calcium free phosphate binders, nephrectomy). These costs and their minimization will substantially influence the relative cost effectiveness of primary therapy in PCKD.

PUB328

APOL1: A "Novel" Gene Underlying Kidney Disease in Chile?

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Introduction: *APOL1* G1 risk allele is common among the African population since they confer resistance to *Trypansoma brucei*. Two G1 alleles are associated with kidney disease with focal and segmental glomerulosclerosis (FSGS). *APOL1* G1 allele is unevenly distributed and is very frequent in the African (American) population, but is considered very rare (<0.6%) in other populations. The genetic basis of FSGS Chilean patients has been associated mainly with *NPHS2*. Since 2014 Chile is experiencing an unprecedented 20-fold increase of Haitian immigrants, looking for better life quality. Haitians have 92% median African ancestry and the role of *APOL1* G1 allele in this population has been barely investigated. Here we describe 3 cases residing in Southern Chile who had proteinuria and resulted to be carriers of the G1 allele.

Case Description: Patient #1: 27yrs old man (APOL1 G1/G1) debuted with nephrotic syndrome when he was 20yrs. His renal biopsy was compatible with FSGS. He was unresponsive to prednisone and cyclosporine A and progressed to ESRD requiring hemodialysis. His younger sister presented hypertension, an FSGS-compatible biopsy and analysis confirmed the same genotype. **Patient #2**: 17yrs old man (APOL1 G1/G0) who had been nephrectomized as a newborn, debuted with nausea and vomits when he was 16yrs. His exams revealed an important persistent proteinuria and biopsy was compatible with FSGS. **Patient #3**: 30yrs old Haitian woman (APOL1 G1/G0) with a 28-wks old pregnancy was admitted at Hospital with moderate hypertension and proteinuria. Given that intrauterine growth restriction was observed, childbirth was induced with an extremely low birth weight (<1000gr).

Discussion: Chilean population has a 3% African ancestry that decreases from North to South, related to the historical Spanish conquest slavery. We confirmed two Chilean patients carrying the *APOL1* G1 allele and a third case of a Haitian pregnant woman, who developed kidney disease as adults. To our knowledge, these are the first cases in Chile, but studies with a more representative cohort are required. The clinical value of APOL1 risk alleles in kidney disease is still uncertain and second hits remain unknown. More evidence is needed before considering the *APOL1* status as an input to define a therapeutic option.

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PUB329

NPHS2 Gene Mutations and Nephrotic Syndrome in Children and Adults in Kuwait

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Background: Genetic testing in nephrotic syndrome (NS) has implications for clinical course, treatment response, risk for post-transplant proteinuria and prenatal diagnosis. The commonly studied rs61747728 NPHS2 gene polymorphism also known as p.R229Q has been reported to be associated with NS. Others failed to report an association, probably due to population differences. Genetics of NS havenot been studied in this part of the globe. We decided to start this journey by investigating the prevalence of the p.R229Q variant.

Methods: Inclusion criteria were: 1. Proteinuria (>3 g/24hrs) in children and >1g/24hrs in adults 2. Biopsy diagnosis of MCD or FSGS 3. No secondary causes of FSGS at the time of diagnosis. 2-5ml of blood were collected from patients. DNA was extracted following standard protocols. Genotyping was performed by Real-time TaqMan Allelic Discrimination Assay (Life technologies, CA, USA).

Results: A total of 51 patients and 4 controls were studied. 19/51 females and 32/52 males. 13/51 were Kuwaiti and the rest from diverse nationalities. 20/51 were > 40 years of age and 31/51 were < 40. 7/51 were < 20. 5/51 patients were heterozygotes for the R229Q gene polymorphism(9.8 %), with a broad age range 15-64. All were females from 3 different nationalities one of whom was Kuwaiti, 15 years of age. 3 had a tissue diagnosis of MCD and 2 were labelled as FSGS. 3 patients improved with steroids and continue to show stable renal function, whilst 2 showed no improvement with steroids or other immunosuppresants and continue to have a rise in serum creatinine. None are on dialysis or have a family history of kidney disease.

Conclusions: The data presented is the first attempt at studying genetic associations of NS in Kuwait. Mutations in NPHS2 in our population account for 9.8% of all our cases, similar to results reported by other groups. Although our sample is comparatively small, the plan is to obtain a total of 100-150 DNA samples by the end of 2018 and study mutations of other genes associated with NS eg INF2, WT-1 etc.. to uncover the genetic susceptibility in our population. Furthermore, we will attempt to sequence these genes to find out if susceptibility loci are similar to other authors. Ultimately we will perform whole exome sequencing to uncover other genes that might be unique to our population.

Funding: Government Support - Non-U.S.

PUB330

Uromodulin Mutation Is the Major Cause of Autosomal Dominant Tubulointerstitial Kidney Disease

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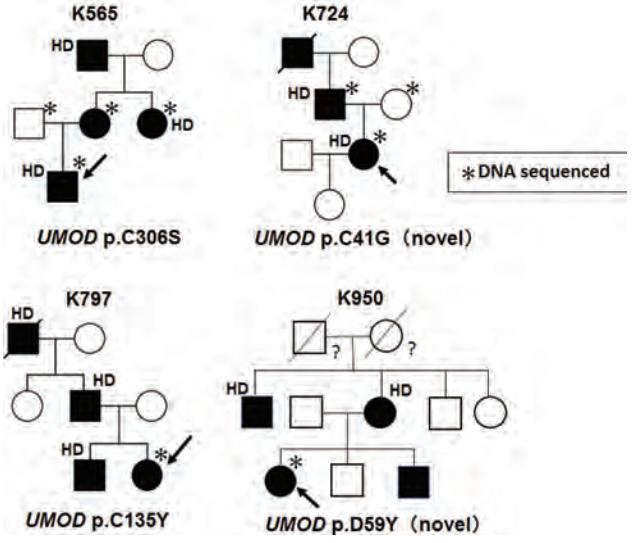
Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of conditions characterized by autosomal dominant inheritance, pathologic changes of tubular and interstitial fibrosis, and progressive renal failure. Uromodulin (UMOD) is known as one of the causes of ADTKD (ADKTD-UMOD) that is also known as juvenile hyperuricemia. Precise diagnosis is difficult without genetic testing.

Methods: We previously developed a comprehensive genetic testing panel using next generation sequencing (NGS) covering 166 genes responsible for vast majority of inherited kidney diseases. Ten families suspected of ADTKD were genetically screened with the panel. Clinical and laboratory data were collected and analyzed.

Results: We identified causal mutations in *UMOD* in four ADTKD families (40%), and excluded simultaneously other candidate genes for ADTKD such as *MUC1*, *REN*, and *HNF1B*. One male and 3 females were included in the four probands (n=4). Age (±SD) at diagnosis was 33.7 (±10.3), and 2 had end-stage renal disease (ESRD). Mean serum urate concentration was 5.42 mg/dl (±1.08). The detail of the detected heterozygous mutations in *UMOD* were C41G, D59Y, C135Y, and C306S, which include two novel mutations (C41G and D59Y).

Conclusions: Four ADTKD-UMOD families including two with novel mutations were detected. We guess a great deal of ADTKD-UMOD cases may be overlooked or misjudged as nephrosclerosis or other kidney diseases because genetic testing on ADTKD is not necessarily conducted. Autosomal inheritance reminds us larger prevalence of ADTKD-UMOD. When we face to cases with familial renal failure with less abnormalities of urine tests, ADTKD should be considered.



PUB331

Alport Spectrum Disorders in Croatia – Preliminary Results of First Genetic Testing in Croatia

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Background: Alport syndrome (AS) and thin glomerular basement nephropathy (TBMN) are part of phenotypic and genotypic spectrum of COL4A3, COL4A4 and COL4A5 mutation disorders. Until beginning of our project "Genotype-Phenotype correlation in Alport's syndrome and Thin Glomerular Basement Membrane Nephropathy", founded by Croatian Science Foundation, genetic testing for Alport spectrum disorders (ASD) was not performed in Croatia and diagnosis of ASD relied solely on kidney biopsy analysis. Here we present preliminary results of first Croatian systematic genetic testing of ASD.

Methods: We are conducting multidisciplinary, nationwide, collaborative research in seven leading Croatian nephrology, pediatric nephrology and nephropathology institutions. We are collecting clinical data, about both renal and extra-renal symptoms, histological data (including staining for collagen IV α1, α3 and α5 chains), as well as, performing genetic counselling and family study data collection on Croatian AS and TBMN patients. The next generation sequencing (NGS) for COL4A5, COL4A4 and COL4A3 gene mutation screening are performed at molecular laboratory at Department of Pathology and Centre for Translational Research, University of Zagreb School of Medicine.

Results: We have identified 337 AS and TBMN patients (age range 2-80) by search of patients' records and data registries. From 337 patients, 158 have accepted to participate in genetic testing. Additionally 87 family members were enrolled in the study. Up to present day we have tested 90 index patients and 40 family members by NGS method. There was 25 (19.2%) patients and family members with mutations in COL4A3, 6 (4.6%) in COL4A4 and 33 (25.4%) in COL4A5. No mutation was found in 66 (50.8%) patients and family members.

Conclusions: Correct and early diagnosis, genetic counselling, and appropriate monitoring and management are essential for management of ASD patients. Our goal is to clarify Croatian Alport spectrum patients histologically, genetically and clinically and ultimately create ASD registry with clinical, histological and genetic and follow up information.

Funding: Government Support - Non-U.S.

PUB332

Two Novel OCRL Gene Mutations in Chinese Patients with Lowe Syndrome and Literature Review

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Background: To analyze the clinical and genetic features of Lowe syndrome carrying *OCRL* mutation.

Methods: The clinical findings and results of genetic studies were retrospectively reviewed for 2 male patients diagnosed with Lowe syndrome, and relevant literatures about *OCRL* mutation were reviewed in this article.

Results: Two male patients all presented with low molecular proteinuria, renal tubular acidosis, hypercalciuria and rickets. Patient 1 did not have obviously extra-renal symptoms, but was found to have mild cataract by a meticulous ophthalmological examination, MRI found cerebral hypoplasia. Patient 2 was found to have abnormal vision and congenital cataract soon after birth and treated by surgery. MRI showed the reduction of brain white matter and the slight dilation of lateral ventricle. Two novel *OCRL* gene mutations were detected. A homozygous missense mutation c.1514G>T(p.G505V) was found in exon 15 of *OCRL* gene in Patient 1, *OCRL* gene 13-24 exon deletion mutation was detected in Patient 2. Both mutations were never reported previously.

Conclusions: Lowe syndrome is characterized by the triad of congenital cataracts, severe intellectual impairment, and renal tubular dysfunction. *OCRL* gene analysis is helpful for the early diagnosis of the disease, as well as providing better genetic counseling and prenatal diagnosis for the proband families.

PUB333

Genetic Variants of Familial Hematuria Associated Genes in Families with Hematuria with Probands Diagnosed with IgA Nephropathy

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Background: Familial hematuria (FH) are genetic disorders characterized by persistent hematuria during childhood, including Alport syndrome (AS) caused by mutations in *COL4A3*/*COL4A4*/*COL4A5*, CFHR5 nephropathy caused by mutations in *CFHR5*, etc. Some FH patients with IgA deposits in the glomerular mesangium could be diagnosed with IgA nephropathy (IgAN) when they either lack examinations of renal ultrastructure or have normal renal ultrastructures. This study aims to examine genetic variants of FH associated genes in 3 families with hematuria with probands diagnosed with IgAN.

Methods: The probands diagnosed with IgAN and their family members from 3 families with hematuria were examined for genetic variants of FH associated genes by next generation sequencing. Genetic variants were verified by Sanger sequencing, and their pathogenicities were verified by bioinformatic analyses.

Results: A heterozygous mutation in *CFHR5*, 533A>G (Asn178Ser), was identified in Family one's proband and his father, but it wasn't found in his mother. A pathogenic mutation in *COL4A5*, 566G>T (Gly189Val), was detected in Family two' proband, and it was also found in his mother, sister and daughter, but it was detected in neither his father nor his nephew. Two heterozygous pathogenic mutations, *COL4A5* 539G>A (Gly180Glu) and *CFHR5* 508G>A (Val170Met), were identified in Family three's proband. *COL4A5* Gly180Glu was also detected in her sister, daughter and maternal nephew, but it was found in neither her oldest son nor youngest son. A heterozygous *CFHR5* Val170Met was found in her oldest son, sister and maternal nephew, but it was detected neither her daughter nor her the youngest son. *CFHR5* Asn178Ser is an uncertain significance. *COL4A5* Gly189Val, *COL4A5* Gly180Glu and *CFHR5* Val170Met were predicted as pathogenic mutations. So Family two' proband was diagnosed with XLAS, and Family three XLAS combined with *CFHR5* nephropathy.

Conclusions: It is necessary to examine genetic variants of FH associated genes in families with hematuria with probands diagnosed with IgAN.

Funding: Government Support - Non-U.S.

PUB334

Opinions of African American Hypertensive Veterans and VA Primary Care Physicians Regarding APOL1 Genetic Testing

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Background: A high-risk apolipoprotein (*APOL1)* genotype predisposes African-American (AA) individuals with hypertension to kidney disease. Although studies have shown that knowledge of genetic risk increases the likelihood of preventive health behaviors, *APOL1* genetic testing is not part of routine hypertension management among AA patients. In order to understand the feasibility of implementing genetic screening at the Veteran Administration (VA), we assessed perceptions of Veterans and VA primary care providers (PCP) about kidney disease, blood pressure (BP) management, race, and genetic testing.

Methods: Ten PCP and ten AA hypertensive Veterans were interviewed at the Saint Louis VA Medical Center. Interview transcripts were coded to identify themes and compared between patients and PCP using a phenomenological approach.

Results: AA subjects had significant awareness of kidney disease and hypertension. They did not have an awareness of the genetic link between race and risk for kidney disease. PCPs had more knowledge of genetic/ancestral risk of hypertension but mostly not of kidney disease. They often stated that they needed more information about the role of *APOL1* variants. PCP tended to believe that AA Veterans generally had poor BP management due to health care habits and compliance. AA patients varied in BP management and were more open to genetic screening while PCP had concerns about cost, insurance, organizational constraints and ethical issues. PCP were agreeable to *APOL1* testing, however, in most cases only if they had more information on how screening would change their practice. Many AA patients said that if they were found to have *APOL1* high-risk genotypes, that they would commit to new strategies to prevent kidney disease.

Conclusions: AA hypertensive Veterans had good knowledge about the pathway from hypertension to kidney disease. Veterans and PCP were mostly agreeable to *APOL1* genetic testing to learn about risk of kidney disease and engage in preventative behavior, but stated a need for more education. These results are preliminary, given the small sample size.

Funding: Veterans Affairs Support

PUB335

Myelin Bodies in LMX1B-Nephropathy

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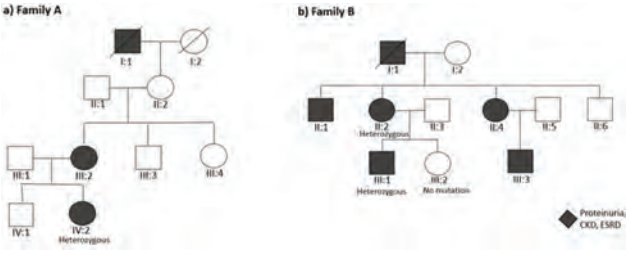
Introduction: Mutations in *LMX1B* have been found in families with isolated nephropathy without extrarenal abnormalities. We describe 2 families with autosomal dominant (AD) nephropathy due to heterozygous *LMX1B* c.737G>A, p.R246Q variant who unexpectedly had myelin figures in electron microscopy.

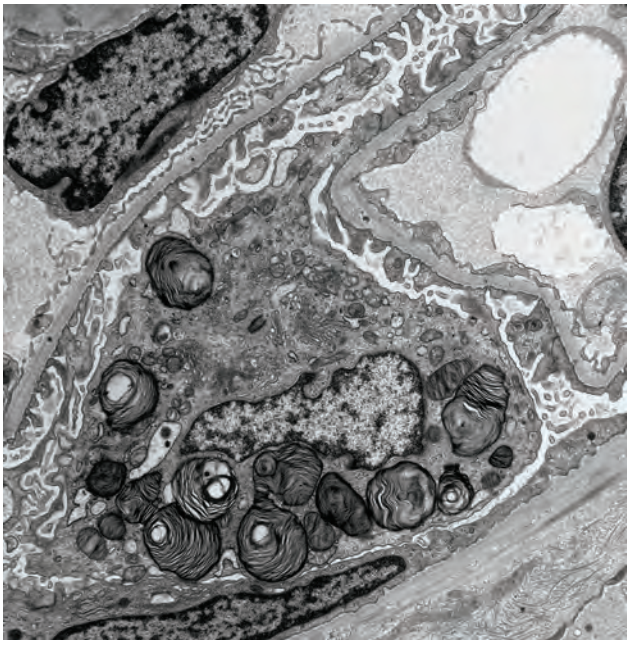
Case Description: Family A (1a). Patient IV:2's biopsy was notable for myelin bodies in podocytes (Figure 2). Her α-galactosidase A activity and *GLA* analyses were normal, thus excluding Fabry nephropathy. Family B (1b). Mother (Patient II:2) and son (Patient III:1) with nephropathy were found to have the p.R246Q variant, while the asymptomatic daughter (Patient III:2) did not have this variant.

Discussion: This is the first case series to report myelin figures in families with *LMX1B*-nephropathy. Consider *LMX1B*-nephropathy in AD glomerulopathy and in differential diagnosis for kidney biopsies with myelin bodies.

Patient	LMX1B Mutation	Age at Diagnosis (y)	Age at Last Follow-up (y)	Up/c at Last Follow-up (mg/mg)	eGFR at Last Follow-up (mL/min/1.73m.sq)	Kidney Histology	Myelin bodies on EM
Family A							
I:1	ND	40	60	ND	ESRD	ND	
III:2	ND	22	35	ND	ND	FSGS	None
IV:2	c.737G>A	3	11	4.2	169	Normal	2+, Podocytes
Family B							
I:1	ND	60	81	ND	ESRD	ND	
II:1	ND	36	50	ND	ESRD	ND	
II:2	c.737G>A	29	45	5.5	118	Mild atrophy	1+, Podocytes
II:4	ND	42	43	0.3	112	FSGS	2+, Podocytes
III:1	c.737G>A	9	15	0.7	132	ND	
III:3	ND	4	20	0.2	141	Normal	None

eGFR, estimated glomerular filtration rate (Schwartz equation K 0.413 in <18yo; CKD-EPI equation in 18y and older); EM, electron microscopy; ND, not determined; Up/c, urine protein/creatinine ratio





PUB336

Genetic Variants of the COL4A5, COL4A4, and COL4A3 Genes in the Children with Familial Hematuria

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Background: The familial hematuric diseases are a genetically heterogeneous group of monogenic conditions, including Alport syndrome (AS) and thin basement membrane nephropathy (TBMN) caused by mutations in the *COL4A5*, *COL4A4* and *COL4A3* genes, etc. This study aims to examine genetic variants of the *COL4A5*, *COL4A4* and *COL4A3* genes in 48 children with familial hematuria (FH).

Methods: The clinical data and blood samples of 48 children with FH and their parents were collected. Genomic DNA was isolated from peripheral blood leucocytes. The 48 children and their parents were examined for genetic variants in all coding exons and exon-intron boundaries of genes by exome sequencing. Variants detected in the *COL4A5*, *COL4A4* and *COL4A3* genes by exome sequencing were further verified by Sanger sequencing. Pathogenicity of the identified variants was verified by bioinformatic analyses. The etiological diagnosis of some children with FH were made according to their genotypes and their phenotypes.

Results: Twenty-five mutations were identified in 29 children with FH by exome sequencing and Sanger sequencing. Among them, 20 nutations, such as *COL4A5* 539G>A, *COL4A5* 3985delC, *COL4A5* 566G>T, *COL4A5* 2822G>A, *COL4A5* EXON 29-30 deletions, *COL4A4* 4421C>T, *COL4A4* 4915G>C, *COL4A4* 2752G>A, *COL4A4* 1030-2A>C, *COL4A4* 2447G>A, *COL4A4* 4481delT, *COL4A4* 4288G>A, *COL4A4* 1567C>T, *COL4A3* 1496G>A, *COL4A3* 3619G>A, *COL4A3* 3627G>A, *COL4A3* 4700T>G, *COL4A3* 898G>A, *COL4A3* 2096T>C and *COL4A3* 4769G>A, were novel, and 5 mutations, such as *COL4A5* 2858G>T, *COL4A5* 530G>A, *COL4A4* 4599T>G, *COL4A4* 3499G>A and *COL4A3* 4235G>T, have already been reported. Muatations in the *COL4A5*, *COL4A4* and *COL4A3* gene were found in 60.4% (29/48) of 48 children with FH. An etiological diagnosis could be made in 56.3% (27/48) of 48 children with FH. Eleven children with FH were diagnosed with X-linked AS, and 1 child with FH was diagnosed with autosomal recessive AS, and 15 cases were diagnosed with either autosomal dominant AS or TBMN.

Conclusions: It is necessary for the children with FH to make an etiological diagnosis by examing genetic variants of the *COL4A5*, *COL4A4* and *COL4A3* genes.

Funding: Government Support - Non-U.S.

PUB337

Complement-Mediated Glomerulonephritis – A Large Spectrum for a Rare Disease

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Introduction: Membranoproliferative glomerulonephritis (MPGN) was recently reclassified as a complement alternative pathway-mediated C3 glomerulopathy (C3G) and immune complex-mediated membranoproliferative GN (IC-MPGN). The primary defect underlying complement-mediated glomerulonephritis is excessive activation of the alternative pathway as a result of either autoimmunity against regulatory components or abnormal genetic variants with a gain of function or loss of normal control of activating pathway.

Case Description: A 59 years old male was admitted to our clinic for anasarca, high blood pressure, oliguria, gross hematuria and worsening of serum creatinine from 2 to 6.2 mg/dl, for five days. A week before admission, he was evaluated in another hospital for a post-traumatic wound consisting in a cut on the left sole and was treated with antibiotics and NSAID. At admission, the biologic evaluation showed anemia, positive inflammatory tests, dyslipidemia, hypoalbuminemia, marked nitrogen retention (creatinine 10.19 mg/ dl, urea 170 mg/ dl), metabolic acidosis and hyperkaliemia, urinalysis with nephrotic proteinuria 9.5 g/ day and macroscopic dysmorphic hematuria. A kidney biopsy was performed, and the patient started RRT with intermittent hemodialysis. The kidney biopsy revealed MPGN with isolated segmental deposits of C3 and extracapillary proliferation. Complement analysis revealed decreased classical and alternative pathway activity. Sequencing of complement genes showed no mutations, but some CFH or CD46 risky variations were identified for both DDD and aHUS. MLPA results suggested that the CFHR1 gene may be present in three copies in the patient. Western blot analysis showed FHR1 bands with higher density than controls, consistent with the presence of an extra *CFHR1* copy. Monoclonal anti-FHR1 antibody did not detect any aberrant protein. He was given pulse therapy with Methylprednisolone and Cyclophosphamide followed by Prednisone with no improvement of renal function, and he remained dialysis dependent.

Discussion: This case demonstrates that C3G can also present with an abrupt loss of kidney function. It is unknown, how the extra *CFHR1* copy affects protein function, further in vitro tests are necessary to analyze its effect.

PUB338

Chronic and Sub-Chronic Hyponatremia and Risk of Serious Falls and Hip Fractures

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Background: Falls and fractures represent serious health concerns in the elderly. Addressing risk factors for falls which may ultimately reduce falls/fractures may help reduce morbidity and mortality. It remains unknown whether the duration of hyponatremia affects serious fall/fracture risk. We sought to evaluate the risk for serious falls and hip fractures among episodes of chronic (≥ 30 days) and subchronic hyponatremia (< 30 days) compared to normonatremia.

Methods: Retrospective cohort study within Kaiser Permanente Southern California (an integrated health system) between 1/1/1998 and 12/31/2016 among individuals ≥ 55 yrs with ≥ 2 outpatient serum sodium (Na) measurements. Hyponatremia defined as a serum Na of <135 mEq/L. Subchronic hyponatremia was defined as 1) a single serum Na measurement <135 mEq/L followed by a normal Na measurement (≥135 mEq/L) on a different day or 2) multiple serum Na values <135 mEq/L with less than 30 days between the first and second and/or last hyponatremia measurement. Chronic hyponatremia was defined as multiple serum Na measurements <135 mEq/L with 30 or more days between first and last serum hyponatremia measurement. Multivariable cox proportional hazards was used to estimate hazard ratios (HRs) for serious falls and/ or hip fractures in 1) subchronic hyponatremia versus normonatremia and 2) chronic hyponatremia versus normonatremia.

Results: Among 1,033,838 persons and 1,799,163 Na measurements, 73,883 (7.1%) serious fall and/or hip fracture events occurred among the cohort. Compared to normonatremia, subchronic hyponatremia and chronic hyponatremia had serious fall and/or hip fracture HRs (95% CI) of 5.77 (5.66 – 5.87) and 1.91 (1.86 – 1.96) respectively.

Conclusions: We observed an increased risk for serious falls and/or hip fractures in persons with chronic and subchronic hyponatremia. Early detection and management of outpatient hyponatremia may provide an opportunity to prevent adverse outcomes including serious falls and fractures.

Funding: Commercial Support - Otsuka Pharmaceuticals

Hazards Ratios (95%) CI for Serious Falls and/or Hip Fractures, Serious Falls, and Hip Fractures in Subchronic and Chronic hyponatremia vs Normal Na

	HR (95% CI)*					
	Serious Falls and/or Hip Fractures		Serious Falls		Hip Fractures	
	Subchronic[a] hyponatremia vs Normal na	Chronic[b] hyponatremia vs Normal Na	Subchronic hyponatremia vs Normal na	Chronic hyponatremia vs Normal na	Subchronic hyponatremia vs Normal na	Chronic hyponatremia vs Normal na
	5.77 (5.66, 5.87)	1.91 (1.86, 1.96)	4.67 (5.98, 5.47)	1.27 (0.60, 2.66)	10.72 (8.94, 12.85)	0.96 (0.24, 3.84)

*Adjusted for age, gender, race, ethnicity, comorbidities, labs, and medication usage (bisphosphonates, other osteoporosis medications, anti-hypertensive medications, anti-arrhythmia medications, anti-coagulation medications, anti-seizure medications, endocrine and hormonal therapies, corticosteroids, thiazide diuretics, benzodiazepines, anti-depressant medications, and proton-pump inhibitors)

[a]Subchronic hyponatremia defined as a single serum sodium measurements <135 mEq/L or multiple serum sodium levels <135 mEq/L with less than 30 days between the first and second and/or last hyponatremia measurement

[b]Chronic hyponatremia defined as multiple serum sodium measurements <135 mEq/L with at least 30 days between first and last serum hyponatremia measurement.

PUB339

A Pilot Study of the Serious Illness Care Program in a Dialysis Population

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Background: Clinician-led conversations about future care priorities are associated with enhanced goal consistent care for individuals with serious illness. However, such conversations occur infrequently with patients with end-stage renal disease (ESRD) on dialysis. The Serious Illness Care Program (SICP) is a multi-faceted, comprehensive initiative to promote serious illness conversations between clinicians and patients centered around a conversation guide. This study aimed to assess the acceptability and feasibility of the SICP conversation for dialysis patients in an outpatient dialysis unit.

Methods: Twelve individuals with end-stage renal disease on dialysis from a single outpatient dialysis unit participated in this study. Average age of participants was 68.8 years. Participants completed a demographics survey and baseline questionnaire on their life priorities and care preferences. Each participant then engaged in a clinician-led SICP structured serious illness conversation and completed an acceptability questionnaire. The conversations were recorded, transcribed and thematically analyzed.

Results: Conversations were an average of 20:53 minutes in length. Ten of twelve participants felt that the clinician had the conversation with them at the right time and only one participant did not feel it was worthwhile to have this conversation with the clinician. Two-thirds reported a neutral ("did not notice" or "neither liked or disliked") reaction to the clinician using a written guide during the conversation. Finally, only one participant noted an increase in anxiety about their illness, while 42% noted that the conversation increased their hopefulness about their quality of life in the future. Thematic analysis revealed common perspectives on dialysis including that it narrowed life experiences and opportunities, was chosen by default, and was expected to be temporary.

Conclusions: The results of this pilot study suggest that clinician-led SICP serious illness conversations may be acceptable and feasible for patients with ESRD on dialysis and support larger scale implementation of the SICP intervention in this population. The lessons

from our thematic analysis can inform future serious illness conversations with dialysis patients.

Funding: Private Foundation Support

PUB340

The Relationship Between Lab Parameters and Patient Reported Outcomes in Pre-ESRD and Dialysis Patients

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Background: Management of pre-ESRD and dialysis patients places major emphasis on monitoring lab parameters. This population suffers from many symptoms, but it is unclear if routinely measured lab values correlate with patient reported outcomes (PROs). We evaluated the relationship between lab and hemodynamic measures and PROs in pre-ESRD and dialysis populations.

Methods: We conducted a cross-sectional study of pre-ESRD and dialysis cohorts. PROMIS surveys on cognitive function, physical function, and fatigue were administered via personal health record (PHR) or in clinic for the pre-ESRD cohort and at the dialysis center for the dialysis cohort. Linear regression analysis of the relationship between PROMIS T-scores (norm=50, SD=10) and labs including eGFR, BUN, hemoglobin (Hb), albumin for the pre-ESRD cohort, and Hb, albumin, Kt/V and intradialytic BP changes in the dialysis cohort. Models were adjusted for demographics and comorbidities.

Results: Our study included 76 pre-ESRD patients and 92 dialysis patients. The mean age (SD) was 61.0 (14.8) and 56.1 (14.8) years for the pre-ESRD and dialysis cohorts, respectively. Pre-ESRD patient mean eGFR (SD) was 18.4 ml/min (11.6). Overall, the pre-ESRD cohort reported no deficits in cognition (51.0 (9.2)) or fatigue (52.8 (10.4)), but did report moderately impaired physical function (39.8 (9.2)). Overall, the dialysis cohort reported no cognitive deficits (50.3 (10.9)), but did report moderately severe fatigue (55.0 (9.8)) and severely impaired physical function (37.9 (7.9)). In Pre-ESRD patients higher BUN and lower eGFR was associated with higher reported cognitive function, $p<0.01$ for both. In dialysis patients lower Hb was associated with greater reported fatigue, $p=0.01$, and higher albumin was marginally associated with higher physical function, $p=0.06$.

Conclusions: Patient reported impairment in physical function was identified in the pre-ESRD and dialysis cohorts. Hb and albumin were associated with increased reported fatigue and reduced physical function in the dialysis cohort. In the pre-ESRD cohort clearance parameters were associated with better reported cognition with unclear relevance. Our results suggest that further research is needed on how to improve PROs in pre-ESRD and dialysis patients.

PUB341

Hemoglobin Variability and Mortality Association in Elder Hemodialysis Patients

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Background: Anemia secondary to Chronic Kidney Disease requires treatment because its impact in mortality; this effects lies within a spectrum that can't be captured by an absolute level of isolated hemoglobin. Controversial results exist in the association between hemoglobin variability and mortality, so we decided to look for this association in elder population.

Methods: We performed a prospective cohort of patients over 60 years in hemodialysis conducted at the Hospital Central Sur de Alta Especialidad in the period from January 2017 to March 2018. Monthly measurement of hemoglobin was recorded and the variability calculated by linear regression model and absolute change model. We documented whether the patient reached the primary (mortality) or secondary outcomes (hospitalizations or visits to the Emergency Room). We performed Cox regression for both models of variability. Secondary outcomes were analyzed by ANOVA. At the end of the study we measured the Granov-Goor Index (GGI) with the NiCaS system, dividing into two groups where <10 is related to asymptomatic left ventricular systolic dysfunction (aLVSD) and compared change in cardiac index and total body water according to tertiles.

Results: Thirty-two patients met the inclusion criteria, 53.1% men with an average age of 72.2(±7.9) years old and a time in hemodialysis of 22(±25.6) months. During the follow-up period 25% of the patients died. The variability of hemoglobin was calculated and divided into tertiles. In the Cox regression there were no significant differences in survival for the linear regression model ($p=0.09$) and for the absolute change model ($p=0.1$). No significant differences were observed in secondary outcomes. At the end of the study, the IGG was measured and the group divided in those with aLVSD (13) and those with IGG>10 (7) without finding significant differences in the cardiac index or body water changes.

Conclusions: Elder patients on hemodialysis represent a vulnerable population exposed to many factors that contributes to fluctuation such as lack of erythropoietin administration or poor compliance of the treatment. In this study we don't observe differences in survival associated with greater variability maybe due to different pre-hemodialysis care, follow-up time or multiple comorbidities. We need to continue analyzing this vulnerable population.

PUB342

Mild Cognitive Impairment in Maintenance Hemodialysis Patients: A Cross-Section Survey and Cohort Study

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Background: Few studies focused on mild cognitive impairment (MCI) with maintenance hemodialysis (MHD) patients. This study was conducted to ascertain whether Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) was more accurate for MHD patients, then survey the prevalence, severity and risk factors of MCI with MHD patients, finally observe the progress of MCI with MHD patients in a period of six-months.

Methods: Referring with guidelines for cognitive impairment in China: the diagnosis and treatment of MCI (2010), MMSE and MoCA were used to assess the cognitive condition.

Results: 64 MHD and 54 non-HD subjects were included in this study. The mean age of the two groups was both beyond 60 years. The cut-off value of MoCA and MMSE were 26 and 27 to screen MCI, respectively. MoCA performed superior to MMSE in sensitivity, specificity and ^{AUC}ROC. The prevalence of MCI in MHD group was significantly higher than that in non-HD group (60.9% vs. 29.6%, MoCA) with OR 3.71. Spearman correlation test indicated that MCI was related with age, comorbidities, education years, uric acid, serum albumin, blood pressure. A multivariate stepwise regression analysis demonstrated that there was no relationship between MCI and the factors tested, except age. After an observation period of six months, MoCA indicated that MCI prevalence tended to augment and aggravate in the MHD group.

Conclusions: MoCA could be a more accurate assessment for screening MCI in both non-HD and MHD population. MHD patients might have a significantly higher prevalence of MCI. Age could be a vital important risk factor for MCI.

PUB343

Relationship Between TGF-β1, TGF-βR I, TGF-βR II, and Coagulation Fibrinolysis Factors and Their Effects on the Process of Renal Fibrosis

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Background: To explore the expressions of transforming growth factor β_1(TGF- β1), and its types I and II receptors (TGF- β Type I, II Receptors, TGF-βR I,II), and their roles and relationships in the mechanism of human glomerulonephritis, their correlation with blood coagulation fibrinolysis factors(FRA,FN, α_1-PI, PLG), and the accelerative effects on glomeruli cirrhosis, so as to identify the key factor that triggers and develops human glomerulonephritis.

Methods: Through immunohistochemistry, SABC, to assay the reflected changes in glomerular expressions of TGF-β_1 and TGF-βR I and II, and in selected biopsy samples of the following 41 disease cases. By applying direct immunofluorescence to assay FN and FRA, indirect immunofluorescence assays α_2-PI, and PLG, in 65 disease cases. Statistical analysis through Ridit and Spearman′s analysis.

Results: (1)Significant close correlations was noted between (TGF-ß1 and TGF-ßR I and II), and (FRA, FN, α_2-PI, PLG) in the sampling disease cases, and the expressions significantly increase in direct correlation to the increased severity of renal tissue inflammation and fibrosis. (2) The glomerular fibrosis is the combined effect of several factors. The key factors include (TGF-β_1 and TGF-βR I and II)and (FRA, FN).

Conclusions: The expressions and correlations within renal tissues of (TGF-β1 and TGF-βR I and II), and (ERA,FN,α_1-PI, PLG), indicate these are significant factors in the developments of renal tissue fibrosis or cirrhosis.

PUB344

Omega-3 Fatty Acid May Stabilize the Podocyte Cytoskeleton and Improve the Survival

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Background: Cytoskeletal disruption is the main issue in podocytopathies. Previous studies reported that omega-3 improved podocyte survival via anti-apoptotic and anti-inflammatory effects. However, the role of omega-3 on the cytoskeleton of the podocyte is yet to be investigated. We studied on the effect of omega-3 on cytoskeleton in a puromycin aminonucleoside (PAN) induced podocyte injury model.

Methods: *In vitro* cultured mouse podocytes were divided into four groups: control, PAN treated, Omega-3 (EPA, DHA) treated, and PAN + EPA/DHA treated. PAN and EPA/DHA were treated by dose and time. Cytoskeletal components including F-actin, synaptopodin, α-actinin-4, and Jo-1 were evaluated. Oxidative stress and autophagic markers and cytoskeleton stains, such as Bax/Bcl2 ratio, caspase-3, phosphorylation (p)-mTOR, phosphorylation (p)-cofillin and RhoA were evaluated.

Results: Compared to control, the PAN-treated group showed decreased expression of f-actin and synaptopodin, α-actinin 4 and Jo-1; and increased (p)-mTOR, (p)-cofillin and RhoA. In the PAN group, treatment with EPA/DHA improved the expression of f-actin and synaptopodin, alpha actinin 4 and Jo-1. EPA/DHA also suppressed (p)-mTOR, (p)-cofillin, RhoA, and Bax/Bcl2 ratio, while activating capase-3.

Conclusions: EPA and DHA treatment improved cell survival and related markers in puromycin-treated mouse podocytes. The results inferred that Omega-3 may ameliorate the podocyte damage by anti-apoptotic and cytoskeleton-stabilizing effects.

Funding: Government Support - Non-U.S.

PUB345

Post Infectious Glomerulonephritis: A Cause of Pulmonary Renal Syndrome

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Introduction: The occurrence of diffuse alveolar hemorrhage (DAH) in association with post streptococcal glomerulonephritis (PSGN) is extremely rare. We present a case of acute kidney injury from PSGN that was initially treated with steroids. DAH developed shortly after stopping steroids. At that time the patient was recovering from the renal injury and was dialysis-independent.

Case Description: Our patient was a 25-year-old lady presented with a history of passing dark brown urine preceded by a vague history of a sore throat two weeks prior to that. He examination was normal. Serum creatinine was 2.4 mg/dl and hemoglobin was 11.6 mg/dl. Urinalysis showed +2 proteinuria, dysmorphic RBC's and several WBCs. Her spot urine protein to creatinine ratio (UPCR) was 1.9 grams/gram. Immunological workup was negative except a high serum anti-streptolysin-O titer (674.9 IU) and a low C3 (0.3 g/l). Kidney biopsy showed diffuse exudative glomerulonephritis. Two glomeruli out of ten showed cellular crescents. Immunoflourescence and electron microscopy were consistent with PSGN. She became anuric and serum creatinine rose to 4.5 mg/dl. Treatment was started with intravenous methylprednisolone 0.5 gram daily for 3 days. She went on to develop anasarca and uremic symptoms with a creatinine of 10.9 mg/dl then dialysis was initiated. Her urine output improved over few days and dialysis was held. During that period steroids were discontinued. Six days later she complained of dyspnea and hemoptysis. Hemoglobin dropped to 8 mg/dl and her oxygen saturation was 75%. Radiographic images were suggestive of DAH which was confirmed by bronchoscopy. The broncho-alveolar lavage was persistently bloody on sequential samples. IV methylprednisolone was restarted again for 3 days. She improved dramatically 2 days into treatment and was discharged on prednisone. Steroids were tapered slowly over 3 months and then stopped. Serum creatinine decreased to 0.4 mg/dl and UPCR improved to 0.32 at 1 year.

Discussion: Our patient had a picture of rapidly progressive glomerulonephritis and was started on high dose steroids. Shortly after stopping steroids she developed DAH which was promptly diagnosed and treated with steroids, raising the question about the role of immune suppression, specifically steroid use in adults with PSGN with DAH. Only five cases were reported in adults and no clear recommendations exist.

PUB346

Catastrophic Antiphospholipid Syndrome Due to Systemic Lupus Erythematosus: The Beneficial Effect of Rituximab Treatment

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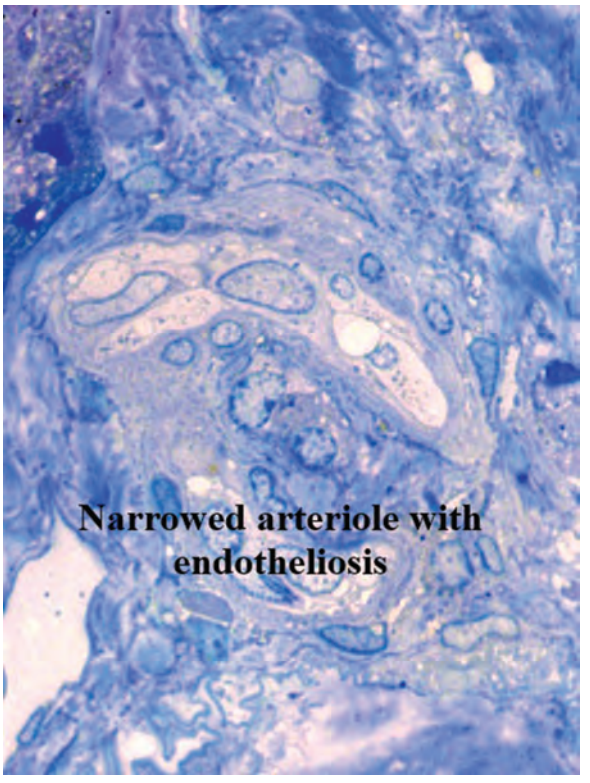
Introduction: Kidney involvement is a frequent complication of systemic lupus erythematosus (SLE). Kidney pathology is essential in differentiating lupus nephritis (LN) from thrombotic microangiopathy (TMA) secondary to antiphospholipid autoantibodies to choose proper treatment.

Case Description: A 61 years male patient with benign polyclonal gammopathy, overlap autoimmune hepatitis–primary biliary cirrhosis, acquired deficiency of factor VIII of clotting due to circulating inhibitors, aortic bioprosthesis for aortic stenosis and SLE with anticardiolipin (ACL) antibodies and lupus anticoagulant, is diagnosed one week before admission with raised serum creatinine (SCr 1.6 mg/dl) and short episodes of diplopia. At admittance he had proteinuria 800 mg/day, microangiopatic anemia, thrombocytopenia 79000/ml and hypofibrinogenemia 119 mg/dl. Kidney biopsy showed no LN but TMA (Image). MHC genotyping showed high risk for autoimmunity (DQB1*02,*05/DRB1*03,*14). For probable cAPS patient received low molecular weight heparin (LMWH), methyl-prednisolone, plasmapheresis, rituximab (two 500-mg infusions at 7-days interval) with resolution of acute kidney injury, diplopia and TMA and complete depletion of CD19+B-lymphocytes (Ly) after one month. Treatment was continued with LMWH and prednisone in tapering dosage. After 18 months we noticed reappearance of ACL and of CD19+B-Ly, followed after 5 months by increase of SCr to 1.4 mg/dl. 500 mg of iv rituximab was administered with SCr normalization.

Discussion: Targeted therapy was possible after kidney pathology exam, improving renal and general prognosis. CD19+B-Ly repopulation preceded biological relapse, so monitoring of CD19+B-Ly may be useful to predict relapses and guide rituximab therapy.



PUB347

New Assay with Enhanced Sensitivity for the Detection of Galactose-Deficient IgA1 Enables Mechanistic Studies Using Human Primary Cells

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis in the world, is characterized by glomerular IgA1 immunodeposits enriched for galactose-deficient IgA1 (Gd-IgA1). These immunodeposits likely originate from the circulation. Patients with IgAN have elevated blood levels of Gd-IgA1, predominantly bound in circulating immune complexes. Current ELISA tests require a significant amount of IgA1 to properly assess IgA1 galactose deficiency. This requirement limits studies with cultured primary cells, such as peripheral blood lymphocytes (PBLs), due to low number of IgA1-producing cells in PBLs and, consequently, low IgA1 production. To circumvent the problem, immortalized IgA1-secreting cell lines were previously established from IgAN patients and controls. This approach enabled studies of O-glycosylation pathways associated with IgA1 galactose deficiency. Translating the finding from immortalized cells into primary cells has proven difficult due to limitations of the current assays. Thus, a more sensitive assay was needed for analysis of IgA1 glycosylation.

Methods: We developed a new chemiluminescent assay for Gd-IgA1 detection using a lectin from Helix pomatia (HPA; specific for terminal N-acetylgalactosamine) conjugated to acridinium ester. Cell-free media were collected post-incubation with PBLs or EBV-immortalized IgA1-producing cells. Galactose deficiency levels were assessed using HPA lectin conjugated to acridinium. Limits of detection were determined for the new assay and compared to that of previously established biotin-labeled HPA and colorimetric detection.

Results: The chemiluminescent assay showed a log-fold increase in sensitivity over the colorimetric assay as well as a two-fold improvement in the limit of detection. This improvement in sensitivity enabled assessment of galactose deficiency of IgA1 secreted by cultured primary PBLs.

Conclusions: We report a new method for analysis of Gd-IgA1 using a highly sensitive chemiluminescent assay. We show that this new assay can accurately assess the degree of galacrose deficiency in IgA1 secreted by cultured PBLs isolated from peripheral blood, a task not feasable with the traditional colorimetric lectin assay.

Funding: NIDDK Support

PUB348

Association of Atypical ANCA with Pauci-Immune Glomerulonephritis

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Background: ANCA are classified into three types based on the indirect immunofluorescence (IIF) pattern in ethanol fixed neutrophils. Whereas c-ANCA and p-ANCA have well established association with systemic vasculitis, atypical ANCA (a-ANCA) have mostly been associated with inflammatory bowel disease. We present the findings of our study to determine if there is any association of a-ANCA with pauciimmune GN.

Methods: This is a retrospective study of patients who had a pathological diagnosis of pauciimmune GN over a five years period. The patients were divided into three groups based on the presence of typical, atypical or no ANCA. Baseline characteristics, clinical presentation, pathological findings and outcomes were compared.

Results: 26 patients were found to have the required diagnosis and data. The results are shown in the table included.

Conclusions: To our, knowledge, this is the first study looking at the association of a-ANCA with pauciimmune GN. Almost a quarter of the patients had positive a-ANCA with negative PR3 and MPO by ELISA. Interestingly, there was only one patient with ANCA negative GN. It is possible that better IIF techniques were able to identify a-ANCA in those sera which would have been ANCA negative with older techniques. These antibodies may have formed against previously unrecognized antigens involved in the disease process. 4 out of 6 patients with a-ANCA had positive ANA which could give false positive ANCA results. But, ANA positivity could give rise to both atypical and perinuclear patterns, whereas, we only saw atypical pattern. Furthermore, the other 2 results with atypical ANCA cannot be explained by this phenomenon. A-ANCA might be associated with pauciimmune GN. In the presence of appropriate clinical presentation, presence of a-ANCA should prompt the clinicians and pathologists to consider the diagnosis of ANCA vasculitis.

Pauciimmune GN	Typical ANCA	Atypical ANCA	P-value
N	19/26 (76%)	6/26 (24%)	-
Age (years) mean±SEM	59.1±4.1	54.3±8.9	0.59
Male N, %	8, (42%)	4, (66.7%)	0.3
Extra renal manifestation N, %	7, (36.8%)	1, (16.7%)	0.36
ANA positive N, %	4, (21.1%)	4, (66.7%)	0.04
Serum creatinine (mg/dL) median (IQ range min and max)	2.7 (1.0, 18.8)	4.3 (1.1, 20.0)	0.34
Necrosis on biopsy N, %	17, (89.5%)	3, (50%)	0.04
HD on presentation N, %	5, (26.3%)	2, (33.3%)	0.74
Treatment with Cytoxan N, %	13, (68.4%)	3, (50%)	0.42
Treatment with anti-CD20 N, %	6, (31.6%)	2, (33.3%)	0.9
Plasma Exchange N, %	10, (52.6%)	2, (33.3%)	0.4
Remission at 90 days N, %	14, (73.7%)	4, (66.7%)	0.74
HD at 90 days N, %	5, (26.3%)	2, (33.3%)	0.74

Comparison of baseline characteristics, findings and outcomes.

PUB349

Pathology Patterns of Paraprotein-Induced Kidney Damage in 168 Patients from a Single Center

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Background: Paraprotein-induced lesions in multiple myeloma (MM) include cast nephropathy (CN), AL amyloidosis, light chain deposition disease (LCDD), light chain proximal tubulopathy (LCPT), proliferative glomerulonephritis with monoclonal Ig deposits (PGMID) and several rarer variants. AL amyloidosis itself is mainly found in the absence of lymphoproliferative disease (LPD). LCDD, PGMID, LCPT and other lesions not related to MM or any LPD are merged under the umbrella of Monoclonal Gammopathy of Renal Significance (MGRS)

Methods: We evaluated 197 patients with LPD, AL amyloidosis and MGRS, who underwent kidney biopsy in 1997-2017. Pathology study included light microscopy and immune stainings with electron microscopy for selected cases. Patients without clear paraprotein deposition were excluded from analysis

Results: Study group included 86 males and 82 females, median age 61 [31; 81] years. Indication for biopsy was nephrotic syndrome in 124 (73.8%) cases, progressive decline of kidney function in 103 (61.3%) cases, or both in 65 (38.6%) cases. Pathology findings and clinical setting are shown in the Table

Conclusions: Most often type of paraprotien-induced renal desease is AL amyloidosis, including that complicates MM and Waldenstrom macroglobulinemia (WM). Patients with MM present also with CN, LCDD and variety of rare lesions, or with the combination of 2 or even 3 patterns. In turn, WM might be complicated by several types of lesions. MGRS and MM share patterns like LCDD and PGMID

Pathology pattern/clinical setting	Multiple myeloma	Waldenstrom macroglobulinemia	Franklin disease	Non-Hodgkin lymphoma	AL amyloidosis	MGRS	Total N (%)
AL amyloidosis	25	1	-	-	102	-	128 (76%)
AH amyloidosis	-	-	1	-	-	-	1 (0.5%)
Cast nephropathy	5	-	-	-	-	-	5 (3%)
Light chain proximal tubulopathy	2	-	-	-	-	-	2 (1%)
Cryoglobulinemic glomerulonephritis	-	1	-	-	-	-	1 (0.5%)
Light chain deposition disease	5	-	-	-	-	9	14 (8%)
Proliferative glomerulonephritis with monoclonal IgG/IgA deposits	1	-	-	1	-	2	4 (2%)
Non-proliferative glomerulonephritis with monoclonal IgM deposits	-	4	-	-	-	-	4 (2%)
Paraprotein-induced anti-GBM nephritis	1	-	-	-	-	-	1 (0.5%)
Paraprotein-induced C3 glomerulonephritis	-	1	-	-	-	-	1 (0.5%)
Cast nephropathy + AL amyloidosis	2	-	-	-	-	-	2 (1%)
Cast nephropathy + Light chain deposition disease	1	-	-	-	-	-	1 (0.5%)
Cast nephropathy + Light chain deposition disease + AL amyloidosis	1	-	-	-	-	-	1 (0.5%)
Cast nephropathy + Light chain proximal tubulopathy	1	-	-	-	-	-	1 (0.5%)
Light chain deposition disease + Light chain proximal tubulopathy	1	-	-	-	-	-	1 (0.5%)
Light chain deposition disease + AL amyloidosis	-	-	-	-	-	1	1 (0.5%)
Total	45	7	1	1	102	12	168

PUB350

Normotensive Scleroderma Renal Crisis (SRC) with Urinary Findings of ATN

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Introduction: SRC can occur in 5-10% of SSc patients. Here we describe a case of normotensive SRC with severe AKI and unequivocal urinary finding of "muddy brown casts" consistent with ATN, presenting dilemma in using ACE inhibitor at initial presentation.

Case Description: A 76-year-old WF with newly diagnosed rapidly progressing diffuse SSC within past year, with failed multiple oral regimens, on prednisolone 12mg qd, and was admitted for Cytoxan infusion. She had recurrent L pleural effusion and pericardial effusion, s/p pericardial window and was normotensive on amlodipine 5 mg and lasix40 mg daily. She had poor po intake over last two weeks and diarrhea. On admission she had LE edemas, was in pain, BP was 172/93 and creatinine level 4.0, increased from baseline 0.8mg/dl two weeks ago. Platelets were 349. She was started on captopril 12.5mg tid for suspected SRC and analgesic doses readjusted with rapid normalization of BP in 120s/70s. Urine studies showed FeNA 1.5%, FeUrea 51.4%, no hemoglobin. Microscopy showed multiple muddy brown casts. She was oliguric but responded to Lasix. Her AKI worsened requiring hemodialysis (HD) over next few days. ACE was stopped after two days briefly when ATN casts were seen in urine and renin level obtained. BP remained in 110s and 120s/70s rest of her Hospital stay, (with or without ACE). ACE was restarted within few days since SRC could not be ruled out. To resolve therapeutic dilemma, we did kidney biopsy, showing thickening of intima in arterioles, thrombotic microangiopathy and mesangiolysis in ischemic glomeruli, consistent with SRC. Renin came back at 61ng/ml/h. Captopril dose was increased to 50 mg po tid as tolerated. She was discharged on HD.

Discussion: Granular casts and dysmorphic red cells can be found in urine in SRC, but sediment is usually bland. This case is unusual since urine sediment showed unequivocally ATN, and with briefly stopping captopril her BP remained within normal limits, despite having very high renin activity in combination with volume overload. Elevated blood pressure at presentation can be explained by uncontrolled pain and normalized within 4 h with pain control. This case demonstrates that when probability of SRC is high, finding ATN on urine microscopy should not preclude ACE/ARB use with or without pathological diagnosis.

PUB351

The Role of Complement in Primary Antiphospholipid Nephropathy

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Background: Renal involvement in the antiphospholipid syndrome has been linked to a spectrum of pathologies, including parenchymal disease known as antiphospholipid (aPL) nephropathy, and although the pathologic features are well-known, the natural history and mechanisms of primary aPL nephropathy have not been established. Recent studies linked thrombotic events to complement and moreover, complement blockade appears promising in severe aPL nephropathy. Here, we investigated primary aPL nephropathy and focused on complement.

Methods: Pathologic and clinical follow-up data were analyzed from adult patients with biopsy-proven aPL nephropathy with no evidence of secondary disease. Complement activation was studied on frozen kidney sections and in vitro after aPL binding to human endothelial cells.

Results: Twenty-one patients (13 female, 8 male) with persistent serum aPL reactivity presented with proteinuria (*n*=19), renal impairment (*n*=17), and/or hypertension (*n*=12). Glomerular disease was noted in 17 cases (thrombotic microangiopathy, *n*=14; focal segmental glomerulosclerosis, *n*=3); the extent of tubulointerstitial and vascular damage varied from mild (*n*=8), moderate (*n*=5), to severe (*n*=8). Electron dense deposits were found in 2 (10%) cases. Four biopsies had C3c co-located with C5b9 along capillaries and/or arteries, all of whom were scored as thrombotic microangiopathy. aPL binding (pooled IgG, *n*=4) to endothelial cells did neither induce C3c nor C5b9. Median follow-up was 5 (range, 1-24) years. Progression to the composite renal endpoint of doubling creatinine and end-stage renal disease occurred in 2 (10%) cases; both patients initially required dialysis. CKD stage 2 (*n*=5), 3 (*n*=12), and 4 (*n*=2) developed in the others. No differences were found regarding activity and chronicity indices on kidney biopsy. New thrombotic events occurred in 5 (24%) patients, one of whom received adequate anticoagulation.

Conclusions: In a large series of primary aPL nephropathy, the disease course appeared quite favorable. Complement activation could not be demonstrated and requires further evaluation.

PUB352

Cryoglobulinemic Membranoproliferative Glomerulonephritis (MPGN) in a Patient with Sjogren's Syndrome and IgM Monoclonal Paraproteinemia

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Introduction: Cryoglobulinemic GN is rare and usually occurs in type II cryoglobulinemia induced by hepatitis C. Here we present Hepatitis C negative patient with Sjogren's syndrome, cryoglobulinemic GN and monoclonal IgM Kappa paraproteinemia.

Case Description: 60 y/o AAF with PMH of dry mouth and eyes and recent increase in dental caries, was seen at Nephrology Clinic with severe LE edemas of 2 weeks duration and proteinuria 11gm/gm of creatinine (Cr). Her Cr increased from 1.1 to 4.5 mg/dl in one month, prompting renal biopsy showing MPGN Type I and extensive hyaline thrombi in glomerular capillaries suggesting cryoglobulinemic GN. Blood cryoglobulin was positive at 2.5% and serum and urine protein electrophoresis with Immunofixation detected two IgM Kappa monoclonal paraproteins. She had negative Hepatitis B DNA PCR, Hepatitis C and HIV tests. Autoimmune w/u showed ANA 1:230, SSA/RO Ab at 14, SSB/LA Ab > 320unit/ml, (normal < 7), low C3 46, low C4 <1mg/dl. Rheumatoid Factor (RF) was elevated at 423 IU/ml. Rheumatology consult confirmed diagnosis of Sjogren's syndrome. Bone marrow biopsy showed Plasma cells comprise less than 5% of the marrow cellularity, flow cytometry did not reveal plasma or B cell clone responsible for paraproteinemia. W/U for malignancies was negative. She was started on plasma exchange (PLEX) and plasma cell therapy, with Velcade, cytoxan and dexamethazone (VCD), discharged after six sessions of PLEX and continued on VCD for two months total of 4 cycles. Her Cr improved to 1.4-1.7mg/dl but kept having proteinuria with Immunofixation showing persistent IgM Kappa paraprotein. 40 days after last VCD she was given Rituximab, (two doses). At one-month F/U after rituximab, her creatinine improved to 0.8mg/dl, paraprotein concentration and proteinuria both decreased to half of pretreatment levels and cryoglobulin tested negative.

Discussion: The patient with Sjogren's syndrome is expected to have polyclonal RF, but she was tested positive on monoclonal IgM kappa. Since source cell clone was unknown, she was initially given plasma cell therapy, resulting in some improvement of kidney function and limited effect on her nephrotic syndrome (NS). She was given anti B cell therapy later on with further improvement in creatinine and proteinuria. If her NS fully resolves remains to be seen.

PUB353

Engineered Immune Complexes Containing Galactose-Deficient IgA1 and IgG Autoantibody, a Renewable Resource in IgA Nephropathy Research

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Background: Circulating immune complexes (CIC) containing galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-specific autoantibodies are considered a key pathogenetic factor in IgA nephropathy (IgAN). To enhance studies of IgAN, we generated engineered immune complexes (EIC) using Gd-IgA1 and a recombinant Gd-IgA1-specific IgG autoantibody derived from a patient with IgAN. The biological effects of EIC on human mesangial cells (hMC) were assessed and compared with those for CIC.

Methods: EIC were prepared from a recombinant IgG autoantibody specific for Gd-IgA1 from an IgAN patient and a Gd-IgA1 myeloma protein. EIC formed in human serum depleted of IgA and IgG and CIC from sera of IgAN patients were isolated by size-exclusion chromatography. hMC were stimulated with EIC or CIC and cellular proliferation and protein-tyrosine kinase (PTK) signaling were evaluated.

Results: EIC and CIC increased cellular proliferation of hMC by 2.88±0.69-fold and 3.97±2.18-fold, respectively. EIC and CIC induced signal transduction in hMC, resulting in enhanced phosphorylation of PDGFR-b, ERK1/2, and AKT1 detected by immunoblotting. Global protein-tyrosine kinome profiling revealed that EIC and CIC activated multiple PTKs. Among the ten kinases with highest phosphorylation indexes (KSTAT and specificity), eight kinases overlapped between EIC- and CIC-activated hMC: ROR1, LCK, LYN, KIT, YES1, BLK, TYK2, and CTK (MATK). Among other activated kinases (P<0.05 compared to negative control), 98% overlapped between EIC- and CIC-activated hMC. Among them, 17% belonged to Src family (a non-receptor protein kinases) and 25% to different growth-factor receptors, including PDGF/PDGFR, VEGFR, FGFR, EGFR, and INSR. Several activated kinases belonged to kinase families, such as Syk, Tec, Axl, and Eph.

Conclusions: EIC and CIC had similar capacity to activate hMC through phosphorylation of multiple kinases and activation of downstream pathways, ultimately resulting in cellular proliferation. EIC may thus serve as a convenient model of IC in the studies of pathogenesis of IgAN.

Funding: NIDDK Support

PUB354

Circulating Antibodies Against M-Type Phospholipase A2 Receptor Can Predict Treatment Response and Outcome in Chinese patients with Primary Membranous Nephropathy

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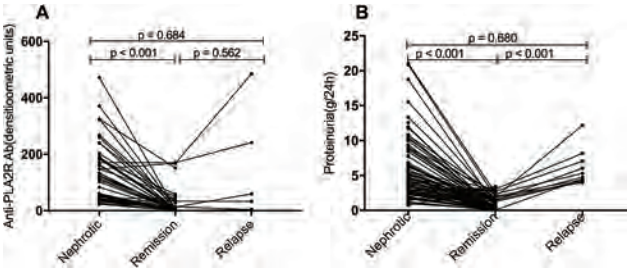
Background: Anti-phospholipase A2 receptor (PLA2R) antibodies are specific to the diagnosis of primary membranous nephropathy (pMN). The prevalence of positive antibodies varies among different cohorts. Discrepancy remains on the association between antibody levels and clinical courses, and the prognostic value of antibodies to treatment responses and kidney outcomes.

Methods: 359 consecutive kidney biopsy-proven pMN patients were enrolled. Anti-PLA2R antibodies were detected by immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA).

Results: The positive rate of anti-PLA2R antibodies in pMN were 65.2% (234/359) by IFA and 56.3% (202/359) by ELISA. Antibody level presented positive correlation with urinary protein excretion (r=0.164, P=0.002). The detectable antibodies (OR=2.99, P=0.007) and higher level of proteinuria (OR=1.11, P=0.009) were independent risk factors to no-remission after treatments. High level (>179U/mL) and moderate level (64-179U/mL) antibodies predicted higher risk to no-remission. Higher level of antibodies (HR=1.002, P=0.019) was the independent risk factor to kidney dysfunction during follow-up. High level (>179U/mL) of antibodies possessed higher risk to kidney dysfunction. The antibodies turned negative in 42/52 (80.8%) patients who achieved clinical remission, while remained positive in all patients of no response (P<0.001).

Conclusions: We documented a lower positivity rate of anti-PLA2R antibodies in this large Chinese pMN cohort and close correlations between antibody levels and clinical severity. The risk stratification of antibody levels could predict treatment responses and kidney outcomes of pMN.

Funding: Government Support - Non-U.S.



Anti-PLA$_2$R antibody levels and proteinuria in pMN patients at the time of kidney biopsy, remission and relapse. Patients who reach a remission had a decrement in the level of anti-PLA$_2$R antibodies and proteinuria. The proteinuria and the level of anti-PLA$_2$R antibodies were increased during relapse.

PUB355

Atypical Anti-GBM Glomerulonephritis with Crescents

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Introduction: Atypical anti-GBM disease is a rare variant characterized by an indolent course, no pulmonary involvement, undetectable circulating antibodies and absence of crescents in kidney biopsy. Here we present a case of rapidly progressive glomerulonephritis due to atypical anti-GBM.

Case Description: This is a 37 year-old man with no past medical history who presented in December, 2016 with bilateral lower extremity swelling and dark urine for 10 days. He denied fever, chills, shortness of breath, hemoptysis, vomiting, diarrhea, joint pain, skin rash or dysuria. Physical examination was remarkable for elevated blood pressure of 160/110 mm Hg and bilateral Lower extremity pitting edema. His labs showed elevated serum creatinine of 270 mmol/L, hypoalbuminemia, hyperlipidemia, microscopic hematuria and 15 g proteinuria. Virologic and immunologic workup was negative including hepatitis B, hepatitis C, HIV, ANA, ANCA, C3, C4 and Anti-GBM antibodies. kidney biopsy showed diffuse proliferation in glomeruli with increased mesangial cellularity and diffuse crescents involving > 50% of glomeruli. Direct Immunofluorescent studies showed diffuse linear GBM staining with IgG (3+) in glomeruli as shown in figure 1. Electron

microscopy showed similar proliferative features and severe foot process effacement, but no immune complex, fibrillary, or paraprotein-related deposits in GBM or mesangial regions. Patient was treated with IV pulse steroids, 8 sessions of plasmapheresis and 6-month of oral cyclophosphamide. He was also maintained on oral steroids. His serum creatinine and proteinuria 1 year post treatment were 117 mmol/l and 3.7 g, respectively.

Discussion: This case is unique because atypical anti-GBM glomerulonephritis is extremely rare and having diffuse crescentic phenotype in atypical anti-GBM hasn't been reported before. Despite high sensitivity of ELISA in detecting serum anti-GBM antibodies, anti-GBM cannot be ruled out completely without kidney biopsy.

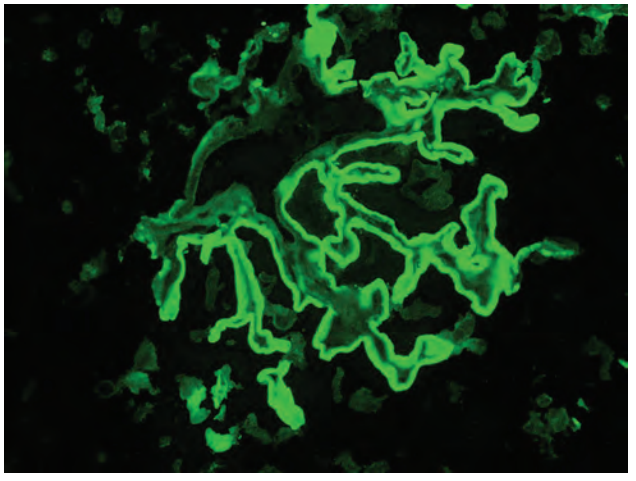

Figure 1

PUB356

Successful Therapeutic Procedure of Two Cases of Monoclonal Immunoglobulin Heavy Chain Deposition Disease (HCDD)

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Introduction: Among monoclonal immunoglobulin deposition disease (<1.0% of biopsy cases), heavy chain deposition disease (HCDD) is considered to be very rare and therapy-resistant glomerular disorder. We recently experienced 2 cases of HCDD who successfully showed clinical remission by immunosuppressive agent and corticosteroid.

Case Description: First case was 37-years-old man, and pointed out sever proteinuria and hematuria on the regular health check at 2 months prior to the admission. Light microscopic (LM) biopsy observation showed membranoproliferative glomerulonephritis (MPGN), and immunostaining showed IgG (+), C1q (+), C3 (+) and IgG3 (+). Light chains were all negative. Electron microscopic (EM) study showed powder-like deposition in the basement membrane. Because CH1 staining was negative, he was final diagnosed as gamma 3-HCDD. He was not satisfied with the myeloma criteria, however, hematologists agreed with the administration of bortezomib+dexamethasone at day-55 and intermittently repeated 12-times. After finishing the 4th therapy, his hematuria was disappeared, and finally his proteinuria was disappeared at day-422. Second case was 30-years-old woman, and she recognized edema on the lower extremities at 2 months prior to the admission. She showed remarkable proteinuria, hematuria and renal dysfunction. Renal biopsy showed MPGN in LM study, and IgG (+), C1q (-), C3 (-), IgG1 (+) in the immunostaining. Light chain staining were both negative, and powder-like deposition was observed in EM study. IgG-Fab and Fc specific staining revealed Fab (-) and Fc (+), suggesting CH1 deficient HCDD. Because hematologists did not agree to use bortezomib, she was started PSL 30 mg/day alone at day-42, and both proteinuria and eGFR were getting to be restored at day-116.

Discussion: Both of our cases responded to the therapy, whereas HCDD is known to show therapy resistance. Bortezomib might show the better efficacy to this disease, however, we sometimes hesitate to use bortezomib in patients in earlier stage because they usually do not agree with the myeloma criteria. However, PSL alone might be sufficiently effective to cases in earlier stage.

PUB357

Anti-Complement Factor H Mediated Glomerulonephritis at a Tertiary Care Centre

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Background: Complement dyregulation has become an important etiology for glomerular diseases. Anti body against complement factor H which regulates the alternate complement pathway can cause atypicical HUS and C3 glomerulopathy

Methods: We studied the clinical profile and outcome of patients with anti complement factor H mediated disease at a tertiary care centre over 18 months. 8 patients were studied and followed up to assess their response to therapy.

Results: Cases were equally distributed between males and females. Mean age was 20.5yrs with 5 patients in the paediatric age group. All patients presented with hypertension with RPGN with active urinary sediments. Mean serum creatinine at presentation was 6.8+/-1.2. Serum c3 was low in all patients with normal c4 levels. LDH was elevated in 50% patients with schistocytes in peripheral smear. 100% patients had oliguria and were dialysis dependent at presentation. Renal biopsy showed thrombotic microangiopathy in 4 patients while features were suggestive of C3 glomerulopathy in 4 patients. Anti complement factor H antibody was elevated in all patients with a mean of 161AU/ml. All patients were managed with pulse steroids followed by oral steroids along with IV cyclophosphamide. Plasmapharesis was done in all patients. All of them showed improvement in renal function after plasmapharesis and were free from dialyisis. Among the 8 patients, one was post transplant thrombotic microangiopathy with low serum c3 with elevated anti cfh antibody. Patient responded well to our treatment and had normal renal function by the 3rd week post transplant. All 5 patients in the paediatric age group are on regular follow up with normal renal function in complete remission. One of the adult patient expired due to sepsis with septic shock. Post transplant patient expired due to intracerebral bleed during follow up. Last patient has a stable creatinine of around 2.2mg/dl and is doing well

Conclusions: Our case series shows that anti complement factor H mediated disease shows good response to immunosuppression and plasmapharesis without the need for eculizumab.

PUB358

Case Report: Recurrence of MPGN Post Transplant – Is This Mere Recurrence of Pattern or Recurrence of Disease?

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Introduction: Recurrence of MPGN is seen in 19-65 % cases of post renal transplant and amounts for graft loss up to 35 to 50 % cases.

Case Description: 31 year old female patient diagnosed to have ESRD 3 years back initiated on MHD three times a week. She underwent deceased donor kidney transplantation after 11/2 yrs with Basiliximab as induction. Post transplant patient had DGF. Post transplant patient achieved nadir creatinine of 0.9 mg/dl by 10 days. 9 months post transplant patient developed fever, anasarca and decrease in urine output. On evaluation found to have active sediments in urine, albuminuria 3+, serum creatinine 3.5mg/dl and 24 hr urine protein 7.5 grams, low C3. Patient underwent graft biopsy. Subsequently patient received pulse steroid for 3 days and 5 sessions of plasmapheresis. Later renal biopsy report was suggestive of MPGN with focal crescents, ATN. IF showed Ig G3+, C3 3+, 3+, negative for or other immunoglobulins or compliments. As her native kidney disease was IC mediated MPGN with no light chain restriction, paraffin tissue of native kidney was reexamined for immunoperoxidase stain for and chains, which were positive. Medical oncologist opinion was taken. Patient underwent extensive work up for paraproteinemias and results were negative. Patient received 4 doses of Bortezomib. Patient's serum creatinine was reduced to 0.8mg/dl and proteinuria reduced to 800mg/day. 2 months later patient was on routine surveillance found to have increase in proteinuria with microscopic hematuria with normal creatinine. As per medical oncologist advice patient was restarted on Bortezomib. Presently her 24 hr urine protein is 600mg/day with normal creatinine.

Discussion: Conclusion: Our case is unique as we were not able to demonstrate monoclonal deposits in native kidney sample with recurrence of MPGN with monoclonal light chain deposits post transplant. Our findings emphasize for thorough evaluation for paraproteinemias in patients with idiopathic MPGN even in the absence of light chain deposition in biopsy

PUB359

Lessons from Comprehensive Analysis of a Factor I (FI) Variant in Atypical Hemolytic Uremic Syndrome (aHUS)

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Introduction: aHUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. Mutations in genes encoding complement proteins have been identified in ~60% of patients. Majority of these variants are variants of uncertain significance (VUS). Herein, we report functional and structural analyses on a FI variant identified in a patient with HUS.

Case Description: **Clinical history:** 22 y/o male had h/o ESRD secondary to *E. coli*-HUS. The patient underwent a renal transplant in 2006. In 2007, he developed non-Hodgkin's lymphoma and his immunosuppression was reduced. Later that year, he lost his kidney to acute cellular rejection. During evaluation for a 2nd kidney transplant, genetic testing for HUS was performed which demonstrated a VUS (R406H) in FI. He received eculizumab post-transplant. One year later, after eculizumab was discontinued, the patient lost his kidney again to acute cellular and antibody-mediated rejection. He is now being evaluated for a 3rd transplant. **Genetic analysis**: The FI variant has been analyzed by several prediction models and due to lack of consensus among these tools, was classified as a VUS. **Antigenic analysis:** The secretion of the variant protein (ELISA) was comparable to wild type (WT). Patient had a borderline low serum FI level. **Functional analysis:** Cofactor assays were performed using purified FI, C3b and with membrane cofactor protein (MCP), Factor H (FH) or Complement Receptor 1 (CR1) as the cofactor protein. WT and variant cDNAs were transfected into human 293T cells. The variant had defective cofactor activity (CA) with FH and CR1 as evident by decreased rate of cleavage of the α-chain of C3b. No defect was observed with MCP. **Structural analysis**: The side chain of R406 in FI forms a salt bridge with the carboxyl group of E123 of FH, thereby stabilizing the FI-FH binding interface. Residue E123 is a unique signature of FH. It is lacking in MCP, possibly accounting for why the R406H mutation impairs FH- but not MCP-mediated CA.

Discussion: **Summary/Lessons Learned:** It is imperative to define the functional activity of a VUS. The variant R406H is pathogenic based on defective CA. Given his clinical course, borderline low FI antigenic levels and these new functional data, we believe that the patient is at high risk of developing a thrombotic microangiopathy or an accelerated rejection in the future.

PUB360

Relapsing IgG4 Related Kidney Disease with Bilateral Ureteral Obstruction by Peri-Renal Tumors – A Case Report of 4-Year Clinical Course

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Introduction: IgG4 related kidney disease (IgG4RKD) is recently established as an interstitial nephritis with IgG4 positive lymphocytes infiltraion. IgG4RKD well responds to corticosteroid therapy, and its prognosis is considered to be good. Here, we report a case with IgG4RKD, in which three times relapses were seen during 4 year duration, with an unusual complication.

Case Description: A 82 year-old male was first admitted in January 2014, because of progressing renal dysfunction. Serum creatinine was 4.77 mg/dL, IgG4 1,130 mg/dL. Renal biopsy showed severe tubule-interstitial nephritis, with typical Bird's eye signs, and with numerous IgG4 positive lymphocytes infiltraion. Intravenous and oral predonisolone (PSL) improved renal function, and he was discharged with serum creatinine around 1.50 mg/dL. One and a half years later, under PSL 5 mg/day, his serum creatinine increased to 2.20 mg/dL. Second renal biopsy revealed active tubulo-interstitial nephritis, again. PSL was increased to 40mg/day, and his renal function was gradually improved. Four years later, in February 2018, his renal function was worsened, again. CT scan revealed bilateral peri-renal retroperitoneal tumors, causing obstruction of bilateral ureters. Bilateral nephrostomy catheters were inserted. At that time, an echo-guided biopsy of the tumors and kidney was performed, revealing numerous patchy infiltrations of IgG4 positive lymphocytes. Intravenous and oral PSL improved renal function, and bilateral nephrostomy catheters were removed on the 40th day, and he was discharged on 70th day, with serum creatinine 1.50 mg/dL.

Discussion: IgG4RKD has been reported to be responsive to steroid therapy (Jap J Nephrol 2011, Saeki T, et al. 2011, Saeki T, et al KI 2013). However, there are very few cases with relapsing IgG4RD in the long clinical course of corticosteroid therapy. Further, there is no case with bilateral ureteral obstruction by tumors with IgG4 infiltration, causing renal failure. The present case indicates that IgG4RKD relapse in the long course of corticosteroid therapy. Also, our case suggests that CT scan should be done to search the cause of renal failure, including retroperitoneal lesions as in the preset case..

PUB361

A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits with Nephrotic Syndrome

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Introduction: In most forms of immune complex–mediated glomerulonephritis, the deposited immunoglobulins are typically polyclonal. Renal disease related to glomerular deposits of monoclonal immunoglobulins includes light- and heavy-chain deposition disease, type 1 cryoglobulinemic glomerulonephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy and proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID). PGNMID is a rare and recently identified disease with a poor prognosis irrespective of the treatment. We report here a case of PGNMID with positive staining for a single light-chain isotype κ and a single heavy-chain subtype IgG3 successfully treated with corticosteroids.

Case Description: A 43-year-old woman with a 3-year history of proteinuria and 2-year history of hematuria was hospitalized because of nephrotic syndrome. At the time of renal biopsy, urinalysis indicated 6.5g/day of urinary protein and microscopic hematuria. Serum creatinine was 1.5 mg/dL. Serum and urine M-protein were negative, and the free light chain κ/λ ratio was within normal limits. Renal biopsy revealed moderate mesangial proliferation and endocapillary cell proliferation. Immunofluorescence staining indicated IgG, C3 and C1q deposits in the mesangium and along the glomerular capillary walls. To rule out secondary MPGN, IgG subclass was elucidated, and detected IgG3 monoclonarity. The light-chain isotype analysis indicated κ-light chain was detected mainly in the glomerular capillary walls. Electron microscopy further showed electron dense deposits in the mesangium and subendothelial space and podocyte foot process effacement. Taken together, we diagnosed as PGNMID. After the treatment with intravenous steroid pulse and consecutive oral steroid, serum creatinine and proteinuria improved to 1.02 mg/dl and under 0.3 g/day, respectively.

Discussion: PGNMID is a novel form of proliferative glomerulonephritis, resembling immune complex–mediated glomerulonephritis. However, the glomerular deposits are a single γ heavy-chain subclass and a single light-chain isotype, most commonly IgG3 κ in the absence of serum M-spike. In patients with PGNMID, about 35% had persistent renal dysfunction, and 22% progressed to ESRD. This case suggested importance of IgG subclass analysis to diagnosis of PGNMID in cases of MPGN.

PUB362

Renal Pathological Analysis Using Galactose Deficient IgA1 Antibody Could Differentiate Secondary IgA Nephropathy from Primary IgA Nephropathy

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Introduction: In several cases with IgA Nephropathy (IgAN), differenatial diagnosis is difficult due to the complication with other diseases that can induce secondary IgAN. Galactose-deficient IgA1 (Gd-IgA1) has been recognized as the key molecules in the pathogenesis of IgAN. Recently, we demonstrated that immunostaining with Gd-IgA1-specific monoclonal antibody (KM55 mAb) could differentiate IgAN from other glomerular diseases including HCV-related nephropathy (HCV-RN). We report a case of HCV-RN successfully treated by Daclatasvir and Asunaprevir by definitive diagnosis using KM55 mAb.

Case Description: A 66-year-old man presented massive proteinuria (5 g/gCr) and admitted to our hospital. He has presented with microscopic hematuria and proteinuria from the age of 56. After 7 years from the onset of urinary abnormalities, levels of urinary protein increased up to 5 g/gCr, and kidney biopsy was performed. Pathological findings of kidney biopsy specimens revealed mesangioproliferative glomerulonephritis with IgA and C3 deposition, and he was diagnosed with IgAN. Blood examination revealed liver dysfunction by HCV infection. Then, we re-analyzed biopsy specimens using KM55 mAb. KM55 mAb was negative in this case and thus he was diagnosed as HCV-RN. Then, he received antiviral treatment with Daclatasvir/Asunaprevir. Microscopic hematuria improved, and proteinuria decreased (1.5 g/gCr) by 24 weeks. After 2 years from treatment with Daclatasvir/Asunaprevir, level of proteinuria was 0.8 g/gCr.

Discussion: Patients with HCV infection have a higher risk of end-stage renal disease. Definitive diagnosis HCV-RN from IgAN is not easy in patients HCV positive. KM55 mAb is a strong tool to differentiate secondary IgAN from primary IgAN

PUB363

An Unusual Case of Serology Negative Crescentic Glomerulonephritis

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Introduction: Anti-GBM (anti-glomerular basement membrane) disease and ANCA vasculitis can coexist but very rare. Seronegative anti GBM disease occurs in 3-4% and seronegative ANCA disease occurs in 10-20% of patients. We describe an unusual renal biopsy showing pathological features of both anti GBM and ANCA crescentic glomerulonephritis; however, serologies were negative for anti GBM antibody and ANCA antibodies.

Case Description: A 46-year-old female presented with history of fatigue and intermittent painless gross hematuria for one month. Physical examination revealed pulmonary congestion and edema. Labs showed hemoglobin 8.7 mg/dl, BUN 85 mg/dl and creatinine 10.8 mg/dl with nephrotic range proteinuria. The patient was emergently started on hemodialysis. Renal imaging showed poor definition of the pelvicaliceal collecting system, normal sized kidneys and bladder wall thickening. Serologies revealed negative ANA, ANCA, anti GBM titers and normal complements. The patient underwent cystoscopy for hematuria, which revealed catheter associated bladder mucosal changes, with no tumors. However, there was light bloody efflux from both ureteral orifices. A renal biopsy was performed and revealed 90% glomerular involvement by active crescents. Immunofluorescence revealed linear glomerular capillary wall staining for IgG. While the majority of the crescents were active and cellular, there was also temporal heterogeneity, with few subacute (fibrocellular) and rare remote/fibrous crescents. This heterogeneity is unusual for anti-GBM nephritis, where all crescents are typically in the same, active stage. Despite the finding of linear GBM staining for IgG, the appearance of the crescentic GN was more consistent with an ANCA-associated vasculitis. The findings raised the possibility of a dual disease process; however, serologic studies for both anti-GBM and ANCA were negative. The patient was treated with pulse dose steroids and cyclophosphamide. Unfortunately, the patient developed infectious complications to cyclophosphamide and treatment was terminated.

Discussion: This case signifies the overlapping features of both anti GBM and ANCA crescentic glomerulonephritis on renal biopsy, but with negative serologies. Although rare, the possibility of atypical anti-GBM and ANCA antibodies, which are not detected by standard commercial assays, should be considered in such cases.

PUB364

Steroid-Resistant Nephrotic Syndrome in a Patient with Lupus: Is It Only Lupus?

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Introduction: Renal involvement in systemic lupus erythematous (SLE) is frequent and it has many therapeutic options. Nephrotic syndrome (NS) is a classic manifestation of class V lupus nephritis (LN), but it can be also due to lupus podocytopathy, a condition with excellent response to steroids. We present a case of steroid-resistant NS with diagnosis

of LN, whose further clinical and laboratory work-up revealed an unexpected cause of nephrosis in LN.

Case Description: A 21 year old woman with history of hypothyroidism, oral ulcers, anemia and foamy urine. Laboratory tests showed: serum creatinine 0.7 mg/dL, albumin 2 g/dL, total cholesterol 297 mg/dL, proteinuria in nephrotic range and positive antinuclear antibodies 1:320. Renal biopsy showed LN class II, with mesangial deposits of IgG, IgM, C1q and C3. Electron microscopy showed diffuse foot processes effacement and immune complexes in mesangium, without subepithelial, subendothelial or membranous deposits. The patient was treated with anti-proteinuric measures, corticosteroids, hydroxychloroquine and azathioprine. She persisted with nephrotic range proteinuria and severe hypoalbuminemia despite normal blood pressure and no clinical or laboratory evidence of active SLE. A change of LN class or lupus podocytopathy was suspected, and immunosuppression was intensified. Since nephrotic proteinuria persisted, a second renal biopsy and genetic study of NPHS2 mutation was performed. Sequencing NPHS2 gene resulted in a compound heterozygous mutation with substitutions on p.R229Q and p.A284V. The renal biopsy showed focal segmental glomerulosclerosis and the electronic microscopy revealed diffuse damage of podocytes, with signs of scarring and resolving immune deposits.

Discussion: A persistent nephrotic syndrome in a patient with controlled SLE despite adequate treatment should raise the suspicion of change in the class of LN and/or the superposition of a lupus podocytopathy. For those cases with no response to treatment, unusual causes of heavy proteinuria should be considered in the differential diagnosis. Genetic causes of nephrotic syndrome in young patients with SLE should be part of the clinical and laboratory work-up of these type of patients.

PUB365

Treatment Response in Membranoproliferative Glomerulonephritis with Negative Immunofluorescence

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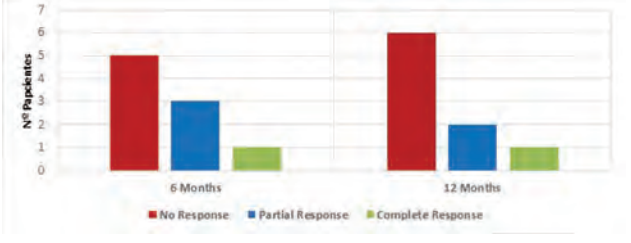
Background: Recent advances in understanding the role of the alternative pathway of complement in membranoproliferative glomerulonephritis (MPGN) consist in evaluating the findings of the immunofluorescence (IF): MPGN immune-complex or complement-mediated. If none of these causes is present, then chronic thrombotic microangiopathy is the main cause of MPGN. However, reports on the clinical evolution of these patients are limited. The objective of this study was to evaluate the treatment response in patients with MPGN and negative IF.

Methods: Analytical and retrospective study. Patients with MPGN pattern through renal biopsy and negative IF were included. Each sample was studied by light microscopy and included Hematoxylin, PAS, and Jones and trichrome stain. The immunofluorescence was performed using direct antibodies against IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, Lightweight Kappa and Lambda chains. Patients were evaluated according to response groups: complete response, partial response and no-response at 6 and 12 months of treatment with Immunosuppressants (MMF or CYC) and glucocorticoids (prednisone).

Results: We included 9 patients with mean age of 33.8 ± 13.1 years, of which 67% were male. 5 (62%) patients started with anemia and thrombocytopenia. The most frequent clinical presentation was asymptomatic urinary alterations (70%). The means values of baseline proteinuria (mg/24h) (1014 ± 1173) at 6 (942 ± 722) and 12 (958 ± 613) months did not show statistically significant differences ($p<0.05$). After 6 months of treatment, 4 (44%) patients achieved response (33% partial and 11% complete). 6 (66%) failed to achieve response at 12 months.

Conclusions: In our study, immunosuppressive therapy did not show statistically significant benefits in MPGN with negative IF at 6 and 12 months of treatment. Chronic thrombotic microangiopathy may be the cause of the MPGN and a formal trial with eculizumab well-characterized patients is warranted.



Response to immunosuppressive treatment of MPGN and negative IF

PUB366

Treatment of Fibrillary Glomerulonephritis with Bortezomib-Dexamethasone: A Case Report

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Introduction: Fibrillary glomerulonephritis (GN) is a poorly understood glomerular disease with no proven treatments and a poor renal prognosis. We present the case of a fibrillary GN successfully treated with bortezomib-based therapy.

Case Description: A 59-year-old Hispanic male had a past medical hypertension and microscopic hematuria for many years, for which he had undergone a renal ultrasound and cystoscopy which did not reveal an etiology. He developed acute kidney injury (SCr 2.3 mg/dL from baseline 1.1 mg/dL). A urinalysis showed moderate blood, 3+ protein, and microscopy showed RBC 50-100 dysmorphic/hpf. Urine protein:creatinine ratio (UPCR) was 1.6 g/g. Serologic testing for hepatitis B and C viruses, HIV, ANCA's, C3 and C4 were negative or normal. A kidney biopsy was diagnostic of fibrillary glomerulonephritis. He was treated with weekly subcutaneous bortezomib 1.3 mg/m2 oral dexamethasone 40 mg on days 1, 8 and 15 repeated every 28 days. The evaluation for monoclonal gammopathy with serum protein electrophoresis and serum free light chain was negative. After his second month of treatment, he developed steroid-induced hyperglycemia requiring insulin therapy. With 5 cycles of therapy, his serum creatinine improved to 1.5 mg/dL, UPCR ratio improved to 0.1 g/g, and microscopic hematuria improved to 2-5 RBC/hpf. At last follow-up, 8 months after stopping treatment, his SCr was 1.8 mg/dL, UPCR was 0.05 g/g, and urinalysis showed 20-50 RBC/hpf.

Discussion: We present a case of fibrillary glomerulonephritis successfully treated with bortezomib-dexamethsone. The effectiveness of bortezomib-based regimens in fibrillary glomerulonephritis requires further exploration.

laboratory trends

	Initial presentation	Treatment start	After 5 cycles	8 months after the end of therapy
sCr (mg/dL)	2.3	1.8	1.5	1.8
Alb (g/dL)	3.5	3.5	3.8	4.2
UPCR (g/g)	1.60	1.30	0.1	0.05
Urine RBC/hpf	50-100		2-5	20-50

PUB367

Cytokine Profile and Renal Response in Lupus Nephritis Women

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Background: The importance of cytokine profile in LN is controversial in spite of their role in disease activity. This study measured six cytokines in LN outpatients and analyzed outcomes.

Methods: Serum cytokines (IL-2; IL-4, IL-6, IL-10, TNF-α, IL-17) from 59 LN and 40 healthy control women were measured by Cytometric Bead Array (CBA) using CBA Human Th1/Th2/Th17 Kit. Renal response and lupus activity were defined according to KDIGO guidelines and SLEDAI respectively. Statistical analyses were done using the GraphPad Prism 6.0.

Results: In LN group mean age was 35y (±10), 68% was non-white women with median LN diagnosis of 88 (62-156) mo and median SLEDAI was 7.7 (0-12) during serum collection. The healthy control group presented mean age of 60y (±5) and 65% non-white women. Their kidney biopsy showed proliferative lesions (class III or IV) in 85% of cases and they were using maintenance therapy in 86% of cases, mostly with Mycophenolate Mophetil (72.4%). Complete or partial response was present at 75.4%, non-response in 14% and decline of renal function in 10.5% of cases. Serum levels of all the cytokines analyzed were significantly increased in LN patients when compared to healthy controls ($p < 10^{-4}$). Similarly, all cytokines were higher in responsive (partial and complete) group than non-responsive group ($p < 10^{-5}$) and IL-17 showed higher values in the responsive group (42.37 ± 7.86 pg/mL). However, statistically significant differences were not found after 4 years of follow-up. Regarding to LN activity, IL-10 showed increased levels in active LN patients (SLEDAI ≥10) (5.07 ± 1.56 pg/mL) in comparison with inactive LN patients (SLEDAI <10) (4.67 ± 1.29 pg/mL) ($p = 0.037$). Additionally, IL-10 levels are correlated with higher values of proteinuria and TNF-α levels ($r = 0.02$ and $p = 0.02$; $r = 0.3$ and $p = 0.02$; respectively). Finally, higher TNF-α levels (4.76 ± 1.24 pg/mL) were correlated to LN class IV ($r = 0.41$; $p = 0.004$) when compared to class III (4.16 ± 0.23 pg/mL).

Conclusions: The anti-inflammatory IL-10 was increased in active lupus probably in effort to control disease activity. Class IV LN had higher TNF-α levels, which may be related an increased inflammatory process and tissue damage. Higher serum six citokines are found in responsives compared to non-responsives, however baseline levels are lacking and this did not predict long term outcomes.

PUB368

Subacute Bacterial Endocarditis (SBE) Presenting as ANCA-Associated Vasculitis (AAV)

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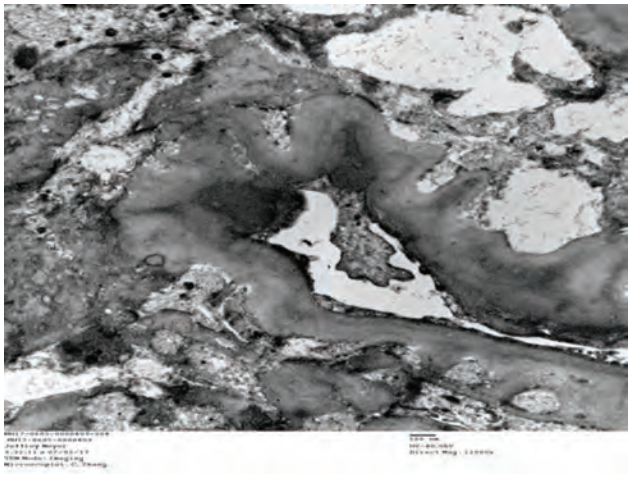
Introduction: The history, and laboratory evaluation may suggest the diagnosis of an AAV, leading the clinician to treat empirically (without renal biopsy). Described is a case of Enterococcus faecalis endocarditis (EFE) masquerading as an AAV.

Case Description: A 73-year-old male presented with a history of hypertension, benign prostatic hypertrophy and new onset anemia. Five months earlier he had experienced onset of hematuria, undergone urologic evaluation showing cortical renal cysts and renal asymmetry. At the time of presentation, serum creatinine was 2.1 mg/dL. Additional labs showed a hematocrit of 23%, and urinalysis dipstick positive for blood. Hepatitis B and C serologies, HIV, ANA, anti-double-stranded DNA, anti-RNP/Sm, anti-SSA/SSB all negative. C3 was initially normal, low on repeat (76mg/dl); C4 was normal. The ANCA returned abnormal (PR3+, MPO-), and a renal biopsy was performed, notable for absence of crescents and necrosis, but positive for subepithelial, intramembranous, and subendothelial electron dense deposits. Blood cultures were positive for Enterococcus faecalis. Echocardiography showed an aortic vegetation, leading to the diagnosis of EFE SBE. He was initiated on antibiotic therapy. Due to continued complaints of back pain, an MRI was performed, revealing discitis/osteomyelitis.

Discussion: The appropriate history, biochemical findings, serologies, and positive PR3Ab must be interpreted with caution as the possibility of an underlying infection needs to be considered. Approximately four reported cases of EFE with PR3Ab positivity have been noted previously. While uncommon, SBE as a cause for PR3Ab positivity needs to be a consideration.



Rare subepithelial immune type electron dense deposits.

PUB369

Rituximab in Minimal Change Disease

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Background: Adults with minimal change disease are often steroid dependent. Rituximab (RTX) is increasingly being used in the treatment of minimal change disease (MCD) but data is lacking. Most studies have had small numbers of patients.

Methods: We retrospectively reviewed 7 consecutive patients with steroid dependent* MCD who received RTX from 2014-2018 at one academic medical center. Five patients (71%) were African American women. Ages range 23-62 (median: 30). RTX was administered 1000 mg IV spaced 2 weeks apart. Notably, 2 patients did not receive a 2nd dose as intended and subsequently relapsed. *defined as relapsing during glucocorticoid taper or within 2 weeks of discontinuation of glucocorticoids

Results: 4 patients achieved complete remission (defined as UP/C ≤0.3 g) and 3 patients had a partial remission (defined as UP/C between 0.3 g and 3.5 g and a 50% reduction of proteinuria) after treatment with RTX. Six patients were nephrotic at the time of treatment with RTX (defined as UP/C > 3.5, hypoalbuminemia and edema). Six patients were on steroids at time of treatment, 1 patient was on tacrolimus monotherapy. 3 patients had relapses of nephrotic syndrome, 2 received repeat doses of RTX, 2 only had one dose initially and 1 was lost to follow up. Follow up has ranged from 2-37 months (median: 24 months). Patient demographics are noted in table. Prior to receiving RTX, 2 patients required short term dialysis, 2 patients had venous thromboses, 4 were hospitalized for sepsis and 6 were admitted to the hospital with volume overload. Adverse events from Rituxan have been limited to 1 patient with alopecia. There were no infusion reactions.

Conclusions: Our small study shows RTX is effective in decreasing proteinuria in a largely African American cohort of patients. Randomized trials are needed but RTX should be considered as a treatment in steroid dependent minimal change disease.

Patient Demographics

Patient	Age at infusion	Sex	Race	Peak UP/C (g)	Most recent UP/C (g)	Current Prednisone dose (mg)	Months since last RTX
1	28	M	White	13	0	0	37
2	57	F	African American	13.1	0	2.5	36
3	23	F	African American	20.2	15*	unknown	27
4	30	F	African American	17.5	0	0	24
5	37	M	White	18.2	0.4	0	20
6	27	F	African American	6.9	0.1	20	2
7	62	F	African American	23.1	2	20	4

*Pt had partial remission (UP/C 0.5) after 1 dose of RTX, returned with disease flare and lost to follow up

PUB370

Individualized Eculizumab Every 3 Months Maintains Successful Remission In Pregnancy-Associated Hemolytic Uremic Syndrome with Hybrid CFHR1/CFH Gene: Case Report and Review of Literatures

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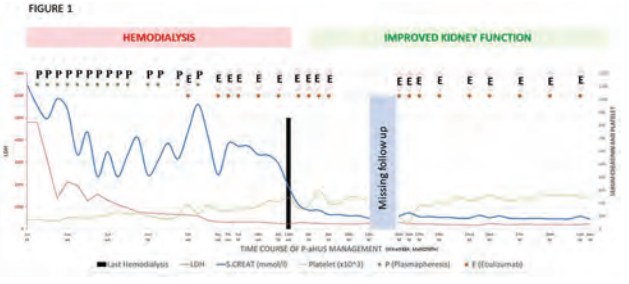
Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) is a rare condition and affects 1 of every 25,000 pregnancies. P-aHUS is characterized by very high maternal mortality as well as severe morbidity. More than half of all patients eventually develop end-stage renal disease in less than 1 month if untreated. Most cases of P-aHUS (79%) manifest in the postpartum period; this is probably due to the complement's involvement in aHUS pathogenesis. Eculizumab, a terminal complement inhibitor, is approved for aHUS treatment. However, its use is limited due to cost, unknown duration of treatment, and vague dose intervals to keep patients in remission.

Case Description: In this case report, we present a 26–year-old female with P-aHUS with hybrid CFHR1/CFH gene. Eculizumab was initiated after 5 weeks of being on hemodialysis and plasmapheresis sessions. Full remission successfully achieved after 6th dose of Eculizumab, within 13 weeks of onset of aHUS. She was in full remission with Eculizumab, however, due to financial issues Eculizumab was set in hold due to inability to financially cover the cost. Within 6 months, she suffered recurrence of the disease and Eculizumab was re-instated. After re-inducing full remission, the patient was switched to Eculizumab every 3 months instead of the recommended manufacture dose interval of every 2 weeks. We followed this patient for 3 years and she continued to be in remission based on clinical and laboratory data.

Discussion: In conclusion, achievement of successful and maintenance of remission of P-aHUS in this patient who had limited access to Eculizumab raise the attention of the efficacy of Eculizumab at longer time intervals. However, it is time to consider conducting a long-term study to learn about the safety and efficacy of this approach, which may have a major financial advantage for patients.



PUB371

Campylobacter Rectus and Cnm-Positive Streptococcus mutans Strains in the Oral Cavity Exacerbate Urinary Protein Levels in IgAN Patients

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Background: Some strains of *Streptococcus mutans*, a major pathogen of dental caries, harbour the *cnm* gene which encodes a collagen-binding protein (Cnm) that has been demonstrated to be associated with urinary protein levels in IgAN patients. Periodontitis-related pathogens, such as *Campylobacter* or *Treponema* species, have recently been shown to be associated with IgAN. The purpose of the present study was to analyse the association of IgAN with *Campylobacter rectus*, *Treponema denticola* and *cnm*-positive *S. mutans* in the oral cavity of humans.

Methods: The presence of *C. rectus*, *T. denticola* and *cnm*-positive *S. mutans* strains in saliva samples of 117 IgAN patients and 56 health controls was evaluated by PCR, and the subjects' clinical parameters were analysed.

Results: *C. rectus* and *cnm*-positive *S. mutans* were significantly more prevalent in the IgAN group than in the control group ($p < 0.05$). Additionally, the *C. rectus*-positive and *cnm*-positive *S. mutans* group was shown to be more closely associated with urinary protein levels than the other groups in IgAN patients.

Conclusions: Our results suggest that harbouring *C. rectus* and/or *cnm*-positive *S. mutans* strains in the oral cavity could be associated with urinary protein levels in the IgAN patients.

PUB372

Acquired Angioedema: A Unique Complication in a Patient with Lupus Nephritis

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Introduction: Acquired angioedema (AAE) is a rare syndrome of recurrent episodes of angioedema without urticaria, which has been associated with B cell lymphoproliferative disorders and rarely with autoimmune diseases. In lupus, AAE may arise from an antibody mediated functional deficiency of C1 esterase inhibitor (C1INH) - a key inhibitor within four interlinked inflammatory cascades.

Case Description: A 28-year-old black woman with quiescent Lupus Nephritis class III & V presented with recurrent edema of the face, arms and abdomen. She had no family history of angioedema and denied allergies. Physical examination revealed bilateral proptosis, edema of the face, arms and abdomen. Respiratory and cardiovascular examinations were unremarkable. CT scan of the head and neck showed periorbital and neck soft tissue swelling with bilateral proptosis. Laboratory data revealed a serum creatinine of 1.7 mg/dl (baseline), leukocyte count of 12,000/microliter and hemoglobin of 10 g/dl. Hypocomplementemia was evident (C3 21 mg/dl and C4 11 mg/dL); anti-DsDNA antibody was 140 IU/ml and urine protein/creatinine ratio was 1700 mg/gm. No clinical improvement was noted after three days of high dose intravenous steroids. Further investigations revealed a C1INH protein level of 23 mg/dL (15-35 mg/dL), functional level of 15 percent (normal > 67 percent), very low C1q level (15 percent) and presence of antibodies to C1INH.Rituximab 1 gram produced an expedient clinical recovery.

Discussion: Angioedema is a life-threatening condition involving the mucosa of the gastrointestinal and respiratory tract. Acquired angioedema differs from hereditary angioedema by absence of family history and late onset of disease. Majority of patients with AAE have been found to have an underlying disorder and about thirty percent test positive for associated antibodies. In lupus patients with angioedema, antibodies to C1INH have been identified. These antibodies lead to an acquired consumption of C1INH resulting in a low or normal C1INH protein level, a low functional percentage of C1INH, low C4 and C1q. Rituximab (a chimeric monoclonal antibody directed at B cells), has been tried in some cases of antibody mediated AAE with a favorable rapid response, when conventional therapies have failed. In summary, we present a case of steroid resistant AAE probably due to Lupus induced antibodies to C1INH and suggest one possible treatment option in Rituximab.

PUB373

An Uncommon Case of Seronegative Primary Membranous Nephropathy in a Young Hispanic Patient

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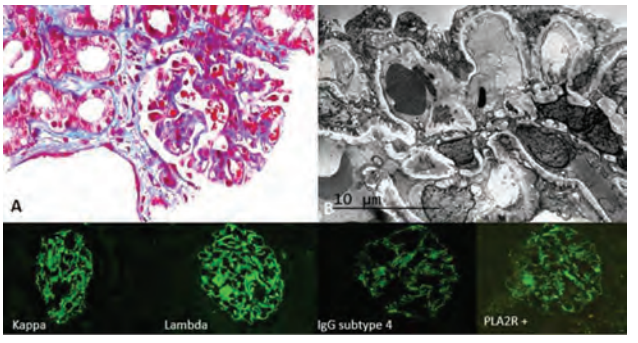
Introduction: Membranous nephropathy (MN) is the most common cause of idiopathic nephrotic syndrome in non-diabetic white adults. The mean age of incidence of Primary MN is between 50 and 60 and is most common in whites followed by Asians, Blacks, and Hispanics. Most cases of PMN have circulating IgG4 autoantibody to the podocyte membrane antigen PLA2R (70%). A minority of the patients have thrombospondin type 1 domain containing 7A (THSD7A) antibodies. It is noteworthy that about 15% cases have biopsy evidence of PLA2R staining indicating recent immunologic disease activity despite negative serum antibody levels. Herein, we present a case of young Hispanic male with biopsy-proven primary MN with positive PLA2R staining but negative circulating antibodies.

Case Description: A 34-year-old Hispanic man with no significant medical history presented with worsening extreme generalized edema. Laboratory data was consistent with nephrotic syndrome with a urine protein-creatinine ratio of 11 g/g, LDL cholesterol 279 mg/dL and serum albumin of 1.1 g/dL. Further work up for HIV, viral Hepatitis, syphilis and common vasculitides was negative. Testing for PLA2R and THSD7A antibodies was negative as well. A renal biopsy was obtained, which demonstrated thickened capillary loops with subepithelial electron dense deposits and diffuse podocyte foot process effacement. Immunofluorescence was strongly positive for PLA2R, suggestive of primary MN [Figure]. He was started on RAAS blockade, statin and diuretic therapy with symptomatic improvement. He was instructed to follow up with Nephrology in a few months to determine the necessity for immunosuppressive therapy.

Discussion: Take home point: Primary MN is typically a disease of middle-aged White men but should be included in the differential diagnosis of nephrotic syndrome in patients of any age and race. Moreover, while serological anti-PLA2R testing has diagnostic value, it must be interpreted in context with patients' clinical characteristics and histological PLA2R staining in seronegative patients is recommended.



PUB374

Clinical Significance on the Difference in Character of Glomerular Tip Lesion in Adult Nephrotic Focal Segmental Glomerulosclerosis (FSGS): A Retrospective Cohort Study

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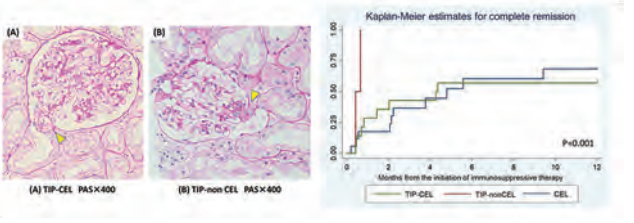
Background: In Columbia classification, locating FSGS lesion in tip domain is prioritized than its pathological character. Hence, patient with glomerular tip lesion (GTL) are usually categorized into tip variant (TIP), not cellular variant (CEL) even if the lesion is cellular type. This diagnostic process on GTL has not been discussed well. We investigated the clinical importance of the GTL among adult nephrotic FSGS patients with TIP.

Methods: A retrospective cohort study; Among 183 biopsy-proven FSGS during 2005-2015, 48 patients who fulfilled the criteria below were included to analyses: ≥20 years old, nephrotic syndrome (serum albumin ≤3.0 and UPCR ≥3.5), received immunosuppressive therapy and whose pathological slides or paraffin blocks were available for review. All pathological slides were reviewed on light microscopy by 3 nephrologists and 1 renal pathologist. Among TIP cases, patients were divided into 2 subgroups based on the dominant character of GTL: cellular type (TIP-CEL) and non-cellular type (TIP-nonCEL). The clinical manifestation and treatment course were compared among the subgroups.

Results: Among 48 patients, 16 were TIP (33.3%) and 17 were CEL (35.4%). Among 16 TIP, 14 cases were categorized into TIP-CEL and 2 cases into TIP-nonCEL. There was no difference in the details of immunosuppressive treatment among the subgroups. Even though TIP-nonCEL, comparing with TIP-CEL or CEL, manifested higher creatinine (1.63 vs 0.99 vs 1.50 mg/dL) and larger urinary protein level (11.31 vs 5.33 vs 7.40 g/gCr), TIP-nonCEL showed excellent therapeutic reactivity which was comparable to that of MCD to attain complete remission. On the other hand, TIP-CEL showed similar treatment response to CEL.

Conclusions: The diagnostic hierarchy of Columbia classification on FSGS may be confusing because it contains both aspects of location and characteristics of FSGS lesions. In adult nephrotic FSGS, therapeutic reactivity of TIP might be depended on their pathological character; presence or absence of cellular lesion.



PUB375

Clinicopathological Features in Lupus and Nonlupus Membranous Nephropathy

Laura Onuchic, Pamela B. Larrea, Ligia C. Battaini, Cristiane B. Dias, Luis Yu, Viktoria Woronik, Lectícia Jorge. *University of Sao Paulo, Brazil, São Paulo, Brazil.*

Background: Membranous nephropathy (MN) is well established as one of the morphologic presentations of systemic lupus erythematosus and idiopathic nephrotic syndromes. The aim of this study was to compare clinical, biochemical and histological characteristics of patients diagnosed with nonlupus MN to class V lupus nephritis (CVLN).

Methods: All MN and CVLN cases diagnosed by kidney biopsy in our center between 2009 and 2016 were retrospectively analyzed. Clinical and laboratorial data were collected at baseline and at the end of follow up.

Results: The prevalence of male gender and older age was significantly higher in the MN group (65.2% *vs* 13.0%, p<0.001 and 48.4±14.7 *vs* 37.0±11.0 years, p<0.001, respectively). The MN group presented higher baseline serum creatinine (Cr, mg/dL) {1.08

(0.79;1,88) *vs* 0.74 (0.58;1.32), p<0.05}, higher proteinuria (g/day) {7.2 (5.1;10.2) *vs* 2.7 (1.1:3.9), p<0.01} and lower serum albumin (mg/dL) (2.1±0.77 *vs* 2.8±0.93, p<0.001) when compared to the LN group. After a mean follow-up of 3.0 years (1.1; 6.9) in the MN group and 2.9 years (1.0; 5.3) in LN, we observed that both groups presented reduction in proteinuria, however the levels were still higher in the MN group {1.7 (0.3;3.8) *vs* 0.5 (0.1;1.2) p<0.001}. Following the same trend, the MN group maintained higher Cr levels {1.36 (0.90; 2.55) *vs* 0.75 (0.50; 1.00)}. Among the optical microscopy findings, the only significant difference was a higher frequency of mesangial hypercellularity in the CVLN than MN group (58.7% *vs* 37.0% of glomeruli; p=0.015). Immunofluorescence (IF) findings are reported in *Figure 1*.

Conclusions: While optical microscopy was scarcely efficient in differentiating MN from CVLN, IF findings were significantly different between the two groups, particularly those related to mensangial deposits. We also underscore the difference in renal function behavior: stable in CVLN while dropping in MN during the follow-up time.

TABLE 1	MN	Class V LN	*p Value*
Biopsies	92	46	
IGA n(%)			
Mesangium			
Present	5 (5.4%)	9 (19.6%)	0.01
Capillary loops			
Present	7 (7.6%)	13 (28.3%)	0.001
IGG n(%)			
Mesangium			
Present	11 (12%)	24 (52,2%)	<0.001
Capillary loops			
Present	90 (97.8%)	42 (91,3%)	0.07
IGM n(%)			
Mesangium			
Present	10 (10.9%)	17 (37%)	<0.001
Capillary loops			
Present	20 (21.7%)	26 (56.5%)	<0.001
C3 n(%)			
Mesangium			
Present	10 (10.9%)	23 (50%)	<0.001
Capillary loops			
Present	54 (58.7%)	32 (69.6%)	0.21
C1q n(%)			
Mesangium			
Present	4 (4,3%)	19 (41,3%)	<0.001
Capillary loops			
Present	8 (8,7%)	28 (60,9%)	<0.001

Table -1- The demographic profiles of patients

Parameters	Perihillar (3)	NOS(80)	Tip(21)	Cellular(6)	P value
Proteinuria	4.80±1.21	4.71±1.11	6.4±1.77	8.39±3.63	<0.001
Creatinine at biopsy(mg/dl)	2.85±0.65	1.79±0.46	1.45±0.35	2.16±0.8	<0.001
Serum Albumin	3.0±0.26	2.96±0.34	2.64±0.47	2.54±0.65	0.003
Hypertension	100%	70%	42.85%	66.66%	

Table-2: Different degree of histopathologic lesions in FSGS glomeruli

Interstitial Fibrosis

Variant	Perihilar	NOS	Tip	Cellular	P value
No. of Cases	3	80	21	6	
Absent	0(0.0%)	6(7.5%)	5(2.38%)	0(0.0%)	0.035
Mild	2(66.7%)	24(30.7%)	9(42.9%)	4(66.7%)	
Moderate	1(33.3%)	39(48.8%)	7(33.3%)	0(0.0%)	
Severe	0(0.0%)	11(13.8%)	0(0.0%)	2(33.3%)	

Tubular atrophy

Variant	Perihilar	NOS	Tip	Cellular	P value
No. of Cases	3	80	21	6	
Absent	0(0.0%)	6(7.5%)	5(2.38%)	0(0.0%)	0.035
Mild	2(66.7%)	24(30.7%)	9(42.9%)	4(66.7%)	
Moderate	1(33.3%)	39(48.8%)	7(33.3%)	0(0.0%)	
Severe	0(0.0%)	11(13.8%)	0(0.0%)	2(33.3%)	

Fibro intimal thickening(%)

Variant	Perihilar	NOS	Tip	Cellular	P value
No. of Cases	3	80	21	6	
Absent	0(0.0%)	6(7.5%)	5(2.38%)	0(0.0%)	
Mild	2(66.7%)	24(30.7%)	9(42.9%)	4(66.7%)	0.035
Moderate	1(33.3%)	39(48.8%)	7(33.3%)	0(0.0%)	
Severe	0(0.0%)	11(13.8%)	0(0.0%)	2(33.3%)	

Glomerular Sclerosis

Variant	Perihilar	NOS	Tip	Cellular	P value
No. of Cases	3	80	21	6	
Absent	2(66.7%)	3(3.8%)	2(9.5%)	0(0.0%)	
Mild	0(0.0%)	42(52.5%)	14(66.7%)	2(33.3%)	0.001
Moderate	0(0.0%)	32(40.0%)	5(23.8%)	0(0.0%)	
Severe	1(33.3%)	3(3.8%)	0(0.0%)	4(66.7%)	

Variant	Perihilar	NOS	Tip	Cellular	P value
No. of Cases	3	80	21	6	
Complete remission	0(0.0%)	23(28.75%)	8(38.09%)	3(50.0%)	
Partial remission	1(33.3%)	23(28.75%)	5(23.8%)	0(0.0%)	0.603
No remission	2(66.7%)	34(42.5%)	8(38.09%)	3(50.0%)	

Table3: 24 hour urinary protein estimation at one year of follow up

PUB376

Clinicopathological Characteristics of FSGS and Their Correlation with Histologic Variants in Selected Population

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Background: FSGS is a histological diagnosis in which there is nephrotic renage proteinuria and that leads to hypertension and renal failure. Five histological variants of FSGS. Not otherwise specified (NOS), perihilar variant, cellular variant, tip variant and collapsing variant.

Methods: Study Design: We have included 110 patient of biopsy proven FSGS diagnosed between January 2010 to December 2012 retrospectively and collected the clinical data and histopathology report of Primary FSGS from institute's hospital information system. who fulfilled inclusion criteria. **Kidney biopsy methods**: Histopathology reports were classified according to Columbia classification guidelines. **Clinical data and definitions:** Standard clinical definition used for data. All patients received oral prednisolone at a dose of 60 mg/m^2 for at least 16 weeks **Statistical Analysis**: Data were analyzed with SPSS version 18.

Results: A total 110 biopsy proven FSGS patient biopsy were recruited retrospectively from January -2010 to December 2012 and clinical finding were noted from our electronic hospital information system. Higher degree of Hypertension and renal failure was seen in perihilar variant and 24 hour proteinuria was maximum in cellular variant. Table 1 Interstitial fibrosis, tubular atrophy and fibrointimal thickening were maximum in perihilar variant. Whereas glomeruloscelerosis was seen in 100% cases of Cellular variant. Table-2. Remission rate after one year is higher in TIP variant as compared other variants. Table 3

Conclusions: In the studied population we found that majority of patient had NOS variant. Cellular variant has highest grade of proteinuria whereas perihilar variants greater degree of renal failure at presentation. One third have complete remission whereas one fourth have partial remission.

PUB377

Significantly Different Patterns of Serum Oxidative Stress Levels in Children with Nephrotic Syndrome and Children with IgA Nephropathy

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Background: Oxidative stress (OS) has been reported to play an important role in several renal diseases, including nephrotic syndrome (NS) and IgA nephropathy (IgAN). However, no comparison study has been reported. This study was conducted to investigate the OS activity in both patient groups.

Methods: Children with NS (n = 5) and those with IgAN (n = 7) at first onset were enrolled. The plasma levels of biological antioxidant potential (BAP) and reactive oxygen metabolite-derived compounds (dROM) were measured. The dROM and BAP levels were <300 U.CARR and 2000 mmol/l higher than normal, respectively. A normal BAP/dROM level was defined as ≥10. The patient groups were compared, and the relationships of BAP and dROM levels to albumin, creatinine, uric acid, urinary protein, total cholesterol, triglyceride, and C-reactive protein levels were studied.

Results: Serum BAP levels were significantly lower in the NS group (1529 ± 259) than in the IgAN group (P < 0.001). The IgAN group had significantly higher dROM levels (394 ± 107) than the NS group (n = 0.003). BAP/dROM level was low, without significant differences, in both groups. A positive correlation was observed between the low CRP and dROM levels in the IgAN group (P = 0.02).

Conclusions: In our study, evaluation was limited to the first episode of the diseases. Even though their potential antioxidant capacities were comparable, the factors involved in the abnormality of the oxidative stress balance differed significantly between the two patient groups. As dROM increases in vasculitis, endothelial cell injury might be involved in the high dROM level in IgAN. A previous study reported a positive relationship between albumin concentration in human preparation and BAP level. Hypoalbuminemia and lipid abnormalities are considered to be involved in the reduction of BAP level, and the same tendency was observed in this study. OS activity significantly differed between the NS and IgAN groups. This helps to clarify the pathophysiological features of NS and IgAN, and support additional treatment for both diseases.

PUB378

Hemolysis-Derived Heme: A Contributing Factor in Thrombotic Microangiopathy

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Background: Although Shiga toxin (Stx)-producing *E. coli* hemolytic uremic syndrome (STEC-HUS) is one of the most common causes of acute kidney injury in children, the exact pathogenesis is still only partially understood. Due to endothelial injury caused by the Stx, the cascade leading to thrombotic microangiopathy (TMA) commences. Yet, there is wide variability in clinical presentation and outcome ranging from no chronic sequalae to severe neurological impairment and end stage renal disease. One possible explanation for this broad range of clinical outcome could be the enhancement of TMA through other additional factors. We hypothesized that extracellular accumulation of heme, as present during extensive hemolysis, could amplify TMA.

Methods: In this study, we measured levels of extracellular heme and its scavengers (hemopexin and heme-oxygenase 1; HO-1) in a cohort of 48 STEC-HUS patients and assessed the effects of these disease specific heme concentration, in combination with Stx, on glomerular microvascular endothelial cells (GMVECs).

Results: Significantly elevated heme levels up till 21.2 μM were found in STEC-HUS patients compared to controls (median of 0.9 μM). These elevated heme levels correlated nicely with plasma hemopexin levels (R^2 -0.737). Furthermore, heme is internalized in GMVECs and subsequently led to a significant increase in reactive oxygen species (ROS). Translocation of NFκB and tissue factor indicated enhancement of pro-inflammatory and thrombotic state. Interestingly, GMVECs showed a clear decrease of HO-1 after co-stimulation with Stx2.

Conclusions: We are the first to show elevated heme levels in patients with STEC-HUS. Moreover, these heme levels contribute and even amplify the cascade leading to TMA. This effect is even more pronounced in STEC-HUS since Stx inhibits the upregulation of HO-1.

PUB379

A Case of Nephrotic Syndrome Secondary to Mercury Poisoning Due to Chronic Usage of Ayurvedic Medications

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Introduction: Acute and chronic mercury exposure represents a potential threat to community health. Mercury poisoning can occur as a result of occupational hazard or herbal medicine. All compounds of mercury are toxic but differ in the routes of absorption, clinical findings, and responses to therapy. The clinical effects of mercury poisoning depend on the form and the route of entry to the organism. Neurologic, gastrointestinal and renal systems are predominantly affected depending on the route of exposure. Traditional Ayurvedic medicines originated in India 2000 years ago. Approximately one billion people use ayurvedic medicines. These medicines contain minerals & heavy metals like lead, Mercury, Selenium, Copper which are known to cause renal failure.

Case Description: 25 year old un-married female engineer came with the chief complaint of peri-orbital swelling and swelling of both feet since two months. On further enquiry patient gives history that since last six months, she had taken ayurvedic medicine for her irregular menses. On examination her vitals were stable except her B.P which was170/110. Her lab reports were Total Protein -2.4 mg/dl, Serum Albumin- 1.5mg/dl, Serum Cholesterol- 281.4mg/dl, Urine protein- ++++, Urine spot protein314, Urine spot creatinine - 93.7. Urine protein creatinine ratio was 3.0. On these basis patient was diagnosed to have Nephrotic Syndrome. As patient is young female considering SLE her Serum ANA & Serum DSDNA was done and her reports came negative. Simultaneously her renal biopsy had done shows membranous glomeruloathy. To rule out primary idiopathic membranous glomerulonephritis, her Anti-Phospholipase A2 receptor IgG(PLA2R) sent which was < 0.6 (> 20 positive) which is negative. Now considering her past history, her serum heavy metal levels were sent and its reports were following Sr. Mercury-16.6μg/L. She was initiated on mercury chelating agent, BAL following which her mercury levels dropped down to 2μg/L. Her proteinuria dropped to normal range over next six months without other therapy.

Discussion: This case report emphasizes the importance of public education on poisoning and specifically, potential hazards of mercury for preventive community health. High risk of suspicion in patients with secondary nephrotic syndrome needs to be kept with history of consumption of Ayurvedic medicines.

PUB380

The Clinical Significance of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) in Patients with Systemic Lupus Erythematosus (SLE)

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Background: To discuss the clinical significance of CRP and ESR in SLE patients by a retrospective analysis.

Methods: 80 SLE cases were divided into 3 Groups,by differences in disease activity, whether complicated by infection and by different organs damaged. To analyse the level of CRP, ESR in different groups.

Results: 1) General data: There was an increased CRP in 36 cases (45%), and an increased ESR in 52 cases(65%). SLE injury multiple systems, the most frequently injuryed organ was the kidney (52 cases, 65%). 2) The CRP level was significantly increased in cases complicated by infection($p<0.05$). The increased level of CRP was significantly correlated with serosa damage($p < 0.05$). There was no correlation with systemic damage such as hematological system, kidney, skin and mucous membrane, joint, nervous system damage ($p > 0.05$). 3) The level of ESR was significantly increased in the patients with organs damage including hematological system, kidney, and serosa damage ($p < 0.05$), but not in the patients with mucous membrane and the skin, joint, nervous system damage ($p > 0.05$).

Conclusions: The level of CRP probably has no relation with SLE disease activity, the level of increased ESR may be associated with SLE disease activity. The level of CRP is associated with SLE with infectious disease. In terms of organ damage, the level of CRP was associated with serosa damage, the level of ESR was associated with blood system, kidney, serosa damage.

PUB381

Complex Regional Pain Syndrome (CRPS) Is Common in Loin Pain Hematuria Syndrome (LPHS)

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Background: LPHS causes severe flank and lower abdominal pain with micro or macro hematuria. We now describe 8/32 patients(pts) with biopsy proven LPHS who often have CRPS associated with attacks of LPHS.

Methods: All medical records of our 32 renal biopsy proven LPHS patients (Pt) were reviewed for episodes of CRPS associated with this syndrome.

Results: Renal bx showed thin glomerular basement membranes in 3 Pts, thick glomerular basement membranes in 4 Pts and normal basement membranes in 1. CRPS occured as ipsilateral (IL) arm, leg, flank or abdominal pain with warm (red) or cool (blue) skin hypersentitive to touch with livedo reticularis & skin swelling on the same side as the loin pain attack. Pt 1: IL arm, back, flank & leg CRPS recurrent many times then finally cured by cervical & splancnic blocks and laparascopic sympathectomy and laparascopic renal denervation. Pt 2: IL arm, back, & flank CRPS before and after renal autotranplant. Abd CRPS occurred at tranpant site and resolved after transplant nephrectomy. Pt 3: Recurrent IL flank CPRS after laparascopic renal neurectomy improved by splanchnic block and duloxetine. Pt 4: Recurrent IL flank CRPS improved with splanchnic blocks. Pt 5: After bilateral renal autotransplant IL back & flank CRPS resolved with splanchnic blocks, gabapentin and pregabalin. Pt 6: IL flank CPRS resolved on its own. Pt 7 After left renal autotransplant, IL CRPS over the autotransplant still recurring. Pt 8: Recurrent L>R flank CRPS treated with an intrathecal pain pump with major improvement.

Conclusions: CRPS occurs in up to 25 % of Pts with LPHS & must be recognized & treated with anti-neuropathic procedures and neuropathy medications rather than opioids. CRPS can occur before and after renal autotransplantation and laparacopic renal neurectomy and may be the cause for failure of these procedures to eliminate pain in LPHS. CRPS in LPHS is self limiting and gradually improves with proper therapy

PUB382

Trends in Glomerular Disease Epidemiology Among Adults in Saudi Arabia, 1997-2017

Abdulkareem Alsuwaida,[1] Lamees I. Al-mezaini,[2] Noura Ahmed,[1] Amaar A. Bakhit,[4] Junaid Wadera,[5] Feras A. Alsuwaida,[6] Mohamed C. Kechrid,[9] Abdulrahman K. Alabdulsalam,[7] Noura Aloudah,[3] Majed M. Alanazi,[10] Talal A. Alfaadhel,[1] Hanadi M. Alhozali,[3] Ghadeer A. Mokhtar.[8] *[1]King Saud University, Riyadh, Saudi Arabia; [2]King Saud University, Riyadh, Saudi Arabia; [3]king abulaziz medical city, Riyadh, Saudi Arabia; [4]King Saud University Medical City, Riyadh, Saudi Arabia; [5]King Khalid University Hospital, Riyadh, Saudi Arabia; [6]King Saud University, Riyadh, Saudi Arabia; [7]National Guard King Abdulaziz Medical City, Riyadh, Saudi Arabia; [8]King Abdulaziz University, Jeddah, Saudi Arabia; [9]Security Forces Hospital, Riyadh, Saudi Arabia; [10]King Abdul Aziz Medical City, Riyadh, Saudi Arabia.*

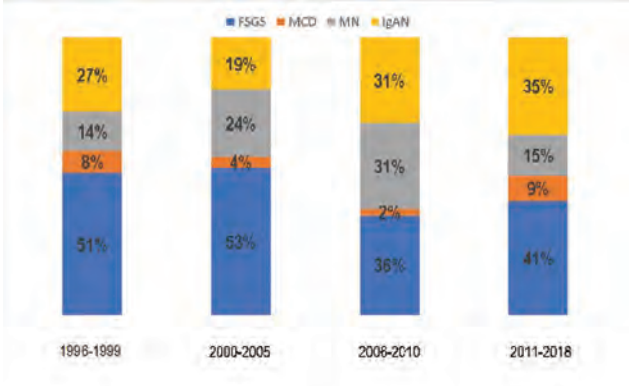
Background: We aimed to examine temporal and demographic trends in renal biopsy glomerular disease diagnosis frequencies in Saudi Arabia over the last two decades.

Methods: In this retrospective, observational study, we identified all patients with a native kidney biopsy between 1996 and 2017. Biopsy era (before 2000, 2001-2005,2006-2010 and 2011-2018) and demographics and the relationship with the prevalence of various glomerular disease were our primaries.

Results: The study included 1481 Saudi patients had a kidney biopsy with 316 patients less than 18 years and 52% were female. The commonest secondary cause of was systemic lupus erythematosus. Focal segmental glomerulosclerosis in renal biopsy specimens continues to be the commonest pathology with preserved frequencies over the three decades (51%, 53%, 36% and 40.0% of diagnoses, respectively; P for trend 0.6). The frequency of IgA nephropathy initially stable but then increased significantly in the last decades. However, the incidence of MPGN declined significantly (27.3%, 11.1%, 9.4% and 3.6%, respectively for trend 0.001). The frequencies of other primary glomerular disease subtypes remained stable (Figure 1).

Conclusions: We have observed a significant change in relative renal biopsy frequencies of many glomerular disease subtypes over the last two decades. There is a significant increase in the prevalence of IgA nephropathy while MPGN continues to decrease. Infection-related forms of GN is declining significantly, in contrast to antigenic related GN

is becoming a predominant disease. This may support the need to investigate more the potential environmental exposures to diet and allergens and it is a role in glomerular disease.



Renal biopsy diagnosis frequencies of the most common primary glomerulonephritis subtypes for biopsy era.

PUB383

A Quartet of ANCA Associated Glomerulonephritis and Vasculitis Cases with Initial Presentation of Gastrointestinal (GI) Symptoms, Which Often Are Missed

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Introduction: Antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, is one of most common causes of new onset glomerulonephritis in adults. The condition is an auto-immune disease characterised by an inflammatory response within the mural vessels of multiple organs leading to extensive inflammation, damage and necrosis. The response produces ANCA autoantibodies against myeloperoxidase (MPO-ANCA) or proteinase-3 (PR3-ANCA). I describe below case report series for patients presenting with GI symptoms leading to delay in diagnosis and management.

Case Description: 1) A 42yrs old patient of Chinese origin, presented through emergency department with >3 weeks of diarrheal illness and acute kidney injury (AKI). 2) A 68 yrs old Caucasian patient admitted to gastroenterology ward with abdominal pain and per rectal (PR) bleeding. AKI noted, fluids given and discharged as gastroenteritis. 3) A 69 yrs old patient of Bangladeshi origin had 3 months history of recurrent admissions to medical admissions unit with history of abdominal pain, diarrhea and weight loss. 4) A 70 yrs old Caucasian elderly patient with preceding symptoms of malaise, weight-loss, presented with (PR) bleeding to the general surgeons with AKI. Initial presentation and symptoms prompted acute medical and surgical teams to focus entirely on the causes of diarrhea, pre-renal causes of AKI and further investigations mainly stool C+S, flexible sigmoidoscopy and colonoscopy. Due to persistent renal impairment on recurrent admissions, nephrology consult was sought where multisystem involvement of ANCA associated vasculitis was diagnosed with immunology and histology. In one case, renal impairment progressed to ESRF, 3/4 have residual CKD.

Discussion: The diagnosis of ANCA associated vasculitides is complicated by marked difference in symptoms, signs, disease activity, chronicity and severity of the disease. Nonspecific symptoms of general fatigue, malaise, weight loss, upper airway and pulmonary symptoms, and renal impairment are neither sensitive nor specific. However diarrheal illness are although not uncommon and documented in MPO vasculitis; may completely distract health professionals, and instead lead them to focus on gastrointestinal causes of diarrhea especially inflammatory bowel disease or cancerous lesions resulting in delay in diagnosis and treating vasculitis.

PUB384

Clinico-Pathological Study of C3 Glomerulonephritis at a Tertiary Care Centre

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Background: Aim - To study the clinico-pathological profile of patients with C3 glomerulonephritis at a tertiary care centre.

Methods: A prospective observational study of all cases of C3 glomerulonephritis was done between August 2016 and December 2017. C3 glomerulopathy was defined by predominant glomerular C3 fragment deposition defined as C3c intensity 2 orders of magnitude more than any other immune reactant on a scale of 0 to 3.

Results: C3 glomerulonephritis was present in 2.68%of all biopsies int he study period. The mean age was 35±2 years of which there was slight male preponderance. Nearly all patients had hypertension (93.7%) while 21.8% had pre existing diabetes. More than two third of patients presented with RPGN (72%). All patients had active urinary sediments. More than half of the patients (56.25%) had low serum C3 levels in our study. All patients had normal serum C4 levels. Anti CFH antibody titres were measured in 6 patients of with it was elevated in 2 patients (33.3%). On LM the dominant lesion was crescentic GN (43.75%). On IF, all patients had dominant C3 staining. Also 3 (9.37%) patients had IgG staining of 1+ intensity. EM study was done in two patients and was suggestive of DDD in one patient (3.15%). All patients were managed with pulse steroids followed by oral steroids. IV Cyclophosphamide was used monthly for 6 doses in 14 patients (43.7%) while oral cyclophosphamide was used in 2 patients (6.25%). Plasmapharesis was done in patients with elevated anti CHF antibody and in patients with diffuse crescents (11 patients -34.37%). Also 11 patients required haemodialysis (34.37%). Among the 11 patients who were dialysis dependent, 4 have recovered completely and are in complete remission with normal renal function. Of these two had elevated anti CFH antibody titers while the other two had diffuse crescents.

Conclusions: C3 glomerulonephritis has emerged as a new entity in the recent past with significant percentage of our patients presenting with RPGN with hypertension. On light microscopy, the most common presentation was crescentic glomerulonephritis, One third of our patients had advanced renal failure requiring haemodialysis. Plasmapharesis was done in one third of patients. Patients with anti CFH antibody were successfully treated with IV cyclophosmamide and plasmapharesis

PUB385

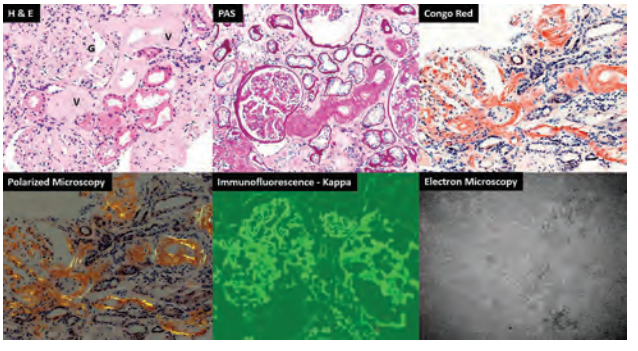
Non-Diabetic Renal Disease in Diabetics: Suspicion Is the Key

Abhilash Koratala, Gajapathiraju Chamarthi, William L. Clapp. *University of Flroida, Gainesville, FL.*

Introduction: Renal biopsy should be considered in diabetic patients who have persistent microscopic hematuria, absence of diabetic retinopathy, immunological abnormalities and/or uncharacteristic course of serum creatinine to exclude non-diabetic renal disease.

Case Description: A 63-year-old White man with a history of diabetes mellitus type 2 diagnosed ~30 years ago associated with non-proliferative diabetic retinopathy, hypertension, CKD stage 3 and CHF was seen in Nephrology clinic for evaluation of worsening kidney function. His diabetes was well-controlled with a hemoglobin A1c of 6.3% and BP in the clinic was 124/75mmHg. Labs showed serum creatinine of 5.1 mg/dL `(~2.7 two months prior and 1.4 a year ago) with an eGFR of 11ml/min and a urine protein-creatinine ratio of 3g/g (no baseline available). Urinalysis was unremarkable except for 3+ proteinuria on dipstick. Obstructive nephropathy was excluded by imaging. Serum and urine electrophoresis and immunofixation were negative for monoclonal protein. Our patient had lost ~ 44ml/min of GFR in just one year in the setting of well-controlled diabetes and hypertension, which is unusual for diabetic nephropathy. Therefore, we obtained a renal biopsy which demonstrated severe κ light chain (AL) amyloidosis [Figure]. A serum free light chain assay obtained retrospectively after the biopsy showed elevated κ/ λ ratio of 8.66. An endomyocardial biopsy excluded cardiac amyloidosis. Bone marrow biopsy was negative for amyloidosis but showed 2% abnormal plasma cells consistent with monoclonal gammopathy of undetermined significance (or more appropriately, 'renal significance' in this case). His renal function continued to worsen requiring initiation of hemodialysis. Chemotherapy with Cyclophosphamide, bortezomib and dexamethasone (CyBorD) is being planned.

Discussion: Take-home points: (a) Non-diabetic renal disease should be suspected in diabetic patients with unexplained worsening of creatinine despite the presence of retinopathy, (b) Serum free light chains should be obtained in addition to immunofixation to screen for paraproteinemia.



PUB386

Changing Patterns of Glomerular Disease in Saudi Children, 1997-2017

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Background: There have been significant changes in the incidence of different glomerular disease in adults. We aimed to trends in renal biopsy glomerular disease diagnosis frequencies in Saudi children over the last three decades.

Methods: In this retrospective, observational study, we identified all patients less than 18 years with a native kidney biopsy between 1996 and 2017. Biopsy era (before 2000, 2000-2009, and 2010-2018) and demographics and the relationship with prevalence of various glomerular disease were our primary outcome.

Results: In total, 289 cases of renal biopsy were analyzed with the median age of the patients was 13 years and 52.6% of the patients were female. Secondary glomerulonephritis accounted for 28.7% and Lupus Nephritis (LN) is the commonest cause noted in 72.3%. Minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS) were the leading primary glomerulonephritis diagnoses observed in 66%. The frequency of membranoproliferative glomerulonephritis (MPGN) decrease significantly to 6.7% in most recent biopsy era versus 35.3% in the era earlier than 2000 ($p < 0.003$). The frequency of IgA nephropathy (IgAN) and membranous nephropathy (MN), doubled in the latest era.

Conclusions: Primary glomerular disease continued to be the predominant kidney disease in Saudi Arabia with MCD and FSGS being the most common pathology. The incidence of MPGN has decreased in the last decades possibly related to improved socioeconomic conditions and decline in regional endemic diseases. LN is the commonest cause of secondary GN.

PUB387

Study of Remission and Relapse in IgA Nephropathy with Steroid Therapy

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Background: Prognosis for the development of end-stage renal disease (ESRD) in the patients with relapsed IgA nephropathy have not fully understood.

Methods: We retrospectively investigated the clinical and histological renal prognostic markers and cause of relapse in the cases of IgA nephropathy whom were performed renal biopsy from January 1980 to December 2013 and were received steroid therapy. We defined that remission was less than 0.3g/gCr or negative in dipstick three times in a row. And we defined that relapse was more than 0.5g/gCr or 1+ in dipstick three times in a row after remission.

Results: One hundred sixty five patients who had the diagnosis of IgA nephropathy were enrolled. Mean age at the time of renal biopsy was 40.2±6.1 years old. Urinary protein was 1.07±0.2 g/gCr. When clinical parameters were evaluated by univariate analysis, relapse was closely associated with the degree of proteinuria. The rate of glomerular sclerosis and cresents at initial biopsy did not contribute to relapse. Relapse had an equally poor prognosis as non-remission.

Conclusions: Our findings demonstrated that remission of proteinuria was a prognostic index for the preservation of renal function. The severity of gromeruli at initial renal biopsy did not correlated with future reccurence of IgA nephropathy.

PUB388

Urinary Myo-Inositol as a Potential Marker for Focal Segmental Glomerulosclerosis: NMR-Based Metabolomics Study

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) have similar histological findings initially, however, response to steroid treatment and long-term prognosis are quite distinct from each other. Therefore, it is of great importance to discriminate FSGS from MCD in the early phase of disease and predict clinical prognosis.

Methods: Discovery set consisted of 185 urine samples (62 healthy controls, 81 MCD, and 42 FSGS) collected at the time of kidney biopsy from 2010 to 2017 at Seoul National University Hospital and Seoul National University Boramae Medical Center. As validation set, we used 61 urine samples (12 healthy controls, 26 MCD, and 23 FSGS) from Gangdong Kyung Hee University Hospital and Gyeongbuk National University Hospital. Characteristic differences of urine metabolites depending on MCD and FSGS were examined using 800 MHz nuclear magnetic resonance (NMR) spectroscopy. After normalization by urine creatinine, the values were transformed to log values.

Results: Of 73 urine metabolites, log-transformed myo-inositol was significantly higher in FSGS patients compared with control patients (2.63-fold; $P < 0.001$) and with MCD patients (2.79-fold; $P < 0.001$). Log-transformed myo-inositol showed an inverse relationship between the initial chronic kidney disease stages ($P < 0.001$) or estimated glomerular filtration rate at baseline ($R^2 = 0.465$, $P < 0.001$). In addition, it was significantly associated with plasma level of soluble urokinase-type plasminogen activator receptor in FSGS patients ($R^2 = 0.228$, $P < 0.001$). Validation set revealed that log-transformed myo-inositol in urine samples of FSGS patients increased by 2.6-fold ($P < 0.001$) and 1.8-fold ($P < 0.05$) than control patients and MCD patients, respectively.

Conclusions: Myo-inositol, as urine metabolite, discriminated FSGS patients from MCD or control patients at the time of early diagnosis and significantly associated with initial renal function. Further studies including the correlation with clinical prognosis and the possible mechanism will be performed.

PUB389

Effect of Epipharyndeal Abrasion Therapy (EAT) on the Remission of IgA Nephritis/Vasculitis

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Background: Epipharyngeal Abration Therapy (EAT) is expected to contribute to the treatment for IgA-nephritis/vasculitis, fibromyalgia, chronic fatigue, atopic dermatitis, Palmoplantar pustulosis.

Methods: Effect of EAT using 0.5%- zinc chloride on the cumulative incidence of complete remission of nephropathy (CR, defined as urinary red blood cell less than 1/HPF and proteinuria less than 30 mg/gCre) was studied on 20 patients with IgA -nephritis/vasculitis (9 male, 32 median-years) [UMIN000009157].

Results: Fifteen patients achieved CR for median treatment duration of 7 months. The time from onset, diagnosis, and initiation of the combination therapy with tonsillectomy and steroid-pulse therapy to EAT did not influence to CR (HR 0.87-1.19, NS). Hematuria (/HPF, p=0.8), proteinuria (mg/gCre, p=0.4), glomerular filtration rate (mL/min/1.73m2, p=0.6), and Oxford-MEST-C score (NS) did not affect the cumulative incidence of CR. Of note, in 19 patients, hematuria was completely diminished. None of the 20 patients experienced adverse event (eg. infectious events).

Conclusions: We defined the CR of hematuria as less than 1/HPF. However, hematuria 1-4/HPF did not demonstrate increased activity of IgA-nephritis/vasculitis because patients with IgA-nephritis/vasculitis can exhibit thin glomerular basement membrane independent of activity of nephropathy. Most patients in our study cannot achieve CR by combination therapy with tonsillectomy and steroid-pulse therapy. Further study is needed to investigate the effect of EAT as initial therapy on CR of IgA-nephritis/vasculitis.

PUB390

Metabolomics Based Biomarkers as Clinical Outcome Indicator in Minimal Change Diseases

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Background: Minimal change disease (MCD) is well known as one of the glomerulonephritis (GN) that recur frequently. We investigated the clinical outcome of Metabolomics based biomarkers in patients with MCD.

Methods: Urine samples from healthy control (n=61), primary MCD (n=81) and MCD follow up (n=35) were analyzed with NMR-spectroscopy. Metabolites were then quantified and compared between groups.

Results: In the urine samples, metabolites that showed a clear difference between the healthy control group and the MCD group were analyzed. In addition, when these metabolites level were completely remission in the MCD follow up group, they were restored to the healthy control group level.

Conclusions: In this study, we suggest that metabolites biomarker is a reliable tool for the prediction of MCD prognosis and guidance of therapeutic plans.

PUB391

Cellular Crescents in Class V Lupus Nephritis: Mere Coincidence or More Than That?

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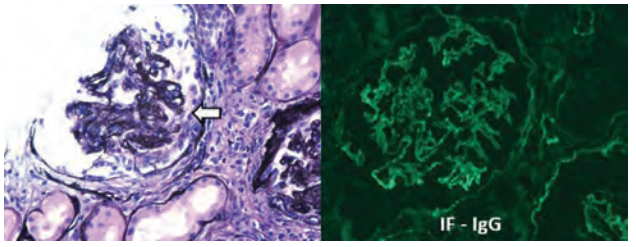
Introduction: Membranous nephropathy (MN) is typically not associated with glomerular crescents. However, crescentic MN has been reported to occur in conjunction with anti-GBM antibody disease, ANCA vasculitis and IgA nephropathy. In membranous (class V) lupus nephritis (LN), cellular crescents may be seen when it occurs together with class III or IV proliferative LN. In addition, fibrous or fibrocellular crescents may be seen in class V as a sequela of previous proliferative, crescentic glomerulonephritis. Herein, we report a unique case of class V LN associated with cellular crescents, but no endocapillary proliferation or necrotizing lesions.

Case Description: A 51-year-old AA woman with a history of SLE presented to our clinic to establish care for LN. She was first diagnosed with class IV LN 6 years prior to presentation, at which time she was treated with prednisone and 6 monthly cycles of cyclophosphamide. Post-treatment biopsy demonstrated class III LN and she was started on Mycophenolate mofetil (MMF) 1000mg bid maintenance therapy but was tapered off after 1 year of treatment. A year later, MMF was restarted when she presented with alopecia and proteinuria of~2 g/g. After 1 year, her proteinuria was 0.6 g/g with preserved renal functuion all this time (Scr <1mg/dL) and her rheumatologist stoped the MMF and initiated belimumab. She was lost to follow up after a few months and the belimumab was stopped. On her own she took MMF 250mg bid for some time, but stopped due to GI side-effects. At presentation to us, her Scr was 1.63 mg/dL with proteinuria of 3.3 g/day. A renal biopsy was

performed, which demonstrated class V LN with cellular crescents [Figure]. We treated her with pulse corticosteroids and started enteric-coated mycophenolic acid.

Discussion: To the best of our knowledge, cellular crescents in association with isolated class V LN has never been reported. In the absence of endocapillary proliferation, the cellular component of these crescents is likely constituted by glomerular parietal and visceral epithelial cells as opposed to macrophages. At this time, the prognostic significance of crescents is unclear.



PUB392

Glomerular Diseases Induced by Medications: Clinical Picture, Histopathology and Outcomes

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Background: The aim of this study was to describe the clinical and histopathological characteristics of patients with drug-induced glomerular diseases along with the related clinical syndrome and the long-term outcome after discontinuation of the offending medicine.

Methods: All cases with any type of biopsy proven glomerular disease, which was associated with administration of a certain medication were studied retrospectively. Demographics and patients' characteristics were recorded along with the related clinical and histopathological picture, the treatment and the outcome during the follow up time.

Results: Eight patients with glomerular diseases associated with medicines were identified. Six of them were females with a mean age of 59.6(±18.8) years. The renal biopsy was performed within 3-17 days from onset of symptoms, which included either nephrotic syndrome (n=4) or nephritic syndrome with acute renal dysfunction (n=4). Patients with acute nephritic syndrome reported general symptoms including fever, arthralgias, fatigue, anorexia and rash. Histopathological evaluation revealed minimal change disease in 3 patients, membranous nephropathy in 1, pauci-immune glomerulonephritis in 2 and lupus like nephritis (WHO Class III, καIV) in 2. The medicines, which were associated were d-penicillamine, tamoxiphen, OH-chlorokine, NSAIDs, propyl-thiouracile, etarnecept, methimazole and infliximab. The median value of serum creatinine was 0.5 (min: 0.5, max: 2.7 mg/dl), of 24-hour proteinuria was 5530 mg (min: 630, max: 240000 mg) while 4 of the patients had active urine sediment. In patients with nephrotic syndrome discontinuation of the offending drug lead to complete remission within a few weeks. Patients with acute nephritis required treatment with cyclophosphamide and glucocorticoids for 3-6 months, in addition to the removal of the offending drug.

Conclusions: In this small series of patients with glomerular diseases associated with medicines discontinuation of the related drug lead to remission of the nephrotic syndrome within a few weeks while patients with acute nephritic syndrome required treatment with cyclophosphamide and glucocorticoids for 3-6 months, in addition to the removal of the offending drug.

PUB393

Eculizumab Improves Outcomes in Patients with Thrombotic Microangiopathy Without ADAMTS-13 Deficiency in Comparison with Therapeutic Plasma Exchange

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Background: Thrombotic microangiopathy (TMA) is a life-threatening disease or complication. Early therapeutic plasma exchange (TPE) is the first line recommended treatment; unfortunately, in patients with TMA without ADAMTS-13 deficiency, the prognosis did not change over time. The introduction of the anticomplement C5 therapy (Eculizumab) indicated for atypical hemolytic uremic syndrome (HUS), may improve the prognosis of TMA. The potential differences on efficacy between TPE in comparison with Eculizumab for the TMA control has not been evaluated. Objective: To compare the efficacy of the use of TPE versus Eculizumab on the risk of chronic renal replacement requirements or death (outcome) in patients with TMA.

Methods: This a retrospective study. Patients of the tertiary referral hospital with TMA and without ADMST-13 deficit or patients with HUS and renal proven biopsy were included. Period evaluated: from January/2008 to February 2018.

Results: 37 patients were evaluated. Mean age 41 years. Sex: Female: 24(64%). TPE was used in 17(46%) and Eculizumab on 20(54%) of the patients. No differences on age, sex, hemoglobin, lactate dehydrogenase, platelets count, urgent dialysis requirements or admission at intensive care unit between groups were observed. 11(27%) patients met study outcome, 8 patients were treated with TPE and 3 with eculizumab. From those treated with TPE, 8 (47%) met outcome (x2:0.04; P=0.82), while in those treated with Eculizumab, it was observed only in 3(15%) patients (x2: 12,65; P<0.01); moreover, in 8 patients initially treated with TPE, the use Eculizumab as a rescue treatment was required. The comparative analysis shows that the odds ratio of chronic renal replacement needs or death in patients treated with TPE versus Eculizumab was 18.4 (95%CI, 3.5 to 97.0).

Conclusions: There is an important difference between TPE in comparison with Eculizumab in the prognosis of the TMA without ADAMTS-13 deficiency. The use of the Eculizumab should be considered as a first line treatment option in these patients.

PUB394

Tonsillectomy with Steroid Pulse Therapy for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most frequent cause of primary glomerulonephritis worldwide. The clinical course of IgAN is extremely variable and ranges from asymptomatic microscopic hematuria to rapidly progressive renal failure. Although the pathogenetic mechanisms of IgAN are still obscure, galactose-deficient IgA1 production may be in the mucosa-bone marrow axis. Indeed, some clinical studies indicated that tonsillectomy plus steroid pulse (TSP) therapy have favorable effects on IgAN. In present study, we evaluated the efficacy of TSP therapy compared with renin-angiotensin system inhibitor (RAS-i) alone for IgAN in our cohort.

Methods: We retrospectively recruited 141 biopsy proven patients with IgAN from 2012 to 2015. The observation period in this study was 24 months. Those patients were divided into three treatment groups; TSP group (n=88), Tons group (n=25) who received tonsillectomy alone, CT group (n=28) who treated with RAS-I, but not any immunosuppressant. Primary evaluation items were the disappearance of urinary protein and microscopic hematuria indicating clinical remission.

Results: At the time of renal biopsy, the amount of urinary protein excretion was 0.7g/gCr in TSP group and 0.4g/gCr in CT group. Degree of hematuria was severe in TSP group than in CT group. Age, gender, serum creatinine, and eGFR were not different between each group. During the intervention period, TSP has the strong effect on improvement of urinary protein compared with CT group (p<0.01). Remission rate of hematuria in TSP group (75.4%) was greater than other groups (Tons group: 55.6%, CT group: 50%). Those therapeutic effect persisted until the final observation. TSP therapy also has an effect to reduce serum level of IgA (26% decreased, p<0.01). The Cox regression model showed that the TSP therapy was more effective in clinical remission than treatment with RAS-I alone.

Conclusions: TSP therapy successfully induced higher clinical remission even in the clinically severe cases of IgAN as compared to sole tonsillectomy or RAS-i therapy.

PUB395

Risk Factors for ESRD in Lupus Nephritis Class IV

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Background: Lupus nephritis (LN) class IV is the most common renal manifestation of SLE and represents an important cause of morbidity and mortality. The purpose of this study was to determine risk factors for ESRD in patients with LN class IV.

Methods: Retrospective cohort of adult patients with biopsy proven LN class IV (ISN/RPS classification). Exclusion criteria were biopsy with <10 glomeruli and follow-up <12 months. Clinicopathological characteristics and long-term follow-up were analyzed.

Results: Baseline characteristics of 89 patients with LN class IV are shown in Table 1. After a follow-up of 57.2± 37.6 months, 73% of patients achieved complete or partial remission and 24.7% progressed to ESRD. The final sCr was 1.9±1.1mg/dl and CrCl was 65.0±41.7ml/min/1.73m^2. The risk factors for ESRD were class IV-G (RR 3.92, 95%CI 1.25–12.24;p=0.006), interstitial fibrosis (IF) ≥25% (RR 2.63, 95%CI 1.19-5.91;p=0.012), chronicity Index (CI) ≥4 (RR 3.64, 95%CI 1.47–9.00;p=0.002) and no remission (NR) in 12 months (RR 9.32, 95%CI 2.98–29.20;p<0.001). In multivariate analyses, NR in 12 months was associated to a risk for ESRD of 9.32 (95%CI 2.96-29.4;p<0.001).

Conclusions: Class IV-G, IF>25% and CI≥4 were associated with higher risk of ESRD. However, the main risk factor of ESRD was NR in 12 months.

Table 1. Baseline characteristics of 89 patients with LN class IV

Baseline characteristics	LN Class IV N=89
Mean age, years	31.0 ± 9.5
Gender (female), %	95.5
Race (non-white), %	65.2
Rapidly progressive glomerulonephritis, %	40.4
Hypertension (BP≥140x90mmHg), %	79.5
Serum creatinine, mg/dl	1.7 (0.9 - 3.0)
CrCl, ml/min/1.73m2	38.8 (19.9 - 77.8)
Proteinuria, g/24h	3.8 (2.2 - 5.9)
Hematuria, %	88.6
Class V, %	39.3
Wire-loops, %	30.3
% biopsy with crescents	61.8
% glomeruli with crescents	25.3 (0.0 - 40.0)
Fibrinoid necrosis, %	4.5
IV-G/IV-S, %	61.8/38.2
Interstitial fibrosis/Tubular atrophy, % Absent 1 – 24% ≥25%	4.5/5.6 50.0/77.5 45.4/16.9
Induction treatment, % Cyclophosphamide Mycophenolate Mofetil	88.9 19.1

PUB396

Can Severe Thrombocytopenia Lead to Kidney Injury

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Background: The gamut of anticoagulation related nephropathy (ARN) has expanded beyond its initial identification as warfarin related nephropathy to include other oral anticoagulants. Idiopathic thrombocytopenic purpura (ITP) is an immune mediated thrombocytopenia diagnosed by exclusion of other causes of thrombocytopenia and characterized by recurrent episodes of severe thrombocytopenia. We undertook this study to assess whether episodes of severe thrombocytopenia are associated with worsening kidney function

Methods: A retrospective study of all patients admitted to a single center between 10/1/2006 and 9/30/2017 and diagnosed with ITP. Mean creatinine levels done in the 5 day period before the nadir were compared with the mean 15 days after to identify a statistically significant trend.

Results: 191 patients were identified that had adequate testing for the analysis. The meain increase in the serum creatinine following the nadir platelet level was 0.156 mg/dl with a 95% confidence interval of 0.021-0.292 and a p value of 0.024.

Conclusions: This exploratory study shows a small but significant mean increase in serum creatinine (0.156 mg/dl), p value= 0.024 at the nadir level of thrombocytopenia. This suggests that severe thrombocytopenia may also contribute to anticoagulation related nephropathy.

PUB397

Urinary Biomarkers in the Prediction of Prognosis and Treatment Response in IgA Nephropathy

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Background: The addition of immunosuppression to supportive care reduces proteinuria in a subset of patients with IgA nephropathy (IgAN) but is associated with an increased rate of adverse events. The present work investigates whether urinary biomarkers are able to identify subjects who benefit from immunosuppression and to predict the progression of disease in a sub-cohort of the STOP-IgAN trial.

Methods: Urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), calprotectin, and the product of tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 (TIMP2, IGFBP7) were measured in all available urine samples obtained at the time point of enrollment in the STOP-IgAN trial (n=113).

Results: Biomarker concentrations in both the overall study population and the subgroup with additional immunosuppression did not differ in subjects reaching vs. not reaching full clinical remission, eGFR loss ≥15, or 30 ml/min/1.73 m² over the 3-year trial phase (p>0.05 each). Receiver-operating characteristic curves showed a poor predictive accuracy of each biomarker for the above mentioned parameters in the overall study population (areas under the curve ≤0.611). Accordingly, there was neither a significant correlation of any biomarker and adverse outcome in linear regression analysis, nor between biomarker concentrations at enrolment and change in the eGFR over the 3-year observation period.

Conclusions: NGAL, KIM-1, calprotectin, and [TIMP-2]x[IGFBP7] had neither a prognostic value for the progression of IgAN, nor for the response to immunosuppression in the present sub-cohort of the STOP-IgAN trial. The search for appropriate biomarkers for an individualized treatment strategy in IgAN continues.

PUB398

Treatment Strategy in a Case of Uncertain Glomerulonephritis

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Introduction: Evaluation of patients with nephrotic range proteinuria usually entails urinalysis, autoimmune/infectious serologies and immunoglobulins. These tests may hint at a potential underlying cause which would lead to a kidney biopsy to confirm the diagnosis. Alsowhen all tests are negative and there is not a clear etiology (e.g. diabetes mellitus), a biopsy is also warranted. This patient presents with multiple potential etiologies of glomerulonephritis (GN) however biopsy may result in an unnecessary risk.

Case Description: 59 year old male with hypertension, diabetes, pulmonary hypertension, hepatitis C (HCV) cirrhosis and prior Hepatitis B infection referred to nephrology for proteinuria evaluation. Uprt/Ucr peaked at 4gm and Cr 2.15 (eGFR 33 ml/min/m²); HCV RNA 3.1M IU/ml, ANA 1:320, cryoglobulin 10%, serum immunofixation with IgM kappa and lambda spike, Urine immunofixation negative; C3 76 mg/dl, C4 8 mg/dl; dsDNA, ANCA, HIV and RPR screens negative; UA 46 RBCs and 6 WBCs. Renal biopsy was considered due to multiple potential etiologies of proteinuria i.e. HCV, MPGN, SLE, IgA, paraproteinemia associate GN, however patient was considered to have high bleeding risk (platelet 87K and INR 1.4). Therefore patient was treated empirically for HCV associated cryoglobulinemia with glecaprevir and pibrentasivir for 12 weeks. Hematology evaluation recommended rituximab therapy for the cryoglobulinemia since the most likely etiology of the abnormal immunofixation result rather than a plasma cell disorder. He also received tenofovir to prevent hepatitis B reactivation. After treatment Cr improved to 1.53 mg/dl and Uprt/Ucr 0.6 gm, complements normalized and UA with 4RBCs and 0 WBC.

Discussion: The standard approach in patients with nephrotic range proteinuria, an active urinary sediment and multiple positive serologies would be to perform a kidney biopsy. In this case after evaluating the potential risks associated with biopsy, the differential and treatment options, we decided to treat empirically. Whilst it is true the patient may have had MPGN or Membranous GN, in this case would be secondary to the HCV infection. If there was underlying lupus nephritis, the patient may have responded to rituximab otherwise biopsy would be reconsidered for lack of response. Therefore it poses less potential harm to treat the most likely underlying etiology and evaluate response in certain situations.

PUB399

Urinary Membrane Attack Complex (UMAC) Perspectives as a Biomarker for Monitoring Response to Treatment in Focal and Segmental Glomerulosclerosis (FSGS)

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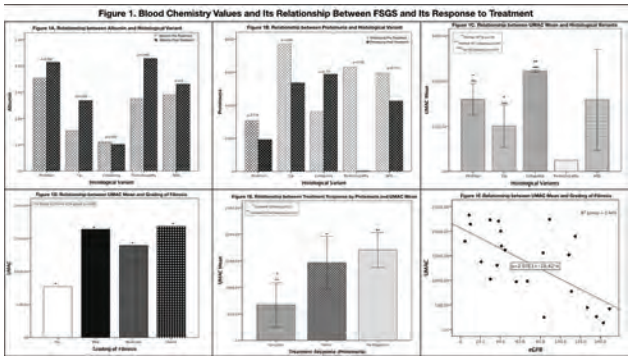
Background: The role of UMAC in the FSGS is unknown. Has been reported that complement activation is present in FSGS patients and associated with disease severity. The aim was assessed the relationship between UMAC and the classification of FSGF and treatment response.

Methods: Longitudinal study in patients with FSGF. We evaluated fibrosis grade, urea, creatinine, albumin, CKD-EPI and UMAC. UMAC was quantified by mass spectrophotometry. Student's t-test, one-way ANOVA, 95% CI, and p <0.05 were performed as statistically significant.

Results: 25 patients with diagnosis of FSGF were evaluated, 9 perihiliar, 10 tip, 2 collapsing, 2 NOS, 2 podocytopathy; the average age was 34±16 years with no significant statistical difference between groups (*p*= 0.81). Significant differences were identified between the groups in the basal and final levels of albumin, while, urea and proteinuria only presented significant difference in basal level. The mean of UMAC was 1258.92±765.19 pg/ml, with significant differences between the groups; although, no differences were found in the UMAC levels with the degree of fibrosis (p= 0.10), subjects without fibrosis had the lowest levels of UMAC 770.1±579 *vs* 1680.31±490.1 severe fibrosis. The 100% of patients received induction treatment with corticosteroids, 88% ACEI, 84% statins, 16% steriods+CNi, 8% calcium channel blockers. The UMAC levels were lower in the group with complete response to treatment, with differences between groups (p= 0.003). UMAC had significant correlation with final proteinuria (r=0.5, p=0.01) and CKD-EPI. **Figure 1.**

Conclusions: The UMAC represents the final stage of activation of the complement system. Our results showed that high levels of UMAC in patients with FSGF with a statistical correlation, had the worst varieties. The patients who had the benign varieties, responded better to treatment; however, these results must be confirmed with a higher number of patients in prospective studies.



PUB400

Clinical Experience with 21 Adults Affected by Post-Infectious Glomerulonephritis

Àlex Favà,[1] Ariel Tango barrera,[2] Isabel Giménez,[3] Aroa Rovira,[4] Rafael Alvarez,[5] Josep M. Cruzado,[4] Joan Torras,[6] Xavier Fulladosa.[7] *[1]Hospital de Bellvitge, Barcelona, Spain; [2]H. Universitario Bellvitge, Barcelona, Spain; [3]Moises Broggi Hospital, Barcelona, Spain; [4]Hospital Universitari de Bellvitge, Barcelona, Spain; [5]Bellvitge Hospital, Barcelona, Spain; [6]Laboratory Experimental Nephrology, IDIBELL. Hospital Universitari de Bellvitge, Barcelona, Spain; [7]Hospital Universitari De Bellvitge, L'Hospitalet de Llobregat, Spain.*

Background: Post-infectious glomerulonephritis(PIGN) is an entity related to childhood and throat infections. It has a well-defined clinical and histological presentation, showing a favourable prognosis. However, in last decades, the improvement in antimicrobial therapies and the population ageing has led to a radical change in this entity in terms of clinical features and prognosis.

Methods: We retrospectively analysed all the PIGN cases diagnosed between 2012 and 2017 from our pathology department archive.

Results: Our study population consisted of 21 cases, with a male:female ratio of 4.25:1. The median follow-up was of 232 days (mean 367). 28% of patients presented chronic kidney disease, 38% diabetes, 62% hypertension, 19% cancer, 33% alcoholism and 10% cirrhosis. The most common site of infection was skin (23%), followed by respiratory tract (19%), preceding in a mean of 15 days the nephritic event. Remarkably, in 28% of the cases, a previous infectious event was unnoticed. Staphylococcus (33%) and Enterobacteriaceae (33%) were the most common identified infectious agents. Hypocomplementemia was present in 57% and was restored in all cases, although 50% occurred after 3 months of nephritis. Nephrotic syndrome was present in 14%. IgA dominiant PIGN occured in 23% of cases, and a "C3 dominant" pattern was presented in 19%. 46% of patients required hemodialysis initially, with 24% finally remaining in chronic hemodialysis program. Only 19% of patients recovered previous renal function. Steroid therapy was used in 76% of cases.3 patients died before six month by infection related causes.

Conclusions: According to our results, PIGN shows a poor prognosis in adult population, and comorbidity burden might be an explanation. In addition, the lack of a previous infectious event, the slow complement restoration and its immunofluorescence patterns akin to other entities make its diagnosis difficult. More evidence is required to define the most appropriate management in these cases.

PUB401

Beverage Intake by US Adolescents: Analysis of National Health and Nutrition Examination Survey (NHANES) Data, 2009-2014

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Background: To examine beverage intake among U.S. adolescents by demographic and health characteristics.

Methods: We analyzed data from 7242 participants aged 14-18 years old (3758 males, 3484 females) with ≥1 day of beverage intake reported in the 2009–2010, 2011–2012, and 2013-2014 U.S.-representative National Health and Nutrition Examination Surveys (NHANES). Beverage types included milks, fruit juices, sports drinks, waters, coffees, and other (combined because of sparsity: protein powder, energy, and cereal drinks). Demographic and health characteristics included sex, age, race/ethnicity, education, household income, body mass index (BMI), diabetes, anemia, sedentary and physical activity time per typical day, waist-to-height ratio, and menses onset age. Analyses accounted for the NHANES survey design and incorporated appropriate weighting. The habitual consumption method was used, along with the Multiple Source Method to estimate usual beverage intake (grams). Proportions of respondents consuming each beverage type and per-consumer mean beverage intake (g/day) were calculated. Because of strong correlations between some variables (e.g., age/education, and BMI/waist-height ratio), univariate logistic models estimated associations with beverage consumption (weighted %). For variables with significant associations (p<.05), t-tests were carried out on least-squares means to assess where differences rested. P-values were Bonferroni-adjusted for multiple comparisons.

Results: Males consumed milks, sodas, and sports drinks more often than females. Blacks consumed juices more often than all other races. Hispanics consumed juices more often than Whites and sodas more often than all others. Significant associations were found between beverage type consumed and sex (p=.01), age (p=.0052), race/ethnicity (p=.0004), education (p=.0015), diabetes (p<.0001), anemia (p=.0092), sedentary time per typical day (p<.0001), BMI (p<.0001), and waist-height ratio (p<.0001).

Conclusions: Few analyses have been conducted to assess beverage intake patterns in adolescents. Results from this study contribute new information to help address the gap, inform future studies of health risks by subgroup, and target education to this age-group.

PUB402

Nutritional and Anthropometric Assessment During and After Ramadan in a Cohort of Hemodialysis (HD) Patients in Jeddah, Saudi Arabia

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Background: During the annual festival of Ramadan (R), Muslims world-wide undergo a period of fasting from sunrise to sunset. Studies suggest that this period of cyclic fasting does not affect the healthy individual but its effect on HD patients is not well documented. Inadequate food intake, muscle loss and inflammation are common in HD. In Saudi Arabia, the number of HD patients increased 14% from 2014 to 2016. While the majority of patients insist on fasting during R, any associated health risks are not well documented. The aim of this pilot study was to assess dietary, anthropometric and biochemical parameters in HD patients over the R period.

Methods: The study was conducted in an out-patient dialysis clinic in Jeddah (n=23, 10 males, age 43±15 yrs, thrice-weekly dialysis, vintage 93±54 months, Kt/V 1.38±0.33). Both 24h diet recall and 3d food records were analyzed using Food Processor ESHA Research. Body mass index (BMI), handgrip strength (HGS) using a Jamar dynamometer, malnutrition-Inflammation Score (MIS) and biochemical parameters were also evaluated during R and two months following R.

Results: Among R participants, the intake of calories, protein, and fat was significantly higher during R while there was no significant difference in carbohydrate intake. Two-months post R, calorie, protein and fat intake had declined by 24%-36% compared to the values noted during R. Absolute carbohydrate intake was not significantly different during or 2 months post R. No differences were noted in BMI, HGS or MIS during this time-period. While there were temporal fluctuations in serum albumin, creatinine and sodium, the values pre and 2 month post R, were not significantly different. Blood glucose, potassium and phosphorus did not change over the course of the study.

Conclusions: Our preliminary data indicates that in HD patients observing R, while alterations in diet and clinical parameters fluctuate, most return to pre R values within 2 months of the end of the R period. The impact on other parameters (e.g. plasma lipoproteins) is currently under evaluation. (BT is a recipient of a scholarship from the Ministry of Education, Saudi Arabia)

PUB403

Hypercholesterolemia as a Risk Factor of Coronary Artery Disease in Hemodialysis Patients: 10-Year Outcome of the Q-Cohort Study

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Background: The prevalence of atherosclerotic diseases including coronary artery disease, peripheral artery disease and stroke is higher in chronic kidney disease (CKD) patients. However, the risk of hypercholesterolemia for cardiovascular disease (CVD) in hemodialysis (HD) patients is still debated. Inflammation and malnutrition may affect dyslipidemia-induced CVD in HD patients. The aim of this study is to investigate the risk of hypercholesterolemia for CVD in a 10-year cohort of hemodialysis patients.

Methods: A total of 3,529 Japanese HD patients aged ≥18 years were prospectively followed for 10 years in this study. Patients were divided into four groups (Q1:<131 mg/dL, Q2:131–152 mg/dL, Q3:152–178 mg/dL, Q4:≥178 mg/dL) by quartiles of serum total cholesterol levels. We estimated the relationship between serum total cholesterol levels and the incidence rate of coronary artery disease (CAD), brain infarction (BI), peripheral artery disease (PAD) and combination of CVDs in 10 years.

Results: During a follow-up period, 460 (13%), 379 (11%) and 261 patients (7%) developed CAD, BI, and PAD, respectively. The incidence of CAD and PAD, and combination of CVDs increased linearly with higher total cholesterol levels. In multivariable-adjusted Cox analysis, a high total cholesterol level was an independent risk of CAD incidence (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.03–1.82; P=0.03 for Q4 vs. Q1) and CVDs combination (HR, 1.26; 95% CI, 1.05–1.51; P=0.02 for Q4 vs. Q1), after adjustment for confounding factors including serum albumin and C-reactive protein (CRP). There is no significant interaction between serum total cholesterol and serum albumin or CRP regarding CAD and CVD.

Conclusions: Serum high total cholesterol level is an independent risk factor for CAD in HD patients. Hypercholesterolemia still has a risk of CAD even after CKD patients have undergone maintenance HD.

PUB404

Correlation Between Dietary Components Measured in 24-Hour Urine Tests and Food Records in Patients with Kidney Disease

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Background: Food Records (FR) are used widely in research and clinical care. Twenty-four hour urine collections (24UV) are considered the gold standard to measure dietary sodium (Na), potassium (K), phosphorus (P), calcium (Ca), magnesium (Mg), and protein. Little research has been done to validate FRs obtained in a clinical setting against biological measurements. The objective of this project was to determine if FR obtained as routine care correlates with 24UV measurements of Na, K, P, Mg, Ca and protein performed at different time points.

Methods: FRs and 24UVs were completed as routine care in the nephrology clinic at University of Chicago Medicine. A Registered Dietitian provided patient instruction and analyzed the FR with National Data Research System, 2017. FR results were compared to a 24UV done closest to the date of the FR. Pearson's correlation was used to compare each nutrient measured via FR and 24UV.

Results: A total of 33 patients were included with a mean age of 50 years, BMI of 25.3kg/m^2 and estimated glomerular filtration rate of 67ml/min (n=28); 91% were Caucasian. Diagnoses included autosomal dominant polycystic kidney disease (45.5%), nephrolithiasis (48.5%) or other (6.1%). Average time between FR and urine was 97 days (range of 0-533); adjustment for time with ANOVA did not improve correlations, therefore was not adjusted for in calculations. Sodium (r=0.55, p=0.001) and Mg (r=0.46, p=0.008) measured via FR correlated significantly with 24UV.Sodium was consistently underestimated by FR; Mg was overestimated. Dietary K (r=0.16, p=0.389), P (r=0.22, p=0.217), Ca (r=0.06, p=0.743) and protein (r=0.26, p=0.138) did not correlate with 24UV.

Conclusions: Sodium and Mg intake measured via FR significantly correlated with 24UV done at separate times. Overestimation of Na by FR is possibly due to underreporting. Underestimation of Mg intake is likely due to low intestinal absorption. Given variability of absorption of Ca and P from hormonal regulation, correlation would not be expected. Lack of correlation for protein and K could be explained by daily variability in intake, unknown physiologic factors, time difference between urine and FR, or difficulty obtaining adequate detail for analysis of a FR.

PUB405

Validation of the Sarcopenia Index to Assess Muscle Mass in the Critically Ill: A Novel Application of Kidney Function Markers

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Background: Adverse outcomes for hospitalized patients with sarcopenia are well documented, and identification of patients at risk remains challenging. The sarcopenia index (SI), previously defined as (serum creatinine/serum cystatin C)x100, could be an inexpensive, readily accessible, objective tool to predict muscle mass and risk for adverse clinical outcomes. The aim of this study was to assess the validity of the SI as a predictor of muscle mass.

Methods: Retrospective study of critically ill adults admitted to Mayo Clinic from 2012 -2015 with suspected sepsis and an available creatinine and serum cystatin C. Muscle surface area was quantified at the L3/4 vertebral level in patients with an abdominal CT scan (CTMSA). Multivariable regression modeling was used to assess the relationship between SI and CTMSA, as well as short-term clinical outcomes.

Results: The 171 included had a mean weight and body mass index (BMI) of 75.2 ± 16.4 kg and 26.0 ± 4.6 kg/m^2 and abdominal CT scans were available for 81 (47%) patients. The SI correlated with CTMSA (r = 0.40). After adjustment for age, sex, severity of illness, and BMI, SI was independently associated with muscle mass (P=0.001). A decrease in the SI (indicative of lower muscle mass) was also associated with frailty and worse short-term clinical outcomes.

Conclusions: The SI, a simple calculation from kidney function markers, is a significant predictor of muscle mass in this validation cohort of ICU patients. A low SI was associated with longer hospital length of stay and frailty. Future studies could explore whether the use of SI assists with identifying patients likely to benefit from pharmacotherapy-, nutrition-, or physical therapy-based interventions.

PUB406

Eating Disorder Nephropathy: A Case Series Study

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Background: Eating disorders (EDs), such as anorexia nervosa and bulimia, are psychiatric disorders frequently found in young women, with a substantially increasing prevalence in recent years. EDs are often intractable and induce the development of various physical disorders, including renal dysfunction and mineral disorder, occasionally progressing to end-stage kidney disease (ESKD). At present, information is limited regarding the renal manifestations, so no consensus has been established regarding the clinical practice guideline for ED patients referred to nephrologists. The study aimed to clarify the clinicopathological characteristics of ED nephropathy (EDN).

Methods: Patients with EDN who were referred to and cared for at our related facilities from January 1992 to December 2017 were retrospectively analyzed. The renal outcomes were defined as doubling of the serum creatinine level and/or progression to ESKD.

Results: The present study included 14 female cases. The mean age at the ED onset was 22.3 years, and the duration from the onset to the initial visit with a nephrologist was 17.8 years. At the first visit with a nephrologist, the serum creatinine level was 1.6 mg/dl, serum potassium level was 2.7 mmol/l, and body mass index (BMI) was 13.1 kg/m^2. All cases showed hypokalemia and either addictive vomiting or diuretics/laxatives abuse. During the average observation period of 5.8 years, renal outcomes occurred in 9 cases, and 2 died due to their ED. The body weight, BMI and estimated glomerular filtration rate at the first visit in the group who developed renal outcomes were significantly lower than in those who did not develop renal outcomes. A renal biopsy was performed in four cases. One early case of ED showed hypertrophy of the juxtaglomerular apparatus, while three advanced cases showed glomerular collapse and interstitial fibrosis predominantly in sub-capsular regions, consistent with peripheral circulatory failure and low-potassium nephropathy.

Conclusions: Advanced renal impairment and a severely lean state at the first visit may be predictors of poor renal outcomes in cases of EDN. In a majority of patients with EDN, the degree of renal injury is already severe at the time of their first referral to a nephrologist. Improving the renal outcomes of EDN may require tighter collaboration with psychiatrists and earlier intervention by nephrologists.

PUB407

A Whole Food Plant-Based Diet Can Be Safe and Beneficial in Dialysis Patients: A Case Report

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Introduction: The demonstrated benefits of a whole food plant-based diet (WFPBD) include weight loss, lipid reduction, improved glycemic control in diabetics and regression of atherosclerosis in patients (pts) with coronary artery disease. Small studies utilizing a WFPBD, low animal protein intake, or addition of fruits and vegetables to the diets of pre-dialysis pts with chronic kidney disease (CKD) have demonstrated lower phosphorus (phos) and FGF 23 levels (both associated with higher mortality), improvement in metabolic acidosis, and less GFR decline without adverse effects. Utilization of a WFPBD in dialysis pts, however, is deemed potentially dangerous due to risk for low serum albumin and hyperkalemia.

Case Description: A 58-year-old woman with type 1 DM, HTN, CAD s/p MI and CVA was denied listing for kidney transplant. Following this, she embarked on a purely WFPBD. Potassium (K) levels in the 6's (often requiring 1K dialysate) were common before she started the diet. Diet included beans, peanut butter, hummus, grains, vegetables, fruits. Her labs improved significantly with the diet (see table). K was checked frequently. PM isulin dose decreased by 38%. Weight decreased from 69 kg to 65.6 kg in 2 months with BMI decline from 26.1 to 24.8. The pt reported improved energy.

Discussion: Potential adverse effects of the standard American diet and animal protein intake in CKD pts include greater phos absorption, inflammation, vacular calcification, a dysbiotic microbiome, acid generation, and high K. The higher fiber WFPBD generates base, reduces serum phos, enhances weight loss, and may improve the microbiome. In this pt, phos decreased rapidly, albumin remained > 4 and potassium did not increase. A WFPB diet may offer significant health benefits without risk for hypoalbuminemia or hyperkalemia.

Patient Labs Before and After WFPBD

Labs:	Month Before WFPBD Started:	Month After WFPBD Started
Potassium	5.8, 5.2	5.5, 5.7, 5.9, 5.5, 5.1
Bicarb	23	29
Albumin	4.5	4.3
Phos	5.4	3.8
intact PTH	1057	846

PUB408

Utilizing Dialysis Clinical and Laboratory Markers to Identify Risk for Major Depression Disorder in Dialysis Patients

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Background: Depression is the most common psychiatric disorder in patients with end-stage renal disease (ESRD) on dialysis. Despite of being widely prevalent, depression is often underdiagnosed in this population. Diagnostic screening surveys are available to identify high risk patients; however, these tools are time consuming and not applied regularly in busy dialysis units. We hypothesize that risk of depression can be predicted using common clinical variables which are screened frequently in dialysis units.

Methods: We conducted a prospective cross-sectional study in ESRD patients receiving either hemodialysis (HD) or peritoneal dialysis (PD) in the main ambulatory dialysis unit in the state of Qatar. Eligibility criteria was all adult ESRD patients who have been receiving dialysis for at least one month duration. All enrolled patients underwent depression screening using the Center for Epidemiologic Studies Depression Scale (CESD-R) which has been validated by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-V) for a major depressive episode. Clinical variables were enrolled of logistic and linear regression models to assess the correlation.

Results: 253 patients with ESRD on dialysis were enrolled. 157 (62%) patients were on HD and 96 (38%) on PD. 122 (48%) patients had depression disorder, defined as CESD-R score ≥ 16. No significantly difference in depression prevalence was detected between HD and PD patients (P=0.55). Bivariate analysis showed that depressed patients have lower hemoglobin levels (mean log Hgb 2.4 (±0.1) vs 2.3 (±0.1), P= 0.04) and higher Hb1AC levels (mean log Hb1Ac 1.8 (±0.2) vs. 1.7 (±0.2), P=0.04) than non-depressed patients. Univariate regression analysis revealed no significant correlation between depression disorder and BMI, serum albumin, Vitamin D level, parathyroid hormone level, serum calcium, phosphate level, nor Kt/V.

Conclusions: Up to 50 % of our adult ESRD patients on dialysis have depressive disorder as per CESD-R score. Our data suggests that Hgb and Hb1AC levels can be utilized to predict patients at increased risk of depression. This will allow early diagnosis and management of depression which can imrpove clinical outcomes.

PUB409

Intradialytic Hypertension and Mortality Risk Among Hemodialysis Patients In National Kidney and Transplant Institute

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Background: Hypertension is prevalent in hemodialysis patients and contributes to cardiovascular morbidity and mortality.

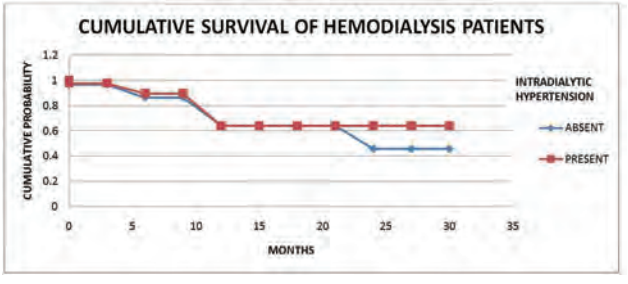
Methods: Blood pressures before and after hemodialysis were recorded and used to classify patients during the baseline period (N=153). Patients were followed for up to 2 years or until death.

Results: The cohort's mean age was 59.3 years old with male predominance (56%) and DM nephropathy (48.4%) as primary renal disease. The intradialytic hypertension group (n=47) had significantly higher change in systolic blood pressure (16.4 vs – 3.2 mmgHg), post dialysis systolic (165.2 vs 147.5mmHg) and mean arterial (106 vs 97.8mmHg) blood pressure compared to 106 patients without intradialytic hypertension. One and two year overall cumulative survival of patients with intradialytic hypertension compared to patients without were 95.1% vs 92.86% and 66.12% vs 63.03%, respectively. Risk for all cause mortality non-significantly trended lower with intradialytic hypertension (HR=0.98, p=0.271), female gender (HR=0.77,p=0.495) and use of calcium channel blockers (HR=0.764, p=0.46).

Conclusions: In this South East Asian national referral center, intradialytic hypertension did not increase the hazard for 2 years all cause mortality of hemodialysis patients.

Characteristics of Patients

Variable	Present IDH (N=47)	Absent IDH (N=106)	p value
Age	59.7	59.1	0.465
Male	36%	59%	0.011
Female	64%	41%	
DM Nephropathy	20(42.6%)	54(50.9%)	0.531
Hypertensive Nephrosclerosis	13(27.7%)	30(28.3%)	
Chronic Glomerulonephritis	10(21.3%)	18(17%)	
Average change in SBP	16.4+4.58	-3.6+11.16	0
Pre HD SBP	148.8+18.24	149.7+23.87	0.810
Post-HD SBP	165.2+17.97	147.5+19.59	0
Dialysis weight gain(L)	2.5+0.73	2.4+0.83	0.491
Calcium Channel Blocker Usage	37(82.2%)	65(69.1%)	0.035
EPO usage (units per week)	7978.7+4188.44	8066+4504.54	0.910
Hemoglobin	11.1+1.84	11.1+1.38	0.886
Albumin	4+0.53	4.1+0.51	0.322
Dialysis vintage	0.7+1.46	0.8+1.62	0.699



PUB410

Prevalence of High Blood Pressure Among Teenagers, With Its Pattern and Related Factors

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Background: Hypertension prevalence is increasing worldwide. Studying the BP among teenagers might give some ideas regarding preventive measures that can decrease the incidence of HTN during adult life. **Aim of this study:** 1-Identify the prevalence of high BP among teenagers. 2-Determine the pattern of the high BP, whether systolic or diastolic. 3-Identify the factors that are related to high BP among this age group.

Methods: This is a cross sectional study with screening of teenagers between 13-20 years attending thirteen middle and high schools in Bahrain. All the students were screened. The consent was obtained from the school administration and the parents. Demographic factors were collected. BP was checked after 3 minutes rest while sitting on an armed chair with both feet on the ground. Two measurements were obtained from the Lt. arm with one minute interval. Ht., wt. and waist circumference were measured for each student. Data were analyzed with SPSS 18. P<0.05 was required for rejecting the null hypothesis.

Results: 2467 students were included. Mean age was 13.5 years (SD 2, SE 0.04). Males were 53%, Mean wt. was 56kg (SD 18.4, SE 0.4). The mean waist circumference was 73.8 cm (SD 17, SE 0.35). Mean Ht. was 157cm (SD 11, SE 0.23). Mean BMI was 22 Kg/m^2 (SD 5.8, SE 0.11). 53% of the students had high BP according to their age, gender and height percentiles. The high BP within the hypertensive ranges were more than the measures within the Prehypertensive range (40% versus 23%). P 0.043 The BP was inversely correlated with age and BMI. The correlation coefficient for age was -0.32, P <0.0001. The correlation coefficient for BMI was -0.068, P 0.003. Systolic BP rather than diastolic BP was more prevalent, 19% versus 4%. P 0.027. Age, gender, waist circumference, nationality and pulse rate were the independent variable related to high BP in mulitvariate regretion model.

Conclusions: There was an unexpected high prevalence of elevated BP among teenagers. The pattern of the high BP was surprisingly systolic rather the diastolic. Hypertensive BP levels were higher than prehypertensive levels. The young age and low BMI were associated with higher BP. These findings would suggest a complete different pattern of BP among teenagers. More research focused efforts are required to elaborate on each of these points to determine significant monitoring and preventive strategies.

PUB411

Real Harakiri Sagliker Effect: Hypertensionologist's Hypertension: Ambulatory Blood Pressure Monitoring of Doctors: Combination-Compilation of Reverse White Coat and Physical Exercise Effects

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Introduction: It is known some normals and hypertensives get higher BP when facing medical environments or devices. Effect called WCE or WCH.We examined if same be also found in doctors in outpatient clinics. This is first medical hypothesis so far on subject

Case Description: 58 Doctors examined daily 12 hypertensives by measuring BP themselves with classical manual recorders by pumping the cuffs, every 10 minutes for two hours first day, then relaxed consecutive day, similarly two hours. Same time doctor's SBP, DBP, MAP, HR (by Mobilograph ABPM machine) were measured, two hours NE,E,VMA, metanephrine in urines and plasma NE,E, PRA, A, A II examined. in doctors. Additionally plasma A II levels examined just before BP recordings in first stress day. Doctors' all those parameters decreased from first stress day to the second relaxation day.. Interestingly plasma AII decreased from time of prerecordings to time of postrecordings in first stres day. P values for differences were less than 0,001.

Discussion: Doctor's had higher SBP,DBP,MAP,HR,PRA,A, cathecolamins in urines and plasma after examinations. Reduction of AII at time of postrecordings be explained by AII's short half life. If AII be examined continously during measurements, could be found higher at first but decreasing tremendously by time till end-point. Staff could face complications, cerebrovascular attacks, myocardial infarctions, blindness if they have hypertension or prone to it. Doctors manual recordings were a reverse white coat effect plus hand grip exercise test and dangerous. In developping countries as Turkey, India, Pakistan, Bengladesh, China, Endonesia, Maleysia where 100-150 patients examined and BP recorded daily only by one doctor, manual recorders be banned by legistlations and started first in history via ASN, ISH, WHO. And this novel phenomenon should be called Sagliker Effect. This is a sine qua non humanity task.

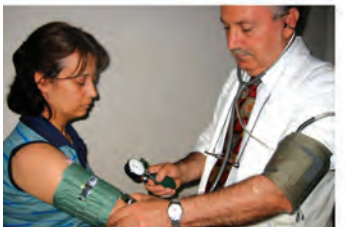

Table 1. Parameters before and after stress and after relaxation

	After Stress	After Relaxation	Before Stress	p Value
SBP (mmHG)	125.9±18.9	112.5±11.5		p<0,001
DBP (mmHg)	78.3±8.2	71.8±8.8		p<0,001
MBP (mmHg)	99.7±9.1	89.6±9.8		p<0,001
Pulse	88.9±9	76.4±10		p<0,001
Urine NE(µg/L)	95.8±117.8	59.2±105.5		p<0,001
Urine E (ug/L)	18.6±19.2	8.1±4.7		p<0,001
Urine VMA (mg/L)	4.9±2.4	2.8±1.4		p<0,001
Urine M (mg/L)	164.8±111.7	100.7±49.6		p<0,001
PRA (ml/L)	37.0±19.8	25.9±13.9		p<0,001
Aldosteron (pg/ml)	106.7±51.7	82.5±33.6		p<0,001
NE (ng/L)	561.5±444.2	347.7±343.3		p<0,001
E (ng/L)	99.2±104.1	62.8±67		p<0,001
A II (pmol/L)	20.5±9.1	25.9±12.7		p=0,35
A II (pmol/L)	20.5±9.1		33.6±8.4	p=0,05
A II (pmol/L)		25.9±12.7	33.3±8.4	p=0,35

SBP sistolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure, VMA vanilyl mandelic acid, PRA plasma renin activity, NE norepinephrine, E epinephrine, AII angiotensin II.

PUB412

Individualized Hypertension Treatment: More Information, Better Results

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Background: High blood pressure (BP) is a leading cause of death and disability in the US and worldwide. Approximately 1 of 3 U.S. adults (75 million) has high blood pressure, and only about half treated with antihypertensive therapy achieve the recommended blood pressure target. Our aim was to observe BP outcomes in standard hypertensive management augmented by hemodynamic information.

Methods: A hemodynamic measurement using noninvasive impedance cardiography (NICaS) was recently added in our hypertension (HTN) clinic, a part of a nephrology group that manages chronic kidney disease (CKD) and referred resistant hypertension patients. Clinicians were informed about measured hemodynamic parameters, however, there were no algorithmic changes made in the HTN treatment protocol. We retrospectively collected

data for patients that had at least one hemodynamic measurement and at least one follow-up visit.

Results: We found 86 eligible patients; mean (SD) number of hemodynamic measurements was 1.6 (0.8). Mean (SD) age was 62.6 (18.1) years, 48 (56%) were female, and 39 (45%) had CKD. Systolic BP (SBP) and diastolic BP (DBP) at time of initial hemodynamic measurement (initial) and at most recent office visit (current) are reported in Figure 1. Target BP results for non-CKD (SDP<140 and DBP<90 mmHg) and CKD (SDP<130 and DBP<80 mmHg) are shown in Figure 2. Mean number of HTN meds was unchanged (2.54 and 2.46, respectively).

Conclusions: Impedance cardiography is a simple, noninvasive method for evaluating underlying hemodynamic drivers of HTN and provides clinically important BP-complementary information for treatment. The encouraging BP reductions prompted us to initiate a new study that compares standard care with a new protocol comprising hemodynamic and pulse wave velocity measurements and a tailored algorithm for medication changes.

Funding: Commercial Support - NiMedical, Ltd.

		initial SBP	current SBP	difference	p-value	initial DBP	current DBP	difference	p-value
	N	mean	mean	mean(CI)		mean	mean	mean(CI)	
All patients	86	160.4	138.8	21.6(17.2,25.8)	<0.001	83.9	74.6	9.3(5.9,12.8)	<0.001
CKD	39 (45%)	164.1	141.3	22.8(14.9,30.6)	<0.001	79.6	71.2	8.5(2.3,14.6)	0.009
non-CKD	47 (55%)	157.3	136.8	20.6(15.6,25.5)	<0.001	87.5	77.4	10.1(6.2,14.0)	<0.001

Figure 1

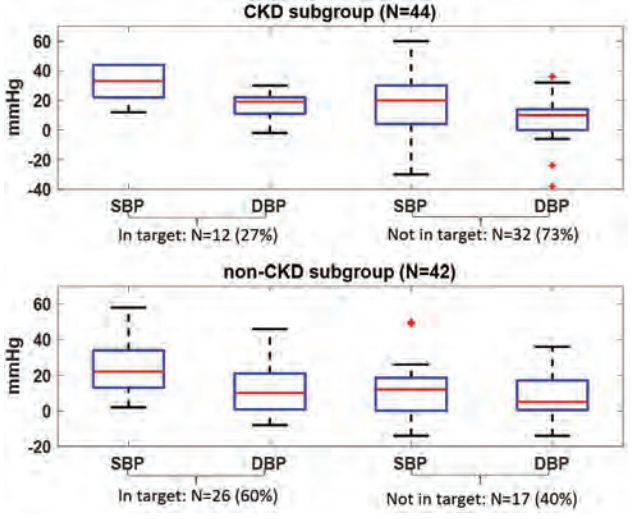

Figure 2: Subgroup results

PUB413

Posterior Reversible Encephalopathy Syndrome (PRES) with Acute and Chronic Kidney Disease (AKI/CKD): Five Cases in Eight Years - Should Nephrologists Consider It More Frequently?

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Introduction: PRES is a clinical and radiological condition with manifestations such as headaches, seizures and altered mental status that shows reversible cortico-subcortical vasogenic edema in Neuroimaging, predominantly bilateral. It is associated with arterial hypertension(AH), autoimmune disease, AKI/CKD, drugs and pregnancy It is usually reversible and recurrent Magnetic resonance(MRI) is the gold standard to diagnose and detect lesions in PRES

Case Description: We present 5 cases of women patients with acute neurological symptoms in the context of AH,AKI/CKD MRI/CT diagnosed PRES Four of them needed RRT All of them recovered after controlled AH (See Summary of the patient's history, MRI findings and final outcome)

Discussion: PRES is a rare disease related to different clinical entities and different pathophysiological origins that causes a delay in diagnosis Our cases are clinical entities with different backgrounds and heterogeneous pathophysiological bases All pacients were women and presented AH and seizures, only one was recurrent and affected 2 or more cerebral lobes Early diagnosis makes a difference in patient outcomes It usually resolves, being the triggers usually identifiable AKI/CKD are cormobid factors for PRES so it is important to consider them at the time of diagnosis in patiens with neurological symptoms

Summary of the patient's history, MRI findings and final outcome

	CASE 1	CASE 2	CASE 3	CASE4	CASE 5
YEAR	2009	2013	2014	2016	2017
GENDER	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE
AGE (years)	33	29	71	20	37
Primary renal disease	Unknown	Unknown	Hypertension	LES	P-ANCA vasculitis
Transplantation	NO	NO	YES	NO	NO
Trigger	Hypertension Abdominal infection	Hypertension	Hypertension Ciclosporine Respiratory infection	Hypertension/ LES with no treatment	First trimester pregnancy/uremic sindrome Hypertension
Clinical findings	Hypertension, seizure, altered mental status	Hypertension, seizure, blindness, altered mental status	Hypertension, altered mental status	Hypertension, seizure, altered mental status	Hypertension, seizure, altered mental status
Renal treatment	CHDF, CHD, plasmapheresis and iHD	Peritoneal Dialysis	NO	eHD, iHD, Plasmapheresis	eHD iHD
Recurrency	NO	NO	NO	YES	NO
CT	Bilateral occipital lobes	No lesion	No lesion	No lesion	Bilateral parietal lobes and right occipital lobe
MRI	MRI was not done	Thalamic, protuberancial and Bilateral parieto-occipital lobes	Bilateral occipital lobes	Bilateral parieto occipital lobes	Bilateral parieto occipital lobes (right predominance)
OUTCOME	Resolution/ Transplantation	Resolution/ Transplantation	Resolution	Resolution/ HD	Resolution/ HD

CHDF, continuous haemodiafiltration; CHD, continuous haemodialysis; CT, computed tomography; eHD, extended haemodialysis; iHD, intermittent haemodialysis; MRI, magnetic resonance imaging; LES Systemic lupus erythematosus; RRT, renal replacement therapy

PUB414

Predictability of Elevated Troponin for Angiographic Coronary Artery Disease in Patients with CKD

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Background: Troponins are elevated in patients with myocardial damage. An association exists between angiographic coronary artery disease (CAD) and troponin elevation in patients with normal kidney function; however, this association remains unclear in patients with chronic kidney disease (CKD). Mild to moderate elevation of troponins are frequently seen in this patients and interpretation for the most part is at the discretion of the treating physician.

Methods: We retrospectively reviewed all coronary angiograms performed at our center between April 2007 to May 2017. Baseline demographic, laboratory, and angiographic characteristics were analyzed using STATA® software. KDOQI staging for CKD was used and GFR was calculated using CKD-EPI formula. Angiographic finding was categorized as normal, mild (<50%), moderate (50-69%), and severe (≥70%) stenosis of any major epicardial coronary artery.

Results: Of the 795 patients, 433 were men (54%). Mean age of the patients was 63 +/- 27 years. Prevelance of hypertension and diabetes mellitus was significantly higher in patients with CKD stages 3-5 compared to normal GFR ($p < 0.001$) but other risk factors for CAD were similar in between groups. Multivariate logistic regression analysis showed no significant difference in mean troponin I (cTnI) levels in severe and non- severe coronary artery stenosis across any CKD stage. However, statistically significant peaks were observed in patients with CKD stages 4 and 5 (20.9 times, P<0.001 [CI 13.5-28.4] and 6.4 times, P=0.007 [CI 1.72-11.1] respectively). Patients with severe (>70% stenosis) CAD had higher mean cTnI levels compared to non-severe stenosis (p<0.02). ROC curve showed cTnI > 0.304 ng/mL had 60% sensitivity, 61.6% specificity and positive likelihood ratio 1.56 for finding severe stenosis.

Conclusions: We found no significant association between modest elevation in Troponin I and angiographically signifcant coronary disease in patients with any stage of CKD. Troponinemia >0.304 ng/mL in proper clinical setting and a rising trend may require additional work up including cardiac catheterization in patients with CKD as per our analysis.

Variables	GFR ≥90 (n = 339)	GFR 60-89 (n = 180)	GFR 30-59 (n = 180)	GFR 15-29 (n = 25)	GFR <15 (n = 71)
Non-severe stenosis (mean; SD)	4.5 ± 0.9	2.0 ± 0.8	6.4 ± 1.4	14.0 ± 11.5	3.0 ± 7.4
Severe stenosis (mean; SD)	4.3 ± 1.4 (p= 0.91)	2.3 ± 1.3 (p=0.83)	3.6 ± 2.2 (p=0.21)	57.9 ± 22 (p=0.06)	18.5 ± 10.6 (p=0.13)

PUB415

Treatment and Prognosis of Malignant Hypertension

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Background: We systematic analyzed the data on treatment of MHT to find a way for best outcome.

Methods: 30 patients diagnosed with MHT were enrolled in this study. The clinic data,treatment strategy and prognosis were analyzed.

Results: The better effect could be expected during 6 months. The plasma level of rennin and aldosterone were higher than the normal at the initiation stage of MHT. However

the presence of thrombotic microangiopathy (TMA) was not found to predict end-stage renal disease(ESRD).

Conclusions: RAAS activation was involved in the pathogenesis of MHT with both primary or secondary origin. RAAS blacker, especially captropril was selected as the first choice for the treatment on MHT despite much higher serum creatinine in the common sense. Long duration at least for 6 months treatment with RAAS blockers could reach the best outcome. The etiology treatment should be initiated for good of patients' future prognosis.

PUB416

Mechanisms of Cardiovascular Complications in CKD: Research Focus of the German Transregional Collaborative Research Center SFB/TRR219

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Background: Patients with chronic kidney disease (CKD) exhibit a massively increased risk for cardiovascular events, and traditional strategies to improve cardiovascular outcome have largely failed in the context of CKD. The classical cardiovascular risk factors such as smoking or overweight have less impact on cardiovascular disease in CKD patients compared to the general population, indicating that in addition to traditional risk factors, novel and hitherto unknown mechanisms may be important in driving cardiovascular disease in CKD and that CKD *per se* represents an independent risk factor for cardiovascular events.

Methods: Reducing cardiovascular mortality in CKD patients through novel therapeutic strategies first requires the identification and understanding of CKD-specific pathological mechanisms. To achieve this goal, two German universities, the RWTH University of Aachen and the Saarland University, have initiated the Transregional Collaborative Research Center 219 (SFB/TRR219) "Mechanisms of Cardiovascular Complications in Chronic Kidney Disease" (www.sfb-trr219.de). This consortium aims to analyze the multi-faceted mechanisms of CKD-related cardiovascular disease in experimental and clinical studies, with a total of 17 interdisciplinary research teams from cardiology, nephrology, biophysics and molecular biology joining forces.

Results: Our current understanding of the increased cardiovascular risk in CKD is based on the interaction of the kidney with the circulation (encompassing the vascular system and blood) and the myocardium. This increases cardiovascular risk by triggering pathological mechanisms. In analyzing these mechanisms and their role in the complex interaction between kidney, vasculature and heart, the SFB/TRR219 is mainly focusing on increased calcification, inflammation, oxidative stress, fibrosis, thrombosis and neurohumoral dysregulation in CKD.

Conclusions: By collaborative and translational research based on existing interactions between groups of different clinical and methodological expertise, the German SFB/TRR219 pursues the overall long-term goal to gain understanding of the renal and cardiovascular interactions that may contribute to the development of novel treatment strategies to decrease cardiovascular risk in CKD patients.

Funding: Government Support - Non-U.S.

PUB417

Pathological Analysis and Serum Reactivity of Anti-GBM Disease/IgG1 Is Dominantly Deposited in the Glomeruli in Anti-GBM Disease

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Background: Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) is caused by circulating autoantibodies against mainly the noncollagenous-1 (NC-1) domain of the alpha 3 chain of type IV collagen. NC-1 domain must be dissociated in order for autoantibody binding to occur. 30% of anti-GBM GN patients are seropositive with anti-neutrophil cytoplasmic antibody (ANCA). Bowman et al reported IgG1 and 4 were dominant in the patient serum and renal eluates, Here we analyze the IgG subclass deposited on GBM in anti-GBM GN cases and patient's serum reactivity to glomeruli in biopsied tissue of ANCA-associated vasculitis (AAV), and other GN cases to evaluate the production of autoantibody formation in anti-GBM GN.

Methods: Kidney biopsy specimens from 16 patients diagnosed with anti-GBM glomerulonephritis between April 2009 and March 2018 were identified in Hokkaido Renal Pathology Center. Renal frozen tissue of AAV (anti-GBM seronegative) and other glomerular diseases were stained by a serum from the patient with anti-GBM disease using indirect immunofluorescence method.

Results: The age range was 15 to 83 years. Serologic titers for anti-GBM were raised (7.1->350) in all cases, and serologic studies for ANCAs were positive in 4 cases. One case superimposed IgA nephropathy, and other one showed remarkable granulomatous inflammatioLight microscopy revealed crescentic formation (80.5±17.8%) and linear GBM staining was detected by immunofluorescence study. The number of preserved glomeruli was correlated with baseline eGFR (R^2=0.4407, p<0.01). 14 renal tissues were available for staining with anti-IgG1,2,3, and 4. IgG1 dominant staining was detected in all 14 cases. Cases with more than 2 times brightness of IgG1 staining were seen in younger cases (p<0.05). Glomeruli of biopsied tissue of AAV cases were stained with serum IgG of anti-GBM disease, although glomeruli of MCNS were negative.

Conclusions: IgG1 was mainly deposited on GBM in anti-GBM disease similar to the previous report (Bowman et al, Clin Exp Immunol 1987). The serum reactivity to GBM in AAV suggests that the rupture of GBM is one of the triggers for the pathogenesis of anti-GBM and ANCA double positive disease.

PUB418

Selection of Housekeeper Genes for Real Time Quantitative PCR (qRT-PCR) Analysis of Rat Kidney Tissues Under Ischaemic and Toxicological Conditions

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Background: Appropriate selection of housekeeper genes (HKG's) is pivotal to obtaining accurate and reproducible results in qRT-PCR. Studies have shown that the more commonly used HKG's are not constant under different experimental conditions. Hence we aimed to determine the most opitmum HKG's and normalization factor (NF) for the study of target gene expression in rat kidney tissues.

Methods: Control and adenine fed Sprague Dawley (SD) rats were equally divided into 6 intervention groups consisting of 8 biological replicates. The intervention groups consisted of a subclinical CKD (sCKD), acute kidney injury (AKI), AKI on a background of sCKD, recovery and a control group. AKI was induced with cisplatin or ischaemia. sCKD was induced with 0.25% adenine. 10 commonly used candidate HKG's from different functional classes were selected.. The stability of gene expression was analyzed utilizing NormFinder, Genorm, BestKeeper and comparative delta Cq statistical algorithms. Weighted rank aggregation by Brute force method and by cross entropy Monte Carlo method was used to achieve a consensus rank of genes.

Results: Results: Ranking of the candidate HKG's by each algorithm is listed below in table 1 below (see table) PABPN1, HMBS, YWHAZ, YWHAG and SDHA were respectively determined to be the 5 most stable HKG's by consensus ranking. The optimum number of HKG's needed for most stable normalization factor (NF) was determined to be 3 with 2 also giving an improved result. By comparison, the commonly used GAPDH and 18S were the least stable of all 10 HKG's studied.

Conclusions: Construction of a normalisation factor by utilizing two or three most stable HKG's which includes HMBS and PABPN1 produces the least variability to control for experimental errors and adjusted for inter-sample variations in rat kidney studies

Funding: Government Support - Non-U.S.

Rank	Comparative delta Cq approach (Standard deviation, SD)	Best keeper (SD)[1]	Best keeper ('r' to bestkeeper index)	Normfinder (M value)	Genorme (M value)
1	The Polyadenylate-binding nuclear protein 1 (PABPN1) (1.26)	PABPN1 (0.88)	Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Gamma (YWHAG) (0.96)	PABPN (0.22)	Hydroxymethylbilane synthase (HMBS) (0.59)
2	HMBS (1.31)	HMBS (0.89)	Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Zeta (YWHAZ) (0.94)	YWHAG (0.27)	PABPN1 (0.64)
3	YWHAZ (1.36)	SDHA (0.95)	PABPN1 (0.92)	HMBS (0.29)	Succinate dehydrogenase (SDHA) (0.68)
4	YWHAG (1.38)	HPRT (0.97)	HMBS (0.90)	YWHAZ (0.33)	YWHAZ (0.72)
5	SDHA (1.42)	ACTB (1.06)	Actin Beta (ACTB) (0.85)	ACTB (0.36)	YWHAG (0.77)
6	Tata Binding Protein (TBP) (1.53)	TBP (1.16)	SDHA (0.85)	HPRT (0.42)	TBP (0.89)
7	ACTB (1.59)	YWHAG (1.21)	Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (0.82)	TBP (0.42)	Hypoxanthine-guanine phosphoribosyltransferase HPRT (0.97)
8	HPRT (1.60)	YWHAZ (1.28)	TBP (0.8)	SDHA (0.51)	ACTB (1.05)
9	18S (2.24)	18S (1.78)	18S (0.75)	18S (0.6)	18S (1.29)
10	GAPDH (2.86)	GAPDH (2.29)	HPRT (0.72)	GAPDH (0.77)	GAPDH (1.56)

PUB419

Double-Negative T Cells in Human Renal Cell Carcinoma – Potential Target for Immune Checkpoint Inhibition

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Background: $CD4^-CD8^-$ double-negative (DN) T cells are an unconventional subset of T cells, that are found in normal human and mouse kidney. Their immunomodulatory potential has been proposed in hematological malignancies and melanoma. Immune cells are involved in the pathogenesis of renal cell carcinoma (RCC). However, whether DN T cells are present in RCC is not known.

Methods: RCC and normal tissue adjacent to the tumor were collected from 11 RCC patients after nephrectomy. Kidney mononuclear cells were isolated immediately following tissue procurement and immunophenotypic analyses was performed for $CD45^+$, TCR^+, $CD4^+$, $CD8^+$, $CD20^+$, $CD16^+$, $CD14^+$, $CD11c^+$ and $CD206^+$ cells using flow cytometry.

Results: The mean age of the cohort was 59.8 years. The average maximal tumor diameter was 6.8 cm. Our results demonstrate the presence of DN T cells in RCC tissue as well as in normal kidney tissue (N) with a similar frequency (N: 5.86%, RCC: 6.17%, p=0.918). This was in spite of a significant increase of $CD45^+$ lymphocytes in the RCC tissue in comparison to the normal kidney tissue (N: 8.22% vs. RCC: 44.76%, p=0.001).

In contrast, B cells ($CD20^+$) and M2 macrophages ($CD206^+$) were significantly decreased in tumor tissue ($CD20^+$: N: 21.2% vs. RCC: 5.91%, p=0.002; $CD206^+$: N: 8.44% vs. RCC: 0.90%, p=0.003). There was no significant difference in TCR^+, $CD4^+$, $CD8^+$, $CD16^+$, $CD14^+$ and $CD11c^+$ cell frequencies between RCC and normal kidney tissue (see figure).

Conclusions: This data demonstrates that DN T cells are present in RCC tissue with a frequency similar to "normal" kidney tissue. Given recent data showing PD1 expression on DN T cells, these cells could be potential targets for checkpoint inhibitors and other immunotherapeutic approaches.

Funding: NIDDK Support, Private Foundation Support

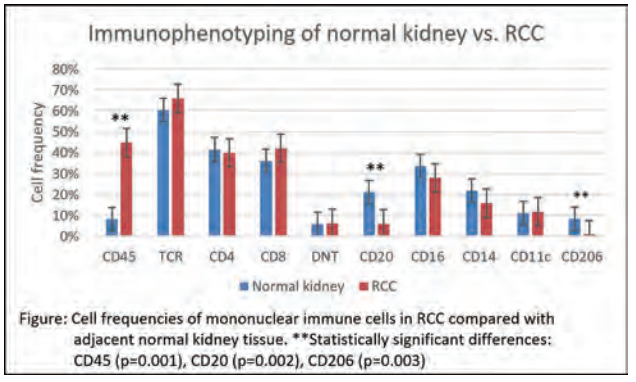

Figure: Cell frequencies of mononuclear immune cells in RCC compared with adjacent normal kidney tissue. **Statistically significant differences: CD45 (p=0.001), CD20 (p=0.002), CD206 (p=0.003)

PUB420

Emerging Role of Post-Translational Modifications in CKD and Cardiovascular Disease

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Background: Post-translational modifications of proteins and peptides have recently gained much attention, as they are involved in the pathogenesis of cardiovascular disease and eventually also in the progression of chronic kidney disease.

Methods: We provide an overview of post-translational protein modifications such as carbamylation, glycation and oxidation, starting with their definitions, mechanisms and clinical relevance in the setting of chronic kidney disease and cardiovascular disease.

Results: The methods currently used for the identification and especially quantification of post-translational modifications are described and potential treatment options in the context of post-translational modifications are reviewed.

Conclusions: We concluded that advancements in mass-spectrometry-based methods will certainly boost the clinical utility of sample analyses, leading to the identification of novel disease markers and/or pathophysiologically relevant factors

PUB421

Angiopoeitin-2 and Procalcitonin as Biomarkers of Atrial Fibrillation in CKD and Sepsis

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Background: Angiopoeitin-2 is a 497 amino acid protein which is involved in vascular remodeling. Procalcitonin (PCT) is a 116-amino acid pro-peptide expressed in non-neuroendocrine tissues. Both biomarkers are upregulated in response to inflammation and cellular injury, particularly in the setting of bacterial sepsis. Ang-2 and PCT are elevated in stage 5 chronic kidney disease on hemodialysis (CKD5-HD), but their relevance with inflammatory cardiac conditions, such as atrial fibrillation (AF), has not been established. Monitoring Ang-2 and PCT levels in CKD5-HD patients may have a dual predictive role in the evaluation of AF and sepsis. Comorbid AF amplifies circulating levels of Ang-2 and PCT are upregulated in CKD5-HD.

Methods: Plasma levels of PCT, CD40-L, CRP, vWF, D-dimer, Ang-1 and Ang-2 were measured in 93 CKD5-HD patients and 50 normal controls using ELISA methods. Patient records established comorbid AF (n=23) and history of sepsis (n=35, mean days from resolution=762, SD=730).

Results: PCT levels were significantly elevated in CDK5-HD patients with comorbid AF (p= 0.0270) but not in patients with a history of sepsis (p=0.3441). In patients with a history of sepsis, PCT levels were elevated only in those patients with comorbid AF (p=0.0405). Notably, of the other inflammatory biomarkers measured, only Ang-2 levels resulted in differentiating between CKD5-HD patients with a history of sepsis (p=0.0138).

Conclusions: In CKD5-HD patients, increased pro-inflammatory processes associated with AF substantially increases PCT and Ang-2 levels. In patients with a history of sepsis, only those with AF demonstrated elevated ANG-2 and PCT levels, therefore measurement of these biomarkers may be useful in the evaluation of AF in post-septic CKD5-HD patients. Sustained inflammation as a result of sepsis may predispose patients at a greater risk of developing AF. Evaluation of this relationship may further elucidate the role of inflammation and the long-term effect of endothelial damage in the pathogenesis of AF.

PUB422

Upregulation of Biomarkers of Neurovascular Diseases in Patients with Stage 5 CKD

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Background: Patients with stage 5 chronic kidney disease (CKD5D) have a higher risk for developing neurovascular complications. Chronic inflammation from renal failure increases the risk for these diseases through oxidative stress and vascular dysfunction. To profile levels of inflammatory and hemostatic biomarkers in CKD5D plasma, and relate measurements to neurovascular diagnoses and demonstrate their relevance to neurovascular deficit.

Methods: Eleven plasma biomarker levels in CKD5D patients (n=97) and healthy controls (n=17-50) were measured using sandwich ELISA method. The biomarkers in this study were of inflammation and hemostatic dysregulation, which included angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), CD40 ligand (CD40L), C-reactive protein (CRP), D-dimer, intercellular adhesion molecule-1 (ICAM-1), NACHT, LRR, and PYD domains-containing protein 3 (NALP3), plasminogen activator inhibitor-1 (PAI-1), procalcitonin (PCT), tumor necrosis factor alpha (TNFα), and von Willebrand factor (vWF). Of the 97 CKD5D patients, 24 had CCAD, 19 had ICAD, and 23 had acute stroke. The results were expressed as mean ± standard error of the mean. Statistics were performed with Mann-Whitney t-tests, Kruskal-Wallis non-parametric ANOVA, and non-parametric Spearman correlations.

Results: All of the biomarkers had elevated levels in CKD5D plasma, except for PAI-1 (p=0.9764), compared to controls. Statistical significance was only found between CKD5D (+) and (-)ECAAD NALP3 (p=0.0299), and between (+) and (-)stroke D-dimer (p=0.0258). Ages between each (+) and (-) disease groups were also significant (p=0.0002 ECAAD; p<0.0001 ICAD; p=0.0157 stroke). D-dimer was correlated with age in CKD5D (r=0.2115, p=0.0375).

Conclusions: Previous studies have demonstrated a relationship between NALP3 expression and the instability of atherosclerotic plaques in ECAAD. NALP3 is a component of inflammasomes, the presence of which elevates IL-1β and IL-18, which subsequently increases risk of ECAAD and stroke. Despite upregulation, biomarker profiling is of limited use in risk stratification of neurovascular diseases among the CKD5D population, with the possible exception of NALP3 for ECAAD.

PUB423

Microdroplets in Minimal Change: A Novel Finding

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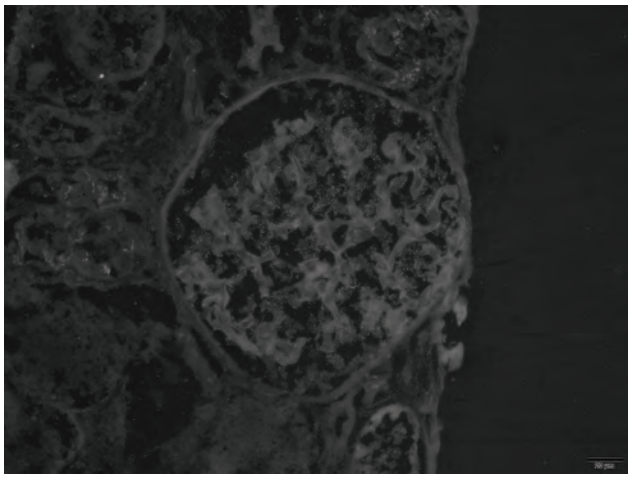
Background: Minimal Change (MCD) is a frequent cause of nephrotic syndrome. MCD results from podocytopathy with filtration barrier changes causing proteinuria. While it is thought circulating mediators lead to podocytopathy, little has been determined about the mediator. In our practice we have noted that many MCD cases have IgG-positive microdroplets in Bowman's space, detectable by IF. We conducted this study to characterize these microdroplets.

Methods: Our database of imaged LM, EM, and IF stains from 2013-16 was reviewed for cases of MCD (n=42), primary FSGS (n=10), collapsing FSGS (n=4), tip lesions (n=5) and normal biopsies (n=12). The presence of microdroplets in images was noted. Additionally, a subpopulation of MCD cases was stained for IgG subtypes and C4d by IF.

Results: Database review revealed 45% (19/42) of MCD cases, 1 out of 10 primary FSGS, and 1 out of 5 tip lesion cases contained IgG dominant microdroplets. Microdroplets were absent in normal biopsies and collapsing glomerulopathy. IgG intensity ranged from weak to 1+. Some microdroplets also stained for IgA (n=1), C3 (n=1), kappa (n=11) and lambda (n=10). A subset of MCD cases (n=8) were stained for IgG subtypes, half which were originally negative for microdroplets. IgG1 microdroplets were present in 88% of cases, 25% were positive for IgG2. All cases were IgG3 and IgG4 negative. A single case, originally negative, showed no subclass staining. One case (13%) had C4d positivity.

Conclusions: To our knowledge the phenomenon of glomerular microdroplets has not been reported. Due to the location and distribution, we believe they represent endocytotic vesicles in podocytes. Subtype restriction suggests there is specific antibody binding to a mediator, possibly involved in causing podocytopathy. Further study to elucidate what the antibodies are binding is warranted. At the very least, we have found these microdroplets helpful in the confirmation of MCD in our practice.



IgG1 stain with diffuse microdroplets within Bowman's space.

PUB424

Kidney Diseases Associated with Tubular Reticular Inclusions (TRI)

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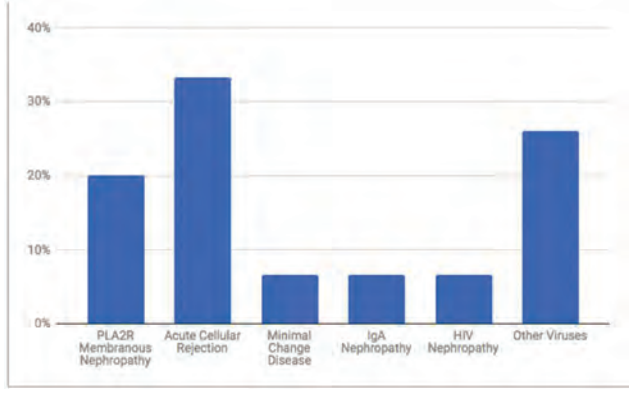
Background: Tubular reticular inclusions (TRI) in kidney biopsies are indicative of a high interferon state. They have been noted in kidney biopsies of patients with HIV nephropathy and lupus nephritis (LN). Literature is limited in other known causes of kidney diseases noted with TRI.

Methods: We reviewed all biopsies performed at our health system with findings of TRI(1 year). Clinical and pathology data were collected by chart review. Comparisons between LN patients and n-LN patients were made using student t-tests and chi-square analysis.

Results: TRI were found in 17% (55/322) of biopsies. 71% of the biopsies had LN (N = 40) & remaining 29% (N =15) had n-LN diagnoses. The 15 n-LN patients comprised of various other diagnoses (Fig). Four patients (26%) of the n-LNpatients had a virus associated disease (BK virus, parvovirus B19, hepatitis C and hepatitis B). The mean age of the LN patients was 31.5 years compared to 40.9 years in n-LN, p = 0.04. The LN were mostly females (80%) compared to the n-LN group, where 50% were females, p = 0.048. Almost 90% of LN presented with hypocomplementemia whereas only 15% of the n-LN presented with hypocomplementemia, p < 0.001. The mean presenting Scr was higher in n-LN compared to LN (2.45mg/dl vs. 1.36 mg/dl, p = 0.01). There was no significant difference in proteinuria at time of biopsy for the LN (3.69 g/day) compared to n-LN (4.82 g/day), p = 0.86. The mean 6 month Scr was 1.94mg/dl in LN patients after treatment and 1.5mg/dl in n-LN, p = 0.78. There was one LN patient and two n-LN patients that required dialysis.

Conclusions: TRI were noted in biopsies of patients with LN but also in a number of n-LN patients. Interestingly, as opposed to commonly being seen in HIV nephropathy, our pathology was mixed with new associations. The n-LN patients presented with higher serum creatinine and normal complement levels. The outcomes appear to be similar in both groups.



Pathology diagnoses of non lupus nephritis patients

PUB425

Xanthogranulomatous Pyelonephritis as a CKD Cause

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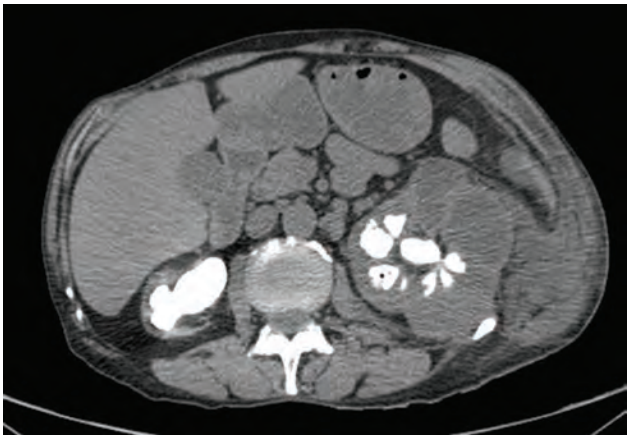
Background: Xantogranulomatous Pyelonephritis (XGP) is a rare chronic inflammatory condition of the kidney that appears as a complication of long-term obstruction and infection of the urinary tract. Renal parenchyma is replaced by xanthoma cells, plasma cells and histiocytes. It accounts for only 0.6% of all histologically documented cases of pyelonephritis. Due to its low frequency, most of the available information comes from case series.

Methods: The study was conducted in the University Hospital Dr. José E. González in Monterrey, during January 2012 to may 2018. All patients with XGP where retrospectively recruited for analysis. Demographics, history and physical examination, biochemical, urinalysis, urine culture and imaging studies information was extracted from patients.

Results: A total of 37 patients were included in our analysis. Females (78.4%) were affected more commonly than man. Prior renal lithiasis and urinary infection affect patients on 51.5% and 44.4% of the cases, respectively. The most common presenting symptom was flank pain (70%) and fever (63.9%). 47.5% of the cases presented with hemoglobin <10 mg/dL and 79.4% had leukocytosis. The mean GFR was 74.1 (47.8–105.3). E. coli and Morganella spp. were the most common cultured bacteria on urine. Nephrectomy was performed on all patients. Bear paw sign was only present on 9.7% of the cases (Fig 1).

Conclusions: XGP is a rare condition, commonly presenting on femele patients with prior renal lithiasis or urinary infection. The most common cultured bacteria on urine were E. coli and Morganella spp. As the main treatment modality is nephrectomy, more information about this disease is needed to improve diagnosis, management and outcomes.



PUB426

The Significance of Serum Soluble Urokinase-Type Plasminogen Activator Receptor in Diagnosing FSGS: A Meta-Analysis

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Background: In the pathogenesis of focal segmental glomerulosclerosis (FSGS), circulating factors have been regarded as a significant factor, since about 40% of the patients recur after transplantation. Soluble urokinase-type plasminogen activator receptor (suPAR) has been suggested as a potential biomarker for FSGS. This study is a meta-analysis on the usefulness of suPAR for the diagnosis of FSGS.

Methods: We performed a PubMed, EMBASE and forward search of the retrieved articles and identified studies that evaluated suPAR levels in patients with FSGS, published until May 1st, 2018.

Results: Of the 187 articles reviewed, 13 fulfilled the criteria of inclusion. We observed increased level of suPAR in the FSGS patients compared to healthy controls (P<0.001, Hedge's g, 3.097, 95% confidence interval(CI), 1.666-4.527). This finding was consistent in comparison with other glomerulonephritis (GN). The suPAR levels were significantly higher in patients with FSGS compared to those with minimal change disease (MCD) (P=0.033, Hedge's g, 1.289, 95% CI, 0.107-2.471), membranous glomerulonephritis (MN) (P=0.013, Hedge's g, 1.372, 95% CI, 0.286-2.457), and IgA nephropathy (IgAN) (P<0.001, Hedge's g, 0.840, 95% CI, 0.488-1.192), respectively. Of note, however, the levels did not differ between FSGS patients with remission compared to those without (P=0.411, Hedge's g, 1.020, 95% CI -1.413-3.453).

Conclusions: The results suggested that suPAR can be a putative diagnostic indicator for FSGS in differential diagnosis of GN.

Funding: Government Support - Non-U.S.

Table 1. Summary of the all meta-analysis data

Groupwise	No. of studies	No. of subjects		Meta-analysis			Heterogeneity			Egger's test
				Hedges's g	95% CI	P-value	I^2 (%)	Tau^2	P-value	P-value
FSGS vs. Control	9	FSGS 418	Control 390	3.997	1.666	4.527	0.000	97.938	4.569	0.000	0.10235
FSGS vs. MCD	10	FSGS 503	MCD 296	1.289	0.107	2.471	0.033	97.469	3.510	0.000	0.80459
FSGS vs. MGN	7	FSGS 430	MGN 238	1.372	0.286	2.457	0.013	96.868	2.049	0.000	0.32793
FSGS vs. IgA nephropathy	2	FSGS 133	IgAN 43	0.840	0.488	1.192	0.000	0.000	0.000	0.906	-
FSGS vs. FSGS remission	2	FSGS 90	FSGS-R 62	1.020	-1.413	3.453	0.411	96.623	2.978	0.000	-

Abbreviations used: SUPAR (soluble urokinase-type plasminogen activator receptor), FSGS (focal segmental glomerulosclerosis), FSGS-R (remission), MCD (minimal change disease), MGN (membranous glomerulonephritis), IgAN (immunoglobulin A nephropathy), *P* values were all two-tailed, Hedges's g was random value

PUB427

Does ABPM Correlate with BP Diagnosis Made at Pediatric Nephrologist's Office?

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Background: ABPM is a helpful tool in evaluating children with variable office BPs, white coat hypertension (WCH) and uncontrolled HTN. In 2017, AAP defined the ABPM role in diagnosing/managing HTN, recommending it for any child with elevated office BP for ≥ 1 yr or with stage I HTN x 3 visits. HTN is a common reason for Ped Nephro referrals from school RN and MD's offices. Limited data exists comparing ABPM diagnosis with Ped Nephro office's BPs in children. Objective: to compare HTN diagnosis made by ABPM vs Ped Nephr office's BP and evaluate by referral source, demographic and clinical data.

Methods: ABPM was done by Welch Allyn 6100 monitor. Soergel criteria were used to define BP percentiles; SBP and/or DBP load ≥ 25% was used to diagnose HTN (% SBP and DBP > 95th). Elevated BP =90-95%, Stage I-≥95-99% and Stage II- ≥99%+5 mm Hg. Retrospective review was done in all children with 24 hour ABPM done from Jan 2011 to May 2017 at our office. IRB approval was obtained for chart access. All children diagnosed with confirmed HTN complete evaluation to r/o secondary causes and evidences of end-organ damage.

Results: 373 ABPMs were done in 361 children aged 3-21yrs (median=14yrs); 73% males; Ethnicity: 152 AA, 117 C, 71 H, 21 other. 73% had positive FH for HTN and 20% were symptomatic at presentation. LVH was seen in 14% and microalbuminuria in 9%. LVH correlated with HTN stage. **Referral source**: 263 (74%) from PMD, 29 from School RN and 63 from Pediatric sub-specialists. **Office BP diagnosis**: 51 wnl, 106 with Elevated BP, 145 Stage I HTN, 58 Stage II HTN and 1 NA. **ABPM diagnosis**:125 WCH, 61 with Elevated BP, 134 Stage I HTN, 47 Stage II HTN and 6 errors. 86 children (23%) with abnormal BP at Nephrologist office had WCH diagnosed by ABPM. **For children with HTN diagnosed by both Nephrologist and ABPM**: office HTN grade was higher in 29 and lower in 45, when compared to ABPM; discordance rate = 74/229 (32%). Masked HTN was noted in 14 children (4%). Degree of HTN and WCH didn't correlate with referral source; children referred by school RNs were more often symptomatic (38% vs 18%, p=0.01).

Conclusions: Children with suspected HTN, often symptomatic were referred from various sources for Ped Nephro consult. ABPM was confirmed as an important tool to diagnose masked HTN, WCH and clearly establish the proper level of HTN. We observed a high discordance rate of HTN Stage diagnosis which was independent from referral source.

PUB428

Trajectory of eGFR Predicts Renal Injury in Children with Multicystic Dysplastic Kidney

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Background: Children with a solitary functioning kidney have a risk of renal injury caused by hyperfiltration. Timely intervention with renin-angiotensin inhibitors may be benefical. We examined whether trajectory of estimated glomerular filtration rate (eGFR) would predict renal injury, defined as microalbuminuria/proteinuria, hypertension, and/or a decline in eGFR.

Methods: Seventeen patients (male 7, female 10) with multicystic dysplastic kidney (MCDK) (median age 13 years, range 6 to 19 years) followed in our clinic were examined retrospectively. Microalbuminuria and proteinuria were defined as urine albumin/creatinine ratio >30 mg/g and urine protein/creatinine ratio >0.15 g/g, respectively. Hypertension was determined when an average of BP measurements was ≥the 95th percentile for age, sex, and height. GFR was estimated by quintic equation for Japanese children by height and gender (2-18 years) or the revised Japanese equation for eGFR (>19 years). An eGFR decline was defined as a fall to <90 ml/min/1.73 m^2 or a decline of >5 ml/min/1.73 m^2/year for those with baseline eGFR of ≥90 ml/min/1.73 m^2 or <90 ml/min/1.73 m^2, respectively. The best-fitting model of eGFR over time was determined in each patient.

Results: Nine patients had renal injury at the time of investigation. Compared with 8 patients without renal injury, those with renal injury tended to be older (14.7±4.2 vs 11.4±4.6 years, meas±SD) and the birth weight was smaller (2538±281 vs 2966±361 g, P<0.05). Frequency of contralateral congenital anormaly of kidney and urinary tract (cyst, hydronephrosis, or vesicoureteral reflux) was not different. Trajectory of eGFR in those without renal injury was either increase (n=3) or unidentifiable (not fitting any statistical significant model but remaining stable, n=5), whereas that in renal injury group was exclusively increase followed by decline (P<0.05). The average age of the onset of eGFR decline was 9.4±4.2 years and that of renal injury (albuminuria/proteinuria 5, eGFR decline 4, hypertension 1) was 12.5±4.2 years.

Conclusions: All the children with MCDK who developed renal injury had eGFR trajectory of increase followed by decline. The peak eGFR was followed by renal injury after 3 years on average. This observation is in agreement with the hyperfiltration theory and underscores the importance of following eGFR trajectory closely especially when eGFR is increasing.

PUB429

An Unusual Case of PHA Type 1

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Introduction: Pseudohypoaldosteronism (PHA) is a rare pediatric condition presenting as either Type 1 or Type 2. Type 1 can be primary or transient whereas Type 2 is often congenital. Transient Type 1 PHA is often due to a UTI or a congenital malformation leading to a UTI. We describe the first documented case of PHA Type 1 in a 2-week old tiger cub at the San Diego Zoo Safari Park

Case Description: A 3-day old tiger cub at the San Diego Zoo Safari Park was rejected by his mother & hand-reared by park keepers using a formula designed for carnivores. The tiger failed to thrive, presenting with acute lethargy at 2 weeks. During initial evaluation, the cub had a cardiac arrest revived with CPR. Initial labs showed a critical K>9 mEq/dL with hyponatremia (120 mg/dL). Subcu 0.9% saline was started. Differential diagnosis included adrenal crisis thus the tiger cub was started on prednisolone and fludrocortisone. Additional testing included a urine culture, which grew *Klebsiella pneumoniae* and *Enterococcus* species. An abdominal U/S revealed hyperechoic debris swirling in the urinary bladder & renal pelvices as well as bilateral pyelectasia. Transient pseudohypoaldosteronism secondary to pyelonephritis was suspected and the tiger was started on amoxicillin and clavulanate. An adrenocorticotropic hormone (ACTH) stimulation test revealed a significantly elevated aldosterone of >4572 pmol/L, confirming the diagnosis. The veterinary staff used pediatric nephrology literature to diagnose and treat. The tiger was given antibiotics until the urine culture was negative and the U/S revealed resolution of debris. Electrolytes normalized. He began to eat, grow & eventually bond with his brother.

Discussion: Severe hyponatremia & hyperkalemia are uncommon during infancy, but can have life-threatening consequences. The differential diagnosis includes congenital adrenal hyperplasia (CAH), congenital adrenal hypoplasia, medication administration and PHA. PHA causes hyponatremia, hypovolemia, hyperkalemia, & metabolic acidosis. Type 1 PHA can either be primary (inherited) or secondary (transient). Transient PHA is reported in infants with UTIs and urinary tract abnormalities (hydroureteronephrosis, vesicoureteral reflux or obstructive uropathy). Patients with PHA should have resolution of their electrolyte imbalances with targeted treatment of the primary infection and appropriate IV fluid resuscitation, even if they are a tiger.

PUB430

Enuresis Is Common, Severe, and Persists to Older Age in Children with Sickle Cell Disease

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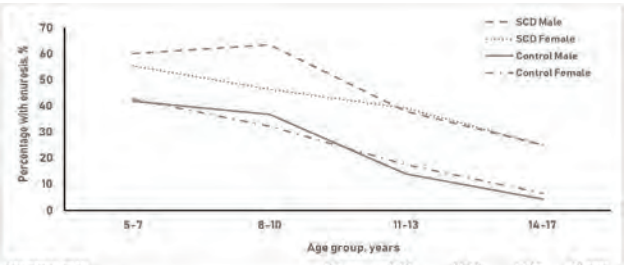
Background: Despite strong association between sickle cell disease (SCD) and enuresis, no large studies have examined, using standardized definitions, the prevalence of enuresis, its variants and risk factors in children with SCD in Sub-Saharan Africa which has the largest burden of SCD. We determined and compared the prevalence of enuresis and its various forms in children with and without SCD and identified its predictors.

Methods: Caregivers of children with SCD attending a hematology clinic in a public hospital in Nigeria were interviewed using a standard case record form. In addition, a separate record form was completed for every sibling aged 5-17 years whose haemoglobin phenotype was known. Enuresis and its variants were defined using the International Children's Continence Society's definitions.

Results: The study involved 256 children with SCD and 256 controls. The mean age of the study cohort was 9.9 (3.4), with 44.5% ≥10 years and 44.5% as females. The prevalence of enuresis was higher at 48.4% in children with SCD than in the controls with a steady decline with age (Fig. 1). The proportions with secondary enuresis (10.5% v 16.2%) were similar in both groups. However, children with SCD and enuresis were older (9.0 v 8.1 year), more likely to be aged ≥10 years (33.9% v 16.2%) and were twice likely to have ≥4 wet nights/week and non-monosymptomatic form than the controls. Pre-adolescence and enuresis in a family member were predictors of enuresis in children with SCD, whereas gender, socioeconomic status, hospitalisation in the past 12 months and receipt of blood transfusion were not.

Conclusions: Enuresis is more frequent, severe, non-monosymptomatic and likely to persist to late adolescence in children with SCD than in controls. These features make enuresis in children with SCD more difficult to treat than in controls. Younger age and enuresis in a family member are risk factors for enuresis in children with SCD.



Age group, years		5-7 n=190 (%)	8-10 n=138 (%)	11-13 n=104 (%)	14-17 n=80 (%)	All ages, n=512 (%)
Percentage of children with SCD with enuresis	Male	60.4	63.4	37.9	25.0	50.7
	Female	55.3	46.4	39.1	25.0	45.6
	Total	57.9	56.5	38.5	25.0	48.4
Percentage of control with enuresis	Male	41.7	36.6	13.8	4.2	28.2
	Female	42.6	32.1	17.4	6.3	29.8
	Total	42.1	34.8	15.4	5.0	28.9
P value*		0.030	0.010	0.008	0.012	0.000

Age and sex prevalence of enuresis

PUB431

Effect of a Gluten-Free Diet on Albuminuria in Patients with Celiac Disease

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Background: Celiac disease (CD) is caused by a gluten-induced increase in zonulin production by the enterocyte. This molecule interacts with protease activated receptor 2, disrupts the tight junction in the gut epithelium, and increases the intestinal permeability to gliadin. PAR2 is expressed in podocytes raising the possibility that this glomerular epithelial cell could be a target of zonulin.

Methods: Patients who were newly diagnosed with CD, based on elevated tissue transglutaminase (tTG) and small bowel histology, were eligible for inclusion in the study. A first morning urine specimen was collected at diagnosis and at the time of the follow-up clinical assessment conducted to assess the response to the gluten-free diet (GFD). Albuminuria was measured using an ELISA kit and expressed as the albumin:creatinine ratio (ACR). Results are provided as mean±SEM.

Results: 17 patients with CD (8M:9F), all white, mean age 9.1±1.1 years old, were included in this study. 16 patients had elevated tTG IgA and the other patient had IgA deficiency with an elevated tTG IgG. At diagnosis, 1 child was receiving escitalopram and a second recombinant human growth hormone. After the initial assessment, 2 patients took lansoprazole but it was discontinued 2 months before the follow-up evaluation. None were receiving immunosuppressive medications. BP, serum creatinine and albumin concentrations were normal in all patients. The mean interval on the GFD was 6.1±0.7 months. The initial ACR was 20.7±5.2 (4 had values above 30 μg/mg) that fell to 10.4±1.5 μg/mg at the repeat evaluation, P=0.035.

Conclusions: Our findings indicate that patients with CD have low-grade albuminuria at the time of diagnosis of their gastrointestinal disease. Initiation of a GFD is associated with a significant decline in albumin excretion. Further study is needed to determine whether assessment of albuminuria should be incorporated into the care of patients with CD as a marker of clinical response and whether this abnormality has any long-term adverse health consequences.

Funding: NIDDK Support

PUB432

The Impact of Pathological Findings of Mitochondrial Disorders in Low Birth Weight Infants

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Background: Preterm infants with a low birth weight (LBW) show reduced numbers of nephrons at birth and a higher risk of developing kidney dysfunction during their lifetime. They demonstrate oligonephronia and focal segmental glomerulosclerosis (FSGS) lesions in their glomeruli. We examined the association between mitochondrial disorders and the pathological characteristics of LBW-related nephropathy.

Methods: We retrospectively evaluated the renal pathology in 6 infants including pairs of twins and 2 LBW infants demonstrating renal dysfunction. In addition to routine staining, the kidney biopsy specimens were analyzed using cytochrome c oxidase subunit IV (COX IV) and transcription factor A (TFAM) staining.

Results: FSGS was diagnosed in 2 and oligonephronia in 4 infants. The mean density of glomeruli was 3.8/mm^2 (0.3–7.2) Granular swollen epithelial cells (GSECs), which have previously been reported exclusively in patients with mitochondrial cytopathy, were observed in the distal tubules and/or collecting ducts in all 6 infants. Electron microscopic examination revealed that these GSECs included an increased number of enlarged mitochondria. Furthermore, we observed unbalanced expression patterns of COX IV and low expression of TFAM in the glomeruli and a part of the tubular cells.

Conclusions: FSGS, a characteristic feature of glomerular involvement in patients with mitochondrial cytopathy is very commonly observed in LBW infants. In our study, all infants did not show FSGS lesions because a renal biopsy was performed in the early stages of the disease in contrast to previous reports. However, most patients revealed similar pathological changes of mitochondrial cytopathy such as unbalanced expression of TFAM, which plays a role in maintaining the mitochondrial DNA. This finding suggests that these lesions could appear during early childhood, resulting in the development of FSGS in the future. These findings could suggest the application of a new approach targeting mitochondrial DNA to prevent the development of LBW-related nephropathy.

PUB433

Molecular Assay to Detect the Pathogenicity of Intronic Variant in NUP93 for Steroid Resistant Nephrotic Syndrome

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Introduction: Advances in molecular genetics have revealed that about 30% of the cases with steroid resistant nephrotic syndrome (SRNS) are caused by single-gene mutations that highly expressed in the podocytes. More than 50 genes are known to be responsible for SRNS. One of the responsible genes is nucleoporin, 93-KD (NUP93). Till date, only few studies reported the mutations of NUP93 in SRNS. Here, we describe a NUP93 biallelic mutation in 9 years old boy with focal segmental glomerular sclerosis (FSGS). Although one was a heterozygous truncating variant, another was a novel heterozygous intronic variant which pathogenicity was unknown. To confirm the pathogenicity of the intronic variant, we conducted in vivo and in vitro analysis.

Case Description: The patient was a 9-year-old boy. He was detected proteinuria at 2 years old, and diagnosed with SRNS. The histological finding was FSGS. At the onset, hypoalbuminemia (2.6 g/dL), high serum creatinine (0.88 g/dL) with decrease renal function (eGFR 53.6L/minute/m^{2}BSA), proteinuria (urine protein creatinine ratio: 2.37), and hematuria was found. He has optic nerve atrophy as his extrarenal symptom. There were no histories of kidney diseases in the family. We found 2 novel heterozygous mutations in NUP93, c.727A>T (p.Lys243*) in exon 8 and c.2137-18G>A in intron 19. To determine the pathogenicity of the intronic variant, we conducted RT-PCR analysis, in vitro splicing assay using minigene construction and in vitro protein expression analysis. Both RT-PCR using patient's sample and in vitro splicing assay showed exon 20 skipping by the intronic variant. The in vitro protein expression analysis result showed abnormal localization in cytoplasm with the particle formation by the intronic variant. From these results, we conclude c.2137-18G>A as pathogenic by causing aberrant splicing.

Discussion: NUP93 variants are quite rare; however, we proved even the intronic variants in NUP93 can cause SRNS. Our results can help identifying more variants in this rare form of SRNS.

PUB434

The Clinical Manifestation of BK Virus Infection in Pediatric Patients with Kidney Transplantation

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Background: Polyomavirus BK is known as a common cause of graft failure in kidney transplant patients. There is rare data in pediatric patients, and the purpose of this study was to evaluate the clinical findings of BK virus infection and risk factor in pediatric patients with kidney transplantation.

Methods: The medical records of 30 children who received kidney transplantation from January 2002 to December 2017 in Samsung medical center were retrospectively reviewed. The screening for BK virus was performed in blood and urine by polymerase chain reaction.

Results: The median age of the kidney transplantation was 11.3 (range, 1.3-18.6) years, and male to female ratio was 2.3:1. The most common underlying disease was congenital abnormalities of kidney and urinary tract. The sixteen patients received the kidney from the deceased donors. BK viremia and viuria were detected in 9 and 6 patients respectively. The median period from kidney transplantation to BK virus detection in blood or urine was 51days (7-3,464days). Among 15 patients with BK infection, 9 patients had the deceased donor kidney. The children with BK virus infection showed the tendency that the age at the time of transplantation was younger compared with those without BK virus infection (median age 8.4 vs 11.3 years). Three patients who had the past medical history with high dose chemotherapy and autologous stem cell transplantation for solid tumor before kidney transplantation showed the high titer of BK virus in blood. However, BK virus infection did not affect the short-term renal function and graft survival in all patients because the dose of immunosuppressant decreased when BK virus was detected.

Conclusions: The results of this study suggest that the risk factors of the BK viremia in the pediatric kidney transplant patients are supposed to be younger age at the time of kidney transplantation, deceased donor kidney, and past medical history with high dose

chemotherapy. Regular monitoring for BK virus and reduction of immunosuppression is necessary to prevent graft function.

PUB435

Classical Fabry Disease in Children

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Background: INTRODUCTION: Fabry disease (FD) is caused by deficient or null activity of the enzyme α-galactosidase A (α-galA) which causes the lysosomal accumulation of complex glycosphingolipids, mainly globotriaosylceramide. Affected children suffer from neuropathic pain, gastrointestinal dysfunction, hypohidrosis and intolerance to cold and heat from early childhood, which may impair quality of life and affect the daily activities of home and school. OBJECTIVE: To describe the organic commitment in children at the time of diagnosis of FD.

Methods: Patients with FD were analyzed from three reference centers in Argentina, with classical mutations of the GLA gene (E398x and p.L415P). Typical manifestations of EF were evaluated after having ruled out other causes of them.

Results: Twenty-one patients, from 2 to 16 years of age (average: 8.2 years), 12 women and 9 men were studied. Renal hyperfiltration was detected in 12/21 (57.1%); 9 girls and 3 boys. Three patients (14.3%) had GFR <90 ml / min / 1.73 m2 (2 children and 1 girl). Albuminuria was evidenced in 2 girls (9.5%). 7/21 children (33.3%) presented neuropathic pain. Cardiac involvement was detected in 4/21 patients (19%); 2 with arrhythmia (sinus bradycardia) and 2 with LVH. 5 patients (23.8%) presented angiokeratomas and only 3 (14.3%) with gastrointestinal involvement. An 11-year-old girl presented CNS involvement (NMR with white matter lesion without any other cause than FD.)

Conclusions: Children in our population experienced symptoms and signs typical of FD at an early age, with a high percentage of renal hyperfiltration. (as a probable glomerular compensation and incipient sign of nephropathy) as the most frequent renal manifestation.

n	Iniciales	Sexo	Edad	Mutación	F.Schwartz	MA	SNC	Arritmia	HVI	GI	SNP	AK
1	NF	F	7	E398x	≥ 140	NO	No	No	No	No	No	No
2	VF	F	9	E398x	120	NO	No	No	No	No	No	No
3	CSP	F	14	E398x	≥ 140	SI	No	No	No	No	No	No
4	MN	F	4	E398x	73	NO	No	No	No	No	No	No
5	SN	F	5	E398x	≥ 140	NO	No	No	No	No	No	No
6	IF	M	3	E398x	≥ 140	NO	No	No	No	No	No	No
7	ANC	M	10	E398x	≥ 140	NO	No	No	No	No	SI	SI
8	YF	M	2	E398x	76	NO	No	No	No	No	No	No
9	CF	M	4	E398x	86	NO	No	No	No	No	No	No
10	JPT	M	4	E398x	108	NO	No	No	No	No	No	No
11	RO	F	11	p.L415P	≥ 140	NO	SI	No	No	No	No	No
12	AE	F	16	p.L415P	≥ 140	SI	No	No	No	No	SI	SI
13	BB	F	4	p.L415P	117	NO	No	No	No	No	No	No
14	AB	F	7	p.L415P	≥ 140	NO	No	No	No	No	No	No
15	OE	F	5	p.L415P	≥ 140	NO	No	No	No	SI	SI	SI
16	PE	F	13	p.L415P	≥ 140	NO	No	Bradicardia	No	No	No	SI
17	LE	F	15	p.L415P	≥ 140	NO	No	Bradicardia	No	No	SI	SI
18	KP	M	4	p.L415P	93	NO	No	No	SI	No	No	No
19	SP	M	9	p.L415P	113	NO	No	No	SI	No	SI	No
20	FO	M	10	p.L415P	112	NO	No	No	No	SI	SI	No
21	AP	M	16	p.L415P	≥ 140	NO	No	No	No	SI	SI	No

PUB436

Ampicillin/Sulbactam as Empiric Monotherapy In Patients Under 24 Months with 1st UTI in the Era of Antibiotic Resistance

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Background: Cephalosporin has been the most commonly used empirical agent for urinary tract infection (UTI) in children. However, the worldwide increase of extended-spectrum beta lactamase (ESBL) producers and its resistance to cephalosporin makes it difficult for physicians to choose empirical antibiotics for UTI.

Methods: All infants and young children 2 to 24 months old who hospitalized to Pusan National University Children's Hospital due to first episode of febrile UTI during the 2-year period (June 2012 to April 2014) were included in the study. The subjects were divided into two groups according to their empirical therapy whether they received cefotaxime or ampicillin-sulbactam. We determined the pathogens of UTI of young children and their antibiotic susceptibilities and compared effectiveness and adverse effect between ampicillin/sulbactam and cephalosporin.

Results: 55 patients of group A were treated with cefotaxime and 44 patients of group B with ampicillin/sulbactam as empirical antibiotics. The most common pathogen was *E. coli* in both groups and isolated *E. coli* of two groups had no significant differences in antibiotics susceptibility rate. In both groups, *E. coli* tends to be more susceptible for ampicillin/sulbactam than cefotaxime. In addition, there was no significant difference in the duration of fever (11.6 ± 15.4 vs 8.7 ± 13.3hrs, P = 0.29) after treatment between the two groups. None of the patients in both groups had initial treatment failure or recurrence due to improper treatment. The most common side effects of antibiotics agents were diarrhea (72.7% vs 74.5%, P = 1.0), elevation of liver function test (47.7% vs 52.7%, P = 0.68), and anemia (11.4% vs 23.6%, P = 0.18). Comparing the cost of treatment, we found that ampicillin-sulbactam is cheaper than cefotaxime.

Conclusions: Ampicillin-sulbactam could be effective alternative to cephalosporins as the empiric treatment in patients with 1st UTI under 24 months.

PUB437

Complement Activation Fragments Levels in Post Infectious Glomerulonephritis

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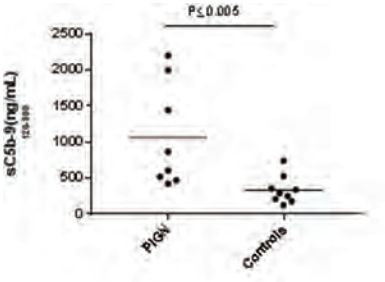
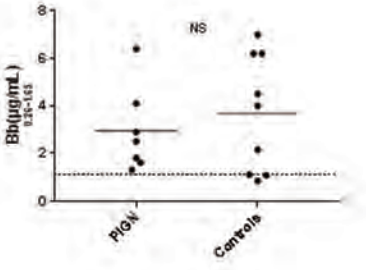
Background: Post infectious glomerulonephritis (PIGN) is the most common cause of acute glomerulonephritis in children, and it is associated with hypocomplementemia (low C3).

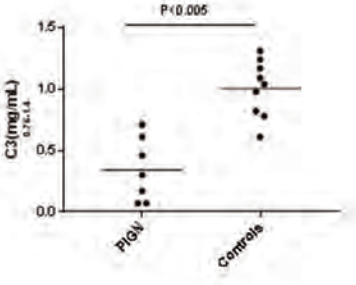
Methods: Children with PIGN (n=8) and controls (acute renal failure n=3, chronic renal failure n=1, typical hemolytic uremic syndrome n=5) were studied for plasma lytic pathway sC5b-9, alternative pathway Bb fragment, and C3 concentrations.

Results: Plasma sC5b-9 concentrations were above the normal range (120-300 ng/mL) in all PIGN patients with a strikingly high mean value of 1067±253ng/mL. The control group showed a mean value of 337±63 ng/mL. Thus, PIGN patients had significantly higher sC5b-9 levels as compared to the control group (P≤0.004). The Bb concentrations were also above the normal range (0.26-1.66 μg/mL) with a mean value of 2.9±0.6 μg/mL in PIGN and of 3.6±0.8 μg/mL in controls, however there was no significant difference in Bb concentration between both groups. C3 concentrations were below the normal range (0.75-1.4 mg/mL) in all PIGN patients with a mean value of 0.34±0.1 mg/mL. The controls had a mean value of 1.0±0.07 mg/mL. Thus, PIGN patients had significantly lower C3 levels as compared to controls (P≤0.01).

Conclusions: PIGN patients had significant higher sC5b-9 levels and significant lower C3 levels as compared to controls. These preliminary data indicate that sC5b-9 levels could be a useful marker to detect ongoing complement activation in the circulation of PIGN patients, which may have utility for therapeutic monitoring, e.g. after administration of complement inhibitors.







- Statistics analysis were done with non-parametric Mann-Whitney test

PUB438

Ethnic Population Variance in Nephron Mass in Neonates: The Miami Cohort versus International References

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Background: Nephron endowment, the number of functioning nephrons at birth, may determine an individual's adult longevity. Preterm birth is associated with developmental programming of hypertension and cardiovascular disease. A non-invasive and economical surrogate of nephron mass is the ultrasound (US) measurement of renal dimensions. Limited studies have suggested subclinical ethnic variations in kidney volume and function in children but not in neonates.

Methods: In a prospective cohort study, 157 neonates were enrolled at birth; 140 singletons [71 term (T), 69 preterm (PT)] and 17 twins. Race/ethnicity were recorded. Renal measures were assessed by US and renal function by serum creatinine (SCr) and cystatin C (CysC) based equations for estimated glomerular filtration rate (eGFR). A table of reference values (RV) for kidney size parameters from 5 countries was extracted from the literature and included 871 healthy term neonates.

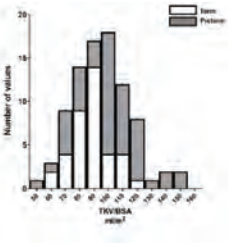
Results: The Miami Cohort is primarily an ethnic/racial minority with an Hispanic/Non-White demographic [144/157=92%]. KL and TKV correlated closely with all body anthropometrics and gestational age (GA) ($p<0.001$). TKV correlated significantly with eGFR. TKV for PT and twins was significantly different from term singletons ($p<0.001$ for all). TKV/BSA (ml/m2) was normally distributed, independent of GA, and similar among T and PT singletons. Both TKV and TKV/BSA were significantly decreased for twins compared to singletons. The Miami Cohort Term infants had lower TKV and TKV/BSA than that of the international RV.

Conclusions: There is a wide regional variation in nephron mass reflective of the gene-environmental influence on nephrogenesis. Absolute TKV is a primary determinant of kidney function; whereas, TKV referenced to BSA (ml/m2) reflects nephron endowment individualized to body size. Support of post-natal nephrogenesis in preterm infants is essential if their nephron endowment is to be maintained. Follow-up of post-natal renal growth and function is warranted in individuals born preterm.

Funding: Private Foundation Support

Group	N	Birth Weight (Kg)	Birth Length (cm)	BSA (m^2)	TKV (ml)	TKV (ml/m^2)
Reference Values						
Term Newborns	871	3.4±0.4	51±2	0.21±0.02	27±6***	128±28***
Miami Cohort						
Singletons						
Term	67	3.0±0.5	50±3	0.19±0.02	17±3**	90±14
Preterm	62	2.1±0.7	45±5	0.15±0.03	16±4**	103±28**
Twins						
Twins	17	2.1±0.4	44±3	0.15±0.02	12±4	81±24

*** p<0,001 Significantly different from all other groups;
** p<0.001 Significantly different from Twins



PUB439

Prediction of the Renal Elimination of Drugs with Cystatin C versus Creatinine: A Systematic Review

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Background: Cystatin C has been proposed as an adjunct or alternative to creatinine for drug dosing. The association of renal function estimated by cystatin C with drug clearance, target achievement, and clinical outcomes is not well defined.

Methods: We conducted a systematic review to synthesize available data for the association between serum cystatin C and drug pharmacokinetics, dosing, and clinical outcomes in adults (≥18 years). PubMed, Ovid MEDLINE, Ovid EMBASE, EBSCO ICNAHL, and Scopus were systematically searched from 1946 to September 2017 to identify candidate studies. Studies of cystatin C as a predictor for acute kidney injury (AKI) or for management of contrast-associated AKI were excluded. Also, studies were excluded if drug concentrations were unavailable and if a reference standard for drug dosing (e.g., serum creatinine) was not concurrently reported. The outcomes of interest included drug clearance (L/h), concentrations (mg/L) target level achievement (%), therapeutic failure (%), and drug toxicity (%).

Results: We included 28 manuscripts that evaluated 16 different medications in 3455 participants. Vancomycin was the most well studied drug. Overall, cystatin C-based estimated glomerular filtration rate ($eGFR_{Cystatin\ C}$) was more predictive of drug levels and drug clearance than $eGFR_{Creatinine}$. In only one study were target attainment and outcomes compared between two drug dosing regimens, one based on $eGFR_{Creatinine\text{-}Cystatin\ C}$ and one dosed with the Cockcroft Gault creatinine clearance. In conclusion, compared with $eGFR_{Creatinine}$, use of $eGFR_{Cystatin\ C}$ to predict elimination of medications via the kidney was as accurate, if not superior, in most studies, but infrequently were data on target attainment or clinical outcomes reported.

Conclusions: Drug-specific dosing protocols which use cystatin C to estimate kidney function should be tested for clinical application.

PUB440

Pharmacological Decision-Making in Gout: A Comparison Between Nephrologists and Other Specialists Using a Script Concordance Test

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Background: Gout commonly coexists with CKD and the presence of CKD often complicates gout management. Gout is treated by providers from many disciplines, hence pharmacotherapeutic heterogeneity may be common in CKD. The goal of this pilot study was to determine whether a validated script concordance test (SCT) for gout, which assesses clinical reasoning in short case scenarios, might detect interprofessional heterogeneity of pharmacological gout therapy.

Methods: Nephrologists (Neph), rheumatologists (Rheum), primary care providers (PCP), and pharmacists (Pharm) at University of Utah and Salt Lake City VA completed the gout SCT. The full SCT consists of 24 case scenarios and responses are obtained using a 5-anchor Likert scale. As we were interested in pharmacological treatment, we used the 10 case scenarios assessing pharmacological decision-making in this study. Response options ranged from the proposed therapy being "strongly indicated" to "strongly contraindicated." SCTs were scored using an aggregate method normed by an expert panel. Mean scores for each discipline were calculated and differences between each discipline and Neph were compared using 2-tailed t-tests.

Results: 29% of invitees (38 of 129) completed the SCT. The number of responses was similar across disciplines (Table). The overall mean (SD) score was 14.69 (2.03); for reference, the maximum score for the 10 case scenarios is 24.39. Rheum had the highest and Neph had the lowest SCT score; the difference approached statistical significance. SCT scores were similar between Neph, PCP and Pharm (Table).

Conclusions: In our study sample, clinical decision-making regarding gout pharmacotherapy was similar between Neph, Pharm, and PCP. In contrast, differences between Neph and Rheum were observed, though confidence is limited by sample size. The results of this pilot study can inform future use of the SCT to detect interprofessional heterogeneity of pharmacological gout therapy in a larger sample across multiple institutions.

Mean SCT score by discipline

Discipline (# of respondents)	Mean (SD) SCT Score	p vs. Nephrology
Nephrology (n=9)	13.77 (2.13)	–
Rheumatology (n=10)	15.67 (1.83)	0.05
PCP (n=10)	15.06 (2.26)	0.22
Pharmacy (n=9)	14.12 (1.48)	0.69

Maximum possible score is 24.39

PUB441

Autosomal Recessive Polycystic Kidney Disease Diagnosed in Adulthood

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Introduction: Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes. Renal cysts arising from collecting ducts and congenital hepatic fibrosis (CHF) are hallmarks, usually in infancy and associated with high mortality in first year of life. For those who survive the neonatal period, the probability of being alive at age 15 ranges from 50-80%, with the majority requiring renal replacement therapy. Approximately 50% of infants have evidence of liver involvement at time of diagnosis. This can lead to progressive portal hypertension. Here, we present a case of an adult female with known CHF believed to be idiopathic, until additional investigation into proteinuria revealed cystic kidney disease, confirmed on genetic testing to be ARPKD.

Case Description: A 38-year-old female with a history of hypertension, bipolar disorder (never on Lithium) and congenital hepatic fibrosis diagnosed at age 20 months presented for evaluation of long standing proteinuria. Albumin was preserved with proteinuria quantification ranging from less than 1 g/g to upwards 3.2 g/g. While a workup was being undertaken, angiotensin receptor blockade was initiated with significant improvement in proteinuria to values less than 200 mg/g. Renal ultrasound revealed relatively large kidneys with bilateral cysts. MRI abdomen confirmed innumerable left kidney cysts, along with several subcentimeter parapelvic cysts on the right kidney. Genetic testing was performed with results consistent with ARPKD. There was no known family history of renal cystic disorder or renal morbidity.

Discussion: The classic presentation for ARPKD is hypertension with progression to ESRD by age of 15. Typicaly a small number of those with ARPKD will live to adulthood with some kidney function, but significant deterioration in liver function. Due to its wide variability, the diagnosis of ARPKD may be made during any stage of childhood and only in rare cases does it present in adolescence or adulthood. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction as the prominent feature. This case highlights the potential spectrum of presenting signs and symptoms associated with ARPKD and the possibility that the diagnosis may need be considered even in adulthood if the scenario seems appropriate.

PUB442

A Novel Presentation of Fabry Disease

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Introduction: Fabry disease (FD) is an X-linked genetic disease due to mutations in the *GLA* gene that lead to deficient or absent α-galactosidase A (α-Gal A) activity and consequent accumulation of globotriaosylceramide throughout the body. Various manifestations of FD include proteinuria, declining glomerular filtration rate (GFR), hypertrophic cardiomyopathy, hypohidrosis, heat intolerance, hearing loss, acroparesthesia, cryptogenic strokes, and cornea verticillata, among others. Renal presentations of FD in classic males typically begin with proteinuria in childhood, followed by a gradual decline in GFR, and ultimately results in end-stage renal disease (ESRD) over the course of a few decades if patients are left untreated. We present an unusual case involving a male patient who had normal GFR at the age of 40, but was diagnosed with ESRD by 42.

Case Description: Our patient was a 42-year-old male, who was first diagnosed with kidney disease when his annual physical lab tests revealed a creatinine of 11 MG/DL. This demonstrated a dramatic elevation from his labs 2 years prior, where the patient's creatinine was measured to be 1.1 MG/DL. At the time of diagnosis, the patient had no history of kidney disease. Meticulous review of the patient's history, in addition to physical examination and work-up did not identify any cause for the observed kidney failure. A kidney biopsy, however, was suspicious for FD. Subsequent screening of α-Gal A enzyme activity and genetic testing confirmed the diagnosis of FD with a P40S mutation. Thus, hemodialysis and enzyme replacement therapy were initiated.

Discussion: Although kidney disease is amongst the most important presentations of FD, this patient demonstrated a unique case with a rapidly progressive disease that has not been reported previously. A review of available natural history data from the Fabry Registry (NCT00196742; sponsor and provider of data: Sanofi Genzyme) showed 14 patients with the same mutation, including 7 males. No renal or cardiovascular events were reported in the male patients. In females, 1 stroke and 1 cardiac event have been reported, but no kidney events. Conclusion: This is a novel presentation of FD in a classic male that will require further investigation.

PUB443

Irreversible Electroporation Treatment of Renal Cell Carcinoma in Von-Hippel Lindau

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Introduction: Irreversible electroporation (IRE) is a non-thermal nephron-sparing technique which offers an alternative treatment for renal tumors in patients previously deemed inoperable or unsuitable for other therapies. It is particularly useful in patients at risk for recurrent renal cell carcinoma (RCC), where it may help prolong renal function and delay requirement for dialysis.

Case Description: A 55 year old female with Von-Hippel Lindau presented in 2009 with a 19mm right midpole RCC, judged unsuitable for partial nephrectomy or thermal ablation due to central location. At time of presentation, the patient previously had one right sided and three left sided partial nephrectomies for confirmed RCCs. In the interests of preserving remaining renal function patient was treated with IRE.

Discussion: In 2009 the patient was enrolled in our department's IRE safety study and underwent two rounds of IRE to the right midpole RCC, which was completely ablated with no residual/recurrent tumor seen for a 6 year interval. In 2015 two further RCCs were detected within right kidney (16mm upper pole, 20mm lower pole), both of which were ablated with a single round of IRE. The inferior pole lesion was completely ablated post IRE while minimal contrast enhancing residual tumor was seen at the upper pole on post-procedural triphasic CT. Two further RCCs were detected within the right inferior pole in 2017, potentially amenable to IRE. However post Urology review patient proceeded to right sided nephrectomy. No major procedural complications of IRE were seen in this patient. This result was in line with results from a further 18 patients and 26 tumors treated. Success was highly correlated to tumor size, with 94% of lesions initially measuring <3 cm in diameter (15 of 16) successfully ablated after ≤2 rounds of IRE versus 63% in lesions ≥3cm (7 of 11). Complete ablation post ≤2 rounds of IRE was seen in 100% of patients at <5 years and 58% of patients at 5-7 years. Partial ureteric stenosis was seen in post-IRE in 1 patient, thought to be related to previous thermal ablation of the same tumor. No other major complications were observed. In conclusion, a previous study performed by our hospital has shown renal IRE is a safe alternative treatment for small renal tumors. IRE is especially useful in patients such as this case at risk for recurrent renal tumors, where a total delay of 8 years to right nephrectomy was achieved.

PUB444

Nephrotic Syndrome in Familial Hyperlipoproteinemia: A "Two-Hit" Hypothesis

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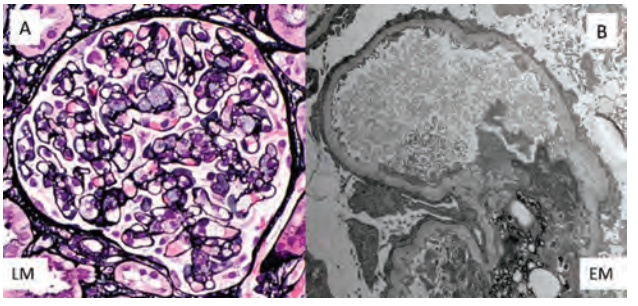
Introduction: Familial hyperlipoproteinemia (FH) Type III is an autosomal recessive disorder caused by mutations of ApoE, which plays a crucial role in lipid metabolism. We discuss a patient with type III hyperlipoproteinemia who developed nephrotic syndrome.

Case Description: A 26 yo female presented with anasarca 2 weeks after pregnancy. She had a urine Protein:Cr ratio (UPCR) of 15 g/g with a serum albumin of 1.2 g/dL. Serum cholesterol (676 mg/dL) and triglycerides (1336 mg/dL) were markedly elevated. Renal biopsy showed diffuse deposition of large lipid droplets in macrophages, mesangial cells, renal tubular cells, and stromal cells (Fig A). Genetic testing revealed familial type III hyperlipoproteinemia (Apo E2/E2 genotype) and she was started on a fibrate. Her nephrosis was presumed to be mediated by FH Type III and thus not responsive to immunosuppression (IS). However, upon referral to our center, review of electron microscopy revealed diffuse foot process effacement suggestive of a primary podocytopathy (Fig B). Treatment with high dose glucocorticoids led to a complete remission (UPCR 0.3) with resolution of dyslipidemia (Cholesterol/Triglycerides). She relapsed twice with steroid tapering and received rituximab for steroid-dependent nephrotic syndrome. She is now in complete remission off glucocorticoids.

Discussion: While patients with FH Type III have lipid deposition in many organs, clinically relevant kidney disease is atypical. Patients with other rare ApoE mutations can develop lipoprotein glomerulopathy, which is a distinct pathologic entity mediated by abnormal deposition of lipoprotein and not responsive to IS. In our case, the patient developed minimal change disease, which unmasked the clinical phenotype of Type III FH. IS led to complete remission and resolution of dyslipidemia. The finding of diffuse foot process effacement serves as a surrogate for a primary podocytopathy. Immunosuppression should not be withheld in such patients, even in the presence of renal lipidosis.



PUB445

Alport Syndrome: A Case of Uncommon Inheritance Pattern

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Introduction: In 1927, Arthur C. Alport first published his description of a triad of symptoms in a family with congenital hemorrhagic nephritis, deafness, and ocular changes. Alport syndrome still inevitably leads to end-stage renal disease (ESRD). It occurs as a consequence of structural abnormalities in type IV collagen, the major constituent of basement membranes. Six genetically distinct chains of type IV collagen have been identified. Mutations in the COL4A5 gene, encoding the alpha-5 chain, is responsible for X-linked Alport syndrome, the most common form of the disease. Mutations in COL4A3 or COL4A4, which encode alpha-3 and alpha-4 chains, are involved in the rarer autosomal recessive and autosomal dominant forms of the disease. Here we describe a female with Alport's syndrome that had an indolent presentation and an uncommon inheritance pattern.

Case Description: 42 year old El Salvadorian female with microscopic hematuria and proteinuria that were persistent for 2 years. Previous cystoscopy was negative. The subject's father and 2 out of 4 brothers had ESRD and passed away (with dialysis initiated at age 50, 45, and 47 respectively). One of these brothers had hearing impaired. Her other 2 brothers, sister, and mother are healthy. Physical examination was unremarkable. Labs revealed serum creatinine of 0.7, 1.3 g/g proteinuria, and urine sediment with 2-3 nondysmorphic RBCs/HPF without cellular casts. Serologic work-up was negative. The renal sonogram showed normal size kidneys. Renal biopsy performed. The light microscopy was notable for glomerulomegaly and routine immunofluorescence was unremarkable. The electron microscopy revealed thin glomerular basement membranes (241 nm) with segmental areas of basement membrane scalloping and microparticles, consistent with Alport syndrome. Staining for alpha 5 chain of type IV collagen was preserved.

Discussion: In this patient, preserved alpha 5 chain staining is consistent with either autosomal dominant or autosomal recessive forms of Alport syndrome. Given her family history she likely has autosomal dominant disease, which accounts for less than 5% of Alport cases. Autosomal dominant disease has a milder renal phenotype, with a median renal survival of 70 years. This case stresses the importance of obtaining an accurate family history and consideration of biopsy in patients with sub-nephrotic proteinuria and family history of ESRD.

PUB446

Late-Onset Bartter Syndrome Type II

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Introduction: Mutations in the ROMK1 potassium channel gene (*KCNJ1*) cause antenatal/neonatal Bartter syndrome (aBS) type II. Bartter syndrome type II is believed to represent a disorder of the infancy, but not in adulthood.

Case Description: We herein describe a female patient with a remarkably late-onset and mild clinical manifestation of BS. Laboratory tests showed hypokalemia (3.0 mmol/L),

low-normal total serum calcium (2.31 mmol/L), hyperaldosteronism (515 ng/L, 847 ng/L) (normal 30-340), hyperreninemia (43.1 ng/L, 25.6 ng/L) (normal 2.0-24.6) and increased calcium excretion in the urine (7.5 mmol/d or 0.13 mmol/kg body weight/day (normal range <6.2 mmol/d or <0.1 mmol/kg body weight/day)). Serum sodium (139 mmol/L), chloride (104 mmol/L), magnesium (0.87 mmol/L) and phosphate (0.9 mmol/L) levels were normal. In arterial blood, pH was high but bicarbonate levels were normal (pH 7.498, HCO3- 25.7 mmol/L, pCO2 30.5 mmHg, PO2 118 mmHg). Fractional excretion of potassium (FEK 22%, 29%) and chloride were increased (FECl 2.52%). The trans-tubular potassium gradient (TTKG 21) was high in our patient considering the presence of hypokalemia, indicating renal potassium wasting. Serum creatinine was 1.10 mg/dL (eGFR [MDRD] 58 mL/min). After 14 hours of water deprivation, our patient had a reduced urine osmolality (392 mOsmol/kg; normal 915±91 mOsmol/kg at a plasma osmolality of 294 mOsm/kg), indicating that our patient cannot concentrate her urine well. Antidiuretic hormone (AVP) in plasma was high. We implemented and evaluated the performance of two different bioinformatics based approaches of targeted massively parallel sequencing (NGS) in defining the molecular diagnosis. Both analyses detected heterozygous *KCNJ1* missense mutations, consisting of a novel c.197T>A (p.I66N) and a previously reported c.875G>A (p.R292Q) *KCNJ1* mutation in our patient. Family analysis revealed compound heterozygosity.

Discussion: Our results demonstrate that aBS II may be suspected in patients with a late-onset phenotype. Our experimental approach of NGS-based mutation screening combined with Sanger sequencing proved to be a reliable molecular approach for defining the clinical diagnosis in our patient. Our results can have a significant impact on diagnosis of other patients with clinical unclassified phenotypes of nephrocalcinosis and congenital renal electrolyte abnormalities.

PUB447

A Case of Autosomal Recessive Alport's Syndrome

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Introduction: Alport Syndrome (AS) is a genetic disorder caused by mutations in Type IV Collagen, which plays a major role in the structural integrity of the glomerular basement membrane. Mutations to the *COL4A3*, *COL4A4*, and *COL4A5* genes can all result in defects to Type IV Collagen. People with AS typically experience a progressive loss of kidney function, and often present with proteinuria and hematuria. Gradual scarring of the kidney eventually leads to ESRD in many people with AS. Type IV collagen is also expressed in important components of the inner ear as well as the eye, thus patients tend to develop extra-renal complications such as hearing loss and visual impairments. Over 80% of AS is inherited in an X-linked pattern due to mutations in *COL4A5*, however AS can also be inherited in an autosomal recessive or autosomal dominant pattern due to mutations in *COL4A3* or *COL4A4*. Compared to autosomal dominant AS, patients with X-linked or autosomal recessive inheritance patterns typically have a more severe disease progression leading to earlier onset of ESRD and extra-renal manifestations

Case Description: Our patient is a 17-year-old male who first presented with persistent 'tea colored' urine, proteinuria, and hematuria at the age of five. His creatinine at the time was measured at 0.27mg/dL and a urinalysis showed protein ≥300mg/dL. At the time there was no family history of renal disease, recurrent hematuria, or hearing loss, therefore a renal biopsy was performed. Renal biopsy showed abnormal basement membrane and an amino histochemistry assay for Type IV collagen was also abnormal, suggesting diagnosis of AS. Genetic testing confirmed the diagnosis of the homozygous autosomal recessive AS. Currently, the patient has a stable renal function with creatinine of 0.57mg/dL, Schwartz estimate 118.7ml/min/1.73m^2, and uACR 1449mg/g.

Discussion: Although our patient is confirmed to have two mutations in the *COL4A4* genes, representing a true autosomal recessive inheritance, his health has been relatively stable. About 50% of untreated males with X-Linked AS develop kidney failure by age 25, increasing to 90% by age 40 and nearly 100% by age 60. Although our patient presents with proteinuria and hematuria, he has stable kidney function, does not present with hypertension, and has no extra-renal complications seen in AS.

PUB448

Two Brothers with ESRD Due to C3 Glomerulopathy – A Case Report

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Introduction: C3 glomerulopathy includes several rare forms of glomerulonephritis (GN) with underlying defects in the alternate complement cascade. The two major subgroups of C3 glomerulopathy are dense deposit disease (DDD) and C3 GN—are distinguished by electron microscopy (EM). DDD is diagnosed at an earlier age than C3 GN. DDD is defined by the EM findings of intramembranous glomerular basement membrane dense deposits. C3 GN encompasses the remainder of the C3G lesions and is defined by some combination of mesangial, sub-epithelial, sub-endothelial, and/or less dense, discontinuous intramembranous deposits. Clinically C3 glomerulopathy presents with proteinuria, hematuria and some degree of renal insufficiency. 35-50% of DDD and 25% C3 GN progresses to ESRD over a 10 year period.

Case Description: Here we describe two brothers who are in their early 20s with ESRD on hemodialysis secondary to MPGN with dominant C3 deposition. Both presented with elevated creatinine and proteinuria. One of them was diagnosed with MPGN at 14 years of age and the other one at 20 years of age. Biopsies revealed electron dense deposits in the mesangium and sub-endothelial space with segmental duplication of basement membrane with mesangial hyper-cellularity and granular C3 staining in the mesangium, and the tubular basement membrane. There were significant interstitial fibrosis and tubular atrophy. See table 1 for results of genetic, functional assay and the biomarkers.

Discussion: There are only few case reports of family members having C3 glomerulopathy. Both of our patients are awaiting kidney transplant. Their genetic analysis revealed variants of unknown significance in genes ADAMTS 13, CFH, SERPINC1 and VWF. There are no effective targeted treatment options for C3 glomerulopathy and there is high recurrence of disease and allograft loss after transplantation. Plasma exchange has been tried with limited success in patients with C3Nefs and greater success in patients with mutations in CFH. Eculizumab has been studied in C3G and DDD with partial response. There needs to be more research into effective treatment as this disease affects younger members of our society.

Genetic Characteristics

	CFH	MLPA (CFH-CFHR5)	FB antibody (titer <200 AU)	NEF activity IFE (<7.5%)	C5 nef C3CSA (<20%)	C3 nef C3 CSAP (<20%)	C3 level (0.9-1.8g/L)	C4 level (0.15-0.57g/L)	Ba level (<1.2mg/L)
Patient A	Allele 1 variation	Heterozygous deletion	425 AU	10.1%	30%	30%	0.4g/L	0.34g/L	6.5mg/L
Patient	Allele 1				Negative				

PUB449

Altered Function of TRPC6 May Contribute to Pregnancy-Associated aHUS

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Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS) has recently become a well-recognized differential diagnosis of aHUS. Postpartal deficiency of complement system inhibitors is suspected trigger endothelial damage and formation of thrombotic microangiopathy (TMA), leading to hemolytic anemia and kidney failure. The presence of preeclampsia is thought to constitute a risk factor for p-aHUS, as the production of soluble Fms-like tyrosinkinase-1 (sFLT-1) promotes TMA formation (Erpenbeck, *JASN* 2016) by inhibiting the angiogenic effect of vascular endothelial growth factor (VEGF). However, since sFLT-1 production normally ceases with delivery and genetic defects in complement regulators can only be found in half of the cases (Bruel, *CJASN* 2018), further mechanisms need to be considered.

Case Description: In a 41 year-old female, delivery by caesarean section was performed in the 25th gestational week, due to preeclampsia (proteinuria 3,4 g/g creatinine, sFLT-1/PIGF 231). Ten days postpartum, she presented with coombs-negative hemolytic anemia (Hb 3.2 mmol/l, platelets 32 Gpt/l, schistocytes 4.3%, LDH >30 mmol/l, haptoglobin <0.1 mmol/l), and acute renal failure (s-creatinine 472 µmol/l). Kidney biopsy revealed glomerular TMA. Genetic testing for mutations of known aHUS genes was unremarkable. However, a previously reported heterozygous 12bp insertion in exon 2 of *TRPC6* was detected (c.253_264dup, p.(Ala85_Phe88dup)) (Weber, *Ped. Neph.* 2015). *TRPC6* encodes an ubiquitously expressed calcium-permeable channel that also plays a crucial role in human podocytes, where defects have been associated with genetic FSGS by mechanisms of both, gain and loss of function (Riehle, *JASN* 2016). Patch clamp analysis and calcium influx assays upon overexpression of wildtype versus Ala85_Phe88dupare ongoing.

Discussion: P-aHUS is a major postpartal condition that takes several triggers in order to develop. We suggest that altered TRPC6 function may constitute an alternative trigger for development of acute TMA-related kidney failure, similar to the proposed mechanism in DGKE-related aHUS/TMA (Ozaltin, *JASN* 2013). As podocytic TRPC6 expression is also influenced by VEGF (Thilo, *NDT* 2012), sFLT-1 mediated VEGF inhibition in the setting of preeclampsia might further provoke an alteration in podocyte and platelet function.

PUB450

Vitamin D Drops Leading to Kidney Failure

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Introduction: Vitamin D toxicity is rare but early recognition may limit complications related to hypercalcemia including acute and chronic renal failure. Hypervitaminosis D can be treated with glucocorticoids, ketoconazole or hydroxychloroquine.

Case Description: A 54-year old man is seen for AKI after his creatinine increased to 376 µmol/L from 132 µmol/L (baseline 100) over a 4-week period despite holding ACEi and diuretic. Medications included perindopril, rosuvastatin, amlodipine, indapamide and febuxostat. Medical history was significant for hypertension and gout. On exam, blood pressure was 149/98 mm Hg with no urgent clinical indications for dialysis. Renal ultrasound was normal. Urine microscopy was normal. Ionized calcium was 1.48 mmol/L and PTH was 0.5 pmol/L. Serum and urine protein electrophoresis studies were negative. Renal biopsy showed tubular atrophy with microcalcifications. He later revealed to be taking 12,000 IU of Vitamin D drops daily for 2.5 years. Measured vitamin D levels were elevated and continued to rise despite stopping supplements (Table 1). He was started on hydroxychloroquine given rise in vitamin D, which only normalized after initiation of hydroxychloroquine. Unfortunately, he is now left with Stage 3B CKD from nephrocalcinosis.

Discussion: Hypervitaminosis D treatment must focus on reducing dietary sources. Alternative strategies to reduce levels by inhibiting conversion to active 1,25-$(OH)_2$D3 must also be considered. If asymptomatic then levels can be monitored expectantly, but may take time to normalize as vitamin D is fat soluble. Glucocorticoids, ketoconazole and hydroxychloroquine have been used to treat hypercalcemia related to sarcoidosis. These medications reduce 1 α-hydroxylase activity and in turn decrease 1,25-$(OH)_2$D3 levels. Given that our patient was reluctant to use glucocorticoid treatment, we successfully used hydroxychloroquine as an alternative to treat his hypervitaminosis D.

Serial clinic labs

Lab Value	Week 1	Week 5	Week 10	Week 16	Week 20	Week 24	Normal Range
Ionized calcium (mmol/L) corrected for pH 7.4	1.48	1.54	1.63	1.47	1.26	1.27	1.12-1.32
Serum calcium (corrected for albumin)	3.04	3.21	3.28	2.87	2.57	2.57	2.20-2.62
PTH (pmol/L)	0.5	0.3	0.4	1.1	-	-	1.3-7.6
1,25 dihydroxyvitamin D (pmol/L)	274	313	234	187	125	102	60-206
25 hydroxyvitamin D (nmol/L)	241	186	152	135	96	108	25-200
Creatinine (μmol/L (mg/dL))	372 (4.21)	241 (2.73)	271 (3.07)	237 (2.68)	199 (2.25)	186 (2.10)	64-110 (0.72-1.24)
Estimated GFR (mL/min/1.73m^2)	<15	25	22	26	32	34	>60

Hydroxychloroquine started at week 5.

PUB451

Dipilumab Induced Acute Interstitial Nephritis

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Introduction: Dupilumab, sold under the trade name Dupixent, is a monoclonal antibody designed for the treatment of allergic diseases, such as eczema. It binds to the alpha subunit of the interleukin-4 receptor (IL-4Rα). Through blockade of IL-4Rα, dupilumab modulates signaling of both the interleukin 4 and interleukin 13 pathway. To our knowledge, renal adverse effects were not reported with this agent.

Case Description: A 59 year old male with achalasia and eczema presented with an elevated serum creatinine of 2.2mg/dl and a bland urine sediment. A few weeks prior to presentation, he was initiated on dupilumab, dosed q2 weeks. His baseline serum creatinine was normal in the past. He was not on any other nephrotoxic agents such as NSAIDs, proton pump inhibitors or antibiotics. Furthermore, he denied any herbal medications. A kidney biopsy was performed which revealed acute moderate allergic interstitial nephritis (AIN) with minimal fibrosis. No other significant pathological findings were noted on biopsy. The patient was started on steroids and dipilumab was subsequently held. The serum creatinine responded to treatment and improved to 1.5mg/dl.

Discussion: AIN is commonly associated with monoclonal antibody agents used for cancer treatment. This is the first reported case of dipilumab-induced AIN discovered during its use for the treatment of eczema. Dermatologists and nephrologists need to be aware of this serious complication associated with IL-4R antagonists.

PUB452

Almond Milk: A Potential Cause of Oxalate Nephropathy?

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Introduction: After Roux-en-Y gastric bypass (RYGB), luminal fatty acid and bile salts increase oxalate absorption. Fecal fat binds calcium that would otherwise bind oxalate. Luminal bile salts enhance colonic epithelial oxalate permeability. These changes cause hyperoxaluria and increase the risk for oxalate nephrolithiasis, although the incidence of oxalate nephropathy remains poorly defined.

Case Description: 62 y.o. woman s/p RYGB in 2012 received DDKT for ESRD from diabetic nephropathy in 3/2014. Her creatinine slowly rose to 2.2 from 8/17 to 11/17. She presented with AKI in 12/17 (Fig. 1). She was asymptomatic except for chronic diarrhea. She also "started to eat healthy", drinking 32 oz. of almond milk a day since 10/17. Biopsy revealed oxalate nephropathy (Fig. 2). The patient was treated with low oxalate diet and citrate supplements. Her creatinine improved to 2.7. Urinary oxalate excretion is now 85 mg/day.

Discussion: This case shows the impact of dietary changes for patients at risk for oxalate nephropathy. We initially suspected almond milk as the source of oxalate that caused AKI. Almond milk is made by filtering water through ground almonds. Many almond milk products contain minimal amounts of almond, though specific data on oxalate content are not available. It is unclear whether consumption of almond milk significantly increases oxalate intake. Therefore, we concluded that the patient's AKI may have been due to other factors such as hypovolemia from diarrhea and RYGB. It's important to note the patient later reported that she had increased her consumption of nuts, hot chocolate, and spinach though the amounts consumed were quite small. In summary, relatively modest increases in oxalate intake may precipitate AKI in patients with RYGB. However, it remains uncertain whether almond milk is a source of dietary oxalate. We hope to arrange formal chemical testing to determine the oxalate content of this popular beverage.

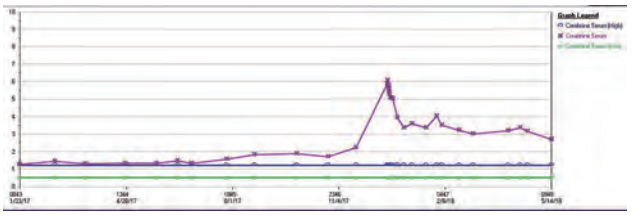

Fig. 1

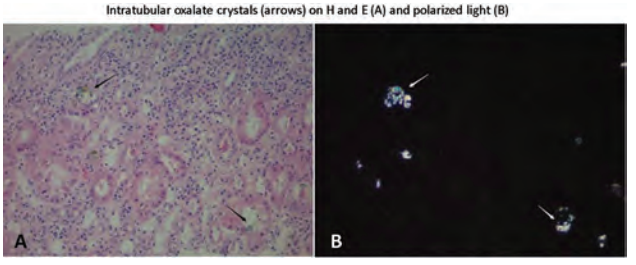

Fig. 2

PUB453

Thrombotic Microangiopathy Associated with Gastric Adenocarcinoma Causing AKI

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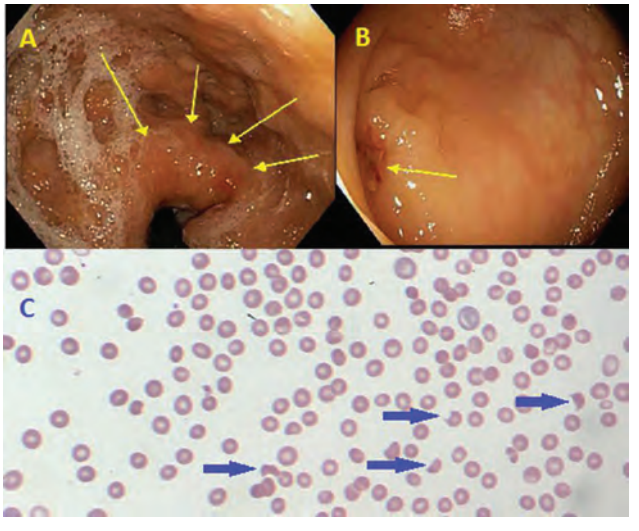
Introduction: Gastric cancer is identified as a cause of thrombotic microangiopathy (TMA), a class of disease occurring with thrombocytopenia and microvascular thrombosis-induced organ damage commonly affecting the kidneys. We present a case of acute kidney injury resulting from TMA due to metastatic gastric adenocarcinoma.

Case Description: The patient is a 46 year old woman complaining of weakness and weight loss admitted with L2 burst fracture and diffuse lymphadenopathy on CT. Blood pressure was elevated to 159/98. Labs showed anemia with hemoglobin of 7.1g/dL and platelets of 67K/uL. Renal function notable for creatinine of 1.45mg/dL and BUN of 38mg/dL. Biopsy of the spine lesion revealed CK7+/CK20+ carcinoma; EGD showed a fungating gastric cardia mass with biopsy showing poorly-differentiated adenocarcinoma. Colonoscopy showed a sigmoid ulcer with ischemic pattern of injury with microthrombi on histology. Additional tests were consistent with microangiopathic hemolytic anemia (MAHA), a feature of TMA. Haptoglobin was <10mg/dL, total bilirubin 2.1mg/dL, and schistocytes seen on blood smear. ADAMTS13 activity was normal at 91% and direct Coombs test was negative. PT and PTT were not prolonged and fibrinogen was normal. Kidney biopsy was felt to be too dangerous at the time. The patient started on chemotherapy but unfortunately her kidney function worsened due to oxaliplatin and she ultimately required hemodialysis.

Discussion: TMA is a recognized complication of gastric adenocarcinoma with kidney injury as a possible result. Kidney biopsy is often not necessary to make the diagnosis. TMA resulting from gastric adenocarcinoma is challenging to treat and is typically refractory to treatment with plasma exchange. Chemotherapy is felt to be the most effective treatment strategy though can itself be nephrotoxic.



A) Gastric cardia massB) Sigmoid colon ulcera

C) Schistocytes on peripheral smear

PUB454

"Zombie" at Home: Rhabdomyolysis Secondary to Synthetic Cannabinoid K2 Withdrawal

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Introduction: Synthetic cannabinoid (SC) use as a marijuana alternative was first reported in the United States in 2008. Multiple variants have been developed that are not recognized as illegal substances, do not appear in routine toxicology screens, and are marketed under a variety of names, including K2, Spice, Joker, and Kronic. Recently, an acute intoxication outbreak was reported in New York City. There have been limited reports on rhabdomyolysis due to K2 withdrawal. We present a case of a 46-year-old African American male with rhabdomyolysis due to severe withdrawal symptoms after acute K2 cessation.

Case Description: A 46-year-old African American male with no PMH presented with a 5-day history of nausea, muscle cramps, irritability, insomnia, auditory and visual hallucinations. Patient's wife described his behavior as a "zombie". Patient had been smoking K2 daily for the past 3 months and symptoms were precipitated after abruptly stopping. Patient was afebrile, BP of 135/85, HR 120 beats per minute, RR of 22 and O2 Sat 100%. He was anxious, tremulous and restless. He was alert and oriented but unable to focus. Patient had dry mucous membranes, pupils < 2 mm, and horizontal nystagmus. Investigation revealed: WBC 22.7 x 10^9/L, Hgb 17.8 g/dL, sodium 126 mEq/L, potassium 3.2 mEq/L, chloride 88 mEq/L, bicarbonate 22 mEq/L, urea nitrogen 21 mg/dL, creatinine 2.16 mg/dL, calcium 10.6 mg/dL, albumin 5.1 g/dL and CPK 3981 U/L. Urinalysis showed a specific gravity of 1.015, trace blood, trace protein, 2-5 red blood cell per high-power field, 2-5 hyaline casts per low-power field. Urine toxicology was positive for THC. Patient was given 2 L of normal saline on admission followed by 200 mL/hr. Management included benzodiazepines due to insomnia and restlessness as well as intravenous hydration due to acute kidney injury. Patient's AKI resolved subsequently; creatinine decrease to 0.74 mg/dL after 72 hours and CPK decreased to 500 U/L at time of discharge.

Discussion: SC use is a public health concern as it has become popular due to low cost, easy availability, and lack of regulation. Acute withdrawal sequelae have not been studied nor understood yet. Rhabdomyolysis should be suspected in patients presenting with acute withdrawal, allowing for prompt initiation of adequate treatment and potentially avoiding acute renal failure.

PUB455

A "Crystal Clear" Case of AKI

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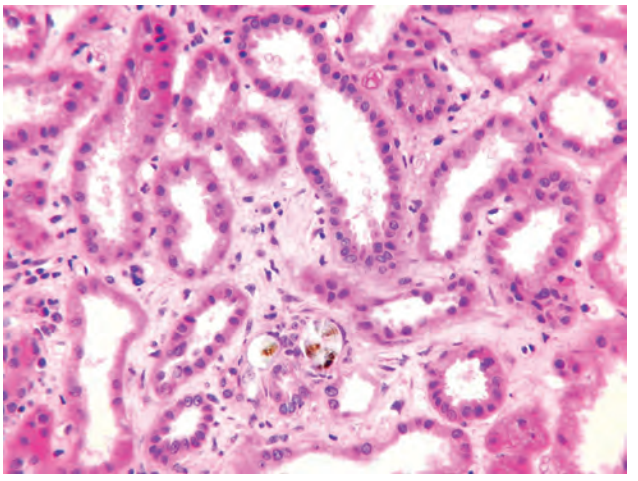
Introduction: A patient was transferred to nephrology with severe acute kidney injury (AKI) requiring dialysis and was subsequently diagnosed with crystal nephropathy (CN) from oral Aciclovir. Intravenous Aciclovir is a well described cause of CN. This case highlights the risk of CN with high dose oral Aciclovir in the setting of volume depletion.

Case Description: A 66 year old female with a medical history of Hodgkins Lymphoma; prior vasculitis with renal and skin involvement; and shingles, on oral Aciclovir prophylaxis; presented with a 1 month history of shortness of breath and palpitations and a 2 day history of gastric upset. She was clinically dehydrated, in rapid atrial flutter and had transient hypotension. She was treated with IV Metoprolol. Over 4 days, she developed anuric AKI; serum creatinine increased from 0.97 mg/dl to 7.68 mg/dl. Oral Aciclovir 200mg three times daily was administered until day 5 of admission when she transferred for haemodialysis. Admission was complicated by an unstable duodenal ulcer bleed, acute confusion and transient inflammatory thrombocytopenia. A renal biopsy was performed after 3 weeks; she remained dialysis dependent but urine output was increasing. Biopsy showed crystals within the tubules and recovering acute tubular necrosis (ATN). By week 4, she was independent of dialysis.

Discussion: The severity of her AKI was out of keeping with the degree of volume depletion and hypotension. Renal biopsy was delayed due to other acute medical issues. Despite the delay, crystals remained within the renal tubules. Oral Aciclovir in this setting contributed to severe anuric AKI. For patients at risk of AKI or with established AKI, physicians should have a low threshold to review Aciclovir indication; if indicated, ensure that the dose is adjusted for the level of renal function.



Renal biopsy showing a crystal within a tubule and recovering ATN

PUB456

Metformin Associated Lactic Acidosis: Identifying Rare Clinical Presentation

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Introduction: Metformin is the one of the most frequently used oral agent in the treatment of Type 2 Diabetes Mellitus. The major toxicity associated with metformin is lactic acidosis, which carries a high morbidity and mortality. While Metformin poisoning can be challenging to diagnose, it requires high index of suspicion. We present one such case.

Case Description: 78 year old Hispanic Female patient with Type 2 Diabetes Mellitus, Hypertension presented to the ER with generalized body aches, diarrhea and flank pain since 3 days associated with severe watery non bloody diarrhea. Patient was initially hypertensive in the triage. Labs reported severe metabolic acidosis with pH of 6.785 with elevated lactic acid 18.0 mmol/L, bicarbonate of 2.0 mmol/L and anion gap of 56. Patient was also noted to have acute kidney injury – with serum creatinine of 6.1 mg/dL (baseline 0.7 mg/dL). Patient was drowsy, providing limited history - said she was taking all of her diabetes and medications including metformin. Pre-dialysis metformin levels were obtained due to high clinical suspicion. Patient was started on IV Bicarbonate replacement, emergency dialysis was arranged with elevated Bicarbonate bath with 40meq/L done in the ER. Pre-dialysis metformin levels later on were found to be 13mcg/mL (theraupetic range 1-2 mcg/mL). Post dialysis metformin levels were noted to be: 5.6 mcg/mL. Patient's septic workup later came back negative pointing that this was a case of Metformin Associated Lactic Acidosis. Patient's renal function and clinical status improved and she was discharged home with serum creatinine of 1.3 mg/dL

Discussion: Metformin poisoning carries a high mortality and morbidity rate. It remains a challenging clinical entity which requires high index of clinical suspicion. Recognizing metformin associated lactic acidosis early on and implementing appropriate therapy would increase patient survival. Dialysis would remain best intervention in patients with Acute kidney Injury with serum creatinine >2 mg/dL and elevated serum lactate levels >15 mmol/L.

PUB457

Mycobacterium Chimaera Infection – A Rare Case of Interstitial Nephritis

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Introduction: Outbreaks of *Mycobacteria chimaera* with cardiac and extra-cardiac manifestations have been reported post cardiac surgery with the use of heater-cooler units in heart-lung machines. Nephritis is a rare presentation of this iatrogenic infection with few reported cases.

Case Description: A 62-year old male developed *Mycobacterium chimaera* spinal infection a year after coronary artery bypass graft and aortic valve replacement. He was started on azithromycin, Rifabutin, Gatifloxacin, and Ethambutol. He developed acute kidney injury that initially improved with IV fluid (figure 1). Gatifloxacin was stopped.10 months later, he presented with altered mental status. Creatinine was 7.1 mg/dl, protein/creatinine ratio of 0.53g/g, urinalysis without pyuria or cellular casts, and a normal WBC count without eosinophilia. Blood cultures grew *M. chimaera*. Mycobacterial urine cultures were negative. Azithromycin, Rifabutin, and Ethambutol were continued. Clofazimine (added 1 month prior to presentation) level was subtherapeutic. Renal biopsy revealed diffuse interstitial inflammation and one small interstitial granuloma with multinucleated giant cells, but AFB stain was negative. Clofazimine was titrated to a therapeutic dose. Mycobacterial blood cultures were subsequently negative. He had a partial improvement in his renal function with Cr of 4.1 mg/dl at the time of discharge.

Discussion: Diagnosis of granulomatous interstitial nephritis in our patient was likely related to the *M. chimaera* infection. Renal function improved with the clearance of bacteremia. Drug-induced interstitial nephritis was less likely since renal function improved despite continuing the 4-drug antimicrobial therapy. *M. chimaera* related interstitial nephritis is a rare condition with poor outcomes. Renal biopsy is crucial to rule out other etiologies of renal dysfunction. Timely initiation of antimicrobial therapy on appropriate doses can prevent deterioration of renal function.

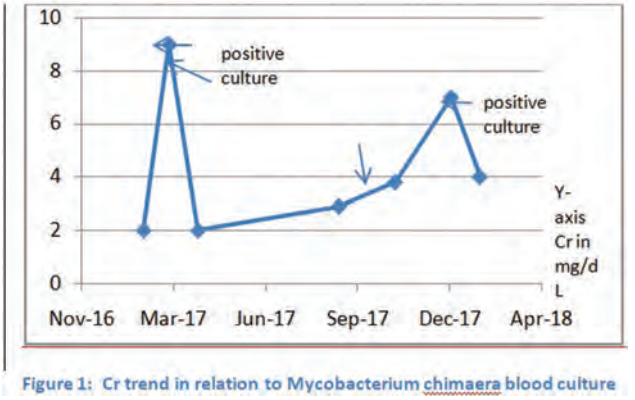

Figure 1: Cr trend in relation to Mycobacterium chimaera blood culture

PUB458

All Fired Up: The Angry Macrophage

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Introduction: Hemophagocytic Lymphohistiocytosis(HLH) is an aggressive and life-threatening syndrome of excessive immune activation characterized by activation and proliferation of uncontrolled macrophages and lymphocytes, culminating in an unrelenting cytokine storm and subsequent tissue infiltration and multi-organ system failure. Here we present a case of a patient who had a dramatic presentation of HLH with severe renal failure and was ultimately found to have a surprising diagnosis.

Case Description: 48 y/o male originally from Ghana, living in US for years with HTN not on treatment who presented with 3 weeks of a variety of symptoms including fever, headache, abdominal pain, poor appetite and a bad taste leading to a weight loss of 20-25 lbs. Also noticed yellowness of his eyes. No sick contacts or travel. Had significant laboratory abnormalities including pancytopenia, severe renal failure with BUN 330 mg/dl and Cr 22 mg/dl, elevated liver enzymes but normal INR, K 7.8mmol/L, CO2 10mmol/L, PO4 17mg/dl,Lipase 4470U/L,lactate 3.2mmol/L,Ferritin 5466ng/ml,TG 451mg/dl and soluble IL-2 43800pg/ml. Imaging revealed pancreatitis, pulmonary edema and bladder calcification. Was started on dialysis. Met criteria for HLH after BM biopsy and was started on steroids. Kidney biopsy revealed ATN.Extensive search for a potential trigger for HLH including all blood/BM cultures was negative. After initial improvement, suffered a PEA arrest after 1 week and continued to rapidly deteriorate and died within hours. Autopsy was performed which showed miliary TB, Schistosomiasis(likely inactive) and HLH.This was very surprising given negative AFB blood and BM cultures and no clear radiological sign of TB.

Discussion: HLH is primarily a pediatric syndrome but is being increasingly recognized in adulthood. Divided into primary and secondary forms, typically associated with a trigger(most commonly infection). Caused by lack of normal downregulation of activated macrophages and lymphocytes leading to a cytokine storm and multi-system injury. Renal manifestations include ATN(most common), pre-renal injury or glomerulopathy(MCD, TMA and collapsing FSGS). High mortality if untreated. No randomized trials to guide treatment, regimens based on HLH-94 protocol with etoposide and steroids. Alternate regimens used especially in the setting of cancer. Triggers should be treated aggressively. TB, a great mimic, has rarely been associated with HLH with a subsequent high morbidity/mortality.

PUB459

Sulfamethoxazole Crystal-Induced AKI

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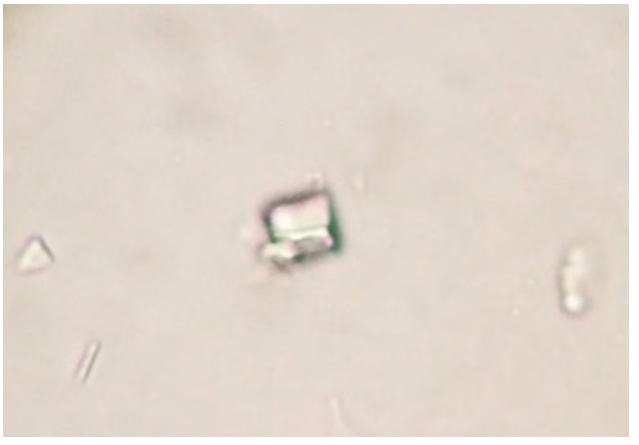
Introduction: In the HIV/AIDS population, TMP/SMX is a frequently used in prophylactic doses, should these patients present with acute illness due to PCP pneumonia, they may require higher dosing, the potential for nephrotoxicity due to sulfa-induced crystalluria is high and vigilance is required for prevention and recognition.

Case Description: We report a 55 year-old woman with PMHx of AIDS, CKD stage III, who presented to the hospital with shortness of breath, cough, CT Chest without contrast showed nodular opacities. The patient was admitted with a suspected diagnosis of PCP pneumonia and was treated with high doses of TMP/SMX, followed by development of anuric renal failure most likely secondary to IV TMP/SMX. Patient was started on IV Lasix to which she was initially not responsive until day 5 when she began making urine, patient's urine was analyzed under microscopy and found to have pleomorphic crystals present. At this point patient's creatinine began to return to baseline and she entered the diuretic phase of AKI, producing 7 liters of urine on days 6 and 7.

Discussion: There are several major risk factors for Sulfadiazine crystalluria and acute kidney injury: volume depletion, administration of higher doses of oral and intravenous formulations, hypoalbuminemia, urine pH <5.5, use of an ACE-inhibitor and the presence of previous underlying kidney disease. In these respects, our patient was exposed to a high IV dose of TMP/SMX (15 mg/kg/day, Patient's weight 110kg), had decreased GFR at baseline and acidic urine (pH = 5.0), along with volume depletion. Management of sulfa-induced kidney injury mainly involves discontinuing the offending drug and aggressive intravenous fluid administration. Urinary alkalization may also play a role; as urine pH increases the crystals more readily dissolve and the obstruction is relieved. It seems prudent to hydrate aggressively during treatment with high dose TMP/SMX to reduce the risk of crystal nephropathy, with increased natriuresis



PUB460

Should You Wait? Taking a Patient with AKI for TAVR Resulting in Dialysis Dependence

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Introduction: Aortic stenosis (AS) is one of the most common cardiac valvular diseases, with a prevalence of 1.3% in patients between 65 and 74 years and ~3% in patients >75 years of age. Trans-catheter aortic valve replacement (TAVR) has shown comparable survival rates in high-risk patients not eligible for open-heart surgery. Given the well-documented complication of AKI in patient's undergoing TAVR, the question arises, in CKD patients with AKI, should you take them for TAVR or try alternative temporizing measures to address the AS and wait for the AKI to resolve?

Case Description: 62 year old female with HTN, T2DM, CKD 3B, CAD status post CABGx4 and history of AS presented with shortness of breath and syncope. She was found to have severe AS and due to her prior cardiac surgeries, deemed a candidate for TAVR. As a part of TAVR workup, she underwent left-heart catheterization and cardiac CT with contrast complicated by Oliguric AKI from a baseline creatinine of 1.7 mg/dL to 3.3 mg/dL. She was initiated on high-dose furosemide bolus, then furosemide infusion without improvement. The following day, she was taken for TAVR. 48 hours post-TAVR, her AKI worsened with creatinine of 6.5 mg/dL and urine output <10ml/hr. Echocardiogram revealed inoperable peri-valvular leak around her new aortic valve. Decision was made to initiate dialysis, and over the following 2 weeks, there was no evidence of renal recovery and patient was discharged with plans for long-term dialysis.

Discussion: Temporary alternatives to aortic valve replacement do exist for patients with AS and have shown to be fairly effective in temporarily improving cardiac function. Since one of the hypothesized etiologies of AKI in patients with AS is decreased renal perfusion, balloon dilation could theoretically provide the time required to resolve any pre-existing kidney injury. Furthermore, spacing out contrast load one week apart from TAVR may potentially be beneficial. Given the mean incidence of AKI post-TAVR to be ~22%, one would assume that CKD patients with a pre-existing AKI prior performing TAVR would be at increased risk for further worsening of their renal function. Further studies should be performed to compare the degree of renal failure in patients with pre-existing renal injury that received temporizing measures versus those that were taken immediately for cardiovascular procedures.

PUB461

AKI Secondary to Enoxaparin Induced Pelvic Hematoma

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Introduction: Pelvic Hematomas have been recognised secondary to pelvic trauma or as a complication of obstetric surgeries and rarely secondary to use of anticoagulation therapy. It is a rare cause of abdominal pain which is often missed and a rarer cause of acute kidney injury.

Case Description: 78 year old female was admitted with shortness of breath and palpitations. A diagnosis of rapid atrial fibrillation was made, and she had AV node ablation after failure of medical therapy. Patient was anticoagulated with enoxaparin injected into the left side of the abdominal wall, as her CHADVASC score was 5. Four days after

admission, she complained of lower abdominal pain and anuria for one day. Physical examination revealed mild abdominal distention and tenderness in the suprapubic region. Labwork showed a sharp rise in serum creatinine and a drop-in hematocrit one day after onset of symptoms. Computed tomography scan of the abdomen revealed a 15x15cm hematoma within the paracolic gutter and pelvis causing bladder compression and left-sided hydronephrosis, patient was diagnosed to have post renal acute kidney injury secondary to pelvic hematoma. Patient was initially managed conservatively with serial physical exams, monitoring of haematocrit, imaging studies and avoidance of anticoagulants. But persistence of abdominal pain and anuria, warranted for a repeat scan which showed expansion in the size of hematoma and new development of right sided hydronephrosis, and hence bilateral nephrostomy tubes were placed. Patient was discharged few days later after removal of nephrostomy tubes and spontaneous reduction in the size of her hematoma.

Discussion: Spontaneous pelvic hematomas are usually missed as a cause of abdominal pain in patients on anticoagulation therapy. They usually develop within 5 days of initiating therapy, symptoms vary depending on the location of the hematoma and are best diagnosed with computed tomography scans. Conservative management should be reserved for patients who are stable, intra-arterial embolization or stent grafting is the treatment of choice when conservative measures fail. In conclusion subcutaneous injections into the abdominal wall increase the risk of hematoma, especially in elderly and thin patients. Healthcare professionals, patients and their relatives using enoxaparin should be advised to avoid deep injections into the abdomen; deltoid region could be a safer alternative.

PUB462

Atypical Hemolytic Uremic Syndrome Overlapping with Antiphospholipid Antibody Syndrome: A Case Report with Four Years Follow Up

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Introduction: Overlapping presentation of atypical hemolytic uremic syndrome (aHUS) and antiphospholipid antibody syndrome (APS) is a rare phenomenon. We present a case with four year follow up.

Case Description: A 57-year-old Caucasian female with a history of APS first diagnosed 10 years prior, presented with a year's history of recurrent abdominal pain and cognitive dysfunction. Laboratory evaluation showed evidence of microangiopathic hemolytic anemia with schistocytes, significant thrombocytopenia and renal insufficiency. Her laboratory studies are summarized below in Table 1. MRI of the brain showed chronic cerebellar and cerebral infarcts. She underwent plasmapheresis for one week without significant improvement in her symptoms or laboratory abnormalities. Given the presentation of thrombotic microangiopathy, the ADAMTS13 activity was > 5%, significant renal insufficiency and the lack of significant response to plasmapheresis, a diagnosis of aHUS was made. She was started on eculizumab infusions, initially 900mg weekly and subsequently maintained on 1200mg every two weeks. After 2 weeks of treatment, her creatinine decreased to 1.2 and hemoglobin stabilized at 9.8g/dl. She has had consistent follow up for 4 years during which period her creatinine has remained stable without the need for renal replacement therapy.

Discussion: aHUS is a condition associated with alternative pathway complement dysregulation. It is characterized by thrombotic microangiopathy(TMA), thrombocytopenia and end organ damage. Clinical presentation of aHUS is difficult to distinguish from other causes of TMA and laboratory differentiation does not always have a quick turnaround time. With an incidence of 1-2 per million, diagnosing aHUS requires a high index of suspicion and the exclusion of thrombotic thrombocytopenic purpura (TTP). APS is a recognized cause of secondary aHUS but may mask its presentation. Timely recognition of aHUS in such cases and the initiation of eculizumab is essential towards modulation of the course of the disease including onset of ESRD and dialysis dependence.

Laboratory parameter	Creatinine	Bun	Hemoglobin	Platelet count	Schistocyte	LDH	Beta-2 glycoprotein	Anti-cardiolipin antibody	Complement C3	Complement C4	ADAMTS 13 Activity
Initial results	1.7mg/dl	45mg/dl	9.4g/dl	37000/ul	1+	341U/L	27.4SGU	>100gpL	57mg/dl	8.3mg/dl	53%
Follow up after 4 years	1.0mg/dl	32mg/dl	11.2g/dl	490000/ul							

Table 1:Laboratory parameters at presentation and at four-year follow up

PUB463

Rhabdomyolysis Secondary to Hypothyroidism

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Introduction: The relationship between Hypothyroidism (HT-H) and Rhabdomyolysis (Rhabdo) is not well-known. This is a case report of a patient that presented with ARF secondary to increased levels of CK and elevated TSH. The connection between both has been mentioned in few case reports but the mechanism is yet to be completely understood.

Case Description: A 71-year-old female with PMH of DM, HTN, and HT-H presented to the ED referred from her primary doctor for a raised Crea of 4.89 mg/dL. The patient was asymptomatic and did not report any changes to medication. On admission, her VS were stable. Repeat Crea in the ED was 4.57 and a BUN of 31. CK was 5403, with a CK MB fraction of 19.7 and a negative Trop. Rest of the labs where normal. UA was consistent with Rhabdo and negative for infection.

Discussion: This case is an example of an asymptomatic patient who presented with Rhabdo and Renal failure secondary to undertreated HT-H. HT-H is a common endocrine with a broad variety of symptoms ranging from asymptomatic to the most serious myxedematous coma. Rhabdo is a syndrome characterized by muscle necrosis and the release of intracellular muscle content into plasma. Most of the time it presents with severe muscle pain, weakness, hematuria, but in some cases, it could be asymptomatic. Diagnosis is made by laboratory results which elicit elevated levels of CK. Different causes for non-traumatic Rhabdo are known such electrolyte imbalances, infections heat exposure. Some endocrine disorders like DM, including DKA and nonketotic hyperglycemia, have also been reported to cause Rhabdo. Other electrolyte imbalances such as hypophosphatemia may also be the cause. There have been very few cases of Rhabdo caused by HT-H, and in most cases, there is an association with precipitating factors like exercise, trauma, drugs, most commonly statins and alcohol. The cause of Rhabdo secondary to HT-H is unclear. Various hypotheses including impaired mitochondrial oxidative metabolism, induction of insulin-resistant state, and decrease muscle carnitine levels including autoimmune mechanism, have been proposed. Thyroxine affects energy metabolism and its deficiency leads to abnormal glycogenolysis, mitochondrial oxidative metabolism and triglyceride turnover, which impair muscle function by causing a switch of fast-twitching type 2 muscle fibers to slow-twitching type 1 fibers, low myosin ATP-ase activity and low ATP turnover in skeletal muscle.

PUB464

Sulfadiazine Related Obstructive Nephrolithiasis and Acute Renal Failure

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Introduction: Renal stones are a known complication of Sulfadiazine but not seen commonly. We report a case of nephrolithiasis and acute renal failure secondary to sulfadiazine.

Case Description: A 73 year old male was evaluated in the Emergency room with complains of hematuria and abdominal pain. He has a past medical history of a cerebello-pontine brain lesion/mass/ abscess and seborrheic keratosis. The patient was admitted in the hospital a month back with ataxia, balance problems and left sided facial weakness/ facial droop. He had extensive workup done including Pan-CT, tumor markers, PSA, blood cultures, Echo - all of which were unrevealing. Toxoplasma IgG was positive, HIV negative. The family refused for a biopsy of the brain lesion based upon location and the risk of procedure. Patient was treated empirically with Ceftriaxone, Metronidazole, Leucovorin, Bactrim and sulfadiazine and discharged on same. One month later, he presented to the ER with abdominal pain and hematuria. In the Emergency room, BUN/Cr was 44/6.4 (baseline serum creatinine 0.8). CT abdomen and Pelvis showed mild left sided hydroureteronephrosis caused by 2mm calculus at the left ureterovesical junction and trace right sided hydroureter caused by a punctate calculus at the right uretero-vesical junction. CT abdomen and Pelvis done one month back was negative for renal stones. He was treated conservatively with intravenous fluids and alkalinization of urine and the BUN/Cr trending down from 44/6.4 to 18/1.3 over the next 6 days. Atovaquone was substituted for sulfadiazine and the patient was advised to continue the meds as MRI showed interval decrease in size of the primary lesion and significant improvement in vasogenic edema and mass effect

Discussion: Sulfadiazine induced nephrolithiasis leading to renal failure is a potentially serious complication that can be managed conservatively in most cases. In our patient BUN/Cr improved dramatically within 1 week. Physicians should be aware of the complication and give their patients a trial of intravenous fluids and controlled alkalinization of urine if clinically warranted.

PUB465

Role of Eculizumab in Postpartum Atypical Hemolytic Syndrome in a Kidney Transplant Recipient

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Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (aHUS) is a rare, potentially lethal condition that can complicate pregnancy in upto 1 in 25000 cases. Given the broad spectrum of conditions that can present similarly in the peripartum period, it is difficult to establish the correct diagnosis in a timely manner. The C5 complement cascade inhibitor eculizumab has been used with considerable success in non-pregnancy aHUS; however, its use in pregnancy associated aHUS is limited to isolated case reports. We present a case of pregnancy associated aHUS in a kidney transplant recipient that was successfully treated with eculizumab with recovery of renal function and safe reintroduction of transplant medications.

Case Description: 33 year old female with history of end stage renal disease due to IgA nephropathy who received a cadaveric kidney transplant 7 years prior, presented at 25 weeks gestation with severe hypertension and acute kidney injury. Immunosuppression included tacrolimus, azathioprine and prednisone. Her baseline Cr was <1.0 mg/dl and was 4.7 mg/dl at presentation. She had thrombocytopenia (58 K/ul, down from baseline normal) and hemolytic anemia with high LDH of 1810 U/L, depleted haptoglobin (< 8mg/dl) and presence of schistocytes. She underwent cesarean section for suspected pre-eclampsia with a non-viable fetus. She remained hypertensive, anemic with high LDH, thrombocytopenic, and had worsened renal function with Cr of 7.7 mg/dl. Schistocytes persisted and ADAMTS13 was normal. Tacrolimus was held with concern of drug induced thrombotic microangiopathy (TMA); however, no improvement occurred. Kidney biopsy, initially avoided due to low platelets, was done at week 4 and confirmed the presence of TMA with no evidence of rejection.

Discussion: After exclusion of other etiologies, a diagnosis of aHUS was made and eculizumab initiated. Patient had rapid improvement in renal function by day 4 of induction (Cr of 3.5 mg/dl), platelets increased to 255 K/ul, and LDH decreased to 200unit/L. While on consolidative phase of eculizumab, azathiorine and prednisone were continued. Tacrolimanus was also safely restarted and subsequently switched to belatacept, which she has been tolerating well. This case provides additional support for the role of eculizumab in the treatment of life threatening post-partum aHUS.

PUB466

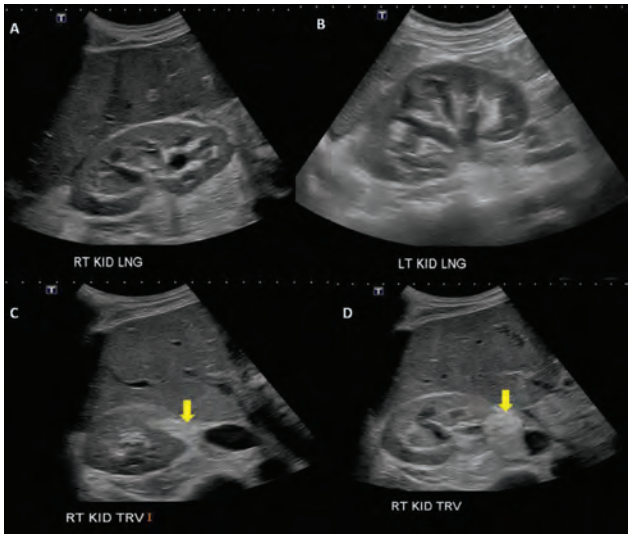
Ultrasonography: Another String to Nephrologists' Bow

Justin Lee Loy, Abhilash Koratala. *University of Florida Gainesville, Gainesville, FL.*

Introduction: Pyonephrosis is a rare purulent infection of the upper urinary tract, which can lead to rapid clinical deterioration. While contrast enhanced CT scan is a sensitive test, point-of-care renal sonography can serve as a quick and valuable bedside tool for diagnosis, especially when iodinated contrast use is contraindicated.

Case Description: A 57-year-old woman presented with fever, abdominal pain and nausea for 6 days. She was hypotensive at presentation and laboratory data demonstrated leukocytosis, pyuria, acute kidney injury requiring renal replacement therapy (RRT) and lactic acidosis. Non-contrast CT scan of the abdomen revealed mild bilateral hydronephrosis with no perinephric stranding or fluid collection. Vasopressors and broad-spectrum antibiotics were initiated. Exploratory laparotomy to identify a possible bowel source of sepsis was unremarkable. A renal ultrasound demonstrated moderate bilateral hydronephrosis with echogenic debris in right renal pelvis, suggestive of pyonephrosis [Figure]. She underwent emergent bilateral nephrostomy tube placement. Her blood and urine cultures were positive for *E coli* and antibiotics were adjusted accordingly. Follow-up ultrasound showed resolution of hydronephrosis. Patient subsequently showed rapid clinical improvement and RRT was discontinued.

Discussion: Pyonephrosis is a rare purulent renal infection due to ureteric blockage, which can lead to septic shock and death. Contrast-enhanced CT scan is commonly used for diagnosis, which may show findings of obstruction with renal pelvic wall thickening and layering of contrast material around the purulent fluid. However, the diagnosis can be missed on unenhanced CT and ultrasonography is a valuable bedside tool for rapid diagnosis as in our case.



PUB467

Amphotericin as Treatment for AKI

Mengyao Tang,[1] Jerald Cherian,[1] Thomas A. Golper,[2] Juan Pablo Arroyo.[2] *[1]Medicine, Vanderbilt University Medical Center, Nashville, TN; [2]Nephrology, Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Histoplasma capsulatum is a fungus endemic to the southeastern United States. Immunocompromised patients are at increased risk for disseminated infection, often presenting with fever, pulmonary disease, hepatosplenomegaly or central nervous system involvement. We report an unusual case of disseminated histoplasmosis presenting with acute kidney injury (AKI), acute liver injury and thrombocytopenia, which resolved upon initiation of amphotericin.

Case Description: A 57-year-old woman with rheumatoid arthritis (on methotrexate and etanercept) presented with 1-month of upper respiratory symptoms and malaise. On admission, she had a creatinine of 11 mg/dL (0.7 mg/dL prior), BUN 127 mg/dL, AST 325 unit/L, ALT 477 unit/L, alkaline phosphatase 313 unit/L, total bilirubin 10 mg/dL, PLT 42 x10^3/mcL. Urine microscopy showed WBC 27/hpf and RBC 129/hpf. Spot urine protein creatinine ratio was 2.42. Ground-glass opacities, as well as mediastinal and right hilar adenopathy were visualized on CT; no hepatosplenomegaly or hydronephrosis was seen. Renal biopsy was deferred due to risk of bleeding. A liver biopsy, performed simultaneously with transjugular dialysis catheter placement, revealed necrotizing granulomas with narrow based budding yeast consistent with histoplasma. Urine histoplasma antigen was 5.98 ng/mL, which confirmed the diagnosis of histoplasmosis. The patient was started on liposomal amphotericin at 3mg/kg daily, and within 5 days the patient no longer required hemodialysis. She was transitioned to itraconazole on discharge, and after 2-months, her renal function, liver function, and platelets had normalized.

Discussion: Our case highlights that, given the right clinical context, nephrotoxic drugs can be given to treat AKI. In this case, although kidney biopsy was not performed, it is hypothesized that either direct damage by histoplasma or the liver failure associated histoplasmosis contributed to the AKI, given that it improved shortly after initiating amphotericin. Although autopsies have shown renal involvement in up to 40% of patients with disseminated histoplasmosis, clinically significant renal disease is rare. In patients with renal failure, renal biopsies have demonstrated several etiologies, including renal papillary necrosis, granulomatous interstitial nephritis, glomerulonephritis, and urinary obstruction. Renal function may recover in such cases with prompt treatment of histoplasmosis.

PUB468

Delayed Bleeding Following Renal Biopsy

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Introduction: Renal biopsy is considered a safe procedure with less than 1% of patients having significant bleeding. Post-procedural bleeding typically occurs within 2-24 hours. Risk factors for bleeding include older age, female gender, renal failure, and bleeding diathesis. There is no consensus on when to resume anticoagulation following renal biopsy, particularly among high-risk patients.

Case Description: We report the case of a 70 yo male with cirrhosis, diabetes and CKD stage 3 admitted for recurrent diffuse alveolar hemorrhage of unknown etiology. On admission, creatinine was at his baseline of 1.7mg/dL. Urine sediment was bland and ANCA titers were negative. A few weeks into his hospitalization, he developed non-oliguric AKI with hematuria, pyuria and 0.8g/day of proteinuria. Repeat PR3 ANCA titers were positive at 26AU/mL (negative<19). A left-sided renal biopsy with CT guidance was performed to evaluate for pulmonary-renal syndromes. At the time of biopsy, the platelet count was $100x10^3$/uL and INR was 1.5. Biopsy results showed diabetic glomerulosclerosis and acute tubular injury. Prophylactic heparin was started 3 days after the biopsy. The patient developed hemorrhagic shock 14 days after the biopsy requiring massive transfusion protocol and pressor support. CT of the pelvis showed left intraparenchymal renal hemorrhage. Angiogram identified left renal artery bleeding pseudoaneurysms that were successfully coiled.

Discussion: Delayed bleeding following renal biopsy is very rare. We report a case of life threatening bleeding that occurred 14 days after the biopsy. This is to our knowledge the second reported case of a bleed occurring more than 10 days post biopsy. Our patient had several bleeding predisposing risk factors including older age, renal failure, coagulopathy, and use of heparin. The benefit as well as timing of initiating anticoagulation must be carefully weighed against the risk of post-procedural bleeding, particularly in high-risk patients who can present with delayed bleeding.

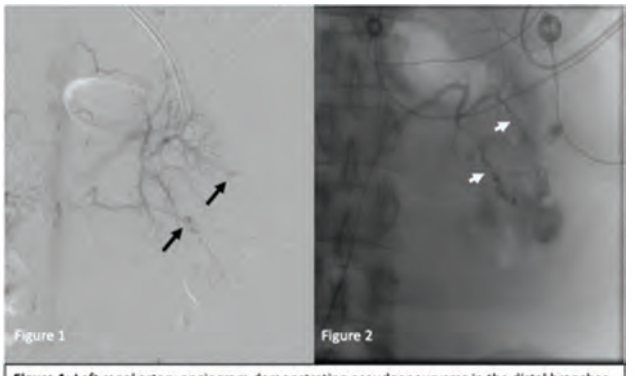

Figure 1: Left renal artery angiogram demonstrating pseudoaneurysms in the distal branches supplying the left mid and lower poles. Black arrows point to the pseudoaneurysms.
Figure 2: Coil embolization of the lower pole pseudoaneurysm and mid pole pseudoaneurysm. White arrows point to the coils.

PUB469

A Unique Approach of Combined Peritoneal Dialysis and Haemodialysis in a Case of Cardiorenal Syndrome

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Introduction: This is a case of renal dysfunction in a pt. with dilated cardiomyopathy(DCM) & cardiac arrythmia. Author was challenged by therapeutic dilemma of DCM, hypotension, acute renal dysfunction needing dialysis & haemodynamic disturbance arising due to haemodialysis(HD). Peritoneal dialysis (PD) & HD were done. It provided efficient solute extraction in volume overloaded pt & corrected diminished renal function.

Case Description: 50-year-old male, k/c/o hypothyroidism, ischaemic heart disease with DCM and CRT-D in-situ came with complaints of palpitations, breathlessness on exertion(NYHA IV), nausea, oliguria and anasarca. Admitted in ICU, systolic BP(SBP) 100 mmHg & temp 100° F; pt. had atrial fibrillation with rapid ventricular rate(RVR). 2D echo showed biventricular systolic dysfunction and EF 30%; Sr. creat1.2 mg/dL. Diuretic and BiPAP ventilator started. Amiodarone dose optimized. Persistence of RVR & hypotension, requiring increasing dose of inotropes. After 48 hrs, sr. creat 5.4. Due to low BP, lung congestion and AKI decision of dialysis was taken Tenckhoff catheter placed in LA. PD exchange with Icodextrin done with ultrafiltration(UF). Azotemia worsened. 4 sessions of short HD & PD over 10 days done. SBP was ≥90 with inotropes which were tapered. Pt. had VAP which was treated. Oliguria persisted 3 wks Pt. was managed in 4 wks with HD & PD. Gradual recovery of renal function with good UOP occurred. CRT-D reprogrammed.

AV Node ablation done & palpitation improved. Sr. Creat was 1.6. Catheter was removed. SBP ≥100 without inotropes. Pt. was fully ambulatory at discharge

Discussion: Cardiac and renal dysfunction often occur together as they share common pathogenic mechanism, known as CRSs. In such case of poor cardiac function & arrythmia, there is risk of intradialytic hypotension & renal hypoperfusion causing worsening of azotemia, which was obviated by combining PD & HD. With a multidisciplinary collaboration between cardiologist and nephrologist, we could achieve symptomatic improvement, improved exercise tolerance, euvolemia, recovery of renal function, and reduction in NYHA class with improvement of EF. It represents a pathophysiologically and conceptually relevant option by simultaneously addressing renal and cardiac dysfunction. The case is first of its kind reported from Indian subcontinent demonstrating safety and efficacy of this therapeutic modality for CRS.

PUB470

A Case of Granulomatous Interstitial Nephritis Likely Associated with Lisinopril

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Introduction: Granulomatous interstitial nephritis (GIN) as a cause of acute kidney injury (AKI) is a rare clinical condition. Drugs, infections and immune processes are among the most common causes.

Case Description: A 61 year old African American female with a history of hypertension and hypothyroidism was admitted with nausea, cough and easy fatigability of 2 weeks duration with decreased urine output. She was found to have a serum creatinine (Scr) of 15 mg/dl from a baseline of 0.8 mg/dl six months prior and was admitted for further workup. She denied NSAID use, did not have any recent contrast studies, illnesses or travel. Her home medications include atenolol, levothyroxine and lisinopril with no new medications. Clinically the patient was uremic with no rashes or edema. She had mild hypertension and was initiated on hemodialysis. Her urinalysis revealed 3+ blood and her sediment review showed many WBC, granular casts and rare RBC. Spot urine protein to creatinine ratio was 2.5 gm/gms. Renal ultrasound showed a 14 cm right kidney and 12.5 cm left kidney but otherwise was normal. Serologies for hepatitis B and C and HIV were negative. Antinuclear antibody, anti-glomerular basement membrane antibodies and ANCA were negative. Complements C3 and C4 were normal. The patient underwent a renal biopsy which showed GIN, so an infectious workup was initiated. A CT scan of the chest was normal, and serum ACE and calcium were normal, largely ruling out sarcoidosis and pneumonia. Blood cultures were negative. Tuberculosis was ruled out with PPD and sputum cultures. Serum protein electrophoresis was negative. The patient's symptoms significantly improved with initiation of HD but her renal function did not recover initially. In total, she received 7 sessions of HD. As infection was ruled out, she was started on 40 mg of oral prednisone and tapered quickly as her Scr improved to 2.1 mg/dl within 3 days of steroid initiation and eventually improved to 1.2 mg/dl. Lisinopril was discontinued on admission and now appears the most likely culprit for the GIN and severe AKI.

Discussion: Although GIN has not been linked with ACEI, captopril has been previously described as a cause of interstitial nephritis. This case opens further discussion for ACEI being a possible inciting agent for GIN among other etiologic association reported thus far.

PUB471

An Unexpected Cause of Hypercalcemia in a Cancer Patient

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Introduction: Primary hyperparathyroidism and malignancy are the most common causes of hypercalcemia, though the differential diagnosis is usually broad. Determining the etiology of hypercalcemia is key to its management and it can be difficult in the presence of multiple confounding factors. We present a case of hypercalcemia in a cancer patient, which was likely secondary to Sarcoidosis.

Case Description: A 59-year-old man with CKD stage 4, hypertension, and prostate cancer on androgen deprivation therapy was admitted to the hospital for worsening renal function and hypercalcemia. Serum creatinine at presentation was 4 mg/dL (baseline 2.8) and calcium was ~12 mg/dL. On chart review, he had varying degrees of hypercalcemia for at least a year that was associated with nephrolithiasis. He was not taking any calcium or vitamin D supplements. Serum parathyroid hormone (PTH) was suppressed and PTH-related peptide, serum protein electrophoresis, free light chain ratio and 1,25-dihydroxy vitamin D level were within normal limits. However, 25-hydroxy vitamin D level was low. Positron emission tomography–CT was negative for bony metastasis but showed lymphadenopathy in mediastinum and abdomen. Inguinal lymph node biopsy surprisingly revealed non-caseating granulomas with asteroid bodies and Schaumann bodies, consistent with sarcoidosis. Corticosteroid therapy was initiated and his calcium and creatinine gradually improved.

Discussion: Sarcoidosis is a multisystem granulomatous disease characterized by non-caseating granulomas. It can affect any organ including kidney. However, granulomatous interstitial nephritis alone is rarely implicated in CKD. Instead, chronic hypercalcemia and hypercalciuria causes tubulointerstitial inflammation with associated calcium deposits leading to nephrocalcinosis, and fibrosis and CKD. Though CKD in our patient was originally attributed to hypertension, hypercalcemia could have contributed. Take-home point from our case is that hypercalcemia in a cancer patient is not always from bone metastases and alternative etiologies should be sought when appropriate. Interestingly, 1,25-dihydroxy vitamin D level was normal in our patient, which is thought to be the main mechanism of hypercalcemia in sarcoidosis. However, 25-hydroxy vitamin D, which is the substrate for the formation of 1,25-dihydroxy vitamin D was low, which could explain this unexpected finding.

PUB472

A Case of Likely Bile Cast Induced Nephropathy

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Introduction: An important non vasomotor (as opposed to hepatorenal syndrome in cirrhosis) mechanism of Acute Kidney Injury in liver dysfunction is the nephro-toxicity of cholephiles (i.e.bilirubin and bile acids). This entity is defined by histologic lesions which include tubular bile cast formation and tubular epithelium injury, associated with jaundice. I describe the case of suspected bile cast induced nephropathy in a patient with obstructive cholestasis caused by stones in the common bile duct, without any prior history of liver disease.

Case Description: This was a seventy two year old male with a history of coronary artery disease s/p coronary artery bypass graft surgery, heart failure with reduced ejection fraction, atrial flutter, atrial fibrillation, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease stage IIIA, who presented with epigastric pain. His work up revealed a creatinine of 1.4 at the time of admission and it rose upto a peak of 2.93 with the total bilirubin peaking at 23.13. He had a CT scan of the abdomen/pelvis without contrast done which showed a suspected stone in the common bile duct after which an ERCP was done which confirmed the suspicion and after relief of the obstruction, both the total bilirubin and creatinine trended down simultaneously. This happened concurrently with the fall in bilirubin in the urine analysis.

Discussion: Kidney injury in the setting of severe cholestasis can result from precipitation of cholephiles in renal tubules with subsequent toxicity to the epithelial cells. In our case, although we did not perform a renal biopsy, but the temporal correlation, as seen in the accompanying table, between the total and direct serum bilirubin levels and the serum creatinine/eGFR and the level of bilirubin in the urine analysis suggest that cholestasis was strongly contributing to the renal injury.

Date/Time	Specimen	CREATi	eGFR	BUN	T BILI	D BILI	ALKP	ALT/WLA	AST	BILIRUB	UROBILI
04/09/18 04:30	Serum ***	1.83 H	37	55 H							
04/08/18 12:41	Serum ***	1.95 H	34	54 H							
04/08/18 06:00	Serum ***	1.86 H	36	51 H	7.51 H		226 H	55 H			
04/07/18 06:00	Serum ***	1.55 H	44	40 H	8.10 H		228 H	51 H	34		
04/06/18 06:00	Serum ***	1.51 H	46	45 H	9.57 H	4.98 H	218 H	47 H	27		
04/05/18 07:30	Urine ***									SMALL	4 H
04/05/18 06:00	Serum ***	2.10 H	31	69 H	13.79 H	7.62 H	264 H	55 H	29		
04/04/18 06:46	Serum ***	2.91 H	21	81 H	23.13 H		330 H	68 H			
04/03/18 02:15	Serum ***	2.59 H	24	76 H		19.99 H			93 H		
04/02/18 12:21	Urine ***									MODERATE	2 H
04/02/18 07:51	Serum ***				21.89 H	17.83 H	351 H	99 H	88 H		
04/02/18 04:18	Serum ***	2.93 H	21	79 H							
04/01/18 06:00	Serum ***	2.50 H	26	71 H	21.33 H	16.55 H	300 H	98 H			
03/31/18 06:00	Serum ***	2.33 H	28	65 H	20.38 H	16.47 H	211 H	98 H	43 H		
03/30/18 17:15	Serum ***	2.13 H	31	56 H	19.18 H	15.38 H	190 H	118 H	39 H		
03/30/18 12:00	Urine ***									SMALL	2 H
03/30/18 07:10	Serum ***				9.95 H				44 H		
03/30/18 06:00	Serum ***	2.12 H	31	50 H	14.99 H		157 H	146 H			
03/29/18 04:01	Serum ***				9.54 H	6.31 H	164 H	225 H	113 H		
03/29/18 04:01	Serum ***	1.37 H	51	35 H							
03/28/18 14:00	Urine (spot)									NEG	2 H
03/28/18 04:24	Serum ***				6.97 H		171 H	328 H	286 H		
03/26/18 04:24	Serum ***	1.30 H	54	33 H							
03/27/18 06:35	Serum ***				1.79 H						
03/27/18 06:35	Serum ***	1.40 H	50	40 H							

PUB473

Temporal Mass and AKI as a Presentation of Multiple Myeloma

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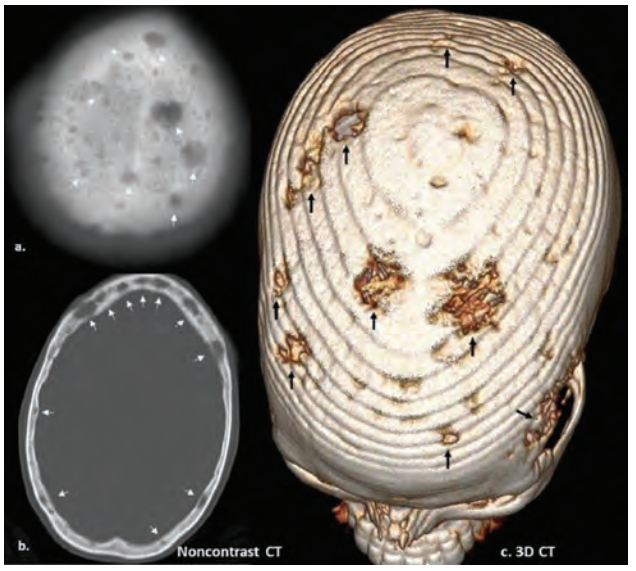
Introduction: Solitary bone Plasmacytoma is a rare malignancy characterized by malignant proliferation of monoclonal plasma cells. It constitutes less than 5% of malignant plasma cell tumors. Herein, we report a case of multiple myeloma that presented with temporal plasmacytoma and found to have acute kidney injury.

Case Description: A 70-year-old female with a history of endometrial cancer s/p hysterectomy, maintained on tamoxifen was brought to our institution for altered mental status of acute onset. She previously told her family about a left temporal mass ~3 weeks ago. Head CT demonstrated left temporal mass centered in the calvarium with intracranial as well as extracranial extension into the left lateral orbit and with associated osseous destruction. In addition, more than 20 calvarial lucent lesions were identified [Figure 1]. Laboratory data demonstrated AKI with a serum creatinine of 13 mg/dL, hypercalcemia with a serum calcium level 11.6mg/dL, anemia with a hemoglobin of 9 g/dL. SPEP showed two distinct monoclonal spikes in the IgA (0.7g/dL) and IgG (1.2g/dL) regions. Serum free kappa light chain (LC) was 1.49mg/dL (Ref: 0.33-1.94) and lambda LC 1339.3mg/dL (significantly elevated). She required initiation of hemodialysis and mental status gradually improved. Temporal mass biopsy demonstrated plasmacytoma with positive kappa LC and bone marrow biopsy was consistent with multiple myeloma. Chemotherapy was initiated with cyclophosphamide, bortezomib and dexamethasone and she is currently dialysis dependent.

Discussion: Plasmacytoma may involve the cranial vault, base or brain parenchyma and rarely, the temporal bone as in our patient. It is important to keep this differential in mind when evaluating a patient for acute kidney injury and cranial mass as not all such patients get appropriate imaging at presentation, especially if the lesion is small.



PUB474

Acute Esophageal Necrosis in a Patient with AKI Due to Acute Pancreatitis

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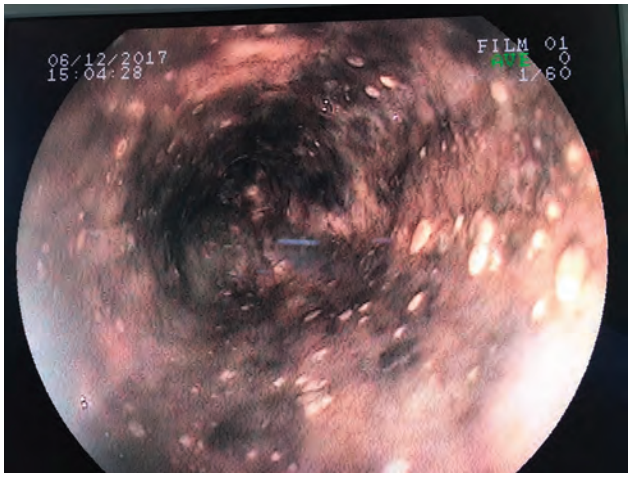
Introduction: The acute esophageal necrosis (AEN), also known as black esophagus, is a rare esophagic complication of many acute criticial illness. Since it has been described by Goldenberg et al in 1990, it has been linked to many critical clinical conditions, like descompensated diabetes mellitus, hypovolemic shock and acute kidney injury (AKI). In this report we aim to describe a case of AEN in a patient with AKI due to acute pancreatitis (AP)

Case Description: A 61 male patient with medical history of severe alcoholism, presented to the emergency department with a history of abdominal pain associated with nauseas and hematemesis for 2 days. He presented with hypotension, tachycardic, diaphoretic, pale and anxious. Labs showed amilasis 780 UI/L, urea 505 mg/dL and a Hb 5,5 g/dL. The patient was promptly resuscitated with saline and received transfusoin of 3 packs of red cells. Posteriorly the patient realized a CT of the abdomen, which confirmed acute pancreatitis, and an upper endoscopy which showed an acute esophagic necrosis. The patient was treated with broad-spectrum antibiotics, was placed on 'nil per os' and received renal replacement therapy. After 3 weeks the patient remained hemodynamically stable, the kidney function restored so that the patient no longer needed renal replacement and was progressively fed back, with good acceptance.

Discussion: Acute esophagic necrosis is a rare complication of many criticall illness. Although imprecise, some studies believe it has a prevalence of 0,2%. AEN is linked with many critical clinical illness, like diabetes mellitus, trauma, any cause of shock and AKI. We presented a case of AEN after a severe AP witch evolved with a AKI requesting renal replacement therapy. Acute GI bleeding is not rare in patients with AKI, normally occurring due to gastric or duodenal ulcer. In the present report we show that AEN is a potential cause of GI bleeding in patients with AKI



PUB475

Primary Renal Lymphoma: An Unusual Cause of Bilateral Nephromegaly

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Introduction: Primary renal lymphoma is a rare disease, which account for only 0.7% of all extra-nodal lymphoma in North America. Amongst the 70 cases reported in the literature to date, it was often reported as unilateral renal involvement in adults. We describe a case of primary renal diffuse large B-cell lymphoma, presenting with acute kidney injury (AKI) and bilateral nephromegaly.

Case Description: A 63 year-old female was admitted with two weeks history of vomiting, legs swelling and weight loss. She has bilateral ballotable kidneys on examination. Initial blood tests showed stage 3 AKI (serum urea: 45.7 mmol/L, creatinine 828 μmol/L) and pancytopenia. Haemolytic, clotting, virology and haematinic screens were unremarkable. Her lactate dehydrogenase was 341 U/L. She had nephrotic syndrome with serum albumin of 27 g/L and random urine protein-creatinine ratio of 413 mg/mmol. Her kappa/lambda ratio was normal with mildly low IgG (5.57 g/L). Ultrasound scan reported bilateral enlarged kidneys (right 14.0cm, left 14.6cm) and homogenous appearance of cortex and medulla. She was started on haemodialysis. Renal biopsy was performed, which showed renal tissue with scattered tubules extensively infiltrated by medium-sized blastoid cells. Bone marrow aspirate showed only slight hypocellularity. Immunophenotyping of the renal biopsy found a diffuse large B-cell lymphoma. She was commenced on CHOP regime with 50% reduction of cyclophosphamide. She had further readmission with pulmonary oedema and hyperkalaemia, which required increased haemodialysis and ultrafiltration. There was no evidence of myocardial infarction, however, the echocardiogram reported severely impaired systolic function. Her chemotherapy regime therefore was altered to R-CEOP. She reported blurred vision following the 2nd cycle of chemotherapy. Though CT and MRI head were unremarkable, cerebrospinal fluid flow cytometry showed evidence of lymphoma infiltration. She was commenced on intra-thecal methotrexate. She has had good response to chemotherapy and is showing signs of potential renal recovery.

Discussion: Although primary renal lymphoma is a rare condition, it must be considered in the differential diagnosis of nephromegaly and AKI. Comparable to previous published cases, our case demonstrated encouraging haematological and renal outcomes following R-CEOP treatment.

PUB476

Methotrexate Crystal Nephropathy in Patients with Rheumatoid Arthritis: An Underrecognized Cause of AKI

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Introduction: Renal dysfunction following administration of high-dose Methotrexate, defined as 1,000-3,000mg/m², has been well described. However, the incidence of nephrotoxicity with low-dose therapy, typically 7.5mg to 25mg weekly prescribed for patients with rheumatoid arthritis, remains largely unknown. Risk factors for nephrotoxicity include high serum Methotrexate level, low urine pH, low urine output and concomitant use of agents known to reduce GFR such as NSAIDs. Crystallization of Methotrexate in the renal tubules, seen as clumps of gold brown needle-like crystals on light microscopy, is urine pH-dependent and occurs in acidic urine. Literature surrounding renal dysfunction from low-dose Methotrexate administration is scarce and crystal formation leading to AKI in this cohort has not been described.

Case Description: We describe a case of a 56 year-old woman with a 10-year history of rheumatoid arthritis on Prednisone 20mg weekly who was referred to our clinic for a rise in serum creatinine from her baseline 0.9 to 1.4 during a 6-month period. Her medical history included hypertension treated with Triamterene-HCTZ and a remote history of asymptomatic nephrolithiasis that was found incidentally on ultrasound. Patient had been on daily Sulindac for many years, which was discontinued only with a transient improvement in creatinine. There was no proteinuria. Patient denied any urinary symptoms. Patient had no history of herbal supplement, smoking, alcohol, or recreational drug use. There was no family history of renal disease. Renal ultrasound was negative for obstruction. Urine dipstick showed specific gravity of 1.015 and pH of 7.0, otherwise negative. Surprisingly urine microscopy showed multiple clumps of brown weakly birefringent crystals, similar to published images of Methotrexate crystals. Upon further questioning, the patient admitted to frequent consumption of Coca Cola.

Discussion: Our case confirms that Methotrexate crystal nephropathy exists even in patients treated with low doses. We postulate that the use of NSAIDs and diuretics led to reduced Methotrexate clearance and consumption of urine pH-lowering foods facilitated crystal formation. The patient recovered renal function after discontinuing Methotrexate. Clinicians must be aware of this clinical entity and be thorough in their history taking including diet and medications.

PUB477

I'm Feeling Swell, and That Is a Complement (Mediated Disease)!

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Introduction: Angioedema is a severe manifestation of complement dysregulation. Hereditary Angioedema (HAE) patients have deficient or non-functional C1 esterase inhibitor (C1-INH). Acquired Angioedema (AAE) patients have autoantibodies or hyper catabolism of C1-INH. Systemic lupus erythematosus (SLE) has a wide array of

complement derangements and angioedema is a rare complication. SLE has been associated with both the hereditary and acquired forms of angioedema. Here we describe a patient with recently diagnosed SLE who presented with a severe case of angioedema and class 3 lupus nephritis.

Case Description: A 33-year-old female with recently diagnosed SLE calls emergency services for tongue swelling, stridor and respiratory distress. She was intubated at the scene and later transferred to the nearest hospital in stable condition. No skin rashes were noted. Initial labs notable for elevated serum creatinine and active urine sediments. She was treated with pulse dose steroids on day of presentation. The next morning, the patient developed respiratory distress after being extubated, so she was re-intubated and then transferred via airlift to our tertiary medical center. On arrival, she was awake, alert and stable on mechanical ventilation. Labs revealed elevated serum creatinine (1.7mg/dL), nephrotic range proteinuria with active sediments, anemia and thrombocytopenia. ANA, Anti-dsDNA titers were elevated, and her complements were low. C1-INH levels were collected but unfortunately the samples never resulted. Imaging of the chest and abdomen were negative for lymphadenopathy. Renal biopsy was performed and revealed class 3 lupus nephritis. She was treated with methylprednisolone pulses and Cyclophosphamide. Patient's respiratory status and renal function improved with therapy and she was extubated after 2 days.

Discussion: Angioedema is a rare complication of lupus flares. Clinicians should be aware of this rare but potentially life-threatening association, to prevent any delay in management

PUB478

Typical Atypical Hemolytic Uremic Syndrome: A Pregnancy-Induced Story

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Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS) is a rare condition that can mimic other clinical conditions in the postpartum period. It is very important for clinicians to promptly recognize and manage this potentially fatal condition to reduce the catastrophic complications that could result if early diagnosis is not made.

Case Description: A 31 year old primigravida African American woman with past medical history of hypertension, asthma and obesity presented to her post-partum follow up clinic 2 weeks after her C-section delivery of a preterm live infant at 29 weeks. Her pregnancy was complicated by premature ROM and chorioamnionitis. She was found to be very hypertensive (220/120 mmHg) with new onset abdominal pain associated with frontal headache and new-onset bilateral lower extremity edema with no fever and normal mental status. She was immediately admitted to the hospital and her initial laboratories showed new onset acute kidney injury (creatinine 2.5mg/dL), new-onset thrombocytopenia (35000), presence of hemolytic anemia with schistocytes on smear, markedly elevated LDH levels (>2000), and undetectable haptoglobin levels. Urinalysis was notable for active sediment with nephrotic range proteinuria and hematuria. Nephrology was consulted and given her classic presentation, she was started on intravenous steroids and hematology was consulted for emergent plasmapheresis the same day of admission. Diagnosis of atypical hemolytic uremic syndrome was confirmed with normal ADAMTS-13 level. Hemodialysis was eventually initiated for worsening kidney function. She was started on Eculizumab 48 hours after being admitted. After 2 doses of Eculizumab, her blood pressure is controlled with normalization of her hemoglobin and platelets and recovery of her kidney function. Patient is currently undergoing genetic workup for identification of inherited complement abnormalities.

Discussion: p-aHUS is a challenging condition that has been known to present in the early postpartum period. It could easily be mistaken for other well-known postpartum complications such as preeclampsia and HELLP syndrome leading to delay in treatment. The bad outcomes of this entity may be mitigated with quick clinical recognition and treatment initiation.

PUB479

Renal Biopsy – Remains an Irreplaceable Tool for the Nephrologist

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Introduction: In the absence of perfect biomarkers for acute kidney injury (AKI), renal biopsy remains an important diagnostic tool despite associated complications. We report a case of non-oliguric AKI with multiple risk factors masquerading the real diagnosis eventually requiring renal biopsy for definitive diagnosis and successful treatment.

Case Description: 63-year-old man with morbid obesity, hypertension, atrial fibrillation, chronic kidney disease and recurrent deep vein thrombosis on warfarin presented with 4 months of intermittent gross hematuria. His BP was 150/90 mmHg with an otherwise normal physical exam. Blood work revealed serum creatinine of 5.9 mg/dl (baseline 1.5 mg/dl). Urine microscopy showed many normal and a few dysmorphic red blood cells (RBCs). 24hr urine protein was 1.6 gm (baseline 1+ on dipstick). INR ranged from 1.5 to 5 in the recent past. He was treated with Ciprofloxacin for presumed urinary tract infection a month prior to presentation with stable creatinine 2 weeks later. He had normal cystoscopy a week prior to presentation. No other exposure to new medications or contrast was noted. Serology work up was negative. CT abdomen was unremarkable except for findings suggestive of liver cirrhosis. Diagnoses of Warfarin related nephropathy (WRN) and IgA nephropathy (IgAN) were entertained and Warfarin was held. Renal biopsy was initially deferred due to morbid obesity and need for anticoagulation but performed a few days later when renal function failed to improve. Despite prophylactic Desmopressin, the biopsy was complicated by a retroperitoneal hematoma requiring embolization of the interlobar artery and blood transfusions. It showed numerous tubules packed with RBCs, severe lymphocytic and eosinophilic interstitial infiltrate, and mesangial expansion with immunofluorescence positive for IgA. The findings were consistent with WRN, acute interstitial nephritis (AIN) and non-crescentic IgAN. He was started on oral steroids and an IVC filter was placed. His serum creatinine was 3.4 mg/dl on discharge, which stabilized around 1.5 mg/dl on follow up. Anticoagulation was resumed with no worsening of renal function.

Discussion: This is a rare case of acute renal failure with a combination of AIN, WRN and IgAN and highlights that renal biopsy remains an essential tool for definitive diagnosis and initiation of timely treatment.

PUB480

Eculizumab: Atypical Treatment of Typical Hemolytic Uremic Syndrome

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Introduction: Typical hemolytic uremic syndrome (HUS) with neurological involvement is a life threatening disease. HUS is caused by E.Coli producing Shiga-toxin damaging endothelial and activating the complement cascade. In atypical HUS, a monoclonal antibody Eculizumab has been effective in treating complement pathway abnormalities. We present a case of typical HUS with severe neurological involvement treated effectively with Eculizumab.

Case Description: An 18 year old Caucasian female was transferred from a Dominican Republic hospital with multiorgan failure including renal failure. She developed bloody diarrhea and was initally hospitalized with presumed acute gastroenteritis. She was started on antibiotics. Her condition worsened as she became anuric despite aggressive fluid resuscitation. She developed seizures and acute encephalopathy requiring ventilatory support. Upon arrival to our hospital, she was in acute renal failure with severe metabolic acidosis. Lactate dehydrogenase was elevated at 9000 with associated anemia and thrombocytopenia. Blood smear showed shistocytes. A clinical diagnosis of HUS was made based on acute renal failure, thrombocytopenia and hemolytic anemia. Stool PCR was positive for Shiga toxin 2. She was initiated on hemodialysis and treated with Eculizumab. Antibiotics were stopped. After 2 weeks in the intensive care unit, her overall condition improved. Her seizures resolved, and she did not require continued treatment with anti-seizure medications. Her renal function started to improve and she came off hemodialysis after 5 weeks. Her renal function though has remained decreased with a GFR around 30.

Discussion: An 18 year old without past medical history presented with a severe form of typical HUS. Shiga toxin as a causative agent was identified. However, neurological manifestations are unusual in typical HUS and thrombotic thrombocytopenia purpura was also considered. She was treated with hemodialysis but plasmapheresis was not offered in this case. Eculizumab was associated with full neurological recovery. After two doses of eculizumab, our patient's seizures resolved and she did not require long term anti-seizure medications. In life threatening cases of HUS with severe neurological symptoms, Eculizumab may be consdered as first line therapy.

PUB481

Postpartum Ruptured Sub-Capsular Liver Hematoma with Dialysis-Dependent AKI and Intracranial Bleed with Delayed Recovery: Is It HELLP or aHUS?

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Introduction: HELLP, a known complication of preeclampsia, can rarely result in ruptured sub-capsular liver hematoma (SLH) and very rarely dialysis-dependent AKI. We present a case of preeclampsia complicated by postpartum ruptured SLH and dialysis-dependent AKI with delayed recovery after delivery.

Case Description: A 33-year-old lady with prior two 1st trimester miscarriages admitted for emergent C-section due to fetal bradycardia and preeclampsia. During surgery hemoperitoneum and ruptured SLH was found. The patient developed AKI and anuria the following day. CVVHD was initiated. Lab workup showed low Hb & platelet counts with elevated LFTs & S.ammonia, resulting in a presumed diagnosis of HELLP syndrome. The patient showed minimal recovery post-delivery with supportive treatment. CVVHD was continued. A CT head was performed due to AMS which revealed sub-arachnoid hemorrhage. Due to persistent thrombocytopenia and anemia, further workup for TTP/aHUS, and APLS were ordered. Schistocytes were seen on peripheral blood with low complement levels and normal ADAMTS 13 activity. A renal biopsy wasn't done due to thrombocytopenia, however, given high suspicion of aHUS treatment with Eculizumab was considered. Just before the treatment initiation, her platelet count and other lab parameters started to improve so the drug was withheld.

Discussion: HELLP syndrome, APLS, TTP, and aHUS, can clinically mimic each other and it can be very challenging to differentiate, although expedited delivery usually improves HELLP and APLS. ADAMTS 13 is low in TTP but the diagnosis of aHUS is solely based on the clinical picture. Our patient didn't respond to expedited delivery and ADAMTS 13 was normal. Given delayed recovery, our patient likely had aHUS which fortunately resolved spontaneously. Henceforth, it is important to exclude aHUS when there is minimal or delayed recovery in patients with severe preeclampsia/ HELLP even after the delivery.

PUB482

Who Did It? An Unusual Case of an AKI MM and CLL in a Patient with Multiple Myeloma and Chronic Lymphocytic Leukemia

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Introduction: Multiple Myeloma (MM) is a notorious malignancy known to cause kidney damage. The range of renal pathology induced by MM range from the effects of tumor lysis syndromes to various types of glomerulonephritis's. It is quick to assume that a patient with MM with an Acute Kidney Injury is likely induced in some way or another from that disease process. However in this case report this particular patient also had Chronic Lymphocytic Leukemia (CLL), a malignancy that is rarely known to cause renal damage.

Case Description: This is a 60 y/o gentleman with a history of MM and CLL. The diagnosis of CLL was made after patient came to the ED for evaluation of chest tightness and palpitations that was attributed to an exacerbation of his known atrial fibrillation. His labs noted to include a WBC count of 175 k, an Absolute Lymphocyte Count of 171 k, with mild anemia and thrombocytopenia. Flow cytometry was ordered and it was consistent with CLL and FISH showed trisomy 12. Patient was asymptomatic so treatment was deferred. 2 months later patient presented with an AKI with a Cr of 3.6, baseline Cr was 1.1. SPEP and UPEP showed 6.3 grams of lamba light chain. Bone marrow biopsy one month later showed CLL with plasmocytic differentiation and plasma cell myeloma. Patient then received a renal biopsy and it showed 3 out of 12 sections that were globally sclerotic. There was prominent but patchy infiltration of the interstitium with lymphocytes (had positive immunoperoxidase staining for CD5, CD20 and CD23). Stainings were negative for kappa and lambda light chains.

Discussion: CLL is a disease entity that is not commonly know to cause an AKI. However going through the literature there are various case reports of CLL induced AKI. What is even more uncommon is AKI secondary to leukemic infiltration but this too is a known entity. In the setting of multiple myeloma one would expect that this disease process would be the etiology of this patient's AKI but the biopsy showed that this was not the case. In a patient with CLL and an AKI, it is important to consider that this disease process could be the cause of a patient's renal damage.

PUB483

Hydralazine Induced ANCA Vasculitis Causing Acute Interstitial Nephritis

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Introduction: This case describes a patient with hydralazine induced autoimmune disease who presented with pulmonary hemorrhage and rapid decline in GFR secondary to biopsy proven acute interstitial nephritis(AIN)

Case Description: A 74-yo male with hypertension on hydralazine for 3 years. He presented with a history of malaise, dark urine and shortness of breath. He had pancytopenia and AKI. Serological tests were positive for anti-histone, anti-MPO antibody and low complements. Bone marrow biopsy was normal. Renal biopsy showed acute interstitial nephritis(AIN) without any glomerular pathology. He was treated with pulsed steroid, and rituximab with the impression of hydralazine associated autoimmune disease. One week later, he had further hemoptysis, significant decline in renal function with proteinuria, RBC, granular casts in the urine. Chest CT revealed new bilateral pulmonary ground-glass infiltrates. He was given pulsed steroids with four plasma exchanges and rituximab. His respiratory status improved but he remained dialysis dependent at the time of discharge with full recovery of AKI at four months.

Discussion: Hydralazine induced lupus glomerulonephritis(GN) causes deposition of immune complexes and complement. Hydralazine induced ANCA associated(AAV) vasculitis cases reported till date have biopsy proven pauci immune crescentic GN. Our patient's history of malaise, pancytopenia, positive anti-histone antibodies and low complements lend weight to lupus syndrome but the rapidly increasing serum creatinine, features of diffuse alveolar hemorrhage(DAH) along with absence of immune deposits at renal biopsy make it most consistent with AAV. However, the presence of only AIN is interesting in this case. Despite adequate sampling, it is still possible that rare crescentic lesion were missed. Alternatively, the findings in our case may represent a drug hypersensitivity-associated AIN. In hydralazine induced lupus, cessation of the drug is sufficient to reverse disease activity. Although there was no histopathological evidence of GN, the patient responded to immunosuppressive therapy that is often used in the treatment of AAV. The uniqueness of this case lies in the development of AIN due to hydralazine induced ANCA vasculitis which recovered fully with immunosuppression. Hence, it is important to recognize the absence of the expected characteristics associated with hydralazine induced autoimmune disease.

PUB484

Calcium Channel Blocker Overdose Revisited: From Insulin to Methylene Blue

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Introduction: Calcium channel blockers (CCB) are commonly prescribed anti-hypertensive agents. CCB's are highly protein bound in the serum with a large volume of distribution and hence not easily dialyzed. Amlodipine, a dihydropyridine CCB, has predominant action on the vascular smooth muscle; overdose of Amlodipine can lead to circulatory shock and may be fatal. Several management strategies have been employed including calcium, insulin and lipid emulsion among others. We describe a case of refractory shock due to Amlodipine overdose, unresponsive to calcium/vasopressors/insulin/lipid emulsion, but stabilized after a single dose of methylene blue (vascular endothelium NO-cGMP inhibitor).

Case Description: A 53-year-old obese male with major depressive disorder and prior suicide attempts brought to the hospital by emergency services after having consumed 15 pills of Amlodipine (75 mg), 5 pills of Valproate and 30 pills of Aspirin (~2500 mg). On arrival, the patient was awake and alert. Following treatment with activated charcoal, he became progressively hypotensive, altered and hypoxemic. He was transferred to the ICU, where he was intubated and started on calcium, Dopamine and Norepinephrine infusions, followed by high dose Insulin infusion (up to 10 IU per kg per hour). CVVHD was started due to oliguric AKI (Cr 1.8) and severe acidosis (pH 7.02 and bicarb of 12). The following day, vasodilatory shock worsened requiring 4 vasopressors while receiving 1000 IU/hr of Insulin infusion. He was given a single dose of methylene blue, along with calcium chloride infusion and a dose of IV Lipid emulsion (aids in the clearance of lipophilic drugs). His mean arterial pressure (MAP) stabilized above 70 soon after, and his vasopressor requirement decreased. Hospital course was complicated by pulmonary edema and hypoxemia due to volume overload, which was successfully managed with CVVHD and ultrafiltration.

Discussion: Summary: Methylene blue (a selective inhibitor of guanylate cyclase, a second messenger for nitric oxide–mediated vasodilation) should be considered in the management of CCB overdose complicated by shock refractory to therapy with calcium, vasopressor and insulin therapy

PUB485

Unique Case of Urinoma After Laminectomy Presenting with Elevated Serum Creatinine

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Introduction: Close to 70% of all ureteral injuries are iatrogenic and occur most commonly subsequent to gynecologic or urologic surgeries. Despite the location of the ureter just lateral to the transverse processes of the lumbar vertebrae, such injury is rare after spinal procedures. If iatrogenic ureteral injury occurs, it usually does not cause acute kidney injury (AKI) in patients with normal baseline renal function. We present a unique case of iatrogenic urinoma after laminectomy which presented with a sustained elevation in serum creatinine.

Case Description: A 64 year old male with Diabetes Mellitus and HTN presented for elective L5-S1 laminectomy. On the first post-operative day, patient complained of back pain and nausea. Physical exam revealed BP of 118/73 mmHg, heart rate of 95-115 beats/minute and normal temperature. Chest was clear and there was no edema. Foley catheter was in place and draining large amounts of yellow urine. Laboratory data showed serum creatinine of 1.5 mg/dL, elevated from pre-operative baseline of 1.0 mg/dl and BUN of 44, elevated from 17 pre-operatively. Rest of the laboratory data including serum potassium and bicarbonate as well as urinalysis were normal. Rise in serum creatinine was attributed to intraoperative hypotension with mean arterial pressures between 50-60 mmHg. Over the subsequent week serum creatinine ranged between 1.5 and 1.8 mg/dL and on postoperative day eight, patient developed abdominal pain. CT abdomen revealed large left sided retroperitoneal collection consistent with urinoma with left sided hydroureteronephrosis. He underwent cystoscopy with ureteral stent placement; after which, serum creatinine normalized to 0.90 mg/dL. Abdominal pain resolved and patient was discharged with urology follow up.

Discussion: Ureteral injury is rare after laminectomy however must be considered in the case of sustained increased serum creatinine post-operatively. As AKI subsequent to unilateral ureteral injury is uncommon in patients with normal baseline renal function, the rise in serum creatinine observed might not reflect a true decline in GFR but rather increased reabsorption from urinoma.

PUB486

Utility of RRT in Reducing Mortality and Morbidity in a Heart Transplant Recipient with Idiopathic Hyperammonemic Encephalopathy

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Introduction: Development of Hyperammonemic encephalopathy is extremely rare in solid organ transplant recipients. Only 3 such cases have been reported in the literature, all due to idiopathic causes [3,4] Since continuous RRT with iHD plays a major role in improving ammonia levels, we hypothesized that similar improvements will be observed in a heart transplant recipient with HAE.

Case Description: A 44-year old male who was POD3 from a heart transplantation for congenital heart disease developed generalized tonic-clonic seizures in the setting of hyperammonemia syndrome. MRI showed diffuse cerebral edema while MR Spectroscopy showed reduced glutamine synthetase activity, N-acetyl aspartate and myo-inositol levels, all of which reflected glial and neuronal dysfunction. All labs were normal except for ammonia levels of 1400 umol/L. Liver and renal studies were also unremarkable. The patient was promptly started on levetiracetam, sodium benzoate, arginine. The patient's ammonia levels on POD4 still remain elevated (1350 umol/L) but decreased to 900 umol/L two days after initiating CVVH with iHD. CRRT was continued for additional 10 days along with sodium benzoate, arginine. Within 2 weeks, ammonia levels had completely normalized (**Table**) and while cerebral edema significantly improved on repeat scans, the

patient still had cognitive impairment (including impulsivity and memory impairment) which was slowly improving.

Discussion: HAE is a rare complication following solid organ and bone marrow transplantation, with an estimated risk of 0.5% and very high mortality. [1,3,4]. Hyperammonia levels can occur in the setting of cirrhosis, inborn errors of metabolism, type 1 RTA, and drugs. Furthermore, metabolic encephalopathy is driven by the effects of glutamate on the brain. Extracellular glutamate activates NMDA receptors and leads to alterations in nitric oxide metabolism and a shortage of ATP. This causes a cascade of events that eventually lead to free radical accumulation and the formation of nitric oxide. As a result, astrocyte swelling and disruption of the blood-brain barrier occurs, along with cerebral vasodilation due to prostaglandin release which causes loss of autoregulatory control in cerebral blood flow and vasogenic edema.

Post-op day	3	4	5	6	7	8	9	10	11
Ammonia level (umol/L)	1392	1250	920	450	344	208	110	45	33

PUB487

Double Whammy - IgM Lambda Multiple Myeloma and Normotensive ATN Abetting AKI

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Introduction: Multiple Myeloma (MM) is a plasma cell disorder characterized by the neoplastic proliferation of plasma cells in the bone marrow producing monoclonal immunoglobulins. We present a case of IgM light chain lambda predominant MM resulting in acute kidney injury (AKI) necessitating long term hemodialysis.

Case Description: A 50 year old male with arterial hypertension and diabetes presented with complaints of nausea, vomiting and fatigue. Vitals signs were stable, and clinical exam was unremarkable. Labs revealed normocytic anemia with hemoglobin 8 g/dl, elevated BUN (78 mg/dl) and creatinine (6.8 mg/dl, baseline 0.9 mg/dl three months back). Serum electrolytes, including calcium, magnesium and phosphorus levels were within normal limits. UA revealed isosthenuria with increased hyaline casts, and absence of hematuria, proteinuria or pyuria. Serum total protein (5.1 mg/dl) and albumin (1.1 mg/dl) levels were low. ESR (87 mm/hr.) and serum viscosity levels were markedly elevated. A 24-hour urine collection revealed proteinuria (848 mg). No osteolytic lesions were noted in a skeletal survey. Quantitative immunoglobulins were significant for elevated IgM levels, with concurrent suppression of IgG and IgA levels. Quantitative serum light chain measurement revealed elevated levels of lambda (6925 mg/L) and kappa (22.56 mg/L), with a Kappa:Lambda ratio of less than 0.01. SPEP, UPEP and serum immunofixation revealed IgM-Lambda Myeloma (MM). Renal biopsy was performed - moderate interstitial fibrosis and tubular atrophy, diffuse acute tubular injury; numerous large intraluminal casts that stained strongly against lambda (3+); diffuse GBM thickening with widespread epithelial foot process effacement was noted. Bone-marrow biopsy with flow cytometry revealed intracytoplasmic lambda-restricted monoclonal plasma cells that occupied 80% of the marrow. He underwent multiple plasma exchanges, and was started on a chemotherapeutic regimen consisting of Bortezomib, Cyclophosphamide, and Dexamethasone. His renal function has not improved, and is dependent on dialysis.

Discussion: Only 10- 20% of all MM are due to light chain disease. Lambda light chain disease is extremely rare, and carries a poor prognosis. Despite aggressive plasma exchange, dialysis, and chemotherapy, our patient did not attain remission. Further research on this rare entity is warranted.

PUB488

ACE Levels – An Unreliable Predictor of Disease Activity in Isolated Renal Sarcoidosis

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Introduction: PTH independent intrarenal calcitriol production by activated macrophages in isolated renal sarcoidosis is an extremely rare cause of hypercalcemia. We describe hypercalcemia with mildly increased serum ACE levels in a patient with isolated renal sarcoidosis.

Case Description: A 63 year old male presented with worsening weakness and polyuria. He was mildly hypotensive, and had no lymphadenopathy. Labs revealed normal hematological indices, moderate hypercalcemia (13 mg/dl), normal total protein and albumin levels, with a preserved hepatic synthetic function. Serum BUN (86 mg/dl) and creatinine (6.9 mg/dl, baseline 1 mg/dl) were elevated. UA revealed no proteinuria, pyuria, or hematuria. Even after aggressive fluid resuscitation with intravenous crystalloids, azotemia persisted with minimal recovery in renal function despite attaining adequate diuresis). Further investigations revealed low serum PTH (9 pg/ml) and 25-hydroxy Vitamin D (14 ng/ml) levels, and mildly elevated ACE (28 IU/L) and 1,25-dihydroxy Vitamin D (38 pg/ml) levels. Serum PTH-related peptide levels were undetectable. SPEP, UPEP, serum complements and immunoglobin levels were normal. RF, ANA, ANCA, anti-dsDNA, anti-MPO, anti-GBM and anti-proteinase-3 antibodies were negative; as were serologies for Hepatitis B & C, cryoglobulins, HIV panel, and RPR. Tuberculin skin test, and cultures for mycobacterium tuberculosis were negative. Chest and abdomen imaging were unremarkable. Renal biopsy demonstrated normal glomeruli with no hypercellularity, mesangial proliferation, necrosis or crescents. Numerous tubulointerstitial granulomas comprising of noncaseating epithelioid and multinucleated giant cells, surrounded by marked infiltration of mononuclear cells were seen. A diagnosis of isolated renal sarcoidosis was made. He was started on Prednisone 60 mg/day with subsequent improvement of hypercalcemia and renal function.

Discussion: Measurement of serum ACE levels is valuable in diagnosing and following disease activity in sarcoidosis. ACE levels in isolated renal sarcoidosis is typically lower than that seen in pulmonary sarcoidosis, likely secondary to reduced numbers of ACE-producing epitheloid cells isolated to the kidney. We illustrate that ACE level elevations may not be a dependable parameter in the diagnosis or evaluation of sarcoid disease activity in those with isolated renal sarcoidosis.

PUB489

Isolated Renal Sarcoidosis Presenting with Granulomatous Interstitial Nephritis

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Introduction: Sarcoidosis is a chronic, inflammatory disorder that affects multiple organs, characterized by noncaseating epithelioid granuloma formation. However, granulomatous interstitial nephritis in the absence of extrarenal sarcoidosis is extremely rare.

Case Description: A 59 year old black male with no significant past medical history presented with acute kidney injury (AKI). Vital signs were stable on admission, and no lymphadenopathy was noted. Labs revealed normal hematological indices, electrolyte levels (including calcium, magnesium and phosphorus levels), total protein and albumin levels, with a preserved hepatic synthetic function. Serum BUN (78 mg/dl) and creatinine (7.6 mg/dl, baseline 1.1 mg/dl) were elevated. PTH (7 pg/ml) and 25-hydroxy Vitamin D (15 ng/ml) levels were suppressed, while Angiotensin Converting Enzyme (69 IU/L) and 1,25-dihydroxy Vitamin D (42 pg/ml) levels were significantly elevated. Serum PTH-related peptide levels were undetectable. Urinalysis revealed no proteinuria, pyuria, or hematuria. ESR was elevated at 80 mm/hr. SPEP, UPEP, serum complements and immunoglobin levels were normal. RF, ANA, ANCA, anti-dsDNA, anti-MPO, anti-GBM and anti-proteinase-3 antibodies were negative. Serologies for Hepatitis B & C, cryoglobulins, HIV panel, and RPR testing were negative. Tuberculin skin test, and cultures for mycobacterium tuberculosis and systemic fungi were negative. CT chest-abdomen-pelvis, renal ultrasound, and pulmonary function tests were unremarkable. Despite aggressive intravenous crystalloid resuscitation, renal function did not significantly improve. Early renal biopsy demonstrated normal glomeruli with no mesangial proliferation, capillary wall abnormalities, or crescents. Numerous tubulointerstitial granulomas comprising of noncaseating epithelioid and multinucleated giant cells, surrounded by marked infiltration of mononuclear cells were seen. Based on laboratory and renal biopsy findings, a diagnosis of isolated renal sarcoid GIN was made. He was started on Prednisone 40 mg/day and renal function normalized to baseline within a month.

Discussion: Isolated renal sarcoidosis is extremely rare and is seen in elderly males unlike systemic sarcoidosis. Our patient did not have hypercalcemia that is frequently associated with this entity. Early diagnosis and prompt steroid therapy lead to normalization of kidney function.

PUB490

From Heart Failure to Light Chain Deposition Disease and Cast Nephropathy in Multiple Myeloma

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Introduction: Light chain deposition contributes to renal failure in multiple myeloma (MM) via 3 main patterns of injury: cast nephropathy (CN), MIDD with light chain deposition disease (LCDD) being a variant, and amyloidosis.

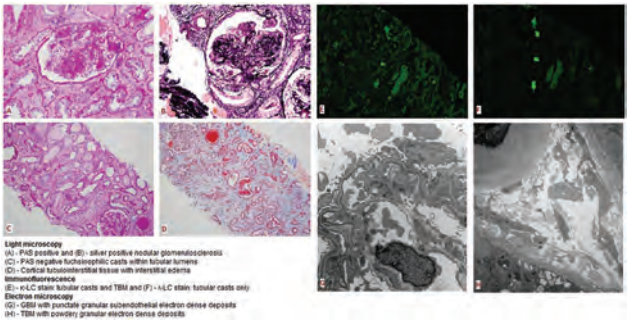
Case Description: 64-year-old man with HFpEF and CKD-3 presented with leg swelling and weight gain. Jugular venous distention and bilateral pitting pedal edema were noted. Labs included creatinine of 5 mg/dl (baseline 1.4), proteinuria, hematuria, glycosuria, raised BNP and anemia of chronic disease. On ultrasound, both kidneys were 16 cm in size. Admission diagnosis was acute cor pulmonale. Further workup revealed abnormal restricted peak in the gamma region on SPEP, elevated κ-FLC and κ- to λ-FLC ratio, and IgG κ monoclonal protein on immunofixation. Renal biopsy detected LCDD-CN and bone marrow analysis confirmed MM.

Discussion: Alternative diagnosis was pursued due to nephrotic-range proteinuria, normoglycemic glycosuria and enlarged kidneys, and MM was diagnosed without albuminocytologic dissociation, hypercalcemia or bony lytic lesions. LCDD-CN is rare and requires detailed microscopy. In contrast to pure LCDD or MIDD, mean age and incidence of AKI and dialysis are higher. Treatment is the same as that of MM and goals include improvement of renal function and prevention of extrarenal deposits.

Literature review of LCDD-CN

Reference	Sample size	LCDD-CN	Comments
Gokden et al	23 with LCDD-CN	100%, 23 cases	13% NGS on LM, 100% positive IF (18 κ & 5 λ), 65% EDD on EM, 35% IF-positive & EM-negative
Lin et al	34 with MIDD	32%, 11 cases	18% NGS on LM, 100% positive IF (10 κ & 1 λ), 36% IF-positive & EM-negative
Pozzi et al	63 with LCDD	16%, 10 cases	NGS on LM unlikely, frequent discrepancy between IF & EM (80% versus 18% with pure LCDD)
Pirani et al	47 with plasma cell dyscrasias	9%, 4 cases	-
Paueksakon et al	121 with monoclonal gammopathy and/or renal biopsy diagnosis related to paraprotein	0.8%, 1 case	-
Qian et al	(CR)	(CR)	MM with CN + heavy and LC deposition disease
Lorenz et al	(CR)	(CR)	MM with LCDD + CN + amyloidosis
Lam et al	(CR)	(CR)	IgD-λ myeloma with λ-LCDD + CN. Post autopsy kidney sections detected amyloid deposits around renal medullary vessels. 2 other specimens showed LCDD + CN and CN + LCDD + amyloidosis

CN - cast nephropathy, CR - case report, EDD - electron-dense deposits, EM - electron microscopy, IF - immunofluorescence, LC - light chain, LCDD - light chain deposition disease, LM - light microscopy, MIDD - monoclonal immunoglobulin deposition disease, MM - multiple myeloma, NGS - nodular glomerulosclerosis, κ - kappa, λ - lambda



LCDD-CN on renal biopsy

PUB491

TMA in Antisynthetase Syndrome

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Introduction: Thrombotic Microangiopathy (TMA) is a syndrome characterized by microangiopathic hemolysis, thrombocytopenia, and kidney injury. Primary causes include Thrombotic Thrombocytopenic Purpura or complement mutations. Secondary causes are due to autoimmune diseases, malignancy, and transplantation. Overall, autoimmune disease causing TMA is extremely rare. A study from Taiwan retrospectively reviewed 2461 cases of SLE in a 10-year span and reported only 25 cases of TMA. This abstract presents a case of an autoimmune phenomenon, Antisynthetase syndrome, causing TMA. As per our literature review, one case of TMA was reported in a patient with Polymyositis. In that case however, the patient also had underlying RA and was on a calcineurin inhibitor which may predispose to TMA.

Case Description: A 64-year-old female with recently diagnosed polymyositis and pulmonary embolism presented for worsening dyspnea. In a prior admission, she presented with arthritis and soft tissue edema. Serology showed elevated JO-1, aldolase, and CPK at the time. Computed tomography of the lungs showed diffuse pneumonitis, due to interstitial lung disease attributed to her autoimmune disease. Her overall presentation and imaging was suggestive of antisynthetase syndrome. During the current admission, her dyspnea was worsening and she had new onset kidney injury. Urinalysis was remarkable for protein and hematuria and she subsequently developed hemolytic anemia and thrombocytopenia. Due to her unexplained proteinuria, renal biopsy was performed revealing thrombi in glomerular capillaries and arterioles, suggestive of TMA. Primary causes of TMA such as TTP, HUS, and drug induced TMA were ruled out. Secondary causes such as malignancy were ruled out with additional CT of abdomen and pelvis. Other secondary autoimmune disorders were ruled out serologically. The only positive test was the >100 JO-1 antibody titers on ENA.

Discussion: TMA is an often fatal disease process. It has been reported in the context of HUS, TTP, autoimmune diseases and malignancy. This case is extremely novel in that the patient met criteria for antisynthetase syndrome by having both autoimmune polymoysitis and interstitial lung disease. Subsequently she developed AKI with biopsy proven TMA. Of note, patient's symptoms and renal function improved following treatment with prednisone. Having ruled out most, if not all causes of TMA, the only culprit was the antisynthetase syndrome.

PUB492

A Catastrophic Sequela of Cryoglobulinemia: Was Bedside Ultrasound Useful?

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Introduction: Intravenous drug usage has a strong correlation with renal failure, as well with chronic viral infections Hepatitis C and HIV respectively. With this risk factors other complications had been describes such as cryoglobulinemia, rhabdomyolysis, disseminated intravascular coagulation (DIC) that in cases could developed Purpura Fulminans as a deadly complication. Several factors had been implicated with renal function deterioration, and one of them is deposition of immune complexes as in cryoglobulinemia. This systemic disease could give rise to distinct clinical manifestations such as hyperviscosity syndrome that could be evidenced by sonography at initial presentation. Hyperpigmented lesions due to direct damage and diffuse anasarca, are early signs of deteriorated renal function. Skin changes could present as well with catastrophic limb gangrene. Here we report a rare case of hepatitis C with HIV related cryoglobulinemia which presented with generalized seizures de novo, rhabdomyolisis, rapidly progressing renal failure, disseminated intravascular coagulation, and purpura fulminant.

Case Description: Case of a 37 year old male with history of intravenous drug usage that presented to the emergency department after having a seizure event in the streets. He developed acute respiratory failure requiring mechanical ventilation within next few hours. Over a period of 24 hours severe renal failure developed, with mucosal bleeding as well bleeding from intravenous sites with bilateral acrocyanosis with pregangrenous changes. During this course, HIV came positive as well Hepatitis C infection.

Discussion: Based on the clinical picture with lab evidence of positive cryoglobulins and association of HCV, we made the diagnosis of HCV related mixed cryoglobulinemia with multi organ failure, glomerulosclerosis, vasculitis in the form of purpura and symmetric distal gangrene of limbs and nose, consistent with Purpura Fulminans. At intial evalaution patient had a bedside echocardiogram, that was relevant for severe hyperviscosity of blood, that is a clinical characteristic othat can be found in cryoglubulinemia. This early sign gave us a clue about patients underlying condition causing this catastrophic presentation, that was later comfirmed with laboratory results. Cryoglobulinemia is a catastrophic event associated with hepatitis C and HIV, early recognition is key.

PUB493

Close Encounters of the Peritoneal Kind: Case Series of Uroperitoneum and Renal Pseudofailure

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Introduction: Uroperitoneum, usually a consequence of bladder rupture, can occur after blunt trauma and surgical procedures or in association with pelvic irradiation, alcohol abuse and bladder anatomic abnormalities. As a result of exchange of solutes across the peritoneal membrane- a reverse autodialysis- an electrolyte milieu mimicking AKI can result

Case Description: Case 1: 74 year old male, day 10 status post robotic assisted radical prostatectomy for prostate cancer presented with increasing abdominal distension. These symptoms progressively worsened since removal of urinary catheter 4 days earlier. He had gross abdominal distension on exam. Labs showed Na 132, K 6.3, Bicarbonate 19, Urea 64 and Creatinine 9.7 mg/dL. Peritoneal fluid creatinine was 9.4 mg/dL. CT abdomen revealed gross ascites continuous with focal fluid at the surgical bed concerning for leak. Subsequent insertion of urinary catheter led to normalization of metabolic disarray in 24 hours Case 2: 32 year old female para 0, 40 weeks pregnant, presented to obstetric unit with reduced fetal movements. Induction was commenced and converted to a cesarean section 2 days later due to failure of descent. On postoperative day 4, patient was noted to have progressively increasing abdominal distension with labs: Na 134, K 3.8, Urea 13, Creatinine 2.4. Peritoneal fluid revealed creatinine of 8.4. A CT abdomen showed evidence of bladder leak and gross ascites. Insertion of urinary catheter led to normalization of creatinine next day Case 3: 37 year old male, with a history of alcohol abuse, presented with increasing abdominal pain and vomiting for 1 week. Labs revealed Na-120, K 6.2, Bicarbonate 20, Urea 151 and creatinine 11.8. Presence of gross ascites on CT led to large volume paracentesis, with subsequent reaccumulation in 8 hours. In light of the same and history of recent fall, a suspicion for bladder rupture was confirmed via cystogram. Insertion of urinary catheter led to correction of renal indices in 24 hours

Discussion: These cases underscore that in the presence of inciting event (trauma/surgery), unexplained ascites, classic electrolyte abnormalities(particularly hyponatremia) and urine:serum creatinine ratio of >1 – uroperitoneum should be suspected. The ensuing elevated creatinine is a consequence of reversed intraperitoneal autodialysis and does not represent a renal injury, thus termed renal pseudofailure

PUB494

Rare Spontaneous Renal Infarction of Unknown Etiology

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Introduction: Spontaneous renal infarction is rare, especially in the absence of thromboembolism secondary to atrial fibrillation. Other potential causes include hypercoagulable states, infective endocarditis, previous endovascular intervention, renal artery dissection, and oral contraceptive use. We report a rare case of spontaneous renal

infarct in a patient with no known risk factors presenting with abdominal pain mimicking a previous endometriosis flare.

Case Description: A 36 y/o African American female with a history of hypertension, possible congenital right renal atrophy, and endometriosis presented with a two-day history of severe left flank and abdominal pain like her prior endometriosis flares. On physical examination, her systolic blood pressure was 160mmHg and she was in significant distress. However, her exam was negative for peritoneal signs or costovertebral angle tenderness. Initial blood work up and urinalysis was unremarkable. Urine pregnancy test was negative. EKG revealed normal sinus rhythm. CT abdomen/pelvis without intravenous contrast was negative for obstructive uropathy but revealed an enlarged left kidney and an atrophic right kidney. MRA of the abdomen/pelvis revealed a previously unknown lower pole infarct in the left kidney without any significant infrarenal atherosclerosis, or aneurysms. Renal ultrasound was significant for an atrophic right kidney (3.3 cm) and an enlarged left kidney (13.5 cm) with decreased echogenicity of the lower pole consistent with known infarction. Left renal artery duplex scan was negative for significant renal artery stenosis. Hypercoagulable and venous thromboembolic work up was negative. Patient was medically managed and discharged home without chronic anticoagulation after symptomatic improvement.

Discussion: Spontaneous renal infarction is rare in the absence of predisposing risk factors such as thromboembolic disorders or hypercoagulable states. Due to non-specific manifestations, diagnosing renal infarction is a challenge and may lead to delayed diagnosis and intervention. Physicians must maintain a high index of suspicion so that timely interventions can be performed to properly assess and maintain kidney function

PUB495

AKI Associated with Acinar Cell Pancreatic Cancer

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Introduction: The kidney plays a large role in the elimination of pancreatic enzymes from the circulation. Acinar cell carcinomas are rare pancreatic cancers associated with lipase hypersecretion. We present a patient with metastatic pancreatic cancer with recurrent acute kidney injury potentially linked to her acinar subtype.

Case Description: A 49 year-old woman was diagnosed with acinar cell cancer and underwent chemotherapy with gemcitabine and abraxane for biopsy-proven metastatic disease with symptomatic ascites. One week after initiating chemotherapy, she developed painful raised bumps on both of her legs. She was hospitalized twice over two months for IV antibiotics for presumed cellulitis. Nephrology was consulted for worsening renal function as her creatinine steadily rose from 1.3 to 2.4 mg/dl. She had 2.8 grams of proteinuria, which was largely tubular, with only 2% of the total being albumin. Urine microscopy showed abundant coarse granular casts and no dysmorphics RBCs. Serologic workup showed no paraproteins, normal complement, and negative screens for hepatitis, ANA, ANCA, and GBM antibodies. Renal imaging showed no evidence of obstruction. A kidney biopsy was performed which showed ATN without any evidence of TMA or GN. Clear cause for ATN could not be identified; there were no hypotensive or nephrotoxic exposures. Without other exposures, she continued to have a rising creatinine to greater than 5 mg/dl along with worsening leg lesions. Another kidney biopsy 5 weeks after her initial one found only progressive ATN. Dermatology skin biopsy of the leg showed necrosis of adipocytes compatible with pancreatic panniculitis. Her serum lipase was 810 U/L (high) with normal serum amylase. She had no symptoms of pancreatitis. A urine lipase was checked and was markedly elevated at 1,112 U/L (Normal < 4).

Discussion: We present a patient with ATN who has acinar cell pancreatic cancer and pancreatic panniculitis. Studies have implicated lipase as pathogenic in panniculitis by its identification in areas of subcutaneous necrosis. 20% of pancreatic enzymes are excreted by the kidneys, with animal studies showing that lipase undergoes filtration, tubular reabsorption, and subsequent intrarenal degradation. We propose a potential novel cause of ATN due to supraphysiologic levels of serum and urinary lipase that should be investigated, similar to that of pancreatic panniculitis.

PUB496

Massive Creatinine Increase in the Setting of Protein Malnutrition

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Introduction: Serum creatinine (SCr) is a marker of kidney function and its elevation is usually associated with a concomitant rise in the blood urea nitrogen (BUN). An isolated rise in SCr has been described with the use of drugs that decrease the secretion of creatinine, with increased muscle mass and interference with its assay. We present the case of a patient with ulcerative colitis (UC) and acute kidney injury (AKI) characterized by an isolated rise in SCr.

Case Description: A 63-year-old man with UC on chronic prednisone and a previous colectomy was admitted to surgery ward after an ileal pouch-anal anastomosis (IPAA) with upstream ileostomy. After IPAA was performed, vancomycin and piperacillin-tazobactam were started for recorded episodes of fever. He was consulted to Nephrology service due to AKI. On evaluation, the patient was hypotensive, tachycardic, with high ileostomy output and decreased urine output. No skin rash was noted. Laboratories showed an elevation in SCr to 6.18 mg/dL from 1.3 mg/dL with associated metabolic acidosis without increase in BUN, electrolyte disturbances or eosinophilia. Albumin levels were 2.8 g/dl. Urine sediment was bland. He had no medications that could alter the secretion of creatinine. Due to signs of volume depletion, he was repleted with intravenous (IV) isotonic saline. SCr continued to rise to 9.44 mg/dL and since he was hemodynamically stable, IV fluids were changed to 0.45% NSS to replace ileostomy losses. Loperamide was added to achieve a solid consistency of ileostomy output. Imaging revealed fluid collections adjacent to IPAA, which identified an infectious focus. Vancomycin and piperacillin-tazobactam were discontinued and meropenem was started. SCr continued to increase up to 13.65 mg/dL while BUN remained at 35 mg/dL without hypervolemia or other electrolyte disturbances, hence dialysis was not considered. SCr levels returned to baseline three weeks later.

Discussion: Reduced muscle mass in patients with UC is associated with inflammation and glucocorticoid treatment. In this setting, BUN is expected to increase at least proportionally to SCr. In our patient, hypovolemia was not associated to an elevated BUN; and despite correction, SCr continued to rise. Severe and prolonged protein malnutrition may explain this unusual presentation.

PUB497

A Rare Presentation of Cocaine Induced Kidney Injury

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Introduction: An estimated 1 out of every 20 young adults in the US abuse cocaine. Case reports have described cocaine related renal impairment manifesting as acute tubular necrosis (ATN), infarction, pigment induced kidney injury and acute interstitial nephritis (AIN). However, hematuria in the setting of cocaine use without evidence of commonly seen cocaine induced renal pathologies has rarely been reported.

Case Description: A 29-year-old female with a medical history of hypertension, cocaine abuse, chronic hepatitis C virus infection and cryoglobulinemic vasculitis (diagnosed 2 weeks prior) was admitted for right lower extremity cellulitis. She was noted to have 1-week history of bloody urine necessitating nephrology team evaluation. She admitted to IV cocaine use few days before presentation. She had mildly elevated blood pressure - 158/69 mm/hg and the rest of her physical exam was unremarkable. Laboratory blood investigations revealed elevated serum creatinine - 3.1 mg/dl and low hemoglobin - 8.6g/dl. Her urinalysis revealed 3+ hemoglobin and 1+ protein. UDS was positive for benzodiazepines and cocaine. Other pertinent lab work up including creatine phosphokinase, urine chemistry and eosinophils, HIV and hepatitis B virus tests and serology for autoimmune disorders was negative. Renal ultrasound scan showed normal kidney size without hydronephrosis or stones. Renal biopsy revealed tubular lumen filled with red blood cells (RBC) and casts with no evidence of fibrosis, sclerosis or tubular atrophy. She was managed supportively with IV normal saline, antibiotics for cellulitis and her outpatient prednisone treatment. Her hematuria resolved, and serum creatinine level improved to her baseline (1.0 mg/dl). She was counseled on cocaine use.

Discussion: Cocaine causes kidney injury by different mechanisms; ATN and renal infarction through severe vasoconstriction and rhabdomyolysis and AIN through idiosyncratic allergic response. Also, chronic cocaine use has been linked to glomerulopathies. Our patient had cocaine related renal injury with RBCs and RBC casts in the tubular lumen without findings to suggest renal abnormalities frequently associated with cocaine abuse and toxicity. This is quite unusual and to our knowledge, has not been reported in the literature. Nephrologists and clinicians should be aware of the various renal manifestations of cocaine use.

PUB498

Suspected Pyelovenous Backflow Causing Acute Anuric Renal Failure (ARF)

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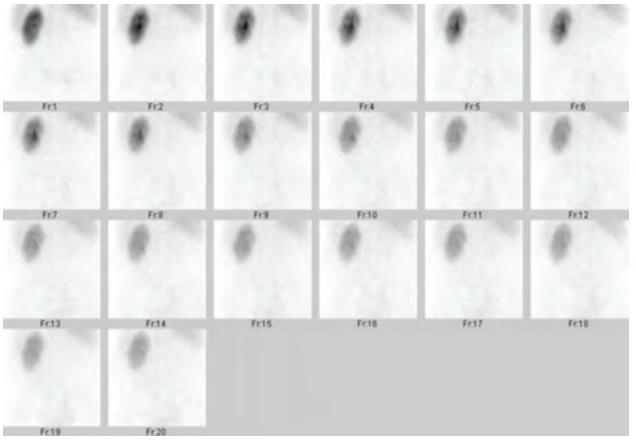
Introduction: The following is a case of ARF requiring dialysis in a man with normal cystatin C and β-2 microglobulin (B2M) levels without evidence of urine leak on imaging.

Case Description: A 72 year-old-man with normal renal function and solitary left kidney after donor nephrectomy 30 years ago underwent prostatectomy for prostate cancer. Surgery was uneventful with EBL 800 mL and intraop SBP remaining over 60. A routine abdominal drain was placed. The patient said he felt well after the surgery, however urine output diminished and he became anuric and creatinine (Cr) increased in the following days. IV fluids had no effect. There was no evidence of hydronephrosis, urine retention, or intra-abdominal fluid collection on CT or US. Urine microscopy showed RBCs without casts. Fluid from the abdominal drain had Cr levels similar to serum. Serum Cr steadily climbed and hemodialysis was initiated on post op day 6 for hyperkalemia. Cystatin C was 1.0 mg/L with a simultaneous Cr of 10.2 mg/dL and two days later B2M was 2.3 mg/dL with Cr 7.8 mg/L. MAG3 renal flow scan showed normal renal perfusion with concentrated tracer in the renal pelvis but not in the ureter and no evidence of urine leak. 2 weeks after the onset of ARF, urine output spontaneously increased and creatinine fell. He was discharged without further dialysis.

Discussion: Although our uninephric patient had ARF, he had normal glomerular filtration as shown by normal cystatin C, B2M, and MAG3 scan. The scan confirmed that freshly-formed urine was reaching the pelvis but not transiting the ureter. There was no evidence of extravasation on MAG3 scan or by analysis of drain fluid. Urine left the renal pelvis by another route: renal veins or renal lymphatics. Most likely postop edema and acute UV junction obstruction caused forniceal rupture and pyelovenous reflux into the arcuate veins. A less likely possibility is pyelolymphatic reflux. Had he been binephric, renal failure would likely have passed unnoticed.



PUB499

Bilirubin Cast Nephropathy Diagnosed by "Liquid Biopsy"

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Introduction: AKI can occur in liver disease through numerous mechanisms; one of them is bilirubin cast nephropathy. Most cases have been diagnosed with kidney biopsy. We present a case of bilirubin cast nephropathy, diagnosed by urine microscopy, in a patient with obstructive cholestasis.

Case Description: A 59 year old woman with past medical history of morbid obesity, type 2 DM, HTN, and CAD was hospitalized for progressive weight loss, nausea, vomiting, itching, and yellow skin. Her vital signs were stable. Physical exam was significant for icteric sclera, jaundice, and scattered excoriations of skin. No ascites or abdominal pain was present. Baseline liver and renal function were both normal. Investigations were remarkable for serum creatinine of 4.7 mg/dL, which later peaked at 8.1 mg/dL. Hepatic panel was significant for total bilirubin of 18.8 mg/dL with direct bilirubin of 14.8 mg/dL, alkaline phosphatase was 568 U/L, ALT was 66 U/L, and AST was 88 U/L, suggesting cholestasis. UPCR was 1.0 g/g. Urine microscopy showed bilirubin-stained granular casts. Abdominal imaging showed cholelithiasis, dilated common bile duct, with normal kidneys and liver. Kidney biopsy was held due to possible renal recovery from planned intervention with ERCP. During ERCP periampullary tumor was found, and CBD stent was placed. Creatinine improved to 2.2 mg/dL afterwards with simultaneous improvement in bilirubin levels. Seven weeks after ERCP with CBD stent placement, creatinine and total bilirubin had returned to baseline.

Discussion: Cases of bilirubin cast nephropathy in the setting of obstructive cholestasis have been underreported. Most reported cases have been diagnosed with kidney biopsy. However, in our case this was a patient with obstructive jaundice, renal failure, and bilirubin-stained granular casts on urine microscopy who then underwent ERCP with CBD stent placement to relieve obstruction, and then had a subsequent improvement in her renal failure. Kidney biopsy was never performed, and may not be necessary to establish a clinical diagnosis of bilirubin cast nephropathy.

PUB500

Role of Eculizumab in Dialysis Dependent AKI Secondary to Atypical Hemolytic Uremic Syndrome

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Introduction: Thrombotic microangiopathies represent 3 syndromes: hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura, and atypical HUS (aHUS). While microvessel wall thickening and intraluminal thrombosis characterizes the pathology, the pathogenesis and prognosis for each disorder is variable. HUS is defined by a triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and AKI. aHUS is then divided into two groups, typical (diarrheal) and atypical (non-diarrheal) HUS.

Case Description: A 65-year-old female with HTN, MDS and MGUS, presented to the ED with fatigue. Refer to Table 1 for lab findings. For the past 6 months, serial peripheral smears demonstrated increasing number of schistocytes. Renal ultrasound ruled out obstruction. Urine studies showed microscopic hematuria and 24h urine protein of 1.1g. As testing ruled out disseminated intravascular coagulation and suggested MAHA, therapeutic plasma exchange was given empirically until ADAMTS13 activity returned normal. Hemodialysis (HD) was then started for volume overload. Renal biopsy showed acute and severe chronic thrombotic microangiopathy-type injury, acute tubular necrosis and focal tubulointerstitial nephritis. Given lack of prodromal diarrhea, aHUS was diagnosed and she received corticosteroids followed by eculizumab. Her renal function and platelet counts recovered requiring 6 weeks of HD although she will require lifelong eculizumab therapy. Genetic testing for abnormal complement factors is pending.

Discussion: aHUS is an uncommon type of microangiopathy with incidence of 1 per million. Dysregulation of complement activation in the alternate pathway secondary to abnormal complement factors, with subsequent endothelial injury, typifies the pathogenesis of aHUS. As more genetic mutations are recognized it is becoming an increasingly understood clinical entity. Previously, standard first-line therapy consisted of plasma exchange followed by immunosuppression. The monoclonal antibody eculizumab has gained popularity in aHUS treatment by binding complement C5. Although eculizumab has been used more often for aHUS our case reflects the efficacy of this agent in a dialysis dependent patient if started immediately after the diagnosis has been made.

Creatinine	BUN	Hemoglobin	Platelets	INR	PTT	LDH	Haptoglobin
7.5 mg/dL	62 mg/dL	10.3 g/dL	69 x 10^3/uL	0.9	30 sec	890 u/L	<8 mg/dL

PUB501

Role of Steroids in Relapsing Light Chain Myeloma Patient with Dialysis Dependent Acute Renal Failure and Interstitial Nephritis

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Introduction: Cast nephropathy and hypercalcemia are the major contributors to renal failure in multiple myeloma patients (MM). Casts result when large amounts of free light chain (FLC) interact with Tamm-Horsfall protein in the urine, blocking glomerular outflow. Conversely, acute interstitial nephritis (AIN) is a rare manifestation of acute kidney injury (AKI) in MM patients. To our knowledge, there are few cases of a MM patient with concomitant cast nephropathy and AIN - here we present one such rare case. Our patient AKI response to steroids highlights the possibility of multiple etiologies for renal failure in MM, and the importance of thorough patient history, workup, and kidney biopsy when caring for these patients.

Case Description: A 61-year-old male with past medical history of IgG kappa MM (relapsed on multiple lines of treatment, most recently Revlimid, not currently on therapy) presented with fevers, generalized fatigue and confusion. He was found to be in acute renal failure (ARF) with an admission creatinine of 4.4 mg/dL, peaking at 6.3 mg/dL. He was empirically given antibiotics, despite negative infectious workup. Urinalysis showed moderate hemoglobin and eosinophil presence. Kappa FLC and kappa:lambda ratio was elevated (1419 mg/L; ratio 61) but had been higher previously (1480 mg/L; ratio 167). Renal ultrasound had no acute findings. His creatinine remained greater than 5 mg/dL without signs of improvement, until he eventually required hemodialysis (HD). Kidney biopsy was pursued; pathology confirmed cast nephropathy with concomitant AIN. As a result of biopsy findings, he was placed on a prednisone taper starting with 60mg QD. He required HD for 6 weeks, but kidney function improved, and his creatinine has since remained 2-3 mg/dL.

Discussion: This case allows us to witness an alternate origin of renal failure in multiple myeloma, in contrast to the classic cast nephropathy. Rapid improvement with steroids reveals AIN as the underlying cause of his renal failure. Without kidney biopsy and diagnosis of AIN, further MM treatment may not have successfully recovered kidney function. Thorough patient history, workup, and kidney biopsy are crucial to prevent oversight of the possible alternate sources of renal failure in MM.

PUB502

A Case of AKI by an Unusual Cause of Rhabdomyolysis

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Introduction: Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. Creatine phosphokinase (CPK) levels are typically markedly elevated, muscle pain and myoglobinuria may be present. The severity of illness ranges from asymptomatic elevations in serum muscle enzymes to life-threatening disease characterized by extreme enzyme elevations, electrolyte imbalances, and acute kidney injury (AKI). AKI is an abrupt and usually reversible decline in the glomerular filtration rate (GFR). This results in an elevation of serum blood urea nitrogen (BUN), creatinine, and other metabolic waste products that are normally excreted by the kidney.

Case Description: We present the case of a 29 year old man with no past medical history that came to our urgency room complaining of muscle pain, malaise and gross hematuria. Pain was more prominent in proximal muscle of upper and lower extremities, cramping, 7/10 in intensity, not radiating, aggravated by movement and affects ambulation due to pain, of 3 days of evolution. Denied any recent medications, toxic habits, fever, nausea, vomiting, diarrhea, chills, seizures, SOB, cough, chest pain, recent travel, sick contacts, sore throat, rhinorrhea, animal contact. He started a new job that demands more physical activity than his usual and have to be prolonged time standing up. He remembers a similar episode when he was 13 year old. Work-up was done at the time as an inpatient elsewhere including muscle biopsy but he doesn't remember any diagnosis. Now initial pertinent laboratory work-up results showed a very high CPK levels, myoglobinuria and GFR of 40 mL/minutes. After history, physical examination and studies a metabolic myopathy was very high in the differential diagnosis. After muscle biopsy and genetic testing were done the diagnosis of McArdle's disease was confirmed.

Discussion: McArdle's disease is a glycogen storage disease affecting the muscle due to muscle phosphorylase deficiency affecting 1:167,000 of the population. It is a type of metabolic myopathy that may cause rhabdomyolysis. Metabolic myopathies represent a very small percentage of cases of rhabdomyolysis with consequent myoglobinuria in which AKI could develop. We as physicians have to be aware about these uncommon conditions that may cause recurrent rhabdomyolysis and therefore recurrent AKI.

PUB503

Cytomegalovirus PCR Levels and Collapsing Glomerulopathy

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Introduction: Collapsing glomerulopathy is a form of focal and segmental glomerulosclerosis (FSGS) which leads to very severe nephrotic syndrome and quickly progresses to end-stage renal disease is usually associated with HIV. We present a case of collapsing glomerulopathy most likely caused by Cytomegalovirus (CMV) as patient had renal function return to baseline during valganciclovir therapy.

Case Description: 21 yo healthy Hispanic patient presented with nausea, headache, myalgia and 8lbs weight gain and noted to have acute kidney injury with serum creatinine of 1.5 mg/dl. Urinalysis revealed 1+ blood and > 500 protein with numerous nondysmorphic RBCs on urine sediment and urine protein/ creatinine ratio of 12.66g/g. CBC showed WBC 12, 14% bands, 15% atypicals, ALT 181 and AST 156. Serologies including complements C3/C4, ANA, anti-DS DNA, HIV, Hepatitis B and C and EBV PCR viracor were negative. CMV PCR viracor was 9,000. Renal ultrasound showed right kidney at 12.5 cm and the left at 12.3 cm. Ct scan abd/pelvis revealed splenomegaly with spleen at 20.1 cm. Kidney biopsy was consistent with collapsing glomerulopathy with moderate to severe interstitial inflammation and negative staining to CMV DNA. He was treated with valganciclovir 900 mg daily, prednisone 60 mg daily and tacrolimus. After 21 days of treatment, CMV PCR viracor was undectected with marked improvement of proteinuria to 0.97 g/g. Prednisone has been tapered down, and tacrolimus was stopped and patient still demonstrated improved serum creatinine a month after undectable CMV PCR viracor.

Discussion: This case describes a patient who was started on valganciclovir which resulted in normalization of serum creatinine. He was also started on tacrolimus and prednisone in addition to the valganciclovir as recommended treatment plan for collapsing FSGS. CMV was more probable cause as there was a correlation with decreased CMV viracor levels and improved serum creatinine even when patient was off tacrolimus. It is still not clearly understood what the proposed mechanism for CMV induced FSGS. The lesion has been proposed to be related to podocyte injury and attachment upon a size from the glomerular basement membrane. This case presented demonstrated rapid improvement in renal function with valcyte administration and decreased CMV PCR viracor levels.

PUB504

Chronic Interstitial Nephritis Associated with e-Cigarette Cannabinoid Consumption

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Introduction: Synthetic cannabinoids (SCBs) are psychoactive designer drugs that bind to the cannabis receptors in the brain more potently than marijuana. Cases reported in the literature with SCBs use have been associated with reversible *AKI* characterized by *ATN* and *AIN*. Here we describe a case of a patient who developed chronic interstitial nephritis associated with habitual synthetic cannabinoid use via vaping.

Case Description: A 37 year old African American male with PMH of Diabetes and Obesity s/p gastric sleeve surgery was referred by PCP due to increased in creatinine from baseline of 1.45. His Social History is significant for frequent use of synthetic cannabinoids and marijuana via e cigarette devices. His creatinine on admission was 6.89 mg/dL and BUN 89 mg/dL and urine was remarkable for + eos in urine and muddy brown casts with minimal proteinuria. Initial serological work up was negative and ultimately underwent renal biopsy and dialysis with a creatinine was 10.86 mg/dL and BUN 110 mg/dL. Results of renal biopsy were consistent with patchy acute tubular injury associated with moderate to severe tubular atrophy and interstitial fibrosis, with chronic inflammation. There was also some evidence of mild changes consistent with diabetic nephropathy.

Discussion: Chronic interstitial nephritis (*CIN*) is a histological entity characterized by progressive scarring of the tubulointerstitium, with tubular atrophy, cellular infiltration, and interstitial fibrosis. There have been multiple case reports in which the use of synthetic cannabinoid (*SCBs*) has been associated with *AKI* via *ATN* or *AIN* but none *CIN*. Many of these cases are attributed to synthetic cannabinoid metabolites XLR-11, AM-2011, UR-144, which are present in these synthetic analogs and are found in e-liquids commercially available. This case illustrates the importance of increased awareness to the potential health risks associated with marijuana use via e-cigarettes, whether synthetic or plant derived.

PUB505

The Deceptiveness of Creatinine as a Measure of Renal Function in Rhabdomyolysis: A Case Report

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Introduction: Rhabdomyolysis associated acute kidney injury (AKI) differs from other etiologies of AKI, as serum creatinine(sCr) represents the measurement of increased generation from muscle lysis and reduced excretion from pigment induced nephropathy. We present a case of dialysis dependent AKI due to rhabdomyolysis with persistently high sCr and eventual normalization of eGFR as demonstrated in a diethylenetriaminepentacetate (DTPA) scan.

Case Description: A 42 year old African American male with no prior medical history presented with progressive weakness and generalized muscle aches which began after phencyclidine use. On initial presentation he was found to have a creatinine of 10.4mg/dL (unknown baseline), potassium 6.9 mmol/L with peaked T waves on EKG, calcium 4.8 mg/dl (5.4, corrected), phosphate 13.4 mg/dl, sodium 127 mEq/L, bicarbonate 20 mEq/L, CK >200,000 IU/L and pH of 7.1. Urine dipstick had 3+ blood and 1-5 erythrocytes on direct microscopy. Renal ultrasound revealed normal renal size and echogenicity. The patient was managed with forced saline diuresis, but was eventually dialyzed for persistent hyperkalemia. After 6 dialysis sessions the patient had increased urine output, normalization of electrolytes and rapid decline of BUN with persistently elevated sCr, see Table 1. Given the patients' clinical improvement a DTPA scan was performed to determine eGFR due to persistently elevated sCr which revealed a GFR of 106 mL/min/1.73m2. Despite cessation of dialysis patient continued to have renal recovery with a sCr of 5.1mg/dL at the time of discharge.

Discussion: Our case demonstrates that sCr is not a reliable marker to monitor recovery of renal function in patients with severe rhabdomyolysis requiring hemodialysis. Nuclear renal imaging such as a DTPA scan is a helpful tool in assessing renal function in similar clinical scenarios. Larger studies are required to assess utility of non creatinine based measurement of GFR in such populations.

Table 1: Lab trend during hospitalization

	Initial labs	HD #1	HD #2	HD #3	HD #4	HD #5	HD #6	Discharge labs
Potassium (mmol/L)	6.9	6.7	4.9	4.5	4.4	4.5	4.6	5.3
BUN (mg/dL)	109	108	104	97	79	47	45	36
sCr (mg/dL)	10.4	11.1	12.8	14.7	14.4	12.0	13.2	5.1
CK (IU/L)	>200,000	>200,000	155,500	7,298	1,865	–	-	-

HD (hemodialysis)

PUB506

From One Page to the Next...

John Ahn,[2] Sandeep Padala,[1] Azeem Mohammed.[1] *[1]Augusta University, Augusta, GA; [2]Medical College of Georgia, Augusta, GA.*

Introduction: Page kidney represents a rare cause of renal dysfunction and secondary hypertension that results from external compression of the kidney immediately after a traumatic or iatrogenic sub-capsular hematoma. We present a unique case of an abnormally delayed development of page kidney after a renal biopsy.

Case Description: A 41year old female with a past history of systemic lupus erythematosus, CKD Stage 3b (baseline serum creatinine of 2.5 mg/dL) and hypertension was admitted for acute kidney injury. After undergoing a percutaneous kidney biopsy that revealed Class IV lupus nephritis, the patient developed hematuria and flank pain. Laboratory results indicated a drop in hemoglobin from 10.2 to 8.6 gm/dL and a rise in creatinine from 2.91 to 4.26 mg/dL. CT scan of the abdomen and pelvis revealed a large right retroperitoneal and sub-capsular hematoma measuring 8.1 x 5.3 cm. CT-guided drainage of 1.2 liter of sanguineous fluid resulted in renal function returning to baseline with minimal residual perinephric fluid on repeat imaging. Patient was discharged on immunosuppression for lupus nephritis. About seven months after the kidney biopsy, the patient presented to the clinic with no specific complaints but noted to have a large right lower quadrant mass. Laboratory results revealed acute kidney injury with serum creatinine at 4.03 mg/dL. Imaging revealed a sub-capsular abscess around the right kidney measuring 15.5 x 13.0 x 14.4 cm, presumed to have developed from the preexisting hematoma. The patient was diagnosed with acute renal failure from page kidney. Percutaneous drainage of the abscess resulted in 1.6 liter of purulent fluid that grew many gram-positive cocci on culture. Repeat imaging showed, the sub-capsular fluid had decreased in size to 5.3 x 2.4 x 5.6 cm with a concomitant decrease in serum creatinine to 3.2 mg/dL. The patient was discharged on oral clindamycin.

Discussion: Page kidney usually results in acute renal failure, pain and hypertension caused by activation of the renin-angiotensin-aldosterone system secondary to a sub-capsular hematoma. The present case is unique since this phenomenon was secondary to an abscess that developed in a preexisting hematoma. The patient's immunosuppressive regimen may have been responsible for her indolent course. Furthermore, in an age of abundant imaging modalities, this case highlights the importance of a physical exam.

PUB507

Acute Renal Failure in a Patient with Acute Lymphoblastic Leukemia (ALL): An Unexpected Combination of Etiologies

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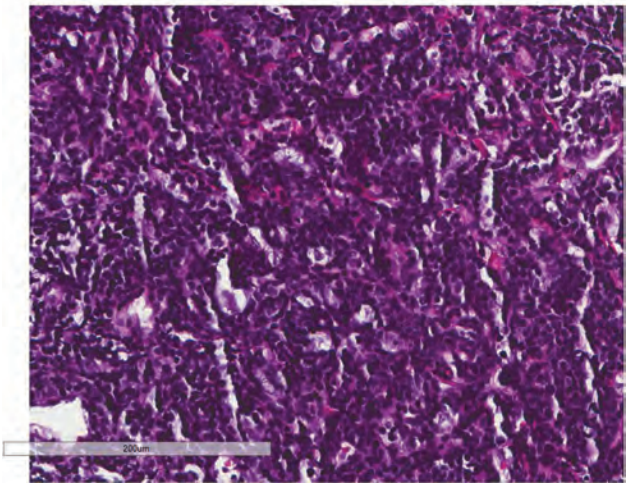
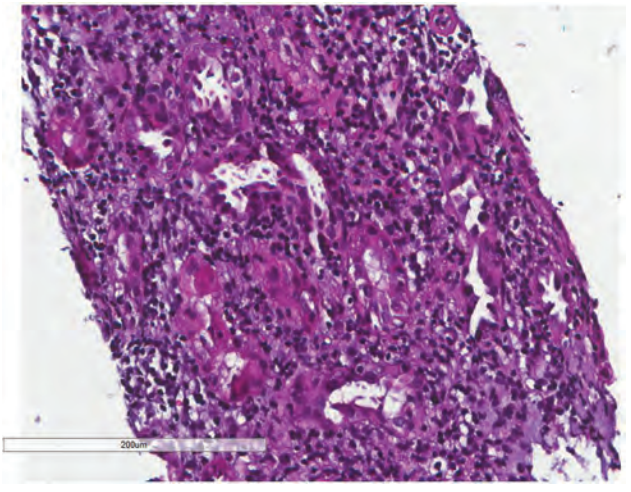
Introduction: We present a case of acute renal failure in an adult patient with relapsed ALL due to lymphomatous infiltration of the kidneys and Blinatumomab induced acute interstitial nephritis (AIN)

Case Description: A 23 year old African male, with relapsed B-cell ALL and chronic Hep B carrier on Entecavir was admitted with acute oliguric renal failure. He was started on Blinatumomab 2 months prior in preparation for stem cell transplant. Outpatient abdominal imaging was concerning for multiple bilateral renal lesions suspicious for secondary Lymphomatous involvement resulting in mass effect. Admission creatinine was 8.4 mg/dl. Renal Ultrasound showed mild bilateral hydronephrosis. Kidney biopsy contained portions of dense interstitial inflammatory infiltrate of CD10-positive and TDT-positive leukemic cells (Figure 1) and a less dense, diffuse interstitial inflammatory infiltrate of CD10-negative and TDT-negative lymphocytes with occasional plasma cells and eosinophils (Figure 2). This was consistent with leukemic infiltration and AIN. Renal failure resolved in a week with supportive measures. Blinatumomab was discontinued.

Discussion: Blinatumomab is a monoclonal antibody used for treatment of relapsed or refractory ALL in adults. It was felt that the most likely etiology of AIN was the recent introduction of Blinatumomab. In addition, ultrasound was concerning for hydronephrosis caused by ALL infiltration which may have contributed to his renal failure To our

knowledge, this is the first reported case of AIN secondary to Blinatumomab. Medications should be considered as a cause of unexplained renal failure.





PUB508

Rapidly Progressing Renal Failure: A Diagnostic Dilemma

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Introduction: AKI though a common diagnosis can pose a diagnostic challenge especially so when it is rapidly progressing like our case

Case Description: A 52-year old lady with recent diagnoses of hypertension, new onset heart failure, cardiomyopathy preserved EF, pericardial effusion and AKI (Creatinine 2mg/dl; last Cr from 2012 – 0.9) presented with complains of generalized weakness and fatigue for a week. Her meds, all recently started were Atorvastatin, Carvedilol, aspirin and Furosemide. Pt denied fever, chills, sputum production, chest pain, orthopnea, palpitations or syncope. She has recent hospitalization with above problems, discharge Cr was 1.4mg/dl. Bone marrow biopsy had shown plasma cells <5% for diagnosis ?cardiac amyloid / pericardial effusion work up, On physical examination vital signs were unremarkable, She was lethargic but oriented to time, place and person. only positive finding was B/L crackles on lung bases and b/l lower extremity swelling. Abnormal Laboratory data : BUN 64mg/dl and creatinine of 2.02mg/l., Urinalysis showed 3+ blood and 2+ protein, Up/UC 0.8, Urine immunofixation revealed Bence Jones kappa protein. Ration of Kappa/Lambda- 1.99. Troponins 1.23, CPK 942 which downtrended. EKG showed T wave inversions in anterior leads. ECHO showed increased left ventricle thickness with ejection fraction of 65-70%. No regional wall motion abnormalities were noted, Moderate circumferential pericardial effusion is noted. CXR for opacity in left lower side of the lung. Renal Ultrasound showed no hydronephrosis with kidney sizes of 10.3 R and 11.1 cm L. Pt required dialysis and Kidney biopsy was done, it was consistent with myoglobin cast nephropathy- acute tubular injury with myoglobin laden casts. Immunoflorescence and electron microscopy identified small amounts of IgG, OgA, C3 and lambda light chain within the mesangium. No evidence of amyloid deposition were noted.

Discussion: In our patient, probable cause of rhabdomyolysis could be immobilization, infection (pneumonia) or the use of statin, hypokalemia(furosemide),. The CPK for the patient was not significantly increased but could have the on the recovering phase at the time of presentation to our hospital

PUB509

Bouquet of Flowers-Deep Inside the Great Pyramids - A Case of Medullary Sponge Kidney in the Elderly

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Introduction: Medullary Sponge Kidney (MSK) is a congenital malformation characterized by dilatation of the collecting ducts of Bellini associated with defective urine acidification and concentration. MSK typically affects papillae in both kidneys. The usual clinical manifestations of hematuria, urinary tract infection and nephrolithiasis are delayed and emerge over a wide age range. 20% of patients with urolithiasis have MSK.

Case Description: 68 years old female admitted with worsening left thigh pain and left lower quadrant abdominal pain of 2 days duration. Past medical history significant for chronic UTIs and kidney stones for 10 years. Labs showed Cr of 1.78 (baseline of 1.2), Urinalysis revealed positive esterase with pyuria. CT showed bilateral renal stones in the calyces without obstruction and small calcifications compared to previous imaging. Bouquets of flowers pattern on CT was characteristic of MSK.Blood and urine cultures grew E. Coli. Patient was treated with targeted antibiotics. Kidney stone analysis revealed calcium phosphate. Potassium citrate was initiated. Creatinine continued to be above her baseline, however urine output remained normal. Despite all efforts, patient continued to have recurrent UTIs. On follow up visits patient reported less episodes of passing stones.

Discussion: MSK is usually asymptomatic. The diagnosis is commonly made as an incidental finding during an imaging test performed for a different indication. Although considered benign, the associated complications of medullary sponge kidney (nephrolithiasis and urinary tract infections) may rarely lead to chronic kidney disease and even renal failure. To identify patients at greatest risk for complications, a grading system based on the number of affected calyxes has been proposed. Our patient was grade 4 on this scale making her most susceptible to complications. CT pattern of MSK developed late in this index case which is uncommon and is described in only 10% of affected subjects. Our case illustrates few reported serious complications of advanced CKD in the setting of late diagnosis of MSK which if diagnosed early may have been salvaged with preventive measures such as use of Potassium Citrate. The concept of prophylactic potassium citrates in MSK remains controversial and further studies are encouraged. MSK should be considered in the differential diagnoses of recurrent UTIs in elderly.

PUB510

Anti-GBM Disease in the Elderly Patient: A Case Report

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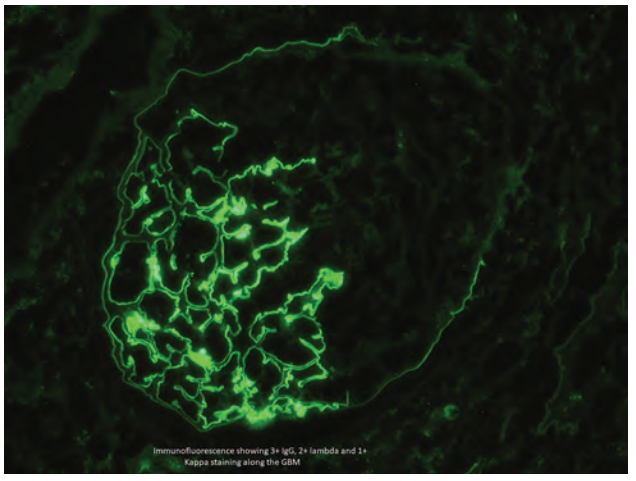
Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a known cause of rapidly progressive glomerulonephritis (RPGN) occurring in the third and seventh decade of life. As life expectancies continue to improve, there may be more cases of RPGN in the elderly. More robust data is needed to guide management in this population.

Case Description: An 81-year-old Caucasian female with history of hypertension and remote tobacco use presented with a two-week history of anorexia, malaise and cough. Home medications included daily atenolol 50 mg, hydrochlorothiazide 12.5mg, amlodipine 5mg and naproxen. Pertinent labs included creatinine 7.7mg/dl, 24-hour urine protein 850mg, urine negative for red or white blood cells, GBM antibody 1.9 AI, and anti-neutrophil cytoplasmic antibody (ANCA) positive with C-ANCA 1:40. She was started on hemodialysis for uremic symptoms and had a renal biopsy done. The biopsy was significant for predominantly acute focal necrotizing and diffuse crescentic glomerulonephritis, crescents in 50% of glomeruli, and minimal tubular changes, consistent with anti-GBM nephritis. She received a two-week course of plasmapheresis, pulse steroids and oral cyclophosphamide. Cyclophosphamide was discontinued after two and a half months due to agranulocytopenia and transient fever but she remains on prednisone taper. Anti-GBM and ANCA became negative after the initial two weeks of treatment with mild improvement of pre-dialysis creatinine but she remains dialysis dependent.

Discussion: Anti-GBM disease in the elderly patient offers a unique challenge due to limited data in this population. Dual-positivity of anti-GBM and ANCA are more likely to occur in the elderly population. Furthermore, elderly patients may be more susceptible to the adverse effects of treatment and this together with comorbidities may limit the duration and intensity of therapy. There is a need for further research to better serve the needs of elderly patients with anti-GBM disease.



PUB511

Metformin Associated Lactic Acidosis (MALA), In Elderly; Are The Prescribing Restrictions Adequate?

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Introduction: Metformin associated Lactic acidosis (MALA), is rare but it has been associated with 40% mortality risk. It is usually related to elevated Metformin levels with overdose. Sustained release(SR) formulation theoretically has a lower risk of MALA, with lower plasma Metformin and lactate levels due to reduced systemic absorption. Our patient developed significant metabolic acidosis and elevated lactate with appropriate use of the drug per current FDA regulations.

Case Description: 78 year old male with a history of diabetes mellitus for >40yrs (on Metformin for 10yrs), heart failure with ejection fraction of 25% and chronic kidney disease with a creatinine of 1.1mg/dl and GFR 45-50ml/min, was admitted to the intensive care with generalized weakness and fall, hyperkalemia, high anion gap metabolic acidosis with elevated lactic acid. He had three admissions in the past three months with reversible serum creatinine (SCr) elevations secondary to CHF exacerbation, GI bleed and pre-renal state with low intake. Exam revealed frail elderly male with stable vitals. Labs showed increase in SCr to 1.7 mg/dl, bicarbonate 10 mmol/L, K 5.7 mmol/L, Anion gap 29mmol/L, sodium 142mmol/L Lactate level was high at 20mmol/L. No other sign of tissue hypo-perfusion and CT abdomen was negative for bowel ischemia. He had emergent hemodialysis for 4 hrs followed by high dose CVVHDF for 48 hrs for presumptive diagnosis of MALA, with improvement in bicarbonate and lactate level. Despite improvement in lab parameters, he developed progressive cardiogenic shock requiring iontropic support, and elected for comfort care. Subsequently, his Metformin level came back supra-therapeutic at 3.8mcg/ml.

Discussion: Recent updates on Metformin safety in CKD has expanded its use in low eGFR patients. Estimated GFR alone, however, may not capture the full risk especially in geriatric population with multiple co-morbidities. Sustained release Metformin compared to immediate release Metfomin, has similar glycemic control, but it is associated with lower systemic levels and thus lower lactate levels. Risk increases, in the presence of other factors like acute kidney injury, heart failure and old age, hence more care and vigilance is needed while prescribing Metformin to this population with multiple co-morbidities.

PUB512

No "Sugar-Coating": A Unique Case of Hyperinsulinemic Hypoglycemia with Renal Cell Carcinoma

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Introduction: Hypoglycemia, as a manifestation of Renal Cell Carcinoma (RCC) is a rare event. Classically described as a paraneoplastic syndrome of non-islet cell tumor hypoglycemia, these patients have suppressed levels of glucose, insulin, proinsulin, C-peptide levels. Characteristically, they have elevated levels of insulin like growth factor (IGF)-2 and suppressed levels of IGF-1. We present a unique case of hypoglycemia from a paraneoplastic, non-islet cell insulin-producing RCC.

Case Description: A 92-year-old Hispanic woman with Chronic Kidney Disease IIIb, presented with recurrent episodes of altered mental status, found to have severe hypoglycemia, with a blood glucose of 37mg/dL on presentation. Her mentation improved with dextrose infusion and work-up for recurrent hypoglycemia was pursued. She denied history of diabetes and testing for inadvertent use of sulfonylureas or insulin was negative. Biochemical workup showed elevated levels of C-Peptide and insulin that was confirmed with repeat readings. In addition, IGF-1, IGF-2 and insulin Antibody were noted to be very low (Table 1). With the working diagnosis of hyperinsulinemic hypoglycemia, MRI abdomen was performed, showing normal pancreas anatomy, with an incidental finding of a 43x44x41mm heterogeneous enhancing right renal mass. Repeat CT abdomen with contrast confirmed the right renal mass with central necrosis and washout, consistent with radiologic features of renal cell carcinoma. Urology was consulted for surgical management, but given the patient's age and medical co-morbidities, nephrectomy was deferred. She was considered for ablation vs excision of the mass, however, her hypoglycemia responded to frequent oral intake, therefore these too were held off in the favor of conservative management.

Discussion: Hypoglycemia can be the initial presenting symptom in patients with renal cell carcinoma. This requires a thorough work-up to rule out other endocrine and medication related etiologies. While resection of the tumor generally resolves the hypoglycemia, the importance of identifying the underlying mechanism is crucial to provide adequate treatment of hypoglycemia in the acute setting while awaiting surgery or in non-surgical candidates like ours.

Table 1

	Insulin (uIU/mL)	C-Peptide (ng/mL)	Pro-insulin (pMol/L)	Insulin Antibody (units/mL)	IGF-1 (ng/dL)	IGF-II (ng/dL)	Growth Hormone (ng/mL)
Patient's labs	58.2	28.38	106	<5	65	147	1.2
Normal range	3-19	0.48-5.15	0-10	<5	50-350	333-967	0.8

PUB513

ANCA Vasculitis Masquerading as FSGS?

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Introduction: We present the case of a 71 yr old man with renal-limited ANCA-associated vasculitis (AAV) with initial presentation of focal segmental glomerulosclerosis (FSGS) on renal biopsy.

Case Description: A 71 yr old non- diabetic white male was referred to renal clinic for evaluation of chronic kidney disease. On initial evaluation his serum Cr (SCr) was 2.2 mg/dl and he had chronic hematuria. Baseline SCr was 0.9-1 mg/dl. He denied NSAID use and had a 40 pack year smoking history. Spot urine albumin/Cr was 169 mg/g. Screens for HIV, Hepatitis B and C were negative. Serum and urine protein electrophoresis showed no para-proteins. C3, C4, ANA and dsDNA were normal. Renal biopsy was reported as Focal Segmental Glomerulosclerosis (FSGS), with some glomeruli showing increased mesangial matrix and 2 of 7 glomeruli being globally sclerosed. Focal mononuclear interstitial inflammation and mild tubulo-interstitial fibrosis were also noted. Patchy foot process effacement was seen on EM. 6 months later, SCr progressively rose to a peak of 5.7 mg/dl and urine alb/Cr increased to 973 mg/g. As the rapid loss of GFR did not correlate with the pathological findings of secondary FSGS, further serologic testing was performed revealing P-ANCA titer of 1:160 and MPO level of 30 AI. Cryoglobulins and anti-GBM were negative. He received IV steroids and underwent renal biopsy. Pathology confirmed pauci-immune glomerulonephritis with crescents in 2 glomeruli, endocapillary hypercellularity, more than 50% IFTA, and interstitial inflammation. He was treated with 4 weekly doses of Rituximab along with steroid taper. SCr eventually improved to 3.7 mg/dl.

Discussion: AAV often presents as a smoldering disease process. We believe that our patient had renal vasculitis masquerading as FSGS at the time of the first renal biopsy. It is possible that glomerular scarring and interstitial fibrosis observed then represented the healing process of active glomerular lesions. Persistent hematuria and the presence of a mononuclear interstitial infiltrate offered support for our theory. Interstitial nephritis has been previously reported to be an atypical histologic presentation of AAV. FSGS is an unlikely and under-reported presentation of AAV. Because AAV may have a relapsing/remitting course, it is possible that FSGS may be seen on pathology rather than typical findings of AAV.

PUB514

Polyclonal Crescentic Fibrillary GN Presenting with Macroscopic Hematuria

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Introduction: A 56 year old female presented with gross hematuria, symptomatic anemia and a serum creatinine of 6 mg/dl. She had a baseline serum creatinine of 2.0 mg/dl and was known to have microscopic hematuria and proteinuria but had never undergone a kidney biopsy. Her biopsy subsequently showed end-stage crescentic fibrillary glomerulonephritis. Given the chronicity of her disease, she was deemed unsuitable for immunosuppression and began work-up for renal replacement therapy. This case illustrates the importance of early diagnosis of glomerulonephritis in patients with chronic kidney disease and an active urinary sediment.

Case Description: A 56 year old obese Caucasian female with poorly controlled diabetes mellitus presented with gross hematuria and a serum creatinine of 6 mg/dl. She had a baseline serum creatinine of 2 mg/dl and had suffered from recurrent episodes of gross hematuria for many years. A urology work-up was negative. She had been given a presumptive diagnosis of IgA nephropathy. A serological work-up was completely negative. Urine protein:creatinine ratio was 8.76 g/g with a urine microalbumin:creatinine ratio of 4274 mg/g. A renal biopsy was performed showing end-stage crescentic GN with 15% cellular and fibrocellular crescents, 15% global glomerulosclerosis and 70% IFTA. IF was negative for IgA but positive for IgG, C3, kappa and lambda. Fibrillary glomerulonephritis was confirmed on electron microscopy. Given the equal kappa and lambda staining, investigations for monoclonal disease were not pursued. Similarly immunosuppression was not commenced given the chronicity of the patient's biopsy findings and clinical renal disease. She was prepared for progression to end-stage kidney disease and renal replacement therapy.

Discussion: This case illustrates the importance of early biopsy-based diagnosis for patients with progressive renal impairment and an active urinary sediment. It also highlights the differences in approach to patients with polyclonal fibrillary glomerulonephritis, compared to those with monoclonal glomerulonephritis for which a work-up for a clonal cell disorder should be pursued. The decision to commence immunosuppression for polyclonal fibrillary glomerulonephritis depends on disease duration as patients with advanced CKD have a poor renal prognosis and do not experience significant benefit from pursuing immunosuppressive therapy.

PUB515

Hydralazine Induced Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Acute Tubulointerstitial Nephritis: A Rare Constellation

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Introduction: Hydralazine is an adjunctive antihypertensive medication that is associated with antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis. Kidney involvement usually comprises a pauci-immune, necrotizing glomerulonephritis with crescents.

Case Description: A 74-year-old Caucasian male on hydralazine, with a history of hypertension, presented with the acute onset of malaise and hematuria. On examination, lower extremity edema was noted. He remained hemodynamically stable. Lab work showed pancytopenia and elevation of serum creatinine (4mg/dl; normal range 0.6-1.1 mg/dl). Urinalysis showed proteinuria, dysmorphic red blood cells, and no red cell casts. Serology showed myeloperoxidase (MPO) positive high ANCA titers; positive anti-histone antibodies, positive cryoglobulins, and negative antinuclear antibodies. Renal biopsy revealed acute tubulo-interstitial nephritis (ATIN). Light microscopy examination revealed no segmental sclerosis, crescents, or areas of necrosis. Infectious work up, hepatitis B & C panel, was negative. Bone marrow biopsy was normal. Even though, he received a pulse dose of steroids and induction therapy with rituximab (375 mg/m2 IV q weekly doses) followed by oral prednisone 60mg daily, his hospital course got further complicated with hemoptysis. Subsequent lab work up revealed markedly elevated serum creatinine (5. 58 mg/dl), and persistent pancytopenia. CT scan of the chest revealed patchy areas of reticulation with ground glass opacities. Bronchoscopy exam revealed the presence of diffuse alveolar hemorrhage. He was started on renal replacement therapy for worsening kidney function. With two months of follow up, he remains on hemodialysis and on maintenance oral prednisone therapy.

Discussion: Hydralazine-induced ANCA vasculitis is a rare occurrence with pulmonary renal syndrome being the most severe presentation. Renal involvement is characterized by focal segmental crescentic and/or necrotizing glomerulonephritis. Mononuclear tubulointerstitial infiltrates have been noted in literature but these have usually been described in conjunction with glomerulitis which was not seen in this case. We report a case of hydralazine induced ANCA vasculitis with ATIN which is rare in the literature.

PUB516

A Rare Case of Pyoderma Gangrenosum Masking Underlying Henoch-Schonlein Purpura

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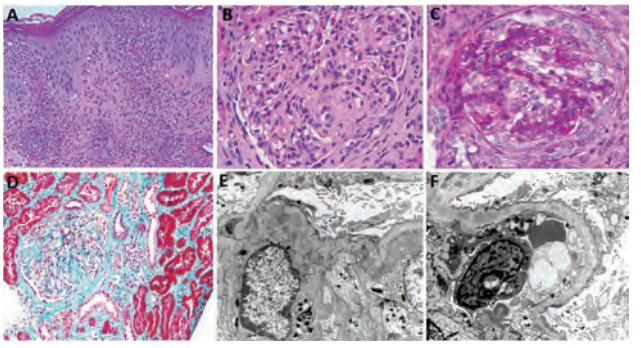
Introduction: Henoch-Schonlein Purpura (HSP) is commonly diagnosed in childhood, however, it can occur in adults where the chances of renal involvement more than double. Here we introduce a unique case where an adult patient with Pyoderma Gangrenosum (PG) underwent further workup and was found to have uderlying HSP.

Case Description: A 21 year old, African American woman with history of hypothyroidism, idopathic heart failure, and recently diagnosed PG rash was admitted for heart failure exacerbation and nausea. Nephrology was consulted on admission for persistent hematuria, proteinuria, and AKI. Upon questioning, she had noticed pink to tea-colored urine and a lower extremity rash. Urinalysis showed protein (100mg/dl) and large blood. She underwent kidney biopsy for persistent, unexplained hematuria which showed focal proliferative and sclerosing glomerular changes with IgA deposits on immunoflourescence study, indicative of HSP. Skin biopsy of her rash showed leukocytoclastic vasculitis, seen in PG. She was treated with mycophenolate and steroids.

Discussion: When PG is diagnosed, 50% of patients have an underlying systemic disease. In this case, PG was diagnosed and clinical symptoms later on are what prompted a workup ultimately diagnosing HSP. Even though HSP is most commonly seen in children, when it occurs in adults renal dysfunction is more common, and consequently, this increases mortality. It is imperative that nephrologists and practicing hospitalists alike are able to keep a wide differential when they see nonspecific findings such as PG. Systemic vasculitides, such as HSP, should be kept in mind if patient's present with symptoms involving multiple organ systems in addition to the characteristic PG rash.



A. Skin biopsy with leukocytoclastic vasculitisB: HE stain showing increased mesangial matrix, cellularity in glomerulus

C: PAS stain suggestive of early crescent

D: Gomori Trichome stain showing global and segmental sclerosis

E&F: Electron microscopy consistent with proliferative immune mediated glomerulonephritis

PUB517

A Cool Case of Cryo

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Introduction: Cryoglobulinemia is a rare but serious cause of vasculitis. Complement activation and inflammation can cause AKI with GN, rash, or alveolar hemorrhage. This case illustrates the recognition and treatment of systemic cryoglobulinemia vasculitis.

Case Description: A 66 year-old woman with history of DLBCL in remission presented with four weeks of lower extremity rash, abdominal pain, anemia, thrombocytopenia and AKI. Exam included palpable purpura over lower extremities, and abdominal tenderness. She was in no distress with unremarkable cardiopulmonary exam and normal vitals. Creatinine was 3.6 (baseline Cr 0.8), Hemoglobin 8.9, and platelets 129,000. UA was active: 6-10 WBCs, 1-3 RBCs, granular casts and mild proteinuria. Infectious workup with cultures, HIV, HVB, and HVC screens were negative. Peripheral smear did not support TTP or HUS. Evaluation with ANA, ANCA, MPO/PR3, anti-GBM were negative. Low C3 and C4 suggested immune complex formation. Steroids were started and a kidney biopsy was performed. After developing hypoxia, a CXR and CT chest were concerning for pulmonary hemorrhage. Bronchoscopy was planned for further evaluation, but was postponed due to hemoptysis requiring intubation. DAH prompted urgent plasmapheresis and Rituximab. Cryocrit returned positive at 1.5%, raising concern for cryoglobulinemic vasculitis. Kidney biopsy confirmed cryoglobulin MPGN, supporting systemic cryoglobulinemic vasculitis, likely a type II crogolbulinemia with unclear etiology. She improved with further plasmapheresis, rituximab and steroids, allowing complete recovery.

Discussion: This case illustrates systemic cryoglobulinemia vasculitis. Cryoglobulin GN manifests as MPGN with characteristic double contoured GBM "tram-tracking" due to membrane disruption and regeneration. "Cryo" immunoglobulins precipitate at low temperatures depositing in small vessels and leading to vasculitis. Causes include HCV, hematologic malignacy, endocarditis or other infalmmatory states. Cryoglobulins are classified as Type I monoclonal Ig, Type II polyclonal IgG monoclonal IgM (rheumatoid factor), or Type III polyclonal IgG polyclonal IgM. Type II or III related to chronic HCV or HBV are most common. Treatment of the underlying condition is paramount. Life or organ threatening cases are treated with steroids, plasmapheresis, and either cyclophosphamide or rituximab. Debate between cyclophosphamide and rituximab exists, but rituximab may be safer and as effective.

PUB518

An Unusual Case of Podocytopathy with Acute Renal Failure and Proximal Tubulopathy

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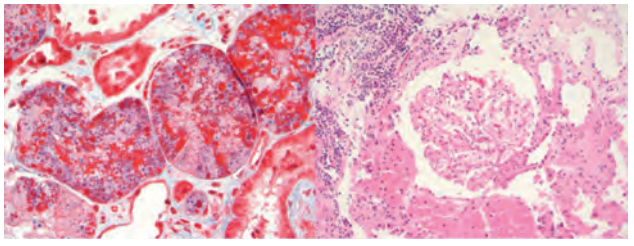
Introduction: Nephrotic syndrome (NS) in adults is most commonly secondary to diabetes, and when primary is predominantly focal segmental glomerulosclerosis. It is unusual for NS in adults to present with acute renal failure, but it has been reported in some cases of minimal change disease. The proposed cause is acute tubular necrosis (ATN) from proteinuria overwhelming proximal tubule reabsorption.

Case Description: 51 year old woman with history of stroke, hypertension, chronic kidney disease stage 3, intravenous drug use, and medical non-compliance presented for 1 day of flu-like illness. Flu testing was negative, and X-ray showed left lower lobe pneumonia. She also had acute kidney injury with creatinine 2.09 (baseline 1.2), oliguria, hematuria, and proteinuria (13.7g in 24 hours). She was diagnosed with ATN which did not respond to fluid, treatment of pneumonia, or later diuretic trial. Hematuria was mild and rapidly resolved, but proteinuria persisted. Renal biopsy showed proximal tubulopathy with accumulation of protein reabsorption droplets. This pattern of tubular injury is typically seen in light chain disease, but immunofluorescence showed no light chain disease. No light chain restriction was noted in our patient and serum protein electrophoresis and bone

marrow biopsy were unremarkable. Renal biopsy also showed 70% podocyte effacement without sclerosis. Hemoglobin A1c, ANA, ANCA, anti-GBM, hepatitis, HIV, and complement testing were normal. Underlying etiology of her NS remains unknown and she remains hemodialysis (HD) dependent.

Discussion: More than half of all NS in adults is secondary, and when presenting with renal failure it typically is transient. In our patient, an underlying cause is unknown and she remains anuric and HD dependent. Her tubulopathy is also unusual, as this degree of tubulopathy in NS is primarily reported in the pediatric population related to mitochondrial disorders and other rare genetic syndromes. Further attention to tubule injury in NS is needed to understand prognostic value and guide therapy.



Left: Proximal tubules with marked protein resorption droplets. Right: Benign light microscopy of glomerulus.

PUB519

Membranous Nephropathy Secondary to Systemic Sclerosis

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Introduction: Systemic sclerosis (SS) has rarely been described in literature as cause of membraneous nephropathy (MN). We hereby present a case of MN secondary to SS.

Case Description: 44 year old African American male with history of SS since2011 was referred to Nephrology clinic in 2016 for nephrotic syndrome and microscopic hematuria (spot urine protein creatinine ratio of 4, serum albumin of 2.9 g/dl, serum creatinine of 0.4 mg/dl and hyperlipidemia with anasarca). SS was manifested as interstitial lung disease, Raynaud's phenomenon, gastroesophageal reflux and hypertension. SS was initially treated with Penicillamine(from 2011 -2014) which was already stopped 2 years before presentation to our clinic. C3, C4, HIV, Hepatitis serology, dSDNA, SPEP, serum PLA2R were negative. Renal biopsy showed Membranous glomerulopathystage 3, with mesangial deposits, tubuloreticular inclusions within endothelial cells and 5-10% interstitial fibrosis. IgG subtype staining was nonspecific and capillary wall PLA2R staining was negative. Lisinopril was initiated butproteinuria continued to worsen, with maximum of 13 gram of urine protein per day in 24 hour urine collection, worsening skin thickening and interstitial lung disease. He was then started on mycophenolate mofetil 500 mg twice a day followed by marked improvement in nephrotic syndrome. As he was already off Penicillamine for 2 years before presentation and serology and other causes of secondary MN were ruled out, we postulate that his SSis the most likely cause of his nephrotic syndrome.

Discussion: Renal involvement is common in SSaffecting about 60-80% of patientswith scleroderma renal crisis being the most serious manifestation(5- 20% patients). 45-60% patients have mild proteinuria, elevated creatinine or hypertension and renal disease is generally not progressive. Most common reasons for impaired renal function are drug toxicity (D- Penicillamine, cyclosporine), prerenal causes (heart failure, pulmonary hypertension NSAIDs), and rarely glomerulonephritis (ANCA positive, secondary amyloidosis). The mean time to resolution of proteinuria after stopping d- penicillamine is 9-12 months and has been reported in some cases to be up to 2-3 years. MN secondary to SS has been reported as exceptionally rare with only few case reports in literature. We suggest including systemic sclerosis as a cause of secondary MN.

PUB520

Diffuse Alveolar Hemorrhage in a Systemic Lupus Erythematosus Patient Treated with Rituximab

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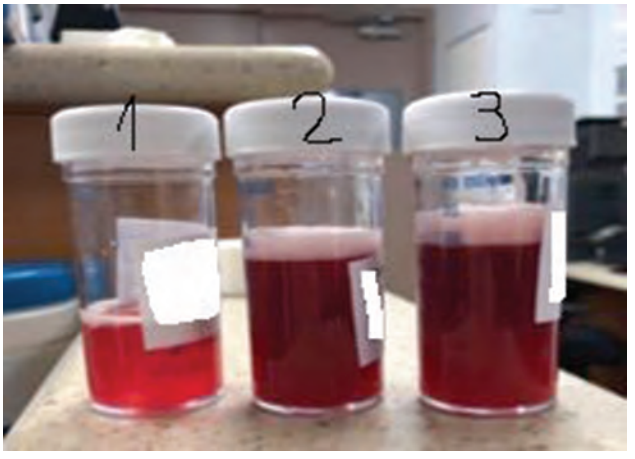
Introduction: Diffuse alveolar hemorrhage (DAH) is a life threatening complication of systemic lupus erythematosus (SLE), it is an atypical manifestation of SLE associated with high rate mortality. Conventional therapy (cyclophosphamide, high-dose corticosteroids and plasma exchange) is recommended as therapy for DAH associated with SLE. Efficacy of alternative therapy such as Rituximab has also been described

Case Description: 36 year old woman with SLE membranous nephropathy, presented with acute onset of shortness of breath (SOB) and respiratory distress in the setting of increasing edema, elevated brain natriuretic peptide (BNP) to 10,000 and chest X-ray with bilateral opacities. Patient required non-invasive ventilation and started Furosemide for presumed fluid overload. Labs were significant for acute kidney injury (AKI) creatinine (Cr) 3.46 mg/dL, microhematuria, proteinuria, low C3 55 mg/dL, anti-ds-DNA 20 IU/mL. Despite aggressive diuresis, patient progressed to acute hypoxemic respiratory failure with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and renal replacement therapy (RRT). She underwent bronchoscopy which showed DAH. The overall clinical picture of AKI and DAH were consistent with acute lupus flare. Conventional therapy was delayed due to concern for active infection. Patient received two doses of Rituximab and did not require long term RRT, with creatinine of 1.4mg/dL a month later

Discussion: DAH is a catastrophic manifestation of SLE with a high mortality rate and treatment should be initiated as soon as the diagnosis is being established. Our patient received two doses of Rituximab with subsequent long term resolution of DAH and improvement of renal function. In summary, this case highlights the importance of early treatment to prevent fatal outcomes in DAH and also suggests that Rituximab might be a valid alternative therapy for DAH with SLE



Bronchoscopy specimen indicates DAH

PUB521

Case Report: Renal Failure Due to IgA Vasculitis with Massive Ascites Accompanied by Small Intestine Inflammation

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Introduction: IgA vasculitis with massive ascites accompanied by small intestine inflammation is very rare.

Case Description: A 26-year-old man with end-stage kidney disease and hypertension presented with headache that had persisted for one year. His visual acuity had decreased over a period of one year, and he visited an ophthalmologist. Physical and laboratory findings at that time revealed hypertension (200/114 mmHg) and end-stage renal failure (serum creatinine 8.06 mg/dL, urinary protein 4+, urinary occult blood 2+). He was admitted on an emergency basis and started on antihypertensive treatment. Anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibodies were negative. Serum complement (C3, C4) values and chest radiography findings were normal. A renal biopsy revealed that half of his glomeruli had global sclerosis. Crescents with endocapillary hypercellularity were found in most glomeruli and fibrilloid necrosis was evident in small arteries. Fluorescent antibody tests were impossible because of the sclerotic glomeruli. We diagnosed vasculitis of unknown cause and started him on treatment with methylprednisolone 500 mg/day for 3 days, followed by oral prednisolone 40 mg/day during seven days of hospitalization. Four days later, the patient complained of severe abdominal pain and abdominal CT revealed remarkable ascites retention and thickening of the small intestinal wall. Therefore, inflammation of the small intestine was diagnosed. Temporary ICU management was implemented and hemodialysis was started because his renal function had not improved. Steroid therapy improved the small intestinal inflammation, but he still needed maintenance dialysis. Renal biopsy specimens were reevaluated, and immunostained paraffin sections revealed IgA, C3-positive staining in the mesangial region, confirming a diagnosis of IgA vasculitis.

Discussion: Teaching Points: This patient had renal failure of unknown etiology complicated by small intestinal inflammation. To conclude a diagnosis was challenging, but IgA vasculitis was finally diagnosed by reassessment of a renal biopsy. Reviews of renal biopsies can be critically important to conclude a concrete diagnosis.

PUB522

An Unusual Case of Interstitial Nephritis in HIV/AIDS

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Introduction: Acute kidney injury (AKI) is a common occurrence in HIV-infected patients with most common etiologies including volume depletion, medication toxicity and acute tubular necrosis. We here describe an interesting case of granulomatous interstitial nephritis (GIN) in HIV/AIDS patient with disseminated mycobacterium avium complex (DMAC) infection.

Case Description: A 35-year-old female with history of HIV/AIDS (CD4 count of 14), DMAC infection (with recurrent positive blood cultures) and CMV retinitis presented for intravenous (IV) Foscarnet therapy. Her baseline creatinine was 1.3-1.4 mg/dL which increased to 3.0mg/dL on admission. Creatinine did not improve beyond 2.7mg/dl after 2 days of IV fluids. Urine studies showed trace leucocyte esterase. Spot urine revealed protein: creatinine ratio of 1.3g/g with microalbumin of 92mg, consistent with tubular

proteinuria. Hepatitis B surface antigen was positive with other serologies being negative. Renal ultrasound showed bilaterally increased renal echogenicity. Renal biopsy done on day 4 showed: interstitial, non-necrotizing granulomatous inflammation; moderate interstitial fibrosis/tubular atrophy, 1/20 glomeruli were sclerotic, non-sclerotic glomeruli were normal on light microscopy, and podocyte foot processes were effaced focally on electron microscopy. Given the patient had MAC bacteremia and MAC associated necrotizing mesenteric lymphadenopathy with chylous ascites, these granulomas most likely were induced by MAC infection. She completed 21 days of IV Foscarnet treatment. Her creatinine on discharge was 2.1mg/dL. We did not treat her with steroids, since benefit:risk ratio was not in favor of treatment. She was continued on MAC treatment with azithromycin 600 mg daily and dose adjusted ethambutol.

Discussion: GIN is an uncommon histological finding, representing ~0.5-1.37 % of native kidney biopsies. Most common etiology of this in developing nations is tuberculosis and fungal infections, however this may be easily overlooked as a cause of AKI in developed nations. GIN can be insidious and may go undetected for several years. Recognition and treatment of underlying cause can lead to improvement in some cases and renal biopsy is key to diagnose and to determine prognosis. Our case represents a complex case with various possible etiologies of AKI. In such a scenario a renal biopsy is imperative to help establish diagnosis and guide therapy.

PUB523

Renal Limited ANCA Vasculitis Can Be a Late Presentation in Patient with Rheumatoid Arthritis and Interstitial Lung Disease

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Introduction: Renal limited mpo anca vasculitis has been rarely reported in patients with Rheumatoid Arthritis Here we present a case of a patient with not only Rheumatoid arthritis but also interstitial lung disease who developed renal limited mpo anca vasculitis glomerulonephritis Renal limited anca vasculitis carries significant morbidity, mortality if not diagnosed and treated promptly

Case Description: 60 year old white man a retired rescue firefighter at world trade center on 911 presented to ER with nausea, lack of appetite, heart burn, weight loss for a month His past history is significant for interstitial lung disease for many years and a diagnosis of Rheumatoid arthritis two years ago Patient was noted with low level anca by his rheumatologist for past year but was thought as bystander Renal sonogram was unremarkable and chest radiograph noted bilateral reticular markings from interstitial lung disease His lab studies reveal a blood urea nitrogen of 119mg/dl, serum creatinine 9.3mg/dl, urinanlysis with rbc casts, normal complement levels, negative hepatitis serology and antiglomerular basement membrane antibody MPO anca later came back high at 50.9u He was immediately started on pulse steroids a kidney biopsy revealed pauci immune crescentic glomerulonephritis. He was diagnosed with MPO Anca vasculitis glomerulonephritis and started on rituximab along with steroids. His symptoms improved, creatinine levels declined and patient went home on prednisine taper and maintenance rituximab infusion. His creatinine declined to 3.5mg/dl over next two months from a high of 9.3mg/dl

Discussion: Renal limited MPO-Anca vasculitis is uncommonly found with other immune mediated entities and creates diagnostic challenges. It can present in patients with rheumatoid arthritis who have disease for years with systemic symptoms Low level anca can also be present in patients with interstitial lung disease In this case patient had no systemic symptoms, had low anca titers noted for a year Anca titers and renal function should thus be closely monitored especially in patients with rheumatoid arthritis, interstitial lung disease without systemic symptoms as overlap can easily be overlooked and or mistaken with serious consequences Understanding of entities can help with early diagnosis, intervention and to avoid catastrophic outcomes as renal dysfunction and need for long term dialysis

PUB524

Cryoglobinemic Glomerulonephritis Post Streptococcal Pharyngitis

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Introduction: The most common inciting event of a post infectious glomerulonephritis (PIGN), from a historical standpoint and in developing countries, is streptococcal infection. Typically, PIGN presents as dominant C3 staining with frequent occurrence of subepithelial humps as well as subendothelial deposits. Diverse histological presentations of PIGN are being increasingly reported. We present a case of cryoglobinemic glomerulonephritis post streptococcal infection

Case Description: A 58 year old female, with a history of type 2 diabetes, presented with sore throat, fever and dysphagia for 2 days. She rapidly developed upper airway edema, and necessitated intubation. Subsequent nasopharyngeal cultures revealed presence of Streptococcus pyogenes and treated with Penicillin G. However, 2 weeks post admission, renal function was noted to be deranged with creatinine of 2.2 mg/dL (baseline 1.3 mg/dL), with presence of 3+ proteinuria (quantified to be 3g/g as per spot protein:creatinine ratio) and 33 RBCs/hpf on urinalysis. The creatinine increased by 1mg/dL each day (with peak at 6.2 mg/dL)-warranting initiation of methylprednisone, due to concerns of rapidly progressive glomerulonephritis. ANA, ANCA, anti-GBM, Hepatitis B/C and HIV were negative with elevated ASO titers (1057 IU/mL) and low C3 (33 mg/dL) and C4 levels (3 mg/dL). Subsequent renal biopsy revealed segmental endocapillary proliferation and occasional endocapillary leukocytes with segmental wire loop-type deposits on light microscopy. Immunoflurescence showed sparse granular peripheral mesangial staining for IgA, IgM, kappa and lambda light chains, C3 and C1q with casts stained 4+ for IgA, IgM, kappa and lambda light chains and protein resorption droplets stain 4+ for albumin. Electron microscopy showed subendothelial and mesangial electron dense deposit with no subepithelial deposits. Within 3 days of initiation of steroids, renal function showed evidence of rapid improvement.

Discussion: This case highlights that, albeit the history and clinical findings most likely point to a classic PIGN- the disease can have varied histologic presentations. Findings indicative of cryoglobinemic GN have been rarely reported and is a sequela to consider, especially in light of decreased C4 out of proportion to decrease in C3 levels and findings based on histology- making it imperative to pursue a renal biopsy if features akin to the aforementioned arise.

PUB525

A Bloody Cough and the Smoking Gun

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Introduction: Goodpasture's Syndrome (GPS) is a rare autoimmune disease due to formation of antibodies targeting the glomerular basement membrane (GBM) in the lungs and kidneys. It is characterized by the presence of anti-GBM antibodies, life-threatening pulmonary hemorrhage and crescentic glomerulonephritis. Treatment of GPS should be initiated as soon as possible with a combination of steroids, plasmapheresis and cytotoxic agents.

Case Description: A 22-year-old breast-feeding female smoker presented to our facility with acute renal failure. She had been seen at an outside facility due to nausea, vomiting, shortness of breath and leg swelling. Preliminary evaluation revealed acute kidney injury. Laboratory data was positive for anti-GBM antibodies and a renal biopsy showed crescentic glomerulonephritis- however she absconded from medical care. She re-presented with worsening dyspnea at rest and oliguria. New laboratory data was notable for a serum creatinine of 10 mg/dL and elevated anti-GBM titers. She was initiated on daily plasma exchange, pulsed intravenous steroids, and rituximab with subsequent negative anti-GBM titers. However despite therapy, she developed hemoptysis and hypoxia necessitating ICU care. We thereafter started her on oral cyclophosphamide and re-instituted plasma exchange and pulsed steroid therapy which lead to the cessation of hemoptysis. Her kidney function did not improve and she remained dialysis dependent at discharge from our care. We discovered, she had returned to smoking cigarettes while hospitalized after we carefully re-interviewed her.

Discussion: Goodpasture's Syndrome has a low incidence with rates <1 per million. Lung involvement is more common in patients who are cigarette smokers and is theorized to be precipitated by denudation of the lung basement membrane. Inhaled smoke is thought to damage capillary endothelium allowing anti-GBM antibodies to reach alveolar basement membranes. The importance of smoking cessation is crucial to prevent life threatening alveolar bleeding and early institution of aggressive immune suppression will dramatically improve prognosis. There are no studies defining the appropriate therapy for GPS in women who are breast feeding due to its relative rarity- especially the appropriate dose of cyclophosphamide in this population. Given limited therapeutic options, it is imperative to develop a safe dosing regimen for cyclophosphamide in this population.

PUB526

Not an UTI! ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis

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Introduction: Pauci-immune crescentic glomerulonephritis, so called due to lack of glomerular immunoglobulin deposition. Is one of the most common causes of rapidly progressive glomerulonephritis (RPGN). Approximately 90% of patients, pauci-immune crescentic glomerulonephritis is associated with ANCA, however 10% of patients with pauci-immune crescentic glomerulonephritis ANCAs are absent. Patients with ANCA-negative, pauci-immune RPGN are considered part of this spectrum, and may have similar clinical features, renal biopsy findings, and prognosis.

Case Description: A 21 year old Puerto-Rican female presents to emergency department complaining of fever. She was previously treated for a urinary tract infection with various antibiotics including sulfamethazole/timethroprim without resolution. Nephrology consultation was requested upon admission due to increased serum creatinine, associated with hematuria and proteinuria. Review of system was only positive for subjective fevers and general malaise. Exam and vital signs were unremarkable. Admission laboratories were remarkable for elevated WBC 12.30x10^3/uL, elevated ESR >140mm/hr, mild anemia with hemoglobin 11.1g/dL. Serum chemistries were remarkable for serum creatinin of 1.87mg/dL, low albumin 2.10g/dL. Analysis of urine revealed RBC 10-12/HPF, granular cast and urine PCR 6212mg/g and ACR 1723 mg/g. Serological workup including hepatitis panel, HIV, ANA, p-and c-ANCA, rheumatoid factor, complement levels were all normal. Given these finding kidney biopsy was performed, showing crescentic glomerulonephritis, involving 90% of viable glomeruli, with no immune deposits. Patient was treated with pulse steroids followed by rituximab 1gm once every 2 weeks for 2 doses and achived remision with improvement in serum creatinine to 1.1mg/dL, PCR 709mg/g and ACR 542 mg/g.

Discussion: We report a case of ANCA-negative vasculitis with cresentic glomerulonephritis, a relatively rare clinical entity that is only present in about 10% of pauci-immune vasculitis. Most patients present with non specific constitutional symptoms of fever and arthalgias. Treatment of this entity is derived from ANCA vasculitis, including non-specific cytotoxic agents. Crescentic glomerulonephritis must be diagnosed promptly so that appropriate treatment can be initiated given the high mortality risk. A better understanding of the pathophysiology is needed.

PUB527

What's the Renal Reason for the Seizin'?

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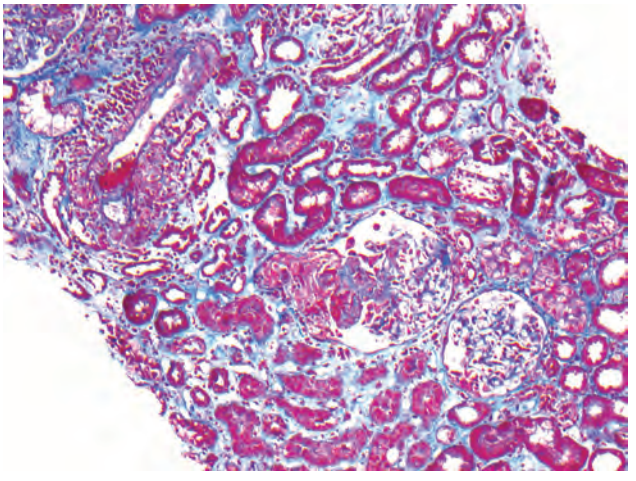
Introduction: ANCA disease is a well-appreciated cause of rapidly progressive glomerulonephritis (RPGN). It can also affect the nervous system, most commonly in the form of peripheral neuropathy, while central nervous system manifestations, including seizures, are exceedingly rare. We describe a case of new seizure in a previously healthy woman whose work-up led to a diagnosis of ANCA-associated RPGN prior to laboratory evidence of renal impairment.

Case Description: A 65 year old woman with hypothyroidism presented with generalized tonic-clonic seizure and was discharged on leviteracetam after an unremarkable brain MRI. One week later, she began to experience fevers prompting re-admission. Lumbar puncture was performed with unrevealing cerebrospinal fluid evaluation. Comprehensive vasculitis work-up including ANCA panel returned with a proteinase-3 titer of 123 u/mL (normally < 21 u/mL) in the setting of normal renal function (creatinine 0.76 mg/dL). Urinalysis revealed numerous dysmorphic red blood cells. Kidney biopsy showed a necrotizing glomerulonephritis with 40% crescents and red blood cell casts. She received intravenous high dose steroids and cyclophosphamide. Although the CNS manifestations of her ANCA vasculitis resolved, her creatinine at clinic follow-up increased to 2.77 mg/dL. She was then re-admitted for plasma exchange followed by a second dose of cyclophosphamide with improvement in creatinine to 1.8 mg/dL.

Discussion: Vasculitis should be included in the differential diagnosis of new onset seizures, especially when brain imaging is nonspecific. Importantly, lack of consideration of ANCA vasculitis as a potential cause of this patient's seizure, coupled with normal renal function at time of presentation, delayed the diagnosis and therapy of her renal disease. Recognition that CNS manifestations of ANCA vasculitis may clue to potential renal involvement prior to a rise in creatinine could have prompted earlier biopsy and treatment, potentially attenuating her renal injury.



PUB528

Case Report: Paraneoplastic FSGS Associated with Acute Lymphocytic Leukemia

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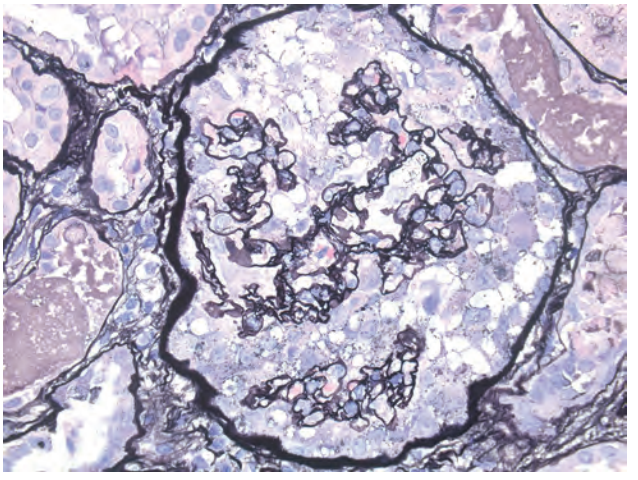
Introduction: Paraneoplastic focal segmental glomerulosclerosis (FSGS) is rarely described in the literature. We report a patient who presented with nephrotic syndrome (NS) and FSGS on kidney biopsy during his initial presentation and recurrence of acute lymphocytic leukemia (ALL).

Case Description: An 11-year-old African American boy presented with NS (urine protein to creatinine ratio (UPCR) 9.7 g/g, serum albumin 2.1 g/dL) and normal renal function. He did not respond to empiric oral prednisone. Kidney biopsy revealed FSGS lesions and widespread podocyte foot process effacement. 6 months later, he developed leukopenia and was diagnosed with ALL. He was treated with Children's Oncology Group Protocol AALL0232 (cytarabine, vincristine, daunorubicin, dexamethasone, methotrexate, pegaspargase, cyclophosphamide, mercaptopurine, doxorubicin, thioguanine) and achieved complete remission of NS and ALL. At age 22, he developed NS again (UPCR 29.7 g/g) and acute kidney injury (serum creatinine(SCr) 14.7mg/dL) requiring hemodialysis (HD). Kidney biopsy showed collapsing FSGS lesions (Figure 1) and extensive podocyte foot process effacement. He also had leukopenia and was diagnosed with recurrent ALL (92% blast cells). He was treated with R-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) and intrathecal Methotrexate and Cytarabine. He was off HD within 9 days and at 7 months after kidney biopsy, SCr was 1.5 mg/dL and UPCR 7.6 g/g. He achieved complete remission of ALL after 3 weeks of chemotherapy and is on maintenance chemotherapy with 6-mercaptopurine, vincristine, methotrexate, and prednisone.

Discussion: We present a rare patient with NS and FSGS coincident with a diagnosis of ALL which occurred again on disease relapse. His kidney disease improved with chemotherapy in both instances.



Glomerulus demonstrating collapsing lesion, with collapsed capillary tuft and epithelial hypertrophy and hyperplasia (Jones silver stain, 400x)

PUB529

Decrypting the Dilemma of the Double Agent: Treating Pulmonary-Renal Syndrome Due to ANCA Vasculitis and Lupus

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Introduction: Anti-neutrophil cytoplasmic antibodies (ANCA) are a group of autoantibodies directed to cytoplasmic constituents of neutrophils and monocytes. Cytoplasmic ANCA is strongly associated with Granulomatosis with Polyangiitis (GPA) while perinuclear ANCA (p-ANCA) is strongly associated with Microscopic Polyangiitis and Renal-limited vasculitis. ANCA-associated vasculitides (AAV) present with pauci-immune rapidly progressive glomerulonephritis (RPGN). Very uncommonly, p-ANCA can be found co existing with other chronic inflammatory diseases, one of which is systemic lupus erythematosus (SLE). This presents a diagnostic and therapeutic dilemma.

Case Description: A 36 year-old Caucasian female presented to our institution with painless, gross hematuria. Laboratory data revealed a hematocrit of 25.2, D-dimer 17.1, platelets 186,000 and an elevated creatinine of 2.65. Her urinalysis showed numerous dysmorphic red blood cells and cellular casts. Her antinuclear antibody (ANA) was positive at a titer of 1:160 and elevated ANCA titers. She was started on pulse steroids and Mycophenolate Mofetil while awaiting for the results of a kidney biopsy. The biopsy report revealed diffuse, segmental proliferative and membranous lupus nephritis (type V) with moderate interstitial fibrosis (35%). She, however, suffered further deterioration in her kidney function which required the initiation of renal replacement therapy. In spite of immune suppression, she developed hemoptysis and then respiratory failure, chest tomographic imaging revealed patchy areas suspicious for pulmonary hemorrhage and bronchoscopy confirmed diffuse alveolar hemorrhage. Plasma exchange therapy was initiated concurrently with another course of pulsed steroids and cyclophosphamide. The patient responded well to therapy with subsequent recovery of kidney function.

Discussion: It is unclear whether patients that have lupus nephritis and positive ANCA antibodies have separate disease entities or whether it is a spectrum of an overlap syndrome. A high index of suspicion must exist for an overlap syndrome, especially if pulmonary symptoms occur in a "lupus syndrome", as the disease can be fulminant and life threatening without early diagnosis and aggressive plasma exchange and immune suppression therapy.

PUB530

Rituximab in a Young African American Female with Stage IV and V Lupus Nephritis: An Exceptional Response to an Unconventional Therapy

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Introduction: Rituximab as a first-line treatment is an unusual, perhaps even wrong choice. Data supporting rituximab in patients resistant to both cyclophosphamide and mycophenolate (MMF) are limited. This case demonstrated its effectiveness in a patient who failed first-tier treatments.

Case Description: A 19-year-old female with a past medical history of SLE with lupus nephritis and G6PD deficiency is admitted to hospital due to worsening kidney function. She was diagnosed with lupus one year prior. Noted to have joint pain and poor kidney function with kidney biopsy confirming lupus nephritis, class IV, she developed worsening renal function while on MMF 500mg BID, hydroxychloroquine, and 30mg daily of steroids. Cyclophosphamide was initiated 1g/month for 5 months prior to current presentation. Kidney

biopsy performed 2 months prior to current admission showed class IV and class V lupus nephritis. She was admitted, started on methylprednisolone 1g/day, and rituximab, 600mg for two doses, one week apart. After completion of this treatment, she was discharged with anticoagulation (warfarin) given low albumin; 60mg of prednisone; pentamidine, while on steroids; and follow-up for contraceptive options. Creatinine improved after a further two doses of rituximab (see figure). She was continued on MMF from 12/20/18 until 3/29/18, when combination therapy with tacrolimus was initiated.

Discussion: This case demonstrates significant improvement in kidney function when treating lupus nephritis with rituximab, which is refractory to first-line treatments. Although initial studies of rituximab involved European populations, this case suggests generalizable, equal effects in African American populations. Additionally, while the use of combination therapy with MMF and tacrolimus is not a common practice, it was effective in this patient as a maintenance therapy.

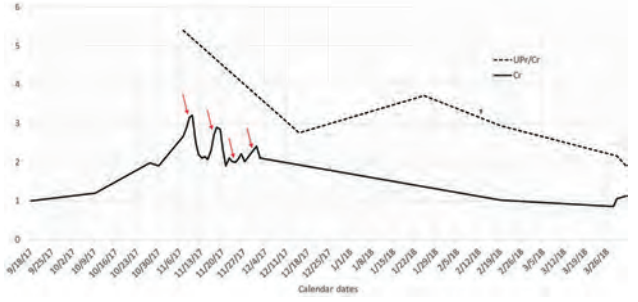

Figure: Kidney function before and after treatment with rituximab.Red arrow = rituximab administration; UPr/Cr = urine protein creatinine ratio; Cr = creatinine; † = 24-hour urine protein.

PUB531

MPO-ANCA Positive Crescentic Glomerulonephritis in a Patient with History of Histoplasmosis

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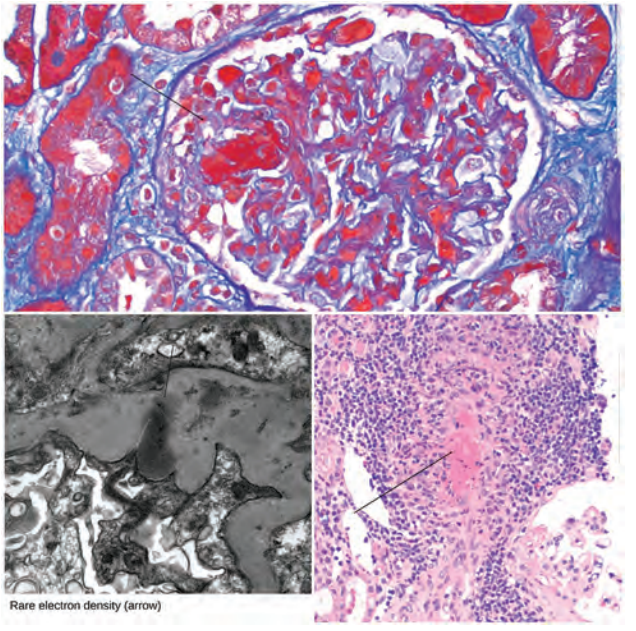
Introduction: Immunosuppression increases risk of opportunistic infections. Here we present a patient with history of histoplasmosis requiring immunosuppresssive therapy for treating vasculitis

Case Description: 82-year-old female patient with remote history of histoplasmosis was evaluated for asymptomatic worsening proteinuria. She was diagnosed with polymyalgia rheumatica three years prior to this presentation when her temporal artery biopsy was negative. Patient was treated with prednisone which was discontinued after tapering over two years. Serologic testing revealed ANCA-MPO, rheumatoid factor was positive and remaining were negative. Kidney biopsy revealed crescentic necrotizing glomerulonephritis with features of vasculitis. Risks and benefits of immunosuppression were discussed with patient especially about the risk of reactivation of histoplasmosis Patient was initially treated with a Methylprednisolone and Cyclophosphamide. Her creatinine improved and proteinuria resolved with treatment. She was continued on low dose prednisone to prevent recurrence of vasculitis. There is no recurrence of histoplasmosis during treatment.

Discussion: The pathologic hallmark of ANCA-associated glomerulonephritis is a pauci-immune necrotizing crescentic glomerulonephritis. Acute lesions such as fibrinoid necrosis or glomerular crescent may completely disappear or reduce significantly after immunosuppressive therapy. Spontaneous remission is rare, and 80 to 90% of untreated patients progress to end-stage renal disease within 6 months. This patient responded to treatment with creatinine improving to near normal and no significant proteinuria. Immunosuppression poses an increased risk for disseminated and severe infection. This patient is being monitored for recurrence of histoplasmosis.



PUB532

Nephrotic Syndrome in Hemophagocytic Lymphohistiocytosis

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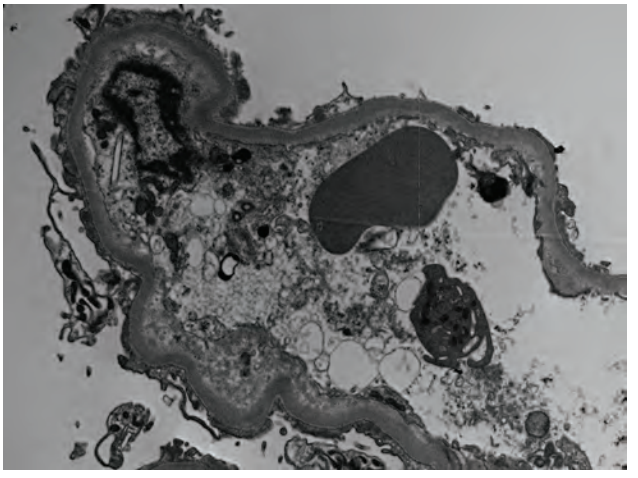
Introduction: Hemophagocytic lymphohistiocytosis (HLH) occurs as a result of dysregulated activation of the immune system and is characterized by infiltration of organs by macrophages that phagocytose RBCs. HLH may be primary or secondary to malignancy, infection, autoimmune diseases. Renal involvement is uncommon, manifesting as ATN or nephrotic syndrome. We present a case of AKI and nephrotic syndrome in the setting of HLH secondary to HIV

Case Description: 33 yo M was transferred with 1 month history of fever, body aches, weight loss, generalized rash, lymphadenopathy and minimal edema. Initial laboratory workup was remarkable for pancytopenia, transaminitis and hyperferritinemia a creatinine 2.5mg/dl and 28gm of proteinuria. Urine analysis showed granular casts. Initial infectious workup including HIV testing was negative; no relief despite antibiotic therapy, lymph node biopsy showed reactive changes. Bone morrow biopsy, was diagnostic for HLH. Renal biopsy only 5 glomeruli were noted and was consistent with MCD or FSGS and acute tubular injury. He required hemodialysis due to worsening renal failure. On further evaluation, his CD4 count was 79/mm^3 and HIV testing for antibodies to p2 antigen was positive, leading to the suspicion that he was initially in the window period he was started on retroviral therapy, leading to enough renal recovery to get off dialysis.

Discussion: AKI with nephrotic syndrome in HLH is believed to be secondary to high pro-inflammatory cytokine levels leading to podocyte injury. ATN associated with collapsing glomerulopathy, minimal change disease or thrombotic microangiopathy are the histological features noted on biopsy and there is no macrophage infiltration of the kidney. If it occurs it is termed histiocytic glomerulopathy presenting as AKI alone. Collapsing glomerulopathy is noted in African Americans while MCD noted in Caucasians. With limited glomeruli on biopsy, collapsing glomerulopathy may have been missed. Management is supportive with treatment of the underlying etiology



PUB533

Lupus Nephritis in Patient with Co-existing SLE and HIV

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Introduction: Immune complex glomerulonephritis has been an increasingly reported phenomena in HIV patients with lupus-like feature but in the absence of histologic and clinical markers of systemic lupus erythromatous (SLE). Also, there are reports of patients with HIV developing autoimmune processes like SLE or a simultaneous diagnosis of HIV and SLE. This is a report of a rare clinical situation of a patient with long-term SLE being diagnosed with HIV and presenting with lupus nephritis.

Case Description: 40 years old black female with SLE for 30 years, and a newer diagnosis of HIV for 4 years. She presented for evaluation of increasing proteinuria (5.3 g/day), hematuria, and increased serum creatinine to 1.3 mg/dl. Patient had a normal CD4 count (1,143) and elevated HIV viral load (5.46 log value). The ds-DNA was elevated with low c3 and c4 levels. She was on an angiotensin coverting enzyme inhibitor, prednisone, plaquenil, and no HIV medications. Patient subsequently had a renal biopsy. The result showed immune complex glomerulonephritis compatible with membranous lupus nephritis (ISN/RPS Class V). The immunofluorescence staining was positive for IgG, IgA, IgM, c3, C1q (full house pattern). Also, she had focal global sclerosis in 31% and focal segmental glomerulosclerosis in 8% of the glomeruli. Interstitial fibrosis and tubular atrophy (IFTA), severe (90% and 80% respectively). The patient was started on mycophenolate mofetil. Unfortunately she had a fast progression of disease and started hemodialysis within 6 months.

Discussion: This is a rare case of a patient with long-term SLE that develops HIV. Some degree of HIV associated nephropathy cannot be excluded, the positive lupus serology and the presence of full house pattern of immunofluorescent staining supports the diagnosis of lupus nephritis. She wasn't on HIV treatment due to a high CD4 count but her HIV viral load was positive. Class V lupus nephritis has a good prognosis but her significant fibrosis and rapidly progressive disease course may have been related to her untreated HIV. Analysis of such individual case reports may lead to important insights into the pathogenic mechanism of both diseases along with solving the therapeutic dilemmas that will assist in the care of patients.

PUB534

Bilateral Facial Palsy as the First Manifestation in Granulomatosis with Polyangiitis (GPA)

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Introduction: Granulomatosis with polyangiitis (GPA: formerly designated Wegener's granulomatosis) is a rare, autoimmune, multi system disease, first described by Friedrich Wegener in 1936. GPA is necrotizing granulomatous inflammation involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels. ANCA is present in >80 percent of patients with a peak age of presentation in the sixth decade of life. Renal disease, at presentation is seen in only 18% of patients; however develops with GPA progression. Bilateral facial paralysis as a primary manifestation of GPA is extremely rare.

Case Description: We present a 67 year old male with bilateral facial palsy, weight loss > 50 lb, dysphagia, anorexia, and depression. Initial extensive neurological evaluation was negative, except for the incidental finding of an abdominal aortic mural thrombosis. Creatinine (Cr) was 0.6 mg/dL. 3 months later he presented to our hospital with the same symptoms as well as increasing shortness of breath, malaise and foul smelling urine. He was diagnosed with acute renal failure and urinary sepsis. Pitting edema and an inability to close both eyes were noted. Cr ws 8.28 mg/dL. Urinalysis showed RBC's cast. ANCA (PR3+) and low C3, C4 were found (Anit GBM-). IV prednisone and cyclophosphamide were started. Head/Neck CT was unremarkable. A kidney biopsy was performed and confirmed the diagnosis of GPA and segmental necrotizing glomerulonephritis. There was mild improvement in renal function and marked improvement in facial palsy, but 2 months after, renal disease worsened and dialysis was initiated.

Discussion: The clinical manifestation of GPA is heterogeneous. The typical triad consists of the upper respiratory tract, lungs, and kidneys involvement. However, bilateral facial palsy as the first manifestation of GPA, like in this patient, is very rare and only a few cases have been reported in the literature. ANCA and PR3 revolutionized the diagnosis of GPA, since they allow early diagnosis. The specificity of positive ANCA testing in GPA is greater than 95%. In such cases, physicians play a crucial role in recognizing the early symptoms of the disease and starting the appropriate therapy to reduce mortality and morbidity.

PUB535

Methicillin-Sensitive Staphylococcus Aureus Bacteremia Associated with Normo-Complementemic, IgA-Predominant, Rapidly Progressive Glomerulonephritis - A Case Report

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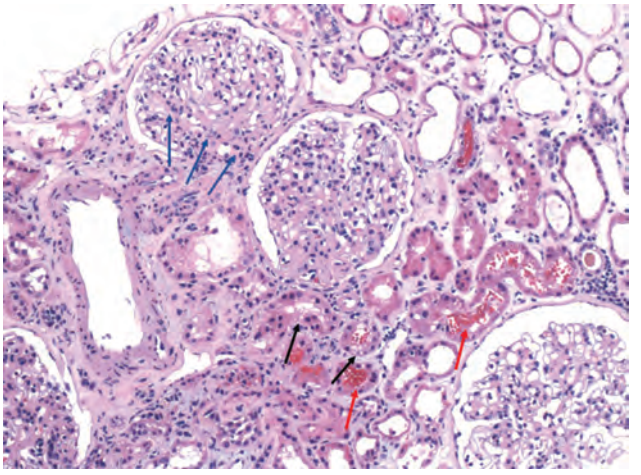
Introduction: Infection associated with Rapidly Progressive Glomerulonephritis (RPGN) tends to be crescentic with hypocomplementemia or pauci-immune. IgA predominant, non-crescentic, post-infectious GN is rarely associated with clinical RPGN. We present a case of normo-complementemic, IgA predominant, non-crescentic, and steroid responsive, RPGN in a patient with Methicillin-sensitive Staphylococcus Aureus (MSSA) bacteremia.

Case Description: A 52-year-old male with past medical history of a chronic left foot wound infection, diabetes type II presented with fevers and found to have MSSA bacteremia. Creatinine on admission was 4.3 mg/dL whereas few months prior, creatinine was 0.6 mg/dL. The patient was started on antibiotics and fluids. In the next few days, creatinine remains above 4 mg/dL. Autoimmune serologies, viral hepatitis panel, and complements were within normal limits. Urine microscopy showed >50 red blood cells (RBC)/field, urine protein to creatinine ratio was 1.4 G/g. A renal biopsy performed for ongoing AKI showed : 1) Light microscopy - mesangial proliferation without endocapillary/extracapillary proliferation, bowman's space hemorrhage with several tubular RBC casts, mild acute, and chronic tubular injury (Figure 1). 2) Electron microscopy - mesangial electron dense deposits. 3) Immunofluorescence- IgA/C3 codominant 3+ staining. The patient was treated with intravenous and oral steroids with significant improvement of renal function.

Discussion: Definitive diagnosis of the cause of RPGN is required to determine the management course. Our case emphasizes the role of renal biopsy as the cornerstone in the diagnosis of RPGN as usual lab investigations may not reveal the diagnosis.



Kidney biopsy (light microscopy): Blue arrows indicating mesangial proliferation, black arrows indicating tubular injury and red arrows indicating tubular red blood cell casts.

PUB536

A Case of Light Chain Nephropathy

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Introduction: The development of proteinuria and deterioration in renal function in a patient with diabetes mellitus and hypertension usually suggests diabetic nephropathy. However, other causes of renal failure should also be considered.Fibrillary glomerulonephritis (FGN) is among the newly recognized primary glomerular diseases. This rare cause of end-stage kidney disease has characteristic electron microscopic findings based upon the deposition of randomly distributed (10-22 nm) microfibrills in the mesangium and less frequently in the capillary basement membrane.Here we report a case of a 67 y/M with DM who was found to have IgG Kappa MGUS with FGN with dramatic improvement in his kidney function after the initiaion of chemotherapy.

Case Description: 67 years old male with type 2 diabetes mellitus since the age of 43 as well as photocoagulated retinopathy, hypertension, gout. He developed nephrotic syndrome. Serum creatinine level was 2.6 eGFR 28, urine protein excretion 6 gram and albumin 24 grams. Physical examination showed 2+ leg edema. His secondary workup for Nephrotic syndrome revealed elevated light chains IgG Kappa M-protein 0.32,Kappa Free light chains 338, Lambda Free light chains 34 and kappa Lambda ratio of 9.95. This prompted B/M biopsy revealing plasma cell dyscrasia(4%). Kidney biopsy confirmed diabetic glomerulosclerosi with superimposed fibrillary glomerulonephritis. The patient was treated with dual RAS blockers initially and then later after discussion with oncology he was started on bortezomib, cyclophosphamide and dexamethasone(CyBorD). After continuing 4 cycle treatment his Cr improved to 1.6 and PCR was decreased to 2.1

Discussion: FGN is a rare glomerular disease seen in 0.5–1% of native kidney biopsy. Clinical features at the time of kidney biopsy commonly include hypertension, proteinuria, hematuria, and varying degree of renal insufficiency. Serum creatinine could also be in normal range. Nephrotic syndrome, as in our patient, can be seen in one-third of the Diagnosis of FGN typically portends a poor prognosis, with approximately half of the patients progressing to end-stage kidney disease within a few years especially if asscoaite with DM. Unfortunately there is no established therapy specific for FGN, However, treating the underlying malignancy is assocaited with good outcomes. In our case we were able to achieve good response after starting the patient on CyBorD therapy for his plasma dyscrasia.

PUB537

Nephrotic Range Proteinuria with Nodular Pattern on Biopsy in a Patient with No History of Diabetes

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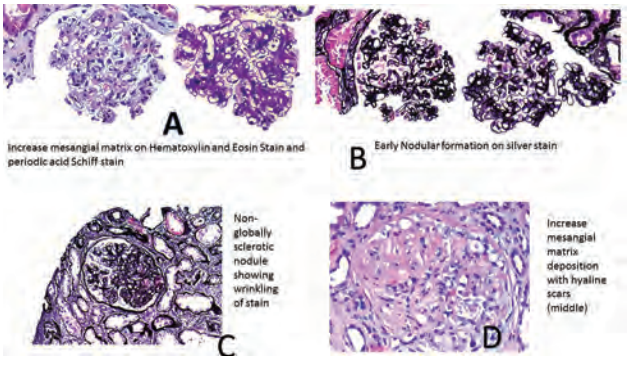
Introduction: Kimmelstiel Wilson nodule had been described extensively in the literature as pathognomonic for patient with diabetes, however it had been also reported in patient who had amyloidosis, multiple myeloma and also reported in idiopathic nodular glomerulosclerosis when diabetes had been ruled out and other causes had been excluded.

Case Description: Herein; our patient is a 70-year-old white man with history of cerebrovascular accident, hypertension, chronic obstructive pulmonary was referred to us for evaluation of elevated creatinine that was 2 mg/dl which was 1.5 mg/dl six months prior, he does have proteinuria on his urinalysis 4 years prior, on his last 24 hour collection, he had nephrotic range proteinuria at 7.4 gm per day, he is a smoker with 54 years pack history and drink occasionally, he presented to us with blood pressure that was 135/63 on lisinopril and diltiazem with pulse of 66 and his BMI was 27. His complements level were normal limit, his hemoglobin A1C off any medication 5.5 -5.8 over the last 2 years, his hepatitis, HIV profile all came back to be negative. Kidney ultrasound showed signs of chronic kidney diseaes with no obstruction.

Discussion: Patient was diagnosed with idiopathic nodular nephrosclerosis on biopsy as shown on figures attached, his serum protein electrophoresis was within normal range, Congo red stain was negative and there had no immune complex deposition seen on his Immunofluorescence. Idiopathic nodular nephrosclerosis is a diagnosis of exclusion, it is seen more commonly in elderly; white males who are hypertensive and has strong correlation to smoking. Studies had showed that people who continued to smoke with idiopathic nodular glomerulosclerosis had higher risk of nephrotic syndrome, lower serum albumin and rapid progression to end stage renal disease. Neovascularization thought to play part in the pathogenesis of idiopathic nodular glomerulosclerosis. We also suggest establishing a pathology bank for future diagnosis and treatment for patients with idiopathic nodular glomerulsclerosis and reporting every case seen.



PUB538

In Bad Company: Crescents and ANCA Are Bad News for Kidney Recovery in Lupus Nephritis

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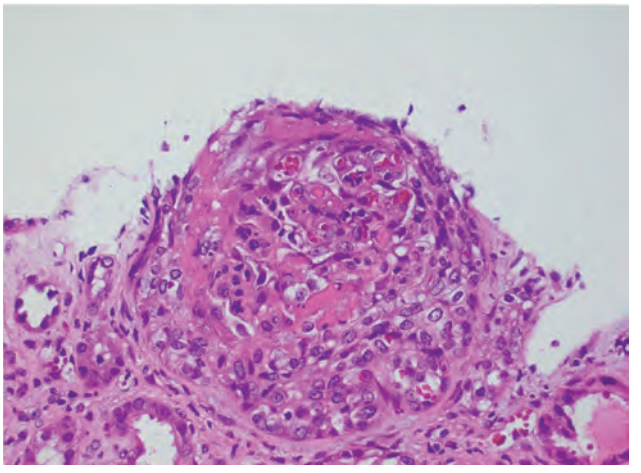
Introduction: Lupus Nephritis (LN) classification highlights the importance of histopathological findings and kidney outcomes. Investigators have found a potential association between positive ANCA serology leading to poor outcome in Lupus GN. This is a case of lupus GN with an impressive biopsy and unexpected serology findings.

Case Description: 40 y/o Caucasian woman with a history of obesity and SLE presented to ER with generalized swelling. On exam, she was very hypertensive (210/120mmgh), with low grade fever (99.1F), sinus tachycardia and anasarca. Initial labs showed a Hgb 6.9 g/dL, Cr 5.4 mg/dL (baseline 1.0 mg/dL), BUN 45 mg/dL, and U/A with overt proteinuria (>300mg) and microscopic hematuria with RBC casts. She reported taking 2-3 ibuprofen daily for several weeks due to joint pain, but denied any other medications or toxic habits. Serology for ANA, anti-dsDNA, **ANCA (MPO&PR3)**, and ASO were **positive. Complements** were **normal.** Biopsy showed **45 of 48 glomerulus with hypercellular crescents** (some with fibrinoid necrosis [image]), full house pattern on IF, except for **negative C1q**. EM showed subendothelial and mesangial deposits. Findings were compatible with **Class IV diffuse lupus nephritis.** She started on dialysis in addition to high dose cyclophosphamide and steroids. She is currently on her third month of treatment with no signs of renal recovery.

Discussion: The amount of crescents in LN is crucial in establishing kidney prognosis. Studies have shown a correlation between the amount of crescents in LN with poor outcome and higher risk for relapse. Fibrinoid necrosis has also been associated with poor recovery. A positive ANCA may occur in about 20% of LN, specially in class IV. Although it suggests to be a bad association, there is not yet enough data available to support a correlation with poor prognosis. The chances of kidney recovery in this patient appear to be low as she remains on dialysis after 3 months of adequate treatment.



PUB539

AKI as the Initial Presentation of Burkitt Lymphoma

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Introduction: Burkitt's lymphoma is a highly aggressive B cell non-Hodgkin lymphoma characterized by the translocation and dysregulation of the *MYC* gene on chromosome 8. Renal involvement in non-Hodgkin's lymphoma is usually seen after the original disease has been diagnosed and has been reported as 30-50 percent at autopsy.The differential for acute kidney injury (AKI) in patients with underlying lymphoma includes tumor lysis syndrome (TLS), tumor infiltration, urate nephropathy etc.Diffuse bilateral kidney infiltration causing acute renal failure as an initial manifestation of NHL is very rare. We present a case of a patient (pt) who presented to an outpatient clinic for workup of AKI and was diagnosed to have lymphoma based on a renal biopsy.

Case Description: A 46 year old male with a PMH of SLE for 5 years presented to an outpatient clinic due to concern for AKI with creatinine (Cr) elevation from 0.8 mg/dL to 3.57 mg/dL over 8 weeks.A detailed history and physical exam did not reveal any etiology for his AKI. Further work up revealed mildly low complement levels and bilaterally enlarged kidneys with symmetric edematous appearance of the renal parenchyma. Renal biopsy was done to ascertain the etiology of AKI which showed high grade B cell lymphoma positive for BCL-6 and CD-10 (weak), while negative for BCL-2 and Ki-67 index greater than 90%.This warranted a PET scan which showed extensive hypermetabolic lymphadenopathy in the cervical, mediastinal, abdominal and pelvic region.The pt was started on chemotherapy, developed acute TLS with worsening of renal function, was started on CRRT later transitioned to IHD after 4 days.His urine output improved by the second week of chemotherapy, AKI resolved and he was able to come off of dialysis.A repeat kidney ultrasound showed decrease in his kidney sizes.

Discussion: Renal infiltration has been reported in 30% to 50% of the cases in autopsy of non-Hodgkin's lymphomas, but is clinically silent, with 0.9% to 23% of them developing renal insufficiency. Impairment of renal function due to tumor infiltration as the initial manifestation of lymphoma is very rare, with only a few cases reported in the literature. Prompt diagnosis and early institution of treatment is imperative, as it can partially or completely reverse AKI.Our patient was fortunate enough to have a complete response to chemotherapy with recovery of renal function to baseline.

PUB540

Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis and Crescentic Glomerulonephritis in Diffuse Systemic Sclerosis: Renal Failure Not Due to Scleroderma Renal Crisis

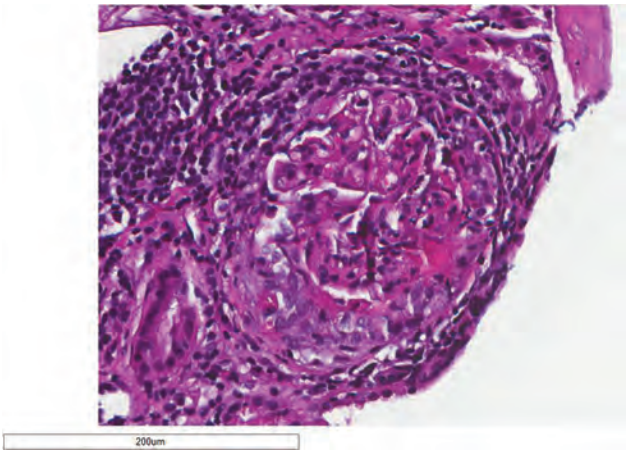
Azza Abdel Hak, Ummerubab Syeda, Rakesh Gulati. *Thomas Jefferson University Hospital, Philadelphia, PA.*

Introduction: Scleroderma renal crisis (SRC) is characterized by rapidly progressive renal failure with severe hypertension. Rarely, a small number of patients with systemic sclerosis develop anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis and renal failure. These patients are usually normotensive. Differentiating between the two entities is important and can be challenging.

Case Description: A 57 year old female with history of diffuse systemic sclerosis, was admitted for evaluation of progressive renal failure, proteinuria and microscopic hematuria. Her blood pressure was 104/63 mm Hg on RAAS blockade. Creatinine level was 2 mg/dl, up from a baseline of 1 mg/dl, and her hemoglobin was 9.2 g/dl. Urine analysis was significant for +1 protein, +3 Blood and 93 red blood cells per high power field. Complement levels were normal. Anti-double stranded DNA and anti-RNA polymerase III antibodies were negative. Anti-Myeloperoxidase (MPO) antibodies were positive. Renal biopsy was consistent with necrotizing, crescentic glomerulonephritis (Figure 1). The patient was started on Rituximab and eventually discharged with plans for outpatient follow-up.

Discussion: Renal involvement in scleroderma is associated with high morbidity and mortality. Scleroderma renal crisis (SRC) is the most serious manifestation and usually presents with abrupt onset of moderate to severe hypertension and rapidly progressive renal dysfunction. The mainstay of treatment of SRC is prompt control of blood pressure in which

ACE inhibitors are the most effective. Rarely, as in our case, patients with scleroderma present with acute renal failure associated with ANCA related crescentic glomerulonephritis. This subset of patients are usually normotensive. Differentiating this from SRC is important as treatment usually involves immunosuppression with cyclophosphamide or rituximab and cautious use of steroids if necessary.



PUB541

Lupus Nephritis with Negative Antinuclear-Antigen-Antibodies

Jaime R. Jimenez Lopez, Samardia Missick, Ivan E. Porter. *Mayo Clinic Jacksonville, Jacksonville, FL.*

Introduction: Immune-complex-mediated membranoproliferative glomerulonephritis (MPGN) with "full house nephropathy" on kidney biopsy is well described on lupus nephritis. Antinuclear antigen (ANA) antibodies are one of the laboratory hallmarks, found in 99%, of patients with systemic lupus erythematosus (SLE). This case challenges the close to obligatory ANA positivity for diagnosing lupus nephritis, and represents a different presentation of an old condition.

Case Description: A 53 year-old Caucasian woman with history of chronic anemia presented with nephrotic range proteinuria, of 6307 mg in a 24 hour urine collection, and an estimated glomerular filtration rate (eGFR) of 87 mL/min. Physical exam was unremarkable, with no evidence of arthritis, skin or any organ system involvement, except for trace dependent edema. Urinalysis showed microscopic hematuria, with 20-40 RBCs per high power of field. Initial serological battery showed decreased C3 at 78 mg/dL (normal range: 90-180 mg/dL), normal C4, negative ANA, rheumatoid factor, HIV serology, hepatitis serologies, factor H, C3 nephritic factor and cryoglobulins. Additionally, workup for paraproteinemias resulted negative as well, and serum albumin was 2.9 g/dL. A kidney biopsy was obtained, showing MPGN type 3 pattern, with diffuse endocapillary GN plus segmental membranous features, and moderate interstitial fibrosis and tubular atrophy. Immunofluorescence was positive at 3+ for IgG and C1q, 2+ for C3, kappa and lambda, and 1+ for IgM, at mesangium, capillary loops and tubulointerstitium. Electron microscopy demonstrated glomerular basement duplication and severe foot process effacement, with no tubuloreticular inclusions. Lisinopril, sodium restriction and mycophenolate mofetil were used, with the latter stopped, due to lack of improvement, after 3 months of treatment. At 3 year follow-up, her eGFR continued to worsen to 27 mL/min, and proteinuria remained unchanged. ANA were consistently negative.

Discussion: ANA-negative cases of lupus nephritis, with no extra-renal involvement, pose a challenging condition to diagnose and treat. Possible explanations to this presentation includes alternative processes, or a different SLE related pathophysiologic mechanism of renal involvement. This case exemplifies the challenge lupus nephritis represents, and contributes to further discussion about new diagnostic and therapeutic options for this condition.

PUB542

A Unique Case of Bilateral Giant Cell Arteritis with Renal ANCA-Associated Vasculitis

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Introduction: Giant cell arteritis (GCA) is an autoimmune vasculitis characterized by infiltration of medium and large vessels by monocyte-derived giant cells leading to local and systemic inflammation. It is a panarteritis preferentially involving the extracranial branches of the carotid artery. Herein, we describe an extremely rare entity of biopsy-proven GCA and renal failure with a kidney biopsy consistent with pauci-immune necrotizing glomerulonephritis (GN).

Case Description: An 81-year-old man presented with weakness, jaw claudication, right temporal artery ache and tenderness, altered mentation, and elevated inflammatory markers. Bilateral temporal artery biopsy revealed active arteritis with transmural inflammation predominantly of mononuclear cells, and disruption of the internal elastic lamina consistent with vasculitis. There were no giant cells or granulomas. He had no vision loss, stroke, or extremity claudication. Imaging of the great vessels and large arteries was negative for vasculitis. He had proteinuria 0.5 g/g, hematuria without casts, and renal insufficiency (creatinine 1.3 from baseline of 0.9). He had a high titer of perinuclear antinuclear cytoplasmic antibodies (ANCA) and antibodies to myeloperoxidase (MPO). Renal biopsy revealed pauci-immune necrotizing GN. He was diagnosed with microscopic polyangiitis. The patient was started on prednisone and also given 2 doses of rituximab 2 weeks apart.

Discussion: Renal involvement with GCA is rare and, to our knowledge, only few cases have been reported of associated pauci-immune necrotizing GN. In contrast to small vessel vasculitides which can be linked to ANCA, large vessel vasculitides have no known associated antibodies. The patient in this case being MPO-ANCA positive with renal vasculitis and GCA represents an extremely rare clinical overlap between small, medium, and large vessel vasculitis. Histologic analysis is the standard for diagnosis; Absence of fibrinoid necrosis and involvement of vasa vasorum favors the diagnosis of GCA over ANCA-associated vasculitis (AAV). All patients diagnosed with GCA should have evaluation for possible associated renal disease. Doing so has important therapeutic implications as the presence of renal vasculitis requires the addition of another immunosuppressant such as rituximab.

PUB543

A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) Presenting with a Rare Pathological Feature

Kotoko Shinya, Akihiro Minakawa, Takashi Iwakiri, Ryuzoh Nishizono, Masao Kikuchi, Yuji Sato, Shouichi Fujimoto. *University of Miyazaki, Miyazaki, Japan.*

Introduction: PGNMID is a recent entity of glomerulonephritis caused by monoclonal IgG gammopathy. Diagnosis of PGNMID requires the presence of a single subclass of IgG heavy and light chains deposition by immunofluorescent study, granular deposits by electron microscopy (EM), and the absence of cryoglobulinemia. We report a patient with PGNMID who presented with a rare pathological feature.

Case Description: A 38-year-old woman was admitted to our department with a 7-month history of moderate proteinuria. A urinary test showed proteinuria of 1.2 g/day and no microscopic hematuria. A blood test showed the following: 0.63 mg/dL of creatinine, 5.98 g/dL of total protein, 3.54 g/dL of albumin, 68 mg/dL of C_3, and 25 mg/dL of C_4. Cryoglobulinemia was not detected. Renal biopsy showed the microscopic feature of membranous nephropathy (MN) with IgG deposition. We performed IgG subclass immunostaining and an EM study because a young adult woman presenting with idiopathic MN is uncommon. Additional immunofluorescence showed monoclonal IgG1-kappa monoclonality. EM showed granular deposits in subendothelial, subepithelial and intra-glomerular basement membranes. A bone marrow examination and serum and urine electrophoresis did not show evidence of underlying hematological disease. We diagnosed the patient with PGNMID and maintained with an angiotensin converting enzyme inhibitor. Her renal function and proteinuria did not worsen until the time of this report.

Discussion: A common pathological feature of PGNMID is MPGN like lesion with deposition of IgG3-kappa, while MN with IgG1-kappa is rare. PGNMID is rarely accompanied by underlying hematological disease, and thus its diagnosis may be difficult without suspicion. To avoid missing this disease, an aggressive immunofluorescence study to detect monoclonality should be performed, even in the case of non-proliferative GN. Mass spectrometric analysis of this case is in progress at the time of writing this report, and we will present the possibility of using this method as an alternative for detecting monoclonal IgG deposition.

PUB544

Hydralazine Induced ANCA Vasculitis - The Dark Side of Medication

Amal Qureshi,[1] Zahra Deen.[2] *[1]Ziauddin Medical College, Karachi, Pakistan; [2]Department of Nephrology, CHI St. Luke's Health - Baylor Medical Center, Houston, TX.*

Introduction: Kidney related side effects of Hydralazine.

Case Description: 82-year-old African American female with PMH of DLD, HTN, CKD III (baseline Cr 1.73 mg/dl) presented to the E.R with abdominal pain, diarrhea and decreased urine output for 2 weeks. On examination, she was lethargic but oriented, appeared anorexic and lungs clear to auscultation. Patient was hemodynamically stable. Her medications included statins, beta blocker and recently started hydralazine. Initial labs perfomed, as mentioned in the table. UA showed microscopic hematuria and proteinuria - prompting further workup as no improvement was seen with 24 hours of IVF. Secondary work up was performed as mentioned in table. These results were confusing for RPGN secondary to lupus nephritis vs ANCA vasculitis with our differential being hydralazine induced lupus with false positive ANCA. After further discussion kidney biopsy was pursued, which to our surprise showed crescentic glomerulonephritis, pauci-immune with moderate to severe interstitial fibrosis and marked arterial sclerosis. Complements were repeated and continued to remain low. Hydralazine was discontinued and the patient was started on Prednisone, Rituximab and initiated on dialysis.

Discussion: Hydralazine is FDA-approved for essential hypertension and recommended by the AHA for the treatment of CHF in African-Americans. The auto-immunogenic capability of hydralazine has been shown through its ability to induce lupus and vasculitis. Hydralazine-induced lupus differs from idiopathic lupus both clinically and serologically. Clinically it rarely involves the kidneys (only 5 %) or nervous system. Serologically while all patients are positive for ANA and can be positive for antihistone antibody, they do not have positive dsDNA or hypocomplementemia. The consideration for hydralazine-induced ANCA vasculitis should be higher for patients who are African-American, if they have positive MPO ANCA antibody at a high titer and positive ANA.

Antibodies to elastase and lactoferrin are also common in hydralazine-induced ANCA vasculitis and hypocomplementemia can be seen.

Initial labs						Secondary workup								
Cr	BUN	Na	K	Cl	CO2	ANA Pattern	ANA titre	ds DNA antibody	Histone antibody	Scl 70 antibody	Myeloperoxidase antibody	C3 levels	C4 levels	Urine protein to creatinine ratio
14.64	117	134	5.1	80	14	+ve Homogenous	1:2560 (1:60)	Positive	9.9	1.2 (<1.0U)	>800.0 (<0.4U)	62 (88-201	9 (15-45	3.1 g/day

PUB545

Crescentic Glomerulonephritis in Henoch-Schönlein Purpura with ANCA: A Therapeutic Dilemma

Rickinder Grewal, Bruce Goldman, Anirban Bose. *University of Rochester Medical Center, Rochester, NY.*

Introduction: The significance of immune complex staining in ANCA-associated glomerulonephritis (AAGN) is unclear and there are no established guidelines for treatment. We report a case of crescentic glomerulonephritis with strong IgA deposition and ANCA positivity.

Case Description: A 49-year-old male with a history of hypertension and rheumatoid arthritis presented to the hospital with a purpuric rash, nephrotic syndrome, and AKI with a very active urine sediment. Serology showed ANA 1:80, c-ANCA 1:640, and PR3 antibody of 180 U. Renal biopsy demonstrated diffuse active necrotizing crescentic glomerulonephritis with dominant IgA deposition (Figure 1). Skin biopsy showed leukocytoclastic vasculitis with focal IgA staining suggestive of Henoch-Schönlein Purpura. He was pulsed with high-dose steroids with plans for outpatient Rituximab (RTX) and cyclophosphamide (CYC) but was soon readmitted with pulmonary symptoms and worsening renal function. He was again treated with high-dose steroids and started on plasmapheresis and hemodialysis. He was then started on IV CYC 500 mg every 2 weeks and weekly IV RTX 375 mg/m^2 for a total of 4 doses every 6 months. However, the patient refused CYC after 2 doses due to concerns for toxicity. Although his PR3 antibody levels normalized on RTX, he has not shown signs of renal recovery and remains on peritoneal dialysis.

Discussion: Concurrent crescentic IgA nephropathy (IgAN) and AAGN is very rare. Our case illustrates the difficulty in treating such patients and the dilemma encountered in determining the predominant pathology. While CYC has been used to effectively treat both IgAN and AAGN individually, there is no data to support the use of RTX in crescentic IgAN. In such cases of concurrent crescentic IgAN and AAGN, primary therapy with CYC should be considered.

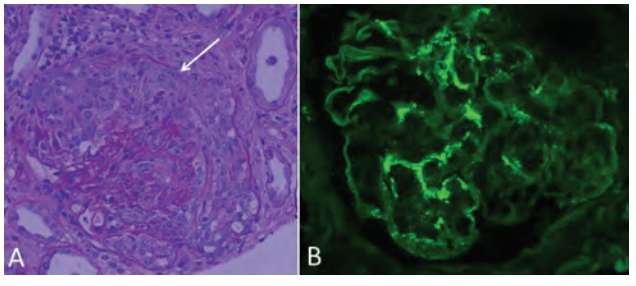

Figure 1: Renal biopsy with a fibrocellular crescent (arrow) on PAS stain (A) and dominant IgA deposition on immunofluorescence (B).

PUB546

Cryoglobulinemic Vasculitis: Unusual Presentation of Multiple Myeloma

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Introduction: Type I cryoglobulins (CGs) are immunoglobulins that precipitate at low temperatures, causing inflammation and tissue damage. They are compounds of a monoclonal immunoglobulin, mainly IgG, and are associated with hematological malignancies. Around 10% of patients with multiple myeloma (MM) present detectable CGs, althoough few develop symptoms. We report the case of a patient with severe cryoglobulinemic vasculitis secondary to MM.

Case Description: This was a female patient, aged 42, with previous hypertension. During the previous four months, she experienced a strong, burning pain in the lower limbs, that developed into purpuric, necrotic lesions at the extremities. She presented a rapid deterioration of renal function, requiring dyalisis. She experienced a mild microscopic hematuria and, due to the risk of crescentic glomerulonephritis, was submitted to pulse therapy with methylprednisolone 1g/day for 3 days. Laboratory tests revealed: ANA, anti-SM, p-ANCA, c-ANCA, anti-HCV, HBsAg, VDRL, anti-HIV, antiphospholipid antibodies, all negative. Only the C3 was discreetly reduced. Hemoglobin 6.0 g/dL; platelets 149,000, with no schizocytes, DHL=696 U/L (125-220) with an ADAMTS-13 activity of 45%. She underwent a kidney biopsy, evolving with bleeding, which resulted in nephrectomy. The biopsy revealed areas of fibrinoid necrosis and intracapillary thrombi with focal granular deposits and in vessels of IgG, C3 and Kappa. CGs research was positive and serum protein electrophoresis revealed a monoclonal peak. The patient presented with pulmonary hemorrhage and a chest CT scan revealed bilateral ground-glass infiltrate. She received pulse treatment with cyclophosphamide and was subjected to plasmapheresis. A bone marrow biopsy and immunohistochemistry were compatible with MM. After a fresh episode of pulmonary hemorrhage, the patient died without receiving treatment for MM.

Discussion: Rarely reported, type I CGs associated with MM appear to worsen the prognosis, especially if diagnosis is delayed. This study emphasizes the need to investigate neoplasms, mainly hematologic, in the presence of cryoglobulinemic systemic vasculitis.

PUB547

A Case of Severe Diffuse Membranoproliferative Glomerulonephritis in Lupus Nephritis with Thrombotic Microangiopathy

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Introduction: Renal involvement is common in patients with Systemic Lupus Erythematous (SLE). An abnormal urinalysis (proteinuria and/or hematuria) is present in up to 75% of patients with SLE. Elevated creatinine develops in ~ 30% and ~ 10% of patients with Lupus Nephritis (LN) develop End Stage Renal Disease (ESRD). Furthermore, Blacks and Hispanics have worse outcomes including death and ESRD.

Case Description: We present a case of a 41-year-old Hispanic male presenting with lower extremity edema, joint pain, high blood pressure and a skin rash. His medical history is noteworthy for SLE diagnosed seven years ago and class IV/V lupus nephritis diagnosed three years ago treated with an incomplete course of IV Cyclophosphamide due to severe infectious complications and was switched to Mycophenolic acid (MMF). He was on MMF 500mg twice a day prior to admission. Patient was in acute renal failure with serum creatinine of 4.0 mg/dL (baseline creatinine around 1.8 mg/dL). Complement levels C3 and C4 were extremely low at 19 mg/dL and < 2 mg/dL respectively. Urinalysis showed active urinary sediments. Urine protein to Cr ratio was 4.0. Repeat kidney biopsy revealed class IV diffuse membranoproliferative glomerulonephritis with focal crescents and thrombotic microangiopathy, moderate interstitial fibrosis and tubular atrophy ~ 30%. Patient was pulsed with Solumedrol for three days and dose for MMF was titrated up to 1.5 gms twice daily. Despite aggressive treatment his renal functions deteriorated leading to initiation of hemodialysis. A course of therapeutic plasmapheresis (TPE) was also initiated. Patient underwent a total of 6 every other day treatments consisting of one plasma volume exchange. He was also continued on intermittent hemodialysis for a total of 4 treatments, at which point his renal function recovered enough to get off the dialysis. Patient was discharged home on MMF, prednisone and plaquenil.

Discussion: In conclusion, our patient with severe proliferative LN with TMA had a favorable outcome from treatment regimen consisting of plasmapheresis and standard immunosuppression. Previous studies have demonstrated variable effectiveness of TPE in patients with lupus nephritis. Additional prospective studies are desired to consolidate the role of plasmapheresis in treatment of severe LN with renal TMA.

PUB548

A Case of an Elderly Patient with IgA Vasculitis

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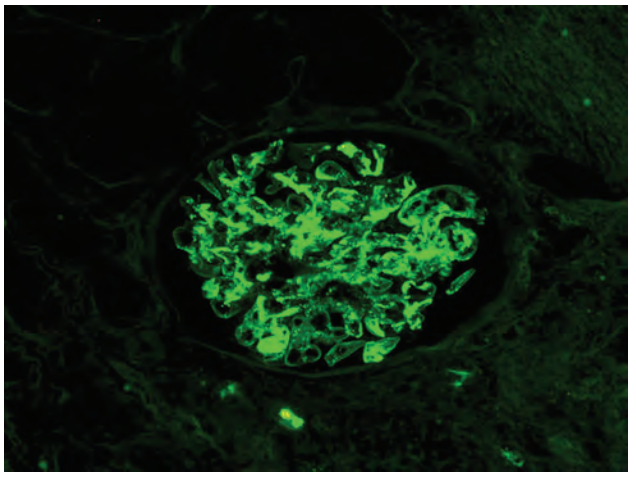
Introduction: IgA vasculitis (Henoch-Schonlein) is primarily seen in children between the ages of 3 and 15 years of age with annual incidence of 15 cases/100,000 compared to 1.3 cases/100,000 per year in adults. HSP is only responsible for 0.6 to 2% of adult nephropathies.

Case Description: A 77-year-old Caucasian male was admitted with septic shock and acute renal failure secondary to duodenal diverticulitis and urinary tract infection. The patient had accompanying confusion, nausea, vomiting, diarrhea, epigastric abdominal tenderness, and decreased urinary output. Physical exam demonstrated palpable purpura on bilateral upper and lower extremities. He was hemodynamically stable and afebrile. Laboratory studies revealed a BUN of 106, Creatinine 6.14 (baseline 1), C3 60.0, C4 14 and normal platelets. Other serologies were negative. Urinalysis was significant for >182RBCs/hpf and protein/creatinine ratio of 0.45mg/dL. Skin biopsy revealed florid acute vasculitis involving small vessels with intramural and perivascular fibrin deposition. Renal biopsy revealed mesangial IgA dominant immune-complex deposits with focal endocapillary proliferation and exudation. The patient received pulse methylprednisolone and was transitioned to 60mg of prednisone with a prolonged taper. He initially improved with reduction of hematuria, proteinuria, and creatinine, but recurrence occurred during the steroid taper.

Discussion: IgA vasculitis prognostication in adults is not well characterized. Steroids shorten the duration of symptoms but do not affect the course of the disease. Glomerular IgA predominantly consists of galactose-deficient IgA1, which is specific to both IgA vasculitis with nephritis and IgA nephropathy, thus distinguishing them from other glomerular diseases. Though IgA vasculitis and IgA nephropathy are distinct clinical entities, they may share a common renal pathogenesis.



IgA immune-complex deposition on immunofluorescence

PUB549

HSP - Not Always Purpura

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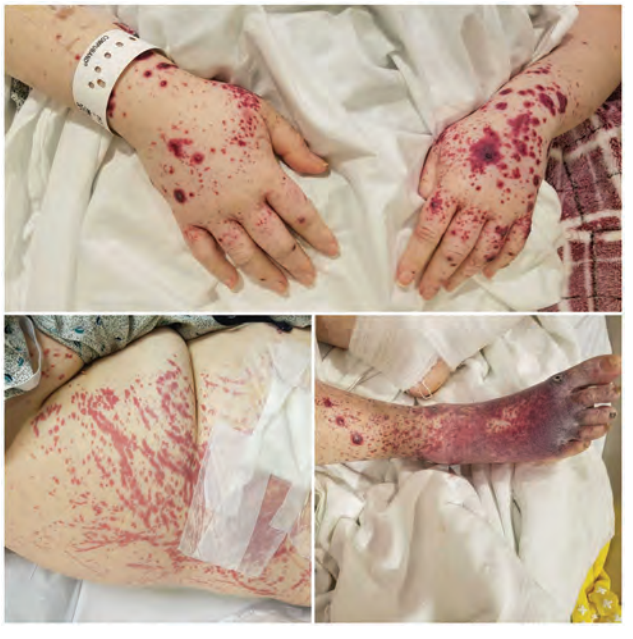
Introduction: Henoch-Schonlein Purpura (HSP), an IgA vasculitis seen in pediatric age group and rarely in adults, manifests as palpable purpura, diffuse abdominal pain, hematuria, arthritis, and in some cases even as bullous rash as seen in our case. It is important to differentiate HSP nephritis which is treated with immunosuppressants from its close proximity diagnosis Staphylococcus associated glomerulonephritis, which needs only antibiotics.

Case Description: This is a case of a 54-year-old female with uncontrolled diabetes mellitus. She was admitted for left foot cellulitis of the left great toe. Both the blood and wound cultured fast-growing staphylococcus aureus and was started on intravenous(IV) antibiotics. On the second day of admission, she developed bullous lesions over her bilateral foot. Succeeding, she complained of abdominal pain accompanied by diarrhea, followed by hematuria and generalized purpuric vasculitic rash. Subsequently, she developed oliguric acute renal failure. Skin and kidney biopsy performed were consistent with the diagnosis of staphylococcal IgA nephropathy/Henoch-Schonlein Purpura. She was started on 500mg methylprednisolone and maintained followed by daily prednisone and continued with IV ertapenem for 42 days. Her hospital course was complicated by paroxysmal atrial fibrillation, electrolyte abnormalities, volume overload leading to a requirement for chronic dialysis.

Discussion: HSP rarely manifests as bullous lesions in contrast to classic purpuric rash. In vasculitis, the blood vessels are already narrowed owing to on-going inflammation, and steroids, in turn, being procoagulant may not be the best drugs of choice. Few studies of similar cases being treated with cyclophosphamide(CYC) has shown better clinical outcome compared to steroids. CYC may be a better drug of choice in these vasculitic conditions, though more studies and further data are needed to change the guidelines.



PUB550

IgA Nephropathy Associated with Chronic Ulcerative Colitis: Clinical Case Report

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Introduction: IgA nephropathy (IgAN) as an extraintestinal manifestation of inflammatory bowel disease (IBD) has a low incidence, during 12 years it has been reported in 24% of 83 patients of kidney biopsy specimens from patients with IBD and acute or chronic kidney failure or proteinuria.

Case Description: A 22-year-old male with CUCI not yet in remission. Maintains treatment with Prednisone 30mg and azathioprine 100mg daily. Ten years ago initiated mezalasin, prednisone and after 6 months suspended for lack of improvement. He also has diagnosis of lithiasis a year ago, and gross hematuria that occurred when running. Hematuria and proteinuria have been reported for 1 year, accompanied by elevation of creatinine and urea. On physical examination the vital signs were normal and he has Cushing appearance, on laboratory exams he has mild leukocytosis, Creatinine 1.3mg/dL, cholesterol 216mg/dL, Uric acid 5.19mg/dL, DHL 506 Ui, urine examn with proteinuria 100mg/dL, hematuria 7 ppf, in collected urine 800mg per 24 hours, ANAs and ANCAs and VIH, VHB, VHC were negative. A renal biopsy was performed that reports IgA nephropathy Oxford MEST-C: M1, S0, E1, T0, C0. Therefore, immunosuppression with Prednisone was increased and Enalapril was initiated, with reduction in creatinine to Cr 1.04 and proteinuria maintain en 860mg per 24 hours

Discussion: The association between IgA nephropathy and IBD is infrequent. A genetic connection has been reported between both diseases, the majority of the loci involved in the pathophysiology of IgAN are directly associated with the risk of IBD or the maintenance of the intestinal epithelial barrier with its response to mucosal pathogens. In addition, genetic linkage has been suggested due to the presence of HLA-DR1 in IgAN and HLA-DR1 / DQw5 in IBD. The reduction of chronic antigenic stimulation of IgA production and blood levels of nephrotoxic cytokines after the elimination of the source of chronic inflammation is the main objective of the treatment, so achieving remission of the disease would allow the improvement of the kidney damage, even when there are extensive sclerotic changes in the kidneys. The aggressive treatment of IBD can improve the manifestations of IgAN, it is important to bear in mind the correlation of glomerulonephritis as an extraintestinal manifestation of IBD.

PUB551

A Case of Severe Renal Impairment with Nephritic/Nephrotic Picture and MPGN Pattern of Injury in a Patient with Monoclonal Gammopathy

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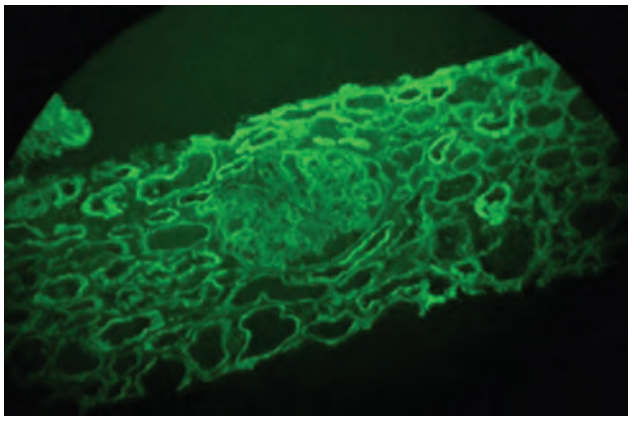
Introduction: In 2012, the term MGRS was introduced to describe patients who had MGUS with Renal dysfunction being the only systemic manifestation. The most recent diagnostic criteria for Multiple Myeloma require the presence >10% clonal Plasma cells in the Bone Marrow plus of one or more CRAB or Myeloma Defining Events. Here we present a patient with Multiple Myeloma whose only presentation was severe Renal impairement (requiring dialysis) with MPGN pattern of Injury on Kidney biopsy who responded well to Chemotherapy and came off Dialysis in about 4 weeks.

Case Description: This is a 64 yr old male with no significant medical Hx. He presented with Lower extremity edema and Hypertension. Wokup showed Nephrotic syndrome (24 hr Urine Protein: 15 g, S. Albumin 2.3, and Edema). Serologic tests were negative (HepC, HepB, HIV, ANA, ANCA, Anti GBM). C3 and C4 were both low. RRT was initiated soon after admission (Cr up to 7, baseline~1). Despite the absence of other CRAB features, SFLC, SPEP and UPEP were obtained. His Kappa/Lambda free light chain ration was 0.11 Kidney Biopsy: LM showed an MPGN pattern of injury, IF with linear Lambda staining and IgG3, EM with moderate effacement of foot the foot processes. Bone Marrow showed 40% clonal plasma cells.

Discussion: Despite the absence of the other classic CRAB criteria, Renal involvement in this patient was severe, with MPGN, Nephrotic/Nephritic picture and AKI requiring RRT. His response to Chemotherapy (CyBorD) was excellent, and he came off dialysis in about 4 weeks (Creatinine now~1.5). Screening for MGRS and Multiple Myeloma in patients with Renal disease is important, Chemotherapy should be initiated as appropriate, and many patients respond well to this approach.



LM, EM and Bone Marrow slides will also be included in the final presentation (not included here due to the size of the images).

PUB552

An Unusual Case of Glomerulonephritis (GN) with Prominent Glomerular Complement Deposition

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Introduction: The presence of glomerular immune complexes (ICs) is critical to determining the correct diagnosis and treatment of GN with prominent complement C3 staining. Although ICs are usually easily shown by immunofluorescence (IF), sometimes this is more complicated.

Case Description: A young white woman developed acute congestive heart failure that was attributed to viral myocarditis. Within 9 months she recovered. She went wilderness hiking and two weeks later developed fever, arthralgias, proteinuria (2.2 g/d), and elevated serum creatinine (SCr) (1.64 mg/dL). Infectious evaluation was negative but she was treated with antibiotics and fever resolved. The kidney disease was felt to be infection-related GN, however it did not clear and 9 months after the febrile illness she had a kidney biopsy. The biopsy demonstrated moderate glomerulosclerosis and interstitial fibrosis on light microscopy, negative IF except for bright glomerular C3, and large subepithelial humps on electron microscopy. C3GN was considered, but no functional or genetic abnormalities of the alternative complement pathway were found. Proteinuria decreased to 0.2 g/d and SCr was stable so the patient was followed closely. Over the next 15 months proteinuria increased to 1.1 g/d. A kidney biopsy was identical to the first biopsy with persistent C3 on IF, subepithelial deposits, and only mild progression of interstitial fibrosis. Paraffin-embedded tissue was protease-digested and repeat IF showed kappa-restricted granular IgG deposits in the mesangium and GBM. Paraffin-embedded tissue was retrieved from her first biopsy, protease-digested, and it showed kappa-restricted IgG deposits. These findings led to a diagnosis of membranous-like glomerulopathy with masked IgG kappa deposits. No circulating or urinary paraproteins were found and bone-marrow biopsy is pending.

Discussion: The diagnosis of this patient's kidney disease rested on the discovery of immune deposits that were unmasked only after IF on protease-digested paraffin-embedded sections. In glomerular diseases with prominent complement deposition the presence or absence of immune complexes will affect treatment decisions. In the absence of staining on routine IF, protease digestion of paraffin tissue should be considered to exclude masked immune deposits.

PUB553

Doxycycline Induced ANCA Vasculitis Causing Crescentic Glomerulonephritis

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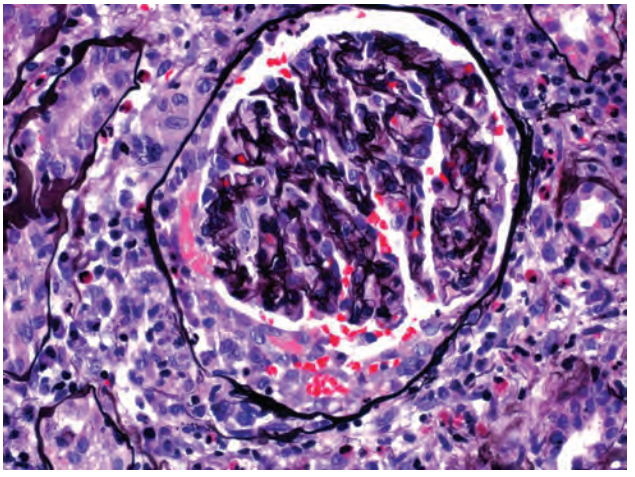
Introduction: ANCA mediated vasculitis is characterized by the absence of immune complex deposition. Certain drugs may be implicated in development of ANCA mediated vasculitis and are associated with constitutional symptoms, arthralgias and cutaneous vasculitis. Rarely, crescentic glomerulonephritis and alveolar hemorrhage may also be present. We describe a rare case of doxycycline induced ANCA vasculitis causing pauci-immune crescentic glomerulonephritis.

Case Description: A 68 year-old female presented with fever and cough and was prescribed levofloxacin followed by moxifloxacin for an upper respiratory tract infection. She failed to respond to these antibiotics and was switched to oral doxycycline 100 mg twice daily. After initiation of doxycycline, she developed a lacy, reticular rash on bilateral lower extremities. Doxycycline was discontinued but she continued to have fevers, arthralgias and fatigue. Labs revealed acute kidney injury with a creatinine of 2.0 mg/dl. Urinalysis showed hematuria along with proteinuria 100+. Serological work-up showed positive c-ANCA (1:1024) along with low C4 (9 mg/dL). Her serum creatinine peaked at 4.39 mg/dL and renal biopsy was performed. Renal biopsy confirmed necrotizing and crescentic glomerulonephritis, pauci-immune type, along with necrotizing arteritis. Patient was initiated on pulse-dose steroids along with Rituximab 375 mg/m2 four weekly doses. Two weeks after the initiation of treatment, patient's renal function showed improvement with a serum creatinine of 2.87 mg/dL with complete resolution of constitutional symptoms.

Discussion: We describe an uncommon presentation of doxycycline causing ANCA vasculitis and leading to pauci-immune glomerulonephritis. In patients developing drug rash and constitutional symptoms with antibiotics like doxycycline, renal function should be assessed. Prompt diagnosis and timely initiation of immunosuppressive agents are essential to renal recovery.



Necrotizing Crescent

PUB554

Occurrence of Post-Infectious Crescentic Glomerulonephritis in a Patient with Small Lymphocytic Lymphoma

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Introduction: Chronic lymphocytic leukemia/ Small Lymphocytic Lymphoma (CLL/SLL) is the most common non-Hodgkin lymphoma associated with glomerular disease but there are only 8 cases of crescentic glomerulonephritis (cGN) associated with CLL/SLL. We are reporting a patient with history of CLL/SLL presenting with acute kidney injury (AKI) and in whom the renal biopsy revealed a crescentic Post Infectious GN (PIGN) with concurrent interstitial infiltration of malignant lymphoid cells. To our knowledge, no such case has been reported in the literature.

Case Description: A 59 y/o diabetic male with history of CLL/SLL, hypertension, seizures, recurrent DVT/PE and CKD was admitted for work up and management of AKI. His only complaint was chronic lower extremity (LE) swelling. His physical exam was remarkable for a BP of 157/106, jugular venous distention, severe pitting edema in the LE's, and a right thigh abscess. Initial labs showed a WBC of 9.9 with 53.7% lymphocytes, Creatinine of 4.10mg/dl, and 24hr urine protein of 8g. Serology for Hepatitis B, C, HIV and ANCA was negative. Complements were normal. He received antibiotics and the abscess was drained. Renal function improved and patient was discharged to follow up with his hematologist. The renal biopsy revealed crescents in 7/20 glomeruli, endocapillary proliferation and rare double contours superimposed on diabetic glomerulosclerosis. A dense interstitial infiltration of neoplastic lymphocytes staining positively for CD20, CD23, CD43 and CD5 was also present. By immunofluorescence microscopy, C3 was deposited along the capillaries. By electron microscopy, a large subepithelial hump was identified. Therefore, the patient was diagnosed with crescentic PIGN with associated interstitial infiltration of SLL.

Discussion: All SLL-associated cGN cases were reported as pauci-immune GN, with one case showing infiltration of neoplastic lymphoid cells within the interstitium. The combination of endocapillary proliferation, glomerular crescents, C3 deposition and a single subepithelial hump characterizes our case as PIGN. Compared to Pauci-immune GN, PIGN is an occurrence not previously reported in this setting, dictating a completely different patient management.

PUB555

Hemoptysis, Renal Failure, and Positive C-ANCA: Is It Truly Wegener's?

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Introduction: Goodpasture syndrome (GPS) is characterized by diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis and positive anti-glomerular basement (Anti-GBM) antibody. Treatment initiation is invariably based on a positive Anti-GBM antibody. We present a case of anti-GBM negative, C-ANCA positive GPS.

Case Description: A 66 year-old male with history of hypertension presented with intermittent hemoptysis for three months and one week of hematuria, fever and chills. On admission he was normotensive and with otherwise normal physical exam. Laboratory abnormalities included: BUN 119mg/dL, creatinine 14.43mg/dL, potassium 3.3mmol/L, hemoglobin 8.4g/dL, ESR 66 and C-reactive protein 3.5mg/dL. CT chest, abdomen and pelvis showed scattered areas of opacities throughout the lungs bilaterally. Urine

microscopy showed RBC casts and 50-100 RBCs/HPF. Work-up revealed an elevated ANA, and negative anti-RNP, scl-70, anti-SM, anti-SSA, anti-LA, and anti-dsDNA. C3 and C4 levels were normal. Patient had a rapid clinical deterioration with increased hypoxemia and worsening hemoptysis. Methylprednisolone was started for suspected Wegener's granulomatosis. Additional tests revealed a positive c-ANCA with a titer of1:320 and negative anti-GBM antibody. Patient had cardiac arrest and expired. Lung autopsy revealed red epithelization and hemorrhage. Histologically, there was minimal necrosis of the alveoli which is expected of Wegener's granulomatosis. The kidneys showed intra-tubular hemorrhage but no crescents or active glomerulonephritis were seen, instead intra-alveolar hemorrhage with organization in the alveolar space was found suggestive of early GPS.

Discussion: GPS is characterized by presence of autoantibodies against α3 chain of type 4 collagen found in alveolar and glomerular basement membrane. Antibody detection rate by ELISA has a false negative rate < 5%. It is important to note that 15%-30% of patients with GPS have positive antinuclear cytoplasmic antibody (ANCA), 3/4th of those cases being C-ANCA. Proper management includes plasmapheresis and immunosuppressive therapy. It is important to differentiate ANCA associated vasculitis from GPS. Serologic testing is the fastest method of diagnosing GPS but carries limitations. Renal biopsy, although gold standard, is difficult to perform in critically ill patients making decision making for timely management challenging for physicians.

PUB556

A Paradox: MPGN After the Treatment of Hepatitis C

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Introduction: Membranoproliferative glomerulonephritis is caused by two main mechanisms: immune complex deposition leading to activation of complement and persistent activation of alternate complement pathway. This dysregulation causes a thickened glomerular basement membrane and increased mesangial and capillary cellularity. MPGN is challenging to treat especially when the underlying cause is unknown.

Case Description: A 66-year-old Asian man with history of hepatitis C cirrhosis presented to the emergency room with increased abdominal distention and lower extremity edema for the past month. On physical exam he had large ascites and 2+ bilateral lower extremity pitting edema. His creatinine was 1.25, but urinalysis revealed >600 protein. Renal ultrasound showed normal kidneys, but there was 13 grams of proteinuria on 24-hour urine collection. Patient's hepatitis C was diagnosed two years ago, and he was treated with Ribavirin and Epclusa with cure. HCV RNA PCR during this admission was undetectable. Serologic work up included HIV, RPR, ANCA panel, RF, complements, free light chains, cryoglobulins, and anti-PLA2R antibody. Kidney biopsy showed MPGN in the setting of sustained viral response from hepatitis C, with no evidence of chronicity or ATN. IF was consistent with immune complex mediated MPGN and EM was consistent with subendothelial deposits. It was positive for IgG, IgA, IgM, C3c, C1q, kappa and lambda. Serologic work-up was normal, serum C3 and C4 were both low and cryoglobulins were negative. He was treated with IV induction steroids and then transitioned to oral prednisone. Repeat 24 hour urine protein was 6.5 grams which improved from 13 grams on admission. Since patient had partial response to steroids, Rituximab was started. Anasarca improved with improving proteinuria and diuresis.

Discussion: MPGN has a variety of causes including infections, autoimmune disease, and monoclonal gammopathies. The IF microscopy showed a "full house" picture with properties of both complement mediated, and immune complex mediated MPGN. This is typically seen in autoimmune disorders, although autoimmune work up was negative. Though HCV has been associated with MPGN, currently there is sparse literature about MPGN in patients after successful treatment of HCV. Thus, this patient with treated HCV most likely developed primary MPGN.

PUB557

Renal-Limited Vasculitis with Unique ANCA Serology: A Great Candidate for Rituximab Therapy

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Introduction: Pauci-Immune glomerulonephritis is the most common cause of RPGN in adults and elderly patients. ANCA serology is usually positive and has shown to play a role in the clinical presentation, kidney manifestations, and renal recovery. Rituximab continues to gain popularity as the first option in treatment. This is the case of ANCA negative pauci-immune glomerulonephritis with good response to Rituximab in combination with methylprednisolone and plasmapheresis.

Case Description: A 65 y/o African American Male with history of hypertension, tobacco use, and prostate CA in remission presented to the ER complaining of progressive general malaise and 15lb weight gain over 2 weeks. He reported sudden uncontrolled BP control in the last 3 months. Physical exam positive for scrotal and +2 pitting edema of lower extremities. Initial labs showed Hgb 14.8 g/dL, Cr 1.4 mg/dL (baseline 0.8mg/dL), BUN 37 mg/dL, Alb 2.3 g/dL and U/A with proteinuria (>600mg) and microscopic hematuria. A 24hr urine collection revealed 45 gm of protein. Serology workup was negative including ANCA, paraproteinemia, and infectious process. Patient denied taking any medicines besides anti-HTN's. Kidney biopsy revealed pauci-immune focal segmental necrotizing glomerulonephritis with one cellular crescent along with 25% tubular atrophy and interstitial fibrosis. He was started on methylprednisolone with weekly Rituximab for 4 weeks. After 2 weeks, his creatinine was still rising. At this time plasmapheresis was initiated and continued for 7 days. After the 3rd dose of rituximab, his Cr went down to 0.8 mg/dL with resolution of edema.

Discussion: Pauci-immune GN usually presents with either positive c-ANCA or p-ANCA. Rarely, it can present with negative serology which can delay diagnosis and initiation of therapy. ANCA negative RPGN presentation is atypical. It usually lacks extra-renal involvement and presents with nephrotic range proteinuria. Kidney biopsy is key to early institution of appropriate therapy that can impact on kidney recovery and long term prognosis. Nephrologists should be highly suspicious of this possibility and be prompt to order kidney biopsy.

PUB558

Treatment of Hashimoto Associated Mesangioproliferative Glomerulonephritis

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Introduction: Mesangioproliferative glomerulonephritis (MesPGN) consists of a group of disorders histologically characterized by an increase in mesangial cells and expansion of the mesangial matrix secondary to deposits of specific immunoglobulins, complements, or immunocomplexes. This insult leads to nephrotic range proteinuria, hematuria, and hypertension (HTN). We present a case in which the deposits consist of immunocomplexes in the setting of autoimmune thyroiditis (AIT).

Case Description: The patient is a 23-year-old female with history of autoimmune thyroiditis and HTN who was referred to Nephrology for evaluation of hematuria and proteinuria. Symptomatically, the patient denied arthralgia and rash. Her family history was positive for lupus and Hashimoto disease. Physical exam was unremarkable. Initial workup revealed: Cr 1.7, microscopic hematuria and proteinuria, urine protein/Cr ratio 3010 mg/g. Serology showed an ANA of 1/40 with negative anti Smith ab and anti ds-DNA. Rheumatology consult ruled out lupus. A kidney biopsy was obtained and revealed immune complex mediated focal mesangioproliferative glomerulonephritis. Immunofluorescence was significant for deposition of IgG, IgM, and C3. The patient was initiated on an ACE inhibitor, mycophenolate mofetile (MMF) 1000 mg BID and prednisone. Microscopic hematuria resolved shortly after starting therapy and proteinuria improved to less than 1000 mg/g. Two years into treatment, prednisone was titrated off. MMF was titrated down 3 years after diagnosis. Patient continues to follow-up in clinic and has been in remission for 4 years status post discontinuation of immunosuppression.

Discussion: AIT has been associated with membranous nephropathy, IgA Nephropathy, and focal segmental glomerulonephritis, but there have been no prior reports of association with MesPGN. Given disease rarity, there are no randomized trials regarding treatment. In patients presenting with mild proteinuria and HTN, ACE inhibitors can prevent progression to nephrotic range proteinuria. For patients with nephrotic range proteinuria, steroids can prevent progression to FSGS. Immunosuppressants have gained popularity as a treatment modality. MMF, in particular, works by improvement of mesangial cell and matrix hypercellularity. The comparative efficacy of MMF in conjunction with steroids to other therapies has yet to be established.

PUB559

Scleroderma Renal Crisis – A Genetic Complementopathy?

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Introduction: Complement dysfunction is a major contributor to the pathophysiology of atypical hemolytic uremic syndrome (aHUS). Scleroderma renal crisis (SRC) shares many clinical and pathologic features with aHUS. We present a case of SRC in a patient with a homozygous mutation associated with aHUS.

Case Description: A 44-year-old woman with a 17-year history of scleroderma presented to rheumatology clinic with new onset hypertension and a rising creatinine. She was admitted to the hospital and started on captopril for blood pressure control; her blood pressure was lowered to her baseline within 48 hours. A 24-hour urine protein demonstrated 1.7 g proteinuria. Given the late presentation of her kidney injury relative to her diagnosis of scleroderma, she underwent a renal biopsy. Blood vessels showed moderate-to-severe wall thickening with semi-occlusive/occlusive changes and some of the vessels revealed "onion skinning," consistent with SRC (Fig 1). Her creatinine stabilized at 2 mg/dl and she was discharged. She was readmitted one week later with recurrent hypertension and an elevated creatinine. The patient underwent genotyping for mutations of the complement pathway and was found to have a homozygous polymorphism within an intron of the membrane cofactor protein/CD46, which has been associated with aHUS. She was initiated on eculizumab. She subsequently developed an infection and had an antibiotic drug reaction that caused her renal disease to progress and she was initiated on dialysis.

Discussion: SRC and aHUS are two entities that are clinically and pathologically similar. SRC pathogenesis may be related to alternative complement pathway dysfunction.

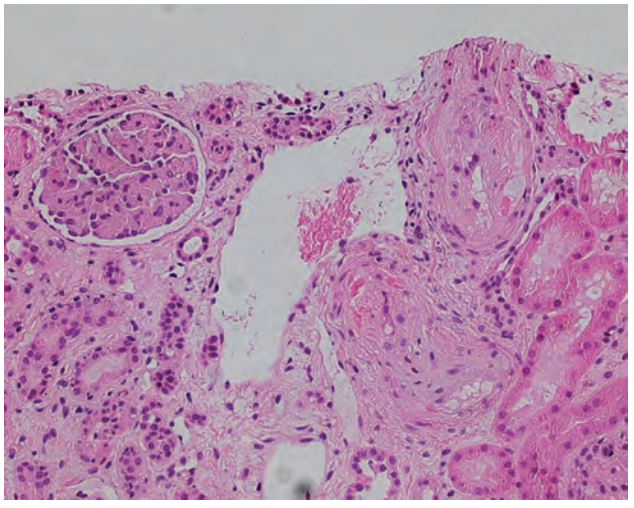

Fig 1

PUB560

The Great Mimicker – A Diagnosis That Should Not Go Undetected

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare disease found in 1% of native kidney biopsies. Most commonly seen in Caucasians, with a predominance of female to male ratio 2:1. Is characterized by glomerular accumulation of non-branching, haphazardly arranged fibrils measuring 10-30 nm in thickness in the mesangium. Undistinguishable from amyloid fibrils except for lack of reactivity to congo red staining. Light microscopy variable patterns that include membranoproliferative, diffuse proliferative, mesangial proliferation and expansion. IF most often reveal polyclonal deposit of IgGs, particularly IgG4 and IgG1. Very little is known about pathogenesis of FGN, however the presence of IgG and complement suggests a glomerular deposition of immune complexes with the ability to undergo fibrillogenesis. Renal outcomes for this disease are poor with progression to ESRD in 4 years in 50% of the patients. No standard therapies are available

Case Description: 71 year old Caucasian male with history of Bladder cancer and Hypertension who developed nephrotic range proteinuria 3.5g/d, serum cr level 1.72 mg/dL, eGFR (MDRD) 39 mL/min/1.73^2. Five months prior with baseline serum creatinine 1.18 mg/dL and eGFR 64.68mL/min/1.73m^2. C3: 123, C4: 32, HIV, Hep B/C, ANA and PLA2R negative. Kappa/lambda 0.78. SPEP and UPEP negative for monoclonal protein. Physical exam significant for +2 lower extremity edema. Kidney biopsy yielded 20 glomeruli. Light microscopy showed diffuse and global mesangial expansion without proliferation. IF was positive for IgG +3, C3 +2, kappa +3 and lambda +3. EM showed sub-epithelial and sub-endothelial densities composed by randomly arranged, non-branching fibrils measuring 20nm consistent with FGN. Patient was treated with two doses of rituximab (1G IV x 2). Six months later, serum creatinine 1.68mg/dL and eGFR 40 mL/min/1.73m^2, with a decrease UPCR to 1.2

Discussion: FGN is an uncommon disease, reason why no controlled clinical trials have been conducted. Small case series propose rituximab as a promising treatment for FGN with the pathology rationale of predominant polyclonal IgG deposits seen in mesangium and glomerular basement. Favorable results were observed in patients with preserved renal function at baseline, similar to our patient suggesting that early diagnosis is necessary to prevent or decrease progression to ESRD.

PUB561

IgA Nephrology After Liver Transplant

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Introduction: IgA nephropathy is the most common biopsied glomerulonephritis worldwide and typically has a slowly progressive course. IgA nephropathy has been associated with end-stage liver disease with biopsies of patients prior to liver transplant or ex-plant in liver-kidney transplant patients demonstrating IgA nephropathy in up to 50% of cases. However, it has been rarely reported as new diagnosis post-liver transplantation. Here, we present a case of IgA nephropathy which developed several years after liver transplantation.

Case Description: Patient is a 62 year-old male with a history of hepatitis C and alcohol-related cirrhosis who underwent liver transplantation in 2009. Prior to transplant, he had no renal dysfunction, hematuria or proteinuria. He presented to nephrology clinic in 2016 with worsening chronic kidney disease (CKD) and proteinuria. His hepatitis C had been successfully treated post-transplantation. Laboratory examination at time of initial consultation showed tacrolimus levels at goal, creatinine of 2.4 mg/dL and urine protein-creatinine ratio of 3.3. Because of his proteinuria, with no clear explanation, he underwent renal biopsy which showed co-dominant IgA and IgG mesangial and segmental capillary loop staining by immunofluorescence as well as subendothelial deposits by electron microscopy and focal nodular hyalinosis. These findings are consistent with IgA focal proliferative glomerulonephritis and calcineurin inhibitor toxicity. He was placed on an angiotensin converting enzyme inhibitor and his creatinine has stabilized with a reduction in his proteinuria.

Discussion: CKD, usually secondary to calcineurin inhibitor toxicity, is a known complication of liver transplantation. There is also a known association of IgA nephropathy with end-stage liver disease. However, the development of IgA nephropathy following liver transplantation has been rarely reported. This case demonstrates the importance of considering other etiologies of chronic kidney disease in post-transplant patients, particularly if hematuria or proteinuria are present.

PUB562

A Case of Malignant Hypertension with Thrombotic Microangiopathy Mimicking Small-Vessel Vasculitic Diseases

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Introduction: Malignant hypertension may present with a number of clinical sequela, however, pulmonary hemorrhage and palpable purpura are rarely associated with the disease presentation. We present a case of malignant hypertension presenting with thrombotic microangiopathy (TMA).

Case Description: A 37-year-old woman presented with a 2-month history of anasarca and a 2-week history of progressive dyspnea with hemoptysis. Her past medical history was significant for untreated hypertension. On arrival, the patient's blood pressure was 230/150 mmHg. She had bilateral inspiratory crackles on lung auscultation and bilateral pretibial slow pitting edema and palpable purpura on her extremities. She had a microcytic anemia (Hb 10.5 g/dl) and mild thrombocytopenia (129,000 platelets/μl) without evidence of schistocytosis. The LDH value was 819 U/l and serum creatinine level was 4.3 mg/dl. The urinalysis demonstrated hematuria and proteinuria with granular casts. The spot urine protein to creatinine ratio was 0.8 g/gCr. Her chest radiograph showed bilateral diffuse ground grass opacities. The patient subsequently received a sequential bronchoalveolar lavage, which demonstrated alveolar hemorrhage. Small-vessel vasculitic diseases were suspected, yet the patient's serum ANA, MPO-ANCA, PR3-ANCA, anti-dsDNA, and anti-GBM antibodies were all negative. A skin biopsy showed the presence of microthrombosis within the dermis. The histology of the renal biopsy was compatible with TMA, revealing glomerular intracapillary fibrinoid necrosis with fibrinoid thrombosis and accumulation of fragmented erythrocytes, mucoid intimal thickening and concentric myointimal proliferation. After initiating treatment with antihypertensive drugs, the patient's serum Hb, platelets and LDH normalized. Her renal function also recovered without dialysis. Follow-up evaluation identified no secondary causes of resistant hypertension.

Discussion: A high index of suspicion of malignant hypertension with TMA is warranted in patients with a history of uncontrolled hypertension and symptoms of pulmonary renal syndrome and purpura, which are typically manifestations of small-vessel vasculitic diseases. Early and aggressive blood pressure control may reduce long-term morbidity and mortality in these patients.

PUB563

Life Threatening Bleeding from Arcuate Kidney Artery Aneurysm as a Rare Complication of Granulomatosis with Polyangiitis

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Introduction: Granulomatosis with polyangiitis (GPA) is a systemic necrotizing inflammation of small and medium-size vessels. It most commonly affects the upper respiratory tract and the kidneys. Bleeding from aneurysms formed during the disease is a rare complication.

Case Description: 50y old patient was transferred to the Department of Nephrology with the suspicion of GPA. The patient was hospitalized for one month with fever, night sweats and progressive pedal edema. The blood test revealed high CRP, the CT scan suggested staphylococcus pneumonia, although patient condition did not improve with antibiotic therapy. Development of kidney failure (creatinine rise from 0.7mg/dl to 3.7mg/dl) and progression of pulmonary infiltrates with cavity formation raised the suspicion of GPA. On admission creatinine was 4.1mg/dl, CRP 211mg/l, cANCA 1:2560, anti-PR3 titer 188RU/ml and among clinical symptoms dominated significant shortness of breath what corresponded with massive pulmonary infiltrates in CT scan. The diagnosis of life-threatening GPA was establish and patient received i.v. methylprednisolone, plasma exchange therapy and pulses of cyclophosphamide. Simultaneously hemodialysis was initiated. On the 15th day of hospitalization patient suffered from a very strong pain in the right flank with significant hemoglobin lowering. Angio-CT scan was performed and showed massive hematoma adjacent to the right kidney with active bleeding from the raptured aneurysm of the arcuate artery. Numerous small non-bleeding aneurysms in both kidneys were also visualized. Urgent embolization of the bleeding vessel was performed which stopped the hemorrhage. After third pulse of cyclophosphamide the condition of the patient improved, regression of the pulmonary infiltrates was observed, although the patient

remained dialysis dependent. The follow up immunosuppressive therapy was planned on an outpatient basis.

Discussion: Clinical manifestations of GPA can be highly varied and are dependent upon which organ is affected by vasculitis. Major hemorrhage from an aneurysm of a medium or large-size artery is a rare manifestation of ANCA-associated vasculitis. Urgent diagnostic CT and intravascular radiology intervention or surgery can ameliorate the patient condition.

PUB564

Lupus Optic Neuritis in ESRD Patient

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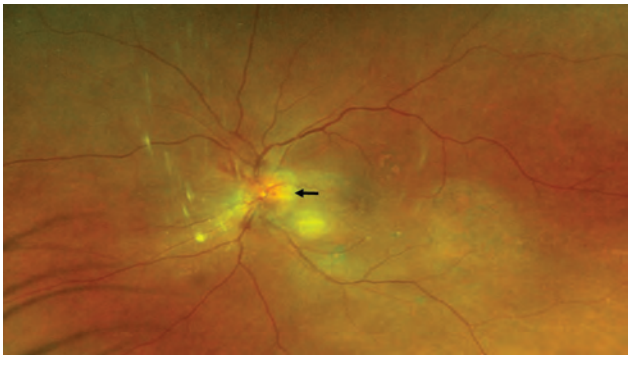
Introduction: Optic neuropathy is an uncommon finding in dialysis patients and has been associated with uremia, ischemia (arteritic and nonarteritic), drugs (isoniazid, ethambutol), infections (tuberculosis) and intracranial hypertension. Inflammatory optic neuritis associated with lupus nephritis is however extremely rare. Herein, we present one such case.

Case Description: A 50-year-old Indian-American female with a history of end stage renal disease (ESRD) secondary to Lupus nephritis, on renal replacement therapy for 2 years presented to the ER with intermittent left eye loss of vision described as "foggy vision, as if looking through a curtain at the edges" for six days without flashing lights. Fundus examination showed optic disc edema with mild obscuration vessels (arrow) and peripapillary flame hemorrhages and retinal pigment epithelial mottling of the macula [Figure], consistent with inflammatory optic neuritis from Lupus. Her dialysis sessions were uneventful and the most recent monthly Kt/V was 1.4.

Discussion: Clinical and serological lupus activity is thought to be substantially reduced after the onset of ESRD and most of the extra-renal manifestations are hematological. The main determinants of lupus activity are age of the patient and time on dialysis therapy, reaching 39% after 5 years on dialysis.Our patient was admitted to the hospital and treated with intravenous methylprednisolone 250 mg pulsed every 6 hours for 3 days and then was transitioned to oral steroids on outpatient basis. Visual symptoms showed gradual improvement. Apart from eye infections related to catheter-related blood stream infections, optic neuritis from Lupus is another important ophthalmologic condition that Nephrologists need to be familiar with to facilitate prompt treatment.



PUB565

An Unusual Cause of Hematuria on a Patient with Granulomatous Polyangiitis

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Introduction: Granulomatous polyangiitis (GPA) is an inflammatory condition characterized by often relapsing hematuria, proteinuria and renal damage. Here, we present a case of an 87 year old man with history of GPA who presented with persistent hematuria, raising concern for a flare of his GPA, and subsequently a bladder wall malignancy when a mass was found in his bladder. However, evaluation, notable for an elevated urine pH and mild leukocyturia, ultimately led to the diagnosis of Corynebarcterium urealyticum cystitis, an uncommon condition seen in immunosuppressed patients.

Case Description: An 87 year old man with an 18 year history of GPA with renal involvement and prostate cancer presented to his rheumatologist with 1 month of intermittent hematuria and weakness. He was found to have elevated serologic titers and was presumptively treated for GPA relapse with high dose steroids and rituximab. Symptoms persisted, however, and he returned with gross hematuria. On admission, he was hemodynamically stable and afebrile. Cr was 2, up from a baseline of 1.5, and the CRP and ESR were normal. Urinalysis showed 3+ blood, 3+ protein, 3+ leukesterase, 20-25 wbc and a pH of 9. Urine sediments was impressive for RBCs and WBCs but no dysmorphic cells were seen. Urine culture was initially negative. Hematuria improved with CBI; cystoscopy demonstrated a calcified bladder mass, and a transurethral resection of bladder tumor was recommended. The culture eventually grew Corynebacterium urealyticum and Nephrology recommended antibiotic therapy. Cystoscopy was nevertheless performed with resection of the mass; pathology showed no evidence of malignancy but predominantly denuded urothelium with reactive changes, atypical stromal cells, necrosis, and active chronic inflammation with calcium deposits.

Discussion: C. Urealyticum is a fastidious, urea-splitting gram-positive organism typically seen in immunosuppressed patients, often introduced by frequent bladder catheterization, as it was in this gentleman. Our patient's presentation, with an encrusted cystitis and pyelitis, is typical. The elevated urine pH and the presence of the bladder mass in a chronically catheterized immunosuppressed patient were clues to the diagnosis and an invasive intervention might have been avoided.

PUB566

Congo Red Positive Fibrillary Glomerulonephritis

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Introduction: Patients with nephrotic range proteinuria and longstanding diabetes mellitus (DM) are often presumed to have diabetic nephropathy (DN). Therefore kidney biopsy is often not performed. However as the prevalence of DM in the general population is rising, the number of cases of nephrotic range proteinuria that are falsely attributed to DN also may be increasing.

Case Description: A 62 year-old female with a history of DM, CKD stage 3, and HTN presented with elevated creatinine and proteinuria. She was noted to have newly diagnosed nephrotic range proteinuria (8 grams/day) which was not consistent with her disease course and therefore kidney biopsy was performed. The light microscopy showed capillary wall and mesangial matrix expansion as well as interstitial fibrosis with a chronic lymphocytic inflammatory infiltrate. Immunofluorescence was significant for smudgy deposition of C3 (1+), IgG (1+), kappa light chain (1+) and lambda light chain (2+). Electron Microscopy (EM) showed fibril deposition with fibril diameters being greater than those typical of amyloid. Furthermore, Congo red staining was weakly positive but did not show green birefringence. Fibril identification by liquid chromatography/mass spectrophotometry (performed at Mayo Laboratories, Rochester MN) was negative for monoclonal light chain but showed positivity for iDNAJB9, a sensitive and specific marker of fibrillary glomerulonephritis (FGN).

Discussion: FGN is defined by the presence of organized fibrils on EM that are usually thicker than those of amyloidosis, usually positive for polyclonal IgG and C3, and importantly are unstained with Congo red. Our patient was found to have this rare diagnosis. This case highlights the importance of renal biopsy in patients with DM and nephrotic range proteinuria, who present with an atypical disease course. Additionally, when renal biopsy shows organized deposits, mass spectroscopy should be considered to ensure an accurate diagnosis.

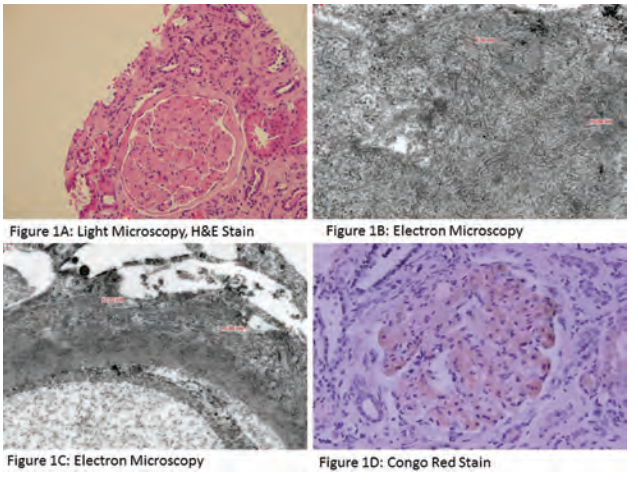

Figure 1A: Light Microscopy, H&E Stain

Figure 1B: Electron Microscopy

Figure 1C: Electron Microscopy

Figure 1D: Congo Red Stain

PUB567

Diffuse Alveolar Hemorrhage, a Rare Complication of Henoch-Schönlein Purpura

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Introduction: Henoch-Schonlein purpura (HSP) is a small vessel vasculitis typically seen in children. Less commonly the disease can occur adults, with renal disease more severe than that seen in children. Diffuse alveolar hemorrhage (DAH) is a rare complication of HSP which if not promptly recognized, carries a high mortality.

Case Description: A 50 y/o male with history of hypertension treated with hydralazine, alcoholic cirrhosis, prior documented leukocytoclastic vasculitis (LCV) presented with lower extremity cellulitis and was treated with vancomycin. On second day of admission he was noted to have significant hypoxia and hemoptysis prompting intubation. There was interval development of purpuric rash in the trunk, bilateral arms and legs. A CT scan demonstrated diffuse lung consolidation and bronchoscopy findings consistent with DAH. Laboratories were remarkable for creatinine: 2.81mg/dL, BUN: 45mg/dL with associated hematuria and minimal proteinuria. Serologies revealed elevated MPO-ANCA (544 AU/ml), double stranded antibodies (119 IU), anti-histone (3.8) but normal anti-GBM and anti-proteinase 3 titers. Intravenous methylprednisolone and plasmapheresis were started for presumed ANCA associated vasculitis (AAV). Renal biopsy revealed diffuse mesangioproliferative glomerulonephritis and acute tubular necrosis without crescents on light microscopy. Immunofluorescence (IF) showed 2+ IgA, 2+ IgM and 2+ C3, all in a mesangial pattern. Electron microscopy demonstrated segmental effacement of foot

processes without tubuloreticular inclusions. Biopsy of his purpuric rash demonstrated LCV but was negative for IgA on IF. Due to development of leukopenia, rituximab was started over cytoxan. Despite treatment, he was unable to recover any renal function requiring dialysis. He was intubated for a prolonged intubation course and was ultimately transitioned to comfort care.

Discussion: HSP with DAH is a fatal complication, with reported prevalence between 1.6%-5% and a mortality rate of 27.5%. Our patient was suspected to have AAV given his positive ANCA and MPO serologies, however kidney biopsy argued against a pauci-immune glomerulonephritis. Instead, a diagnosis of HSP with DAH was felt most likely, and treated with corticosteroids, plasmapheresis and rituximab. The poor outcome in this case, highlights challenges in treatment of this particularly devastating disease.

PUB568

A Case of a Pregnant Woman Carrying Dichorionic Diamniotic Twins and Having Nephrotic Syndrome Eventually Diagnosed as IgA Nephropathy and Preeclampsia After Delivery

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Introduction: A 35-year-old Chinese pregnant with dichorionic diamniotic (DCDA) twins developed nephrotic syndrome (NS). However, her blood pressure (BP) continued to be normal throughout her gestation and puerperium. After delivery, her NS got worse. A renal biopsy (RBx) revealed IgA nephropathy (IgAN) and preeclampsia. She was treated with steroid therapy and her NS improved. This is a rare case presenting a combination of IgAN and preeclampsia pathologically but not meeting preeclampisa criteria in the clinical course.

Case Description: A 35-year-old Chinese female with no history of renal disease was pregnant with DCDA twins. At 31 weeks of pregnancy, she presented with nephrotic range proteinuria (8.9 g/day) and hypoalbuminemia (1.7 g/dL) for the first time. However, her BP was normal, at approximately 110/80 mmHg. She did not match the criteria of preeclampsia. At 34 weeks of pregnancy, she delivered twins by cesarean section. At 16 days after delivery, she presented with syncope and her NS got worse; her proteinuria was 21.1 g/day. She underwent an RBx, and we started treatment with m-PSL pulse followed by conventional prednisolone therapy. Her pathological findings were extracapillary cell proliferation and 3+ staining for IgA over the mesangial area on immunofluorescence, and electron microscopy revealed electron dense deposits in the paramesangial area along with endotheliosis and epithelial cell changes. Therefore, her pathological diagnosis was a combination of IgAN and preeclampsia. After beginning steroid therapy, her NS gradually improved.

Discussion: This case showed development of severe proteinuria without hypertension, which is rare. IgAN cases diagnosed as a result of NS comprise less than 10% of all IgAN cases. In addition, NS due to renal diseases reportedly occurs in 0.028% of pregnant women. Therefore, if pregnancies present severe gestational proteinuria without hypertension, a pathological preeclampsia diagnosis should be considered.

IgAN and Pregnancy

Maternal age(yr)/gestation age (wk)	Past History	Hypertension During pregnancy	Cr at presentation	Peak proteinuria During/After pregnancy(g/day)	Serum Albumine During/After pregnancy (g/dL)	Diagnosis	Pathology
27/19	IgAN	(-)	0.9	8.3/not discribed	2.7/3.9	Aggrivation of IgAN	Mesangial cell proliferation, Cellular crescent, IgA deposition
26/18	IgAN	(+)	0.88	1.2/9	2.9/4.5	A combination of IgAN and preeclampsia	Mesangial cell proliferation, Fibrous cellular crescent, IgA deposition
28/29	IgAN	(+)	0.61	5.6/7.2	2.5/not discribed	A combination of IgAN and preeclampsia	Cellular crescentendotheliosis, thrombus, IgA deposition
35/33 (This case)	None	(-)	0.82	1.3/21.1	1.6/1.0	A combination of IgAN and preeclampsia	extracapillary cell proliferation, endotheliosis and epithelial cell changes, IgA deposition

PUB569

Podocyte Infolding Glomerulopathy: A Rare Cause of Proteinuria in SLE

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Introduction: Podocyte infolding glomerulopathy (PIG) is a pathologic entity characterized by diffuse podocyte infolding into the glomerular basement membrane (GBM) associated with ultrastructurally demonstrable microspherular aggregates. The clinical features, significance, and pathogenesis of this condition are still not well delineated because only a few cases have been documented to date, all from Japan and India. We report a case of PIG associated with SLE in an AA woman who presented with nephrotic syndrome.

Case Description: A 25 year old AA female was seen in nephrology clinic as a transition of care from pediatrics. She had a diagnosis of SLE for over 10 years. She had a kidney biopsy 5 years ago that showed Class III+V lupus nephritis that required treatment with tacrolimus monotherapy. Since, her renal function was normal and her proteinuria minimal at <1gm/24 hours tacrolimus was discontinued. Over the next one year, her proteinuria progressed to 3gm. A kidney biopsy revealed PIG along with Class 1 lupus nephritis. EM analysis of the biopsy specimen revealed unusual subepithelial aggregates of microspherules admixed with few microtubules alongside extensive infolding of podocyte foot processes into the underlying GBMs. Characteristic clustering of these microparticles near the invaginated tips of podocyte foot processes in the GBM was observed on EM. With elevated dsDNA levels, and normal secondary workup of all viral etiologies, it was presumed to be secondary to SLE and treatment was initiated with rituximab (2 doses) 1gm over 2 weeks apart. She was maximized on conservative therapy with enalapril. Her proteinuria peaked at 5gm and the most recent is 2gm. Her dsDNA levels have been down-trending as well.

Discussion: PIG is a rare entity initially described as a nucleopore glomerulopathy in the 1980s. Most of the recent cases described have been in the Japanese and the Indian population. Majority of the patients had a contaminant diagnosis of SLE or other autoimmune diseases. The diagnosis is made with findings on EM as IF shows minimal reactivity to immunoglobulins. Response to immunosuppression can be variable. In our case, there was a partial response to rituximab therapy. Nephrologists and rheumatologist need to be aware of this rare form of glomerular disease in patients with SLE and other connective tissue disorders.

PUB570

Immunological Remission in PLA2R-Antibody–Associated Membranous Nephropathy in a Kidney Transplant Patient After Excision of Breast Cancer

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Introduction: M-type phospholipase A_2 receptor(PLA_2R) is the major antigen in primary membranous nephropathy(MN). It is suggested that coexistent PLA2R-positive MN and cancers are coincidental since previous reported cases did not achieve remission of proteinuria after tumor resection. We present a case of coexistent PLA2R-positive MN and breast cancer after kidney transplant(KTx), who subsequently had immunological remission in PLA2R-Ab and reduction of proteinuria after excision of breast cancer.

Case Description: A 76-year-old Caucasian female, who was a recipient of a deceased donor zero-ABDR mismatch kidney, developed worsening proteinuria over the first year post KTx. Long-standing HTN was the presumed cause of her ESRD. She received induction with rabbit anti-thymocyte globulin and was maintained on cyclosporine, prednisone and mycophenolic acid. At 2-month follow-up, she developed 2+ (100 mg/dL) proteinuria. Thus, lisinopril was initiated and was titrated up to 20 mg daily. Her serum Cr had been 1.0 mg/dL which was her baseline. However, her proteinuria had been gradually worsening, measured at 4 g/24h at 8-month post-KTx. Renal allograft biopsy revealed MN with +glomerular PLA2R deposition. The PLA2R Ab in the serum was also positive. IgG subtyping showed intense IgG4 staining along the glomerular capillary walls. Lab testing showed negative for monoclonal protein, ANA, HBV, HCV, and HIV. She underwent age-appropriate screening for malignancy, and was found to have newly diagnosed ductal Carcinoma in Situ of left breast. She underwent lumpectomy and did not require chemotherapy. The patient did not receive higher immunosuppression or any additional treatment for her MN. On 9-month follow-up studies, proteinuria in a 24-hour urine collection decreased to 1.1 g/24h with stable serum Cr. Serum PLA2R-Ab was repeated and came back negative.

Discussion: The coexistence of MN, solid tumors, and PLA2R positivity has been previously reported, and is suggested that the coexistence could be coincidental. In addition, recent studies showed that appearance of PLA2R-Ab post-KTx may suggest a more resistant MN. To our knowledge, this is the first case of KTX patient, who achieved immunological remission in PLA2R-Ab and reduction of proteinuria after excision of breast cancer.

PUB571

Crescentic Lupus Nephritis Treated with MMF, a Promising Outcome: 2 Patient Series

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Introduction: Crescentic lupus nephritis is a severe disease that requires an aggressive approach to treatment. Recent randomized clinical trials showed that mycophenolate mofetil compared favorably with cyclophosphamide (traditional approach) for remission induction. However, the role of mycophenolate mofetil in treating **crescentic lupus nephritis** remains unclear, because such patients were excluded from these trials. Many nephrologists still prefer to treat this patient population with cyclophosphamide despite its known toxicities. Here, we present a case series of two patients with severe crescentic lupus nephritis (class 4 G) treated with MMF –as an induction therapy-with an excellent response within 6 months of treatment.

Case Description: Patient 1: 34 year old African American female with class 4 lupus nephritis complicated by crescents as evidenced by her renal biopsy. Upon induction with MMF and steroids, she has had marked improvement in serological markers of activity including dsDNA titers (173 to 15) and improvement in serum albumin (1.7 to 3.6) within 3 months of treatment. Patient 2: 30 year old African American female with crescentic lupus nephritis class 4, was also initiated on MMF and steroids. Her kidney function has markedly improved with creatinine dropping from 3.5 mg/dL to 1.33 mg/dL. Her proteinuria has markedly decreased from 9.5g to 1.2g within 3 months of induction.

Discussion: Lupus nephritis represents a significant complication of SLE with substantial morbidity and mortality. Although treatment has improved, treating crescentic lupus nephritis portends a challenge to nephrologists that they fall back to old therapies like cyclophosphamide despite its significant morbidity, including an increased risk of serious infections and amenorrhea. In clinical practice, MMF is now the preferred induction regimen for patients with lupus nephritis (not crescentic) who wish to preserve fertility, which is a large patient population given that the disease commonly presents in women of child-bearing age. Unfortunately, most randomized controlled studies of lupus nephritis do not offer insight on treating cases complicated by crescents given their reduced occurrence. Our abstract sheds the light on the use of MMF as induction therapy for crescentic lupus nephritis which offers these patients a drug with less toxicity.

PUB572

Crescentic Primary Membranous Glomerulonephritis

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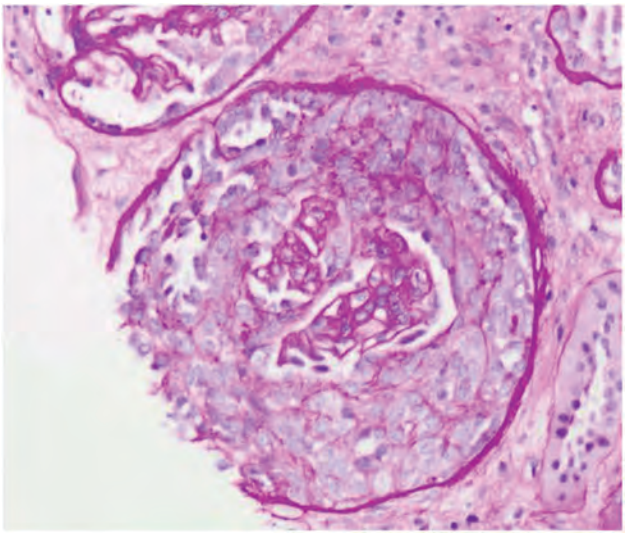
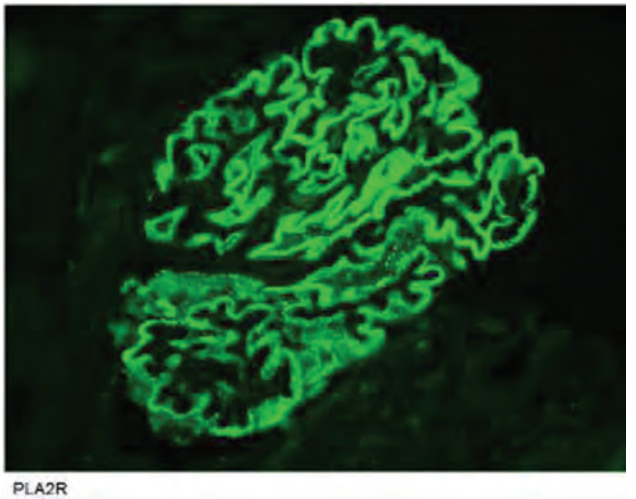
Introduction: Membranous nephropathy (MN) is one of the common causes of nephrotic syndrome in adults and is most often primary (pMN). Kidney function is usually normal at presentation. Mild mesangial hypercellularity may be seen in pMN but significant proliferation and crescent formation raise suspicion of a secondary process. This case illustrates an unusual presentation of pMN.

Case Description: A 20 year old black woman presented with swelling. Diagnostic work up was significant for AKI with Scr 3.9 mg/dl, active urine sediment and nephrotic syndrome (24h urine Protein/Creatinine 15.7g/g and serum albumin 1.8g/dl). Kidney biopsy showed crescentic GN with IgG1, IgG4, and PLA2R staining on IF, and electron dense subepithelial deposits along the glomerular capillary loops (figures 1 and 2). Serum anti-PLA2R was 338 units/ml. Work up for secondary or additional etiology was negative. She received 2g IV methylprednisolone. Ten days later her Scr improved to 1.2mg/dl. She is currently on cyclophosphamide and prednisone, anticoagulation and lisinopril.

Discussion: pMN with rapidly progressive and crescentic glomerulonephritis is unusual. The predominant IgG1 and IgG4 staining and the positive serum anti-PLA2R and tissue PLA2R with negative work-up for secondary/additional etiology support the diagnosis.





PUB573

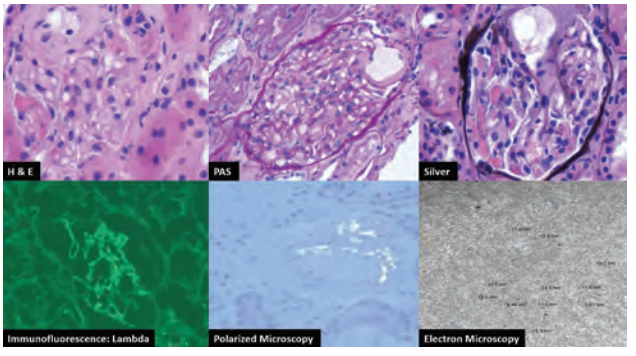
Elderly White Man with Proteinuria Does Not Always Have Membranous Nephropathy or Minimal Change Disease

Justin Lee Loy, Gajapathiraju Chamarthi, Abhilash Koratala. *University of Flroida, Gainesville, FL.*

Introduction: Heavy proteinuria with or without overt nephrotic syndrome may occur in association with a wide variety of primary and systemic diseases. Kidney biopsy is not always indicated, especially when secondary cause is suspected but the serologic work up should be 'complte' prior to making a decision. We describe a case where incomplete serological work up with respect to serum immunofixation (IFE) delayed the diagnosis and appropriate treatment.

Case Description: A 70-year-old White man without any known systemic disease was seen for second opinion regarding worsening proteinuria and edema. His symptoms started 1 year ago at which time, he had 700 mg/g proteinuria. SPEP, UPEP and Serum Free light chain assay (FLC) were negative for monoclonal protein. Screening for common vasculitides and viral hepatitis was negative. However, serum/urine IFE was not obtained. His proteinuria worsened to 5g/g in 1 year and developed hypoalbuminemia with relatively preserved creatinine. The patient was told by his prior nephrologist that it's most likely membranous nephropathy vs. minimal change disease and the plan was to empirically treat with prednisone. Therefore, patient was resistant to undergoing renal biopsy and requested us to obtain serum PLA2R autoantibody testing. Eventually, he agreed and the biopsy revealed λ light chain (AL) amyloidosis. Bone marrow biopsy revealed abnormal plasma cells with monotypic λ light chains and he was referred for bone marrow transplant.

Discussion: Most patients with AL amyloidosis have little or no intact monoclonal immunoglobulin, but are characterized by the presence of monoclonal free light chain. IFE of serum and urine is required because the monoclonal peaks in amyloid tend to be small and frequently do not produce a spike detectable with electrophoresis alone. It's noteworthy that in one series, the diagnostic sensitivity of the FLC κ/λ ratio was 76%, that of IFE of both serum and urine was 96%, and their combination correctly identified the amyloidogenic light chains in 100% of patients.



PUB574

Tacrolimus and Intravenous Cyclophosphamide as Effective Therapy for Membranous Nephropathy in a Patient with Mixed Connective Tissue Disease

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Introduction: Renal involvement occurs in about 25% of patients with mixed connective tissue disease (MCTD), and it usually takes the form of membranous nephropathy (MN).

Case Description: A 61-year-old woman was admitted to our hospital complaining of lower extremities edema. She was diagnosed with MCTD because of Raynaud's phenomenon and positive anti-RNP antibody at the age of 39 years old. Since no organ involvement was observed, she did not receive any glucocorticoid or immunosuppressant. She developed nephrotic syndrome at the age of 60, and renal biopsy revealed the association of MN. PAM staining of renal histopathology showed spiking of the glomerular basement membrane and Masson trichrome staining showed diffuse sub-endothelial deposit. Anti-phospholipase A2 receptor antibody was negative. Oral prednisolone (PSL) 30mg and mizoribine (MZB) 100mg daily were initiated, but failed to achieve remission. Switching MZB to tacrolimus (TAC) 3mg daily decreased urine protein/creatinine ratio (UPCR) to 2.0-4.0 g/gCr, but persistent proteinuria remained. Because she developed cellulitis of her left lower extremity due to severe edema and became unable to walk, intravenous cyclophosphamide (IVCY) was added expecting immediate improvement. UPCR was reduced to 0.5-1.0 g/gCr and walking difficulty was significantly ameliorated following IVCY. TAC + IVCY combination therapy was continued and PSL was tapered.

Discussion: Efficacy of TAC + mycophenolate mofetil combination therapy for lupus nephritis (LN) has been well documented. Since Asian LN patients have much higher response rate to CY than black or white patients, IVCY could be a beneficial treatment for the LN. TAC is also safe and effective for class V LN. Although no standard therapy has been established at this point, TAC + IVCY could be a beneficial therapeutic option for MN associated with MCTD according to treatment strategy for LN.

PUB575

IgA Nephropathy Associated with Evans' Syndrome

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Introduction: IgA nephropathy (IgAN) is associated with autoimmune diseases. Evans' syndrome (ES) is characterized by immunological hemolytic anemia (HA) and thrombocytopenia (TCP), and may be idiopatic or secondary. Systemic lupus erythematosus (SLE) is associated with IgAN and ES. We report the case of a patient with primary ES and IgAN, treated for SLE

Case Description: Female patient aged 23. At 13, after a viral infection, she was diagnosed with SLE due to edema, macroscopic hematuria and hypertension. At the time, she presented: creatinine 2.0 mg/dL, hemoglobin 7.0 g/dL, positive direct Coombs test, platelets 95,000. The urine analysis: 3+ protein and numerous red blood cells; proteinuria (PTN) 500mg/24h; negative ANA, anti-DNA, VDRL. C3 46 (NR 90-180 mg/dL). A kidney biopsy (KB) in her medical records described lupus glomerulonephritis. After treatment with methylprednisolone (methyl) and cyclophosphamide (CP), the glomerular filtration rate (GFR) was normalized. Maintenance treatment was azathioprine. She continued with subnephrotic PTN, microscopic hematuria, intermittent HA and TCP, negative ANA and no other clinical manifestations of SLE. A myelogram was performed, which was normal. At 16, mycophenolate mofetil was initiated. After 3 years with no remission of PTN, she did a KB that showed mesangial expansion and hypercellularity, segmental sclerosis and adherence to the Bowman's capsule, with no endocapillary proliferation; immunofluorescence: intense granular deposits of IgA in the mesangium and capillary loops, characterizing IgAN. At 23, she suffered a rapid GFR decline, with HA and TCP. A new KB confirmed a diagnosis of crescentic IgAN. The treatment was methyl and CP for 5 months. With no clinical response, a KB was performed with electron microscopy (EM): chronic IgAN, with no lesions suggestive of SLE. There was a need for dialysis.

Discussion: This is the first report of IgAN associated with idiopatic ES. We emphasize the importance of EM for an adequate diagnosis of glomerulonephritis, especially when the clinical signs are not definitive

PUB576

Use of Rituximab as a Steroid Sparing Agent to Achieve and Maintain Complete Remission in an Initial Episode of Minimal Change Disease

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Introduction: Adults with minimal change disease (MCD) will experience complete remission over 80% of the time with corticosteroids. Data for using steroid sparing regimens to treat the initial episode is limited mostly to case reports, with most experience involving Cyclophosphamide (CYC) or Cyclosporine (CsA). We report a case of adult MCD where steroids were not given, and nephrotic syndrome persisted despite nearly 1 year of CsA. It was only after administering Rituximab that complete remission was achieved and maintained.

Case Description: A 26 year old female with history of type I diabetes mellitus developed sudden weight gain and edema. Workup revealed albumin of 1.3 g/dL and 13 g/g of proteinuria. Kidney biopsy (54 glomeruli) showed diffuse podocyte effacement with normal light microscopy and immunoflorescence, consistent with MCD. Due to glycemic concerns, steroids were avoided and CsA initiated. Peak albumin on this therapy was 2.6 g/dL, with nadir proteinuria 4 g/g. When proteinuria again rose to 11 g/g after 8 total months, Rituximab was given as 2 doses of 1000 mg, 2 weeks apart. Proteinuria 6 weeks later was 21 mg/g, and remained <100 mg/g over subsequent months. After 6 months she received a single maintenance dose of Ritiximab 500 mg, while CsA was being weaned down. She now remains in complete remission with the latest proteinuria <100 mg/g and albumin 4.5 g/dL.

Discussion: There are scenarios whereby relative contraindications to high dose steroids exist, despite being considered the mainstay of therapy for MCD. There is little literature to guide alternative treatment strategies. Relapses occur frequently with patients becoming steroid resistant, steroid dependant (SD), or frequently relapsing (FR). In these settings, evidence for using alkalating agents or calcineurin inhibitors exists. The use of Rituximab to effectively prevent relapses of SD or FR MCD has been reported as well. Insights into how exactly Rituximab works in the treatment of MCD may help elucidate details of pathogenesis. Some hypotheses include protective actions on podocytes or targeting of B-cell subsets that secrete humoral factors injurious to podocytes. These ideas may lead to a novel approach to therapy, with this case an example of achievement of remission despite the first line agent never having been administered.

PUB577

A Case of ANA, dsDNA Negative Anti-Ro/SSA, Anti Smith Positive Lupus Nephritis

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Introduction: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder that is characterised by antibodies to nuclear and cytoplasmic antigens. Renal involvement in SLE is known as lupus nephritis and is associated with anti-nuclear antibody (ANA) positivity. ANA is negative in 5% of cases of SLE.

Case Description: We present a case of a 56 year old burmese refugee who presented to hospital with hypertensive crisis. Her blood pressure on admission was 220/120 mmHg with urinary protein studies revealing a protein excretion rate of 11grams/day. Furthermore urine cytology revealed dysmorphic red blood cells consistent with glomerular bleeding. Serum creatinine was 156 micromol/L with previous blood tests showing normal creatinine levels 6 months prior to hospital admission. Serum ANA, dsDNA were negative but anti ro/ssa and anti smith antibodies were positive. Renal biopsy was performed with histology revealing membranoproliferative glomerulonephritis suggestive of class III/IV nephritis.

Discussion: SLE is a multisystemic autoimmune disease that is characterised by nuclear and cytoplasmic antibodies to antigens. Antibodies to DNA play a role in the pathogenesis and activity of lupus nephritis. There are few cases of lupus nephritis described in the literature with no detectable antibodies. The role of anti ro/ssa and anti smith antibodies in lupus nephritis is not established. In this report we highlight the possible role of anti ro and anti smith antibodies in the pathogenesis of lupus nephritis. The mechanism of this is still misunderstood with further studies required.

PUB578

PCSK9 Inhibitors: A Novel Therapy for FSGS?

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Introduction: Alirocumab, an anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody is used for the treatment of primary dyslipidemia. PCSK9 is implicated in the pathogenesis of hyperlipidemia associated with nephrotic syndrome. In experimental models of focal segmental glomerulosclerosis, (FSGS) lipid infiltration in glomerular cells was found to induce podocyte injury and proteinuria.

Case Description: We present the case of a 60 year old African American man with obesity (BMI 42) and history of hypertension, hyperlipidemia, chronic kidney disease (CKD) with nephrotic range proteinuria. He previously had an episode of acute kidney injury due to statin-induced rhabdomyolysis that required temporary hemodialysis. He subsequently recovered and stabilized his renal function at CKD stage 3. His creatinine was 1.7 (eGFR: 45), had 5 g/g proteinuria, without hematuria and normal serum albumin (3.8 g/dL). Viral serologies were negative for HIV, Hepatitis B and C. He had biopsy-proven secondary FSGS thought to be related to obesity and possibly APOL1 due to his African American ethnicity. He was tried on a weight loss regimen and started on maximum RAAS blockade without improvement in his proteinuria. Given his poorly controlled hyperlipidemia (Chol: 345, LDL: 238, HDL: 73, TG: 171) while on ezetimibe, colesevelam, and niacin, he was started on PCSK9 inhibitor-Alirocumab. His proteinuria improved to 1 g/g soon after Alirocumab was initiated and has remained stable.

Discussion: PCSK9 levels correlate with the severity of hyperlipidemia and the degree of proteinuria. Once in remission, patients with nephrotic syndrome have decreased PCSK9 levels. Inhibition of the PCSK9 pathway should be investigated further as a novel therapeutic option in patients with proteinuria.

PUB579

Between a Rash and a Hot Knee: Distinguishing IgA Vasculitis from IgA Dominant Post-Infectious Glomerulonephritis

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Introduction: Methicillin-resistant Staphylococcus aureus (MRSA) bacteremia has been associated with post infectious glomerulonephritis (PIGN) and dominant IgA deposits. On the other hand, infections can precipitate a de novo IgA vasculitis. Distinguishing between the two is critical, since management options are different.

Case Description: A 61-year-old male was admitted with MRSA bacteremia and septic arthritis of the knee. Urinalysis and renal function were normal. Three weeks later he developed a non-pruritic erythematous rash on his extremities (Fig 1A), nephrotic range proteinuria and creatinine increased to 1.5 mg/dl. Serologies were negative with normal complement levels. Renal biopsy revealed focal areas of neutrophil infiltration (Fig 1C). Immunofluorescence (IF) showed heavy granular mesangial and glomerular capillary loop staining for IgA (Fig 1B), and focal C3 deposition. Electron microscopy revealed focal subepithelial and subendothelial mesangial deposits and a single large sub-epithelial deposit (Fig 1D).

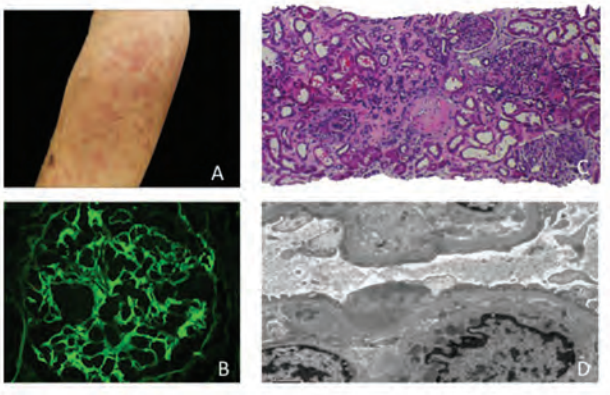
Discussion: Distinguishing MRSA associated GN from IgA vasculitis can be challenging. The pertinent distinguishing features and our patient's clinical features are summarized in Table-1. Given the clinical picture favoring MRSA related GN, persistent bacteremia and lack of convincing evidence favoring immunosuppressive therapy in IgA vasculitis, we elected for conservative treatment. Follow up showed stable creatinine at 1.4 mg/dl, despite persistent bacteremia, arguing for a cautious approach to treatment in such patients.

Table 1: Comparison of clinical characteristics of Staphylococcus infection-associated glomerulonephritis and idiopathic IgA nephropathy

Clinical Characteristics	Staphylococcus Infection Associated GN	IgA Vasculitis
Demographics		
Age	50-89 years*	20-30 years
Sex	80-90% males	~70% males
Race	Japanese, Caucasian*, Hispanics	Highest Asians, Low in blacks
Association with infection	Usually active infection*	History of infection in 30-40%
	Deep seated infections* about 70% MRSA*	Upper respiratory or mucosal infection Viral or Bacterial infection
	Latent period 5-10 weeks*	Latent period 1-2 days
Clinical Features	Low complements (30-40%)	Normal complements*
	Nephrotic range proteinuria*	Nephritic sediment
	Cryoglobulins may be present	Cryoglobulins are absent
	Renal dysfunction is common*	Renal failure is rare
Pathology	Endocapillary proliferation*	Mesangial proliferation
	Neutrophil infiltration*	Crescentic glomerulonephritis
	Stronger staining for C3 than IgA	Dominant IgA staining*
	IgA polyclonal	Ig A monoclonal (Ig A1)
	Sub-epithelial humps on EM*	EM: Mesangial deposits occasionally extending to peripheral capillary loops

* Clinical characteristics associated with our patient EM: Electron microscopy

Figure 1:



PUB580

A Case Series of Rituximab for Resistant Focal Segmental Glomerulosclerosis in Adults

Ellia Zhong,[1] Siavash Ghadiri,[1] Judith G. Marin,[2] Sean Barbour.[1] *[1]University of British Columbia, Richmond, BC, Canada; [2]Providence Health, North Vancouver, BC, Canada.*

Introduction: Adults with primary focal segmental glomerulosclerosis (FSGS) are frequently resistant to multiple immunosuppressive (IS) agents. Rituximab (RTX) is considered a last resort treatment, however there are few successful cases reported in adults. As such, we reviewed all patients with FSGS in the province of British Columbia (Canada) who were treated with RTX from January 2014 – April 2018. We included patients >19 years old with FSGS in the native kidney. RTX dosing was decided by the treating physician. Chart reviews were performed to extract clinical and laboratory data.

Case Description: Of the 121 patients who applied for RTX funding, 10 had FSGS of whom 3 met our inclusion criteria and 7 did not because they were children or had kidney transplants. Patient 1, a 41 year old female, was on prednisone, MMF and tacrolimus (TAC) and had previously failed galactose. Her creatinine (sCr) was 71 μmol/L, albumin (alb) 23g/L and proteinuria (prot) 4.95g/d. She was treated with RTX 375mg/m^2 weekly for 4 doses followed by single 375mg/m^2 doses with CD20 reconstitution. After RTX she was tapered off all other IS, with sCr 69μmol/L, alb 34g/L and prot 0.33g/d. Patient 2, a 21 year old male, was on prednisone and MMF, and had previously failed TAC, cyclosporine, cyclophosphamide, infliximab and galactose. His sCr was 168μmol/L, alb 30g/L and prot 8.69g/d. He was treated with RTX 375mg/m^2 weekly for 4 doses followed by single 375mg/m^2 doses with CD20 reconstitution. After RTX he was tapered off all other IS, with sCr 187μmol/L, alb 39g/L and prot 1.68g/d. Patient 3, a 26 year old female, was steroid sensitive but unable to taper prednisone without a disease flare despite concurrent use of cyclophosphamide, cyclosporine and TAC. At the time of being treated with RTX 1g every 2 weeks for 2 doses she was on TAC 3mg BID and prednisone 20mg/d, with sCr 63μmol/L, alb 35g/L and prot 0.38g/d. After RTX treatment, her prednisone has been tapered to 2.5mg every 2 days (the lowest dose without a flare in the previous 8 years) and TAC 2mg BID, with sCr 61μmol/L, alb 36g/L and prot 0.37g/d.

Discussion: By systematically evaluating all adults in a large Canadian province treated with RTX for FSGS, we have shown that RTX can be effective in FSGS resistant to multiple other IS agents. These findings support the need for a prospective trial in adults with resistant FSGS.

PUB581

Monoclonal Immunoglobulin-Associated Renal Disease Diagnosed by Liquid Chromatography-Tandem Mass Spectrometry: A Report of Three Cases

Yasuhisa Matsushita,[1,2] Hideki Inoue,[1] Keiko Okamura,[1] Mami Sugimoto,[1] Yoshimi Nakashima,[1] Takehiro Ko,[2] Yutaka Kakizoe,[1] Takashige Kuwabara,[1] Masataka Adachi,[1] Yushi Nakayama,[1] Masashi Mukoyama.[1] *[1]Nephrology, Kumamoto University Hospital, Kumamoto, Japan; [2]Tamana Central Hospital, Tamana, Japan.*

Introduction: Monoclonal immunoglobulin (MIg)-associated renal disease (MIg-ARD) results from direct deposition of nephrotoxic MIg or its light- or heavy-chain fragments in various renal compartments. Immunofluorescence (IF) and electron microscopy (EM) are essential to identify MIg and define its tissue distribution. We here report three cases of MIg-ARD diagnosed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Case Description: Case 1: A 73-year-old woman was referred due to proteinuria and hematuria. She had been diagnosed with non-ischemic cardiomyopathy 6 years before. Plasma electrophoresis showed the presence of IgGκ monoclonal protein. Light-chain amyloidosis was suspected upon renal biopsy, but MIg heavy-chain deposition was revealed by IF and LC-MS/MS. We finally diagnosed her with renal heavy- and light-chain amyloidosis. Case 2: A 75-year-old woman with Sjögren syndrome was referred because of proteinuria and hematuria. Cryoglobulinemia, hypocomplementemia, and IgMκ monoclonal protein were detected. Renal biopsy showed membranoproliferative glomerulonephritis (MPGN). Although there was positivity for IgM and C3 with negative staining for κ and λ light chains on IF, MIg light-chain deposition was revealed by EM and LC-MS/MS. We diagnosed her with cryoglobulinemic glomerulonephritis with light-chain deposition. Case 3: A 70-year-old woman was referred because of proteinuria. Although serum immunoglobulin levels were especially low, none of MIg proteins were shown by plasma and urine electrophoresis. However, on the basis of high κ/λ free light-chain levels in serum and hyperplastic bone marrow, multiple myeloma was diagnosed. Renal biopsy showed MPGN. Although there was weak positivity for IgM with negative results for κ and λ light chains on IF, light-chain deposition disease was finally revealed by EM and LC-MS/MS.

Discussion: LC-MS/MS is effective to identify MIg deposits in renal tissue compartments, especially when the findings of IF and EM are inconsistent with the background of monoclonal gammopathies.

PUB582

Goodpasture's Syndrome Superimposed on Autosomal Dominant Polycystic Kidney Disease

Matthew Day, Khaled Abdel-Kader, Beatrice P. Concepcion. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by multiple, bilateral renal cysts associated with cysts in other organs. The average rate of GFR decline is 4.4-5.9 mL/min/year. Here, we report a case of unexplained AKI with nephrotic syndrome in a patient with known ADPKD.

Case Description: 56/F with a history of ADPKD presented with 2 wks of worsening abdominal pain, lethargy, and oliguria described as darker than usual. Vitals were T-36.7, BP 163/84, HR 85, RR 20, O2sat 96% on RA. PE was significant for diffuse abdominal tenderness. Lungs were clear, and she had no edema nor any rashes. Admission SCr was 15 mg/dL with a prior normal baseline in 2010. Labs were significant for nephrotic-range proteinuria (PCR of 12.2) and microscopic hematuria. CXR revealed patchy perihilar and bibasilar opacities. No improvement in renal function was noted with IV fluids. Serological workup revealed normal complements, negative ANA, ANCA, SPEP/UPEP, HIV, and hepatitis panel. Worsening anemia thought to be secondary to hemoptysis complicated her hospital course. Chest CT revealed evidence of diffuse alveolar hemorrhage prompting a bronchoscopy that demonstrated blood throughout the tracheobronchial tree. Anti-GBM antibody levels were subsequently found to be elevated (209 AU/mL). Renal biopsy was not pursued due to technical difficulty and high risk of bleeding complications. She was started on high dose methylprednisolone (1 mg/kg/day) followed by plasma exchange and cyclophosphamide 25 mg PO BID. Her pulmonary symptoms improved with the above-stated therapy. However, she ultimately progressed to end stage renal disease requiring maintenance hemodialysis.

Discussion: In most patients with ADPKD, renal function is maintained despite relentless growth of cysts until the 4th to 6th decades of life. When renal function begins to decline, this occurs at an average rate of 4.4-5.9 mL/min/year. Unexplained AKI should prompt an evaluation for coexisting etiologies, which includes examination of the urinary sediment, a serologic work-up and possibly a renal biopsy, if technically feasible. In this case, the patient's clinical picture and positive anti-GBM titer led to the diagnosis of Goodpasture's syndrome superimposed on ADPKD. Her pulmonary symptoms improved with high dose steroids, plasma exchange, and cyclophosphamide therapy.

PUB583

Posterior Reversible Encephalopathy Syndrome Complicating Therapy of Membranous Nephropathy

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a rare, poorly-understood, reversible syndrome characterized by headache, altered mental status, seizures, visual disturbances and radiologically by vasogenic brain edema, predominantly

in the parietal and occipital lobes. PRES is frequently associated with severe hypertension, hemolytic uremic syndrome, lupus, ANCA vasculitis and several drugs including calcineurin inhibitors (CNI). We report a case of PRES, in a young male with membranous nephropathy associated with tacrolimus use and highlight the importance of early recognition as treatment involves withdrawal of the offending agent.

Case Description: A 27-year-old male presented with generalized tonic-clonic seizures, altered mental status and hypertensive emergency with blood pressure of 270/130 mm Hg. Medical history was known for biopsy proven membranous nephropathy on immunosuppression with tacrolimus and prednisone in the past one year. Exam revealed pallor and profound anasarca. Labs revealed acute kidney injury (AKI), hypoalbuminemia and tacrolimus level of 10.3 ng/ml (target range 5-8 ng/ml). Brain MRI showed symmetrical posterior subcortical vasogenic edema consistent with PRES. Management included discontinuation of immunosuppression with goal-directed optimization of blood pressure and volume status. He recovered well, with partial resolution of his AKI and without recurrence of seizures. Repeat renal biopsy showed advanced membranous nephropathy with mild tubular atrophy and interstitial fibrosis. Patient was conservatively managed without use of alternative immunosuppression due to higher risk of PRES associated with their use.

Discussion: PRES, also known as reversible posterior leukoencephalopathy syndrome was first described by Hinchey et al in 1996 and refers to a clinical conundrum of reversible subcortical vasogenic edema and severe hypertension. Tacrolimus is a macrolide derived immunosuppressant that competitively inhibits calcineurin and associated with severe vasoconstriction, hypertension, AKI and neurotoxicity. The estimated incidence of neurotoxicity is 7-32% in transplant recipients on CNI. It needs to be emphasized that PRES is a non-dose dependent adverse effect. Prompt recognition and discontinuation of the offending agent, with goal directed supportive care is paramount for complete neurological recovery.

PUB584

A Case of IgA and Bronchiolitis Obliterans in a Young Dialysis Patient

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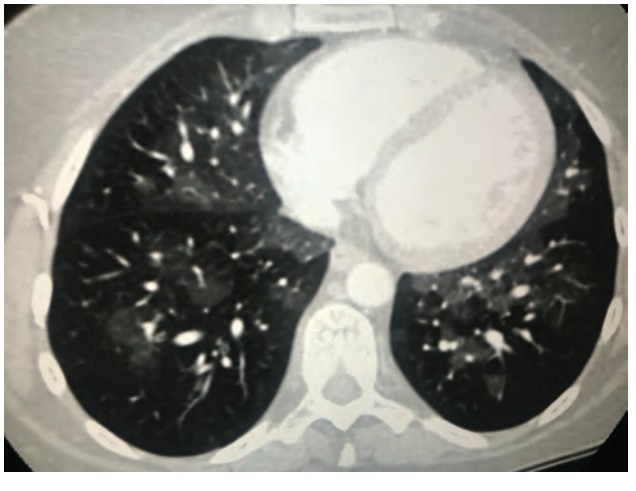
Introduction: IgA Nephropathy is the commonest cause of glomerulonephritis worldwide, with typical presentation ranging from microscopic haematuria to rapidly progressive glomerulonephritis. It is estimated that 20% of people with IgA nephropathy(IgA GN)will progress to ESRD over10-15 years. The exact pathophysiology remains unknown %given the spectrum of disease, other associations including pulmonary disease have been described.

Case Description: A 36 year old female with ESRD%biopsy proven IgA GN had been haemodialysis(HD) dependent since 2010. One year after starting HD, she developed dyspnoea&reduced exercise tolerance. Investigations, including pulmonary function tests revealed a marked reduction in transfer factor (FEV1 0.7L, 24% predicted). CT Thorax demonstrated bilateral ground glass opacification consistent with small airways disease(Image I). Pulmonary screen was negative&the patient underwent two bronchoscopies, however no organism or abnormality was detected. Echocardiogram showed preserved left ventricular function&no evidence of pulmonary hypertension. A diagnosis of Bronchiolitis Obliterans was made&it was felt that this may be related to her underlying renal disease. The patient was assessed at a tertiary Lung transplant centre with view to potential combined lung/kidney transplant. She received a trial of steroids with minimal benefit.

Discussion: This young patient has already received 8 years of HD treatment, undoubtedly impacting on her length of life. She has a chronic irreversible lung condition, which has shown some stability in the last6years. Whilst she remains functionally better than investigations would suggest, the lung transplant team do not feel she is in need of urgent lung transplantation due to risk/benefit factors. Whilst systemic complications of IgA GN are uncommon, cases of interstitial pneumonitis, pulmonary haemosiderosis&bronchiolitis obliterans have been reported and an increased index of suspicion for multi-organ disease is needed in this patient group.



PUB585

Renal Thrombotic Microangiopathy: A Rare Complication of Castleman's Disease

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Introduction: Castleman's disease (CD) is a lymphoproliferative disorder characterized by excessive cytokine production. It is classified based on the extent of lymph node involvement, histologic features and associated diseases (HHV8). The pathogenesis of Castleman's disease involves excess IL-6 production in response to viruses, autoinflammation, or neoplasms. We present a rare case of renal thrombotic microangiopathy secondary to CD.

Case Description: A 51-year-old female presented with three months of worsening fevers, ascites and pedal edema. She was recently hospitalized for abdominal pain and imaging revealed multifocal circumferential colonic masses with diffuse abdominal and pelvic lymphadenopathy. Colonoscopy was completed two weeks prior to presentation, and there were no intraluminal abnormalities or evidence of malignancy. On admission she was noted to have acute kidney injury with serum creatinine 3.95mg/dL (baseline 1mg/dl) and non-nephrotic range proteinuria without active sediments. Lab findings notable for anemia (Hb 8.6 g/dL) and thrombocytopenia (platelets 26,000/uL), without evidence of hemolysis. Secondary workup revealed elevated ANA titers. Complements and other autoimmune serologies were normal. HIV and Hepatitis studies were negative. Fine needle aspiration of a supraclavicular lymph node returned as lymphoid tissue with polyclonal plasmocytosis. On Day 4, renal biopsy was performed, and histology revealed acute glomerular thrombotic microangiopathy. She was empirically treated with 5 sessions of therapeutic plasma exchange (TPE) with improvement in renal function (serum creatinine 1.2mg/dL). ADAMSTS13 eventually returned as equivocal (>32%) and genetic complement testing was unavailable. Bone marrow biopsy and peripheral blood smears were negative for a myeloproliferative process. On Day 20, she underwent excisional biopsy of cervical lymph node, which confirmed HHV8 negative Castleman's disease, mixed hyaline vascular and plasmocytic type. She was referred to hematology clinic for treatment but unfortunately lost to follow up.

Discussion: Multicentric Castleman's disease can present with a wide range of symptoms. Our patient presented with TAFRO syndrome (a unique subtype of idiopathic MCD) characterized by Anasarca, Fever and thrombocytopenia. Clinicians should be aware that CD can be a rare cause of thrombotic microangiopathy.

PUB586

Promising Treatment of Membranous Nephropathy Followed by Anti-Glomerular Basement Disease

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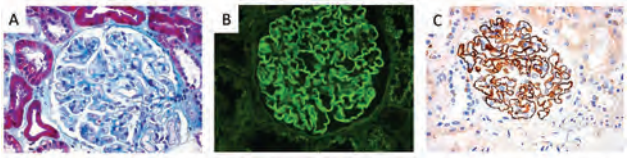
Introduction: Until now, a few studies reported evidence that both, simultaneous and consecutive occurrence of MN and anti-GMB disease can appear. The pathogenesis is still unclear and there is no algorithm in therapy. Here, we discuss a case of anti-GBM disease following MN with respect to clinical presentation and treatment options.

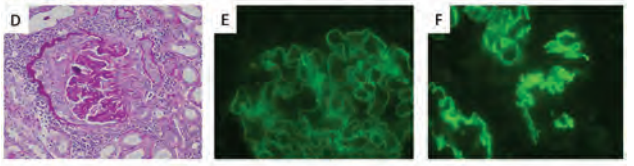
Case Description: We report a 55-year-old man with biopsy-confirmed MN 6 years ago and a base-line creatinine (Cr) of 1.3 mg/dl. The first kidney biopsy showed a MN with immune complex deposits (Figure 1A-C). Currently, the patient was admitted with new onset limb edema. Serum Cr level was 4.1 mg/dl and the protein/Cr ratio 119 g/molCr. Except the anti-GBM antibodies (titer 1:2560), the immunological screening was inconspicuous. In summary, we made the diagnosis of a rapidly progressive glomerulonephritis (GN). Thus, a second kidney biopsy was performed and the diagnosis of an anti-GBM GN superimposed on pre-existing MN could be established (Figure 1D-F). Immediately, therapy with i.v. methylprednisolone (MP) and cyclophosphamide (CYC) once per week in a dose of 250 mg for 3 times was started. Further, immunoadsorption (IA) was conducted 18 times. As a maintenance therapy, oral MP combined with another three times CYC 750 mg monthly was scheduled. Under therapy, the renal function improved and the serum Cr recovered to 1.6 mg/dl after 2 months.

Discussion: In a few cases with MN followed by anti-GBM, different therapy strategies were administered, having a poor patient outcome in common. For the first time, we report a patient with a favorable follow-up. An early biopsy-proven diagnosis followed by an immediate regimen of immunosuppression containing i.v. MP and CYC combined with IA seems to be encouraging. This case report underlines the fact that an early second biopsy should be considered in MN patients with an unusual clinical course.

Figure 1



The first renal biopsy in 2009 revealed a typical MN with thickening of glomerular basement membranes in the Masson-Trichrome stain (A), diffuse granular IgG deposits in subepithelial localization (B), and PLA2R-psotivity (C).



The current biopsy in 2017 disclosed an active crescentic GN (D, PAS stain)), with finely granular (E) and co-existing linear (F) IgG deposits along the GBM on immunohistology.

PUB587

Great Masquerade: Para-Neoplastic Pauci-Immune Glomerulonephritis

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Introduction: Pauci-immune glomerulonephritis associated with neoplasia has been described in the literature. Fain et al reported the largest case series of 60 patients with malignancy and vasculitides and found 23.3% renal involvement. The most common cancer described in this series were hematologic followed by solid tumors. We describe a case series of 4 patients who presented with pauci-immune glomerulonephritis diagnosed by renal biopsy and four different malignancies which have not been commonly associated with pauci-immune glomerulonephritis.

Case Description: Three patients had diagnosis of malignancy and pauci-immune glomerulonephritis during the same hospital visit. One patient had cancer approximately 18 months after diagnosis of pauci-immune glomerulonephritis (Table 1). Only one patient recovered renal function leaving three patients dialysis dependent. Malignancy was treated in all patients without any recurrence to date.

Discussion: Malignancy should be considered at the time of diagnoses of antineutrophil cytoplasmic antibody associated pauci-immune glomerulonephritis as an ideopathic cause is often thought responsible. Physicians need to be vigilant to perform a thorough history and physical examination to identify the presence of clinical cues for any associated malignancies. Renal outcomes for patients with paraneoplastic pauci-immune glomerulonephritis are poor as in our case series. Nephrologists need to continue to strive to determine the best treatment when a combination diagnosis is present.

Table 1: Details about patients with Paraneoplastic pauci-immune glomerulonephritis

Abbreviation: IFTA, PLEX, CyBorD

Age & Sex	Serum Creatinine at presentation (mg/dl)	Antibody Positivity & Titer at time of diagnosis (units)	Renal Biopsy findings	Malignancy associated	Time interval between diagnosis of GN & Malignancy	Treatment (Malignancy and GN)	Renal function
50 years, Female	12.42	ANCA, MPO titer 26	Glomeruli 8/17 with cellular crescents, 2/17 globally sclerosis, 30% IFTA	Invasive ductal Carcinoma of right breast	Simultaneous	Prednisone + Cyclophosphamide + PLEX	Dialysis dependent
54 years, Female	1.59	ANCA, MPO 51	Glomeruli 6/17 fibrous crescents, 3/27 globally sclerosis, 20% IFTA	Malignant Melanoma of Left ear lobe	18 months	Methotrexate + Prednisone pre-biopsy – transitioned to Rituximab post biopsy	Renal function recovered completely
73 years, Female	5.41	ANCA, PR3 55	Glomeruli 2/6 with fibrinoid necrosis (inadequate specimen)	Adrenal Carcinoma	Simultaneous	Prednisone + PLEX, Rituximab	Dialysis dependent
75 years, Female	7.10	ANA 6.2, Anti DsDNA Ab 87.9 ANCA negative	Glomeruli 5/17 cellular crescents, 1/17 segmental fibrinoid necrosis, 7/17 global sclerosis, 70% IFTA	Multiple Myeloma (IgG Lambda)	Simultaneous	Prednisone + CyBorD	Dialysis dependent

PUB588

Treatment Options for Relapsing ANCA Associated Crescentic Glomerulonephritis (GN)

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Introduction: KDIGO 2012 guidelines recommends treatment of first episode or severe ANCA associated GN with cyclophosphamide and corticosteroids and alternatively the use of rituximab and corticosteroids in patients without severe disease or in whom cyclophosphamide is contraindicated. According to the RAVE TRIAL, neither treatment is superior for induction of remission in severe ANCA associated vasculitis and that perhaps rituximab may be ***superior in relapsing disease***. This case looks at the clinical application of these findings.

Case Description: A 26 year old female with history of ANCA (MPO) crescentic GN 2 years prior presents to ophthalmology clinic with a red eye and is found to have scleritis. Labs work reveals a Cr 1.62 mg/dl, Uprt/Ucr 4.4gm and UA >182 WBCs, >36 RBCs. Her initial episode of GN was treated with cyclophosphamide and steroids and she achieved remission with a Cr 0.70 and proteinuria 0.3 gm. She was maintained on and compliant with azathioprine until this second episode. Repeat kidney biopsy showed relapse of ANCA GN with 30% active crescents and secondary focal and segmental sclerosis. Anti-MPO titers increased from 4 to 31.4 and PR3 Ab negative. After discussion of therapy with cyclophosphamide and its potential risks of infertility vs. rituximab, patient opted for rituximab 375 mg weekly for 4 weeks with plan for biannual rituximab maintenance. Cr was 1.2 and proteinuria 2gm after 2 months.

Discussion: Cyclophosphamide with glucocorticoids has been the mainstay of therapy for ANCA associated vasculitis for many years. Most nephrologists are more comfortable with its use due to experience especially in very severe cases. The data does shows that rituximab is as effective as cyclophosphamide in treating ANCA associated vasculitis and maybe more effective for relapsing disease. After deciding to use rituximab for this patient's relapse, she questioned why we didn't use it for her first episode as she would have preferred a therapy that would not potentially affect her fertility. Although the study did not look at the fertility aspect, this is an advantage that rituximab haswhen choosing therapy. It is standard that we discuss all risk and benefits however we sometimes sway patients that cyclophosphamide might be better for severe disease. However clinically for younger female patients with severe disease, rituximab may be the superior option.

PUB589

Catastrophic Antiphospholipid Syndrome Presenting with Subacute Renal Thrombotic Microangiopathy

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Introduction: Renal thrombotic microangiopathy (TMA) can be the initial presentation of various systemic diseases including catastrophic antiphospholipid syndrome (CAPS).

Case Description: A 28-year-old Caucasian woman with history of asthma presented with two weeks of abdominal pain and new-onset jaundice, anorexia, and gross hematuria. Labs revealed a creatinine of 4.6 mg/dL (baseline 0.5 mg/dL), direct hyperbilirubinemia, hypoalbuminemia, leukocytosis, and elevated LDH. Extensive imaging was notable only for hepatosplenomegaly. Hepatitis panel, anti-nuclear antibody, and complement levels were unremarkable. Her renal failure worsened despite supportive measures and hemodialysis was initiated. A renal biopsy was performed, and she was transferred to our institution. The patient developed progressive anemia and thrombocytopenia with rare schistocytes seen on peripheral blood smear. Hematology recommended against empiric plasmapheresis given lack of clear evidence for microangiopathic hemolytic anemia and platelet count of 69 K/μL. Renal biopsy demonstrated glomerular endocapillary hypercellularity and segmental mesangiolysis, but no obvious fibrin thrombi or fibrinoid necrosis. Immunofluorescence staining was unremarkable and electron microscopy showed subendothelial widening concerning for subacute TMA. ADAMTS13 level and Shiga toxin PCR later returned normal. A liver biopsy was planned but the patient became encephalopathic and hypotensive following a platelet transfusion. She developed pressor-dependent shock and passed away hours later from cardiac arrest. On the day of death, her lupus anticoagulant resulted positive (anticardiolipin and anti-beta-2 glycoprotein antibodies negative). Autopsy findings included cerebral, adrenal, omental, and renal thrombi by CD61 staining, consistent with CAPS.

Discussion: The diagnosis of CAPS requires laboratory confirmation of the presence of antiphospholipid antibodies (APLA), thromboses in three or more organs in less than one week, and histopathologic confirmation of TMA. We describe an atypical case of a patient with rapid clinical deterioration in the absence of imaging consistent with thrombosis or infarction, delayed APLA positivity, and renal biopsy without active fibrin thrombi. Given the very high mortality rate associated with CAPS, a high index of suspicion is needed in patients with subtle features of TMA on renal biopsy.

PUB590

A Breathless Herring: Goodpasture's Presenting as Chronic Pulmonary Fibrosis

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Introduction: Goodpasture's syndrome involves rapid progressive glomerulonephritis and diffuse alveolar hemorrhage due to anti-glomerular basement membrane (anti-GBM) antibodies. We describe a case of Goodpasture's that presented as chronic pulmonary disease prior to renal involvement and was co-positive for anti-GBM and MPO/ANCA.

Case Description: A 73-year old man presented for 2 weeks of progressive weakness and oliguria. He had a 10-year history of pulmonary fibrosis, which did not require treatment or supplemental oxygen. On exam, he had asterixis and bibasilar crackles. Labs revealed a creatinine 23.7 mg/dL, BUN 256 mg/dL, potassium 7.0 mEq/liter and sedimentation rate (ESR) 98 mm/hr. Chest x-ray showed bibasilar fibrosis, in a usual interstitial pneumonia pattern, with superimposed edema. He became tachypneic with frothy hemoptysis, requiring intubation, and emergent continuous renal replacement therapy was started. Methylprednisolone was empirically started and ANCA, PR3, MPO and anti-GBM antibody labs were ordered. Anti-GBM antibodies and MPO/ANCA were positive. Plasmapheresis and cyclophosphamide were initiated. The patient improved and was extubated. Renal biopsy revealed necrotizing and crescentic glomerulonephritis with positive linear IgG basement membrane staining by immunofluorescence, confirming Goodpasture's syndrome. The patient was discharged on plasmapheresis, cyclophosphamide, prednisone and hemodialysis, with plans to switch to peritoneal dialysis.

Discussion: Goodpasture's has an estimated incidence of 1 case per million per year. However, Goodpasture's presenting as chronic pulmonary fibrosis prior to renal disease with anti-GBM, MPO/ANCA positivity is rare; as of 2017, only 7 cases had been reported. The significance of this presentation is unclear but may relate to the development and prognosis of the disease. While the trigger for Goodpasture's is unknown (proposed risk factors include hydrocarbon fumes and smoking), previous studies suggest MPO/ANCA positive pulmonary fibrosis may induce anti-GBM antibodies. The average 1-year survival rate of these 7 cases was 29%, in contrast to Goodpasture's 5-year survival rate of 50%. In either case, mortality rates improve with early treatment. Thus, early recognition of Goodpasture's presenting as chronic pulmonary fibrosis is key to improved outcomes.

PUB591

A Rare Case of Crescentic Fibrillary Glomerulonephritis

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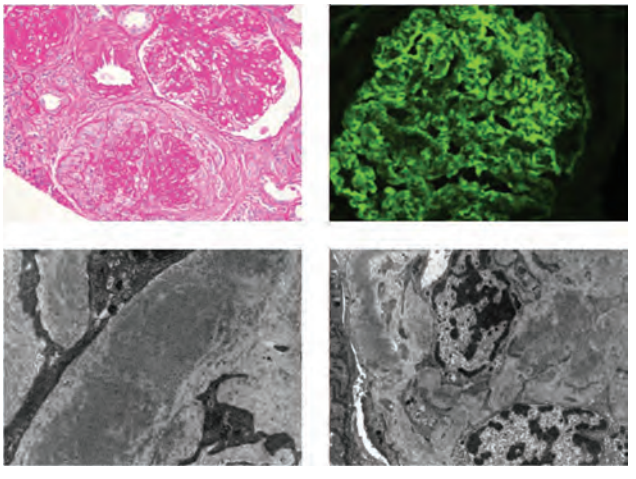
Introduction: Fibrillary glomerulonephritis (FGN) is a rare, primary, progressive glomerular disease that was first described by Rosenmann in 1977. Glomerular deposition of polyclonal IgG in the form of random fibrils of 15-20 nm size is pathognomonic of FGN and is distinguished from amyloidosis by negative congo red staining. We report a rare case of FGN in a middle-aged female with progressive renal failure and crescents on biopsy.

Case Description: A 58-year-old woman with hypertension was admitted with pneumonia and creatinine of 1.4 mg/dl with hematuria and 1.9 grams proteinuria. Extensive serological work up for secondary causes was negative. A diagnostic renal biopsy revealed FGN and patient was treated conservatively with ACE-inhibitor therapy, given stable renal function. A year later, she had steady rise in creatinine and a repeat biopsy showed FGN with active crescents. Repeat serological work up was unrevealing and patient was initiated on immunosuppression with cyclophosphamide and prednisone in anticipation of a favorable outcome.

Discussion: Patients with FGN are typically middle-aged and present with proteinuria, hematuria and renal insufficiency. FGN carries a poor prognosis with progressive renal disease and ESRD in over 50% of patients. Older age, higher creatinine and higher percentage of globally sclerotic glomeruli are poor prognostic indicators. FGN is a morphologically defined entity and without electron microscopy, it can be indistinguishable from other deposition diseases. Due to its rarity and diagnostic difficulty, there are not many clinical trials evaluating treatment efficacy. Immuno-staining with DNAJB9, a heat shock protein with >98% sensitivity and specificity for FGN has shown promise. With increased awareness and testing with DNAJB9, there can be hope of identifying viable treatment options for patients with FGN.



PUB592

Treating Antineutrophil Cytoplasmic Antibody Associated Vasculitis (AAV) with Rituximab: A Double-Edged Sword

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Introduction: Rituximab is a monoclonal antibody directed against the CD20 antigen of B-lymphocytes used for the treatment of AAV. B-cell depletion with rituximab in AAV results in decreased production of pathogenic antibodies but also renders the patient immunocompromised. We report here a case of Invasive Pulmonary Aspergillus (IPA) after rituximab administration for AAV.

Case Description: A 27-year-old male with recently diagnosed AAV (based on anti-PR3 level of 528 AU/mL and pulmonary cavitary lesions on chest CT) s/p IV rituximab (375 mg/m^2 weekly x 4 doses) plus prednisone (60 mg q day), was transferred to our hospital. Four weeks after initial diagnosis, the patient continued to have persistent cough, anemia (Hb 8.7 g/dL, Plts 497 10^3/ uL) and leukocytosis (wbc 25.7 10^3/ uL), plus microscopic hematuria, and proteinuria (2.9 gm/ 24 hrs), with preserved renal function (Cr 0.91 mg/dL), and undetectable CD 19(+) B cells. Bronchoscopy was performed and bronchoalveolar lavage was positive for *Aspergillus*. Renal biopsy was done 6 weeks after the first dose of rituximab to determine the degree of activity of AAV and was consistent with pauci-immune focal segmental necrotizing (2/22 glomeruli) and crescentic glomerulonephritis (4/22 glomeruli with fibrocellular crescents). Voriconazole was started for IPA, followed by cyclophosphamide for active vasculitis despite induction therapy with rituximab. The patient had improvement in pulmonary symptoms and stable renal function, with resolution of microscopic hematuria but persistent proteinuria (2.2 gm/24 hr).

Discussion: AAV is an aggressive small vessel vasculitis that needs urgent treatment with immunosuppressive agents i.e. rituximab and cyclophosphamide, which increase the risk of opportunistic infections. Additional risk factors for infections in patients receiving rituximab include corticosteroids > 15 mg/day, creatinine clearance ≤ 45 mL/min, low IgG level, and low CD19(+) B cell count. Undetectable CD19(+) B cells (utilized to monitor B cell subset depletion after rituximab) in our patient implies that rituximab associated immunosuppression may have increased the risk of IPA. Therefore, while persistent pulmonary symptoms in patients with AAV can be due to active vasculitis, opportunistic and fungal infections such as *Aspergillus* must be ruled out.

PUB593

ANCA-Positive Crescentic Glomerulonephritis with Associated IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) can present with positive ANCA in 10% of cases. Most of them are considered as false positives. The proposed mechanism is that pathogenic IgA immunocomplexes would predispose to ANCA positivation. Those patients with ANCA positive IgAN have poorer outcomes compared to those ANCA negative. Otherwise, in crescentic IgAN, ANCA correlates with better outcome.

Case Description: A 38-year-old Bolivian male patient presented malaise, vomits, oliguria and uveitis. He had a rapidly worsening renal function, from baseline serum creatinine (sCr) 0.84 mg/dL to admission sCr 11.06 mg/dL. His general condition deteriorated and emergency haemodialysis was initiated. He also showed hematuria (86 erythrocyte /c), which was present for the last 5 months, subnephrotic proteinuria (0.15 g/day) and severe anemia (7.0 gr/dL). Other relevant exams were normal Complement (C3 137mg/dL; C4 36 mg/dL), positive c-ANCA antigen (1/320), ANA 1/160, positive anticardiolipin IgG antibody (14.93 GPL U/mL), positive rheumatoid factor (61.8 UI/mL) and negative Anti-DNA. Kidney biopsy sample included twenty-eight glomeruli, eighteen of which were globally sclerotic, eight containing cellular glomerular crescents, two with fibrinoid necrosis and segmental cellular proliferation. Light microscopy demonstrated necrotizing glomerulonephritis with ANCA-associated pattern. Immunofluorescense revealed IgA mesangial diffuse granular staining (3+), suggesting IgA glomerulonephritis.

Discussion: We report a rare association between ANCA-associated vasculitis and IgAN. The previous finding of hematuria suggests that our patient could have IgAN as a previous undiagnosed condition. We could speculate that IgAN may trigger an immunologic response for developing an ANCA-associated vasculitis. More studies are needed to determine if this overlap would define a new condition, its physiopathology as well as the best therapeutic approach.

PUB594

Drug Resistant Focal Segmental Glomerulosclerosis (FSGS)

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Introduction: Focal Segmental Glomerulosclerosis (FSGS) accounts for approximately 40% of cases of nephrotic syndrome in adults. Most cases of FSGS are primary while others include genetics, infection/inflammation associated, or drug induced. The initial treatment of idiopathic FSGS is corticosteroid therapy. For steroid resistant FSGS, KDIGO guidelines recommend therapy with cyclosporine or Mycophenolate Mofetil (MMF) with corticosteroids. About 40% of the patients relapse after the initial therapy of FSGS. Relapses occur less frequently in those who have complete remission. We present a case of idiopathic FSGS resistant to multiple therapies.

Case Description: A 59-years-old male with medical history of CAD, hypertension, diabetes mellitus type 2, chronic obstructive pulmonary disease presented with proteinuria. Initial kidney biopsy confirmed FSGS thought to be primary. Patient could not tolerate steroid therapy due to side effects and was started on cyclosporine to which he responded well after prolonged therapy but relapsed after it was discontinued. At this time, repeat kidney biopsy was preformed showing predominantly FSGS with mild diabetic glomerulosclerosis. After reinstituting cyclosporine, he had an episode of Acute kidney Injury (AKI) requiring hospitalization and cyclosporine was changed to prednisone in combination with MMF for 12 months. Patient did not respond with worsening proteinuria. Patient was again restarted on cyclosporine with persistent nephrotic range proteinuria. Eventually therapy with corticotropin was also attempted but failed to show any benefit and had significant side effect of weight gain. Patient continues to be treated with cyclosporine.

Discussion: Our patient failed to show response with multiple immunosuppressive regimens and remains a challenge to achieve remission. Another option with Rituximab was also considered but with given underlying CKD, history of multiple AKI episodes and failure to show response with multiple regimens, we thought not to pursue Rituximab given lack of strong evidence. Larger studies and research is needed to better understand this disease and develop more effective therapeutic options.

PUB595

A Unusual Case of Nephrotic Syndrome Post Allogenic Bone Marrow Transplant (aBMT) Secondary to Focal Segmental Glomerular Sclerosis (FSGS)

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Introduction: Allogenic bone marrow transplantation is a widely used treatment modality for many hematological diseases. Nephrotic syndrome post allogenic bone marrow transplant is extremely rare with an incidence of 1%. The development of nephrotic syndrome usually happens in the late post-transplant period of more than six months. When present, membranous nephropathy is the typical microscopic finding in 2/3 of cases followed by minimal change disease. In general, this develops after the cessation or tapering of immunosuppressive therapy, which suggests that nephrotic syndrome could be a manifestation of chronic graft versus host disease.

Case Description: A 75-year-old gentleman had a history of hypertension, prostate cancer and myelodysplastic syndrome with transformation into acute myeloid leukemia. He underwent matched unrelated donor allogenic bone marrow transplant as part of his treatment. Ten months later, the patient presented with symptomatic nephrotic range proteinuria (edema and hypoalbuminemia). A spot urine protein creatinine ratio was 12g and 24hr urine collection was 18g protein. Serologic workup was positive for ANA with negative ANCA, anti GBM, anti dsDNA, Smith, RNP, SSA, SSB. Free kappa lambda was elevated with normal ratio. The serum and urine protein electrophoresis reflected the presence of intensely stained bands in the beta-gamma region which may have represented a monoclonal protein. PLA2R was negative. Kidney biopsy revealed acute tubular injury with cytoplasmic vacuolization on light microscopy. Immunofluorescence had no specific immunoglobulin or complement deposition. Electron microscopy showed podocyte injury with diffuse foot process effacement and no electron dense deposits. These findings were suggestive of focal and segmental glomerulosclerosis, primary or secondary. After steroid treatment proteinuria improved to 1.5g/g.

Discussion: We presented this case of nephrotic syndrome post bone marrow transplant, with FSGS as microscopic evidence, because it was distinct from the most commonly found lesion. Further studies are needed to determine if FSGS might represent a chronic graft versus host phenomenon. Single agent steroid use was successful in this patient and ultimately this case expanded our knowledge on renal complications post bone marrow transplantation.

PUB596

Fulminant Acute Renal Failure in IgA Nephropathy

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Introduction: IgA nephropathy (IGAN) has been described as a disease with invariable histopathologic findings but highly variable clinical outcomes (Rodrigues JC et al, CJASN, 2017). Here we describe a patient a new diagnosis of IGAN that caused fulminant acute renal failure.

Case Description: A 20-year-old Hispanic woman with childhood epilepsy presented with two days of right flank pain, nausea and vomiting. Current medications were levetiracetam and topiramate. Physical exam was normal except for obesity. Abdominal CT scan was unrevealing. She was admitted without an explanation for her symptoms, which rapidly improved, but her serum creatinine rose from 0.88 mg/dL to 11.8 mg/dL with oliguria in one week. Nephrology was consulted. Urine sediment showed a few granular casts with numerous WBCs and RBCs. Urine culture grew E.coli > 100K. Ultrasound showed normally sized kidneys with increased echogenicity. Initial serologic tests were negative. She was treated with antibiotics for cystitis, dialyzed twice and then underwent kidney biopsy. Microscopy revealed mesangial hypercellularity, no crescents or fibrinoid necrosis, and a large number of red cell casts within tubules along with epithelial flattening. In addition there was a diffuse lymphoplasmacytic infiltrate with eosinophils. IF showed 3-4+ mesangial and glomerular capillary staining for IgA, C3 and fibrinogen. EM showed numerous mesangial dense deposits. MEST-C score: M0, E1, S1, T1, C0. Her interstitial nephritis was treated by changing her anti-epileptic medication and also with 1 month prednisone 60mg. Dialysis was held, and within a week she was discharged with improving renal function. Four weeks later in clinic her creatinine was 0.88mg/dL.

Discussion: Our patient had a new diagnosis of IGAN with acute renal failure due to intra-tubular obstruction from RBC casts. This rare variant of IgA is not incorporated into the Oxford classification. The prognosis is excellent because renal function recovers once RBC casts start degenerating. How glomerular hematuria becomes sufficient to cause cast obstruction is unclear. Similar to other case reports (Friedlaender MM et al, Isr J M Sci 1986; Lee HS et al, AJKD, 1988; August C et al, J Neph, 2001) our patient's infectious trigger was cystitis rather than a URI, a correlation that bears further consideration.

PUB597

Crescentic IgA Nephropathy in an African American Man on Warfarin

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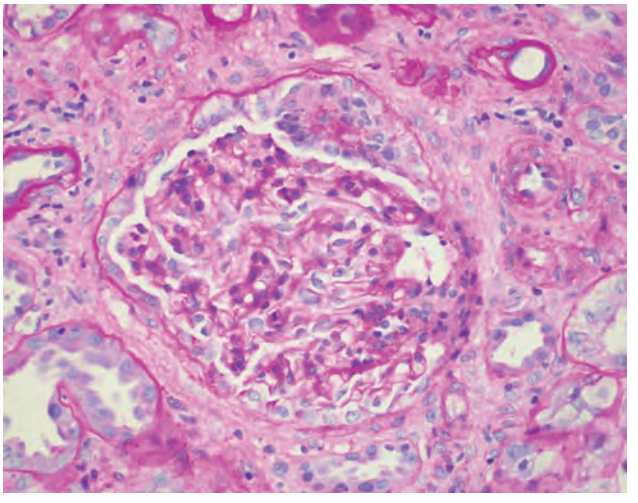
Introduction: Immunoglobulin A Nephropathy (IgA Nephropathy) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA.Its more commonly seen in Asians, caucassians and hispanics but the prevalence of IgAN is very low among African Americans. Anticoagulant related nephropathy is more common in patients with IgA Nephropathy.

Case Description: This is a 57 y/o AA man with a past medical history of thromboembolic disease on warfarin therapy, hypertension, and CKD stage 3 presented to our hospital with foot pain and gross hematuria with no other symptoms. On exam he was afebrile with a B/P of 140mm/hg with clear lungs and no edema. His admission labs showed a creatinine of 15.17mg/% (baseline 1.6mg/%), BUN of 100mg/% with a HCO3 of 14meq/dl. U/A showed large blood, with RBC casts and nephrotic range proteinuria of 4.1gms. His serologic work up was normal. His INR was 3.8. A renal ultrasound showed echogenic kidneys without hydronephrosis. After reversing the anticoagulation a Kidney Biopsy was done and is was consistent with IgA nephropathy with cellular crescents and moderate interstitial fibrosis. The patient was treated with methylprednisolone 1gm/daily for 3 days. He was then started on Prednisone 60 mg daily. He also received 1gm of cyclophosphamide, with recommendations to continue cyclophosphamide once a month for 6 months. His creatinine improved throughout his admission from 16.15mg/% to 6.60mg/% on discharge without the need for dialysis. The patient was discharge on Apixaban instead of Warfarin.

Discussion: Anticoagulant related nephropathy (ARN) is defined as an acute increase in serum creatinine of >0.3 mg/dl within 1 week of an INR >3.0. Chronic kidney disease and particularly patients with IgA Nephropathy are risks factor for ARN. We must be aware of the relationship of these two conditions and include IgA nephropathy in the differential diagnosis of glomerulonephritis in African American patients.



PUB598

Nephrosarca Causing Anasarca in an Elderly Male with Minimal Change Disease

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Introduction: Minimal Change Disease (MCD) rarely presents with nephrotic range proteinuria and acute kidney injury in adults. Nephrosarca, or severe edema of the kidney, has been proposed as a pathophysiological mechanism for this.

Case Description: A 75 year old male with chronic back pain (on long-term NSAIDs) presented with generalized body swelling, 10 kg weight gain, progressive dyspnea and decreased urine production worsening over a week. Vital signs were stable, and clinical exam revealed anasarca. Serum BUN (96 mg/dl) and creatinine (8.7 mg/dl, baseline 1 mg/dl) were elevated. Serum electrolytes, calcium, phosphorus, and magnesium were normal. Total protein was 5.3 mg/dl and albumin was 1.1 mg/dl. UA revealed 4(+) protein. A 24 hr. urine collection showed 5.9 g of protein, mainly albumin, and a creatinine clearance of 10 ml/min. SPEP and UPEP demonstrated hypoalbuminemia and hyperalbuminuria respectively. Serological workup including RF, ANA, ANCA, anti-dsDNA/anti-MPO/anti-GBM/anti-proteinase-3 antibodies, Hepatitis B & C panel, HIV, cryoglobulins, RPR, and complements C3/C4 was negative. Serum immunoglobulins levels were normal. Renal ultrasound showed kidneys' of normal size and echogenicity, but with moderate perinephric fluid. Renal biopsy depicted extensive and global foot process effacement with significant interstitial edema, consistent with MCD (likely secondary to chronic NSAID use). High doses of intravenous diuretics were ineffective, and early hemodialysis aided in achieving evolemia. He was started at 60 milligrams of prednisone per day, and his proteinuria and renal function improved in 4 weeks. Repeat renal ultrasound revealed no perinephric fluid.

Discussion: *Lowenstein et al.* proposed the theory of nephrosarca as a root cause in the pathophysiology of MCD by physically abetting vascular and tubular occlusion, consequently causing filtration failure. Our patient's nephrosarca and AKI did not revert by prompt reinstitution of euvolemia alone, but was temporarily concomitant with proteinuria remission in response to corticosteroids. Interestingly, our patient's nephrosarca resolution was captured on repeat renal imaging, which has not commonly been cited in the medical literature so far.

PUB599

Oxalate Nephropathy Leading to Acute Renal Failure

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Introduction: Hyperoxaluria is implicated in the development of nephrolithiasis and nephrocalcinosis and has also been shown to cause renal parenchymal disease with progression to end-stage renal disease. We present a patient with underlying CKD and pancreatic insufficiency who developed AKI secondary to oxalate nephropathy.

Case Description: A 75-year old man with a history of CKD IV and pancreatic adenocarcinoma s/p pancreaticoduodenectomy nine months ago presented to the emergency room complaining of nausea, fatigue, shortness of breath, and leg swelling for two weeks as well as decreased urine output for four days. Initial work-up revealed creatinine 11 mg/dL (baseline 2.5 mg/dL), hyperkalemia 6 mmol/L, and metabolic acidosis. Patient reported that since surgery he had been eating spinach daily and taking an herbal supplement containing kelp, thistle, rhubarb, and spinach. In addition, he stopped taking his pancreatic enzymes two months ago. He had also avoided dairy intake for many years. He has a history of kidney stones with analysis showing calcium oxalate, calcium phosphate, and uric acid. Urine microscopy was notable for pyuria, WBC casts, and muddy brown casts. Urine culture was negative. Patient underwent a percutaneous kidney biopsy which revealed acute tubular injury with extensive tubular calcium oxalate deposition and diffuse interstitial inflammation consistent with oxalate nephropathy. His diet has been adjusted to a low-fat, low-oxalate, high-calcium diet in addition to restarting pancreatic enzyme replacement. Patient has remained anuric requiring regular hemodialysis.

Discussion: Secondary hyperoxaluria often results from enteric hyperoxaluria (due to increased intestinal absorption), endogenous production, and/or increased dietary intake. Enteric hyperoxaluria results when intestinal oxalate is absorbed and is excreted in the urine, where it binds with calcium and deposits in the tubules. Renal parenchymal disease secondary to hyperoxaluria manifests as diffuse tubular deposition of calcium oxalate crystals and interstitial inflammation. Our patient, along with underlying CKD, also had malabsorption due to a pancreaticoduodenectomy as well as high oxalate and low calcium intake. Oxalate nephropathy has a poor prognosis and in this case the patient became dialysis-dependent. This case highlights the importance of gathering dietary habits as part of routine history-taking.

PUB600

Cocaine Induced Perinephric Hematoma

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Introduction: Cocaine causes devastating effects on multiple organ systems. Renal complications range from kidney injury from rhabdomyolysis, progression of atherosclerosis, hypertensive nephrocalcinosis, end stage renal disease to rarely renal infarction. We present a rare case of perinephric hematoma associated with cocaine abuse in a young patient

Case Description: A 37-year-old Hispanic female with history of depression, hepatitis C and polysubstance abuse presented with left flank pain that started few hours after using intravenous cocaine. Pain was intermittent, colicky, 10/10 in intensity, aggravated by deep inspiration without any nausea or vomiting. On physical examination, she was febrile but hemodynamically stable, had left lower quadrant and costovertebral angle tenderness. Laboratory studies revealed leukocytosis with normal liver, renal and pancreatic function tests. Urinalysis revealed numerous RBCs. Renal ultrasound showed enlarged kidneys bilaterally with decreased echogenicity in left capsule without any evidence of hydronephrosis, tumor or calculi. Computed tomography (CT) of abdomen and pelvis with contrast showed large fluid collection surrounding left kidney originating from parenchymal defect in the inferior pole. Patient underwent CT guided aspiration of hematoma and aggressive blood pressure control. She was eventually discharged to rehabilitation facility

Discussion: Perinephric hematoma is defined as collection of blood in the subcapsular and perinephric space. It is a rare condition associated with renal neoplasms(renal cell carcinoma, angiomyolipoma), vasculitis, pyelonephritis, kidney stone, preeclampsia, eclampsia or coagulation disorders but it is a common complication of percutaneous nephrolithotripsy. Perinephric hematoma is rare complication seen in cocaine abusers. Most likely mechanism could be from severe hypertension associated with sympathetic stimulation in patients with cocaine abuse. The morbidity and mortality associated with this condition is high. CT scan is the diagnostic modality of choice. Conservative management with close follow-up is the mainstay of treatment but patients with associated tumor or those with uncontrollable hemorrhage are treated with nephrectomy. Our patient presented with left perinephric hematoma without any evidence of hemodynamic compromise or findings suggestive of malignancy. We managed our patient conservatively with frequent hemoglobin and hematocrit monitoring and fluid resuscitation

PUB601

A Case of Renin-Mediated Hypertension

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Introduction: Renin-secreting tumors are a known rare cause of secondary hypertension with hypokalemia and metabolic alkalosis. Evaluation is remarkable for elevated plasma renin activity (PRA) and, in most cases, secondary hyperaldosteronism. Treatment options are limited with variable effectiveness data on the use of renin angiotensin aldosterone system blockers, making tumor resection the definite treatment. Our case highlights the importance of early recognition of reversible causes of hypertension, and its potential reduction of cardiovascular risk.

Case Description: A 23-year-old female with history of hypertension and hypokalemia, presented with 2 weeks of dyspnea on exertion, decreased exercise capacity, and mid-sternal sharp chest pain exacerbated by dry cough. On admission, her blood pressure was 195/144mmHg and she had jugular venous distention with clear lungs and no evidence of peripheral edema. Labs showed K 2.9mmol/L, CO2 29mmol/L, Cr 0.88mg/dL, pH 7.46, BNP 1492.3pg/mL, and UA >500 protein. EKG showed left ventricular hypertrophy. Chest x-ray revealed cardiomegaly and mild pulmonary edema. Findings were suggestive of new onset heart failure (HF) thus she was treated with aggressive diuresis. TTE confirmed left ventricular systolic and diastolic dysfunction. Evaluation of secondary causes of hypertension included Renal US and CT Abdomen/Pelvis which revealed an enhancing well-circumscribed 2.8cm renal mass arising from the left kidney. US doppler and CT angiogram showed no signs of high-grade renal artery stenosis or fibromuscular dysplasia. PRA was elevated to 29.794ng/mL/hr and aldosterone 52.4ng/dL. 24hr urinary collection of catecholamines and metanephrines was negative. A diagnosis of hypertension with end-organ damage due to renin-secreting tumor was made and our patient was referred for surgical tumor removal.

Discussion: Approximately 5% of patients with hypertension have reversible secondary causes. Renin-secreting tumors are considered a rare cause of secondary hypertension that should be considered in patients with concomitant hypokalemia and elevated PRA, especially when renovascular disease is ruled out. Our patient presented with HF and proteinuria in the setting of a suspected renin secreting tumor. Timely evaluation and treatment of secondary causes of hypertension is paramount to avoid mechanical injury, oxidative stress, and fibrosis along the renal and cardiovascular system.

PUB602

Amyloid Cast in a Case of Multiple Myeloma

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Introduction: Cast nephropathy is the most frequent pathologic pattern of renal involvement in Multiple myeloma (MM), characterized with distal tubular casts that are composed of monotypic light chains. Here we present a case of MM with unusual cast.

Case Description: A 74-year-old Chinese male was referred to our hospital with complaint of extremities edema and fatigue for 4 months. He denied fevers, rashes, joint pain or weight loss. On admission, blood test showed WBC count 71600 with no shift, and platelets count 18000, and hemoglobin 98g/L. Urine test showed trace protein with no hemauria. Total urine protein in 24 hours was 12.43g/d with serum albumin 41g/L and normal renal function. ANCA, anti-GBM antibody, PLA2R antibody, autoantibodies and hepatitis virus were negative. Serum protein electrophoresis showed 5% M-protein. Both serum and urine immunofixation electrophoresis showed a band of lambda light chain. Bone marrow aspirate and biopsy confirmed multiple myeloma with 51% plasma cell. Renal biopsy: The specimen for light microscopy contained renal cortex with 10 glomeruli without globally sclerosis. The GBMs were almost normal without endocapillary hypercellularity or mesangial proliferation. No fuchsinophilic deposition was found. Tubular lumina contained several casts, and the interstitium was edematous with focal inflammation cells infiltration, mostly lymphocytes and monocytes. Arteries were almost normal. Congo Red and Oxide-Congo Red were only positive for several casts, with spicule formation at the rims. No immunoglobulin or complement components were positive by immunofluorescence microscopy (IF). Immunohistochemistry (IHC) test revealed lambda positive for certain casts. Electron microscopy (EM) showed 1glomeruli without any sign of amyloidosis or light chain deposition disease, but no casts were found. There were no electron dense immune complex deposits. This case was diagnosed Multiple myeloma (Stage III, lambda type), with amyloid cast nephropathy. He received PAD therapy (Bortezomib + Pirarubicin + Prednisolone) and revealed a good response.

Discussion: Cast nephropathy is characterized with casts of monotypic light chains. But there are rare cases showing amyloid casts, with spicule formation at the rims. Congo red staining, IHC and EM are helpful to confirm the diagnosis.

PUB603

Myeloma Cast Nephropathy in Elderly Patient Presenting as AKI

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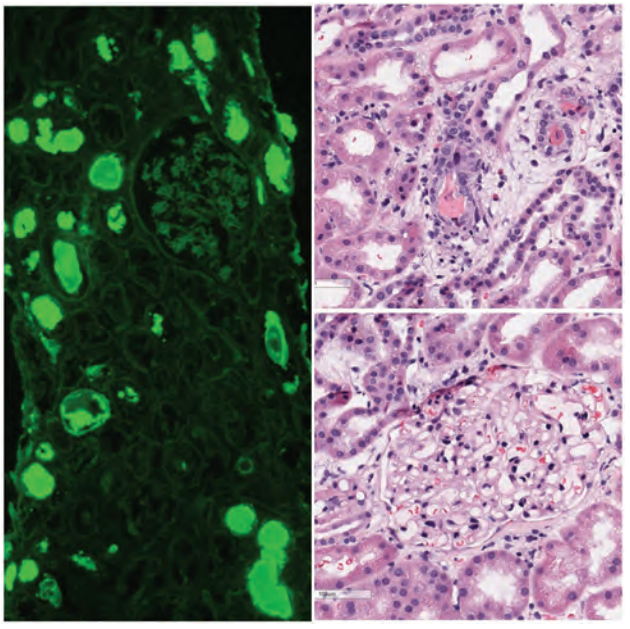
Introduction: Multiple myeloma can present with various renal manifestations. Here we present a patient with acute kidney injury diagnosed as Myeloma cast nephropathy on kidney biopsy.

Case Description: 90-year-old healthy female with a history of treated endometrial cancer and osteoarthritis presented with creatinine of 7mg/dl (baseline creatinine 0.7mg/dl) and potassium 5.3mmol/l on routine laboratory testing done by her primary care physician. Urine is clear with specific gravity of 1.010. Renal ultrasound is normal with no hydronephrosis or renal artery stenosis. Complement levels are normal, c-ANCA negative and p-ANCA positive 1:320. Despite adequate hydration her creatinine improved only to 6.4mg/dl. Kidney biopsy showed Acute tubular necrosis and myeloma cast nephropathy with normal glomerulus. Protein electrophoresis demonstrated monoclonal lambda light chains in serum and free lambda light chains of 10934mg/l in urine. Bone scan showed lytic lesions suggestive of multiple myeloma. Bone marrow biopsy is diagnostic of monocytic lambda-expressing plasma cell neoplasm (65.6% plasma cells) with coexpression of CD56, CD38 and CD138. Patient is requiring hemodialysis and is being considered for specific regimen to treat myeloma.

Discussion: Despite increased risk of bleeding at her age, kidney biopsy was performed as diagnosis is unclear. The diagnosis of cast nephropathy is based on the demonstration of

tubular casts in distal nephron that are composed of immunoglobin light chains. Light chain casts generate intense inflammation via the activation of c-Src and NF-κB, and subsequent chemotaxis of immune cells further damaging the kidney tubules. If the obstruction is not eliminated, the damage becomes irreversible. Patients who are promptly diagnosed with myeloma cast nephropathy and rapidly commenced on disease-specific therapy have better outcomes.



PUB604

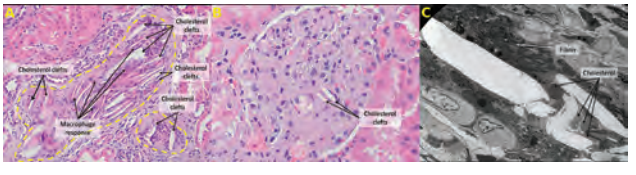
Severe Atheroembolic Renal Disease (AERD) Contributing to Renal Failure

Vidhit Puri,[1] Pridvi Kandagatla,[1] Nishant K. Puri,[1] Gunjan Garg,[1] Tina Nigam,[1] Sowmya Goranta,[2] Evan A. Farkash,[1] Rachel Perlman.[3] *[1]University of Michigan, Ann Arbor, MI; [2]Hurley Medical Center, Canton, MI; [3]UM Health Center, Ann Arbor, MI.*

Introduction: AERD is the occlusion of renal arterioles by cholesterol crystal emboli. These emboli often originate from atherosclerotic plaques along major arteries. They can circulate after an endovascular procedure or the initiation of anticoagulation. We present a case of severe AERD with an unusually extensive cholesterol burden associated with remarkably notable histopathological findings.

Case Description: A 74 year old male presented with weakness, anorexia, and low urine output. His recent history was notable for iliac artery stenting four months prior for claudication, and an interval ICU admission for burns, sepsis, and AKI. At admission, exam findings were significant for eschars on bilateral great and fifth toes. Lab values showed leukocytosis (16.9 x 10^9/L), eosinophilia (13%), and creatinine of 4.37 mg/dL (baseline 1.2). Work-up revealed bland urine sediment, minimal proteinuria, and normal renal US and complement levels. Despite fluid resuscitation, his renal function declined with no clear etiology. A renal biopsy revealed cholesterol clefts with a phagocytic reaction in the arcuate and intra-lobular arteries, arterioles, and glomerular capillaries across multiple tissue cores. Electron microscopy (EM) also showed occluded arteries with crystalline voids and intact cholesterol crystals. Imaging demonstrated an unstable aortic dissection presumed to be source for the atheroemboli. Not being a surgical candidate, his renal function continued to deteriorate, and hemodialysis was initiated.

Discussion: AERD can be challenging to diagnose; it requires a biopsy, the clefts can mimic processing artifacts, and it is frequently an incidental finding. Our case uniquely illustrates not only some of the common clinical findings associated with this entity, but it also exemplifies severe manifestations of this disease on pathology. Extensive cholesterol emboli involving vessels of multiple sizes, including documentation of cholesterol crystals by electron microscopy (Fig.1), is truly a rare presentation of this disease.



Cholesterol emboli present in multiple arteries in multiple cores: Large Intralobular Artery and Branches (A), Glomeruli (B), and EM (C).

PUB605

Cryofibrinogen-Associated Glomerulonephritis in a Patient with Rheumatoid Arthritis: A Rare Disease Without Immune Complex Type Electron Dense Deposits, but with Fibrillary Organized Deposits

Saeko Hatanaka,[1] Kentaro Koike,[1] Nobuo Tsuboi,[1] Ryuji Ohashi,[2] Tetsuya Kawamura,[1] Akira Shimizu,[3] Takashi Yokoo.[1] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Setagaya-ku, Japan; [2]Department of Diagnostic Pathology, Nippon Medical School Musashikosugi Hospital, Kanagawa, Japan; [3]Department of Analytic Human Pathology, Nippion Medical School, Tokyo, Japan.*

Introduction: Cryofibrinogen (CF) is a cryoprecipitate produced during the process of plasma refrigeration via the structural alteration of serum fibrinogen. To date, there are only a few reported cases of glomerulopathy associated with CF, and thus its clinicopathological aspects remain uncertain. Herein, we present a case of membranoproliferative glomerulonephritis (MPGN), characterized by the absence of immunoglobulin deposits and the presence of organized electron dense deposit (EDD), suggestive of CF-induced glomerulonephritis associated with rheumatoid arthritis (RA).

Case Description: A 72-year-old man, who had been followed-up for RA, visited our hospital with proteinuria and microscopic hematuria lasting over the last 1 year. At presentation, his serum creatinine (Cr) level was 1.69 mg/dL, and urinalysis found protein excretion of 4.6 g/day and many red blood cells. By laboratory work-up, all autoantibodies were negative except anti-cyclic citrullinated peptide antibody, and plasma cryoglobulin or M-protein were not present. Renal biopsy found MPGN, accompanied by glomerular basement membrane (GBM) rupture with fibrin exudation. By immunofluorescence microscopy, no immunoglobulin, or light or heavy chain deposition was found; however, subendothelial and subepithelial EDD were observed along GBM by electron microscopy. Of note, fibrillary materials with luminal diameter ranging from 50 to 100 nm were focally recognized within EDD. Those histological findings were suggestive of CF-associated glomerulonephritis. Subsequently, the patient was treated with corticosteroid, and the serum Cr decreased and the hematuria and proteinuria resolved in 12 weeks.

Discussion: CF-associated glomerulonephritis is an extremely rare disease as only a few cases are reported in the English literature. In the present case, we speculated that CF was produced in association with the patient's long standing RA. Our findings may provide insight into the underlying etiology and further help reveal morphological spectrum of this unique disease entity.

PUB606

Fibrillary Glomerulonephritis (GN) with Amyloid-Like Fibrils Confirmed by Mass Spectrometry

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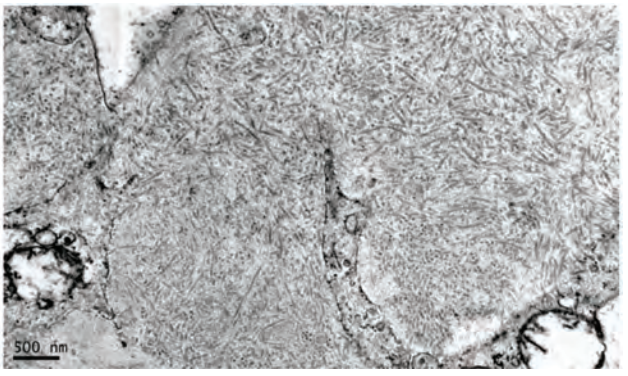
Introduction: Fibrillary GN is a nephritic syndrome characterized by Congo red negative glomerular fibrillary deposits. On electron microcopy (EM) the fibrils are oriented randomly, lack hollow centers, and are generally 16-24 nm in diameter. DNA heat shock protein family member B9 (DNAJB9) has been identified as a potential protein marker for this disease on biopsy.

Case Description: A 54 YOF was seen in clinic because of elevated serum creatinine (2.1 mg/dL). She was obese with uncontrolled hypertension but no evidence of diabetes. UA revealed 3+ protein with 3 RBCs/hpf. The UPCR ratio was 4.94 g/g with UACR of 3.3 g/g. Biopsy yielded 16 glomeruli; 5 showed mild mesangial expansion, 3 segmental sclerosis, and 8 global sclerosis. Congo red staining was negative. No glomeruli were present in tissue sent for IF. EM showed non-branching fibrils measuring between 8.8 - 15 nm in width localized in the mesangial matrix (Figure). Since the fibril size overlapped with that seen in amyloid, laser microdissection-tandem mass spectrometry (LMD-MS/MS) was used to determine the composition of the fibrils. This yielded abundant protein corresponding to DNAJB9. There was no evidence of monoclonal gammopathy. Renal function has continued to deteriorate and she is being evaluated for renal transplantation.

Discussion: Fibrillary GN is a rare cause of GN. Traditionally, Congo red stain and EM are used to distinguish between fibrillary GN and amyloid deposits; however, amyloid deposits may show variable affinity for Congo red stain. By EM, amyloid fibrils are typically 8-12 nm wide while fibrils in fibrillary GN are usually twice this size (16-24 nm), although there is considerable overlap with amyloid. Before interpreting fibrillary deposits as amyloid in specimens where Congo red stain is negative additional testing is prudent. Studies have shown that DNAJB9 is found in almost 100% of fibrillary GN by LMD-MS/MS and immunostains. In view of the absence of IF data, LMD-MS/MS demonstrating DNAJB9 protein was used to verify the diagnosis of fibrillary GN in this patient.



EM

PUB607

An Unexpected Cause of Acute Oxalate Nephropathy – or Is It?

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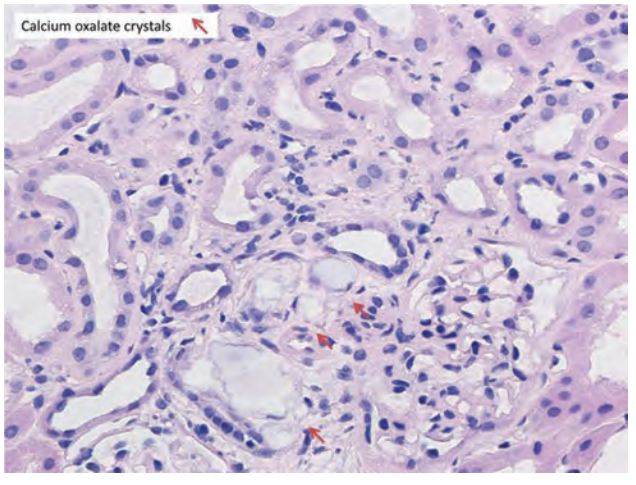
Introduction: Acute oxalate nephropathy may result from increased intestinal absorption of oxalate due to: 1) excessive oxalate intake 2) fat malabsorption syndromes enteric hyperoxaluria or 3) alterations of gut flora depleting oxalate degrading bacteria including the obligate anaerobe Oxalobacter formigenes. During small bowel transplantation (SBT) the gut microbiome is destroyed and the new gut flora with ileostomy is composed of facultative anaerobes.

Case Description: 55 y/o female with h/o SMA rupture requiring SBT and ileostomy presented with multiple episodes of non-oliguric AKI 1yr post txp attributed to high stoma output with volume depletion. Baseline cr pretxp was 0.7mg/dl, peaked at 3.3 and improved to 1.44mg/dl with IVFs but never returned to baseline. U/A and abd CT w/o contrast unremarkable. A small intestinal biopsy ruled out rejection. After the third episode of AKI a native renal biopsy was performed that revealed ATN with calcium oxalate crystals suggesting a possible dx of acute oxalate nephropathy. The patient was treated with increased fluid intake, low oxalate diet, calcium supplementation with meals and a low fat diet. Another clinician questioned how a patient with an ileostomy could develop acute oxalate nephropathy since most oxalate absorption occurs in the large bowel. A relook at the biopsy revealed only sparse crystals in the tissue not refractile under polarized light (as would be expected with calcium oxalate). A von Kossa stain (which picks up phosphate) was not performed. The dx of acute oxalate nephropathy was deemed unlikely contrary to the initial preliminary report.

Discussion: Nephrology remains a fascinating field because it demands that we understand pathophysiology and that things "make sense". This case illustrates that nephrologists must use their clinical knowledge of the patient and be skilled in interpreting renal biopsies even if they are not pathologists. This includes being aware of the limitations and possibilities that a biopsy may offer.



PUB608

Acute Renal Infarction – A Diagnostic Challenge in a Young Female

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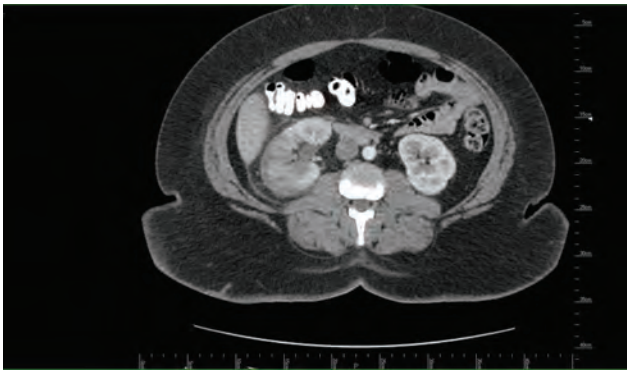
Introduction: Acute renal infarction is a rare but serious event that continues to present a challenge in diagnosis and treatment.

Case Description: A 37-year-old morbidly obese female was admitted to an outside hospital with acute onset of severe right flank pain with nausea and vomiting. Past medical history was notable for dysfunctional uterine bleeding, migraine and psoriatic arthritis. Medications included Topiramate and OCP (high estrogen content) that were started 6 weeks prior to presentation. No history of miscarriages, but family history was significant for SLE. Physical exam was remarkable for mild hypertension, BMI 50, and RLQ tenderness. Laboratory tests: Cr 1.19mg/dL, LDH 2124 and normal PTT. CT scan showed right renal multifocal peripheral areas of decreased enhancement, consistent with infarction, confirmed by CT angiography. She was discharged on enoxaparin injections, and presented 3 months later for a second opinion. Livedo reticularis was noted on lower extremities. Echocardiogram was normal. Laboratory tests: normal LDH, platelets $289x10^9$/L; anti cardiolipin, anti b2 glycoprotein-1, lupus anticoagulant, anti-ds DNA, ANA, C3/C4, were all WNL. Repeat testing at 12 weeks was all negative.

Discussion: Although the most common etiology for renal infarction is thromboembolic originating from the heart or aorta, obesity, high estrogen OCP, or a hypercoagulable state can be associated with in situ thrombosis. In this reported case, clinical findings point to the diagnosis of antiphospholipid syndrome: history of migraines, no cardiac pathology, presence of livedo reticularis and thrombocytopenia during acute presentation. However, auto antibodies (anti-cardiolipin, anti b2 glycoprotein and lupus anticoagulant) were negative. The etiology of renal infarct was therefore attributed to morbid obesity and high estrogen OCP. Long-term aspirin use was recommended by hematology. Conclusion: With negative cardiac source and APLS workup, morbid obesity and high estrogen OCP should be considered in the differential diagnosis for acute renal infarction.



PUB609

Adenovirus Associated Acute Interstitial Nephritis (AIN) in a Patient with Follicular Lymphoma

Jessica M. Nelson, Isabelle Ayoub, Sergey V. Brodsky, Jason Prosek, Salem Almaani. *Ohio State Wexner Medical Center, Columbus, OH.*

Introduction: Adenovirus is a non-enveloped, double-stranded DNA virus known to cause upper respiratory, gastrointestinal, and conjunctival infections in healthy individuals. However, more significant disease is commonly observed in immunosuppressed patients. Those with renal allografts commonly develop adenoviral urinary tract infections. Patients can have disseminated disease, but this is quite rare. Bendamustine-Rituximab combination is a therapy option for the treatment of Follicular Lymphoma. Bendamustine is an alkylating agent that causes DNA damage. Its action is more pronounced in rapidly proliferating cells such as lymphocytes, causing rapid and sustained depletion. This case describes an unusual presentation of pyelonephritis secondary to adenovirus in a patient without a history of transplantation.

Case Description: A 70-year-old Caucasian female presented to our medical center for evaluation of persistent unilateral flank pain with radiological evidence concerning for pyelonephritis. Her medical history is significant for a recent diagnosis of stage IV follicular lymphoma the previous year, treated with 6 months Bendamustine-Rituximab that she completed 6 weeks prior to presentation. She had sought medical care weekly for three weeks, with right flank pain sans dysuria. She described one episode of gross hematuria at her initial presentation but no further episodes. CT and PET scans revealed unilateral perinephric stranding, concerning for pyelonephritis, that persisted on repeat imaging despite adequate antibiotic therapy. Renal biopsy was performed to rule out renal lymphoma. Renal biopsy was consistent with adenoviral interstitial nephritis. At the time of presentation her CD4 count was 86 cells/mm3. Her serum adenoviral load was 4696 copies/mL, urine 96,631 copies/mL. She was treated with Cidofovir. Current serum and urine viral loads are less than 500 copies/mL, or within normal limits.

Discussion: Bendamustine is a chemotherapy agent known to cause prolonged lymphocyte depletion. Therefore, these patients are at a higher risk for the development of common bacterial and viral infections including CMV, EBV, and adenovirus. Physicians

should be vigilant about the prolonged immunosuppressive effects of chemotherapeutic agents, and keep a low index of suspicion for unusual culprits of infection in this population.

PUB610

Know Your HBsAg Testing Method

Karthik Kovvuru, Prakrati C. Acharya, Pradeep Vaitla, Divya Monga. *University of Mississippi Medical Center, Ridgeland, MS.*

Introduction: Center for Medicare and Medicaid services (CMS) requires isolation of Hepatitis B surface antigen(HBsAg) positive patients on dialysis. We encountered a unique situation with our patient's (pts) positive screening HBsAg, negative confirmatory HBsAg and negative Hepatitis B (Hep B) PCR.

Case Description: 41 Yr old male with HIV (on Rx, undetectable HIV RNA, CD4 - 186)) and untreated Hepatitis C (viral load 3,500,000) was admitted to the hospital for worsening CKD requiring initiation of dialysis. He reportedly received last dose of Hep B vaccination series 3 months prior to admission and his screening HBsAg turned positive both immediately and a month after the vaccination series with a negative confirmatory HBsAg and Hep B PCR. Dialysis was initiated and Hep B status re-checked to help with outpatient dialysis placement. His screening HBsAg came back positive again with negative results for confirmatory HBsAg, Hep B antibody and Hep B PCR twice. His placement became challenging as our lab reported that his screening HBsAg is positive despite his confirmation test being negative. We requested CDC assistance and sent them blood samples. Meanwhile we arranged outpatient dialysis at our hospital with a dedicated machine and chair, in accordance with CMS regulations. CDC reported that the surface antigen and Hepatitis B PCR are negative and he was subsequently placed in a non isolation chair at outpatient dialysis center.

Discussion: Our lab uses Abbott architect which tests for HBsAg in two steps "HBsAg Qualitative" and "HBsAg Qualitative confirmatory". The first test is highly sensitive and gives false positive results when Hepatitis C viral load is high or other antibodies are present. The second test uses a reagent to neutralize the false positives and is specific. Our pt had very high Hepatitis C viral load and this was responsible for the false positive screening test. Due to the multiple testing modalities used (CDC uses Ortho Clinical Vitros HBsAg) we should learn how to interpret the local lab and incorporate into clinical practice. Also we need broader guidelines from CMS so that these tests can be interpreted without confusion.

PUB611

Placental Passage of Eculizumab and Complement Blockade in a Newborn

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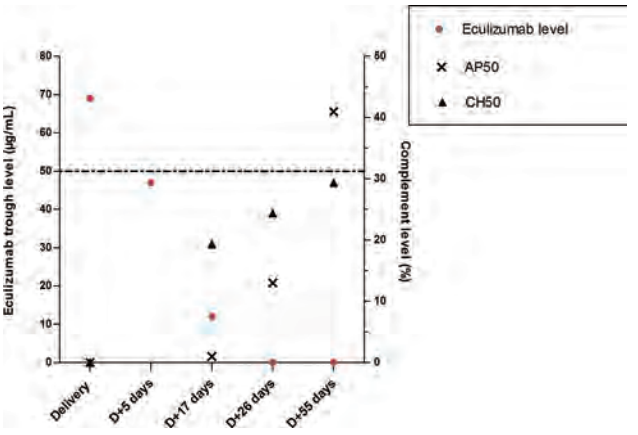
Introduction: Atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH) are rare complement mediated disorders, often affecting women of childbearing age. Because of severe maternal and fetal morbidity and mortality, pregnancy used to be discouraged. The introduction of the complement inhibitor eculizumab has contributed to successful pregnancies. Eculizumab can cross the placenta, and thus may inhibit the complement system of the newborn.

Case Description: A 30 year-old mother, known with aHUS and without treatment, presented at 8 weeks of gestation, with a rise in serum creatinine (from 100 µmol/L to 219 µmol/L), progressive proteinuria and evidence of thrombotic microangiopathy (thrombocytes $91x10^9$/L, undetectable haptoglobin and LDH 309 U/L). Treatment with eculizumab was started (900 mg weekly for four weeks, followed by 1200 mg biweekly), resulting in normalization of hematological parameters and improvement in renal function. At 36^{+1} weeks, after a spontaneous vaginal delivery, a healthy infant of 2010 gram was born. The mother had received her regular eculizumab dose 1 day before delivery. The eculizumab trough level was 262 µg/ml. Eculizumab was detectable in the cord blood of the newborn: free eculizumab level was 69 µg/ml. Evaluation of the complement cascade revealed complete blockade (Figure). Recovery was slow, and lasted > 3 weeks. The newborn was prophylactically treated with amoxicillin until normalization of the complement.

Discussion: Passage of eculizumab resulted in a therapeutic eculizumab level and full complement blockade in the newborn. During follow-up the alternative complement pathway remained blocked for several weeks while eculizumab levels decreased. This may be the result of physiologically low neonatal complement levels. Based on our observation we recommend assessment of drug levels and complement activity in newborns from eculizumab-treated mothers. Prophylactic treatment of newborns with antibiotics should be considered.



PUB612

Complement Factor I Gene Mutation with Normal Factor I Activity in a Child with ESRD Secondary to Atypical HUS

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Introduction: Complement factor I (CFI) regulates the deleterious cytotoxic and inflammatory activity of the alternate complement pathway. CFI deficiency is a rare cause of atypical HUS (aHUS). We report a child diagnosed with ESRD secondary to aHUS who was found to have a CFI gene mutation with normal CFI activity.

Case Description: Our patient is a 10 yo boy with history of an encephalocele, seizures and hypertension who presented with hypertensive urgency and acute deterioration of renal function (serum creatinine 8.7 mg/dL) requiring CRRT. Following admission, his hemoglobin and platelets declined, requiring multiple blood product transfusions. Work-up for causes of acute on chronic renal failure were negative, including duplex US without renal artery stenosis, negative renal angiography, and negative serologies (ANA, anti-double stranded DNA and hepatitis panel). C3 was low at 64 mg/dl and C4 was normal on admission. Renal biopsy was significant for global glomerulosclerosis and tubular atrophy. HUS evaluation showed elevated LDH, normal haptoglobin, smear with schistocytes, and a normal ADAMTS13. Whole exome sequencing (GeneDx, OPKO Health) showed heterozygosity for a G119R variant classified as "likely pathogenic" in the CFI gene inherited from the paternal side. TMA complement panel (Cincinnati Children's Hospital) revealed normal Factor H and B activity. Factor I activity was also normal at 3.2 mg/dl (reference range 2.4-4.9 mg/dl). The patient received a deceased donor renal transplant ~10 months after initial presentation. Due to genetic mutation in CFI, he has been treated with IV eculizumab at time of transplant and every 2 weeks since transplant. He had one episode of anemia requiring blood transfusion but has maintained his platelets in normal range with excellent allograft function (creatinine 0.5 mg/dl).

Discussion: In this patient with a known variant in the CFI gene and a history of ESRD, Factor I activity as measured on a TMA complement panel was within normal range. However, clinical presentation is consistent with aHUS, and he has remained stable on biweekly IV eculizumab infusions -post-transplant. This case supports the value of genetic investigation for causes of aHUS, even in the setting of normal factor H and/or I levels, in order to prevent disease recurrence after renal transplantation.

PUB613

Acute Antibody-Mediated Rejection in a Zero Mismatch Living Donor Pediatric Kidney Transplant Due to an Anti-HLA-DP Donor-Specific Antibody

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Introduction: Donor-specific antibodies (DSAs) against human leukocyte antigens (HLA), particularly anti-HLA-DP, have been associated with development of acute/chronic rejection in highly sensitized (due to a previous transplant) HLA-matched renal allografts recipients. We present a case of a 6 year-old male with **no** prior sensitization, who received a zero mismatch living-related donor kidney transplant from his mother and developed acute antibody mediated rejection (AMR) due to an anti-(HLA)-DP DSA.

Case Description: The recipient and donor were a 10/10 antigen match for HLA-A, B, C, DR, and DQ and the flow cytometric T- and B-cell crossmatches were negative. The recipient was given induction immunosuppression with five daily doses of antithymocyte globulin (total dose of 4.7 mg/kg) and steroids tapered over 6 days. Maintenance immunosuppression included mycophenolate mofetil (MMF) and tacrolimus every 12 hours. Our maintenance immunosuppression protocol targets the following goal tacrolimus troughs: 7-12 ng/mL for months 0-3 and 5-10 ng/mL for months 4-6. Due to our recipient's low immunological risk, we reduced the goal to ≥5 ng/mL for months 0-3. Furthermore, his MMF dose was reduced during this time due to neutropenia. No DSAs were identified in

the first 6 months. Over the next year, the recipient had a slow increase in serum creatinine from 0.4 mg/dL to 0.6 mg/dL. He developed a *de novo* DSA to HLA-DPB1(MFI = 8377) at 14 months post-transplant. Pathology met Banff 2013 criteria for acute AMR. He received two doses of 1 g/kg intravenous immunoglobulin (IVIG) and one dose of 375 mg/m2 Rituximab. His serum creatinine has remained stable and unchanged after treatment.

Discussion: Due to low immunological risk (10/10 HLA antigen match) our patient received reduced maintenance immunosuppression for the first 3 months post-transplant. However, despite being a *pediatric* non-sensitized recipient with an apparently well-matched renal allograft and receiving complete induction immunosuppression, the patient developed acute AMR after developing DSA against the mismatched HLA-DP antigen. This report highlights a role for evaluating DP antigen mismatch before making adjustments to immunosuppression protocols.

PUB614

Arginine Induced Metabolic Acidosis and AKI

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Introduction: Arginine (Arg) among multiple OTC supliments used for various medical conditions. Under appropriate dose and chemical form it is not toxic to cells**,** high doses >9 gm/day are associated with adverse effects in some subjects.

Case Description: 65 years old female patient self treating her hypertension with OTC Arg, for 10 years with poor efficacy, increased her dose gradualy to a total of 45 – 60 mg/day. Presented confused, lab workup showed a Non Anion Gap Metabolic acidosis, with elevated Creatinine, Arg over dose revealed from history and the patient was started on NaHCO3 infusion and hydration, condition improved gradually till completely resolved.

Discussion: Arginine is available in different structures, among which is Arg-HCL, HCL group is added to improve solubility, Side effects are largely related to the HCl group resulting in rapid drop in pH causing metabolic acidosis leading to hyperkalemia, Arginine markedly impairs bicarbonate reabsorption in the proximal convoluted tubules, hence inducing proximal renal tubular acidosis with hypophosphatemia without a renal phosphate leak. Infusion of Arg-HCL causes profound impairment of bicarbonate reabsorption. Management is mainly supportive with IV NaHCO3 and hydration with correction of electrolyte abnormalities. Fatal dose have been reported in pediatric population

Table 1: Patient's Abnormal lab results on admission and on discharge

	Reference	Admission	Discharge
pH	7.32 – 7.45	7.15↓	
PCO2	35 – 45 mmHg	14↓	
HCO3:	22 – 24 mmol/L	<5↓	35
creatinine:	0.6-1.3 mg/dL	2.4↑	1.0
Blood Urea Nitrogen	7-21 mg/dL	87↑	40
Na	136-144 mmol/L	143	145
K	3.6-5.1 mmol/L	3.4↓	2.6
Anion Gap	5.5-14.6 mmol/L	14	7
Phosphorus	2.3 – 7 mg/dL	5.3	3.5
Mg	1.8-2.5 mg/dL	2.9↑	1.8
Glucose	70-100 mg/dL	L 143↑	123

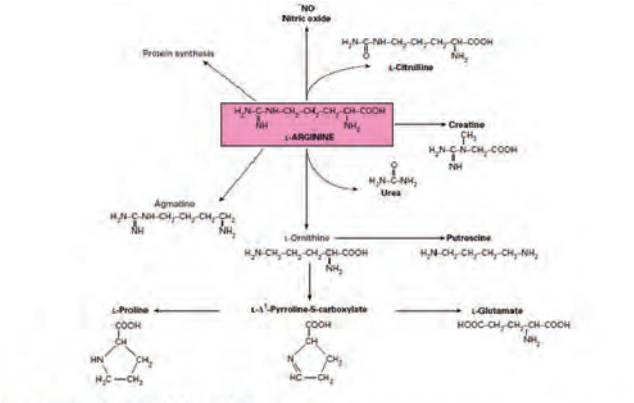

Figure 1 Metabolic fates of arginine in mammalian cells

The five enzymes on which the central fluxes of the pathways are based include tetrahydrobiopterin from the rapid nitric oxide synthase (NOS), arginine:glycine amidinotransferase, arginase, ornithine decarboxylase and arginyl-tRNA synthetase.

PUB615

Hepatorenal Failure with Mushroom (Amanita) Poisoning

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Introduction: Toxic mushroom ingestions can lead to many symptoms including gastroenteritis, seizures and multiorgan failure depending on the toxins involved. Here, we describe a case of acute hepatorenal failure secondary to amatoxin.

Case Description: A 75-year-old male with hyperlipidemia presented to the emergency department (ED) with nausea, vomiting, and diarrhea for two days following ingestion of wild mushroom. Symptoms started 24 hours after a plateful of cooked mushrooms from his backyard. He also complained of inability to urinate. Temp 36.4 C, BP 116/87, Pulse 97, RR 24, Sao2: 99% room air. Physical exam did not have any gross abnormality. Foley yielded 400 cc urine. Labs: hemoglobin19, hematocrit 54.1, platelet 155, sodium 127, Potassium 4.6, chloride 91, bicarbonate 16, bun 75 and creatinine 5.48 Aspartate aminotrasferase 4879, Alanine aminotransferase 9212, Total bili 2.6. Patient had normal kidney function at baseline per his recollection. Given the patient's hepatic injury and unknown mushroom type, he received N-acetylcysteine to reduce potential toxic conversion in the liver, methylprednisolone for potential interstitial nephritis, silymarin to interrupt the enterohepatic circulation of amatoxin, charcoal to absorb the toxin, and penicillin G to increase renal toxin excretion. Plasmapheresis was performed given case reports of successful toxin removal in amatoxin ingestions. Dialysis was initiated given profound azotemia, and he was set up for outpatient hemodialysis (HD) prior to discharge. Amanita virosa was identified based on photos.

Discussion: Amatoxin manifests with symptoms of nausea, vomiting and diarrhea occurring within 24 hours after ingestions followed by multiorgan failure, most notably fulminant hepatic failure and rarely renal failure. Amatoxin is a peptide with molecular weight 900 DA, and it has a high affinity for charcoal as well as polymers found in hemoperfusion cartridges and HD. The best way to remove amatoxin would be hemoperfusion or HD because of its small molecular weight and large volume of distribution. Plasmapheresis in theory would not provide any benefit. Teaching point: It is important to note that the efficacy of treatments of mushroom toxicity is based on small series and there are no randomized controlled trials to address the efficacy of treatments. Given the uncertain role of extracorporal support in toxin management, one should carefully weigh the risks and benefits of these procedures.

PUB616

Appearances Should Not Deceive the Nephrologist

Gajapathiraju Chamarthi, Abhilash Koratala. *University of Flroida, Gainesville, FL.*

Introduction: Hydroxocobalamin causes reddish discoloration of the urine, mimicking hematuria. Clinicians should be aware of this common side effect of the rarely used drug to prevent unnecessary consultations and work up. Additional benign causes of red urine include foods such as beets, rhubarb and medications such as rifampin, phenazopyridine.

Case Description: A 70-year-old woman with a history of multiple abdominal surgeries in the past was admitted for incisional hernia repair and adhesiolysis. The procedure was complicated by bowel injury leading to peritonitis and refractory septic shock with a mean arterial pressure less than 60 mmHg. A trial of intravenous Hydroxocobalamin 5g was given, in an attempt to improve the blood pressure as a last resort, as she was hypotensive despite being on multiple vasopressors. Subsequently, she developed reddish discoloration of the urine, which appeared to be gross hematuria [Figure]. However, urine microscopy was negative for red blood cells and the chromaturia was due to hydroxocobalamin administration.

Discussion: Hydroxocobalamin is the hydroxylated active form of vitamin B12, which is approved for the treatment of cyanide poisoning. Approximately 18-28% of healthy subjects receiving hydroxocobalamin develop elevated blood pressure as a side effect. This moderate pressor effect is likely due to its nitric oxide scavenging effects and this drug is sometimes used as an off-label treatment for vasoplegic syndrome. Hydroxocobalamin can impart reddish to purple color to the urine, which can persist for up to 35 days following intravenous infusion. While this side effect is benign, it is important to note that it can alter colorimetric laboratory measurements and interfere with hemodialysis by triggering a false blood leak alarm.

PUB617

The Ups and Downs of Diarrhea

Krystahl Z. Andujar, Ileana E. Ocasio Melendez, Fatima B. Cintron-Rosa. *Nephrology, University of Puerto Rico - Medical Sciences Campus, San Juan, Puerto Rico*.

Introduction: Despite increased intestinal transit times, a paradoxical rise in tacrolimus levels is a rare complication in diarrheal illness. We present the case of a renal transplant patient on a stable dose of tacrolimus that had to be adjusted after the onset of severe diarrhea.

Case Description: A 70-year-old man with end stage renal disease secondary to hypertension status-post renal transplant in 2007 presented to the emergency department with more than 20 episodes of watery diarrhea, anorexia and abdominal pain. He had travelled from Massachusetts to Puerto Rico two days prior and had been treating his symptoms unsuccessfully with oral hydration. He had no sick contacts and onset of symptoms occurred hours after consuming a sandwich containing mayonnaise during his flight. Long term immunosuppressive regimen included tacrolimus 2 mg every 12 hours, mycophenolate mofetil (MMF) and prednisone. Upon evaluation, he had dry mucous membranes, tachycardia and a tender abdomen. Laboratory results demonstrated severe metabolic acidosis and creatinine levels of 7.3 mg/dL from his baseline creatinine of 2 mg/dL. He was started on intravenous (IV) isotonic fluids and bicarbonate; however, due to refractory metabolic acidosis, intermittent hemodialysis (HD) was started. HD was placed on hold after one session and IV hydration was continued for hypovolemia. Tacrolimus trough levels were supratherapeutic at 37.9 ng/dL and dose was decreased. MMF was placed on hold. Stool and blood cultures, fecal leukocytes, clostridium difficile toxin and CMV titers were negative. After the resolution of diarrhea, tacrolimus trough levels were subtherapeutic and dose was readjusted. He was discharged with stable dose of tacrolimus and baseline renal function.

Discussion: Due to intestinal metabolism by cytochrome P450 (CYP3A4) and active secretion from enterocytes into intestinal lumen by P-glycoprotein, tacrolimus has low oral bioavailability. In the setting of diarrhea, enterocytes are damaged, leading to both increased absorption and decreased gut metabolism of tacrolimus. The impaired gut mucosa leads to increased drug levels despite increased transit times. As the gut heals, CYP3A4 and P-glycoprotein begin to function normally, and tacrolimus levels fall. Therefore, as tacrolimus trough levels may abruptly rise and fall during diarrhea, their intense monitoring is recommended.

PUB618

Hypernatremia and Neurosurgery: Not Always What It Seems

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Introduction: After a neurosurgical procedure, the expected etiology of hypernatremia would be central diabetes insipidus (CDI). However, in a patient with psychiatric illness, poor water access may reveal another culprit for electrolyte disturbance. We present the case of nephrogenic diabetes insipidus (NDI) in a patient on chronic lithium use.

Case Description: A 63-year-old woman was admitted to the neurosurgical unit following a left temporal lobe mass resection. Nephrology service was consulted two days after surgery for a sodium of 172 mEq/L. Medical history was significant for bipolar disorder on chronic lithium therapy for more than 20 years. A direct medical history could not be obtained due to altered mental status but her son reported that she had complained of thirst, increased fluid intake and urinary frequency. Upon evaluation, patient had dry mucous membranes. Urine output was charted at 5 liters per day (L/d). Laboratories showed hypernatremia that followed an increasing trend with associated low urine osmolality of 176 mOsm/kg. Despite lithium discontinuation upon admission and fluid repletion, patient persisted with severe hypernatremia. A water deprivation test was not performed. Desmopressin administration failed to elevate urine osmolality above 300 mOsm/kg, which confirmed NDI. A thiazide diuretic was started to increase urine osmolality by reducing distal water delivery and upregulate aquaporin receptors. Patient showed significant improvement, decreasing urinary output to 3 L/d and reaching normal sodium levels. A positive response to the thiazide diuretic without further symptoms or electrolyte disturbances was observed in the outpatient follow up.

Discussion: NDI is a rare condition that can become irreversible in patients with chronic lithium use. This case highlights the importance of thorough history taking and differential diagnosis formulation; as in our patient, the etiology of hypernatremia was lithium use and not brain mass or surgery. It is important for patients on chronic lithium to be monitored closely for medication complications.

PUB619

Multisystemic Manifestations of Lithium Therapy

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Introduction: Chronic lithium use has been associated with multiple complications, including nephrogenic diabetes insipidus (NDI), hyperparathyroidism, thyroid disease and dysrhythmias. Patients on chronic lithium therapy experience at least one episode of toxicity during treatment. Unfortunately, lithium concentrations may not correlate with signs of toxicity.

Case Description: A 53-year-old woman with bipolar disorder was admitted to the Internal Medicine Ward due to acute changes in mental status. She was diagnosed with bipolar disorder 20 years prior and was treated with risperidone and lithium. Laboratories showed leukocytosis, sodium 164 mEq/L, calcium 11.3 mg/dL, creatinine 2.6 mg/dL and BUN 36 mg/dL. Brain imaging and lumbar puncture ruled out any acute pathology to explain symptoms. Nephrology service was consulted due to hypernatremia and kidney disease. Upon evaluation, patient reported increased thirst, dry mouth and urinary frequency. She was oriented only to person and had dry mucous membranes. Additional workup revealed lithium levels 1.4 mmol/L, serum osmolarity 325 mOsm/kg, urine osmolarity 104 mOsm/kg and PTH 191 pg/mL. Urinalysis showed decreased specific gravity 1.003. Renal ultrasound was remarkable for left non-obstructive nephrolithiasis and findings of renal parenchymal disease. Suspecting NDI, lithium was discontinued. Patient was volume repleted and intravenous fluids were then changed to hypotonic dextrose solution, which resulted in a steady decline in sodium and calcium levels.

Discussion: Lithium leads to NDI by inhibiting aquaporin insertion into the apical membranes, which affects urine concentration and decreased parathyroid gland sensitivity to calcium resulting in an increased incidence of adenomas and hyperplasia. The mainstay of therapy is discontinuation of lithium. Although our patient had only mild elevation of lithium levels, she had a unique presentation with three simultaneous complications from lithium therapy: NDI, hyperparathyroidism and chronic kidney disease. As the unusual multisystemic manifestations of lithium therapy may be observed regardless of its levels, close monitoring for possible complications is of utmost importance during therapy with this drug.

PUB620

An Extended Lithium Saga

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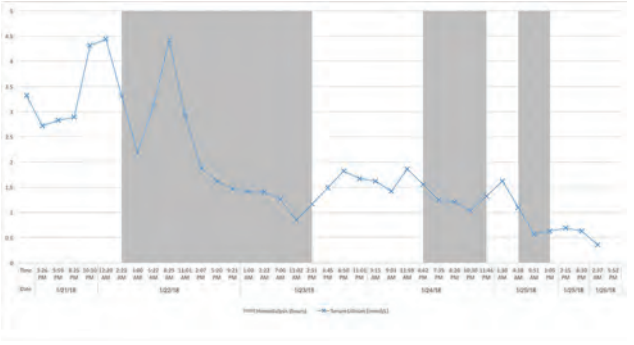
Introduction: Despite its narrow therapeutic window and toxic effects, lithium continues to be an effective treatment for bipolar disorders. Severe lithium intoxication (levels > 2.5 mEq/L) can cause altered mentation, seizures or death and almost universally requires hemodialysis for removal if renal function is compromised. Proper management is essential

to avoid permanent complications. We present a case of acute on chronic lithium toxicity that necessitated a total of 45 hours of hemodialysis to appropriately reduce lithium levels.

Case Description: A 29-year-old male with bipolar disorder presented with altered mental status, emesis, and tachycardia following an intentional overdose with 470 tablets of lithium carbonate 300 mg extended release. Initial lithium level was 3.32 mEq/L. After 2 liters of saline administration, repeat lithium levels were improving to 2.72 mEq/L therefore a decision to track levels instead of starting hemodialysis was made. Intermittent hemodialysis (IHD) was initiated 12 hours after the presentation when patient's UOP decreased and QT began to prolong. Repeat lithium level had increased to 4.4 by the start of dialysis. After 36 continuous hours of hemodialysis a lithium level of 0.85 mEq/L was achieved. Rebound lithium levels necessitated two additional sessions of dialysis, with an additional 9 hours in total. Upon discontinuation of IHD, the lithium level remained below 1 mEq/L.

Discussion: This case illustrates the therapeutic role of prolonged IHD in extended release lithium intoxications. Realizing the pharmacokinetics of extended release lithium, the care team astutely continued tracking lithium levels even after they were noted to be decreasing. It is imperative for practitioners to understand the pharmacodynamics of lithium, including the changing volume of distribution for chronic use in comparison to acute overdose. It is also important to understand how extended release formulations might alter predictions on how to best provide intoxication management.



PUB621

Glass Green Colored Urine: Is It Benign or a Cause for Alarm!

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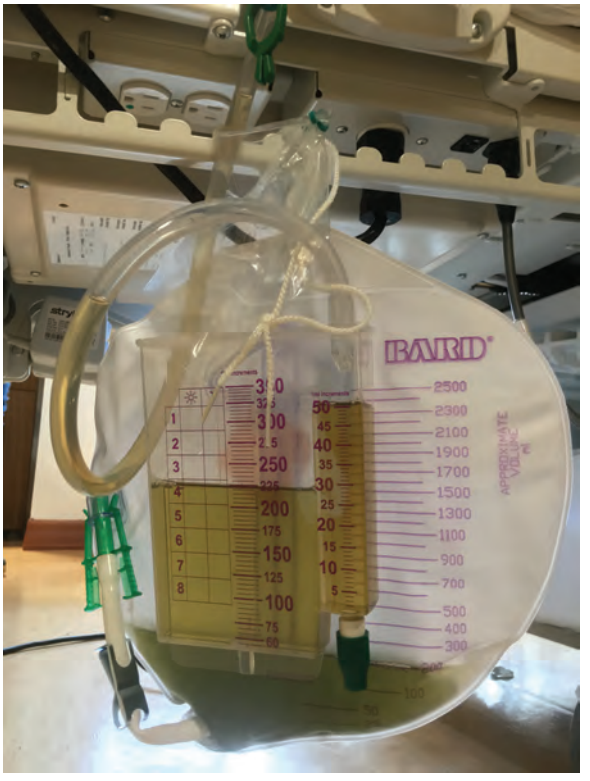
Introduction: Urine analysis is an integral part of the evaluation of any illness. A change in the urine color always makes a clinical contemplate. The cause could be an underlying illness or simply a new medication or dietary changes. We present an interesting case of green urine which developed after propofol.

Case Description: A 22-year-old male was admitted with an acute onset of difficulty in breathing that started 3 hours prior to admission and was debilitating to the extent that he couldn't speak in full sentences. On examination, he was tachypneic, breathing at 34 breaths per minute and required oxygen 6L/minute to maintain>90% saturation. He was subsequently intubated. Propofol5mcg/kg/min and Fentanyl25mcg/hr were used for sedation. Propofol was gradually increased to 20mcg/kg/min to achieve RAAS score of -2. On the day 2, his condition improved and he was extubated. Interestingly, during this period his urine bag showed glass green colored urine. Initially, urine infection was suspected. Although clinically he was normal. All his sedations including Propofol were stopped.6 hours after discontinuation, the green color cleared and his urine returned to a pale yellow color.

Discussion: Propofol is extensively used in intensive care medicine for sedation. It is metabolized in the liver and predominantly excreted in urine as phenolic metabolites. The green discoloration of urine is attributed to these phenolic metabolites and is reversible on discontinuation. Total dosage or length of infusion does not correlate with discoloration. The total dose of propofol leading to green urine may range from 200 mg to 14,000 mg. Our patient received total 3035mg over 34 hours. Some of the other causes of green color urine could be urine infection or drugs like promethazine, thymol etc. Therefore, urine color should be interpreted with an acumen considering all benign and pathological conditions so as not to miss a disease and also avoid unnecessary diagnostic evaluation.



Urine bag

PUB622

Systemic Absorption of Oral Vancomycin in C. difficile Colitis

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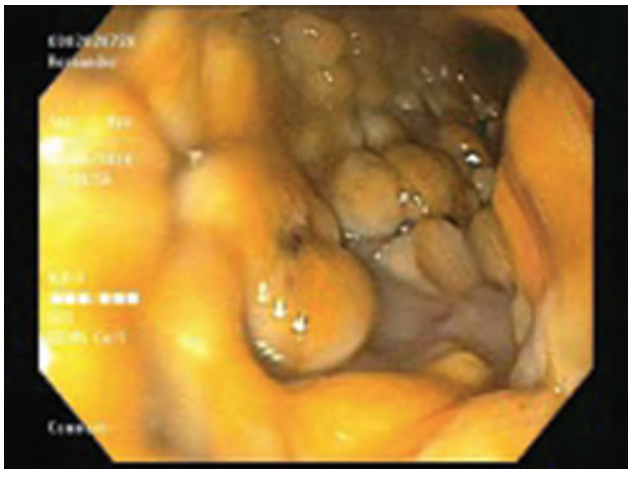
Introduction: Oral vancomycin is generally considered safe to use in patients with kidney disease due to its minimal absorption in the gut <5%. This has led to a widespread approval of the oral form of the drug in treating *Clostridium difficile* infection (CDI). Some case reports indicate unpredictable absorption in renal failure. Here we report a case of nearly supratherapeutic levels in a patient with severe CDI and stable renal function.

Case Description: 50-year-old female with hypertension, diabetes, and CKD 4 presented to the hospital with chief complaint of diarrhea and abdominal pain. After completing two weeks of levaquin developed profound loose, watery stools. Labs showed a leukocytosis 25k and stable CKD (Cr~3.0). CDI tests were positive for toxin and GDH antigen. Oral vancomycin and IV metronidazole were started immediately, however, symptoms persisted one week later. Vancomycin dose was increased and given both oral and rectally with only mild improvement in symptoms. Prolonged vancomycin taper was initiated. Trough levels were measured 19 mg/L. Due to concern for nephrotoxicity the dose was not increased. Flexible sigmoidoscopy showed diffuse pseudomembranes indicating severe CDI refractory to antibiotics. Fecal transplant was performed 35 days into admission and diarrhea resolved.

Discussion: IDSA guidelines recommend oral vancomycin for treating several stages of CDI. This case raises the question of whether inflammatory states or altered bowel anatomy (rectal ulcers in this case) and renal insufficiency play roles in unpredictable vancomycin levels. Few case reports have been published on this matter, most report detectable drug concentrations when vancomycin is used at high doses >2 g/day and long durations >10 days. Currently there are no guidelines for monitoring serum vancomycin levels when given orally. Serum drug monitoring in patients with severe or fulminant CDI is an area necessitating further research and may reveal an issue of toxic absorption.



sigmoid pseudomembranes

PUB623

Cefepime Induced Non-Convulsive Status Epilepticus in ESRD Patients

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Introduction: Cephalosporin induced neurotoxicity is well described in the literature but it remains an under-recognized phenomenon clinically. Studies have shown that up to one-third of patients (pts) on hemodialysis (HD) are prescribed a drug at an inappropriate dose resulting in adverse reactions. Cefepime is predominantly cleared by renal excretion; impaired renal function increases the risk for cefepime-induced neurotoxicity leading to an array of symptoms including slurred speech, tremors, confusion, coma, and non convulsive status epilepticus (NCSE). We present a case of a pt with ESRD who developed NCSE from cefepime toxicity and aim to highlight the importance of medication adjustment in patients with renal failure.

Case Description: A 60 year old woman, with ESRD on HD, was transferred to our facility for management of persistent encephalopathy while being treated at an outside hospital for health care associated pneumonia (HCAP). She was receiving cefepime at the regular dose rather than the ESRD -adjusted dose. Imaging excluded acute intracranial abnormalities and CSF studies were unrevealing. Continuous EEG monitoring showed 2Hz generalized periodic discharges (GPD), a pattern characteristic of NCSE. The patient was dialyzed daily for several days with high flux dialyzer. Gradually, GPD were replaced with generalized rhythmic delta activity, marked improvement in neurological status was noted and eventually the pt was extubated.

Discussion: Physicians need to be aware of the importance of medication dose adjustment in patients with renal failure. This case highlights a common neurotoxic effect of cefepime due to high levels in an ESRD pt but a similar scenario can be envisioned with any medication that needs renal adjustment, if they are not dosed properly. To prevent such adverse events, we suggest the use of eGFR calculators in all electronic medical records, involvement of clinical pharmacists on the inpatient teams as well as increased vigilance on the part of the inpatient pharmacy along with early involvement of nephrology team. Keeping in view the shortage of fellows opting for nephrology resulting in a decrease of qualified physicians to care for the ever increasing population with ESRD, it is imperative to stress this issue when residents rotate on the nephrology service since they will often be on the frontlines to treat such patients.

PUB624

Recurrent Proliferative Glomerulonephritis with Monoclonal IgG Deposits in a Renal Allograft - Still a Dilemma

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin G deposit (PGNMID) is a recently described pathological entity of native kidneys which falls in the spectrum of monoclonal immunoglobulin deposition disease, whose clinical course resembles glomerulonephritis. Occurence in renal allografts is exceedingly rare and appears as a recurrent or de novo disease.

Case Description: A 56 year old Caucasian female with history of End Stage Renal Disease due to biopsy proven membranoproliferative glomerulonephritis 12 years ago on dialysis, underwent a deceased donor kidney transplant on maintenance prednisone, tacrolimus and myfortic with baseline allograft function at 0.9mg/dl, presented 4 months later for a routine visit and was found to have worsening allograft function with serum creatinine at 1.35 mg/dl. Urinalysis showed 3+ blood and >500 protein. Urine sediment revealed dysmorphic red blood cells with urine protein/creatinine ratio of 1.5 g/g. Complements C3/C4, SPEP, UPEP and serum immunofixation were normal, prompting a diagnostic allograft biopsy. Findings were consistent with endocapillary proliferative and exudative glomerulonephritis accompanied by diffuse glomerular immune deposits comprising IgG, kappa light chain and C3 localized to capillary walls and mesangial areas confirming the diagnosis of PGNMID. Bone marrow biopsy was negative. She was treated with 4 doses of Rituximab 3.75mg/ m2 given 2 weeks apart, and prednisone 60mg. 5 months after treatment, repeated urinalysis still showed 3+ blood and 100 protein with improving allograft function and serum creatinine at 1.1 mg/dl.

Discussion: Our patient has recurrent PGNMID in allograft due to its rapid appearance after transplant, supporting the theory that it recurs within 2 years after transplant due to circulating abnormal IgGs in patient sera. Diagnosis is based on electron microscopy and immunofluorescence of biopsy specimen as it can be misdiagnosed as transplant glomerulopathy. There is no definite treatment yet. Amongst case reports of PGNMID of native kidneys, the most successful outcomes were with Rituximab perhaps because it targets plasma cells secreting these abnormal immunoglobulins. Hence, we chose this treatment option in our patient. A follow up biopsy may be helpful to assess the pathological response to Rituximab.

PUB625

Primary Nonfunction of a Renal Allograft Secondary to Primary Hyperoxaluria and Systemic Oxalosis

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Introduction: The primary hyperoxalurias are rare genetic abnormalities of the hepatic enzymes involved in glyoxylate metabolism leading to overproduction of oxalate which is renally excreted. There is deposition of calcium oxalate in various tissues, primarily the kidney, leading to nephrolithiasis, nephrocalcinosis and ESRD.We present a case of primary nonfunction of a renal allograft due to primary hyperoxaluria type 1 (PH1).

Case Description: 52 yo M with ESRD due to recurrent staghorn calculi s/p DDKT remained dialysis dependent. Allograft biopsy showed an eosinophilic infiltrate, interstitial nephritis and acute tubular necrosis (ATN). There were a few crystals under polarized light but no interstitial fibrosis/rejection. Two months later he still required dialysis so a second biopsy was done. This showed marked ATN with casts and birefringent crystals enhancing under polarized light. Immunofluorescence and electron microscopy were negative for light chains and the amyloid stain. He remained anemic despite erythropoietin and transfusions. The erythropoietin level was 459 mIU/mL.A bone marrow biopsy showed normocellular marrow, oxalate crystals, myelodysplasia of the megakaryocytes and erythroid precursors that was classified as refractory cytopenia with multilineage dysplasia. FISH markers for myelodysplastic syndrome were negative.With evidence of oxalate crystals on the kidney/ bone marrow biopsies and history of recurrent nephrolithiasis, primary hyperoxaluria was worked up. Genetic tests showed an alanine-glyoxylate aminotransferase gene mutation consistent with PH1 causing primary nonfunction of his renal allograft.

Discussion: Systemic oxalosis causes deposition of oxalate crystals in the kidneys, blood vessels, bones, heart and central nervous system. The earliest manifestations are renal due to direct tubular toxicity from the crystals, nephrolithiasis, infection and nephrocalcinosis. Once the GFR <30-45 mL/min, serum oxalate levels rise and deposit in tissues. Bone marrow involvement causes ineffective erythropoiesis, resistance to erythropoietin, other cytopenias and hepatosplenomegaly. PH with ESRD requires daily dialysis along with nocturnal peritoneal dialysis. Oral pyridoxine is helpful as a suppressive therapy in PH1. Definitive treatment with liver-kidney transplantation supplies the missing enzyme for glyoxylate metabolism.

PUB626

CNS Aspergilloma Mimicking Pituitary Adenoma in a Renal Transplant Recipient

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Introduction: Fungal infections of the CNS are frequently seen immunocompromised hosts however, CNS Aspergillomas are rare. Aspergillosis commonly presents as a primary opportunistic infection of the lungs/paranasal sinuses with systemic hematogenous spread. Primary CNS infection without extracranial involvement is rare. MRI Brain and CT sinuses are essential for diagnosis. Surgical resection with voriconazole are the best treatment. We present a case of an isolated CNS Aspergilloma mimicking a pituitary adenoma in an immunosuppressed kidney transplant recipient.

Case Description: 68 yo F with HTN, DM, ESRD s/p DDKT with CKD due to allograft nephropathy, maintained on immunosuppression, presented with frontal headache. She did not exhibit neurological deficits. Labs showed baseline Cr 2 mg/dL.Brain MRI showed a sellar mass consistent with a pituitary macroadenoma. She had no clinical findings of an endocrinopathy. Due to limitations of contrast administration given her CKD imaging was limited. Later she presented with sudden onset decreased vision and L sided proptosis. Repeat imaging showed increased size of the lobulated sellar mass with supra-sellar extension, optic chiasmatic compression and invasion of the L cavernous sinus. Trans-sphenoidal resection showed a fibrous and purulent mass. Frozen section biopsy revealed necrotizing granuloma, septate fungal hyphae and conidia consistent with aspergilloma. Fungal cultures were also positive. She was treated with IV amphotericin B and voriconazole and was maintained on lower immunosuppression. However she suffered a stroke and renal allograft dysfunction post-operatively. Given her complex condition the family decided to withdraw care.

Discussion: CNS aspergillosis is an uncommon infection seen in immunocompromised hosts. Manifestations include focal deficits, cranial nerve palsies, strokes, and intra-cranial hemorrhage. Radiographic findings include sino-nasal disease, intracranial mass lesions and cavernous sinus invasion. Biopsy reveals branching septate hyphae and conidia of Aspergillus. Sellar space occupying lesions can be confused with pituitary adenomas and endocrine involvement must be considered. Craniocerebral aspergillosis is treated with Voriconazole which has been shown to have good CNS penetration in combination with surgical resection. Mortality rates are higher in immunosuppressed patients with intracerebral involvement.

PUB627

Azathioprine and Allopurinol Combination Therapy in Renal Transplantation

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Introduction: Azathioprine is rarely used in renal transplant recipients outside of pregnancy, but options for immunosuppression are limited in this setting. Thiopurine-allopurinol co-therapy represents an alternative treatment strategy in the setting of azathioprine-associated hepatotoxicity in women with transplants who desire pregnancy

Case Description: A 32 year old female with a history of ESRD secondary to unknown etiology received a preemptive unrelated renal transplant in 2014. She received Campath induction and was on tacrolimus and mycophenolate mofetil. She was initially prednisone-free; however, was transitioned off mycophenolate mofetil to azathioprine in anticipation of desired pregnancy. Thiopurine methyltransferase (TPMT) activity was normal. Unfortunately, soon after the initiation of azathioprine she developed hepatotoxicity with transaminitis and biliuria. She subsequently had normalization of her liver function tests after the azathioprine was switched back to mycophenolate mofetil. She was then found to have a borderline cellular rejection on protocol biopsy, necessitating steroid treatment. After another year of therapy with stable graft function, she again wanted to discuss the possibility of pregnancy and different options were considered for immunosuppression, including prednisone and tacrolimus dual therapy or sirolimus in place of mycophenolate mofetil. Finally, a third alternative was chosen of using low-dose azathioprine in combination with daily allopurinol to minimize the hepatotoxicity of azathioprine

Discussion: Thiopurine-allopurinol co-therapy has been successfully used as immunosuppressive strategy in renal transplant recipients, but is rarely used now due to risks of bone marrow suppression. Azathioprine is metabolized to 6-MP, which is metabolized to form 6-thioguanine nucleotides (TGN), the main therapeutic metabolites. 6-MP can also be deactivated by TPMT to form 6-methylmercaptopurine (MMP). High levels of 6-TGN are associated with disease remission, but also with myelosuppression when in excess, whereas high levels of 6-MMP are associated with hepatoxicity. TPMT activity does not predict hepatoxicity in the same way that it predicts myelosuppression. Approximately 15% of patients will preferentially metabolize 6-MP to 6-MMP instead of 6-TGN. Allopurinol helps circumvent this hypermethylation and will reduce 6-MMP levels and increase 6-TGN levels

PUB628

Daily Self-Administered Intravenous Fluids Prevent Recurrent Acute Kidney Allograft Dysfunction in a Patient with Short Bowel Syndrome

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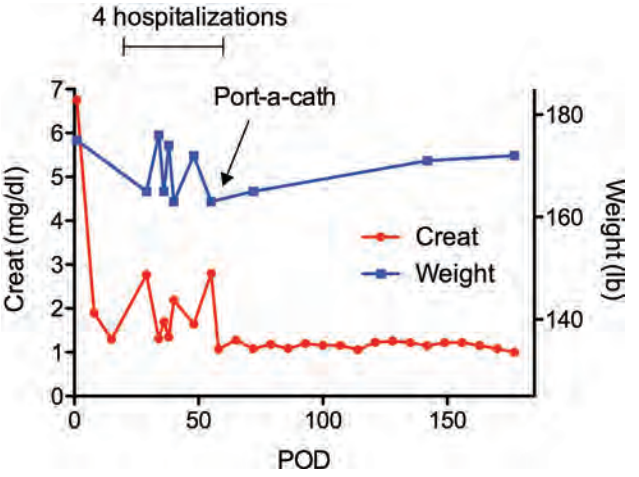
Introduction: Short bowel syndrome (SBS) is a relative contraindication for kidney transplantation (KT). Few cases of dual kidney and intestinal transplantation are reported, whereas there are no data to help manage similar patients who end up receiving KT alone.

Case Description: A 59 y/o man with ESRD on HD for 10 years in the setting of Crohn's disease and SBS (150 cm of small bowel, subtotal colectomy), underwent a deceased donor KT. He received basiliximab induction and maintenance mycophenolate, tacrolimus, and prednisone; discharged on POD 4, after requiring one session of HD for hyperkalemia. Subsequent course was complicated with recurrent acute kidney injury (AKI) from diarrhea, with stool output >3.5L at times, and weight loss before each AKI, despite aggressive oral hydration. A kidney biopsy showed acute tubular injury with rare tubular oxalate crystals. Despite transition to azathioprine, aggressive motility inhibition including DTO, he continued to have high output diarrhea and required 4 hospitalizations (average length of stay was 5 days) for work up and volume expansion, which on every occasion led to the swift resolution of the AKI. Eventually, he received an internal jugular port-a-cath and was discharged on a daily 1L Ringer's lactate infusion. This resulted in a sustained recovery up to 7 months after transplantation (at the time of this report) with steady serum creatinine and weight, no additional hospitalizations, and return to work full time (figure).



Discussion: We report for the first time stable kidney allograft function in a patient with SBS with self-administered daily IV fluids. Although this case is short-termed, the trend is meaningful and shows that select patients with SBS, could still undergo kidney transplant, but will rely on daily parenteral volume expansion, which can be done at home safely and consistently.

PUB629

Recurrent MGRS in a Renal Transplant: Importance of Knowing the Primary Disease

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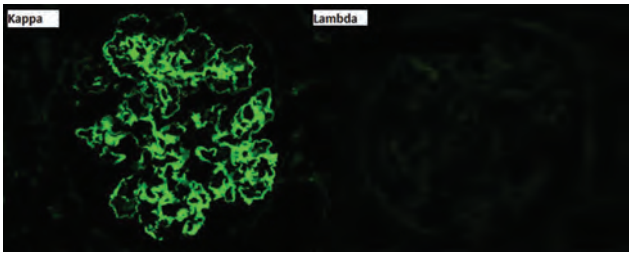
Introduction: The term monoclonal gammopathy of renal significance (MGRS) was developed to encompass renal lesions associated with a monoclonal immunoglobulin (mIg) that do not fit the typical lesions of cast nephropathy and AL amyloidosis etc. While some are associated with a mIg in the serum or urine, some are identified only on renal biopsy by demonstrating light chain restriction indicating an abnormal cellular clonality. These lesions have a high recurrence rate in allografts and the clonal cell line should be treated prior to transplantation. We present a case of MGRS that was identified as such only after recurrence in the renal transplant.

Case Description: A 61 year-old woman presented with nephrotic-range proteinuria and creatinine (Cr) of 0.8 mg/dl. Renal biopsy revealed MPGN with IgG kappa restriction (Figure 1). This was not appreciated to be a MGRS and was treated with cyclophosphamide (CP) and steroids. Three years later, she presented with ESRD. A renal biopsy was identical but with advanced fibrosis felt to be ESRD secondary to idiopathic MPGN and she remained on hemodialysis without further treatment. After 5-years she received a cadaveric renal transplant (CRT). At 4 months post CRT, her Cr was 2.1 mg/dl. An allograft biopsy showed mesangial hypercellularity with glomerular IgG kappa restricted deposits and her disease was finally clinically recognized as a MGRS. Serum and urine immunofixation failed to show a mIg and a bone marrow with flow cytometry could not identify an abnormal cell clone. Despite this, she was treated with bortezomib, dexamethasone and CP. An allograft biopsy 4 months later had persistent mIg deposits but her Cr improved to 1.2 mg/dl. Due to concern for failure of first line therapy and future allograft loss, second line therapy with Daratumumab vs. autologous stem cell transplant is being considered.

Discussion: MGRS has high allograft recurrence rates and needs to be identified and treated prior to renal transplantation. This patient appears lucky in that the clonal production of mIg was indolent enough that treatment post CRT may be successful.



PUB630

Discovery of Functioning Native Kidneys with a Failed Renal Allograft 5 Years After a Simultaneous Liver Kidney Transplant (SLKT)

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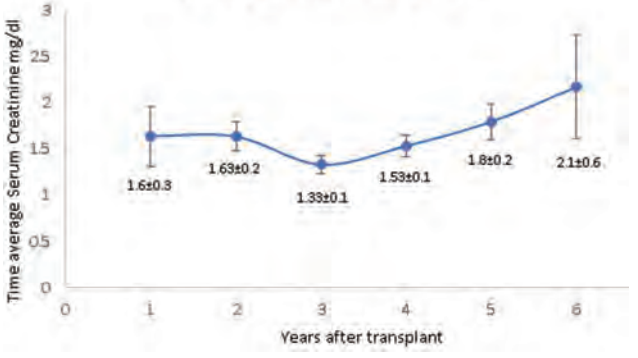
Introduction: Renal function has been found to recover in 11.5% of single organ liver transplant recipients who required pre-transplant renal replacement therapy for more than 90 days. There are reports of SLK recipients regaining significant native kidney function post transplantation. We report a discovery of native renal function in a patient with renal allograft failure 5 years after SLKT who required pre-transplant renal replacement therapy for 5 months.

Case Description: A 70-year-old man with a PMH of end stage liver disease from HCV cirrhosis, HCC, HTN, T2DM and HRS pre-transplant, requiring hemodialysis, who received a SLKT in 2013. His post-transplant course was complicated by acute cellular

rejection of the liver in 2013 which was successfully treated. Five years post transplant, patient developed AKI with creatinine rising to 2.0mg/dl. See figure 1 for the trend of creatinine post transplantation. US revealed an atrophic renal allograft with significant cortical thinning and abnormal doppler waveforms of the main renal artery that was consistent with a failed renal allograft. US of the renal allograft performed 2 years prior was normal in size but increased in echogenicity. Biopsy revealed chronic inflammation, 60% globally sclerosed glomeruli with severe interstitial fibrosis and tubular atrophy. MAG3 furosemide renal scan was performed to investigate native renal function which revealed left kidney, 55.2% and right kidney, 44.8% without activity in the renal allograft.

Discussion: We discovered renal allograft failure which resulted in the unmasking of native renal function as demonstrated by the furosemide renal scan 5 years after SLKT. This patient met UNOS criteria for dual organ transplantation, having sustained AKI requiring hemodialysis for 5 months prior to SLKT. More studies are warranted to investigate better predictors of native renal recovery in SLKT in the era of the new UNOS policy.

Figure 1: Creatinine trend



PUB631

A Case with Muir-Torre Syndrome: Concurrent Sebaceous Carcinoma with Multiple Visceral Malignancies in a Kidney Transplant Recipient

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Introduction: Sebaceous carcinoma (SC) is a rare but progressive malignant skin cancer, and the incidence is approximately five times higher in post-transplant patients. SC is sometimes found concurrently with visceral cancers and a genetic abnormality called Muir-Torre syndrome (MTS).

Case Description: The patient was a 43-year-old woman who had received a living kidney transplantation from her father at the age of 33 due to end-stage kidney disease caused by IgA nephropathy. The transplanted kidney function was stable, with a serum creatinine of 1.5 mg/dl. Ten years after transplantation, a rapidly enlarged skin tumor developed in the left occipital region, which was totally resected. The tumor was diagnosed as SC. In addition, subsequent examination revealed the development of multiple visceral malignancies, including sigmoid colon cancer, rectal SC, and cervical cancer. Immunohistochemical study revealed the absence of mismatch repair (MMR) proteins and the development of microsatellite instability in the SC, suggesting MTS. DNA sequence analysis for MMR genes revealed a genetic mutation of 1226_1227delAG in the MSH2 Exon 7 lesion, which confirmed MTS.

Discussion: SC is relatively common in transplant recipients with visceral malignancies due to MTS. Our case suggests that careful and frequent follow-up and thorough evaluation by a dermatologist is important for an accurate diagnosis in transplant recipients.

PUB632

Adenovirus Nephritis in the Transplanted Kidney

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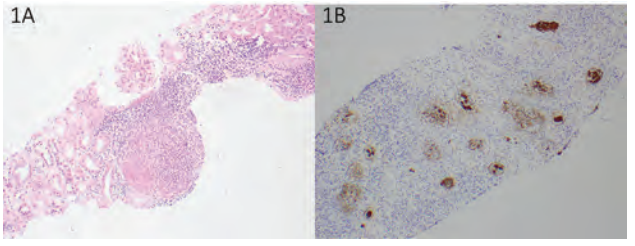
Introduction: Adenovirus infection can manifest as disease involving the upper respiratory tract, gastrointestinal, ophthalmologic, genitourinary, and/or neurologic systems. Most cases are self-limited; however, serious and disseminated infections can occur in immunocompromised patients.

Case Description: We report the case of a 69-year old male with end-stage renal disease attributed to diabetic nephropathy who underwent a deceased donor kidney transplant six years prior and presented with weakness, fever, chills, and gross hematuria. Laboratory work-up revealed acute kidney injury with a serum creatinine of 2.1 mg/dL, up from his baseline of 1.3 mg/dL. Urine studies were notable for >1000 red blood cells/high-power field and proteinuria of 0.58 g/g. Cystoscopy showed clots in the bladder, cystitis, and bloody efflux from the ureteral orifice of the transplanted kidney. Adenovirus DNA was detected in the urine by PCR and serum adenovirus viral load was elevated at 1630 copies/mL. An allograft kidney biopsy was performed, which demonstrated diffuse and severe interstitial inflammation with tubulitis and vague granulomas on light microscopy (Figure 1A). Immunostaining for adenovirus showed numerous foci of nuclear and cytoplasmic staining of tubular epithelial cells (Figure 1B). Given these findings, the patient was diagnosed with adenovirus nephritis and treated with intravenous cidofovir 2.5 mg/kg twice a week for 3 weeks. The dose of his mycophenolate was also reduced by 50%. With this treatment, his hematuria resolved, serum creatinine returned to baseline, and serum adenovirus viral load became undetectable.

Discussion: Adenovirus is an opportunistic infection frequently seen in kidney transplant recipients. Clinical manifestations of adenovirus involving the genitourinary system include hemorrhagic cystitis and, rarely, tubulo-interstitial nephritis. A kidney biopsy is necessary for definitive diagnosis of adenovirus nephritis. Treatment includes antiviral therapy and reduction of immunosuppression.



PUB633

Rituximab Success in Management of Recurrent GVHD of the Kidney Post Allogeneic SCT

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Introduction: GVHD of the kidney is a rare complication post allogeneic stem cell transplant usually manifests clinically as a nephrotic syndrome after around 6-12 months of transplant. It is estimated that the incidence of the nephrotic syndrome in adult recipients ranges 0.4-6 %. Majority of the cases has evidence of Mimimal change disease(65.5%), followed by membranous (19%) then FSGS (7.7%). Steroids used alone or in combination with calcineurin inhibitor reported to induce favorable response in around 75% of the cases. Rituximab had good outcome in management of GVHD with membranous nephropathy. There is a very limited data about the incidence and treatment of recurrent GVHD of the kidney after initial remission. We present a case of FSGS as a presentation of GVHD of the kidney with three relapses who has failed tacrolimus and steroids in the past and successfully treated with rituximab each time with full remission.

Case Description: 66 year old hispanic male with history of hypertension, non-ischemic cardiomyopathy and Mantle cell lymphoma status post allogenic SCT (7 years ago) with renal GVHD at 1 and 3 years post-transplant. Renal biopsy consistent with Minimal change disease and FSGS respectively, treated successfully with rituximab. Patient presented with volume overload with anasarca. Urine analysis was positive for hematuria and pyuria. Proteinuria peaked at 11g and albumin of 2.2 g/dl. Patient had AKI on admission with creatinine was of 3.3 mg/dl (with baseline 1.4 mg/dl, 5 months prior to admission) patient was started on empiric therapy with 1m/kg of prednisone daily and underwent renal biopsy with finding of FSGS. He was started on weekly dose of rituximab 375 mg/m^2 but his creatinine peaked at 7.7 mg/dl and underwent dialysis for three weeks at which point he had improved urine output, creatinine decreased to 1.0 mg/dl, and UPC decreased from 11g to 1g.

Discussion: Renal GVHD after stem cell transplant can be of a recurrent nature, even after 7 years of transplant. Rituximab successfully induced remissions in patient with FSGS despite severe AKI that required. A possible theory on how B cells can contribute to chronic GVHD is that the reconstituted B cells after myeloablative conditioning may have impaired immune tolerance of peripheral B cells, leading to the production of autoantibody in chronic GVHD.

PUB634

A Case of High Output Heart Failure Secondary to an Arteriovenous Fistula in a Renal Transplant Patient

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Introduction: The presence of an arteriovenous (AV) fistula in a patient leads to decreased systemic vascular resistance and a compensatory increase in cardiac output which may result in clinical heart failure.

Case Description: A 72-year-old lady with history of end stage renal disease secondary to ANCA vasculitis post renal transplant 2 weeks ago was admitted with worsening

peripheral edema and dyspnea on exertion. She had gained 19 kg since transplant. She was on tacrolimus, mycophenolate sodium and prednisone. Physical examination showed elevated jugular venous pressure, bilateral crackles, 2+ pitting lower extremity edema, 1+ pitting upper extremity edema, greater on the right side, and a right brachiocephalic arteriovenous fistula with thrill and bruit. Echocardiogram showed an ejection fraction of 63%, diastolic dysfunction, an elevated pulmonary artery systolic pressure of 53 mmHg and a dilated inferior vena cava. Right upper extremity duplex was negative for deep vein thrombosis. Serum creatinine (SCr) was 1.64 mg/dl, (baseline 1 mg/dl). She was treated with intravenous (iv) furosemide and improved clinically. She was transferred to inpatient rehab after 5 days, by which time SCr was down to 1.2 mg/dl and she had lost 2 kg. In rehab, she lost another 10 kg. 2 weeks after transfer, she developed worsening hypoxia and was transferred back to the floor. She received iv diuresis and was discharged after 5 days. She was readmitted 3 weeks later for volume overload, and her weight was up by 9 kg. Labs showed SCr of 2.34 mg/dl. Vascular duplex of AV fistula showed a high flow rate of 2.7 L/min. She was treated with iv furosemide. The patient lost 12 kg and underwent right heart catheterization. Her cardiac output was 8.6 L/min at baseline and decreased to 6.6 L/min after right arm fistula occlusion. Her fistula was ligated 4 days later. At the time of clinic visit 2 weeks post-discharge, SCr was down to 0.6 mg/dl, and the patient had lost another 3 kg and was back to her pre-transplant weight.

Discussion: High output heart failure secondary to an AV fistula can be confirmed by right heart catheterization with dynamic measurements. An elevated baseline cardiac output with a significant decrease upon transient fistula occlusion, such as in our patient, helps confirm the diagnosis.

PUB635

Invasive Mucormycosis Causing Gastrointestinal Bleed in a Renal Transplant Patient

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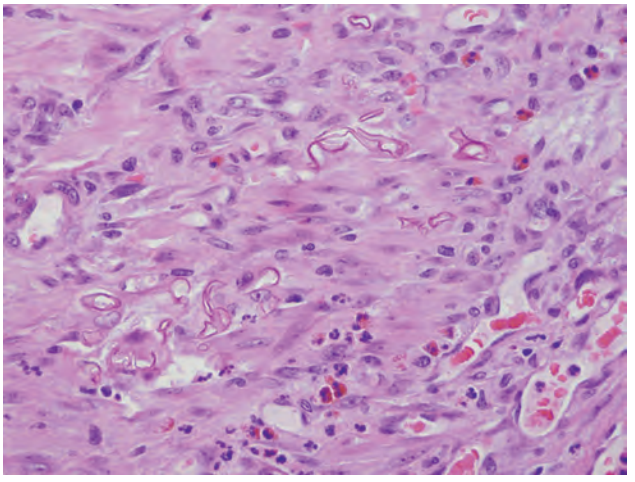
Introduction: Mucormycosis refers to a serious infection by fungi in the order Mucorales. It presents most commonly as rhino-orbital-cerebral and pulmonary infections. It predominantly affects patients with diabetes mellitus and immunocompromised patients.

Case Description: A 43-year-old lady with a history of end stage renal disease secondary to lupus nephritis post second kidney transplant (with alemtuzumab induction) 2 weeks prior to presentation was admitted with severe anemia. She was on tacrolimus, mycophenolate sodium and prednisone. She had blood tinged stools but stable vital signs. Hemoglobin was 5.6 g/dl for which she received two units of packed red blood cells. Colonoscopy revealed two large ulcers. Biopsies showed invasive mucormycosis. She was started on amphotericin therapy and subsequently underwent a subtotal colectomy with creation of an ileostomy. The resected specimen had multifocal ulcerations on gross examination. On histologic examination, the mucor invaded the muscularis propria and was associated with an extensive giant cell reaction, acute inflammation and ulceration. Her clinical course was further complicated by antibody mediated rejection after immunosuppression was decreased. She developed a pulseless arrest during plasmapheresis therapy necessitating resuscitation. She developed hypoxic brain injury and was eventually transferred to a long term assisted care living center with a tracheostomy.

Discussion: Invasive mucormycosis can rarely affect the gastrointestinal tract. The stomach is most frequently reported as a site of involvement, followed by the colon. The typical lesions seen are ulcers with necrosis. Opportunistic infections such as mucormycosis should be part of the differential diagnosis for solid organ transplant patients with gastrointestinal symptoms. There should be a low threshold to pursue definitive diagnosis with tissue biopsy.



Colon biopsy showing invasive mucormycosis

PUB636

Type III Hypersensitivity Reaction (HSR3) from Rabbit Anti-thymocyte Antibody (ATGAM) Induction

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Introduction: We report a rare complication of thymoglobulin use and importance of its early recognition and treatement.

Case Description: A 38 year old male during his 3rd kidney transplant received 6 mg.kg of ATGAM for induction immunosuppression. He presented 1.5 weeks after last dose with 102 F fever and fleeting joint pains. Examination revealed tender joints with effusions. Day 2 of hospital admission, targeted question of jaw pain was elicited, which was positive. Clinical diagnosis of serum sickness due to ATGAM was made, empiric antibiotics discontinued and treatment with Solumedrol, daily plasmapheresis was initiated. Day 4 of treatment, all symptoms were resolved. Steroids were tapered over 2 weeks.

Discussion: Incidence of HSR3 or serum sickness due to ATGAM ranges 2-27%, but severe reaction needing treatment is rare. Prior ATGAM exposure, raising or ingesting rabbits, increase its incidence. Jaw pain is a distinct clinical symptom. No commercial diagnostic test is available in the US: personal communication, Sanofi. Complements may be low. IgM, IgG, but mainly IgG antibodies bind to the F(ab) part of IgG thymoglobulin forming immune complexes (IC). Excess IC escaping degradation by liver and Kupffer cells, precipitate in tissues. Fenestrated endothelial lining(synovial membrane)are most susceptible. Fc part of the IC binds to the Fcγ receptor on endothelial lining activating classical complement pathway, recruiting inflammatory cells, cytokines resulting in a systemic reaction. Corticosteroids, physical removal of IC by plasmapheresis is mainstay of treatment. Rapid resolution of symptoms after plasmapheresis, correlates with reduction of IC *in vivo*. Our case demonstrates need to identify this rare clinical syndrome due to ATGAM. Theoretically, reduced immunosuppressive potency of ATGAM due to IC formation may increase risk of early rejection; no such effect was observed in our case.

Lab data

WBC	25 k/uL
Hemoglobin	11.7 g/dL
Platelets	279 k/uL
Creatinine	2.3 mg/dL
Urine	11-19 rbcs/hpf
C3	119 (80-150)
C4	27.5 (15-50)
CRP	217 mg/dL (0-8)
Autoimmune panel	ANA, ANCA, anti ds DNA negative

PUB637

Deep Dermatophytosis in an Immunosuppressed Kidney Transplant Recipient: A Case Report

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Introduction: Dermatophytosis is a common, superficial skin, hair and nail infection caused by a diverse group of filamentous fungi. In contrast, deep dermatophytosis is a rare and invasive form, whereby deeper dermal structures are invaded and/or there is dissemination to other tissues (e.g. lymph nodes, brain and lung). Risk factors for this include CARD9 deficiency, human immunodeficiency virus infection and immunosuppression. We report a case of deep dermatophytosis involving the fungus, *Trichophyton rubrum*, in an immunocompromised patient.

Case Description: A 66 year-old man of Indian descent, presented to our rapid access clinic with fevers, left buttock pain, dry cough and a nodular lesion on his right leg. He had a recent diagnosis of type 2 diabetes mellitus and received a live unrelated donor kidney transplant one-year prior. He was on tacrolimus, mycophenolate and prednisolone therapy for antibody-mediated rejection. The patient had a fever (38.6ºC) and was temocillin and vancomycin for a presumed urinary tract infection. Admission blood testing revealed an elevated C-reactive protein (45.9mg/L), a high tacrolimus level (14.9 ug/L), graft dysfunction (creatinine 184 umol/L), normocytic anaemia (Hb 106g/L, MCV 89.4fL) and normal white cell count ($6.4x10^9$/L). EBV and adenovirus DNA were detected in blood. Biopsy of the nodular lesion demonstrated granulomatous inflammation and fungal hyphae within the granulomas. *Trichophyton rubrum* was isolated in culture. High-resolution CT imaging of the chest revealed progressive ground-glass opacities in the right peri-hilar region. Bronchoscopy was negative for malignant cells, *M. tuberculosis* and fungi. He was treated with liposomal amphotericin B and voriconazole, topical terbinafine and meropenem.

Discussion: This case highlights the plethora of opportunistic infections that immunosuppressed kidney transplant patients are at risk of. A high index of suspicion, thorough investigation and good dialogue between specialists are required to offer the best patient outcomes. In addition, we feel that any undefined skin lesion in this patient group warrants a skin biopsy.

PUB638

Recurrence of Hypertension and Hypokalemia Following Renal Transplant Uncovers Inadequately Treated Primary Hyperaldosteronism

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Introduction: Persistent or recurrent primary hyperaldosteronism after renal transplant has only rarely been reported which makes this case unique.

Case Description: 49-year-old man received a deceased donor renal transplant in November 2016 after being on hemodialysis for 18 months. Potassium in blood was 4 on admission and he was on amlodipine 10 mg daily (changed to nifedipine late November to allow for up titration), carvedilol 25 mg twice a day, doxazosin 8 mg daily, furosemide 80 mg daily (later discontinued), and spironolactone 50 mg twice a day for blood pressure. He developed hypertension, 1 day after transplant up to 160s systolic blood pressure and manifested hypokalemia by day 52 post- transplant, despite being on tacrolimus, trimethoprim-sulfamethoxazole & heparin. Review of his prior records indicated that he had been diagnosed with primary hyperaldosteronism leading to ESRD. His CT scan in August, 2015 showed bilateral adrenal lesions, most likely simple adenomas, medullary nephrocalcinosis & concurrent renal atrophy, left greater than right. His aldosterone to renin ratio was 20 in 2013 & 71.9 in 2015. He had been treated with carvedilol 12.5 mg twice a day, doxazosin 8 mg daily and spironolactone 100 mg twice a day, until he developed ESRD. TTKG was 4.5, aldosterone 22 ng/dl, renin 0.7 ng/ml/h and renin to aldosterone ratio 31 on 11/28/17. He is currently more than 1.5 year out from renal transplant with an eGFR in ml/minute/square meter of 71 per MDRD. His hypertension is treated with spironolactone 50 mg twice a day, carvedilol 12.5 mg twice a day and doxazosin 16 mg daily. His last serum potassium level was 3.8 and blood pressure 140s/90s last checked at home.

Discussion: The cardinal manifestations of primary hyperaldosteronism may be lost or masked by the onset of ESRD because of end organ resistance to aldosterone and because maintenance dialysis can efficiently manage hypertension and disordered electrolytes. Since the abnormality arises from autonomous secretion of aldosterone, the successful replacement of renal function with a functioning renal transplant will inevitably lead to recurrence of the resistant hypertension & hypokalemia. Patients with a history of primary hyperaldosteronism should be recognized and appropriately managed prior to a kidney transplant and if pre-transplant cure is not possible, then recurrence should be anticipated

PUB639

Early Listeria Monocytogenes Infection Post-Kidney Transplantation

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Introduction: *Listeria monocytogenes* is a facultative anaerobic, gram-positive bacillus commonly found in soil, water, sewage, animal feces and domestic animals. It most commonly affects immunocompromised individuals such as those with HIV, cancer, and those who are immunosuppressed. Invasive form of *Listeria monocytogenes* infection usually occurs during the intermediate phase of post-renal transplantation. However on rare incidences, it can affect recipients during early phase of post renal-transplantation.

Case Description: This is a 67-year-old female with history of end-stage renal disease secondary to type 2 diabetes mellitus who was admitted 9 days post deceased donor renal transplantation for symptoms of fever, diarrhea, nausea and lethargy. Patient had received 3 doses of anti-thymocyte globulin on Days 0-2 of renal transplantation, and was started on tacrolimus, mycophenolic acid and prednisone. Septic workup showed blood culture and cerebrospinal fluid study was positive for *Listeria monocytogenes*, and CAT Scan of the head was overall unremarkable. Thus, she was diagnosed with meningitis due to *Listeria monocytogenes* and was treated with parenteral ampicillin and gentamycin. Her course was complicated by acute hypoxic respiratory failure requiring brief intubation for 2 days, and an episode of tonic-clonic seizures. Her condition gradually improved and was discharged to rehabilitation with total 4 weeks course of ampicillin and gentamycin.

Discussion: This case highlights that even though opportunistic infections occur during intermediate phase of post-renal transplantation, they can manifest during early phase as it did with this patient who presented within 10 days of renal transplantation. In this case, it is presumed that patient had acquired *Listeria monocytogenes* prior to her transplantation since the average incubation period of *Listeria monocytogenes* is 11 days. The invasive form manifested earlier due to T cell activity suppression via anti-thymocyte globulin and tacrolimus. Such cases like this are rare but needs increased awareness when considering etiology of fever in transplant recipients.

PUB640

Successful Use of Ruxolitinib for Graft-versus-Host Disease in a Simultaneous Liver-Kidney Transplant Recipient

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Introduction: Graft-versus- host disease (GVHD) is a rare and lethal complication of solid organ transplants (SOT). It occurs more commonly from donor grafts with larger amounts of lymphoid tissue such as liver transplants. Its occurrence after simultaneous liver-kidney (SLK) transplant has not been described. We describe the first successful case of Ruxolitinib use in steroid refractory GVHD in SOTs.

Case Description: A 66 year old Caucasian male with end stage renal disease and non-alcoholic steatohepatitis related cirrhosis received a SLK transplant with Basiliximab induction and was maintained on tacrolimus, mycophenolate and prednisone. On post-transplant day (PTD) 14, he was readmitted for fever and abdominal pain due to an E. Faecium biloma which was treated with linezolid, cefepime and surgical drainage. At PTD 26, he developed a diffuse maculopapular rash and a biopsy showed interface dermatitis; initially thought to be due to drug eruption and was treated with 3 days of IV methyl prednisone (MP) at 1mg/kg then prednisone taper. His rash worsened, and he complained of nausea and watery diarrhea. Infectious workup was negative. Hepatic and renal function were normal and immunosuppression was continued. However on PTD 31, he was noted to be pancytopenic. Bone marrow biopsy revealed normocellular marrow without evidence of GVHD. Short tandem repeats (STR) enriched for CD3+ cells from peripheral blood showed mixed chimerism. His diarrhea became intractable, and a colon biopsy revealed Grade 1 GVHD. MP 2mg/kg/ day was started, but he became neutropenic requiring filgrastim. He had persistent mixed chimerism on repeat testing a week later. Ruxolitinib 5mg twice daily (a selective Janus kinase inhibitor used in steroid refractory GVHD, where it inhibits T cell activation) was added. 3 days later, leucopenia and thrombocytopenia resolved and diarrhea ceased. His rash improved and steroids were gradually tapered. 6 wks post treatment there was no evidence of peripheral blood donor chimerism.

Discussion: Knowledge of the clinical features of GVHD in SOT is limited and delayed diagnosis contributes to the high mortality. This case demonstrates the value of early recognition and initiation of treatment. The treatment however, is quite heterogenous and no guideline exists.

PUB641

First Report of Successful Kidney Transplantation in a Patient with Job's Syndrome

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Introduction: Autosomal dominant hyper-IgE syndrome (AD-HIES), commonly referred as Job's syndrome, is a rare immune disorder associated with mutations in the STAT3 gene with high blood levels of IgE. Recurrent infections affecting multiple body systems characterize the disease. Little is known of the renal disease that occurs in patients with Job's syndrome; however, there have been documented reports of lupus nephritis and interstitial disease occurring in these patients. The survival of patients receiving hemodialysis (HD) is poor and can be decidedly improved with transplantation, but due to the high risk of infections kidney transplantation has not been generally considered as an option for patients with AD-HIES.

Case Description: A 26-year-old African American female with a history of Job's syndrome, asthma, and recurrent skin and lung infections developed end-stage renal disease (ESRD) due to immune-complex nephritis. She received HD for 5 years prior to accepting a living related kidney transplant from her mother. She received induction with thymoglobulin, and was subsequently placed on tacrolimus, mycophenolate, prednisone along with standard infection prophylaxis. She had immediate graft function and was discharged home on post-operative day 4 with a serum creatinine (SCr) of 1.26 mg/dL, down from a pre-transplant value of 11.73 mg/dL. Infectious complications during her post-transplant course included several urinary tract infections, an episode of influenza, CMV, BK, and EBV viremia. She also experienced periodic asthma exacerbations and pneumonia, which required brief hospitalizations. She developed acute kidney injury after some of the infectious complications, never requiring dialysis. After 14 months post-transplant she has not experiend allograft rejection and maintains good renal function, the most recent SCr was 1.08 mg/dL at the time of this report.

Discussion: We present the first and only case of successful kidney transplantation in a patient with Job's syndrome. Despite the various infectious episodes complicating her post-transplant course, she has been able to overcome them and her renal function remains excellent. The decision to transplant should be highly personalized with the involvement of experts who are familiar with the disease. Close monitoring for infectious complications and avoidance of over-immunosuppression would be advised.

PUB642

A Case of Myeloma Cast Nephropathy Unmasked by Volume Depletion in a Renal Transplant

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Introduction: Acute kidney injury (AKI) in a renal transplant patient should prompt investigation for reversible causes, such as volume depletion, ureteral obstruction, or supra-therapeutic calcineurin inhibitor levels. If no clear cause is identified, allograft biopsy can help elucidate a diagnosis and potentially guide treatment decisions.

Case Description: A 51 year-old Caucasian female with Alport syndrome underwent deceased donor renal transplant at age 37. She had chronic allograft dysfunction with baseline creatinine 1.8-2.0 mg/dL. Medications included tacrolimus 2mg q12h, mycophenolate mofetil 500mg BID, and lisinopril 5mg daily. She presented with 5 days of profuse diarrhea and poor oral intake. Her daughter was recently sick with similar symptoms. Labs showed creatinine of 6.5 mg/dL, HgB 6.7 mg/dL, calcium 8.0 mg/dL, albumin 4.1 g/dL, and FK trough of 2.9. Stool infectious workup was unrevealing. Transplant ultrasound showed no evidence of hydronephrosis. She received IV fluids without improvement in renal function. Allograft biopsy showed numerous intra-tubular, periodic acid-Schiff-negative casts with surrounding cellular reaction and diffuse interstitial edema/inflammation. Moderate tubular atrophy/interstitial fibrosis were present. No glomerulitis/tubulitis, or crescent formation were seen. Staining for C4d was negative in peri-tubular capillaries. Bone marrow biopsy showed plasma cell infiltrate of 30% with associated kappa restriction, consistent with light chain myeloma. She was started on induction chemotherapy and plasmapheresis. She required hemodialysis due to progressive decline in renal function and associated hyperkalemia.

Discussion: Light chain cast nephropathy can be unveiled in certain settings, such as intravascular volume depletion or receipt of potentially nephrotoxic agents (iodinated contrast, NSAID's, etc.). Severe renal insufficiency at diagnosis is generally associated with worse overall survival. However, recovery of renal function with disease-specific therapy can have prognostic significance. Thus, it should remain a diagnostic consideration in patients with AKI that does not improve with conservative interventions, especially in the setting of volume depletion.

PUB643

Unusual Case of Encapsulated Sclerosing Peritonitis(ESP) in Renal Transplant Recipient

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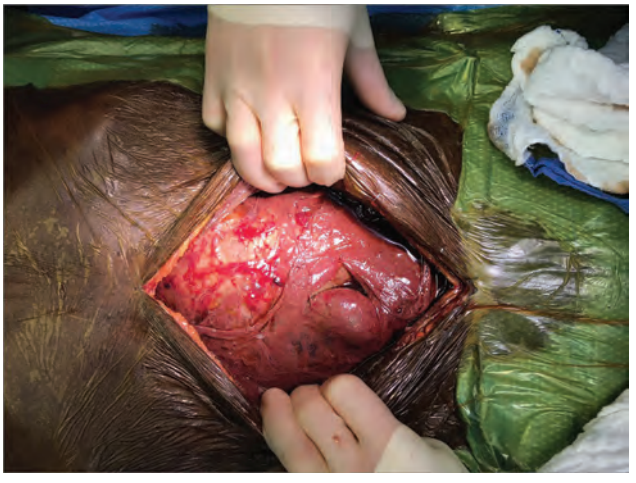
Introduction: ESP is a rare complication of Peritoneal Dialysis(PD) with annual mortality 51%. Likely causes are prior episode of severe peritonitis, using acetate as dialysate buffer, prolonged exposure to glucose degradation products from glucose-containing solutions, withdrawal from PD and long duration of PD.

Case Description: 35 year old man admitted with intractable nausea(N), vomiting(V), odynophagia, abdomen distension and weight loss for few months. **PMH**:ESRD from FSGS s/p LRKT in 2003 failed due to noncompliance and recurrent FSGS, HTN, on PD for >10 years, DDKT12/2016. **P/E**:BP 90/50; weight loss 50 lbs ;tender distended abd, no guarding, sluggish bowel. **Labs**:K 5.4, HCT 35. Frequent readmission for abd pain, N&V.Multiple CT abd-loculated collections, large hemoperitoneum, no bowel obstruction. Ba swallow- delayed gastric emptying;bone marrow biopsy -neg. IR guided angiogram- no active bleeding or aneurysm. Managed conservatively and started on TPN. **Exploratory Laporotomy**:Dense fibrovascular tissue with chronic inflammation, hemorrhage, hemosiderin deposition and fibrin;fibrous tissue with fibrinous exudate and necrosis **Treatment:**Tamoxifen. Now tolerating po intake. Stable renal graft function on tacrolimus& prednisone.

Discussion: ESP cause extensive intraperitoneal fibrosis & encasement of bowel loops. It is associated with progressive loss of ultrafiltration, causing fluid retention and edema. It is slowly progressive, mostly asymptomatic. Presentations are abd pain, N&V, appetite loss, constipation, diarrhea, abdominal mass, ascites, weight loss and fatigue. CT abd shows peritoneal calcification, bowel thickening, bowel tethering and dilatation. Diagnostic confirmation with laparotomy/laparoscopy-characteristic peritoneal thickening that encloses intestinal contents. Histopathology: dense fibrocollagenous tissue +/- lymphocytic/plasma cell infiltration. Treatment is switching from PD to hemodialysis, bowel rest with TPN, immunosuppressive therapy (corticosteroids/azathioprine/tamoxifen)+/- surgery.



Abdominal Cocoon

PUB644

External Iliac Artery Stenosis Causing Resistant Hypertension and Acute Renal Allograft Dysfunction

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Introduction: Renal artery stenosis (RAS) in kidney transplant is a reversible cause of hypertension (HTN) and acute kidney injury. Although RAS usually presents between the first three months to two years after transplantation, it can manifest at any point during the post-transplant course. We present a rare case of external iliac artery stenosis presenting as transplant RAS.

Case Description: A 52 year-old man with end stage renal disease due to IgA nephropathy and diabetes underwent living unrelated renal transplant (right lower quadrant placement) 9 years prior to presentation. Baseline lab values showed creatinine of 1.4 mg/dL and urine protein/creatinine ratio of <500mg/g. His tacrolimus trough level was maintained at 6-7 ng/mL. Over the past several years he developed worsening HTN, for which he was treated with lisinopril but this required discontinuation on several occasions due to worsening renal allograft function. He developed worsening HTN and renal allograft function with creatinine as high as 2.7 mg/dL. On physical examination, a bruit was appreciated over the allograft. Renal ultrasound showed a parvus-tardus waveform. Angiography performed by Interventional Radiology showed high-grade stenosis of the right external iliac artery that was successfully stented with no residual post-procedural stenosis identified. No stenosis of the transplanted renal artery was seen. Prior to the procedure he disclosed worsening right leg claudication that improved after vascular intervention. His creatinine subsequently improved to 1.3mg/dL and blood pressure was controlled on minimal anti-hypertensive therapy.

Discussion: Stenosis of the transplanted renal artery is a common complication after renal transplantation. It can occur in up to 23% of patients and present as uncontrolled hypertension with AKI. Stenosis of the anastamosed external iliac artery, which can have similar hemodynamic effects on the renal allograft, can also occur but has rarely been reported. This case highlights the importance of thorough vascular examination in the renal transplant recipient to help identify signs of poor flow to the ipsilateral limb of the allograft. Such vascular changes can unmask a stenosis that is proximal to the renal artery and can have clinical manifestations of RAS.

PUB645

Cystic Degeneration of Metastatic Lymph Nodes in Renal Cell Carcinoma (RCC) in a Renal Transplant Patient

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Introduction: Increased risk of malignancy is a major post-transplant complication. The incidence of *de novo* RCC is 4.6% in the renal transplant compared to 3% in the general population and 25% of which are incidentally discovered. We present a case of incidental RCC associated with rare cystic degeneration of metastatic lymph nodes in a renal transplant patient.

Case Description: A 53 y/o AAM with obesity and h/o kidney transplantation 5 years ago secondary to ESKD from hypertensive nephrosclerosis requiring prior hemodialysis was admitted with advanced renal failure. He presented with nausea, vomiting and anuria after defaulting on immunosuppression for few weeks and was found with blood pressure 220/100, creatinine 33.16 mg/dl, BUN 180 mg/dl, hyperkalemia, severe metabolic acidosis, and microangiopathic hemolytic anemia on workup. Allograft kidney biopsy revealed thrombotic microangiopathy, acute tubulitis, intimal vasculitis, and positive C4d staining consistent with acute antibody-mediated rejection (AMR). Hospital course was complicated by incidental finding of diffuse mediastinal and cervical lymphadenopathy with cystic degeneration. Cytology of the cyst aspirate revealed papillary cancer. Further imaging showed atrophic native kidneys with innumerable bilateral complex cysts and normal allograft kidney. Immunohistochemistry profile favored papillary RCC – likely arising from native kidneys. During AMR treatment, he developed life-threatening spontaneous hemorrhage from left native kidney needing percutaneous embolization.

Discussion: In renal transplant recipients, RCC is the most common urologic malignancy and multiple factors such as age, gender, race, dialysis duration, glomerular disease has been shown to affect RCC risk. However, most transplant guidelines either recommend against or do not include RCC screening recommendation citing limited cost-effectiveness of screening strategies. A regular post-transplant surveillance would have detected RCC in a much earlier stage with probable chance of cure. This case emphasizes the need for further awareness and clear cancer surveillance guideline with special attention to high risk post-transplant population. This case also highlights two other rare presentations – a cystic degeneration in metastatic lymph nodes, and spontaneous hemorrhage of RCC in a transplant recipient.

PUB646

De Novo Crescentic IgA Nephropathy Along with Antigen and Antibody Mediated Rejection in a Renal Allograft

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Introduction: Acute rejection is the common cause of allograft dysfunction in a kidney transplant. Rejection can be either antigen or antibody mediated. De Novo IgA nephropathy can happen in tranplant kidney. We report a unique case of de novo crescentic IgA Nephropathy with both acute cellular and antibody mediated severe allograft rejection.

Case Description: 36-year-old male with history of ESRD secondary to recurrent AKI from sepsis related to MRSA hip osteomyelitis and contrast exposure s/p deceased donor kidney transplant in 2014, h/o biopsy proven cell and antibody mediated rejection in 2015 due to non-compliance with immunosuppressants which was successfully treated. He was admitted with nausea, diarrhea and dark colored urine. Labs revealed AKI with creatinine of 11 mg/dL (baseline 1.8), BUN of 96 mg/dL, CO2 of 11 mEq/L, K of 5.6 mEq/L and subtherapeutic tacrolimus level of 1.6 ng/ml. UA and microscopy revealed dysmorphic RBC's and protein without any infection. On exam, he had a systolic murmur and 1+ bilateral lower extremity edema. Pan cultures and ECHO were negative. Due to worsening acidosis and hyperkalemia, hemodialysis was initiated. Transplant ultrasound was normal. A kidney biopsy revealed mesangial expansion, IgA deposition, mesangial immune complex deposits, severe lymphoplasmacytic tubulointerstitial infiltration, transplant arteritis, positive C4d staining along peritubular capillaries consistent with both cell mediated as well as humoral rejection. Also crescents were seen. Donor specific antibodies were positive. Further workup revealed weakly positive anti-nuclear antibodies (1:160). C3, C4, ds-DNA, C-ANCA, P-ANCA, anti-GBM, HIV, hepatitis panel, RPR, EBV, CMV, Adenovirus, BK virus and Influenza were negative. Treatment was initiated with high dose steroids, thymoglobulin followed by plasmapheresis and IVIG. Cyclophosphamide was not used. Despite aggressive management, patient had no response and required hemodialysis as outpatient.

Discussion: Our case reports occurrence of de novo crescentic IgA nephropathy along with both cellular and antibody mediated rejection in a kidney transplant patient. IgA nephropathy with mesangial deposits only may have a favorable prognosis but presence of crescents heralds a bad prognosis. Crescentic IgA nephropathy along with transplant rejection is associated with worse prognosis.

PUB647

Successful Combined Liver and Kidney Transplant in a Patient with Primary Hyperoxaluria and Thrombophilia: A Management Conundrum

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Introduction: Primary hyperoxaluria (PH) is a rare autosomal recessive disorder caused by a deficiency of the liver-specific enzyme alanine: glyoxylate aminotransferase (AGXT). This is characterized by oxalate overproduction, leading to kidney failure due to nephrocalcinosis, and is eventually responsible for systemic oxalosis. We present a case of PH with known factor V Leiden and prothrombin 20210G mutation, who underwent combined deceased-donor liver and kidney transplant (CLKT).

Case Description: A 27-year-old Syrian female, with a history of PH type 1 (positive AGXT mutation), factor V Leiden and prothrombin gene mutation was scheduled for CLKT. Over the past 1 year, patient developed end-stage renal disease in the setting of nephrocalcinosis secondary to PH and was started on hemodialysis (HD). Preoperative laboratory tests showed serum creatinine, 5.63 mg/dL (0.6-1.2 mg/dl); international normalized ratio (INR), 1.1; and activated partial thromboplastin time (aPTT), 29 seconds. Model for End-Stage Liver Disease score was 21. Intermittent HD was done 6-24 hours before surgery to adjust electrolyte balance and to optimize intravascular volume. Continuous venovenous hemofiltration (CVVHD) was started after induction of anesthesia to remove oxalate crystals. She received methylprednisolone and thymoglobulin for immunosuppression. In view of the patient's history of prothrombin gene mutation and factor V Leiden mutation, she was maintained on a heparin infusion with an aim of maintaining the partial thromboplastin time in the range of 70-75. She remained stable throughout, maintaining a mean arterial pressure goal of > 80-85 mmHg after reperfusion. CVVHD was continued in post-operative period to enhance oxalate removal followed by intermittent daily HD. As per institutional policy she was on maintenance immunosuppression with tacrolimus, steroid taper and mycophenolate mofetil. The functions of both grafts remained stable throughout the entire 2-month post-transplant period.

Discussion: Inherited prothrombotic risk factors predispose to thromboembolic events and are significantly associated with acute vascular rejections. There is currently no consensus on optimal management for CLKT in the setting of prothrombin gene mutation. More prospective studies are needed to elucidate ideal treatment strategies for an uncommon, but important clinical scenario.

PUB648

A Case of PTLD 27 Years After Kidney Transplantation in a Failing Allograft

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Introduction: The deterioration of allograft function in kidney transplant recipients can lead to over immunosuppression due to relative immunosuppressant overdosing for kidney function. We report a case of EBV-positive post transplantation lymphoproliferative disorders (PTLD) 27 years after transplantation in a failing allograft, which immediately responded well only to withdrawal of immunosuppressant (IS).

Case Description: A 59-year-old female, who received an ABO-compatible living kidney transplantation 27 years ago, was admitted to initiate dialysis for allograft failure. Six months prior, she had developed pancytopenia, which was caused by bone marrow suppression from accumulation of mycophenolic acid and CMV infection, and was recovered by reducing mycophenolate mofetil (MMF). When admitted, she was found to have asymptomatic low-grade fever. Computed tomography (CT) showed multiple liver masses without lymphadenopathy or other organ involvement, which was not present six months before. We at first diagnosed it as liver abscess and treated her with antibiotics, only in vain. We then punctured the liver mass, which showed diffuse large B-cell lymphoma (DLBCL) with positive EBV in situ, leading to a final diagnosis of PTLD. MMF and cyclosporine were stopped immediately, and subsequently she became afebrile and the liver masses were completely disappeared within 4 months without requiring chemotherapy.

Discussion: Although there are a growing number of late-onset PTLD, most reported cases were occurred earlier than twenty years post-transplant and were not so associated with EBV, partly because ISs are usually reduced in very late phase. In these perspectives, our case seems exceptional. Teaching points in our case include that PTLD can occur even very long after the transplant, and that late onset PTLD can be associated with EBV. We speculate the pathogenesis of our case is over-immunosuppression not because of absolute IS overdosing but because of relative overdosing due to advanced allograft dysfunction, in which renally excreted MPA could accumulate. The fact that only IS withdrawal resolved the PTLD suggests the over-immunosuppression rather than dysregulated proliferation is the cause of PTLD in our case. In conclusion, failed transplant patients may have risk of PTLD due to relative IS overdosing, which may be prevented by therapeutic drug monitoring.

PUB649

Chronic Interstitial Nephritis with IgG Tubular Basement Membrane Staining in a Allogeneic Stem Cell Transplant Patient: Renal Graft vs Host Disease?

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Introduction: GVHD of the kidney is a rare complication post allogeneic SCT usually manifests clinically as a nephrotic syndrome. Renal GVHD can present as minimal change disease, membranous nephropathy, or FSGS. We are presenting an allogeneic SCT patient who developed tubulo-interstitial nephritis with IgG and C3 granular tubular basement membrane deposits with negative brush border autoantibodies. To the best of our knowledge, this is the first case report of renal GVHD associated with antibodies against an unknown tubular antigens in humans.

Case Description: 56-year-old woman with history of plasma cell leukemia who underwent an allogeneic SCT in 2016. Her transplant course was complicated by GVHD of the skin and GI tract, treated successfully with steroids and continued on prophylactic sirolimus. She has developed progressive renal dysfunction with creatinine increasing to 2.5mg/dl from baseline of 1mg/dl. She was noted to have proteinuria of 1g she underwent a renal biopsy that indicated chronic tubulo-interstitial nephritis with granular tubular basement membrane deposits. No evidence of BK Polyomavirus infection or IgG4 subtype. Patient had normal complements and lupus serologies. Based on a similar case report in a kidney transplant recipient with interstitial infiltrate and anti-brush border antibody we tested our patient's serum for ABBA; however, was negative. We have started patient on prednisone 1mg/kg to treat for the interstitial infiltrate with improved creatinine and have started her on Rituximab in hopes to help with the antibody mediated process.

Discussion: We postulate that autoantibodies to an unknown tubule antigen likely caused cellular injury in our patient with granular basement membrane deposits. Autoantibodies against proximal tubular brush border in mice with experimentally induced chronic GVHD has been reported, but no similar findings in humans. In recent studies, the presence of autoantibodies after allogeneic SCT in association with GVHD provides evidence for B-cell involvement. It has been shown in autoimmune disease that more than half of the developing B cells in the bone marrow express autoreactive B-cell receptors. This case presents yet another possible form of renal GVHD after allogeneic SCT.

PUB650

AT1R Antibodies: Time to Think Outside the HLA Box

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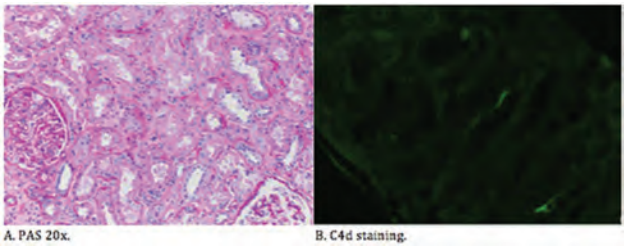
Introduction: In renal transplantation, elevated levels of anti-angiotensin II type 1 receptor (AT1R) antibodies have been associated with antibody-mediated rejection (AMR) in the absence of HLA (human leukocyte antigen) donor specific antibodies (DSA). The majority of these patients present early after transplantation with elevated serum creatinine (SCr) in the setting of accelerated hypertension. Renal biopsy typically shows C4d negative vascular rejection. Treatment with an angiotensin receptor blocker (ARB) has been successful in children but is not well-documented in adults.

Case Description: We present a unique case of a 29-year-old male with end-stage renal disease due to Alport syndrome who underwent a living related renal transplant with nadir SCr 1.2mg/dl. He received thymoglobulin induction with tacrolimus, mycophenolate mofetil, and corticosteroids maintenance therapy with an uneventful post-transplant course. At one year follow-up, urine protein-to-creatinine ratio (UPC) increased to 0.8, and lisinopril was started. Six weeks later, UPC was 2.24. Renal biopsy showed moderate glomerulitis and peritubular capillaritis (Image A) with minimal C4d staining of the peritubular capillaries (Image B) consistent with an AMR. Pre and post-transplantation sera were negative for HLA DSAs, so non-HLA antibody testing was sent. Anti-AT1R antibodies were detected at 33 U/ml (strong positive). Patient was switched to losartan and then treated with intravenous methylprednisolone 500mg for three doses followed by four sessions of plasmapheresis. The response to treatment was excellent with a decrease in UPC to 1.2 and in anti-AT1R antibodies level to 8U/ml (<10 normal). SCr and blood pressure remained well-controlled throughout the treatment.

Discussion: AMR in renal transplantation due to non-HLA antibodies, like anti-AT1R antibodies, has gained interest in recent years. The diagnosis is often missed or delayed, leading to more aggressive therapy and a poor prognosis. Our patient had an unusual presentation with proteinuria, but prompt diagnosis and early initiation of therapy achieved a good outcome with relatively modest immunosuppression.



PUB651

A Case of Serous Lymphoma Post Renal Transplant

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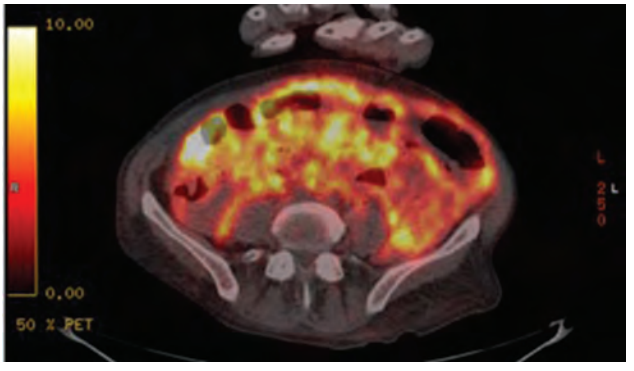
Introduction: Post-transplant lymphoproliferative disorder (PTLD) is one of the most feared consequences of long term transplantation. We present a case occurring late in the post transplant period with an unusual distribution. The case highlights the utility of PET CT in facilitating diagnosis and guiding tissue diagnosis in suspected PTLD.

Case Description: Our case is a 62 year old man who presented with anorexia, weight loss, night sweats, fevers, and altered bowel habit. End stage renal disease was secondary to IgA nephropathy. He was a deceased donor transplant recipient from 2000 with early biopsy proven antibody mediated rejection. Maintenance immunosuppresion was Tacrolimus and Mycophenolate mofetil. Clinically he had ascites and lower limb oedema. CT-TAP showed dense ascites and small bowel thickening. Colonoscopy was normal. A large pleural effusion caused respiratory compromise and chest drain insertion was performed. Empiric cover for TB was added due to his clinical status and pending a tissue diagnosis. PET-CT showed extensive FDG avid peritoneal disease (Figure 1) as well as in the pleura and pericardium. Ascitic fluid had abundant inflammatory cells but no malignant cells. Pleural aspirate revealed atypical lymphoid cells positive for CD20 consistent with high grade B cell lymphoma. Peritoneal biopsy revealed atypical cells staining positive for CD20, CD10 and BC16. Immunosuppression was discontinued and he is being treated with R-CHOP with an excellent clinical response to date. Graft function remains stable

Discussion: Given the heterogeneity of PTLD presentations the clinician must maintain a high index of suspicion. This case demonstrates an unusual distribution of a post transplant lymphoma as well as highlighting the increasing utility of PET-CT in the work up of these patients. Earlier use of PET-CT in the work up of suspected PTLD may facilitate earlier instigation of treatment and improve prognosis.



PUB652

A Case of Lymphocele Associated Kidney Graft Impairment

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Introduction: Lymphocele is well established as an early renal transplantation complication and may seriously impair graft function due to graft vessel compression. Venous compression may increase the pressure gradient and therefore cause kidney graft associated proteinuria.

Case Description: A 46 year-old male, on hemodialysis for the past 3 years due to hypertensive nephrosclerosis, was admitted for deceased donor kidney transplantation. We followed institutional protocols for surgery and immunossupression, with no apparent complications. At discharge, the patient serum creatinine was 1.53mg/dL and urine tests for proteinuria were negative. Four months after transplantation, the serum creatinine increased to 2.56 mg/dL and the protein/creatinine ratio rose to 4.3 (g/g), with no hematuria. Renal graft biopsy revealed interstitial fibrosis and mild focal tubular atrophy, BANFF grade I, and immunofluorescence for C4d was negative. Computerized tomography of the abdomen revealed two lymphocells, localized posterior to the graft (18.0 x 10.0 x 10.0 cm) and adjacent to the left iliac vessels (8.5 x 6.0 x 6.0 cm), leading to compression of the left external iliac vein close to the venous anastomosis of the renal graft. In this scenario, marsupialization of the lymphocele was performed due to worsening renal function and progressively ascendant protein/creatinine ratio (12.1 g/g). Two days after surgery, the patient evolved with reduction in proteinuria (protein/creatinine levels of 0.2g/g) and serum creatinine dropped to 1.98 mg/dL, suggesting early recovery.

Discussion: This is an atypical case of massive urinary protein loss secondary to lymphocele compression leading to high pressures in the renal vein. Graft rejection and glomerulopathy relapses are widely discussed as etiologies of proteinuria in transplant patients; however in this case we underscore the importance of including anatomical causes among the differential diagnosis.

PUB653

Acute Respiratory Distress in a Renal Transplant Recipient: Think Toxoplasmosis

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Introduction: *Toxoplasma gondii (T. gondii),* an intracellular protozoan parasite is an important cause of opportunistic infection in transplant recipients associated with high mortality. Herein, we present a case where physicians' knowledge gaps and diagnostic difficulties resulted in unfavorable outcome.

Case Description: A 38-year-old man with ESRD due to congenital vesicoureteral reflux underwent deceased donor kidney transplant. Alemtuzumab was used for induction immunosuppression (IS), followed by maintenance IS consisting of mycophenolate mofetil, tacrolimus and prednisone. Inhaled pentamidine was used for post-transplant *P. jirovecii* prophylaxis instead of the standard therapy with trimethoprim-sulfamethoxazole (TMP-SMX) because of hyperkalemia. At 1-month follow up visit, he appeared ill and was febrile to 102 F, hypotensive and tachycardic. He was admitted to the hospital for further evaluation and soon after that, he developed acute respiratory distress requiring intubation, later extracorporeal membrane oxygenation and also dialysis requiring AKI. He was started on broad-spectrum antibiotics/antifungals and antivirals. Blood and urine cultures were negative. Respiratory viral panel, CMV, EBV and HSV serologies were negative. Clinical status deteriorated rapidly and he passed away. Autopsy revealed multiple intracellular organisms consistent with *T. gondii* in both lungs and the heart.

Discussion: The clinical presentation of toxoplasmosis in renal transplant recipients is variable. Fever is the most frequent clinical sign (80%), followed by pneumonia and headaches. It can be transmitted from a seropositive donor to a seronegative recipient or occur as a *de novo* infection or as a reactivation of latent infection. Our patient was seronegative prior to the transplant and donor was positive. Interestingly, post-mortem testing revealed both serologic and histologic positivity for *T. gondii*. The data on prevention of toxoplasmosis is sparse and TMP-SMX at a dose of 1 single-strength tablet daily is considered sufficient for both Pneumocystis and Toxoplasma prevention. Pyrimethamine + TMP-SMX may be considered in high-risk recipients. Toxoplasmosis should be considered in the differential diagnosis of pneumonia, culture-negative sepsis, and encephalitis in renal transplant recipients, especially when the history suggests inadequate prophylaxis.

PUB654

A Rare Case of JC Virus Nephropathy in a Kidney Transplant Recipient

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Introduction: Acute kidney injury after renal transplantation is usually attributed to acute cellular or antibody medicated rejections or viral nephropathy (BKV). However rarely we can be confronted with the unexpected conditions. We are reporting a rare case of biopsy proven JCV nephropathy in a kidney transplant recipient.

Case Description: A 57-yo female, ESRD due to ADPKD, had deceased donor renal transplant (DDRT) in 2011. She was on azathioprine, tacrolimus and prednisone as the maintenance therapy with serum creatinine level 1.8 to 2.0mg/dL. In 2017 SCr elevated to 3mg/dL for 3 months without urinary symptoms. BKV PCR was negative in both serum and urine. Kidney biopsy show acute tubular injury, acute interstitial inflammation, and scattered prominent atypical tubular epithelial cells. SV40 stains was positive in many cells (figure 1). JCV DNA was detected by in situ hybridization in the allograft biopsy tissue. JCV DNA was also detected by PCR in both blood (81661copies/ml) and urine (>35000000 copies/ml). Spinal fluid was negative for JCV. MRI of the brain was unremarkable. JCV blood level became undetectable 4 months after reduction in tacrolimus dosage and initiation of iv IG. Prednisone and azathioprine were continued. Transplant kidney function remained stable with SCr 2.8mg/dL.

Discussion: Up to 36% of renal transplant recipients were found to be positive for JCV in their urine. Reactivation of JCV post-transplant could be associated with PML in immunosuppressed patients, but rarely causes JCV nephropathy. Less than a dozen cases of JCV nephropathy were ever reported in renal transplant recipients after the first case in 2003. Reduction in immunosuppression remains the mainstay of treatment for JCV nephropathy. Use of iv IG was reported to be helpful as well. It is important to look for JCV nephropathy in DDRT recipients with unexplained AKI.

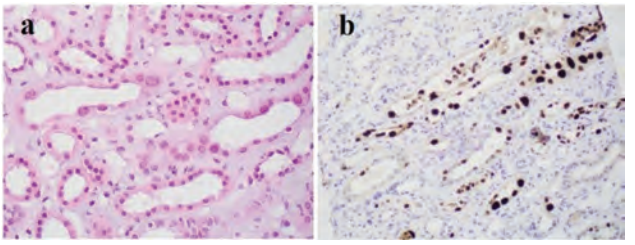

Figure 1: kidney allograft biopsy. (a): acute interstitial inflammation (HE staining). (b): Simian virus 40 positive nuclear staining of tubular cells.

PUB655

Native Kidney BK Nephropathy in Lung Transplant Patient

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Introduction: BK nephropathy (BKN) usually affects renal allografts and is rarely seen in non-renal solid organ transplant patients. We present the rare case of a lung transplant patient who developed BK nephropathy in the native kidney.

Case Description: 62 yo AAF with sarcoidosis received a bilateral lung transplant in 2007 complicated by bronchiolitis obliterans syndrome stage III and CKD stage IV secondary to calcineurin inhibitor toxicity. Her immunosuppression was sirolimus, mycophenolic acid, and prednisone. She presented with severe sepsis, Pseudomonas pneumonia, and acute kidney injury (AKI) Cr up to 4.3. Renal function did not improve despite improvement of pneumonia and sepsis. Native kidney biopsy showed tubulitis and viral nuclear inclusions and serum BK PCR was 8,000,000 copies/ml. Her renal function rapidly declined (Cr 6.8). She was treated for BKN with lower immunosuppression, IVIG and cidofovir. Her renal function improved without need for dialysis and her serum BK PCR decreased to 849,000 copies/ml. Three weeks after discharge, she was re-admitted with progressive acute respiratory failure and severe oliguric AKI requiring hemodialysis. BK levels increased back to 1,700,000 copies/ml and sepsis work up was negative. She was later transitioned to comfort measures per family wishes.

Discussion: The poorer outcomes seen with BKN in non-renal solid organ transplants maybe due to the lack awareness of native BKN and its relative rarity in this population. This leads to late diagnosis, advanced irreversible disease and poorer response to treatment. A higher suspicion for BKN in non-solid organ transplant patients with AKI seems warranted. Peripheral blood testing for BK virus and kidney biopsy for early diagnosis may avoid irreversible injury and yield a more favorable outcome.

PUB656

Preserved Renal-Allograft Function and Successful Treatment of Metastatic Merkel Cell Cancer Post Nivolumab Therapy

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Introduction: Checkpoint inhibitors like Programmed cell death 1 (PD-1) inhibitors are found to be efficacious even in difficult-to-treat cancers, has fewer side-effects and sustained therapeutic benefit. PD-1 is a cell surface receptor that has a vital role in down-regulating the immune system and enhancing self-tolerance by suppressing T cell activity. The major shortcoming in Kidney transplant recipient is the severe rejection and immediate graft loss making it somewhat taboo to use these agents in this population.

Case Description: 71-year-old female, status post deceased donor Kidney transplant in 2004 for Autosomal Dominant Polycystic Kidney disease with coincident native nephrectomy received a 5/6 HLA-mismatched kidney, induction with ATG and steroid, and maintenance therapy of tacrolimus and myfortic. She was diagnosed with Merkel cell cancer in 01/2016 and underwent lateral neck dissection and radiation therapy (05/2016). Tacrolimus was discontinued, mycophenolate was reduced to half dose twice daily, and prednisone 5 mg daily was initiated. In April 2017, she was diagnosed with the metastatic disease to the liver and spine. Her prognosis was deemed marginal and she was initiated on Nivolumab and was maintained on 10 mg of Prednisone. She completed a total of 13 cycles of Nivolumab (240 mg based on a dose regimen of 3 mg/kg, every month) without any significant side-effects and significant improvement in the quality of life. Her renal function remained stable with the creatinine of 1.5 (egfr 35), absent donor-specific antibodies and no disease progression on subsequent imaging.

Discussion: To date, the literature reports five kidney transplant recipients treated with PD-1 inhibitors. To our knowledge, the case presented here is only the second case of a kidney transplant patient treated with a PD-1 inhibitor(s) who did not experience acute rejection. One similarity between our situation and previously reported case is the history of native nephrectomy. It is unclear if native Kidneys have a role to play in rejections and thus nephrectomy is giving an added benefit. Additionally, our patient was on a reduced frequency of Nivolumab (monthly compared to bi-monthly). If these drug regimens have any significant role to play in avoiding rejection, is again a topic for future research and debate.

PUB657

Stuck Between a Rock and a Hard Place - The Challenging Management of Metastatic Renal Cell Carcinoma in a Kidney Transplant Recipient Using Checkpoint Inhibitors

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Introduction: The incidence of Renal Cell Carcinoma(RCC) in a renal transplant is 100 times higher than the general population. Metastatic RCC is a dreaded complication and currently there is no one specific agent used in its management. Due to marked success of immunotherapy and checkpoint inhibitors (CPIs) specifically the program cell death ligand inhibitors (PD-1)in treatment of melanomas, these agents have been proposed for metastatic RCC also. Their effects on organ transplant recipients are unknown.

Case Description: 58 y/o Caucasian male with h/o End Stage Renal Disease on hemodialysis for 2 years s/p Deceased donor kidney transplant 18 years ago, maintained on tacrolimus, azathioprine and prednisone, with excellent allograft function with baseline creatinine of 1.5 presented with shortness of breath. Medical history included bilateral nephrectomies performed 4 years ago with both kidney biopsied and showing RCC. A CT Chest this admission revealed multiple nodules to the lungs and a left sided pleural effusion. Surprisingly, a nodule biopsy was consistent with metastatic RCC. Oncologists initiated pazopinib(a tyrosine kinase inhibitor) but disease progressed on the drug. Hence, the decision to switch to Nivolumab(a PD-1L inhibitor) was made while decreasing dose of tacrolimus. Within 2 weeks of drug initiation, patient became oliguric and developed an acute kidney injury with a creatinine of 4.5. An allograft biopsy showed banff grade 2A/2B acute cellular rejection and dialysis had to be resumed. Unfotunately, patient could not tolerate dialysis due to hypotension, had recurrent admissions for pleural effusions and finally opted for inpatient hospice.

Discussion: Our case is unique in several ways. It is an exceedingly rare one where metastatic RCC was found even years after bilateral nephrectomy. It is also highlights the association of CPIs with acute cellular graft rejection. PD-1 ligand inhibitors increase effector T-Cell activity, promote tumor regression, but may also be responsible for the cell mediated rejection of the allograft, using the same pathway. Hence, it becomes necessary to weigh the risks of graft rejection with mortality benefit from immunotherapy in organ transplant recipients because of significant morbidity that follows.

PUB658

Nivolumab-Induced Kidney Transplant Allograft Rejection Requiring Nephrectomy

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Introduction: Many types of cancers have developed mechanisms to activate immune checkpoints in order to evade the immune system. Immune checkpoint inhibitors allow a patient's immune system to overcome such a blockade in order to target and eradicate tumor cells. Although checkpoint inhibition holds a promising future in cancer treatment, side effects can include severe autoimmune-mediated reactions, including against transplanted organs. We report a case of a patient treated with nivolumab who developed acute on chronic kidney allograft rejection necessitating nephrectomy.

Case Description: A 47-year-old female who had chronic kidney disease stage V secondary to renal dysplasia received a living donor kidney transplant and was maintained on prednisone, cyclosporine (CSA), and mycophenolate mofetil (MMF). Her creatinine post-transplant ranged from 1.8-2.5 mg/dl. She was diagnosed with anal squamous cell carcinoma 15 years later and underwent chemoradiation with simultaneous reduction of CSA and discontinuation of MMF. Her kidney function declined over this time. Unfortunately, her cancer recurred 2 years later and was deemed unresectable, prompting her oncologist to start nivolumab. In preparation for immunotherapy, the patient's prednisone and CSA were stopped. By then, her creatinine was 6.1 mg/dl. Shortly after she began maintenance hemodialysis for uremic symptoms, though she continued to make about a liter of urine per day. Two days after receiving her first nivolumab dose, she abruptly became anuric other than small streaks of gross hematuria. Five days post nivolumab treatment she was admitted to the hospital with fever and unrelenting allograft tenderness and swelling. Renal ultrasound showed an enlarged, echogenic allograft of 14 cm with abnormal perfusion, consistent with severe acute rejection. She initially underwent IR-guided embolization of the transplant but ultimately required surgical nephrectomy to control her inflammation.

Discussion: Literature is scarce on protocols for administration of immune checkpoint inhibitors to transplant recipients. We report an interesting case of nivolumab-induced rejection that acutely blossomed two days post-administration. Future studies should evaluate whether transplant nephrectomy should be considered prior to immune checkpoint inhibition, particularly in patients with planned minimization or withdrawal of immunosuppression.

PUB659

AKI from Aspergillus Triggering Antiphospholipid Syndrome

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Introduction: Thrombotic microangiopathy (TMA) is commonly encountered following kidney transplant, however anti-phospholipid syndrome (APS) causing TMA is rare. We present a case of transplant AKI from APS triggered by *Aspergillus*.

Case Description: 52 yo M with lupus nephritis status post kidney transplant on tacrolimus and MMF was admitted for 3 days of progressive cough and hemoptysis. Medical history significant for APS with stroke and DVT, paroxysmal a fib on chronic warfarin, HTN and thrombocytopenia. Initial EKG had a fib with RVR and CXR with multifocal pneumonia. Labs: BUN and cr of 32 and 1.9 mg/dL, plt 26 (baseline 80), hgb 12.7 g/dL and INR 1.9 with a PTT of 73. Urinalysis had 2+ protein and hyaline casts. Given IV levofloxacin, oral β-blocker, heparin drip, and platelet transfusions. On day 2, chest CT and bronchoscopy done. No evidence of DAH. CT revealed multifocal ground glass and peribronchial airspace opacities with bronchial thickening and bronchiectasis bilaterally; concerning for atypical fungal infection. Fibrinogen and D-dimer elevated, +ANA (1:160 titer) with normal C3, C4 and ds-DNA. Anti-microbials switched to meropenem and voriconazole. By day 3, renal function deteriorated (cr trend 1.9>4.4>9.8 mg/dL). Due to acute thrombocytopenia, a high concern for TMA even though initial labs not suggestive (LDH 144, hagptoglobin 189). Tacrolimus was held. DRVVT screen, anticardiolipin antibodies, beta 2 glycoprotein resulted very high titers. On day 5, transplant biopsy done and IV methylprednisolone given. Biopsy showed TMA and APS. The biopsy findings mimicked a severe antibody mediated rejection (DSA neg). He received 5- sessions of plasmapharesis (PP) and HD. Bronchoscopy cultures were negative and voriconzale stopped. On day 7, his galactomannan testing from BAL was positive. Given the high specificity of this test, CT findings, and hemoptysis, diagnosed with invasive pulmonary aspergillosis. Voriconazole restarted. 1g/kg of IVIG and 5 more PP was used for refractory thrombocytopenia. Over next 3 weeks, Cr improved, HD stopped, and he was discharged to rehab.

Discussion: This case of AKI induced by TMA and APS triggered by invasive aspergillosis had none of classical features of TMA. A low threshold for kidney biopsy and high suspicion of fungal infection were helpful to reach the diagnosis. The management of APS post-kidney transplant lacks evidence and trials are needed.

PUB660

Wondering Why It Wandered: Pacemaker Lead Perforation in a Renal Transplant Patient on Sirolimus

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Introduction: Pacemaker lead perforation of the ventricle is a rare but potentially fatal event, we present the first reported case of pacemaker lead perforation in a renal transplant patient on sirolimus.

Case Description: A 63 year-old man, end stage renal disease from diabetes, status-post living-related renal transplant 17 years ago, on sirolimus and prednisone, presented to the hospital with dyspnea and flank pain. Medical history included bi-ventricular permanent pacemaker (PPM) 3 months prior. He was hemodynamically unstable, in respiratory distress, requiring intubation and vasopressors. Labs showed acute kidney injury, creatinine of 6.0 mg/dL (baseline 1.3) and hyperkalemia, requiring dialysis. Chest X ray revealed left pleural effusion and displaced right ventricular (RV) pacer lead. Thoracentesis showed hemorrhagic effusion and echocardiogram revealed perforated, thin-walled RV apex, with pericardial effusion. Hemopericardium was evacuated in the OR, RV perforation repaired, and PPM generator/leads were removed. Patient had a favorable post-operative course and underwent reinsertion of pacemaker with no complications. Renal allograft function returned to normal and immunosuppression was changed from sirolimus to tacrolimus. Outpatient follow-up confirmed stable PPM location and function.

Discussion: Ventricular perforation following PPM placement is rare and perforation greater than 1 month after implantation is infrequent. Predictors of perforation include steroid use, temporary pacemaker, active fixation of PPM lead and antiplatelet therapy. Proposed mechanisms include characteristics of the ventricular wall (thinner walls have increased risk of perforation) and intrinsic characteristics of PPM leads. No cases of RV perforation on mammalian target of rapamycin (mTOR) inhibitor therapy have been documented. It is well described that mTOR inhibitors impair fibrosis and wound healing. Furthermore, murine models show less fibrosis, hypertrophy and lower levels of TGF-β and collagen type I and III in rat myocardium on mTORs compared to controls. In this case, sirolimus may have favored conditions in the myocardium (less fibrosis and thinner wall) that allowed RV perforation to occur. This case highlights the importance of considering this infrequent complication in patients on mTOR inhibitor therapy to prevent potentially catastrophic consequences.

PUB661

Unusual Case of Abdominal Pain in Kidney Transplant Patient

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Introduction: Gastrointestinal histoplasmosis is likely manifestations of disseminated disease but only rarely comes to clinical attention due to the lack of specific signs and symptoms. We report the unusual case of abdominal pain found to be histoplasmosis in duodenum in kidney Transplant patient

Case Description: 65 year female with history of ESRD Secondary to Alport's Syndrome s/p kidney transplant X2, last DDKT 9/2013. Presented to ED with generalized weakness, and abdominal pain, no change in bowel habit, no dysphagia or odynophagia. physical exam notable for abdominal tenderness. Labs notable for mild leukopenia wbc 3.2. Abdominal CT imaging demonstrated 'misty' mesenteric LAD, as well as some mild duodenal thickening. GI was consulted regarding CT findings and performed endoscopy noting some gastric erythema and nodular/polypoid mucosa of the duodenum.biopsy was done and Path returned notable for histoplasmosis at the duodenal biopsy site. no evidence of pulmonary involvement based on CT imaging and CXR. Serum histoplasmosis ag negative, urine histoplasmosis ag positive; She was started on PO liquid Itraconazole and tolerated it. Her abdominal pain has resolved.

Discussion: Disseminated histoplasmosis may involve the gastrointestinal tract in 70-90% of cases, nearly 90% of lesions involve the lower GI tract, most commonly the ileocecal region or colon. Given the risk of dissemination of histoplasmosis and the potential to lead to considerable mortality and morbidity if not identified in early, suggesting that clinicians should consider fungal infections as part of their assessment for transplant patients, presenting with non-specific symptoms, including abdominal pain to improve patient outcomes and prevent disease recurrence.

PUB662

Successful Treatment of Refractory Severe Acute Humoral Rejection (AMR) in a Renal Transplant with Double Filtration Plasmapheresis and Immunoadsorbtion

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Introduction: AMR is a major threat to renal allograft survival in the early transplant period as it accounts for up to 40% of graft losses within the first year. Although various immunomodulatory treatments are implemented to treat AMR, there is no golden standard. In every clinical situation regarding mismatch, serological follow-up, severity of AMR and long- and short-term adverse events of immunosuppressive treatment, careful consideration which therapy to choose is imperative. Here we present a case of severe, sustained early AMR, treated w/ the various immunomodulatory agents and techniques, eventually AMR being successfully resolved by an extensive plasmapheresis approach.

Case Description: Immunosuppressive treatment has been initiated w/ Cyclosporin, Methylprednisone and Mycophenolate. While the patient (pt.) developed no graft function postoperatively, she underwent the first renal transplant biopsy (Bx) at d6 which revealed severe AMR. Despite sequentially initiated treatment w/ a course of anti-thymocyte immunoglobulin, plasma exchange, Rituximab, Immunoadsorption (IA) and intravenous immunoglobulin, the pt. remained anuric still. We then decided to serial-connect the double filtration plasmapheresis (DFPP)- w/ an IA system, treating the pt. every other day. After the 2nd treatment the transplant developed excretory function, accompanied by significant decline in SCr. Follow-up Bx at d50 still showed AMR but w/ significantly lesser activity. The pt. was dismissed at d60 w/ improved and stable renal function. We performed DFPP+IA thrice weekly for 2 months and weaned the pt. over one year. The last SCr was 1,52 mg/dl (2,5y).

Discussion: The capability of DFPP+IA in clearing main effectors of AMR was the rational to adopt this approach in an experimental treatment intent. Although we cannot rule out the impact of long-term effects of the preliminary treatments, the chronological relationship of DFPP+IA initiation and renal recovery appears convincing. To our knowledge, this is the first report of DFPP+IA for treatment of severe AMR. Thus, we consider the implications of this case to be twofold: 1st, treatment of severe AMR could be successful in long-term graft dysfunction. 2nd, DFPP+IA should be considered a rescue-treatment option for selected high-risk pts. w/ proven severe AMR in which other treatments failed.

PUB663

Myeloma Cast Nephropathy in the Kidney Transplant: A Rare Reversible Cause of Kidney Transplant Dysfunction

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Introduction: Multiple Myeloma (MM) is commonly associated with kidney injury through multiple mechanisms, most importantly cast nephropathy. Although kidney transplant recipients (KTR) have a higher incidence of malignancy, *de novo* MM is infrequent. Likewise, cast nephropathy is relatively frequent in the population with MM and kidney dysfunction (KD), but exceedingly rare as a cause of KD in the transplanted kidney.

Case Description: The authors present a case of a 62 year old men submitted to a deceased donor kidney transplant 12 years ago for end stage diabetic nephropathy, presenting a stable baseline serum creatinine (sCr) of 1.2mg/dL therafter. He presented to the clinic with mild progressive KD, with sCr increasing to 2.2mg/dL over a 5-month period. His laboratory workup was unremarkable except for mild anemia and borderline hypercalcemia. At this time his renal biopsy discarded rejection and was otherwise inconclusive. No other causes of KD were found. He maintained rapidly progressive RD over the next 4 months, to a maximum sCr of 8.3mg/dL, leading to initiation of hemodialysis. At this point, investigation revealed a IgA kappa MM with 48% bone marrow plasmacytosis. A second biopsy confirmed myeloma cast nephropathy in the transplanted kidney. He started treatment with bortezomib and cyclophosphamide and switched to high cut-off hemodialysis until disappearance of free light chains. He presented a surprisingly favorable evolution with progressive and sustained renal function recovery (RFR), being dialysis-free after 5 weeks of treatment and 21 dialysis sessions. Presently, 2 months after treatment initiation, he maintains a lowering sCr of 1.9mg/dL.

Discussion: The better survival of KTR results in older patients with associated longer immunosuppression times, which will possibly lead to previously infrequent types of malignant disease in this population. Our patient case is unique in reflecting both a rare case of MM cast nephropathy in KTR and the possibility of a good outcome regardless

of advanced disease/known negative predictive factors of RFR in the general population. Novel myeloma treatments should be promptly considered in KTR, as should the use of high cut-off membranes in dialysis-dependent patients. A high index of suspicion and early institution of curative treatment may potentially revert kidney injury and lead to complete RFR in the transplanted kidney.

PUB664

A Case of RPGN Due to Alport Post-Transplant Anti-GBM Nephritis

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Introduction: Studies show recurrent Anti-GBM disease in up to 50% of renal allografts after transplantation. De-novo occurrence of anti-GBM in transplanted Alport patients remains a rare phenomenon. We present a case of RPGN due to de novo anti-GBM disease post-transplantation in a patient with Alport syndrome.

Case Description: A 20-year-old African American male was diagnosed with Alport syndrome by renal biopsy at age 5, progressed to ESRD by age 13, and received a deceased donor renal transplant at age 14. Post-transplant, he developed 2A ACR after 1 year, AMR after 4 years, and acute and chronic AMR after 6 years. These biopsies had no evidence of glomerular disease. He presented to the hospital with AKI, hematuria, and hypervolemia 7 years post-transplant. Creatinine was 4.6mg/dl from baseline of 2.5mg/dl with 4.7g/g proteinuria on spot check. Renal allograft ultrasound was unremarkable. His clinical course rapidly deteriorated, requiring initiation of dialysis for electrolyte and volume management. Allograft biopsy immunofluorescence demonstrated 3+ IgG, kappa, and lambda linear staining with granular IgM staining in the mesangium and capillary walls. Serology was positive for anti-GBM antibodies. Diagnosis of anti-GBM disease was made. He received solumedrol, plasmapheresis, and was discharged on dialysis.

Discussion: COL4A5 gene mutations cause a defect in the alpha 3(IV)NC1 domain of the basement membrane component of type IV collagen. Anti-GBM alloantibodies bind only to this alpha 3(IV)NC1 domain. Anti-GBM antigen consists of the noncollagenous domain (NC1) of the α-3 chain of type IV collagen, indicating a connection in the pathogenesis between anti-GBM nephritis and Alport syndrome. This has implication towards allograft loss in transplanted patients with this underlying defect. Additionally, Anti-GBM pathology is consistent with linear IgG deposition along the GBM, which our patient demonstrated in addition to granular IgM staining on immunofluorescence. This may indicate an additional concommitant underlying process contributing to the de-novo appearance of anti-GBM disease in our Alport patient. Renal outcomes are reportedly poor in patients with anti-GBM in a renal allograft. Plasma-exchange and amplified immune suppression has been initiated to mitigate disease severity temporarily and improve pathologic findings, but evidence of anti-GBM has shown to inevitably result in graft loss.

PUB665

Out of Window: Late Disseminated Nocardiosis in Renal Transplant

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Introduction: Opportunistic infections in solid organ transplantation cause high morbidity and mortality in our patients. When we talk about Nocardiosis we refer to an infectious, rare, localized or systemic affectation, produced by Nocardia spp, a genus of ubiquitous environmental saprophytes actinomyces. This group of Gram-positive bacteria, which in the microscope present an appearance of branched filamentous cells, are found in soil, There are more than 50 species generating infectious tables, the most important taxonomic groups being the complex N. asteroids complex producing mainly respiratory and disseminated infections, N. brasiliensis responsible for disease located in skin and soft parts. N. Nova and N. farcinica can produced Nocardiosis in patients transplanted from solid organ, with an approximate frequency that varies between 0.7 to 3.5%. The incidence of thes desease is high during firsts 6 moths post trasplant.

Case Description: Given this premise, we review our series of patients with kidney transplant from 2000 to 2007 with disseminated Norcardiosis; finding a total of 8 cases. All of them presened compromise of two or more organs; being the most frequent skin, lung and Central Nervous System. In all cases fever was dominant. The diagnosis was made by Staining Kynyoun (+). As a therapeutic scheme, doble and triple antibiotic therapy was started, including Ceftriaxone, Trimetroprim Sulfamethoxazole and Minocycline. All of the patients survival. The clinical resolution was equally frequent. The average time of the beging of the symphtoms in our population was 64 months after trasnsplant.

Discussion: Our conclution is that Nocardia may present in late period after kindey transplantation, and the early diagnosis and treatement contributed to a low mortality of this patology.

PUB666

How Low Can You Go? A Case Report of Disseminated Cryptococcus in a Kidney Transplant Recipient

Goni Katz Greenberg, Pooja Singh, Anju Yadav. *Thomas Jefferson University and Hospital, Philadelphia, PA.*

Introduction: In patients following solid organ transplantation, wider differential of infectious etiology is warranted as the presentation can be nonspecific.

Case Description: We present a 68 years old Caucasian male, with past medical history of hypertension and end stage renal disease due to polycystic kidney disease, status post deceased donor kidney transplant (DDKT) in Sept 2016, admitted following two weeks of malaise, fatigue and recurrent falls, with one fall leading to a wound on his right shin. His post-transplant period was also complicated by BK nephropathy in early post-transplant period, which was managed by reduction of his immunosuppression. He was maintained on tacrolimus and prednisone. On physical examination the patient was alert, with a mild cognitive deficit. An open wound of about 6 cm was seen on the anterior aspect of his right shin. The patient underwent irrigation and debridement of the wound. Patient was started on antibiotics for community acquired pneumonia for right side infiltration seen on chest X-ray. Wound pathology came back positive for Cryptococcus. Cerebrospinal fluid analysis which was done at this time, was consistent with Cryptococcus meningitis, and chest CT showed also showed right lower lobe cavitatary lesions and small calcification. Empirical treatment was initiated with IV liposomal amphotericin B and 5 flucytosine for disseminated Cryptococcus, later switched to IV fluconazole following results of cultures. Additionally, patient's remaining immunosuppression was further decreased, and is maintained on tacrolimus monotherapy at lower trough goal levels.

Discussion: Cryptococcosus neoformans is the third most common invasive fungal infection in organ transplant recipients after candidiasis and aspergillosis. Reports indicate that Cryptococcus usually presents as a symptomatic disease and despite therapy the mortality remains high. A common risk factor for Cryptococcal infection is the lifelong immunosuppression. We believe our case is unique as our patient's immunosuppression was reduced about 18 months prior to diagnosis of disseminated Cryptococcus following renal biopsy proven BK nephropathy. Furthermore, our patient's atypical presentation caused delay in the diagnosis.

PUB667

An Unusual Cause of Life-Threatening Bleeding in a Patient with Bladder Drained Kidney-Pancreas Transplant

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Introduction: The optimal method of exocrine pancreatic transplant drainage has been highly debated. Enteric drainage was preferred from 1960s-1990s and regained popularity in the 2000s being more physiological. There was a transient shift during the 1990's when bladder drainage became popular as it allowed monitoring of graft rejection by detecting hypoamylasuria. However, pancreatic secretions can be inflammatory to the bladder wall and the duodenal stump anastomosed to the bladder. This can lead to ulceration or anastomotic dehiscence. Inflammatory erosion of artery leading to exsanguination is one of the most dreaded complications of bladder drainage. Since this technique is becoming rare, the experience to manage these catastrophic presentations might be meager. We report a case of successful management of arterial erosion in a bladder drained kidney-pancreas transplant.

Case Description: A 45-year-old female, status post combined bladder drained Kidney-Pancreas transplant in 2006 with repeat living unrelated renal transplant in 2012 presented with gross hematuria and acute blood loss anemia (Hemoglobulin 5.3 from baseline of 10.1). On presentation, she was hemodynamically stable but deteriorated into hemorrhagic shock requiring massive transfusion (5 units PRBC, 1 FFP, 1 Platelet) and transfer to ICU. Emergent exploratory laparotomy was performed showing grossly distended bladder containing one liter of blood. There was a 4mm ulcer on the duodenum eroding into a branch of the renal artery with active pulsatile bleed. Repair and transplant pancreatectomy was performed with resolution of hemorrhage. Post-procedure she was hemodynamically stable and was discharged on insulin.

Discussion: Inflammatory erosion into major arteries following KP transplant appears to be related to graft pancreatitis or leakage of pancreatic secretions in the region. This can result in pseudoaneurysms, fistulae formation (arterio-enteric or arterio-vesicular) and erosions. Fortunately, this is a rare complication but need to be considered in any patient with gross hematuria or blood clots. A high index of suspicion needs to be maintained by clinicians since it is treatable, at the expense of the pancreas allograft. Although our patient had pancreas anastomosed to the urinary bladder wall, this complication has been reported even in enteric-drained pancreas transplants.

PUB668

A Rare Case of Pneumonia in a Combined Kidney and Pancreas Transplant Recipient

Massini Merzkani, Momina M. Ahmed, Aleksandra Kukla. *Mayo Clinic, Rochester, MN.*

Introduction: Rhodococcus equi is an unusual cause of infection in humans. Patients on immunosuppressive medications that affect the cell-mediated immunity are susceptible for acquiring this infection. We present an unusual case of pneumonia in a combined kidney and pancreas transplant recipient.

Case Description: 72 year old male with a history of diabetes mellitus type 1 complicated by end stage renal disease. Patient received a living donor kidney transplant in 2002, followed by pancreas after kidney transplant six months later with Thymoglobulin (ATG) induction. He was maintained on Cellcept, Tacrolimus and prednisone. Post transplant course was complicated by two acute cellular rejections of the pancreas in 2012 and 2015 treated with ATG. He present to outside hospital with productive cough, fever and diaphoresis of 3 weeks duration. He traveled to Arizona 2 months prior. He denied contact with animals or desert activities. Three weeks prior symptoms his neighbor started to use horse manure for farming. Chest CT showed a 5 cm consolidation in the left upper lobe. Bacterial, fungal and mycobacterial sputum cultures were negative. Biopsy done by bronchoscopy showed noncaseating granulomatous inflammation. Mycobacterial culture of the biopsy showed Rhodococcus equi infection and was started on azithromycin and rifampin. He came to our institution after 4 weeks without improvement. Vital signs and oxygen saturation were unremarkable. Lungs were clear to auscultation. Serum Cr was

stable at 0.7 mg/dL, lipase and amylase were elevated (157 U/L, 105 U/L). Chest CT had an increase in size of the consolidation 10.7cmx 9.1cm. He was started IV vancomycin, meropenem and PO azithromycin. The Tacrolimus level was undetectable due to use of rifampin. Tacrolimus was adjusted to a through level 7-9 and pancreatic enzymes improved. He completed 5 months of IV antibiotics with improvement of the infection.

Discussion: Rhodococcus equi is a gram-positive coccobacillus can cause pulmonary and extrapulmonary infection. Inhalation of soil contaminated herbivore manure is the most common route infection. Combination of 2–3 antibiotics is recommended for immunocompromised patient. Antibiotics interact with transplant medications; therefore levels need to be carefully monitored to avoid rejection. This case reminds us the importance educate our transplant patients the risk of exposure to manure

PUB669

Ganciclovir-Resistant Cytomegalovirus Treated with Foscarnet in a Pediatric Renal Transplant Recipient

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Introduction: Human Cytomegalovirus HCMV poses significant morbidity in CMV-negative recipients (R) who receive a kidney transplant from a CMV-positive donor (D), (mismatch D+/R-). The usual treatment for CMV infection/disease is ganciclovir/valganciclovir. With molecular testing of resistance markers, we have been able to identify strains of HCMV resistant to ganciclovir and tailor treatment to prevent morbidity. In this report, we describe a case of a patient with CMV infection with a ganciclovir-resistant strain of CMV treated with foscarnet.

Case Description: We describe the case of a 6-year-old-girl with ESRD secondary to congenital nephrotic syndrome post deceased donor kidney transplant at age 3 years. Her serostatus at the time of transplant was CMV D-/R-, and she was maintained on prednisone, tacrolimus and Mycophenolate mofetil. CMV infection was first diagnosed 35 months post-transplant when quantitative CMV PCR was at detected 3.7 x 10^ 4 genome copies per ml. Treatment with ganciclovir 5 mg/kg/dose bid, titrated to 10mg/kg/dose bid failed with increasing CMV PCR load to 8.2 x 10^4 genome copies per ml. Initial resistance testing at 3 months was negative. Cytomegalovirus Immune Globulin infusions (twice/week) was commenced and continued for 2 months with no improvement in viral load. Repeat resistance testing showed CMV UL97 mutation (L595S) and no UL54 mutation confirming ganciclovir resistance and possible foscarnet susceptibility. Treatment was thus changed to foscarnet at 90mg/kg daily induction dose. After 1 month of foscarnet, CMV was undetectable but reappeared after a reduction in the dose of foscarnet to 60mg/kg daily. Foscarnet dose was re-increased to 90mg/kg daily and CMV was undetectable after 3 weeks of at this dose. She completed a further 2 months of treatment at this dose. The most notable side effect of foscarnet was a transient rise in her serum creatinine that improved with pre- and post-medication hydration with 0.9%NaCl.

Discussion: The effects of CMV disease can lead to significant allograft-related and systemic effects to the transplant recipient. We highlight the utility of resistance testing to detect de-novo ganciclovir resistance in newly acquired drug-resistant HCMV in the seronegative renal transplant patient, and the use of foscarnet in the successful eradication of CMV infection.

PUB670

Eculizumab as Salvage Therapy in a Patient with APLS Undergoing Renal Transplantation

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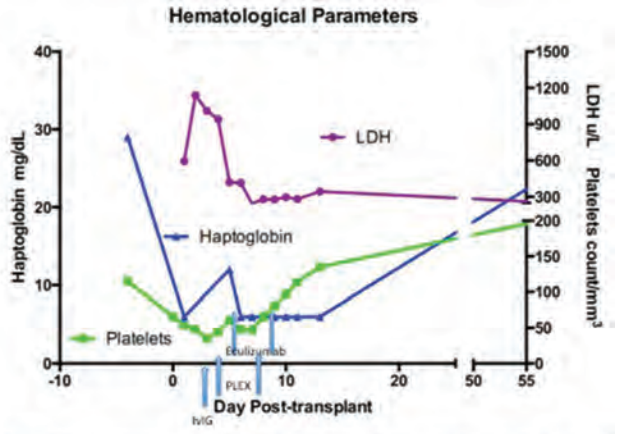
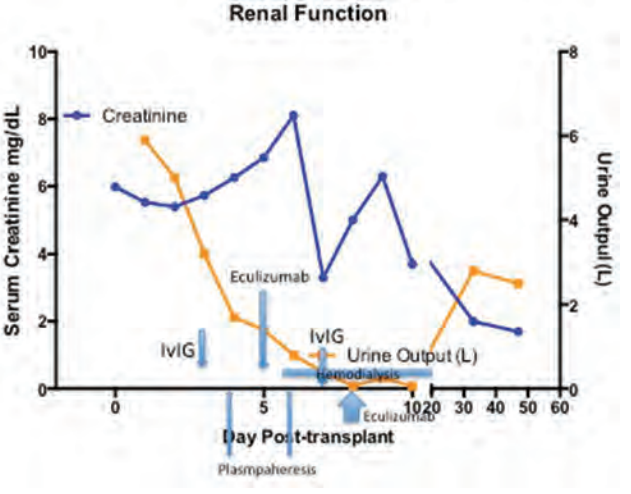
Introduction: APLS is associated with an increased risk of kidney allograft loss. We describe a patient with high titer APLS who developed oliguric renal failure post living donor transplant and was treated with Eculizumab.

Case Description: A 63 y/o sensitized F with triple positive antibody APLS underwent a living donor transplant with no donor specific antibodies (DSA). She received Hydroxychloroquine, Mycophenolate Mofetil and Rituximab as immunomodulatory therapy pre-transplant and steroid /ATG induction with anticoagulation with unfractionated heparin. On POD 6, she developed oliguric AKI necessitating hemodialysis. Labs were notable for a rise in LDH, decrease in platelets, and low haptoglobin (Figure 1). Thrombocytopenia precluded the possibility of biopsy. She received IvIg 200 mg/kg, 2 sessions of plasmapheresis followed by Eculizumab. Approximately 1 month after starting Eculizumab, she recovered her renal function and continues to have excellent graft function (Table 1, Figure 1).

Discussion: Although patients with APLS are at increased risk for acute kidney injury and allograft loss, anticoagulation remains the mainstay of management. The role of preemptive immunosuppression remains unclear. In our patient, despite pre-transplant immunosuppressive therapy, she developed an acute hemolytic syndrome with AKI that resolved with a combination of plasmapheresis and Eculizimab therapy. Our data suggests that the use of Eculizumab modulated the development of APLS associated TMA despite significantly high antibody titers.



APLS antibody	Pre-transplant	Day 10	Day 60
B_2 Glycoprotein IgG	149.6	125.8	135.3
Phosphatidylserine IgG	100	>100	>100
Phosphatidylserine IgA	4	1	3
Phosphatidylserine IgM	61	18	34
Cardiolipin IgG	132.1	79.4	91.8
Cardiolipin IgA	4.4	0.7	1.6
Cardiolipin IgM	36.2	14.4	26.9



PUB671

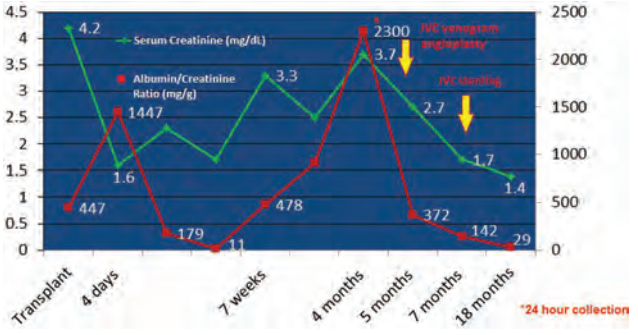
Recurrent FSGS? Maybe the Problem Is in the Plumbing

Massini Merzkani, Matthew R. D'Costa, Momina M. Ahmed, Mary E. Fidler, Hatem Amer. *Mayo Clinic, Rochester, MN, Rochester, MN*.

Introduction: Primary Focal Segmental Glomerulosclerosis (FSGS) in adults can recur in up to 40% of first transplants and >90% with a repeat transplant. Here we present a patient who had a third kidney transplant with worsening proteinuria that was not due to recurrence.

Case Description: A 40-year-old male with ESRD disease received his third living donor transplant from his father. His two prior renal allografts had developed recurrent FSGS. The first lasted for 12 years, and the second for 8 years. During his second transplant he developed an iliofemoral thrombosis in the setting of heavy proteinuria. During his evaluation for the third transplant, he was noted to have an occluded inferior vena cava but with extensive collaterals and underwent the third renal transplant by removing the second renal allograft and attaching the new kidney to site of the second allograft. He underwent conditioning with pre-transplant plasma exchange and received two doses of Rituximab. His post-transplant course was characterized slow graft function and fluctuating proteinuria, punctuated by repeated episodes of acute kidney injury (See fig 1). Several biopsies performed showed acute tubular injury with only mild focal foot process effacement. Ultrasound revealed no hydronephrosis and renal vein was patent. He was transitioned to Belatacept with no change in his course. Noting the thrombosed IVC and dependence on collaterals we proceeded to venography and pressure measurements. The IVC was canalized and stented with an improvement in venous pressures of the renal allograft vein. Subsequent to this there was a marked improvement in renal function with resolution of proteinuria.

Discussion: This is a case shows that although recurrent FSGS the most likely cause for the increasing proteinuria, it was important to rule out other pathologies. An important sign in this case was the focal foot process effacement arguing against as systemic permeability factor affecting all the podocytes diffusely.



PUB672

Deceased Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome Without Preemptive Eculizumab Use

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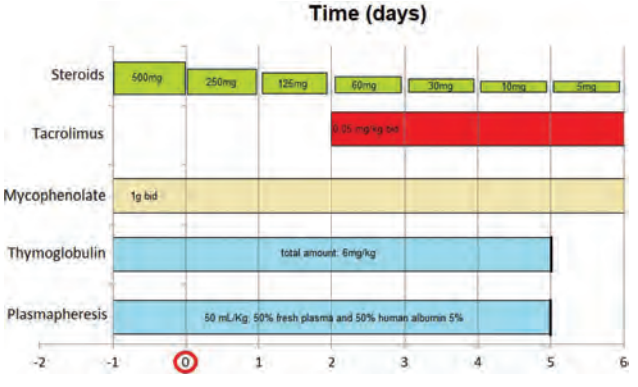
Introduction: Atypical hemolytic uremic syndrome(aHUS) has been associated with high risk for recurrence after kidney transplantation. In 2017, a consensus report on aHUS was published by KDIGO working group whereby eculizumab prophylaxis should be recommended in renal transplantation. However, it has recently been described the potential benefits from living kidney donors and low tacrolimus use to minimize recurrence rates in aSHU, thereby averting endothelial injury. Here we report two cases of successful deceased donor kidney transplantation in atypical hemolytic uremic syndrome without preemptive eculizumab treatment.

Case Description: They are a 58 and 46-yr old women with a history of CKD stage V in hemodialysis due to aHUS diagnosed in 1991 and 1993 respectively. The first one showed a total complement factor I(CFI)deficiency of 100% (mutation c.-173C>T), whereas in the second case, a complement factor B mutation (c.858C>G) was identified. Both underwent renal transplantation from cadaveric donor, sharing two HLA identities(class I and II) in each case. Cold ischemia time (CIT) were of 19h18' and 23h30', respectively. Our immunosuppressive strategy, based on preemptive plasmapheresis, is depicted in the attached image. The clinical course was uneventful, without hemodialysis requirements nor biochemical microangiopathic anemia signs. Actually, they show a normal renal function under tacrolimus (5-6pg/L), mycophenolate and steroid treatment, one month and four years after transplantation, respectively.

Discussion: According to our experience, preemptive plasma therapy could be effective in the prevention of disease recurrence in patients with high risk mutations with deceased kidney donors and long CIT. We need more evidence to define risk groups and tailor current treatments to each case to make better cost-effective decisions.



PUB673

Study of Factors Related to Survival of the Renal Graft in Rejection, by Means of Plasma Exchange Treatment: Experience in the Hemodialysis Unit of the National Medical Center November 20 ISSSTE

Monica Lopez Mendoza, Diana Maldonado Tapia, Ana Karen Garro Almendaro. *ISSSTE, Ciudad de Mexico, Mexico.*

Introduction: The therapeutic plasma exchange (TPE) is an extracorporeal blood purification, which consists of extracting plasma, to eliminate particles of great molecular weight, from a replacement with colloids or crystalloids. The use in the renal patient is indicated to desensitize or reject a renal transplant compatible with ABO and not compatible with terms of evidence levels. Currently there is no information in Mexican population under this treatment compared to the universal literature.

Case Description: A retrospective analysis during the period from 2016 to 2018 at the CMN November 20 ISSSTE, 9 patients, with TPE, under treatment with plasma exchange, Collection of demographic characteristics, filters, volume and fluid replacement, number of sessions and HD sessions performed. 9 patients being 44.4% female and 55.5% male, the mean age was 34 ± 12.1, the predominant type of donor was alive in 66.7% and cadaveric in 33.3%, most of the patients, 66.7%, did not have a reported immunological risk of the reference hospital and 3 ones were classified as low (11.1%), and intermediate (22.2%), the creatinine value previously recorded at the event of transplant rejection was 1.9 ± 2.3, with BUN at 22.4 ± 25.2. In the CMN, the mean in the reference time was 35.7 ± 26.1, the creatinine value was 8.4 ± 5.9, with BUN 61.2 ± 32.8, registering anuria in 33.3% and uresis preserved in 66.7 %, performing plasma exchange treatment in Hemodialysis Unit with a mean of sessions of 3.3 ± 1.6, during their stay required conventional hemodialysis sessions in 55.6% and recovery of kidney function after treatment was 44.4%, a creatinine of 4.5 ± 4 and BUN 31.5 ± 19.4 was reported. Analysis of categorical variables, chi square was occupied, finding a significant difference between the recovery of the renal function of the patient with the type of living or cadaveric donor, with a value of p 0.048.

Discussion: Within 3 years of experience of the Hemodialysis Unit, CMN November 20, the use of theTPE technique is a useful and effective treatment for transplant rejection, however the survival is influenced to risk factors, type of donor, the reference time and creatinine at the beginning of treatment. Currently patients are being collected for their subsequent analysis.

PUB674

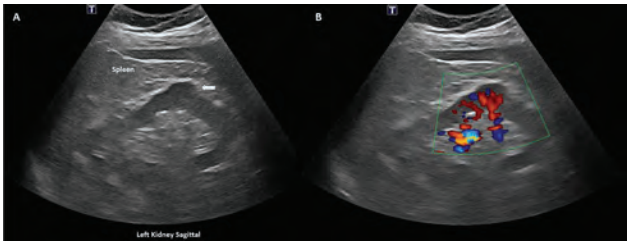
Dromedary Hump

Justin Lee Loy,[2] Gajapathiraju Chamarthi,[1] Abhilash Koratala.[1] *[1]University of Flroida, Gainesville, FL; [2]University of Florida Gainesville, Gainesville, FL.*

Introduction: Point-of-care renal ultrasonography, performed by clinicians at bedside assists in the management of kidney disease by allowing rapid evaluation of hydronephrosis, nephrolithiasis and other major structural abnormalities. It is being increasingly performed by internal medicine physicians as well as nephrologists, who typically do not have a formal training in radiology. As such, it is important for these physicians to have a thorough understanding of renal anatomy and the sonographic appearance of normal kidneys and various pathologies that can mimic one another. Herein, we describe a case of dromedary hump, a benign anatomic variant.

Case Description: A 58-year-old man with a history of hypertension, obstructive sleep apnea and mildly elevated serum creatinine underwent renal ultrasonography for evaluation of kidney size and structure. The scan reported no structural abnormalities except for a 'protuberance' in the left kidney [Figure 1A], for which Nephrology input was sought. The patient was reassured that this was a benign finding called 'dromedary hump' and no follow up imaging was indicated.

Discussion: Dromedary hump appears as a focal bulge on the lateral border of the left kidney, caused by molding of the normal renal parenchyma by the adjacent spleen. It is similar in appearance to the hump of a dromedary camel and thus the name. The incidence of this normal anatomic variant is estimated to be about 0.5%. It can sometimes mimic a kidney neoplasm and therefore considered a 'renal pseudotumor'. The hump demonstrates the same echogenicity as adjacent normal renal parenchyma on the sonogram unlike renal cell carcinoma, which typically appears as a heterogeneous mass with areas of necrosis, cystic changes, and hemorrhage. In addition, colour doppler ultrasonography demonstrates a normal blood flow within the hump [Figure 1B]. Failure to recognize this benign entity may result in unnecessary consultations and investigations.



PUB675

Spontaneous Bleeding in a Patient on Enoxaparin with Overestimated GFR

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Introduction: Creatinine-based equations are commonly used to estimate glomerular filtration rate (GFR). Unfortunately, creatinine varies depending on factors such as age, gender, and muscle mass. Overestimation of renal function by creatinine-based equations can be dangerous for renally-dosed medications. We present a patient who developed spontaneous bleeding on enoxaparin with kidney function overestimated by creatinine-based equations.

Case Description: A 73-year-old woman with chronic obstructive pulmonary disease on home oxygen was admitted with sudden swelling, pain, and discoloration in her right hand. She was completing an enoxaparin bridge to warfarin for history of recurrent pulmonary embolism. Examination showed a hematoma on the dorsum of her right hand. Labs revealed hemoglobin 10.8 g/dL, creatinine 0.98 mg/dL, INR 1.2, and cystatin C 1.80 mg/L. She underwent two hematoma evacuations and required 2 units of packed red blood cells. Therapeutic enoxaparin was stopped, and she was resumed on warfarin at discharge.

Discussion: Creatinine-based formulas overestimated our patient's kidney function. Creatinine-based equations, such as Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) study, and CKD-EPI, placed her at Stage 2 or 3a CKD. Cystatin C, a low-molecular weight protein, can better predict kidney function independently of creatinine. Using the cystatin C equation, our patient had more severe renal dysfunction of Stage 3b CKD. The discrepancy between the equations can be due to creatinine variability from her older age, female gender, and decreased muscle mass with poor functional status. The dosing of enoxaparin sodium was likely too high for her renal function, placing her at increased risk of bleeding. Clinicians should be aware of the variability in using creatinine-based equations to estimate GFR, including patients with low functional status, and should consider using cystatin C to guide clinical decision-making.

	Range	
Serum Creatinine	0.86-0.98 mg/dL	
Serum Cystatin C	1.68-1.83 mg/L	
Equation		
Cockcroft-Gault	67-76 mL/min	Stage II
MDRD	59-69 mL/min/1.73m2	Stage II/IIIA
CKD-EPI	57-67 mL/min/1.73m2	Stage II/IIIA
CKD-EPI Cystatin C	31-35 mL/min/1.73m2	Stage IIIB

PUB676

Calciphylaxis in CKD: The Need for Vigilance in Nondialysis Patients

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Introduction: Calcific uremic arteriolopathy (CUA) or calciphylaxis is a small-vessel vasculopathy, primarily seen in end-stage renal disease, and although rare, it can also occur in patients with early stages of CKD. Calciphylaxis results in skin ulcerations and ischemia due to thrombosis of small arteries and arterioles triggered by intimal hypertrophy, medial calcification and endovascular fibrosis. We present a case of extensive calciphylaxis in CKD stage 3.

Case Description: A 48-year-old female with PMHx of CKD 3, DM, PVD, HLD, MI, DVT (on anticoagulation with warfarin), and PSHx of multiple vascular procedures including femoral-popliteal bypass and CABG presented with multiple painful ulcerations. Then ulcerations initially starting on the right inner thigh, and left breast, and later involved the left thigh and gluteal area. Serum creatinine was 0.86 mg/dL at the time of presentation, and calcium, phosphorus and PTH were 8.8 mg/dL, 3.5 mg/dL, and 137 pg/ml, respectively. Skin biopsy revealed sclerosing dermatitis and angioendotheliomatosis, concerning for calciphylaxis. The focal findings of arteriole wall calcium deposition supported the diagnosis of calciphylaxis, however ischemic changes and calcification of small arterioles were not seen. Warfarin was discontinued and the patient was started on intravenous sodium thiosulfate 25 gm three times a week, with subsequent dose titration to 50 gm three times a week. Therapy, including sodium thiosulfate and hyperbaric oxygen, were limited by patient compliance on discharge, with continued progression of lesions and untimely death at 6 months after initial diagnosis.

Discussion: Calciphylaxis should be suspected in patients with early to moderate CKD presenting with suspicious skin findings including non-healing ulcerations with surrounding areas of induration circumferentially, or painful subcutaneous nodules, especially in areas of increased adiposity (thighs, abdomen). Risk factors that have been associated with calciphylaxis include warfarin, obesity, and vitamin D analogues. Skin biopsy can help confirm the diagnosis of calciphylaxis[4], but carries risks of superimposed infections, and should not be performed with actively infected lesions. Timely diagnosis and identification of risk factors, along with therapeutic interventions i.e. sodium thiosulfate is key to slow progression.

PUB677

The Case: CKD Unmasked

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Introduction: We present a 42-year-old Caucasian man with a body mass index (BMI) of 32 kg/m^2, who was referred because of heavy proteinuria and decreased renal function. We were impressed by his markedly muscular physique.

Case Description: A renal biopsy was performed, which showed advanced focal segmental glomerular sclerosis (FSGS). The patient is a professional bodybuilder who was not fat despite BMI criteria that classified him an obese (Obesity Class 2) person. He used progressive resistance exercise to develop his musculature from age 18 to 39 years. As part of his bodybuilding regimen, he consumed anabolic steroids, muscle-growth stimulating substances, and high-protein, low-fat diets. For more than six months until admission to our hospital, he resumed progressive resistance exercise and also regularly used anabolic androgenic steroids. We performed laboratory examinations and anthropometric data (BodPod) monitoring over time. Laboratory tests revealed a serum creatinine of 6.37 mg/dL (CKD-EPI, eGFR <15 mL/min) and a serum urea of 185 mg/dL. Endogenous creatinine clearance (CrCl) was 33 mL/min. Intact parathyroid hormone was 580.3 ng/L. There was an albuminuria of 3.01 g albumin/creatinine 1 g. The total proteinuria was 3.98 g protein/creatinine 1 g. Serum creatine kinase (CK, 5995 U/l, normal <190 U/l) (with CK-MB activity 66.4 U/l) and myoglobin (1554 μg/L) were elevated. Serum albumin (36 g/l) and protein (64 g/l) levels were in the low-normal range. Over a six-month period, our patient's renal function failed to improve despite reduction in lean body mass, discontinuation of anabolic steroid drugs, and muscle growth-stimulating substances. We developed and validated a new custom-targeted NGS gene panel (Ion Ampliseq FSGS panel) in two patient cohorts with FSGS, and detected several common DNA variants in FSGS genes, which could represent candidates for renal risk variants in our patient.

Discussion: We conclude that increased BMI due to increase muscle mass and/or body fat in combination with long-term anabolic steroid use and growth promoting substances should be included as risk factors in the differential diagnosis of secondary FSGS. Bodybuilders are a unique patient population that are fixated upon their behavior. Simple counseling is well meaning; however, nephrologists may have to recruit other health-care professionals when dealing with these patients.

PUB678

Homocysteine-Induced Renal Microvascular Injury in a Case with Vitamin B12 Deficiency Following Gastrectomy

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Introduction: High Homocysteine levels are established as an independent risk factor for atherosclerotic vascular diseases because of its atherogenic and prothrombotic properties. Although in ESRD patients the level is known to elevate, it has not fully been elucidated the mechanism how high concentration of plasma homocysteine affects the function of the kidney in human. We report a case with edema, proteinuria and renal function impairment, whose renal histopathology showed thrombotic microangiopathy (TMA) like lesions. Furthermore he was associated with marked hyperhomocysteinemia and vitamin B12 deficiency related to total gastrectomy.

Case Description: A 56 year-old man presented progressive systemic edema and weight gain by 7.2 kg over one month. Hypertension, diabetes mellitus or kidney disease including proteinuria had never been pointed out, except for the history of total gastrectomy. Laboratory data showed proteinuria of 3.2 g/day, u-occult blood 3+ and RBC casts in the sediment. Renal function was impaired as serum Cr 1.35 mg/dL, eGFR 44 mL/min/1.73 m^2, and were serum albumin 3.4 g/dL and LDH 246 IU/L. Blood cell count indicated mild anemia, RBC 3.46×10^6 /μL, Hb 9.3 g/dL and Ht 29.1%, and normal Plts count (266×10^3/μL). Both serum ferritin and vitamin B12 were low, 4.3 ng/mL and 95 pg/mL (normal: 180-914), respectively. In further tests, IgG, IgM, IgA, C3 and C4 were within normal limits, and ANA, ANCA and anti-GBM were all negative. Renal biopsy revealed endothelial cell swelling and mesangiolysis in glomeruli. Later his homocysteine level in plasma was reported to be very high, 55.8 nmol/mL (normal: 5-15). Treatment with cyanocobalamin injection was started.

Discussion: Vitamin B12 plays a crucial role as a cofactor in the metabolism of homocysteine. Its deficiency, thus, leads to very high homocysteine concentration of the amino acid in plasma. The level is also related to serum Cr in patients with renal diseases, partially because the elimination is dependent on the clearance in the kidney. Our case indicates the relationship between hyperhomocysteinemia and the pathological findings of glomerular endothelial cell damage similar to TMA, suggesting homocysteine-induced renal microvascular injury. We propose hyperhomocysteinemia is one of important causes in unexplained renal TMA, especially in vitamin B12-deficient adults.

PUB679

"It's Not Always Lupus": A Case Report

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Introduction: Autoimmune hemolytic anemia (AIHA) can be a clinical manifestation as well as a sequel to lupus flares. Mechanical valves can cause hemolytic anemia due to shearing of red blood cells (RBCs). Here we are presenting a case of a patient with active lupus and mechanical mitral (MVR) and aortic valves (AVR) presenting with jaundice.

Case Description: 37-year-old female with prior history subacute bacterial endocarditis with mechanical MVR and AVR on anticoagulation, systemic lupus erythematosus (SLE) complicated by non-biopsy proven lupus nephritis, transaminitis, hemolysis. In August 2017 she was hospitalized with severe anemia requiring multiple blood transfusions, worsening fatigue, 1+ blood on urine dipstick associated with hypocomplementemia while on MMF. She developed frank hematuria and high dose steroids were initiated. UA illustrated RBC casts and Cytoxan was initiated given presumed class IV lupus nephritis. Due to her being anticoagulated a biopsy could not be performed. In January she was found to have scleral icterus, jaundice, transaminitis, anemia and gross hematuria. At this time our differentials were lupus induced hemolysis vs mechanical shearing. Her LDH was high and her haptoglobin was low indicating hemolytic anemia. Her ESR/ANA/C3/C4/dsDNA were at normal. Her anti-cardiolipin, Parvovirus, direct and indirect Coombs were negative. Her Glucose 6 Phosphate Dehydrogenase (G6PD) levels were normal. On physical exam no murmurs detected. Her first echo showed a well-seated MVR, AVR was with a normal gradient across the valve, no pericardial effusion, and EF 60-65%. Repeat cardiac echo less than 2 weeks later which illustrated moderate medial paravalvular leak and severe anterio/lateral paravalvular leak of the MV, in addition, her AVR illustrated elevated AVR gradients likely of obstructive physiology. She was taken to the operating theater with a diagnosis of aortic and mitral paravalvular leak, pseudoaneurysm between the aortic and mitral valve where she underwent a third sternotomy with redo mechanical MVR and redo AVR with repair of pseudoaneurysm at the base of the heart. She is post-op from her open heart surgery.

Discussion: Here we would like to emphasize that in the setting of existing and recently active Lupus nephritis, all etiologies must be considered and ruled out. Hemolytic anemia is a known complication of SLE however not all are due to an autoimmune etiology.

PUB680

A Mysterious Case of Hypercalcemia

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Introduction: Hypercalcemia is often associated with endocrine dysfunctions, sarcoidosis, and malignancies. Among malignancies, the physiologic processes resulting in hypercalcemia differ. Bony metastases cause lysis of bone calcium deposits, or tumors can release parathyroid hormone (PTH) or parathyroid hormone-related protein (PTHrP), altering hormonal axes. Rarely, malignancies secrete Vitamin D_3 (Calcitriol), causing increased intestinal absorption of calcium and increased osteoclastic bone activity.

Case Description: A 47-year-old female with no significant past medical history presented with palpitations and dyspnea on exertion. On physical exam, she was tachycardic at 144 bpm, hypertensive at 195/129 mmHg, and had palpable splenomegaly. Lab values showed a calcium level of 17.7mg/dL. Blood smear showed normal erythrocyte morphology with normocytic anemia and some tear-drop cells. White blood cells were without inclusion bodies. Platelets were unremarkable. Calcium was stabilized with IV fluids and pamidronate. A CT revealed 25cm heterogeneous splenomegaly. A bone marrow biopsy demonstrated normocellular marrow with lymphoid aggregate and no evidence of an infiltrative process. Microscopic examination showed normocellular marrow with moderately decreased iron and no evidence of acute leukemia or lymphoproliferative disorder. PTH was depressed at 5.2 pg/mL (reference range 14-64 pg/mL), and PTHrP was 19 pg/mL (reference range 14-27 pg/mL). An acetylcholinesterase (ACE) level was negative. A 24-hour urine calcium was elevated. No monoclonal spikes were identified on SPEP and there was no abnormal distribution of immunoglobulins on immunofixation. Abnormally high calcitriol levels at 118 pg/mL were noted. Subsuqently, a total splenectomy was performed. Post-operative calcium corrected to 8.5 mg/dL. Surgical pathology of the spleen revealed a high grade diffuse large B cell lymphoma. She received systemic chemotherapy. Follow-up PET-CT was without residual or recurrence of tumor burden.

Discussion: Primary Splenic Lymphomas are uncommon and presenting symptoms are often non-specific. This case is an example of Splenic B Cell Lymphoma presenting with hypercalcemia secondary to ectopic calcitriol production. With splenectomy the ectopic calcitriol was eliminated and calcium levels abruptly corrected. This case demonstrates that with application of basic physiologic principles even a mysterous cause of hypercalcemia can be unveiled.

PUB681

Mesenteric Ischemia in Post-Kidney Transplant Patient Associated with the Use of Sevelamer

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Introduction: It is well known that hyperphosphatemia leads to vascular calcification, increasing mortality in chronic kidney disease(CKD)patients. Sevelamer is a phosphate binder, widely used to control hyperphosphatemia. One of the barriers to the use of Sevelamer are the gastrointestinal(GI)symptoms. As other resin-based binders, it can crystallize, deposit and injure the GI mucosa through mechanisms not yet well established. In this paper, we will report a case of a post kidney transplant patient that presented intestinal perforation with the presence of sevelamer crystals(SC)on the GI mucosa.

Case Description: AMSR,41 years old, female, with a history of Systemic Lupus Erythematosus, with prolonged use of corticosteroids, Hypertension, CKD due to Lupus Nephritis, in haemodialysis(HD)since 2010, and Secondary Hyperparathyroidism. To treat bone mineral disease the patient used Sevelamer, CaCO3 and Cinacalcet. The patient underwent kidney transplant(deceased donor), progressing to delayed graft function, requiring HD for 2 weeks. During that period, she presented with severe abdominal pain. The pain ceased with interruption of HD, leading to the suspicion of mesenteric ischemia. Contrast tomography was performed, showing perforation of the colon and ileum, and she underwent exploratory laparotomy. When analysed by optic microscopy, the lesions showed multiple ulcers, micro thrombi and foci of fibrinoid necrosis in the small vessel walls, and yellow-brownish intramural deposits, suggestive of drug resin, with eosinophilic background and presence of a fish scale curvilinear pattern in the haematoxylin-eosin and Ziehl-Neelsen stains. Calcium deposit were not characterized on vessel walls submitted to Von Kossa's stain.

Discussion: Comparing Sevelamer with the resin found in the patient's mucosa and current data, we conclude the lesion in question is a SC deposit, since the patient had used this medication. These lesions should be considered in patients with CKD and GI symptoms, once other causes have been ruled out. Although rare or underdiagnosed, the complications of resin deposition in GI tract are severe and increase patient mortality. Further studies should be performed so that these complications can be detected and prevented.

PUB682

An Infectious Case of Calciphylaxis Prior to Renal Replacement Therapy

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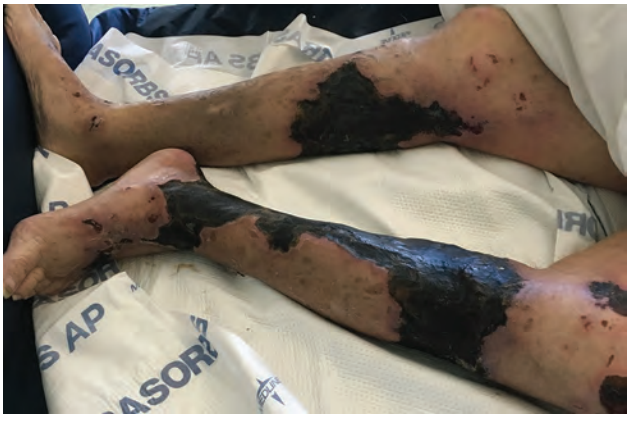
Introduction: Calciphylaxis is a rare disorder characterized by slowly progressive necrosis of skin and subcutaneous tissue. It is rarely reported in patients with chronic kidney disease (CKD) before the initiation of renal replacement therapy.

Case Description: A 62 year old male presented with multiple rapidly spreading skin lesions. His past history is significant for hypertension, diabetes mellitus type 2 and CKD stage 4 with baseline creatinine 2.8 with eGFR 25 ml/min/1.73m^2. Physical examination was notable for multiple lesions manifesting as hard black eschars with violaceous and purpuric borders on both legs. The glans penis was indurated and necrotic. Laboratory data revealed creatinine 5.9 mg/dl, BUN 85 mg/dl, Ca 6.8 mg/dl, phosphorus 4.5 mg/dl and albumin of 2.6 g/dl. Blood cultures grew Methicillin Sensitive Staph Aureus. Biopsies of the lesions demonstrated degeneration of adipose tissue with necrotic leukocytic infiltrate and thrombosis of the subcutaneous small vessels. Von Kossa staining highlighted vascular and adipocytic calcification. Biopsy findings were compatible with calciphylaxis with superimposed staphylococcal scalded skin infection. He was started on intrravenous antibiotics. Aggressive daily hemodialysis was initiated with administration of Sodium Thiosulfate three times a week. Repeat cultures were negative but the lesions continued to worsen. The patient passed away two months later.

Discussion: Calciphylaxis should be included in the differential diagnosis of skin lesions in patients with CKD. Dialysis vintage is one of the main risk factors reported in literature but the absence of this risk factor doesnn't rule it out. The patient didn't have any uremic signs or symptoms but the presence of biopsy proven calciphylasxis necessitated dialysis initiation. The rapid progression of CKD along with the superimposed staphylococcus infection are potential culprits. High morbidity and mortality are observed in both uremic and non-uremic cases of calciphylaxis.



Calciphylaxis lesions involving lower extremities

PUB683

A Case of Tumoral Calcinosis After Renal Allograft Failure

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Introduction: Tumoral calcinosis is a rare manifestation in chronic renal failure patients. This report describes a case of patient who had a living unrelated kidney transplant, but developed allograft failure within a year and developed tumoral calcinosis of the left thigh.

Case Description: A 45-year-old male was admitted to the hospital due to a five-day history of progressive left thigh swelling and pain, with no recent trauma. His medical history was notable for coronary artery disease, end-stage renal disease from membranous nephropathy, and a living unrelated kidney transplant in 2013, but developed allograft failure in 2014 and resumed home hemodialysis. Physical examination revealed normal vital signs. The left upper leg revealed swelling and tenderness over the anterior and lateral thigh, with an ill- defined palpable mass; however, no erythema, ecchymosis or wounds were noted. Sensation and reflexes were intact. Initial laboratory assessment revealed serum calcium 8.5 mg/dL (ref: 8.6-10.3 mg/dL), serum phosphorus 7.9 mg/dL (ref: 2.5-4.5 mg/dL), serum creatinine 7.20 mg/dL and intact serum PTH 636.5 pg/mL (ref: 15-65 pg/mL). MRI revealed large multi-locular cystic calcified masses occupying the anterolateral, medial and posterior compartments of the left thigh, and extending into the left gluteal region with fluid-fluid levels. The multifocal areas on MRI with hypointense T1 and T2 signal suggested osteoid matrix/calcification.

Discussion: Calcinosis develops in the soft tissues, and is usually distributed along the extensor surfaces of the large joints such as the hip, elbow, shoulder or foot. It can be differentiated from other soft tissue masses by evidence of hemorrhage and/or septations on imaging, as well as the T1/T2 high intensity signal seen on MRI with synovial sarcomas. Evidence of bone involvement is characteristic of osteosarcomas, and is not seen with calcinosis. The greater trochanteric bursa has been cited as the most common area affected for calcinosis; however, the extensive involvement of soft tissue on this patient was unlike others reported in literature, especially since the masses extended beyond the previously described periarticular distribution. Management of tumoral calcinosis from renal failure includes phosphate lowering therapy and intensification of hemodialysis treatments.

PUB684

Calciphylaxis in Non-Dialysis Patient

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Introduction: The patient is a 57 y.o. male with PMHx of alcoholic liver cirrhosis, HFpEF, CKD stage 4, recent admission due to hepatic encephalopathy, VDRF and dialysis

dependent AKI with recovery of renal function who presented from rehab in the setting of AMS and AKI.

Case Description: Patient initially presented on 2/18/18 for hepatic encephalopathy and respiratory failure due to pneumonia and hepatic hydrothorax requiring intubation. Per outside hospital records patient had baseline CKD stage 4. He developed anuric AKI thought to be secondary to ATN. He was dialysis dependent from 2/20-3/14. He was discharged to sub acute rehab off dialysis on 3/18/18 with a creatine of 1.9. On follow up visit on the outpatient clinic creatinine was 2.4. It appears that he was advised to hold diuretics for a couple of days and then resume. He had a second hospitalization on 4/16/18 due to AMS and he was found to have a creatinine of 4.6. Pt was being treated for hepatic encephatlopathy again. He was noted to have necrotic lesions on lower extremities. Necrotic lesions on the thighs and calf have been present for 2-3 weeks per wife. Biopsy confirmed calciphylaxis.

Discussion: Unique presentation of calciphylaxis in non dialysis patient with rapid progression of lesions over weeks.

PUB685

Overlap of Type 1 Diabetes (DM) and Systemic Lupus Erythematosus (SLE) – A Perilous Combination in Pregnancy and Postpartum

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Introduction: Patients with type 1 DM are at increased risk for developing other autoimmune diseases and renal biopsy remains the gold standard for diagnosing diabetic nephropathy (DN). SLE can present at any time during pregnancy and should be suspected with atypical presentations of underlying disease.

Case Description: A 24-year-old African American female with type 1 DM, hypertension (HTN), and proteinuria presented to clinic at 24 weeks gestation for new edema. Her DM was complicated by poor glycemic control (A1c 11%), retinopathy and neuropathy. Nephrotic proteinuria in her first trimester was attributed to DN. Urine sediment was unremarkable. Labs revealed creatinine (Cr) 0.85mg/dL, albumin 3.0mg/dL, hemoglobin (Hgb) 7.6g/dL, ferritin 107, iron sat 18%, normal B12 and folate. ANA was >1:640 with normal C3 and C4. She was started on oral iron. Two weeks later, Hgb was 7.6g/dL and she was admitted. Hgb electrophoresis, bilirubin and LDH were normal. Direct coombs test was negative and peripheral smear showed rare schistocytes. Double stranded DNA antibody (dsDNA) was pending at discharge but returned positive. She was re-admitted a week later with headaches and HTN. Cr was 1.11mg/dL and UP/C was 8.5g. She delivered via c-section at 29 weeks and 6 days due to superimposed preeclampsia. Five days post-discharge, she presented with fatigue. Blood pressure was 150/89, Hgb 8.1g/dL, glucose 336mg/dL, Cr 1.73mg/dL and UP/C 11.7g. CXR showed cardiomegaly and echocardiogram (TTE) revealed a large circumferential pericardial effusion. Rheumatology felt she met criteria for SLE and began pulse corticosteroids. Following therapy, glucose rose to 970mg/dL requiring the ICU. Renal biopsy was performed and revealed DN with nodular glomerulosclerosis with segmental tuft sclerosis and moderate to severe interstitial fibrosis and tubular atrophy. She was treated with a steroid taper and hydroxychloroquine. One month later, TTE showed decreased effusion and dsDNA was negative.

Discussion: This case highlights the diagnostic conundrum of coexisting autoimmune diseases and the cumulative adverse maternal outcomes that can arise from both diseases and their treatments. Failure to respond to iron therapy in pregnancy should prompt further investigation and may suggest a misdiagnosis. Earlier renal biopsy may have allowed for lower steroid dose and avoided ICU transfer.

PUB686

Prolonged Hemodialysis for Refractory Lactic Acidosis Secondary to Metformin Overdose

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Introduction: Metformin is a biguanide oral antihyperglycemic agent that has been used in the United States since 1995 for treatment of type 2 diabetes mellitus. According to the American Diabetic association, recommended as the first drug of choice. Except in overdose situations, the association of metformin with lactic acidosis is quite rare with an estimated incidence of 3 per 100,000 patient-years. When it does occur, metformin-associated lactic acidosis is most often associated with an intercurrent disease and renal insufficiency. A 2009 review article could identify only 22 cases of metformin overdose. We describe a patient with metformin overdose who was successfully treated with hemodialysis.

Case Description: A 57 year old male with past medical history of type 2 diabetes mellitus and hypertension was brought to the emergency department with altered mental status. His wife reported that he has become increasingly lethargic and fatigued over the course of a week. In the emergency department, due to low Glasgow Coma scale, he was intubated. The laboratory test revealed severe metabolic acidosis secondary to lactic acidosis and acute renal failure. His values were: BUN 103 mg/dL, serum creatinine 11.2 mg/dL, carbon dioxide 7 mEq/L, anion gap 40, pH 6.78 with a lactic acid level greater than 12.7 mmol/L. He was evaluated by Nephrology and underwent emergent hemodialysis, which he underwent twice without improvement in his lactic acid. Upon re-evaluation, his wife revealed that he was taking metformin 2000 mg daily. A third hemodialysis decreased the value for lactic acidosis. After 7 days of inpatient treatment with antibiotics and hemodialysis, he was finally extubated. His renal function improved with creatinine of 1.7 mg/dl on the day of discharge.

Discussion: Metformin is cleared by the kidney with about 90% of drug eliminated by glomerular filtration and tubular secretion in 12 hours. Thus, renal insufficiency is a risk factor for drug accumulation. Treatment includes use of NaHCO3. Dialysis therapy has benefit of correcting the acidosis while removing the toxin. Prolonged hemodialysis is indicated in patients with severe overdose.

DATE	TIME	PH	HCO3 (MEQ/L)	DIALYSIS	LACTIC ACID (MMOL/L)	pCO2(mmHg)
11/28	1710	6.78	7	4 hrs	12.7	14.6
11/28	1935	6.63	5	4 hrs	14.0	16.3
11/29	0100	7.03	7	3 hrs	12.9	22.9
11/29	2037	7.25	14	stopped	5.1	21.4

PUB687

Achieving Equilibrium Is Not That Easy: A Case of Dialysis Disequilibrium Syndrome

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Introduction: Dialysis disequilibrium syndrome (DDS) is an increasingly rare neurological syndrome attributed to cerebral edema and osmotic shifting following dialysis. Symptoms vary in severity from restlessness and headache to less commonly seizure, coma, or death. Risk factors include first dialysis session, markedly elevated BUN, and severe acidosis. As there is no specific treatment, prevention is essential.

Case Description: A 27-year-old female with end stage renal disease (ESRD) on hemodialysis (HD) and antiphospholipid syndrome on warfarin presents with generalized weakness, anasarca, fatigue, and gingival bleeding in the context of noncompliance with HD for four weeks. She was afebrile and hypertensive with blood pressure of 188/120. Labs significant for BUN/creatinine 231/22.6 mg/dL, sodium 141 mEq/L, potassium 7.2 mEq/L, bicarbonate 7 mEq/L, hemoglobin 5.2 g/dL, platelets 119,000/mm^3, and INR 1.8. DIC screen was negative. She was transfused and emergent HD initiated. Shortly after her 3-hour HD session, the patient had a seizure complicated with hypoxia and subsequent cardiac arrest. She was resuscitated for two minutes with return of spontaneous circulation and was intubated. Once she was stabilized, CT head was negative for hemorrhage or stroke, BUN 83 mg/dL, bicarbonate 15 mEq/L, glucose 122 mg/dL, sodium 141 mEq/L, potassium 3.3 mEq/L, calcium 8.3 mg/dL, magnesium 1.9 mg/dL. The patient was diagnosed with DDS and she was initiated on continuous renal replacement therapy (CRRT) without ultrafiltration. She ultimately achieved neurological recovery, was extubated and transitioned back to intermittent hemodialysis successfully after two days.

Discussion: Prevention of DDS involves initiating HD cautiously with low flow rates, short duration, and increased frequency. Care must be taken on initiation of HD not only in new dialysis patients, but also in noncompliant ESRD patients with marked metabolic disturbances as presentd in this case. Treatment is largely supportive as no benefit has been proven with agents aimed to decrease intracranial pressure such as mannitol or hypertonic saline.

PUB688

Calcium - To Drip or Not to Drip: The Curious Case of Masked Hypercalcemia on Regional Citrate

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Introduction: Continuous renal replacement therapies (CRRT) has several short-term advantages. However, there is a paucity of data on the long-term effects when used in End Stage Renal Disease (ESRD). Anticoagulation is frequently required to maintain filter patency. Regional citrate is the recommended form and functions most effectively when the post-filter ionized calcium (iCa) is kept ~ 0.2-0.4 mmol/L while a calcium drip maintains the systemic iCa ~ 1.0-1.3 mmol/L. We describe a case of a patient on regional citrate with hypercalcemia secondary to prolonged immobilization and history of tertiary hyperparathyroidism(THP) which was masked by the use of the regional citrate protocol.

Case Description: A 67-year-old male with ESRD and THP presented for shortness of breath. His hospital stay was prolonged due to development of small bowel obstruction associated with perforation and hemodynamic compromise, hence was initiated on CRRT. Due to frequent filter clotting, a regional citrate protocol with prefilter Anticoagulant Citrate Dextrose Solution A (ACD-A) was initiated and a 2% calcium gluconate drip was used systemically. While on CRRT with regional citrate, he was requiring only minimal calcium gluconate at 20ml/hr. In subsequent days, this drip was stopped due to elevated systemic iCa. We continued his pre-filter citrate drip and were able to maintain his post-filter iCa between 0.2-0.4 mmol/L per protocol. In evaluating his hypercalcemia, he was found to have 25-OH vitamin D level of <7.0 ng/mL, 1,25-OH Vitamin D was <8pg/mL, PTH was 260.9 pg/mL (off cinacalcet) with a level of 777.8 pg/mL on admission. Alkaline phosphate was 242 IU/L, Bone-specific alkaline phosphate was 53.7 mcg/L, iCa while off the calcium drip was 1.33-1.24 mmol/L with a total calcium of 9.7-9.4 mg/dL and a citrate requirement of 280cc/hr.

Discussion: Regional citrate is the recommended form of anticoagulation on CRRT. Prolonged immobilization in patients with ESRD and THP can liberate calcium from bone which can be further exacerbated by the effect of chronically elevated PTH. This hypercalcemia may be masked if citrate is used for CRRT. If left up to the protocol, patients can come off calcium drips with their bone calcium stores acting effectively as a calcium drip. Given this increased bone mineral loss alternate therapy must be instituted as soon as the subject becomes hemodynamically stable.

PUB689

Cardiac Arrest from Baclofen Overdose: Dialysis to the Rescue

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Introduction: Baclofen overdose often presents with CNS and respiratory depression, leading to coma requiring mechanical ventilation. Seizures, hypothermia and cardiac instability have also been reported. Treatment is primarily supportive in those with normal kidney function. We report a case of baclofen overdose complicated by bradycardia, sinus pause, and cardiac arrest treated with hemodialysis.

Case Description: A 54 year old African American female with history of bipolar and schizoaffective disorder was found unresponsive and brought to the emergency department. The patient had allegedly overdosed on 40 tablets of baclofen (10 mg) 2 hours prior. On arrival, her GSC was 3/15, pupils dilated, with agonal breathing. Patient was intubated promptly and placed on mechanical ventilation. Laboratory data were normal; including creatinine of 0.76 mg/dl and negative urine drug screen. Poison control recommended supportive care. 9 hours after admission, patient became hypotensive, bradycardic and was noted to have frequent sinus pauses lasting 20-30 seconds leading to asystole. Following successful resuscitation she was emergently dialyzed which resulted in marked improvement of her clinical status and extubation the next day.

Discussion: Baclofen acts as an inhibitory neurotransmitter and is commonly used to treat spasticity. The kidney primarily excretes Baclofen. However there have been reports where hemodialysis has been used for Baclofen overdose even in patients with normal renal function. Properties that enhance dialytic clearance include its low molecular weight, low volume of distribution and relatively low protein binding. 79% of the drug is cleared with a 4 hour dialysis session leading to a reduction in half life from 7 to 3 hours. This shortens recovery time. This case teaches us that dialysis should be considered early in those with life threating manifestations.

PUB690

Acute Hepatic Encephalopathy: An Underexplored Indication for Renal Replacement Therapy

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Introduction: Hepatic encephalopathy (HE) is associated with high mortality. While the key role of serum ammonia level (SAL) in development of HE has long been recognized, emerging evidence points to distinct mechanisms underlying chronic alterations in neural metabolic functions and acute changes in cerebral perfusion. In acute HE, formation of glutamine, a strong osmolyte, leads to cerebral edema as ammonia crosses the blood–brain barrier at high levels.

Case Description: A 52-year-old man with liver cirrhosis and esophageal varices presented with hematemesis and decline in mental status. He was afebrile, normotensive, and confused. Laboratory studies showed hemoglobin level 6.8 g/dL, platelets 9000/mm^3, serum creatinine 0.5 mg/dL and SAL 176 μmol/L (normal <35). He received intravenous fluids, blood transfusion, and antibiotics. However, his mental status deteriorated further with development of decerebrate posturing; he was intubated. Head CT was unremarkable. Bleeding varices precluded nasogastric tube placement while administration of lactulose per rectum was high risk due to thrombocytopenia. Hence, the decision was made for renal replacement therapy (RRT), starting with hemodialysis (HD) followed by continuous venovenous hemofiltration (CVVH). Despite 4 hours of HD with a high flux filter, the post-HD SAL was as high as 262 μmol/L making it unlikely for the patient to survive had the RRT started with delay. SAL progressively declined to 71 μmol/L, 19 hours post-RRT. Improvement in his mental status closely mirrored the reduction in SAL. Endoscopy could be performed to stop the bleeding, RRT was stopped, and he was extubated.

Discussion: Rapid lowering of SAL remains the primary goal of therapy in HE. Ammonia is readily dialyzable as it is a non-protein-bound small molecule. While HD is a plausible option when less invasive medical options are not feasible, post-HD rebound could represent a major drawback. To minimize this effect, we used CVVH in conjunction with HD, which could also portend a salutary impact through temperature control. Using a combined RRT strategy helped stabilize the patient so the underlying cause of HE (i.e. bleeding varices) could be treated. This case coupled with previous reports represents an underexplored indication for RRT and highlights the significance of an interdisciplinary approach for efficient treatment of these patients.

PUB691

Liver Dysfunction from Immune Reconstitution Syndrome After Treatment of Hepatitis C Virus Infection in ESRD Patient

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Introduction: Hepatitis C virus (HCV) infection is associated with worse outcomes in ESRD patients. Elbasvir/grazoprevir-a combination direct antiviral agent (DAA) demonstrated safety and effectivines in treating ESRD individuals with genotype(GT)-1 HCV infection. We report a case of autoimmune liver injury in a hemodialysis(HD) patient after successful HCV eradication.

Case Description: A 57-year old female with ESRD was noted to have yellow discoloration of the dialyzer filter at the end of HD session 2 days prior to completion of a 12-week elbasvir/grazoprevir course for chronic HCV GT-1A infection resulting in a sustained virologic response. She reported insidious onset of pruritus, vague abdominal pain, nausea and reduced appetite. On exam she had scleral icterus and diffuse abdominal tenderness. Laboratory investigations showed hypercholesterolemia, alkaline phosphatase rise from baseline of 184U/L to 548U/L with liver-specific fraction of 64%. Total and direct bilirubin were 4.6mg/dL and 3.9mg/dL. Computed tomogrpahy scan revealed new hepatomegaly. Cholestasis symptoms persisted 8 months after completion of DAA. In addition, the patient had new elevated antimitochondiral antibodies (AMA 68U, normal <20U). A liver biopsy was performed as a part of kidney transplant evalution. Unexpectadly, it showed the biliary pattern of liver injury consistent with primary biliary cholangitis (PBC). Ursodeoxycholic acid was initiated but stopped due to intolerable gastrointestinal side effects. Despite no additional therapy, pruritus and hyperbilirubinemia gradually resolved 18 months after completion of DAA; however, AMA levels remained elevated.

Discussion: HCV infection is associated with chronic state of antigenemia and resultant immune activation and impaired function of several immune cell populations. It was shown that HCV eradication can lead to reactivation of chronic hepatitis B and recurrent hepatocellular carcinoma. We hypothesize that PBC-like liver injury in the present case was due to immune reconstitution inflammatory syndrome and imbalance of immune-regulatory mechanisms associated with eradication of HCV infection rather than *de novo* PBC. Potential benefits of HCV treatment in ESRD patients should be balanced with possible complications, reduced ability to receive HCV positive organ for kidney transplantation and increased cost of care.

PUB692

Unexpected Allergic Reaction in a Patient Receiving Chronic Hemodialysis

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Introduction: Anaphylactic reactions usually occur during the initial dialysis session. We present a patient on chronic hemodialysis who suddenly develops an anaphylactic reaction to a part of the dialysis apparatus.

Case Description: 34-year-old man with ESRD presented to the emergency department with hyperkalemia and dyspea secondary to volume overload after missing outpatient dialysis. Hemodialysis was started using his outpatient prescription (1). Two minutes after initiating dialysis, the patient became hypoxic and hypotensive, requiring emergent intubation and vasopressors. He was started on CRRT (2) and had no adverse reactions. The next day, he was weaned from pressors and extubated. Hemodialysis was again attempted (3), but he developed hypotension and hypoxia. At this point, there was suspicion for a dialysis-related issue. Hemodialysis was attempted using a different dialyzer (4), double priming of the extracorporeal circuit, and pre-medication with antihistamines, but he again developed anaphylactic symptoms. Since he tolerated CRRT with NxStage, hemodialysis using the NxStage machine was ultimately performed with no issues (5). He is currently dialyzing at his outpatient unit with this set up without incident.

Discussion: This chronic dialysis patient likely had a severe allergic reaction to ethylene oxide sterilant used for dialyzer components. Type A reactions (anaphylactoid) occur within the first five minutes, and are an IgE medicated process, causing hypotension and possibly shock. Patients with prior history of allergic reactions during dialysis are at higher risk of type A reactions, so it is unexpected that this patient developed a reaction after receiving outpatient dialysis treatments for several years without incident. Because this patient tolerated CRRT with the Purema cartridge, the reaction was thought to be due to the sterilization method, specifically to the tubing. It is unclear why he suddenly developed these symptoms. One should always consider Type A reactions in patients on chronic dialysis who develop instability while receiving dialysis.

	1	2	3	4	5
Machine	Fresenius	NxStage	Fresenius	Fresenius	NxStage
Dialyzer/Sterilant	Optiflux-e beam	Purema-gamma	Optiflux	Exceltra-gamma	Purema
Circuit/Sterilizer	Medisystems Streamline-ethylene oxide	Purema	Medisystems Streamline	Medisystems Streamline	Medisystems Streamline Expressv-gamma
Modality	HD	CVVH	HD	HD	HD
Reaction	Y	N	Y	Y	N

PUB693

Effect of Intermittent Hemodialysis (iHD) on Patient and Left Ventricular Assist Device (LVAD) Hemodynamics: A Case Report

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Introduction: IHD in patients with a LVAD is challenging due to non-physiological and complex circulatory hemodynamics, especially in modern LVAD which have continuous instead of a pulsatile blood flow. There is a general lack of literature in this field. We present a case of an ESRD patient with LVAD in whom we studied the hemodynamics effect of iHD.

Case Description: 42-year-old male with past medical history of Non ischemic cardiomyopathy with Ejection Fraction of 10-15% on Destination LVAD (Heart ware continuous flow, centrifugal), ESRD on IHD for 1.5 years due to cardiorenal syndrome. We prospectively collected pre and post dialysis Mean Doppler Pressure (MDP, mmHg), Cardiac Output (CO, Liters/min), Heart rate (HR, beats per min BPM) Dialysis time, and Ultrafiltration volume; from 35 consecutive treatments. MDP mmHg was measured as first brachial artery doppler signal after manual cuff deflation (Lanier et al), CO were recorded from LVAD device monitor and HR was collected using continuous chest lead telemetry. Paired 2 tailed T-test was used for within group difference, Pearson's r was used for correlation analysis. There was a statistically significant improvement in CO, reduction in MDP and

increase in HR(table 1). The average Ultrafiltration volume was 3.4±0.7 Litres and average dialysis time was 3.7±0.6 hours. There were 3/35 post ultrafiltration hypotensive episodes (MDP < 55mmHg), all were asymptomatic and resolved spontaneously. Midodrine was not required in any instances. Interestingly there was no correlation between ultrafiltration volume and change in cardiac output (r2 = 0.013) or change in MDP (r2 = 0.002).

Discussion: Hemodialysis in LVAD patients remains challenging. Our case showed that iHD is tolerated well and significant increased in CO occurred after UF despite decrease in the MDP. We recommend further larger scale studies in this regard.

Patient Hemodynamic and LVAD CO changes with hemodialysis

n=35 (no of treatments)	Pre dialysis, average± stdev	Post dialysis, average± stdev	post-pre dialysis, average± stdev	p value
MDP (mmHg)	66.9 ± 5.3	62.7 ± 5	-4.2±5.8	<.0001
Cardiac Output (L/min)	6.5±1.5	7.2±0.4	0.65±0.5	<.0001
Heart Rate (bpm)	68±9.6	73.4±12	5.3±10	<.004
UF volume (liters)	3.4±0.7			
Dialysis time (hours)	3.7±0.6			

Stdev= standard deviation

PUB694

Dialyzing Massive Metformin Overdose

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Introduction: Metformin is a biguanide oral antihyperglycemic, prescribed to over 120 million people globally. Metformin associated lactic acidosis (MALA) is a serious complication of metformin overdose. We present a case of massive metformin overdose and MALA successfully managed with sequential rounds of hemodialysis (HD) and continuous venovenous hemodialysis (CVVHD).

Case Description: A 19-year-old male was admitted after taking approximately 360 pills of 500 mg metformin in a suicide attempt. Initial serum lactic acid (LA) level was 5.0 mmol/L and metformin level was 350 mcg/mL (therapeutic 0-2 mcg/mL). He was started on a bicarbonate drip and underwent emergent HD for 4 hours; however, LA worsened to 27 mmol/L and developed acute respiratory failure and hemodynamic compromise requiring mechanical ventilation and vasopressor support. LA had worsened to 39 mmol/L with an anion gap (AG) of 40. Patient also developed acute kidney injury (AKI) with a peak creatinine of 4.4 mg/dL. Blood gas analysis showed pH 7.02, pCO2 23 mm Hg and bicarbonate 6.0 mmol/L. Patient underwent successive rounds of HD for 6 hours with a high flux dialyzer and then switched to CVVHD with a dialysate flow rate of 112 ml/kg/hr. The total duration of renal replacement therapy (RRT) was 60 hrs after which AKI resolved and serum bicarbonate, LA and AG normalized.

Discussion: Metformin has a relatively high volume of distribution (1-5L/kg) and its toxicity is associated with a mortality of >38% with levels above 50 mcg/mL. MALA poses a multifaceted challenge including drug removal, correction of acidosis and prevention of rebound. Our case was unique for various reasons. The magnitude of toxicity was massive and patient was dialyzed three times in 24 hrs using a high flux, high surface area dialyzer and metformin level decreased from 350 mcg/mL to 8.7 mcg/mL. To prevent rebound, patient was continued on high volume dialysate at 112 ml/kg/hr with CVVHD achieving clearance rates of approximately 130 mL/min. The total duration of RRT of 60 hours was much shorter compared to previously reported cases involving low flux, low-efficiency dialyzers that required RRT for days to weeks. This resulted in earlier resolution of MALA and may have influenced renal recovery. Sequential use of high flux, high surface area dialyzer and high volume CVVHD can decrease metformin levels precipitously, prevent rebound MALA and promote early renal recovery.

PUB695

Baclofen Neurotoxicity: A Case for More Stringent Guidelines

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Introduction: Baclofen is a Y-aminobutyric acid (GABA) derivative whose inhibitory effect at the motor neuron synaptic reflexes is utilized in muscle spasticity reduction. Baclofen elimination occurs primarily through the kidneys (69% +/- 14%) and therefore is severely reduced in patients with renal insufficiency; hemodialysis (HD) clearance of Baclofen is 128mL/min. Baclofen neurotoxicity in end stage kidney disease (ESKD) is a major concern.

Case Description: A 44 year-old male with ESKD on scheduled HD, diabetes mellitus II, hypertension, and diastolic heart failure was admitted for acute encephalopathy. One day prior to presentation, the patient visited a local clinic for leg pain for which he was prescribed Baclofen 10mg two times daily. After taking two tablets as instructed, he had progressive encephalopathy leading to hospital admission. At presentation, he had notable dyskinesia and encephalopathy and was emergently intubated for airway protection. Head and chest imaging was unremarkable and infectious workup was negative. Nephrology was consulted for emergent HD for metabolic clearance. EEG was consistent with metabolic-toxic etiology. He received three consecutive daily HD sessions, was successfully extubated, returned to baseline mental status, and was discharged on day five of hospital admission.

Discussion: Our case highlights potentially lethal Baclofen neurotoxicity in patients with ESKD. Avoidance of Baclofen in this population has been recommended. However, if necessary, prescribers are advised to start at a low dose with close monitoring for adverse effects. From our experience and detailed literature review, even a small/renal-adjusted dose of Baclofen in an ESKD patient may lead to rapid subsequent neurotoxicity. Despite recognition by nephrologists of this severe adverse effect, Baclofen is still being prescribed to ESKD patients. This may be due to the fact that there is no clear contraindication for its use in this population. Very often, nephrologists are not the providers first in line treating common complaints such as muscle spasms/pain for which Baclofen is often prescribed. Our case highlights the need for clearer Federal Drug Administration (FDA) guidelines for the cessation of Baclofen use in patients with ESKD and advises for greater education to primary care and emergency care providers of baclofen neurotoxicity in patients with ESKD.

PUB696

Methotrexate Toxicity Following Treatment of a Caesarean Scar Pregnancy

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Introduction: Caesarean scar pregnancies(CSP) require treatment with methotrexate(MTX). Local MTX was not thought to be systemically absorbed. Our end stage renal failure(ESRF) patient developed severe MTX toxicity following local MTX therapy.

Case Description: A 30-year-old woman with ESRF maintained on haemodialysis(HD) presented with an unplanned pregnancy. She previously had a vaginal delivery followed by a caesarean section. An ultrasound scan at 8 weeks showed an ectopic CSP. This was managed with an intra-sac injection of 50mg MTX Post-procedure she deteriorated with fever, mucositis, rash, neutropenia and thrombocytopenia. On Day 5 MTX toxicity was considered and a MTX level was 0.30umol/L. Folinic acid and granulocyte colony stimulating factor were started. Despite this she developed severe neutropenia had a prolonged hospital admission with a protracted recovery.

Discussion: Management of pregnancy in dialysis patients is challenging. This case was further complicated by a CSP, a condition where ongoing pregnancy is ill-advised and complications of uterine rupture, severe haemorrhage and death can occur. Treatment options include systemic or local MTX, uterine artery embolization and surgery. MTX preferentially affects rapidly dividing cells, e.g. blastocysts and stem cells. In those with normal renal function MTX toxicity can be seen in patients receiving very high doses. Pre-emptive folinic acid and careful monitoring of MTX concentration may prevent toxicity. There are reports of MTX toxicity and death in patients on dialysis. There have been 2 cases of MTX toxicity in dialysis patients after systemic MTX administration for ectopic pregnancy, 1 fatal. There have been no reported cases of MTX toxicity following intra-sac MTX administration. Local administration of MTX for management of CSP has the theoretical advantage of less systemic exposure to MTX. However, a previous study in tubal ectopic pregnancies showed the mean peak serum level of MTX after local injection to the ectopic amniotic sac was not lower compared with systemic dosing. Caesarean scar ectopic incidence is increasing with the growing trend of operative deliveries. Improved outcomes and reduction of systemic toxicity in ESRF may be achieved with dose reduction, methotrexate concentrations, early folinic acid therapy, increased frequency of high flux dialysis and strong clinical index of suspicion for MTX toxicity.

PUB697

Excessive Elevation of Serum Phosphate During Tumor Lysis Syndrome: Lessons Learned from a Particularly Challenging Case

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Introduction: Tumor lysis syndrome in the modern era of allopurinol and recombinant uricase administration may present to Nephrologists with predominant abnormalities of phosphorus and calcium. Indications and choices of renal replacement therapy (RRT) may need to be customized to individual scenarios.

Case Description: An 18-year-old male received first cycle intensive chemotherapy for Burkitt lymphoma and developed massive tumor lysis syndrome. Lactate dehydrogenase peaked at 9,105 [130-250 U/L] with undetectable serum haptoglobin values. Initial medical therapy consisted of recombinant uricase enzyme, intravenous isotonic sodium-bicarbonate administration and oral phosphorus binders. Nonetheless, within 4 days he developed excessive hyperphosphatemia (up to 21.4 mg/dl) with acute kidney injury (serum creatinine 2.2 mg/dL), oliguria, hyperkalemia (6.2 mM), hypermagnesemia (3.1 and hypocalcemia (corrected calcium 7 mg/dL). The competing risk of dialysis disequilibrium syndrome vs. insufficient control of hyperphosphatemia prompted us to utilize an initial session of conventional dialysis session (HD) (4 hour session, with blood flow 200 mL/min, dialysate flow of 400 mL/min; electrolyte composition: sodium 150 mM/L; calcium 2.5 mEq/L), with simultaneous mannitol administration (12.5 gm) at two and four hours after start. Stability of serum osmolality was demonstrated (322 and 319 mOsm/kg before and after, respectively). Serum phosphate improved to 8.7 mg/dL; this improvement, however, may also partially represented test interference by mannitol. Thereafter, high-volume slow continuous hemofiltration started (initial hemofiltration rate 30 mL/kg/h, [2 L/h]); subsequently escalated to 3.5 L/h), where serum phosphate remained difficult to control and even rose transiently (13; 11 mg/dL) during the next 24 h. He had excellent tolerance of these therapies and recovered renal function uneventfully.

Discussion: The presented exceedingly high phosphorus remains the highest serum phosphorus witnessed in our institution. Early and aggressive RRT may involve upfront administration of both an initial conventional HD session to debulk phosphorus load and subsequent continuous modality, until full correction is achieved.

PUB698

Bullous Pemphigoid in Patients with ESRD: A Case Series

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Introduction: Bullous Pemphigoid (BP) is an uncommon autoimmune subepithelial blistering disease. Very few single case reports of BP have been described in ESRD population. Prevalence and etiology of BP in hemodialysis (HD) patients (pts) is unknown. We describe a case series of 3 pts with ESRD from a single outpatient dialysis center diagnosed with BP.

Case Description: Case 1: 62 yo woman (W) developed BP during cessation of immunosuppression (IS) for her failed second kidney transplant (KTx). Native kidney failure was presumed secondary to HTN, first kidney allograft worked for 6 years and failed due to non compliance. She was on HD for 9 years before getting a second KTx which failed after 4 years due to rejection. She was restarted on HD and her IS decreased. She developed BP as her IS was decreased. She was restarted on high dose prednisone with prolonged taper. She is now on low dose prednisone and mycophelonate mofetil (MMF). Case 2: 44 yo W with type 1 DM and HTN, ESRD on HD who also developed BP immediately after cessation of IS for her 16 yr old failed KTx. She was treated with prednisone 60 mg with prolonged taper. She was unable to get MMF due to insurance issues and did not tolerate azathioprine. She could not be tapered off steroids and was kept on maintenance low dose prednisone with intermittent high doses for flares. Case 3: 52 yo W with DM, HTN, ESRD on HD who underwent bilateral below knee amputations due to recurrent infections and osteomyelitis. Her wound healing was slow and required prolonged wound care. She developed acute onset of blisters in both stumps about 2 years after surgery. Skin biopsy confirmed stump-related BP which resolved with short length of prednisone taper.

Discussion: Etiology of BP in HD pts remains to be determined. It has been speculated that unmasking of epitopes at the AV fistula/graft site could be playing a role. In KTx pts, cessation of IS could unmask de novo BP or allograft epitopes from a kidney undergoing rejection. BP should be considered high in the differential for blistering disease in HD pts (especially those with failed KTx) as early diagnosis would initiate appropriate therapy.

PUB699

Dialysis Disequilibrium Syndrome with Proper Precautions: A Case Series

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Introduction: Dialysis disequilibrium syndrome (DDS) is an increasingly rare syndrome in modern dialysis practice. It can manifest as altered mentation, seizure, coma and even brain death. Pathogenesis is believed to be the result of rapid reduction in serum osmolality, and water movement into brain leading to cerebral edema. Among the risk factors is first dialysis session and significantly elevated blood urea nitrogen (BUN). To prevent DDS, small dialyzers and slower blood flow rates are employed whenever possible. We present two cases of DDS that developed following proper dialysis initiation precautions.

Case Description: Patient A: 70-year-old female with no significant history of renal disease presented with slurred speech and malaise. Laboratory workup revealed elevated BUN and creatinine (cr), hyperkalemia and severe metabolic acidosis (Table-1). After pretreatment with mannitol, dialysis was started with plan for 2 hours of slow hemodialysis (blood flow 200 ml/min). 90 minutes into the dialysis session the patient developed altered mentation. Dialysis was stopped and her symptoms resolved shortly after. Delivered hemodialysis dose: Kt/V of 0.61 (URR = 43%). **Patient B:** 56-year-old female with no significant history of renal disease presented with headaches and somnolence. Laboratory workup revealed elevated BUN and cr, hyperkalemia, and severe acidosis (Table-1). Dialysis was started with plan for 2 hours of slow haemodialysis (blood flow 250 ml/min) via small dialyzer (F16). 90 minutes into the dialysis session, she had a witnessed seizure. Dialysis was stopped and lorazepam was administered with subsequent resolution of seizure. Delivered hemodialysis dose: Kt/V of 0.71 (URR = 48%).

Discussion: DDS, although rare, is still a possible complication in new start dialysis patients. Dialysis initiation precautions that include small dialyzers and slower blood flow rates should be employed whenever possible. In spite of these precautions, DDS can occur with Kt/V and URR well below the target of 1.2 and 65% respectively. Larger studies are required looking into traditional and novel mechanisms and risk metrics of DDS in modern dialysis practice.

Table-1

Patient	Initial Laboratory Workup	BUN, cr after Dialysis
A	BUN: 249, cr: 23.6 K: 7.1, pH: 6.9	BUN: 142 cr: 13.6
B	BUN: 144, cr: 27.2 K: 6.1, pH: 7.093	Bun: 80 cr: 17.7

BUN & cr (mg/dL), K (mmol/L)

PUB700

A Tale of Two Cryptococcoses: Risks in HIV-Negative Hemodialysis Patients

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Introduction: Cryptococcosis is an opportunistic fungal infection typically associated with advanced HIV/AIDS. We report two cases in HIV-negative patients with end-stage renal disease (ESRD) on hemodialysis (HD).

Case Description: Patient 1 is a 47-year-old male with a history of ESRD secondary to type 2 diabetes mellitus and hypertension on maintenance HD with a tunneled dialysis catheter (TDC) who presented with two weeks of headache and fever. Lumbar puncture revealed an elevated opening pressure, and diagnosis of cryptococcal meningitis was made by cryptococcal antigen positivity in the cerebrospinal fluid. Peripheral and TDC blood cultures were negative. The patient improved with antifungal therapy and placement of a ventriculoperitoneal shunt due to persistent intracranial hypertension. Patient 2 is a 67-year-old male with a history of hepatitis C related cirrhosis and ESRD on maintenance HD with a TDC who presented with subacute abdominal pain, progressive ascites, and fever. Paracentesis was not consistent with spontaneous bacterial peritonitis; however, cultures of the peritoneal fluid grew *Cryptococcus neoformans*. Further workup revealed disseminated disease in the ascites, cerebrospinal fluid, and serum. His hospital course was complicated by sepsis and death four weeks after initiating antifungal therapy.

Discussion: Although ESRD is associated with immune dysfunction, the pathogenesis of cryptococcal infections in HIV-negative HD patients is not well described. Both patients presented here were HIV-negative Hispanic males from low socioeconomic backgrounds who had initiated HD within the last six months via TDC, and were found to have CD4 T-lymphocyte counts less than 400. ESRD is associated with both impaired T-lymphocyte function and lymphocytopenia, likely predisposing patients to fungal infections. Practice guideline recommendations for treatment in this population are limited. Catheter removal is associated with improved mortality in peritoneal dialysis patients, but this has not been studied in TDCs. Though challenging, early diagnosis improves morbidity and mortality. In conclusion, ESRD patients are at increased risk for cryptococcal infections, regardless of HIV-status. Further studies are needed to better understand the pathogenesis and treatment of cryptococcosis in ESRD patients.

PUB701

Treatment of Idiopathic Hyperammonemia Syndrome in a Post-Lung Transplant Patient

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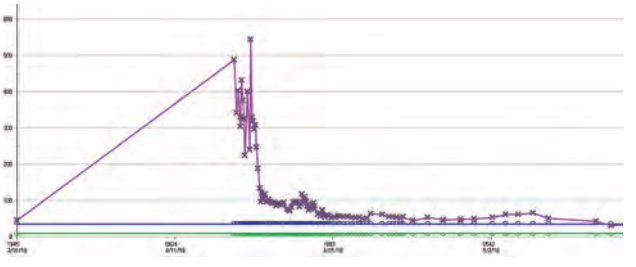
Introduction: Idiopathic hyperammonemia syndrome (IHS) is a rare but well-described phenomenon occurring after solid organ transplantation. Here, we describe a case of IHS in a lung transplant recipient, which required renal replacement therapy as well as antibiotics and nitrogen-scavenging agents and was eventually attributed to donor-derived infection with a urea-splitting organism.

Case Description: A 62-year-old gentleman with a history of chronic obstructive pulmonary disease underwent bilateral orthotopic lung transplantation. He became acutely obtunded on post-operative day 13, and labs revealed an ammonia level of 489 umol/L (post-op day 0 ammonia level was 45). Renal replacement therapy was initiated with intermittent hemodialysis followed by continuous venovenous hemodialysis, with marked reduction in blood ammonia levels to less than 100 umol/L within 48 hours. He was empirically started on levofloxacin as well as Ammonul, and he was noted to have a large pericardial effusion. The pericardial fluid grew *Mycoplasma hominis*, which is a urea-splitting organism that has been associated with hyperammonemia. With the combination of prompt renal replacement therapy, nitrogen-scavenging agents, and antibiotics, the patient's ammonia levels returned to normal, and he was discharged home on post-operative day 59.

Discussion: (1) Review the metabolism of ammonia in normal and pathologic states (2) Recognize IHS due to urea-splitting organisms in the immediate post-operative period following lung transplant (3) Discuss renal replacement therapy options for lowering blood ammonia levels Ammonia is produced by amino acid metabolism and converted to urea by the liver. The brain and skeletal muscle also metabolize small amounts of ammonia by generating glutamine, which is then metabolized by the kidney to regenerate ammonia and subsequently excreted in the urine. Ureaplasma and Mycoplasma species produce urease and generate ammonia, and disseminated infection or transmission from a donor organ can cause IHS. There are no current guidelines to initiate dialysis in patients with hyperammonemia, though intermittent hemodialysis removes ammonia most efficiently.



PUB702

Renal Replacement Strategy in a Critically Ill Patient with Severe Azotemia and Hyponatremia

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Introduction: Severe Azotemia and hyponatremia in AKI with CKD is always difficult to manage in critically ill patients who end up requiring renal replacement therapy. Rapid correction of hyponatremia and reduction of BUN can lead to osmotic demyelination and dialysis disequilibrium syndrome. We are presenting a case of 66 year old female with multiple comorbids requiring Continuous Venovenous Hemodialysis(CVVHD) for severe uremia and hyponatremia.

Case Description: A 66 year old female with past medical history of CKD stage 3b with baseline creatinine(Cr) of 1.2 mg/dL, DM2, hypertension, depression, hepatitis C, CVA with residual aphasia, seizures, and dysphagia presented from nursing home with bradycardia, hypothermia and hypotension was found to have non-oliguric AKI over CKD with significantly raised BUN of 327 mg/dL, Cr of 4.17 mg/dL, hyperglycemia of 430 mg/dL with a serum sodium(Na) of 116 meq/L corrected for glucose to 121 meq/L, potassium of 5.5 meq/L, chloride of 80 meq/L, HCO3 of 15 meq/L with high anion gap metabolic acidosis secondary to lactic acidosis, respiratory acidosis and anemia with hemoglobin of 3.9 gm/dL due to upper GI bleed. She was initially resuscitated with IV fluids, IV bicarbonate, started on pressors, insulin infusion for hyperglycemia, IV Proton pump inhibitors for the GI bleed and later on intubated due to respiratory distress. She was started on CVVHD due to diffuse EKG changes. Her calculated dialysate dose was 2.5 L/hr (30ml/kg for a 88kg) but we started her at 1L/hr. We also calculated the urea reduction ratio(URR) via Kt/V= -ln(1-URR) which we estimated of 29%, but her URR came out to be 43% after the first day of treatment, after which we held the CVVHD for 8 hours and then restarted it again. Adequate sodium correction was monitored by obtaining ABGS with critical care panels every 2 hours, which showed a rise from 121 meq/L to 128 meq/L in first 24 hours and to 136 meq/L in the next 24 hours. Her BUN was gradually reduced from 327 mg/dL to 103 mg/dL over a period of 2 days and she was extubated with adequate urine output, EKG normalized and CVVHD discontinued.

Discussion: Our experience showed that frequent use of URR equation and low dialysate rate can be a useful tool in patients on CVVHD with severe azotemia and hyponatremia to avoid dialysis disequilibrium syndrome and osmotic demyelination.

PUB703

An Unusual Case of Hemodialysis-Associated Thrombocytopenia and Severe GI Bleeding

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Introduction: Transient, mild, and asymptomatic thrombocytopenia (TCP) from hemodialysis (HD) has been reported. Clinically significant bleeding from HD-associated TCP has not been previously described.

Case Description: An 82-year-old Caucasian male with baseline TCP (120,000-150,000/μL) and no prior history of GI bleeding (GIB) was initiated on HD. Thereafter he was admitted 5 times for worsening TCP and severe GIB, requiring 40 units of PRBCs and 13 units of platelets. Workup revealed AV malformations. Patient complained of severe fatigue and chills during dialysis and associated each GIB event with HD treatment. A pre- and post-HD CBC revealed profound post-HD TCP, prompting concern for a dialyzer reaction. His polysulfone (PS) electron beam (EB)-sterilized dialyzer was switched to a polyarylethersulfone (PAES) and polyvinylpyrrolidone (PVP) steam-sterilized dialyzer with marked improvement in post-HD TCP and cessation of GIB (Figure 1).

Discussion: Severe and sustained TCP has been described in case reports. Most cases have been associated with PS EB-sterilized dialyzers. One prospective observation study revealed a significant improvement in post-HD TCP after switching to non-EB-sterilized dialyzers. EB-sterilization may alter the surface property of PS-dialyzers, thereby increasing platelet activation. Modified PS dialyzers appear to be associated with less TCP. We are describing the most severe case of HD-associated TCP that has been documented with use of an EB-sterilized PS dialyzer. Unexplained TCP with HD should prompt workup for a dialyzer reaction. Further research is needed to better characterize the mechanism of HD-related TCP and its risk factors.

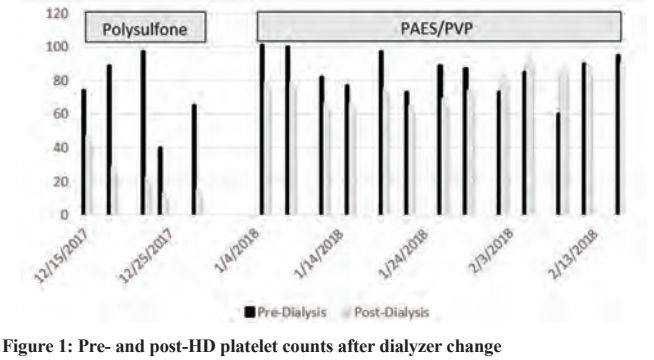

Figure 1: Pre- and post-HD platelet counts after dialyzer change

PUB704

Nocardia Peritonitis: A Rare Case of Peritoneal Dialysis Associated Peritonitis

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Introduction: Nocardia is a very rare cause of peritoneal dialysis (PD) associated peritonitis with only a few case reports reported. It is ubiquitous in soil, water and vegetable matter and known to cause infection in immunocompromised hosts. We report a rare case of PD associated peritonitis caused by Nocardia Asteroides.

Case Description: A 76 year old female with a history of ESRD on PD using a cycler for 4 years presented with symptoms concerning for peritonitis on day 1 received 2 doses of ceftazidime and 3 doses of vancomycin as an outpatient. She was admitted to the hospital on day 10 for a diffuse skin eruption thought to be a drug reaction to the cephalosporin. She was afebrile with stable vitals but a WBC count of 31, 000. Outpatient peritoneal cultures reported growing a gram positive organism, AFB positive. Repeat peritoneal fluid analysis showed no evidence of peritonitis with a cell count of 70/mcL and negative culture. However, she had an increasing WBC count with abdominal pain so cultures were repeated a third time. The culture was positive for Nocardia Asteroides sensitive to Sulfamethoxazole/Trimethoprim (TMP-SMX). CT scan of the abdomen-pelvis was concerning for a pancreatic mass. MRI with contrast showed 1cm intra-ductal pancreatic neoplasm, with benign appearance and recommended 1 year follow up. She was scheduled to follow up with Surgical -Oncology after discharge. She was treated with IV TMP-SMX for three weeks and her PD catheter was removed as she transitioned to hemodialysis at which time she began to improve clinically.

Discussion: Nocardiosis is an opportunistic infection and because of the slow growth, difficult to isolate. Partially acid fast, filamentous branching rods are pathognomonic of Nocardia. TMP-SMX is the drug of choice. The peritonitis has been treated successfully with both removal and retention of the PD catheter. Optimum duration of treatment for Nocardia Peritonitis is not known, usually 3 weeks is recommended and treatment is tailored to individual patients. Duration may need to be prolonged as it has the propensity to relapse on appropriate treatment. Our patient may also have an undiagnosed pancreatic malignancy causing her to be susceptible to this organism.

PUB705

A Rare Cause of Outflow Tract Obstruction in Peritoneal Dialysis, Pleuroperitoneal Leakage

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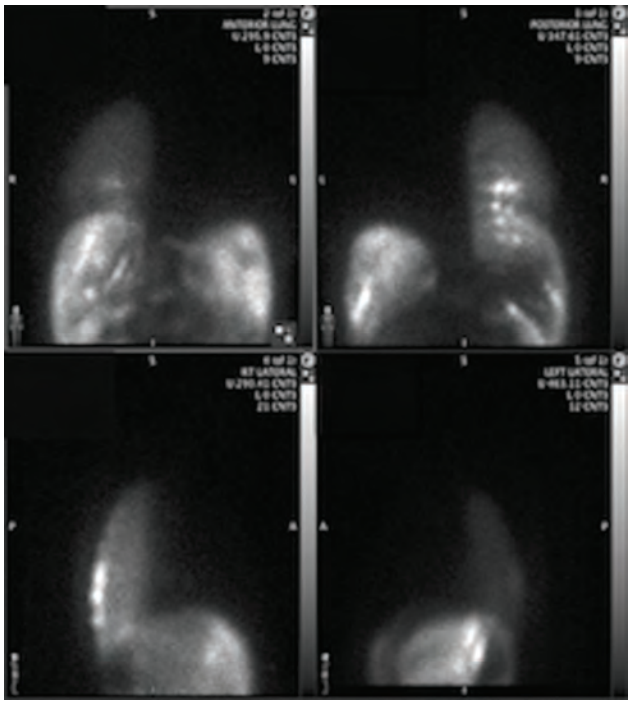
Introduction: Pleuroperitoneal leakage is a complication in peritoneal dialysis(PD). Although it is rare, we should be familiar with this condition.

Case Description: A 54-year-old woman with ESRD on PD presented with inability to drain the dialysate. PD was started 10 months ago without issues and she was converted to automated cycler 2 months ago. She reports mild dyspnea, chest discomfort when lying flat and dry cough for 1 month. The physical exam showed decreased breath sound on right with dullness to percussion. Abdomen was soft, no tenderness. No redness, discharge at exit and tunneled site. Chest x-ray showed right sided pleural effusion. Right sided Thoracocentesis showed pleural fluid protein <0.2 g/dL LDH 15 IU/L Glucose 642mg/dL and pH 7.51. Cell differential and count did not suggest infectious process. High glucose level and alkaline pleural fluid gave the suspicion of dialysate pleuroperitoneal leakage. A radiotracer(Tc-99m DTPA) was injected via PD catheter in supine position. The images showed uptake above the diaphragm on right pleural space suggesting the leakage(figure). Video-assisted thoracic surgery (VATS) was performed, found 1.5 mm pore on the dome of diaphragm. The pore was sutured and doxycycline pleurodesis was done. PD was terminated and patient was converted to hemodialysis for 4 months, PD eventually was resumed again successfully.

Discussion: Pleural effusion with high glucose level and alkaline pleural fluid is suggesitve of this condition. It tends to occur early after initiating PD or change to cycler as this patient. Radionuclide scan, CT and MRI with tracer can be used to diagnose with moderate sensitivity(40-50%). Conservative treatment with PD interruption should be done for at least 4-6 weeks and if it has failed, invasive procedures such as pleurodesis or VATS can be applied.



PUB706

Candida albicans Peritonitis with Urgent Start Peritoneal Dialysis in a Patient with aHUS Treated with Eculizumab

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Introduction: Fungal peritonitis occurs in about 2-13% of patients who undergo peritoneal dialysis (PD). Although rare, fungal peritonitis is a very serious complication with high rates of hospitalization, catheter removal, transfer to hemodialysis and death. The most commonly isolated species with fungal peritonitis is candida sp., with *Candida albicans* being the most frequently isolated organism. Common risk factors associated with the development of fungal peritonitis include episodes of bacterial peritonitis, recent antibiotic use, and immunosuppression. Atypical hemolytic uremic syndrome (aHUS) is a hereditary disease process that occurs due to dysregulation in the complement cascade. It typically presents with a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure secondary to thrombotic microangiopathy. Eculizumab, a monoclonal antibody against C5, is the mainstay in the treatment of aHUS and its introduction has made prevention of ESRD a possibility. However, some patients do develop ESRD despite the treatment and require chronic renal replacement therapy (RRT). Although Eculizumab is known to increase susceptibility to meningococcal infections, case reports of intraabdominal fungal infection while being treated with eculizumab have been rare.

Case Description: We present a case of *Candida albicans* fungal peritonitis within 24 hours of a fluoroscopically placed peritoneal dialysis catheter in an ESRD patient maintained on Eculizumab for aHUS. The patient was given surgical prophylaxis for bacterial pathogens, but not for fungal pathogens prior to the PD catheter placement. Patient clinically improved after removal of PD catheter and was treated with IV then oral fluconazole.

Discussion: Perhaps surgical prophylaxis for bacterial and fungal pathogens is indicated in patients undergoing PD catheter placement who are treated with eculizumab.

PUB707

A Typical Peritoneal Dialysis Patient with an Atypical Cause of Hyperparathyroidism

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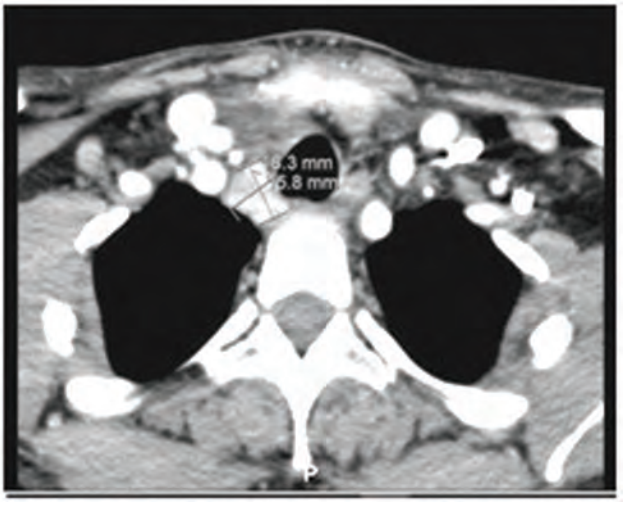
Introduction: We present a patient on peritoneal dialysis with a combination of normal gland; hyperplasia, a gland replaced by fibrous tissue and an ectopic gland, emphasizing that there may be role of dual imaging prior to surgical intervention.

Case Description: A 58 y/o women on peritoneal dialysis developed severe Tertiary hyperparathyroidism. She was unable to tolerate cinacalcet. Surgical resection was done after Ultrasound showed enlarged glands. Upon resection, ¼ glands were normal, 2/4 glands had hyperplasia and 1/4 glands pathology revealed fibrous tissue. However post-resection PTH did not change significantly even one month after surgery. Contrast CT of neck showed 2 cm x 1 cm ectopic gland in right superior mediastinum located between vertebral and subclavian artery. Resection of ectopic gland through transcervical approach was planned. However patient refused surgery which was deemed high risk given the critical location of the gland.

Discussion: End Stage Renal Disease patients usually have hyperparathyroidism secondary to hyperplasia or adenomas or a combination. If unable to tolerate medical management they undergo subtotal or total parathyroidectomy (1). Ectopic adenomas are commonly in thymus, retroesophageal and intrathyroidal areas (3). Accurate localization is needed to improve outcomes [1]. Sestamibi (MIBI) has higher sensitivity (89%) than USG (59 %) for detecting ectopic glands. MIBI accurately locates ectopic glands in the thymus, mediastinum or retroesophageal space and USG accurately detects intrathyroidal glands [2].This suggests that combining preoperative USG and Sestamibi can help locate ectopic parathyroid glands effectively and prepare for focussed surgical intervention which is both time and cost effective.

PTH Trend(pg/ml)	804 (3/17/16)	1958 (12/18/17)	2754 (2/28/18)
Intraoperative PTH trend (12/1/17)	2138	1311	1383
Calcium(mg/dl)	9.8	11	9.9



Ectopic parathyroid adenoma close to apex of right lung

PUB708

Peritoneal Dialysis (PD) Cell Count May Not Always Diagnose Intra-Abdominal Catastrophe

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Introduction: Abnormalities in PD fluid, e.g. high white or red cell counts, bilious or chylous peritoneum, and particulate matter etc. can assist in early diagnosis of intra-abdominal events. A benign PD fluid in a patient with otherwise stable abdominal examination makes the diagnosis of intra-abdominal catastrophe highly unlikely. We present an unusual case, where equivocal radiological findings and benign PD fluid cytology contributed to uncertain diagnosis and adverse patient outcome.

Case Description: A 60-year-old female with end-stage renal disease on PD was admitted with nausea and vomiting. She had benign abdominal examination, no exit site abnormality, peritoneal signs, or evidence for focal findings. CT scan revealed small bowel obstruction with free intraperitoneal air and a transition point in the right lower quadrant, concerning for internal hernia. Repeated PD fluid analysis revealed 62-73 WBC with 3-5% neutrophils. After 3 days of conservative management and unchanging clinical course, exploratory laparotomy was performed which showed matted bowel lumens in right lower quadrant requiring resection of ileum and right hemi-colon. Pathology examination showed the features of early Encapsulating Peritoneal Sclerosis (EPS). Post-operative course was complicated by recurrent intra-abdominal bleedings, multiple laparotomies, splenectomy, and death by day 14.

Discussion: Encapsulating Peritoneal Sclerosis (EPS) is an uncommon but well-reported complication of chronic peritoneal dialysis (PD). History of recurrent peritonitis, indolent onset, malnutrition, and radiological findings are typical presenting findings in these patients. However, acute abdomen presentation with non-inflammatory PD cytology with or without EPS is considered unlikely and has been rarely reported. We present a unique case where incongruent symptomatology, radiological findings and benign PD cell counts could not definitively rule out an internal herniation requiring a surgical approach and adverse outcome. Through this case, we conclude that a non-inflammatory PD fluid cytology could provide an important indication for EPS in PD patients who present with CT findings of possible acute abdomen but are clinically stable. Special considerations for an ongoing trial for conservative management may save lives in such situations.

PUB709

Low Dose Gabapentin Therapy Resulting in Bilateral Lower Extremity Edema in a Young Female Peritoneal Dialysis Patient

Alissa Ice, Farshid Yazdi, Mihran V. Naljayan. *Louisiana State University Health Sciences Center New Orleans, New Orleans, LA.*

Introduction: Peripheral edema is a known side effect of gabapentin with an incidence of roughly 6-8%. This adverse effect has mainly been noted in elderly patients at high (>1200 mg/d) doses of gabapentin. It is unclear whether renal dysfunction may contribute to this clinical finding. We report the first case of gabapentin induced lower extremity edema in a young female patient on peritoneal dialysis.

Case Description: A 36 year old female with end stage kidney disease secondary to lupus glomerulonephritis syndrome, WHO class IV and V, on peritoneal dialysis presented to clinic with bilateral lower extremity edema one month after initiating gabapentin therapy with symptomatic resolution upon discontinuation. The patient began experiencing progressive edema approximately two weeks after starting gabapentin 100-300 mg/d for her peripheral neuropathy. She presented to clinic with 2+ bilateral pitting lower extremity edema and an 8 kg increase in weight one month after beginning therapy. Prior to the onset of her lower extremity edema, there were no recent significant changes to her prescribed medications, continuous cyclic peritoneal dialysis (CCPD) regimen, or laboratory results (albumin remained between 3.3-3.7 g/dL). She had no history of lower extremity edema since beginning peritoneal dialysis in 2016. Upon discontinuing the drug, the patient's swelling resolved over the course of one week, and she returned to her target weight. The patient was then started on pregabalin 25 mg/d with no subsequent edema.

Discussion: The incidence of gabapentin related peripheral edema has been shown at higher doses and tends to increase with age. This unique case illustrates the necessity to consider this medication effect in younger populations and at lower doses, particularly with decreased renal clearance such as in patients on peritoneal dialysis. Gabapentin is frequently used in this patient population due to multiple comorbidities that increase the risk of developing peripheral neuropathy; therefore, we must remain cognizant of this particular side effect as these patients are prone to develop peripheral edema due to other various etiologies. Interestingly, despite some studies showing an increased prevalence of peripheral edema in patients using pregabalin compared to gabapentin, this patient did not develop edema after initiation of pregabalin.

PUB710

Sweet Hydrothorax: Comparing Pleural Effusions in Two Peritoneal Dialysis Patients

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Introduction: Pleural effusion in patients receiving peritoneal dialysis (PD) has a prevalence ranging from 1.2%-10%. When hypertonic dialysate enters the pleura it forms a 'sweet hydrothorax' (transudative effusion with elevated glucose compared to serum glucose). Underlying mechanisms include an increased intra-abdominal pressure with acquired weakening of the diaphragm and impaired lymphatic drainage. We report two cases of patients receiving PD with right-sided pleural effusions.

Case Description: Patient 1- A 59 year old female with ESRD on PD presented to the ED with shortness of breath and nonproductive cough. Four days prior to presentation she fell and sustained a left 10th rib fracture. Following her fall she noticed reduction in ultrafiltrate volume and increasing shortness of breath. She was found to have a significant right pleural effusion associated with hypercapnia (pCO2 62.7 mmHg) and hypoxia (pO2 59 mmHg). Thoracentesis removed 1700 mL of fluid in the ED followed by 1500 mL the following day. Pleural fluid was transudative with elevated glucose compared to serum glucose (502 mg/dL and 169 mg/dL, respectively). Patient 2- A 64 year old female with ESRD on PD for 2 months presented to the ED with shortness of breath and nonproductive cough worsening over several days. She was found to have a large right sided pleural effusion that was removed with thoracentesis (1200 mL). Pleural fluid was transudative with elevated glucose compared to serum glucose (148 mg/dL and 82 mg/dL, respectively). She resumed PD with lower volumes and returned to the ED the following day with shortness of breath and a re-accumulated right-sided pleural effusion for which she did not undergo thoracentesis.

Discussion: These cases highlight etiology of the PD effusion (trauma and congenital diaphragmatic abnormality) and the use of pleural fluid glucose levels in identification of the 'sweet hydrothorax'. Although the site of trauma in patient 1 was on the left, the PD effusion was present on the right indicative of the consistent laterality of such effusions. Furthermore, while patient 2 had a glucose level that was not notably elevated as in patient 1, it was sufficiently raised from her serum glucose. This suggests body fluid glucose content alone should not be so heavily relied upon for diagnosis of pleuroperitoneal leak.

PUB711

Using Indocyamine Green to Diagnose Hydrothorax in Peritoneal Dialysis

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Introduction: Massive hydrothorax is uncommon, but important complication of peritoneal dialysis. Several methods were used to diagnose hydrothorax in peritoneal dialysis patients. However, there was no single definite method to diagnose hydrothorax with peritoneal dialysis patients. Here we report two cases who were diagnosed hydrothorax by using indocyanine green mixing test.

Case Description: CASE 1 A 50-year-old female with PD secondary to diabetic nephropathy visited the emergency room because of abdominal pain and diarrhea. She was treated already for five months with CAPD. Her chest radiograph showed a right-sided pleural effusion. Thoracentesis was performed and her pleural fluid was transudate (Table 1). There was no evidence of heart failure and liver cirrhosis. CAPD peritonitis was improved by intraperitoneal antibiotics. Peritoneal scintigraphy showed no definite abnormality. To confirm the origin of pleural fluid, we mixed ICG on the peritoneal fluid in infused through Tenkhoff catheter. After injected ICG mixed (green color) peritoneal fluid, pleural fluid was drained with green color. **CASE 2** A 78-year-old female with ESRD on PD secondary to diabetic nephropathy visited the emergency room because of shortness of breath. She had been started CAPD for 33 months. On brief sonography demonstrated a massive right-sided pleural effusion and pleural fluid revealed transudate (Table 1). There was no evidence of heart failure and liver cirrhosis. ICG was mixed in peritoneal fluid and injected (2L) to peritoneum then green color pleural fluid was drained via the pleural fluid.

Discussion: ICG is non-toxic, water soluble dye that is used for cardiac output measurement, hepatic function estimation, and retinal microcirculation assessment. Toxicity of ICG is low incidence and mild allergic reactions. In conclusion, we recommend that ICG mixing test may be a reliable, simple, non-harmful, and non-expensive method in differentiating pleuroperitoneal communication from other causes of transudate hydrothorax in PD patients.

Table 1. Results of serum, pleural fluid in two cases of CAPD related hydrothorax.

	Glucose (mg/dL)		TP (mg/dL)		LDH (U/L)	
Cases	PF	Serum	PF	Serum	PF	Serum
1	109	67	0.8	5.0	56	343
2	336	117	0.2	5.9	34	343

LDH=lactic dehydrogenase; PE=pleural fluid; TP= Total protein.

PUB712

Conversion from Peritoneal Dialysis (PD) to Hemodialysis (HD) in Patients with Calciphylaxis

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Introduction: Calciphylaxis is a rare but devastating skin disease in the end-stage renal disease (ESRD) population. Treatment options are limited, and the utility of conversion from PD to HD in patients diagnosed with calciphylaxis remains unclear.

Case Description: A 46-year-old female with morbid obesity, paroxysmal atrial fibrillation on warfarin, poorly controlled diabetes mellitus (DM), ESRD on PD presented to a hospital with painful skin lesions over bilateral thighs. Her outpatient clinic reported gradual loss of renal reserve over the past year resulting in up-titration of her PD prescription. Her parathyroid hormone and phosphate level were refractory to medical therapy. Her skin examination revealed indurated plaques over both thighs. Skin biopsy was consistent with a new diagnosis of calciphylaxis. Her home medications containing calcium and vitamin D were discontinued. Warfarin was substituted with a direct anti-Xa inhibitor. After discussion of the risks and benfits, the patient agreed to convert from PD to HD with a plan to start intravenous sodium thiosulate.

Discussion: It remains unclear if patients on PD will benefit from converting to HD when calciphylaxis is diagnosed. Concerns have been raised with some studies suggesting a higher incidence of calciphylaxis reported in the PD population when compared to the HD population. Furthermore, experts at the first calciphylaxis consensus meeting supported intensifying dialysis treatment which included switching from PD to HD. However, outcome data surrounding dialysis intensification is mixed. While Baldwin et al. published a case series of successful treatment of calciphylaxis by utilizing intense HD, Santos et al. conducted a retrospective analysis of single center data showing increased risk of mortality associated with intense HD. In order to provide the best care for PD patients who develop calciphylaxis, further studies to compare outcomes between continuation of PD versus conversion to HD are needed.

PUB713

Sweet Hydrothorax

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Introduction: Peritoneal dialysis (PD) Patients can develop various complications, one such rare complication is hydrothorax.

Case Description: A 35-year-old man with a history of hypertension, and end-stage renal disease secondary (ESRD) on peritoneal dialysis (started six-weeks earlier) presented due to right-sided pleuritic chest pain that started one day before admission. Over the preceding days, he had noticed an unexplained low drainage volume of dialysate. Vital signs were normal. Physical examination revealed decreased air entry on auscultation at the right side. Chest X-ray revealed a massive right-sided pleural effusion. Laboratory evaluation demonstrated renal dysfunction indicative of his ESRD status with unremarkable complete blood count and liver function test. Ultrasound-guided thoracentesis was performed, and 2300 ml of clear pleuritic fluid was removed without complications. The fluid analysis revealed a high glucose concentration of 447 mg/dl. The fluid was a transudate according to the Light's criteria (Table 1). PD dialysis was temporarily ceased, with very close monitoring of his labs and plan to re-introduce peritoneal dialysis with low-volume exchanges.

Discussion: PD related hydrothorax is rare and can be seen in 2% of the PD patients due to congenital or acquired diaphragmatic defects with a consequent peritoneo-pleural migration of the dialysate. Effusion can develop shortly or several weeks to months after commencing PD. The pleural-fluid analysis is usually diagnostic, revealing a clear fluid with a low protein and a high glucose concentration (sweet hydrothorax). Pleural-serum glucose gradient of more than 50 mg/dL has a 100% sensitivity and specificity to detect PD related pleural effusion. Temporary (2–6 weeks) interruption of CAPD is recommended as a first-line conservative option which can prevent effusion recurrence in approximately 50% of the cases. Other treatment options include chemical pleurodesis via chest drain, limited thoracotomy, and video-assisted thoracoscopy. **Teaching points** Hydrothorax can occur at any time after PD initiation. The pleural-fluid analysis is diagnostic. Interruption of PD is recommended as a first-line therapy.

Table 1. Chemical analysis of the simultaneously drawn serum and pleural fluid

Variable	Serum	Pleural Fluid
Glucose (mg/dl)	89	447
Total protein (g/dl)	6.4	< 3
Lactic dehydrogenase (U/L)	< 25	215

PUB714

Treatment of Mycobacterium Abscesses Exit Site Infection: Looks Can Be Deceptive

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Introduction: Exit site infections (ESI) caused by *Mycobacterium abscessus* (a rapidly growing nontuberculous mycobacterium) in patients on peritoneal dialysis (PD) are uncommon and difficult to treat. Successful intraperitoneal (IP) antimicrobials regimen for *M. abscessus* ESI has not been established and most patients require systemic therapy with switch to hemodialysis. We report a case of *M. abscessus* ESI that resolved clinically following 9-month therapy with IP agents, only to relapse within a short-time of discontinuation of therapy leading to catheter removal.

Case Description: A 55-year-old man with a history of IgA nephropathy, on PD for 2 years without any prior peritonitis, presented with a large ulcer surrounding the exit site with hypertrophied granulation tissue. M. abscessus was isolated from the exit site without any evidence of peritonitis. Because of patient's strong desire to continue PD to maintain his sailing lifestyle, IP amikacin and imipenem with oral azithromycin was commenced. IP antimicrobial levels were serially checked and amikacin was discontinued after 3 weeks because of ototoxicity. Because of clear clinical improvement and absence of peritonitis, the patient was continued on imipenem and azithromycin for a total of 9 months and discontinued once the ulcer appeared healed circumferentially. Within one month of discontinuation of therapy, he suffered an ESI relapse with expanding erythema and ulcer margins. This led to surgical removal of the PD catheter, surgical debridement, conversion to HD, and need for intravenous and oral therapy.

Discussion: We report an unusual case of M. abscessus ESI in an otherwise immunocompetent patient with no previous history of peritonitis or ESI. We found that though an extended course of IP antimicrobial therapy led to ostensibly complete ESI resolution, rapid relapse occurred once treatment was discontinued. In conclusion, extended courses of IP antimicrobial therapy with attention to therapeutic drug monitoring may enable successful therapy of certain infections in PD patients. However, for patients with M. abscessus ESI, PD catheter removal should be strongly considered.

PUB715

Treatment of Acyclovir Neurotoxicity for a Patient with ESRD on Peritoneal Dialysis

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Introduction: Neurotoxicity is a rare side effect of acyclovir therapy. Because of its renal clearance, adjustment of acyclovir dosage is necessary for patients with End Stage Renal Disease (ESRD) on hemodialysis or peritoneal dialysis. We report a case of the successful treatment of acyclovir neurotoxicity in a patient on peritoneal dialysis (PD).

Case Description: A 39 year old female with a past medical history of ESRD on PD was hospitalized because of new onset agitation, anxiety, visual and auditory hallucinations. Two days prior to initiation of symptoms, patient was unfortunately started on acyclovir with dosage of 1000mg three times a day for herpes zoster. CT and MRI of the head and blood work did not reveal any abnormalities. Neurotoxicity of acyclovir was suspected. Acyclovir blood level however, was 2.6 (normal therapeutic level 0.12-10.8). Since no other obvious cause, acyclovir was discontinued and patient was initiated on CAPD with 2.5% Dianeal 1.5 liters fills and every 4 hours exchanges. After 2 days of CAPD acyclovir blood level decreased to zero. Symptoms of agitation, anxiety and hallucination improved in 24 hours and resolved in 48 hours after initiation of more frequent PD treatments.

Discussion: In this case, successful treatment of acyclovir toxicity with peritoneal dialysis was achieved without having to transition to hemodialysis. Herpes zoster is a common condition seen quite often in the offices of primary care providers or urgent clinics and obvious care needs to be taken when prescribing acyclovir to patient with ESRD. In addition to discontinuing acyclovir and close neurological monitoring, we validate that acyclovir neurotoxicity will improve by increasing manual PD exchanges and is an acceptable approach in treatment of this potentially fatal complication. We do also suggest that more research needs to be done to validate therapeutic acyclovir drug levels in patients with ESRD.

PUB716

Tuberculous Peritonitis Masquerading as Diabetic Gastroparesis

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Introduction: The incidence of tuberculosis (TB) in patients from industrialized nations is relatively low. However, patients on dialysis have a five to fifteen times higher risk of developing TB compared to the general population. This is attributed to malnutrition, alterations in cellular immunity and associated comorbidities.

Case Description: A 42-year-old male Filipino immigrant with end stage renal disease secondary to diabetic nephropathy on peritoneal dialysis (PD) was admitted with hypotension, progressive weakness and worsening abdominal pain. He had been hospitalized multiple times previously with anorexia, weight loss, nausea, vomiting and abdominal pain. After extensive work up, his symptoms were attributed to gastroparesis. A week prior to admission, the patient underwent peritoneal fluid testing for worsening hypotension which showed WBCs >200/μL and he was started on intraperitoneal vancomycin and ceftazidime. Blood and peritoneal fluid cultures remained negative. Repeat peritoneal fluid analysis on admission showed WBC 265/μL with 56% neutrophils, 13% lymphocytes and 19% monocytes. He was started on IV vancomycin and ceftazidime and the PD catheter was removed. A tunneled hemodialysis catheter was placed and patient was transitioned to hemodialysis. Interferon (IFN)-gamma release assay was indeterminate, but peritoneal fluid acid fast bacillus culture came back positive for Mycobacterium tuberculosis. Treatment was initiated with Rifampicin, Pyrazinamide, Isoniazid and Ethambutol. Two months after treatment for peritoneal TB, he was readmitted with back pain. MRI demonstrated osteomyelitis of T5-T6 with complex paraspinal abscess and epidural extension causing spinal canal narrowing. Infectious disease service recommended a total of 9 months of treatment for his vertebral tuberculosis.

Discussion: Peritoneal TB is less commonly reported than other forms of TB. It is very challenging to diagnose since regular aerobic cultures do not grow the organism and even culture for acid fast bacillus has a yield of only 15-30%. The diagnosis of tuberculous peritonitis in PD patients is frequently delayed and this increases morbidity and mortality. It is important to consider this differential diagnosis in the setting of culture negative peritonitis in patients from endemic regions.

PUB717

Successful Management of Dislodged/Floating Venous Hardware in ESRD Patients

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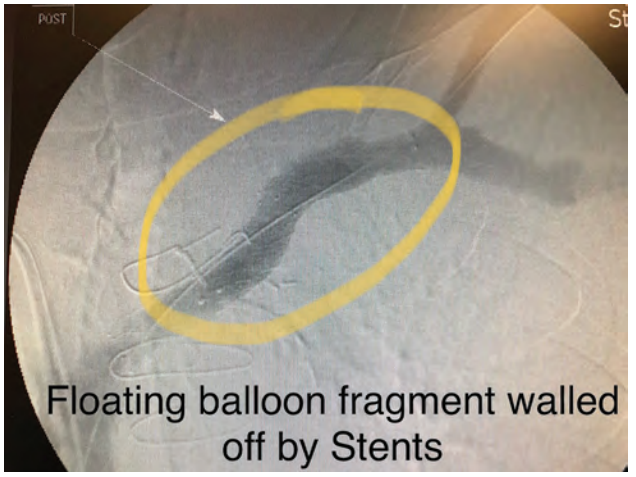
Introduction: Interventional nephrology procedures are performed to maintain functional hemodialysis accesses. A functional access is critical in ESRD patients and complications associated with interventional nephrology procedures include arterial and venous ruptures, clot embolizations, dislodged vascular stents, and ruptured balloon fragments. We present two cases of successful management of dislodged and floating venous hardware in ESRD patients.

Case Description: Case 1: A 80 year old female on hemodialysis for more than 7 years with a left upper arm brachial cephalic fistula who was referred for left upper extremity swelling. Angiogram revealed 80% stenosis of the left innominate vein (in STENT stenosis), and angioplasty was done with a 14x40mm balloon which ruptured and then degloved in the process of being removed. A sizeable portion of the balloon was free floating in the left innominate vein distal to the previously placed stent. Multiple retrieval attempts with a snare were unsuccessful. At this time a second 14x60mm Bard E. Luminexx bare metal biliary stent was placed and seated with a 14x40mm Vaccess balloon. Post angiogram showed good results with re-established flow (see figure1). Case 2: A 67 year old male with ESRD on hemodialysis via a left femoral thigh AVG who presented with a clotted access. In the process of placing a 8x50mm FLAIR stent graft, the stent dislodged and ended up in the left Iliac vein. Multiple retrieval attempts with a snare were unsuccessful. A WALLSTENT by Boston Scientific was placed and the floating stent was prevented from wandering into the pulmonary artery. For both cases, six week follow-up revealed a functional access and no extremity swelling.

Discussion: Dislodged vascular stents and ruptured balloon fragments are unfortunate complications of interventional nephrology procedures. Both of these complications can be successfully managed by placement of a second stent and in essence walling it off from the circulation.



Post Angiogram

PUB718

Preemptive Treatment with Sodium Thiosulfate May Offer Value as Prophylactic Treatment for Calciphylaxis

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Introduction: Calciphylaxis is a poorly understood disease process which has challenged the medical community since its discovery and continues to plague patients to this day. Although previously considered rare, incidence appears to be rising with current prevalence of ~4% in end stage renal disease (ESRD) patients. Optimal treatment for calciphylaxis is unknown, but sodium thiosulfate (STS) appears to be an emerging therapeutic option. Traditionally, this agent has been utilized once disease has already manifested as well as for secondary prevention following resolution. Here we describe two cases in which ESRD patients were treated with STS infusions preemptively before the development of painful wounds and have thus far avoided materialization of the disease.

Case Description: Case#1 28 years old black female with ESRD from lupus nephritis developed bilateral painful thigh lesions. She was hemodialysis dependent for 9 years, and required systemic anticoagulation with Coumadin since 2015 following aortic valve replacement. At the time of symptoms development patient had tertiary hyperparathyroidism which prompted partial parathyroidectomy. Preemptive therapy with STS was initiated and after 15 infusions patient had significant improvement in pain. She has not developed open wounds even though hard subcutaneous lesions are persistent. Her PTH have not improved significantly and complete parathyroidectomy is planned. Anticoagulation alternative to Coumadin have not been approved by hematology. Patient is now status post 22 STS infusions and stable. Case#2 37 year old black female with ESRD from lupus nephritis developed bilateral lower extremities hard painful lesions involving thigh and lower calves. She was on peritoneal dialysis for 18 months at the time of symptoms development. She had poorly controlled secondary hyperparathyroidism. MRI of lower extremities demonstrated calcified areas, Doppler was negative for thrombosis. Preemptive infusions of STS were initiated for 12 treatments. Patient had significant improvement in pain and almost completer resolution of subcutaneous hardening. Cinacalcet was used for suppression of hyperparathyroidism. She is at present sustains in remission for almost two years.

Discussion: Given the highly morbid nature of calciphylaxis, further investigation into preventative strategies and prophylactic agents such as STS are worthwhile.

PUB719

A Novel Use of Teduglutide in Treating Persistent Hypomagnesemia

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Introduction: We present a patient with hypomagnesemia due to chronic diarrhea and proton pump inhibitor (PPI) use. She required weekly intravenous (IV) magnesium infusions. In 2017, she was given a trial of Gattex® (Teduglutide) which improved her magnesium levels and provided better symptom control.

Case Description: Our patient is a 59 year old woman referred to nephrology clinic in 2012 for evaluation of hypomagnesemia. She reported abdominal pain and loose stools since 2009. Upper endoscopy revealed gastric ulcers. Omeprazole was prescribed. Colonoscopy showed collagenous colitis in 2010. Despite controlling her loose stools to a manageable level with budesonide and supplementing with oral magnesium, her low magnesium persisted. In 2013, her urine Magnesium was <42mg, indicating appropriate renal conservation of Magnesium. She had gained 25 pounds in the last 5 years. Her serum albumin is 4g/dL. Celiac's disease serologies were negative. Her other nutritional deficiencies included iron deficiency and vitamin D deficiency. Omeprazole therapy was not able to be discontinued due to recurrence of pain. In 2015, she was started on weekly IV magnesium replacement. Her magnesium remained in the 0.5mg/dL to 1mg/dL range. In November 2017, her gastroenterologist referred her to a Gattex® (Teduglutide) representative to test the efficacy of Teduglutide in reducing her symptoms. She was able to take the drug for 2 months before she could no longer afford the medication. Remarkably, her loose stools decreased and her magnesium levels were maintained at the highest levels in 5 years (1.5md/dL to 1.9mg/dL). Unfortunately, after she discontinued the medicine her loose stools have returned and her magnesium levels have dropped once again.

Discussion: Our patient's low magnesium is likely multifactorial from her PPI use as well as chronic diarrhea. Teduglutide was FDA approved to treat Short Bowel Syndrome in 2012. Teduglutide is a glucagon like peptide 2 analog that promotes intestinal growth and reduces the necessity for parental infusions in patients with malabsorption. Despite not having generalized malabsorption, our experience suggests that Teduglutide may have a role improving magnesium absorption in those with hypomagnesemia due to gastrointestinal losses. Further studies on its safety profile and efficacy in other nutritional and electrolytes deficiencies are warranted.

PUB720

Iatrogenic Diabetes Insipidus

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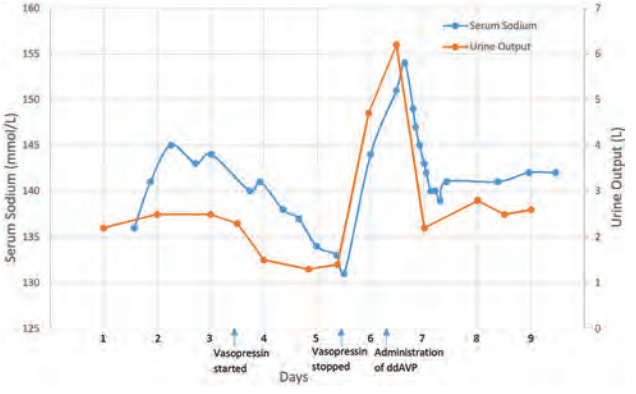
Introduction: Arginine vasopressin (AVP) is a peptide hormone with multiple critical roles. Exogenous AVP is often used in the treatment of septic shock, ventricular arrhythmia, and diabetes insipidus (DI).

Case Description: A 23 year old woman was admitted with septic shock due to MRSA bacteremia. On physical examination, temperature 37.3°C, HR 90 beats per minute, BP 90/50 mmHg, RR 30 per minute, and oxygen saturation 96% on FiO2 70%. Examination was otherwise unremarkable. She received intravenous vancomycin, cefepime, and norepinephrine. On day 3, ivs vasopressin was added for refractory hypotension. Prior to vasopressin, creatinine was 0.6 mg/dL, sodium (Na) 144 mmol/L, and urine output 2.5 L in preceding 24 hours. Over the next 48 hours, Na decreased to 131 mmol/L, with decrease in urine output to 1-1.5 L per day (Figure 1). Vasopressin was discontinued on day 5, and sNa rose from 131 to 154 mmol/L in 24 hours with urine output of 6 L. Measured serum osmolality was 317 mOsm/kg with simultaneous urine osmolality 76 mOsm/kg. Serum AM cortisol level was 22 mcg/dL. Non-contrast head CT was unremarkable. Transient DI upon vasopressin withdrawal was diagnosed. A single 4 mcg iv dose of desmopressin acetate was administered in addition to iv 5% dextrose water (D5W) at 200 ml/hour. A total of 4 L D5W was given over the next 24 hours, and urine output decreased to 2-3 L with normalization of the Na to 140 mmol/L. Her Na remained 138-143 mmol/L for the remainder of her hospitalization.

Discussion: Transient DI is a very rare event. The precise mechanisms, however, are unknown. Leading mechanistic theories include insufficient endogenous AVP production, as well as downregulation of renal V2 receptors upon prolonged intense vasopressin exposure. In the latter, the abrupt withdrawal of exogenous vasopressin may result in inadequate V2 receptor signaling. Providers should be knowledgeable of this uncommon but serious side-effect of vasopressin.



PUB721

A Rare Cause of Hypercalcemia Post Influenza Vaccination

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Introduction: Multiple myeloma (MM) is characterized by the neoplastic proliferation of immunoglobulin-producing plasma cells. Several cytokines, including IL-1, IL-6 and TNF-beta, derived from myeloma cells are thought to accelerate osteoclastic bone resorption and cause hypercalcemia through a paracrine mechanism.

Case Description: A 65 year old female presented with subjective myalgias lasting 2 days. She had received an inactivated influenza vaccine 5 days ago. Vital signs were stable. CBC & BMP were unremarkable. Serum calcium was 10.8 mg/dl. She was discharged on supportive therapy. She presented a day later with persistent flu-like symptoms. Labs revealed serum calcium being above 22 mg/dl, normal renal function, total protein, albumin, ACE levels; clear UA with no albuminuria; low PTH and 1, 25-(OH)2-Vitamin D3 levels; elevated PTHrP & viscosity levels. 24-hour urine collection revealed proteinuria (550 mg). Peripheral blood smear revealed rouleaux formation. CT scans of the chest, abdomen and pelvis revealed no obvious malignancy. Quantitative immunoglobulins revealed elevated IgA (2415 mg/dl), and concurrent suppression of IgG and IgM levels. Quantitative serum light chain measurement revealed normal levels of kappa and lambda, with an elevated Kappa:Lambda ratio of 2:1. SPEP, UPEP, and serum immunofixation

revealed IgA-Kappa MM. Given her severe-symptomatic hypercalcemia, she was treated with aggressive intravenous crystalloids, loop diuretics, calcitonin, pamidronate, and hemodialysis. Her calcium subsequently normalized to 10.1 mg/dl. Bone-marrow biopsy revealed intracytoplasmic kappa-restricted monoclonal plasma cells that occupied 40% of the marrow. Bone survey was negative for lytic lesions. She was started on bortezomib, lenalidomide, dexamethasone and monthly zoledronic acid; and she has not attained remission from myeloma yet.

Discussion: Our case is unique in that the patient initially had a normal serum calcium level that had increased rapidly to over 22 mg/dl within a period of 24 hours, had no renal failure or any bone involvement; and had a normal quantitative serum light chain measurement. It is theorized that the inactivated influenza vaccine given prior to presentation unmasked an atypical presentation of MM. This may be attributed to a vaccination induced cytokine storm, especially IL-6 mediated, that may be the key in the pathophysiology of hypercalcemia related to MM.

PUB722

Cryptogenic Adrenal Infarction

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Introduction: Adrenal infarction is a rare event in pregnancy and in most reported cases, it is bilateral and associated with a thrombophilic state such as antiphospholipid syndrome. We report the first case of unilateral adrenal infarction in a pregnant female, without thrombophilia, secondary to paradoxical embolization.

Case Description: 21-year-old obese G1P0 female presented at 28 4/7 week of gestation with 1-week history of worsening, right-sided abdominal pain associated with nausea and non-bloody non-bilious emesis. No history of thrombophilia, denied smoking or OCP use. No family history of clotting disorders or spontaneous abortions. Physical exam significant for pregnant abdomen with right upper and lower quadrant tenderness. Lab work revealed Hgb 8.0g/dL, Hct 28%, WBC count 13.5k/mm3 and alk. phos. 124U/L. MRI abdomen/pelvis showed a normal appendix and gallbladder but an abnormal right adrenal gland with increased T2 signal and surrounding edema concerning for non-hemorrhagic adrenal infarct. This was confirmed by a contrast-enhanced CT. She was started on anticoagulation with enoxaparin. An extensive thrombophilia workup including lupus anticoagulant, anti-cardiolipin & anti-beta-2 glycoprotein antibodies and JAK2 mutation were negative; haptoglobin and homocysteine levels were within normal limits; lower extremity duplex did not reveal any deep vein thrombosis. A morning cortisol level of 16.3ug/dL ruled out adrenal insufficiency. An echocardiogram with bubble study revealed a patent foramen ovale (PFO). She delivered a healthy neonate at 39 weeks. Following delivery, she was bridged to coumadin for a total 6-week course and started on lifelong aspirin therapy for the PFO.

Discussion: Unilateral adrenal infarction in pregnancy is extremely rare, with only 5 cases reported in medical literature so far. Diagnosis is challenging because of presentation as an acute abdomen with a broad differential further complicated by pregnancy. MRI and CT scan are preferred imaging modalities for the adrenal glands. Once the diagnosis is made, anticoagulation is of paramount importance to prevent recurrent thrombotic events and LMWH like enoxaparin is preferred in pregnancy as it does not cross the placenta. Management of PFO is controversial with unclear benefit of surgical closure vs. medical therapy.

PUB723

Drugs Masking Follicular Lymphoma as the Cause of Severe Symptomatic Hyponatremia

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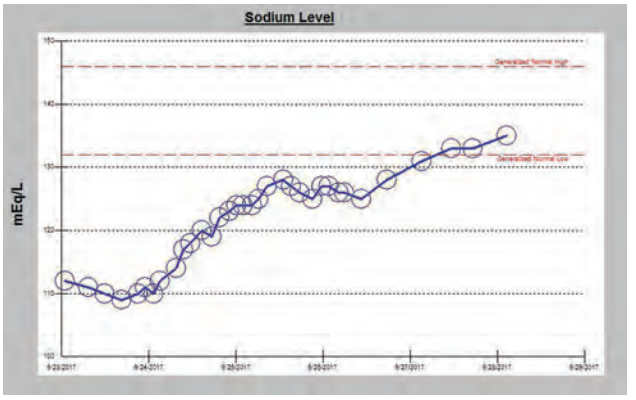
Introduction: The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) is a common cause of hyponatremia. It may be predisposed by certain drugs, nervous system disorders or pulmonary diseases. Malignancy especially small cell lung cancer has also been related to SIADH. Finding the underlying etiology is critical in management.

Case Description: A 58 year old Caucasian lady with a past medical history of depression presented with acute neurological symptoms of headache, dizziness and unsteady gait. CT scan head was reported negative for any acute abnormality. Routine investigations revealed hypotonic hyponatremia with hyperosmolar urine. Careful review of home medications identified Citalopram and Trazodone. The diagnosis of hypo-osmolar euvolemic hyponatremia secondary to SIADH was established and thought to be caused by anti-depressants. The drugs were stopped and she was successfully treated with hypertonic saline with appropriate correction of hyponatremia and complete resolution of symptoms. Later, significant weight loss of 20 lbs in last one year prompted work up to rule out underlying malignancy as a cause of SIADH. She underwent CT scan chest, abdomen and pelvis which showed enlarged mesenteric lymph nodes. Subsequent CT guided biopsy confirmed Grade II Follicular lymphoma. PET scan revealed pleura and cervical lymph nodes involvement.

Discussion: SIADH induced hyponatremia is a common presentation, but the underlying cause needs to be carefully investigated. In our case, initially drugs were thought to be associated with SIADH. But later detailed work up revealed a rare and serious etiology of metastatic follicular lymphoma. Few cases have been previously reported where lymphomas were associated with SIADH. We suggest an open minded and aggressive approach to look for underlying malignancy in all patients irrespective of obvious associations, in order not to miss the dire causes.



Serum Na correction with hypertonic saline

PUB724

Unusual Etiology of Hypokalemia in a Patient with New Onset of Diabetes Mellitus

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Introduction: Hypokalemia can be due to renal or non-renal wasting. Here we are presenting a patient with hypokalemia due to rare cause of renal wasting.

Case Description: 27-year-old healthy male patient presented with generalized weakness, lower extremity edema and shortness of breath gradually worsening over three weeks. He was diagnosed with Diabetes mellitus about a month prior to this presentation. His blood glucose levels remained elevated despite treatment with Metformin and diabetic diet. Past medical and surgical history are negative. Family history is unknown as patient is adopted. Patient is non-smoker, no history of alcohol or recreational drug use or licorice ingestion. On examination temperature 97F, heart rate 93 bpm, regular, BP 144/93mmHg. Patient is noted to have 1+bilateral pitting pedal edema, proximal muscle wasting and areas of ecchymosis over back. Examination is otherwise unremarkable. Laboratory data: Sodium 140mEq/l, Potassium 2.2mEq/l, Chloride 91mEq/l, Bicarbonate 39meq/l, BUN 16mg/dl, Creatinine 1.0mg/dl, Glucose 334mg/dl, Calcium 8.2mg/dl, WBC 17.5/µl, neutrophils 93%, HB 14.8g/dl, Urine Potassium 45.9mmol/l, Transtubular Potassium Gradient (TTKG) 14.46, AM cortisol- 69.9ug/dl, ACTH: 325pg/ml, TSH, free T4, T3: low. Intact PTH, Renin, Aldosterone, FSH, LH, CEA, prolactin, IGF-1, c peptide is within normal limits. Low and high dose dexamethasone suppression test did not suppress ACTH and cortisol levels. Echocardiogram LVEF 55- 60%, trivial pericardial effusion; CT chest, MRI Brain and Abdomen (with and without contrast) normal without any lung mass, pituitary tumor or adrenal mass respectively.

Discussion: Elevated TTKG is suggestive of renal potassium wasting. The generation of hypokalemia, metabolic alkalosis and hypertension are likely the result of sustained activation of mineralocorticoid receptors by high levels of circulating cortisol. Elevated ACTH levels in this case is either due to ectopic ACTH secretion or pituitary microadenoma. Patients with ectopic ACTH secretion often lack the clinical manifestations of Cushing's syndrome as in this patient. Management from Nephrology standpoint is maintaining potassium levels within normal limits and treating the underlying cause. Ectopic ACTH secretion is a rare cause of hypokalemia. Prognosis depends upon the underlying cause.

PUB725

Severe Hypercalcemia Secondary to Histoplasmosis: A Report of an Interesting Case

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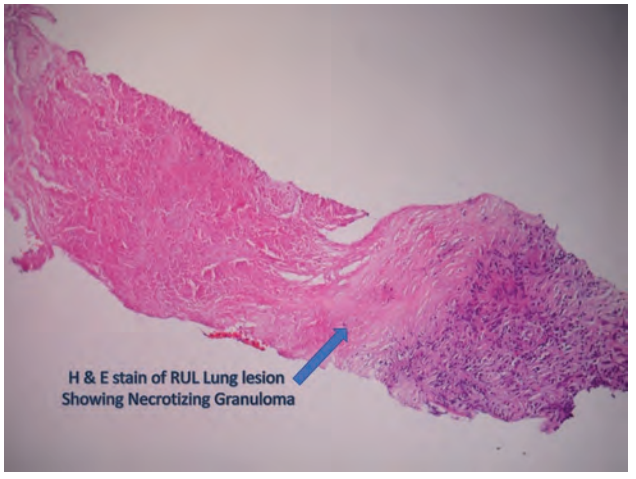
Introduction: Hypercalcemia(↑Ca^{+2}) is an uncommon presentaion of Histoplasmosis. ↑Ca^{+2} associated with Histoplasmosis is usally mild.Here in we present an interesting case of severe ↑Ca^{+2} leading to diagnosis of Histoplasmosis.

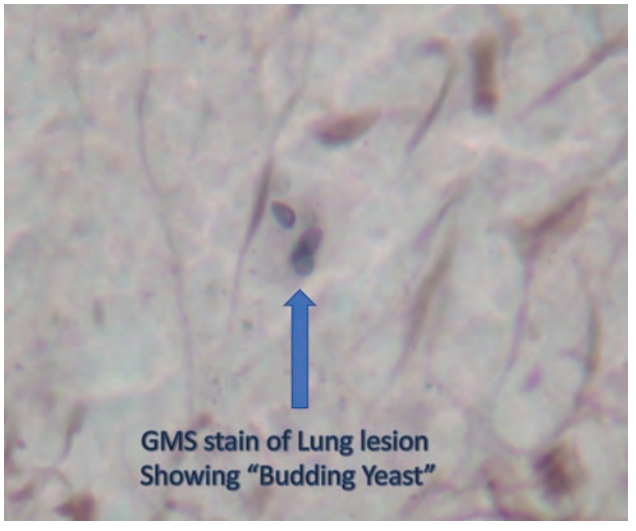
Case Description: 76 yr old female PMH significant for HTN, hypothyroidism, smoker, chronic cough & weight loss presented with syncope & fall, found to have serum Ca^{+2} of **17.7mg/dl** & creatinine of **2.3mg/dl**. PTH was suppressed at 5.4 pg/ml. Urine Ca^{+2} /Cr ratio was 0.26. 25-OH Vit D was 81ng/ml & 1-25-OH VIT D3 was 32pg/ml. PTH-rp was normal at 25 pg/ml. TSH was normal, SPEP/UPEP & serum immunofixation were negative. She was taking oral Ca^{+2} supplementation. She was found to have a RUL Lung mass. She underwent RUL biopsy showing necrotizing granuloma with Budding yeast identified as Histoplasmosis.She was treated for ↑Ca^{+2} with aggressive IV fluids and calcitonin. She was evaluated by ID & was started on itraconazole & oral Ca^{+2} was stopped. Her Ca^{+2} came down to 8.8 mg/dl & creatinine improved to 1.2mg/dl eventually.

Discussion: Histoplasmosis like other granulomatous diseases can cause ↑Ca^{+2} through increased intestinal calcium reabsorption. But severe ↑Ca^{+2} is uncommon. Our case depicts a rare presentation of Histoplasmosis with severe hypercalcemia behaving

like a malignancy. To our knowledge this is the **highest Ca^{+2} level reported** in literature associated with non metastatic Histoplasomosis.



Necrotizing Granuloma



Budding Yeast

PUB726

Marginal Zone B-Cell Lymphoma: A Rare Cause of Central Diabetes Insipidus

Ruby Zhao, Kamal Nayyar, Win Win Moe, James Drakakis, Nobuyuki (Bill) Miyawaki. *NYU Winthrop Hospital, Mineola, NY.*

Introduction: While hyponatremia is often considered in association with paraneoplastic syndromes including SIADH, hypernatremia from central diabetes insipidus (CDI) is a rare neoplastic complication. Metastasis to hypothalamus-pituitary region from breast cancer, lung cancer, acute myelocytic leukemia and disseminated squamous cell carcinoma have been previously described. Leukemia and lymphoma rarely affect the pituitary gland with an estimate of 0.6%. This is the first reported case of CDI from splenic marginal zone lymphoma (MZBCL).

Case Description: A 67-year-old female with a relatively new diagnosis from 6 months ago of splenic MZBCL was admitted to the hospital with thirst, generalized weakness and vertigo and increased urination over 1 week despite doing well prior on Rituxan maintenance therapy for her splenic MZBCL. Her admission Na was normal. Serum Na hovered between 145-149mEq/L on admission days 2-10. With worsened nausea and inability to keep oral intake, Na level suddenly soared from 147 to 169mEq/L overnight accompanied by severe thirst without notable reduction in urine output. Her serum potassium level was 4.2mEq/L, CO2 35mEq/L and creatinine was 0.6 mg/dL. Concurrently obtained urine osmolality was inappropriately low to 224mOsm/L with urinary Na of 62 mEq/L. After administration of dDAVP 2 micrograms IV, urine osmolality increased to 457mEq/L overnight as the serum Na improved from 169 to 143mEq/L over the next 12 hours. The patient subjectively noted a significant decrease in urine output though accurate output was not kept. MRI showed a new enhancing inferior hypothalamic lesion and further testing confirmed the diagnosis of splenic MZBCL with central nervous system involvement.

Discussion: Splenic MZBCL account for less than 1% of non-Hodgkin lymphomas, and are often indolent in nature. Cerebral localized MZBCL has been reported as a rare cause of CDI but our literature search failed to discover CDI or hypothalamic complication from splenic MZBCL. As MZBCL can present with fevers mimicking infections, especially with hemophagocytic lymphohistiocytosis, development of hypernatremia may be inappropriately dismissed as simple case of 'dehydration' without proper history and diagnostic assessments. Concurrence of vertigo with CDI may indicate neoplastic disorder involvement of CNS, including extremely rare entities such as splenic MZBCL.

PUB727

A Simple Approach to the Management of Chronic Polydipsia-Induced Hyponatremia

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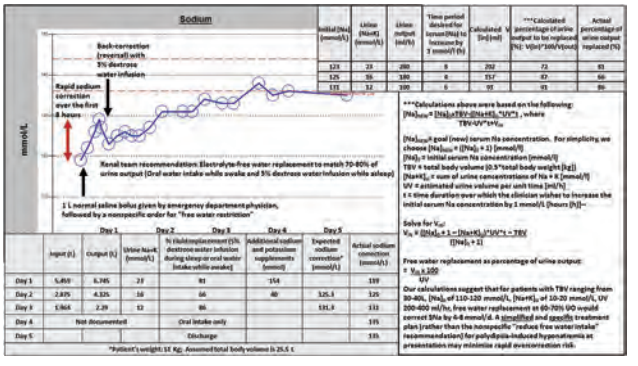
Introduction: Chronic polydipsia-induced hyponatremia (cPIH) is often rapidly overcorrected due to inappropriate strict free water restriction. Current recommendation to "reduce free water intake" (e.g. 500 ml less than daily urine output [UO]) is difficult to apply due to the lag of daily UO measurement.

Case Description: 48-year old female with chronic allergies presented with increasing lethargy and unsteady gait. Patient reports 12-20 L of water intake daily. Medication: diphenhydramine, up to 2 "bottles" daily in recent weeks Exam: Blood pressure 132/97 mmHg, pulse 90/min; oriented, drowsy; moist mucosa, unremarkable cardiopulmonary, abdominal, and extremity exams; neurological exam nonfocal Labs/imaging studies: Brain CT, chest X-Ray: negative Serum Na 119, K 3.3 mmol/L, osmolality 250 mosm/kg, blood urea nitrogen 7 mg/dl, creatinine 0.49 mg/dl. Thyroid stimulating hormone and morning cortisol levels: normal In the emergency room, patient received 1L normal saline bolus, followed by strict free water restriction. Serum Na increased to 129 mmol/L within 8 h. Renal team was consulted. Hyponatremia was attributed to the increased thirst associated with high dose diphenhydramine (anticholinergic). Free water was given to reverse the rapid correction. Urine studies revealed urine Na+K persistently <25 mmol/L and urine osmolality <100 mosm/kg; UO ranges at 200-350 ml/h. Further recommendation was to match 70-80% of patient's UO with electrolyte-free water (calculations were based on estimated UO rate and urine Na+K concentrations, Figure). Patient's serum Na steadily and safely corrected and UO tapered nicely over 3 days.

Discussion: cPIH may be rapidly overcorrected with inappropriate free water restriction. In this condition, patient continues to lose high volume of electrolyte-free UO despite being water restricted due to the loss of optimal renal concentrating ability. Our simple recommendation to replace free water at a specified percentage of UO to the primary care team allowed for a steady and safe correction of the presenting hyponatremia.



PUB728

Back to the (Acidosis) Basics: CRRT Masking DKA

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Introduction: We present a case of diabetic ketoacidosis (DKA) obscured by continuous venovenous hemofiltration (CVVH).

Case Description: A 33-year-old male with type I diabetes mellitus (DM) and ESRD was admitted with cardiac ischemia and had urgent coronary artery bypass grafting. Postoperatively, he required continuous renal replacement therapy (CRRT) because of persistent hypotension. CVVH was initiated at 25 ml/kg/h using NxStage PureFlow dialysate (glucose 100 mg/dL). His diabetes was managed with an insulin infusion titrated via a computerized glucose management system. On postoperative day 5, the patient developed worsening metabolic acidosis. Laboratory studies revealed arterial pH 7.17, PaCO2 38 mmHg, sodium 141 mEq/L, potassium 5.0 mEq/L, chloride 109 mEq/L, total CO_2 15 mmol/L, glucose 140-185 mg/dl, anion gap 17, albumin 3.2 g/dl, and lactate 1.0 mmol/L. Despite glucose levels <200 mg/dL, the serum beta-hydroxybutyrate (BHB) level was found to be elevated to 7.9 mmol/L, consistent with euglycemic DKA. Further review of his record revealed that he was receiving minimal calories via tube feed. In addition, the rate of the insulin infusion rate averaged only 0.2 Unit/hr over the preceding 72 hours. The patient was started on dextrose infusion until tube feeds could be advanced to goal and the insulin rate was increased accordingly. His acidosis resolved and the BHB level normalized.

Discussion: Euglycemic DKA describes the clinical triad of anion gap metabolic acidosis, positive serum or urine ketones, and serum glucose <250 mg/dl. Coutrot *et al.* described 18 cases of euglycemic DKA in patients receiving CRRT with glucose-free replacement fluids. We are not aware of previously described cases in which near

normalization of serum glucose by CRRT using glucose-containing replacement fluid yielded euglycemic DKA. In this case, the development of DKA was multifactorial, including inadequate provision of insulin and carbohydrates. The diagnosis was initially missed by an experienced critical care staff because glucose levels were <200 mg/dL. Methodical acid-base analysis prompted measurement of BHB, confirming the diagnosis of DKA. In this case, the near normalization of serum glucose by CVVH masked the diagnosis of this common acid-base disturbance. An increased suspicion for DKA is warranted in patients with insulin-dependent DM on CRRT even when glucose levels are <200 mg/dL. Reference: Coutrot, Intensive Care Med. 2018.

PUB729

Water Balance Disorders as an Early Sign of Acute Myeloid Leukemia

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Introduction: Central diabetes insipidus (DI) commonly is idiopathic or may be due to tumors, infections, trauma or infiltrative diseases affecting the brain. It is rare in patients with acute myeloid leukemia (AML).

Case Description: A 52 year old female with past history of high risk myelodysplastic syndrome was admitted because she progressed to AML. She was started on IV Cytarabine. Her serum sodium (Na) was 139 mEq/L on admission. She became steadily more hypernatremic, her Na peaked at 167 mEq/L, then improved to 156 mEq/L with IV dextrose. She reported polyuria and polydipsia of 4-6 L of water daily for few weeks prior to presentation. Initially her urine output (UOP) was not adequately recorded but later she was noted to make 5L of urine a day. Labs showed normal kidney function, serum osmolarity of 320 mOsm/L and urine osmolarity of 104 mOsm/L. DI was highly suspected so DDAVP test was done with marked drop in UOP and rise in urine osmolarity to 534 mOsm/L. All were consistent with Central DI. Other workup showed low serum ADH, FSH, LH, ACTH and TSH. MRI head showed pituitary stalk thickening of 6 mm. She was started on intranasal DDAVP at night time and her serum Na normalized. Her hospital stay was complicated by septic shock due to E.coli bacteremia, AKI and hyponatremia. DDAVP was stopped and she was started on CRRT. She continued to deteriorate and died shortly thereafter.

Discussion: DI may occur any time in the course of AML, but often precedes initial diagnosis. The mechanism is unknown but one theory is that leukemic cells infiltrate the hypothalamic-pituitary stalk, however some patients have such infiltration without DI and vice versa. Thrombocytosis can lead to pituitary micro-infarction. It may lead to platelet dysfunction with increased risk of pituitary hemorrhage. Also may interfere with ADH action because > 90% of circulating ADH is bound to platelets. Leukostasis can lead to pituitary infarction as well. Association with specific chromosomal abnormalities has also been reported in AML. Anomalies of chromosome 3, particularly 3q26 breakpoint with inv(3)(q21q26), in AML patients have been associated with DI. Outcomes are poor in patients with AML who present with DI, regardless of the cytogenetic profile. AML diagnosis should be suspected in the evaluation of patients with central DI with hematologic abnormalities. It can be a good clue for early diagnosis and treatment.

PUB730

A Case of Nafcillin Induced Hypokalemia

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Introduction: Hypokalemia is a frequent clinical finding. Most common causes are diuretic use and gastrointestinal losses; Less common causes include: RTA, DKA, insulin excess, ectopic ACTH production and medications.

Case Description: We present a case of severe hypokalemia secondary to treatment with Nafcillin for a Methicillin Sensitive Staphylococcus aureus (MSSA) infection. Patient presented with right sided weakness and bilateral shoulder pain for 1 day. Physical examination showed decreased muscle power in both lower extremities; upper extremity strength was preserved. MRI of cervical spine showed an epidural abscess. Initial laboratory tests were: pH 7.43, Na^+ 133 mEq/L, K^+ 4.0 mEq/L, HCO_3^- 23 mEq/L, BUN 20 mg/dL, Creatinine 0.7 mg/dL. Patient was started on Vancomycin, Ceftriaxone, Metronidazole and cord decompression/abscess drainage was performed. Blood/abscess cultures were positive for MSSA and Nafcillin was started. As showed in graphic and table 1, the patient persisted hypokalemic in despite of repeated replacement with high doses of intravenous Potassium Chloride. A 24 hours urine electrolytes showed: K^+ 63.9 mEq/L and Mg^{+2} 102 mg/dL. Oral K^+ and Mg^{+2} supplements were started, and thereafter both serum K^+ and Mg^{+2} normalized.

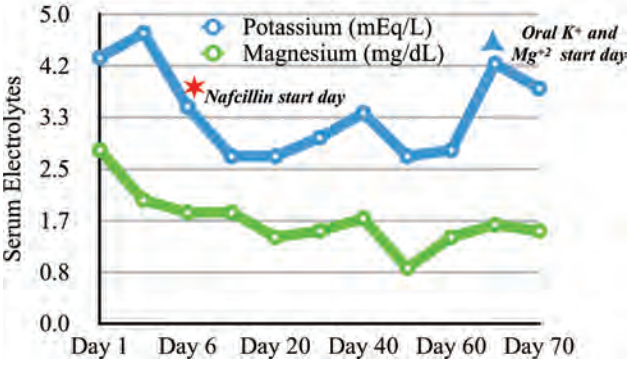
Discussion: Reviewed literature suggests that drug-related hypokalemia is rare after starting therapy with penicillin antimicrobials (i.e, Nafcillin) and baseline serum K^+ level is a key determinant. Nafcillin associated hypokalemia is related to non absorbable ion effects in the distal tubule and/or intracellular redistribution due to volume depletion. Hypokalemia in this setting needs aggressive K^+ replacement and may be also corrected by decreasing the dose of Nafcillin. Clinicians should be aware of hypokalemia when using Nafcillin.

Table 1. Serum electrolytes during hospital course

	Hospital day													
Electrolyte	#1	#3	#6 %	#11 €	#20	#25	#30	#40	#45	#50	#55	#60	#65 ¥	#70
K^+	4.3	4.7	3.5	2.7	2.7	2.9	3.0	3.4	3.0	2.7	2.9	2.8	4.2	3.8
Mg^{+2}	2.8		1.8	1.8	1.4	1.7	1.5	1.7	1.6	0.9	1.3	1.4	1.6	1.5

Reference values (serum): K^+ :3.5-5.0 mEq/L, Mg^{+2}:1.5-2.7 mg/dL.
Symbols: %:Nafcillin day #1; €: Nafcillin day #4; π: Oral K^+ and Mg^{+2} day #1

Graphic 1. Electrolytes trend



PUB731

Treatment of Refractory Metabolic Alkalosis and AKI with Reinfusion of Gastric Drainage

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Introduction: Gastrointestinal (GI) hydrogen loss is a common cause of metabolic alkalosis. It is usually treated with proton pump inhibitor (PPI) or H2 blocker along with volume replacement. For refractory patients, methods such as dialysis or intravenous (IV) infusion of hydrochloric acid (HCl)/ ammonium chloride can be considered. We describe a case of severe metabolic alkalosis caused by massive gastric drainage that was successfully treated by reinfusion of the drainage into the jejunostomy tube.

Case Description: A 50-year-old female was admitted with 3 days of worsening confusion. She had a complicated surgical history after a jejunal diverticulum perforation. As a result, her small intestine was left in discontinuity, with a duodenostomy draining tube, a jejunostomy tube and a venting gastrostomy tube. She had been receiving a liquid diet as well as total parental nutrition (TPN). Six days prior to the admission, her TPN was taken out for a break. On admission, she complained of markedly increased gastric drainage of about 2.5L daily from the duodenostomy tube. Further evaluation revealed pH 7.52, HCO3 51.6 mmol/L, base excess 24.0 mmol/L, Na 119 mmol/L, K 2.3 mmol/L and Cl 48 mmol/L with creatinine of 6.67 mg/dL (baseline 0.8mg/dL). She received IV fluids, PPI and TPN with potassium chloride repletion. Her electrolyte disturbances quickly corrected. However, she remained in metabolic alkalosis with high GI output of around 3L. Given the acidic nature of her gastric drainage (pH < 5), we decided to re-infuse the gastric drainage from the duodenostomy tube into the J tube to correct the metabolic alkalosis. The patient's acid-base disturbance and renal function normalized over the next few days.

Discussion: Conventionally, metabolic alkalosis caused by excessive GI fluid loss is treated with H2 receptor blocker or PPI, along with IV fluids. However, they were ineffective in our patient. IV HCl or ammonium chloride is the next line of therapy; but they are associated with narrow therapeutic windows and fatal complications. Reinfusion of gastric secretion into distal small bowel has been well described, but mainly for the purpose of nutritional support in patients with high output fistula or stoma to eliminate the dependence of TPN. Our report shows this could be a practical alternative in patients to treat refractory metabolic alkalosis as well.

PUB732

Hyponatremia in ESRD: Look Before You Leap

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Introduction: Hyponatremia in patients with end stage renal disease (ESRD) who receive hemodialysis (HD) is frequently attributed to interdialytic fluid intake as they primarily depend on HD for removal of excess water. Measuring serum sodium (SS) as a part of plasma component, instead of plasma water content (PWC), can lead to erroneously low SS measurement.

Case Description: A 76-year-old ESRD patient treated with HD, anoxic brain injury, and recurrent bacteremia presented with severe hyponatremia despite lack of access to free

water. In order to avoid rapid correction of SS, low dialysate sodium (135 mmol/L) was used albeit with no notable impact. Persistence of hyponatremia and patient's physical inability for excessive water intake prompted further evaluation that revealed a serum osmolality of 285 mOsm/Kg in the presence of SS of 127 mmol/L. Further work up showed total protein 10.4 g/dL with albumin 2.9 g/dL. Interestingly, serum protein electrophoresis found large and broad polyclonal hypergammaglobulinemia due to multiple chronic infections, with IgG 5106 mg/dL (N: 635-1616), Ig A 1310 mg/dL (N: 70-433). Total serum lipid level (including triglycerides) was 450 mg/dL. PWC was then calculated [PWC=0.991–(0.73Xprotein Kg/L)-(1.03Xlipid Kg/L)] which revealed reduction in PWC (i.e. 91%) as the source of erroneously reported SS.

Discussion: Plasma dilution technique is used for conventional SS measurement; sodium concentration is adjusted by a fixed factor of 0.93, taking into consideration that the usual plasma composition is 93% water and 7 % solids. This method could result in clinically relevant measurement artifacts even with trivial changes in PWC due to significant increase in plasma lipids or plasma proteins such as in this patient. This case is a reminder that erroneous reporting due to PWC changes should be considered for unexpected low SS levels. This is particularly relevant in ESRD patients where a chronically modified HD approach might portend potentially adverse consequences.

PUB733

Metformin-Associated Lactic Acidosis (MALA): A Rare but Fatal Clinical Entity

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Introduction: Metformin is widely used as first line therapy for type 2 diabetes mellitus and is the most prescribed oral hypoglycemic agent in the world. While metformin reduces the risk of diabetic complications and cardiovascular mortality, it is also associated with the risk of life-threatening lactic acidosis, particularly in patients with renal or hepatic insufficiency. Metformin associated lactic acidosis (MALA) is a rare but serious complication with a remarkably high mortality rate of 30-50% in affected individuals. The incidence of MALA is reported to be about 4-9 cases per 100,000 patient-years in metformin users. We report a case of metformin associated lactic acidosis in the setting of renal insufficiency.

Case Description: A 55-year-old man with past medical history of DM II, HTN, CKD III presented with sudden onset of dyspnea, chest and abdominal pain associated with nausea, vomiting and poor oral intake for a few days. He takes metformin, losartan and atenolol at home. His vital signs were notable for a temperature of 35.5 C, blood pressure of 176/94, pulse of 94 and oxygen saturation of 99% on BiPAP. He was in moderate respiratory distress and had a resting tremor in his distal upper extremities bilaterally. The rest of his systemic examination was unremarkable. He was initially started on hemodialysis but subsequently developed hypotension requiring transition to continuous venovenous hemofiltration (CVVH). His renal function, metabolic acidosis and hemodynamics improved within 24 hours of treatment with CVVH. He subsequently recovered from lactic acidosis. His renal function improved to his previous baseline upon discharge and he did not require long-term renal replacement therapy.

Discussion: In the setting of renal insufficiency, metformin can induce lactic acidosis by promoting the conversion of glucose to lactate in the splanchnic bed of the small intestine and also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate and pyruvate. There is no specific antidote for metformin overdose. Gastrointestinal decontamination with activated charcoal can be used in acute overdose but not in patients with chronic toxicity. Extracorporeal treatment (ECTR) is the key component of management, hemodialysis being the modality of choice.

PUB734

Pseudohyperkalemia - A Hoax

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Introduction: Pseudohyperkalemia is a factitious elevation of serum potassium (K^+) which is caused by many factors including mechanical trauma due to blood draw, due to reagent of blood collection tube, delay in collected sample transport to the lab, leakage of K^+ from the hypermetabolic cells in vitro (i.e. myeloproliferative disorders).

Case Description: A 63 years old Afro-American male with history of Mantle Cell Lymphoma status post 13 cycles of chemotherapy got admitted for stem cell transplant with a white blood cell (wbc) count of 276000/uL. He was persistently hyperkalemic K^+ of 6.4> 8.0 > 9.8 mEq/L; got reversed on dialysis but reappeared again. All causes of hyperkalemia were excluded. He had normal EKG, normal creatinine 0.97mg/dl and had good urine output. K^+ q4h and wbc count daily were monitored. Interestingly observation was distinct when blood sample turnaround time to laboratory for K^+ check was 5 minutes, K^+ value turned out to be normal as opposed to value reported after regular 4-hour delay from a lab technician draw. Therefore, unnecessary dialysis and medical treatments for high K+ were discontinued. When his WBC count came down from 276000/ul to 31000/ul with chemotherapy his K^+ became normal.

Discussion: K^+ leak from hypermetabolic cells (leukemia, lymphoma, thrombocytosis, Polycythemia Vera) occurs in vitro while no changes seen in vivo. Serum K^+ in cases of hyperkalemia especially in setting of myeloproliferative disorders should be evaluated to differentiate true hyperkalemia from pseudohyperkalemia by minimizing the time delay in turnaround of samples to the laboratory. ***Key Words***: Pseudohyperkalemia, myeloproliferative disorders

PUB735

Voriconazole Induced Refractory Hyperkalemia and Adrenal Insufficiency

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Introduction: Voriconazole, member of the azole family, acts by inhibiting lanosterol 14-alpha-demethylase, a cytochrome P450 dependent enzyme. It demonstrates enhanced activity against aspergillus and superior activity against certain fluconazole-resistant candida species. Hepatotoxicity is common side effect of the azoles with neurotoxicity and cardiac arrhythmias more specific to voriconazole. Electrolyte abnormalities and adrenal dysfunction have been reported with voriconazole. In our literature review we found a case report of adrenal insufficiency associated with the concomitant use of voriconazole and inhaled glucocorticoids [1], a case series of severe hyponatremia associated with voriconazole use [2] and a case of iatrogenic Cushing syndrome associated with concomitant use of voriconazole and budesonide [3]. Hyperkalemia is a rare adverse reported not well reported in the literature. We present here a case of intractable hyperkalemia resulting from voriconazole use.

Case Description: A 47-year-old Caucasian male presented with progressively worsening shortness of breath that required mechanical ventilation within 24 hours of presentation. The patient was diagnosed with acute respiratory distress syndrome and was empirically treated with broad spectrum antibacterial coverage but failed to show improvement. Voriconazole was added to his regimen for anti-fungal coverage. Over the next 3 days the patient developed worsening hyperkalemia with normal renal functions and output, not responding to standard pharmacological treatment and emergent continuous renal replacement therapy was instituted. Voriconazole was stopped and the patient could be taken off continuous renal replacement therapy with no further electrolyte imbalances. Throughout this entire period his kidney function remained normal and his urine output was excellent.

Discussion: Hyperkalemia resulting from voriconazole use is an uncommon adverse effect occurring in less than 2% of cases but is important because of the serious and potentially life-threatening consequences. It should be kept in mind whenever initiating treatment especially in patients with compromised renal function; in kidney transplant recipients receiving tacrolimus and other hyperkalemia inducing drugs requiring careful serum potassium monitoring.

PUB736

Hypoparathyroidism Concomitant with Macrothrombocytopenia in an Elderly Woman with 22q11.2 Deletion Syndrome

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Introduction: Although hypocalcemia is common, its etiology is complex. Common causes of hypocalcemia are vitamin D deficiency, hypomagnesemia, critical illness, drugs, and hypoparathyroidism. Among these, congenital hypoparathyroidism has rarely been reported. Chromosome 22q11.2 deletion syndrome (22q11.2DS) associated with congenital hypoparathyroidism can result in hypocalcemia and hyperphosphatemia.

Case Description: We describe the case of a 62-year-old woman with schizophrenia and intellectual disability, who presented with intermittent muscle cramping for 2 weeks. A dysmorphic face and a positive Trousseau's sign, but without ecchymosis or petechial lesion were noted. Laboratory data revealed impaired renal function (creatinine level = 1.6 mg/dL), severe hypocalcaemia (total calcium level = 5.7 mg/dL) with low urinary calcium excretion (13.2 mg/day), hyperphosphatemia (phosphate level = 7.3 mg/dL), and low intact parathyroid hormone level (52.5 pg/mL)—indicating primary hypoparathyroidism. A blood smear revealed thrombocytopenia (30,000 thrombocytes/μL) and giant platelets—indicating macrothrombocytopenia. Chromosome 22q11.2 deletion syndrome (22q11.2DS) in the deficient chromosome 22 was confirmed using multiplex ligation-dependent probe amplification showing haploinsufficiency in *GP1BB* and *TBX-1*.

Discussion: The estimated prevalence of 22q11.2DS is 1:2000 to 1:6000. The clinical manifestations of 22q11.2DS are characterized by facial dysmorphism, congenital cardiac defect, palatal abnormalities, thymic hypoplasia and immunodeficiency, parathyroid hypoplasia, developmental delay and learning disability, schizophrenia, and hearing loss. However, another one of its manifestations, macrothrombocytopenia, has rarely been discussed. Cooccurrence of hypoparathyroidism and macrothrombocytopenia in 22q11.2DS is rare and can easily be misdiagnosed as idiopathic thrombocytopenia purpura. Inappropriate splenectomy or chemotherapy can aggravate hypoparathyroidism. Early diagnosis of 22q11.2DS, characterized by hypoparathyroidism and macrothrombocytopenia, in elderly patients with schizophrenia can facilitate in avoiding circuitous diagnosis and inappropriate management.

PUB737

Dramatic Changes of Water Metabolism

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Introduction: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and central diabetes insipidus are recognized complications following craniotomy or craniectomy.

Case Description: A 29-year-old man with prior resection of metastatic left frontal poorly differentiated sarcoma on dexamethasone 4 mg orally every 4 hours, presented with altered mental status associated with bulging of his left eye and seizures three weeks after procedure. History included end stage renal disease status-post renal transplant in 2011. He was hemodynamically stable without tachycardia or fever. Physical exam revealed left eye proptosis and euvolemia. Due to altered mental status, he was placed on mechanical ventilation. Laboratories revealed sodium 131 mEq/L, creatinine 1.0 mg/dL, urine osmolarity 682 mOsm/Kg, urine sodium 181 mmol/L and TSH levels were normal. Since patient was clinically euvolemic, SIADH was diagnosed and fluid restriction started. Despite fluid restriction, serum sodium levels continued to decrease, and a 3% hypertonic saline solution was started. Serum sodium levels rose 15 mEq/L in a 72-hour period, the patient became more alert and hypertonic saline was discontinued. In addition, transplant immunosuppression was decreased, and doxorubicin initiated. Despite therapy, he had a rapid deterioration in mental status and another emergent decompressive craniectomy was done. At the time of surgery, sodium levels were 143 mEq/L. Within 24 hours, he developed urine output higher than 300 mL/hr associated with serum sodium levels of 162 mEq/L and urinary specific gravity of 1.006. Volume repletion was started, and desmopressin provided, which reduced polyuria and raised urine specific gravity to 1.025. Brain imaging revealed transtentorial and tonsillar herniation. Rapid progression of malignancy may have been associated with pituitary ischemia, resulting in decreased antidiuretic hormone secretion.

Discussion: Our case highlights dramatic changes of water metabolism that patients with brain lesions undergoing neurosurgery can experience. In the post-operative period, frequent monitoring of serum sodium levels is essential including close attention to urine output and tonicity to avoid dysnatremia and delay in treatment.

PUB738

Biopsy Proven Acute Interstitial Nephritis in a Patient with Hashimoto's Thyroiditis Presenting with Concurrent Distal Renal Tubular Acidosis (dRTA) and Severe Lower Extremities Weakness

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Introduction: Distal RTA is a common clinical manifestation of a multitude of autoimmune disorders like Sjögren's syndrome, Chronic active hepatitis, Takayasu arteritis and SLE. dRTA is also a common presenting feature of chronic tubule-interstitial nephritis from any cause; however, there is scant data on the association of autoimmune thyroid disease and lymphocytic interstitial nephritis. Our case is unique in a manner that a patient presenting with no other autoimmune processes except for Hashimoto's comes to have a positive biopsy finding favoring acute interstitial nephritis as being the cause of her dRTA.

Case Description: 39 year old Female with history of Hashimoto's thyroiditis status hemi thyroidectomy and CKD stage 2 presented with severe weakness of her lower extremities. Her admission relevant pertinent labs had revealed a potassium (K+) of 2.1mmol/L and bicarbonate (Hco3-) of 12mmol/L. Her TSH levels were found to be subtherapuetic at <0.03 thought to be as a result of unmonitored thyroxin use. Concurrent Bicarb and potassium supplementation improved her muscle weakness while endocrinology managed her hyperthyroid state. Despite the above measures, hypobicarbonatemia persisted with Nephrology evaluation revealing a urine pH>7.0 and a UrineNa+K (92.8)> UrineCl (83). With the above findings, the diagnosis of dRTA was made with a recommendation of autoimmune evaluation. Serologic studies were only positive for speckled ANA (250) while Ophthalmologic exam was unrevealing for uveitis. Given the above and the ongoing reduced GFR, a renal biopsy was performed which revealed the presence of a lymphoplasmacytic interstitial process with an element of tubulitis as well as some tubular atrophy and fibrosis.

Discussion: Recent studies show that thyroid hormones have several effects on expression of acid-base transporters and are associated with defects in distal nephron handling of acid-base balance. An underlying autoimmune etiology is almost always associated with dRTA, although the exact mechanism is unknown. Our report highlights the importance of recognizing the autoimmune association of dRTA and that there is likely an as-of-yet unidentified autoimmune condition vs currently-known, but serologically negative autoimmune disease resulting in both hypothyroidism and dRTA.

PUB739

Incomplete Proximal Tubular Dysfunction in Acute Myeloid Leukemia (AML): Thinking Outside the Box

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Introduction: Acute kidney injury (AKI) is common in hematological malignancies. AML in particular can cause acquired defects within the kidney, notably the proximal tubule which results in wasting of amino acids, uric acid, bicarbonate, sodium, potassium and phosphate. In this report, we present a patient with complex myelo-monocytic AML who developed an unusual kidney complication of his malignancy with its associated electrolyte abnormalities.

Case Description: A 58 yo male presented to ER for syncope. Labs revealed BUN 37 mg/dl, serum creatinine (Cr) 5.0 mg/dl, potassium 3.3 mmol/L, phosphate 4.0 mg/dl, uric acid 16.1 mg/dl, LDH 1500 IU/L, WBC 156,000, Hb 10.0 g/dl and platelets 36,000. His AKI was deemed pre-renal and creatinine improved to 0.9 by day 10, with intravenous fluid administration. Flow cytometry confirmed AML. He completed 1 session of leukapheresis and began chemotherapy. By day 13, he developed hypophosphatemia (1.9 mg/dl), hypokalemia (3.3 mmol/L) and hypouricemia (<1.5 mg/dl). Urine pH was 6.0, with new-onset glycosuria >500 mg/dl and proteinuria. Spot urine phosphate was 63 mg/dl, with fractional excretion 38% confirming urinary wasting. Repeat urinalysis continued to exhibit glycosuria in the setting of normoglycemia. 24-hour urine showed phosphaturia of 2.1 g/d (normal 0.9-1.3 g/d) and proteinuria (3 g/d). These findings pointed to the diagnosis of Fanconi's Syndrome except his serum bicarb was 27, with arterial pH 7.43 and pCO 40 mmHg. Serum lysozyme concentration on day 23 was normal. Simultaneous WBC was 900. He was determined to have incomplete proximal renal tubular acidosis, due to lysozyme mediated tubular injury, which persisted despite the lysozyme levels that presumably returned to normal. His serum phosphate improved with oral phosphate replacement to 3.3 mg/dl at discharge.

Discussion: Lysozyme originates from monocytes and macrophages. Increased levels are seen in monocytic leukemia. When excreted in large quantities in the urine various types of renal tubular dysfunction are observed. The combination of AKI, proteinuria, hypokalemia, and hypophosphatemia appears to be characteristic for patients. Our patient's initial AKI masked the typical electrolyte imbalances, which became apparent as his kidney function improved. Even after chemotherapy and normalization of lysozyme levels, the proximal tubular damage persisted.

PUB740

Sporadic Hypocalciuric Hypercalcemia Caused by De Novo CaSR Mutation

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Introduction: Hypercalcemic disorders with hypocalciuria are caused primarily by chronic thiazide or lithium use, acquired antibody to the calcium-sensing receptor (CaSR), familial hypocalciuric hypercalcemia (three types: type 1 (*CaSR*), type 2 (*GNA11*) and type 3 (*AP2S1*)) or sporadic type. It is crucial to distinguish among these causes due to different treatment strategy.

Case Description: A 51-year-old man was referred because of hypercalcemia of unknown cause for > 5 years and progressive decline in eGFR. Family and personal history were non-revealing. There were no obvious symptoms related to hypercalcemia but easy fatigue, constipation and deteriorating renal function. Laboratory testing revealed hypercalcemia (12.5 mg/dL; range, 8.6-10.2) with hypocalciuria (spot urine Ca/Cr ratio was 0.019 in mg/dl/mg/dl, 24-hour urinary calcium excretion was 32 mg/day), and inappropriately elevated iPTH (65 pg/mL; range, 10.0-69.0). Parathyroid and abdominal sonography was normal. Direct sequence analysis of the relevant genes inclusive of *CaSR*, *GNA11*and *AP2S1* showed a heterozygous missense T>A nucleotide substitution at c.1661, resulting in an amino acid change I554N in the extracellular domain of CaSR. I554 is well conserved in all species and this novel mutation is not inherited from his parents. In addition, this *CaSR* gene mutation was not found in 200 healthy subjects and should be pathogenic based on the predictive tools via PROVEAN and Polyphen2 score. Calcimimetics with cinacalcet (25 mg daily) reduced his serum calcium concentration to 11.2 mg/dL and iPTH level to 9.7 pg/mL, coupled with an increased urine calcium excretion (spot urine Ca/Cr ratio to 0.06) and eGFR four months later.

Discussion: Genetic diagnosis for idiopathic or sporadic hypocalciuric hypercalcemia is warranted. Calcimimetics by sensitizing the CaSR to calcium rather than parathyroidectomy can be used to treat symptomatic or moderate to severe hypercalcemia patients with loss of function mutation in CaSR.

PUB741

A Fatal Prescription: Metformin Associated Lactic Acidosis

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Introduction: Metformin has become the most widley prescribed type two diabetes medication in the United States, Europe, and Australia. A Cochrane review, and accompanying conclusion, found that the incidence of metformin associated lactic acidosis is 5 cases per 100,000 patient years. This review's conclusions were drawn from patients taking metformin per an established study protocol. Of concern, is the patient population that have a metformin exposure outside the defined prescribing parameters with risk factors for the development of MALA.

Case Description: 58 year old male with end-stage renal disease (ESRD) from unknown etiology, non-insulin dependent type two diabetes, and coronary artery disease presented to a tertiary care medical intensive care unit in trasfer from rural emergency department for managmeent of severe metabolic acidosis and cardiogenic shock. A high anion gap acidosis of 46 and serum osmolar gap of 23 were present on admission which was concerning for toxic alcohol ingestion. Patient was immediately treated with CVVHD in addition to Fomepizole. Approximately 6 hours after admission to the ICU the patient was found to be hemorrhaging from multiple sites and was diagnosed with disseminated intravascular coagulation. 8 hours after admission the patient developed PEA cardiac arrest and expired. Toxic alcohol levels returned negative prompting further post-mortem investigation and a serum metformin level was collected from admission blood work was found to be at a toxic level.

Discussion: The patient had been living transiently through various states receiving compassionate dialysis for several months after being newly diagnosed with ESRD. His fragmented care lead him to continue to take a previously prescribed metformin prescription. This lead to chronic metformin accumulation and the development of MALA, cardiogenic shock, and DIC.

Table 1

	LAB VALUE	REFERENCE	UNITS
Sodium	136	136-145	mmol/L
Potassium	6.9	3.5-5.1	mmol/L
Chloride	88	98-107	mmol/L
C02	<2	22-29	mmol/L
Glucose	153	70-99	mg/dL
BUN	58	6.0-20	mg/dL
Creatinine	8.60	0.8-1.3	mg/dL
Calcium	7.2	8.6-10.0	mg/dL
Albumin	3.8	3.5-5.2	g/dL
Magnesium	2.0	1.6-2.6	mg/dL
Phosphorus	7.6	2.5-4.5	mg/dL
Lactic Acid	14.9	0.5-1.9	mmol/L
Osmolality	324	275-295	mOsm/kg
Ethanol	0	<10	mg/dL
Salicylate	<1	0	mg/dL
Acetaminophen	<5.0	10-30	mcg/mL
pH Arterial	6.81	7.35-7.45	
pC02	20	36-44	mmHg
p02	111	75-85	mmHg
WBC	8.26	4.0-11.0	th/mm3
Hemoglobin	5.1	14.0-18.0	g/dL
Platelets	30	150-450	th/mm3
LDH	1.280	122-222	U/L
Haptoglobin	19	30-200	mg/dL
Fibrinogen	<60	199-495	mg/dL
Protime	>120.0	12.2-15.1	mg/dL
APTT	>150.0	21.0-37.0	seconds
Ethylene Glycol	Not Detected	>20	mg/dL
Methanol	Not Detected	>20	mg/dL
Metformin	44	<5	mcg/mL

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PUB742

Syndrome of Inappropriate Antidiuretic Hormone Secretion Preceding the Diagnosis of Occult Tonsil Cancer

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Introduction: Syndrome of inappropriate secretion of ADH (SIADH) is associated with broad spectrum of malignancy, most notably small cell lung cancer and brain tumors. Still, SIADH patients who lack signs of overt malignancy could be a daunting challenge. Simple correction of hyponatremia without further investigation could miss true etiology of hyponatremia and delay the diagnosis of underlying malignancy. Here we present a case presenting with unexplained SIADH, which led to the diagnosis of occult tonsil cancer.

Case Description: A 59-year-old man presented with chronic dizziness and hyponatremia for two years. He had no previous medical and family history. Review of medication did not find possible offending drugs. He was euvolemic, nonedematous, and normotensive. Cardiac, abdominal and neurologic exams were unremarkable. Laboratory investigations showed serum Na^+ 113 mmol/L, K^+ 4.1 mmol/L, Cl^- 90 mmol/L and osmolality 243 mOsm/kg.H_2O. Serum cortisol, thyroid function and ACTH were normal. Urine biochemistries were osmolality 407 mmol/kg.H_2O, Na^+ 140 mmol/L, K^+ 9.7 mmol/L and Cl^- 157 mmol/L. Chest x-ray, MRI of brain and CT scan of chest were unremarkable. SIADH was diagnosed by the inappropriately concentrated urine during serum hypotonicity and exclusion of hormonal disorders. His hyponatremia was refractory to fluid restriction and loop diuretics. Selective vasopressin receptor antagonist with tolvaptan raised the serum Na^+ to 130 mmol/L. However, hyponatremia recurred quickly after the discontinuation of tolvaptan. To search for occult malignancy, whole body positron emission tomography (PET) scan using 18F-fluorodeoxyglucose identified strong uptake at tonsillar regions. Tonsillectomy was performed and the pathological exam proved the diagnosis of moderately differentiated squamous cell carcinoma. Immunohistochemical staining of ADH was negative in the tumor cells. The patient received concurrent chemoradiotherapy, and his hyponatremia resolved eventually.

Discussion: Thorough workup for the hidden malignancy is important in patients with unexplained SIADH. PET scan could be a useful tool in catching occult cancer, which may not easy to be found by conventional image. Early diagnosis and treatment of the underlying malignancy, instead of simply correcting serum Na^+, should always be kept in mind while managing patients with unexplained SIADH.

PUB743

Hidden Type B Lactic Acidosis in a Patient with Known Underlying Malignancy

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Introduction: Type B lactic acidosis is an uncommon recognized acid base disorder in patients with malignancies including leukemia and lymphoma. We present a patient with non-Hodgkin's lymphoma and monoclonal gammopathy of undetermined significance (MGUS) with mixed acid base disorder including type B lactic acidosis.

Case Description: 83-year-old female patient with multiple medical problems including stage IV low grade non-Hodgkin lymphoma, double band IgM kappa monoclonal gammopathy of undetermined significance (MGUS), hypertension, type 2 diabetes mellitus and dementia presented with altered mental status worsening over three days. On arrival to Emergency Room patient was minimally responsive, afebrile with a heart rate 120 bpm, blood pressure 110/62 mmHg, respiratory rate 23/min. Her initial BUN 96 mg/dl, creatinine 2.4 mg/dl, Sodium 145 mEq/l, Potassium 5.8 mEq/l, Chloride 105 mEq/l, Bicarbonate 31 mEq/l, Lactic acid 4 mmol/l, anion gap 9 mEq/l, Albumin 2.4 g/dl, Lactate dehydrogenase 688 U/l. Arterial blood gas PH 7.09, CO2 77 mmHg, PO2 95 mmHg, bicarbonate of 22.7 mg/dl. Patient required dialysis for oliguria, uremia and severe acidosis which didn't respond to medical treatment. We felt it is more likely to be type B lactic acidosis as patient was not significantly hypotensive and not septic. Patient's mental status improved to her baseline.

Discussion: Type B lactic acidosis is a rare complication of solid tumors and hematological malignancies. Patient has respiratory acidosis with compensated metabolic alkalosis, Despite the elevated lactic acid level, the anion gap was within normal limits even after correcting for albumin. Increased anion gap metabolic acidosis was hidden even with significant lactic acidosis and uremia. Patient's anion gap was 3 after resolution of lactic acidosis and acute kidney injury. Low anion gap in MGUS is probably the reason why her anion gap was within normal limits despite elevated lactic acid level. Type B lactic acidosis in patients with cancer seems to be a marker of poor prognosis regardless of the treatment offered. Limited studies are available specifically addressing management of type B lactic acidosis.

PUB744

Ifosfamide-Induced Fanconi Syndrome in a Patient with von Recklinghausen's Disease

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Introduction: Ifosfamide is an alkylating agent used to treat many solid tumors. Fanconi syndrome secondary to ifosfamide use has been described in the pediatric literature. We report an unusual case of ifosfamide-induced Fanconi syndrome with self-remitting and recurrent proximal tubulopathy with each chemotherapeutic cycle in an adult patient with neurofibromatosis.

Case Description: A 36-year-old female with history of von-Recklinghausen's disease underwent laparotomy and resection of retroperitoneal malignant nerve sheath tumor arising from a neurofibroma. She was initiated on chemotherapy with doxorubicin and Ifosfamide at a dose of 5 gm/m^2 and Mesna for prophylaxis of hemorrhagic cystitis. Of note, 10 years ago she was treated with same chemotherapy agents and had received 2 doses of ifosfamide at 9 g/m^2. She had normal renal function and electrolytes at baseline. A week following chemotherapy, she was admitted for neutropenic fever, and she was noted to have hypokalemia and hypophosphatemia which were refractory to electrolyte replacement. Other laboratory data revealed: sodium 136 meq/l, chloride 109 meq/l, bicarbonate 18 meq/l, BUN 14 mg/dl, Cr 0.55 mg/dl, magnesium 1.5, glucose 94 mg/dl. Urine studies showed pH of 8.5, glucosuria, albuminuria and evidence of urine phosphorus wasting. She was diagnosed with ifosfamide induced proximal tubular injury. Her electrolyte and urinary abnormalities improved over the next week. With the second cycle of chemotherapy a week later, she developed similar pattern of self-remitting proximal tubular injury. She received a third cycle of non-modified chemotherapy with which she had persistent proximal tubulopathy at 4 week follow up.

Discussion: Ifosfamide-induced tubular toxicity is common among children under 4 years and cumulative doses greater than 60 g/m^2. Mechanisms of ifosfamide-induced proximal tubular injury are not well understood, but chloroacetaldehyde, a metabolite of ifosfamide, is implicated. Oxidative stress mediated by glutathione depletion by both ifosfamide and mesna may also contribute. The older age and limited cumulative dose makes this an interesting presentation. Although the long term renal prognosis is good, caution should be exerted in repeated exposure. Apart from dose reduction, limited data is available for other preventive therapies. Cimetidine and n-acetylcysteine are potential options that lack clinical data.

PUB745

Hyponatremia: The Key to Diagnosing a Lung Abscess in an Asymptomatic Patient

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Introduction: Lung pathology such as malignancy or infection can commonly result in inappropriate ADH secretion, causing hyponatremia. This case highlights a unique presentation of a lung abscess, where hyponatremia was the key clinical abnormality suggesting the infectious process.

Case Description: 85 y/o F with PMH of smoking, bronchiectasis, bladder cancer (in remission) presented to the hospital with a chief complaint of acute on chronic lower back pain with new onset radiation to right leg and associated weakness. She was incidentally found to have severe hyponatremia of 120 mmol/L on admission labs. The patient denied any recent illness, fever, chills, confusion, seizure-like activity, productive cough, hematemesis, night sweats or weight loss. On admission, she was afebrile with HR of 89, RR 22, BP 125/106 and O2 of 95% on RA. On exam, she was frail-appearing, with moist mucous membranes, regular heart rate and rhythm, clear lung fields bilaterally and no lower extremity edema. Additional lab work showed serum osmolality of 269 mOsm/kg, urine sodium of 118 and urine osmolality of 467. Uric acid was 3.5 mg/dL, TSH 4.35 uIU/ml and cortisol was not checked. She had leukocytosis of 18.9 K/uL with 95.7% neutrophils. Lumbar spine and femur x-rays were negative for fracture and a right leg duplex ultrasound was negative for DVT. Based on these labs, SIADH was diagnosed and the patient was placed on a 1.5L fluid restriction. On day 2 of hospitalization, Urea-Na 15 g/d was added by nephrology and later increased to 30 g/d for persistent hyponatremia. As part of the SIADH work-up, a Chest CT was performed to rule out lung malignancy due to the patient's history of smoking and bladder cancer. It revealed a 3.4 x 3.9 cm mass in the right middle lobe. The patient underwent a CT guided biopsy of the mass demonstrating an abscess, which grew Pseudomonas aeruginosa. She was started on a prolonged course of Ciprofloxacin and continued on Urea-Na 30 g/d with a fluid restriction. This resulted in a sodium correction to 128 at discharge, and to 135 after completing one month of antibiotic therapy for the lung abscess.

Discussion: Lung abscesses can cause hyponatremia due to SIADH. However, only a few cases are reported. This asymptomatic patient's severe hyponatremia helped identify the lung abscess, hence guiding therapy.

PUB746

5-Oxoprolinemia - An Underdiagnosed Cause of High Anion Gap Metabolic Acidosis

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Introduction: 5-oxoprolinemia was first identified in 1989 as a cause of high anion gap metabolic acidosis (HAGMA) but is rarely considered as a part of initial differential. After ruling out important causes of HAGMA, one can consider this rare entity in patients with certain risk factors such as malnutrition, pregnancy, vegan diet, and hepatic or renal disease. 5-oxoprolinemia is caused by deficiency of glutathione synthetase and 5-oxoprolinase deficiency related to drug toxicity like acetaminophen. Our case highlights the importance of considering 5-oxoprolinemia early in patients with unclear etiology of HAGMA.

Case Description: 71 year old female with recently treated gallstone pancreatitis, pancreatic abscess status post drain placement was readmitted for 5 days of abdominal pain and vomiting. On admission, she was in acute distress with unstable vital signs (heart rate-113, respiratory rate-30) with diffuse abdominal tenderness. Initial laboratory data showed: HCO3 4mmol/l, Creatinine 1.89 mg/dl, glucose 242 mg/dl, anion gap(corrected) 22, white blood cell count 26.9 KU/L, lipase 2323 U/L, INR 1.7, lactic acid 3.6mmol/l, negative urine and serum ketones, and an arterial blood gas showing pH 6.81, PaCO2 27 mmHg, HCO3 <7.9 mg/dl. Imaging showed improved peripancreatic fat stranding compared to previous CT scan. She was treated with IV fluids, antibiotics and a bicarbonate infusion. Despite above measures, her HAGMA persisted, prompting consideration of other causes including drugs. Her serum acetaminophen level was 240.8mcg/ml thus she was started on N-acetylcysteine and her liver function test were monitored. Due to worsening INR, she was transferred to a liver transplant center for evaluation. High acetaminophen level with concurrent high 5-oxoproline level in setting of malnutrition identified acetaminophen as the culprit for this HAGMA.

Discussion: 5-oxoprolinemia is an important cause of HAGMA, hemolytic anemia and central nervous system dysfunction. Higher acetaminophen level leads to increase in 5-oxoproline levels by directly depleting glutathione levels in the liver. Treatment is mainly IV hydration and N-aceytlcysteine (regenerates glutathione). Meticulous history and awareness of rare etiologies is important and can significantly reduce morbidity and mortality in patients with HAGMA.

PUB747

Cerebral Salt Wasting in Neurosurgical Patient

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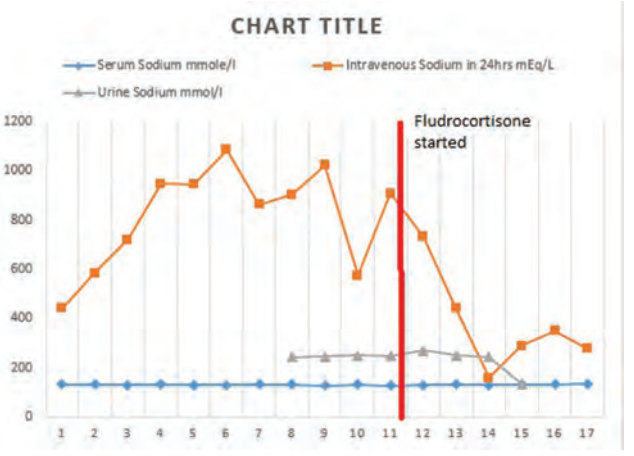
Introduction: We report a case of cerebral salt wasting as an uncommon cause of hyponatremia. Making the diagnosis rapidly is vital as its treatment requires volume and sodium restoration rather than the water restriction as in SIADH. Hyponatremia is common in neurosurgical patients and is associated with substantial morbidity and mortality. Diagnosis of the cause and its correction are essential to prevent severe hyponatremia, which can substantially worsen cerebral edema and increase risk of seizures.

Case Description: 44 yr old male with past medical history of traumatic brain injury at 14 yrs of age with multiple infections of ventriculo peritoneal shut in the past admitted with altered mental status. VP shunt was removed along with washout of ventricle due to repeat CNS infection. Post op serum sodium 131 mmol/L started on 3% NaCl to prevent cerebral edema, serum and urine osmolality were 265 and 569 respectively with urine sodium 245mmol/L. We suspected CSW due to clinical volume depletion, low CVP, urine sodium >200 and large volume urine output. Fractional excretion of Uric acid and phosphorus were high 33%, 29% respectively. After starting fludrocortisone on day 11 his requirement of IV Na and urine Na improved.

Discussion: CSW is a disorder of sodium and water homoeostasis which occurs as a result of cerebral disease in the setting of normal renal function. CSW results in inappropriate primary sodium losses which are not related to volume expansion. The pathogenesis of CSW remains unclear; however any injury to the brain cells releases atrial, brain C type and dendroapsis natriuretic peptides appears to be the driving factor in pathogenesis of CSW. It is postulated that these substances reduces the efficacy of aldosterone and leads to decreasing ability of the kidneys to resorb sodium causing very high urine sodium concentration, a high urine output leading to low volume state. High fractional excretion of uric acid and phosphorus occurs CSW.



PUB748

Renal Salt Wasting (RSW) with Normonatremia Secondary to Acquired Mineralocorticoid Deficiency

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Introduction: RSW is a syndrome represented by hypovolemia, hyponatremia in face of excess urinary sodium loss resulting in ECV contraction. We demonstrate a case of Polyuria with excess urinary sodium loss without significant hyponatremia (net water gain from excess ADH).

Case Description: 44-year-old male with PMH of HTN presented with persistent fevers and AMS. He was found to have bacterial meningitis and brain abscess. His hospital course was complicated by septic shock requiring vasopressor support but baseline urine output remained roughly around 3 L per day, with evidence of euvolemia and normal renal function. Following improvement of his hemodynamics and overall clinical status, he developed significant polyuria as well as renal salt wasting coupled with hypovolemia and hypotension not explained by intake and previously infused crystalloid.

Discussion: The literature addressing etiology of polyuria in the ICU population is scarce. In such contexts, the differential diagnosis should include auto-diuresis from previously given IV fluids, polyuria of sepsis, polyuria of recovery from ATN, diabetes insipidus (DI), cerebral salt wasting (CSW), and mineralocorticoid deficiency among others. In this particular patient, given his normonatremia, DI and CSW alone would not explain these findings; however, a combination of the two is possible. On Day 3, patient had urine output of 9.5 L with urine sodium of 166 mEq/L resulting in total sodium loss of 1577 mEq (1577/154 = 10.2 L of 0.9% saline). This degree of ECV salt loss is associated with profound hemodynamic instability and cannot be replaced without massive volume repletion. In this situation given preserved renal function, acquired transient mineralocorticoid deficiency from sepsis appears to be the best plausible explanation, hence decision to start low dose Fludrocortisone was made with dramatic clinical and hemodynamic response. Absence of hyponatremia can possibly be explained by not allowing to progress to the threshold for ADH release (10-15% ECV volume loss) by constant 0.9% saline and probably hampered CRH and ADH production resulting in decreased ACTH and adrenal steroid production. This case highlights complexity of polyuria in critically ill patients. Fludrocortisone presents a reliable alternative of massive volume repletion in select cases with acquired transient mineralocorticoid defect of sepsis.

PUB749

A Case of Cisplatin Induced Salt Wasting Nephropathy

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Introduction: Salt wasting nephropathy is a rare cause of polyuria and hyponatremia and is associated with cisplatin and other platinum based chemotherapy. Patients with salt wasting nephropathy typically present with hyponatremia, hypovolemia and orthostatic hypotension. This is a case of a patient who presented with salt wasting nephropathy secondary to cisplatin.

Case Description: A twenty-eight year old male with history of recurrent non-seminoma testicular cancer with metastasis to the lungs presents to the hospital with a right sided empyema. He underwent decortication and washout and was admitted to the intensive care unit for hypoxic respiratory failure. On admission, serum sodium was 133 mmol/L. His sodium worsened to 126 mmol/L one month into hospitalization. At that time, the hyponatremia was suspected to be due to low solute intake along with SIADH in the setting of paroxetine use and malignancy. His urine sodium was 73 mmol/L and urine osmolality was 490 mOsm/kg. Paroxetine was tapered off and sodium improved to 136 mmol/L. He was also receiving cisplatin chemotherapy for cancer treatment. Shortly after his initial hyponatremia resolved, he developed polyuria of 9 L in 24 hours. At onset of polyuria, serum sodium was 124 mmol/L, urine sodium was 95 mmol/L, and urine osmolality was 292 mOsm/kg. His urinary losses were replaced with fluids at a one to one replacement rate. Over the next two days, his urine sodium rose to 180 mmol/L and urine osmolality rose to 402 mOsm/kg. He continued to make between 9 and 15 L of urine daily, so replacement rate of fluids was decreased to two thirds of urinary losses. Despite this, four days later his urine osmolality was 381 mOsm/kg, which led to high suspicion for salt wasting nephropathy. In addition, he was orthostatic and tachycardic, further correlating with salt wasting nephropathy.

Discussion: Salt wasting nephropathy is a rare cause of chemotherapy induced hyponatremia and can be seen with cisplatin and other platinum based chemotherapy. In one study of 70 patients treated with cisplatin for 18 months, 7/70 developed salt wasting nephropathy. All of these patients presented with severe orthostatic hypotension. Their urine sodium ranged from 85-145 mmol/L and urine osmolality ranged from 340-619 mOsm/kg. It is important to recognize salt wasting nephropathy, as management includes replacing water and salt loss.

PUB750

Diabetes Insipidus: Diagnosing Dilemma in a Patient with Cerebral Palsy

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Introduction: Diabetes Insipidus (DI) is a disease in which the secretion of or the response to the pituitary hormone vasopressin is impaired, resulting in the production of large amounts of dilute urine, often associated with dehydration and avid thirst. DI can be central vs nephrogenic (CDI and NDI respectively) subdivided further into partial vs complete. In general, a stepwise approach will help differentiate in most adult patients. Here we present a challenging case in which an accurate diagnosis was delayed in part related to the patient's mental and physical disability.

Case Description: 33 year old Latin male with history of cerebral palsy epilepsy and inflammatory arthritis, presented with sepsis secondary to pneumonia. Due to the patient's mental disability, history was obtained from his mother. He was started on Methotrexate, leflunomide, and steroids approximately 7 months ago. In addition, persistent polyuria of 12-15 diaper changes per day and polydipsia started around the same time. Labs on admission showed a sodium 152 mmol/L, potassium 3.5 mmol/L, chloride 116 mmol/L, bicarbonate 26 mmol/L, glucose 95 mg/dL, and creatinine of 0.47 mg/dL. Urinalysis: specific gravity 1.002, pH 7.0, negative glucose, ketones, blood, RBC or WBC. Hemoglobin A1C was 4.4%. He was volume replete with crystalloids for sepsis, however hypernatremia remained and polyuria persisted. Desmopressin (DDAVP) was given on day 2 of admission with only mild decrease in urine output (UOP) and rise in urine osmolality. Water deprivation test was not possible due to agitation and insomnia, so another approach was taken. DDVAP and intravenous fluid were withheld for 2 days, and patient was allowed to drink to thirst. Urine and serum osmolalities with electrolytes were trended showing reoccurrence of hypernatremia and polyuria. Prior to giving DDAVP again, urine osmolality automatically improved from 131 to 451, and after restarting DDAVP, there was further rise in urine osmolality. This data suggested Partial CDI, so MRI brain was done which showed a central germinoma infiltrating the posterior pituitary stalk.

Discussion: This case shows the difficulty in diagnosing partial NDI vs partial CDI in patients with mental disabilities who are unable to comply with routine methods used for diagnostic purposes. DDAVP will increase urine osmolality with overlapping values in both partial CDI and partial NDI which makes diagnosis a challenge.

PUB751

Central Diabetes Insipidus Preceding Thrombocytosis Caused by Acute Myelogenous Leukemia

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Introduction: Central diabetes insipidus (CDI) is commonly caused by organic lesions affecting the hypothalamic-pituitary regions. However, CDI preceding the thromobocytosis uncovering acute myeloid leukemia (AML) was rarely reported and could go unrecognized, leading to delayed diagnosis with inappropriate treatment

Case Description: A 61-year-old man was referred for the unknown cause of CDI with sudden polyuria, polydipsia, and thirst for 3 months. His family and personal history were unremarkable. There was no visual field defect. CDI was confirmed by water deprivation and desmopressin test. Magnetic resonance imaging of the brain revealed loss of the posterior pituitary bright spot on T1 weighted sequences without other abnormality. At that time, a thorough examination including complete blood count, immune, tumor, infection, and inflammation survey was non-revealing. On laboratory examination, a markedly high platelet count (1,038,000μL) was found despite normal platelet counts 3 months ago. The leucocyte count was 19,400μL with 62.3% blast. Bone marrow examination showed hypercelluler marrow plus megakaryocytes and infiltration with 25% blast cells. The immunohistochemical and flow cytometry results were consistent with AML-M2. He achieved complete remission with resolution of CDI after induction and consolidation chemotherapy. To date, there were only five cases presenting with CDI, thrombocytosis and AML, all showing the association with chromosome 3 or 7 abnormalities. Cytogenetic analysis in this patient was normal despite positive CEBPA and negative FLT3 and NPM1 gene mutations.

Discussion: CDI may be the preceding and presenting feature of thrombocytosis and/or AML. A regular check-up of complete blood count test is necessary for early diagnosis of hematologic abnormalities. The mechanism connecting abnormality of the hematopoietic cells, impact on the neurohormonal cells in the hypothalamus, chromosomes abnormality and platelets warrants further investigation.

PUB752

Unique Case of Severe Metabolic Alkalosis from a Gastro-Ileal Fistula: The Role of PPIs

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Introduction: Metabolic alkalosis is the most common acid-base abnormality seen in-hospital. It results from the loss of extracellular acids or the gain of bicarbonate. Persistent vomiting has been known to cause alkalosis through the loss of hydrochloric acid rich gastric secretion. We report a case of gastro-ileal fistula causing severe alkalosis through a similar mechanism.

Case Description: 53-year old man with history of rectal cancer, Crohn's Disease with total colectomy, ileostomy, and short gut syndrome, was admitted for severe hypokalemia (serum potassium 2.3 mEq/L) and metabolic alkalosis with bicarbonate of 49 mEq/L. He reported increased quantity of watery stool in his ileostomy for one month. Exam was significant for dry oral mucosa, and ileostomy bag with clear liquid. Labs revealed acute kidney injury (creatinine 1.20 mg/dL from baseline of 0.77 mg/dL) and normal anion gap. Arterial gas showed pH of 7.567 and pCO2 50.0. Urinalysis was normal with pH of 7.0. Ileostomy content was very acidic with pH less than 6.0 and beyond the lab range. CT abdomen with oral and IV contrast showed normal appearing bowel loops and ileostomy. However, there was no trace of oral contrast. Acidic ileostomy fluid, electrolyte abnormalities, and absence of oral contrast on imaging were suggestive of gastro-ileal fistula. Severe metabolic alkalosis was thought to be due to continuous loss of gastric hydrochloric acid. Electrolytes were replaced and he was aggressively hydrated. He was started on a proton pump inhibitor (PPI), and his alkalosis improved rapidly in 48 hours. Ileostomy output decreased and labs normalized over the next 5 days. He was discharged on pantoprazole.

Discussion: Acidity of the GI tract varies based on location with the lowest pH in the stomach which gradually increases down the small bowel. In our patient, severe alkalosis was thought to be due to the continuous loss of gastric acid containing a significant amount of H+ ions. Hypovolemia and hypokalemia also contributed to his alkalosis. PPIs are pro-drugs which concentrate in the gastric parietal cell canaliculi and bind irreversibly to the H+/K+ pumps. They have been shown to induce profound hypochlorhydria in the stomach, with a single dose shown to raise the pH from 2.0 to 6.0 in the stomach. This supported the use of PPI in our patient to prevent the acid loss, preserve H+ ions, and help correct the alkalosis.

PUB753

Acid-Base Disorder in Extremis

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Introduction: In physiological conditions, normal acid-base homeostasis is maintained by an interplay of respiratory or metabolic compensation to counteract the primary disorder. We present a case of severe acute on chronic hypercapneic respiratory acidosis that was compensated to near normal pH by an extreme elevation of serum bicarbonate.

Case Description: A 43-year-old male with a history of chemoradiation for recurrent Hodgkin's lymphoma complicated by pulmonary fibrosis and right hemidiaphragmatic paresis leading to chronic respiratory acidosis on BiPAP treatment at home, and constrictive pericarditis treated with pericardiectomy presented with increased somnolence. He was on bumetanide 3 mg twice a day at home. On exam, he was afebrile, hemodynamically stable with an oxygen saturation of 100% on room air. He was difficult to arouse, oriented to time and person with normal cardiorespiratory exam and 2+ lower extremity pitting edema. His blood gases showed a pCO_2 of 126 mmHg, bicarbonate of 68 mEq/L and pH of 7.34 on arrival. Renal function was normal with creatinine of 0.6 mg/dL and potassium and chloride were low at 3.4 mEq/L and 77 mEq/L respectively. Given that his pCO_2 in prior admissions had always been >110 mmHg and bicarbonate >55 mEq/L with near normal pH and no symptoms, it was decided to lower pCO_2 only slightly using intermittent BiPAP in a controlled fashion with concomitant acetazolamide for a brief alkaline diuresis. The patient's mental status rapidly improved with this intervention and at the time of discharge his blood gas showed pH 7.46, pCO_2 99 mmHg and bicarbonate 69 mEq/L. Given his persistent fluid overload, he was maintained on a reduced dose of bumetanide 2 mg orally twice a day to avoid diuretic-induced metabolic alkalosis.

Discussion: In patients with chronic respiratory acidosis secondary to pulmonary diseases, obstructive sleep apnea and obesity hypoventilation syndrome, it is not unusual to find some degree of metabolic compensation in the presence of normal renal function. However, it is rare to find an asymptomatic patient who has chronic respiratory acidosis with a pCO_2 consistently above 100 mmHg and a serum bicarbonate above 60 mEq/L as compensation with near normalization of pH. In treating such patients, caution should be exercised in correcting chronic respiratory acidosis aggressively as the resulting severe metabolic alkalosis can lead to life-threatening complications such as disorientation, seizures and coma.

PUB754

A Puzzling Case of Severe Hypokalemia in Pregnancy

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Introduction: Hypokalemia is a dangerous electrolyte disturbance in pregnancy. It is defined as a serum potassium level less than 3.5 mmol/L and is associated with EKG abnormalities, arrhythmias, or rarely rhabdomyolysis. We present an interesting case of a 25-year-old pregnant female with severe hypokalemia.

Case Description: A 25-year-old G1P0 female at 32 weeks gestation was admitted with potassium less than 1.8mmol/L. She had decreased oral intake, nausea, and vomiting for four days which was initially thought to be the cause of hypokalemia. However, she also had polyuria with urine output up to 400 cc/hr. She had hypernatremia (Na of 147 mmol/L). Liver function tests were elevated and CK trended up to 28,786 U/L. EKG revealed prolonged QT interval. Urinalysis showed +1 protein, +3 ketone, and pH 6.5. Urine potassium and sodium were 77.9 and 152 mmol/24 hours respectively with dilute urine (65 mosm/kg H_20) likely in the setting of diabetes insipidus (DI) despite no known prior history. In addition to pain in lower extremities, she had jaw pain and headache. MRI brain was notable for diffuse myositis of the muscles of mastication and nonvisualization of T1 hyperintensity of neurohypophysis. Hypotonic Intravenous fluids were used initially with both oral and IV potassium supplementation. Urine output decreased and urine osmolality rose to 228 mosm/kg H_20 after a dose of desmopressin (DDAVP). Serum potassium improved with continued oral supplementation and high potassium diet. Her pain and hypernatremia resolved. She was discharged home on oral potassium and nasal DDAVP with close follow up.

Discussion: This case highlights the complex etiology of hypokalemia and associated complications in pregnancy including unusual presentation of rhabdomyolysis for which clinicians should remain vigilant. Our patient's combination of polyuria with increased urinary potassium loss in the setting of likely prior undiagnosed diabetes insipidus and gastrointestinal losses led to severe hypokalemia. As a result, she developed the rare complication of rhabdomyolysis affecting the muscles of mastication as well. She will need MRI imaging of the pituitary after delivery to confirm central DI diagnosis. Such patients need close monitoring throughout pregnancy in a multidisciplinary approach for effective treatment and avoidance of complications.

PUB755

Hypercalcemia as Presentation of Renal B Cell Lymphoma

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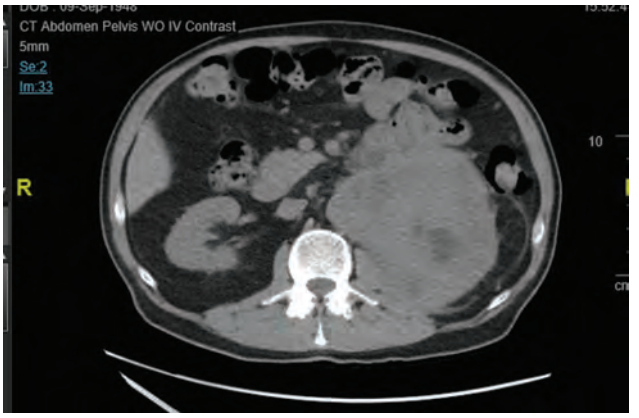
Introduction: Primary renal lymphoma (PRL) is a rare condition that mimics renal cell carcinoma. We describe a patient who presented with hypercalcemia and acute renal failure who was found to have a large mass in his kidney that was biopsied and showed diffuse large B cell lymphoma (DLBCL). He was started on rituximab, cyclophosphamide, vincristine, doxorubicin prednisone (R-CHOP) and radiation. We report this case to highlight the pitfalls in diagnosis of this rare entity as well as the peculiar presentation of hypercalcemia

Case Description: 69 year old man with history of hypertension presented with 4 months of nausea, weakness, and weight loss. He was found to have serum calcium 13.3mg/dL and serum creatinine of 4mg/dL (baseline 0.9mg/dL 6 months ago). Workup showed suppressed PTH, and PTH-rp, a normal ACE, vitamin D 25 and mildly elevated vitamin D1, 25. His paraprotein workup was negative. He received 0.9% normal saline, calcitonin and pamidronate. CT scan abd/pelvis showed a 15 cm mass in the left renal fossa. There was high suspicion of renal cell carcinoma but due to technical difficulty in surgical approach, a decision was made to do a renal biopsy instead of nephrectomy. Kidney biopsy was consistent with DLBCL. A PET scan showed a large area of intense FDG uptake only in the left renal lesion. He completed 6 cycles of R-CHOP with improvement in serum creatinine to 1.3mg/dl, normal calcium and a repeat PET scan after R-CHOP completion that showed improved FDG uptake. He is to receive radiation.

Discussion: PRL are extremely rare extranodal lymphoma. It usually presents as flank pain, hematuria, renal failure and diagnosed after nephrectomy. This is an aggressive cancer with grave prognosis. This case is unique as our patient presented with hypercalcemia, got a renal biopsy, was started on chemotherapy and radiation and responded well. We highlight the importance of high index of suspicion when faced with renal mass and hypercalcemia, to think about PRL as the management is completely different from renal cell carcinoma



PUB756

Seminoma Presenting as Acute Renal Failure and Hypercalcemia

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Introduction: Hypercalcemia is commonly associated with various solid and hematologic malignancies, but rarely associated with seminoma. Similarly rare is 1,25 dihydroxyvitamin D (calcitriol) mediated hypercalcemia, which is more commonly associated with lymphomas and sarcoid-related granulomatous disease. Here we describe an atypical presentation of a patient with seminoma patient presenting with acute renal failure and hypercalcemia.

Case Description: The patient is a 55-year-old Caucasian male with history of left orchiopexy for undescended testis as a child presented to the nephrology clinic for acute renal failure with Cr to 2.37 mg/dL on a routine laboratory test with no recent baseline. His only complaint was a dull abdominal discomfort and constipation for 2 months. Abdominal exam revealed a fixed large abdominal mass. CT scan showed a 9.4 cm x 15 cm x 18.4 cm retroperitoneal mass and mild left hydronephrosis. Serum calcium (SCa) elevated at 12.3 mg/dL. His SCa rapidly normalized with IV saline infusion, and Cr downtrended. Work up revealed suppressed PTH (3 pg/mL), normal 25-OH Vitamin D3 (30.3 ng/mL), low PTHrP (1.1 pmol/L), and an elevated 1,25 dihydroxyvitamin D level to 119 pg/mL. Serum ACE level elevated to 73 units/L. Pathology showed a metastatic seminoma. Patient received Cycle 1 of cisplatin and etoposide (CE). He was discharged with SCa of 8.0 mg/dL with no additional therapy and improved kidney function (Cr 1.28 mg/dL). Patient recently underwent cycle 2 of chemotherapy with stable renal function and normal SCa.

Discussion: This case is unique in illustrating an atypical cause of acute renal failure due to hypercalcemia associated with seminoma due to a tumor sarcoid-like reaction. Hypercalcemia normalized with CE chemotherapy regimen which included steroids, the typical treatment of sarcoid-associated hypercalcemia.

PUB757

Isolated Hyperkalemia During Anesthesia

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Introduction: Hyperkalemia can occur during anesthesia even in the absence of renal failure and may result in cancellation of surgery. We would like to present a case and discuss possible mechanisms.

Case Description: A 62 year old African American male with a past medical history of hypertension, type 2 diabetes mellitus, chronic hepatitis C and recently diagnosed duodenal cancer was admitted for elective pancreaticoduodenectomy. This was his first time receiving general anesthesia. He was not on an ACE inhibitor because of a single episode of hyperkalemia in the past. Pre-operative potassium from 2 weeks prior was normal as were several other measurements in the past. His CKD-EPI eGFR was 93 ml/min/1.73 m2. In the operating room, he was given Isoflurane, Sevoflurane, Propofol, Rocuronium and Vecuronium. He was found to have hyperkalemia (7.0-7.6) on intra-operative blood gases repeated x3. A basic metabolic panel confirmed a serum potassium of 7.3 meq/L with tall tented T waves on electrocardiographic monitoring. There was no evidence for tumor lysis, rhabdomyolysis, hemolysis or hematoma. He also did not develop any features of malignant hyperthermia during observation. Surgery was cancelled before the first scalpel. Hyperkalemia resolved with furosemide administration.

Discussion: There may be several reasons for isolated hyperkalemia in this patient. Firstly, he may have had impairment of extra-renal potassium disposal secondary to increased alpha adrenergic tone as has been described in the past. Secondly, he may have had a genetic predisposition to hyperkalemia as is found in patients who develop malignant hyperthermia in association with anesthetic agents. However, the whole syndrome of malignant hyperthermia was not present in this patient.

PUB758

Much Ado About Nothing

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Introduction: Sirolimus is a mTOR (mammalian target of rapamycin) inhibitor that is used for immunospression in solid organ transplant recipients. Common side effects include pancytopenia, thrombotic microangiopathy, proteinuria and delayed wound healing. We present a case of massive hemothorax following automated implantable cardioverter-defifrillator (AICD) placement from sirolimus use.

Case Description: 49 year old female with history of childhood glomerulonephritis (unkown etiology) with third kidney transplant and h/o 2 failed kidney transplants in the past, who presented for elective AICD placement. During immediate post operative period, patient developed massive bleeding from AICD site causing hemothorax requiring bilateral chest tube placement. Past medical history includes: diabetes mellitus, hypertension, asthma and schizoaffective disorder. Her labs include: BUN/CR 49/1.8 mg/dl (baseline 1.1 mg/dl prior to procedure). Hemoglobin was 8.1 g/dl, platelets 202,000/UL, WBC 11,400/UL. Her albumin level was 1.3 g/dl. Donor specific antibody was not elevated. Renal ultrasound showed increased resistive indices without hydronephrosis. Home immunosupression includes: mycophenolate 750 mg twice a day, prednisone 5 mg and sirolimus 2 mg daily. Nephrology was consulted for the management of postoperative acute kidney injury following the procedure. We first recommended to hold sirolimus and started patient on tacrolimus 1 mg twice a day. Patient required 18 units of PRBC transfusion and multiple units of fresh frozen plasma. Hospital course was complicated by respiratory failure requiring intubation, hemodnamic acute tubular necrosis requiring dialysis. After a prolonged ICU stay, patient continued to fail spontaneous breathing trials. She was thus transferred to longterm assisted care with tracheostomy and on maitenance hemodialysis three times a week.

Discussion: This is the first case of massive hemothorax following AICD placement from sirolimus use per our literature review. Through this case we would like to suggest that sirolimus should be held for atleast 2-4 weeks prior to any kind of surgical procedure. Nephrology has to be involved early in the preoperative care of kidney transplant recipients even when they are going for minor elevtive procedures.

PUB759

The Effects of Rituximab on Atherosclerotic Biomarkers in Kidney Transplant Recipients

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Background: Cardiovascular disease is the leading cause of mortality in renal transplant (tx) recipients. Rituximab is widely used in kidney transplantation. There are few reports about the relationship between rituximab and atherosclerotic process in rheumatologic disorders. The aim of the study was to evaluate the efficacy of rituximab on atherosclerotic biomarkers in kidney tx recipients.

Methods: Forty renal tx patients who did not have a history of cardiovascular event were included to study. All of the patients in the treatment group (n:27) were received at least of one dose of 375 mg/m^2 rituximab. The control group (n:13) were selected by historically and donor type matched patients. Quantitative measurement results were compared between rituximab and control group of kidney tx recipients for atherosclerotic biomarkers: interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-alpha), transforming growth factor beta (TGF-beta) and oxidized low-density lipoprotein (anti-oxLDL) antibody. Counts of B lymphocytes, T lymphocytes and natural killer cells were measured in both groups.

Results: Demographic parameters, laboratory results of the patients were demonstrated in Table. Counts of B, T lymphocytes and natural killer cells were significantly lower in rituximab group compared to control group. Serum IL-10 levels were significantly higher in the rituximab group compared to the control group, although anti-oxidized low-density lipoprotein levels were lower in the rituximab group compared to the control group though this did not achieve statistical significance.

Conclusions: Rituximab treatment may decrease lymphocyte counts and IL-10 levels, however significant decreases in all atherosclerotic biomarkers has not been shown.

Demographic parameters, laboratory results of the patients

	Patients with rituximab (n=27)	Control group (n=13)	p
Age (years) (mean ± SD)	43±13	43±15	0.623
Sex (n, %)	-	-	-
Female	10 (37%)	5 (38.5%)	0.931
Male	17 (63%)	8 (61.5%)	
Previous renal replacement history	-	-	-
Hemodialysis (n, %)	13 (48%)	11 (85%)	0.027
Peritoneal dialysis (n, %)	3 (11%)	1 (8%)	0.736
Duration of dialysis (years) (mean ± SD)	4±4	5±4	0.427
Indications of rituximab (n, %)	-		
Antibody mediated rejection	17 (63%)		
Desensitization therapy	6 (22%)		
Post-transplant FSGS recurrence	3 (11%)		
Membranous glomerulonephritis	1 (4%)		
Laboratory Results (mean ± SD)	-	-	-
CD19+ B lymphocyte count	27.4±50.2	145.5±149.9	0.001
CD3+ T lymphocyte count	1175±700	1908±622	0.008
CD16+ 56+ natural killer cell count	94.6±90.0	713.9±1996.2	0.049
CD45+ T lymphocyte count	1333±777	2219±781	0.005
Serum level of IL-10 (pg/ml)	6.1±2.4	4.6±0.9	0.043
Serum level of TNF-alpha (pg/ml)	58.3±111.1	10.5±3.4	0.112
Serum level of TGF-beta (ng/L)	465.6±395.7	613.1±496.7	0.254
Anti-oxLDL antibody level (ng/L)	3845±3386	4597±4167	0.634

Abbreviations: FSGS; Focal segmental glomerulosclerosis, CD; Cluster of differentiation, IL; Interleukin, TNF; Tumor necrosis factor, TGF; Transforming growth factor, oxLDL; Oxidized low-density lipoprotein.

PUB760

Antioxidant Capacity in Mexican Kidney Transplant Recipients

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Background: Kidney transplant (KT) offers a better quality of life in patients with Chronic Kidney Disease (CKD). Despite the benefits of KT, long-term survival rates have shown none satisfying status due to graft failure. KT prone to oxidative stress mediated injury by diverse pre- and post- transplant conditions affecting the allograft and other clinical disorders in kidney recipients. The aim of this study was to determine the total antioxidant capacity in post transplantation anemia kidney transplant recipients (KTR).

Methods: The study included 41 adult patients during the maintenance period (>1 year) following renal transplantation, treated with different combinations of immunosuppressive agents. The total antioxidant capacity (TAOC) of plasma was measured using Trolox-equivalent antioxidant capacity (TEAC) assay

Results: A higher proportion of female KTR, mean age was 29.53 ± 7.24 years. They had a TAOC 326.77 - 473.12 ± 399.95 µmol/L. There was a significantly negative correlation between TAOC and plasma creatinine (R^2 = -0.551, p = 0.033) and a positive correlation between TAOC and hematocrit in patients treated with tacrolimus but not with cyclosporine.

Conclusions: This study could asses that TAOC values were associated with immunosuppressive therapy and anemia, and these could be determinant risk factors to increase of oxidative stress. Further studies are needed to determine oxidative stress pathways and if it can improve the allograft survival.

Funding: Government Support - Non-U.S.

PUB761

Considering Kidney Function When Screening for Hepatitis C Virus at Temple University Hospital

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Background: State mandates have prompted hospitals to implement Hepatitis C Virus (HCV) screening programs to capture high-risk individuals and facilitate treatment. It is not standard to screen kidney function before treating HCV, despite evidence of increased risk of chronic kidney disease (CKD). Individuals living with HCV and CKD may eventually require a kidney transplant, and can receive a cadaver HCV positive kidney significantly sooner if they delay HCV treatment until after the transplant.

Methods: The goal of this project was to identify the proportion of HCV patients with kidney disease at Temple University Hospital (TUH) and use that data to design a tool within the hospital's electronic health record system to facilitate proper nephrology care. Data were collected from the electronic health records of HCV patients at TUH that were seen for the first time in 2017 for HCV treatment. Demographic information, data about kidney function, and information about the referring department were collected. Patients that would have benefitted from a nephrology consultation before HCV treatment were identified.

Results: Of the 637 patients seen for HCV treatment at TUH, 29 (4.6%) were seen by a nephrologist. An additional 84 (13%) patients were identified as having an estimated glomerular filtration (eGFR) rate less than sixty, making them candidates for nephrology care before HCV treatment. Twenty-five patients were found to have an eGFR less than thirty, warranting urgent nephrology care.

Conclusions: New technology to identify late stage CKD patients would increase the number of HCV patients receiving nephrology care at TUH.

PUB762

Comparison of Immunohistochemical Staining for Large T Antigen and VP1 in Polyomavirus Nephropathy After Kidney Transplantation

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Background: Banff Working Group on Polyomavirus Nephropathy (PVN) proposed a new histological classification consisting of pvl and ci scores, and recently demonstrated that the classification is a useful predictor of graft dysfunction. Most transplant centers use SV40 large T antigen (TAg) staining for pvl scoring, while the expression of TAg is decreased and VP1 is increased on the course of viral replication in the tubular epithelial cells (TECs). In addition, TAg and VP1 staining in biopsy specimen of PVN has not been clearly compared.

Methods: From 1996 through 2017, 16 patients developed biopsy-proven PVN in Kyushu University Hospital. We performed immunohistochemical staining using commercially available anti-SV40 TAg and anti-BKV VP1 antibodies in the serial sections of 16 index biopsies and 12 follow-up biopsies. We compared the patterns of positive staining, and the number of positive tubulus (%) in all biopsies. In 16 index biopsies, we investigated the correlation between serum creatinine increase from the baseline and the number of positive tubulus determined by SV40 TAg and BKV VP1 staining.

Results: In BKV VP1 stained section, positive staining was observed not only in the nuclei of TECs, but also in the cytoplasm, cells shedding into the lumen, and intratubular casts. Two of 28 biopsies (7.1%) showed negative staining for BKV VP1, in which SV40 TAg positive tubulus were detected in less than 1%. The median (interquartile range) percentage of positive tubulus was 2.8 (0.7-9.8) % in SV40 TAg and 1.4 (0.5-3.9) % in BKV VP1 staining (P=0.2). In 16 index biopsy, serum creatinine increase significantly correlated with the number of BKV VP1 positive tubulus (r=0.49, P<0.05), while it did not with the number of SV40 TAg positive tubulus.

Conclusions: In BKV VP1 staining showed various pattern of positive cells, but it could detect approximately half as many tubulus as SV40 TAg staining, which might cause a false negative results in the specimen with minimal BKV replication. On the other hand, increased BKV VP1 positive staining means advanced damages of TECs and has possible association with graft dysfunction.

PUB763

Predonation Laparoscopic Sleeve Gastrectomy for Morbid Obese Kidney Donors

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Background: The prevalence of obesity is increasing in the general population so number of living donor transplants due to elevated BMI have declined by 13%. This procedure is required to reduce the future complications of the donor including CKD and increase the donor pool. According to a study by Locke et al obese donors had a 1.9 fold increased risk of ESRD post donation and this cohort was free of diabetes and hypertension at the time of donation which are conditions known to contribute to ESRD. This data suggests that obese living donors should be counseled for weight loss programme. Laparoscopic sleeve gastrectomy(LSG) is used as a procedure for treating morbid obesity. However we have seen very few reports of LSG as a procedure for weight loss to improve chances of donation in a morbidly obese donor. Published analysis(Brooks et al) suggests that a live donor though obese is more cost effective than a deceased donor even if LSG is used to reduce the weight.

Methods: We intentionally performed LSG in preparation of kidney donation. We reviewed charts of these ten donor nephrectomy patients who were subjected to LSG between 2012 and 2017.

Results: The age range of donors was 32 to 65 years(mean 41.1 years). Presurgery BMI ranged from 35.3kg/sqm to 46kg/sqm(mean 41) and post surgery BMI ranged from 27 to 36 kg/sqm (mean 32.3kg/sqm) at the time of donation. LSG did not give rise to significant perioperative complications. Two donors became non-diabetic and weight loss continued in the subsequent months following surgery also. It did not influence the subsequent laprascopic donor nephrectomy(LDN).

Conclusions: This procedure allowed morbidly obese donors to donate and subsequently expanded the donor pool without impacting the outcome of subsequent LDN. We will recommend this for obese live kidney donors.

Demographics of donors who underwent LSG before laparoscopic donor nephrectomy

Case	Age (Yrs)	Sex	Time interval with donation (Months)	Pre-BMI (kg/ m2)	Post-BMI (kg/ m2)	Weight loss, %	Comorbidity
1	32	F	5	40.3	29.8	27.5	DM REVERSED
2	37	F	4	42.9	32	25.2	NIL
3	50	M	Did not donate as patient died	36.2	27	25.7	NIL
4	40	F	6	44	36.4	20.5	NIL
5	33	F	Did not donate as patient died	42.8	34.5	20	NIL
6	46	F	5	35.3	28.9	18.8	DM REVERSED
7	44	F	4	42	35.3	15.8	NIL
8	65	F	Did not donate as patient died	46	31.6	31.8	NIL
9	42	F	6	38.7	30.2	21	NIL
10	49	F	5	42.9	34.5	20.3	NIL

PUB764

Explant Biopsy and Allocation Based on Remuzzi Scoring Permits Selection of Extended Criteria Donor Kidneys for Single Implantation with Excellent Outcomes

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Background: While Extended Criteria Donors (ECD) increase deceased donation (DD) rates, allocation of ECD kidneys is challenging due to difficulty in predicting post-transplant outcomes.

Methods: Since November 2009, kidney DDs were stratified as ECD if Age>60(ECDAge); if meeting UNOS criteria(ECDUNOS); Diabetic(ECDDM) or other renal conditions(ECDOthers); the rest were Standard Criteria Donors(SCD). ECD underwent explant biopsy, rapid biopsy processing and histological scoring of Glomeruli, Tubules, Interstitium and Arteries to derive a Total Remuzzi Score (TRScore). TRScore of 0-4 or 5-7 were generally allocated as single (ECDSingle) or dual Implants (ECDDual) respectively. This study evaluated impact of our allocation strategy on longterm outcomes. Of 118 DD, 55(46.6%) were ECD; 21(38.2%), 11(20%), 12(21.8%) and 11(20%) were ECDAge, ECDUNOS, ECDDM and ECDOthers. After evaluating TRScores, 30 ECD(54.5%) were allocated as ECDDual, preferentially to kidney transplants (KTX)>45 yrs. After excluding 1 ECDSingle with staghorn calculus that was discarded and 5 SCD that were allocated to paediatric KTX, 200 adult KTX (30 ECDDual, 49 ECDSingle and 121 SCD) were analysed.

Results: TRScores from ECD explant biopsies and from 61 of 63 SCD with implant biopsies were 5.2±1.2, 2.8±1.1 and 2±1.7 for ECDDual, ECDSingle and SCD respectively (P<0.001). ECD KTX were older (52.4±7.5, 49.1±9.4 and 47±9 yrs for ECDDual, ECDSingle and SCD respectively; p=0.01), but sex, ethnicity, incidence of Delayed Graft Function (DGF) and Biopsy Proven Acute Rejection by 6 mths (BPAR6) were not significantly different between groups. 5 yr overall survival was worse for ECDDual (64.4%, P=0.05), but comparable for ECDSingle and SCD (84.8% and 84.7% respectively). After adjusting for age, gender, ethnicity, DGF and BPAR6, ECDSingle had lower hazard for overall failure (OR 0.29, [95%CI 0.114-0.741]).

Conclusions: Stratifying ECD with explant biopsy and allocation based on Remuzzi scoring yields outcomes comparable to SCD for ECD Single kidneys.

PUB765

Cutaneous Polyarteritis Nodosa (PAN) After Kidney Transplantation: A Case Report, Sepsis Induced or Primary Disease?

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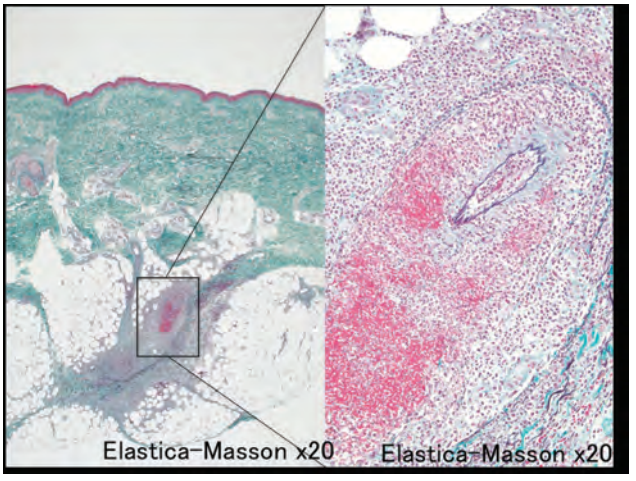
Introduction: Polyarteritis nodosa (PAN) is a systemic vasculitis characterized by necrotizing inflammatory lesions that affect medium and small-sized arteries. The pathogenesis of PAN is not well known, but Hepatitis B virus (HBV) and other viruses are thought to be causative agents. We present a biopsy proven case of PAN, which developed 20 months after a kidney transplant. Development of an autoimmune disease after transplant is a rare phenomenon.

Case Description: A 53 year-old woman received a living kidney transplant on March, 2016. Her kidney disease was speculated to be caused by IgA nephropathy. The patient's perioperative course was uneventful. Her induction regimen was basiliximab, mycophenolate mofetil (MMF), tacrolimus, and prednisolone. Nineteen months after transplantation, the patient had a parathyroidectomy for primary hyperparathyroidism. She was discharged on postoperative day 4. One day after discharge, the patient returned to our hospital for Escherichia coli (E.coli) urinary tract infection (UTI) and sepsis (extended-spectrum beta-lactamase). The patient was treated with carbapenem and second generation cephem antibiotics for14 days. Twenty-one days after discharge, she presented to our hospital for second time with a UTI caused by E.coli, but not associated with sepsis. On this second presentation, Carbapenem was initiated with resolution of the UTI symptoms. On hospital day13, the patient noticed pain in her bilateral lower legs as well as in her left forearm and right arm. On day15, a small painful nodule appeared, which was biopsied.

Discussion: PAN is a very rare complication after transplant. We found six other cases of PAN after transplantation in the literature; one case was related to HBV infection. Take away points: In a transplant patient, de-novo autoimmune diseases, such as PAN, may present atypically.



PUB766

Late Onset JC Virus Allograft Nephropathy (JCVAN)

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Introduction: JC virus (JCV) is a member of the Polyomaviridae family. Few studies were published regarding the replication of JCV in transplant recipients. The incidence of JCV viruria, viremia, and allograft nephropathy is unknown. Most reported cases of JCV infection occurred during the first 24 months after transplantation. We describe two cases of JCVAN occurring beyond 24 months post-transplant.

Case Description: CASE 1: 66-year-old Polish male with ESRD due to hypertensive nephrosclerosis on hemodialysis for 6 years and peritoneal dialysis for 1 year, underwent a deceased donor kidney transplant in 4/2014. His post-operative course was complicated by nephrolithiasis that required a nephrostomy tube. In 11/2017, he developed acute kidney injury (AKI) with a creatinine of 2.1mg/dl. Renal allograft biopsy showed Polyoma Virus allograft nephropathy (PAVN). His immunosuppression at that time was Astagraf and Myfortic. His Myfortic dose was reduced. Blood BK virus PCR was not detected. Blood JCV PCR was 270,000 copies/ml and urine JCV PCR >100 million copies/ml. His Astagraf dose was reduced to maintain a trough of 3-5ng/ml. His Myfortic was stopped. Prednisone 10mg daily was added. Two-months follow-up JCV PCR was 338,000 copies/ml. He did not exhibit neurologic symptoms. His creatinine remained around 2mg/dl. CASE 2: 48-year-old Filipino male with a history of polycystic kidney disease underwent deceased donor kidney transplant in November 2003 with stable good kidney function on maintenance tacrolimus and mycophenolate mofetil (MMF). He underwent a renal allograft biopsy in 6/2017 to evaluate AKI, microscopic hematuria, and albuminuria. The biopsy showed PAVN. Blood BK virus PCR was undetectable. Blood JCV PCR peaked at 4,200 copies/ml and urine JCV PCR 24 million copies/ml. His MMF was stopped, prednisone 7.5mg daily was added, and tacrolimus dose was adjusted to maintain a trough level between 2 and 5ng/ml. Blood JCV PCR decreased to 1,500 copies/ml and urine JCV PCR decreased to 9.9 million copies/ml 11 months after diagnosis of JCVAN. He continues to have stable renal allograft function with no neurologic symptoms.

Discussion: PAVN should be considered as a cause of late-onset AKI in kidney transplant recipients. JCV should be considered as the cause of PAVN, particularly when BK virus infection is excluded. Neurologic symptoms are absent. Reduction in immunosuppression remains the mainstay of management of JCVAN.

PUB767

A Significance of Serum Albumin in Kidney Transplant Recipient: Association with Cardiovascular Event and Mortality

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Background: Serum albumin is a marker of malnutrition, inflammation and proteinuria. The aim of this study is to investigate the association between serum albumin and outcomes in kidney transplant (KT) recipient.

Methods: We reviewed a total of 387 patients over 15 y.o. who received KT from 2006 through 2012 in Kyushu University. The patients divided into 3 groups according to serum albumin one year after KT (ALB1y); T1 1.4-4.1 g/dL, n= 93, T2: 4.1-4.3 g/dL, n=145, T3: 4.4-5.6 g/dL, n=149. We investigated various events after one year, consisting of all cause mortalities, new onset cardiovascular disease (CVD), graft dysfunction (doubling serum creatinine and/or development of end-stage kidney disease), new onset malignancy and infectious episode need administration.

Results: The patients consisted of 233 male and 154 female with median age (IQR) of 44 (35-56) years. A number of patients received transplantation from deceased donors was 56, those with diabetes mellitus as primary disease was 82. ALB1y was associated positively with LDL cholesterol and eGFR, and negatively with age, dialysis duration, proportion of diabetic mellitus as primary disease, incidence of rejection episode within one year, and C reactive protein. Cox hazard models revealed all cause mortalities and new onset of CVD in T1 was significantly worse than those in T3. Hazard ratio (HR) for mortalities was 4.82 and 95% confidential interval (95%C.I.) was 1.62-17.70, and P=0.004 for T1 vs T3. HR for CVD was 5.20, 95%C.I. was 2.12-14.60, and P=0.0002 for T1 vs T3. The association between ALB1y and graft dysfunction was weak; HR of T1 was 2.16, P=0.042. However, ALB1y was not associated with malignancy nor infectious episodes.

Conclusions: Low serum albumin was a strong risk factor of all cause mortalities and new onset CVD.

Outcomes	Event	n	Mutivariate model HR (95%CI)	P Value	P for trend
All cause mortality					
T3	4	149	(Reference)		
T2	5	145	1.32 (0.35-5.38)	P=0.680	0.005
T1	12	93	4.82 (1.62-17.70)	P=0.004	
Cardiovascular disease					
T3	6	149	(Reference)		
T2	13	146	2.04 (0.80-5.84)	0.140	0.0004
T1	17	93	5.20 (2.12-14.60)	0.0002	
Doubling creatinine					
T3	17	149	(Reference)		
T2	17	145	0.84 (0.41-1.71)	0.635	0.071
T1	18	93	1.96 (0.98-3.92)	0.056	
Malignancy					
T3	12	149	(Reference)		
T2	15	146	1.27 (0.60-2.78)	0.275	0.268
T1	10	93	1.61 (0.68-3.76)	0.530	
Infectious					
T3	39	149	(Reference)		
T2	39	145	0.96 (0.60-1.54)	0.872	0.727
T1	21	93	0.91 (0.51-1.55)	0.724	

ALB1y and outcomes.

PUB768

Outcomes of Switching Renal Transplant Recipients to Generic Mycophenolate Mofetil: A Single Center Study

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Background: The aim of the study was to investigate the clinical and economic outcomes of switching clinically stable renal transplant recipients to a lower-cost generic Mycophenolate Mofetil.

Methods: From January 2017, all renal transplant patients receiving mycophenolate mofetil (CellCept, Roche) were switched to same doses of another generic (APO-Mycophenolate, Apotex) at the Armed Forces Hospitals Southern Region, Khamis Mushait, Saudi Arabia. Patients were followed up for one year for changes in serum creatinine, incidence of infections, acute tubular necrosis, renal biopsy, acute rejection, changes in tacrolimus or ciclosporin levels and death. Besides, direct cost saving was calculated.

Results: During the study period, 161 renal transplant patients (58.4% males, 41.6% females, mean age = 45.5 ± 15.5 years, mean duration since transplantation = 11.4 years) were switched to APO-Mycophenolate. Among them, 19 patients were diagnosed before switching with chronic allograft nephropathy (CAN). The baseline serum creatinine of the study sample was 100.24 ± 42.64 mcmol/l. After switching, serum creatinine did not change significantly after 3 months (94.48 ± 57.62), 6 months (98.97 ± 59.5), 9 months (99.75 ±56.93) and one year (106.21 ± 76.34) (p=0.5). For the CAN patients, the serum creatinine also did not change significantly from baseline (185±52.63 mcmol/l) till the end of the study period (220.74 ± 139.3 *p=0.76)*. For the patients on Tacrolimus (n=101), trough levels did not differ significantly before and after one year of switching (5.63 ± 1.44 ng/ml vs 5.62 ± 1.49 ng/ml, p=0.73). Similarly, C0 for Ciclosporin patients did not change significantly (265.54±245.22 vs 270.27 ± 277.84, p=0.87). Fifteen patients developed 16 infectious episodes, one of which was life threatening (cerebral toxoplasmosis). Four patients experienced Gastrointestinal symptoms (2.48%) that lead to mycophenolate discontinuation in two of them (1.24 %). No patients underwent renal biopsy, experienced acute tubular necrosis/acute rejection or died during the study period. Besides, Use of APO-Mycophenolate was associated with a direct cost saving of 431309 Saudi Riyals compared to Cellcept.

Conclusions: Using generic Mycophenolate Mofetil in clinically stable renal transplant recipients was associated with similar efficacy and safety profile with significantly reduced cost.

PUB769

Can You Reject Your Own Kidney?

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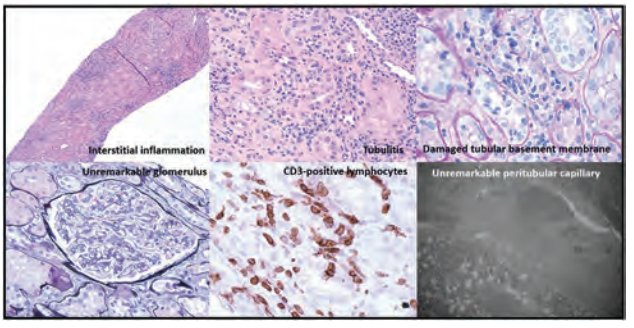
Introduction: Renal involvement secondary to Graft-versus-host disease (GVHD) is considered rare and membranous nephropathy and minimal change disease are considered to be the most common glomerular lesions associated with GVHD. Herein, we present a unique case of renal GVHD with isolated involvement of the tubulointerstitium.

Case Description: A 64-year-old Caucasian woman was seen for evaluation of proteinuria and gradually worsening serum creatinine (Scr) over a period of 4 months. Her medical history was significant for hypertension, diabetes and myelofibrosis s/p matched

unrelated donor peripheral blood allogenic stem cell transplant 2 years ago. Her post-transplant course was complicated by severe chronic GVHD involving skin, buccal mucosa, eyes and lung, all manifested within the first year of transplant. Chronic GVHD was initially managed with tacrolimus, ruxolitinib (JAK inhibitor), prednisone and extracorporeal photopheresis. 3 months prior, tacrolimus was switched to sirolimus due to recurrent non-melanoma skin cancers. Scr was 1.94 mg/dL and 24-hour urinary total protein was 3.5 g (~1.6 g albumin) at presentation. Because of the persistent tubular proteinuria despite ACEI therapy and decrease in sirolimus dosage, renal biopsy was obtained. It demonstrated severe GVHD resembling an acute T-cell mediated rejection in a transplanted kidney [Figure]. The disease was confined to tubulointerstitium without any glomerular lesions or peritubular capillaritis, confirmed by EM. As there is no clear consensus on the optimal management of renal GVHD, our patient was treated with 3 days of pulse steroids, in line with treatment of acute cell-mediated rejection in a renal allograft. A week after the treatment, 24-hour urinary protein improved to 1.1 g.

Discussion: Renal GVHD may be underdiagnosed in patients with HCT, as they are not frequently biopsied owing to multifactorial nature of the renal dysfunction and relative contraindications to biopsy such as low platelet counts. Keeping low treshold for biopsy may pave way for the development of better and effective treatment regimens.



PUB770

Hypercalcemia and Pneumocystis Pneumonia After Kidney Transplantation: A Non-Fortuitous Association

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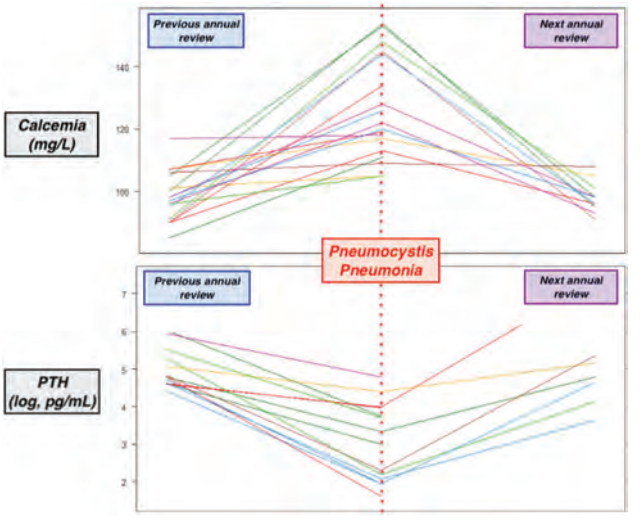
Background: Hypercalcemia may persist beyond the first year after transplantation in 5 to 10% of the kidney transplant recipients (KTR), mainly due to persistent hyperparathyroidism. Recently, a few scattered observations of hypercalcemia associated with *Pneumocystis* pneumonia (PCP) in KTR have been reported but its prevalence and potential pathophysiological mechanisms remain unknown.

Methods: This retrospective cohort collected all proven cases of PCP in adult KTR, that occurred between January 2005 and August 2017 in our center.

Results: Among the 49 confirmed cases of PCP, 18 patients experienced hypercalcemia (12.0±1.6 mg/L), which represented a prevalence of 36.7%. The clinical presentation was different between hypercalcemic and normocalcemic patients (29.4% only presented febrile dyspnea *versus* 66.7%, respectively, p=0,02). In the hypercalcemic group, eGFR was significantly lower (26.5±10 *versus* 36.1±16.2 mL/min/1.73m^2, p=0.013), while 25-OH vitamin D levels and calciuria-on-creatininuria-ratio were higher (respectively 28.1±8.8 *versus* 14.2±8.6 ng/mL, p=0.008 and 0.28 [0.16-0.39] *versus* 0.05 mg/mg [0.02-0.07], p=0.001). In the hypercalcemic group, 1,25-OH vitamin D levels, also higher at the time of PCP, collapsed after healing, while PTH levels, initially lower, increased secondarily after PCP (Figure).

Conclusions: To the best of our knowledge, this is the first reported cohort of adult KTR suffering from PCP-associated hypercalcemia. The evolution of vitamin D and PTH levels around the infectious episode pleads in favour of an extra-parathyroid mechanism and suggests a granulomatous reaction. Acute hypercalcemia after renal transplantation may be related to PCP and should lead to enlightened investigations, even in the absence of infectious or respiratory symptoms.



Evolution of calcium and PTH serum levels before and after PCP.

PUB771

An Unusual Cause of AKI in a Renal Transplant Recipient

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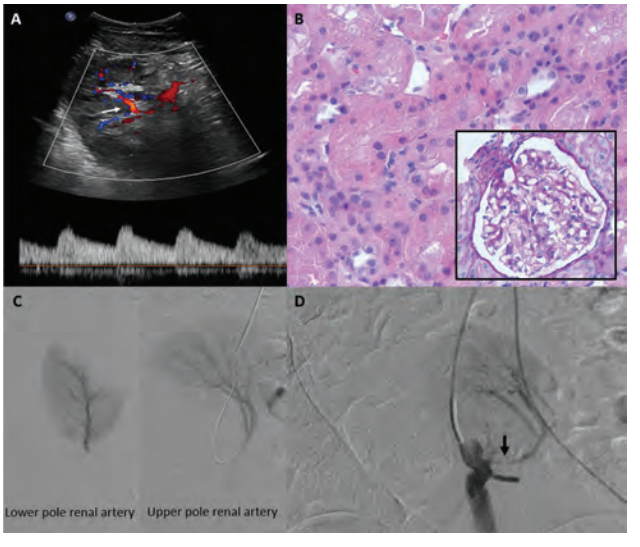
Introduction: Acute kidney injury is one of the major determinants of graft survival in kidney transplantation and has to be promptly addressed with appropriate investigations.

Case Description: A 43-year-old Asian man with a history of ESRD, status post deceased donor kidney transplantation in China 3 months ago, was sent to the ER for elevated Scr of ~3.1 mg/dL. Reportedly, his post-transplant baseline creatinine was about 1.5 mg/dL. He was told in China that the blood vessel supplying the transplanted kidney was 'shrunk'. Doppler ultrasonography of the allograft done in the ER demonstrated a single renal artery with slight blunting of the systolic upstroke, but otherwise unremarkable flow [Figure-1A]. There was no evidence of renal infarction and the resistive indices were wnl. His BP was well controlled. As the renal function failed to improve with supportive measures, a biopsy of the allograft was performed, which showed no evidence of acute rejection or tubular injury [Figure-1B]. Based on the patient's history that something might be wrong with his renal artery, a carbon dioxide (CO_2) angiogram of the pelvic and renal arteries was performed, which revealed 2 separate renal arteries anastomosed to the right external iliac artery [Figure-1C]. There was good flow through the lower pole renal artery with minimal pressure gradient across the anastomosis but the upper pole artery demonstrated more than 75% stenosis with a significant pressure gradient of 107 mmHg. The gradient reduced to 21 mmHg after successful balloon angioplasty [Figure-1D]. The patient's Scr improved back to the baseline value of 1.5 mg/dL at 1-week follow up.

Discussion: Take home message from our case: High index of suspicion is required for ischemic nephropathy in renal transplant patients presenting with unexplained acute kidney injury, as it is potentially reversible.



PUB772

Performance on Longevity Matching Using Current KAS

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Background: To improve longevity matching, current kidney allocation system(KAS) allots top 20% Kidney Donor Profile Index(KDPI) kidneys to top 20% Estimated Post Transplant Survival(EPTS) recipients. Among KDPI<85% kidneys, some fulfil Expanded Criteria Donor(ECD) status. We evaluate the outcome of ECD kidneys compared to standard criteria donor(SCD) ones and in whom ECD kidneys are transplanted.

Methods: Using data from Scientific Registry of Transplant Recipients, we retrospectively calculated EPTS of recipients and KDPI, SCD/ECD status of kidneys transplanted from 1/02 to 9/16. We assessed the graft outcome of KDPI<85% kidneys stratified by ECD vs SCD status and determined the distribution of these kidneys across EPTS deciles.

Results: Among 146,912 kidneys with KDPI<85%, 15,820(11%) were ECDs. Significant differences existed in baseline characteristics of recipients(Table1). ECD kidneys had 65% higher risk of graft failure than SCD ones and were transplanted across all EPTS deciles(Figure1).

Conclusions: As ECD kidneys have worse allograft survival and are transplanted across all EPTS deciles, we recommend to 1)identify individuals who may not benefit from receiving ECD kidneys 2)counsel those who will receive them about higher risk of graft failure.

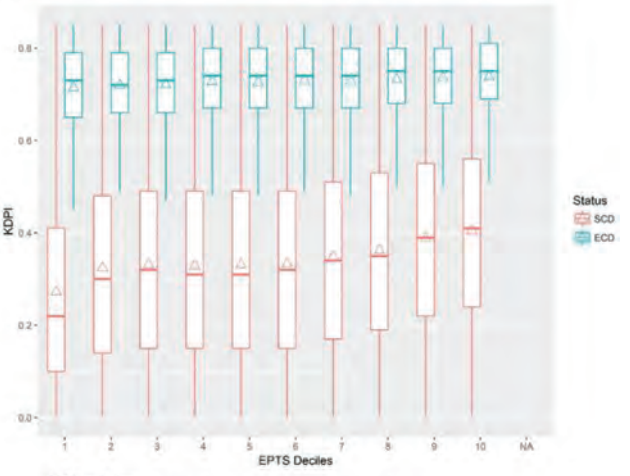
Funding: Commercial Support - Dialysis Clinic Inc

Table 1: Baseline characteristics of recipients of KDPI<85% kidneys

	KDPI <85		
	SCD (n=127,493)	ECD (n=15,506)	p-value
Age	45.90 ± 15.11	57.18 ± 10.70	< 0.001
Gender (Male)	76,327 (59.87)	9,924 (64.00)	< 0.001
Race			< 0.001
White	80,228 (62.93)	9,453 (60.96)	
African American	38,077 (29.87)	4,650 (29.99)	
Hispanics	20,142 (15.8)	2,153 (13.88)	
Asians	6,864 (5.38)	1,091 (7.04)	
Native Americas	1,289 (1.01)	193 (1.24)	
Others	1,035 (0.81)	119 (0.76)	
Body Mass Index	28.17 ± 313.6	28.18 ± 5.6	0.991
Cause of kidney disease			< 0.001
Diabetes	38,765 (30.41)	5,461 (35.22)	
Hypertension	26,722 (20.96)	3,922 (25.29)	
Glomerulonephritis	24,515 (19.23)	2,158 (13.92)	
Polycystic Kidney Disease	8,911 (6.99)	1,216 (7.84)	
Other	28,580 (22.42)	2,749 (17.73)	
Comorbidities:			
Diabetes	49,353 (38.71)	7,169 (46.23)	< 0.001
Hypertension	88,949 (69.77)	11,514 (74.26)	< 0.001
Coronary Artery Disease	8,243 (6.47)	1,444 (9.31)	< 0.001
Peripheral Vascular Disease	6,181 (4.85)	1,024 (6.6)	< 0.001
Malignancy	5,863 (4.6)	1,087 (7.01)	< 0.001
On dialysis	96,824 (78.32)	12,484 (80.57)	< 0.001
Years on dialysis	3.22 ± 3.44	3.33 ± 3.1	< 0.001
Peak Panel Reactive Antibody	20.22 ± 32.44	12.84 ± 24.7	< 0.001
On expanded donor list	43,332 (41.5)	13,879 (93.29)	< 0.001
Donor Characteristics			
Age	32.6 ± 14.24	57.76 ± 5.21	< 0.001
Kidney Biopsy			
Kidney GS	3.24 ± 6.23	10.76 ± 10.93	< 0.001
Left kidney GS			< 0.001
0-5%	28,992 (77.35)	8,691 (65.23)	
6-10%	4,553 (12.15)	2,428 (18.22)	
>10%	3,936 (10.5)	2,204 (16.55)	
Right kidney GS			< 0.001
0-5%	29,965 (78.24)	8,702 (64.71)	
6-10%	4,411 (11.52)	2,462 (18.31)	
>10%	3,925 (10.24)	2,283 (16.98)	
Machine perfusion			
Left kidney resistance	0.22 ± 0.13	0.28 ± 1.47	0.003
Right kidney resistance	0.21 ± 0.13	0.26 ± 1.39	0.011
Transplant Characteristic			
Cold ischemic time	17.29 ± 9.03	18.24 ± 9.5	< 0.001

Continuous variables are expressed as mean ± SD while categorical variables are expressed as n (%)

Figure 1: Allocation of Kidneys with KDP<85% and stratified by ECD/SCD status in each EPTS Deciles



*Abbreviations:
SCD = Standard Criteria Donor, ECD = Expanded Criteria Donor

PUB773

Histomorphometric Analyses of Preimplantation Needle Biopsies of Paired Kidneys from the Same Deceased Donors

Marcin Adamczak,[1] Katarzyna Kwiecien,[1] Magdalena E. Szotowska,[1] Wojciech Wystrychowski,[2] Robert Król,[2] Andrzej Wiecek.[1] *[1]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, Katowice, Poland; [2]Department of General, Vascular and Transplant Surgery, Medical University of Silesia, Katowice, Poland, Katowice, Poland.*

Background: Both donor and recipient factors influence kidney graft function. Integrated histo-morphometric assessment of transplanted kidney might better predict graft survival. The aim of the study was to determine differences in histomorphometric analyses of preimplantation needle biopsies of paired kidneys from the same donors.

Methods: Forty pairs of kidneys harvested from 40 donors (17F/23M; median age 42.3 and 95% CI 37.6-47.0 years) in which diagnostic preimplantation biopsies were done, were included into the analysis. Mean glomerular volume, mean glomerular density and mean capillaries density in the interstitium were estimated. For statistical analyses Wilcoxon tests were used. Results were presented as mean and 95% CI.

Results: Paired kidneys harvested from the same deceased donor did not differ in mean glomerular volume [2.59 (2.24-2.93) vs 2.49 (2.15-2.84) μm^3 x10^6], glomerular density [3.43 (3.07-3.80) vs 3.24 (2.87-3.61) n/mm^2] and capillaries density in the interstitium [233.58 (211.26-255.90) vs 217.80 (199.45-236.47) n/mm^2].

Conclusions: In daily clinical practice assessment of only one from both harvested kidneys from the donor seems to be sufficient for histomorphometric analysis.

Funding: Government Support - Non-U.S.

PUB774

Post-Transplant Vitamin D Deficiency: Comparison of Two Repletion Regimens

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Background: Vitamin D deficiency is common post-transplant associated with immune impairment and ongoing metablic bone disease.(1)

Methods: We randomized 62 patients who had 25-OH D levels < 20, 1 month post-transplant to vitamin D3 4000 units daily (low dose) or 50,000 units daily (high dose) for 30 days. Patients were followed for 2 years. Immunosuppression was 3 mg/kg thymoglobin induction followed by tacrolimus, mycophenolate and prednisone.

Results: There were no differences in graft or patient survival between groups. Only the high dose group had >100 ng/ml 25-OH D levels after 1 month (63%). There were no evident clinical sequelae.

Conclusions: Both regimens were safe and effective. There is a tendency for less rejection on the high dose regimen suggesting the possibility that vitamin D may have beneficial immune modulatory effects. This needs to be tested prospectively. Reference: 1. Chung BH, Kim B-M, Doh KC, Min J-W, Cho M-L, Kim KW, Yang CW. Suppressive effect of 1α,25-Dihydroxyvitamin D3 on Th17-immune responses in kidney transplant recipients with tacrolimus-based immunosuppression. Transplantation 2017; 101:1711-1719.

Demographic Data and Results

	High Dose (n=30)	Low Dose (n=32)
Median Age	49.5	51.3
Gender	M=17, F=13	M=20, F=12
Baseline 25-OH Vitamin D (ng/ml)	14.3	14.0
2 Year Post-transplant 25-OH Vitamin D (ng/ml)	54.5	61.3
Hypercalcemia (>11 mg/dl)	4	6
Biopsy Proven Rejection	2	7
2 Year eGFR (ml/min/1.73m^2)	54	56
Fractures	0	0

PUB775

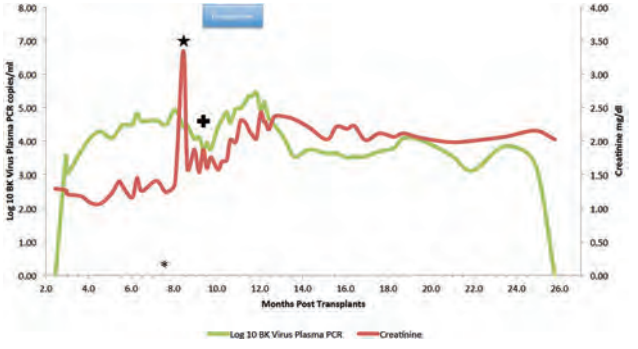
Combined Polyoma Virus-Associated Nephropathy (PVAN) and Rejection Treated with Thymoglobulin and Brincidofovir (CMX) in a Renal Transplant Recipient

L Parker Gregg,[1,2] Nashila AbdulRahim,[1] Bekir Tanriover,[1] Ricardo M. La Hoz,[1] Venkatesh Kumar Ariyamuthu.[1] *[1]UT Southwestern Medical Center, Dallas, TX; [2]VA North Texas Healthcare System, Dallas, TX.*

Introduction: PVAN occurs in 1-10% of kidney transplant recipients. Concomitant rejection and PVAN is a challenging scenario for immunosuppression (IS) management. We present a case of biopsy-proven PVAN and acute cellular rejection (ACR) treated with CMX and aggressive augmentation of IS.

Case Description: A 49 year-old man with ESRD from type 2 diabetes and hypertension received a DDRT with ATG induction and maintained on tacrolimus (TAC)/MMF and Prednisone. Six weeks after his transplant he had a mild acute antibody-mediated rejection (AMR) that was treated with methylprednisolone, IVIG, and plasmapheresis. His serum BK PCR came positive in 6 months and reached 85,560 copies/mL in 8 months, and mycophenolate (MPA) was stopped, but continuing prior doses of Tac. Two weeks later, his creatinine rose to 3.3, and biopsy showed Banff 1B (ACR) and AMR. He was treated with steroids, plasmapheresis, and IVIG. His creatinine returned to a nadir of 1.9, but again rose to 2.1. BK titer at this time was 12,799 copies/mL. Repeat biopsy showed persistent ACR Banff 1B and AMR, and positive for SV40 staining and was treated with ATG 4.5 mg/kg, methylprednisolone and IVIG. He was also started on CMX100 mg twice a week. His creatinine decreased to 1.5 and he was discharged home on Tac, prednisone and MPA. Repeat kidney biopsy showed AMR and BKVAN. His IS was decreased and continued on CMX. In 3/2016 he developed leukopenia, BK titer rose to 269,659 copies/mL, and creatinine rose to 2.4 in the setting of sub-therapeutic tacrolimus levels. CMX and MPA were discontinued, and he was given IVIG. Over last 18 months his creatinine has been stable and his serum BK titers have most recently been just detectable.

Discussion: We report the first case when CMX was used with aggressive augmentation of IS for concurrent PVAN and ACR. We believe CMX allowed us to augment IS in the setting of PVAN and preserve the allograft.



Log$_{10}$BKV Plasma PCR and Serum Creatinine vs. Time post-transplantation

PUB776

100% cPRA Renal Transplant Recipients Are at Increased Risk of Polyoma BK Viremia but Not Graft Loss

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Background: We investigated whether 100% cPRA sensitized kidney transplant recipients are at increased risk of polyoma BK viremia due to enhanced postoperative immunosuppression.

Methods: Plasma PCR monitoring for BKV was performed monthly in all recipients. Immunosuppression for all patients included thymoglobulin induction and maintenance sirolimus (rapamycin), low-dose CellCept (Mycophenolate Mofetil), and low-dose tacrolimus. BK viremia was defined as viral DNA >1,000 copies/mL. Recipients identified to have BK viremia underwent an immediate reduction in immunosuppression. We analyzed BK viremia rates in 100% cPRA recipients (19) versus non-100% cPRA recipients (96) between December 2014 and March 2017.

Results: Of the 100% cPRA patients, 31.6% were found to be positive for BK viremia versus only 15.6% with <100% cPRA (Fisher's exact test: p=0.112). Despite the increased incidence in BK viremia in 100% cPRA patients, the mean time to detection and mean serum creatinine at 12 months was not statistically significant (Two-sample t-test: p=0.302 and p=0.999). Through reducing immunosuppression, BKV resolved in all patients without progression to BK nephropathy or acute reactivation. None of the viremic patients experienced acute rejection following immunotherapy reduction.

Conclusions: BK viremia rate was greater in 100% cPRA recipients than those in the non-100% cPRA group. However, this was not detrimental to one-year graft survival and function over time with our monthly screening protocol. Graft survival and function in BKV positive 100% cPRA patients was similar to that of the non-100% cPRA group. This data indicates that monthly screening of BK viremia in 100% cPRA patients is effective in preserving one-year graft function outcomes.

Demographics and Clinical Characteristics of Renal Transplant Recipient Population

Patient Group	100% cPRA	Non-100% cPRA
Number of Patients, N	19	96
Mean Age at Time of Transplant (Years)	44.1±12.4	49.1±13.9
Male (%)	9 (47.3)	64 (66.7)
Race (% Caucasian)	13 (68.4)	76 (79.2)
Primary Transplant (%)	5 (26.9)	93 (96.9)
Diagnosis of Diabetes (%)	6 (31.6)	27 (28.1)

PUB777

Elimination of Chronic Hepatitis B in a Kidney Transplantation Recipient via Lamivudine Monotherapy: A Case Report

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Introduction: Numerous studies have investigated lamivudine use for the treatment of hepatitis B virus (HBV) infection after kidney transplantation (KT). However, the efficacy and safety of lamivudine after KT remain unclear. A meta-analysis of 14 clinical trials (184 patients) demonstrated a hepatitis B envelope antigen (HBeAg) seroconversion rate of 27% (16 - 39%) and a HBV-DNA clearance rate of 91% (86 - 96%) in lamivudine-treated HBV-infected KT recipients; however, maintaining HBsAg clearance over 10 years has not been reported previously.

Case Description: A 56-year-old HBV-infected man had undergone KT for chronic glomerular nephropathy 20 years prior. Before KT, serological markers of HBV revealed that the patient was hepatitis B surface antigen (HBsAg)-positive and HBeAg-negative. A daily dose of 25 mg lamivudine monotherapy was started 8 weeks before KT. After KT, 100 mg of lamivudine was prescribed daily for 16 years, but was stopped 4 years prior to presentation. After 42 months of lamivudine treatment, HBsAg cleared, and 32 months later hepatitis B surface antibody (HBsAb) appeared. Four years after lamivudine therapy termination, serological markers revealed that the patient was HBsAg-negative, HBsAb-positive, and HBeAg-negative.

Discussion: HBsAg-positive KT recipients are at increased risk of mortality and graft failure compared to seronegative patients. Natural immunity to HBV may not protect against reactivation in immunocompromised patients. Currently, lamivudine is not the treatment of choice in chronic HBV-infected KT recipients because of its relatively lower treatment rate than other anti-viral agents. Furthermore, it can lead to increase in lamivudine resistance due to mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) locus. We report a case in which chronic hepatitis B remission was sustained for over 10 years via lamivudine monotherapy without YMDD mutation and any adverse effects. This case describes a sustained cure of chronic HBV infection in a KT recipient without a YMDD mutation via lamivudine monotherapy.

PUB778

Significance of Donor-Specific Antibodies in Sequential Liver-Kidney Transplantation from the Same Donor

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Background: Donor-specific antibodies (DSA) occur in recipients of sequential liver-kidney transplantation from the same donor. In simultaneous liver-kidney transplantation, the liver's protective effect on the kidney results in a lower acute rejection rate and better renal allograft survival than in isolated kidney transplantation (KT). Our aim was to determine the significance of DSA in recipients of sequential liver-kidney transplantation from the same donor.

Methods: We retrospectively analyzed data on patients aged <20 years who underwent sequential liver-kidney transplantation from the same donor between November 2005 and March 2017 at our institute. All patients were screened for DSA using complement-dependent cytotoxicity, flow-cytometry crossmatch, flow panel reactive antigen, and Luminex single antigen before KT.

Results: The cohort included five recipients. The primary disease comprised autosomal recessive polycystic kidney disease (3 cases), primary hyperoxaluria (1 case), and nephronophthisis (1 case). The median age at liver transplantation (LT) and KT was 5.6 years (range 0.7-7.5) and 6.1 years (range 3.0-7.9), respectively. The median duration between the procedures and the median follow-up duration was 1.1 years (range 0.4-2.4) and 2.4 years (range 1.2-8.1), respectively. Four patients were positive for DSA after LT prior to KT and had the DQ6 (6592MFI) and DR15 (7050MFI), B44 (2892MFI) and DQ6 (8946MFI), DQ7 (21263MFI) and DR53 (22080MFI), and DQ6 (7088MFI) antigens. One patient received plasmapheresis and intravenous immunoglobulin, and two patients received rituximab, plasmapheresis, and intravenous immunoglobulin before KT. One patient did not receive desensitization therapy. All patients except one received standard immunosuppressant therapy with prednisolone, tacrolimus, and mycophenolate mofetil as did the non-sensitized patients. One patient was targeted for the ABO incompatible

protocol. Although two patients showed the DSA antigen after KT, they showed no histologic evidence of antibody-mediated rejection, and their allograft function was similar to that in non-sensitized patients. All patients had good liver function. Two patients who received a liver biopsy showed no sign of rejection.

Conclusions: In sequential liver-kidney transplantation from the same donor, DSA may not contribute to antibody-mediated rejection.

PUB779

Histopathological Examination of Removed Kidney Allografts: Is It Useful?

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Background: The rate of allograft nephrectomy after graft failure varies between 4.5% and 84.4%, reflecting the lack of a standard policy. The incidence and relevance of histological findings in removed grafts is unknown. In this study, we investigated the outcome of histopathological examination of removed grafts.

Methods: We performed a retrospective cohort study in patients who underwent a kidney transplantation between 1981 and 2015, and in whom the graft failed ≥ 3 months after transplantation. In these cases, our policy is to remove the graft only on indication (e.g. graft intolerance syndrome). We routinely send the removed graft for histopathological examination. In total, 198 allograft nephrectomies were performed. In 31 cases, no pathology report was available, leaving 167 cases for analysis. Pathology reports were especially reviewed for recurrences of primary disease and for unexpected findings. Moreover, the consequences for clinical management of these findings were examined in the patient charts.

Results: In 17 of the 167 examined grafts, gross necrosis due to infarction or thrombosis precluded adequate interpretation. Signs of acute and/or chronic rejection were reported in 137 of the remaining 150 allografts. Recurrence of the original disease was the main finding in 8 cases: primary focal segmental glomerulosclerosis (n=4) and membranoproliferative glomerulonephritis (n=4). In all cases, the recurrence was already known from prior kidney graft biopsies. Relevant secondary findings were present in 8 cases: renal cell carcinoma (n=2), urothelial cell carcinoma, candida pyelonephritis (n=2), PTLD, polyomavirus inclusions, and oxalate deposition. All these conditions were already diagnosed before the graft nephrectomy, with the exception of one case of papillary renal cell carcinoma of 0.8 cm. The clinical consequence of the latter finding was that retransplantation for this patient was withheld for 9 months.

Conclusions: As expected, acute and/or chronic rejection is the main histopathological finding in grafts that are removed after late graft failure. Unexpected secondary findings are very rare. We therefore question whether routine histopathological examination of removed kidney allografts is useful and cost-effective.

PUB780

A Single Center Experience of Kidney Transplantation in Jehovah's Witness Patients

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Background: Jehovah's witness patients refuse blood products due to religious implications, but they do accept organ transplantation, albumin, immunoglobulin and some even accept clotting factors. We present a case series of Jehovah's witness patients who successfully received renal transplantation in our bloodless center for surgeries and transplantation.

Methods: We performed a single center retrospective study of renal transplants in Jehovah's witness patients from 2001 to 2018.

Results: A total of 13 patients received renal transplantation. One recipient received a kidney from a living donor and the others received deceased donor kidneys. Donor quality (average kidney donor profile index scores reported 37 ± 29%). No patients required blood products. Nine received erythropoietic stimulating agents and 2 received IV iron. Eight patients received Basiliximab and 5 received thymoglobulin for induction. All were on calcineurin inhibitors, 12 were on mycophenolate mofetil, 1 was on sirolimus and 3 were on steroid withdrawal protocol. Two patients were treated for rejection: 1 had a combination of both cellular and humoral rejection and required additional thymoglobulin, plasmapheresis and IVIG in the first year, while the other was preemptively treated for cellular rejection with methylprednisolone. The average length of hospital stay was 7.7 days. Five patients required readmission within 30 days; no readmissions were related to anemia. Patient and graft survival at 1 and 3-year were 100%. 6 allografts continue to function, 2 died with functioning graft, 3 have failed allografts and 2 patients were lost to follow up.

Conclusions: Although kidney transplantation does not generally require blood products, except in the case of surgical complications, our experience showed that Jehovah's witness patients can safely undergo transplantation with similar allograft outcomes as the general population while respecting their religious beliefs.

Table 1: Patient characteristics

Age (years)	51.23±19.52
BMI	28.47±5.97
Pre Hgb gm/dL	12±1.84
Post Hgb gm/dL	10.52±2.02
Creatinine 1 month mg/dL	1.26±0.38
Creatinine 1 year mg/dL	1.14±0.45
Allograft survival (months)	60.69±37.93

PUB781

Leptin and Adiponectin Serum Levels in Kidney Transplant Recipients: Preliminary Results

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Background: Adipokines modulate endocrine and immune processes; they are regulated in turn by nutritional parameters. There is controversy between the findings of diverse studies that evaluate outcomes in Chronic Kidney Disease and its association with adipokines, including kidney transplant. The aim of this study was to evaluate the relationship between adipokines serum levels with the type of rejection in patients with kidney transplant (KT) as well as their immunosuppressive treatment.

Methods: In this cross-sectional study, 36 patients with KT were included. The measurement of leptin and adiponectin were on serum samples with an ELISA Kit, these measures were compared with the result of the KT biopsy (Banff 2017 criteria), nutritional parameters and the type of immunosuppressant (Tacrolimus, Sirolimus, Ciclosporin). This study complies with the WMA Declaration of Helsinki, and Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Results: There was a tendency for patients treated with calcineurin inhibitors (CNI) to have higher levels of leptin (21.6 ng/ml) than those of sirolimus (18.2 ng/ml). Regarding adiponectin, it was inversely showing tendencies at higher levels those of the sirolimus group (13.1 µg/ml) with respect to the CNI (10.8 µg/ml). A positive correlation of adiponectin was found with the post transplant time (r=0.477, *P*=0.016) and with the Proteinuria/Creatininuria index (r=0.563, *P*=0.005). Regarding the type of rejection, no significant differences were found, but it was observed that patients with active humoral rejection had a tendency to lower leptin concentrations (15.5 ng/ml) and those with only IF/TA had higher concentrations (25.3 ng/ml). Likewise, patients who presented chronic humoral rejection showed intermediate values (20.5 ng/ml). Regarding the concentrations of adiponectin the values were homogeneous in the range of 12.4-13.1 µg/ml.

Conclusions: The immunosuppressive treatment would influence levels of adipokines. Chronicity changes of the allograft would be determined by leptin levels, but not by adiponectin, whose levels apparently did not influence the type of rejection or chronic changes inherent to the graft, however they are correlated with post-transplant time and proteinuria.

PUB782

Predictors and Outcomes of Calcium Oxalate Crystals in Kidney Transplant Recipients with AKI and Delayed Graft Function

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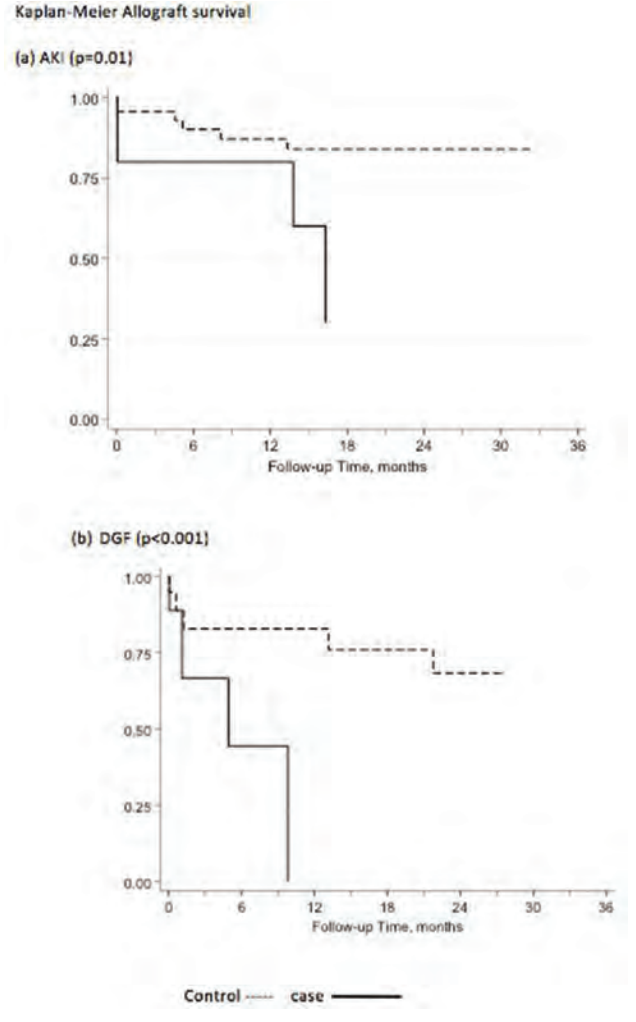
Background: The predictors of calcium oxalate (CaOx) deposits associated with Acute Kidney Injury (AKI) and Delayed Graft Function (DGF) and the impact of CaOx crystals on allograft survival are unclear. The aim of the study is to evaluate predictors and impact of CaOx crystals in kidney (KT), simultaneous liver kidney (SLK) and simultaneous pancreas and kidney (SPK) transplants with AKI and DGF.

Methods: We abstracted data for all KT, SLK, and SPK recipients who had for cause biopsies in a single center from 1994-2017. CaOx crystals were identified in 9 recipients with DGF and 15 recipients with AKI. These were matched on time since transplantation with 19 and 46 controls without DGF or AKI, respectively

Results: Median follow-up was 28 days for DGF and 502 days for AKI. Stepwise logistic regression models identified a nearly significant association between Banff i+t score (sum tubulitis and interstitial inflammation) and CaOx crystals in DGF (OR 9.9, p=0.072), while a history of native kidney nephrolithiasis was an independent predictor of CaOx in AKI (OR 20.03, p=0.037) table 1. CaOx was significantly associated with inferior death-censored allograft survival in both DGF (p<0.001) and AKI (p=0.01) fig 1 (a & b).

Conclusions: CaOx crystals in allograft biopsies with AKI and DGF are associated with inferior allograft survival. Pre-transplant nephrolithiasis, tubulitis, and interstitial inflammation may be risk factors for CaOx crystals in allograft with AKI and DGF. These observations suggest a need to better understand the pathogenesis of CaOx crystals to develop preventive and therapeutic strategies in kidney transplant recipients

	AKI			DGF		
	OR	p	95% CI	OR	P	95%CI
Age	1.02	0.504	.96 – 1.08	1.07	0.218	.959 – 1.2
Female	3.5	0.102	.780 – 15.79	0.17	0.197	.011 – 2.5
h/o Native Nephrolithiasis	17.1	0.067	.812 – 359.9	3.5	0.425	.162 – 75.5
I+t	0.41	0.262	.088 – 1.93	5.7	0.221	.349 – 94.14
Ptc+g	0.34	0.10	.094			



PUB783

Association of Anti-retroviral Therapy Following Kidney Transplantation on Incident BK Viremia

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Background: BK polyomavirus is an opportunistic virus that can cause polyomavirus-associated nephropathy and graft failure after kidney transplantation (KT). Given interactions of anti-retroviral therapy (ART) with calcineurin inhibitors, many HIV+ KT recipients receive integrase inhibitor (II) based ART. We investigated BK viremia and nephropathy rates in HIV+ KT while on II ART.

Methods: We performed a single center retrospective study of 28 HIV+ KT recipients, transplanted between 2009 to 2017. We compared incidence of BK viremia after KT based on whether patients were on II-based ART or not. **Study Population:** All patients had undetectable HIV viral load and CD4 count > 200 cells/mm3. Standard HIV+ immunosuppression (IS) protocol at our center included basiliximab induction, CNI-based IS, mycophenolate, and steroid taper. After 2011, IVIG was added to induction IS. One recipient received anti-thymocyte globulin, secondary to increased PRA and re-transplantation. BKV monitoring was performed by protocol for all patients following KT.

Results: Of the 28 recipients, 12 (43%) were maintained on II-based ART after KT (table 1). One-year post-KT, BK viremia (range: 2770 - 71150 copies/ml) rates were higher in the II-based ART group compared to the non-II group (3/12,vs.0/16, p=0.067). No allografts were lost from BK virus nephropathy; Rejection was noted to be higher in non-II group (2/12 vs 9/16 vs p=0.054). Graft survival at 1- and 3- year follow-up was 100/100% in the II-ART group vs. 100/94% in the comparative group. Median eGFR at 1 year for both groups were > 60 mL/min.

Conclusions: BK viremia is generally uncommon in the HIV+ KT population. Based on our follow-up, we have seen a slight increase in the incidence of clinically relevant BK viremia. Long-term follow-up is needed to monitor this HIV+ KT cohort.

Table-1

	No Integrase Inhibitor (-) ART (16)	Integrase Inhibitor (+) ART (12)
BK viremia	0 (0%)	3 (25%)
Median Age	51 yrs (IQR)	48 yrs (IQR)
Male	13 (81%)	8 (67%)
African American	12 (75%)	10 (83%)
Deceased donors	14 (88%)	11 (92%)
Delayed graft function	6 (38%)	4 (33%)
Median KDRI scores	0.9166	1.074
Acute cellular rejection at 1 year	6 (38%)	1 (8%)
Acute antibody rejection at 1 year	3 (19%)	1 (8%)

PUB784

Continuation of Immunosuppression (IS) Protects Against Allosensitization in Recipients of Kidney Transplant (KT) After Previous Non-Liver Solid Organ Transplantation (SOT)

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Background: Following kidney allograft loss, current standard of care involves discontinuing IS to prevent risks of more exposure. We hypothesized that continuation of IS after graft failure in candidates for another transplant would lower the risk of allosensitization.

Methods: We retrospectively analyzed calculated panel reactive antibodies (cPRA) on KT recipients at our center from January 2009 to March 2017 after having undergone a prior non-liver SOT. Patients with > 2 prior KT's were excluded. We compared sensitization between those who continued IS, and those who did not, based on cPRAs at times of listing and pre-transplant, using Risk Ratio (RR) and Chi square or Fishers exact test for statistical significance.

Results: 87 cases met inclusion criteria. 70 had a prior KT, 10 simultaneous kidney and pancreas, 1 pancreas, 1 lung and 5 heart transplants before being listed for a second organ (KT). Table shows that in the 50 cases where IS was discontinued after failure of the first graft, 45 of 50 (90%) had a cPRA ≥ 20 at the time of their second organ (index kidney) transplant, whereas 18 of 37 cases with continued IS (48.6%) had a cPRA ≥ 20 (RR = 1.85 [1.31-2.61], p < .0001, for proportion of sensitized cases when IS was discontinued). Among the 42 cases with available cPRA results at listing for the first transplant and the index KT, discontinuing IS after failure of first graft significantly increased the interim sensitization level compared to continuing IS (RR = 2.36 [1.23-4.51], p = 0.0008).

Conclusions: In this single center retrospective analysis, continuation of IS protects against the risk of allosensitization at listing for a second transplant. Both the proportion of sensitized patients and the magnitude of sensitization are significantly greater in cases that discontinued IS. Additional studies of IS management after graft failure are needed to determine whether the benefit of continued IS in candidates eligible for a second KT includes improved access to transplant and reduced morbidity.

Comparison of cPRA in cases continuing versus discontinuing IS

IS Treatment	cPRA <20	cPRA 21-50	cPRA 51-80	cPRA 81-100	cPRA mean (SD)	Median
IS Continued	19	7	6	5	32.2 (35.8)	18.0
IS Discontinued	5	8	11	26	70.4 (34.3)	83.5

PUB785

Efficacy and Safety of Ultra-Low Dose Valganciclovir Chemoprophylaxis for CMV Infection in High Risk KTP

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Background: CMV syndrome and disease are one of the major causes of decreased graft and patient survival for kidney transplant(KT) recipients. CMV syndrome is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen. CMV disease consists of CMV syndrome plus the presence of sign or clinical symptoms in the end organs. Valganciclovir (VGCV) prophylaxis to prevent CMV infection is recommended for solid organ transplant patients. Most transplant centers perform universal prophylaxis only in high risk groups including ABOi KT and DDKT. Most studies recommend administration of VGCV 900 mg twice a day. However, compliance can be reduced due to expensive medication, or hematologic side effects can occur. Therefore, we studied whether an ultra-low dose and short duration of VGCV (450 mg,

every other day, 3 months after KTP) is sufficient to prevent CMV infection in ABOi KT and DDKT recipients

Methods: We retrospectively evaluated 74 CMV seropositive donor/seropositive recipient(D+/R+) adult ABOi KTP recipients and 78 CMV seropositive donor/seropositive recipient(D+/R+) adult DDKT recipients from June 2009 to July 2016 who received ultra-low dose VGCV (450 mg every other day) prophylaxis for 3months. The primary outcome was occurrence of CMV syndrome and CMV disease. The secondary outcome was patient survival and graft survival.

Results: Follow-up durations were 2 to 52 months, respectively. CMV syndrome occurred in 1 case (1.4%) in ABOi KT and 2 cases (2.7%) in DDKT, but this was not statistically significant(p-value = 0.38). However, CMV disease occurred in one case (1.4%) in the ABOi KTP group and in 12 cases (16%) in the DDKT group, which was statistically significant(p-value 0.001). The CMV disease in ABOi was CMV pneumonia. CMV pneumonia was found in 8/12 (66.6%) and CMV colitis in 4/12 (33.3%) among the CMV disease in DDKT. Patient survival and graft survival(Fig.1) did not differ significantly between the two groups

Conclusions: Using an ultra-low dose VGCV, CMV prophylaxis was found to be effective in ABOi KTP, but DDKT increases the incidence of CMV disease. To reduce CMV disease after DDKT, the dose or duration of VGCV may be increased or preemptive treatment may be more effective

PUB786

Nocardia Infection in Renal Transplant Patients: Report from Transplant Center in India

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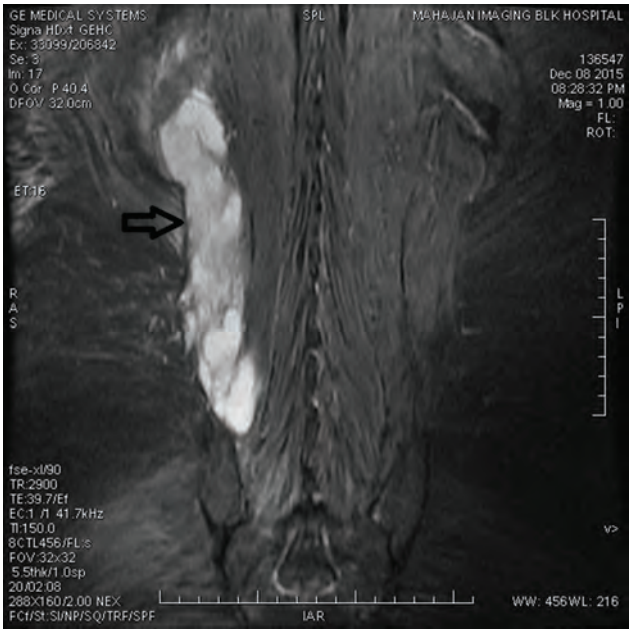
Background: Nocardosis is an uncommon but important cause of Infection in renal transplant recipients. There is scarce data regarding Nocardisis from Indian Subcontinent. Here we present spectrum of Nocardia infection from our center in India.

Methods: A retrospective analysis of all transplant performed from July 2012 to June 2017 was performed. Patients with diagnosis of Nocardia infection were identified. Their immunosupressive regimen, clinical presentation and outcome was examined.

Results: During the study period total 346 transplant were performed including Live, cadeveric, ABO-Incompatible. 3 patient (0.86%) developed Nocardia infection. Mean age at diagnosis was 58 years. 2 patients had Diabetes Mellitus and one had chronic Glomerulonephritis as native Kidney disease. All 3 received ATG as Induction and were on Tacrolimus, Mycophenolate and Prednisolone as maintenance immunosupression. Mean duration of presentation was 12 to 48 weeks after transplant. 1 patient was treated for acute cellular rejection in recent past with injection Methylprednisolone, one patient had recurrent infection including episode of CMV disease and tuberculosis in form of subcutaneous cold abscess and 3rd was largely asymptomatic prior to presentation.. One patient presented with Pulmonary Nocardiosis, one with epidural abscess at Dorsal Spine D3-D4 level and 3rd presented with paraspinal intramuscular abscess at lumbo-sacral level. All 3 were treated with combination antibiotic. 2 patients improved and one expired.

Conclusions: Nocardia infection is associated with significant morbidity and mortality. Pre transplant diabetes, treatment of rejection, ATG induction may be risk factor for Nocardia infection. High index of suspicion is essential for diagnosis as presentation is varied and patient may present late after transplant.



PUB787

Pre- and Post-Transplant Albumin Levels and Kidney Transplant Survival

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Background: Survival of ESRD patients continues to be lower than the general population even after kidney transplant (KT). Predictors of outcomes are important guides in the proper referral and postoperative care among KT patients. We examined the association of pre- and post-KT albumin levels on patient survival.

Methods: We retrospectively enrolled patients who underwent KT from 2005 to 2015 in our institution. Demographics, date of transplantation and death, albumin levels and preoperative comorbidities were obtained from medical records and kidney transplant program database. Cox regression, Kaplan Meier and ROC analyses were performed to determine the effect of pre- and post-KT levels on survival. Mean pre- and post-KT albumin levels were also compared using T-test for paired variables.

Results: A total of 705 patients underwent KT during the study period, 589 of which had both pre-KT and post-KT albumin data points. Mean pre-KT and post-KT albumin levels were 3.6±0.7 and 3.9±2.3 g/dL, respectively. Median follow-up time was 3.3 years (IQR 1.2-5.4 years). Cox regression analyses showed that both higher levels of pre-KT albumin (HR 0.67, p=0.01) and post-KT albumin (HR 0.28, p<0.001) were significantly associated with improved survival. KM survival analysis showed that a chosen pre-KT and post-KT albumin cut-off of 3.6 g/dL (log rank p=0.04) and 3.7 g/dL, (log rank p<0.001) were able to predict survival (Figure 1). After KT, 321 (54.6%) patients had improvement in albumin (mean increase of 0.3±2.4 g/dL, p=0.003). Improvement in albumin levels was not associated with improvement in survival (log rank p=0.55)

Conclusions: Our results showed that higher pre- and post-KT albumin levels are associated with improved survival. Although albumin levels imrove slightly after KT, this was not associated with improvements in surival. Optimization of nutrition and proper preoperative selection based on albumin levels may be keys to better risk stratification and improvement in survival of KT recipients.

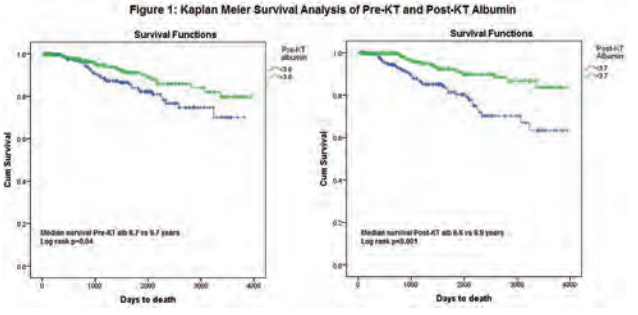

Figure 1: KM Survival analyses for Pre- and Post-KT albumin levels

PUB788

Advice Given to Moslem Kidney Recipients by Moslem Nephrologists About Potentially Medically Risky Religious Rites

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Background: Moslem patients often ask their nephrologists if performing certain religious obligations may be harmful to their health. Permissibility as advised by an expert Muslim physician religiously acceptable waiving of such rites.

Methods: This is a cross-sectional survey of the nephrologists' advices to posttransplant patients regarding fasting Ramadan, performing pilgrimage, Omrah, marital relations and pregnancy. The survey was sent to Moslem nephrologists in different countries.

Results: Of the respondents (n=58), 78% follow up posttransplant patients; 35% form Saudi Arabia, 19 % from USA and 20 % from Pakistan. 60% of the respondents would let stable patients, fast Ramadan after one year of transplantation whereas just one fifth would not recommend fasting at any time. If the patient is diabetic those who would not recommend fasting at any time increased to 32%. Three quarters would let patients perform Omrah after 6 to 12 months and only 1.7% would not recommend that at any time. Obligatory Hajj, would be allowed by 58% after 1 year after transplantat, additional 22% will allow it after 2 years and 5% would not recommend that at any time. The responses for nonobligatory Hajj were 47%, 23 % and 23% respectively. The majority felt that marital relationship could be resumed once the surgical incision has healed, 6% felt there should a period of one year of abstinence. 61% of the respondents would delay the pregnancy in primigravida with stable renal function for one year, 28% for 2 years, about 2 % would allow it immediately and none

would not recommend it at any time. In multiparous recipients, the respective frequencies were 45%, 25%, 3% and 20% The presence of controlled hypertension in the absence of proteinuria is not a contraindication to pregnancy except in only 3% of, whereas 71% would allow it after one year of transplantation. There was no statistical difference between the advice given by transplant nephrologist and general nephrologist on pregnancy or fasting Ramadan for the recipients or donors.

Conclusions: To our knowledge this the first study exploring the consensus among Moslem nephrologists regarding the advice they would give regarding performing potentially risky religious rites by Moslem posttransplant patients.

PUB789

When to Treat Hepatitis E in Renal Transplant Patients?

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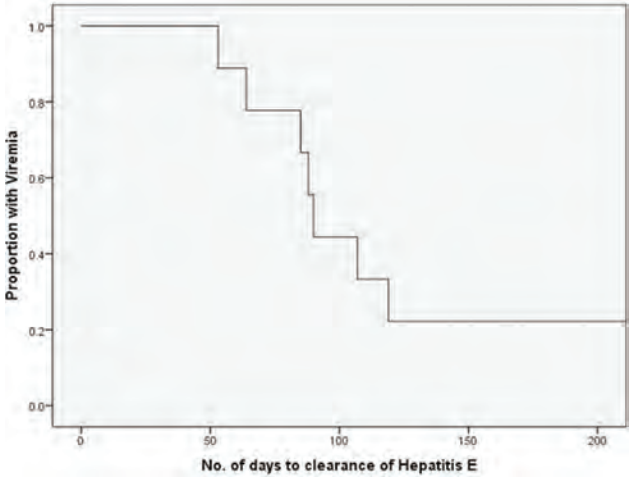
Background: Whereas Hepatitis E (HepE) is a self-limiting illness in the immunocompetent, chronicity is increasingly reported among immunocompromised patients. In the absence of established therapy, current approach is initial monitoring with treatment for viral persistence. We hypothesized that spontaneous resolution is infrequent among immunocompromised renal transplant recipients(RTX), warranting early treatment.

Methods: This single-centre, retrospective study evaluated clinical and laboratory characteristics and outcomes for RTX with HepE.

Results: 10 RTX (90% Male, Median age 55years, 80% Chinese, 20% Indian) were diagnosed with HepE from 2013-2018, yielding a yearly incidence of up to 1,082/100,000 population among RTX, in comparison to 0.92/100,000 in the general population. 2 reported intake of Chinese sausages or raw oysters. 1 Indian male was exposed to plasma products. Diagnosis of HepE was made on viral load (VL) detection in 9 RTX and by serology in 1 RTX at an interval of 111-8,770 days. At diagnosis, median AST was 80IU/mL, ALT 133IU/mL, ALP 102.5IU/mL and VL was 1,140,000IU/ml. Immunosuppression decrease (IsD) alone achieved viral clearance in 1 RTX with low VL of 4,380 copies; another RTX did not achieve clearance despite a 188 day trial of IsD. The remainder could not undergo IsD for clinical reasons and received Ribavirin (Rb) within 50 days of diagnosis. Of 9 treated with Rb, 4(44.4%) developed anaemia, majority requiring erythropoietin. 7 out of 8 (87.5%) achieved viral clearance within 105 days after initiation, 2(22.2%) had relapse/reinfection requiring re-treatment. 1 had treatment failure due to treatment-limiting side effects.

Conclusions: HepE has a high incidence among RTX, presenting with mild transaminitis and responding to Rb in the majority. As viral clearance with IsD is not effective or feasible in the majority, our results advocate for early treatment of HepE among RTX.



PUB790

The Aftermath of Chemotherapy for Burkitt Lymphoma in a Renal Transplant Recipient

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Introduction: Burkitt lymphoma is a very rare post-transplant lymphoproliferative disorder (PTLD) in adults. It behaves aggressively requiring cessation of conventional immunosuppression and urgent start of combination chemotherapy.

Case Description: A 44 year old man was diagnosed with CKD 5 secondary to ADPKD for which he underwent pre-emptive ABO compatible single haplotype matched live related renal allograft surgery in Jan'11 at our centre. He was on tacrolimus, azathioprine and steroids. He had an uneventful course for 5 years. In Apr'16, he was diagnosed with Burkitt lymphoma of the caecum (CD 20 and Ki67 positive) for which he received 6 cycles of chemotherapy (rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide and prednisolone). He was on 5mg prednisolone daily as maintenance therapy. He was cured of lymphoma in Nov'16 (sr creatinine 0.8 mg%). However, in Dec'16 he developed gross hematuria with graft dysfunction (sr creatinine 3.8 mg%) and pancytopenia. Peripheral smear and bone marrow examination were normal. Blood and urine cultures were negative. Urine TB PCR, geneXpert and culture were negative. Cystoscopy was normal. Serology (ELISA) showed: Parvovirus IgM-negative; EBV VCA IgM and IgG and EBNA IgG positive; HIV, HBsAg and anti HCV negative. Plasma and urine BK viral load, plasma CMV viral load were undetectable. However, his urine was positive for JCV and CMV (by NAAT). Renal biopsy showed acute interstitial nephritis with lymphocytic infiltrate of 10-15% with no tubulitis or peritubular capillaritis and with C4d, SV40 and CMV negative with no chronic changes. Though no strong evidence, we presume that his graft succumbed to JC virus in just three months (contrary to current understanding of JCV nephropathy having a favourable graft outcome). The patient continues to be on hemodialysis. He developed orbito-cerebral mucormycosis in Aug'17 requiring left orbital exenteration and antifungals to which he responded.

Discussion: Despite recovering from Burkitt lymphoma, our patient suffered two opportunistic infections within a year of completion of chemotherapy, though he was not on calcineurin inhibitors and antiproliferative agents. It was tragic that he didnot lose the graft to rejection but to infection highlighting that immunity can remain suppressed as long as 9 -12 months post chemotherapy.

PUB791

Multimodal Individualised Treatment for Recurrent FSGS After a Third Kidney Transplantation Using Rituximab and Belatacept

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Introduction: Recurrent nephrotic syndrome due to FSGS is associated with poor transplant outcomes, its optimal management is not yet established.

Case Description: We report the case of a 48 years old patient treated by hemodialysis since 1992 due to ESRD caused by biopsy proven FSGS. A first kidney transplant failed after four months due to severe recurrence of his initial disease. The second transplantation was lost rapidly due to surgical complications. The patient had not developed significant HLA immunization before his well-matched third graft. Immunosuppression consisted of an association of tacrolimus, mycophenolic acid (MA) and steroids at usual doses. Rituximab was injected at day 1 after transplantation and induced a deep depletion in CD19 positive B cells. During the first 2 months kidney function remained stable with GFR levels estimated by CKD-EPI between 35-40 ml/min/1.73 m2 and urine protein/creatinine ratio did not exceed 0.1 g/g while serum-albumin was in the normal range. However during the third month after transplantation positive viremias for BK virus were observed and the patient developed pneumonia and pyelonephritis which required adapted antibiotic treatment. Despite stopping MA and lowering tacrolimus doses BK viremia and viruria remained positive. Proteinuria tended to increase, clinical significant edema developed despite normal serum albumin and kidney function worsened. A kidney biopsy performed at month (M) 7 showed slight signs of calcineurin toxicity and podocyte foot-process fusion. We therefore decided to start plasmapheresis (3 sessions during the first week followed by 1 session every month during 6 months and switch to monthly belatacept injections, while lowering tacrolimus trough levels < 2 ng/l. Under this treatment BK viremia disappeared (M 12), proteinuria could be maintained in the non-nephrotic range and kidney function recovered and is stable at a follow-up of 18 months.

Discussion: This case indicates that Rituximab is able to prevent severe recurrence of FSGS after kidney transplantation but infectious complications are frequent and can have deleterious consequences. Belatacept treatment seems to be a safe in this condition and might permit to lower concomitant immunosuppressive treatment. Further studies and probably individualized strategies are needed to optimize management of recurrent FSGS.

PUB792

The Impact of Hurricane Maria on Transplant Outcomes in Puerto Rico: A Retrospective Chart Review

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Background: On September 20th, 2017, Hurricane Maria made landfall on the island of Puerto Rico, leading to a high number of deaths, destruction of property, and adverse health outcomes. This study aims to characterize the effect of Hurricane Maria on Kidney Transplant Recipients through the Veterans Affairs (VA) Health Care System.

Methods: The electronic health records of all kidney transplant recipients through the Veterans Affairs since 2005 were reviewed. Patients who had lived on Puerto Rico in the year of 2017 were included. All notes and laboratory values were abstracted prior and after the hurricane, including creatinine, urinalysis, urine protein-to-creatinine ratios and drug levels, as well as demographic and historic data on transplant status.

Results: 31 patients were identified Puerto Rico residents in 2017. All 31 were males (100%) and Hispanic/Latino (100%). The mean age was 65.5 ± 7.0 years. 29 were kidney transplants while 2 were kidney-pancreas transplants. The mean time since transplant was 8 ± 3.5 years. End-Stage Renal Disease was most frequently due to diabetes mellitus (11; 35%), hypertension (8; 25.8%), and glomerulonephritis (4; 12.9%). Only 4 patients had proteinuria on urinalysis. Prior to the hurricane, serum creatinine levels were 1.3 mg/dL ± 0.4, urine protein-to-creatinine ratio was 0.45 ± 0.79. Tacrolimus and sirolimus levels were 6.4 ± 1.3 and 11 ± 0.2, respectively. After the hurricane, contact was established with all 31 patients. Serum creatinine levels were 1.4 mg/dL ± 0.55 and UPC were 0.31 ± 0.38, which were not statistically significant (p= 0.33 and 0.38, respectively). Three patients had creatinine elevations greater than 0.3, of which only one had persistent elevations one

month afterwards. Tacrolimus and sirolimus levels three months after the hurricane were 7.3 + 1.3 and 10 ± 0.8, respectively. None was subtherapeutic.

Conclusions: Despite the destruction and degradation of infrastructure in Puerto Rico after Hurricane Maria, the vast majority of kidney transplant recipients through the VA were not adversely affected. Only one recipient had sustained creatinine elevations, which may or may not have been a consequence of disruption of healthcare services after the hurricane.

PUB793

Comparison of Outcomes One Year After Renal Transplant Between Alemtuzumab and Basiliximab for Induction Immunosuppression

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Background: Induction immunosuppression has become increasingly utilized to improve early graft function and decrease rejection rates. The aim of our study was to compare the outcomes one year post-transplant in renal transplant patients who received either alemtuzumab or basiliximab for induction therapy.

Methods: At our center, alemtuzumab is given to all patients with a calculated panel of reactive antibody (CPRA) > 25% and basiliximab is given when CPRA < 25%. We included all patients (N=27) who received induction with alemtuzumab for renal transplant between 2011 and 2016. These were matched 1:2 to basiliximab recipients by age and date of transplant. Continuous variables were compared using t-tests or Wilcoxon rank-sum tests and categorical variables using Fisher's tests or chi-square tests. Binary outcomes were compared using Cochran-Mantel-Haenszel tests. Time-to-event outcomes were plotted using the Kaplan-Meier method and compared between groups using log-rank tests.

Results: Baseline demographics are described in Table 1. Most patients were maintained on tacrolimus, mycophenolate, and prednisone. No statistically significant differences in the following outcomes were detected: delayed graft function (p = 0.76), graft loss (p = 0.99), or rejection (p = 0.2). Opportunistic infection rates were not significantly different at 1-year post-transplant (p = 0.83). Time-to-infection (p = 0.84) and time-to-death (p=0.21) were similar in both groups, but time-to-rejection was longer in the basiliximab group vs alemtuzumab group (p = 0.04).

Conclusions: Despite a difference in immunological risk between the 2 groups, we did not detect any significant differences in outcomes at 1-year post-transplantation between higher immunological risk patients receiving alemtuzumab and lower risk patients receiving basiliximab. Early opportunistic infectious rates were similar.

	Alemtuzumab (N=27)	Basiliximab (N=54)	p-value
Age, mean (SD)	50.78 (11.98)	50.83 (11.72)	0.98
Gender - female, n (%)	20 (74.07)	19 (35.19)	0.001
Race			
Black	1 (3.7)	11 (20.37)	0.02
White	21 (77.78)	41 (75.93)	
Other	5 (18.52)	2 (3.7)	
Number of transplants, n (%)			
1	21 (77.78)	51 (94.44)	0.054
>1	6 (22.22)	3 (5.56)	
CPRA, median (range)	80 (0, 100)	0 (0, 47)	<0.0001
CMV serostatus n, (%)			
High risk	2 (7.41)	9 (16.67)	0.18
Intermediate risk	22 (81.48)	33 (61.11)	
Low risk	3 (11.11)	12 (22.22)	
Any opportunistic infection, n (%)	5 (18.52)	11 (20.37)	0.83
HLA Mismatch, n (%)			
Level 1	2 (7.69)	1 (1.85)	0.12
Level 2	3 (11.54)	3 (5.56)	
Level 3	3 (11.54)	17 (31.48)	
Level 4	18 (69.23)	33 (61.11)	

PUB794

Low-Dose Mycophenolate Mofetil in Kidney Transplant Recipients and Its Association with Infectious Diseases and Acute Rejection

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Background: Current immunosuppression schemes have improved the overall kidney transplant (KT) survival; however, the adverse events associated with maintenance of immunosuppressive therapy have not been modified. The use of Mycophenolate mofetil (MMF) has unfavorable dose-related effects (gastrointestinal, hematological and infectious). **OBJECTIVE:** Determinate the incidence of infectious diseases and acute rejection (AR) with two different doses of MMF.

Methods: A prospective cohort (March 1, 2017 - March 1, 2018) in first-time live donor kidney transplant (LDKT) recipients. Patients with low dose of MMF (1.5 gr/day) and standard dose of MMF (2 gr/day) were compared. Anthropometric measures, presence of post-transplant infections, hospitalizations, AR and adverse events associated with MMF were collected.

Results: 81 low risk posttransplant patients were included (31±11 y/o), from which 39 were in the low dose group (LD-G) and 42 in the standard dose group (SD-G), both of them with tacrolimus and prednisone. At the end of follow up, an incidence of infectious diseases was reported (46.2% vs 47.6% p=0.9), [RR=1.06, CI (0.44-2.5)], and AR proved with biopsy of (4.8% vs 2.6% p=0.6), [RR=1.9, CI (0.17-19.6)]. The LD-G had a higher tendency for risk of AR without statistical significance and other complications (gastrointestinal manifestations and hematologic diseases) that required hospitalization, which were more frequent in the SD-G (9.5% vs 56.4% p<0.001) [RR= 2.07, CI (1.43- 3.04)].

Conclusions: The use of low doses of MMF has an adequate safety profile in the Mexican population, without increasing the risk of AR or having a significant impact on infections in the post-transplant period, therefore, reducing the presence of adverse effects that require hospitalization.

PUB795

Characteristics of Long-Term Renal Allograft Survivors

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Background: We studied the characteristics and the predictors of survival in Bahraini renal transplant recipients with an allograft that functioned for more than 10 years.

Methods: Seventy-eight patients underwent renal transplantation between 1982 and 2007. Among them, 179 patients maintained functioning allografts for more than 10 years (range 10-35 years). Characteristics of the surviving patients, data on graft survival, and determinants of outcome were obtained by reviewing all medical records.

Results: The mean age at time of renal transplantation was 40.1 ± 14.4 years and 70% were males. The cause of end-stage renal disease was diabetic nephropathy in 24.6% and 84% received dialysis therapy before transplantation. The source of the graft in 119 (66%) recipients was from living related donors with a mean age of 29.8 ± 6.6 years, and it was the first graft in 172 recipients. The primary immunosuppression regimen was cyclosporine (CsA) base in 129 patients, tacrolimus (Tac) based in 46 patients while four patients received steroids and azathioprine only. Induction therapy was administered to 96 patients. Acute rejection episodes occurred in 25 patients (14%), of whom three experienced two episodes. During the last follow-up in January 2018, the mean serum creatinine was 118.3 ±46.5 μmol/L. A history of cancer was noted in two patients, whereas hypertension was encountered in 54% and diabetes mellitus in 24%. We compared the graft functioning group with the graft failure group and found that the independent determinants of long-term graft survival included time of late acute rejection episodes and histopathologic findings of chronic allograft damage, post-transplant hypertension and serum creatinine at one year.

Conclusions: We conclude that renal transplantation even in its earliest years and despite the associated numerous complications has provided a ten-year or more of near-normal life to patients with end-stage renal disease.

PUB796

Serum β2-Microglobulin May Predict the Change of Renal Function After Kidney Transplantation

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Background: Several perioperative factors including histological findings of allograft biopsy are known to be associated with graft function and graft survival after kidney transplantation (KTx). It is unclear what factors in post-KTx period predict the longitudinal change of renal function.

Methods: The data from post-KTx patients who are followed at The University of Tokyo Hospital were collected retrospectively. Patients followed-up less than 6 months after KTx were excluded. To identify predictors of the longitudinal change of renal function, we analyzed data including clinical parameters measured at each outpatient visit. The primary outcome was determined as the eGFR decline (more than 10% or 2 ml/min/1.72m^2 reduction from baseline) during 12 months period.

Results: A total of 38 post-KTx recipients were analyzed in this study. Age and eGFR at baseline of these patients were 51.0 ± 15.4 years old and 43.0 ± 16.1 ml/min/1.73m^2 (mean ± SD), respectively. The duration from KTx to collection of clinical parameters was 7.9 ± 7.3 years. Estimated GFR changes were evaluated 12 months after. When patients were divided into two groups with (N = 14) and without (N = 24) eGFR decline after 12 months, percentage of male (93% vs 63%), serum uric acid (UA, 7.48 vs 6.18 mg/dl), and β2-microglobulin (β2MG, 5.78 vs 2.85 mg/L) were significantly higher and serum albumin (3.98 vs 4.22 g/dl) was significantly lower in the eGFR decline group. On ROC analysis, β2MG and UA predicted eGFR decline after 12 months (AUC [95%CI] = 0.75 [0.58-0.92] and 0.72 [0.53-0.92], respectively). On multiple regression analysis, logarithm of β2MG was significantly correlated with the relative eGFR changes during 12 months observation period (β = -0.50, p = 0.001).

Conclusions: β2MG and UA measured at outpatient clinic may predict the change of renal function of post-KTx patients.

PUB797

Effects of Late Cyclosporine Withdrawal on Graft Function and Survival

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Background: Attempts to discontinue calcineurin inhibitors (CNI) early after renal transplantation without conversion to an alternative immunosuppressive have failed due to high rates of acute rejections. Data on "late CNI withdrawal" are lacking so far.

Methods: The present work provides a matched case-control study on the effects of CNI withdrawal on graft loss and mortality in 90 patients (1500 screened) with advanced graft dysfunction (serum creatinine > 3.5 mg/dl) and a cyclosporine based triple immunosuppressive regimen at the Charité University Hospital, Berlin.

Results: Cyclosporine was withdrawn at a mean of 54.0±32.8 months posttransplant in 45 subjects. Whereas eGFR did not significantly differ between the groups at this time (12.4±2.7 vs. 14.7±8.9 in the control group, p=0.08), it was significantly higher in subjects undergoing withdrawal after 120 months (D 4.1 ml/min; p<0.001). In a Cox regression analysis adjusted for age, gender and eGFR patients with CNI withdrawal showed better survival rates for the combined endpoint death/graft loss (HR (95% CI): 0.19 (0.12-0.33), p=0.001) compared to matched controls. The survival benefit was significant for the endpoints death (p=0.01) and graft loss (p=0.001).

Conclusions: CNI withdrawal was associated with improved survival rates in patients with advanced graft dysfunction in this retrospective analysis.

PUB798

All That Glitters Is Not Gold: CKD Stage 4 Disguised as CKD Stage 4T

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Introduction: Steroid-resistant focal segmental glomerulosclerosis (FSGS) is the primary renal disease in approximately 10% of pediatric renal transplant recipients (RTR). While immunosuppressive medications (ISM) are essential for prevention of allograft rejection, they could also potentially portend salutary impact on the underlying disease of the native kidneys.

Case Description: A 38-year-old African American man referred to nephrology clinic to re-establish care for his transplanted kidney after he was lost to follow up for about 20 years. He had a history of end-stage renal disease secondary to FSGS and received a living-related donor kidney transplant at the age of 10. Although he was on dialysis briefly prior to transplant, he was never anuric. Post-transplant, he received azathioprine and prednisone for about 10 years with a baseline serum creatinine (Scr) of 1.6 mg/dL. Then, the patient stopped taking all ISM and lost follow up. At the time of current presentation (Scr 3.4 mg/dL and urine albumin-creatinine ratio 75 mg/g) he was presumed to have developed allograft rejection leading to chronic kidney disease stage 4T as he was taking no ISM for 2 decades. Surprisingly, ultrasound of the right lower quadrant, performed twice, could not identify any allograft tissue due to its significant atrophy and blending in with the hyperechogenic surrounding fat tissue. Therefore, a radionuclide renogram was obtained which confirmed complete absence of flow to the right lower quadrant allograft while perfusion to the native kidneys was present; his renal function was entirely provided by the native kidneys rather that the allograft. Seven years later, his Scr has remained stable with medical therapy without ISM.

Discussion: This patient received azathioprine and steroids for 10 years after transplant prior to stopping ISM. While he lost his allograft afterwards likely due to rejection, the salutary impact of ISM on underlying FSGS of the native kidneys resulted in partial recovery that has lasted for more than 25 years. The main teaching point in this case is that renal function in RTRs could still be partially (or completely) provided by the native kidneys even decades later, as post-transplant ISM could induce remission in certain underlying diseases. In cases where there is a doubt, complementary studies such as radionuclide renogram could be beneficial.

PUB799

Clinical Phenotype of CAKUT May Predict Clinical Course After Kidney Transplantation

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Background: Clinical and pathological differences in transplant (tx) recipients, where the cause of end stage renal disease (ESRD) was vesicoureteral reflux nephropathy (VURN) or other congenital anomalies of the kidney and urinary tract (CAKUT) or biopsy confirmed glomerulonephritis (GN) were compared to test the hypothesis that the tx outcomes may differ among these various groups.

Methods: We compared post-tx outcomes of 150 renal tx recipients with non-syndromic VURN (VURN group, 52% male, mean age:28±9 years), 52 tx recipients with CAKUT other than VURN (CAKUT group, 73.1% male, mean age:30±11 years) and 150 tx recipients with GN as the cause of ESRD (GN group: 55.3% male, mean age:31±10 years). Randomly selected renal allograft indication biopsies in each group [VUR (n=16), CAKUT (n=7) and GN (n=19)] were evaluated. Primary outcome was allograft loss and secondary outcome was biopsy-confirmed rejection.

Results: Demographic characteristics of study groups were similar except higher number of males in CAKUT group (p=0.028). Allograft survival rates by Kaplan-Meier analysis at 10 year for VURN, CAKUT and GN groups were 83%, 77.4% and 71.3%, respectively (p=0.21). Patient survival rates were similar among VURN (100%), CAKUT (96.2%) and GN (98.7%) groups during follow up (p=0.08). There was a trend in CAKUT group to develop post-tx donor specific antibodies (9, 17.3%) compared to VURN group (12, 8%) (p=0.05). Biopsy-proven acute rejection rate (BPAR) in VURN, CAKUT and GN groups were 14%, 26.9% and 16%, respectively (p=0.09). BPAR rate and total inflammation score in biopsy were significantly higher in CAKUT group than VURN group (p=0.03 and p=0.05, respectively). Incidence of post-tx VUR was significantly higher in VURN group (19, 12.7%) compared to CAKUT (2, 3.8%) and GN (4, 2.7%) groups (p=0.002). Recurrent allograft pyelonephritis was significantly higher in VURN group (23, 15.3%) compared to CAKUT (2, 3.8%) and GN (6, 4%) groups (p=0.001).

Conclusions: Primary diagnosis of VURN poses an increased risk of VUR and urinary tract infections in kidney allograft and the sustained infection related inflammation may account for reduced rejection rates compared to non-VURN CAKUT and GN patients.

PUB800

Effects of Different Thymoglobulin (r-ATG) and Mycophenolic Acid (MPA) Dosing Regimens on Acute Rejection and BK and CMV Infections

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Background: There are no randomized clinical trials comparing outcomes of different r-ATG and MPA dosing regimens, as induction and maintenance immunosuppression agents respectively, in renal transplant recipients maintained on tacrolimus, MPA and prednisone.

Methods: We retrospectively reviewed the charts of all adult kidney transplant recipients at our institution from January 2015 to December 2017. We divided our patient cohort into 2 groups. Group-1 received r-ATG 5 mg/kg (standard dose), MPA 540 mg BID (low dose), standard tacrolimus BID dosing, and a fast taper of prednisone down to 5 mg qd in 1 month (N=49). Group 2 underwent r-ATG 3-4.5 mg/kg (low dose), MPA 720 mg BID (standard dose), standard tacrolimus BID dosing, and a slow taper of prednisone down to 5 mg qd in 3 months (N=46). Plasma BK and CMV PCR were checked monthly within 1 year of transplant. Acute rejection (AR) was defined as biopsy proven and treated rejection within 1 year of transplant.

Results: A total of 95 patients were followed post-transplant with a mean follow up of 10 months. The overall graft survival (graft failure or patient death) for both groups is 100% at 1 year. There was no significant difference in 1 year BK & CMV viremia between both groups (BK Group-1 18 % vs. Group-2 15%, p=0.68; CMV Group-1 4% vs. Group-2 13%, p=0.12). Moreover, AR at 1 year did not differ between groups (Group-1 19.5% vs. Group-2 24%, p=0.36). The mean tacrolimus levels at discharge differed significantly between Group-1 (5.9 ng/ml) and Group-2 (7.15 ng/ml) with p=0.04. Of the patients who were BK positive, CMV positive, and rejection positive, there was no significant difference in their mean tacrolimus levels at the time of their positive tests. Lastly, the mean eGFR at 6 months and 1 year were not significantly different between Group-1 and Group-2.

Conclusions: Overall, the rates of BK/CMV viremia and AR at one year in kidney transplant recipients were not significantly different between the standard dose of r-ATG / low dose MPA and low dose r-ATG / high dose MPA groups.

PUB801

Understanding Barriers to Kidney Transplantation Among Adults on Maintenance Dialysis: A Cross-Sectional Study

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Background: Kidney transplantation (KT) is the treatment offering the best possible long-term outcomes for patients with end-stage renal disease. In Saudi Arabia, KT accounted for only 4.5% of total renal replacement therapy in 2016; the number of KTs performed outside Saudi Arabia in 2016 is not known. The main objective of this study was to evaluate the barriers to KT experienced by patients in Saudi Arabia.

Methods: This cross-sectional study was conducted during the period of September 2017 to January 2018. Direct interviews using a specifically pre-coded and pre-tested online questionnaire were used to examine reasons for low KT rate and the possible barriers to KT in Saudi Arabia.

Results: A total of 321 adult hemodialysis (HD) patients eligible for KT were selected from 4 HD units in Jeddah, representing 11% of the total HD population in Jeddah. Mean patient age was 49.9 ± 14.9 years, 62.1% were male, and 26% were employed. Most patients were of Saudi nationality, only 38 (11.8%) were non-Saudi. Upon interviewing, 90.7% had been counseled for KT. The majority of counselling (86.5%) was done by nephrologists after the start of HD. 178 (55.5%) were referred for pre-transplant evaluation. Among the cohort, 92 (28.6 %) were on the active transplant list. The most common barrier to KT was lack of donor availability (n=107, 40.5%), followed by misconceptions regarding long-term complications for donors (n=58, 22%), and concerns regarding surgical complications (n=24, 9.1%). Only 17 patients (6.4%) reported financial constraint as the main reason for not having a KT; this occurred more frequently among non-Saudi patients.

Conclusions: Misconceptions about KT still represent a substantial barrier among dialysis patients. Most patients are educated about KT after initiation of dialysis. Initiatives to promote and improve pre-dialysis education and knowledge about KT are needed to improve the low transplant rate in Saudi Arabia.

Funding: Commercial Support - DaVita

PUB802

Kidney Transplantation in Patients with Neurogenic Bladder

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Background: Neurogenic bladder is a condition associated with high incidence of urinary tract infections (UTI) and is a rare cause of end stage renal disease (ESRD), for which kidney transplantation (KT) is performed. There is lack of data in the recent literature on the outcome of KT in adult recipients with neurogenic bladder.

Methods: During 2009-2018 period, six patients with neurogenic bladder were transplanted at the Merkur Hospital. Their medical records were retrospectively analyzed, with aim to evaluate long-term patient and graft survival, as well as UTI and rejection frequency.

Results: The mean ± SD (range) age of the study cohort was 31.6± 11.0 (20-50) years at the time of transplantation. Cause of neurogenic bladder in three patients was spinal cord injury, meningomyelocele in one patient, detrusor areflexia after bladder surgery in one and neurological disorder in one patient. Mean dialysis vintage was 59 ± 32 (0-96) months. All patients had repeated urinary tract infections before and after transplantation. One-year patient and graft survival was 100%. Five-year patient survival was 67%. One patient died 30 months after transplantation due to squamous cell bladder cancer, with a functioning graft and one kidney graft lost its function 60 months after transplantation due to BKV nephropathy. 5/6 patients required either intermittent, or permanent bladder catheterization after KT. During the mean follow-up of 1206 ± 1106 (102-3092) days, there was a mean number of 14.3±10.4 (5-34) urinary infection episodes requiring antibiotic therapy and mean number of 3.8±1.5 (2-6) urinary tract infections requiring hospitalization and intravenous antibiotic therapy. Two patients had one episode of acute cellular rejection (IA), which was treated by bolus of steroids. Mean serum creatinine in patients with graft function on the last visit was 84.6 ± 21.8 (56-109) μmol/L.

Conclusions: Acceptable long-term patient and graft survival, graft function and serious UTI rates can be achieved in patients with ESRD attributable to neurogenic bladder. The fact that KT can be successfully performed in patients with neurogenic bladder is especially important, because this population often consists of younger patients with longer life expectancy.

Funding: Government Support - Non-U.S.

PUB803

Adenovirus Infection Case-Series in Kidney Allograft Recipients at Hospital do Rim

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Background: Adenovirus infection is an important cause of complications in renal transplant patients that carries potential risks of loss of graft function and death. Hence, we attempted to describe the main characteristics of the affected patients with such a disease in our population during 2017.

Methods: We described the clinical and laboratory features of renal transplantation recipients coursing with adenovirus infection after kidney transplantation at the time of diagnosis at Hospital do Rim during 2017. These included main symptoms at onset, duration, time from transplantation to disease, time from onset to negative viremia, time to creatinine improvement, time to clinical response, association with other infections and immunosuppression description.

Results: Adenovirus infection occurred in 6 patient transplanted during 2017. All of the patients received 3 mg x kg of rabbit anti-thymocyte globulin as induction, all of them used prednisone and calcineurin inhibitor according to institutional protocols, 4 used azathioprine and 1 received everolimus as third drug. All of the living donor kidney recipients who developed infection did it during the first year(n=3), two of them during the first month, compared with deceased recipients (23rd month, range 17-30 months). The main symptoms at onset where fever (n=6), macroscopic hematuria (n=5) and dysuria (n=5). The mean time to negative viremia from onset of symptoms was 21 days. Interestingly, the duration of the symptoms was 13 days (7-18 days) meanwhile the lowest creatinine value after the event was reached at 26th day (14-39 days). The loss of allograft function was 9 ml/min/1.73m2 (8-32 ml/min/1.73m2) assessed by CKD-Epi formula. Co-infection with CMV happened in 1 case. The mean hospitalization time was 26 days (9-55days). Management of adenovirus infection included adjusting immunosuppression in all the cases. Two patients suspended azathioprine, one suspended everolimus and two patients received IV immunoglobulin. All of the patients survived to infection and one of them developed a new episode subsequently.

Conclusions: Adenovirus infection in transplant patients must be considered as an alternative hypothesis to urinary tract infection, mainly during the first months of transplantation in living donor recipients. Its prompt management could preserve allograft function.

PUB804

Severe Hyponatremia with Intraoperative Desmopressin Use in (Deceased and Living Donor) Renal Transplant Recipients

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Background: Desmopressin (DDAVP) is used for hemostasis in patients with factor VIII deficiency, von Willebrand disease and platelet function defects including that seen in patients with chronic kidney disease. A serious consequence of its use is water intoxication with attendant hyponatremia. We studied the incidence of hyponatremia in patients who received desmopressin during kidney transplant (KT) surgery.

Methods: We retrospectively analyzed the incidence of hyponatremia (Na < 135) and severe hyponatremia (Na < 130) in the first 48 hrs following DDAVP used during KT surgery at our center between 2009-2018. We compared the incidence of hyponatremia in the first 48 after surgery with a control group of living and deceased KT recipients who did not receive DDAVP but were administered the same post-operative fluid protocol that the study group received. Relative risk (RR) and Fishers exact t test p values were used to determine the significance of differences between the two groups.

Results: 22 patients met the inclusion criteria. 17 (77.3%) patients developed hyponatremia, and 8 (36.4%) developed severe hyponatremia (Mean 125.3, SD 3.93) (Table 1). In 25 controls (living donor 4; deceased donor 21) hyponatremia was noted in 17 (68%), but no patient developed severe hyponatremia. There was no significant difference between the groups for the incidence of hyponatremia (RR 1.13 [0.7-1.62], p=0.35). However, severe hyponatremia was noted only in patients who received DDAVP; 3 out of 4 living KT recipients (75%) and 4/18 (22.2%) deceased donor recipients (p = 0.0027).

Conclusions: In this retrospective analysis of the incidence of hyponatremia, among KT recipients who were given DDAVP for intraoperative hemostasis, there was a significantly higher incidence of severe hyponatremia (75% of living KT recipients, and 22.2% of deceased recipients) compared to patients who did not receive DDAVP. Although larger retrospective analyses are required to further validate these findings, the risk of severe hyponatremia should be acknowledged and anticipated if patients are administered DDAVP during KT surgery.

Recipients	Na (mEq/L)	DDAVP (%)	No DDAVP (%)
Living Donor	< 135	4/4 (100)	3/4 (75)
	<130	3/4 (75)	0 (0)
Deceased Donor	< 135	13/18(72.2)	14/21 (66.67)
	<130	4/18 (22.22)	0 (0)

Table 1

PUB805

Early Evidence of the Association Between Gout and Higher Mortality Rates in the Prevalent Solid Organ Transplant Population

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Background: There is evidence that gout may be associated with higher mortality risk in kidney transplant recipients, though little data is available in other transplant types. Existing literature has focused on the association between new onset gout and mortality in the incident transplant population. Important questions remain regarding the impact of gout on transplant outcomes beyond the initial post-transplant timeframe and on other solid organ transplant (SOT) types. This retrospective patient claims data analysis was performed to determine whether an association between gout and mortality exists in the prevalent SOT population.

Methods: 2015 gout prevalence among the prevalent SOT population was assessed in 2 administrative claims databases: Medicare Fee-For-Service Limited Data Set (5% sample) and a commercial claims sample (IQVIA™ Real-World Data Adjudicated Claims – US). Definitions used were – SOT: a claim with an SOT procedure code OR any claim with a history of SOT status diagnosis code, limited to kidney, liver, and heart; Gout: ≥1 claim with any gout diagnosis code. Univariate analysis included 2016 mortality for patients in the gout / non-gout SOT cohorts identified in calendar year 2015 and still living in 2016.

Results: In the Medicare SOT population, 2016 mortality was higher among kidney transplant patients with gout vs. those without gout (9.6% vs. 7.1%, p=0.013). In the commercially insured SOT population, 2016 mortality was higher among patients with gout for both kidney (3.0% vs. 2.3%, p=0.022) and heart (5.3% vs. 3.2%, p=0.045) recipients. No significant differences in mortality were observed in either population for liver transplant recipients.

Conclusions: The higher mortality risk observed in the surviving kidney transplant population for those with vs. without gout, regardless of insurance provider, reveals an important initial finding and demonstrates a potential unmet need in this population. While gout appears to be associated with a greater risk in this analysis, further risk-adjusted studies are warranted to determine whether gout is an independent driver of mortality, as well as other poor outcomes, in the prevalent SOT population.

Funding: Commercial Support - Horizon Pharma

PUB806

Impact of Cardiac Function on Allograft Survival in a Cohort of Mexican Transplant Recipients

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Background: Cardiovascular disease is a major cause of morbidity and mortality among patients who undergoes kidney transplant (KT). Asymptomatic cardiac changes cause during CKD, could lead to perioperative complications and mortality as well as poor graft and patient survival. The purpose of this study was to evaluate the impact systolic ventricular function and pulmonary arterial pressure in patients with CKD and the outcomes after KT.

Methods: The study included 150 patients over 18 years of age with CKD who had a successful KT. Ventricular function and pulmonary arterial pressure were assessed by echocardiographic standard parameters before and 6 months after transplant.

Results: Mean age was 31.99 ± 11.28 years, and 65% were women. Before transplant, mean ventricular ejection fraction (VEF) was 58% and pulmonary arterial pressure was 32 mmHg. Ventricular dysfunction was associated with unclamping donor renal vessels at 107.8 ± 7.96mmHg, and lower perioperative hemodynamics values. The LVEF group increased from 25% to 72.5%, and serum creatinine decrease from 2.25 ± 3.76 mg/dl to 1.98 ± 2.65 mg/dl ($p<0.001$) by 6 months after kidney transplant. The best set of predictors in multiple regression analysis for renal function were the onset of diuresis and the use of diuretics ($R2 = 0.4$; $p < 0.001$).

Conclusions: Patients with LVEF should not be excluded from KT. These results showed the relationship between ventricular function and lower perioperative vasopressors and diuretics and its association on the graft function. Further studies are needed to determine if after KT there is an improvement as well on cardiac structure.

Funding: Government Support - Non-U.S.

PUB807

Short-Term Outcomes of Kidney Transplantation in Patients with Preformed DSA: University Malaya Medical Centre Experience

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Background: The shortage of deceased donors led to an increase of living related renal transplant (LRRT) performed in the presence of donor-specific antibodies (DSAs) or ABO incompatibility (ABOi). Various desensitization protocols have been used in order to reduce the incidence of antibody mediated rejection (ABMR). Here, we described our short-term outcomes in patients with preformed DSAs using our desensitization protocol.

Methods: This is a prospective, cohort study recruiting all kidney transplant recipients from August 2016 till February 2018. Cadaveric, ABO incompatible and those sensitized patients who were not prescribed on our desensitization protocol were excluded. Our desensitization protocol consisted of anti-CD20 (Rituximab) and plasma exchanges post transplantation. However, MFI≥3000 or positive flow cytometry will receive extra cycles of plasma exchanges prior to transplantation. Clinical outcomes: immediate graft function, serum creatinine at 3 months, incidence of acute rejection (borderline, acute T-cell mediated and ABMR), de novo DSAs and infections (CMV and BKV) were documented.

Results: A total of 26 LRRT patients were recruited (11 patients DSAs positive and 15 patients in low risk group). Mean age was 37.45 ± 11.68 and 37.07 ± 12.09 for DSAs' group and low risk group respectively. Both groups had 3 HLA mismatches (median). Immediate post-transplant 1 patient from DSAs' group had slow graft function (prolong warm ischaemic time) and 1 patient from low risk group also had slow graft function (TTP/HUS secondary to CNI). All other patients had immediate graft function. Mean creatinine at 3-month was 109.25 ± 27.28 mmol/L for DSAs' group and 124.47± 40.16mmol/L in low risk group. At 3-month 2 patients (18%) had borderline rejection from DSAs' group and 7 patients (47%) from low risk group, 1 patient from low risk group had acute T-cell mediated rejection and none developed ABMR. Two patients from low risk group had also developed de novo DSA. There was no incidence of BKV. However, 5 patients had CMV viraemia and 1 patient had disease.

Conclusions: We demonstrated favorable short-term allograft survival and function after renal transplantation (immediate graft function, stable serum creatinine and no development of denovo DSA at 3-month) using desensitization with anti-CD20 and plasma exchange in patients with preformed DSA.

PUB808

Intestinal Perforation by Schistosoma mansoni in a Kidney Transplant Patient: Case Report

Saulo J. Feitosa,[1,2] Frederico C. Cavalcanti,[2] Ana C. Souza.[2] *[1]Universidade Federal de Pernambuco, Recife, Brazil; [2]Real Hospital Português de Beneficência em Pernambuco, RECIFE, Brazil*.

Introduction: Schistosomiasis is endemic in several regions of Brazil and is a public health problem. Caused by *Schistosoma mansoni*, it can present with gastrointestinal symptoms in its chronic form; its presentation with colitis and intestinal perforation is rare, even more so among kidney transplant patients.

Case Description: We present the case of a 56-year-old female patient who underwent kidney transplant in October 2013 and developed chronic allograft nephropathy due to chronic rejection. In February 2018 she was hospitalized with complaints of severe abdominal pain and intestinal constipation for 3 days, and had signs of peritonitis on physical exam. Computed tomography of the abdomen showed signs of colitis and pneumoperitoneum. On the same day of hospitalization, the patient was submitted to exploratory laparotomy, with the finding of a rectum-sigmoid perforation. Hartmann's colectomy with biopsy of the lesion were performed. The patient developed septic shock and acute-on-chronic kidney injury requiring hemodialysis in the postoperative period. The patient was treated with Meropenem based on results of peritoneal fluid cultures. Because Cytomegalovirus (CMV) is a more common cause of intestinal perforation among kidney transplant patients, serum PCR for CMV was performed and came back positive with 6656 copies and the patient was treated with intravenous Ganciclovir until a result with zero copies was obtained. The histopathological study showed active peritonitis with active granulomatous colitis associated with serosal perforation and the presence of viable eggs of *Schistosoma mansoni* in the intestinal mucosa. The patient was treated with praziquantel evolving with clinical improvement and partial recovery of kidney graft function, being discharged in April 2018, awaiting reconstruction of the intestinal transit.

Discussion: In endemic regions for schistosomosis, all kidney transplant candidates must be empirically treated with praziquantel for one month before the transplant, and schistosomosis must be included in the differential diagnosis of intestinal perforation in immunossupressed patients.

PUB809

Impact of the Kidney Donor Profile Index (KDPI) on Kidney Transplants Outcomes in a Tertiary Hospital in Brazil

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Background: Due to the disproportionate relationship between supply and demand of organs, a more complete analysis of the deceased kidney donor is necessary to avoid organ discard. The KDPI is used to estimate how long a deceased donor kidney is expected to function relative to all of the kidneys recovered in the United States of America during the last year, but there is a lack of data regarding KDPI in Brazil.

Methods: A retrospective analysis of medical records of 73 patients submitted to kidney transplant from deceased donors was performed. The transplants ocurred between January and December 2014 in a referral tertiary hospital in Brazil. Stratified KDPI values (less than 20%, 20-40%, 41-60%, 61-80% and more than 80%) were correlated with recipients glomerular filtration rate (CKD-EPI), biopsy-proven rejection episodes and loss of graft function at 1 and 3 years post transplantation. All statistical analysis were made using StatPlus for Mac version 6.

Results: Kidney recipients mean age was 46.2 (SE +/- 1,3) years and 76.7% were male. They had 6.6 (SE +/- 0,4) years of dialysis prior to transplantation and 83.5% had low immunological risk (PRA: 0%). Mean KDPI value was 48.4% (SE +/- 3,2). The mean GFR distribution at 1 year was: less than 20%: 74.5 (SE +/- 8) ml/min (N = 10), 20-40%: 66.5 (SE +/- 6,7) ml/min (N = 17), 41-60%: 62.9 (SE +/- 8,6) ml/min (N = 13), 61-80%: 49.1 (SE +/- 8,3) ml/min (N = 9) and more than 80%: 42.1 (SE +/- 7,3) ml/min (N = 7), $p = 0.09$. In the 3-year analysis we observed: less than 20%: 68.4 (SE +/- 7,3) ml/min (N = 10), 20-40%: 59.4 (SE +/- 5,3) ml/min (N = 17), 41-60%: 53.6 (SE +/- 6,7) ml/min (N = 13), 61-80%: 42.3 (SE +/- 8,6) ml/min (N = 9) and more than 80%: 33.6 (SE +/- 7,1) ml/min (N = 7), $p = 0.03$. The percentages of biopsy-proven rejection episodes at 3 years were: less than 20%: 16.6%, 20-40%: 15%, 41-60%: 26.6%, 61-80%: 35.7%, more than 80%: 66.6%, and regarding complete loss of graft function at 3 years: less than 20%: 16.6%, 20-40%: 10% 41-60%: 13.3%, 61-80%: 35.7% and more than 80%: 41.6%.

Conclusions: In our study, patients who received kidneys from donors with higher KDPIs did have worse outcomes regarding GFR, biopsy-proven rejection episodes, and loss of the allograft.

PUB810

Clinical Significance of C4d Deposition in ABO-Compatible Renal Allografts Without Histologic or Serologic Evidence of Antibody Mediated Rejection

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Background: Antibody-mediated rejection (AMR) is a leading cause of allograft loss in kidney transplant recipients (KTRs). C4d, a product of the classical complement pathway, with morphologic changes on graft biopsy and/or detectable circulating donor specific antibodies (DSAs) is diagnostic of active AMR. The clinical significance of C4d positivity alone is undetermined. We aimed to evaluate clinical outcomes in adult and pediatric ABO-compatible, DSA negative, KTRs with isolated C4d positivity.

Methods: This was a retrospective chart review to identify adult and pediatric KTRs transplanted between 2009-2017 with isolated C4d positivity on biopsy and at least 1 year of post-biopsy follow up. Isolated C4d positivity was defined as C4d + (> 1+ by immunofluorescence in peritubular capillaries) without other findings of AMR and without DSA positivity. Patients with concomitant acute cellular rejection (ACR) were included. Protocol biopsies were performed on pediatric KTRs at 6, 12, and 24 months post-transplant and for clinical suspicion of rejection. Only clinically indicated biopsies were performed in adult KTRs.

Results: 11 patients had isolated C4d positivity. C4d was focal in 7/11 (75%) and diffuse in 4/11 (36%). 4/11 (36%) had ACR and were all treated with steroids, 1 patient received anti-thymocyte globulin (ATG), and 1 patient received IVIG. At 1-year post-biopsy, 6/11 (55%) had repeat biopsies and 6/11 (55%) had DSA testing. None of these patients developed AMR and 2 patients developed DSAs (Figure 1A). The mean change in eGFR between time of biopsy and 1 year post-biopsy was +6.1mL/min/1.73m^2(Figure 2A).

Conclusions: This case series provides preliminary evidence that isolated C4d positivity in ABO-compatible, DSA negative allografts does not correlate with deterioration of renal function, development of DSA, or development of AMR within 1 year following the incident biopsy. Further studies are needed to better understand the impact of isolated C4d positivity on allograft outcomes to better tailor monitoring and treatment.

Patient	C4d	C4d Intensity	ACR	Treatment	AMR in repeat biopsies	DSAs in repeat labs
1	Focal	2+	No	NA	Not tested	No
2	Focal	2+	No	NA	No	No
3	Diffuse	1+	Borderline	Steroids, ATG	No	Yes
4	Focal	3+	Borderline	Steroids	Not tested	Not tested
5	Diffuse	3+	Borderline	Steroids	No	No
6	Focal	1+	No	NA	No	Yes
7	Focal	1+	ACR1A	Steroids	No	No
8	Focal	2+	No	Steroids	Not tested	Not tested
9	Diffuse	1+	No	NA	No	Not tested
10	Diffuse	2+	No	IVIG	Not tested	Not tested
11	Focal	3+	No	NA	Not tested	Not tested

Figure 1A: Patient Biopsy and Clinical Characteristics. Characteristic of C4d positivity, presence or absence of ACR, treatment regimen and presence or absences and AMR and HLA DSA within 1 Year post-biopsy are shown.

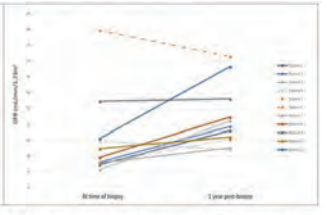

Figure 2A: Renal Function at Time of Biopsy and 1Year Post-Biopsy. GFR was measured at time of biopsy and 1-year post-biopsy to trend renal graft function.

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FR-OR142

Effect of Linagliptin on Kidney and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Kidney Disease: CARMELINA®

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Background: Type 2 diabetes (T2D) is a common cause of ESKD so the effects of glucose-lowering therapies on kidney outcomes are of great interest, especially in people with CKD.

Methods: CARMELINA (NCT01897532) randomized people with T2D and prevalent CKD (UACR >30 mg/g with concomitant CV disease, OR eGFR 45-75 ml/min/1.73m^2 and UACR > 200 mg/g OR eGFR 15-45 regardless of UACR) to receive double-blind linagliptin (5 mg, a DPP inhibitor) or placebo QD. The primary CV endpoint was 3P-MACE, with a key secondary kidney endpoint (adjudicated ESKD, renal death, or sustained ≥40% decrease in eGFR from baseline). Other renal outcomes included albuminuria and eGFR slope. Subgroups were assessed by baseline eGFR (≥/<45 and ≥/< 30, 45 or 60 ml/min/1.73m^2).

Results: 6979 participants (mean age 66 yrs, HbA1c 8.0%, eGFR 54.6 ml/min/1.73m^2, 43% eGFR ≤45, and 80% UACR ≥30 mg/g) from 27 countries were followed for median 2.2 yrs. Linagliptin reduced albuminuria progression and albuminuria levels (table), but eGFR-slope was unaffected. Rates of the secondary kidney endpoint (HR 1.04 [0.89, 1.22]) and renal death, or sustained ESKD (0.87 [0.69, 1.10]), as well as 3P-MACE and hospitalization for heart failure (table) were similar between groups. Incidence rates were higher with reduced eGFR, however, results were consistent across subgroups (p heterogeneity >0.1).

Conclusions: Linagliptin slowed progression of albuminuria, without affecting eGFR slope or other kidney outcomes. Linagliptin also demonstrated CV safety including in patients with advanced CKD where clinical evidence has been particularly scarce.

Funding: Commercial Support - Boehringer Ingelheim and the Eli Lilly diabetes alliance

Effects on kidney surrogate parameters	Linagliptin		Placebo			
	n (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years	*HR for progression*	*P-value*
Albuminuria progression[1] *(n=4291)*	783 (35.3)	21.36	819 (38.5)	24.54	0.86 (0.78, 0.95)	0.0034
	Baseline, median (IQR)				*Difference at week 36*	*Difference at week 84*	*p-value*
Absolute change in UACR[2]*, mg/g*	158.41 (43.36, 684.07) (n=3258)		154.87 (42.48, 706.19) (n=3231)		0.87 (0.81, 0.93)	0.88 (0.82, 0.95)	Both p < 0.01
eGFR slope (MDRD), estimate±SE (n=6740)	*eGFR-slope from baseline to last value on treatment/year*				*Between-group difference*		
	-2.459±0.108		-2.284±0.108		-0.175±0.151		0.2485
Effects on CV and kidney outcomes	**Linagliptin (*N* = 3494)**		**Placebo (*N* = 3485)**		**HR (95% CI)**		***P*-value**
	n (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years			
3P-MACE (CV death, non-fatal myocardial infarction, or non-fatal stroke)	434 (12.4)	5.77	420 (12.1)	5.63	1.02 (0.89, 1.17)		0.7398
eGFR < 45 (n=3000)	250 (16.6)	7.61	241 (16.2)	7.49	1.02 (0.85, 1.21)		0.9361 (p-for interaction)
eGFR ≥ 45 (n=3979)	184 (9.3)	4.34	179 (9.0)	4.23	1.03 (0.84, 1.26)		
Hospitalized heart failure	209 (6.0)	2.77	226 (6.5)	3.04	0.90 (0.74, 1.08)		0.2635
eGFR < 45 (n=3000)	135 (8.9)	4.13	153 (10.3)	4.81	0.87 (0.69, 1.10)		0.5933 (p-for interaction)
eGFR ≥ 45 (n=3979)	74 (3.7)	1.73	73 (3.7)	1.72	0.97 (0.70, 1.34)		
Key secondary kidney endpoint (Renal death, sustained ESKD or sustained decrease of 40% or more in eGFR from baseline)	327 (9.4)	4.89	306 (8.8)	4.66	1.04 (0.89, 1.22)		*0.6164*
eGFR < 45 (n=3000)	222 (14.7)	7.83	219 (14.7)	7.93	0.97 (0.80, 1.17)		0.2398 (p-for interaction)
eGFR ≥ 45 (n=3979)	105 (5.3)	2.72	87 (4.4)	2.29	1.19 (0.89, 1.58)		
Renal death, or sustained ESKD	136 (3.9)	1.78	154 (4.4)	2.04	0.87 (0.69, 1.10)		0.2371
eGFR < 45 (n=3000)	124 (8.2)	3.78	146 (9.8)	4.54	0.82 (0.64, 1.04)		0.2004 (p-for interaction)
eGFR ≥ 45 (n=3979)	12 (0.6)	0.26	8 (0.4)	0.19	1.50 (0.61, 3.67)		
Renal death, sustained ESKD, or sustained ≥ doubling of se-creatinine from baseline[3]	219 (6.3)	3.21	229 (6.6)	3.43	0.92 (0.77, 1.11)		*0.4011*
eGFR < 45 (n=3000)	165 (10.9)	5.69	180 (12.1)	6.38	0.87 (0.70, 1.07)		0.3261 (p-for interaction)
eGFR ≥ 45 (n=3979)	54 (2.7)	1.38	49 (2.5)	1.27	1.08 (0.73, 1.59)		

HR based on Cox regression analyses in patients treated with ≥1 dose of study drug.
1: change from normoalbuminuria to micro-/macroalbuminuria, or change from microalbuminuria to macroalbuminuria.
2: gMean ratio of relative change for linagliptin versus placebo.
3: doubling of se-creatinine accompanied by eGFR < 60 ml/min/1.73m^2 (MDRD).

FR-OR143

High-Dose Versus Low-Dose Intravenous Iron Therapy in Hemodialysis: The PIVOTAL Trial

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Background: Intravenous (IV) iron is widely used in the management of anemia in hemodialysis (HD) patients, but very little scientific evidence guides its appropriate use. The Proactive IV irOn Therapy in haemodiALysis patients (PIVOTAL) trial (EudraCT 2013-002267-25) was designed to compare the effects of 2 distinct IV iron dosing regimens on "hard" clinical outcomes, including mortality and cardiovascular (CV) events, as well as infection risk among HD patients.

Methods: In this multicenter, open-label, blinded endpoint, controlled trial, 2141 incident HD (<12 mo) patients receiving erythropoiesis-stimulating agents (ESAs) were randomly assigned (1:1) to a proactive, high-dose IV iron regimen (iron sucrose 400 mg monthly unless ferritin >700 µg/L and/or TSAT ≥40%) or a reactive, low-dose IV iron regimen (iron sucrose administered if ferritin <200 µg/L or TSAT <20%). The primary outcome was nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, analyzed as time to first event. The hazard ratio (HR) for noninferiority was set at 1.25. Secondary endpoints included all-cause death, infection, and ESA dose.

Results: The median duration of follow-up was 2.1 years (max: 4.4 yr). Patients in the proactive, high-dose IV iron arm received a median (lower quartile [LQ], upper quartile [UQ]) monthly iron dose of 264 (200, 336) mg compared with 145 (100, 190) mg in the reactive, low-dose arm. Median monthly ESA doses were 19.7% lower in the high-dose arm (P<0.001). The incidence of the primary outcome was numerically lower in the high-dose arm than the low-dose arm (30.5% vs 32.7%; adjusted HR [95% CI]: 0.88 [0.76–1.03]; P<0.001 for noninferiority; P=0.11 for superiority). Rates of all-cause death, hospitalization, and infection were similar between the two arms (Table).

Conclusions: Among HD patients, the use of higher doses of IV iron significantly reduced ESA dose requirements without negatively affecting mortality or the incidence of nonfatal CV endpoints.

Funding: Government Support - Non-U.S.

Selected secondary endpoints

Outcome	Proactive, High-Dose IV Iron (N=1093)	Reactive, Low-Dose IV Iron (N=1048)	Estimated Treatment Effect	P Value
All-cause death	22.5%	25.7%	HR (95% CI): 0.84 (0.71–1.00)	0.054
All-cause hospitalization	59.6%	58.8%	HR (95% CI): 1.01 (0.90–1.12)	0.90
Hospitalization for infection	29.6%	29.3%	HR (95% CI): 0.99 (0.85–1.16)	0.92
All-cause death or myocardial infarction or stroke or hospitalization for heart failure as recurrent events, rate per 100 patient-years	20.63	26.10	Rate Ratio (95% CI): 0.78 (0.66–0.92)	0.003

FR-OR144

Safety and Effectiveness of Bexagliflozin in Type 2 Diabetes Mellitus and Stage 3a/3b CKD: A Phase 3 Randomized Clinical Trial

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Background: Hyperglycemia exacerbates the progression of chronic kidney disease (CKD), but most glucose-lowering therapies seldom address morbidities associated with CKD. Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer potential benefits to diabetics with CKD but their utility may be diminished with impaired renal function.

Methods: A phase 3, double-blind, placebo-controlled, multi-center, multi-national, randomized trial was conducted to evaluate the safety and effectiveness of bexagliflozin, a novel SGLT2 inhibitor, in patients with type 2 diabetes and stage 3a/3b CKD. Patients were randomly assigned to receive bexagliflozin or placebo for 24 weeks. The placebo-adjusted change in hemoglobin A_{1c} was the primary endpoint. Secondary endpoints were changes in body weight, systolic blood pressure, albuminuria, fasting plasma glucose and hemoglobin A_{1c} stratified by CKD 3a/3b status. Efficacy data were analyzed using repeated measures methodology with intent to treat population to demonstrate treatment effects at 24 weeks.

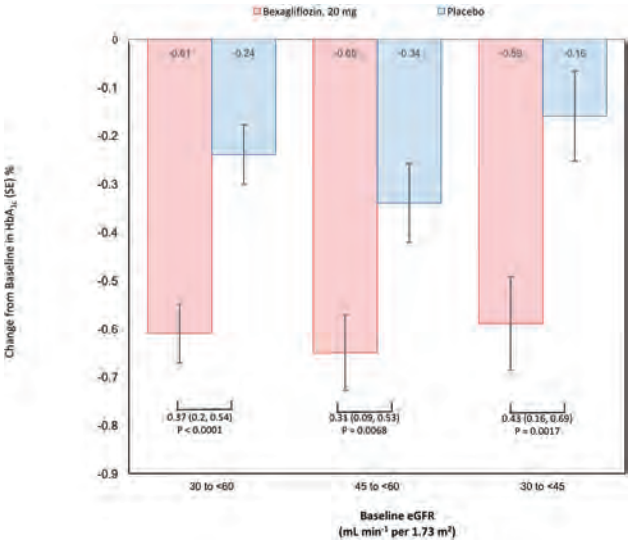
Results: 312 patients across 54 sites were analyzed. Bexagliflozin lowered hemoglobin A_{1c} by 0.37% (95% CI 0.20, 0.54, p <0.0001) compared to placebo. Patients with CKD stage 3a (eGFR 45 to <60) and 3b (eGFR 30 to <45) had reductions in hemoglobin A_{1c} of 0.31% (p = 0.0068) and 0.43% (p = 0.0017), respectively. Bexagliflozin lowered body weight (1.61 kg, p <0.0001), systolic blood pressure (3.8 mmHg, p = 0.02), fasting plasma

Underline represents presenting author/disclosure.

glucose (0.76 mmol/L, p =0.0029) and albuminuria (geometric mean ratio reduction of 20.1%, p = 0.027). Adverse events were comparable between groups.

Conclusions: Bexagliflozin was effective for lowering hemoglobin A_{1c} in diabetic patients with stage 3a/3b CKD and was well tolerated. Additional benefits in this population were reduction in body weight, systolic blood pressure, fasting plasma glucose and albuminuria.

Funding: Commercial Support - Theracos LLC



FR-OR145

Cardiovascular Safety of Methoxy Polyethylene Glycol-Epoetin Beta in Treatment of Anemia of CKD

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Background: Erythropoiesis-stimulating agents (ESAs) may increase the risk of cardiovascular events when used in the treatment of anemia of CKD. We compared cardiovascular outcomes and all-cause mortality for monthly methoxy polyethylene glycol-epoetin beta (continuous erythropoietin receptor activator, C.E.R.A.) with those of reference ESAs epoetin alfa/beta and darbepoetin alfa in the MIRCERA Post-Approval Safety Study (PASS).

Methods: MIRCERA PASS was a prospective, multicenter, open-label, blinded endpoints, non-inferiority trial. CKD patients with anemia were randomized either to start or switch to C.E.R.A., or to a reference ESA for correction or in the maintenance setting. The primary endpoint was the composite of all-cause mortality and non-fatal myocardial infarction or stroke, adjudicated by an independent committee unaware of treatment assignment. Non-inferiority was defined as the two-sided 95% confidence interval (CI) upper boundary of the hazard ratio [HR] <1.2.

Results: 2825 patients were randomized between December 2008 and November 2011 and 2818 were treated for a median of 3.4 years (maximum 8.5 years). The primary endpoint occurred in 640/1409 patients (45.4%) in the C.E.R.A. arm and 644/1409 (45.7%) in the reference ESAs arm (HR 1.03; 95% CI, 0.93–1.15; p=0.0039 for non-inferiority). Subgroup analyses showed no significant differences between treatment groups for patients on dialysis or not, those with or without diabetes, or in the maintenance or correction setting. Similar findings were seen for individual components of the primary endpoint, all-cause mortality (HR 1.06, 95% CI 0.94–1.19), and non-fatal myocardial infarction or stroke (HR 0.91, 95% CI 0.74–1.12). Mean hemoglobin was maintained at 10–12 g/dL throughout the trial and was comparable between treatment arms, as were serum iron parameters. Gastrointestinal bleeding and thromboembolic events were also similar between treatment groups. No patient developed antibody-mediated pure red cell aplasia.

Conclusions: In patients with anemia of CKD, long-term treatment with monthly C.E.R.A. resulted in overall rates of major cardiovascular events and all-cause mortality similar to those associated with reference ESAs administered more frequently. Study registered at clinicaltrials.gov (NCT00773513).

Funding: Commercial Support - F Hoffmann-La Roche Ltd

FR-OR146

Comparison of Lanthanum Carbonate and Calcium Carbonate in the Cardiovascular Mortality and Morbidity of Hemodialysis Patients

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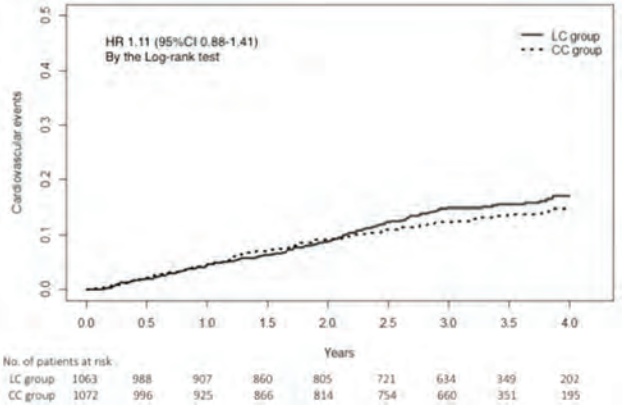
Background: The multicenter LANDMARK study (NCT01578200/UMIN000006815) is a randomized, open-label, parallel assignment study comparing the effects of a non-Ca P binder, lanthanum carbonate (LC), with the effects of calcium carbonate (CC) on cardiovascular mortality and morbidity in hemodialysis (HD) patients.

Methods: A total of 2309 hemodialysis patients with at least one risk factor for vascular calcification (VC) (age >65 years, postmenopausal women, type 2 diabetes); intact parathyroid hormone ≤240pg/mL; and life expectancy >1 year were randomly assigned to the LC (n = 1154) or CC (n =1155) group. In the LC group, patients initially received 750 mg/day of LC (or their previous dose) and were titrated up to a maximum of 2250 mg/day to achieve serum P levels of 3.5 to 6.0 mg/dL. In the CC group, patients received 3 g/day of CC (or their previous dose), and were titrated to achieve the same target serum P levels. If these levels were not achieved with the maximum tolerated dose, non-Ca P binders were given to those in the LC group, and P binders other than LC to those in the CC group. The primary endpoint was survival time free of cardiovascular events (CVEs), including cardiovascular death, nonfatal myocardial infarction or stroke, and unstable angina.

Results: A total of 2135 patients (female 40.5%, 68.4 years, diabetes 56.1%) were analyzed in this study. After a median follow-up of 3.16 years, the incident rates of CVEs were 4.80 (/100 patient-years) in the LC group and 4.30 in the CC group, and there was no significant difference in the adjusted hazard ratio (HR) between the two groups (1.11 [95%CI, 0.88–1.41], P = 0.366; log rank test. There is also no significant difference in all-cause death between the LC and CC groups (HR 1.10 [95%CI, 0.88–1.37], P = 0.424).

Conclusions: The non-Ca P binder, LC, did not reduce CVEs as compared with CC among long-term HD patients with high risk of VC.

Funding: Commercial Support - Bayer Yakuhin, Ltd.



FR-OR147

Effect of a Restrictive Versus Liberal Approach to Red Blood Cell Transfusion on AKI in Patients Undergoing Cardiac Surgery

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Background: Safely reducing red blood cell transfusions avoids transfusion-related adverse effects, conserves the blood supply, and reduces healthcare costs. We conducted a prespecified substudy of the Transfusion Requirements in Cardiac Surgery-III (TRICS-III) trial to determine if a restrictive approach to red blood cell transfusion is as safe as a liberal approach on the risk of acute kidney injury [protocol Can J Kid Health Dis 2018 Jan 3; 5].

Methods: This was a randomized trial of 4531 moderate-to-high–risk patients undergoing cardiac surgery with cardiopulmonary bypass from 73 centers in 19 countries between January 2014 and March 2017. Patients were assigned to a restrictive red blood cell transfusion threshold (transfuse if hemoglobin level was <7.5 g/dL, intraoperatively and postoperatively until day 28 or hospital discharge; n=2251) or a liberal threshold (transfuse if hemoglobin level was <9.5 g/dL in the operating room or intensive care unit, or <8.5 g/dL on the non-intensive care ward; n=2280). Acute kidney injury was defined as an increase in the postoperative serum creatinine concentration (from the preoperative value) of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hrs of surgery, or ≥50% within 7 days of surgery. The prespecified noninferiority margin for the absolute risk difference was 3.5%.

Results: Perioperative acute kidney injury occurred in 27.7% of patients in the restrictive-threshold group and in 27.9% of patients in the liberal-threshold group; absolute risk difference, -0.2% (95% CI, -2.8% to 2.4%). Results were consistent

Underline represents presenting author/disclosure.

with multiple alternative definitions of acute kidney injury, and in the subgroup with preoperative chronic kidney disease (Table).

Conclusions: A restrictive approach to red blood cell transfusion was as safe as a liberal approach on the risk of acute kidney injury in patients undergoing cardiac surgery. Trial Registration: NCT02042898

Funding: Government Support - Non-U.S.

	Number of Events (%)		
	Restrictive (n=2251)	Liberal (n=2280)	Risk difference (95% CI)
AKI (primary outcome)	624 (27.7%)	636 (27.9%)	-0.2% (-2.8% to 2.4%)
Alternative Definitions			
AKI or death	636 (28.3%)	662 (29.0%)	-0.8% (-3.4% to 1.9%)
≥ Stage 2 AKI	166 (7.4%)	150 (6.6%)	0.8% (-0.7% to 2.3%)
Stage 3 AKI	75 (3.3%)	84 (3.7%)	-0.4% (-1.4% to 0.7%)
Acute dialysis	54 (2.4%)	66 (2.9%)	-0.5% (-1.4% to 0.4%)
Subgroup			
Chronic Kidney Disease	258/767 (33.6%)	252/755 (32.5%)	1.1% (-3.6% to 5.8%)

AKI=Acute Kidney Injury

FR-OR148

Comparative Efficacy of Therapies for Depression for Patients Undergoing Hemodialysis

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Background: Depression is common in patients undergoing hemodialysis but limited data exist on increasing treatment acceptance or efficacy of various anti-depressant therapies. We sought to determine the effect of an engagement interview on treatment acceptance, and compare efficacy of cognitive behavioral therapy (CBT) or sertraline for treating major depressive disorder (MDD) or dysthymia in patients undergoing hemodialysis.

Methods: In a multi-center randomized controlled trial, 2569 patients in 41 dialysis facilities in 3 metropolitan areas were screened with Beck Depression Inventory (BDI). In those who scored ≥ 15, MDD/dysthymia was diagnosed using MINI Neuropsychiatric Interview. Participants were randomized to engagement interview, to increase treatment acceptance, vs. control visit, with proportion starting anti-depressant treatment within 28 days as the primary outcome. Willing individuals were further randomized to 12-weeks of CBT or sertraline, with Quick Inventory of Depressive Symptoms (QIDS-C) at 12 weeks as the primary outcome.

Results: Of 636 patients with BDI score ≥ 15, 310 (49%) eligible subjects were evaluated further, 184 were randomized to engagement vs. control, and 120 subsequently randomized to CBT vs. sertraline. There was no difference in the proportion initiating treatment for depression in engagement arm or control (66% vs. 64%, respectively, p=0.77). Compared with CBT, sertraline resulted in a greater decrease in depressive symptoms (12-week QIDS-C, -1.84, (-3.54, -0.13), p=0.04). There was also greater improvement in 5 of 9 secondary patient-reported outcomes with sertraline (BDI, Sheehan Disability, SF-36 Energy/Vitality, Satsifaction with Life, and Pittsburgh Sleep Quality Index scales). The incidence of serious adverse events was similar but non-serious adverse events were more frequent with sertraline (56 events, 25 patients) than with CBT (17 events, 12 patients).

Conclusions: In participants undergoing hemodialysis, there was no effect of an engagement interview on patients' acceptance of treatment for depression. There was greater improvement in depressive symptoms and other patient-reported outcomes with sertraline compared to CBT.

Funding: NIDDK Support, Other U.S. Government Support, Commercial Support - Dialysis Clinic, Inc.

FR-OR149

Interventions to Reduce Early Dialysis Initiation in Canada: A Cluster Randomized Trial

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Background: There are higher healthcare costs and poorer outcomes when patients initiate dialysis earlier at a higher level of kidney function compared to when they initiate dialysis later. Despite the publication of The Initiating Dialysis Early and Late (IDEAL) study and concurrent clinical practice guidelines recommending an intent-to-defer dialysis initiation strategy, the estimated glomerular filtration rate (eGFR) at dialysis initiation varies widely.

Methods: We conducted a national cluster randomized controlled trial of a multifaceted knowledge translation intervention in 55 multi-disciplinary advanced chronic kidney disease (CKD) clinics in Canada. The intervention included academic detailing, audit and feedback, and provision of visual aids for patients and providers promoting the intent-to-defer strategy. The primary efficacy outcome was the proportion of patients who started dialysis early (eGFR > 10.5 ml/min/1.73m^2) and the primary safety outcome was the proportion of dialysis starts occurring in the acute inpatient setting. Absolute risk differences were estimated using generalized-estimating-equations analysis of clustered binary data using the difference-in-differences approach.

Results: There were 6,836 patients that started dialysis during the study period, 3,521 people who started in the 1 year before the intervention and 3,314 people who started in the 1 year following the intervention. Prior to the intervention, the proportion of early dialysis starts was 28.1% in the intervention group and 31.1% in the control group, and following the intervention was 30.6% and 31.0% in the intervention and control groups respectively. In unadjusted and analyses adjusted for patient-level characteristics no differences in early initiation were observed (adjusted absolute risk difference 3.7%; 95% confidence interval [CI] -0.07% to 8.1%; p = 0.10). Similarly, no differences in acute inpatient dialysis starts between the intervention and control group were detected (adjusted relative risk 1.11; 95% CI 0.96-1.29; p = 0.17).

Conclusions: A multifaceted knowledge translation intervention did not result in further declines in early dialysis initiation in Canada. Secular trends in dialysis initiation from uptake of the IDEAL trial findings may have limited the impact of this intervention.

Funding: Government Support - Non-U.S.

TH-PO1147

Canagliflozin Reduces the Risk of Renal Events in People with Type 2 Diabetes Mellitus and Normoalbuminuria

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Background: It has been postulated that the renoprotective effect of SGLT2 inhibitors is primarily due to restoration of tubuloglomerular feedback, which ameliorates glomerular hyperfiltration and lowers albuminuria. As a result, these agents might not be as effective in people with type 2 diabetes mellitus (T2DM) and normoalbuminuria (urinary albumin:creatinine ratio [UACR] <30 mg/g). Ongoing renal outcome studies are including participants who mostly or entirely have macroalbuminuria. We therefore sought to determine the renal effects of canagliflozin in people with normoalbuminuria in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

Methods: The CANVAS Program randomized people with T2DM and high risk of cardiovascular disease to canagliflozin or placebo. We included participants with normoalbuminuria in this analysis, and further divided them into tertiles according to baseline UACR (low, mid, or high normoalbuminuria), and into subgroups based on estimated glomerular filtration rate (eGFR; <45, 45-<60, 60-<90, and ≥90 mL/min/1.73m^2). We analyzed the effects of canagliflozin on renal outcomes in people with normoalbuminuria overall and across these subgroups.

Results: Among 10,142 CANVAS participants, 7,007 (69%) had normoalbuminuria (mean age 63 years, BP 135/77 mmHg, HbA1c 8.2%, eGFR 78.3 mL/min/1.73m^2). In this population, canagliflozin reduced average UACR by 9% (95% CI 7-12%) compared to placebo over 338 weeks. Mean annual change in eGFR for placebo and canagliflozin treated participants was –0.47 and +0.59 mL/min/1.73m^2, respectively (placebo-subtracted difference 1.06 mL/min/1.73m^2). Canagliflozin reduced the risk of the composite renal outcome of 40% decrease in eGFR, end-stage kidney disease, or renal death by half (HR 0.50, 95% CI 0.33-0.77). The effect on the composite renal outcome appeared broadly consistent across UACR and eGFR subgroups (*P* heterogeneity = 0.16 and 0.10, respectively).

Conclusions: Canagliflozin reduces the risk of eGFR decline and renal outcomes in people with normoalbuminuria despite modest albuminuria reductions. Multiple mechanisms of renal benefit from SGLT2 inhibition might be important in T2DM.

Funding: Commercial Support - Janssen Research & Development, LLC

TH-PO1148

Effects of Selonsertib in Patients with Diabetic Kidney Disease (DKD)

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Background: Increased oxidative stress in the kidney and the resulting activation of apoptosis signal-regulating kinase 1 (ASK1) in glomerular and tubular cells has been implicated in progression of acute and chronic kidney diseases. This Phase 2 trial

evaluated the safety and efficacy of selonsertib (SEL), a potent and selective ASK1 inhibitor, in 334 pts with treatment-refractory moderate to advanced DKD.

Methods: Pts were randomized to receive SEL (2, 6, or 18 mg oral daily) or PBO. Primary outcome was change from baseline eGFR with SEL compared with PBO at 48 wks.

Results: SEL appeared safe with no dose-dependent adverse effects over 48 wks. Although there was no significant difference in SEL group mean (±SE) eGFR compared with PBO (0.38±1.21, 0.84±1.22, and -0.87±1.23 mL/min/1.73m^2 in the 2-, 6-, and 18-mg groups, respectively; p>0.4 for all pairwise comparisons; n=333 dosed; full analysis set [FAS]), differences in eGFR at 48 wks were confounded by acute effects related to SEL's inhibition of creatinine secretion. To account for this unanticipated effect, we used piecewise linear regression and found two dose-dependent effects: an acute, more pronounced decline in eGFR from 0-4 wks (creatinine secretion effect) and an attenuated decline in eGFR between 4-48 wks (therapeutic effect) seen with higher doses of SEL. Between 4-48 wks, rate of eGFR decline was reduced 71% for the 18-mg group relative to PBO (difference 3.11±1.53 mL/min/1.73m^2 annualized over 1 year, 95% CI, 0.10-6.13; nominal p=0.043; n=313; FAS excluding data from 2 sites with GCP compliance findings).

Conclusions: Although the trial did not meet its primary pre-specified endpoint, post-hoc analyses indicate that SEL appears to slow the progression of DKD (ClinicalTrials.gov: NCT02177786).

Funding: Commercial Support - Gilead Sciences, Inc.

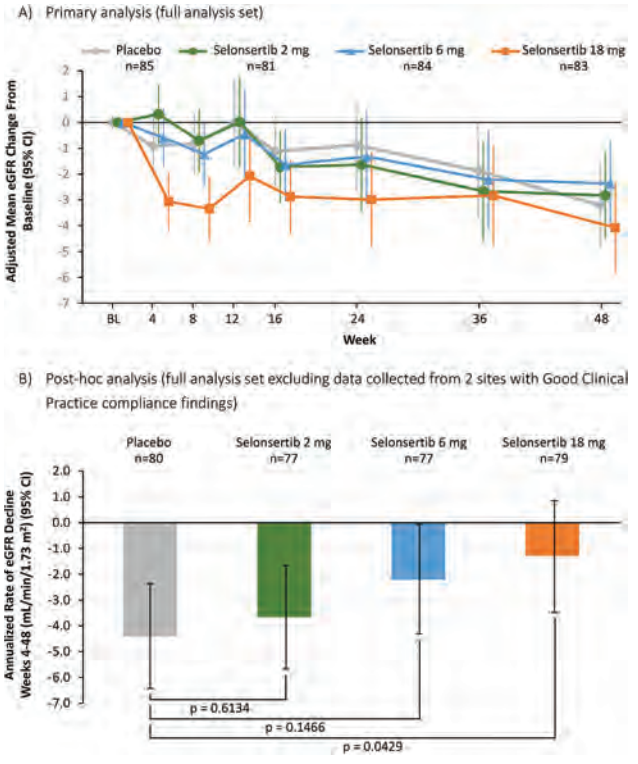

Figure 1 Adjusted Mean (95% CI) Change in eGFR (MDRD)

TH-PO1149

Primary Results of the Quality of Life in Peritoneal Dialysis and Conventional In-Center Hemodialysis (China Q) Study: A Prospective, Randomized, Open-Label, Multicenter, Noninferiority Trial

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Background: There may be differences in health-related quality of life between hemodialysis (HD) and peritoneal dialysis (PD) for incident end-stage renal disease (ESRD) patients, but this hypothesis has not been adequately tested.

Methods: Open-label clinical trial from 21 centers in China, in adults diagnosed with new ESRD requiring maintenance dialysis, randomized 1:1 to receive in-center HD (≥3 x 4 hour sessions/week) or PD (3-5 exchanges/day). Primary end-point was burden of kidney disease score from the KDQoL-SF at 48 weeks; main secondary endpoint was all-cause mortality at 48 weeks. This dataset was supplemented by 235 patients (142 PD, 93 HD) from the previously terminated SURinD trial, who had complete measures of burden of kidney disease at both baseline and 48 weeks. The primary endpoint was assessed in the per protocol (PP) population, with a sensitivity analysis in the intention-to-treat (ITT) population. The treatment effect between arms was represented by the geometric mean (GM) ratio, and non-inferiority defined by the lower bound of 1-side 95% CI of GM ratio > 0.9 after 48 weeks follow-up. The main secondary end-point was assessed only in the China Q ITT population (NCT02378350, NCT01413074).

Results: 336 incident patients allocated to HD (237 per protocol), 332 to PD (253 per protocol) between Apr 2014 to Jun 2016. Patients were representative of those in China, with a pooled mean (SD) age of 49.5 (14.7) years, and 370 females (41.0%). For the primary endpoint, the GM ratio (95% CI) of PD *vs.* HD was 1.06 (0.91, 1.24), exceeding the limit for non-inferiority (p=0.43). The result of the sensitivity analysis was similar. There were 13 deaths in the PD group, and 19 deaths in the HD group, with no difference between groups (p=0.94).

Conclusions: In this study, burden of kidney disease was not inferior with PD *vs.* in-center HD, suggesting comparable perceptions of frustration and interference of kidney disease in one's life. Mortality risk was not different, although the study was not powered for this end-point. Analysis of other KDQoL-SF endpoints, clinical endpoints, and hospitalization are ongoing.

Funding: Commercial Support - Baxter Healthcare Corporation

TH-PO1150

A Randomized Trial of Magnesium Oxide for Coronary Artery Calcification in Pre-Dialysis CKD

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Background: Although coronary artery calcification (CAC) predicts cardiovascular events among patients with CKD, effective therapeutic strategies for CAC have not yet been established. Animal studies have revealed that magnesium inhibits vascular calcification whereas indoxyl sulfate aggravates it. We explored whether magnesium supplementation or oral carbon adsorbent (AST-120) mitigates the progression of CAC in CKD.

Methods: In this 2-year, open-label, randomized controlled trial with a 2 by 2 factorial design, the efficacy of magnesium oxide and AST-120 for the progression of CAC was separately evaluated. We enrolled stages 3-4 CKD patients with known risk factors of CAC (diabetes mellitus, prior history of cardiovascular disease, hyper-low-density lipoprotein cholesterolemia, or current smoking). These patients were randomly assigned to magnesium oxide or control group and to AST-120 or control group. The primary outcome was a percent change in CAC score (Agatston score).

Results: The study was terminated prematurely after a planned interim analysis of the first 125 enrolled patients, showing that the percent change in CAC score in the magnesium oxide group was lower than that in the control group (median: 11.3% vs 39.5%; P<0.001). The proportion of patients whose annual percent change in CAC score over 15% was significantly lower in the magnesium oxide group (23.9% vs 62.0%; P<0.001). Magnesium supplementation increased serum magnesium levels from 2.0 to 2.3 mg/dL (P<0.001; vs control group) but did not alter serum calcium, phosphate, or parathyroid hormone levels. The progression rate of CAC was not significantly different between patients in the AST-120 and control groups (23.1% and 31.9%, respectively; P=0.57).

Conclusions: Oral magnesium oxide retards the progression of CAC among pre-dialysis CKD patients with a high risk of vascular calcification.

TH-PO1151

Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Conversion Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan

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Background: Roxadustat, an oral HIF-PHI, is in late-stage development for treatment of CKD anemia. This phase 3 study evaluated non-inferiority of roxadustat efficacy to darbepoetin alfa (DA) as treatment of CKD anemia on hemodialysis (HD).

Methods: Multicenter, 24-week, Japanese study of CKD anemia patients on HD for ≥12 weeks and treated with ESA. Patients were randomized to roxadustat (70mg and 100mg) three times weekly or DA (10-60μg) once weekly; dose was adjusted to maintain Hb at 10-12g/dL. Primary endpoint was change of average Hb from baseline to Weeks 18-24 (ΔHb_{18-24}). Roxadustat efficacy was confirmed if the 95% CI of average Hb at Weeks 18-24 was within 10-12g/dL; non-inferiority to DA was confirmed if the lower limit of the 95% CI of the difference between roxadustat and DA was above –0.75g/dL. Secondary endpoints were average Hb at Weeks 18-24, proportion of patients with Hb of 10-12g/dL at Weeks 18-24 (maintenance rate), and iron parameters (ie, serum iron, ferritin, TSAT, transferrin, and TIBC). Safety was assessed as occurrence of adverse events (AEs) including ophthalmological examination (color fundus photography and optical coherence tomography [OCT]).

Results: 303 patients were randomized to roxadustat (n=151) or DA (n=152). The average Hb at Weeks 18-24 was 10.99 g/dL (95% CI: 10.88, 11.10) with roxadustat,

Underline represents presenting author/disclosure.

confirming its efficacy. The difference between roxadustat and DA in $\Delta Hb_{18\text{-}24}$ was –0.02g/dL (95% CI: –0.18, 0.15), confirming non-inferiority of roxadustat to DA. Maintenance rate of target Hb in patients with ≥1 Hb value at Weeks 18-24 was 95.2% (roxadustat) and 91.3% (DA). With roxadustat, serum iron, ferritin, and TSAT showed no remarkable change; transferrin and TIBC increased through Week 4 and then remained stable. No remarkable changes in iron parameters occurred with DA. The most common AEs in both groups were nasopharyngitis, shunt stenosis, diarrhea, contusion, and vomiting. New/worsening retinal hemorrhage occurred in 32.4% (roxadustat) and 36.6% (DA) of patients; no clinically meaningful change in retinal thickness by OCT were observed over time between groups.

Conclusions: Roxadustat maintained target Hb in HD patients and its efficacy was non-inferior to DA. AEs were consistent with previous reports.

Funding: Commercial Support - Astellas Pharma Inc

TH-PO1152

A Phase 3, Randomized, Open-Label, Active-Controlled Study of Efficacy and Safety of Roxadustat for Treatment of Anemia in Subjects with CKD on Dialysis

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that regulates erythropoiesis and iron metabolism.

Methods: In this phase 3 trial, Chinese pts (hemoglobin-Hb 9-12g/dL) on hemo/peritoneal dialysis with previous erythropoiesis stimulating agent (ESA) therapy for >6 weeks were randomized 2:1 to roxadustat or epoetin-alfa thrice-weekly for 26 wks; IV iron was withheld except for rescue. Primary endpoint was the average Hb change from baseline to wks 23-27 ($deltaHb_{23\text{-}27}$) tested for non-inferiority vs epoetin-alfa. Both arms were titrated to maintain/achieve Hb 10-12g/dL. All randomized subjects who received ≥2 weeks of study treatment with baseline and post-baseline Hbs w/o rescue therapy 6 wks prior to assessment and w/o important protocol deviation comprised the per protocol set (PPS); all randomized subjects with baseline and post baseline Hbs comprised the full analysis set (FAS) population.

Results: The safety population consisted of 304 pts (204 roxadustat, 100 epoetin-alfa); 256 pts (162 roxadustat, 94 epoetin-alfa) completed the 26-week treatment period. Average baseline Hb overall was 10.4g/dL. Roxadustat produced a numerically greater mean $deltaHb_{23\text{-}27}$ of .8g/dL(±1.1) than epoetin-alfa, (.5 g/dL±1.0) and was noninferior and superior (p=.037) to ESA in the PPS population and non-inferior but not superior in the FAS population. The Hb change in the roxadustat group wasn't clinically affected by baseline CRP. Roxadustat increased transferrin, maintained serum iron, and attenuated decreases in TSAT versus epoetin-alfa (all p<0.01). At wk 27, the decline from baseline in both total and LDL cholesterol was greater with roxadustat (both p<0.0001). Roxadustat reduced hepcidin from baseline by a mean of 30.21ng/ml (p=.0028) compared to 2.28ng/ml in the epoetin-alfa group (p=.1228). Roxadustat was well tolerated.

Conclusions: Roxadustat was efficacious as oral anemia therapy in Chinese pts receiving dialysis. Roxadustat's reduction in hepcidin levels with iron mobilization likely contributes to its efficacy in erythropoiesis irrespective of inflammation.

Funding: Commercial Support - FibroGen

TH-PO1153

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Subjects with CKD Not on Dialysis

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Background: Roxadustat (FG-4592) is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism.

Methods: In this phase 3 trial, Chinese patients with hemoglobin (Hb) between 7.0-10.0 g/dL and CKD not requiring dialysis were randomized and treated in a double-blind manner to roxadustat thrice-weekly or placebo (2:1) for 8-weeks; parenteral iron was withheld except for rescue. The primary endpoint was the average change in Hb from baseline to week 7-9. Following, all patients were offered open-label roxadustat for 18-weeks.

Results: The safety population included 152 patients (101=roxadustat, 51=placebo) in the initial 8-weeks, during which subjects in the roxadustat arm had a greater mean (±SD) change from baseline in hemoglobin of 1.90 g/dL (±1.175)(mean baseline Hb 8.87 ±0.81 g/dL), as compared to placebo -0.39 g/dL (±0.786)(mean baseline 8.93 ±0.73 g/dL) (p<0.000000000000001). At week 9, patients randomized to roxadustat had a greater mean reduction in hepcidin at -56.14 (±63.40)(p<0.00001) vs. -15.10 (±48.06) ng/ml (p=0.172) in the placebo group (p<0.00001 between groups). At week 9, the decline from baseline was greater for lipid fractions (total cholesterol and LDL cholesterol) in the roxadustat arm (p<0.00001). The most frequent treatment-emergent adverse events were typical for this population and without trend in individual or composite events. Ninety-eight subjects completed the 18-week open-label period. Roxadustat performed similarly in the open-label as in the initial treatment period with respect to correction and maintenance of hemoglobin.

Conclusions: Roxadustat was well tolerated in patients with CKD not requiring dialysis in China and superior to placebo in correcting anemia and maintaining Hb levels.

Funding: Commercial Support - FibroGen

TH-PO1154

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Treat Metabolic Acidosis in CKD Patients with TRC101, a Novel, Non-Absorbed, Hydrochloric Acid Binder

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Background: Metabolic acidosis increases risk of chronic kidney disease (CKD) progression and adversely affects muscle and bone. TRC101, a non-absorbed, sodium-free polymeric drug that selectively binds and removes hydrochloric acid from the gastrointestinal tract, is being developed for the treatment of metabolic acidosis in CKD and slowing CKD progression.

Methods: 217 CKD patients (eGFR 20 - 40 mL/min/1.73m^2) with metabolic acidosis (serum bicarbonate [HCO_3] 12 - 20 mEq/L) were randomized 4:3 to TRC101 (6 g) or placebo once-daily for 12 weeks. Algorithmic dose titration was performed to achieve a normal serum HCO_3 (22 - 29 mEq/L). The primary endpoint was the between-group comparison of the proportion of patients with a ≥4 mEq/L increase in serum HCO_3 or a normal serum HCO_3 at Week 12. The secondary endpoint evaluated the change from baseline in serum HCO_3. Two exploratory endpoints evaluated effects of acidosis correction on physical functioning using the Kidney Disease Quality of Life Short Form-36 Physical Functioning subscale and a timed repeated chair stand test.

Underline represents presenting author/disclosure.

Results: The mean (SD) baseline serum HCO3 and eGFR were 17.3 (1.5) mEq/L and 28.6 (6.0) mL/min/1.73m2, respectively. 96% of patients completed treatment. Comorbidities included hypertension (97%), diabetes (65%), left ventricular hypertrophy (44%), and congestive heart failure (31%). More TRC101 (59.2%) than placebo (22.5%) patients met the primary endpoint response definition ($p<0.0001$). From baseline to Week 12, mean serum HCO3 increased +4.5 mEq/L (TRC101) vs. +1.7 mEq/L (placebo), $p<0.0001$. More TRC101 compared with placebo patients had improvement in self-reported physical functioning ($p = 0.012$) and there was a trend toward improvement in standardized chair stand time ($p=0.063$). There were no effects of TRC101 on creatinine or other electrolytes. Overall treatment-related adverse events occurred in 9.7% of placebo and 13.7% of TRC101 patients, most of which were gastrointestinal (e.g., diarrhea, flatulence, nausea and constipation).

Conclusions: TRC101 effectively and safely treated metabolic acidosis and improved self-reported physical functioning in CKD patients.

Funding: Commercial Support - Tricida, Inc. San Francisco, CA, USA

TH-PO1155

Effect of Everolimus with Reduced-Exposure Calcineurin Inhibitor in De Novo Kidney Transplant Recipients: 24-Month Results from the US Cohort of the TRANSFORM Study

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Background: To present 24-month (M) efficacy and safety data from the US cohort of the TRANSFORM study (NCT01950819).

Methods: In this 24M, multicenter, open-label study, *de novo* kidney transplant recipients (KTxRs) were randomized to receive either everolimus + reduced-exposure calcineurin inhibitor (EVR+rCNI: 1022) or mycophenolic acid + standard-exposure CNI (MPA+sCNI: 1015) with induction and steroids. The binary composite of tBPAR or eGFR <50 mL/min/1.73 m^2, composite efficacy failure (CEF: tBPAR/graft loss/death) and individual components, eGFR (MDRD4), and safety were assessed at M24.

Results: Of 2037 KTxRs in overall study, 352 (EVR+rCNI: 173; MPA+sCNI: 179) were included in the US cohort. Except for younger donors and lower proportion of extended criteria donors (ECD) in the US cohort, other characteristics were similar for both populations. Similar to the overall population, CNI trough levels (C0) were towards the upper limit/above the target C0 throughout the study. In contrast to overall population, the incidence of binary composite efficacy was significantly higher in the EVR+rCNI vs MPA+sCNI arm in the US cohort at M24. The CEF and individual components were comparable between arms in both populations (**Table**). Mean eGFR was higher in the US cohort vs overall population for both arms. Incidence of viral infections were lower in EVR+rCNI vs MPA+sCNI.

Conclusions: Similar to 24M data from the TRANSFORM study, US cohort showed comparable efficacy and safety with lower viral infection rates in the EVR+rCNI vs MPA+sCNI arm; higher mean eGFRs in the US cohort may be attributed to differences in donor type and age in the population.

Funding: Commercial Support - Novartis

Table: Efficacy, renal function and safety outcomes in KTxRs at M24

Parameters	US cohort			Overall population		
	EVR+rCNI (N = 173)	MPA+sCNI (N = 179)	Difference (95% CI); *P*-value*	EVR+rCNI (N = 1022)	MPA+sCNI (N = 1015)	Difference (95% CI); *P*-value*
Demographic and baseline characteristics						
Recipient age (years), mean±SD	50.1±13.09	49.1±13.54	–	48.8±14.12	48.8±14.52	–
Male, n (%)	128 (74.0)	126 (70.4)	–	710 (69.5)	707 (69.7)	–
Race, n (%)			–			–
Caucasian	125 (72.3)	128 (71.5)	–	743 (72.7)	735 (72.4)	–
Black	21 (12.1)	24 (13.4)	–	43 (4.2)	35 (3.4)	–
Asian	14 (8.1)	20 (11.2)	–	136 (13.3)	157 (15.5)	–
Donor age (years), mean±SD	43.7±14.16	40.5±12.91	–	48.4±15.11	48.2±15.48	–
Donor category, n (%)			–			–
Living related	46 (26.6)	56 (31.3)	–	302 (29.5)	315 (31.0)	–
Living unrelated	71 (41.0)	65 (36.3)	–	209 (20.5)	192 (18.9)	–
Deceased heart beating	55 (31.8)	57 (31.8)	–	506 (49.5)	505 (49.8)	–
SCD	50 (90.9)	56 (98.2)	–	354 (70.0)	345 (68.3)	–
ECD	5 (9.1)	1 (1.8)	–	152 (30.0)	160 (31.7)	–
Deceased non-heart beating	1 (0.6)	1 (0.6)	–	5 (0.5)	3 (0.3)	–
Efficacy outcomes, n (%)						
eGFR <50 mL/min/1.73 m^2 or tBPAR	67 (38.7)	48 (26.8)	11.6 (1.4, 21.9); 0.026	489 (47.9)	443 (43.7)	4.2 (–0.3, 8.7); 0.067
tBPAR, graft loss, or death†	23 (13.7)	14 (11.7)	2.0 (–8.3, 12.3); 0.707	169 (18.0)	147 (17.3)	0.8 (–4.6, 6.1); 0.782
tBPAR‡	17 (10.3)	9 (9.0)	1.3 (–8.7, 11.2); 0.804	118 (12.8)	98 (12.1)	0.7 (–4.4, 5.8); 0.794
Graft loss‡	4 (2.4)	2 (1.1)	1.2 (–1.5, 4.0); 0.377	37 (3.7)	32 (3.2)	0.5 (–1.1, 2.1); 0.572
Death‡	4 (2.5)	3 (1.8)	0.7 (–2.4, 3.8); 0.667	32 (3.7)	36 (4.2)	–0.5 (–2.7, 1.6); 0.634
Renal function	**EVR+rCNI (N = 173)**	**MPA+sCNI (N = 179)**	**Difference (95% CI); *P*-value**	**EVR+rCNI (N = 1022)**	**MPA+sCNI (N = 1015)**	**Difference (95% CI); *P*-value**
eGFR (mL/min/1.73 m^2), mean±SE	56.7±1.89	63.8±1.72	–7.06 (–12.1, –2.01); 0.006	52.6±0.74	54.9±0.72	–2.28 (–4.32, –0.24); 0.028
Safety outcomes, n (%)	**EVR+rCNI (N = 169)**	**MPA+sCNI (N = 179)**	**RR (95% CI)**	**EVR+rCNI (N = 1014)**	**MPA+sCNI (N = 1012)**	**RR (95% CI)**
Any AE/infection	169 (100)	179 (100)	-	1000 (98.6)	992 (98.0)	1.01 (0.99, 1.02)
Any infection	82 (48.5)	111 (62.0)	0.78 (0.65, 0.95)	584 (57.6)	664 (65.6)	0.88 (0.82, 0.94)
Viral	40 (23.7)	60 (33.5)	0.71 (0.50, 0.99)	208 (20.5)	357 (35.3)	0.58 (0.50, 0.67)
BKV	17 (10.1)	30 (16.8)	0.60 (0.34, 1.05)	46 (4.5)	87 (8.6)	0.53 (0.37, 0.75)
CMV	6 (3.6)	6 (3.4)	1.06 (0.35, 3.22)	44 (4.3)	158 (15.6)	0.28 (0.20, 0.38)

*P-value to test for no difference ([EVR+rCNI] – [MPA+sCNI] = 0). †Kaplan-Meier incidence rates

AE, adverse event; BKV, BK virus; CI, confidence interval; CMV, cytomegalovirus; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; EVR, everolimus; KTxRs, kidney transplant recipients; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; RR, risk ratio; SCD, standard criteria donor; SD, standard deviation; sCNI, standard-exposure calcineurin inhibitor; SE, standard error; tBPAR, treated biopsy-proven acute rejection.

TH-PO1156

Effect of Adding Dapagliflozin as an Adjunct to Insulin on Urinary Albumin-to-Creatinine Ratio over 52 Weeks in Adults with Type 1 Diabetes

Steven Edelman,[1] Johan Jendle,[2] Paresh Dandona,[3] Chantal Mathieu,[4] Diethelm Tschoepe,[5] Fredrik A. Thorén,[6] Markus F. Scheerer,[6] John Xu,[6] Anna Maria Langkilde.[6] DEPICT-1 and -2 Investigators *[1]Division of Endocrinology and Metabolism, University of California, San Diego, CA; [2]Orebro University, Örebro, Sweden; [3]State University of New York at Buffalo, Buffalo, NY; [4]KULeuven, Leuven, Belgium; [5]Herz- und Diabeteszentrum NRW, Ruhr-Universitaet Bochum, Bad Oeynhausen, Germany; [6]AstraZeneca, Gothenburg, Sweden.*

Background: DEPICT-1 and DEPICT-2 studies, where dapagliflozin (DAPA) was added as adjunct to insulin in adults with inadequately controlled type 1 diabetes (T1D) (glycated hemoglobin: 7.5%–10.5%), reported improvements in glycemic control and weight, and was well tolerated.

Methods: In this pooled post hoc analysis of the DEPICT-1 and -2 studies, we evaluated the effect of dapagliflozin on Urinary Albumin to Creatinine Ratio (UACR) in individuals with T1D with baseline albuminuria.

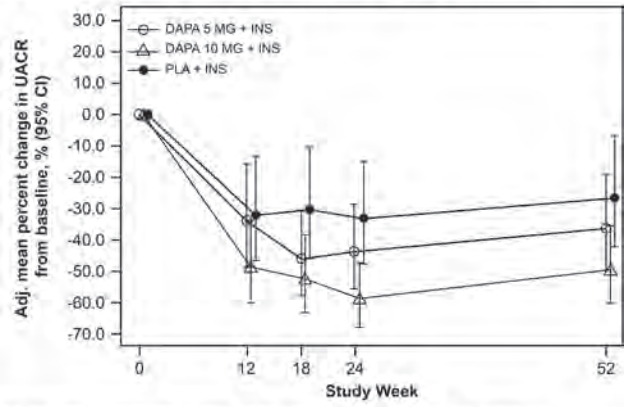
Results: In total, 548 individuals treated with DAPA 5 mg, 565 with DAPA 10 mg, and 532 with placebo had UACR recorded at baseline. Albuminuria at baseline was found in 80, 84, and 87 individuals in the DAPA 5 mg, 10 mg, and placebo arms, respectively. Of these 251 individuals, baseline renal function measured as estimated glomerular filtration rate (eGFR) was normal in 93 individuals (eGFR ≥90 mL/min/1.73 m^2), mildly impaired in 131 individuals (eGFR ≥60 or <90 mL/min/1.73 m^2), and moderately impaired in 27 individuals (eGFR <60 mL/min/1.73 m^2). Changes in eGFR appeared similar across the treatment arms (data not shown). However, treatment with DAPA resulted in a dose-dependent reduction in UACR at weeks 12, 18, 24, and 52 (Figure). The difference in UACR between DAPA 10 mg vs placebo was significant from weeks 18 to 52. At week 52, the differences in UACR between DAPA 10 mg and placebo and DAPA 5 mg and placebo were –31.12% (95% CI: –49.94, –5.22) and –13.30 (95% CI: –37.24, 19.79), respectively.

Conclusions: Treatment with DAPA appears to provide a dose-dependent benefit in reducing UACR, suggesting renoprotective effects in individuals with T1D with baseline albuminuria.

Funding: Commercial Support - AstraZeneca, Gaithersburg, MD, USA.

Underline represents presenting author/disclosure.

Figure: Adjusted mean percent change in UACR (mg/g) from baseline



Adj, adjusted; CI, confidence interval; DAPA, dapagliflozin; INS, insulin; PLA, placebo; UACR, Urinary Albumin to Creatinine Ratio

TH-PO1157

Correction of Serum Potassium with Sodium Zirconium Cyclosilicate in Japanese Patients with Hyperkalemia: A Dose-Finding Study

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Background: Sodium zirconium cyclosilicate (SZC) is an oral potassium (K) binder approved to treat hyperkalemia (HK) in adults in the US and EU. We evaluated SZC doses for correcting serum K (sK) in Japanese patients (pts) with HK in a multicenter, double-blind, placebo-controlled phase 2/3 trial.

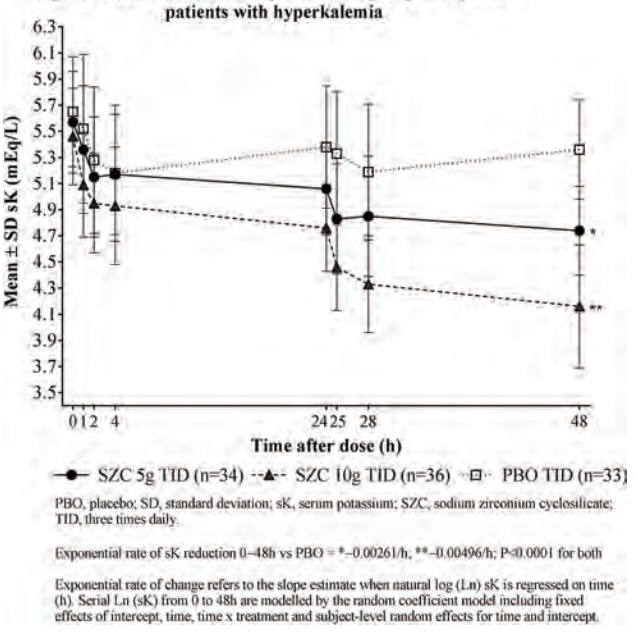
Methods: Pts aged ≥18y with sK ≥5.1–≤6.5mEql/L were randomized 1:1:1 to SZC 5g, SZC 10g, or placebo (PBO) administered (as powder in water) thrice daily for 48h. Primary endpoint was exponential rate of change in sK over 48h. Pts (%) with normokalemia (sK 3.5–5.0mEq/L) at 48h (secondary endpoint), multiple time points (1, 2, 4, 24, 25, 28, and 48h), and adverse events (AEs) were evaluated.

Results: At baseline, the 103 randomized pts (mean age 73y; 75% male) had mean sK of 5.6 mEq/L, mean eGFR of 26.1 mL/min/1.73m^2 (29%, 40%, 28%, and 3% had eGFR <15, 15–<30, 30–<60, and ≥60, respectively). All pts (34 on SZC 5g; 36 on SZC 10g; 33 on PBO) completed the study except 2 PBO pts discontinued due to HK. Exponential rate of sK change from 0–48h vs PBO was –0.00261/h with SZC 5g and –0.00496/h for SZC10g (Figure; both P<0.0001). At 48h, 85% of pts had normokalemia with SZC 5g, 92% with SZC 10g, and 15% with PBO. More pts had normokalemia with SZC 5g vs PBO at 4h through 48h and with SZC 10g vs PBO at every time point. AEs occurred in 4, 5, and 1 pt in the SZC 5g, 10g, and PBO groups; all AEs were mild and single occurrences in individual patients. sK <3.5 mEq/L occurred in 2 pts in the SZC 10g group, and none in the SZC 5g or PBO groups.

Conclusions: SZC 5g and 10g were well tolerated and corrected HK in most Japanese pts within 48h; SZC 10g had the most rapid sK reduction and highest response rate.

Funding: Commercial Support - AstraZeneca

Figure. Mean sK over time by treatment group in Japanese patients with hyperkalemia



PBO, placebo; SD, standard deviation; sK, serum potassium; SZC, sodium zirconium cyclosilicate; TID, three times daily.

Exponential rate of sK reduction 0–48h vs PBO = *–0.00261/h, **–0.00496/h; P<0.0001 for both

Exponential rate of change refers to the slope estimate when natural log (Ln) sK is regressed on time (h). Serial Ln (sK) from 0 to 48h are modelled by the random coefficient model including fixed effects of intercept, time, time x treatment and subject-level random effects for time and intercept.

TH-PO1158

Sodium Zirconium Cyclosilicate for Hyperkalemia: Results of the Randomized, Placebo-Controlled, Multi-Dose HARMONIZE-GLOBAL Study

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Background: Sodium zirconium cyclosilicate (SZC) is an odorless, tasteless, inorganic, oral, potassium (K) binder approved for the treatment of hyperkalemia in adults in the US and Europe. In the HARMONIZE trial (Kosiborod, JAMA 2015), SZC rapidly corrected and maintained control for 28 days in Caucasian patients with few dose-related adverse events (AEs). Presented here is the HARMONIZE Global study; a 28-day, multicenter, randomized, double-blind, placebo-controlled phase 3 study that evaluated the efficacy and safety of SZC for hyperkalemia in primarily Asian patients.

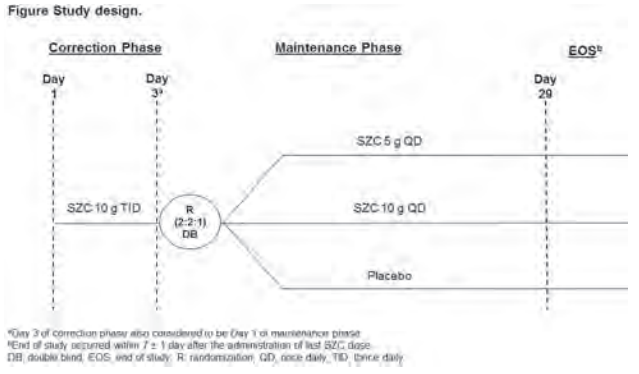
Methods: Outpatients (≥18 yrs) with K ≥5.1mEq/L (measured by the point-of-care device iSTAT) were enrolled from sites in Japan, South Korea, Russia and Taiwan. During the open-label correction phase (CP), patients received SZC 10 g thrice daily for 48 hours (**Figure**), changes in serum K (sK) were evaluated serially. Patients with K 3.5–5.0 mEq/L in the CP entered the 28-day maintenance phase (MP) and were randomized 2:2:1 to receive 5 g SZC, 10 g SZC, or placebo once daily. Background renin angiotensin aldosterone system inhibitors and diuretic use were kept stable. The primary endpoint was the mean serum K (measured by central laboratory) during days 8–29 in MP. Secondary endpoints included changes in sK, proportion of patients who achieved normokalemia (sK 3.5–5.0 mEq/L) in CP and those who maintained normokalemia in MP, quality of life (assessed using EuroQol-5D questionnaire), and changes in aldosterone and renin. Safety parameters included adverse events, vital signs, ECG, and clinical laboratory evaluations.

Results: Efficacy and safety data will be available for presentation.

Conclusions: A randomized, controlled trial of two doses of SZC for hyperkalemia versus placebo was conducted over 28 days in a population of primarily Asian patients; the results will be important for the use of this potassium binder in this population.

Funding: Commercial Support - AstraZeneca

Underline represents presenting author/disclosure.



TH-PO1159

Kidney Injury Biomarkers and Contrast-Associated AKI: A Substudy of the PRESERVE Trial

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Background: The utility of novel biomarkers in contrast-associated AKI (CA-AKI) is unknown. Among PRESERVE trial participants, we evaluated novel proteins of kidney injury and repair to risk stratify post-angiography CA-AKI and 90-day major adverse kidney events and death (MAKE-D); predict pharmacodynamic response to the trial interventions (bicarbonate and acetylcysteine) and; inform clinical trial design.

Methods: We collected plasma and urine 1-2 hours pre- and 2-4 hours post-angiography and measured injury (KIM-1, NGAL, IL-18) and repair (MCP-1, UMOD, and YKL-40) proteins at both time points. We analyzed the association of pre-, post-, and delta (Δ) biomarker levels with 90-day MAKE-D (dialysis, persistent kidney impairment, death) and with CA-AKI. We also evaluated the association of the trial interventions with Δ biomarker levels, and examined whether biomarkers could enrich the primary MAKE-D event rate to improve trial efficiency.

Results: Among 860 PRESERVE participants, pre-angiography levels of four plasma and four urine biomarkers were significantly associated with MAKE-D (Table). Absolute and relative Δ in biomarker levels were modest and were not associated with MAKE-D or CA-AKI. None of the biomarkers demonstrated significant changes with trial interventions. Incorporating the 50th percentile pre-angiography plasma KIM-1 or YKL-40 value into patient screening would have enriched the MAKE-D event rate and reduced the required sample size by ~2000 (30%) participants (prognosticenrichment.com).

Conclusions: Pre-angiography levels of injury and repair biomarkers predict the development of post-angiography MAKE-D outcomes and could improve efficiency of future CA-AKI trials. Changes in biomarker levels did not predict MAKE-D, CA-AKI, or pharmacodynamic response to the trial interventions. The modest change in biomarker levels following angiography suggests that most cases of CA-AKI reflect hemodynamic effects rather than intrinsic kidney damage.

Funding: Other NIH Support - NIDDK RO1 grant, Veterans Affairs Support

	Plasma Median (IQR)			Urine Median (IQR)		
	MAKE-D	No MAKE-D	P-value	MAKE-D	No MAKE-D	P-value
KIM-1	504 (306, 948)	321 (189, 586)	<0.001	1804 (961, 3558)	1409 (722, 2744)	0.06
NGAL	259 (209, 420)	229 (173 296)	0.001	37 (16, 97)	23 (11, 49)	0.009
IL-18	332 (238, 445.81)	318 (246, 408)	0.51	33 (16, 54)	21 (12, 37)	0.003
MCP-1	229 (167, 280)	217 (181, 271)	0.98	289 (159, 565)	205 (118, 363)	0.01
UMOD	59 (41, 81)	71 (51, 98)	0.006	2300 (1462, 3642)	2484 (1558, 3973)	0.46
YKL-40	141987 (98750, 284819)	91574 (53544, 174552)	<0.001	902 (272, 4474)	394 (127, 1166)	<0.001

Preagiography biomarker levels (pg/ml) and their association with primary outcome

TH-PO1160

Alemtuzumab for Relapsing and Refractory Primary Systemic Vasculitis: A Trial of Efficacy and Safety (ALEVIATE)

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Background: Primary systemic vasculitis encompassing ANCA associated vasculitis (AAV) and Behcet's Disease (BD) has considerable morbidity & mortality. Inadequate response and relapses are common. There is an unmet need for safer therapy that leads to sustained remission in patients with relapsing or refractory disease (RD). Alemtuzumab(ALZ), an anti-CD52 mAb depletes lymphocytes for prolonged periods and was shown in observational studies to induce remission in RD. This trial's aim is to determine the efficacy and safety of ALZ in patients with RD.

Methods: Randomized, prospective, open label, dose ranging clinical trial. 24 patients with RD randomized to receive either 60mg or 30mg of ALZ. Eligible patients were required to have failed to respond to standard therapies (cyclophosphamide/rituximab in AAV or anti-TNF therapy in BD). Patients > 60 yrs, creatinine >150umol/L, requiring intensive care unit support were excluded. Treatment was repeated at 6 months(M) or earlier where clinically appropriate. Each patient was followed up for 12M or until withdrawal. Co-trimoxazole and acyclovir prophylaxis was administered. Primary end-points: Proportion of patients with treatment response at 6M(Complete remission-CR: BVAS/WG of 0 for > 1M. Partial remission-PR: No severe BVAS/WG items and >=50% fall in BVAS/WG from entry) & proportion with a severe adverse event(SAE; CTCAE grade >=3).

Results: Evaluable patients:23. Mean age 36.8(10.9) yrs; M:F=9:15; AAV:12; BD:11; withdrawals:6/23(26%)-all due to progressive disease. Response(CR/PR) at 6M:15/23(65.2%; 95%CI: 0.43-0.84); 5/23(22%; 95%CI: 0.08-0.44) had remission that lasted to 12M. 10/15 (66.6%, 95% CI: 0.38-0.88) achieving remission had a relapse during the follow-up period. Of the 8 SAEs in 6 patients(26%), 5 were treatment related (1 CMV colitis, 1 viral gastroenteritis, 1 c.difficile infection; 2 infusion related reactions) and the other 3 were due to relapse. Small sample size precluded dose comparison analysis.

Conclusions: In this small phase II RCT testing the efficacy and safety of ALZ to treat RD, 65% of the patients achieved clinical remission at 6M. Even though relapses were common, 22% achieved sustained remission. SAEs were seen in 26% of the patients. This study indicates that ALZ is a safe therapy in a select group of patients.

Funding: Commercial Support - Genentech

TH-PO1161

Insulin Therapy for the Prevention of Posttransplantation Diabetes Mellitus: Preliminary Results from an International Multicenter Study (ITP-NODAT)

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Background: In our previous proof-of-concept trial, basal insulin therapy early after kidney transplantation significantly reduced the odds of posttransplantation diabetes mellitus (PTDM) throughout 1 year of follow-up (PMID22343119). The ITP-NODAT study aimed at reproducing these findings (NCT03507829).

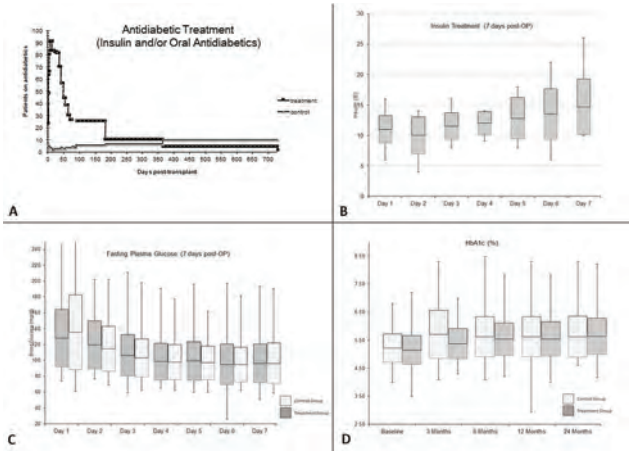
Methods: Kidney transplant recipients without diabetes history were randomized to receive immediate insulin isophane treatment for pre-dinner glucose ≥140 mg/dL, or short-acting insulin and/or oral antidiabetics for fasting glucose ≥200 mg/dL. Primary endpoint: PTDM incidence at 12 months.

Results: Of 263 patients enrolled at 4 centers, N=205 completed month 24 by 5/2018. 119 of 133 treatment patients received insulin for a median duration of 49 days while 18 of 130 control patients received insulin and/or oral antidiabetics for a median duration of 730 days (Figure: A/B). We observed 17 versus 1 episodes of hypoglycemia in treatment versus control patients (none clinically concerning). While results from oral glucose tolerance tests are currently being evaluated, fasting glucose and HbA1c data indicate that treatment and control patients did not separate well in terms of glycemic control (Figure: C/D). Based on HbA1c (≥6.5 %) and antidiabetic treatment, 13 patients in each group classified as diabetics at 12 months.

Conclusions: (1) Exogenous insulin therapy was relatively safe; (2) treatment and control patients had a similarly low PTDM incidence and a low rise in HbA1c over follow-up; (3) there were more control group than treatment group patients who required prolonged antidiabetic therapy. Result (2) differs from our previous trial, where PTDM incidence had been higher, and significantly different between groups. The lower glucocorticoid regimen in ITP-NODAT and increased PTDM awareness likely contributed to this difference.

Funding: NIDDK Support, Commercial Support - Astellas Pharma, Eli Lilly

Underline represents presenting author/disclosure.



TH-PO1162

RITUXILUP: An Open-Label Randomised Multicentre Controlled Trial of Rituximab and Mycophenolate Mofetil (MMF) Without Oral Steroids for the Treatment of Lupus Nephritis

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Background: A key challenge in lupus nephritis (LN) is to treat effectively whilst minimising treatment related toxicity. The investigator led RITUXILUP trial hypothesised that rituximab (RTX), methyl prednisolone (MP) & mycophenolate mofetil (MMF) but without oral steroids (OS) would be non-inferior to standard of care (MP, MMF & OS) in inducing complete remission (CR) at 1yr.

Methods: The trial primary objective was CR at 1yr defined by urine protein/creatinine ratio (uPCR) of ≤50mg/mmol, eGFR (CKD-Epi) ≥60mls/min, or without a fall of >20% if baseline <60mls/min, & without extra steroids above a strictly defined limit. Inclusion criteria: age 12-75yrs, renal biopsy within 8 weeks (ISN/RPS Class III or IV, (A or A/C) or class V), uPCR ≥100mg/mmol & not on maintenance OS. Patients randomised 1:1 all received MP 500mg d1+d15 & MMF with (SoC arm) tapering OS (from 0.5mg/kg) or (RTX arm) RTX 1g d1+d15 & no OS

Results: We needed to recruit minimum 210 patients for 80% power. However, over 2 yrs only 25 (13 RTX, 12 SoC; Female 88%; Non white 68%) were enrolled as the majority of otherwise eligible patients were on longterm OS. The trial terminated early due to slow recruitment & withdrawal of funding. **Median (IQR) days follow up (f/up) for primary endpoint**: RTX arm 336(253,356); SoC arm 354.5(306,365). **Key results n (%): CR at 1 yr or latest f/up if <1yr: RTX** 6 (**46**) vs **SoC** 4 (**33**) (1 randomised to SoC, withdrew & received RTX) **CR (+steroid deviation): RTX** 2 (**15**) vs **SoC** 1 (**8**) **PR: RTX** 3 (**23**) vs **SoC** 6 (**50**) **Non response: RTX** 2 (15) vs **SoC** 1 (8) **Significant difference in median total OS exposure over trial : 0mg in RTX vs 3570mg in SoC & equivalent daily dose including the MP 3.6mg/day in RTX vs 13.7mg in SoC SAEs: RTX** 4 in 3 pts & **SoC** 2

Conclusions: Doing trials in LN remains challenging. Whilst limited, RITUXILUP provides the first RCT data ever to support our hypothesis that LN can be effectively treated without oral steroids. The RTX arm CR is superior to that in most trials despite minimal steroids. A pragmatic future trial will include patients on longterm low dose OS with no dose increase in RTX arm

Funding: Commercial Support - F.Hoffman-La Roche Ltd

TH-PO1163

Failure of Regulatory B Cells to Repopulate After Rituximab Associates with Lack of Efficacy in Renal Transplant Patients with CAMR: Evidence from the RituxiCAN-C4 Trial

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Background: Immune-mediated late failure of kidney allografts is a significant problem, usually presenting as progressive dysfunction with histological features of chronic antibody-mediated rejection (CAMR). RituxiCAN-C4 was an open-labelled randomised controlled phase IV clinical trial running in 13 UK centres from 2007-2017, to assess efficacy of Rituximab in stabilising graft function after failure of optimised oral immunosuppression.

Methods: Of 59 patients meeting eligibility criteria who underwent optimisation, 23 consented to randomisation, 11 to no additional treatment (control), and 12 to Rituximab. In the pre-specified second interim (per protocol) analysis of the 9 who received rituximab vs. 11 controls, there was no significant difference in the primary endpoint (short-term stability of function), so recruitment was halted in 2015. Follow-up ended in 2017.

Results: The median reduction in circulating B cells post Rituximab was 98.2% (IQR 3.8%), with no significant recovery in circulating B cells over 3 years. Analysis of remaining B cells showed normalisation of the proportions of different subpopulations, except for transitional cells expressing higher levels of CD24 and CD38, which remained disproportionately low compared to controls. ELISPOT analysis of indirect alloresponses to donor proteins in all 59 patients confirmed that B dependent CD4+ IFNγ production associated with greater decline in eGFR. Optimisation of immunosuppression that resulted in conversion to non-responsiveness or to anti-donor responses regulated by CD19+ or CD25+ cells was associated with slower decline in eGFR. Regulation by CD19+ cells associated with higher proportions of the same transitional B cells that failed to repopulate in Rituximab-treated patients, none of whom showed this pattern of ELISPOT responsiveness.

Conclusions: This analysis illustrates the importance of B cells and indirect alloresponses in CAMR, confirms the functional heterogeneity of B cells and association with eGFR decline in these patients, and suggests an explanation for the lack of efficacy of Rituximab in CAMR.

Funding: Commercial Support - Roche provided the rituximab free of charge, Government Support - Non-U.S.

TH-PO1164

A Randomized Trial of Mild Hypothermia and Machine Perfusion in Deceased Organ Donors for Protection Against Delayed Graft Function in Kidney Transplant Recipients

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Background: Machine perfusion (MP) of kidneys from deceased donors has been increasingly adopted by many centers even though clinical and cost effectiveness studies remain uncertain in the United States. We investigate the effectiveness of MP compared to mild hypothermia which recently has been shown to be protective against DGF (1).

Methods: The trial was approved by the IRB of UCSF (# 17-21768). Donors are not considered human subjects under federal regulations. A waiver of informed consent for recipients is acceptable based on the same federal regulations. A pragmatic multi-site randomized controlled trial that bases enrollment on each Organ Procurement Organization (OPO) current pumping criteria. There are two main groups of deceased donors (DNDDs), (1) those that are "pump eligible" based on current practice and (2) those that are lower risk and whose kidneys do not receive MP ("not pump eligible"). In this trial, "pump eligible" DNDDs are randomized to one of three groups : (1) normothermia (36.5-37.5 C) plus MP of both kidneys (standard of practice control group), (2) mild hypothermia (34-35 C) plus MP of the left kidney only, and (3) mild hypothermia plus MP of the right kidney only. In this manner, the same number of kidneys are randomized to each of the three treatment strategies (MP alone, mild hypothermia alone, or MP+hypothermia). NCT02525510

Results: Three OPOs joined the trial within the first 12 months and 709 donors were screened for eligibility, 559 (78.8%) had research authorization. 353 were excluded with DCD, age the most common reason for exclusion. 203 DNDDs were enrolled in the trial. There were 2 reportable events (bradycardia and ectopy with low BP) with no adverse events that required intervention. In 40 kidneys randomized to pump-eligibility, intended pump assignment could not be followed. Notably, 28 kidneys (22.5% of pump eligble) could not be pumped when supposed to, mainly because of anatomy and logistics.

Underline represents presenting author/disclosure.

Conclusions: Additional OPOs will join within the next 6 months allowing enrollment to increase above 10/week. Importantly, a significant portion of pump eligble kidneys could not be pumped which demonstrates the need to identify additional protective strategies for kidneys at risk for DGF and poor function. 1. N Engl J Med. 2015 Jul 30;373(5):405-14

Funding: Private Foundation Support

TH-PO1165

Enteric-Coated Mycophenolate Sodium Versus Mycophenolate Mofetil in Combination with Calcineurin Inhibitors in Chinese Renal Transplant Recipients: An Observational Phase 4 Study

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Background: This phase IV observational study (ERL080A2424) compared efficacy and safety of enteric coated mycophenolate sodium (EC-MPS; myfortic®) vs mycophenolate mofetil (MMF; Cellcept®) in Chinese renal transplant recipients (RTxR).

Methods: In this 12-month (M) study, 600 adult RTxR received EC-MPS (N=401) or MMF (N=199) + cyclosporine(CsA)/tacrolimus(TAC) + steroids post-Tx. Usage of mycophenolic acid (MPA) dosing regimen, efficacy, and safety at M12, and MPA exposure ($AUC_{0\text{-}12h}$; EC-MPS) in a pharmacokinetic (PK) subset at days 14 and 90 post-Tx were assessed.

Results: Most patients in EC-MPS (78.4%) and MMF (87.8%) cohorts received a starting daily dose ±25% of recommended dose (EC-MPS: 1440 mg/day; MMF: 2000 mg/day). Efficacy events were similar in both cohorts (**Table 1**). Patients receiving lowest range of starting daily doses (EC-MPS: 360-<720 mg; MMF: 500-<1000 mg) had numerically higher acute rejection (AR) rates than patients with higher MPA exposure (EC-MPS, *P*=0.200; MMF, *P*=0.670). MPA exposure ($AUC_{0\text{-}12h}$; EC-MPS) increased in CsA subset from days 14 to 90, but was similar in TAC subset (**Table 2**). Probability of developing serious infections was low with starting doses ±25% of recommended dose for both cohorts.

Conclusions: EC-MPS and MMF cohorts showed similar efficacy and safety at M12; lowest dose ranges, but not higher, were associated with AR rates in EC-MPS cohort. These results will facilitate informed decision-making for EC-MPS-based regimen in China and for patients of Chinese ethnicity in the US.

Funding: Commercial Support - Novartis

Table 1. Tolerability, efficacy, and safety of EC-MPS vs MMF at M12

Parameters	EC-MPS group	MMF group
Tolerability – PPS	**N = 399**	**N = 197**
Duration of use in days, mean (SD)	344.2 (73.53)	338.6 (90.97)
Mean dose in CsA patients*, mg, n (mean±SD)	112 (977.1±207.44)	43 (1255.8±338.45)
Mean dose in TAC patients*, mg, n (mean±SD)	190 (910.9±207.66)	117 (1237.2±262.30)
Number of dose reductions, n (mean±SD)	322 (2.2±1.21)	162 (2.5±1.30)
Time to first dose reductions*, days, n (mean±SD)	322 (39.2±56.20)	162 (49.7±71.71)
Patients switched from EC-MPS to MMF and vice versa, n (%)	72 (18.0)	17 (8.6)
Efficacy – PPS		
eGFR (mL/min/1.73 m² by MDRD4), mean±SD	65.0±16.65	70.2±17.65
BPAR, n (%)	12 (3.0)	7 (3.6)
Suspected or confirmed AR episodes (at least 1), n (%)	40 (10.1)	18 (9.1)
Graft loss, n (%)	1 (0.25)	1 (0.50)
Death, n (%)	3 (0.75)	6 (3.04)
Safety – FAS/SAF	**N = 401**	**N = 199**
Overall AEs, n (%)	322 (80.3)	172 (86.4)
Infections and infestations	182 (45.4)	76 (38.2)
Gastrointestinal disorders	91 (22.7)	55 (27.6)
Overall SAEs, n (%)	149 (37.2)	66 (33.2)
Discontinuation of study	36 (9.0)	17 (8.5)
AEs leading to study discontinuation	1 (0.2)	2 (1.0)

*At M12, total number of patients in the CsA arm were 139 (EC-MPS cohort) and 48 (MMF cohort); total patients in the TAC arm were 228 (EC-MPS cohort) and 137 (MMF cohort).
AE, adverse event; BPAR, biopsy-proven acute rejections; CsA, cyclosporine; EC-MPS, enteric coated mycophenolate sodium; eGFR, estimated glomerular filtration rate; FAS, full analysis set; M, month; MDRD4, 4-variable modification of diet in renal function disease; MMF, mycophenolate mofetil; PPS, per-protocol set; SAE, serious AE; SAF, safety analysis set; SD, standard deviation.

Table 2. Pharmacokinetics of MPA at Days 14 and 90 post-Tx

Parameters	EC-MPS (MPA) in CsA subset				EC-MPS (MPA) in TAC subset			
	Day 14 (N = 15)		Day 90 (N = 13)		Day 14 (N = 16)		Day 90 (N = 14)	
	n (mean±SD)	CV (%)	n (mean±SD)	CV (%)	n (mean±SD)	CV (%)	n (mean±SD)	CV (%)
Daily dose, mg	15 (1750±127)	7.2	13 (1160±216)	18.5	16 (1160±271)	23.4	14 (874±263)	30.1
T_{max}, hr	15 (2.96±2.47)	83.5	13 (3.64±3.91)	107.4	16 (3.26 ±2.93)	89.8	14 (2.50±1.02)	40.9
C_{max}, µg/mL	15 (10.2±10.4)	102.6	13 (12.7±10.0)	79.2	16 (18.5±14.0)	75.4	14 (20.9±12.7)	61.0
$AUC_{0\text{-}12h}$, (hr*µg/mL)	7 (29.5±16.3)	55.3	9 (39.2±16.4)	41.7	14 (53.8±25.2)	46.8	12 (52.0±23.0)	44.2
Dose-normalized $AUC_{0\text{-}12h}$ (h*µg/mL)	7 (24.3±13)	53.3	9 (49.6±20.8)	41.9	14 (64.8±23.1)	35.7	12 (86.7±28.9)	33.4

AUC, area under the curve; CsA, cyclosporine; C_{max}, maximum concentration; CV, coefficient of variation; EC-MPS, enteric-coated mycophenolate sodium; MPA, mycophenolic acid; SD, standard deviation; Tx, transplantation; TAC, tacrolimus; T_{max}, time to maximum concentration.

TH-PO1166

Is High-Dose Telmisartan for Proteinuria Better and Safe?

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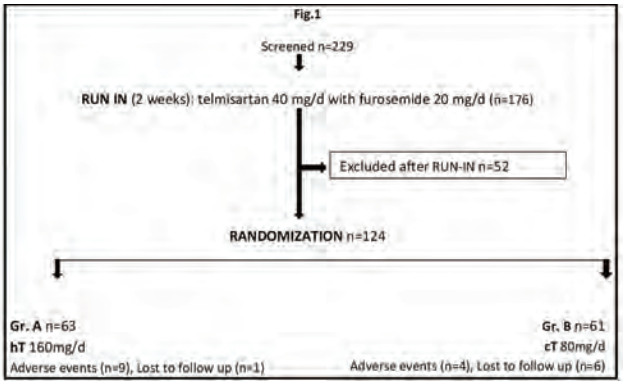
Background: Renal and CV outcomes correlate with proteinuria(PU) reduction with ARB therapy in diabetic(DN) and non diabetic(non DN) proteinuric diseases. Combining ACEI with ARB for maximal RAAS blockade and PU reduction failed to meet safety criteria. This trial aims to compare benefit [of PU reduction] vs risk (rising creatinine, declining eGFR or hyperkalemia)of using **high dose Telmisartan(hT) 160 mg/d** i.e. Gr. A versus **conventional dose Telmisartan 80mg/d(cT)** i.e. Gr. B in treatment of DN and non DN proteinuric patients(pts).

Methods: This is hospital based RCT. Pts with persistent PU ≥1 gram/day, due to DN and non DN disease, neither on any disease specific therapy nor on RAAS blockers for prior 6 wks were screened. Fig 1 shows protocol of study. Furosemide 20mg/day was given in both groups. End point: completion of 6 mo. of follow up or discontinuation of therapy (K>5.5, Sr. Cr rise >30%, eGFR <30). Primary outcome: % change in PU within and between groups. Secondary outcomes:change in Sr.Cr,eGFR by MDRD,BP and occurrence of adverse effects. Intention to treat analysis was done.

Results: No. of pts after randomization and subsequent incidence of adverse effects has been shown in table 1. Dose-related adverse events eg.K+ > 5.5 mEq/L were comparable in both groups but decline in eGFR to <30 ml/min/1.73 m² was more in Gr.A compared to Gr.B (6 vs 2).

Conclusions: Effectiveness of **cT** versus **hT** for PU reduction is comparable in proteinuric diseases. Adverse effects like hyperkalemia were similar, however higher events of dose related decline in eGFR occurred with hT.

Funding: Government Support - Non-U.S.



Study protocol

	Gr.A; median		Gr.B; median		% Change in parameter		
	#	##	#	##	Gr.A	Gr.B	Pvalue
PU*	4206	1400;p0.00	3260	1344;p0.00	45.88	48.71	0.42
SBP mmHg	140	122;p0.00	140	124;p .00	10.62	9.63	0.46
DBP mmHg	90	80;p0.00	84	80;p .00	9.57	8.53	0.45
eGFR	57.77	50.39;p0.27	57.4	53.82;p0.42	6.88	3.93	0.70
Sr.Cr**	1.27	1.55;p0.00	1.4	1.48;p 0.03	15.67	5.64	0.00
K;mmol/l	4.3	4.3	4.45	4.4	3.43	1.26	0.28

#: Baseline; ## at end point,*in mg/d, **in mg/dl

RESULTS

TH-PO1167

PHYOX: A Safety and Tolerability Study of DCR-PHXC in Primary Hyperoxaluria Types 1 and 2

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Background: Primary Hyperoxaluria (PH) is a family of rare diseases characterized by hepatic overproduction of oxalate due to 3 distinct genetic mutations. Clinical manifestations include nephrocalcinosis, recurrent kidney stones, progressive renal impairment, and systemic oxalosis (primarily PH1). DCR-PHXC is an investigational RNAi therapeutic targeting LDHA enzyme, which is involved in the ultimate step of hepatic oxalate production and has the potential to treat all 3 known genetic forms of PH.

Underline represents presenting author/disclosure.

Methods: This abstract includes preliminary data from the ongoing PHYOX study (ClinicalTrials.gov: NCT03392896), a two-part, single-ascending dose study conducted in 25 normal healthy volunteers (NHVs, Group A) and 16 PH patients (Group B). Eligible PH patients have PH1 or PH2, urinary oxalate (Uox) ≥0.7 mmol/24Hr, and eGFR ≥30 mL/min/1.73m^2. Group A is randomized including placebo with 5 cohorts dosed at 0.3, 1.5, 3, 6, and 12 mg/kg DCR-PHXC or placebo. Group B is open label and has 3 PH1 Cohorts dosed at 1.5, 3, and 6 mg/kg DCR-PHXC and a 4th PH2-only cohort. The primary objective is safety and secondary endpoints include change in 24Hr Uox from baseline defined as the mean of two 24Hr urine collections during screening.

Results: Group A is complete with no observed safety or tolerability issues and no serious adverse events (SAEs). Two mild injection site reactions (ISRs) occurred and resolved within 48Hrs. Dosing is complete in Group B Cohorts 1 (1.5 mg/kg, n=4) and 2 (3.0 mg/kg, n=4) and in the Cohort 4 sentinel PH2 subject (1.5 mg/kg). To date, only adults have been dosed. No SAEs have occurred in Group B. Two mild ISRs resolved within 48Hrs. Preliminary results following a single administration of 1.5 mg/kg DCR-PHXC in Cohorts 1 and 4 shows maximum 24Hr Uox reductions from baseline between 39%-57% between postdose Days 43 and 95. Cohort 2 has shown 40-62% reductions in Uox between Days 15 and 43 and 2/4 patients have 24Hr Uox values in the normal range. Follow-up in all Cohorts is ongoing.

Conclusions: Preliminary PHYOX data show DCR-PHXC is safe and well-tolerated in this ongoing study. Observed reduction of 24Hr Uox following a single administration of DCR-PHXC in both PH1 and PH2 patients is a promising sign of DCR-PHXC's potential potency and duration of action.

Funding: Commercial Support - Dicerna Pharmaceuticals

TH-PO1168

Short-Term Medium-Chain Triglycerides Supplementation on the Nutritional Status and Muscle Strength of Patients on Chronic Dialysis

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Background: One of the major risk factors for cardiovascular disease is lipid abnormalities among hemodialysis patients. We prospectively evaluated the effects of medium chain triglycerides (MCT) supplementation on the nutritional status, muscle strength and anthropometrics of patients on chronic dialysis.

Methods: This study was randomized, double-blind comparison of placebo and active treatment for dialysis patients with MCT. In this full scale of the evaluation study, chronic dialysis patients who have malnutrition (serum albumin less than <3.8 g/DL) and did not have the active infection disease were included. Dietary supply with MCT and by daily dietary record review, we estimated the amount of dietary components in participants. Patients were supplied with the powder of MCT, 9.1g, (100kcal) daily while the control group received start (100 kcal) daily. The biochemical data, nutritional status, muscle power and anthropometrics were evaluated at baseline and 4 months later.

Results: Totally 84 patients (male, 43.8%; mean age, 62.7 years) of chronic dialysis with malnutrition (albumin 3.42± 0.32 g/dL) were included. Forty-two patients received MCT treatment (100 kcal daily) and another fourth-two patients received starch 100 kcal daily. After MCT treatment, the SGA 7-point nutritional score (5.22± 1.53 to 6.19 ± 1.36, p=0.001) and the estimated carbohydrate amount (127.7± 69.8 to 165.9± 42.5g, p=0.004) augmented. Additionally, the hand-grip strength (18.0± 6.8 to 19.2± 7.5kg, p =0.048) as well as the middle arm circumference (25.4 ± 2.72 to 26.9 ± 3.7 cm, p= 0.025) improved. However the patients received starch supplement did not improve muscle power or nutritional score.

Conclusions: In chronic dialysis patients with malnutrition, short- term daily oral MCT supply could improve the nutritional status in term of nutritional score and carbohydrate amount. It will contribute to the positive effect of muscle thickness and muscle power.

TH-PO1169

Effect of Hemodiafiltration (HDFIT) on Physical Activity and Self-Reported Outcomes: Primary Results of the Brazilian HDFIT Trial

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Background: Advantages of hemodiafiltration (HDF) in solute removal and clinical outcomes compared to hemodialysis have been reported. HDFIT investigated the effects of HDF on physical activity (PA), quality of life (QOL) and other outcomes.

Methods: HDFIT (NCT02787161) is a multicenter RCT conducted in 13 clinics in Brazil that studied if HDF effects PA measured by accelerometry (ActiGraph, Pensacola, USA), self-reported QOL as per SF-36, and laboratories. Stable HD patients (vintage 3-24 months) were randomized to either high-volume online HDF or high-flux HD (control). We compared differences in changes from baseline (BL) at months 3 and 6 for 1) step counts and moderate-to-vigorous PA (MVPA) over 24 hrs after HD (primary outcome) and 2) self-reported SF-36 vitality scores and post-dialysis recovery time (secondary outcome), and 3) laboratory parameters. Linear mixed-effects models (LMM; adjusted for age, sex, and baseline values) quantified effect sizes of switching to HDF. Data are reported as percentage of the effect size to the BL mean value (control) with 95% CIs.

Results: We randomized 195 patients (age 53±15 yrs; 71% male; 29% diabetes) from Aug/16 to Oct/17. Exchangeability at BL was achieved for the primary outcomes (BL step count 5184±3374 (HDF) vs 5050±4262 (HD), P=0.69; min of MVPA 27±32 (HDF) vs 27±42 (HD), P=0.95). HDF tended to increase the step count by 3.0% (95%CI -2.3 to 8.3) and the min of MVPA by 2.3% (95%CI -6.9 to 11.5; Figure 1A), and reduce the recovery time by 15% (-31 to 2) vs HD (Figure 1B). SF-36 Vitality scores were not affected by HDF. Effect sizes of HDF on laboratories are consistent with increased solute clearance (Figure 1C).

Conclusions: HDF produces higher clearance of solutes compared to HD. Despite borderline significance, HDF has a positive absolute effect on increasing step counts and minutes of MVPA, and reducing post-dialysis recovery time compared to HD.

Funding: Commercial Support - Fresenius Medical Care and Pontificia Universidade Catolica do Parana

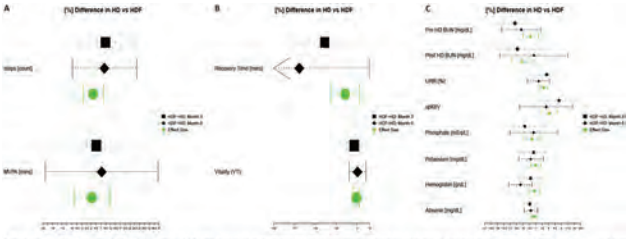

Figure 1: Forest plots depicting the differences in change between HDF versus HD from baseline (reference) to months 3 (black square) and 6 (black diamond). Data are presented as the percentage of the effect size in reference to the baseline mean value in the control group . Linear mixed effects models estimate the effect size of HDF compared to HD adjusted for baseline value, age and sex (green circle). A) step counts and mins of MVPA during 24 hours after the treatment. B) post-dialysis recovery time and SF-36 vitality scores. C) selected laboratory parameters.

Underline represents presenting author/disclosure.